CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF HEART FAILURE 2023

5th Edition

Ministry of Health Malaysia

Academy of Medicine Malaysia

National Heart Association of Malaysia

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STATEMENT OF INTENT

This clinical practice guideline (CPG) is meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her patient based on the clinical picture presented by the patient and the management options available locally.

PERIOD OF VALIDITY

This CPG is issued in 2023 and will be reviewed in 5 years or sooner if new evidence becomes available.

CPG Secretariat
c/o Health Technology Assessment Unit
Medical Development Division
Ministry of Health Malaysia
4th Floor, Block E1, Parcel E
62590, Putrajaya.

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This is the 5th update to the Clinical Practice Guidelines on Heart Failure (published 2000, 2007, 2014 and 2019). It supersedes the previous CPGs on Heart Failure.

MESSAGE FROM THE DIRECTOR GENERAL OF HEALTH

Heart failure is a condition associated with significant morbidity and mortality. In recent years, there have been advancements in both treatment and diagnostics, to enable all stakeholders in healthcare to improve the management of this condition.

Over 23 years have passed since the publication of the first Clinical Practice Guidelines in Malaysia for Heart failure. Subsequent editions in 2007, 2014, and 2019 reflected the growing body of evidence generated both internationally and locally. This latest edition incorporates the latest science in this field.

I am pleased to see that the goal of management has evolved, from reducing symptoms, improving functional capacity, quality of life and patient survival, to reducing heart failure-related hospitalisation, and reducing the socio-economic impact. The paradigm shift is timely to reduce the burden of hospital admissions due to heart failure.

In addition, I can see new approaches to managing heart failure, including the introduction of early implementation and optimization of foundational heart failure medications, and a structured, multidisciplinary strategy is essential to embark seamless care between hospitals and primary care.

With 25 key messages and 22 key recommendations, I am sure these guidelines will provide all healthcare providers the necessary information that will lead to optimal care of patients with heart failure in Malaysia.

I congratulate the Writing Committee members who have worked hard to produce these guidelines, and I thank all stakeholders who have contributed to its publication. I look forward to the active dissemination of the new information, and its translation into clinical practice.

Dr Muhammad Radzi Abu Hassan
Director-General of Health Malaysia

MEMBERS OF THE EXPERT PANEL

CHAIRPERSON:

Dr. Jeyamalar Rajadurai	Consultant Cardiologist, *Subang Jaya Medical Center, Selangor*

MEMBERS (in alphabetical order)

Dr. Abdul Raqib Abd Ghani	Consultant Cardiologist & Electrophysiologist, *Hospital Sultan Idris Shah, Selangor*
Dr. Azmee Mohd Ghazi	Consultant Cardiologist, *Institut Jantung Negara*
Dr. Anwar Suhaimi	Consultant Cardiac Rehabilitation Physician, *Pusat Perubatan Universiti Malaya*
Dr. Cham Yee Ling	Consultant Cardiologist, *Sarawak Heart Center*
Dr. David Chew Soon Ping	Consultant Cardiologist, *Cardiac Vasuclar Sentral Kuala Lumpur*
Dr. Feisul Idzwan Mustapha	Consultant Public Health Specialist, *Kementerian Kesihatan Malaysia, Putrajaya*
Dr. Geetha Kandavello	Consultant Pediatric & Adult Congenital Cardiologist, *Institut Jantung Negara*
Dr. Izwan Effendy Ismail	Family Medicine Specialist, *Klinik Kesihatan Puchong Batu 14*
Dr. Liew Houng Bang	Consultant Cardiologist, *Hospital Queen Elizabeth II, Sabah*
Dr. Ma Soot Keng	Consultant Cardiologist & Electrophysiologist, *Island Hospital*
Dr. Mohd Rahal Yusoff	Consultant Cardiologist & Physician, *Universiti Teknologi MARA (UiTM)*
Dr. Noel Ross Thomas	Consultant Physician, *Hospital Kuala Lumpur*
Dr. Ong Mei Lin	Consultant Cardiologist, *Gleneagles Hospital Penang*
Dr. Rohana Abdul Ghani	Consultant Endocrinologist, *Universiti Teknologi MARA (UiTM)*
Dr. Sunita Bavanandan	Consultant Nephrologist, *Hospital Kuala Lumpur*
Dr. Vengketeswara Rao Seetharaman	Family Medicine Specialist, *Klinik Kesihatan Serendah*
Dr. Wardati Mazlan Kepli	Pharmacist & Research Fellow (Cardiovascular), *Universiti Malaya*
Dr. Wan Azman Wan Ahmad	Consultant Cardiologist, *Pusat Perubatan Universiti Malaya*
Dr. W. Yus Haniff W. Isa	Consultant Cardiologist, *Hospital Universiti Sains Malaysia*

LIST OF EXTERNAL REVIEWERS (in alphabetical order)

Dr. Aizai Azan Abdul Rahim	Consultant Cardiologist, *Institut Jantung Negara*
Dr. Chong Kuck Meng	General Practitioner, *Klinik Chong, Slim River, Perak*
Dr. Kamaruddin Mohd.Yusoff	Former Professor & Head of Biochemistry, *Universiti Malaya*
Dr. Koh Kok Wei	Consultant Cardiologist & Electrophysiologist, *Subang Jaya Medical Center*
Dr. Martin Wong Ngie Liong	Consultant Paediatrician, *Sarawak Heart Center*
Dr. Mastura Ismail	Timbalan Pengarah (Kesihatan Primer), Bahagian Pembangunan Kesihatan Keluarga, *Kementerian Kesihatan Malaysia*
Dr. Narul Aida Salleh	Family Physician, *Klinik Kesihatan Kuala Lumpur*
Dr. Ong Loke Meng	Consultant Physician & Nephrologist, *Island Hospital Penang*
Dr. Ong Tiong Kiam	Consultant Cardiologist, *Sarawak Heart Center*
Dr. Paras Doshi	Consultant Physician & Head of Medical Department, *Hospital Tuanku Fauziah, Perlis*
Dr. Rokiah Ismail	Head, Department of Dietetics, *Pusat Perubatan Universiti Malaya*
Dr. Sahimi Mohamed	Head of Pharmacy, Cardiology Center, *Hospital Sultan Idris Shah, Selangor*
Dr. Saiful Safuan	Consultant Physician (Acute Internal Medicine) & Head of General Internal Medicine Unit, Department of Medicine & Head of Clinical Research Center, *Hospital Kuala Lumpur*
Dr. Saari Mohamad Yatim	Consultant Rehabilitation Physician, Rehabilitation Medicine, *Hospital Sultan Idris Shah, Selangor*
Dr. Saravanan Krishinan	Consultant Cardiologist, *Hospital Sultanah Bahiyah, Kedah*
Dr. Tan Maw Pin	Consultant Geriatrician, *Pusat Perubatan Universiti Malaya*
Dr. Wan Jumani Paizi	Head of Programme (Foreign Languages), Center for Modern Languages, *Universiti Malaysia Pahang*
Dr. Wong Ping Foo	Family Medicine Specialist, *Klinik Kesihatan Cheras Baru*
Dr. Zanariah Hussein	Consultant Endocrinologist, *Hospital Putrajaya*

RATIONALE AND PROCESS OF GUIDELINES DEVELOPMENT

Cardiovascular disease is an important cause of morbidity and mortality in Malaysia. Heart Failure (HF), the end stage of most diseases of the heart, is a common medical problem encountered in primary care and is an important cause of hospital admissions and readmissions with a significant impact on hospital expenditure. As the population ages, the prevalence of HF is expected to increase.

The 1st Clinical Practice Guidelines (CPG) in HF was published in 2000 with revisions in 2007, 2014 and 2019. Since then, there have been many new developments in this field. Thus, the publication of this 5th edition is timely. This CPG stresses on the early implementation and optimization of the "Foundational HF" medications. It also proposes a structured multidisciplinary strategy for the seamless care of patients with HF between hospital and primary care.

This CPG was drawn up by a committee appointed by the National Heart Association of Malaysia and Ministry of Health. It comprises cardiologists, nephrologists, family medicine and general physicians and pharmacists from the government, private sectors, and the public Universities.

Objectives:

The objectives of this CPG are to:

- Critically review the latest scientific evidence, since the last CPG, in the diagnosis and management of HF.
- Incorporate this new evidence in the daily management of our patients and adapt it to our local needs and available resources.
- Develop clinical pathways for HF.
- Establish HF Clinics and provide guidance on step down care of these patients within primary healthcare.

Process

The last CPG published in 2019 was used as a basis. Apart from addressing previous clinical questions that needed to be updated, the Expert Panel also formulated new questions that needed to be addressed. These clinical questions have been divided into sections and each member was assigned one or more topics.

A review of current medical literature on HF from 1st Sept 2018 (the date of the last CPG) till 31st August 2022 was performed. Literature search was carried out using the following electronic databases - PubMed and Cochrane Database of Systematic Reviews.The following Medical Subject Headings (MESH) terms or free text terms were used either singly or in combination:

"Heart Failure", "Congestive Cardiac Failure", "Acute Heart Failure, "Chronic Heart Failure" "Right Heart Failure", "Left Heart Failure" [MeSH], "Heart Failure Reduced Left Ventricular Function", Heart Failure Preserved Left Ventricular Function" [MeSH], Acute decompensated heart failure, tachycardio-induced cardiomyopathy, heart failure mid-range, refractory heart failure, terminal heart failure, end stage heart failure, cardio-oncology

The search was filtered to clinical trials and reviews, involving humans, and published in the English language. The relevant articles were carefully selected from this huge list. In addition, the reference lists of all relevant articles retrieved were searched to identify further studies. Experts in the field were also contacted to obtain further information. International guidelines on HF - the American Heart Association / American College of Cardiology and European Society of Cardiology - were also studied.

All literature retrieved was appraised by members of the Expert Panel and all statements and recommendations made were collectively agreed by the group. The grading of evidence and the level of recommendation used in this CPG was adapted from the American College of Cardiology / American Heart Association and the European Society of Cardiology (Page10).

After much discussion, the draft was then drawn up and submitted to the Technical Advisory Committee for Clinical Practice Guidelines, Ministry of Health Malaysia and key health personnel in the major hospitals of the Ministry of Health and the private sector for review and feedback.

Clinical Questions Addressed:

There were several topics and subtopics that were formulated addressing the diagnosis and therapy of HF.

For ***diagnosis***: In a person presenting with shortness of breath:

- What features in the history and clinical examination would make one suspect this patient is having HF?
- What diagnostic tests help confirm the clinical suspicion of HF with reasonable sensitivity and specificity?
  - ECG
  - Chest X-ray
  - Natriuretic peptides
  - Echocardiogram
  - Lung ultrasound

For ***therapy***, the topics and subtopics were formulated using the Population Intervention Comparison and Outcome (PICO) method as follows:

P: Population - Persons with confirmed HF (including both gender and the elderly) and who had:

- Reduced left ventricular (LV) function (LVEF < 40%) - HF*r*EF
- Preserved LV function (LVEF > 50%) - HF*p*EF
- Mildly reduced LV function (LVEF: 40-50%) - HF*mr*EF
- HF with improved LV function - HF*imp*EF

These patients could be:

- Congested (Volume overload),
- Hypotensive (Cold) or,
- Combination of congestion and hypotension.

The etiology could be: (either singly or in combination)

- Coronary artery disease
- Atrial Fibrillation (AF)
- Diabetes

- Chronic Kidney disease
  - Not on renal replacement therapy
  - On renal replacement therapy

I: Intervention:
- Non-pharmacological therapy
- Pharmacological therapy:
  - Diuretics
  - Angiotensin Converting Enzyme Inhibitors (ACE-I),
  - Angiotensin Receptor Blockers (ARB)
  - Angiotensin Receptor and Neprilysin Blockers (ARNI)
  - β-blockers
  - Mineralocorticoid Antagonists (MRA)-both steroidal and non steroidal
  - Sodium Glucose cotransporter-2 inhibitors (SGLT2-i)
  - Statins
  - etc
- Surgery :
  - Valve surgery/percutaneous intervention
  - Coronary artery bypass surgery
- Device therapy
  - Cardiac resynchronisation therapy
  - Catheter ablation
  - Pacemaker therapy

C: Comparison:
- Non-pharmacological therapy vs no non-pharmacological therapy
- Diuretics vs no diuretics
- ACE-I vs no ACE-I
- etc

O: Outcome:
- Improvement in symptoms.
- Reduction in:
  - Hospital readmissions for HF
  - Major Adverse Cardiovascular (CV) Events - MACE - (Myocardial Infarction (MI), stroke, CV death).
  - All-cause mortality

Type of Question - Involves:
- Therapy - pharmacotherapy, surgery, device therapy
- Harm -
  - Worsening of symptoms and readmission rate.
  - Increase in MACE.
  - Increase in bleeding risk and stroke rate.
  - Adverse effects due to pharmacotherapy.
- Prognosis - reduction in MI, heart failure, CV death and improvement in all-cause mortality.

Type of Study
- Systematic review and meta-analysis.
- Randomised controlled studies.
- Cohort studies.

Thus, there were numerous clinical questions formulated.

Examples of some of these Clinical Questions:

- For a person with HF*r*EF and congested (volume overload) will the use of diuretics lead to an improvement in symptoms, hospital readmission, cardiac event rate and / or all-cause mortality?
- For a person with HF*r*EF and not congested (volume overload) will the use of diuretics lead to an improvement in symptoms, hospital readmission, cardiac event rate and / or all-cause mortality?
- For a person with HF*r*EF and congested (volume overload) will the use of ACE-I lead to an improvement in symptoms, hospital readmission, cardiac event rate and / or all-cause mortality?
- For a person with HF*r*EF and CAD, will coronary artery bypass surgery lead to an improvement in symptoms, hospital readmission, cardiac event rate and / or all-cause mortality?
- For a person with HF*p*EF and congested (volume overload) will the use of ACE-I lead to an improvement in symptoms, hospital readmission, cardiac event rate and / or all-cause mortality?

Target Group and Target Population:

This guideline is developed for all healthcare providers involved in the management of HF in individuals (> 18 years) with and at risk of HF.

Facilitators and Barriers:

The main barrier for the successful implementation of this CPG is:

1. The lack of knowledge of healthcare providers in the:
   - Diagnosis of HF.
   - Management of HF - initial treatment and long-term follow-up.
   - Optimization of therapy and when to refer to tertiary centers.
2. Availability of Natriuretic Peptide testing - BNP, NTProBNP - for early diagnosis of HF in Primary Health Care Clinics.
3. Availability of Foundational HF Medications in Primary Health Care Clinics (ARNI - Not available, SGLT2- available in small quota and only for use in diabetic patients.)

Applicability of the Guidelines and Resource Implications:

These guidelines were developed considering our local health resources. Blood investigations, chest radiographs, ECGs and echocardiograms are common in almost all public health facilities. Most of the drugs used to treat HF - diuretics, ACE-I, ARB, β-blockers have been approved for use in Malaysia and available in public hospitals as generics.

This guideline aims to educate health care professionals on strategies to optimize existing resources in the timely management of patients with HF.

Implementation of the Guidelines:

The implementation of the recommendations of a CPG is part of good clinical governance. To ensure successful implementation of this CPG we suggest:

- Increasing public awareness of CVD and HF in general and educating them on the importance of seeking early medical attention.
- Continuous medical education and training of healthcare providers on the implementation and optimization of the Foundational HF medications. This can be done by road shows, electronic media, and in-house training sessions.
- Clinical audit by individual hospitals and units to ensure compliance using the suggested performance measures in Section 19, pages 160.

Period of Validity of the Guidelines:

These guidelines need to be revised at least every 5 years to keep abreast with recent developments and knowledge that is being learnt.

Dr. Jeyamalar Rajadurai
Chairperson

Table 1: GRADES OF RECOMMENDATIONS AND LEVELS OF EVIDENCE

GRADES OF RECOMMENDATION	
I	Conditions for which there is evidence and/or general agreement.
II	Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure/therapy.
II-a	Weight of evidence/opinion is in favor of its usefulness/efficacy.
II-b	Usefulness/efficacy is less well established by evidence/opinion.
III	Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective and, in some cases, may be harmful.

LEVELS OF EVIDENCE	
A	Data derived from multiple randomized clinical trials or meta-analyses.
B	Data derived from a single randomized clinical trial or large non-randomized studies.
C	Only consensus of opinions of experts, case studies or standard of care.

Adapted from the American College of Cardiology Foundation/ American Heart Association and the European Society of Cardiology

(Available at: http://assets.cardiosource.com/Methodology_Manual_for_ACC_ HA_Writing_Committees and at http://www.escardio.org/guidelines-surveys/escguidelines/about/Pages/rules-writing.aspx).

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WHAT'S NEW IN THE GUIDELINES

What is new is:

1. The concept of "Foundational Heart Failure" medications and advising on the strategy of:
   - Initiating all about the same time.
   - Titrating them up relatively quickly (preferably within 3 months) to maximally tolerated or target doses.
2. The class of SGLT2-i as a HF medication based on recent clinical evidence.

	4th Ed CPG Heart Failure 2019 (Old)	5th Ed CPG Heart Failure 2023 (New)
Goal of management	Focused on reducing symptoms, improving functional capacity, quality of life and patient survival.	• In addition to the previously mentioned goals, the emphasis is on making a reduction in HF related hospitalizations as an important goal of management to reduce the socio-economic impact of the disease.
Definition of HF	Was defined solely based on clinical symptoms and signs.	• Is defined based on clinical symptoms and signs that should be supported objectively by either an elevation of natriuretic peptides and/or evidence of pulmonary or systemic congestion.
Classification of HF	Was classified by clinical presentation only.	• Is classified by clinical presentation as well as LVEF categories and Stages of HF.
Diagnosis of HF	-	• Places more emphasis on using objective testing with Natriuretic Peptides for the diagnosis of HF in addition to clinical symptoms & signs.
Acute HF	-	• Introduces the concept of 3 phases: ➢ **Phase 1** - Urgent treatment and stabilization usually in the emergency department. ➢ **Phase 2** - In-hospital management. ➢ **Phase 3** - Discharge and Post discharge. • Recognizes that in the period immediately following discharge, the patient is "vulnerable" for decompensation and advises closer follow up, preferably in the HF clinic. • Provides a discharge care plan & summary to facilitate follow up. (Appendix III, IV, pages 164-165)

Precipitating Factors	-	• Introduces the acronym **"CHAMPION"** as a quick reminder of the precipitating factors for acute HF. (page 73)
Pharmacotherapy HF*r*EF	-	• Introduces the concept of **"Foundational HF Medications"**: ➢ RAS blockers (ACE-I, ARB, ARNI) ➢ β-blockers ➢ MRA ➢ SGLT2-i • Recommends that these be initiated while the patient is in hospital and up titrated to maximally tolerated or target doses as soon as possible, preferably within 12 weeks post- discharge. • Recommending that the dose of diuretic be reduced when the patient is no longer congested. • Provides a section on patient profiling (section 10.2) and how to initiate and titrate **"Foundational HF Medications"**. This is complemented with Flowcharts III, IV and V, pages 37-39
SGLT2-i	-	• Introduces this class of medications in the management of all categories of LVEF to reduce HF hospitalizations and improve CV outcomes.
Diuretics		• Recommends that the dose of diuretics be reduced when the patient is no longer volume overloaded.
Atrial Fibrillation	-	• Recommends rhythm control instead of rate control for recent onset AF of < 1 year duration, wherever possible.
HF*p*EF		• Provides more recommendations on the diagnosis and management of HF*p*EF.
New Sections		11. Chronic HF due to HF*mr*EF 12. Chronic HF due to HF*imp*EF 14.2 Valvular Heart Disease and HF 14.3 Cardiomyopathy and HF 14.8 Coronavirus 2019 (Covid-19) +/- Vaccine and HF 15.3 Palliative and End of Life Care 16. Heart Failure Rehabilitation 17.4 Telemedicine/Telehealth

GLOSSARY

Abbreviation	Description
ACC	American College of Cardiology
ACE-I	Angiotensin Converting Enzyme Inhibitor
ACHD	Adult Congenital Heart Disease
ACS	Acute Coronary Syndrome
ADHF	Acute Decompensated Heart Failure
AF	Atrial Fibrillation
Acute HF	Acute Heart Failure
AHA	American Heart Association
AMI	Acute Myocardial Infarction
ALCAPA	Anomalous left coronary artery from pulmonary artery
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor-Neprilysin Inhibitor
ASD	Atrial Septal Defect
ASV	Adaptive Servo-Ventilation
AV Node	Atrioventricular Node
AVM	Arteriovenous Malformation
AVSD	Atrio-Ventricular Septal Defect
Bd	Bis Die (twice daily)
BiPaP	Bi-level Positive Airway Pressure
BNP	B-Type Natriuretic Peptides
BP	Blood Pressure
BT Shunt	Blalock-Taussig shunt
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
cCTGA	Congenitally Corrected Transposition of the Great Arteries
CCU	Cardiac Care Unit
CHD	Coronary Heart Disease
CIN	Contrast Induced Nephropathy
CKD	Chronic Kidney Disease
cMR	Cardiac Magnetic Resonance
CPG	Clinical Practice Guidelines
CR	Cardiac Rehabilitation
CrCl	Creatinine Clearance
CRT	Cardiac Resynchronisation Therapy
CSA	Central Sleep Apnea
cTn	Cardiac troponins
CV	Cardiovascular

Abbreviation	Description
CVD	Cardiovascular Disease
CPAP	Continuous Positive Airway Pressure
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
DOAC	Direct Oral Anticoagulants
DVT	Deep Venous Thrombosis
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenator
ED	Erectile Dysfunction
EF	Ejection Fraction
EOD	Every Other Day
EP	Electrophysiology
ER	Emergency Room
eGFR	Estimated Glomerular Filtration Rate
ERA	Endothelin Receptor Antagonists
ESC	European Society of Cardiology
FiO2	Fraction of Inspired Oxygen
GFR	Glomerular Filtration Rate
GLP-1	Glucagon Like Peptide 1
HCM	Hypertrophic Cardiomyopathy
HF	Heart Failure
HFimpEF	Heart Failure with Improved Ejection Fraction
HFmrEF	Heart Failure with Mildly Reduced Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HFpEF	Heart Failure with Preserved Ejection Fraction
HIIT	High Intensity Interval Training
HR	Heart Rate
HRQoL	Health Related Quality of Life
ICD	Implantable Cardioverter-Defibrillator
IHD	Ischemic Heart Disease
IMT	Inspiratory Muscle Training
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcomes
LBBB	Left Bundle Branch Block
LV	Left Ventricle
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
LVT	Left Ventricular Thrombus

Abbreviation	Description
MACE	Major Adverse Cardiovascular Events
MI	Myocardial Infarction
mPCWP	Mean Pulmonary Capillary Wedge Pressure
MOH	Ministry of Health Malaysia
MRI	Magnetic Resonance Imaging
MRA	Mineralocorticoid Receptor Antagonist
NP	Natriuretic Peptides
NTProBNP	N-terminal (NT)-pro hormone B-Type Natriuretic Peptides
NSAIDs	Non-Steroidal Anti- inflammatory Agents
NYHA	New York Heart Association
Od	Once daily
OMT	Optimal Medical Therapy
OSA	Obstructive Sleep A
PA	Pulmonary Artery
PAH	Pulmonary Arterial Hypertension
PCI	Percutaneous Coronary Interventions
PCWP	Pulmonary Capillary Wedge Pressure
PDA	Patent Ductus Arteriosus
PLE	Protein Losing Enteropathy
PPCM	Peripartum Cardiomyopathy
PDE-5 inhibitors	Phosphodiesterase-5 Inhibitors
PSG	Polysomnography
PUFA	Polyunsaturated Fatty Acids
RAS	Renin Angiotensin System
RHD	Rheumatic Heart Disease
RV	Right Ventricle
SBP	Systolic Blood Pressure
SC	Subcutaneous
SCD	Sudden Cardiac Death
SCr	Serum Creatinine
SDB	Sleep Disordered Breathing
SGLT2-i	Sodium-Glucose Cotransporter-2 Inhibitor
SpO2	Pulse Oximeter Oxygen Saturation
STEMI	ST Segment Elevation Myocardial Infarction
Tds	Ter die sumendus (three times per day)
TOF	Tetralogy of Fallot
VAD	Ventricular Assist Device
VHD	Valvular Heart Disease
VPC	Ventricular Premature Contraction
VSD	Ventricular Septal Defect
VT	Ventricular Tachycardia

KEY MESSAGES

 # 1: Epidemiology and Goals of Management

- In Malaysia, patients with HF are almost 10-15 years younger than those in western countries. Comorbidities such as hypertension, diabetes and chronic kidney disease are common in our patients.
- HF is associated with a huge socio-economic and humanistic burden.
- Most of the costs related to HF are related to re-hospitalizations and inpatient hospital care.
- Important goals of management include:
  - Preventing readmissions thus reducing both the socio-economic and humanistic burden of the disease.
  - Improving symptoms, functional capacity, and quality of life of these patients.
  - Improving patient survival.

#2: Definition

- HF is a clinical syndrome due to any structural or physiological abnormality of the heart resulting in its inability to meet the metabolic demands of the body or its ability to do so only at higher-than-normal filling pressures.
- The diagnosis is made by the presence of characteristic symptoms and/or signs and supported by the findings of either an elevation of natriuretic peptides and/or evidence of pulmonary or systemic congestion.

#3: Classification & Stages of HF

- HF can be **classified** according to:
  - **Clinical Presentation:**
    - Acute heart failure (Acute HF)
    - Chronic heart failure (Chronic HF)
  - **Left ventricular ejection fraction (LVEF):**
    - ***Reduced (LVEF ≤ 40%)*** - Heart failure with reduced ejection function (HF*r*EF).
    - ***Mildly reduced (LVEF 41% - 49%)*** - Heart Failure with the LVEF being in the mildly reduced range (HF*mr*EF).
    - ***Preserved (LVEF > 50%)*** - Heart failure with preserved ejection fraction (HF*p*EF).
    - ***Improved Ejection Fraction*** - HF with an initial baseline LVEF of ≤ 40%, a ≥ 10-point increase from baseline LVEF following treatment, and a second measurement of LVEF of >40%.(HF*imp*EF).
  - **Stages of HF** are:
    - A - “At Risk”
    - B - “Pre HF”
    - C - “Symptomatic HF with previous or current symptoms”
    - D - “End Stage HF”
- The severity of symptomatic HF and the exercise capacity of the patient can be assessed using the New York Heart Association (NYHA) functional Class. (Table 9, page 50)

#4: Pathophysiology

- The main pathophysiology of HF is the inability of the heart to provide sufficient cardiac output to meet the perfusion and oxygenation requirements of the body while maintaining normal filling pressures.
- This results in compensatory mechanisms which can also aggravate HF by increasing ventricular afterload and preload to the point where pulmonary and/or systemic congestion and edema occur.
- HF may be due to either impaired cardiac contractility or impaired relaxation and compliance. Both mechanisms may co-exist in the same patient and depending on the predominant pathophysiology, the patient may present as **HF*r*EF** or **HF*p*EF**.
- In **HF*r*EF**, cardiac output is reduced due to depressed myocardial contractility, irrespective of the etiology.
- In **HF*p*EF**, there is impaired left ventricular (LV) filling due to decreased relaxation (during early diastole) and/or reduced compliance (early to late diastole) leading to elevated LV filling pressures at rest or during exercise resulting in dyspnea.
- **HF*mr*EF**, is a clinical entity between **HF*r*EF** and **HF*p*EF**. With regards to etiology, it is more like **HF*r*EF** (high prevalence of CAD) but in terms of prognosis, it is like **HF*p*EF**.
- In **HF*imp*EF**, patients have resolution of symptoms and signs of HF either spontaneously or with treatment, but HF is known to frequently relapse especially after withdrawal of pharmacological treatment. These patients have a lower mortality and risk of hospitali zation compared to **HF*r*EF** and **HF*p*EF**.

 # 5: Etiology

- The common underlying causes of HF in adults are:
  - Coronary artery disease (CAD) - accounting for almost 60-66% of HF in Malaysia.
  - Hypertension.
  - Dilated cardiomyopathy - idiopathic, familial.
  - Valvular heart disease - an important cause is rheumatic heart disease (RHD) among the rural and urban poor.
  - Diabetic cardiomyopathy.
- Comorbidities are common and include hypertension, diabetes, and dyslipidemia.

#6: Prevention of HF

- Prevention and early intervention, wherever appropriate, should be the primary objective of management.
- There is robust clinical data that by appropriate and timely interventions, HF can be prevented, and cardiac function improved.
- It should focus on those who are in:
  - **Stage A - "At Risk"** - Individuals who are at high risk of developing cardiac disease but who do not have symptoms or signs of HF and still have structurally normal hearts.
  - **Stage B - "Pre HF"** - Individuals with structural cardiac disease and who have either normal or impaired cardiac function but do not, yet, have signs and symptoms of HF.

 # 7: Acute HF

- Acute HF may present as:
  - De Novo HF - first occurrence of HF or,
  - Acute decompensated HF (ADHF) - this is a more common presentation occurring in a previously stable patient with HF who has now deteriorated.
- Three important phases should be considered in the management of these patients.
  - **Phase 1** - Urgent treatment and stabilization usually in the emergency department.
  - **Phase 2** - In-hospital management.
  - **Phase 3** - Discharge and Post discharge.

 # 8: Chronic HF due to LV reduced Function (HF*r*EF)

- **Optimal HF medications are:**
  - Diuretics- to be titrated according to the presence of congestion.
  - **Foundational HF medications:**
    - Renin-angiotensin system (RAS) blockers:
      - Angiotensin converting enzyme inhibitor (ACE-I) ***or***
      - Angiotensin receptor blocker (ARB) ***or***
      - Angiotensin receptor neprilysin inhibitors (ARNI).
    - β-blockers.
    - Mineralocorticoid Antagonists (MRA).
    - Sodium glucose cotransporter 2 inhibitors (SGLT2-i).
  - Other drugs (when necessary) include:
    - Ivabradine.
    - Nitrates.
- For the doses and the Grades of Recommendation and Levels of Evidence of these medications for HF*r*EF, see Table 3 & 4, page 40-42).

 # 9: Arrhythmias

- Arrhythmias are common in HF. These include:
  - Atrial Fibrillation.
  - Ventricular arrhythmias.
  - Bradyarrhythmias.

 # 10: Surgery for HF

- Patients with HF should undergo surgery if the pathology causing the HF (e.g., CAD, valve lesions) is amenable to surgical treatment.

#11: HF*mr*EF

- HF*mr*EF includes symptomatic HF patients with LVEF between 41-49% and is a clinical entity between HF*r*EF and HF*p*EF.
- There are a limited number of randomized control trials focusing on management of this category of patients - most of the evidence is derived from post-hoc or sub-group analysis of previous HF trials.

#12: Chronic HF due to HF*imp*EF

- HF*imp*EF includes patients with a:
  - Baseline LVEF of <40% and a
  - >10-point increase from baseline LVEF following treatment to
  - A second measure of LVEF > 40%.

- LV function and structural abnormalities do not fully normalize despite improvement in symptoms, functional capacity, and near normalization of biomarkers.
- Symptoms and signs may however relapse and cardiac biomarkers may increase if HF treatment is withdrawn.
- Foundational HF medications should be continued to prevent relapse of symptoms and subsequent deterioration of LV function.

#13: Chronic HF due to HF*p*EF

- HF*p*EF is a heterogenous disease that is highly prevalent, accounting for up to 50% of all patients with HF and is becoming the dominant form of HF in aging populations worldwide.
- In this guideline HF*p*EF refers to LVEF≥ 50%. LVEF is a continuous variable and the EF cut-offs used in definitions are therefore arbitrary.
- HF*p*EF differs from HF*r*EF in that HF*p*EF patients are older, more often female with AF, CKD and have more non-CV comorbidities.
- The main hemodynamic finding in HF*p*EF is an elevation in LV filling pressures i.e. end diastolic LV pressure (LVEDP), initially only on exertion and later even at rest resulting in dyspnea.

 # 14: HF and Diabetes

- HF and diabetes mellitus (DM) often co-exist, each increasing the likelihood of developing the other. Whether this indicates a causal effect or just a comorbidity is still unclear.
- HF per se is associated with a high morbidity and mortality and concomitant DM compounds this risk. This is particularly so in patients with HF*p*EF.

 # 15: HF and Valvular Heart Disease (VHD)

- VHD is an important cause of HF.
- In the young, RHD is an important cause. The incidence of RHD in rural and urban poor is high.
- In the older population, degenerative valve disease is more common.

 # 16: HF and Cardiomyopathies

- Cardiomyopathies are a heterogeneous group of myocardial disorders which frequently present as HF.
- They can be inherited (familial/genetic) or acquired.
- They are usually classified according to anatomic and physiologic features into:
  - Dilated cardiomyopathy (DCM)
  - Hypertrophic cardiomyopathy (HCM)
  - Restrictive cardiomyopathy (RCM)
  - Arrhythmogenic cardiomyopathy
  - Unclassified cardiomyopathy
- In general, treatment of patients with cardiomyopathy encompasses the Foundational HF Medications as well as etiology-specific therapy (if available).

 # 17: HF Due to Arrhythmias and Conduction Abnormalities

- HF due to arrhythmias and conduction abnormalities are potentially reversible.
- Successful treatment of the arrhythmia by drug therapy or catheter ablation can result in normalization of LV function.

#18: Cardio-Oncology

- Heart disease and cancer are often linked due to common etiologic factors and chemotherapeutic treatment strategies.
- Chemotherapy-induced cardiotoxicity is not common:
  - Clinical HF occurs in 1-5%.
  - An asymptomatic decrease in LV function occurs in the range of 5% to 20%.
- It can develop in a subacute, acute (within 2 weeks of termination of drug administration) or in a chronic manner.
- One must consider both drug efficacy and toxicity in choosing chemotherapeutic agents.

#19: HF and Chronic Kidney Disease

- Cardiac and chronic kidney disease often occur together, and this increases the complexity and costs of care, and may interact to worsen prognosis.
- During treatment of Acute HF, a significant proportion of patients will develop varying degrees of worsening renal function (WRF) usually in the first three to five days of hospitalization.
- WRF may not always indicate a poor outcome-especially if it is due to overdiuresis and hypotension or due to drug therapy.

#20: HF and Pregnancy

- About 0.5 - 4% of pregnant women have cardiac disease. HF remains the most common complication among these women regardless of the cause.
- Women with cardiac disease should be assessed:
  - Before conception to assess their risk and to be advised accordingly ***and***
  - Early in the pregnancy to optimize the outcome of the pregnancy.
- Maternal cardiovascular risk can be assessed using the modified World Health Organization (WHO) or NYHA classification. (Appendix XI & XII, page 171-173)
- Level of Care will depend on the maternal CV risk.
  - **Low risk:** can be managed at their local center after review by a family medicine specialist/physician or cardiologist.
  - **Moderate risk:** should be managed at a tertiary center by a multidisciplinary team with cardiac expertise.
  - **High risk:** should be referred early to a tertiary center for assessment.
- Patients with LVEF < 30% and those in NYHA Class III and IV should be strongly advised not to get pregnant. If pregnant, termination should be considered.

 # 21: HF and Covid - 19 Infection and Vaccine

- In hospitalized patients with COVID-19, the prevalence of HF varied between 4% and 21%. About 8% - 33% of these patients required critical care.
- Patients with HF who develop COVID-19 had an overall mortality rate between 20% and 40%.
- Myocarditis is a rare but serious complication of SARS-CoV-2 infection as well as COVID-19 mRNA vaccination.
- The rate of myocarditis or pericarditis across different age groups:
  - After SARS-CoV-2 infection - 12.6-114 per 100,000 for males and 5.4-61.7 per 100,000 for females.
  - After mRNA COVID-19 vaccination - 0-35.9 per 100,000 for males and 0-10.9 per 100,000 for females.

 # 22: HF and Acquired Congenital Heart disease (ACHD)

- HF is the most common cause of mortality in ACHD patients, accounting for 17- 42% of all deaths.
- Patients with isolated simple defects generally do well with mortality rates like those in the general population.
- Patients with complex heart defects such as systemic RV, single ventricle palliated with Fontan circulation, and unrepaired cyanotic CHD with Eisenmenger physiology comprise the majority of HF- related deaths.

#23: Advanced HF

- All patients with severe symptomatic HF despite OMT and no other alternative therapeutic options have a poor prognosis. There should be a discussion with the patient and family on the choice of further management.
- Further options include:
  - Heart transplant if the patient is eligible.
  - If they are not eligible or a donor heart is not available, a Left Ventricular Assist Device (LVAD) as a destination therapy or a bridge to heart transplant.
- Patients who either choose not to or are ineligible for the available options, should be referred for palliative care.

 # 24: HF Rehabilitation

- Fatigue & breathlessness leads to individuals restricting their physical activity and this in turn, leads to deconditioning.
- Exercise training in patients with HF is safe and leads to an improvement in functional capacity, exercise duration, and health related quality of Life.
- HF is now endorsed as an indication for Cardiac Rehabilitation, and it spans through out the continuum of HF care.

 # 25: Level of Care, Shared Care, Monitoring and Follow - Up & Telemedicine /Telehealth

- The care of patients with HF should ideally take place in a multidisciplinary system, allowing for shared care between the hospital (secondary or tertiary settings) and community (primary setting).
- HF clinics will serve as an intermediary between in-patient hospital care and community primary care.
- When stable with optimized **Foundational HF medications**/treatment plans, patients can be discharged to the community with appropriate care plans to primary care.
- Telemedicine services may improve healthcare accessibility and geographical limitations. It can complement existing HF clinic services and provide venues for early escalation of HF therapy before decompensation.

KEY RECOMMENDATIONS

Recommendations	Grade of Recommendation/ Level of Evidence
#1: Diagnosis & Essential Investigations	
• In making a diagnosis of HF, a detailed history and a thorough physical examination are important.	I,C
• The clinical suspicion of HF should be supported by either raised natriuretic peptides and/or evidence of pulmonary or systemic congestion.	I,C
• Important basic investigations: ➢ Echocardiogram ➢ ECG ➢ Chest Radiograph ➢ Blood - Full Blood Count, urea, creatinine, serum electrolytes (sodium and potassium) liver function, serum glucose, lipid profile.	I,C
➢ Natriuretic Peptides: NT - Pro BNP or BNP ◆ They are a useful "rule out" test in the diagnosis of HF in patients presenting with acute dyspnea. ◆ In chronic HF, NPs may be persistently elevated and show substantial biological variation. In this setting, NPs should be interpreted with careful clinical assessment and with all other clinical information. ◆ A value of NT - Pro BNP of ≤1,000 pg/ml during treatment was associated with better CV outcomes.	I,A
#2: Prevention of HF	
• In the prevention of HF in patients in **Stage A**: ➢ All CV risk factors should be treated to target - BP, Lipids, and glucose.	I,A
➢ Optimal profiles of the 7 CV risk factors - smoking, body mass index, physical activity, diet, cholesterol, blood pressure, and glucose have been shown to be associated with a lower lifetime risk of HF.	I,A
• In the prevention of HF in patients in **Stage B**: ➢ Patients with Acute Coronary Syndrome, Hypertension, Stable CAD and arrhythmias should be treated timely and according to the guidelines. ➢ In patients who have impaired LV function (LVEF<40%): ◆ Treat the underlying cause and avoid/treat precipitating factors early. ◆ The following medications should be instituted early to prevent progression of the HF and improve CV outcomes. ❑ In the **asymptomatic patient in NYHA Class I**: - ACE-I	I,A

- β-blockers - SGLT2-i ❑ In **symptomatic patients in NYHA Class II-IV**: - All the Foundational HF medications (RAS blockers, MRA, β-blockers and SGLT2-i)	**I,A** **I,A** **I,A**
#3: Non-pharmacological Measures ● In managing HF, non-pharmacological measures play a vital role. It is important to: ➢ Educate the patient and family about the disease, treatment options and prognosis. There should be frank end-of-life discussions and advanced care planning with the patient and family. This is important as there is a potential risk of sudden death, and they should put their affairs in order. ➢ Encourage lifestyle measures: ◆ Proper balanced diet to prevent malnutrition and cardiac cachexia. ◆ Weight management -avoid obesity. ◆ Regular physical activity and exercise training. ◆ Smoking cessation. ➢ Individualize fluid intake - A general recommendation is 1-1.5 Liters per day in patients with normal renal function. During periods of acute decompensation and in patients with more advanced stages of HF, more fluid restriction may be necessary. ➢ Provide advice regarding sexual activities and pregnancy. ➢ Address psychosocial problems encountered by the patient and the family.	 **I,B** **IIa,B** **I,B** **I,B** **I,A** **I,C** **IIa,B** **I,C**
#4: Acute HF ● Phase 1 - Urgent treatment and stabilization ➢ Assessment and management must be prompt and done concurrently. ➢ Rapid recognition and making the diagnosis of HF based on symptoms and signs and quickly assessing its severity. Precipitants are as in the acronym: **"C H A M P I O N"** ◆ **C** - Coronary Artery Disease - Acute Coronary Syndrome (Myocardial infarction/Ischemia). ◆ **H** - Severe and uncontrolled hypertension. ◆ **A** - Arrhythmias. ◆ **M** - Mechanical e.g., Acute valvular dysfunction (e.g., acute mitral regurgitation from chordal rupture); cardiac tamponade. ◆ **P** - Pulmonary embolism, pulmonary infections. ◆ **I** - Infections e.g., urinary tract, Covid. ◆ **O** - Other medications (medications that increase fluid retention and/or have negative inotropic effects). ◆ **N** - Non-compliance with treatment especially oral diuretics and or dietary/fluid restriction.	**I,C**

➢ Look for non-cardiovascular comorbidities- Diabetes, chronic kidney disease, thyroid disease (both hyper and hypothyroidism), chronic lung disease, anemia.	
#5: Acute HF	
● **Phase 2 - In-hospital management**	
➢ After initial clinical assessment, management should be instituted as in Flow Chart II, Page 35.	
➢ For grading of recommendations and levels of evidence, see Table 2, Page 36.	
● **Phase 3 - Discharge and Post discharge**	
➢ Discharge planning is a very important process after an episode of hospitalization for HF to reduce HF related readmissions.	
➢ The patient should be given a discharge summary and a discharge care plan. (Appendix III & IV, pages 164-165)	**I,C**
➢ **Prior to discharge**, the patient should be:	
◆ Carefully assessed to ensure that there are no longer signs of congestion ***and***	**I,C**
◆ If the LVEF < 40%, already initiated on Foundational HF medications i.e., RAS blockers, MRA, β-blockers and SGLT2-i ***and***	**I,A**
◆ Given a discharge care plan and summary (Appendix III & IV, pages 164-165) ***and***	**I,C**
◆ Informed of the need and, if indicated, given appointments for further cardiac work up e.g., coronary angiography and cardiac rehabilitation.	**I,C**
➢ **At the Follow up visit**:	
◆ The first FU visit should be within 2 weeks of discharge.	**I,C**
◆ Review that instructions in the discharge care plan (Appendix III & IV, pages 164-165) were followed and identify/determine reasons if otherwise.	
◆ The Foundational HF medications should be up titrated to maximally tolerated or target doses as soon as possible, preferably within 12 weeks post-discharge.	I,A
#6: Chronic HF due to HFrEF: Pharmacotherapy	
● **Foundational HF Medications - For doses of the medications, Grades of recommendation and Levels of Evidence, see Table 3 & 4, pages 40-42)**	
➢ The Foundational HF Medications should be initiated at about the same time and up titrated to their target or maximally tolerated doses.	**I,A**
➢ Once the patient is stable and no longer volume overloaded, the dose of diuretics may be down titrated to the lowest maintenance dose and in selected patients, may be discontinued especially if LVEF has improved to > 40-45% following treatment.	
➢ In general, starting low doses of the 4 different classes would be preferred over up titration of each of the individual drugs	

to the maximally tolerated dose before initiating the next drug. ➢ These drugs are preferably all initiated, albeit at low doses, when the patient is admitted with HF so that at the time of discharge, the patient is on all of them. ➢ In elderly patients who often have multiple comorbidities, it is important to consider pill burden, compliance, and the potential of adverse events due to drug-drug interaction. Education of the patient, family and caregivers is important. ➢ For the initiation and up titration of these HF drugs see section 10.2 and Flowcharts III, IV & V, pages 37-39.	
#7: Arrhythmias ● In HF patients who present **with palpitations, near faints and syncope**, arrhythmias are sometimes difficult to detect. If the clinical suspicion is high, the following may be considered: ➢ Prolonged ECG rhythm monitoring using 3-day, 7-day or even 1-month rhythm monitors ***or*** ➢ An implantable loop recorder ***or*** ➢ Using a smart watch that can monitor ECG heart rhythm.	
● **Atrial Fibrillation** ➢ To be treated by: ◆ Rate ***or***	**IIa,B**
◆ Rhythm control (if onset < 1 year)	**IIa,A**
◆ To anticoagulate with DOAC or Vitamin K antagonists	**I,A**
● **Ventricular arrhythmias** ➢ Identify contributing factors such as electrolyte imbalances, ischemia and drugs.	**I,C**
➢ Consider an Implantable cardioverter defibrillator (ICD) for secondary prevention in: ◆ Patients resuscitated from SCD due to ventricular fibrillation or hemodynamically unstable sustained ventricular tachycardia.	**I,A**
◆ Prior MI (> 40 days) and LVEF ≤ 40% with non-sustained VT **AND** inducible sustained VT or VF during an EP study.	**I,A**
◆ Patients with chronic HF and LVEF ≤ 35% who experience syncope of unclear origin.	**IIa,B**
◆ Prior MI (> 40 days) and 3 months after revascularization, LVEF ≤ 35% and NYHA class II-III.	**I,A**
◆ No prior MI, LVEF ≤ 35%, on optimal medical treatment, and in NYHA II or III	**I,B**
● **Bradyarrhythmias** ➢ The following patients should be considered for pacemakers: ◆ Significant symptomatic bradyarrhythmias. ◆ Trifascicular bundle branch blocks. ◆ Permanent or paroxysmal third-or high-degree atrioventricular (AV) blocks.	**I,A**
➢ Prior to implanting a conventional pacemaker, the need for an ICD or Cardiac Resynchronisation Therapy (CRT) device should be considered.	**I,A**

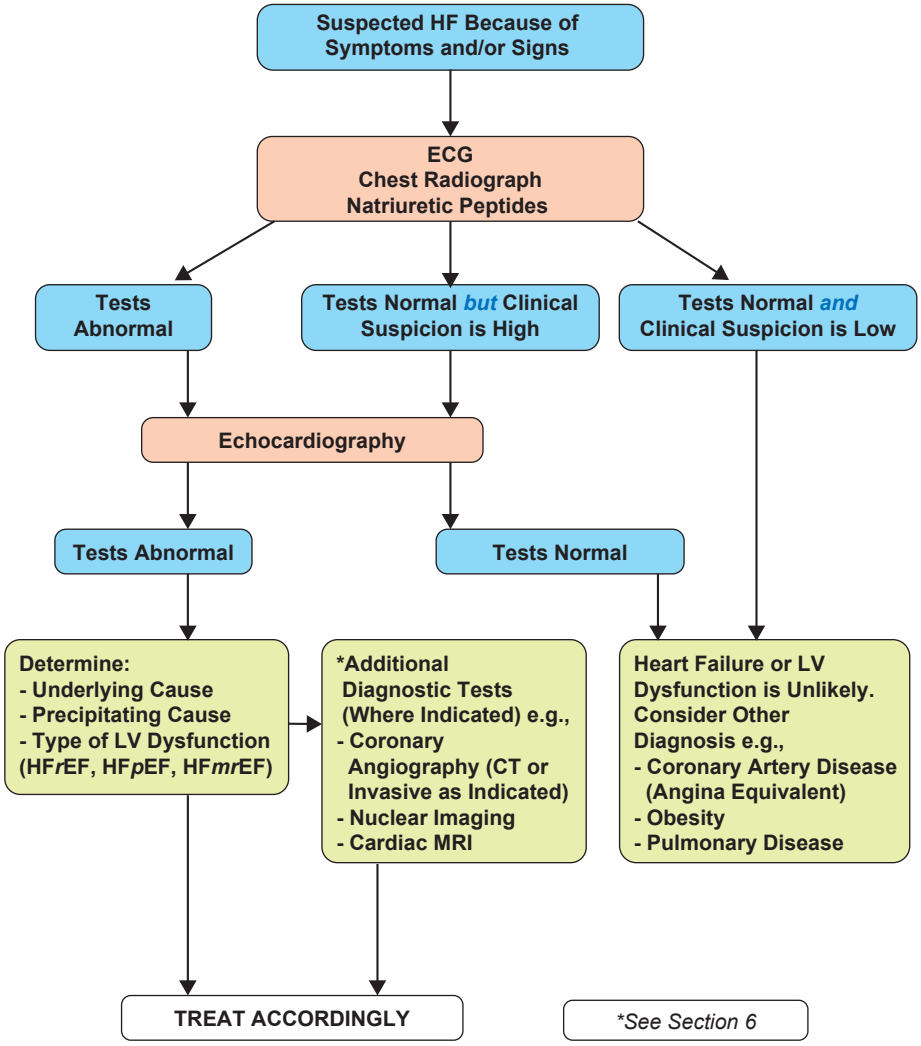
➢ Conduction system pacing (which includes His bundle and left bundle branch area pacing) is a new pacing modality. The early results appear promising but evidence on its indications, safety and efficacy is still lacking.	
#8: Chronic HF due to HF*r*EF ● Surgery For HF ➢ **CAD** ◆ Patients with HF should undergo surgery if they have: ❑ Ischemia demonstrated as angina or on non-invasive testing ***and*** ❑ An anatomy that is suitable for revascularization (left main stem or triple vessel disease). ➢ **Valve Heart Disease (VHD)** ◆ All patients with VHD should be assessed periodically on the need for early intervention before they begin to develop symptoms of reduced effort tolerance and decompensate. ◆ Patients who are assessed to require intervention should be seen by a heart team to help decide the timing and type of intervention. ◆ The indications for valve intervention are as in the Appendix V, page 166.	**I,C** **I,C** **I,C**
#9: Chronic HF due to HF*mr*EF ● The management of these patients include: ➢ Optimal treatment of CV risk factors. ➢ **SGLT2- i**. ➢ **Diuretics** for patients who remain symptomatic and show signs of congestion. ➢ **β-blockers**, **RAS blockers** (ARNI, ACEI or ARB) and **MRAs** can be considered to reduce the risk of HF hospitalization and CV death.	**I,C** **I,A** **I,C** **IIa,B**
#10: Chronic HF due to HF*imp*EF ● Symptoms and signs may relapse, and cardiac biomarkers may increase if HF treatment is withdrawn. ● Foundational HF medications should be continued to preven relapse of symptoms and subsequent deterioration of LV function.	 **IIa,B**
#11: Chronic HF due to HF*p*EF ● Timely and early diagnosis of HFpEF leads to a better outcome. ● The management of patients with HFpEF includes: ➢ Encouraging lifestyle measures ◆ Weight reduction ◆ Exercise training ➢ Managing comorbidities such as hypertension, CAD, CKD, atrial fibrillation, obesity according to guidelines. ➢ Pharmacotherapy: ◆ **Diuretics** - for volume overload.	 **I,B** **I,A** **I,C** **I,C**

◆ **SGLT2-i** - decreases HF hospitalizations and CV mortality. ◆ **RAS blockers** (ARB, ACE-I, ARNI) - As a group, RAS blockers have not been shown to reduce total or CV mortality. There was a suggestion of benefit with ARNI in women with LVEF< 60%, while for men the benefit was restricted to LVEF<45%. ◆ **MRA** - it may be considered to decrease combined CV mortality and HF hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. ◆ **β-blockers** - No good data that they are beneficial in the treatment of HFpEF although they are often prescribed for the management of comorbidities such as CAD or AF.	**I,A** **IIb,B** **IIb,B**
#12: HF and Diabetes	
● **Prevention of HF**:	
➢ Lifestyle measures are important. They have been shown to lower the risk for HF, particularly HFpEF. These measures include:	
◆ Attainment of appropriate weight, ***and***	**I,A**
◆ Increased physical activity ***and***	**I,B**
◆ Smoking cessation.	**I,B**
➢ The BP and LDL-C should be treated to target:	
◆ BP 130-139/70-79 mmHg	**I,A**
◆ LDL-C according to CV risk category.	**I,A**
● **Treatment of Diabetes - Glucose lowering Agents**	
➢ Glycemic targets for patients with DM and HF should be individualized.	**I,A**
➢ Current recommendations suggest a target range of HbA1c 7%-8%, while minimizing adverse effects of treatments particularly hypoglycemia.	**I,A**
➢ Glucose lowering drugs:	
◆ With proven CV benefits:	
❑ SGLT2-i.	**I,A**
❑ GLP-1 receptor agonists.	**IIa,A**
❑ Metformin.	**IIa,B**
◆ With no proven CV benefits but which will help with glucose control:	
❑ DPP4 inhibitors.	**IIa,B**
◆ With no proven CV benefits and need to be used with caution:	
❑ Insulin -This has been associated with increased all-cause mortality and hospitalization for HF especially in patients with low HbA1c < 7%.	**IIa,B**
❑ Sulfonylureas.	**IIa,B**
◆ That need to be avoided:	
❑ Thiazolidinediones	**III,A**
#13: HF Due to Arrhythmias and Conduction Abnormalities	
● In managing cardiomyopathy due to arrhythmias (SVT, AF or frequent PVCs or VT), radiofrequency ablation is the preferred	**I,A**

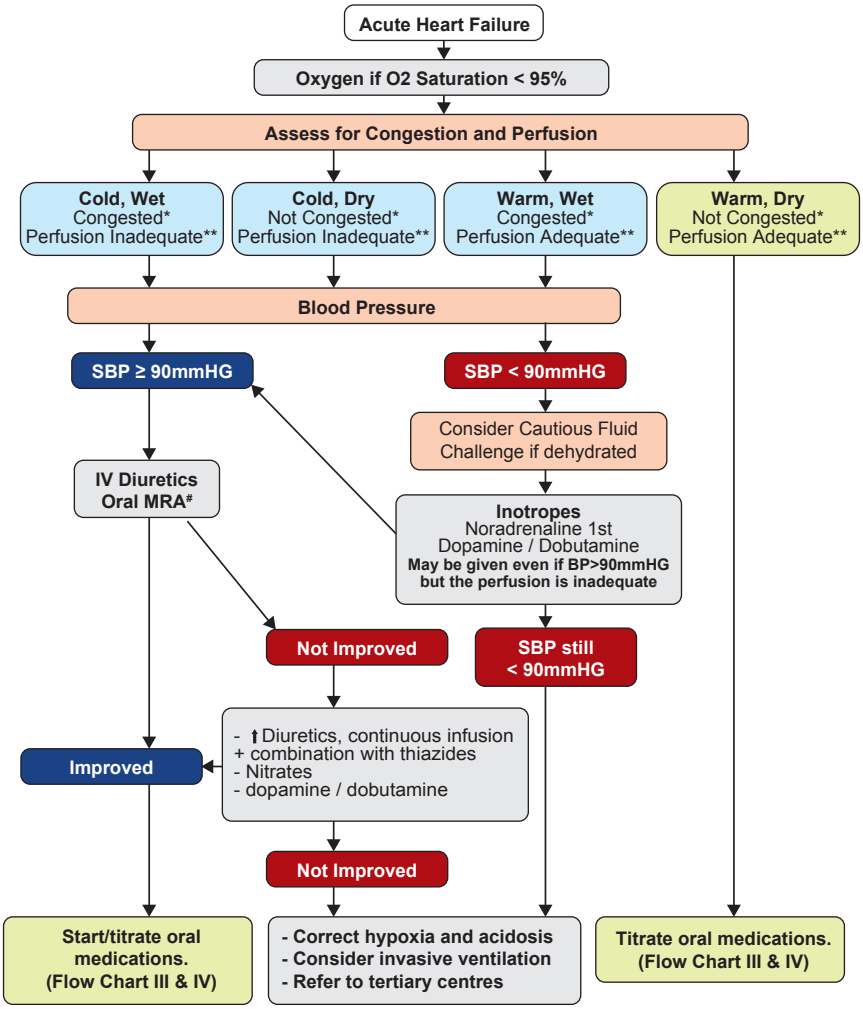
therapy, since most antiarrhythmic drugs are contraindicated in the presence of HF.	
• In patients with HF who have bradyarrhythmias and where pacing is indicated, biventricular pacing (Cardiac Resynchronisation Therapy) is the pacing mode of choice.	**I,A**
#14: Cardio-Oncology	
• Close collaboration between the oncologist and the cardiologist is important.	**I,C**
• Patients undergoing chemotherapy should have careful clinical evaluation and assessment. Specifically:	
➢ All CV risk factors should be treated adequately.	**I,C**
➢ High risk patients should be identified and in these patients:	
◆ A pre-treatment cardiac echocardiogram is advisable. If the LVEF < 50%, they should be referred to a cardiologist.	
◆ Reassessing and repeating (if necessary) imaging studies during and after treatment.	
◆ Assessing cardiac biomarkers when indicated - troponins and/or Natriuretic Peptides.	
➢ Considering cardio-protection prior to/or during treatment using β-blockers, MRA and/or ACE-I/ARB if:	**IIa,B**
◆ EF < 50%,	
◆ EF drops by > 10%	
◆ Abnormal global longitudinal strain (GLS) (> 15% drop).	
#15: HF and CKD	
• A multi-disciplinary approach with early referral to a nephrologist is recommended.	**I,C**
• Almost all **Foundational HF Medications** can be used in patients with eGFR ≥ 30mls/min/1.73m^2	**I,A**
• In patients with eGFR < 30mls/min/1.73m^2, the following drugs can be used:	
➢ Diuretics - usually higher maintenance doses.	**I,B**
➢ Careful use of RAS blockers.	**I,B**
➢ β-blockers.	**I,B**
➢ SGLT2-i (eGFR >20mls/min/1.73m^2).	**IIa,B**
• Closely monitor electrolytes and kidney function. The baseline renal function will determine how frequently this should be done.	
• RAS blockers and SGLT2-i can lead to an initial drop in eGFR but this should not be a reason to automatically stop or down titrate these agents. See table 18, page135 for the management of RAS blockers in response to changes in renal function.	**I,C**
• Occasionally ultrafiltration and renal replacement therapy (hemodialysis) may be necessary.	**I,C**
#16: HF and Pregnancy	
• HF in pregnancy should be managed by a multidisciplinary team consisting of physicians, obstetricians, and pediatricians.	**I,C**

• HF that develops during pregnancy can be managed with the judicious use of diuretics, digoxin, nitrates, β-blockers (most commonly metoprolol) and/or hydralazine.	**I,C**
• For postpartum women with severe acute HF caused by Peripartum cardiomyopathy and LVEF <35%, Foundational HF medications to improve LVEF recovery and prophylactic anticoagulation are recommended.	**I,A**
#17: HF and ACHD (Appendix XIII-XV, pages 174-177)	
• The principles of managing HF in ACHD HF are:	
➢ First to access and address all reversible causes.	**I,C**
➢ If HF control is still not optimal, initiate pharmacotherapy.	**I,C**
➢ Arrhythmias to be treated appropriately by pacing or ICD as indicated.	**I,B**
➢ To consider cardiac resynchronization and more advanced therapies if these patients continue to have worsening HF despite optimal medical therapy.	**IIa,C**
#18: Advanced HF	
• Heart transplantation is well-established for refractory end stage HF.	**I,A**
• Patients with severe symptomatic HF despite OMT and no other alternative therapeutic options should be considered for palliative care.	**I,C**
• Older people with multiple comorbidities and generally poor prognosis, should be considered for palliative care even at an early stage of the disease.	**I,C**
# 19: HF Rehabilitation	
• Cardiac Rehabilitation should be recommended to all stable HF patients, in NYHA II-III.	**IIa,B**
#22: Performance Measures	
• Performance measures are used with the goal of improving quality of care for HF.	
• This includes:	
➢ Process performance which measures the aspects of care that are delivered to a patient and	
➢ Outcome measures which focus on hard endpoints such as mortality and hospitalization.	
• For the quality indicators in HF, see section 19, page 160 & Appendix XVI, page 178)	

Flow Chart I: Algorithm for the Diagnosis of Heart Failure*



Flow Chart II: Management of Acute Heart Failure

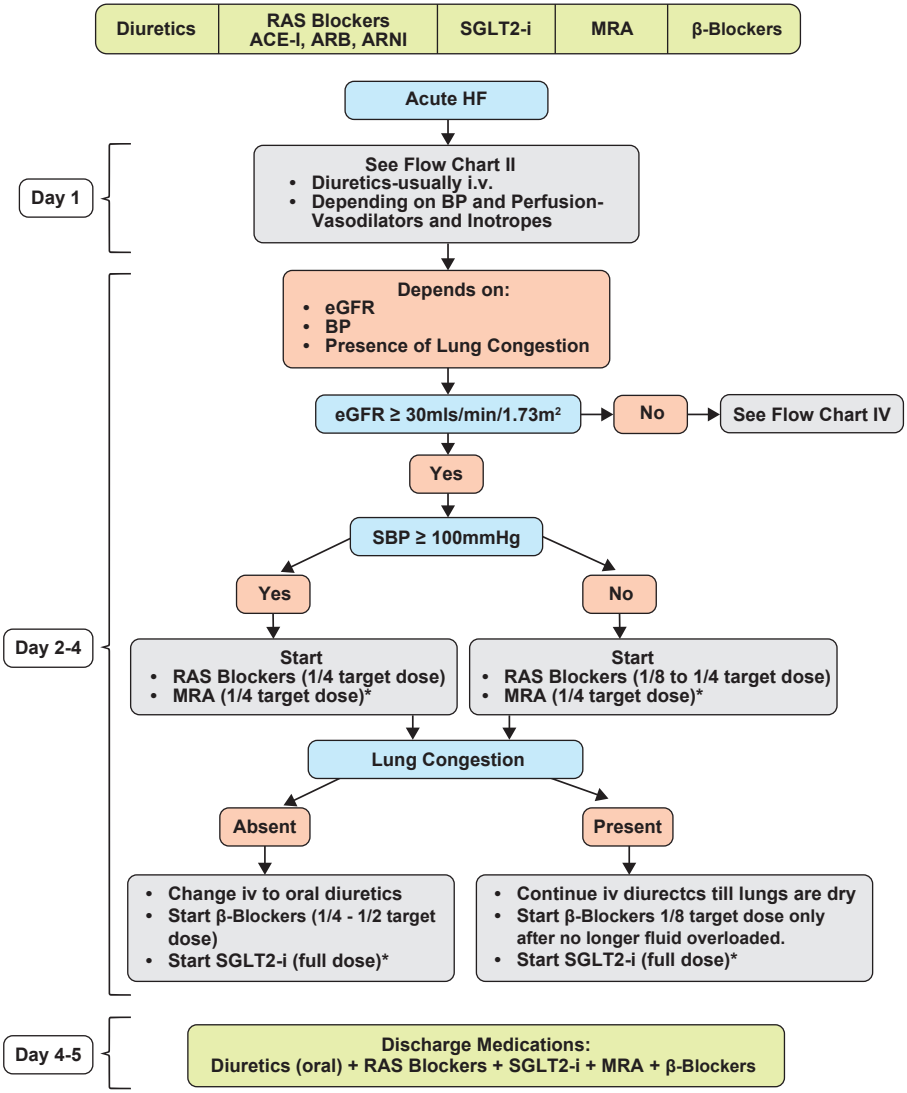


***Congestion**: Peripheral oedema, orthopnoea, paroxysmal nocturnal dyspnoea, lung crepitations, jugular venous dilatation, hepatojugular reflux, congested hepatomegaly, gut congestion, ascites.
****Hypoperfusion**: Cold peripheries, capillary refill time more than 2 seconds, diaphoresis, oliguria, dizziness, Confusion, narrow pulse pressure, hypotension.
#Administration of MRA will depend on eGFR ≥ 30 mls/min/1.73m^2 and serum potassium levels < 5.0 mmol/l
From onset, evaluate to identify correctable/reversible lesions - C H A M P I O N

Table 2: Grading of Recommendations in the Management of Acute HF

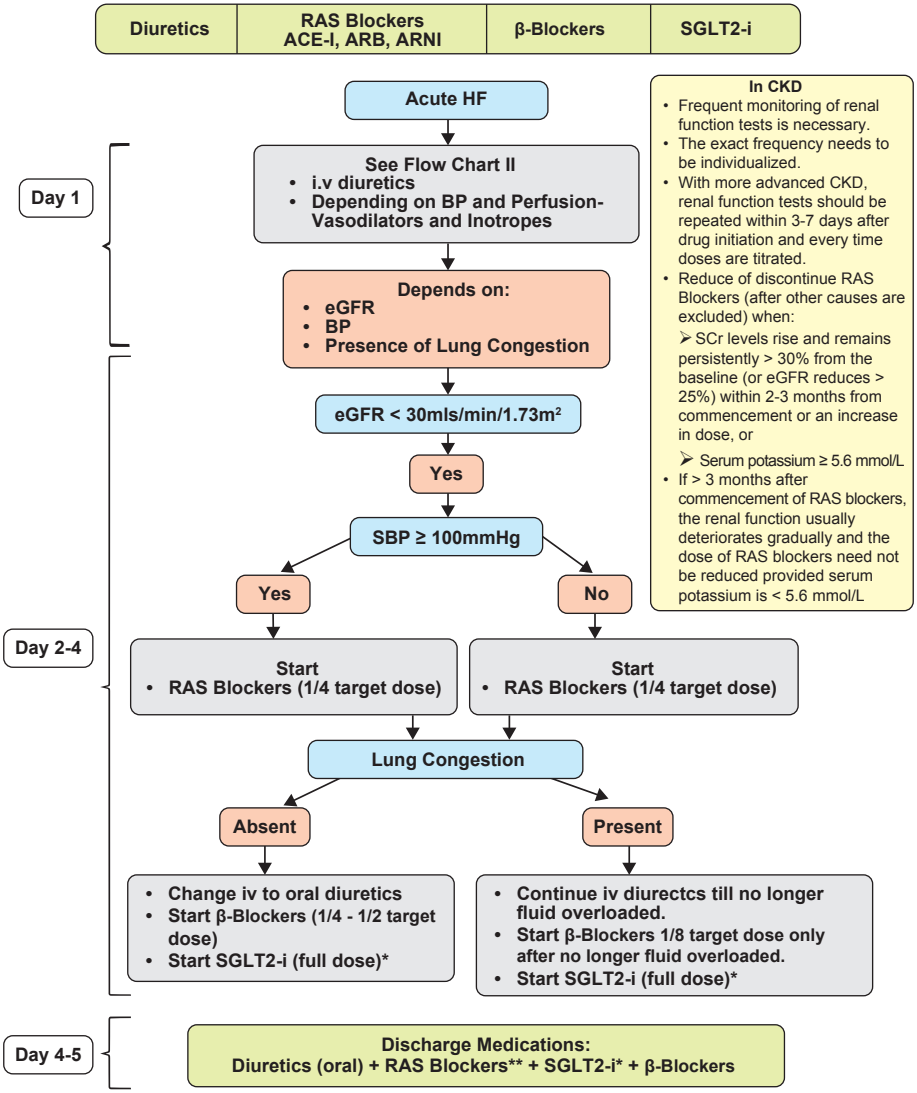
Intervention	Grades of Recommendation	Levels of Evidence	Comments
INITIAL MANAGEMENT CONSISTS OF:			
Oxygen	I	C	Maintain the oxygen saturation ≥ 95%.
Diuretics	I	B	To be given preferably when SBP ≥ 90mmHG.
MRA	I	A	To be given if eGFR ≥ 30 mLs/min/1.73m^2 and serum potassium levels < 5.0mmol/l. May be initiated within 24-48 hours of admission.
NOT RESPONSIVE TO INITIAL TREATMENT AND SBP ≥ 90mmHg			
Diuretics	IIa	B	Continuous infusion +/- combination with thiazides.
Nitrates	I	B	Most useful if there is concomitant myocardial ischemia, severe hypertension or aortic or mitral regurgitation.
Noradrenaline	IIa	B	Indicated for peripheral hypoperfusion despite an adequate filling status.
Dopamine	IIb	B	Indicated for peripheral hypoperfusion despite an adequate filling status.
NOT RESPONSIVE TO INITIAL TREATMENT AND SBP < 90mmHg			
Noradrenaline	IIa	B	Indicated to increase the BP.
Dopamine	IIb	B	Indicated to increase the BP.
IABP	IIa	B	Indicated as a bridge till myocardial recovery or heart transplant.
Ventricular Assist (VAD)	IIa	B	Indicated as a bridge till myocardial recovery or heart transplant. Occasionally as destination (definitive) therapy.
ORAL MEDICATIONS IN ACUTE HF (Initiated when patient is hemodynamically stable, off all i.v. inotropes and SBP ≥ 100mmHG)			
RAS blockers (ACE-I or ARB in ACE-I intolerant patients)	I	A	
ARNI	IIa	B	
β-Blockers	I	A	
SGLT2-i	I	A	No increase in i.v. diuretic dose and off all iv vasodilators, including nitrates within the last 6 hours. The dose of diuretics may need to be reduced on initiation of SGLT2-i.

Flow Chart III: Initiating Foundational HF Medication



*The dose of diuretics may need to be down titrated upon initiation of SGLT2-i and MRA. The initiating drug doses may occasionally need to be modified depending on the patient's clinical condition. SGLT2-i should be initiated when patients have not been on inotropes for at least 24 hours, SBP > 100mmHg and there is no increase in the diuretic dose in the last 6 hours. SGLT2-i may also be initiated post discharge .

Flow Chart IV: For Patients with eGFR < 30mls/min/1.73m² (Initiating Foundational HF Medication)



*SGLT2-i should only be initiated if eGFR ≥ 20mls/min/1.73m². Caution should be exercised when it is started concurrently with the RAS-blocker. The dose of diuretics may need to be down titrated upon initiation of SGLT2-i.
**ARNI should be used with caution if eGFR < 30mls/min/1.73m². It is not recommended in patients with end-stage renal disease.

Flow Chart V: Optimizing Management of HF*r*EF
Foundational HF Medications

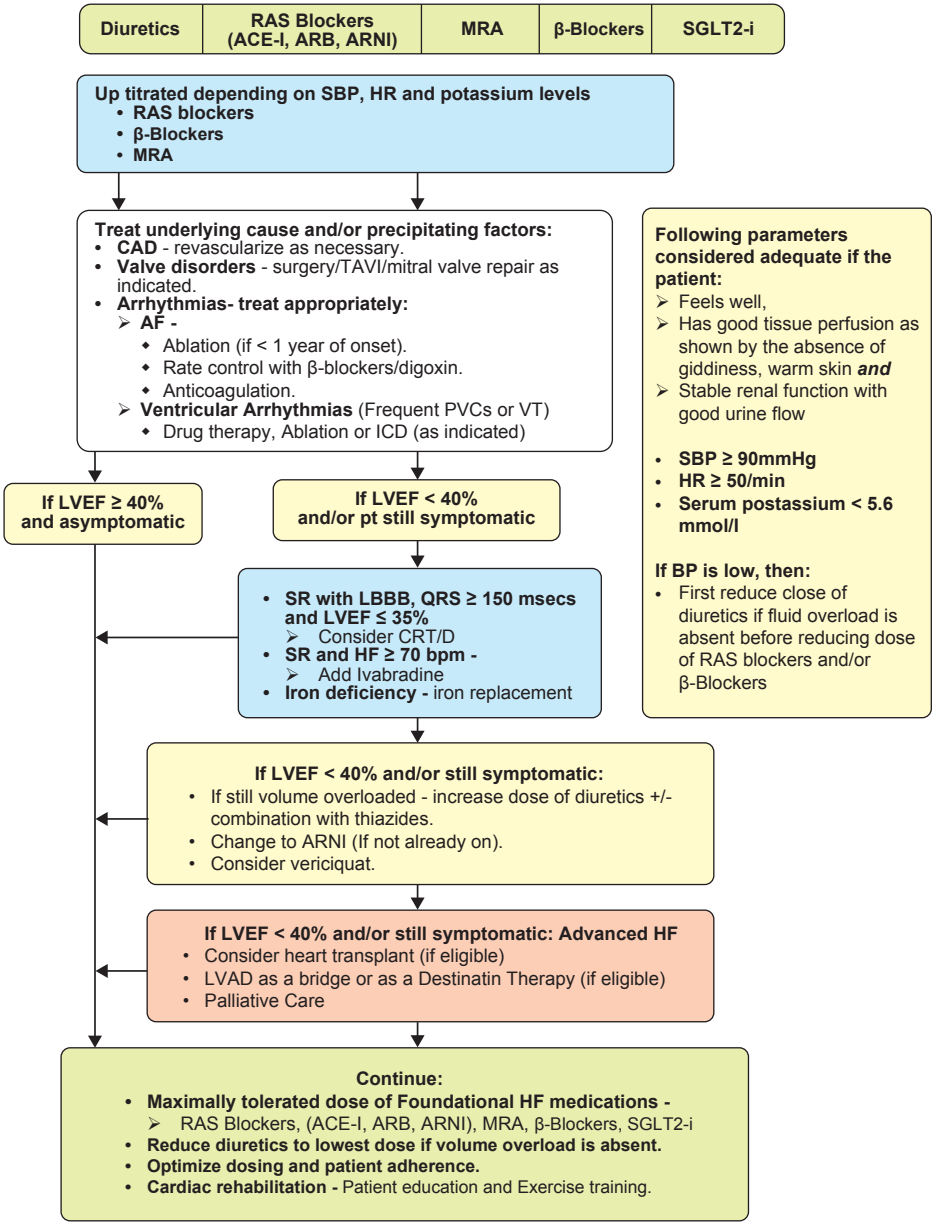


Table 3: Doses of Foundational HF Medications

Drug	Initial Daily Dose(s)	Target Dose(s)	1/8 Target Dose	1/4 Target Dose	1/2 Target Dose	Tablet Strength Available		Renal Dose For CrCl < 30ml/min
ACE-I								
Captopril	6.25mg BD	50mg TDS	6.25mg	12.5mg	25mg	12.5mg, 25mg	Yes	6.25mg-12.5mg bd/tds
Enalapril	2.5mg OD	10-20mg BD		2.5-5mg	5-10mg	5mg, 10mg, 20mg	Yes	2.5mg OD
Lisinopril	2.5–5mg OD	20-40mg OD	2.5mg	5-10mg	10-20mg	5mg, 10mg, 20mg	Yes	2.5mg OD CrCl 10-30:5mg OD CrCl<10: 2.5mg OD
Perindopril	2mg OD	8-16mg OD		2-4mg	4-8mg	2mg, 4mg, 8mg	Yes	CrCl 15-30: 2mg eod CrCl <15 & HD: 2mg on dialysis day**
Ramipril	2.5mg OD	10mg OD	1.25mg	2.5mg	5mg	2.5mg, 5mg, 10mg	Yes	1.25mg OD CrCl <40: 25% normal dose
ARBs								
Candesartan	4-8mg OD	32mg	4mg OD	8mg	16mg	8mg, 16mg	Yes	4mg OD
Losartan	25-50mg OD	50-150mg OD		12.5-37.5mg	25-75mg	25mg, 50mg, 100mg	Yes	No adjustment
Valsartan	40mg OD	160mg BD		40mg	80mg	40mg, 80mg, 160mg	Yes	Use with caution
ARNI								
Sacubitril/ valsartan	100mg (49/51mg) BD*	200mg (97/ 103mg)BD	25mg	50mg	100mg	50mg,100mg, 200mg	Yes	50mg BD

Drug	Starting Dose	Target Dose	1/8 Target Dose	1/4 Target Dose	1/2 Target Dose	Tablet Strength Available		Renal Dose For CrCl < 30ml/min
β-Blocker								
Bisoprolol	1.25mg OD	10 mg OD	1.25mg	2.5mg	5mg	2.5mg, 5mg, 10mg	Yes	No adjustment
Carvedilol	3.125mg BD	25 mg BD	3.125mg	6.25mg	12.5mg	6.25mg, 12.5mg, 25mg	Yes	No adjustment
Metoprolol Tartrate*	12.5-25mg BD	100 mg BD	12.5mg	25mg	50mg	50mg, 100mg	Yes	No adjustment
Nebivolol+	1.25mg OD	10 mg OD	1.25mg	2.5mg	5mg	5mg	Yes	No adjustment
MRA								
Spironolactone	12.5-25mg OD	50 mg OD		12.5mg	25mg	25mg	Yes	Contraindicated
Eplerenone	25 mg OD	50 mg BD		12.5mg	25mg	25mg, 50mg	Yes	Contraindicated
Finerenone	20mg OD	20mg OD				10mg, 20mg	Yes	eGFR 25-60: 10mg OD eGFR <25: contraindicated
SGLT2-i								
Dapagliflozin	10mg OD	10mg OD						CrCl <25: limited experience
Empagliflozin	10mg OD	10mg OD						CrCl <20: not recommended

** The evidence-based form of metoprolol in HF is metoprolol succinate (CR/XL), which is not available in Malaysia. The only form of metoprolol available in Malaysia is metoprolol tartrate*
+ Shown to reduce the composite endpoint of all-cause mortality and CV hospitalization, but not all-cause mortality.
IBM Micromedex Drug Ref (2023) (cited 14th January 2023) & product leaflet available from Quest3 (accessed date: 13th January 2023)
*** At the discretion of the attending physician*
CrCl unit: ml/min; eGFR unit: ml/min/1.73m²

Table 4: Grading of Recommendations and Levels of Evidence in the Management of HFrEF (LVEF<40%

Intervention	Grades of Recommendation	Levels of Evidence	Comments
INDICATED FOR FLUID RETENTION IN NYHA II - IV			
Diuretics	I	B	No randomized trial to show improvement in survival.
INDICATED IN ALL PATIENTS			
ACE-I	I	A	Improves survival and delays progression in all classes of HF.
ARB	I	A	In ACE-I intolerant patients.
ARNI (Instead of ACE-I)	I	B	Improves survival and delays progression in all classes of HF when compared to ACE-I.
β-Blockers	I	A	Improves survival and delays progression in all classes of HF.
SGLT2-i	I	A	Improves survival and delays progression in all classes of HF.
Mineralocorticoid Receptor Antagonists	I	A	Improves survival and reduces hospitalizations in moderate to severe HF and in post MI patients with mild HF.
IN ADDITION TO THE ABOVE, THE FOLLOWING ARE INDICATED IN SELECTED PATIENTS			
ARB (instead of ACE-I)	I	B	In patients post MI and LVEF < 40%, Valsartan was shown to be comparable to captopril.
Digoxin	I	B	In patients with HF and AF
	IIa	B	No effect on survival. Reduces hospitalizations when added to optimal medical therapy.
Ivabradine	IIa	B	Reduces hospitalizations when added to optimal medical therapy in patients in sinus rhythm and heart rate ≥ 70bpm
ICD (Implantable Cardioverter Defibrillator)	I	A	Improves survival in patients with resuscitated cardiac arrest, VF, or sustained VT
	I	A	Improves survival in patients > 40 days post MI, LVEF ≤ 30%, with non-sustained VT **AND** inducible sustained VT or VF during an EP study and on optimal medical treatment, and in NYHA II or III
	I	A	Improves survival in patients with prior MI and > 40 days post MI and 3 months after revasculari zation, LVEF ≤ 35% and NYHA class II-III
	I	B	Improves survival in patients (no prior MI), LVEF ≤ 35%, on optimal medical treatment, and in NYHA II or III
CRT (Cardiac Resynchronisation Therapy)	I	A	Improves survival in patients having **all of the following:** sinus rhythm, LVEF ≤ 35%, LBBB ***and*** QRS duration on resting 12-lead ECG: ≥ 150ms
	IIa	B	≥ 120-149ms
Pacemaker	I	A	For significant symptomatic bradyarrhythmias, trifascicular BBB, third-or high-degree AV blocks.

Table 5: Patient Profiling and Titration of "Foundational HF Medications"

Blood Pressure	**Systolic BP < 90 mmHG**	• Detect and treat causes of hypotension, such as hypovolemia from over diuresis, bleeding, infection etc. • If the patient is euvolemic, reduce the dose of diuretics to the lowest maintenance. Occasionally it may be possible to remove the diuretic completely especially if the LVEF > 40-45%. • Remove all non "Foundational HF" Medications that may also cause hypotension e.g., - nitrates, calcium channel blockers, alpha blockers. • The dose of "Foundational HF" Medications only needs to be reduced or temporarily stopped if there is symptomatic hypotension. • SGLT2-i and low-dose MRA have minimal effects on BP and may be continued.
	Systolic BP > 110 mmHG	• The dose of RAS blockers and β-blockers should be up titrated in turn till the target or maximally tolerated dose. • Whether the RAS blocker or the β-blocker should be up titrated first will depend on the patient's heart rate, renal function, and potassium levels.
Heart rate (Sinus Rhythm)	**HR > 70/bpm**	• The dose of β-blocker should first be up titrated to the target or maximally tolerated dose. • Ivabradine may be added to the β-blocker to achieve the target HR.
	HR < 50/bpm	• Discontinue non-dihydropyridine calcium channel blockers e.g., diltiazem and verapamil, digoxin, or other antiarrhythmic drugs such as amiodarone. • If the HR is still < 50/bpm, the dose of ivabradine should first be reduced. • If the HR is still < 50/bpm or the patient has symptomatic bradycardia, then the dose of β-blocker should be reduced or temporarily discontinued.
Atrial Fibrillation	**Heart Rate (HR)**	• The optimal resting ventricular rate in patients with AF and HF is unknown. It is not unreasonable to aim for a HR < 110bpm. • If the patient is troubled by palpitations or there is deterioration of LV function, then a more strict rate control of 80bpm may be targeted. • The ventricular rate should however, be maintained > 70 bpm. Lower HR have been associated with worse outcomes. • Excessive rate control, which may be associated with an increase in pauses, carries a risk. • The optimal ventricular rate during exercise is also uncertain, but may be < 110bpm during light exercise.
	Systolic BP < 90mmHg	• β-blockers may be stopped and replaced with digoxin for rate control. • This action may allow for the up titration of RAS blockers as the SBP improves to ≥ 90mmHG.
Renal Function months	**Potassium**	• RAS blockers and MRA to be sequentially initiated if serum potassium is < 5.5 mmol/l. • Consider reducing or discontinuing the dose of RAS Blockers and MRA if serum potassium is persistently > 5.5 mmol/l despite other measures to reduce hyperkalemia.
	Serm Creatinine	• Consider reducing or discontinuing RAS Blockers (after excluding other precipitating factors) when SCr levels remain ≥ 30% from the baseline (or eGFR reduces ≥ 25%) and if these occur within two from commencement or dose increase.

Table 6 Grading of Recommendations and Levels of Evidence in the Management of HF*p*EF (LVEF > 50%)

Intervention	Grades of Recommendation	Levels of Evidence	Comments
LIFESTYLE MEASURES			
Overweight / Obesity	I	B	• A caloric restriction diet is feasible and safe and should ideally be combined with exercise. • Bariatric Surgery in patients with HFpEF and obesity was associated with improved symptoms and reduction in HF hospitalizations.
Exercise Training	I	A	• This is safe and improves exercise capacity and quality of life.
IDENTIFYING AND TREATING THE UNDERLYING CAUSE(S) AND CO-MORBIDITIES			
Hypertension	I	A	• Improved BP control has been shown to reduce morbidity and hospitalizations for HF.
Tachyarrhythmias (Persistent or Paroxysmal AF)	IIa	B	• **Rate Control** with β-blockers or non-dihydro pyridine calcium channel blockers (verapamil, diltiazem) alone or in combination.
	IIa	A	• **Rhythm Control** in patients with recent onset AF < 1 year duration or paroxysmal AF.
Anti Coagulation	I	A	• To reduce the risk of thromboembolic events.
Others	I	C	• Treat CAD, Diabetes, CKD appropriately according to guidelines.
PHARMACOTHERAPY			
Diuretics	I	C	• To relieve congestion.
RAS Blockers	IIb	B	• Trial data show a reduction in HF hospitalizations, but no reduction in all-cause or CV mortality in HF*p*EF. • With ARNI, there was a suggestion of benefit in patients with LVEF < 57% (in women benefits of ARNI were sustained up to LVEF 60%, while for men the benefit was restricted to LVEF 45%).
MRA	IIb	B	• It may be considered to decrease HF hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.
SGLT2-i	IIa	A	• These have been shown to decrease HF hospitalizations and CV mortality. • As more trial data becomes evident, the grading ***may*** more upwards to I, A
β-Blockers			• No good data to show that β-blockers are beneficial in the treatment of HF*p*EF. • Often prescribed for treatment of co-morbidities.

1. INTRODUCTION

1.1 Epidemiology of Heart Failure

Heart failure (HF) is a clinical syndrome and is the end stage of most heart diseases. Globally, it affects more than 60 million individuals and in Asia, the prevalence is estimated to be between 1.3% and 6.7%.[1] In general, the incidence of HF has stabilized but the prevalence appears to be increasing due to the ageing of the population and increasing number of survivors post myocardial infarction.[1-4]

In Asia, patients with HF are younger with a mean age of 60 years and two-thirds are < 65 years.[5] This is 10 to 15 years younger than patients in Europe (71-79 years) and the USA (mean 72 years).[6-10] Most of the Asian patients were males and about two-thirds (64%) had 2 or more comorbid conditions such as hypertension (51.9%), coronary artery disease (CAD, 50.2%), or diabetes (40.4%).[5] There were regional variations but Southeast Asians (Malaysia, Indonesia, Singapore, Thailand, and Philippines) had the highest burden of comorbidities, particularly CAD, hypertension, diabetes mellitus, obesity and chronic kidney disease.[11]

In the ASIAN-HF registry, the 1-year all-cause mortality for the whole population was 9.6%, varying from 4.4% in Japan to 21.4% in Indonesia.[11] Southeast Asians had the highest mortality (13.6%) compared with South Asians (8.3%) and Northeast Asians (8.9%).[11]

In Malaysia for Acute HF, (see Table 7, page 48), the:[11-17]

- **Median age** of patients was 59-64 years. In Thailand, the mean age of patients with HF was 65.3 years.[34]
- **Median length of hospital stay** (LOS) was 3-5 days - comparable to that in the US.[18]
- **In-hospital mortality** varied from <3% to as high as 7.5%. In the European Society of Cardiology (ESC) HF-Long term (LT) registry, the in-hospital mortality was 4.9% and in the Get With The Guidelines-HF (GWTG-HF) registry, the in-hospital mortality was <3%.[18,19]
- **30-day mortality** was high at 11-15%.
- **1-year mortality** was also similarly high at 33-49.5%.
- **30-day and 1-year all cause readmission rates** were 4-18% and 24-76% respectively compared to the 19% and 53% seen in a meta-analysis of 27 HF registries.[20]

In general, in addition to hospitalizations due to HF, all-cause hospitalizations were also increased and observed in up to 60% of patients.[21] In Malaysia, cardiovascular causes accounted for half of all 30-day readmissions (50.1%) with HF specifically accounting for 27.8%.[17] Readmission rates were higher in the older age and those with CKD.[17] Length of stay increased with each hospitalization and the time in between hospitalizations decreased with each subsequent hospitalization.[17]

The prognosis of HF has improved over time, but mortality remains high.[1,6-9,22,23] In the European Society of Cardiology (ESC) HF-Long term (LT) registry, 1-year mortality was 23.6% for acute HF and 6.4% for chronic HF between 2011 and 2013.[19] In ambulatory patients with HF, pooled analysis of cohorts from three North-western European countries, showed that outcomes have significantly improved during the last two decades. (Period 1:1995-2005 vs period 2: 2006-2015).[24] Improvement in all-cause mortality can be explained partly by demographic differences and also by better utilization of Optimal Medical Therapy.[25]

1.2 Socio-Economic Consequences of Heart Failure

The socio-economic burden of HF is huge. In high-income countries, 1-2% of the total healthcare expenditure is spent on HF.[21] In the US, total cost for HF was estimated to be $30.7 billion in 2012, with 68% attributable to direct medical costs.[26] A more contemporary review estimated annual healthcare costs for HF patients in the western world, to amount to 25,000 Euro.[1] Most of the costs was linked to inpatient care and re-hospitalizations. In Malaysia, in 2014, it was estimated that 3.6% of the GDP is being spent on total healthcare with only 1.8% spent on HF.[27] This cost is expected to rise with an ageing and rapidly expanding population.

The overall global economic cost of HF is highly variable from country to country.[21,28] In general, the costs of treatment of a HF patient is higher:[28-30]

- than other diseases such as asthma, coronary artery disease, chronic obstructive pulmonary diseases, diabetes, hyperlipidemia and hypertension.
- in the presence of comorbidities such as diabetes, obesity and chronic kidney disease.

Healthcare costs for HF include:[27]

- Direct costs - this accounts for 60% of total costs.
- Indirect costs - account for 40%. This includes premature mortality, 'presenteeism' (the lost productivity that occurs when employees are not fully functioning in the workplace because of an illness, injury, or other condition), disability, sick absenteeism (short- and medium-term absence from work) and costs of caregiver's absenteeism.

In general, in most low and medium economies like Malaysia, the indirect costs of HF in terms of premature mortality, morbidity, lost earning potential and unpaid care costs outweigh the direct costs.[27]

In Asia, there is substantial variations in healthcare spending. In a non-interventional, retrospective study conducted through medical chart audit for the year 2014, the average cost of HF hospitalization varied from USD 4,513 in Taiwan to USD 1,443 in public hospitals in Malaysia (adjusted to 2015 USD).[31] This wide variation in costs could be partly explained by the fact that in Malaysia, healthcare is heavily subsidized by the government and the wide use of generic medications. There was also less use of more expensive medications such as Angiotensin Receptor Neprilysin Inhibitors and device therapy.

In a costing study on HF conducted in Hospital Queen Elizabeth II, Kota Kinabalu, the mean and median annual cost of HF per person were USD 5,428 (MYR 22,649) and USD 591 (MYR 2,466) respectively in 2017.[32] This is much higher than that seen in the earlier study because it includes interventional procedures. Inpatient cost accounted for 90.6% of the total cost and was mainly attributable to percutaneous coronary intervention (PCI) procedures and hospitalization.[32]

In another cost analysis done in 3 public hospitals in Sabah, Kelantan and Pulau Penang looking only at patients with chronic HF from 2016-2018, the mean total cost per HF patient per-year (PPPY) was USD 1,971 (MYR 8,224) ± USD 1,255 (MYR 5,236), of which inpatient cost accounted for 74.7% of the total cost.[33] Medication costs (42.0%) and procedure cost (40.8%) contributed to the largest proportion of outpatient and inpatient costs. HF patients with preserved LVEF had the highest mean total cost of PPPY, at USD 2,410 (MYR 10,056) ± USD 1,226 (MYR 5,115).[33]

Thus, an important goal in management of HF is to prevent readmissions, reducing both direct and indirect costs.

1.3 Humanistic Burden of Heart Failure

A diagnosis of HF also has a huge humanistic burden.[21,27] This refers to the impact of an illness on the patient's health-related quality of life (HRQoL), activities of daily living, caregiver(s) 's health, caregiver(s)'s quality of life, patients' treatment satisfaction and compliance with their specific treatment regimens.[21,28] In general, most patients prefer improved HRQoL to length of survival.

The goals of management of HF include:

- Preventing hospitalizations and unplanned hospital visits - this will reduce both the socio-economic and humanistic burden of HF.
- Reducing symptoms, improving functional capacity and quality of life, and thus improving the humanistic burden of HF.
- Improving patient survival.

This guideline provides evidence-based recommendations to help health care providers in the management of their patients with HF. Beyond the Clinical Practice Guidelines (CPG), clinical management needs to be individualized considering the patient's overall health goals, values, perspective, and preferences.

Sound clinical judgment plays an important role in formulating appropriate patient-centered care plans.

Key Message # 1: Epidemiology and Goals of Management

- In Malaysia, patients with HF are almost 10-15 years younger than those in Western Countries. Comorbidities such as hypertension, diabetes and chronic kidney disease are common.
- HF is associated with a huge socio-economic and humanistic burden.
- Most of the costs related to HF are related to inpatient hospital care and re-hospitalizations.
- Important goals of management include:
  - Preventing readmissions thus reducing both the socio-economic and humanistic burden of the disease.
  - Improving symptoms, functional capacity, and quality of life.
  - Improving patient survival.

Table 7 : Epidemiology of HF in Asia & Malaysia

	Asian HF registry[11]	Lim YMF et al[12]	MYHF[13,14]	Sharif RER et al[14]	Ling HS et al[15]	Azmee et al[16]
Source of Data	Prospective longitudinal study of outpatient (at least 1 episode of decompensated HF in the previous 6 months) and hospitalized patients 1st Oct 2012 - 31st Oct 2016	10 years retrospective data from 1st Jan 2007 to 31st Dec 2016 of pts hospitalized with HF	Prospective observational study on hospitalized patients from Aug 2019 - Dec 2020	Single center Retrospective data Jan 2012 - Dec 2016	Single center Prospective observational study on hospitalized pts Sept 2017 to Oct 2018	Single center Retrospective on hospitalized pts 1st Jan 2009 to 31st Dec 2018
Population	6480 patients aged > 18 years With symptomatic HF	105,399 > 20 years incident HF hospitalizations in a MOH hospital	2673 patients > 18 years	1307 patients > 18 years Acute HF patients	117 patients >18 years Acute HF patients	3923 patients Adult HF pts
Mean Age	61.6 years	64.1 years	60.17 years	63.4 years	59 years	62 years
% Women	27%	44%	33.2%	53.6%	41.1%	37.7%
% HF*r*EF	81%	NA	64.6%	40.8%	48.6%	62.9%
Length of Hospital Stay	NA	3 days (median)	7.3 days (mean) 3 - 4 (median)	5.3 ± 3.4 days (mean).	5 days (median)	9.2 days (mean)
All Cause Readmission 30 days 1 year	NA NA	18.1% NA	12.9% NA	4.1% 76.1%	11.2% NA	6.8% 24.7%
In Hospital Mortality		5.3%	2.8%	1.7%	7.5%	7.2%
30 days Mortality		11.2%	7.8%	15.7%	13.1%	NA
1 year Mortality	9.6% HF*r*EF:10.6% HF*p*EF: 5.4%,	33.1%	NA	49.7%	NA	NA

2. DEFINITION

HF is a clinical syndrome due to any structural or physiological abnormality of the heart resulting in its inability to meet the metabolic demands of the body or its ability to do so only at higher-than-normal filling pressures. This is supported by either an elevation of natriuretic peptides and/or evidence of pulmonary or systemic congestion.[35]

This may be accompanied by signs and symptoms of systemic hypoperfusion and/or volume overload. Patients may have typical symptoms (e.g., breathlessness, ankle swelling and fatigue) and signs (e.g., elevated jugular venous pressure, ankle edema, pulmonary crackles and displaced apex beat). Occasionally, some patients may present without signs or symptoms of volume overload. Older patients, often, present with atypical symptoms such as delirium, reduced appetite, immobility, incontinence, and falls.

Most commonly, HF is due to myocardial dysfunction- either systolic, diastolic, or both. However, pathology of the valves, pericardium, and endocardium, and abnormalities of heart rhythm and conduction can also cause HF.

Occasionally, non-cardiac disease, e.g., anemia, pulmonary, renal, thyroid, or hepatic disease may have symptoms and signs like those of HF, but in the absence of cardiac dysfunction, these do not fulfil the criteria for HF. However, these pathologies can coexist with HF and exacerbate the condition.

Key Message #2: Definition

- HF is a clinical syndrome due to any structural or physiological abnormality of the heart resulting in its inability to meet the metabolic demands of the body or its ability to do so only at higher-than-normal filling pressures.
- This is supported objectively by either an elevation of natriuretic peptides and/or evidence of pulmonary or systemic congestion.

3. CLASSIFICATION

HF can be classified by phenotypes. These descriptions may reflect the:

- Temporal characteristics (e.g., acuteness, chronicity)
- Affected circulatory systems (e.g., left vs right)
- Clinical context and trajectory (e.g., decompensated, improved, advanced, end-stage).

Another commonly used classification is by the severity of LV systolic function as assessed by LV ejection Fraction (LVEF).[35] (Table 8, page 50)

Table 8: Classification Of Heart Failure According To LVEF

Ejection Fraction Terminology	LVEF
Heart Failure with Reduced Ejection Fraction (HF*r*EF)	≤ 40%
Heart Failure with mildly reduced LVEF (HF*mr*EF)	41 - 49%
Heart Failure with Preserved Ejection Fraction (HF*p*EF)	≥ 50%
Heart Failure with Improved Ejection Fraction (HF*imp*EF)	HF with a baseline LVEF of ≤ 40%, a ≥10-point increase from baseline LVEF following treatment, and a second measurement of LVEF of > 40%.

Stages of HF include[35]:

- **A** - 'At Risk"
  - Asymptomatic without structural cardiac disease but 'at risk' of developing HF.
- **B** - "Pre HF"
  - Asymptomatic but with structural and functional cardiac abnormalities that can lead to HF. They may have normal or mildly reduced LV function.
- **C** - "HF"
  - Symptomatic HF, either previous or current symptoms.
- **D** - "Advanced HF"
  - Marked symptoms interfering with daily activities of living and with recurrent hospitalizations.

The severity of symptomatic HF can be assessed by the New York Heart Association (NYHA) Functional Class. (Table 9, page 50)

Table 9: New York Heart Association Functional Classification for Patients with Heart Disease

CLASS	FUNCTIONAL CAPACITY	1 YEAR MORTALITY
CLASS I	No limitation. Ordinary physical activity does not cause undue fatigue, dyspnea or palpitation.	5 - 10%
CLASS II	Slight limitation of physical activity. Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or angina.	10 - 15%
CLASS III	Marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.	15 - 20%
CLASS IV	Inability to carry on any physical activity without discomfort. Symptoms of congestive failure are present at rest. With any physical activity, increased discomfort is experienced.	20 - 50%

Key Message #3: Classification & Stages of HF

- HF can be classified according to:
  - **Clinical Presentation:**
    - Acute heart failure (Acute HF)
    - Chronic heart failure (Chronic HF)
  - **Left ventricular ejection fraction (LVEF)**:
    - ***Reduced (LVEF ≤ 40%)*** - Heart failure with reduced ejection function (HF*r*EF).
    - ***Mildly reduced (LVEF 41%-49%)*** - Heart Failure with the LVEF being in the mildly reduced range (HF*mr*EF)
    - ***Preserved (LVEF > 50%)*** - Heart failure with preserved ejection fraction (HF*p*EF)
    - ***Improved Ejection Fraction*** - HF with a baseline LVEF of < 40%, a >10-point increase from baseline LVEF following treatment, and a second measurement of LVEF of >40%.(HF*imp*EF)
  - **Stages of HF** are:
    - **A** - "At Risk"
    - **B** - "Pre HF"
    - **C** - "Symptomatic HF with previous or current symptoms"
    - **D** - "Advanced HF"
- The **severity of symptomatic HF** and the **exercise capacity** of the patient can be assessed using the New York Heart Association (NYHA) functional Class (Table 9, page 50).

4. PATHOPHYSIOLOGY

The **main pathophysiology** of HF is **the inability of the heart to provide sufficient cardiac output to meet the perfusion and oxygenation requirements of the body while maintaining normal filling pressures. This may be due to either impaired cardiac contractility or impaired relaxation and compliance**. Both mechanisms may co-exist in the same patient and depending on the predominant pathophysiology, the patient may present as HF*r*EF or HF*p*EF.

This will result in the following compensatory mechanisms:

- A higher ventricular end diastolic pressure - This is a compensatory mechanism to increase stroke volume by the Frank Starling mechanism.
- Increasing ventricular volume and wall thickness through ventricular remodelling.
- Neuro-hormonal activation of the:
  - Sympathetic nervous system
  - Renin-angiotensin-aldosterone system
  - Vasopressin

This neuro-hormonal activation is aimed at increasing stroke volume and cardiac output by:

- An increase in heart rate and ventricular contraction.
- Vasoconstriction of arterial resistance vessels to maintain blood pressure.
- Venous constriction to increase venous preload.
- Salt and water retention to increase preload.

In general, these neuro-hormonal responses are compensatory mechanisms. However they can also aggravate HF by increasing ventricular afterload and increasing preload to the point where pulmonary and/or systemic congestion and edema occur.

4.1 HF*r*EF

In HF*r*EF, cardiac output is reduced due to depressed myocardial contractility, irrespective of the etiology. This leads to a cascade of pathophysiological changes as outlined above. There are effective medical and device therapies that have been shown to have a survival benefit in HF*r*EF. In this group of patients, their LVEF can remain as < 40% or improve to ≥ 40% when they are reclassified as Heart Failure with Improved Ejection Fraction (HF*imp*EF).

4.2 HF*p*EF

In HF*p*EF there is impaired left ventricular (LV) filling due to decreased relaxation (during early diastole) and/or reduced compliance (early to late diastole) leading to elevated LV filling pressures at rest or during exercise. These hemodynamic changes are accompanied predominantly by signs of pulmonary and/or venous congestion and occasionally systemic hypoperfusion as well.

Clinical studies seem to indicate that HF*r*EF and HF*p*EF are mechanistically distinct pathophysiological entities.[36] The transition from HF*p*EF to HF*r*EF is rare.[37]

HF*p*EF appears to be a multi-organ, systemic syndrome with heterogeneous clinical manifestations and high comorbidity burden.[36]

There is limited data available on therapies that improve survival in HF*p*EF unlike those with HF*r*EF. In this group of patients, their LVEF can deteriorate to between 41 to 49% (HF*mr*EF) or rarely < 40% (HF*r*EF).

4.3 HF*mr*EF

The prevalence of HF*mr*EF is between 10-25%.[38] (Table 10, page 53). It is a clinical entity between HF*r*EF and HF*p*EF. With regards to etiology, it is more similar to HF*r*EF (high prevalence of CAD) but in terms of prognosis, they are more like HF*p*EF in terms of survival rates, low risk of CV events but a higher risk of non-CV adverse events than those with HF*r*EF.[36,38,39]

HF*mr*EF represents a transitional phase and the LVEF can:

- Remain in the 41 to 49% range (HF*mr*EF) or
- Worsen to ≤ 40% (HF*r*EF) or
- Improve to ≥ 50% (HF*imp*EF).

Patients with HF*mr*EF had the best outcomes, compared to the high rates of mortality seen in patients with HF*r*EF and the high rates of HF readmissions seen in patients with HF*p*EF.[6] Only 1/3 of patients with HF*mr*EF transitioned during follow up, with the lowest mortality seen in patients transitioning to HF*p*EF.[40]

Clinical trials on therapies for HF*p*EF that enrolled patients with an LVEF of >40% or ≥45% did not demonstrate a clear treatment effect. Post hoc analysis however suggests that some therapies for HF*r*EF might also be effective in HF*mr*EF.

4.4 HF*imp*EF

In HF with improved EF (HF*imp*EF), the baseline LVEF is ≤40% but either spontaneously or following treatment, there is a ≥10% increase from baseline LVEF, and a second measurement of LVEF is >40%. [35] These patients have resolution of symptoms and signs of

HF. "HF in remission" is a term that is sometimes used but **the HF is known to frequently relapse especially after withdrawal of pharmacological treatment**.[41]

In a large meta-analysis, the prevalence of HF*imp*EF was 22.64%.[42] They had a lower mortality and risk of hospitalization compared HF*r*EF and HF*p*EF.[42]

Key Message #4: Pathophysiology

- The main pathophysiology of HF is the inability of the heart to provide sufficient cardiac output to meet the perfusion and oxygenation requirements of the body while maintaining normal filling pressures.
- In **HF*r*EF**, cardiac output is reduced due to depressed myocardial contractility, irrespective of the etiology.
- In **HF*p*EF** there is impaired left ventricular (LV) filling due to decreased relaxation (during early diastole) and/or reduced compliance (early to late diastole) leading to elevated LV filling pressures at rest or during exercise and dyspnea.
- **HF*mr*EF** is a clinical entity between HF*r*EF and HF*p*EF. With regards to etiology, it is more like HF*r*EF (high prevalence of CAD) but in terms of prognosis, it is more like HF*p*EF.
- In **HF*imp*EF**, patients have resolution of symptoms and signs of HF but HF is known to frequently relapse especially after withdrawal of pharmacological treatment. They have a lower mortality and risk of hospitalization compared HF*r*EF and HF*p*EF.

Table 10: Prevalence of HF*r*EF, HF*p*EF and HF*mr*EF in Registries

	ESCHF-LT[43] HF[44]	GWTG-HF[45]	Swedish Registry[5]	ASIAN HF	MYHF[13]
Source of Data	Prospective Observational study of Outpatients and hospitalized patients April 2011 to Jan 2015	Prospective Observational study of hospitalized between Jan 2005 and Sept 2013	Prospective Observational study of Outpatients and hospitalized patients between 2000 - 2018	Prospective longitudinal study of outpatient (at least 1 episode of decompensated HF in the previous 6 months) and hospitalized patients 1st Oct 2012-31st Oct 2016	Prospective observational study on hospitalized patients from Aug 2019 - Dec 2020
No	16,354	99,825	75,518	6,480	2,673
HF*r*EF	59.8%	49.0%	52.5%	81.0%	64.6%
HF*mr*EF	24.2%	12.8%	23.5%	NA	11.3%
HF*p*EF	16.0%	38.1%	24.1%	19.0%	21.6%

5. ETIOLOGY

HF is not a complete diagnosis. **It is important to identify the underlying disease and the precipitating cause(s), if present**, so that disease-specific treatment can be initiated early.

The common underlying causes of HF in adults are:

- Coronary artery disease (CAD)
- Hypertension
- Dilated cardiomyopathy-idiopathic, familial
- Valvular heart disease
- Diabetic cardiomyopathy

The commonest cause in Malaysia is CAD accounting for almost 60-66% of HF.[14,15,17] Comorbidities are common and include hypertension, diabetes, and dyslipidemia.[14,15,17] Valvular Heart Disease, especially rheumatic heart disease, is an important cause among the rural and urban poor.

Other causes of HF include:

- Congenital heart disease
- Cor pulmonale
- Pericardial disease: constrictive pericarditis, cardiac tamponade
- Hypertrophic cardiomyopathy
- Viral myocarditis
- Acute rheumatic fever
- Toxic:
  - Alcohol
  - Cardiotoxic chemotherapy e.g., doxorubicin, cyclophosphamide, trastuzumab (Herceptin), immune checkpoint inhibitors,
  - Radiotherapy
  - Medications such as clozapine
  - Substance abuse: methamphetamine and cocaine
- Endocrine and metabolic disorders: thyroid disease, acromegaly, phaechromocytoma.
- Collagen vascular disease: systemic lupus erythematosis, polymyositis, polyarteritis nodosa.
- Tachycardia induced cardiomyopathy e.g., uncontrolled atrial fibrillation.
- Infiltrative cardiac disease e.g., amyloid, hyper-eosinophilic syndrome, Sarcoid.
- Neuromuscular Disorders: Friedreich's Ataxia, Muscular Dystrophy.
- Storage Disorders: Haemochromatosis, Glycogen Storage Disease, Fabry disease.
- Endomyocardial disease: Carcinoid, Endomyocardial Fibrosis.
- Miscellaneous
  - High output HF e.g., severe anemia, large A-V shunts/malformations.
  - Peripartum cardiomyopathy.
  - Stress (Takotsubo) cardiomyopathy.

Patients with Chronic HF may occasionally develop acute decompensation. Factors that can contribute to this acute decompensation are listed in Table 11, Page 55. The more important causes that need to be recognized and treated appropriately are as in the acronym:

C H A M P I O N

C - **C**oronary artery disease - Acute myocardial infarction/myocardial ischemia
H - **H**ypertensive emergencies
A - **A**rrhythmias (e.g., atrial fibrillation)
M - **M**echanical causes such as acute valve regurgitation
P - **P**ulmonary - e.g., pulmonary embolism, pneumonia
I - **I**nfections - e.g., urinary tract infection, Covid
O - **O**ther medications such as NSAIDs and COX-2 inhibitors,
N - **N**on-compliance to medications

Key message #5: Etiology

- The common underlying causes of HF in adults are:
  - Coronary artery disease (CAD) - accounting for almost 60-66% of HF in Malaysia
  - Hypertension
  - Dilated cardiomyopathy-idiopathic, familial.
  - Valvular heart disease
  - Diabetic cardiomyopathy
- Comorbidities are common and include hypertension, diabetes, and dyslipidemia.

Table 11: Factors Contributing to Decompensation in a Patient with Stable HF

Patient factors • Non-compliance to medications • Dietary indiscretion especially salt and fluid intake • Inappropriate medications e.g., NSAIDs and COX-2 inhibitors • Alcohol consumption
Cardiac causes • Superimposed myocardial ischemia or infarction (often asymptomatic) • Hypertensive emergencies • Arrhythmias • Pulmonary embolism • Secondary mitral or tricuspid regurgitation
Systemic conditions • Superimposed infections • Anemia • Thyroid disease • Electrolyte disturbances • Worsening renal disease
Others • Urinary retention • Severe emotional or physical stress • Medications with negative ionotropic effect, e.g., Verapamil

6. DIAGNOSIS

I, C **The diagnosis of HF depends on a detailed history focusing on symptoms, risk factors and a thorough physical examination**. Patients with HF may present differently but tend to be consistent in their presentation whenever they develop a recurrent episode.

6.1. Symptoms and Signs

I, C **The clinical suspicion of HF should be supported by objective evidence of cardiac dysfunction**. Breathlessness with orthopnea, paroxysmal nocturnal dyspnea (PND), reduced exercise tolerance and ankle swelling are the characteristic symptoms of HF. Orthopnea and paroxysmal nocturnal dyspnea are markers of high filling pressures and contribute to sleep-disordered breathing.

Signs which are more specific for HF are an elevated jugular venous pulse (JVP), and a third heart sound. These signs are associated with adverse outcomes in patients with HF and asymptomatic LV dysfunction.[46,47] The presence of a raised JVP, a positive jugulo-venous reflux and hepatomegaly generally indicate a raised right atrial pressure of > 8 mmHg.[48] A raised JVP has a good sensitivity (70%) and specificity (79%) of left sided congestion.[48]

A fourth heart sound is due to atrial contraction and is more frequent in patients with HF*p*EF. It is absent in patients with atrial fibrillation (AF).

These signs may be accompanied by a laterally displaced apical impulse and a cardiac murmur. Other supportive signs include peripheral edema, tachycardia, narrow pulse pressure, pulmonary crepitations, hepatomegaly and ascites. These clinical findings may be transient and resolve completely following initial therapy.

However, these signs are difficult to detect and are not always easily reproducible in the elderly, the obese and in patients with chronic lung disease. In a small study on patients with chronic HF, signs of congestion (rales, edema and JVP elevation) were absent in 42% of patients with a PCWP ≥ 22 mmHg.[49] Occasionally symptoms and signs of volume overload may be absent, and the patient may present with fatigue only.

In the elderly, as exertional dyspnea increases, they begin to lead more sedentary lives. Fatigue is common and this is likely due to low cardiac output, peripheral hypo-perfusion and skeletal muscle deconditioning and should not be considered due to ageing only.[50] Atypical symptoms, such as confusion, memory deficit, sleepiness, episodes of delirium, irritability, syncopal states, fatigue, anorexia, and reduced level of activity are common manifestations of HF especially after age 80.[50] Other co-existing conditions such as infections, anemia, delirium etc may complicate the clinical picture making the diagnosis of HF difficult.[51] Bilateral leg edema is common in the elderly and may be due to other causes such as venous insufficiency, chronic kidney disease or lymphedema besides HF.[51]

In patients presenting with dyspnea, acute LV failure can sometimes mimic an acute exacerbation of bronchial asthma or chronic obstructive pulmonary disease. Thus, a proper history and clinical examination is essential. Similarly, in patients with CKD presenting with dyspnea, a concomitant diagnosis of HF may be missed.

Exercise capacity in a patient with heart disease is assessed by the New York Heart Association (NYHA) functional classification. (Table 9, page 50)

I, A The clinical suspicion of HF should be supported objectively with either raised natriuretic peptides and/or evidence of pulmonary or systemic congestion.[35] A value of NT-Pro BNP > 125pg/ml or BNP >35pg/ml is used as a cut off value for the diagnosis of HF in the non-acute setting.[35] (Table 12, page 60)

Objective evidence of cardiac dysfunction by diagnostic tests will further support the diagnosis of HF. It will help establish the etiology and the precipitating factors of the syndrome.

Key message # 5:

- In making a diagnosis of HF, a detailed history and a thorough physical examination is important.
- The clinical suspicion of HF should be supported objectively with either raised natriuretic peptides and/or evidence of pulmonary or systemic congestion.

6.2 Investigations (Flowchart 1, page 32)

BASIC INVESTIGATIONS	
12 Lead Electrocardiogram Chest Radiograph	- To assess heart rate, rhythm, QRS morphology, QRS duration, QRS voltage, evidence of ischemia, LV hypertrophy and arrhythmias. - To look for pulmonary congestion, cardiomegaly, and presence of underlying lung pathology. - Patients with HFpEF may have a normal cardiac size.
Blood Tests	Full Blood Count, urea, creatinine, serum electrolytes (sodium and potassium) liver function, serum glucose, lipid profile.
Urinalysis	To look for proteinuria.
OTHER IMPORTANT INVESTIGATIONS	
Echocardiography	This will allow assessment of: ● LV chamber size, volume, and systolic function. ● LV wall thickness, evidence of scarring and wall motion abnormalities. ● Diastolic function of the heart. ● Valvular structure and function. ● Congenital cardiac abnormalities. ● LV mechanical dyssynchrony. ● Pulmonary hypertension. It is the most useful and widely available test to establish the diagnosis in patients suspected of HF.
Natriuretic peptides in **(NP):** ● **Brain Natriuretic Peptide (BNP) or** ● **N-Terminal Pro BNP (NT-Pro BNP)**	BNP and NT-Pro BNP are a family of hormones secreted by the ventricles response to wall stress. They are useful in the following situations: **DIAGNOSIS OF HF** **A) <u>De Novo HF-1st episode of HF</u>** **A1. Emergency Setting** ● **NPs are useful as a 'rule out' test for patients presenting with acute dyspnea.** A level of < 100pg/ml for BNP and < 300pg/ml for NT-Pro BNP makes the diagnosis of acute HF unlikely.[52-56] ● There is no statistical difference between the diagnostic accuracy of plasma B type natriuretic peptide (BNP) and NT-Pro BNP.[55] ● These levels are affected by renal function and gender.[55-57] (See Table 12, Page 60 for the optimal cut off values of NP to exclude or diagnose HF in patients with dyspnea.) ● A high level supports the diagnosis of acute HF and very high levels correlate with the severity of HF and adverse outcomes.[52-57] ● The values of both BNP and NT-Pro BNP are predictive of both in-hospital and 1-year mortality, irrespective of LVEF.[55-60] ● The discharge value as well as percent change from admission to discharge were more predictive of subsequent mortality and/or rehospitalization than admission values.[61] A decrease by > 30% at discharge indicates a better prognosis than when values fail to decrease or actually increase.[62]

A2. In the community setting (Primary Care):

- **They are a useful "rule out" test in the diagnosis of HF in patients presenting with dyspnea**.[57,63,64] A point-of-care test allows early diagnosis.
- Changes in the levels of BNP and NT-Pro BNP predict risk of hospital admissions for HF.[57,65]
- A decline in NT-ProBNP over time suggests favourable LV remodeand improved clinical outcomes.[66,67]

B) <u>Acute Decompensation in patients with Chronic HF</u>

- In patients with chronic HF, NPs may be persistently elevated and show substantial biological variation.[68]
- When these patients present with acute symptoms, a change of 100% or more from the stable concentration suggests decompensation.[57]
- **A combination of symptoms, weight gain and NP concentration may, however, be the best way to diagnose early decompensation in these patients.**

NP levels are affected by:

- Atrial fibrillation (AF)[69,70] - levels are increased even in the absence of HF.
- Age [71, 72] - Levels of NP increase with age.
- Renal function.[57,73,74]
- Obesity [75, 76] - Levels are reduced in obesity.
- Certain medications such as Angiotensin Receptor Neprilysin Inhibitor (ARNI) may interfere with the interpretation of BNP levels.

In cases of suspected HF, a point-of-care NP test allows early confirmation of the diagnosis. However:

- A raised NP level may be due to other causes besides HF. (Appendix I, Page 161)
- For this reason, NPs should only be used in conjunction with careful clinical assessment and investigation and interpreted with all other clinical information.

GUIDING THERAPY:

- The results of studies on the use of NP to guide therapy in HF are conflicting.[57,77-80]
- A value of NT-Pro BNP of ≤ 1,000 pg/ml during treatment was associated with better CV outcomes.[81]

ADDITIONAL INVESTIGATIONS WHEN INDICATED:	
Blood Tests	• Serum cardiac biomarkers: to look for myocardial necrosis - troponins, creatine kinase - muscle/brain band (CKMB). • Iron studies (ferritin, serum iron, transferrin saturation). • Serum calcium and magnesium. • Thyroid function tests.
	Other less common tests that may be considered include: • Gamma-glutamyl transferase (GGT) • Viral studies
Tests for Myocardial Ischemia and/or Viability	• Treadmill exercise test • Stress echocardiography (exercise or pharmacological) • Radionuclide studies • Cardiac magnetic resonance imaging (Cardiac MRI)
Invasive Tests	• Coronary angiography • Cardiac catheterisation • Endomyocardial biopsy
Others	• Holter electrocardiography, loop recorders • Pulmonary function test

Table 12: Optimal Natriuretic Peptide Cut Points for Diagnosis or Exclusion of Heart Failure among Patients with Dyspnea. [56,57,64]

	BNP (ng/L)	NT-Pro BNP (ng/L)
Emergency Setting		
Heart Failure Rule Out	< 100	< 300
Heart Failure Possible	> 400	Age < 50 y: > 450
		Age 50 - 75: > 900
		Age > 75: > 1800
Community Setting (Primary Care)		
Heart Failure Rule Out	< 35	< 125

Key Recommendations # 1: Diagnosis & Essential Investigations

- In making a diagnosis of HF, a detailed history and a thorough physical examination are important.
- The clinical suspicion of HF should be supported objectively by either raised natriuretic peptides and/or evidence of pulmonary or systemic congestion.
- Important basic investigations:
  - Echocardiogram.
  - ECG.
  - Chest Radiograph.
  - Blood - Full Blood Count, urea, creatinine, serum electrolytes (sodium and potassium) liver function, serum glucose, lipid profile.
  - Natriuretic Peptides: NT-Pro BNP or BNP
    - They are a useful "rule out" test in the diagnosis of HF in patients presenting with acute dyspnea.
    - In chronic HF, NPs may be persistently elevated and show substantial biological variation. In this setting, NPs should be interpreted with careful clinical assessment and investigation and with all other clinical information.
    - A value of NT-Pro BNP of ≤ 1,000 pg/ml during treatment was associated with better CV outcomes.

7. PREVENTION

FOUNDATION OF MANAGEMENT OF HEART FAILURE

Stage A "At Risk"	**Individuals who do not have structural cardiac disease but are at high risk of developing HF/CAD.** Hypertension Diabetes Obesity and the Metabolic Syndrome Cigarette smoking Familial hypercholesterolemia Multiple CV risk factors Family history of Cardiomyopathy Thyroid Disease Renal Disease Cardiotoxins *Others:* Sleep Disordered breathing, Connective Tissue Disease, Chronic Pulmonary disease and Pulmonary Hypertension
Stage B "Pre HF"	**Individuals with structural cardiac disease and who either have normal or impaired myocardial function.** Established CAD Hypertension with LVH Cardiac Valve disease Congenital Heart disease Arrhythmias

Prevention of HF should always be the primary objective and the foundation of management. It should focus on those who are in:

- **Stage A - "At Risk"** - Individuals who are at high risk of developing cardiac disease but who do not have symptoms or signs of HF and have structurally normal hearts.
- **Stage B - "Pre HF"** - Individuals with structural cardiac disease and who have either normal or impaired cardiac function but do not have signs and symptoms of HF.

There is robust clinical data that by appropriate and timely interventions, HF can be prevented in these individuals and cardiac function improved.

7.1 STAGE A - "AT RISK"

Individuals who are at high risk of developing HF/CAD but who do not yet have structural heart disease. These include individuals with:

- **Hypertension -**
  - This is an important risk factor for the development of HF especially in the elderly.
  - In the Framingham Heart Study, 91% of the participants with HF had a previous diagnosis of hypertension.[82] In multivariable analysis, the population-attributable risk of HF in the Framingham population was 39% and 59% for male and females respectively.[82]
  - In a meta-analysis of 23 hypertension trials, the risk of development of HF was comparable to that of stroke: 8.5 and 9.1 events per 1000 patients respectively.[83]
- **Diabetes -**
  - This is a risk factor for the development of HF independent of the presence of coexisting hypertension or CAD and after adjusting for other CV risk factors such as age, hyperlipidemia, and smoking.[84]
  - In the Framingham population cohort, the presence of diabetes increased the risk of HF by 2x in men and 5x in women.[85]
  - The prevalence of HF in individuals with diabetes is 4x higher than that of the general population.[86]
- **Obesity and Mmetabolic Syndrome -**
  - In the Framingham Heart Study, obese individuals had a doubling of the risk of HF when compared to those with a normal body-mass index.[85] There was a continuous gradient of the risk of developing HF with increasing body-mass index in both sexes which persisted even after adjusting for other CV risk factors, presence of Left Ventricular Hypertrophy and CAD.[87]
  - A meta-analysis showed that there was a 41% increase in HF per 5-unit increment in BMI and a threshold of risk at 23-24 kg/m^2.[88]
  - HF*p*EF is more common than HF*r*EF in obese individuals. Those who are overweight and with class 1 obesity have 38% and 56% higher risk of HF*p*EF, respectively, independent of other CV risk factors.[89,90]
  - However, there exists an obesity paradox in HF - Patients with overweight or class 1 obesity have better clinical outcomes than patients with normal weight for similar degrees of HF.[90]
  - Metabolic Syndrome - After adjusting for other risk factors for HF, the presence of metabolic syndrome at baseline was also a strong predictor of the development of subsequent HF.[91,92]

- **Cigarette Smoking -**
  - This is a risk factor for HF independent of traditional CV risk factors.
  - Current smoking, smoking ≥20 cigarettes/day and smoking burden (≥15 pack-years) were significantly associated with incident HF hospitalization in comparison with never smoking.[93]
  - In older adults, both current and past cigarette smoking was shown to increase HF risk after adjusting for other HF risk factors.[94]
  - Smokers had 2x the risk of developing HF*r*EF and HF*p*EF compared to never / nonsmokers after a median of 13 years of follow up.[95]
- **Familial Hypercholesterolemia -**
  - This leads to premature CAD and subsequent HF.[96]
- **Multiple CV Risk Factors** or who already have evidence of atherosclerotic disease in other vascular beds (e.g., cerebral, peripheral vascular disease).
- **Family History of Cardiomyopathy -**
  - These usually manifest in younger individuals as HF, arrhythmias, or syncope.
  - A family history of premature cardiomyopathy death was associated with an increase in the risk of developing cardiomyopathy ranging from 6 - to 400-fold, depending on age, kinship, gender, and number of affected family members.[97]
  - In the Framingham Offspring Study, parental HF was connected to asymptomatic left ventricular dysfunction and increased the likelihood of overt HF in the offspring.[98]
- **Thyroid Disorders -**
  - Both hyper and hypothyroidism increase the risk of HF.[99]
  - A meta-analysis showed that the risk of HF is increased with a TSH < 0.10 mIU/L and > 10.0 miu/l among older adults.[99-101] The risk of a low-output HF in hyperthyroid patients has been reported to be between 6 and 15%.[99]
- **Kidney Disease -**
  - Microalbuminuria is a strong and independent indicator of increased risk of CV events and death among individuals with and without diabetes, with stable CAD and those with HF.[102-104] It is a CV risk marker - reflecting subclinical vascular damage in the kidneys and other vascular beds.[105]
  - There is a close relationship between the heart and the kidneys, each condition causes or exacerbates the other, compounded by the accompanying anemia.[106]
  - The incidence of de novo HF in known CKD is in the range of 17% to 21% and for post-kidney transplant it is 18% at 3 years.[107]
  - The prevalence of HF increases greatly as the patient's renal function deteriorates, and, at end-stage kidney disease, can reach 65-70%.[106]
- **Cardiotoxins -**
  - Alcohol - Heavy drinking has been shown to increase the risk of HF, whereas light-to-moderate drinking (up to 1 drink per day for women and up to 2 drinks per day for men) has been associated with a lower risk of HF.[108]
  - Chemotherapeutic agents.
  - Substance abuse such as cocaine, amphetamine, antidepressants.
- **Healthy Sleep Pattern -**
  - In a prospective study, adherence to a healthy sleep pattern was associated with a lower risk of HF, independent of the conventional risk factors.[109] Healthy sleep factors were defined as early chronotype (“morning” person or “morning” than “evening” person); sleeping 7 to 8 hours/day; never/rarely or sometimes insomnia symptoms; no snoring; and no excessive daytime sleepiness.

- The National Sleep Foundation recommends 7 to 9 hours for young adults and adults, and 7 to 8 hours of sleep for older adults.[110]
- Sleep-disordered breathing includes Obstructive Sleep Apnea (OSA) and Central Sleep Apnea (CSA) with Cheyne-Stokes respiration.
- The relationship between sleep disordered breathing and HF is complex. It may just be an association rather than a cause-and-effect relationship.[111,112]
- It is a frequent comorbidity in HF, the prevalence ranging from 11% to as high as 40-50% in symptomatic HF.[111,112]

- Connective tissue diseases such as rheumatoid arthritis, SLE -
  - There is a high prevalence of atherosclerotic coronary disease in these systemic inflammatory conditions.[113] In addition, HF can occur secondary to chronic myocardial and pericardial inflammation, valvular disease and/or pulmonary hypertension.
  - Chronic pulmonary disease with pulmonary hypertension- These lead to right HF which in turn also affects left heart function and causes a complex clinical syndrome affecting multiple organ systems.[114]

7.1.1 Preventive Strategies in Stage A

- **Treating Hypertension to Target -**

I,A
- Reducing systolic BP to 140-145mmHg, has been shown in several trials in older patients with systolic hypertension to reduce new onset HF from 36-64%.[115-118]

IIa,B
- Further lowering of the target SBP from ≤ 140 to ≤ 120 in non-diabetic hypertensive individuals who were age ≥ 50 years and at high CV risk was also shown to reduce the development of HF by as much as 37%.[119]

- **Diabetes -**

I,A
- Treat A1c to target - Poor glycaemic control increases the risk of HF, each 1% increase in A1c increases the risk by 8-32%.[120,121]

I,A
- In patients at high CV risk and/or with established CVD, sodium-glucose cotransport-2 inhibitors (SGLT2-i) have been shown to reduce hospitalization for HF and improve CV outcomes.[122-127]

- **Smoking Cessation -**

I,B
- Quitting smoking appears to have a substantial and early effect (within two years) on decreasing morbidity and mortality in patients with left ventricular dysfunction mainly due to a reduction in CV events.[128]
- After > 15 years of smoking cessation, the risk of HF and death for most former smokers becomes like that of never-smokers.[129]

- **Familial Hypercholesterolemia -**

I,A
- Treating lipid levels to target reduces risk of MI and thus prevents the development of HF.[130,131]

- **Multiple CV Risk Factors -**

I,A
- Optimal profiles in the 7 CV risk factors -smoking, body mass index, physical activity, diet, cholesterol, blood pressure, and glucose- are associated with a lower lifetime risk of HF.[132,133]

- **Family History of Cardiomyopathy -**
  - Screening and early treatment of first-degree relatives of patients with known heritable cardiomyopathy.

I,C
- **Thyroid Disease -**
  - Detecting and treating thyroid disease early especially in older adults to prevent thyroid heart disease.

I,C
- **Kidney Disease -**
  - Early detection and appropriate management of kidney disease and the coexisting anemia. In adult CKD patients, however, KDIGO has advised that the Hb be maintained < 11.5 gm/100ml.[134] These levels are associated with lower mortality and less frequent hospitalization rates.[134]
  - Preservation of kidney function by avoiding nephrotoxic agents such as non-steroidal anti-inflammatory agents and the use of proven kidney-protective agents.

- **Alcohol -**
  - In the absence of large, randomized trials, light-to-moderate drinking cannot be recommended to lower the risk of HF. Advise abstinence.

I,C
- **Chemotherapy -**
  - Identifying and monitoring at risk individuals prior to administration of cardiotoxic chemotherapy.

III,B
- **Sleep Disordered Breathing -**
  - To date, the use of servo-ventilation and/or Continuous Positive Airway Pressure (CPAP) for central and /or obstructive sleep apnea (OSA) has not been shown to prevent HF or to improve CV outcomes.[135-140]

- **Others:**

I,A
  - Regular exercise - A minimum physical activity of at least 150 minutes per week of moderate intensity activity has been recommended to reduce CV risk and prevent ischemic heart disease.[89,141]

I,A
  - Maintain ideal body weight - Maintenance of normal weight and physical activity during adult life have been associated with lower incidence of HF.[89,141,142]
  - n-3 Polyunsaturated Fatty Acids (PUFA) supplements -
    - To date, there have been no primary prevention trials on the use of these supplements to prevent cardiac disease.[143]

IIb,B
    - The cumulative findings from RCTs on the prevention of HF and or CV events in patients at high CV risk and or established CVD have been mixed.[143]

7.2. STAGE B - "Pre HF"

Individuals with structural cardiac disease but who do not have signs and symptoms of HF. Cardiac function may be normal or impaired. The following strategies have been shown to prevent the development of HF.

7.2.1. In the presence of normal cardiac function

I,A
- Timely triage and appropriate treatment of patients with acute coronary syndromes.[144,145]

I,A
- Patients with CAD should be treated appropriately with guideline directed medical therapy (antiplatelet agents, statins, β-blockers, and Renin Angiotensin System blockers) and intervention as necessary.[146]

I,A
- Patients with hypertension and left ventricular hypertrophy (LVH) should have their blood pressure control optimized. Regression of LVH has been shown to be associated with a lower incidence of new onset HF.[147,148]

I,C
- Patients with significant valve disease (moderate and above) should be assessed for

progression and undergo timely intervention as indicated.

- Patients with arrhythmias, when indicated, should be referred for evaluation and treatment. I,C
- Patients with congenital heart disease should have their cardiac lesions corrected with appropriate follow-up looking for progression and sequelae.

7.2.2. In the presence of impaired LV function (LVEF< 40%) irrespective of symptoms:

- Treat the underlying cause wherever possible. I,A
- The evidence for the benefits of pharmacotherapy in patients with **asymptomatic LV dysfunction in NYHA Class** I has been mainly derived from studies conducted in patients with LVEF < 40% with β-blockers and ACE-I.[149-152] I,A
- SGLT2-i reduce hospitalization for HF in patients with and without established CVD, irrespective of diabetes status.[127,128,153.154] I,A
- In **symptomatic patients in NYHA Class II-IV**- All the 4 Foundational HF medications (RAS blockers, MRA, β-blockers and SGLT2-i) improve CV outcomes.[155,156]

Key message #6: Prevention of HF

- Prevention and early intervention, wherever appropriate, should be the primary objective of management of patients at risk for HF.
- There is robust clinical data that by appropriate and timely interventions, HF can be prevented in these individuals and cardiac function improved.
- It should focus on those who are in:
  - **Stage A - "At Risk"** - Individuals who are at high risk of developing cardiac disease but who do not have symptoms or signs of HF and have structurally normal hearts.
  - **Stage B - "Pre HF"** - Individuals with structural cardiac disease and who have either normal or impaired cardiac function but do not have signs and symptoms of HF.

Key Recommendations #2: Prevention of HF

- In the prevention of HF for patients in **Stage A**:
  - All CV risk factors should be treated to target.
  - Optimal profiles of the 7 CV risk factors - blood pressure, glucose, cholesterol, absence of smoking, body mass index and physical activity has been shown to be associated with a lower lifetime risk of HF.

- In the prevention of HF for patients in **Stage B**:
  - Patients with Acute Coronary Syndrome, Hypertension, CAD, arrhythmias, valve, and congenital heart disease should be treated timely and according to the guidelines.
  - In patients who have impaired LV function (LVEF<40%):
    - Treat the underlying cause and avoid/treat early precipitating factors.
    - In **asymptomatic patients in NYHA Class I**: ACE-I, β-blockers, and SGLT2-i.
    - **Symptomatic patients in NYHA Class II-IV**: All the 4 Foundational HF medications (RAS blockers, MRA, β-blockers and SGLT2-i) should be instituted early to improve CV outcomes.

8. NON-PHARMACOLOGICAL MEASURES

8.1 Education

I,B **HF patients and their family members should be educated on the definition, causes, signs, symptoms, and the progressive and relapsing nature of the disease, emphasizing self-care wherever possible**. Increased awareness helps patients adhere to therapeutic instructions whereas knowledge leads to reduced anxiety and better sense of control.[157] Self-care is important and improves long term adherence to management strategies.[157]

Patients and their family should[158]:

- Be educated on self-care which includes:
  - Maintenance (e.g., taking medication, exercising, and adhering to a healthy diet)
  - Monitoring (e.g., regular weighing) ***and***
  - Management (e.g., changing diuretic dose in response to symptoms)
- Recognize the changes in their signs and symptoms - a sudden weight gain - more than 2kg in 3 days is a sign of worsening HF.
- Know when to contact their healthcare provider.
- Understand the indication, dosing, side effects and drug interaction of each medication they are prescribed.
- Be warned about self-medication and potential drug interactions.
- Adhere to treatment and be informed of the potential complications resulting from non-adherence to prescribed medications.
- Be provided with prognostic information to enable them to make realistic long-term decisions and plans. There should be frank end-of-life discussions and advanced care planning with the patient and family. This is important as there is a potential risk of sudden death, and they must put their affairs in order.

In advanced HF, treatment options must be discussed tactfully and realistically with the patient and family.

Structured telephone support and non-invasive home telemonitoring have been shown to reduce all-cause and cardiac hospitalizations, length of hospital stays and all-cause and cardiac mortality.[159-161] Patients involved actively in educational process through telemedicine are more likely to accept positive lifestyle changes.[157]

Telemedicine (See also section 17.4)

- Allows more frequent monitoring of the patient's status using smart phones and other mobile devices.
- Has been found to be effective in improving patient's self-care abilities.[159]
- Enables HF patients to be cared for while staying at home, thus reducing hospitalizations.

They are however barriers for the widespread implementation of telemedicine. These include:[162]

- Issues related to patient privacy and data safety although recently, many platforms have been developed to address these issues.

- Costs- it would be more cost effective to identify:
  - The most relevant biological parameters to monitor.
  - The HF sub-populations who may gain from telehealth interventions (e.g., older patients with more comorbidities).
  - In which specific healthcare subsets these interventions should be implemented e.g., immediate post discharge.

8.2. Exercise training-see also Section 16 - HF Rehabilitation

I,B Several systematic reviews and meta-analyses support **exercise training as an integral part of the non-pharmacological treatment of HF**.[163-169] Exercise also leads to an improvement in the patient's Health Related Quality of Life (HRQoL) - symptoms, a greater sense of wellbeing, and better functional capacity.[163]

Exercise training:

- Is safe in patients with stable HF.[163-170]
- In patients with HF*r*EF, has been shown to reduce overall and HF-specific hospitalizations.[163-169]
- In patients with HF*p*EF has limited clinical data. Small trials show that exercise training leads to an improvement in exercise capacity and quality of life.[169,170]

Exercise-based rehabilitation:

- Reduced the risk of hospital admissions.[163-169]
- Improved health related quality of life. (HRQoL).[163-170]
- Enhanced exercise capacity.[163-170]
- Did not result in an obvious improvement in cardiac function although in some small studies, it has been shown to reverse left ventricular remodelling.[171]

Regular aerobic exercises are encouraged in NYHA I - III patients. These include:[172]

- Aerobic and endurance training - Moderate intensity continuous exercises such as walking, treadmill, stationary bicycle as well as swimming with a target goal of 5 days per week, 30 minutes per session.
- Interval training and high intensity interval training (HIIT) - This has been shown to be safe and results in greater improvements in exercise tolerance in selected patients with HF. In a trial on patients with HF*p*EF, however, HIIT did not confer any advantage compared to guideline based physical exercise.[173]
- Inspiratory muscle muscle training (IMT) - the addition of IMT has been shown to reduce dyspnea, improve exercise time and HRQoL.

8.3 Diet and nutrition

I,B It has been widely accepted that sodium intake should be restricted in patients with HF especially in those with symptoms. **However, there is little clinical evidence to support this**.[174-176] Sodium restriction to < 100gm/day did not reduce clinical events.[175]

IIa,C **The current recommendation is to avoid adding salt and flavouring sauces such as soya sauce, tomato ketchup and chilli sauce while cooking or at the table**. Refer to Appendix II, Page 162-163 on salt content of common Malaysian food.

IIa,B A good balanced diet plays an important role in preventing energy depletion which can lead to cardiac cachexia and malnutrition. Cachexia is associated with increased mortality.[177]

A review found that the combination of personalized nutrition intervention with conventional treatment led to a decrease in all-cause mortality and hospital readmission.[178]

There are at present, however, few existing dietary strategies proven to improve clinical outcomes in HF.[179,180] The role of routine supplementation of micronutrients as a component of HF management is unclear.[179,180]

8.4 Fluid restriction

IIa,C **The current evidence on fluid restriction is mixed**.[181,182] As with salt, excessive fluid restriction can also lead to worse outcomes.[181,182] This may also be due to reverse causality - sicker patients tend to take less salt and water.

I,C Fluid intake should be individualized. **A general recommendation is 1-1.5 liters per day in patients with normal renal function.**

In older persons, particularly those living with dementia and at the end of life, fluid intake may be more liberal.

Temporary fluid restriction can be considered in decompensated heart failure and/or patients with hyponatremia.[182]

8.2.1.5 Lifestyle measures

These include:

I,B
- **Weight Monitoring** - Patients should be encouraged to monitor their own weight. In obese patients, weight loss should be encouraged.[183]

IIa,B
- **Alcohol** - Heavy binge drinking should be avoided in patients with HF as it can predispose to supraventricular arrhythmias especially atrial fibrillation and lead to acute cardiac decompensation.[184.185] Patients with alcoholic cardiomyopathy should abstain from alcohol.[185]

I,B
- **Smoking** should be stopped.[128,186]

8.2.1.6 Sexual activity, pregnancy, and contraception

As many as 60% to 87% of HF patients have sexual problems.[187] Erectile dysfunction (ED) is common and many have misconceptions that their symptoms (20%) or medications (10%) is the cause.[185] Proper counselling is necessary to address these concerns, to allay anxiety, avoid skipping medications and prevent the use of traditional potency enhancing drugs or herbs.[187]

IIa,B **It is imperative that enquiries on sexual activities or dysfunction be addressed to provide a holistic approach to patient care**.[188] The physician must take over the initial approach since patients are often embarrassed to initiate the topic. Some helpful tools to initiate the conversation include:

- PLISSIT (permission, limited information, specific suggestion, and intensive therapy).[189]
- Needs of Sexual Counselling Scale for Chronic Heart Failure (NSCS-CHF).[190]
- Sexual Adjustment Scale (SAS).[190]

Patients should be taught:

- To pay attention to their symptoms of HF.
- The potential dangers (worsening chest pain, dyspnea, giddiness and/or palpitations) and how to manage them when they occur during sexual activities.
- To defer sexual activities if in NYHA III-IV.
- Not to resume until his/her heart condition stabilizes.
- To modify sexual practices to accommodate impaired effort tolerance.

HF patients need to be told that certain cardiac medications have important side effects and drug interactions:

- Nitrates may dangerously interact with drugs for erectile dysfunction - phosphodiesterase - 5-inhibitors (Viagra, Cialis, Levitra).
- β-blockers may contribute towards worsening erectile dysfunction, but it is important that HF patients remain compliant to them.

I,C **Patients with LVEF < 30% and those with NYHA III and IV should be advised against pregnancy because of high maternal mortality.**[191,192] If pregnant, termination of pregnancy should be considered.[192]

I,C When pregnancy is contraindicated, a multi-disciplinary approach with pre-conception counselling and proper contraceptive advice becomes paramount to the safety of the patient by preventing an unwanted pregnancy. Contraceptive counselling should begin early. In the absence of randomized controlled studies, the choice of contraceptive method is almost always based on expert opinion of the attending cardiologists, obstetrician, and the patient's choice.

Generally, Tier I methods which includes permanent sterilization and long-acting reversible contraceptives such as intrauterine devices [IUDs] and implants, have typical-use 1-year failure rates of < 1%. Given their excellent safety and efficacy profile, they should be recommended for women with underlying CVD. The risk of infective endocarditis with IUD is low.[193,194]

8.2.1.7 Sleep disorders

Sleep disorders are common in HF with prevalence rates of 50-75%, the prevalence increasing with age, obesity, male sex, Atrial Fibrillation, and poorer LV systolic function.[195] These sleep disorders include short sleep time, low sleep quality, and sleep-disordered breathing.[196] Sleep disordered breathing (SDB) includes either:

- Central Sleep Apnea (CSA) or
- Obstructive Sleep Apnea (OSA) or
- Coexisting OSA and CSA.

Sleep disturbances could also be due to pulmonary congestion leading to breathlessness and cough, and nocturnal diuresis due to diuretics and anxiety.

OSA may occur in the normal population or in HF patients, while CSA, which may present as Cheyne-Stokes respiration, is more associated with HF.[197] Independent predictors of SDB include older age, male gender, obesity, low ejection fraction and the presence of AF.[196] Attended in-hospital polysomnography (PSG) is the gold standard in diagnosing OSA and CSA. However, a screening using overnight pulse oximetry is useful to preselect a patient for PSG.

SDB affects HRQoL and leads to harmful effects on cardiac function, arrhythmias (both atrial fibrillation and malignant ventricular arrhythmias) and poorer prognosis due to the repetitive hypoxemia, hypercapnia and swings in blood pressure and intrathoracic pressure.[196,197]

I,C **OSA patients are encouraged to lose weight and to exercise moderately. Alcohol and sedatives before sleep are best avoided**.[196] These patients are best managed in a multi-disciplinary manner.

IIa,B **CPAP** improves daytime sleepiness. However, **none of the evidence so far indicates an improvement in terms of cardiovascular or all-cause mortality or hospital admissions**.[196,198-201]

In patients with HF and CSA, the use of Adaptive Servo Ventilation (ASV) was associated with an increase in all cause and CV mortality mainly driven by an increase in sudden cardiac death.[137]

III,B **ASV is contraindicated in patients with HF and CSA**.[135-140]

I,C **As CSA tends to worsen when HF worsens, optimizing medical therapy remains the main strategy in CSA**.[197]

8.2.1.8 Psychosocial support

About 35% patients with HF have clinical depression and about 40% have severe anxiety.[202,203] There is an association between HRQoL scores and survival.[204] Most patients prefer improved HRQoL to longevity.[205,206]

Patients with HF who have psychological problems have been shown to have increased morbidity and hospital readmission rates, to be less adherent to their medical regimen, and to have an overall increase in cost of care. Effective, homebased HF management, has been shown to improve HRQoL, reduce expenditure and re-hospitalization rate.[207,208]

I,C **Thus, it is important that family members and carers are included during counselling sessions**. Depressive symptoms may affect adherence and should prompt referral to the appropriate specialists for psychological support. Inpatient treatment and hospitalizations are the main drivers for a decrease of HRQoL and efforts should be made to avoid this.[21]

Key Recommendation # 3: Non-Pharmacological Measures

- In managing HF, non-pharmacological measures play a vital role. It is important to:
  - Educate patient and family about the disease, treatment options and prognosis. There should be frank end-of-life discussions and advanced care planning with the patient and family. This is important as there is a potential risk of sudden death, and they should put their affairs in order.
  - Encourage lifestyle measures:
    - Proper balanced diet to prevent malnutrition and cardiac cachexia.
    - Weight management - avoid obesity.
    - Regular physical activity and exercise training.
    - Smoking cessation.
  - Individualize fluid intake - A general recommendation is 1-1.5 liters per day in patients with normal renal function.
  - Provide advice regarding sexual activities and pregnancy.
  - Address psychosocial problems encountered by the patient and the family.

9. ACUTE HEART FAILURE

Acute heart failure is a heterogeneous clinical syndrome of new or worsening symptoms and signs of HF. It may occur as:

- **De Novo HF** - first occurrence of HF ***or***,
- **Acute decompensated HF (ADHF)** - this is a more common presentation occurring in a previously stable patient with HF who has now deteriorated.

In general, patients presenting with De Novo HF tend to do better than previously stable HF patients admitted with worsening symptoms ie ADHF.[209,210] Patients admitted with ADHF tend to have a greater comorbidity burden and are symptomatic despite being on proven medical therapy.[209]

When previously stable patients present with ADHF, their risk of death is increased.[211] Only one quarter to one third of these patients survive 5 years after a HF related hospitalization. Patients who have decompensated because of under or suboptimal treatment tend to do better when compared to those who have decompensated on OMT.[212-214]

The onset can be:[215]

- **Sudden** with the patient presenting in acute respiratory distress and/or cardiogenic shock - This is a more common presentation of De Novo HF following an acute cardiac injury e.g., Acute MI ***or***
- As a **slow progressive deterioration over days (up to weeks)** prior to hospital admission - this is a more common presentation of ADHF.

Three important phases should be considered in the management of these patients.[216]

- **Phase 1** - Urgent treatment and stabilization usually in the Emergency Room. (ER).
- **Phase 2** - In-hospital management.
- **Phase 3** - Discharge and Post discharge “vulnerable” period.

9.1 PHASE 1- Urgent treatment and stabilization (See Flowchart II, page 35)

Assessment and management must be prompt and done concurrently.

- Rapid recognition and making the diagnosis of HF based on symptoms and signs and quickly assessing its severity.
- Maintaining adequate oxygenation and perfusion of vital organs.
- Identification and stabilization of life-threatening hemodynamics (heart rate and rhythm, blood pressure and organ/tissue perfusion).
- Relieving clinical symptoms, signs and preventing end organ damage.

Once the diagnosis of Acute HF has been made, the **initial management** should focus on: (see also section 8.2 & Flowchart II, page 35)

- Adequate oxygenation-SpO2 ≥ 95%.
- Intravenous (i.v.) diuretics to relieve congestion if present.
- Stabilization of hemodynamics and perfusion with vasodilators +/- inotropes.
- Identifying and treating the precipitating factors. An aide memoire to common precipitants is: (see Table 11, Page 55)

C H A M P I O N

- **C** - Coronary artery disease - Acute Coronary Syndrome (Myocardial infarction/Ischemia).
- **H** - Severe and uncontrolled hypertension.
- **A** - Arrhythmias.
- **M** - Mechanical e.g., Acute valvular dysfunction (e.g., acute mitral regurgitation from chordal rupture); cardiac tamponade
- **P** - Pulmonary embolism, pulmonary infections.
- **I** - Infections e.g., urinary tract, Covid.
- **O** - Other medications (Medications that increase fluid retention and/or have negative inotropic effects).
- **N** - Non-compliance to treatment especially oral diuretics and or dietary/fluid restriction.

In 40% of patients admitted with Acute HF however, a clear underlying precipitant may not be identified.[217]

- **Identify non-cardiovascular comorbidities** - These can complicate management affecting the choice and doses of medications used. The presence of these non-cardiovascular comorbidities tends to worsen the prognosis. The more common comorbidities include:
  - Diabetes (Section 14.1)
  - Chronic kidney disease (Section 14.6)
  - Thyroid disease (Both hyper and hypothyroidism)
  - Chronic lung disease
  - Anemia
- It is important that **precipitating factors be identified as soon as possible after presentation and treated immediately** according to guidelines.
- The patient **should be seen by a specialist as soon as possible after admission** to co-ordinate the initial and further management. In the United Kingdom National Heart Failure Audit 2022, in-hospital mortality was lower in patients who had been seen by a specialist especially a cardiologist.[218]

9.1.1. Classification of Acute HF

Based on the initial clinical assessment, the patient may be classified as:[215,219]

- Wet or dry depending on their fluid status.
- Cold or warm depending on their perfusion status.

Table 13: Classification of Acute HF According to Clinical Presentation and a Guide to Management

Warm / Wet	Warm / Dry
SBP : Adequate (≥ 90mmHg) **Perfusion** : Adequate **Fluid Status** : Congested **Management**: ● **Diuretics** - Yes ● **Vasodilators** - Yes ● **Inotropes** - No	**SBP** : Adequate (≥ 90mmHg) **Perfusion** : Adequate **Fluid Status** : Not congested. **Management:** ● **Diuretics** - No ● **Vasodilators** - No ● **Inotropes** - No ● **Adjust Oral Medications**
Cold / Wet	**Cold / Dry**
SBP : Low (< 90mmHg) or Adequate (≥ 90mmHg) **Perfusion** : Poor **Fluid Status** : Congested **Management:** ● **Diuretics** - Yes ● **Vasodilators** - If BP ≥ 90mmHg ● **Inotropes** - Yes irrespective of the BP	**SBP** : Low (< 90mmHg) **Perfusion** : Poor **Fluid Status** : Not congested **Management:** ● **Diuretics** - No ● **Vasodilators** - If BP ≥ 90mmHg ● **Inotropes** - Yes **Consider fluid challenge cautiously**

The classification in the table above will help guide the initial management.

Thus according to the clinical presentation, the patient may be: (Table 13, Page 74)

- **Warm and Wet** - Adequate perfusion but congested** (lungs and/or periphery).
- **Cold and Dry** - Hypoperfusion* and dehydrated/not congested**.
- **Cold and Wet** - Hypoperfusion* and congested** (lungs and/or periphery).
- **Warm and Dry** - Adequate perfusion and dehydrated/not congested.** These patients have either mild HF or are in the compensated stage of HF.

***Hypoperfusion**: cold peripheries, capillary refill time more than 2 seconds, diaphoresis, oliguria, dizziness, confusion, narrow pulse pressure, hypotension.

****Congestion**: peripheral edema, orthopnoea, paroxysmal nocturnal dyspnea, lung crepitations, jugular venous dilatation, positive hepatojugular reflux, congested hepatomegaly, gut congestion, ascites.

Most patients admitted with Acute HF are in the 'wet-warm' category.[220]

The goal of therapy is to make them 'dry-warm'- optimal perfusion and fluid status.

9.1.2. Investigations

I,C **Essential Investigations** in Acute HF include: (See Section 6.2)

- **Electrocardiogram** - ECG.
- **Chest Radiograph** - Chest X-Ray - About 20% of patients with congestion, however, may exhibit a normal Chest X-Ray.[221]
- **Blood Investigations** - FBC, serum electrolytes, urea, creatinine, cardiac biomarkers (troponins, CKMB, BNP or NT-Pro BNP), liver function tests.
- **Echocardiography** - To assess LV function, Pulmonary Artery Pressure and to estimate right and left sided filling pressures. An IVC diameter less than 21 mm and which collapses > 50% suggests normal right atrial pressures.[222]

Other Investigations which may be performed if indicated and/or available:

- **Blood Investigations** - Thyroid function tests, serum lactate and pH.
- **Blood Gases** - If oxygen saturation is still < 90% despite initial treatment.
- **Lung Ultrasound** - To look for extravascular fluid in the lungs (B-lines). These are often observed in patients with HF, but can also occur in other conditions, such as non-cardiogenic pulmonary edema and interstitial lung disease.[223] Lung ultrasound is, in general, more sensitive in ruling out interstitial edema and pleural effusions than Chest X-Ray.[224]

9.1.4. Decision for hospitalization and care-setting

I,C Initial care in the **critical care unit (ICU/CCU) should be considered for high-risk patients** with features such as:

- Hemodynamic instability.
- Arrhythmias.
- Hypoperfused state-cold peripheries, capillary refill time more than 2 seconds, diaphoresis, oliguria, dizziness, confusion, narrow pulse pressure, hypotension.
- Need for invasive ventilatory support.
- Oxygen saturation (SpO_2) < 90% despite supplemental oxygen.

I,C **The remaining patients with Acute HF can be managed in a high-dependency unit or normal ward** depending on the clinical circumstances. However clinical deterioration may occur and hence, frequent re-assessments are necessary.

I,C Step-down care from the ICU/CCU is dictated by clinical improvement. Similarly, should the patient not improve, he should be considered to be transferred to a tertiary hospital with a Cardiology Unit.

9.1.5. Response to Therapy

Response should be assessed continuously using the following parameters:

- **Symptoms and signs of HF** - this requires repeated thorough clinical examinations looking for resolution or worsening of clinical signs.
- **Vital signs**
  - Oxygen saturation - SpO_2.
  - Heart rate.
  - Blood pressure - including looking for a postural drop whenever possible.
  - Respiratory rate.

- Urine output.
- Body weight.

- **Investigations**
  - Urea, creatinine, serum potassium and sodium.
  - Invasive hemodynamic monitoring may be considered in patients if there are uncertainties in diagnosis, or, for the more severe cases, that despite pharmacological treatment, present refractory symptoms (particularly with hypotension and hypoperfusion). Invasive monitoring includes:
    - Arterial pressure line.
    - Central venous pressure line and pulmonary artery catheter (PAC). This would allow a more accurate assessment of the fluid status of the patient and allow better titration of medications. It is only recommended in cardiogenic shock and in this setting, PAC is associated with lower mortality and in-hospital cardiac arrest.[225-227]

IIb,B

An adequate response would be reflected by ***all*** the following:
An improvement in the patient's clinical condition and symptoms,

- Warm peripheries,
- Decrease in heart rate,
- Decrease in respiratory rate,
- An improvement in oxygen saturation ***and***
- An improvement in the urine output.

Generally, **a SBP ≥ 90mmHg would be considered adequate** if the patient has all the following:

- Feels well,
- Has good tissue perfusion as shown by the absence of giddiness, warm skin ***and***
- Stable renal function with good urine flow.

9.2. PHASE 2: In - Hospital Management (Flow Chart II, page 35, Table 2, page 36 & Table 14, page 80)

The management of patients with Acute HF is largely based on clinical judgement and experience rather than on randomized controlled trials. Most clinical trials have been small and of low quality.

9.2.1. Pharmacotherapy

9.2.1.1. Oxygen

I,C
- Measurement of oxygenation by pulse oximetry (SpO_2) is recommended.

I,B
- **Supplemental oxygen therapy is recommended when the SpO_2 < 94% and should be titrated to achieve SpO_2 ≥ 95%.**

III,B
- Routine use in non-hypoxic patients is not recommended as it can cause deleterious effects such as vasoconstriction and a reduction in cardiac output.[228-235]

IIa,B
- **Supplemental oxygen therapy** can be delivered as:[236]
  - **Nasal Prongs** - at a flow rate of 2-6 l/min gives approximately 24-50% FiO_2.
  - **Simple Face Mask** - at a flow rate 5-10 l/min gives 35-60% FiO_2. Low flow rates below 5 l/min may cause carbon dioxide rebreathing and increased resistance to inspiration and thus should not be used.

- **Venturi Masks** - Gives concentrations of 24-60% FiO_2. A 60% venturi mask gives approximately 50% FiO_2.
- **Non-Rebreathing Reservoir Mask** - gives concentration of between 60-80% FiO_2.

IIa,B

- **Non-Invasive ventilation (NIV)** reduces respiratory distress and may decrease the need for intubation although data regarding mortality are less conclusive.[237,238] It includes:[238,239]
  - **High Flow Nasal Cannula (HFNC)** -This seems more effective and better tolerated than conventional oxygen therapy using nasal prongs or mask.[240-242]
  - **Continuous Positive Airway Pressure (CPAP)** - can be used without a ventilator and does not require specialized training.
  - **Non-Invasive Pressure Support Ventilation (NIPSV - Also Called Bilevel or BiPAP)**. This requires a ventilator and specialized training.
- CPAP and NIPSV should be considered early in patients with respiratory distress (respiratory rate > 25 breaths/min, SpO_2 < 90%) despite high-flow oxygen administration. There are no significant differences in clinical outcomes when comparing CPAP with BiPAP and the choice will depend on the equipment and expertise that is available.[237,243,244]

I, C

- Intubation may be considered in patients with respiratory failure, who cannot be managed with NIV techniques and who show signs of exhaustion and respiratory muscle fatigue.
- **Some helpful indicators of respiratory failure include**:
  - Hypoxemia (PaO_2 < 60mmHg),
  - Hypercapnia ($PaCO_2$ > 50mmHg), and
  - Acidosis (pH < 7.35)

9.2.1.2. Diuretics

- **Diuretics is the cornerstone of therapy in patients who are fluid overloaded (wet).**
- i.v. diuretics should be administered as early as possible to relieve congestion and provide symptomatic relief. Studies on the impact of early administration of i.v. diuretics on in-hospital mortality, however, have shown mixed results.[245,246]

I, B

- **i.v. furosemide 40-100mg is the diuretic of choice**.[48,247,248] This initial dose should be individualized depending on the severity of the clinical condition.
- **In individuals who are diuretic naive, a reasonable initial dose is 20-40 mg**.

IIa,B

- **Patients who have already been on diuretics or have chronic kidney disease**, may require a higher dose. A reasonable initial strategy in these patients is **a daily dose of 2.5 times the previous oral dose on a mg-to-mg basis**, administered as twice-daily boluses.[48,247]
- Further doses can be adjusted according to clinical response, blood pressure, urine output and renal function.
- In general, with a sufficient dose of a loop diuretic agent, urine output should measurably increase within 2 hours. If there is not an adequate response to the initial dose, there is no need to wait until the next scheduled dose to increase dosing.[48]
- An adequate response is a urine output >100ml/ hour during the first 6 hours.[48]
- If the urine output is:
  - **Excessive (a negative balance of > 3L/day)** and associated with a drop in systolic BP, then consider:
    - Temporarily stopping the diuretic ***or***
    - Reducing the dose by 50% ***or***
    - Increasing the dosing interval ***or***
    - Changing to oral administration.

- If worsening renal function occurs after the 1st i.v. dose, then:
  - Stop the diuretic ***and***
  - Rehydrate the patient with i.v. fluids ***and***
  - Restart later after the renal function improves, at a much lower preferably oral dose.

➢ **Adequate** and patient is:
- **Still congested** - continue the same i.v. dose of diuretic at 12 hourly intervals.
- **No longer congested but patient is still dyspneic** - consider other causes of dyspnea e.g., pulmonary embolism, chest infection etc.

➢ **Inadequate (< 600ml in the first 6 hours) (rule out urinary retention as a cause)** - As HF progresses, diuretic resistance may develop and responsiveness to loop diuretics diminish. Diuretic resistance is defined as an impaired sensitivity to diuretics resulting in reduced natriuresis and diuresis limiting the possibility to achieve euvolemia.[48]

This can be overcome by:

I,C
- **Uptitration of the dose of loop diuretics** - this is the preferred strategy. This can be done by:
  - Increasing the dose of i.v. furosemide and/or dosing intervals.
  - Continuous infusion - To date, there has been no difference between continuous infusion or bolus dosing of furosemide for all-cause mortality, length of hospital stay and electrolyte disturbances, but continuous infusion was superior to bolus administration with regard to diuretic effect, safety profile and reduction in brain natriuretic peptides.[249-252]

IIa,B
- **Combination of low dose dopamine and low dose furosemide** was as effective as high-dose furosemide with a suggestion of less worsening of renal function.[252,253] The addition of dopamine however, did not result in any difference in CV outcomes.[252]

IIa,B
- **Using bumetanide**, a second generation loop diuretic,because of its more predictable absorption.[254]

IIa,B
- **Combination of thiazides and loop diuretics for "total nephron block**." [255-257] It may also be used in patients with refractory edema and advanced renal impairment.[258,259] However, this combination has been associated with hypokalemia, hyponatremia, worsening renal function and increased mortality.[255]

IIb,B
- **Metolazone** is a once-daily oral thiazide diuretic. It is given in combination with a loop diuretic in patients with severe HF and refractory edema.[260-262] At present, there is inadequate data to show that it is superior to the other thiazides in this setting.[262] It can be used in advanced renal impairment.[263]

IIa,B
- **Other agents, when used in combination with i.v. loop diuretics**, that have been shown to produce rapid and persistent diuresis and weight loss but without, however, an impact on CV outcomes. These include :
  - **Tolvaptan**[264-266]
  - **Nesiritide**[267,268]
  - **Acetazolamide**[269]
- When combination therapy is used, there can be a marked diuresis. Careful monitoring of fluid and electrolyte balance and BP, including orthostatic hypotension,is essential.

IIa,B
- **Target 0.5 - 1kg decrease in body weight/day when the patient is volume overloaded.**[48] **Less than 0.5kg of weight loss/day may indicate inadequate diuretic dose or diuretic resistance.**[48]

9.2.1.3. Vasodilators (Table 14, page 80 for dosing)

- Vasodilators can confer symptomatic relief and an improvement in hemodynamics but there is, however, a lack of data to draw any firm conclusions concerning their effects on CV outcomes.[270-273]
- In patients with pulmonary congestion who are normotensive, emphasis should be placed on adequate diuresis, with vasodilators reserved for patients who fail to show clinical improvement or have poor perfusion and cool extremities.[274]
- **Nitrates**

I,B
  - Nitrates are the most widely studied vasodilators.[270,271]
  - It should be considered if the BP is adequate (SBP > 100mmHg).
  - Early i.v. nitroglycerin administration pre-hospital or in the ER was associated improved post-discharge event rate.[275]
  - It is most useful if there is concomitant myocardial ischemia, severe hypertension or aortic or mitral regurgitation.

I,C
  - It should be administered preferably intravenously for ease of titration.
  - Patients should be closely monitored for hypotension. This commonly occurs with concomitant diuretic therapy.

IIb,C
  - Extreme caution should be exercised in patients with aortic and mitral stenosis.

III,C
  - Nitrates are contraindicated in severe valvular stenosis.

9.2.1.4. Inotropes (Table 14, page 80 for dosing)

- Inotropes are not routinely administered to patients with an adequate BP.
- They are indicated in the presence of persistent signs of hypoperfusion (hypotension and low cardiac output - "cold patients") despite an adequate filling status.
- These patients are best managed in specialized tertiary centers.
- These agents are best administered via central lines, inserted aseptically with proper infection control.
  - **Noradrenaline infusion**:

IIa,B
    - Noradrenaline was as efficacious as dopamine with a trend towards a lower 28-day mortality and safer especially in the subset of patients with cardiogenic shock.[276,277]

IIa,B
    - The combination of noradrenaline-dobutamine appeared to be associated with more favorable hemodynamics and a safer strategy than adrenaline alone.[278]
    - The use of adrenaline in HF complicated with cardiogenic shock should be avoided because of increased mortality.[279]
  - **Dopamine infusion**:

IIb,B
    - Dopamine has been shown to improve renal flow and promote natriuresis in patients with HF.[280]
    - The role of low-dose dopamine in helping to improve renal function is still not well proven.[252] Studies seem to indicate that "low-dose' dopamine can worsen renal perfusion in patients with acute renal failure.[281]

Table 14: Drugs Commonly Used in Acute HF

	Route of Admin	Dosages
Diuretics		
Furosemide	i.v.	40-100mg **Initial dose:** New onset Acute HF and furosemide-naive: 20-40mg Known HF and on oral furosemide: 2.5 times the daily oral dose
	Infusion	5-20mg/hour (better than intermittent very high bolus doses)
Vasodilators		
Nitroglycerin	Infusion	5-200mcg/min
Isosorbide dinitrate	Infusion	1-10mg/hr
Inotropes		
Noradrenaline	Infusion	0.02-1mcg/kg/min till desired blood pressure is attained
Dopamine	Infusion	< 2-3mcg/kg/min - renal arterial vasodilation 2-5mcg/kg/min - inotropic doses 5-15mcg/kg/min - peripheral vasoconstriction
Dobutamine	Infusion	2-20mcg/kg/min
Adrenaline	Infusion	0.05-0.5µg/kg/min

➢ **Dobutamine infusion:**

- Started at 2-5mcg/kg/minute and titrated by 1-2mcg/kg/minute increments at 30 - minute intervals until the desired clinical and hemodynamic response is attained.

IIb,B

- Dobutamine, when used alone, improved cardiac output but there was a trend towards an increase in mortality.[220,283]

9.2.1.5 Morphine

- i.v. 1-3mg bolus (repeated, if necessary, up to a maximum of 10mg) reduces pulmonary venous congestion although its effect on venodilation has been shown to be minimal.[284]

IIb,B

- May reduce anxiety and dyspnea however due to paucity of data, routine use cannot be recommended.[284,285]
- Dose-dependent side effects include nausea, hypotension, bradycardia, and respiratory depression.
- Consider co-administrating i.v. antiemetics (metoclopramide 10mg or prochlorperazine 12.5mg).
- In a small study there were no significant difference in mortality between i.v. midazolam and i.v. morphine although the use of morphine was associated with a significantly higher rate of adverse side effects.[286]

If the blood pressure is low at initial presentation (SBP < 90 mmHg) or drops during treatment:

IIa,B
- Noradrenaline infusion[276,277] - initial inotrope and if BP is still low, add:

IIa,B
- Dopamine[278]

I,C
- Avoid vasodilators (nitrates) and morphine until the blood pressure has stabilized.
- Over diuresis or hypovolemia - correct accordingly. In Right Ventricular (RV) infarction, the hypotension may respond to volume loading.

Other measures to be considered

I,C
- Intubation and mechanical ventilation

IIa,C
- Correction of acidosis

IIb,C
- Invasive hemodynamic monitoring

If the patient is still unwell with poor perfusion "cool" and/or congested "wet", Mechanical Circulatory Support may need to be considered:

9.2.2 Mechanical Circulatory Support

This includes:

- **Intra-aortic balloon pump (IABP):**

IIa,B
  - This would be useful in patients with ADHF and cardiogenic shock who are not responding optimally to medical therapy and as a bridge to definitive treatment. IABP would be particularly useful in patients with intractable myocardial ischemia or acute moderate to severe mitral regurgitation. [287-289]

IIb,B
  - In patients with acute MI complicated by cardiogenic shock and undergoing percutaneous coronary intervention, the use of IABP has not been shown to reduce mortality.[287,290,291] There was however a trend of benefit in patients in Killip class 3 & 4 undergoing reperfusion by fibrinolytic therapy.[292,293]

III,C
  - IABP is contraindicated in patients with aortic regurgitation or aortic dissection.

- Others - These include the Impella system, the TandemHeart, and venous-arterial extracorporeal membrane oxygenation (ECMO). These are not widely available in Malaysia.
- Ventricular Assist Devices (VAD) - see also Section 15.2
  - These would be useful as a bridge in patients for whom recovery from Acute HF is expected or for whom heart transplant is an option. It may also be used as a destination therapy in selected patients.[294]

9.2.3 Treat precipitating factors for the Acute HF - "C H A M P I O N"

C Coronary Artery Disease - Myocardial Ischemia / Infarction:
- Reversible myocardial ischemia causing Acute HF needs early recognition, rapid stabilization and referral for urgent coronary angiography.
- In STEMI, reperfusion therapy by fibrinolytic or primary Percutaneous Coronary Intervention (PCI) may significantly improve or prevent Acute HF.
- Long term management strategy should include adequate coronary revascularization, antiplatelet therapy, ACE-I and/or ARB, β-blockers and statins.

H Hypertensive Emergency:
- Typically presenting as "flash pulmonary edema". Systolic LV function tends to be normal.
- The blood pressure needs to be reduced relatively quickly.

- This is best achieved with parenteral drugs such as intravenous nitrates.
- No attempt should be made to restore "normal" values of BP as this may cause deterioration of organ perfusion.
- Look for secondary causes of hypertension such as renal artery stenosis and phaeo chromocytoma.

A Arrhythmias

- Unstable tachy - or bradyarrhythmias need to be identified and treated appropriately e.g., electrical or pharmacological cardioversion or temporary pacemaker.

M Mechanical causes eg Valvular Heart Disease

- Acute HF can be caused by valvular conditions such as acute mitral or aortic valve incompetence or stenosis, bacterial endocarditis, aortic dissection and prosthetic valve thrombosis.
- Vasodilator therapy would be beneficial in acute valvular regurgitation, but is contraindicated in severe valvular stenosis.
- Early access to echocardiography is crucial for the diagnosis and management.
- Percutaneous intervention such as mitral valve commissurotomy can be life saving in patients with severe mitral stenosis.

P Pulmonary Embolism/Pulmonary infections

- Acute pulmonary embolism can mimic Acute Coronary Syndromes and Acute HF.
- Natriuretic peptides may be raised in acute pulmonary embolism.[295]
- Patients with previously stable HF are also predisposed to deep vein thrombosis which can lead to pulmonary embolism.

I Infections

- Severe sepsis can lead to HF by many different mechanisms - inflammatory cytokines, deranged celluar metabolism etc.
- In addition, type 2 MI may also occur as a result of myocardial oxygen supply - demand mismatch as a consequence of hypotension, hypoxia etc and lead to Acute HF.
- Sepsis in a patient with previous stable HF is a management dilemma especially with regards fluid administration and use of HF medications. It tends to be associated with poor clinical outcomes.

O Other medications

- These include medications that have negative inotropic effects and/or cause water retention and include agents such as Non Steroidal Anti Inflammatory Agents, Calcium channel blockers, Itraconazole, minoxidil, thiazolidinediones etc.

N Non compliance to Therapy

- The reasons for this may be multifactorial and some reasons include poor patient understanding of the disease, financial or transport constraints in getting refills, fears of polypharmacy and the effects of the medications on the kidney etc.
- Patient and family education is important prior to discharge.

9.2.4 Comorbidities

Other comorbidities should be identified, and treatment optimized. This includes:

- Diabetes
- Hypertension
- Iron deficiency
- Chronic lung disease

- Chronic Kidney Disease (see section 14.6)
  - Acute HF and renal impairment can co-exist and either may give rise to the other.
  - Renal impairment influences the response to drug therapy.[296] In these patients with refractory fluid retention, continuous ultrafiltration may be considered.

If the patient improves and is now "warm and dry" (no longer congested and with good perfusion), he moves to Phase 3. (Section 8.3)

9.3 PHASE 3: Discharge and Post discharge "vulnerable" period

9.3.1. Pre - Discharge

Following "decongestion", the challenges are to:[297]

- Provide guidance on how to start OMT,
- How to perform up titration at discharge and
- Correctly prioritize or select the most appropriate titration schedule according to the patient profile. (Section 10.2)

9.3.1.1 Conversion to oral therapy

Following adequate response to intravenous therapy, the patient should be converted to optimal oral medications. If the LVEF < 40%, they should be initiated on Foundational HF medications (RAS blockers, β-blockers, MRA and SGLT2-i) as outlined below.

- **Diuretics** [48]
  - **Oral diuretics may be commenced following resolution of symptoms of congestion and the patient achieving his "dry weight"**.

I, C
  - The initial dose of oral diuretics required is generally higher than the intravenous dose.[298] A reasonable guide is to use a mg-to-mg i.v. to oral conversion.
  - In patients who are suspected to have diuretic resistance, bumetanide may be considered as it is better absorbed.[254]

I, C
  - The dose of diuretics at discharge needs to be individualized.
  - Many patients are discharged with residual clinical congestion, and this is a strong predictor of readmission.[299,300]
  - Residual clinical congestion is often difficult to assess. Absence of dyspnea, peripheral edema, the amount of fluid lost during i.v. diuretic therapy and the patient achieving his "dry weight" are inadequate signs to assess decongestion.[48,299,301] This is further compounded by the inter-individual variation in the amount of fluid retention that can precipitate symptoms.[299]
  - Determining the most appropriate outpatient dose of diuretic can be difficult and requires careful follow-up, particularly early in the post-discharge period.[48]

I, C
  - **It would be prudent to discharge the patient on the same dose of oral diuretics as the individual was on as in - patient and then only cautiously reduce the dose in the post discharge period after careful assessment of the patient's congestion status.**

I, A
- **MRA**[302-304]
  - **These can be commenced within 24-48 hours of admission**.[48]
  - Renal function and potassium levels need to be monitored.

I, A
- **Renin Angiotensin System Blockers (RAS blockers)-Angiotensin Converting Enzyme Inhibitor (ACE-I) or Angiotensin Receptor blockers (ARB)**[305,306]
  - **Renin Angiotensin System (RAS) Blockers may be commenced at admission if the initial BP is adequate. (systolic BP ≥ 100mmHg)**

- In all other cases, it is best to defer for at least 24 hours till the BP is stable. (systolic BP ≥ 100mmHg)
- If the patient is already on a RAS blocker, it is advisable to stop it for at least 24 hours if the BP is low. It can be recommenced at a lower dose once the BP is stable. If the BP is adequate (systolic BP ≥ 100mmHg), it can be continued at the same dose.
- **Start at a low dose depending on the BP and renal function and up titrate as tolerated.**

I, A

- **β-blockers**[307-313]
  - **It is advisable to commence oral β-blockers if the BP is adequate (systolic BP ≥ 100mmHg) and the patient is no longer congested i.e. his lungs are clear and there is no more edema**. If β-blockers are initiated in a patient who is still congested, it can worsen the congestion.
  - If already on a β-blocker, this can be continued depending on the patient's symptoms and hemodynamics.
  - **Whenever possible, β-blockers should be continued**. A meta-analysis showed that discontinuation of β-blockers in patients admitted with ADHF was associated with significantly increased in-hospital mortality, short-term mortality, and the combined endpoint of short-term rehospitalization or mortality.[314]

IIa,B

- **RAS blockers- Angiotensin Receptor Neprilysin Inhibitor (ARNI)**[315,316]
  - **ARNI can be commenced as first line therapy in Acute HF in lieu of RAS Blockers.** In the clinical trial, it resulted in a greater reduction in NT-Pro BNP levels than an ACE-I (enalapril) without improvement in clinical end points.[315]
  - It can be commenced if the systolic BP ≥ 100mmHg.
  - Registry data indicates that among patients hospitalized for HF*r*EF, sacubitril/valsartan at discharge was independently associated with reduced post discharge mortality.[316]
  - In-hospital initiation of ARNI in patients with Acute HF in lieu of ACE-I is safe.
  - Substituting ARNI for ACE-I/ARB during the in-hospital stay can be considered if the patient is already on the latter drugs and is admitted with decompensation.
  - ACE-I needs to be stopped at least 36 hours prior to the initiation of ARNI. ARB can be switched to ARNI at the next dosing interval.

I, B

- **SGLT2- Inhibitor (SGLT2-i)**[317,318]
  - **These can be initiated after stabilization of the patient during the in-hospital stay.**
  - In most of the clinical trials, SGLT2-i was initiated when patients were:
    - No longer on inotropes for the last 24 hours *and*
    - SBP > 100mmHg *and*
    - No increase in the diuretic dose in the last 6 hours *and*
    - Vasodilators have been stopped for at least 6 hours.
  - The diuretic dose may need adjustment taking into consideration the degree of diuresis induced by this drug.

9.3.1.2 Worsening renal function.

Worsening Renal Function may occur during treatment.[319] See Section 14.6

Following conversion to oral therapy, the patient should be observed for at least 24 hours for the stability of symptoms, weight and hemodynamics prior to discharge. The follow-up plans must be tailored according to the availability of facilities and expertise to manage the patient on an outpatient basis.

9.3.1.3. Deep vein thrombosis (DVT) prophylaxis

IIa,B HF patients especially if they are bed-bound for protracted periods are at risk for DVT. Prophylactic measures include:[320,321]

- TED stockings
- Direct oral anticoagulants (DOAC)
- Unfractionated or low molecular weight heparin.

9.3.1.4 Comorbidities

Other comorbidities should be identified, and treatment optimized according to guidelines. This includes:

- Diabetes[322]
- Hypertension[147]
- Iron deficiency -
  - In patients with HF, iron deficiency (ID) is defined as:[155,323]
    - Serum ferritin <100 ng/mL or,
    - Serum ferritin:100-299 ng/mL and a transferrin saturation (TSAT) <20%.

IIa,B
  - In patients hospitalized with HF and having ID, treatment with i.v. iron improved symptoms and reduced the risk of HF hospitalizations but did not reduce the risk of CV death.[324,325]

- Chronic lung disease

Discharge planning is a very important process after an episode of hospitalization for HF to reduce HF related readmissions. The patient has transitioned into a vulnerable period during which he may develop complications such as hypotension, worsening renal function, electrolyte imbalance or decompensate into HF due to inadequate fluid restriction. If this phase is not optimally treated, it will lead to re-admission. The patient should be given an early follow-up, within 2 weeks of discharge, preferably in the HF clinic. The following steps are recommended:

I,C
- A care plan needs to be agreed upon by the patient, family, and main caregiver with the treating physician. (Appendix III & IV, page 164-165)

I,C
- A summary of the care plan must be made available to the doctor in the out-patient clinic. (Appendix III & IV, page 164-1654)

Hospitalization is a key opportunity to initiate Foundational HF medications.[326] A large trial showed that starting and optimizing Foundational HF medications as in- patient, followed by regular check-ups and monitoring after hospital discharge, cuts the rate of all-cause death and HF readmissions within 6 months.[327]

9.3.2 Post-discharge phase (vulnerable period)

At the time of hospital discharge, the patient should be:

- On all the foundational HF medications as tolerated.
- Given a discharge summary and discharge care plan. (Appendix III & IV, page 164-165)
- Informed of the need and, if indicated, given appointments for further cardiac work up e.g., coronary angiography and cardiac rehabilitation.

At the Follow up visit:

- The instructions in the discharge care plan should be followed and identify/determine if otherwise.
- The Foundational HF medications should be up titrated to maximally tolerated or target doses as soon as possible, preferably within 12 weeks post-discharge. (Section 12.2 - Patient profiling and titration of Foundational HF Medications)
- After each up titration, there should be a safety check of hemodynamics and renal function within one to two weeks.
- Where available, NT-Pro BNP measurements may be used to risk-stratify and guide management.
- The presence of any of the following features has been shown to predict re-congestion and re-hospitalization:[328]
  - Orthopnea,
  - Edema,
  - A raised JVP,
  - Weight gain ***and***
  - The need to increase daily diuretic dose because of fluid overload.
- Patients who had none of these at 1-month post discharge had good 2-year survival.[328]
- The presence of any of these clinical features is an indication of the need for optimization of Foundational HF medications.

Key Message # 7: Acute HF

- Acute HF may present as:
  - De Novo HF - first occurrence of HF *or*,
  - Acute decompensated HF (ADHF) - this is a more common presentation occurring in a previously stable patient with HF who has now deteriorated.
- Three important phases should be considered in the management of these patients.
  - **Phase 1** - Urgent treatment and stabilization usually in the emergency department.
  - **Phase 2** - In-hospital management
  - **Phase 3** - Discharge and Post discharge

Key Recommendation #4: Acute HF

- Phase 1 - Urgent treatment and stabilization
  - Assessment and management must be prompt and done concurrently.
    - Rapid recognition and making the diagnosis of HF based on symptoms and signs and quickly assessing its severity.
    - Maintaining adequate oxygenation and perfusion of vital organs.
    - Identification and stabilization of life-threatening hemodynamics (heart rate and rhythm, blood pressure and organ/tissue perfusion).
    - Relieving clinical symptoms, signs and preventing end organ damage.
  - Identification and treatment of the underlying cause and precipitating/ aggravating factors. The more important precipitants are as in the acronym:

    "C H A M P I O N"
    - **C** - coronary artery disease - Acute Coronary Syndrome (Myocardial infarction/Ischemia)
    - **H** - Severe and uncontrolled hypertension
    - **A** - Arrhythmias
    - **M** - Mechanical e.g., Acute valvular dysfunction (e.g., acute mitral regurgitation from chordal rupture); cardiac tamponade
    - **P** - Pulmonary embolism, pulmonary infections
    - **I** - Infections e.g., urinary tract, Covid
    - **O** - Other medications (medications that increase fluid retention and/or have negative inotropic effects)
    - **N** - Non-compliance to treatment especially oral diuretics and or dietary/fluid restriction
  - Look for non-cardiovascular comorbidities- Diabetes, chronic kidney disease, thyroid disease (both hyper and hypothyroidism), chronic lung disease, Anemia.

Key Recommendation #5: Acute HF

- Phase 2 - In-hospital management
  - After initial clinical assessment, management should be instituted as in Flow Chart II, Page 35.
  - For grading of recommendations and levels of evidence, see Table 2, Page 36.
- Phase 3 - Discharge and Post discharge
  - Discharge planning is a very important process after an episode of hospitalization for HF to reduce HF related readmissions.
  - The patient should be given a discharge summary and care plan. (Appendix III & IV, page 164-165)
  - If the LVEF < 40%, they should be initiated on the Foundational HF medications (RAS blockers, β-blockers. MRA and SGLT2-i) as in-patient.

10. CHRONIC HEART FAILURE – HF DUE TO REDUCED LV FUNCTION, LVEF<40% (HF*r*EF)

10.1 PHARMACOLOGICAL MANAGEMENT

There are five essential classes of medications (Optimal Medical Therapy) in the management of patients with HF*r*EF. These are:

I, B
- Diuretics

I, A
- Renin-angiotensin system (RAS) blockers:
  - Angiotensin converting enzyme inhibitors[305,306,329,330] *or*
  - Angiotensin receptor blockers[331-334] *or*
  - Angiotensin receptor neprilysin inhibitor[335]

I, A
- β-blockers[307-313]

I, A
- Mineralocorticoid Antagonists (MRA)[302-304]

I, A
- Sodium glucose cotransporter 2 inhibitors (SGLT2-i)[127,336-343]

- Diuretics, by relieving congestion, **are the initial step** in the management of patients with symptomatic HF.
- The other four medications (RAS blockers, β-blockers, MRA and SGLT2-i) have been shown to improve survival, reduce hospitalizations for HF and improve quality of life in patients with HF*r*EF. SGLT2-i has been shown to be effective irrespective of diabetic status.[340-342] For these reasons, these 4 medications are referred to as **"Foundational HF" Medications.**
- The **initiation and up titration** of these 4 Foundational drug classes should be guided by the patient's:
  - Clinical status,
  - Heart rate,
  - Blood pressure,
  - Fluid overload status,
  - Renal function,
  - Electrolytes and
  - Tolerance.
- **Comorbidities** such as atrial fibrillation, diabetes, chronic kidney, and pulmonary disease are also important conditions to be considered.
- These 4 Foundational HF Medications **should be initiated at about the same time** and up titrated if needed to their target or maximally tolerated doses.
  - In general, **starting low doses of the 4 different classes** would be preferred over up titration of each of the individual drugs to the maximally tolerated dose before initiating the next drug.
  - These drugs are **preferably all initiated, albeit at low doses, when the patient is admitted with HF** so that at the time of discharge, the patient is on all the "Foundational HF" Medications.
- These drugs should be **"up titrated" as outpatient to the maximally tolerated dose** according to the patient's profile - hemodynamic and renal function. (Section 10.2 and Flowcharts III, IV & V, page 37-39)

- Drugs with less proven survival benefits (e.g., diuretics) should be re-evaluated for reduction in dosage **when Foundation HF medications are not well tolerated due to a low BP**. If the **patient is no longer congested and appears clinically to be euvolemic, the doses of diuretics can be reduced**. Alternatively, **administering drugs at different timing** may be considered for those with symptomatic hypotension.
- Wherever possible, Foundational HF medications should be continued during an acute illness. If discontinued, they should be restarted as soon as the condition has stabilized.

10.1.1 Diuretics (Table 15, page 90)

I,B

- Diuretics are **indicated in all patients in whom there are signs and/or symptoms of congestion** to alleviate symptoms, improve exercise capacity, and decrease hospitalizations for HF.[344,345]
- The goal is **to achieve and maintain euvolemia with the lowest dose of a diuretic**. Euvolemia is, however, often difficult to assess clinically. Important **features to look for clinically** are:[345]
  - Resolution of symptoms and signs of congestion - subclinical congestion is sometimes, however, difficult to detect.
  - Improvement in effort tolerance and walking distance.
- Other useful **investigative tools which may be helpful to assess euvolemia**, if available, include:
  - **Chest X-ray** - this is a specific but not a very sensitive indicator of volume status.[346,347]
  - **Echocardiographic parameters** - such as:
    - Decrease in chamber sizes.
    - Decrease in the diameter of the IVC and a 50% decrease with inspiration.
    - Normalization or at least a decrease in doppler indices of LV and RV filling pressures.
  - **Natriuretic peptides** - These may, however, be persistently elevated in patients with Chronic HF and in addition, there is biological variability. A decrease in levels compared to admission would be a helpful guide although relying on this alone can lead to a false assurance that decongestion has been achieved.[48]
  - **Lung ultrasound (LUS)** - In a small study, tailored LUS-guided diuretic treatment of pulmonary congestion reduced the number of decompensations and improved walking capacity in patients with HF.[348]
- Most of these investigative tools-such as echocardiographic parameters and natriuretic peptides - measure filling pressures and not volume status. These tests, however, may sometimes be insufficient to detect subclinical volume excess without accompanying increases in filling pressures.[349]
- The dose of diuretic used is variable and dependent on individual requirements. In the presence of:
  - **Severe congestive HF and ADHF**, oral diuretic therapy may be ineffective. **Intravenous therapy may be preferred**. The diuretic of choice in these patients with fluid overload is a loop diuretic i.e., furosemide. The **goal is a reduction of body weight of about 1kg/day**.
  - **Mild fluid retention, thiazide diuretics may be preferred** especially in the presence of co-existing hypertension. Thiazides, however, are weak diuretics.
- For most patients however, **a loop diuretic is often required**. Other **Foundational HF Medications** - ARNI, MRAs, and SGLT2-i - **also have diuretic characteristics and this may help modify the dose of the diuretic**.[350-353]

- Patients on diuretics should be monitored closely as over diuresis can cause intravascular volume depletion leading to hypotension and deterioration of renal function. Hypokalemia is a common problem with diuretic use and oral potassium supplementation is usually necessary.
- Patients should be **educated in 'dry weight' management** and advised to record their daily weight. If there is a **consistent increase in weight of more than 2kg in 3 days, patients should be educated to self-adjust their diuretic (furosemide) dose together with restriction of their fluid intake until their "dry weight" is regained**. However, if the weight increase is associated with worsening symptoms or the patient fails to respond to these measures, the patient should seek medical help immediately.
- Diuretic therapy may be reduced as the clinical condition of the patient improves and they are assessed to have attained euvolemia using the indicators listed earlier. In one study, however, these indicators had limited predictive capability to determine down titration success/failure.[349]
- In selected patients who have stable symptoms and have been taught to manage their volume status and modify their diuretic dose accordingly, diuretic therapy may be discontinued. This is more likely to succeed if their LVEF improves to above 40-45%. In a study of a small number of patients with stable CHF on OMT, diuretic withdrawal did not result in dyspnea or adverse CV events up to 90 days.[354]

Table 15: Diuretics Used In Heart Failure

	Route of Administration	Starting Dose	Usual Daily Dose
LOOP DIURETICS			
Furosemide	i.v. / Oral	20 - 40mg	20 - 80mg
Bumetanide	i.v. / Oral	0.5 - 1mg	0.5 - 2mg
THIAZIDES			
Hydrochlorothiazide	Oral	25mg	12.5 - 50mg
Metolazone	Oral	2.5mg	2.5 - 10mg

10.1.2 Renin-angiotensin system (RAS) blockers (Table 3, page 93)

These include:

- Angiotensin Converting Enzyme Inhibitors (ACE-I)
- Angiotensin Receptor Blockers (ARBs)
- Angiotensin Receptor Neprilysin Inhibitor (ARNI)

10.1.2.1 ACE-I and ARB

I,A
- ACE-I improve survival and reduce HF hospitalizations in patients with mild, moderate, and severe symptoms of HF*r*EF.[305,306,329,330] **They are recommended in all HF*r*EF** patients. There are no differences among available ACE-Is in their effects on symptoms or survival.[305]
- In head-to-head analysis, there was no difference between ACE-I and ARBs in terms of CV outcomes such as mortality and HF hospitalization, in patients with HF*r*EF.[355-357]

I,A
- **ACE-I are, however, the preferred agents because the data for reduction in mortality and HF hospitalizations are more robust**.[356,357]

- ARBs are however better tolerated because of their better side effect profile.[356,357]

I,A
- **ARBs are indicated in HF*r*EF in ACE-I intolerant patients** and can be considered in patients who develop angioedema with ACE-I or ARNI.[332-334]

IIa,B
- In patients post MI with impaired LV function, the ARB, Valsartan, was found to be as effective as captopril.[331]

In the initiation of ACE-I/ARB, the following should be considered:

- Patients with underlying low systolic BP < 100mmHg and/or elevated serum creatinine or potassium (>5.0 mmol/l) should be initiated with a low-dose of ACE-I/ARB cautiously.
- Avoid excessive diuresis before treatment. If patients are on large doses of diuretics, the BP and renal function should be monitored.
- Start with a low dose. The dose should be increased gradually to the target dose (Flowchart III & IV, pages 37-38, Table 3, page 93) or the maximum tolerated dose.
- Orthostatic hypotension should be avoided. Wherever possible, the BP should be measured in the lying and standing position. The consensus definition of orthostatic hypotension is a reduction of systolic BP of at least 20 mm Hg or a reduction of diastolic BP of at least 10 mm Hg within 3 minutes of erect standing.[358] In the elderly, the presence of orthostatic hypotension should be interpreted cautiously due to both its high prevalence in this population and its low association with underlying pathology directly related to volume status.[345]
- Renal profile should be checked periodically. Serum creatinine may increase up to 30% (or estimated Glomerular Filtrate Rate (eGFR) may decrease by 25%) from baseline at 7-14 days, after introduction of either an ACE-I or an ARB.[359] Dose adjustments is not required if the increase in serum creatinine stabilizes at < 30% (or eGFR reduces < 25%) and serum potassium < 5.5 mmol/l. The renal function should however be monitored periodically on a regular basis. Other causes of deteriorating renal function such as infection, drug therapies or worsening HF should be excluded.
- There is no significant difference in rates of hypotension, hyperkalemia, or renal dysfunction between ACE-Is and ARBs.

I,A
- ACE-I intolerance denotes the presence of a bothersome cough (most commonly, 5% - 20% although it can be as high as 64.9%) or the experience of angioedema (uncommon, < 1%) with ACE-I therapy.[360,361] Patients with these conditions may be switched to an ARB, although, some may still develop angioedema.[362,363]

III,A
- **Routine combined use of both ACE-I and an ARB should be avoided**, as this combination causes more adverse effects (hypotension, hyperkalemia, and renal dysfunction).[364,365]

10.1.2.2. ARNI

- ARNI is a **combination of angiotensin receptor blocker (ARB) and a neprilysin inhibitor** (an enzyme that degrades natriuretic peptides-bradykinin, adrenomedullin, and other vasoactive peptides). The only drug in this class is sacubitril/valsartan.

I,B
- ARNI has been **shown to improve symptoms, reduce HF hospitalizations and increase survival in patients with HF*r*EF** who have previously tolerated ACE-I.[335,366]
- ARNI has also been shown to be safe in patients who are ACEI-naive and in hospitalized patients who have just recovered from Acute HF.[315]

I,B
- **ARNI is recommended as a replacement to ACE-I in patients with HF*r*EF who remain symptomatic despite OMT**. It has been shown to decrease CV death, HF hospitalizations, and symptoms.[335] The benefit of ARNI over an ACE-I, was consistent

regardless of background therapy and irrespective of previous coronary revascularization or β-blocker dose.[366] It has also been shown to have favorable effects on cardiac remodeling.[367]

IIa,B
- ARNI may also be considered as a first-line RAS blocker in ACE-I-naïve patients.[315]

IIa,B
- ARNI in Post MI patients with LVEF <40% was not superior to the ACE-I ramipril.[368]
- The tolerability of ARNI and its side effect profile is like that of ACE-I or ARB. Laboratory monitoring is also similar.
- The use of ARNI is, however, associated with hypotension but a low incidence of angioedema.
- When initiating an ARNI, the initial dosing and rate of titration:
  - Is dependent on pre-existing treatment, hemodynamic profile, and associated comorbidities. It should be individualized.
  - Should not be initiated if systolic BP < 100mmHg and used with caution if eGFR < 30 mL/min/1.73m^2.
  - When switching from ACEI to ARNI, a washout period of at least 36 hours is required to decrease the risk of angioedema.
  - No washout period is required for conversion between ARB and ARNI.
- The drug should be up titrated to the target or maximally tolerated dose shown to improve important HF outcomes.
- Among patients with HF*r*EF, similar improvement in prognostic biomarkers, health status, and cardiac remodeling were observed across various ARNI doses - average daily dose: 112 mg in Tertile 1 (low dose), 342 mg in Tertile 2 (moderate dose), and 379 mg in Tertile 3 (high dose).[369]
- In patients taking ARNI, NT-Pro BNP is a more reliable biomarker than BNP. BNP levels may be spuriously elevated as the drug prevents its breakdown.

10.1.3 β-blockers (Table 3, page 94)

I, A
- In major clinical trials, β-blockers, on top of standard therapy, have been shown to improve symptoms, reduce hospitalizations and improve survival in patients with HF*r*EF, regardless of their NYHA Functional class.[307-313,370-372]

I, A
- **All patients with HF*r*EF should be on β-blockers unless there is a contraindication**.[307-313,370-372]
- Objective improvement in cardiac function might not, however, be apparent for 6-12 months after β-blocker initiation. Hence, early initiation of β-blockers for all stable patients with current or prior symptoms of HF upon diagnosis is warranted, unless contraindicated.
- **When initiating a β-blocker, the patient should be in a non-congested state** ie. out of Acute HF and preferably euvolemic with clear lung fields. Caution should be exercised when initiating β-blockers in a patient in NYHA class III-IV.

IIa,B
- **Patients who decompensate and are admitted in Acute HF should be maintained on the same dose of β-blockers unless the clinical condition (hypotension or significant bradycardia) warrants a temporary stopping or reduction in the dose.**[314]
- After the patient has been stabilized, an attempt should be made to titrate to the **target or maximum tolerated dose**.
- The contraindications for β-blocker use include:
  - Second- or third-degree atrioventricular block (without a pacemaker).
  - Bronchial asthma (relative contraindication - use with caution).
  - Symptomatic bradycardia or hypotension.
  - Critical limb ischemia.

IIa,B

- **Initiating therapy with a β-blocker first is non-inferior to the standard approach of starting with an ACE-I.**[310] The benefits seen with both these drugs are additive.

Table 3: Doses of Foundational HF Medications

Drug	Initial Daily Dose(s)	Target Dose(s)	1/8 Target Dose	1/4 Target Dose	1/2 Target Dose	Tablet Strength Available		Renal Dose For CrCl < 30ml/min
ACE-I								
Captopril	6.25mg BD	50mg TDS	6.25mg	12.5mg	25mg	12.5mg, 25mg	Yes	6.25mg-12.5mg bd/tds
Enalapril	2.5mg OD	10-20mg BD		2.5-5mg	5-10mg	5mg, 10mg, 20mg	Yes	2.5mg OD
Lisinopril	2.5–5mg OD	20-40mg OD	2.5mg	5-10mg	10-20mg	5mg, 10mg, 20mg	Yes	2.5mg OD CrCl 10-30:5mg OD CrCl<10: 2.5mg OD
Perindopril	2mg OD	8-16mg OD		2-4mg	4-8mg	2mg, 4mg, 8mg	Yes	CrCl 15-30: 2mg eod CrCl <15 & HD: 2mg on dialysis day**
Ramipril	2.5mg OD	10mg OD	1.25mg	2.5mg	5mg	2.5mg, 5mg, 10mg	Yes	1.25mg OD CrCl <40: 25% normal dose
ARBs								
Candesartan	4-8mg OD	32mg	4mg OD	8mg	16mg	8mg, 16mg	Yes	4mg OD
Losartan	25-50mg OD	50-150mg OD		12.5-37.5mg	25-75mg	25mg, 50mg, 100mg	Yes	No adjustment
Valsartan	40mg OD	160mg BD		40mg	80mg	40mg, 80mg, 160mg	Yes	Use with caution
ARNI								
Sacubitril/valsartan	100mg (49/51mg) BD*	200mg (97/103mg)BD	25mg	50mg	100mg	50mg,100mg, 200mg	Yes	50mg BD

Drug	Starting Dose	Target Dose	1/8 Target Dose	1/4 Target Dose	1/2 Target Dose	Tablet Strength Available		Renal Dose For CrCl < 30ml/min
β-Blocker								
Bisoprolol	1.25mg OD	10 mg OD	1.25mg	2.5mg	5mg	2.5mg, 5mg, 10mg	Yes	No adjustment
Carvedilol	3.125mg BD	25 mg BD	3.125mg	6.25mg	12.5mg	6.25mg, 12.5mg, 25mg	Yes	No adjustment
Metoprolol Tartrate*	12.5-25mg BD	100 mg BD	12.5mg	25mg	50mg	50mg, 100mg	Yes	No adjustment
Nebivolol+	1.25mg OD	10 mg OD	1.25mg	2.5mg	5mg	5mg	Yes	No adjustment
MRA								
Spironolactone	12.5-25mg OD	50 mg OD		12.5mg	25mg	25mg	Yes	Contraindicated
Eplerenone	25 mg OD	50 mg BD		12.5mg	25mg	25mg, 50mg	Yes	Contraindicated
Finerenone	20mg OD	20mg OD				10mg, 20mg	Yes	eGFR 25-60: 10mg OD eGFR <25: contraindicated
SGLT2-i								
Dapagliflozin	10mg OD	10mg OD						CrCl <25: limited experience
Empagliflozin	10mg OD	10mg OD						CrCl <20: not recommended

** The evidence-based form of metoprolol in HF is metoprolol succinate (CR/XL), which is not available in Malaysia. The only form of metoprolol available in Malaysia is metoprolol tartrate*
+ Shown to reduce the composite endpoint of all-cause mortality and CV hospitalization, but not all-cause mortality.
IBM Micromedex Drug Ref (2023) (cited 14th January 2023) & product leaflet available from Quest3 (accessed date: 13th January 2023)
*** At the discretion of the attending physician*
CrCl unit: ml/min; eGFR unit: ml/min/1.73m²

10.1.4. MRA (Table 3, page 94)

I,A

- MRAs improve symptoms, reduces HF hospitalizations and mortality in patients with HF*r*EF.[303-305] **It is indicated in all symptomatic HF*r*EF patients (NYHA II-IV) in addition to other Foundational HF Medications.**
- Caution should be exercised in the following conditions :
  - Hyperkalemia
  - Renal dysfunction
  - Concomitant use of:
    - Potassium-sparing diuretics
    - Potassium supplements
    - ACEI/ARB/ARNI
    - NSAIDs

IIa,B

- **MRAs have also been shown to be beneficial in patients with HF and comorbid conditions such as diabetes and chronic kidney disease despite a greater risk of hyperkalemia and acute renal insufficiency**.[373]
- It has also been shown to improve CV outcomes in elderly HF patients > 75 years.[374]
- **Potassium supplements may need to be reduced or discontinued**. If despite these measures, hyperkalemia persists (serum potassium >5.5mmol/l), then the dose of MRA should be reduced or stopped. Alternatively potassium binders may be used. (Section 14.6)
- Spironolactone may uncommonly cause gynaecomastia in men. The incidence of gynae comastia is lower with epleronone as it is more selective for aldosterone blockade.
- Finerenone is a non-steroidal MRA which has less risk of hyperkalemia and BP-lowering effects. It has been shown to reduce first and recurrent HF hospitalizations in patients with Type 2 diabetes and CKD.[375-378]

10.1.5. SGLT2-i (Table 3, page 94)

I,A

- **SGLT2-i, particularly dapagliflozin and empagliflozin, lower the risk of HF hospitalizations, cardiovascular mortality, and improve quality of life in patients with HF*r*EF, irrespective of diabetes status**.[340-342,379-381]
- The diuretic/natriuretic characteristics of SGLT2-i may provide further benefits in decreasing congestion and may allow for a reduction in loop diuretic dosage.[351-353]
- In the initiation of SGLT2-i, the following should be considered:
  - Renal profile should be checked periodically and monitored regularly. Although renal function is known to decrease modestly following initiation, SGLT2-i tends to be renoprotective in the long term.[382] A slight decrease in eGFR following initiation is expected, but this should not lead to discontinuation of treatment.
  - Monitor glycemia regularly, especially in diabetic patients. Consider modifying other diabetic medications.
  - Identify and eliminate risk factors for ketoacidosis e.g., fasting, inadequate fluid intake.
  - Monitor fluid balance regularly, especially when a patient is on diuretics, is elderly, and/or frail. Adjust diuretic therapy and fluid intake as necessary.
- Uro-genital infections may occur during treatment with SGLT2-i. Patients should be educated on the signs and symptoms of uro-genital infections as well as the appropriate preventive measures.

10.1.6. I_f channel inhibitor- Ivabradine (Table 16, page 96)

- Ivabradine selectively inhibits the I_f current in the sinoatrial node, resulting in a reduction in heart rate.
- **It is effective in patients in sinus rhythm**. Ivabradine may, however, be associated with an increased incidence of AF.[383,384]

IIa,B
- Ivabradine resulted in a reduction in the combined endpoints of CV mortality and HF hospitalizations in patients who were still symptomatic while on OMT with an ACE-I (or ARB), a β-blocker and an MRA and:[385]
  - ➢ With an LVEF ≤ 35% *and*
  - ➢ An episode of HF hospitalization in the past 12 months *and*
  - ➢ Who were in sinus rhythm with a heart rate of ≥ 70 beats per minute (bpm).
- The magnitude of heart rate reduction by β-blocker plus ivabradine, rather than the background dose of β-blockers, appeared to determine the effect on CV outcomes.[386]
- In patients with a heart rate of ≥ 75 bpm, ivabradine has been shown to improve CV outcomes, the best risk reduction being seen in those achieving a heart rate < 60 bpm or a heart rate reduction > 10 bpm.[387]

IIa,B
- **In patients with stable CAD and LVEF < 40%, ivabradine did not reduce CV outcomes**. In a subgroup of patients with a heart rate > 70bpm, there was a reduction in the secondary end point of the incidence of CAD (fatal and non-fatal MI and coronary revascularization).[388]
- **Every effort should be made to achieve target or maximally tolerated doses of β-blockers before initiation of ivabradine**. It would be useful in patients who have contraindications to β-blockers or who are not able to tolerate higher dose of β-blockers due to its side effects. Ivabradine has no effect on BP or myocardial contractility.
- Patients should be educated to measure and record their pulse regularly, to monitor for bradycardia. Side effects of ivabradine include symptomatic bradycardia (dizziness, fatigue, or hypotension) and visual disturbances.

Table 16: Other Drugs Recommended for HF Management and Their Dose Regime

Drug	Starting dose	Target dose
I_f channel inhibitor		
Ivabradine	5mg bd†	7.5mg bd
Others		
Isosorbide dinitrate‡	10mg tds	40mg tds
Digoxin	0.0625mg od	0.25mg od
Vericiguat	2.5mg od	10mg od

†In patients >75 years old, lower starting dose of 2.5mg bd can be used.
‡(PO) Hydralazine-nitrate combination is not available in Malaysia.

10.1.7. Soluble guanylate cyclase stimulator- Vericiguat

IIa,B
- Vericiguat may be considered in patients in NYHA classes II to IV, who despite being on OMT with a RAS blocker, a β-blocker and an MRA, have evidence of worsening HF. It has been shown to reduce CV mortality or HF hospitalizations.[389]

10.1.8. Nitrates (Table 16, page 96)

IIa,C
- Symptoms of HF such as orthopnea, paroxysmal nocturnal dyspnea, exercise-induced dyspnea and/or angina may be relieved with the use of nitrates alone, in the form of tablets, sprays, or transdermal patches.
- Continuous (i.e., around the clock) use should generally be avoided to prevent nitrate tolerance and pseudotolerance.[390]
- Nitrates are mainly used in Acute HF.

I,A
- In chronic HF, the trials on nitrates have been in combination with hydralazine. This combination has been shown to improve survival in the African American population with HF.[391,392]

10.1.9. Digoxin

- In patients with HF, digoxin may be considered in the following situations:

IIa,B
  - ➢ To relieve symptoms and lower the risk of hospitalization in patients with symptomatic HF*r*EF and already on OMT with an ACE-I (or ARB), a β-blocker and an MRA.[393-395] It has no survival benefit.

IIb,B
  - ➢ Rate control in patients with AF.[396-398]

IIa,B
- Where rate control is the preferred strategy, β-blocker alone or in combination with digoxin was associated with a similar decrease in the risk of mortality.[396-398]
- Digoxin alone was associated with an increase in mortality.[399,400]

IIa,B
- **Digoxin may be considered in patients with HF and AF** in the following situations:[397,398]
  - ➢ Rate control is inadequate on β-blockers alone.
  - ➢ β-blockers are contraindicated.
  - ➢ Rapid control of the ventricular rate with parenteral drugs is required.
- **Digoxin has a narrow therapeutic range** and thus close monitoring of renal function and serum electrolytes (particularly potassium and magnesium levels) is required, prior to initiation of digoxin and periodically during its use.
- No loading dose is required for the management of chronic HF. Lower doses of digoxin and lower levels of serum digoxin (0.5-0.8ng/ml or 0.65 to 1nmol/L) are efficacious and appear adequate in most patients with compensated HF.[401-403] The **maintenance dose of digoxin may range between 0.0625mg to 0.25mg daily**, which may be lower in elderly patients, women, and those with renal impairment.
- **Regular monitoring of digoxin levels is not required** other than to assess for toxicity as the levels should not be used to guide dose adjustment in chronic therapy. Digoxin levels may be elevated in the presence of worsening renal function, electrolyte imbalance (hypokalemia, hypomagnesemia, or hypocalcemia) or interacting drugs (e.g., amiodarone), which may lead to atrial and ventricular arrhythmias particularly in the presence of hypokalemia.

10.1.10. Antiplatelet and Anticoagulation Therapy

IIb,B
- **There is no role for routine antiplatelet or anticoagulant therapy in patients with HF**.[404-412]
- The decision to treat patients with HF with antiplatelet therapy **is largely influenced by the presence or absence of concomitant arterial disease**.
- In patients with HF and sinus rhythm, anticoagulation, when compared to antiplatelet therapy, did not significantly influence the primary outcome of death and stroke, but reduced ischemic stroke rates.[409-411] Treatment with warfarin however, was associated with a higher risk of major bleeding complications.[409]

- HF patients with the following risk factors for thromboembolism should be given an appropriate anticoagulant, unless contraindicated:
  - **Atrial fibrillation (AF)**

I,A

    - **All patients with AF, HF and CHA_2DS_2-VASc score > 2 in men or > 3 in women should be given an anticoagulant indefinitely, unless contraindicated.**[412-416]
    - **Direct-acting oral anticoagulants (DOACs) are recommended over warfarin** in patients with HF who are eligible, with the exception of those with moderate or severe mitral stenosis and those with mechanical prosthetic heart valves.[412,416]

- **Left ventricular thrombus (LVT)**.
  - The 1-year risk of stroke with LVT is high (10%) even with anticoagulation.[417] There was no statistically significant difference in thrombus resolution, risks of bleeding complications, stroke, or systemic embolization and mortality in LVT patients treated with warfarin compared to those treated with DOACs.[418,419]
  - If an LVT is detected, **the duration of anticoagulation will depend on clinical judgment, including the following factors**:

IIa,C

    - **If following an acute MI, then anticoagulation (especially for a duration > 3 months)** was associated with an overall lower risk of MACE or all-cause mortality.[417] A recent review has suggested that if the LV thrombus has resolved, anticoagulation can be discontinued and dual antiplatelet therapy continued per management of MI.[420] If the LV thrombus is persistent, anticoagulation should continue with repeat imaging every 3 months. Once anticoagulation has been discontinued, repeat imaging 3 months later is advised.[420]
    - **If there is no obvious acute event and the thrombus was detected during a routine examination**, then the duration of anticoagulation becomes more difficult to decide since the risk of embolisation decreases over time although still present. In these cases, clinical judgment taking into account the bleeding risk and clinical profile of the patient can help in decision making.

10.1.11. Antiarrhythmic Drug Therapy

- Arrhythmias are common in HF. The more common ones are:
  - Atrial fibrillation
  - Ventricular tachyarrhythmias
  - Bradyarrhythmias

10.1.11.1. Atrial fibrillation (AF)

- **New-onset AF in a patient with established HF is associated with a poor prognosis irrespective of the LVEF**.[421,422] On the other hand, patients who develop AF first, followed by HF usually have a more benign course.[423]
- Combination of HF and AF may increase the risk of stroke, dementia, HF hospitalization and all-cause mortality.[416,424]
- Patients with AF and HF can be managed **by identifying and treating potential causes of AF and optimizing HF treatment - i.e., Optimal Medical Therapy**.

IIa,A

- **The AF can be treated by either rate control or rhythm control although in patients with recent onset of AF < 1 year duration, rhythm control is preferred to rate control**.[155,398,416,425]

10.1.11.1. A Rate control

- **The optimal resting ventricular rate in patients with AF and HF is unknown**. There was no significant difference in clinical events between a strict rate control of < 80bpm vs a more lenient < 100/bpm.[416,426,427]
- **A reasonable approach is to aim for a HR < 110/bpm** unless there are symptoms or a deterioration in LV function, in which case, one should try to target a HR < 80 bpm.[416,427]
- **The optimal ventricular rate during exercise is also uncertain, but may be < 110 bpm during light exercise**.[416,426]
- **In the rate control of AF:**
  - IIa,B β-blockers should be considered for both short - and long-term rate control.[396,428-430] β-blockers are preferred over digoxin as it provides better rate control during exercise and improves morbidity and mortality in patients with HF although the latter effect is attenuated in patients with AF.[396,426,429]
  - IIa,B Digoxin should be considered if the ventricular rate remains elevated despite treatment with β-blockers, or if β-blockers are contraindicated or intolerable.[397,426,429,431,432]
  - Intravenous amiodarone may be used for rate control, but only in the acute setting.[416,433]
  - The initial target heart rate for rate control therapy should be < 110 bpm.[416]
  - IIa,B Combination therapy may be considered if a single rate control therapy does not achieve the target heart rate.[416] Rate control is better when digoxin and β-blockers are used in combination rather than with each drug individually.[396-398,432]
- In patients with marked congestion who cannot tolerate β-blockers, suggest:
  - Oral or IV digoxin
  - Oral or IV amiodarone [433,434]

10.1.11.1. B Rhythm control

- In patients with permanent AF and HF and LVEF < 35% (HF*r*EF), there was no difference in all-cause mortality or secondary outcomes (death from any cause, worsening HF or stroke) comparing a strategy of rate or rhythm control.[435,436]
- IIa,A In patients with early onset AF of < 1 year duration and/ or paroxysmal AF, and/or cardiovascular problems who received early rhythm-control, there was a significantly decreased primary end point of a composite of CV death, stroke or hospitalization due to HF or ACS than those who received standard care.[416,425] The study included 28% stable HF patients.[425] At 2 years,however, symptoms and LV function did not differ significantly between the groups.[399,437]
- The primary indication for rhythm control is reduction in AF-related symptoms and improvement of quality of life.[399]
- Rhythm control can be achieved by:
  - IIa,B Pharmacotherapy:
    - Amiodarone is preferable compared to other antiarrythmic drugs as others are associated with worse outcomes in HF*r*EF.[433,434,438]
  - Electrical therapy:
    - IIa,C Electrical cardioversion and/or
    - IIa,A Radiofrequency ablation.[416,425]

10.1.11.2 Ventricular Arrhythmias

- The exact prevalence of sudden cardiac death (SCD) in patients with HF in the contemporary era is not known. It varies depending on the etiology of the HF and the LVEF.[439] Patients with HF and reduced (< 30 or 35%) LVEF (HF*r*EF) account for < 20% of all SCDs.[440]

- SCD is most often due to either sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) although sometimes it may be due to a bradyarrhythmia or electromechanical dissociation.[440,441] Occasionally rapid supraventricular tachycardias may deteriorate to malignant ventricular tachyarrhythmias.[442]
- Patients with HF with ventricular arrhythmias must be treated aggressively with OMT.
- **The following medications have been shown to reduce the risk of SCD:**

I,A
- **β-blockers**: have been shown to reduce SCD in the clinical trials done on patients post MI as well as in the HF trials.[311,313,443]

IIa,B
- **ACE-I or ARB**: clinical trials done following MI and heart failure with EF < 40% showed that ACE-I or ARB reduced SCD.[444-449]

IIa,B
- **ARNI**: reduced both SCD and deaths due to worsening HF.[450,451]

IIa,B
- **MRA**: have been shown to reduce the incidence of SCD.[303,304,452,453]
- **Statins**: do not prevent SCD or overall mortality, however statins may minimize hospitalization for worsening heart failure in patients with HF.[454,455]

- In addition to the above, in patients with ventricular tachyarrhythmias, the following are important:

I,C
- Identify contributing factors such as electrolyte imbalances, ischemia and drugs.

I,A
- Implantable cardioverter defibrillator (ICD).[456-460] (Section 8.2.3.2)

IIa,B
- Antiarrhythmic drug therapy with amiodarone can be considered as adjunctive therapy in patients with ICD to reduce the number of shocks and in patients who are not candidates for ICD.[461,462]

IIb,B
- Radiofrequency ablation may be considered in the event of VT storms.[463]

10.1.11.3 Bradyarrhythmias- see section 10.3.3

10.1.12. Calcium Channel Blockers (CCBs)

IIb,B
- Routine use of CCBs is not recommended in patients with HF*r*EF as they do not confer any morbidity or mortality benefit but worsen HF outcomes.[464-469]

III,A
- Diltiazem, verapamil and nifedipine should be avoided.[462-467]

IIa,B
- However, amlodipine and felodipine may be considered for other indications such as persistent hypertension despite OMT.[468,470]

10.2 PATIENT PROFILING AND TITRATION OF "FOUNDATIONAL HF MEDICATIONS" (Table 5, page 43)

The "Foundational HF" drug classes should be initiated in all patients, preferably prior to discharge. These "Foundational HF" Medications are:

- Renin-angiotensin system (RAS) blockers:
  - Angiotensin converting enzyme inhibitor (ACE-I) or
  - Angiotensin receptor blocker or
  - Angiotensin receptor neprilysin inhibitor (ARNI)
- β-blockers
- MRA
- SGLT2-i

These drugs should be up titrated cautiously depending on the patient's BP, heart rate, renal function, and potassium levels.[297] The following is a guide to titration and modifying the doses of these medications depending on the patient's profile.

10.2.1 Blood Pressure:

If systolic BP < 90 mmHG

- Detect and treat causes of hypotension, such as hypovolemia from over diuresis, bleeding, infection accordingly.
- If the patient is euvolemic using the criteria in section 10.1.1, an attempt may be made to reduce the dose of diuretics to the lowest maintenance level e.g. furosemide 20 mg EOD or use a mild thiazide diuretic such as hydrochlorothiazide 12.5-25 mg daily. Occasionally it may be possible to remove the diuretic completely especially if the LVEF > 40-45%.
- Remove all non "Foundational HF" Medications that may also cause hypotension eg - nitrates, calcium channel blockers, alpha blockers.
- The dose of the "Foundational HF" Medications only needs to be reduced or temporarily stopped if there is symptomatic hypotension.
- SGLT2-i and low-dose MRA have minimal effects on BP and may be continued. Spironol actone at a mean dose of 26 mg daily had no significant hemodynamic effects in the RALES trial.[303] However when used as a fourth line drug in patients on a mean of 2.9 other anti-hypertensive drugs, at a mean dose of 25 mg daily, it can drop the SBP/DBP by 21.9/9.5 mm Hg.[471]

If systolic BP > 110 mmHG

- The dose of RAS blockers and β-blockers should be up titrated in turn till the target or maximally tolerated dose.
- Whether the RAS blocker or the β-blocker should be up titrated first will depend on the patient's heart rate, renal function, and potassium levels.

10.2.2 Heart Rate (HR)

10.2.2.1 Sinus Rhythm

- The optimal HR for patients with HF and in sinus rhythm is 50-60/bpm.[416]

If the HR > 70/bpm

- The dose of β-blocker should first be up titrated to the target or maximally tolerated dose.
- Ivabradine may be added to the β-blocker to achieve the target HR.[386,387]

If the HR < 50/bpm

- Discontinue non-dihydropyridine calcium channel blockers e.g., diltiazem and verapamil, digoxin, or other antiarrhythmic drugs such as amiodarone.
- If the HR is still < 50/bpm, the dose of ivabradine should first be reduced.
- If the HR is still < 50/bpm or the patient has symptomatic bradycardia, then the dose of β-blocker should be reduced or temporarily discontinued.

10.2.2.2 Atrial Fibrillation

Heart rate (HR)

- The optimal resting ventricular rate in patients with AF and HF is unknown.
- It is not unreasonable to aim for a HR < 110bpm.[416]

- If the patient is troubled by palpitations or there is deterioration of LV function, then a more strict rate control of 80bpm may be targeted.[416] The ventricular rate should however, be maintained > 70 bpm.[297] A lower HR has been associated with worse outcomes.[472]
- Excessive rate control, which may be associated with an increase in pauses, carries a risk.[416]
- The optimal ventricular rate during exercise is also uncertain, but may be < 110bpm during light exercise.[416,426]
- In patients with persistent AF and HF*r*EF, heart rate is not a predictor of mortality unlike in patients in sinus rhythm.[416,426,429,431,472]
- There is no clear evidence for a prognostic benefit of β-blockers in HF patients with AF.[155,416,426]

Systolic BP < 90mmHg

- β-blockers may be stopped and replaced with digoxin for rate control.
- This may allow for the up titration of RAS blockers.

10.2.3. Chronic Kidney Disease - see section 14.6

Key Message# 8: Chronic HF due to LV reduced Function (HF*r*EF)

- Optimal HF medications are:
  - Diuretics - to be titrated according to presence of congestion.
  - Foundational HF medications:
    - Renin-angiotensin system (RAS) blockers:
      - Angiotensin converting enzyme inhibitor (ACE-I) or
      - Angiotensin receptor blocker or
      - Angiotensin receptor nephrilysin inhibitor (ARNI)
    - β-blockers
    - Mineralocorticoid Antagonists (MRA)
    - Sodium glucose cotransporter 2 inhibitors (SGLT2-i)
  - Other drugs (when necessary) include:
    - Ivabradine
    - Nitrates
  - For doses of these Foundational HF medications, Grades of recommendation and Levels of Evidence of these medications, see Tables 3 & 4, page 40-42.

Key Message # 9: Arrhythmias

- Arrhythmias are common in HF. These include:
  - Atrial Fibrillation
  - Ventricular arrhythmias
  - Bradyarrhythmias

Key Recommendations #6: Chronic HF due to HF*r*EF: Pharmacotherapy

- For Grades of recommendation and Levels of Evidence, see Table 4, page 42
- **Foundational HF Medications**
  - The Foundational HF Medications should be initiated at about the same time and up titrated if needed to their target or maximally tolerated doses.
  - Once the patient is stable and no longer volume overloaded, the dose of diuretics may be down titrated to the lowest maintenance dose.
  - In general, starting low doses of the 4 different classes would be preferred over up titration of each of the individual drugs to the maximally tolerated dose before initiating the next drug.
  - These drugs are preferably all initiated, albeit at low doses, when the patient is admitted with HF so that at the time of discharge, the patient is on all of them.
  - For the initiation and up titration of these HF drugs see Flowchart III, IV & V, page 37-39.

Key Recommendation #7: Arrhythmias

- **Atrial Fibrillation**
  - To be treated by rate or rhythm control (if onset < 1 year).
  - Anticoagulation with DOAC or Vitamin K antagonists.
- **Ventricular arrhythmias**
  - Identify contributing factors such as electrolyte imbalances, ischemia and drugs.
  - Implantable cardioverter defibrillator (ICD)
- **Bradyarrhythmias**
  - Device Therapy as indicated.

10.3. DEVICE THERAPY IN HEART FAILURE

10.3.1. Cardiac Resynchronisation Therapy (CRT)

Patients who remain symptomatic (NYHA class II-III) despite OMT should be considered for CRT.

CRT has been shown to improve symptoms, hospitalizations, and mortality. though up to 30% of patients may be non-responders.[473-477]
Patients **with all the following criteria** can be considered for CRT:[475-484]

- Sinus rhythm
- LVEF ≤ 35%
- LBBB
- QRS duration on resting 12 - lead ECG:
  - ≥ 150ms
  - ≥ 120-149ms

I,A

IIa,B

Mechanical ventricular dyssynchrony is no longer a criterion in selecting patients for CRT.[485-487]

Patients with AF are less likely to respond to CRT. They may be considered for CRT along with atrio-ventricular node ablation.[488-490]

Conduction system pacing may be an alternative to biventricular pacing in patients with pacing indications (expected RV pacing of > 40%) and HF not fulfilling criteria for CRT or with unsuccessful coronary sinus lead implantation.[491-494]

Regular monitoring of the patients after device implantation is mandatory to adjust medical therapies and reprogram the device as necessary.

10.3.2. Implantable Cardioverter Defibrillator (ICD)

Sudden cardiac death (SCD) in patients with HF is often due to ventricular fibrillation or ventricular tachycardia. This risk can be reduced with the implantation of an ICD.

An ICD is recommended for secondary prevention in patients with previous sudden cardiac arrest or documented sustained ventricular arrhythmias.[456-460]

It should be considered in patients who fulfil the eligibility criteria, who otherwise have good clinical function and prognosis to improve their survival.

Secondary prevention:

The following should be considered for implantation of ICD:[456-460,495-498]

I,A
- Patients resuscitated from SCD due to ventricular fibrillation or hemodynamically unstable sustained ventricular tachycardia. These cardiac arrest survivors have a high risk of recurrent events and implantation of an ICD has been shown to reduce mortality.

IIa,B
- Patients with chronic HF and LVEF ≤ 35% who experience syncope of unclear origin have a high risk of subsequent SCD should also be considered for placement of an ICD.

I,A
- Prior MI and LVEF ≤ 40% with non-sustained VT **AND** inducible sustained VT or VF during an electrophysiological (EP) study.

Primary prevention (prophylactic ICD implantation)

Prophylactic ICD implantation to reduce the risk of SCD may be considered in patients with:

I,A
IIa,B
- Prior MI and at least 40 days after an MI and 3 months after revascularization by PCI or CABG and:
  - LVEF ≤ 35% with mild to moderate HF symptoms (NYHA class II-III).[496]
  - LVEF ≤ 30% regardless of NYHA class, to reduce mortality.[495]

I,B
IIa,B
- Non ischemic cardiomyopathy LVEF < 35%, on guideline directed medical therapy with no reversible causes, and
  - Mild to moderate HF symptoms (NYHA class II-III)[497,498]
  - No HF symptoms (NYHA class I)[497,498]

- Additional risk factors shown to further increase the risk of sudden cardiac death and ventricular arrhythmias that may be factored to further support prophylactic implantation of a defibrillator device (ICD/ CRTD) are:
  - Syncope/ presyncope
  - LVEF < 25%
  - Non sustained Ventricular Tachycardia
  - PVCs > 10/hr on Holter monitoring

10.3.3. Pacemakers

I,A

- Patients with significant bradyarrhythmias, trifascicular bundle branch blocks and permanent or paroxysmal third-or high-degree atrioventricular (AV) blocks should be considered for pacemaker therapy.[479] Prior to implanting a conventional pacemaker, the need for an ICD or Cardiac Resynchronisation Therapy (CRT) device should be considered.
- Conduction system pacing (which includes His bundle and left bundle branch area pacing) is a new pacing modality. The early results appear promising but evidence on its safety and efficacy is still lacking.[479]

Key Recommendation #8: Arrhythmias

- **Device Therapy For HF**
  - ➢ The grade of recommendations and levels of evidence for device therapy (ICD, CRT, pacemakers) are as in Table 4, page 42.

10.4. SURGERY FOR HEART FAILURE

Patients with HF should undergo surgery if the pathology causing the HF is amenable to surgical treatment. The decision to subject a patient to surgery should however consider the functional status, prognosis, and comorbid conditions of the patient.

Surgical procedures include the following:

10.4.1. Revascularization Procedures

Patients with CAD and HF may benefit from revascularization particularly if they have angina and anatomy that is suitable for revascularization (left main stem or triple vessel disease). The benefit of revascularization is likely to be more in younger patients with more severe left ventricular dysfunction, severe CAD with angina, viable myocardium, and reversible ischemia.

The STICH trial did not find any difference in survival between optimal medical therapy and CABG in patients with CAD amenable to surgery and LVEF < 35% at the end of the trial at a median follow up of 56 months.[499] An extended follow up of the trial, however, after a median follow-up of 9.8 years, found lower total mortality, CV death and the combined outcome of all cause death and CV hospitalizations in patients with severe HF (LVEF < 35%) who underwent CABG.[500] There was an early risk of mortality following CABG, but the benefits of CABG were seen after 2 years, and these were seen whether myocardial viability or angina was present or absent.

IIa,B Coronary revascularization by CABG should be considered in patients with HF and suitable coronary anatomy.

A recently completed trial comparing PCI to OMT in patients with demonstrable myocardial viability and LVEF< 35% did not result in an improvement in CV outcomes.[501]

These high-risk patients undergoing CABG have a high surgical morbidity with longer intensive care unit stays, a median in-hospital stay of 9.0 days and higher 30-day mortality.[499] The treatment decision should be individualized after a discussion with the patient and family and considering the recommendations of the Heart Team.

10.4.2 LV Reduction Surgery

In the STICH trial, surgical ventricular restoration (SVR) resulted in a significant reduction of the end-systolic volume index but despite this, there were no differences in symptoms, exercise tolerance, rate of death or hospitalization compared with patients who underwent CABG alone.[502]

III,B As such, SVR is not routinely recommended in patients with HF who have areas of LV dyskinesia or akinesia and undergoing CABG.[502]

IIb,B LV aneurysmectomy may be considered in patients with a large discrete LV aneurysm who develop HF, angina pectoris, thromboembolism, and tachyarrhythmias due to the aneurysm.[503]

10.4.3. Valve Surgery

Please see section Section 14.2.5.1

10.4.4. LV Assist Devices

Left ventricular assist devices have been used to:

- Bridge patients with HF to heart transplant.[504]
- Support patients as a bridge to recovery.[505]
- Provide long term hemodynamic support in patients ineligible for heart transplantation (destination therapy).[506] In this group of patients, permanent treatment with LVADs improves survival and quality of life compared with optimal medical therapy alone. It is however expensive and is associated with significant adverse events.[507-509]

IIa,B Patients awaiting heart transplant who have become refractory to medical therapy and requiring inotropic support should be considered for a mechanical support device as a bridge to transplant.[507-509]

Key Messages # 10: Surgery for HF

- Patients with HF should undergo surgery if the pathology causing the HF is amenable to surgical treatment.
- This is particularly so if they have ischemia demonstrated as angina or by non- invasive testing and an anatomy that is suitable for revascularization (left main stem or triple vessel disease).
- The decision to subject a patient to surgery should however consider the functional status, prognosis, and comorbid conditions of the patient.

Key Recommendations #8: Chronic HF due to HF*r*EF

- Surgery For HF
  - **CAD**
    - Patients with HF should undergo surgery if they have angina and anatomy that is suitable for revascularization (left main stem or triple vessel disease).
  - **Valve Disease**
    - All patients with VHD should be assessed periodically on the need for early intervention before they begin to develop symptoms of reduced effort tolerance and decompensate.
    - Patients who are assessed to require intervention should be seen by a heart team to help decide the timing and type of intervention.
    - The indications for valve intervention are as in the Appendix V, page 166.

11. HEART FAILURE WITH MILDLY REDUCED LV EJECTION FRACTION (HF*mr*EF)

Symptomatic HF patients with LVEF between 41-49% are now classified under this category (previously known as heart failure with mid-range ejection fraction).[35] HF*mr*EF, makes up about 10-20% of patients with HF.[510]

There are limited number of randomized control trials focusing on this category of patients specifically. Hence, the evidence for treatment of this group of patients are derived from post-hoc or sub-group analysis of previous HF trials conducted in patients with HF*r*EF and HF*p*EF.

HF*mr*EF is a clinical entity between HF*r*EF and HF*p*EF. The LVEF can:

- Remain 40 - 49%.
- Improved to > 50% - HF*imp*EF.
- Worsen < 40% HF*r*EF.

It may be helpful to re-evaluate the LVEF periodically to determine the trajectory of the disease process. It is important to appreciate that these trajectories may not be linear and uni-directional.

In the management of these patients:

I,A
- SGLT2-i have been shown to reduce the combined end point of worsening HF or CV death.[511-513]

I,B
- Diuretics are recommended in patients who remain symptomatic and show signs of congestion despite a SGLT2-i.[514,515]

IIa,B
- Sub-group analysis of large trials indicates that β-blockers, RAS blockers (ARNI, ACEI or ARB) and MRAs can be considered to reduce the risk of HF hospitalization and CV death.[516-519]
- CV risk factors must be optimized.

Key Messages # 11: Chronic HF due to HF*mr*EF

- HF*mr*EF includes symptomatic HF patients with LVEF between 41-49% and is a clinical entity between HF*r*EF and HF*p*EF.
- There are limited number of randomized control trials focusing on this category of patients - most of the evidence is derived from post-hoc or sub-group analysis of previous HF trials.

Key Recommendations #9: Chronic HF due to HF*mr*EF

- The management of these patients include:
  - Optimal treatment of CV risk factors.
  - SGLT2- i
  - Diuretics for patients who remain symptomatic and show signs of congestion.
  - β-blockers, RAS blockers (ARNI, ACEI or ARB) and MRAs can be considered to reduce the risk of HF hospitalization and CV death.

12. HEART FAILURE WITH IMPROVED LV EJECTION FRACTION (HF*imp*EF)

This is a new category which includes patients with a:[520]

- Baseline LVEF of < 40% ***and***
- > 10-point increase from baseline LVEF ***and***
- A second measure of LVEF > 40%.

Patients with a baseline LVEF of 41-49% who have improved to a new baseline of LVEF > 50% may be categorized in this group.[35]

LV function and structural abnormalities do not fully normalize despite improvement in symptoms, functional capacity, and near normalization of biomarkers. Symptoms and signs may however relapse and cardiac biomarkers may increase if HF treatment is withdrawn.[41] This "remission" status requires continued treatment for HF.

IIa,B Hence in patients with HF*imp*EF, Foundational HF medications should be continued to prevent relapse of symptoms and subsequent deterioration of LV function.[41]

Key Messages # 12: Chronic HF due to HF*imp*EF

- HFImpEF includes patients with a:
  - Baseline LVEF of < 40% ***and***
  - >10-point increase from baseline LVEF ***and***
  - A second measure of LVEF > 40%.
- LV function and structural abnormalities do not fully normalize despite improvement in symptoms, functional capacity, and near normalization of biomarkers.

Key Recommendations #10: Chronic HF due to HF*imp*EF

- Symptoms and signs may relapse, and cardiac biomarkers may increase if HF treatment is withdrawn.
- Foundational HF medications should be continued to prevent relapse of symptoms and subsequent deterioration of LV function.

13. CHRONIC HEART FAILURE - HF DUE TO PRESERVED LV SYSTOLIC FUNCTION, LVEF > 50% - (HF*p*EF)

HF*p*EF is a heterogenous disease with various phenotypes and comorbidities.[521-524] It is highly prevalent, accounting for up to 50% of all patients with HF and is becoming the dominant form of HF in aging populations worldwide.[525,526]

In this guideline HF*p*EF refer to LVEF ≥ 50%. Importantly, clinicians should be aware that LVEF is a continuous variable and the EF cut-offs used in definitions are therefore arbitrary.[155,527,528]

HF*p*EF differs from HF*r*EF in that HF*p*EF patients are older and more often female. AF, CKD, and non-CV comorbidities are more common in patients with HF*p*EF than in those with HF*r*EF.[529]

In the ASIAN-HF registry, patients with HF*p*EF were younger and leaner. They, however, carried a high comorbidity burden, with 70% of patients having a least two comorbidities -most commonly hypertension, followed by anemia, CKD, diabetes, ischemic heart disease (IHD), AF, and obesity.[525] Similarly in the MyHF registry, patients with HP*p*EF had a high comorbidity burden, commonly hypertension, diabetes, IHD and CKD.[530]

13.1. Diagnosis

The diagnosis of HF*p*EF is challenging as symptoms and signs can be attributable to other co-existing conditions and LVEF is normal. Chronic obstructive pulmonary disease and obesity per se can also contribute to dyspnea in these patients.

The main hemodynamic finding in HF*p*EF is an elevation in LV filling pressures i.e. end diastolic LV pressure (LVEDP). In the early stages of the disease, these become elevated only during exercise or exertion giving rise to exertional shortness of breath.[531] As the disease progresses, it becomes elevated even at rest.

As outlined previously, the definition of HF includes the presence of:

- Clinical symptoms and signs of HF ***and***
- Raised NP - In general, the level of elevation of these peptides are less than that seen in patients with HF*r*EF.[532] NP levels may be normal in patients with HF*p*EF who are obese and falsely raised in patients without HF*p*EF but with AF.[533-535] Thus the diagnosis of HF*p*EF cannot be relied on solely on elevated NP levels.

If the patient has HF as per above definition, then basic investigations should be performed as outlined previously to look for possible etiology and the presence of comorbidities:

- ECG
- Chest X-ray
- Lab investigations
- Echocardiogram - Some features supporting the diagnosis of HF*p*EF include:[536]
  - LVEF ≥ 50% within 72 hours of the clinical event.
  - Left ventricular hypertrophy (increased LV wall thickness or LV mass index > 115g/m^2 for men and > 95g/m^2 for women).
  - Left atrial enlargement (LA volume index > 34ml/m^2 or > 40 mL/m^2 in the presence of AF).
  - Diastolic dysfunction if E/e′ ≥ 15.[536] A mean E/e' index >15 at rest has good diagnostic value for identifying a high mean pulmonary capillary wedge pressure (mPCWP), supporting the likelihood of HF*p*EF but an E/e' ratio within the intermediate range (9-14) is less sensitive. The E/e' index cannot be recommended as a single diagnostic index above all other non-invasive measures of filling pressures (such as retrograde pulmonary venous flow).[536]
  - Tricuspid valve regurgitation velocity > 2.8m/s.

HF*p*EF may be suspected in patients who have dyspnea and in whom non-cardiac causes of breathlessness have been excluded. In addition, the:

- The LVEF > 50% ***and***
- There is no significant heart valve disease or cardiac ischemia.

Many patients who are elderly, obese and who have hypertension, diabetes and/or AF presenting with dyspnea would fall into this category.

The diagnosis of HF*p*EF is often not clear cut. It does not depend on a single parameter but on a combination of parameters derived from clinical presentation, laboratory results and imaging tests that together will give a probability for the diagnosis.[536,537]

In difficult diagnostic situations, 2 scores have been proposed to aid in the initial assessment of patients suspected of having HF*p*EF (Appendix VI & VII, page 167-168)

- H2FPEF score[538]
- HFA-PEFF score[536]

In cases of intermediate probability of the disease based on the scores, confirmatory tests such as exercise echocardiography, invasive measurement of intracardiac pressures i.e. the mPCWP at rest and sometimes with exercise is necessary to make the diagnosis. (Appendix VI, page 167)

These tests are best performed in specialized cardiology centers and most doctors may not have access to them. This limits the broad clinical applicability of the scores and demonstrates the ongoing difficulty in making the diagnosis of HF*p*EF.[539]

The following patients who continue to have dyspnea may be referred to these centers for further evaluation and management:

- Cases where the diagnosis is unclear.
- Non responders to treatment especially those with multiple comorbidities.

13.2. Etiology and Associated Comorbidities

- HF*p*EF may also share similar clinical characteristics with valvular heart disease, pericardial disease, and high-output HF. In all these conditions, patients present with HF and have normal LVEF and even normal LV dimensions. In HF*p*EF however, the HF is due to myocardial disease resulting in abnormal myocardial relaxation, decreased compliance, and increased filling pressure.[539] For this reason, a basic echocardiogram is essential in the initial work up of these patients.
- The etiological factors affecting HF*p*EF and HF*r*EF seem to be different. When compared to patients with HF*r*EF, patients with HF*p*EF are more likely to have hypertension, valvular heart disease (e.g., aortic stenosis) and AF and are less likely to have a MI or left bundle branch block.[540]
- Comorbidities play an important role in the pathophysiology of HF*p*EF. These contribute to systemic and endomyocardial inflammation with fibrosis which are important in the pathogenesis of the disease.[524] It is these comorbidities that primarily correlate with outcome in patients with HF*p*EF rather than NP levels or echocardiographic parameters.[541]
  - Hypertension remains the most prevalent comorbidity of HF*p*EF, with a prevalence of 60% to 89%.[542-544]
  - Other comorbidities include :[542-544]
    - Overweight or obesity- Obesity is not only a comorbidity, but it is also an important risk factor for HF*p*EF development. The mechanisms involved are complex and include neurohormonal mechanisms and oxidative stress.[545] Morbid obesity also has an adverse effect on cardiac remodeling.[545]
    - Diabetes mellitus (DM)
    - Chronic obstructive pulmonary disease (COPD)
    - Obstructive sleep apnea (OSA)
    - Anemia
    - Coronary artery disease (CAD)
    - Chronic kidney disease (CKD)
  - The presence of diabetes, a lower systolic BP, lower hemoglobin and a lower eGFR were associated with a poorer outcome.[541]
  - AF is common in HF*p*EF and increases the risk of adverse outcomes.[546]

13.3 Management (Table 6, page 44)

Compared with HF*r*EF patients, hospitalizations, and deaths in patients with HF*p*EF are more likely to be due to non-cardiovascular causes. As LVEF increases, the proportional contribution of non-cardiac and non-HF events to death or hospitalization increases, highlighting the importance of managing comorbidities.

The important aim of therapy is to alleviate symptoms, improve well-being and reduce hospitalizations. Screening for comorbidities and treating these appropriately is important.

13.3.1 Lifestyle measures

- **Overweight or obesity** are important comorbidities in HF*p*EF.

I,B

  - A caloric restriction diet is feasible and safe in older, obese patients with HF*p*EF. It has been shown to significantly improves patient's dyspnea, peak oxygen consumption, and quality of life.[547]
  - Caloric restriction should ideally be combined with exercise, such as walking exercise for one hour three or more times per week.[169,547,548]
  - Bariatric Surgery in patients with HF*p*EF and obesity was associated with improved symptoms, reduction in HF hospitalizations, reverse cardiac remodelling, and improved LV distensibility.[549-551]

- **Exercise training**:
  - I,A ➢ This is safe and improves exercise capacity and quality of life.[169,547,551,552]
  - ➢ Combined endurance/resistance training appears safe for patients with HF*p*EF and improves exercise capacity (as reflected by an increase in peak oxygen consumption), physical functioning score and diastolic function.[169,548,549] It should consist of dynamic isotonic (e.g., walking or cycling) and not static exercise.
  - ➢ High-intensity interval training or moderate continuous training has not proved to be better than guideline-based physical activity for patients with HF*p*EF.[173]

13.3.2 Identifying and treating the underlying cause(s) and co- morbidities.

- I,A **Hypertension** should be treated to target goals.[147] Improved BP control has been shown to reduce morbidity and hospitalizations for HF.[119,554-555] More intensive BP control in patients with high CV risk including those > 75 years of age, significantly reduces HF and other cardiovascular outcomes.[553,556,557]
- **CAD** is common in patients with HF*p*EF and this should be treated appropriately.
- **Diabetes** - See section 14.1
- **Chronic Kidney Disease** - See Section 14.6
- **Tachyarrhythmias** should be treated, and sinus rhythm restored whenever possible.
  - IIa,B ➢ If the patient remains in persistent AF, β-blockers or non-dihydropyridine calcium channel blockers (verapamil, diltiazem) alone or in combination are the usual first line agents used for rate control.
  - IIa,A ➢ In patients with recent onset AF < 1 year duration or paroxysmal AF who received early rhythm-control, there was a significantly decreased primary end point of a composite of CV death, stroke, or hospitalization due to HF than those who received rate control.[416,425]
- I,A **Anticoagulation** - Patients with paroxysmal or persistent AF should be anticoagulated to reduce the risk of thromboembolic events.[412,416]

13.3.3 Pharmacological options

Pharmacotherapy has not been shown to reduce total or CV mortality. These include:

- I,C **Diuretics**: These are necessary to control pulmonary congestion and peripheral edema but should be used cautiously so as not to lower preload excessively and thereby reduce stroke volume and cardiac output. One should aim to use the lowest dose of a diuretic necessary to maintain euvolemia.
- **β-blockers**: β-blockers are often prescribed for the management of comorbidities such as coronary artery disease or atrial fibrillation. At present, however, there is no good data to show that β-blockers are beneficial in the treatment of HF*p*EF.[558] Furthermore, the type of β-blockers (non-selective and vasodilating, such as nebivolol and carvedilol, vs. rate controlling only) may have differential effects in different HF*p*EF phenotypes.[559] β-blocker withdrawal was shown to improve maximal functional capacity and chronotropic incompetence in patients with HF*p*EF.[560] Further studies are warranted on the use of β-blockers in these patients.
- **RAS blockers**
  - ➢ Current evidence does not support their routine use in HF*p*EF in the absence of an alternative indication.[561,562] Trial data show a reduction in HF hospitalizations, but no reduction in all-cause or CV mortality in HF*p*EF.[559]
  - IIb,B ➢ **ARB** - the use of ARB may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[563]
  - IIb,B ➢ **ACE-I** - may be considered to reduce hospitalization in patients with HF*p*EF.[564]

IIb,B

- **ARNI** - did not reduce the composite endpoint of CV death and total hospitalizations for HF in patients with a LVEF> 45% when compared to an ARB.[565] In a combined analysis of 2 large ARNI trials, there was a suggestion of benefit in patients with LVEF < 57% and in women (benefits of sacubitril-valsartan in women were sustained up to LVEF 60%, while for men the benefit was restricted to LVEF < 45%).[566]

IIb,B

- **MRA:** MRAs improve diastolic function in patients with HF*p*EF.[567] It may be considered to decrease HF hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[562,568,569] Benefits were seen in patients with LVEF > 45%, elevated BNP level or HF admission within 1 year, eGFR > 30 mL/min/1.73 m^2, creatinine < 2.5 mg/dL, and potassium < 5.0 mEq/L).[323] MRAs showed a greater benefit in patients who demon strated more functional impairment, obesity, diabetes, CKD, concentric LV hypertrophy, high renin, and biomarkers of tumor necrosis factor-alpha-mediated inflammation, liver fibrosis, and tissue remodeling.[570] Hyperkalemia was more common in those on MRA and close monitoring of potassium is important.

I,A

- **SGLT2-i** - These have been shown to decrease HF hospitalizations and CV mortality.[511-513] There was also a decrease in the slope of the eGFR decline, and a modest improvement in quality of life at 52 weeks.[511-513] The benefit was similar irrespective of the presence or absence of diabetes at baseline. In a subgroup analysis by LVEF, there was a signal for lower benefit on the primary composite endpoint, first and recurrent HF hospitalizations, at higher LVEF > 62.5%.[511]
- **Non-dihydropyridine Calcium Channel Blockers (verapamil and diltiazem)**:
  - Clinical data regarding use of calcium-channel blockers in HF*p*EF is sparse. Its use is mainly to treat hypertension or for rate control in AF.

Key Message #13: Chronic HF due to HF*p*EF

- HF*p*EF is a heterogenous disease that is highly prevalent, accounting for up to 50% of all patients with HF and is becoming the dominant form of HF in aging populations worldwide.
- In this guideline HF*p*EF refer to LVEF ≥ 50%. LVEF is a continuous variable and the EF cut-offs used in definitions are therefore arbitrary.
- HF*p*EF differs from HF*r*EF in that HF*p*EF patients are older, more often female with AF, CKD and non-CV comorbidities being more common.
- The main hemodynamic finding in HF*p*EF is an elevation in LV filling pressures i.e. end diastolic LV pressure (LVEDP), initially only on exertion and later even at rest.

Key Recommendation # 11: Chronic HF due to HF*p*EF

- Timely and early diagnosis of HF*p*EF leads to a better outcome.
- The management of patients with HF*p*EF includes:
  - Lifestyle measures
    - Weight reduction
    - Exercise training
  - Managing comorbidities such as hypertension, CAD, CKD, atrial fibrillation, obesity according to guidelines.
  - Pharmacotherapy:
    - Diuretics - for volume overload.
    - SGLT2-i - decreases HF hospitalizations and CV mortality.
    - RAS blockers (ARB, ACE-I, ARNI) - As a group, RAS blockers have not been shown to reduce total or CV mortality. There was a suggestion of benefit of ARNI in women up to LVEF 60%, while for men the benefit was restricted to LVEF < 45%.
    - MRA - it may be considered to decrease HF hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.
    - β-blockers - No good data that they are beneficial in the treatment of HF*p*EF although they are often prescribed for the management of comorbidities such as CAD or AF.

14. SPECIAL GROUPS

14.1. DIABETES AND HEART FAILURE

- HF and diabetes mellitus (DM) often co-exist, each increasing the likelihood of developing the other.[571] Diabetes is one of the risk factors for the development of HF and similarly among patients with HF there is a high prevalence of often unrecognized dysglycemia.[572-574]
- In Malaysia, about 60-65% of patients admitted with HF, have diabetes as a comorbidity.[13-15]
- Almost all the epidemiological and clinical trial data on DM and HF have been based on trials done on patients with type 2 DM.

14.1.1 Risk of developing dysglycemia in Patients with HF

- Patients with HF irrespective of ejection fraction phenotype, were shown to be at an increased risk of developing dysglycemia- both prediabetes and DM.[573,574]
- The prevalence of DM varies[571]:
  - 6-25% in patients with left ventricular systolic dysfunction (LVSD).
  - 12-30% in patients with symptomatic HF.
  - Up to 40% in patients hospitalized with HF.
- In the clinical trials, however, the incidence of new onset diabetes varied from 6-7%.[571,575,576]
- Predictors for developing new onset DM among patients with HF include:[573,574,577-581]
  - Severity (as reflected by a higher NYHA functional class) and duration of HF.
  - Elevated body mass index and waist circumference.
  - History of smoking.
  - Higher systolic blood pressure.
  - Certain medications such as loop diuretics, metoprolol.
- The presence of DM has been shown to be linked to adverse outcomes in HF of both ischemic and non-ischemic etiologies, irrespective of LVEF.

- All patients at Risk (Stage A) and who already have HF (Stage B-D) should be screened for dysglycemia and this should be treated appropriately according to guidelines.[322]

14.1.2 Risk of developing HF among patients with dysglycemia

- Diabetic patients have between 2-5x risk of developing HF.[572] Whether this indicates a causal effect or just a comorbidity is still unclear. It is an important CV complication and the prognosis of diabetic patients admitted to hospital for HF were worse than those admitted with MI.[582,583]
- The prevalence of HF ranges between 4-30% in various diabetic drug trials, with almost a third of patients being undiagnosed.[584]
- Even pre-diabetics (depending on the definition used) have a 9-58% risk of developing HF.[585] It is often the first manifestation of a CV event.[571]
- Predictors for the development of HF in patients with DM include:[571,586-589]
  - Female sex
  - Longer duration of DM
  - Older age
  - Increased body mass index
  - Poorer glycemic control
  - Insulin use
  - Renal impairment

14.1.3. Prognosis of patients with Dysglycemia and HF

- HF per se is associated with a high morbidity and mortality and concomitant DM compounds this risk.[590-593]
- This is particularly so in patients with HF*p*EF who have co-existing microvascular complications.[594] Both poor glycemic control (HbA1c >9.5%) and tight glycemic control (HbA1c <5.5%) are associated with increased all-cause mortality in this group of patients.[595]
- In Acute HF, incidence of hospitalization (adjusted for age and sex) is 2x higher in patients with DM compared with those without.[596,597] It is an independent predictor for overall mortality in acute HF.[598]
- Every 1% HbA1c reduction is associated with a 15% relative risk reduction in hospitalization for HF.[599]
- Inadequate glycemic control (HbA1c ≥ 7.0%) within one year after hospital discharge for HF, was significantly associated with a higher risk for all-cause mortality compared with an adequately controlled diabetes (HbA1c < 7.0%).[598]
- Once HF develops, the clinical course is marked by frequent hospitalizations and eventually death.[600-602] Most sudden deaths are due to LV dysfunction rather than a new ischemic event.
- Advanced age, duration of the disease, insulin use, the presence of CAD and an elevated serum creatinine are all independent risk factors for the development of HF.[603]
- However, despite having five risk factor variables within the target range i.e. glycated hemoglobin level, low-density lipoprotein cholesterol level, blood pressure, absence of albuminuria and smoking, the risk for hospitalizations for HF was increased by almost 45% over a 5.7-year period.[604]

14.1.4. Pathophysiology of HF in DM

- The development of HF in DM involves a complex interconnected process between systemic, myocardial, and cellular mechanisms that lead to coronary atherosclerosis, myocardial ischemia and infarction, with co-existing hypertension and dyslipidemia.[605]
- Diabetic cardiomyopathy is defined as the presence of diastolic or systolic dysfunction in a patient with DM without other obvious causes for cardiomyopathy, such as CAD, hypertension, or valvular heart disease.[605-607] However, whether diabetes directly causes a cardiomyopathy is, however, uncertain.[582,584]

14.1.5. Diagnosis of HF in diabetes

- The diagnosis of HF in patients with diabetes is like those without diabetes (see section 6).
- In those patients suspected of having HF, appropriate investigations as outlined in section 6 should be performed.

14.1.6. Management

14.1.6.1. Prevention of HF

- Diabetes is a CVD defining disease, and patients should have their other CV risk factors treated aggressively and closely monitored.[322]
- Lifestyle measures are important and have been shown to lower risk for HF, particularly in patients with HF*p*EF.[608] These include:[322]
  - I,A ➢ Weight reduction,
  - I,B ➢ Increased physical activity; and
  - I,B ➢ Smoking cessation.
- The BP and LDL-C should be treated to target:[322]
  - I,A ➢ BP 130-139/70-79mmHg, SBP < 130 in those without pre-existing CAD (but not < 120 mmHG) and who are at a higher risk of CKD or stroke.
  - I,A ➢ LDL-C according to CV risk category.
- Ambulatory or home BP monitoring should be encouraged as undetected hypertension and masked hypertension is highly prevalent among patients with DM.[609]
- In asymptomatic patients, routine screening for CAD is not recommended. Routine screening does not improve outcomes if CV risk factors are not treated to target.[322]

14.1.6.2. Treatment of HF

- The treatment of both Acute and Chronic HF in patients with DM is similar to those without DM with the use of the Foundational HF medications.

14.1.6.3. Treatment of Diabetes -Glucose Lowering Agents

- IIb,B Intensive glucose lowering is not associated with any significant reduction in CV risk.[610] In fact, tight control of DM especially with the occurrence of hypoglycemia is associated with increased mortality.[611-613]
- I,A In addition, HbA1c variability, has been shown to be an independent risk factor for CVD in T2DM patients, even when the HbA1c is within the target range.[614]
- Glycemic targets for patients with DM and HF should be individualized to include consid erations of comorbidities, severity of HF, and to balance benefits versus potential risks.[322,605]

I,A
- However, due to limited HF-specific data in DM patients, current recommendations suggest a target range of HbA1c 7%- 8%, while minimising adverse effects of treatments particularly hypoglycaemia.[322,584,605] This target however should be individualized based on patient characteristics and comorbidities.

A) Sodium-glucose cotransporter-2 inhibitors (SGLT2-i)

- SGLT2 -i showed a reduced risk of major adverse CV events, with the greatest benefit being seen for reduction in hospitalizations for HF.[615,616] This is the most consistent observation in CV outcome trials across this class.[615,616]

I,A
- In patients with DM and established CVD or at high CV risk, SGLT2-i should be given to prevent hospitalizations for HF.[155]
- SGLT2-i with the strongest with the strongest proven benefits for HF hospitalizations should be used.
- However, SGLT2-i should be used with caution, taking into consideration recognized side effects including genital candidiasis, euglycemic diabetic ketoacidosis, as well as lower-limb amputation and fractures with Canagliflozin.[605]

B) Glucagon-Like Peptide 1 (GLP-1) Receptor Agonists

IIa,A
- In patients with DM and established CVD or multiple risk factors for CVD, GLP-1 receptor agonists with proven CV benefits is recommended to reduce the risk of major adverse cardiovascular events.[322,584,617]
- GLP-1 receptor agonists show a 9%-12% reduction of the risk of HF hospitalization.[618,619] However, to date, there is insufficient data to include GLP-1 receptor agonists in the recommended treatment of patients with diabetes for HF risk reduction.[620,621]

C) DPP4 inhibitors

IIb,B
- DPP4 inhibitors confer no added benefit for therapy of DM in HF patients compared to placebo.[617]

III,A
- Saxagliptin and Alogliptin are not recommended in patients with DM and HF.[155,156,622]

D) Biguanides (Metformin)

IIa,B
- Observational studies indicate that metformin can be safely used in HF with no increased mortality even in those with NYHA class III and IV.[623]
- It also reduced the risk of hospitalization due to HF and all-cause hospitalization.[623,624]
- Lactic acidosis during hospitalization was uncommon.[625]
- Metformin should be discontinued when the eGFR is <30ml/min/1.73m^2.
- In older patients with DM who were hospitalized for HF, metformin initiation was independently associated with a significant reduction in HF hospitalization particularly in patients with LVEF > 40%.[626] Conversely, sulfonylurea initiation was associated with excess risk of death and HF hospitalization, regardless of LVEF.[626]

IIa,B
- Metformin is recommended for the treatment of DM in patients with HF if the eGFR is stable and ≥ 30 mL/min/1.73m^2.
- It should be used cautiously in unstable or hospitalized patients with HF.[584,617,627]

E) Sulfonylureas

IIb,B

- Current evidence based on observational cohort studies, suggests that sulfonylureas (including 2nd generation drugs) increase the risk of HF and therefore should be avoided if possible.[605,628-631]
- Sulfonylureas have been shown to be as safe as the DPP4 inhibitors as an add-on therapy to metformin or other diabetic medications for atherosclerotic CVD end points i.e. CVD death, nonfatal MI or nonfatal stroke. The occurrence of HF, however, was either not a key end point or not reported in these trials.[632-634] A large cohort study however, found the use of the second-generation sulfonylurea, glimepride to be safe in patients with diabetes and chronic HF.[635]

F) Insulin

IIb,C

- Insulin therapy may be considered in patients with advanced systolic HF*r*EF for better glycemic control.[584]
- However, insulin has been associated with increased all-cause mortality and hospitalization for HF.[636,637] This is especially in patients with low HbA1c < 7%.[636]

G) Thiazolidinedione

III,A

- TZD use including pioglitazone and rosiglitazone should be avoided in patients with T2DM and symptomatic NYHA class III & IV heart failure.[584,617,638,639]

Key Messages #14: HF and Diabetes

- HF and diabetes mellitus (DM) often co-exist, each increasing the likelihood of developing the other. Whether this indicates a causal effect or just a comorbidity is still unclear.
  - ➢ Patients with HF irrespective of ejection fraction phenotype, have been shown to be at an increased risk of developing dysglycemia.
  - ➢ Also, diabetic patients have between 2-5x risk of developing HF.
- HF per se is associated with a high morbidity and mortality and concomitant DM compounds this risk. This is particularly so in patients with HF*p*EF.

Key Recommendations #12: HF and Diabetes

- **Prevention of HF**:
  - Lifestyle measures are important. They have been shown to lower the risk for HF, particularly HF*p*EF. These measures include:
    - Attainment of appropriate weight,
    - Increased physical activity and
    - Smoking cessation.
  - The BP and LDL-C should be treated to target:
    - BP 130-139/70-79mmHg, SBP < 130 in those without pre-existing CAD (but not < 120 mmHG) and who are at a higher risk of CKD or stroke
    - LDL-C according to CV risk category.
- **Treatment of HF**
  - The treatment of both Acute and Chronic HF in patients with DM is similar to those without DM with the use of the Foundational HF medications.
- **Treatment of Diabetes - Glucose lowering Agents**
  - Glycemic targets for patients with DM and HF should be individualized.
  - Current recommendations suggest a target range of HbA1c 7%- 8%, while minimizing adverse effects of treatments particularly hypoglycemia.
  - Glucose lowering drugs:
    - With proven CV benefits:
      - SGLT2-i
      - GLP-1 receptor agonists
      - Metformin
    - With no proven CV benefits but which will help with glucose control:
      - DPP4 inhibitors
    - With no proven CV benefits and need to be used with caution:
      - Insulin -This has been associated with increased all-cause mortality and hospitalization for HF especially in patients with low HbA1c < 7%.
      - Sulfonylurea
    - That need to be avoided:
      - Thiazolidinediones

14.2. VALVULAR HEART DISEASE (VHD) AND HF

14.2.1. Etiology

Common etiological factors are:

- Rheumatic Carditis and Rheumatic Heart disease (RHD)
  - In a patient with acute rheumatic carditis, the early detection and appropriate treatment of beta-hemolytic streptococcal infections of the pharynx (positive throat swab and raised ASOT) during the infection and with subsequent appropriate penicillin prophylaxis against recurrent infection will help prevent the development of RHD in later life.
  - RHD is a sequela of acute rheumatic carditis. It occurs because of inflammation and scarring of the heart valves leading to fusion of the commissures and/or fusion and shortening of the chordae and deformation of the valve cusps. The incidence of Rheumatic Fever and RHD is still high among the rural and urban poor.[640]
- Infective Endocarditis
  - This can result in acute valvular damage or may exacerbate an underlying valve pathology.
  - A common source is poor oral hygiene.
  - An often-unrecognized source is i.v. lines.

- Congenital
  - This includes congenital bicuspid aortic valves, congenital mitral valve prolapse (Barlow's disease) and pulmonary stenosis.
- Degenerative disease
  - Commonest cause in the elderly.
  - This includes calcific aortic stenosis, aortic regurgitation secondary to aortic root dilatation from any cause, and degenerative mitral regurgitation.

14.2.2. Valve pathology

- **Mitral Valve Disease**
  - Mitral stenosis (MS)
    - This is almost always due to RHD.
  - Mitral Regurgitation
    - Primary mitral regurgitation is a disease of the mitral valve leaflets or chordae. It is the most common primary VHD seen locally.
      - In young adults and middle-aged persons, it is commonly due to RHD. It may also be secondary to collagen disorders such as Marfan's.
      - In the older age group (>70 years of age), degenerative causes leading to fibroelastic deficiency, myxomatous degeneration, chordal elongation and rupture are more common.
    - Secondary mitral regurgitation also known as functional MR, is a consequence of LV dysfunction with normal mitral valve leaflets and chordae. The LV dilatation may be secondary to CAD or any other non-ischemic etiology.
- **Aortic Valve Disease**
  - Aortic stenosis (AS)
    - May occur due to congenital bicuspid aortic valve.
    - More commonly develops in the elderly due to progressive degeneration, scaring and calcification of the valve.
  - Aortic regurgitation (AR)
    - Locally it is commonly due to RHD.
    - Bicuspid aortic valve is the commonest congenital cause.
    - Other causes include infective endocarditis or secondary to dilatation of the ascending aorta due to Marfan's or idiopathic aortic dilatation etc.

14.2.3. History and Physical Examination

- Common presenting symptoms are dyspnea, reduced effort tolerance and palpitations.
  - The presence of symptoms of HF in a stenotic lesion is a strong indication for intervention.
  - In regurgitant lesions, particularly with aortic regurgitation, it is usually a late presentation.
- The presence of valvular AF indicates significant valve pathology - usually due to mitral valve disease.

14.2.4. Investigations

Essential investigations include:

- ECG
- Chest Radiograph - Chest X-rays
- Echocardiography -
  - Transthoracic echocardiography is usually adequate to make the diagnosis and plan management.

- Transesophageal echocardiography may be required if the transthoracic echocardiography is of suboptimal quality or occasionally for prosthetic valve dysfunction, prosthetic valve endocarditis or left atrial thrombi. It is also necessary preoperatively when detailed valve anatomy is required to assess valve repairability.

14.2.5. Management

I,C All patients with VHD should be assessed periodically on the need for early intervention before they begin to develop symptoms of reduced effort tolerance and decompensate. This can be achieved by:

- Serial Chest X-rays to look for progressive cardiac enlargement.
- Serial echocardiograms are more sensitive to look for progressive deterioration. It can assess valve severity, chamber dilatation, pulmonary artery pressures and cardiac (both LV and RV) function.
- Objective assessment of the patient's effort tolerance and symptoms in doubtful cases.

Patients with VHD who are assessed to require intervention should be seen by a heart team to help decide the timing and type of intervention.[641] Valve intervention include:

- Surgical repair or valve replacement.
- Percutaneous intervention.

The initial medical management of patients with VHD and HF (especially those with secondary mitral regurgitation) is as outlined earlier with the Foundational HF medications.

III,C In addition,

- Vasodilators should be avoided in severe valve stenosis.

IIa,B
IIb,B
I,A
- Atrial Fibrillation should be managed with:
  - Rate control using:
    - β-blockers and/or
    - Digoxin for rate control
  - Anticoagulation with DOAC or vitamin K antagonists to prevent thrombo-embolism.

14.2.5.1. Valve Intervention in patients with HF

The indications for valve intervention are listed in Appendix V, page 166.

- Mitral valve intervention
  - Mitral stenosis
    - If the anatomy is suitable, percutaneous balloon mitral valvuloplasty is the procedure of choice.
    - If not suitable, then open mitral commissurotomy or mitral valve replacement may be indicated.
  - Mitral Regurgitation (MR)
    - Patients with HF of non-ischemic origin and severe functional mitral regurgitation may have symptomatic improvement after mitral valve surgery.[641] If the LVEF < 30%, mitral valve repair is preferred as mitral valve replacement is associated with poorer outcomes.[642]
    - Patients with LV systolic dysfunction undergoing surgical coronary revascularization who also have severe mitral regurgitation secondary to ventricular dilatation (functional mitral regurgitation) may be considered for concomitant mitral valve repair or replacement.[643,644]

- In patients with functional moderate to severe MR and who are not surgical candidates, the use of a MitraClip on a background of Foundational HF medications is superior to medical therapy alone.[645-647] At 2 years, there was a reduction in HF hospitalization and mortality in symptomatic HF patients with grade 3-4+ MR.[648]
- Compared to surgery, MitraClip demonstrated a similar safety profile and shorter length of stay in high-risk patients, at the expense of increased residual mitral regurgitation and higher reoperation rate.[649]
- The other landmark transcatheter mitral valve intervention study, however, did not meet its primary end point although there was a trend towards benefit in the cumulative rate of HF hospitalization between 12 and 24 months among the treated patients.[650,651]
- In view of the conflicting results, additional studies are needed to identify patients who will benefit the most from transcatheter mitral valve interventions.[641]

IIa,B

- At present, it may be considered in patients with moderate to severe MR and who are not surgical candidates and in high volume centers where this is done routinely.[645-651]

- **Aortic valve intervention**
  - **Aortic stenosis (AS)**
    - Severe AS has been defined as a:[641]
      - Valve area < 1.0 cm^2,
      - A mean transvalvular gradient > 40 mm Hg, and
      - Peak flow velocity > 4.0 m/s.
    - In the absence of symptoms and adverse prognostic features, watchful waiting has generally been recommended with prompt intervention at symptom onset.[641]
    - Variants include:
      - Severe AS with high gradient.
      - Severe AS with low gradient and poor LV function.
      - Severe AS with low/ normal gradient and preserved LV function.
    - Low dose dobutamine stress echocardiography can help in the diagnosis when the LVEF < 50% and the stroke volume index < 35 mL/m^2.[641,652]
      - In patients with true AS, the increased flow across a fixed valve orifice results in increased transvalvular flow velocity and gradients, without a change in calculated valve area.
      - In pseudo-AS, the augmented flow results in only a mild increase in transvalvular gradient and an increase in valve area to ≥1.0 cm^2.
    - In the presence of preserved LV function, LVEF>50%, the diagnosis is more challenging.[641]

IIa,B

    - In elderly patients > 70 years of age at moderate to high surgical risk, transaortic valve replacement is a reasonable alternative to surgical valve replacement.[641,653-658]
  - **Aortic Regurgitation**
    - In patients not reaching the thresholds for surgery, close follow-up is advised. They should be considered for surgery if:[641]
      - Exercise testing indicates borderline symptomatic patients or
      - There is progressive enlargement of the left ventricular end-diastolic diameter (LVEDD) > 65 mm), *or*
      - Progressive decrease in LVEF.

Key Messages # 15: HF and Valvular Heart Disease (VHD)

- VHD is an important cause of HF.
- In the young, RHD is an important cause. The incidence of RHD in rural and urban poor is high.
- In the older population, degenerative valve disease is more common.

Key Recommendations #8: HF and Valvular Heart Disease

- All patients with VHD should be assessed periodically on the need for early intervention before they begin to develop symptoms of reduced effort tolerance and decompensate.
- Patients who are assessed to require intervention should be seen by a heart team to help decide the timing and type of intervention.
- The indications for valve intervention are as in the Appendix V, page 166.

14.3. CARDIOMYOPATHY AND HEART FAILURE

Cardiomyopathies are a heterogenous group of myocardial disorders which frequently present as HF.[659] They can be inherited (familial/genetic) or acquired and may be accelerated by disease modifiers such as infection, immunological diseases, drugs, and comorbidities such as hypertension and diabetes mellitus.[659-661] In clinical practice they are usually classified according to anatomic and physiologic features into:

- Dilated cardiomyopathy (DCM)
- Hypertrophic cardiomyopathy (HCM)
- Restrictive cardiomyopathy (RCM)
- Arrhythmogenic cardiomyopathy
- Unclassified cardiomyopathy

As the presentation of arrhythmogenic cardiomyopathy is typically ventricular arrhythmias rather than HF, it will not be discussed further in this document.

It is worthwhile noting that specific etiologies of cardiomyopathy can have overlapping clinical phenotypes or transform from one clinical phenotype into another. For instance, Anderson-Fabry disease can have overlapping features of HCM and RCM, while RCM due to amyloidosis may transform into DCM as the disease progresses.

Where applicable, genetic testing and family screening should be considered.

14.3.1 Dilated Cardiomyopathy (DCM)

- DCM is one of the leading causes of HF*r*EF globally.[662]
- It is characterized by systolic dysfunction and ventricular dilatation in the absence of abnormal loading conditions (e.g., hypertension, valvular stenosis) or CAD[659]. Other morphological changes include atrial dilatation, reduction in ventricular wall thickness, and functional mitral and tricuspid regurgitation.
- The etiologies are myriad but can generally be classified into genetic or non-genetic causes (Appendix VIII, page 169). In some circumstances these causes can overlap and interact with one another e.g., cardiotoxicity from chemotherapeutic agents in a patient predisposed genetically to DCM.

- A family history can be detected in 30-50% of cases[663] and a genetic determinant in up to 40% of DCM patients.[659,664] More than 60 genes coding for various myocardial proteins and molecules have been implicated in the pathogenesis of DCM.[664,665] The most common inheritance pattern is autosomal dominant.
- The clinical course of DCM is variable, but it generally follows of one these pathways[666]:
  - Recovery following incident HF.
  - Remission with improvement or stabilization of LV systolic function.
  - Progression to advanced HF and death.
- Reverse remodeling is usually observed in DCM resulting from potentially reversible causes such as alcohol-related cardiomyopathy, peripartum cardiomyopathy and tachycardia-induced cardiomyopathy.

14.3.1.1. Management

- Management of dilated cardiomyopathy is as outlined in the earlier sections with the Foundational HF Medications.

14.3.2. Hypertrophic Cardiomyopathy

- HCM accounts for 2-3% of HF[667]. Etiologies of HCM are shown in (Appendix VIII, page 179-180)
- It is characterized by an increase in LV wall thickness (commonly defined as >15 mm, or >13 mm in adult first degree relatives of HCM patients) in one or more myocardial segments which cannot be explained by abnormal loading conditions.[668,669]
- The predominant form of HF in HCM is HF*p*EF. A small number of patients develop HF*r*EF later in the disease.
- HCM can be obstructive or non-obstructive. HF is prevalent in the majority of obstructive HCM and in 10% of non-obstructive HCM.[670]
- The LV outflow tract obstruction may be due to:[671]
  - Systolic anterior motion (SAM) of the mitral valve with prolonged septal contact.
  - Midcavity muscular apposition, usually caused by anomalous papillary muscle insertion directly into anterior mitral leaflet.
- Dynamic Left Ventricular outflow tract obstruction (gradient, ≥ 30 mm Hg) may be associated with mitral regurgitation. It is a strong independent determinant of HF.[671] Surgical myomectomy has been shown to reduce mortality in these patients.[672]
- About 3.5-17% of HCM patients progress to advanced HF. The pathophysiologic processes leading to progression of HF include severe LV obstruction, hypertrophy and adverse remodeling.[673-676]

14.3.2.1 Management [668,670,677]

- Referral to multidisciplinary HCM centers can help optimize care for patients with HCM.
- Genetic counseling of the patient and family is important.
- In patients with:
  - Arrhythmias:
    - Assessment of the individual's risk for sudden cardiac death (SCD) and consideration for ICD implantation.[678]
    - To treat AF by rate or rhythm control and appropriate anticoagulation.
  - Significant Left Ventricular Outflow Tract Obstruction:
    - Septal reduction procedures by either:
      - Surgical myomectomy - procedure of choice in experienced centers.[672]
      - Trans-catheter alcohol ablation in patients with advanced age or significant comorbidities.

- Pharmacotherapy - drugs that have negative inotropic effects such as β-blockers, verapamil or disopyramide. Emerging novel agents for obstructive HCM include agents such as mavacamten - a first-in-class cardiac myosin inhibitor. This has been shown to improve symptoms, physical and social function, and quality of life in a phase 3 study.[679,680] It has been approved for the treatment of symptomatic New York Heart Association (NYHA) class II-III obstructive HCM.

➢ HF - to treat accordingly as per clinical presentation as HF*p*EF or HF*r*EF.

14.3.3. Restrictive Cardiomyopathy

- RCM is characterized by restrictive physiology with normal or reduced diastolic volumes, and normal or reduced systolic volumes (in LV, RV or both).[669]
- There is typically no LVH, but some forms of infiltrative or storage diseases such as amyloidosis or Fabry-Anderson disease can cause an increase in LV wall thickness.[681]
- The etiology of RCM is heterogenous. It comprises infiltrative or non-infiltrative myocardial disorders, storage diseases and endomyocardial disorders that are either idiopathic, hereditary, or acquired (Appendix VIII, page 169).
- The prevalence of HF in RCM has been reported to be as high as 83%.[682] The predominant form of HF in RCM is HF*p*EF. HF*r*EF may manifest late in the disease and is more prevalent in amyloidosis and hemochromatosis.[683,684]
- The pathophysiology of HF in RCM is increased myocardial wall stiffness, resulting in diastolic dysfunction with subsequent predisposition to AF[681]. The LV systolic function is usually preserved but may be reduced at late stages of the disease, such as in cardiac amyloidosis.[685]
- The prognosis of RCM is generally poor, regardless of the underlying etiology.[686]

14.3.3.1 Management

- Management includes:
  - ➢ The Foundational HF medications are generally used but caution should be exercised as these patients tolerate over diuresis and hypotension poorly.
  - ➢ Consider disease-specific therapy if available e.g., amyloidosis and Fabry's disease.

Key Messages # 16: HF and Cardiomyopathies

- Cardiomyopathies are a heterogenous group of myocardial disorders which frequently present as HF.
- They can be inherited (familial/genetic) or acquired.
- They are usually classified according to anatomic and physiologic features into:
  - ➢ Dilated cardiomyopathy (DCM)
  - ➢ Hypertrophic cardiomyopathy (HCM)
  - ➢ Restrictive cardiomyopathy (RCM)
  - ➢ Arrhythmogenic cardiomyopathy
  - ➢ Unclassified cardiomyopathy
- In general, treatment of patients with cardiomyopathy encompasses the Foundational HF Medications as well as etiology-specific therapy (if available).

14.4. CARDIOMYOPATHY DUE TO ARRHYTHMIAS OR CONDUCTION ABNORMALITIES

14.4.1 Arrhythmia Induced Cardiomyopathy

Arrhythmia-induced cardiomyopathy (AiCM) includes:[687,688]

- Tachycardia-induced cardiomyopathy.
- Atrial Fibrillation (AF) induced cardiomyopathy.
- Premature Ventricular Complexes (PVC) induced cardiomyopathy.

Arrhythmia-induced Cardiomyopathy is a reversible cause of HF characterized by LV dysfunction resulting from an increased ventricular rate. The degree of LV dysfunction correlates with the duration as well as rate of the tachyarrhythmia. The cardiomyopathy may present weeks, months, or years after the onset of the tachycardia.687,689 It can occur in the setting of either an incessant or paroxysmal tachycardia and it should be suspected if no other cause of LV dysfunction is identified.[687]

Recognition of this entity is important clinically, as treatment of the underlying arrhythmia can result in either partial or complete recovery of LV function which, in turn, would result in an improvement in morbidity and mortality.[687]

In managing arrhythmias in patients with HF:

I,A
- Initiate the "Foundational HF" Medications to improve LV function and optimize reverse LV remodeling.

I,C
- Identify and treat arrhythmias accordingly. Arrhythmia recognition and suppression should be considered as part of the holistic evaluation and management of HF.

I,C
- Treat non cardiovascular comorbidities particularly, lung disease, obstructive sleep apnea and obesity.

14.4.1.1. Detection of Arrhythmias

Arrhythmias are sometimes difficult to detect, especially if they are paroxysmal and infrequent. In any person who presents with a deterioration in cardiac function, paroxysmal palpitations, near faints or syncope and the clinical suspicion that these could possibly be due to arrhythmias are high, the following modalities may be considered to aid in the diagnosis:

- Prolonged ECG rhythm monitoring using 3-day, 7-day or even 1- month rhythm monitors.
- Using a watch that can monitor ECG heart rhythm or
- An implantable loop recorder.

14.4.1.2. Supraventricular Arrhythmias

Any supraventricular tachycardia (SVT) with a rapid ventricular response may induce HF. Commonly encountered SVTs in clinical practice include:

- Incessant atrial tachycardia (AT),
- Very frequent episodes of atrioventricular nodal re-entrant tachycardia (AVNRT), and
- Atrioventricular re-entrant tachycardia (AVRT).

Arrhythmia-induced Cardiomyopathy has been reported in 10% of patients with AT, and as high as 37% of patients with incessant AT.[688,690]

I,A Successful treatment, usually via electrophysiological study and radiofrequency ablation, could potentially restore LV function.[416]

14.4.1.3. Atrial Fibrillation

AF is the commonest cardiac arrhythmia encountered in clinical practice.[691] AF and atrial flutter with rapid ventricular response is the most common cause of tachycardia induced cardiomyopathy.[687] AF induced cardiomyopathy may be suspected if LV function improves after rhythm control has been achieved and no other underlying cause has been identified.[687]

Management of AF in patients with HF would include the use of:[690]

IIa,B
- Anti-arrhythmic drugs for either rate control or rhythm control. Most anti-arrhythmic drugs are however contraindicated in the presence of HF.

IIa,A
- Catheter ablation - This has a higher chance of achieving rhythm control in patients with AF than anti-arrhythmic drugs.[437] Catheter ablation has been shown to reduce the risk of death and HF hospitalization in patients with AF and HF when compared to standard therapy with anti-arrhythmic drugs.[692,693] The success of the procedure and benefits seen were more likely in patients who underwent the procedure within 1 year of diagnosing AF.[692]

14.4.1.4. Ventricular Arrhythmias

Ventricular arrhythmias, including frequent PVCs or VT, may also induce HF.[689] It is however, sometimes difficult to ascertain whether the PVCs caused LV dysfunction or whether progressive LV dysfunction caused the frequent PVCs.[694,695] Even if the PVCs are the result of LV dysfunction, if frequent, may contribute to and increase the risk of HF and mortality even after adjusting for age and other ECG abnormalities.[689]

I,B Thus, maintenance of sinus rhythm and/ or control of ventricular rate is important in treating patients with HF.[689,694,695]

PVC induced cardiomyopathy is a diagnosis of exclusion, to be suspected in patients with frequent PVCs > 10%, especially in the nonischemic setting. Generally, LV dysfunction has been associated with greater PVC burden (>10% and usually > 20%).[694]

Curative or suppressive therapies with either radiofrequency ablation or anti-arrhythmic drugs may be considered in patients with PVC burden of:

IIb,C
- > 10% over 24 hours (high) - The prevalence of PVC induced cardiomyopathy in this group of patients has been reported to be about 7% but this could be an underestimate.[687,696]

IIb,B
- > 20% over 24 hours (very high) - The exact prevalence in this group is not known.[694,696,697]

I,C In patients with cardiomyopathy suspected to be caused by frequent and predominately monomorphic PVCs, catheter ablation is recommended.

IIa,B Anti-arrhythmic drug therapy that may be considered include β-blockers and class 3 anti-arrhythmic drugs such as amiodarone and sotalol.[696,698]

I,B Radiofrequency ablation is preferred, since most anti-arrhythmic drug therapy are contraindicated and may be pro-arrhythmic in the presence of HF.[694,699,700]

14.4.2. Cardiomyopathy due to Conduction Abnormalities

This will include cardiomyopathy due to conduction abnormalities/dyssynchrony, such as chronic RV pacing and left bundle branch block.

14.4.2.1. Pacing induced Cardiomyopathy

Pacing induced cardiomyopathy is defined as a reduction in LVEF of > 10% after pacemaker placement.[701] Paced QRS durations ≥ 150 milliseconds was associated with an increased risk.[701]

It is a complication of single-and dual-chambered pacemakers and may be present in up to 9% of patients. It is most prevalent within the first year after implantation and is associated with more pronounced intraventricular dyssynchrony.[702] The prevalence of this condition varies, depending on its definition, from 9% at 1 year, 7 up to 15% at 25 years.[703]

A high RV pacing percentage of > 40% and long-term pacing may exacerbate HF symptoms, increase hospitalization for HF, and increase mortality.[704-709]

I,A In patients with HF who have bradyarrhythmias and where pacing is indicated, biventricular pacing (Cardiac Resynchronisation Therapy - CRT) is the pacing mode of choice.[708-710]

14.4.2.2. Others:

This would include left bundle branch block (LBBB) - induced cardiomyopathy and other dyssynchronopathies.

Key Messages # 17: HF due to Arrhythmias and Conduction Abnormalities

- Cardiomyopathy due to arrhythmias and conduction abnormalities are potentially reversible causes of HF.
- Successful treatment of the arrhythmia by drug therapy or catheter ablation can result in normalization of LV function.

Key Recommendations #13: HF Due to Arrhythmias and Conduction Abnormalities

- In managing cardiomyopathy due to arrhythmias, radiofrequency ablation is the preferred therapy, since most antiarrhythmic drugs are contraindicated in the presence of HF.
- In patients with HF who have bradyarrhythmias and where pacing is indicated, biventricular pacing (Cardiac Resynchronisation Therapy) is the pacing mode of choice.

14.5 CARDIO-ONCOLOGY AND HEART FAILURE

Heart disease and cancer are often linked due to:

- Common risk factors (e.g., increasing age and cigarette smoking)
- Treatment strategies
  - Chemotherapy drugs has been associated with HF, arrhythmias, vasculitis and throm boembolic disease.
  - Radiotherapy of the mediastinum and left chest can lead to CAD, myopericardial fibrosis and valvular dysfunction.
  - New oncological therapeutic agents like targetted therapies affecting signalling pathway and immune checkpoint inhibitors.

Dyspnea in cancer patients could be due to:

- Fluid overload.
- Cardiomyopathy due to chemotherapeutic agents, stress (Takotsubo), underlying CAD, coronary vasospasm or pericardial diseases.
- The primary cancer causing anemia, lung and pericardial involvement.

Chemotherapy-induced cardiomyopathy is not common, clinical HF occurs in 1-5% and an asymptomatic decrease in LV function in the range of 5% to 20%.[711]

Cardiotoxicity can develop in a subacute, acute, or chronic manner. Acute or subacute cardiotoxicity may occur at any time from the commencement of therapy up to 2 weeks after termination of treatment.[709] Chronic toxicity can occur early (within 1 year) or late.[711,712] Prognosis in the patients who develop HF, especially late onset HF, is poor.[712,713]

The anthracycline class of chemotherapeutic agents remain the major cause of chemotherapy -induced cardiomyopathy.[712,713] In the current era, newer agents have also been implicated in a reversible form of cardiomyopathy.[714-716]

At present, there is no consensus definition of cardiotoxicity.[717] The definition that is currently most often used is by the Cardiac Review and Evaluation Committee of trastuzumab -associated cardiotoxicity.[718] By this defintion, chemotherapy-induced cardiomyopathy is said to occur in the presence of at least one or more of the following: [714,718]

1. Cardiomyopathy characterised by a decrease in Ejection Fraction (EF) globally or due to regional changes in interventricular septum contraction.
2. Signs and symptoms of HF.
3. Signs associated with HF including but not limited to S3 gallop, tachycardia, or both.
4. Decline in initial EF of at least 5% to < 55% with signs and symptoms of HF or asympto matic decrease in EF of at least 10% to < 55%.

Chemotherapy drugs that have been associated with HF are as listed in the (Appendix IX & X, pages 170-171)

One must consider both drug efficacy and toxicity in choosing chemotherapeutic agents. Many of the newer targeted agents cause a reversible form of HF and symptoms usually resolve after the initiation of anti-failure medications.[715,718-720]

Risk factors for anthracycline toxicity include:[713,721-726]

- The total cumulative dose- there is however, no safe dose for doxorubicin.[713]
- Intravenous bolus administration versus infusion.
- Higher single doses.
- History of prior irradiation.
- Use of concomitant agents known to have cardiotoxicity.
- Female gender.
- Underlying CV disease.
- Age (children and elderly > 65 years).

An increase in cardiac biomarkers such as troponins during and after administration is an indication of toxicity.[726,727]

14.5.1 Management

I,C
- Patients undergoing chemotherapy should have a careful clinical evaluation and assessment and treatment of CV risk factors.[714-716]

I,C
- Blood pressure control is important in all patients especially in those being considered for Vascular endothelial growth factor signaling pathway (VSP) inhibitors.

I,C
- All patients with potentially cardiotoxic chemotherapy should have an echocardiogram prior to treatment. An important parameter is the LVEF determined using the biplane method of discs (Simpson's method) or three-dimensional echocardiography (preferred) where available. Newer techniques to detect and quantitate regional and global myocardial dysfunction (strain assessment with global longitudinal strain) can be used to detect pre-clinical and subtle changes in function.[724,727,728] A 15% change from the baseline global longitudinal strain measure indicates an abnormality.[724]

IIb,C
- Biomarkers such as troponin and natriuretic peptides can help identify patients at higher risk.[729]

Close collaboration between the oncologist and the cardiologist is important.

For the oncologists, the strategy (prior to commencement) includes:[724]

I,C
- Identifying high risk patients (pre-existing heart disease, presence of CV risk factors, age-both the very young and old- female gender, use of high dose anthracycline regimens).

I,C
- High risk patients should:
  - Have a pre-treatment cardiac function evaluation. If the LVEF is < 50%, refer to the cardiologist.

I,C
  - Be considered for non-cardiotoxic alternatives.

I,C
  - Have their therapy protocols adjusted where necessary (e.g., reduction in doses, continuous infusions rather than bolus injections, liposomal doxorubicin, dexrazoxane etc).

I,C
  - Have regular echocardiography evaluation to detect deteriorating myocardial function.

For the cardiologists/general physicians, the strategy includes:

I,C
- Treating CV risk factors.

I,C
- Assessing, repeating (if necessary) imaging studies. (e.g., using high quality LVEF measurement, strain evaluation etc).
- Assessing cardiac biomarkers (troponin and/or Natriuretic Peptides).

IIa,B
- Considering cardio-protection prior to/or during treatment using β-blockers, MRA and/or ACE-I/ARB if:[726,730-733]
  - EF < 50%,
  - EF drops by > 10%
  - Abnormal global longitudinal strain (GLS) (> 15% drop).[724]
- Monitoring LVEF during therapy is important with repeat echocardiography at 3-monthly intervals and/or according to symptoms. If cardioprotective medications are given, monitoring may be necessary at closer intervals of time depending on the clinical condition of the patient e.g., at monthly intervals.
- Withholding cardiotoxic therapy is a last resort. (for anthracycline LVEF < 45%, for anti-HERS2 therapy LVEF < 40%).
- Monitoring after completion of therap y:
  - Obtain post therapy LVEF.
  - Repeat echocardiography in 6 months or 1 year. Most cases of treatment-associated cardiac dysfunction develop within the first year after completion of therapy.[733]
  - If EF remains abnormal, follow guidelines for management of HF.[725]

Key Message # 18: Cardio-Oncology

- Heart disease and cancer are often linked due to common etiologic factors and chemotherapeutic treatment strategies.
- Chemotherapy-induced cardiotoxicity is not common:
  - Clinical HF occurs in 1-5% and
  - An asymptomatic decrease in LV function in the range of 5% to 20%.
- It can develop in a subacute, acute (within 2 weeks of termination of drug administration) or a chronic manner.
- One must consider both drug efficacy and toxicity in choosing chemotherapeutic agents.

Key Recommendations #17: Cardio-Oncology

- Close collaboration between the oncologist and the cardiologist is important.
- Patients undergoing chemotherapy should have a careful clinical evaluation and assessment. Specifically:
  - All CV risk factors should be treated adequately.
  - High risk patients should be identified and in these patients:
    - A pre-treatment cardiac echocardiogram is advisable. If the LVEF < 50%, they should be referred to the cardiologist.
    - Reassessing and repeating (if necessary) imaging studies during and after treatment.
    - Assessing cardiac biomarkers when indicated - troponins and/or Natriuretic Peptides.
  - Considering cardio-protection prior to/or during treatment using β-blockers, MRA and/or ACE-I/ARB if:
    - EF < 50%,
    - EF drops by > 10%
    - Abnormal global longitudinal strain (GLS) (> 15% drop).

14.6. HEART FAILURE AND CHRONIC KIDNEY DISEASE (CKD)

14.6.1. Epidemiology, definitions, and classifications

HF and CKD frequently co-exist. The presence of both at the time of admission for HF, varies from 45.4% in patients with chronic HF to > 60% in those with Acute HF.[734,735]

In addition, during treatment of acute HF, a significant proportion of patients will develop varying degrees of worsening renal function.

The definition of worsening renal function is:[219]

- An increase in serum creatinine by ≥ 26.5μmol/ L (0.3mg/dl) ***and/or***
- A ≥ 25% increase in serum creatinine or a ≥ 20% drop in eGFR.

The rise in serum creatinine usually occurs in the first three to five days of hospitalization.

The incidence of worsening renal function is estimated to be between 19 and 45%.[736] This large observed range is due to variations in the definitions of worsening renal function, the observed time-at-risk, and the study population.[736]

Risk factors for worsening renal function during admission for HF include:[737]

- A prior history of HF or diabetes ***and/or***
- An admission serum creatinine of > 133µmol/L ***and/or***
- Systolic blood pressure > 160mmHg.

Worsening renal function may fulfill criteria for type 1 or type 2 cardiorenal syndrome (CRS). The term "cardiorenal syndrome" refers to disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic impairment of the other.[736]

This syndrome has been classified by the Acute Dialysis Quality Initiative working group into 5 subtypes as shown in Table 17, page 133.[736] Many patients, however, may belong to more than one subtype and may move between subtypes during the course of their disease.[736]

14.6.2. Pathogenesis of Cardio-Renal Syndrome (CRS)

Multiple mechanisms are involved in the pathogenesis of CRS. These include:

- Increased renal venous pressure - venous congestion is probably the most important factor.[738]
- Right ventricular dysfunction.
- Reduced renal perfusion due to reduced cardiac output.
- Volume overload.
- Neurohumoral adaptations (e.g., activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, increases in vasopressin and endothelin-1).
- Anemia.
- Metabolic abnormalities e.g., disorders of calcium, magnesium, and potassium metabolism.

14.6.3 Clinical significance /Impact of kidney dysfunction in HF

The combination of cardiac and kidney disease increases the complexity and costs of care and may interact to worsen prognosis.

A. Pharmacologic considerations

- Safety:
  - Dosing of renally-excreted cardiac drugs need adjustment in the presence of renal impairment (e.g., digoxin, insulin, low molecular weight heparin, direct oral anticoagulants).
  - Patients with HF are at increased risk of contrast-induced acute kidney injury.
  - Safety of newer drugs:
    - ARNI - safety has been demonstrated for eGFR > 30 mls/min/1.73m^2. A small study found that it was as safe as irbesartan in patients with eGFR > 20 mls/min/1.73m^2.[739]
    - SGLT2-i - safety has been shown for eGFR> 20 mls/min/1.73m^2.[740,741]
    - MRA - only finerenone has been shown to be safe in patients with eGFR down to 25 mls/min/1.73m^2.[373-376]
  - There is a lack of published data on newer drugs such as ARNI and SGLT2-i at eGFR < 20 mls/min/1.73m^2. If the patients are already on this drug and the eGFR drops to < 20 mls/min/1.73m^2, or if there is a compelling need for initiation despite eGFR < 20 mls/min/1.73m^2, shared decision-making with patients for off-label use is necessary.
- Efficacy:
  - Impaired renal function affects drug choices and dosing. If eGFR < 30mls/min/1.73m^2, most thiazide diuretics are no longer effective and loop diuretics are preferred.
  - Higher doses of loop diuretics may be required with increasing renal impairment.

B. Prognostic implications

- CKD is a risk multiplier in patients with HF - as the disease severity worsens, the risks of CV events, hospitalizations, and mortality increase.[742] In patients with HF, worsening renal function may not always indicate a poor outcome.[743] The prognostic value of worsening renal function is mainly determined by:
  - ➢ The presence of persistent congestion.
  - ➢ Baseline renal function and magnitude of renal changes.
  - ➢ Duration - a persistently worsening renal function is usually associated with hemody namic derangements and poor prognosis as compared with a transient worsening of renal function as a result of aggressive decongestive therapy.[744-746]

14.6.4 Management

A) General Considerations:

I,C
- A multi-disciplinary approach with an early referral to a nephrologist is recommended.

I,C
- Exclude potentially reversible causes for increasing renal dysfunction such as hyper - or hypovolemia, concomitant medications such as aminoglycosides and NSAIDs, and renal artery stenosis.

Table 17: Classification of Cardiorenal Syndrome (CRS)

Cardiorenal (CRS) Subtypes	Description
CRS Type 1 (Acute CRS)	Rapid worsening of cardiac function leading to acute kidney injury e.g., MI with cardiogenic shock.
CRS Type 2 (Chronic CRS)	Chronic abnormalities in cardiac function leading to progressive Chronic Kidney Disease (CKD) e.g., chronic HF*r*EF or HF*p*EF.
CRS Type 3 (Acute Renocardiac Syndrome)	Worsening of renal function leading to acute cardiac dysfunction e.g., in Acute Kidney Injury.
CRS Type 4 (Chronic Renocardiac Syndrome)	Primary chronic kidney disease contributing to decreased cardiac function and an increased risk of CV events e.g., CKD leading to LVH, CAD.
CRS Type 5 (Secondary CRS)	Presence of comorbid cardiac and renal dysfunction due to either acute or chronic systemic disease e.g., diabetes, sepsis, amyloidosis.

Adapted from Ronco C, McCullough P, Anker SD, et al. Cardio-renal syndromes: report from the consensus conference of the Acute Dialysis Quality Initiative. Eur Heart J 2010;31:703-11.

I,C
- Closely monitor electrolytes and kidney function, especially during acute illnesses, dehydration and when increasing doses of cardiac drugs including diuretics. The baseline renal function will determine how frequently this should be done.
- The recommended range for serum potassium is 4 - 5.5mmol/L.[747]

I,C
- Wherever possible, avoid nephrotoxins, e.g. contrast media for angiography.

B) Choice of Pharmacotherapy

I,B
- Intravenous diuretics
  - Loop diuretics are the first choice.

IIa,B
  - Continuous infusion may not have greater benefits compared with bolus dosing.[247, 249-252]
  - Start initially with 2.5 x the usual oral dose.

IIa,B
  - Combination therapy (loop diuretic and thiazide/thiazide-like diuretic/mineralocorticoid) may be required to enhance diuresis.[255,256, 748] However, care is required to avoid electrolyte disturbances, hypovolemia and worsening renal function.

I,A
- Foundational HF Medications in patients with concomitant CKD:
  - Foundational HF Medications have been proven to be equally efficacious in patients with CKD.
  - Many of these agents can still be initiated in patients with lower GFR (Table 19, page 136).
  - However, most of the treatments used for HF can cause worsening renal function and/or hyperkalemia. Therefore, close monitoring of renal function is essential:
    - In the landmark MRA trials, potassium was checked after 7 days (and again after 72 hours if dose reduction was needed).
    - In the RAS blocker (ACE-I/ARB/ARNI) and SGLT2-i trials, laboratory assessment of creatinine, urea, eGFR and electrolytes was typically done after 14 days during drug titration and every 4 months thereafter.
    - The interval for monitoring renal function tests needs to be individualized depending on baseline renal function, concomitant medications and comorbidities. With more advanced CKD at baseline, renal function tests should be repeated within 3-7 days after drug initiation and every time doses are titrated.
  - ACE-i/ARB/ARNI and SGLT2-i can lead to an initial drop in eGFR but this should not be a reason to automatically stop or down titrate these agents. For HF*r*EF, both ARNI and SGLT2-i have renoprotective effects.[749]
  - ACEi/ARB should be up titrated to the maximum recommended dose to achieve optimal dosing provided:[750]
    - SCr levels remain < 30% from the baseline (or eGFR reduces < 25%) ***and***
    - Serum potassium < 5.5 mmol/L
  - Consider reducing or discontinuing ACEi/ARB within two months from commencement (after excluding other precipitating factors) when:[750]
    - SCr levels remain ≥ 30% from the baseline (or eGFR reduces ≥ 25%) ***or***
    - Serum potassium ≥ 5.5 mmol/L
  - A decrease in eGFR over time (beyond 2 months from commencement of medication) may reflect the underlying disease process and is not necessarily a signal to automatically discontinue or down titrate the RAS blocker or SGLT2-i.[749]

I, C

- In patients with advanced renal disease, the decision to start or stop RAS blockers should be individualized.[751] The discontinuation of RAS blockers in patients with advanced and progressive CKD did not make any significant difference in kidney disease progression and the long-term rate of decrease in the eGFR.[752] Hence the decision to continue or discontinue RAS blockers should be made according to the individual patient's level of proteinuria, blood pressure control, tolerability and cardiovascular risk profile.

IIa,B

- Novel potassium binders such as sodium zirconium cyclosilicate and patiromer have been proven to be safe and efficacious even with long term use of up to one year. These new agents may be considered to allow continuation or dosing optimization of Renin Angiotensin Aldosterone System (RAAS) inhibitors in patients with hyperkalemia.[155]
- A guide to adjustment of dose of RAS blockers with changes in eGFR is as in Table 18, below.

Table18: Management of RAS Blockers in response to changes in renal function

Compared to baseline, serum creatinine increases by:	HF*p*EF	HF*r*EF
< 30%	Consider stopping RAS blocker Review Dosage of MRA	Continue unless there is symptomatic hypotension
30 - 50%	Stop RAS Blocker	Consider reducing the dose of RAS blocker and/or temporary withdrawal
< 50%	Stop RAS Blocker	Temporarily stop RAS blocker. Exclude other causes and consider re-challenge.

Adapted from Clark AL, Kalra PR, Petrie MC, Mark PB, Tomlinson LA, Tomson CR. Change in renal function associated with drug treatment in heart failure: national guidance. Heart. 2019 Jun;105(12):904-910.

C) Ultrafiltration

- This involves the removal of plasma water across a semi-permeable membrane in response to a transmembrane pressure gradient.
- It may be considered for congestive symptoms refractory to diuresis but should be used in consultation with a nephrologist.[753]

IIa,B

- Evidence for its efficacy in fluid removal is, however, mixed at present.[753]

D) Renal Replacement Therapy (Hemodialysis or Peritoneal Dialysis)

- Criteria for possible need to initiate renal replacement therapy include:
  - Oliguria (urine output < 200mls/12 hours) or anuria unresponsive to judicious fluid resuscitation.
  - Intractable pulmonary edema.
  - Hyperkalemia refractory to medical therapy or where urgent correction is required (serum potassium > 6.5mmol/L).

- Severe acidemia (pH < 7.2).
- Serum urea > 25mmol/L.
- Serum creatinine > 300µmol/L.
- Uremic symptoms or signs e.g., uremic pericarditis

Table 19: Initiation of HF drugs in relation to baseline CKD status*

Medications	EVIDENCE ACROSS eGFR STRATA			
	eGFR > 60 mls/min/1.73m^2	eGFR 30-60 mls/min/1.73m^2	eGFR 15-30 mls/min/1.73m^2	ESRD
ACE-i/ARB	Strong evidence		Moderate evidence	Moderate evidence if on dialysis, weak if not on dialysis
ARNI	Strong evidence		Weak evidence Small study only for eGFR > 25 mls/min/1.73m^2	Not recommended
β-blockers	Strong evidence		Moderate evidence	
MRA	Strong evidence		Only finerenone at eGFR > 25 mls/min/1.73m^2	Not recommended
SGLT2-i	Strong evidence (From eGFR > 20 mls/min/1.73m^2)			No Evidence
Ivabradine	Strong evidence		No Evidence	
Vericiguat	Strong evidence			No Evidence

**Adapted from Mullens W, Martens P, Testani JM, et tal. Renal effects of guideline-directed medical therapies in heart faiure: a consensus document from the Heart Failure Association of the European Society of Cardiology. Eur J of Heart Fail 2022;24: 603-619*

Key Message # 19: HF and CKD

- Cardiac and kidney disease frequently co-exist, and this increases the complexity and costs of care, and may interact to worsen prognosis.
- During treatment of Acute HF, a significant proportion of patients will develop varying degrees of worsening renal function usually in the first three to five days of hospitalization.
- In patients with HF, worsening renal function may not always indicate a poor outcome-especially if it is due to overdiuresis and hypotension or drug therapy.

Key Recommendations #15: HF and CKD

- A multi-disciplinary approach with early referral to a nephrologist is recommended.
- Almost all Foundational HF Medications can be used in patients with eGFR > 30mls/min/1.73m^2
- In patients with eGFR < 30mls/min/1.73m^2, the following drugs can be used:
  - Diuretics- usually higher maintenance doses
  - Careful use of RAS blockers
  - β-blockers
  - SGLT2-i (eGFR > 20mls/min/1.73m^2)
- Closely monitor electrolytes and kidney function. The baseline renal function will determine how frequently this should be done.
- RAS blockers and SGLT2-i can lead to an initial drop in eGFR, but this should not be a reason to automatically stop or down titrate these agents. See table 18, page 135 for the management of RAS blockers in response to changes in renal function.
- Occasionally ultrafiltration and renal replacement therapy (hemodialysis or peritoneal dialysis) may be necessary.

14.7 HEART FAILURE IN PREGNANCY

About 0.5-4% of pregnant women have cardiac disease.[754] HF remains the most common complication among all pregnant women with heart disease regardless of the cause (valvular, congenital, cardiomyopathy or pulmonary hypertension).[755]

In Malaysia, in 2020, the maternal mortality ratio was at 24.9 maternal deaths per one hundred thousand live births.[756] This refers to the annual number of female deaths caused by or related to pregnancy per one hundred thousand live births.

In general, pregnancy is well-tolerated in women with cardiomyopathy and NYHA class I pre- pregnancy. Factors increasing maternal and fetal risks include:[757-761]

- Previous cardiac events
- NYHA class III to IV ***or***
- LVEF < 40%.

In the ROPAC Registry, women with pre-pregnancy or peripartum cardiomyopathy had the highest mortality rate (2.4%)[762,763]

Normal hemodynamic changes that occur in pregnancy are:

- An increase in cardiac output by 30-50% during normal pregnancy.
- An increase in cardiac output to 80% above baseline during labour and delivery.
- Hemodynamic changes return to baseline 2-4 weeks after vaginal delivery and up to 6 weeks after Caesarean delivery.

In women with heart disease, these changes may have a deleterious effect on their cardiovascular system and may precipitate HF.

The periods of greatest risk for cardiac events during pregnancy are early third trimester, at delivery and in the immediate post partum period.

HF may develop in pregnancy:[192,764]

- For the first time in a patient with pre-existing heart disease (congenital and/or valvular) due to decompensation from the stress.
- May occur in a patient who had HF previously and still has a depressed myocardial function. (LVEF < 40%).
- In a patient with a previously unrecognized genetic cardiomyopathy or a latent cardiac viral infection which has been unmasked or activated by the stress of pregnancy.[765-768]
- In a patient with a previously normal heart due to:[769-771]
  - Hypertensive complications of pregnancy i.e. gestational hypertension and the more severe forms preeclampsia, the HELLP syndrome.
    (H: hemolysis, EL: elevated liver enzymes, LP: low platelet count).
  - Peripartum cardiomyopathy.
  - Takotsubo syndrome.[755]

14.7.1. Diagnosis

Most forms of cardiac disease can be detected by physical examination, ECG and echocardiography. In cases of new HF or if there is diagnostic uncertainty, non-contrast CMR may be considered.

14.7.2. Risk stratification

- Pregnant women with cardiac disease are at risk of adverse maternal and fetal outcomes.

I,C

- Their risk should be assessed before conception or early in the pregnancy to optimize the outcome of the pregnancy.[192,764]
- Maternal cardiovascular risk can be assessed using the modified World Health Organization (WHO) or NYHA classification.[192] (Appendix XI & XII, page 172-173)
- Level of Care will depend on the maternal CV risk:[192]
  - **Low risk**: can be managed at their local center after review by a family medicine specialist/physician or cardiologist.
  - **Moderate risk**: should be managed at a tertiary center by a multidisciplinary team with cardiac expertise.
  - **High risk**: should be referred early to the tertiary center for assessment. If termination of pregnancy is considered, it can be performed up to 22 weeks.

14.7.3. Management

The management of HF in pregnancy is more difficult than in the non-pregnant state and should be managed by a multidisciplinary team consisting of physicians, obstetricians, and pediatricians.[789,754,755,764]

In the management of HF in pregnancy, the following issues need to be considered:[192,755,764]

- Gestational age at presentation.
- Clinical presentation, either as Acute HF or Chronic HF.
- Response to medical therapy.
- Potential maternal and fetal risks.
- Review and replace all fetotoxic drugs
- Timing and mode of delivery.

Predictors of maternal cardiac complications are as in Table 20, Page 139.

14.7.3.1. Preconceptual counselling

I,C
- Patient-centered counselling regarding contraception and the risks of cardiovascular deterioration during pregnancy should be provided to all women in the childbearing age with known or suspected heart disease.[192-194,764]
- Patients with LVEF < 30% and those in NYHA Class III and IV should be strongly advised not to get pregnant.[192,772] If pregnant, termination should be considered.

14.7.3.2. Management of HF during pregnancy

This includes:

- **Non-pharmacological measures**

I,B
The management of patients with mild symptoms consists mainly of non-pharmacological measures such as:[192]
- ➢ Limiting strenuous exercise.
- ➢ Adequate rest - maintaining a low salt diet.
- ➢ Treating anemia and infections early.
- ➢ Frequent antenatal examinations.

- **Pharmacological measures**

The following drugs may be used in the pregnant patient with HF:[192]

I,C ➢ Diuretics are the first line therapy in patients who are fluid overloaded.

IIa,C ➢ Nitrates and/or hydralazine are used for preload and afterload reduction.

IIa,C ➢ β-blockers can be used cautiously, most commonly metoprolol.[773,774]

IIa,C ➢ Digoxin is safe in pregnancy and during breast feeding.

III,C ➢ ACE-I, ARB, ARNI, MRA, SGLT2-i and ivabradine are contraindicated in pregnancy.[755,775,776]

IIa,C ➢ ACE-I (enalapril and captopril) can be used in the post partum period.[775,776]

➢ In the postpartum period, Foundational HF medications may be given. The patient should however be advised not to breast feed.

Table 20: Predictors of Maternal Risk for Cardiac Complications[192,754,768,769]

• Cyanosis (oxygen saturation < 90%)
• Repaired or unrepaired cyanotic heart disease
• History of HF before pregnancy
• Prior cardiac event (HF, transient ischemic attack, stroke, arrhythmia)
• Prior arrhythmia (symptomatic sustained tachyarrhythmia or bradyarrhythmia requiring treatment)
• NYHA class > II
• Valvular stenosis (aortic or mitral valve area < 1.5cm^2) and LV outflow tract obstruction (peak gradient > 30mmHg)
• Reduced systemic ventricular dysfunction (LVEF < 40%)
• Mechanical valve
• High risk aortopathy
• Reduced subpulmonary ventricular function (TAPSE < 16 mm)
• Pulmonary arterial hypertension
• Systemic and pulmonary atrio-ventricular valve regurgitation (moderate to severe)
• Natriuretic peptide levels (NT-Pro BNP > 128pg/mL at 20 weeks predictive of event later in pregnancy)
• Cardiac medication before pregnancy
• Maternal history of smoking
• No prior cardiac intervention

- **Other treatment considerations in the pregnant patient.**
  - Patients with AF who are hemodynamically unstable should be promptly electrically cardioverted. This is safe in pregnancy.
  - Anticoagulation is indicated in the presence of AF, dilated left atrium or mechanical prosthetic heart valve.
  - Patients with valvular lesions who remain symptomatic despite optimal medical treatment may be considered for percutaneous valve intervention or surgery.

I,C

  - Commonly recommended antihypertensive drugs include methyldopa, labetalol, calcium channel blockers and hydralazine.[192,775]
  - Echocardiographic reexamination may be considered:
    - In the third trimester for reassessment of myocardial structure and function before labor.
    - When there are significant changes in HF symptoms or signs during pregnancy.
    - When HF medications are reduced or discontinued.
  - In selected patients, Natriuretic peptide (BNP or NT-Pro BNP) monitoring may have some value for prediction of cardiovascular events.[777,778]

A. Antenatal care

The principles of management of HF in pregnancy are like that in the non-pregnant state. If the patient is in decompensated HF requiring inotropes, she should be transferred to a cardiac center.[192,754]

B. Labour and delivery

Timing and mode of delivery should be carefully planned by a multidisciplinary team. In the majority of patients, vaginal delivery with epidural anesthesia is the preferred mode of delivery.

- Cesarean section is indicated:[192]
  - For obstetric reasons.
  - In patients on warfarin or who have discontinued their warfarin for < 2 weeks and who now are in imminent labour.
  - In patients with severe pulmonary hypertension.
- It is beneficial to shorten the second stage of labour by forceps or vacuum assisted delivery.[192]
  - Left lateral decubitus position is preferred to attenuate the hemodynamic effects in the supine position.
  - A slow i.v. infusion of oxytocin immediately after birth, (2 U of oxytocin given over 10 min followed by 12 mU/min for 4 h) reduces the risk of post-partum hemorrhage and has a minimal impact on cardiovascular parameters.[192]
- Routine antibiotic prophylaxis is not recommended in patients with valvular heart disease undergoing uncomplicated vaginal delivery or Cesarean section.

C. Post partum care

- After delivery, careful monitoring of hemodynamic status should be done for at least 24 hours, or longer in high-risk patients. In patients with severe cardiac lesions, hemody namics may be abnormal up to 10 days after delivery.[192]
- These patients should be evaluated post-partum to assess the need for corrective surgery.

- The risk of recurrence of HF in subsequent pregnancies should also be made known to the patient.
- Follow-up visit at 6 weeks post-partum should be attended by the multidisciplinary team, a full cardiac assessment should be done, and appropriate contraception should be advised.
- Postpartum women who breast feed can start ACE-I (enalapril or captopril preferred). Metoprolol remains the preferred β-blocker.[773-776]

14.7.4 Peripartum Cardiomyopathy (PPCM)

- PPCM presents as HF secondary to LV systolic dysfunction, usually shown by an LVEF < 45% occurring during the third trimester or in the months following delivery without any other identifiable cause.
- The majority of PPCM cases are diagnosed in the post-partum period. PPCM frequently presents with Acute HF but may also present with ventricular arrhythmias and/or cardiac arrest.
- Cardiac recovery may occur in the first 3-6 months though it may be delayed up to 2 years. Recovery rates vary among regions, from 75% to less than 50%.[779-781]
- Subsequent pregnancies for women with previous peripartum cardiomyopathy have been associated with further decreases in LV function, maternal death, and adverse fetal outcomes.[779] The strongest prognostic determinant is LVEF <50% before a subsequent pregnancy.[780-782]
- The incidence of intracardiac thrombi during Acute HF caused by peripartum cardiomyopathy has been reported to be around 16%-17% with a 9% thromboembolic event rate.[782]
- Predictors of adverse pregnancy outcomes include:[780,781]
  - LVEF < 30%
  - RV involvement.
- Prognosis is related to the initial LVEF, presence of LV thrombus, RV involvement, preeclampsia, geographical region, and race.[779,780]

14.7.4.1. Management:

- This is as listed in section 14.7.3.2
- In addition:
  - In those patients presenting with severe HF and cardiogenic shock requiring inotropic or vasopressor support, it is advisable to transfer them to an advanced HF center. Urgent delivery by cesarean section (irrespective of gestation) should be considered.
  - Bromocriptine has been proposed for patients with acute PPCM to reduce the production of a cleaved 16 kDa prolactin fragment, which may contribute to the pathophysiology of PPCM. The efficacy and safety of bromocriptine for acute PPCM treatment, however, remains uncertain currently, particularly in the setting of contemporary HF and cardiogenic shock management.[780,783] The use of bromocriptine increases thromboembolic risk and thus, adequate anti-coagulation is important.
  - Some patients may present with HF late post-partum and thus, they should be followed up closely long-term. They should also be counselled about subsequent pregnancies and the risk of relapse.

Key Message #20: HF and Pregnancy

- About 0.5-4% of pregnant women have cardiac disease. HF remains the most common complication among all women with heart disease regardless of the cause.
- Women with cardiac disease should be assessed:
  - Before conception to assess their risk and to be advised accordingly and
  - Early in the pregnancy to optimize the outcome of the pregnancy.
- Maternal cardiovascular risk can be assessed using the modified World Health Organization (WHO) or NYHA classification. (Appendix XI & XII, page 172-173)
- Level of Care will depend on the maternal CV risk.
  - **Low risk**: can be managed at their local center after review by a family medicine specialist/physician or cardiologist.
  - **Moderate risk**: should be managed at a tertiary center by a multidisciplinary team with cardiac expertise.
  - **High risk**: should be referred early to the tertiary center for assessment.
- Patients with LVEF < 30% and those in NYHA Class III and IV should be strongly advised not to get pregnant. If pregnant, termination should be considered.

Key Recommendations #16: HF and Pregnancy

- HF in pregnancy should be managed by a multidisciplinary team consisting of physicians, obstetricians and pediatricians.
- HF that develops during pregnancy can be managed with the judicious use of diuretics, digoxin, nitrates, β-blockers (most commonly metoprolol) and/or hydralazine.
- For post-partum women with severe acute HF caused by Peripartum cardiomyopathy and LVEF < 35%, Foundational HF medications to improve LVEF recovery and prophylactic anticoagulation are recommended.

14.8. CORONAVIRUS 2019 (COVID 19) +/- VACCINE AND HEART FAILURE

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

In hospitalized patients with COVID-19, the prevalence of HF varied between 4% and 21% and about 8% - 33% required critical care admissions.[784] Patients with HF who develop COVID-19 had an overall mortality rate between 20% and 40%.[784,785]

HF is an independent predictor of mortality in hospitalized COVID-19 patients and these patients were more likely to be sicker and develop complications. Patients with HF*r*EF did worse than those with HF*mr*EF or HF*p*EF.[784]

Patients hospitalized for COVID-19 may develop both an acute decompensation of chronic HF as well as new onset HF. New onset HF was observed in as much as a quarter of hospitalized COVID-19 patients and about one-third of those admitted to the intensive care unit (ICU).[786]

New onset HF may be due to multiple mechanisms. These include myocardial injury due to the direct effects of the virus, myocardial ischemia (Type 1 or 2 Myocardial infarction), multisystem inflammatory syndromes, cytokine storm, stress cardiomyopathy, acute cor pulmonale from micro and macro pulmonary emboli.[787,788] Myocardial injury occurred in at least 10% of unselected COVID-19 cases and up to 41% in critically ill patients or in those with concomitant CV comorbidities.[789]

14.8.1. Myocarditis and Myocardial Involvement

This is a rare but serious complication of SARS-CoV-2 infection as well as COVID-19 mRNA vaccination.[788]

Myocarditis is defined by the presence of all of the following:[788]

- Cardiac symptoms (e.g., chest pain, dyspnea, palpitations, syncope),
- Elevated cardiac troponin (cTn) ***and***
- Abnormal electrocardiographic, and /or echocardiographic, cardiac magnetic resonance imaging (CMR), in the absence of flow-limiting coronary artery disease.

There may also be myocardial involvement only without myocarditis and this is defined by: [788]

- An abnormal myocardium manifest by electrocardiographic, echocardiographic, CMR and /or histopathologic findings, with or without symptoms and with or without an elevated cTn.

Prevalence

The Center for Disease Control (CDC) reported the rate of myocarditis or pericarditis after SARS-CoV-2 infection ranged from 12.6 - 114 per 100,000 for males and 5.4 - 61.7 per 100,000 for females across different age groups.[790]

Myocarditis following COVID-19 mRNA vaccination is rare. The rate of myocarditis or pericarditis after mRNA COVID-19 vaccination was 0 - 35.9 per 100,000 for males and 0 - 10.9 per 100,000 for females across different age groups and vaccine cohorts.[790] The highest observed rates have been in young male individuals (aged 12-17 years) after the second vaccine dose.[791] Vaccination-linked myocarditis is milder than that associated with the virus itself.[791] Myocarditis following administration of the COVID-19 vaccine have a significantly lower rate of mortality compared with myocarditis associated with non-COVID-19 viral infection.[792]

Despite this, COVID-19 vaccination is associated with a very favorable benefit-to-risk ratio for all age and sex groups evaluated thus far.

Management[788]

- Hospitalization is recommended for patients with definite myocarditis, ideally at an advanced HF center.
- Patients with myocarditis and COVID-19 pneumonia (with an ongoing need for supplemental oxygen) should be treated with corticosteroids.
- For patients with suspected pericardial involvement, treatment with nonsteroidal anti- inflammatory drugs, colchicine, and/or prednisone is reasonable.
- Intravenous corticosteroids may be considered in those with suspected or confirmed COVID-19 myocarditis with hemodynamic compromise or multisystem inflammatory syndrome in adults.

- As appropriate, guideline-directed medical therapy for HF should be initiated and contin ued after hospital discharge.
- In general, vaccine-associated myocarditis should be diagnosed, categorized, and treated in a manner similar analogous to myocarditis following Covid-19 infection.

Long-term cardiovascular outcomes of COVID-19

- The risk and 1-year burden of cardiovascular disease in survivors of acute COVID-19 are substantial.[793]
- Individuals with COVID-19 are at increased risk of other CV diseases such as cerebrovas cular disorders, arrhythmias, ischemic and non-ischemic heart disease, pericarditis, myocarditis, HF, and thromboembolic disease.
- These risks and burdens were evident even among individuals who were not hospitalized during the acute phase of the infection.
- Patients with more severe initial illness were more likely to develop long-term CV complications and this increased in a graded fashion according to the care setting during the acute phase (non-hospitalized, hospitalized and admitted to intensive care).
- Care pathways of those surviving the acute episode of COVID-19 should include attention to CV health and disease.

Key Message # 21: HF and Covid 19 Infection and Vaccine

- In hospitalized patients with COVID-19, the prevalence of HF varied between 4% and 21% and about 8%-33% required critical care admissions.
- Patients with HF who develop COVID-19 had an overall mortality rate between 20% and 40%.
- Myocarditis is a rare but serious complication of SARS-CoV-2 infection as well as COVID-19 mRNA vaccination.
- The rate of myocarditis or pericarditis across different age groups:
  - After SARS-CoV-2 infection:
    - 12.6-114 per 100,000 for males and 5.4-61.7 per 100,000 for females.
  - After mRNA COVID-19:
    - 0-35.9 per 100,000 for males and 0-10.9 per 100,000 for females.

14.9. HEART FAILURE IN ADULT CONGENITAL HEART DISEASE (ACHD)

Majority of pediatric patients with congenital heart disease are now surviving into adulthood due to advances in medical and surgical treatment.[794,795] However many of these adults with congenital heart disease (ACHD) are at risk of long term sequalae with increased morbidity and morbidity.

14.9.1. Definition

Definition of HF in the ACHD in patients with biventricular circulation is like that of those with acquired heart disease.[796]

However, defining HF in patients with Fontan circulation, may be more complicated.[797]

14.9.2. Burden of disease

- Prevalence of HF in ACHD ranges from 3.3% (median follow up of 27.5 years)[798] to 6.4% at a mean age of 35 years.[799]
- HF is the most common cause of death in ACHD patients, accounting for 17- 42% of all deaths.[800-803]
- The median age of death from HF was 48.4 years (range 20.2- 91.2 years)[798] and varied based on the complexity of the underlying lesions and interventions.[799,800,804,805]
- Those patients with more complex CHD including systemic RV, single ventricle palliated with Fontan circulation, and unrepaired cyanotic CHD with Eisenmenger physiology comprise the majority of HF- related deaths.[799,803,806]
- Hospitalization related to ACHD associated HF has increased significantly over the recent years accounting for 11.8%-20% of all ACHD admissions.[806,807]
- ACHD patients with HF had longer length of stay, higher burden of arrhythmias and were more likely to die.[807] One-year mortality after HF admission was 24% and 3-year mortality was 35%.[808] Male gender, pacemaker implantation, admission duration, non-cardiac medication use, and high serum creatinine were identified as independent risk factors for 3-year mortality.[808]

14.9.3. Predisposing risk factors

- The risk factors for developing HF and related mortality in ACHD patients includes advancing age, worsening NYHA functional class, complexity of the underlying congenital heart defect(s), pulmonary hypertension/ Eisenmenger syndrome, endocarditis, atrial arrhythmias, ventricular dysfunction, end organ dysfunction and previous interventions e.g., Fontan surgery.[799,802,803]

14.9.4. Pathophysiology of HF in ACHD

- Unlike acquired heart disease, the underlying mechanism for HF is more heterogenous and complex.
- It is highly dependent on the underlying anatomy, presence of pulmonary arterial hypertension, timing and type of intervention, myocardial protection during surgery, presence of residual hemodynamic lesions and acquired comorbidities.
- The most common reasons for ACHD-HF include presence of native, new, or residual hemodynamic lesions, myocardial failure and arrhythmias.
- For the different causes of ACHD-HF based on the underlying pathophysiology, related congenital heart disease and etiology tailored management see Appendix XIII, pages 174-175. [186-187796,809,810]

14.9.5. Diagnosis of HF in ACHD

- Diagnosing HF is challenging as typical clinical findings may not be present and most patients do not report symptoms of decreased functional capacity due to chronic adaptation since childhood.[811]
- Interpreting the routine investigations also poses a challenge as many are abnormal even at baseline.
- Assessment of HF in these ACHD patients should include a comprehensive review of clinical history, underlying congenital heart defect, previous interventions, signs, symptoms, and relevant investigations.
- Due to the multifactorial etiology of HF in these patients, a patient-centered approach is crucial.

- Signs and symptoms of HF are non-specific. It can vary depending on whether it is due to biventricular failure, systemic or sub pulmonary ventricle failure.[812,813] See Section 6.
- Chronic lymphatic dysfunction in failing Fontan circulation causes plastic bronchitis and protein losing enteropathy (PLE) characterized by enteric protein loss.[814]
- Right sided HF is more prevalent in ACHD compared to other acquired heart disease.
- Patients with palliated or unrepaired cyanotic congenital heart disease, Eisenmenger syndrome or pulmonary to systemic shunts may have worsening cyanosis contributing to impaired functional capacity with or without HF. These patients are also at risk of thromboembolic events.[815]
- Arrhythmias may be the cause or the first manifestation of HF in these patients.
- Identifying the cause of HF is important as it may be reversible (e.g., new or residual hemodynamic lesions, acute arrhythmias, compounding medical conditions like iron deficiency anemia or thyrotoxicosis.)

14.9.6. Investigations

- Investigations are like that of acquired heart disease as outlined earlier in Section 6. In addition, the following investigations are important to assess both structural and hemodynamic anomalies: (Appendix XIV, page 176)
  - Transthoracic and transesophageal echocardiogram
  - Cardiac magnetic resonance (CMR)
  - Computer tomography scan
  - Cardiac catheterization for invasive hemodynamic assessment.
  - Rhythm monitoring and analysis.
- Patients with ACHD are usually well adapted to their functional limitations. Thus, objective assessment of their functional capacity and response to therapy is important. This can be done by exercise tests (Cardiopulmonary exercise test (CPET) or a six-minute walk test). The CPET predictive values of poor prognosis may, however, be different in ACHD compared to acquired heart disease especially in single ventricle physiology[816,817] and in patients with cyanotic heart disease.[818,819]

14.9.7. Management (Appendix XV: Flowchart of the management of ACHD-HF, page 177)

- The aim of treatment is to alleviate symptoms, improve quality of life and to improve survival. These patients are preferably managed by a multidisciplinary team that includes both the ACHD and HF cardiologist.
- The principles of managing HF in ACHD HF are:
  - First to access and address all reversible causes.
  - To initiate pharmacotherapy if HF control is still not optimal.
  - To consider cardiac resynchronization and more advanced therapies if these patients continue to have worsening HF despite optimal medical therapy.
- Potentially reversible causes in ACHD-HF are:
  - Native, new, or residual structural anomalies that are amenable to surgical or catheter interventions. These include:
    - Shunts (VSD/ASD/PDA)
    - Valvular lesions (free flow Pulmonary regurgitation post TOF repair/aortic regurgitation e.g., post arterial switch)
    - Outflow tract obstruction (conduit stenosis/ LV outflow tract obstruction).[820]
  - Arrhythmias- atrial[821] or ventricular tachyarrhythmias
  - Other medical problems such as-sepsis, thyrotoxicosis, anemia, uncontrolled hypertension.

- **Pharmacotherapy** [809,810,812]

In general, drug therapy for HF in ACHD lacks evidence unlike that in acquired HF. The medical treatment is based on the varying subgroups of ACHD-HF.

A) Impaired systolic function

- **Systemic left ventricle failure (LVEF<40%)**
  - The treatment is similar as acquired HF.
  - Patients with HF*r*EF may be treated with RAS blockers (ACE-I, ARB, ARNI), β-blockers, MRA and SGLT2-i. Loop diuretics are given for symptom relief.
- **Systolic failure of subpulmonic RV (RVEF<40%)**[822]
  - No medical treatment is indicated for asymptomatic patients.
  - There is limited evidence for the use of RAS blockers or β-blockers.
  - Diuretics are the mainstay treatment for symptomatic patients.
  - It is important to identify hemodynamically significant lesions and to address these.[820]
  - Patients with Right Heart Failure (RHF) due to Pulmonary Arterial Hypertension (PAH)/Eisenmenger would benefit from PAH targeted therapy.[823]
- **Systolic failure of systemic RV**[824,825]
  - There are no standard guidelines for medical therapy for asymptomatic patients.
  - In symptomatic patients, standard heart failure medications may be given but evidence for their use in this setting is lacking.
  - An increase in biomarkers and worsening VO2 max may be useful parameters to consider for initiating medical therapy.
- **Systolic failure of single ventricle**[826-828]
  - There are no guidelines for the use of standard drugs in asymptomatic patients.
  - Loop diuretics may be used judiciously in symptomatic patients.
  - PAH targeted therapy (Phosphodiesterase-5 Inhibitors and Endothelin receptor antagonists) may improve pulmonary blood flow and improve cardiac output.[819]

B) Arrhythmias[829]

- Diagnostic and interventional catheter and device-based electrophysiologic procedures in adults with moderate or complex CHD or complex arrhythmias should be performed in a regional ACHD center by a cardiac electrophysiologist with expertize in CHD, and in a laboratory with appropriate personnel and equipment.[821,830]

I,C
- These should be managed promptly and aggressively with appropriate antiarrhythmic drug therapy, catheter, or surgical ablation.

- Permanent pacing is recommended in:[829-831]

I,B
  - Advanced second- or third-degree AV block associated with symptomatic bradycardia, ventricular dysfunction, or low cardiac output.

I,B
  - Post operative advanced second- or third-degree AV block that persists more than 7days after cardiac surgery.

I,B
  - Congenital 3rd degree AV block.[831]

- Cardiac implantable cardioverter defibrillator (ICD) may be considered for the secondary prevention of sudden death in:

I,B
  - High risk ACHD patients resuscitated from cardiac arrest due to VT/VF *and*

IIa,C
  - In those with spontaneous sustained ventricular tachycardia with no clear reversible cause.[832]

- CRT may be helpful in managing HF in patients with subpulmonary and systemic RV.[833,834]

C) Cyanosis[815]

- Iron deficiency anemia is common in those with cyanotic heart disease and may be missed due to secondary erythrocytosis.
- Routine phlebotomy based on a predetermined hematocrit should be avoided.
- These patients are also at risk of thromboembolic events and bleeding. Anticoagulants should be given with caution.

D) Advanced therapies for ACHD- HF[835,836]

- The use of mechanical circulatory support (MCS), total artificial heart, and heart transplantation in ACHD patients are challenging due to:
  - Complex anatomy with abnormal pulmonary arteries, anomalous pulmonary or systemic venous drainage, aortopulmonary collaterals.
  - Prior surgical intervention/repeated sternotomies.
  - Allosensitization due to blood transfusion, use of homografts.
  - Pulmonary hypertension - thus a heart-lung transplant may be required.
  - End organ involvement e.g. Fontan associated liver disease (may need heart-liver transplant).

E) General measures

- Infective endocarditis[837]
  - Optimal oral hygiene is recommended to prevent infective endocarditis which has been identified as a predisposing risk for ACHD-HF.[837]
  - Antibiotic prophylaxis should be considered in selected high-risk patients to prevent endocarditis during invasive dental procedures.
- Pregnancy (refer to section 14.7).
  - It is important that in all women in the childbearing age with ACHD, preconception counselling should be initiated early, and all pregnancies should be pre-planned.
  - Exercise rehabilitation[838] (refer to section 16)
  - Even though the evidence is less extensive in ACHD-HF, individualized exercise programs have been shown to be beneficial.[839]
  - Cardiopulmonary exercise testing is a useful tool performed both at baseline and post exercise training.

F) Palliative care and advance care planning (refer to section 15.3)[840]

- Advanced care planning is preferably done in an ACHD center with support from a multidisciplinary team involving both the ACHD cardiologist and palliative care specialist.
- It should be patient-tailored and age appropriate due to the heterogenous nature and chronicity of ACHD and counselling should be given based on the projected course of the respective disease and prognosis.[841]

Key Message # 22: HF and ACHD

- HF is the most common cause of death in ACHD patients, accounting for 17- 42% of all deaths.
- Patients with isolated simple defects generally do well with mortality rates like those in the general population.
- Patients with complex heart defects such as systemic RV, single ventricle palliated with Fontan circulation, and unrepaired cyanotic CHD with Eisenmenger physiology comprise the majority of HF-related deaths.

Key Recommendations #17: HF and ACHD

- The principals of managing HF in ACHD HF are: (see Appendix XV, page 177)
  - First to access and address all reversible causes.
  - To initiate pharmacotherapy if HF control is still not optimal.
  - To consider cardiac resynchronization and more advanced therapies if these patients continue to have worsening HF despite optimal medical therapy.

15. ADVANCED HEART FAILURE

15.1. Heart Transplant

I,A Heart transplantation is well-established for refractory end stage HF. It is the gold standard for the treatment of advanced HF in the absence of contraindications. World-wide the 1-year survival rate is 91% and the median survival post-transplant is 12 to 13 years.[842]

This definitive therapy for HF is however limited by the lack of donor organs.[843] To address this, worldwide, efforts are being made to increase this organ donor shortage by increasing the donor age limit criteria, improving donor recovery strategies and being more stringent in the selection criteria.[155,843]

All patients with severe symptomatic HF despite OMT and no other alternative therapeutic options should be considered for heart transplant. They need to be referred to a HF specialist hospital for further evaluation.

Assessment for heart transplant is done by a multispecialty, multidisciplinary team and appropriate work up will be performed for eligibility.

Eligibility criteria to be considered for heart transplant include:

- Poor LVEF (< 25%).
- Recurrent HF hospitalizations.
- Major limitation of the patient's daily activities.
- Poor effort tolerance i.e. peak VO2 (maximal oxygen consumption or peak oxygen uptake) < 10ml/kg/min (or < 50% predicted). VO2 max is the maximum rate of oxygen consumption measured during incremental exercise i.e. exercise of increasing intensity. This is widely used as an indicator of cardiorespiratory fitness.
- Intravenous inotropic dependence for symptomatic relief or to maintain end organ function.
- Motivated, psychologically stable, and compliant with therapy.

Contraindications to heart transplant:

- Active infection.
- Severe peripheral arterial or cerebrovascular disease.
- Malignancy within 5 years.
- Diabetes mellitus with widespread microvascular complications.
- Systemic disease with multi-organ dysfunction.
- Irreversible chronic kidney, liver, or lung disease.
- Pharmacologically irreversible pulmonary hypertension.
- Other medical or psychosocial issues that would impact survival.

15.2. Mechanical Circulatory Support (MCS)-see Section 9.2.2.

The use of a mechanical circulatory support (e.g., Left Ventricular Assist Device -LVAD) may be considered as a:[844-848]

- Bridge to recovery in patients with potentially reversible or treatable conditions ***or***
- Bridge to heart transplant in suitable candidates ***or***
- Destination therapy in candidates who are not suitable for transplant.

Patients have improvement in their symptoms when compared to OMT.[844,845]

However, the rate of rehospitalizations due to complications of bleeding, thrombosis and infections are high.[844-846,848] Many patients also go into major depression. Thus, extensive discussion with the patient and family is necessary prior to LVAD implantation.

15.3. Palliative and End of Life Care

Despite recent advances in therapy, for some patients, HF remains a progressive disease and carries a poor prognosis. Patients with refractory symptoms despite guideline-directed medical therapy, should be considered for cardiac transplantation or LVAD implantation if deemed eligible. This includes:

- Those with < 50% survival at 1 year (using established scoring tools)
- Persistently elevated natriuretic peptide levels and/or
- A low V02 max measurement (if available) and
- other eligibility criteria as stated in section 15.1.

In patients who are unable to receive advanced therapy, palliative care consultation should be considered.[219,849] The aim of palliative care in HF is to prevent and relieve suffering and to promote the best quality of life for patients and their families.[850]

Although majority of guidelines do not specifically address when best to refer end-stage HF patients for palliative care consideration, due to the often-unpredictable trajectory in decline over time, palliative care is particularly important in a subgroup of patients. A recent international consensus referral criterion for specialist palliative care for patients with advanced HF includes 6 major categories:[851]

- Patients suffering from advanced HF alongside complications including cardiac cachexia or multiorgan failure, having concurrent non-cardiac life-threatening diseases, or being intolerant to guideline-directed therapies.
- Patients likely eligible for advanced therapies but not receiving them due to various factors.
- Patients with repeated hospitalizations or emergency department visits within the past 3 months.
- Patients with poor prognostic estimate, with estimated life expectancy of 6 months or less.
- Patients suffering from refractory symptoms requiring palliative sedation, severe emotional or physical symptoms, and severe spiritual or existential distress.
- Patients, their families, or care teams requesting palliative care, including assistance in discussing goals of care and other planning surrounding withdrawal or de-escalation of life-prolonging interventions.

End-of-life issues surrounding advanced HF remains complex to this day, with minimal evidence in the literature to guide management.[852] Nonetheless, there exists several

position papers and expert consensus documents highlighting key components in providing palliative care for HF patients, including the following:[853,854]

- **Advanced care planning**
  - Clearly define goals of care and preference for future and pre-existing treatment, especially those which are life-sustaining. (e.g., intubation and mechanical ventilation, ICD implantation, etc)
  - Address disease-specific aspects of care with clear limits to escalation.
  - Record and clearly document these plans in the medical records.
  - When requested and possible, clearly nominate a personal representative for medical decision-making.
  - When available, clearly indicate where palliative care is to be provided (home versus healthcare facility).[855]
- **Medical management**
  - Medical management with clear goals of care, prioritizing symptom control over disease control, and maximizing quality of life.
  - Common symptoms and signs to be addressed include dyspnea, fatigue, pain, irregular bowel habits including constipation, urinary retention, or incontinence, and most importantly depression and anxiety.
  - Validity of previous medications used in disease control should be continuously re-evaluated for benefit and harm, with appropriate adjustment.
  - Religious and spiritual needs, values and existential quest need to be continually addressed during each consultation or visit.
  - Professional help offered by specialists in spiritual care should be engaged when requested for.
  - Care for the dying.
  - Understanding that dying is a medical diagnosis that should neither be neglected nor postponed.
  - Understanding that dying is a complex and dynamic process.
  - Counselling, support, and reassurance should be provided to patients and their families.
  - The aim should be to provide the highest level of comfort to the patient and their families, and therapy that contradict this should be discontinued (e.g., ICD deactivation)
- **Managing ethical dilemma**
  - An ethical dilemma arises when at least two of the four ethical principles conflict with one another.
  - Patient autonomy remains central in the decision making for palliative care, although the 3 other ethical principles remain paramount (beneficence, non-maleficence, and justice).
  - In the event of an ethical dilemma, ethical consultation through palliative care services or a professional ethics committee should be sought.

Key Messages #23: Advanced HF

- All patients with severe symptomatic HF despite OMT and no other alternative therapeutic options should be considered for heart transplant.
- If they are not eligible or a donor heart is not available, they may be considered for LVAD as a destination therapy or a bridge to heart transplant.
- Patients who are unable to receive either should be considered for palliative care.

Key Recommendations #18: Advanced HF

- Heart transplantation is well-established for refractory end stage HF.
- Patients with severe symptomatic HF despite OMT and no other alternative therapeutic options should be considered for palliative care.

16. HEART FAILURE REHABILITATION

Fatigue and breathlessness lead to individuals restricting their physical activities. This in turn leads to deconditioning - a phenomenon of reduced capacity to perform physical, mental, and cognitive tasks. This adds to the humanistic burden of HF, increasing morbidity and recurrent hospitalizations.

- Exercise training in HF addresses 3 main impairments:
  - Exercise intolerance due to muscle wasting leading to a loss of strength and endurance.[856]
  - Cardiopulmonary and musculoskeletal deconditioning.[857]
  - Exertional dyspnea that occurs from:[857]
    - Increased respiratory muscle work because of excessive ventilation to compensate for increased muscle lactate release.
    - Increased lung dead space.
    - Decreased lung compliance caused by chronic pulmonary congestion and fibrosis.
- Exercise training in HF is safe and effective.[858] Long-term exercise training leads to improvement in quality of life, functional capacity and survival rates.[155,164,165,859-865]

16.1 Cardiac rehabilitation (CR) in HF

- HF is now endorsed as an indication for CR.[866] CR spans throughout the continuum of HF care.[862]
- A formal cardiac rehabilitation program usually includes:
  - A medical and functional evaluation.
  - Education of the patient and family on the importance of:
    - Medical adherence
    - Lifestyle changes
    - Fluid management
    - Dietary recommendations ***and***
    - Addressing psychosocial concerns
  - Exercise prescription, training, counselling on physical and daily activities.
  - Functional training and work hardening.
  - Stress management and adaptation.

IIa,B

- CR should be recommended to all stable HF patients, in NYHA II-III. This includes patients with no recent (≤ 6 weeks) or planned (≤ 6 months) major CV hospitalizations or procedures.[858]
- There is insufficient data at present to recommend outpatient CR for patients in NYHA IV.
- CR involves:
  - An **inpatient phase** which aims towards safe home discharge. Compared to routine care, early CR significantly improves the effect of physical capacity, physiological outcomes, and clinical outcomes in acute HF patients.[867]

- An **outpatient phase** to improve functional gains. Three exercise training modalities in HF include:[862]
  - Endurance aerobic training.
  - Resistance strengthening - this addresses skeletal muscle alterations and sarcopenia.
  - Respiratory muscle training.
- A **maintenance phase** that aims at improving long term survival by focusing on identifying and treating CV risk factors and optimizing HF treatment.[868]

- Hydrotherapy or aquatic exercise training can improve exercise capacity, muscle strength and quality of life like land-based training programs. It is a safe and effective alternative for those unable to participate in traditional exercise programs.[869]
- Active participation in any kind of exercise training program is sufficient to improve the prognosis, quality of life and functional capacity.[870] Active participation is a more important factor in achieving improvement than how the exercise is performed.[871]
- The details of the Cardiac Rehabilitation program in HF can be obtained from several resources.[868,872]

16.2. Settings for CR in HF

- A community-based CR program provides patients with a structured exercise training intervention alongside educational support and psychological counselling.[873]
- Settings for CR in HF include:[874]
  - Traditional center-based CR programs are safe and effective but are resource intensive and of limited availability. It is recommended during the initial sessions following discharge particularly in patients with severe HF symptoms.
  - Home-based programs are available for stable and well-treated patients. It is a cost-effective treatment option even in HF*r*EF.[165]
  - Emerging CR models include:
    - Hybrid CR that combines short-term center-based CR with home-based CR.[875]
    - Mobile phone based CR[876]
    - Telerehabilitation services.[877] There is still inadequate evidence at present on the impact of this modality on hospitalization and CV death reduction.[878]

16.3. Heart failure CR in special populations

These include:

- Individuals with implantable devices
  - CR in HF patients with ICD and CRT is safe and beneficial.[862,879-881]
  - Activities such as hydrotherapy or pronounced arm - shoulder movements should be avoided as this may lead to an ICD discharge and loss of consciousness.
- Elderly patients with HF
  - Frailty is common among the elderly and is associated with increased morbidity and mortality. It is partially reversible and potentially preventable in HF with early rehabilitation referral.[882]
  - Rehabilitation non-enrolment results in worsening frailty status.[883]
  - Cognitive impairment and HF frequently coexist - either as acute delirium with decompensated HF during hospital admission or dementia.
  - Patients with a high frailty score and cognitive impairment will benefit from closer contact with the HF specialist team, more frequent follow-up and monitoring and individualized self-care support.

16.4 Barriers to HF rehabilitation

- Despite benefits, cost-effectiveness, and strong practice guideline recommendations, CR remains underused.[172]
- Barriers include[884]
  - Physician Factors:
    - Fewer referrals from cardiologists.
    - Fewer well trained CR staff.
    - Overworked doctors.
  - Patient Factors:
    - Lack of motivation
  - Reluctance to change in lifestyle.
    - Transport difficulties.
    - Lack of family support.
    - Time constraints.
  - Service Factors:
    - Lack of insurance coverage.
    - Accessibility of programs.

Key Messages # 24: HF Rehabilitation

- Fatigue and breathlessness lead to individuals restricting their physical activities and this in turn, leads to deconditioning.
- Exercise training in patients with HF is safe and leads to an improvement in functional capacity, exercise duration, and health related quality of life.
- HF is now endorsed as an indication for Cardiac Rehabilitation, and it spans through out the continuum of HF care.

Key Recommendations #19: HF Rehabilitation

- Cardiac Rehabilitation should be recommended to all stable HF patients, in NYHA II-III.

17 ORGANISATION OF CARE

17.1 LEVEL OF CARE AND SHARED MANAGEMENT

The care of patients with HF should ideally take place in a multidisciplinary system, allowing for shared care between the hospital (secondary or tertiary settings) and community (primary setting). A multidisciplinary approach encompasses patient education, cardiac rehabilitation, psychosocial support and palliative care, and has been proven to reduce HF hospitalizations and mortality in discharged patients.[884-886]

The multidisciplinary team usually consists of cardiologists and/or general physicians, HF nurses, pharmacists, dieticians, physiotherapists, primary care providers, social workers as well as geriatricians, psychologists, cardiac rehabilitation physicians, occupational therapists and when necessary, palliative care specialists.

Care can be done in two different settings:

- In the patient's own home - home-based interventions are associated with significantly lower healthcare costs, reduced hospital readmissions and an improvement in the patient's quality of life.[855] This may now be possible with telemedicine.
- Specialist outpatient clinic - the HF clinic.

HF clinics can either be:

- Nurse-directed - these are run by nurses with special training in HF.
- Physician-directed - run by general physicians and/or cardiologists.

HF clinics can be established in the tertiary hospitals or in the primary care setting. The minimum human resource requirements are:

- A cardiologist or general physician with an interest in cardiology and heart failure,
- A dedicated nurse and
- A medical technologist for blood taking, doing echocardiography and 6 minute-walk tests.

In bigger clinic settings, the involvement of a cardiac rehabilitation team and physiotherapists to encourage physical activities, pharmacists and counsellors for end-of-life care would be advisable. The needs of these patients vary, and these may need to be addressed by a multidisciplinary team.

These clinics will be the intermediary between in-patient hospital care and community primary care. Patients who can be seen in these clinics include those:[887]

- Recently discharged after an admission for decompensated HF (a waiting time of 7-12 days post discharge has to be the maximum wait-time).
- Who are in the early decompensation phase and need treatment modification.
- Who are stable but need up titration of HF medications.
- With ICD or CRTs.
- With comorbidities, such as renal dysfunction, diabetes and COPD.
- With advanced HF who may benefit from:
  - Heart transplant.
  - Left Ventricular Assist Device (LVAD).
  - Palliative care.

The objectives of these HF clinics may vary based on local settings. They include:[887,888]

- Optimization of Foundational HF medications particularly the up titration of β-blockers, ACE-I and MRA.
- Initiating referral for Cardiac Rehabilitation
- Education of the patient and caregiver on the nature of the disease and its progression.
- Promotion of self-care such as :
  - Compliance to medical therapy and fluid restriction.
  - Regular weighing and adjusting diuretic doses according to symptoms and body weight.

Patient with optimized HF medications/treatment plans can be discharged to the community with appropriate care plans to primary care. Close partnership between these HF clinics and primary care helps to reduce unnecessary admissions to hospital.

Moving forward, it may be timely, to suggest establishing community medical care centers for chronic illnesses such as diabetes, HF, CKD etc. This could serve as a resource and

rehabilitation center for individuals with chronic illnesses. It could be run by both volunteers - doctors, nurses, physiotherapists, rehabilitation physicians - with funding from government and Non Government Organizations and offering tax incentives to all those participating in the program.

In 2018, the Heart Failure Medication Therapy Adherence Clinic (MTAC) was introduced. These clinics are conducted by pharmacists in collaboration with doctors and other healthcare providers to improve heart failure management. The objectives of the Heart Failure MTAC are:[889]

- Enhance patient's adherence to HF pharmacotherapy and non-pharmacological interventions.
- To reduce unscheduled emergency department visits or hospitalizations of HF patient due to acute decompensation.
- To provide consultative service to doctors on evidence-based HF pharmacotherapy and related issues.
- To collaborate with doctors and other health care professionals in HF management program.

17.2. MONITORING AND FOLLOW-UP

Patients with HF require regular follow-up and monitoring. Serial evaluations serve to assess a patient's status, response to therapy, development of complications and disease progression.

17.2.1. Assessment during Follow Up Visits

Key components of assessment include:

- **History:**
  - Functional capacity - NYHA functional class or 6-minute walk test
  - Cognitive status and nutritional status
  - Diet and sodium intake
  - Consumption of alcohol or illicit drugs
  - Smoking history
- **Physical examination:**
  - Fluid status and body weight
  - Blood pressure, heart rate and rhythm
  - Examination of the cardiovascular and respiratory systems
- **Investigations:**
  - Blood tests - serum urea, electrolytes, creatinine and eGFR as necessary.
  - Serial brain natriuretic peptide measurements to guide and tailor HF therapy cannot be recommended at the present time due to a lack of consistent evidence.[77,81,891,892]
  - Echocardiogram:
  - Routine serial echocardiogram is not recommended. However, if there has been a recent change in clinical status (e.g., episode of acute coronary sydrome) or if the patient has received treatment (e.g., revascularization or device therapy) that might significantly change certain echocardiographic parameters, a follow-up echocardiogram is reasonable to re-assess the LVEF, degree of valvular function and structural remodeling.
- **Others:**
  - Review of pharmacotherapy - compliance, side effects and titration of dosages as necessary.
  - Control of disease specific management - hypothyroidism, hyperthyrodism, acromegaly, connective tissue disease, HIV, sarcoidosis, amyloidosis, hemochromatosis.
  - Review use of potentially detrimental medication to HF control - e.g., NSAIDs.

- Education:
  - Another key component during follow up is education regarding the name, dose and function of each medication the patient is on. This is not only important in terms of enhancing compliance, but this is also to avoid polypharmacy from a different facility the patient may also be seeing.

17.2.2. Frequency of follow-up

This will depend on:

- The patient's clinical stability ***and***
- Need for pharmacotherapy optimization.

A patient with a recent episode of decompensation or clinical instability, for instance, should ideally be seen again soon, usually within 2 weeks. Ultimately, the intensity and type of follow-up would be determined by the local organization of care and resources.

17.3. CARDIOLOGY REFERRALS

HF patients with stable symptoms may be managed at the primary care level.

Referral to the cardiologist should be considered in the following situations:

- De novo HF for a comprehensive workup to confirm the diagnosis and determine the etiology, and to devise a management plan.
- Episodes of acute decompensation
- Worsening HF symptoms despite appropriate therapy
- HF that is complicated with symptomatic hypotension or excessive bradycardia, limiting up titration of pharmacotherapy.
- Symptomatic stable CAD and/or acute coronary syndrome for consideration of revascularization (PCI or CABG)
- Resuscitated cardiac arrest.
- Documented or suspected significant arrhythmias e.g., AF, VT
- ECG demonstrating a LBBB morphology with a QRS duration of > 150ms for consideration of device therapy.
- Significant valvular disease not previously assessed or worsening valvular dysfunction.
- Preconception assessment and counselling of women with significant structural heart disease and a history of HF or LV dysfunction.
- Complex congenital cardiac lesions and/or Eisenmenger's syndrome.

17.4. TELEMEDICINE/TELEHEALTH

Telemedicine services may improve healthcare accessibility and geographical limitations. In the unforeseen circumstances of a future pandemic, telemedicine may provide uninterrupted patient consultation when community lockdowns or social distancing is required.[893]

Early escalation of HF care with a multidisciplinary team is possible without the need for face-to-face consultation.

17.4.1. Telemedicine Strategies

Requirements

- Home Monitoring Equipment -The following are required:
  - Computer, tablet, or smart phone
  - BP machines
  - Weighing scales
  - Optional:
    - ECG recording device on smart phone.
    - Mobile monitor (e.g., Cardio Mobile)

Patients, and/or their younger family members can record and transmit the information to the physician.

Virtual visits

- This will help maintain the doctor-patient relationship.
- These virtual visits can be performed via audio-visual telecommunication system or through an online portal to review the following:
  - Assessment of symptoms.
  - Review information from the Home Monitoring devices.
  - Where available, laboratory results from a laboratory close to the patient's home.
  - Optimization of Foundational HF Medications.

Telerehabilitation

Telemedicine can allow:

- Initiation of dietary and physical cardiac rehabilitation.
- Identification of cardiac decompensation and advise hospitalization, when necessary.

Key Messages # 25: Level of Care, Shared Care, Monitoring and Follow - Up & Telemedicine/Telehealth

- The care of patients with HF should ideally take place in a multidisciplinary system, allowing for shared care between the hospital (secondary or tertiary settings) and community (primary setting).
- Heart Failure clinics will serve as an intermediary between in-patient hospital care and community primary care.
- HF clinics can either be:
  - Nurse-directed - these are run by nurses with special training in HF.
  - Physician-directed
- At these clinics, patients with HF undergo close follow-up and monitoring to evaluate their status, response to therapy, development of complications and disease progression.
- When stable with optimized HF medications/treatment plans, patients can be discharged to the community with appropriate care plans to primary care.
- Where necessary, (decompensation, development of significant arrhythmias) they can be referred to the cardiologists/specialists.
- Telemedicine services may improve healthcare accessibility and geographical limitations. It can complement existing HF clinic services and provide venues for early escalation of HF therapy before decompensation.

18. OTHER THERAPIES FOR HEART FAILURE

Despite taking conventional HF therapy, patients may seek alternative therapy and healing approaches that are not considered as allopathic medicine. The National Center for Complementary and Alternative Medicine (NCCAM) defines complementary and alternative medicine (CAM) as a group of diverse medical and healthcare interventions, practices, products, or disciplines that are not generally considered part of conventional medicine.

18.1. Enhanced External Counter Pulsation (EECP)

There is inadequate evidence of clinical effectiveness of EECP in HF.[894-898] Data seem to indicate that there is improved functional status, walk distance, and symptoms and NYHA Functional class.[896-897] There is however, concern that it could precipitate or exacerbate symptoms in those with a history of HF.[898]

18.2. Stem cell therapy

Stem cells, which are derived from bone marrow or umbilical cord blood, have been infused into the coronary arteries or injected directly into the myocardium. The original hypothesis was that stem cells would engraft in the myocardium and replace damaged cardiomyocytes. Subsequent research has suggested that stem cells probably do not differentiate into functional cardiomyocytes, but as an alternative hypothesis, it was hoped that they might have paracrine effects that would benefit myocardial function.

There is still limited knowledge on the optimal cell type, dosing, route of administration, patient parameters, patient safety, and other important variables that contribute to successful stem cell therapy. There is, however, still a lot of research left to do into the effectiveness and safety of these interventions.[899-901]

18.3. Omega 3 fatty acids

This may be considered as an adjunctive therapy to standard HF therapy, based on observations and clinical trials which showed a small benefit in CV death and/or hospitalizations especially among diabetics.[902-907]

18.4. Coenzyme Q10

There is some evidence that coenzyme Q10 probably reduces all-cause mortality and hospitalization for HF. However there still needs to be further research to determine the role of Coenzyme Q10 in patients with HF, the optimal dose, and the duration of Coenzyme Q10 supplementation.[908-910]

18.5. Tai Chi

Tai Chi may improve 6 minute walk test distance, quality of life and LVEF in patients with HF.[911-914] Its effect on hard CV outcomes such as rehospitalization, MI and mortality is not known.

18.6. Yoga

Yoga improves peak VO2 (exercise capacity) and quality of life in chronic HF patients.[915] In addition, it has been reported to reduce cardiovascular events, morbidity, and mortality although the evidence supporting these conclusions is somewhat limited.[916]

19. PERFORMANCE MEASURES

Performance measures should be used with the goal of improving quality of care for HF and conversion of scientific evidence into clinical practice.[155,917] It has been shown that higher hospital performance measures were inversely associated with HF readmissions.[918,919]

Process performance measures focus on the aspects of care that are delivered to a patient, while outcome measures focus on the endpoints such as mortality or hospitalization.

Process performance indicators for in-patients with HF includes:[155,917-919]

- % of patients who had documentation of NYHA Functional Class.
- % of patients who had LVEF measurement.
- % of patients with current or prior LVEF < 40% and without contraindications discharged with ACE-I/ARB/ARNI.
- % of patients with current or prior LVEF < 40% and without contraindications discharged on β-blockers.
- % of patients with current or prior LVEF < 40% and without contraindications discharged on MRA.
- % of patients with chronic or paroxysmal AF/Atrial Flutter without contraindications on anticoagulant therapy at discharge.
- % of patients given a post discharge appointment within 14 days.
- % of patients who had up titration of their Foundational HF medications to target or maximally tolerated doses at 3 months.

The accepted performance measure is 60%.

Outcome Measures indicators include:

- In-hospital mortality
- 30-day readmission for heart failure

Refer to Appendix XVI, page 178 for calculation of these measures.

Key Recommendations #20: Performance Measures

- Performance measures are used with the goal of improving quality of care for HF.
- This includes:
  - Process performance which measures the aspects of care that are delivered to a patient and
  - Outcome measures which focus on hard endpoints such as mortality or hospitalization.
- For the Quality indicators in HF, see section 19 & Appendix XVI, page 178.

Appendix I: Causes of Elevated Natriuretic Peptide Levels*

Cardiac
• Heart Failure, including RV syndromes • Acute coronary syndromes • Heart muscle disease, including Left Ventricular Hypertrophy • Valvular heart disease • Pericardial disease • Atrial fibrillation • Myocarditis • Infective Endocarditis • Cardiac surgery • Cardioversion • Toxic-metabolic myocardial insults, including cancer chemotherapy
Non-cardiac
• Advancing age (Table 12, page 60 for optimal cut off values according to age) • Anemia • Renal failure: ➢ NTProBNP loses its prognostic value in patients with GFR < 30ml/min/1.73 m^2. ➢ BNP levels are relatively independent of GFR. • Right ventricular overload from: ➢ Pulmonary causes: obstructive sleep apnea, severe pneumonia ➢ Pulmonary hypertension whatever the cause • Shock • Critical illness • Bacterial sepsis • Severe burns • Liver cirrhosis • Intracranial pathologies • Thyrotoxicosis

**Adapted from*

- *Yancy WC, Jessup M, Bozkut B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017;136:e137-61.*
- *Goei D, Schouten O, Boersma E, et al. Influence of renal function on the usefulness of N-terminal pro-B-type natriuretic peptide as a prognostic cardiac risk marker in patients undergoing noncardiac vascular surgery. Am J Cardiol 2008;101:122-6.*
- *Tagore R, Ling LH, Yang H, Daw HY, Chan YH, Sethi SK. Natriuretic peptides in chronic kidney disease. Clin J Am Soc Nephrol 2008;3:1644-51.*
- *Tsai SH, Lin YY, Chu SJ, Hsu CW, Cheng SM. Interpretation, and use of natriuretic peptides in non-congestive heart failure settings. Yonsei Med J. 2010:51(2):151-63*

Appendix II: Salt Content of Common Malaysian Foods
Daily Reference Intake (DRI) for salt: 5 g per day (1 teaspoon)

SALT CONTENT IN FOOD					
LOW (< 5% of DRI)		**MODERATE (5% - 20% of DRI)**		**HIGH (> 20% of DRI)**	
Tosai without Gravy (1 piece)	0.5g	Preserved Bean Curd (16g)	0.8g (16% of DRI)	Fried Chicken (3 pieces), Coleslaw, Mashed potato, Soft Drink	10.4g (208% of DRI)
Cereal (Cornflakes) (1 cup, 30g)	0.4g	Luncheon Meat (1 piece)	0.9g (18% of DRI)	Curry Mee (1 large bowl)	8.2g (164% of DRI)
Fresh Fruit (1 medium)	<0.15 (3% of DRI)	Beef Burger Patty (1 piece,74g)	0.8g (16% of DRI)	Wonton Noodle Soup (1 large bowl)	4.5g (90% of DRI)
Fresh Vegetables (1 cup, cooked)	<0.3g (5% of DRI)	Nuggets (2 pieces,40g)	0.7g (14% of DRI)	Bihun Soup (1 large bowl)	4.0g (80% of DRI)
Tuna In Water, no salt (1 can)	0.2g (4% of DRI)	Chili Sauce (1 tbsp,15g)	0.56g (11% of DRI)	Char Kway Teow (1 plate)	3.6g (72% of DRI)
Low Fat Milk (1 packet)	0.2g (4% of DRI)			Fried Hokkien Noodles with prawn (1 plate)	3.6g (72% of DRI)
Putu Mayam (1 piece,50g)	0.15g (3% of DRI)			Pizza with Tomato Sauce, Chicken, and Mushroom	2.75g (55% of DRI)
Baked Potato (1 whole)	<0.15g (<3% of DRI)			Chicken Burger + Fries and Soft Drink (1 regular set)	2.6g (52% of DRI)
Fresh Fish (1 whole)	<0.13g (2.6% of DRI)			Budu (1 tbsp)	2.2g (44% of DRI)
Oat Crackers (3 pieces)	0.11g (2.2% of DRI)			Salted Egg (1/2 piece)	2.0g (40% of DRI)
Low Salt Biscuit (3 pieces)	0.09g (2% of DRI)			Beef Noodles (789g)	9.9g (198% of DRI)
Chicken Breast Part (1 piece, 38g)	0.06g (1% of DRI)			Hot Dog Set	3.9g (78% of DRI)
Margerine Reduced Salt (1 tsp)	0.05g (1% of DRI)			Nasi Lemak (210g)	2.1g (42% of DRI)
Unsalted Nuts (1 cup)	0.04g (0.9% of DRI)			Yong Tau Fu (324g)	4.3g (86% of DRI)
Chapatti with Gravy (1 pc)	0.04g (0.8% of DRI)			Instant Noodles (85g)	3.8g (76% of DRI)
White Rice (1 scoop)	0.04g (0.8% of DRI)			Chinese Sausage (1 piece, 68g)	2.6g (52% of DRI)
Soy Milk (1 glass, 250ml)	0.01g (0.2% of DRI)			Instant Porridge (1 cup, 35g)	2.4g (48% of DRI)
Tau Kua (1 pc)	0.005g (0.1% of DRI)			Instant Soup (1 packet ,63g)	2.0g (40% of DRI)
Oat (6 tbsp, 35g)	0.001g (0.06% of DRI)			Cube/Stock Powder (110% of DRI)	5.52g (1 cube,12g)

Appendix II: Salt Content of Common Malaysian Foods,cont'd
Daily Reference Intake (DRI) for salt: 5g per day (1 teaspoon)

SALT CONTENT IN FOOD					
LOW (< 5% of DRI)		MODERATE (5% - 20% of DRI)		HIGH (> 20% of DRI)	
				Light Soya Sauce (1 tbsp,15g)	3.14g (63 % of DRI)
				Fish Sauce (1 tbsp,15g)	2.58g (52% of DRI)
				Salted Fish (1 piece, 25g)	1.1g (22% of DRI)
				Dried Anchovies (¼ cup)	1.2g (24% of DRI)
				Cheddar Cheese (2 slices)	1.2g (24% of DRI)
				Oyster Sauce (1 tbsp)	1.6g (32% of DRI)
				Spaghetti Sauce (½ cup)	1.3g (26% of DRI)
				Baked Beans (¾ cups)	1.3g (26% of DRI)
				Belacan (1 tbsp)	1.7g (34% of DRI)
				Asam Jawa (1 tbsp)	1.5g (30% of DRI)
				Taucu (1 tbsp)	1.4g (28% od DRI)
				Dried Prawn (1 tbsp)	1.2g (24% of DRI)
				Cheese Sausage (2 pieces,70g)	1.4g (28% of DRI)
				Meatballs (5 pieces)	1.4g (28% of DRI)
				Keropok Lekur (4 pieces,120g)	1.0g (20% of DRI)
				Salted Nuts (1 cup, 155g)	1.6g (32% of DRI)
				Canned Chicken Curry (150g)	1.4g (28% of DRI)
				Pickled Lettuce (9 pieces,30g)	1.3g (26% of DRI)
				Mono Sodium Glutamate (1 tsp,5g)	1.54g (31% of DRI)
				Dark Soya Sauce (1 tbsp,15g)	1.41g (28% of DRI)

Source: Malaysian Food Composition Database

Appendix III: Discharge Care Plan

The following discharge care plans should be discussed and agreed upon by the patient and treating physician.

NO	PARAMETER	TICK
1	Discussion on: ● The precipitating factor(s) leading to this current exacerbation, ● How to avoid such circumstances and ● Other precipitating factors for decompensation.	
2	To re-enforce education regarding: ● The current status of the patient and the disease trajectory	
3	To establish the role of: ● Fluid management and ● Daily weight measurement at the same time each day (if possible). If weight measurement is not able to be done daily, at least 2-3 times a week is encouraged. A sudden weight gain of more than 2kg in 3 days is a sign of worsening HF. Patients should be educated to increase their diuretic (furosemide) dose together with restriction of their fluid intake until their "dry weight" is regained. However, if the weight increase is associated with worsening symptoms or fails to respond to these measures, the patient should seek medical help immediately.	
4	To ensure compliance with medication by explaining the reason and why the medication is integral to the patient's wellbeing.	
5	To encourage: ● Appropriate physical activity and exercise. ● Lifestyle modification: ➢ Healthy balanced diet with no "added salt and flavoring sauces." ➢ Weight management. ➢ Ssmoking cessation.	
6	Stressing on the importance of follow up visit to ensure a safe post discharge period.	
7	Referral for cardiac rehabilitation as soon as possible.	

Appendix IV: Discharge Care Summary

A summary of the discharge care plan should be made available to the physician at the outpatient clinic upon follow up.

NO	PARAMETER	TICK
1	Establish: ● Type of HF (HF*r*EF, HF*p*EF, HF*mr*EF) ● Underlying cause ● Precipitating factors (if any)	
2	Brief synopsis of admission with pertinent findings: ● Blood results ● ECG abnormalities ● Echocardiogram findings with LVEF	
3	Highlight: ● Blood tests that need to be re checked - e.g., electrolytes ● Tracing blood results e.g., iron studies	
4	Medication progress ● Outline plans for resuming medications that had been stopped temporarily. ● Up titrating Foundational HF Medications and titration goals)	
5	Further cardiac work and referrals if indicated: ● Appointment for further cardiac investigations e.g., coronary angiography, cardiac imaging etc.	
6	Management of non-cardiac diseases (pulmonary disease, substance abuse).	
7	Identify problems like poor psychosocial support, impaired health literacy, cognitive impairment, frailty.	
8	Additional services needed like rehabilitation, device therapy, palliative care and destination therapy discussed.	
9	List of patient's and family expectations	

Appendix V: Indications for Valve Intervention*

Valve	Pathology	Recommendations
Mitral	Stenosis	**Intervention** is indicated in patients with MVA < 1.0 cm^2 and who are: ● Symptomatic ● Asymptomatic but have new onset AF, Pulmonary Hypertension or planning a pregnancy.
	Regurgitation	Surgery **is recommended** for: ● Acute severe mitral regurgitation ● Chronic severe mitral regurgitation with: ➢ Symptoms of decreasing effort tolerance ➢ Asymptomatic but: ◆ LVEF ≤ 60%, ◆ LVESD ≥ 40 mm ◆ LA volume ≥ 60 mL/m^2 or diameter ≥ 55 mm ◆ Systolic pulmonary arterial pressure > 50 mmHg and/or ◆ AF
Aortic	Stenosis	Surgery **is recommended** for patients who are: ● Symptomatic ● Asymptomatic patients with severe aortic stenosis and: ➢ Impaired LV function of no other cause ➢ Those who are asymptomatic during normal activities but develop symptoms during exercise testing.
	Regurgitation	Aortic valve replacement **should be advised** for: ● Symptomatic patients irrespective of the LVEF ● Asymptomatic patients with: ➢ LVEF ≤ 50% *or* ➢ Left ventricular end-systolic diameter (LVESD) > 50 mm Aortic valve replacement **may be considered** in asymptomatic patients and: ● LVEF< 55% without any other cause ● Sustained fall in systolic BP < 20 mmHg on exercise testing

**Adapted from:Vahanian, A., Beyersdorf, F., Praz, F., Milojevic, M., Baldus, S.et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2022; 43(7), 561-632.*

Appendix VI: ESC Heart Failure Association algorithm (HFA–PEFF)

P - Pretest Assessment

This includes a detailed clinical evaluation, electrocardiogram, laboratory tests, and basic echocardiogram. HF*p*EF is suggested by:

- Normal LVEF ***and***
- Nondilated left ventricle with concentric remodelling, or left ventricular hypertrophy ***and***
- Left atrial enlargement.

E - Diagnostic Workup

This will include a more detailed echocardiographic study and measurement of natriuretic peptides. They have proposed a scoring system using major and minor diagnostic criteria as outlined below.

Natriuretic Peptides:

- **NT-Pro BNP:**
  - *Major Criterion:* > 220 pg/mL - sinus rhythm; > 660 pg/mL - in AF
  - *Minor Criterion:* 125-220 pg/mL - sinus rhythm; 375-660 pg/mL - in AF
- **BNP**
  - *Major Criterion:* > 80 pg/ml - sinus rhythm; > 240 pg/mL - in AF
  - *Minor Criterion:* 35-80 pg/mL - sinus rhythm; 105-240 pg/Ml - in AF

Echocardiographic Criteria:

HF*p*EF cannot be diagnosed from a single echocardiographic measure. Suggestive criteria include:[16]

- **Septal e':**
  - *Major Criterion:* e' < 7 cm/s; or lateral e' < 10 cm/s (subjects aged < 75 years)
  - *Major Criterion:* e' < 5 cm/s; or lateral e' < 7 cm/s (subjects aged ≥ 75 years)
- **Average Septal-Lateral E/e' Ratio: -** The E/e' index cannot be recommended as a single diagnostic index above all other non-invasive measures of filling pressures (such as retrograde pulmonary venous flow).[16]
  - *Major Criterion:* ≥ 15 -This has good diagnostic value for identifying a high mean pulmonary capillary wedge pressure rest has (mPCWP) supporting the likelihood of HF*p*EF
  - *Minor Criterion:* 9 -14 - This is less sensitive in identifying a high mPCWP.
- **Tricuspid Regurgitant (TR) Peak Velocity**
  - *Major Criterion:* > 2:8m/s
- **Pulmonary Artery Systolic Pressure** - This is estimated 4x peak TR velocity plus estimated right atrial pressure.
  - *Major Criterion:* > 35mmHg
- **Left Atrial Volume Index:** This is an indirect correlate of LV filling pressures. It is more accurate as a marker of chronic LA remodelling than either LA area or diameter.
  - *Major Criterion:* > 34mL/m^2 - in sinus rhythm
  - *Major Criterion:* > 40mL/m^2 - in atrial fibrillation
  - *Minor Criterion:* 29-34mL/m^2 - in sinus rhythm
  - *Minor Criterion:* 34-40mL/m^2 - in atrial fibrillation
- **Left Ventricular Mass Index and Relative Wall Thickness (RWT)**
  - *Major Criterion:* LVMI ≥ 149 g/m^2 in men or ≥ 122 g/m^2 in women and RWT > 0:42
  - *Minor Criterion:* LVMI ≥ 115 g/m^2 in men or ≥ 95 g/m^2 in women or RWT > 0:42 or LV end-diastolic wall thickness ≥ 12mm

Scoring System Based on Echocardiographic and Natriuretic Peptide Levels:

For each major criterion met, 2 points are awarded, and 1 point is awarded for a minor criterion.

- A score of ≥ 5 is diagnostic of HF*p*EF.
- A score of ≤ 1 makes a diagnosis of HF*p*EF very unlikely.
- A score of 2-4 makes the diagnosis uncertain and additional work up is recommended.

F- Advanced Work Up

This includes functional testing in cases of uncertainty:

- Exercise echocardiogram - To assess diastolic dysfunction during exercise.
  - An average E/e' ratio at peak stress of ≥ 15, with or without a peak TR velocity > 3.4 m/s
- Invasive hemodynamic assessment - If criteria for diastolic dysfunction during an exercise echocardiogram through E/e' ratio and TR velocity are not met, then a right heart catheterization at rest and/or with exercise is the next step.
  - Invasive hemodynamic assessment through a right heart catheterization at rest or at exercise. The following are diagnostic of HF*p*EF:
    - At rest PCWP ≥ 15 mmHg
    - At rest left ventricular end-diastolic pressure (LVEDP) ≥ 16mmHg
    - Exercise PCWP ≥ 25 mmHg

F- Final Etiological Workup

This consists of establishing the etiology of the HF*p*EF. This includes assessment of blood pressure control, chronotropic competence, arrhythmias, and ischemia. Cardiac magnetic resonance imaging should be considered where specific etiology such as amyloidosis or hypertrophic cardiomyopathy are suspected.

In general, **steps E, F, F** are best performed in specialized cardiology centers. The following patients who continue to have dyspnea may be referred for further evaluation and management:

- Cases where the diagnosis is unclear.
- Non responders to treatment especially those with multiple comorbidities.

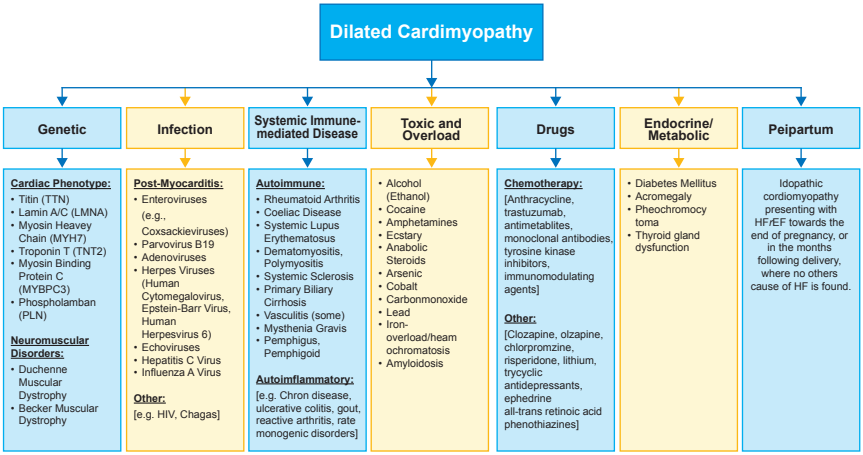
Appendix VII: H2FPEF score

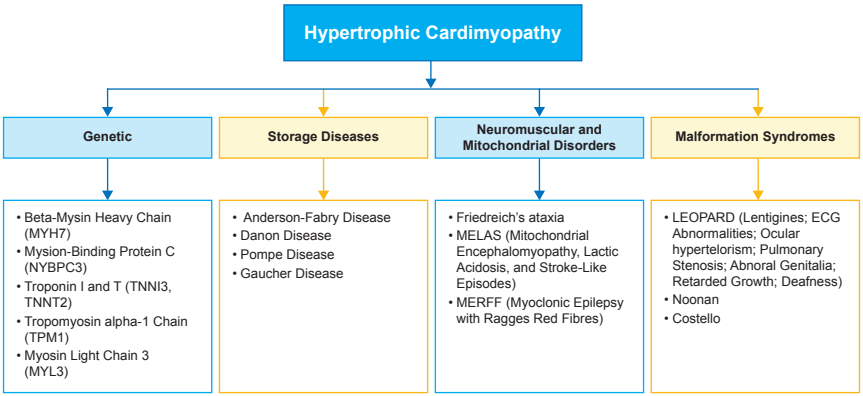
	Characteristic	Measurement	Score
H	Heavy	Body mass index > 30 kg/m^2	2
H	Hypertension	Two or more hypertensive medications	1
F	Atrial Fibrillation	Paroxysmal or persistent	3
P	Pulmonary Artery Pressure	Pulmonary artery systolic pressure > 35 mmHg	1
E	Elderly	Age > 60 years	1
F	LV filling pressure by echocardiogram	Echocardiographic E/e' > 9	1

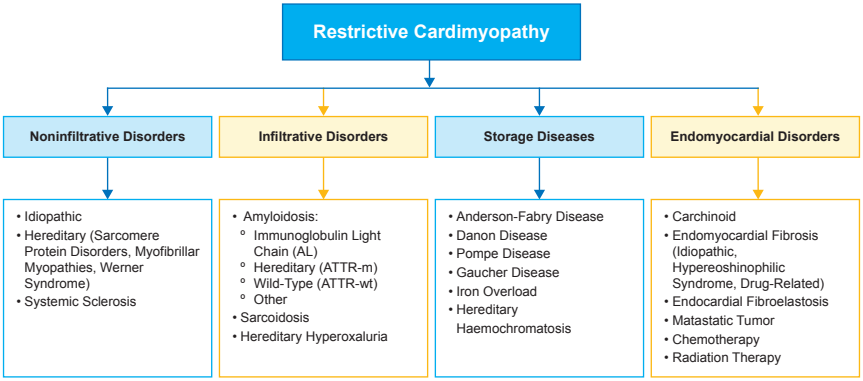
Score	Probability of HF*p*EF
6-9	>90%
0-1	≤ 23%
2-5	Intermediate probability and require additional testing to determine the cause of dyspnea.

Appendix VIII: Etiology of Cardiomyopathies

Adapted from "Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology")







Appendix IX: Anticancer Agents Associated with Heart Failure / LV Dysfunction)

Chemotherapy Agents	Prevention/Treatment
Anthracyclines Doxorubicin Epirubicin Idarubicin	Monitor LVEF, strain assessment with global longitudinal strain. Measure troponins. Consider use of dexrazoxane, continuous infusion, liposomal preparations, β-blockers, ACE-I.
Alkylating Agents Cyclophosphamide Ifosfamide	
Antimetabolites Decitabine Clofarabine	
Antimicrotubule Agents Docetaxel	
Monoclonal Antibody-Based Tyrosine Kinase Inhibitors Trastuzumab Bevacizumab Adostratuzumab emtacine Pertuzumab	Avoid concomitant use with anthracyclines.
Small Molecule Tyrosine Kinase Inhibitors Pazopanib Sorafenib Sunitinib Lapatinib	Treat hypertension aggressively
Proteasome Inhibitor Carfilzomib Bortezomib	

Appendix X: Chemotherapy drugs that have been associated with HF

Class of Drugs	Examples
Anthracyclines	Doxorubicin, daunorubicin, epirubicin,
Antimetabolite	Capecitabine, 5 Fluorouracil
Alkylating Agents	Cisplatin, cyclophosphamide
Vinca Alkaloids	Vincristine, vinblastine
Taxanes	Paclitaxel, docetaxel
Immune Checkpoint Inhibitor	Pembrolizumab, nivolumab
Targeted Therapies	Herceptin, imatinib, bevacizumab

Appendix XI: Modified World Health Organization Maternal Cardiovascular Risk Assessment[a-f]

WHO CLASS I: No Increase or a Mild Increase in Morbidity

- Uncomplicated, small, or mild
  - Pulmonary stenosis.
  - Patent ductus arteriosus.
  - Ventricular septal defect.
  - Mitral valve prolapse (with no more than trivial mitral regurgitation).
- Successfully repaired simple lesions (secundum atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage.
- Isolated Atrial ectopic beats or ventricular extrasystoles.

WHO CLASS II: (If otherwise well and uncomplicated)
Moderate Increase in Maternal Morbidity
Small Increase in Maternal Mortality (< 1%)

- Unoperated atrial or ventricular septal defect (moderate size, velocity < 4m/s).
- Repaired tetralogy of Fallot (without significant residual lesions).
- Most asymptomatic arrhythmias without cardiac decompensation - atrial fibrillation, supraventricular tachycardia, Wolff Parkinson White syndrome, long QT syndrome without any cardiac decompensation.

WHO CLASS II-III: Maternal Mortality, (1-5%)
Depending on the individual or other co-existing conditions

- Mild left ventricular dysfunction (LVEF 40-50%).
- Hypertrophic cardiomyopathy.
  - No LV outflow tract obstruction: WHO II
  - LV outflow tract obstruction present: WHO III
- Marfan syndrome without aortic dilation.
- Aorta < 45 mm in aortic disease associated with bicuspid aortic valve.
- Native or tissue valve disease not considered WHO I or IV.
- Mild native or repaired coarctation of aorta (without hypertension or significant obstruction.

Appendix XI: Modified World Health Organization Maternal Cardiovascular Risk Assessment (cont'd)[a-f]

WHO CLASS III: Severe Increase in Maternal Morbidity
Significant Increase in Maternal Mortality (5-15%)
Expert counselling required. If pregnancy is decided upon, needs an individualized pregnancy care plan with a multidisciplinary team management.

- Left ventricular dysfunction (LVEF 35-40%).
- Mechanical valve.
- Systemic right ventricle (cCTGA, post Senning/Mustard).
- Fontan circulation.
- Repaired Tetralogy of Fallot with severe pulmonary regurgitation, right ventricular failure, right ventricular outflow tract obstruction.
- Cyanotic heart disease (unrepaired).
- Other complex congenital heart disease.
- Aortic dilatation 40 - 45 mm in Marfan syndrome.
- Aortic dilatation 45 - 50 mm in aortic disease associated with bicuspid aortic valve.

WHO CLASS IV: Maternal mortality is 25-50%
Pregnancy Is Not Recommended or Is Contraindicated.
If pregnancy occurs, termination should be discussed.
If pregnancy continues, care as for class III.

- Severe pulmonary arterial hypertension of any cause (mortality 17-33%).
- Severe systemic ventricular dysfunction (LVEF < 30%, NYHA III-IV).
- Previous peripartum cardiomyopathy with any residual impairment of left ventricular function.
- Severe mitral stenosis (MVA < 1.0 cm^2), severe symptomatic aortic stenosis (AVA < 1.0cm^2).
- Marfan syndrome with aorta dilated > 45 mm .
- Aortic dilatation > 50 mm in aortic disease associated with bicuspid aortic valve.
- Uncorrected severe coarctation.

Modified from:

a) *Thorne S, MacGregor A, NelsonPiercy C. Risks of contraception and pregnancy in heart disease. Heart 2006; 92:15205;*
b) *RegitzZagrosek V, Blomstrom Lundqvist C, Borghi C et al. European Society of Cardiology guidelines on the management of cardiovascular diseases during pregnancy. Eur Heart J 2011; 32:314797*
c) *Siu SC, Sermer M, Colman JM, Alvarez AN, Mercier LA et al. Prospective multicentre study of pregnancy outcomes in women with heart disease. Circulation 2001; 104: 515-521.*
d) *Drenthen W, Boersma E, Balci A, Moons P, Roos-Hesselink JW et al. Predictors of pregnancy complications in women with congenital heart disease. Eur Heart J 2010; 31: 2124-2132.*
e) *Khairy P, Ouyang DW, Fernandes SM, Lee-Parritz A, Economy KE, Landzberg MJ. Pregnancy outcomes in women with congenital heart disease. Circulation 2006; 113:517-524*
f) *Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd,Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD; ACC/AHA Task Force Members. 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:2440-2492*

Appendix XII: New York Heart Association (NYHA) Functional Classification

Functional Class	Symptoms	Maternal Cardiovascular Risk
CLASS I	No limitation. Ordinary physical activity does not cause undue fatigue, dyspnea or palpitation.	**Low**
CLASS II	Slight limitation of physical activity. Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or angina.	**Low**
CLASS III	Marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary will activity lead to fatigue, palpitation, dyspnea or angina.	**High**
CLASS IV	Inability to carry on any physical activity without discomfort. Symptoms of congestive heart failure are present at rest. With any physical activity, increased discomfort is experienced.	**High**

Modified from:

The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Appendix XIII: The different causes of ACHD-HF based on the underlying pathophysiology, related CHD and etiology tailored management

Etiology	Pathophysiology	Congenital heart defect	Management
Systemic left ventricle failure	**Pressure overload**	Sub, supravalvular or valvular aortic stenosis, coarctation of the aorta, congenital MS, Shone syndrome	**Surgical or catheter intervention** to address obstructive or regurgitant valve lesions, persistent shunts, coronary anomalies. For coarctation of aorta - correct residual lesion,` treat hypertension **Medical therapy** ACEi, ARB ± sacubitril, RAS blockers Beta blockers Mineralocorticoid receptor antagonist Loop diuretics for symptom relief **CRT/ Biventricular pacing** in patients with chronic RV pacing and desynchrony
	Volume overload	Aortic/mitral valve regurgitation, persistent shunts: VSD, ASD, PDA atrioventricular valve regurgitation (post AVSD repair) Aorto-pulmonary collaterals	
	Myocardial injury /ischemia	Inadequate myocardial protection during surgery, supply-demand mismatch, ventriculotomy, myocardial hypertrophy, cyanosis, coronary anomalies (ALCAPA)	
	Sub-pulmonary Ventricle - systemic ventricle interaction	Severe pulmonary regurgitation in TOF, Chronic right ventricular pacing	
Sub-pulmonary morphological right ventricle failure [a,b]	**Volume overload**	Severe pulmonary regurgitation in TOF, atrial septal defect with large left-to-right shunt Ebsteins with severe tricuspid regurgitation	**Surgical or catheter intervention** to address obstructive or regurgitant valve lesions, persistent shunts, conduit stenosis **Medical therapy** PAH targeted therapy if RV failure due to PAH Loop diuretics for symptom relieve
	Pressure overload	Severe RV outflow tract obstruction, RV to PA conduit stenosis, double chambered RV Pulmonary arterial hypertension	
Morphological systemic right ventricle failurec	**Pressure Overload Volume Overload Myocardial architecture - RV morphology, Tricuspid systemic atrioventricular valve/ Ebsteinoid**	Congenitally corrected transposition of the great arteries, transposition of the great arteries after atrial switch repair (Mustard or Senning)[d,e] systemic atrioventricular valve regurgitation - Tricuspid Regurgitation	**No standard guidelines for medical therapy**[f,g] **Medical therapy if symptomatic Treat arrhythmias, correct residual hemodynamic lesions** E.g,baffle stenting / systemic TV replacement where appropriate CRT may have a role
Systemic single ventricle failureh	**Complicated multifactor etiology Volume overload (valve regurgitation, collaterals) Decrease in preload - post Fontan Myocardial injury / underlying morphology Elevated systemic venous pressure Diastolic dysfunction (impaired relaxation and ventricular filling)[i], Tachy & bradyarrhythmias**	Single ventricle physiology (unrepaired) Heterotaxy Single ventricle physiology palliated (BTshunt, Glenn, PDA stenting) Post Fontan - PLE, valve regurgitations, arterial desaturation fenestration.	**Transcatheter Intervention** eg fenestration closure or creation of fenestration, coil occlusion of aorto - pulmonary collaterals pulmonary artery stenting **surgical Fontan conversion Manage arrhythmias** - EPS ±RFA, pacemaker implantation **No standard guidelines for medical therapy** Judicious use of Loop Diuretics for symptom relief **PDE5 inhibitors & ERA** to decrease PA pressures and to improve cardiac output

Appendix XIII: The different causes of ACHD-HF based on the underlying pathophysiology, related CHD and etiology tailored management

Etiology	Pathophysiology	Congenital heart defect	Management
Cyanotic systemic and/or sub-pulmonary ventricle failure with or without pulmonary hypertension (PH)	**Myocardial injury by chronic hypoxia** **Pulmonary to systemic shunts**	Uncorrected or palliated cyanotic congenital heart disease (TOF, TOF with pulmonary atresia, single ventricle) Baffle leak (post atrial switch) Veno-veno collateral, pulmonary AVM	**Surgical Correction/repair** all hemodynamic lesions **Transcatheter intervention** to occlude any veno-veno collateral, occlude baffle leaks **Treat iron deficiency anemia** Routine **phlebotomy not recommended PAH targeted therapy**
	Pressure overload	**Eisenmenger syndrome**	
Systolic dysfunction of the systemic ventricle due to arrhythmias [k]	**Atrial or ventricular tachyarrhythmias** **Sinus node dysfunction/AV node dysfunction** **Interatrial re-entrant tachycardia**	Post TOF repair, Senning/Mustard (Atrial switch) cCTGA, Ebstein Anomaly, post Fontan [l]	**Antiarrhythmic medication** Electrophysiology study and **catheter or surgical ablation** **Devices:** Pacemaker, ICD, CRT
Acquired ischemic heart disease and ventricular dysfunction	**Coronary artery disease & Cardiovascular risk factors** [m]	Systemic hypertension, hyperlipidemia, diabetes mellitus, smoking	**Treat appropriately**
	Congenital coronary artery abnormalities	Anomalous origin and/or course, extrinsic compression by a dilated pulmonary artery, coronary kinking after re-implantation of coronary arteries	**Treat appropriately**
Non cardiac cause of ventricular dysfunction	**Anemia, Thyroid diseases, renal failure, Liver failure**	Can affect any CHD Fontan associated liver disease Iron deficiency anemia more common in cyanotic heart disease	**Treat appropriately**

a) *Konstam MA, Kiernan MS, Bernstein D, Bozkurt B, Jacob M, Kapur NK, Kociol RD, Lewis EF, Mehra MR, Pagani FD, Raval AN, Ward C; American Heart Association Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; and Council on Cardiovascular Surgery and Anesthesia. Evaluation and Management of Right-Sided Heart Failure: A Scientific Statement From the American Heart Association. Circulation. 2018 May 15;137(20):e578-e622.*

b) *Santens B, Van De Bruaene A, De Meester P, D'Alto M, Reddy S, Bernstein D, Koestenberger M, Hansmann G, Budts W. Diagnosis and treatment of right ventricular dysfunction in congenital heart disease. Cardiovasc Diagn Ther. 2020 Oct;10(5):1625-1645.*

c) *Brida M, Diller GP, Gatzoulis MA. Systemic Right Ventricle in Adults With Congenital Heart Disease: Anatomic and Phenotypic Spectrum and Current Approach to Management. Circulation. 2018 Jan 30;137(5):508-518..*

d) *Lubiszewska B, Gosiewska E, Hoffman P, et al. Myocardial perfusion and function of the systemic right ventricle in patients after atrial switch procedure for complete transposition: long-term follow-up. J Am Coll Cardiol 2000;36:1365-70.*

e) *Roos-Hesselink JW, Meijboom FJ, Spitaels SE, et al. Decline in ventricular function and clinical condition after Mustard repair for transposition of the great arteries (a prospective study of 22-29 years). Eur Heart J. 2004;25(14):1264-70*

f) *Ladouceur M, Segura de la Cal T, Gaye B, Valentin E, Ly R, Iserin L, Legendre A, Mousseaux E, Li W, Rafiq I, Kempny A, Barradas-Pires A, Babu-Narayan SV, Gatzoulis MA, Dimopoulos K. Effect of medical treatment on heart failure incidence in patients with a systemic right ventricle. Heart. 2021 Sep;107(17):1384-1389.*

g) *Dos L, Pujadas S, Estruch M, Mas A, Ferreira-González I, Pijuan A, Serra R, Ordóñez-Llanos J, Subirana M, Pons-Lladó G, Marsal JR, García-Dorado D, Casaldáliga J. Eplerenone in systemic right ventricle: double blind randomized clinical trial. The evedes study. Int J Cardiol. 2013 Oct 15;168(6):5167-73. .*

h) *Perrin N, Dore A, van de Bruaene A, Mongeon FP, Mondésert B, Poirier N, Miró J, Khairy P, Ibrahim R, Chaix MA. The Fontan Circulation: From Ideal to Failing Hemodynamics and Drug Therapies for Optimization. Can J Cardiol. 2022 Jul;38(7):1059-1071..*

i) *Book WM, Gerardin J, Saraf A, Marie Valente A, Rodriguez F 3rd. Clinical Phenotypes of Fontan Failure: Implications for Management. Congenit Heart Dis. 2016 Jul;11(4):296-308*

j) *CheungYF, Penny DJ, RedingtonAN(2000) Serial assessment of left ventricular diastolic function after Fontan procedure. Heart Br Card Soc 83:420-424.*

k) *Motonaga KS, Khairy P, Dubin AM. Electrophysiologic therapeutics in heart failure in adult congenital heart disease. Heart Fail Clin. 2014 Jan; 10(1):69-89.*

l) *Egbe AC, Connolly HM, Khan AR, et al. Outcomes in adult Fontan patients with atrial tachyarrhythmias. Am Heart J 2017;186:12-20.*

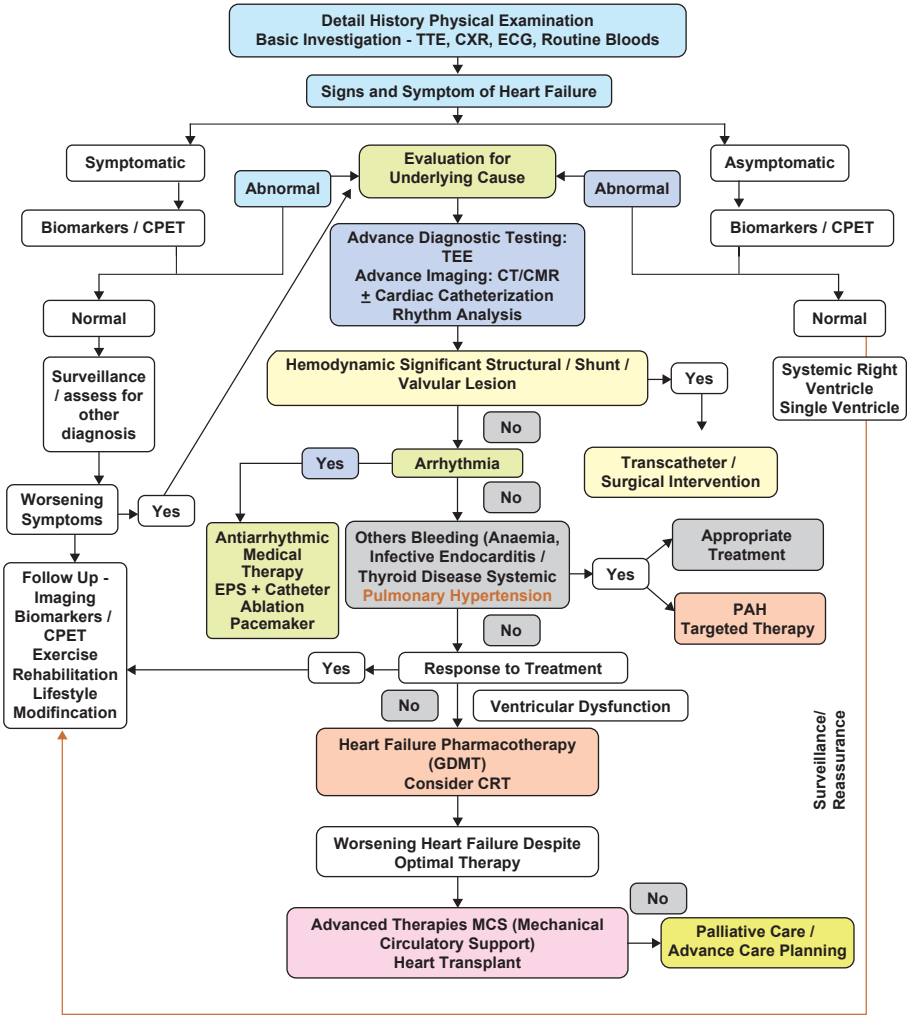
m) *Fedchenko M, Z. Mandalenakis, K.W. Giang, A. Rosengren, P. Eriksson, M. Dellborg, Long-term outcomes after myocardial infarction in middle-aged and older patients with congenital heart disease-a nationwide study, Eur. Heart J. 2021: 42 (26): 2577-2586.*

Appendix XIV: Investigations in ACHD[a]

Investigations	Important	Values/Parameter
Electrocardiogram (ECG)	To identify new onset/change in baseline ECG e.g., right/left ventricular hypertrophy, Conduction abnormalities.	Baseline ECG is abnormal to begin with in many ACHD. New or recent change in baseline ECG should trigger further review.
Chest X-ray (CXR)	Abnormalities in pulmonary artery and cardiac size, lungs(oligemic/plethoric) and thorax/skeletal	Baseline CXR may be abnormal.
Transthoracic echo	Anatomical diagnosis, identify residual or new lesions and sequelae, assess ventricular function, screening for pulmonary hypertension (PH).	Poor echo window (obesity, multiple scars, skeletal anomalies, lung pathology.) Echo parameters for left ventricular assessment are not suitable for single/ Right Ventricle (RV) function. Extracardiac lesions may not be clearly visualised.
Transesophageal echo	Anatomical diagnosis, conduits, valvular lesions	Useful to assess intracardiac shunts (especially ASD), valvular lesion, anomalous venous return. Used to assist in transcatheter interventions
CMR	Ventricular volumes and function especially RV Flow and regurgitation fractions. Perfusion defects/fibrosis. Cardiac and extracardiac anatomy.	Excellent tool for assessment of RV and to study flow in Fontan and calculate shunts. Artifacts if patients have coils/ pacemakers that are not MRI compatible. Not optimal for coronary anatomy.
Cardiac CT	Assessment of extracardiac anomalies. pulmonary artery anatomy. stents, conduit and aorto- pulmonary collateral arteries & shunts, aortic anomalies, coronary arteries	3D reconstruction is invaluable in planning surgical intervention and assessing surrounding non cardiac structures. Risk of radiation and contrast induced nephropathy. Tachycardia impairs resolution.
Cardiac catheterisation	Hemodynamic assessment of shunts. Pressure gradients across stenotic lesions, extracardiac shunts severity of PH and vasoreactivity .	Allows for transcatheter interventions for appropriate lesions.
Biomarkers (BNP/NT ProBNP)[b,c,d]	Reflects hemodynamic significant lesions, ventricular dysfunction.	Levels may be raised at baseline - increasing trends/acute rise may suggest HF. Assess response to treatment.
Cardiopulmonary exercise test[e]	Objective exercise capacity-peak Vo2, chronotropic competence, exercise induced arrhythmias, desaturation on exercise.	Heterogenous population[f] (Trending may be more important than absolute values) Prognostic values not standardized. Assess response to treatment.
Rhythm Analysis (24 hours & up to 7 days ECG monitoring, loop recorders	Identifies baseline and new onset conduction abnormalities (atrial/ventricular premature contractions, tachy/bradyarrhythmias, pauses, heart rate variabilities	May miss paroxysmal arrhythmias.

a) *Burchill LJ, Mertens L, Broberg CS. Imaging for the assessment of heart failure in congenital heart disease: ventricular function and beyond. Heart Fail Clin. 2014 Jan;10(1):9-22*
b) *J.A. Eindhoven, A.E. van den Bosch, P.R. Jansen, E. Boersma, J.W. Roos-Hesselink, The usefulness of brain natriuretic peptide in complex congenital heart disease: a systematic review, J. Am. Coll. Cardiol. 60 (21) (2012) 2140-2149.*
c) *Giannakoulas G, Dimopoulos K, Bolger AP, Tay EL, Inuzuka R, Bedard E, Davos C, Swan L, Gatzoulis MA. Usefulness of natriuretic peptide levels to predict mortality in adults with congenital heart disease. Am J Cardiol 2010;105:869 - 873*
d) *KochAM, ZinkS, SingerH, DittrichS.B-type natriuretic peptide levelsinpatients with functionally univentricular hearts after total cavopulmonary connection. Eur J Heart Fail 2008;10:60-62.*
e) *Inuzuka R, Diller GP, Borgia F, Benson L, Tay EL, Alonso-Gonzalez R, Silva M, Charalambides M, Swan L, Dimopoulos K, Gatzoulis MA. Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the*
f) *Kempny A, Dimopoulos K, Uebing A, Moceri P, Swan L, Gatzoulis MA, Diller GP. Reference values for exercise limitations among adults with congenital heart dis- ease. Relation to activities of daily life-single centre experience and review of published data. Eur Heart J 2012;33:1386 -1396.*

Appendix XV: Flow Chart of the Management of ACHD-HF



APPENDIX XVI Calculation of Performance and Outcome Measures

% of patients who had documentation of NYHA Functional Class	=	Number of patients who had documentation of NYHA Functional Class / Number of HF patients who were seen during that time period	x 100
% of patients who had LVEF measurement	=	Number of patients who had LVEF measurement / Number of HF patients who were seen during that time period	x 100
% of patients discharged with ACE-I / ARB	=	Number of patients who ere on ACE-I / ARB at discharge / Number of HF patients who were discharged during this time period who had no contraindications to ACE-I/ARB	x 100
% of patients discharged on β-blockers	=	Number of patients who were on β-blockers at discharge / Number of HF patients who were discharged during that time period who had no contraindications to β-blockers	x 100
% of patients discharged on MRA	=	Number of patients who were on MRA at discharge / Number of HF patients who were discharged during that time period who had no contraindications to MRA	x 100
% of patients with chronic or paroxysmal AF/Atrial Flutter on anticoagulant therapy (OAC) at discharge.	=	Number of patients who had AF/Atrial Flutter who were on OAC at discharge / Number of HF patients who had AF/Atrial Flutter during that time period who had no contraindications to OAC at discharge	x 100
% of patients given a post discharge appointment within 14 days	=	Number of patients who were given a post discharge appointment / Number of HF patients who were seen during that time period	x 100
% of patients who had their Foundational HF medications up titrated to maximally tolerated doses by 3 months post discharge	=	Number of patients who Had the HF medications up titrated within 3 months / Number of HF patients who were seen during that time period	x 100

REFERENCES

1. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res 2022:cvac013. doi:10.1093/cvr/cvac013
2. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. Cardiac Failure Review 2017;3:7-11.
3. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. Eur J Heart Fail. 2020 Aug;22(8): 1342-1356
4. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. Lancet 2018;391:572–580.
5. Lam CS, Teng TK, Tay WT, Anand I, Zhang S et al. Regional and Ethnic Differences among Patients with Heart Failure in Asia: The Asian Sudden Cardiac Death in Heart Failure Registry. Eur Heart J 2016: 37: 3141-53.
6. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A et al. The EuroHeart Failure survey programme - a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J 2003;24:442-463.
7. Buddeke, J., Valstar, G.B., van Dis, I. et al. Mortality after hospital admission for heart failure: improvement over time, equally strong in women as in men. BMC Public Health 2020: 20, 36
8. Conrad N, Judge A, Canoy D et al. Temporal Trends and Patterns in Mortality After Incident Heart Failure. A Longitudinal Analysis of 86 000 Individuals. JAMA Cardiol. 2019;4(11):1102-1111
9. Cunningham LC, Fonarow GC, Yancy CW, Sheng S, Matsouaka RA, DeVore AD, Jneid H, Deswal A. Regional Variations in Heart Failure Quality and Outcomes: Get With The Guidelines-Heart Failure Registry. J Am Heart Assoc. 2021 Apr 6;10(7):e018696.
10. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database.J Am Coll Cardiol 2006;47:76-84.
11. MacDonald MR, Tay WT, Teng TK,et al: Regional Variation of Mortality in Heart Failure With Reduced and Preserved Ejection Fraction Across Asia: Outcomes in the ASIAN-HF Registry. J Am Heart Assoc 2020 Jan 7;9(1):e012199.
12. Lim YMF, Ong SM, Koudstaal S, Hwong WY, Liew HB, Rajadurai J et al: Trends for Readmission and Mortality After Heart Failure Hospitalisation in Malaysia, 2007 to 2016. Glob Heart. 2022 Mar 8;17(1):20
13. Ahmad, W. A. Wan, M. A. S. K. Abdul Kader, N. T. Ross, et al. "Demographic and Characteristic of Patients Admitted with Heart Failure: Interim Analysis of Malaysia Heart Failure (MYHF) Registry." Int J Cardiology 2021: 345:(December 1, 2021): 13-14. https://doi.org/10.1016/j.ijcard.2021.10.057
14. Malek, A.M. Abd, M.A.S. Abdul Kader, T.K. Ong, A.W. Ramli, H.H. et al. "Clinical Characteristics of Hospitalized Heart Failure Patients with 30 Days Mortality: Insights from Malaysian Heart Failure (MYHF) Registry." Int J Cardiology 2022: 369: 21-22. https://doi.org/10.1016/j.ijcard.2022.10.070.
15. Raja Shariff RE, Kasim S, Borhan MK, Yusoff MR. Acute heart failure - The 'real' Malaysian experience: An observational study from a single non-cardiac centre. Proceedings of Singapore Healthcare 2021, Vol. 30(3) 218-224
16. Ling, H.S., Chung, B.K., Chua, P.F. et al. Acute decompensated heart failure in a non cardiology tertiary referral centre, Sarawak General Hospital (SGH-HF). BMC Cardiovasc Disord 2020:20, 511
17. Azmee Mohd Ghazi, Chee Kiang Teoh and Aizai Azan Abdul Rahim: Patient profiles on outcomes in patients hospitalized for heart failure: a 10-year history of the Malaysian population ESC Heart Failure (2022) Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/ehf2.13992
18. Ambrosy AP, Fonarow GC, Butler J, Chioncel O. The global health and economic burden of hospitalizations for heart failure lessons learned from hospitalized heart failure registries. J Am Coll Cardiol. 2014;63:1123-1133
19. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, et al. European Society of Cardiology heart failure long-term registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. Eur J Heart Fail 2016;18:613-625.
20. Lan T, Liao Y-H, Zhang J, Yang Z-P, Xu G-S et al. Mortality and Readmission Rates After Heart Failure: A Systematic Review and Meta-Analysis.Therapeutics and Clinical Risk Management 2021:17 1307-1320
21. Hessel FP. Overview of the socio-economic consequences of heart failure. Cardiovasc Diagn Ther 2021;11(1):254-262
22. Jones NR, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ. Survival of patients with chronic heart failure in the community: a systematic review and metaanalysis. Eur J Heart Fail 2019;21:1306-1325
23. Taylor CJ, Ordóñez-Mena JM, Roalfe AK, Lay-Flurrie S, Jones NR et al., Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population based cohort study. BMJ 2019;364:l223
24. Frohlich H, Rosenfeld N, Tager T, Goode K, Kazmi S, Hole T, et al. Epidemiology and long-term outcome in outpatients with chronic heart failure in Northwestern Europe. Heart 2019:105:1252-1259.
25. Lund LH, Carrero J-J, Farahmand B, Henriksson KM, Jonsson A et al. Association between enrolment in a heart failure quality registry and subsequent mortality-a nationwide cohort study. Eur J of Heart Failure 2017:19,1107-1116.
26. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, Nichol G, Pham M, Piña IL, Trogdon JG. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail. 2013; 6:606-19.
27. Cook C, Cole G, Asaria P, Jabbour R, Francis DP.The annual global economic burden of heart failure. Int J Card 2014:171(3):368-76.
28. Giles L, Freeman C, Field P et al. Humanistic burden and economic impact of heart failure - a systematic review of the literature [version 2]. F1000Research 2020, 8:859 (doi: 10.12688/f1000research.19365.2)
29. Alva ML, Gray A, Mihaylova B, et al.: The impact of diabetes-related complications on healthcare costs: new results from the UKPDS (UKPDS 84). Diabet Med. 2015; 32(4): 459-66.

30. Nichols GA, Ustyugova A, Déruaz-Luyet A, O'Keeffe-Rosetti M, Brodovicz KG. Health Care Costs by Type of Expenditure across eGFR Stages among Patients with and without Diabetes, Cardiovascular Disease, and Heart Failure. J Am Soc Nephrol. 2020 Jul;31(7):1594-1601
31. Yingchoncharoen T, Wu T-C, Choi D-J, Ong TK, Liew HB, Cho M-C. Economic Burden of Heart Failure in Asian Countries with Different Healthcare Systems. Korean Circ J. 2021 Aug;51(8):681-693
32. Shafie AA, Tan YP, Liau SY, Yang SL, Liew HB, Chaiyakunapruk N. Registry based analysis of cost-of-illness study among stage C heart failure patients at Hospital Queen Elizabeth II, Sabah, Malaysia. Health Policy and Technology 2019; 8 : 51-60
33. Ong SC, Low JZ, Yew WY, Yen CH, Ali MSK et al. Cost analysis of chronic heart failure management in Malaysia: A multi-centred retrospective study. Front. Cardiovasc. Med. 9:971592. doi: 10.3389/fcvm.2022.971592
34. Janwanishstaporn, S., Karaketklang, K. & Krittayaphong, R. National trend in heart failure hospitalization and outcome under public health insurance system in Thailand 2008-2013. BMC Cardiovasc Disord 2022: 22, 203
35. Bozkurt B, Coats AJ, Tsutsui H, et al. Universal Definition and Classification of Heart Failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail 2021;27:387-413
36. Roh J, Hill JA, Singh A, Valero-Muñoz M,Sam F. Heart Failure With Preserved Ejection Fraction: Heterogeneous Syndrome, Diverse Preclinical Models. Circulation Research. 2022;130:1906-1925
37. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction.Nat Rev Cardiol. 2017; 14:591-602
38. Savarese, G., Stolfo, D., Sinagra, G. et al. Heart failure with mid-range or mildly reduced ejection fraction. Nat Rev Cardiol 2022: 19:100-116.
39. Koh AS, Tay WT, Teng THK, Vedin O, Benson L, Dahlstrom U, et al. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. Eur J Heart Fail 2017;19:1624-1634
40. Webb J, Draper J, Fovargue L,Sieniewicz B, Gould J et al. Is heart failure with mid range ejection fraction (HF*mr*EF) a distinct clinical entity or an overlap group? IJC Heart & Vasculature 2018: 21: 1-6.
41. Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. Lancet 2019;393:61-73.
42. He Y, Ling Y, Guo W, Li Q, Yu S, Huang H, Zhang R, Gong Z, Liu J, Mo L, Yi S, Lai D, Yao Y, Liu J, Chen J, Liu Y, Chen S. Prevalence and Prognosis of HFimpEF Developed From Patients With Heart Failure With Reduced Ejection Fraction: Systematic Review and Meta-Analysis. Front Cardiovasc Med. 2021 Nov 25;8:757596.
43. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC heart failure long-term registry. Eur J Heart Fail. 2017:19:1574-85.
44. John R. Kapoor JR, Kapoor R, Ju C, Heidenreich PA, Eapen ZJ et al. Precipitating Clinical Factors, Heart Failure Characterization, and Outcomes in Patients Hospitalized With Heart Failure With Reduced, Borderline,and Preserved Ejection Fraction. J Am Coll Cardiol HF 2016;4:464-72
45. Lindberg F, Lund LH, Benson L, Schrage B, Edner M et al. Patient profile and outcomes associated with follow-up in specialty vs. primary care in heart failure. ESC Heart Failure 2022; 9: 822-833
46. Drazner MH, Rame JE, Stevenson LW, et al; Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. N Engl J Med. 2001;345(8):574-81.
47. Drazner MH, Rame JE, Dries DL. Third heart sound and elevated jugular venous pressure as markers of the subsequent development of heart failure in patients with asymptomatic left ventricular dysfunction. Am J Med 2003;114:431-7.
48. Mullens W, Damman K, Harjola V-P, Mebazaa A, La Rocca HBP et al. The use of diuretics in heart failure with congestion - a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Failure 2019:21:137-155
49. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. JAMA1989;261:884-888.
50. de Freitas EV, Batlouni M, Gamarsky R. Heart failure in the elderly. J Geriatr Cardiol. 2012 Jun;9(2):101-7.
51. S. Katsanos, G. Bakosis, A. Frogudaki .Acute heart failure syndrome in the elderly.Cont Cardiol Educ 2017:3: 87-87 https://doi.org/10.1002/cce2.60
52. Maisel AS, Krishnaswamy P, Nowak RM, et al for Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 002;347(3):161-7.
53. Maisel AS, McCord J, Nowak RM, et al. Bedside B-type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. Results from the Breathing Not Properly Multinational Study. J Am Coll Cardiol 2003;41(11):2010-7.
54. Januzzi JL, van Kimmenade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J 2006;27(3):330-7.
55. Roberts E, Ludman AJ, Dworzynski K, Al-Mohammad A, Cowie MR, et al NICE Guideline Development Group for Acute Heart Failure. The diagnostic accuracy of the natriuretic peptides in heart failure: systematic review and diagnostic meta-analysis in the acute care setting. BMJ 2015;350:h910.
56. Kim H-N, Januzzi JL, Jr. Natriuretic peptide testing in heart failure. Circulation 2011;123:2015-19.
57. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF et al. Heart Failure Association of the European Society of Cardiology. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail 2019;21:715 731.

58. Fonarow GC, Peacock WF, Phillips CO, et al. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. J Am Coll Cardiol 2007;49:1943-50.
59. Januzzi JL, Jr., Sakhuja R, O'Donoghue M, et al. Utility of amino-terminal pro-brain natriuretic peptide testing for prediction of 1-year mortality in patients with dyspnea treated in the emergency department. Arch Intern Med 2006;166:315-20.
60. Lam CSP, Gamble GD, Ling LH, Sim D, Leong KTG, Yeo PSD, Ong HY, Jaufeerally F, Ng TP, Cameron VA, Poppe K, Lund M, Devlin G, Troughton R, Richards AM, Doughty RN. Mortality associated with heart failure with preserved vs. reduced ejection fraction in a prospective international multi-ethnic cohort study. Eur Heart J. 2018 May 21;39(20):1770-1780
61. Kociol RD, Horton JR, Fonarow GC, et al. Admission, discharge, or change in B-type natriuretic peptide and long-term outcomes: data from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) linked to Medicare claims. Circ Heart Fail 2011;4:628-36.
62. Bettencourt P, Azevedo A, Pimenta J, Frioes F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. Circulation. 2004; 110:2168-2174
63. Booth RA, Hill SA, Don-Wauchope A, Santaguida PL, Oremus M, McKelvie R, Balion C, Brown JA, Ali U, Bustamam A, Sohel N, Raina P. Performance of BNP and NT-proBNP for diagnosis of heart failure in primary care patients: a systematic review. Heart Fail Rev 2014;19:439-451
64. Zaphiriou A, Robb S, Murray-Thomas T, Mendez G, Fox K, McDonagh T, Hardman SM, Dargie HJ, Cowie MR. The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. Eur J Heart Fail 2005;7:537-541.
65. Savarese G, Musella F, D'Amore C, et al. Changes of natriuretic peptides predict hospital admissions in patients with chronic heart failure. A meta-analysis. JACC Heart Failure 2014:2(2):148-58.
66. Aimo A, Gaggin HK, Barison A et al (2019) Imaging, biomarker, and clinical predictors of cardiac remodeling in heart failure with reduced ejection fraction. JACC Heart Fail 7:782-794.
67. Daubert MA, Adams K, Yow E et al (2019) NT-proBNP goal achievement is associated with significant reverse remodeling and improved clinical outcomes in HFrEF. JACC Heart Fail 7:158-168.
68. Meijers WC, van der Velde AR, Müller Kobold AC, Dijck-Brouwer J, Wu AH, Jaffe A, de Boer RA. Variability of biomarkers in patients with chronic heart failure and healthy controls. Eur J Heart Fail 2017;19:357-365.
69. Morello A, Lloyd-Jones DM, Chae CU, van Kimmenade RRJ, Chen AC, Baggish AL, O'Donoghue M, Lee-Lewandrowski E, Januzzi JL. Association of atrial fibrillation and amino-terminal pro-brain natriuretic peptide concentrations in dyspneic subjects with and without acute heart failure: results from the ProBNP investigation of dyspnea in the Emergency Department (PRIDE) study. Am Heart J 2007;153:90-97
70. Richards M, Di Somma S, Mueller C, Nowak R, Peacock WF, Ponikowski P, Möckel M, Hogan C, Wu AH, Clopton P, Filippatos GS, Anand I, Ng L, Daniels LB, Neath SX, Shah K, Christenson R, Hartmann O, Anker SD, Maisel A. Atrial fibrillation impairs the diagnostic performance of cardiac natriuretic peptides in dyspneic patients. JACC Heart Fail 2013;1:192-199
71. Keyzer JM, Hoffmann JJ, Ringoir L, Nabbe KC, Widdershoven JW, Pop VJ. Age- and gender-specific brain natriuretic peptide (BNP) reference ranges in primary care. Clin Chem Lab Med 2014;52(9):1341-6.
72. Wang TJ, Larson MG, Levy D, Leip EP, Benjamin EJ, Wilson PW, Sutherland P, Omland T, Vasan RS. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. Am J Cardiol 2002;90:254-258.
73. Kimmenade RRJ van, Januzzi JL, Baggish AL, Lainchbury JG, Bayés-Genis A, Richards AM, Pinto YM. Amino-terminal pro-brain natriuretic peptide, renal function and outcomes in acute heart failure. J Am Coll Cardiol 2006;48:1621-1627.
74. Anwaruddin S, Lloyd-Jones DM, Baggish A, Chen A, Krauser D, Tung R, Chae C, Januzzi JL. Renal function, congestive heart failure, and amino-terminal pro-brain natriuretic peptide measurement: results from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. J Am Coll Cardiol 2006;47:91-97
75. Bayes-Genis A, Lloyd-Jones DM, van Kimmenade RR, Lainchbury JG, Richards AM, Ordonez-Llanos J, Santalo M, Pinto YM, Januzzi JL. Effect of body mass index on diagnostic and prognostic usefulness of amino-terminal pro-brain natriuretic peptide in patients with acute dyspnea. Arch Intern Med. 2007; 167:400-40
76. Daniels LB, Clopton P, Bhalla V, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA, Maisel AS. How obesity affects the cut-points for B-type natriuretic peptide in the diagnosis of acute heart failure: results from the Breathing Not Properly Multinational Study. Am Heart J. 2006; 151:999-1005.
77. Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, Januzzi JL, Mark DB, Piña IL, Passmore G, Whellan DJ, Yang H, Cooper LS, Leifer ES, Desvigne-Nickens P, O'Connor CM. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction. JAMA 2017;318:713-720.
78. Bajaj NS, Patel N, Prabhu SD, Arora G, Wang TJ, Arora P. Effect of NT-proBNP-guided therapy on all-cause mortality in chronic heart failure with reduced ejection fraction. J Am Coll Cardiol 2018;71:951-952.
79. Pfisterer M, Buser P, Rickli H, Gutmann M, Erne P, Rickenbacher P, Vuillomenet A, Jeker U, Dubach P, Beer H, Yoon SI, Suter T, Osterhues HH, Schieber MM, Hilti P, Schindler R, Brunner-La Rocca HP; TIME-CHF Investigators. BNP-guided vs symptom-guided heart failure therapy: the trial of intensified vs standard medical therapy in elderly patients with congestive heart failure (TIME-CHF) randomized trial. JAMA 2009;301:383-392.
80. Januzzi JL, Rehman SU, Mohammed AA, Bhardwaj A, Barajas L et al. Use of amino-terminal pro-B-type natriuretic peptide to guide outpatient therapy of patients with chronic left ventricular systolic dysfunction. J Am Coll Cardiol 2011;58:1881-1889
81. Januzzi JL Jr, Ahmad T, Mulder H, Coles A, Anstrom KJ et al. Natriuretic Peptide Response and Outcomes in Chronic Heart Failure With Reduced Ejection Fraction. J Am Coll Cardiol. 2019 Sep 3;74(9):1205-1217
82. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA. 1996;275:1557-62.

83. Tocci G, Sciarretta S, Volpe M. Development of heart failure in recent hypertension trials. J Hypertens. 2008;26:1477-86
84. Dunlay SM, Givertz MM, Aguilar D, Allen LA, Chan M et al. Type 2 Diabetes Mellitus and Heart Failure: A Scientific Statement From the American Heart Association and the Heart Failure Society of America. Circulation. 2019;140:e 294-e324
85. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA. 1979; 241:2035-2038.
86. Kenny HC, Abe ED. Heart Failure in Type 2 Diabetes Mellitus. Circ Research. 2019;124:121-141
87. Kenchaiah S, Evans JC, Levy D, Wilson PWF et al. Obesity and the Risk of Heart Failure. N Engl J Med 2002; 347:305-313
88. Aune D, Sen A, Norat T, Janszky I, Romundstad P et al. Body mass index, abdominal fatness and heart failure incidence and mortality: a systematic review anddose-response meta-analysis of prospective studies. Circulation 2016;133:639-49.
89. Pandey A, Cornwell WK, Willis B, Neeland IJ, Gao A, Leonard D, DeFina L, Berry JD. Body mass index and cardiorespiratory fitness in mid-life and risk of heart failure hospitalization in older age: findings from the Cooper Center Longitudinal Study.JACC Heart Fail. 2017; 5:367-374
90. Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P et al. Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation. 2021;143:e984-e1010
91. Ingelsson E, Arnlöv J, Lind L, Sundström J. Metabolic syndrome and risk for heart failure in middle-aged men. Heart. 2006;92:1409-1413.
92. Tang ZH, Wang L, Zeng F, Zhang K. Association and predictive value analysis for metabolic syndrome on systolic and diastolic heart failure in high-risk patients. BMC Cardiovasc Disord. 2014;14:124
93. Kamimura D, Cain LR, Mentz RJ, White WB, Blaha MJ et al. Cigarette Smoking and Incident Heart Failure. Insights From the Jackson Heart Study. Circulation. 2018;137:2572-2582
94. Gopal DM, Kalogeropoulos AP, Georgiopoulou VV,Smith AL, Bauer DC et a. for the Health ABC Study. Cigarette Smoking Exposure and Heart Failure Risk in Older Adults: The Health, Aging, and Body Composition Study. Am Heart J. 2012 Aug; 164(2): 236-242.
95. Ding N, Shah AM, Blaha MJ, Chang PP, Rosamond WD, Matsushita K. Cigarette smoking, cessation, and risk of heart failure with preserved and reduced ejection fraction. J Am Coll Cardiol. 2022;79(23):2298-2305.
96. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2017;38:2459-2472
97. Ranthe MF, Carstensen L, Øyen N, Jensen MK, Axelsson A et al. Risk of Cardiomyopathy in Younger Persons With a Family History of Death from Cardiomyopathy. Circulation. 2015;132:1013-1019
98. Lee DS, Pencina MJ, Benjamin EJ, Wang TJ, Levy D, O'Donnell CJ et al. Association of parental heart failure with risk of heart failure in offspring. N Engl J Med 2006: 355(2):138-147
99. Gencer B, Collet TH, Virgini V, Bauer DC, Gussekloo J, Cappola AR, Nanchen D, den Elzen WPJ, Balmer P, Luben RN, Iacoviello M, Triggiani V, Cornuz J, Newman AB, Khaw KT, Jukema JW, Westendorp RGJ, Vittinghoff E, Aujesky D, Rodondi N, Thyroid Studies Collaboration . Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from six prospective cohorts. Circulation 2012 126 1040-1049.
100. Rodondi N, Newman AB, Vittinghoff E, et al. Subclinical Hypothyroidism and the Risk of Heart Failure, Other Cardiovascular Events, and Death. Arch Intern Med. 2005;165(21):2460-2466.
101. Rodondi N, Bauer DC, Cappola AR, Cornuz J, Robbins J, Fried LP, Ladenson PW, Vittinghoff E, Gottdiener JS, Newman AB. Subclinical thyroid dysfunction, cardiac function, and the risk of heart failure. The Cardiovascular Health Study. Journal of the American College of Cardiology 2008 52 1152-1159.
102. Gerstein HC, Mann JFR, Yi Q et al. Albuminuria and Risk of Cardiovascular Events, Death, and Heart Failure in Diabetic and Nondiabetic Individuals. JAMA. 2001;286(4):421-426.
103. Solomon SD, Lin J, Solomon CJ, Jablonski KA, Rice KM et al.for the Prevention of Events With ACE Inhibition (PEACE) Investigators. Influence of Albuminuria on Cardiovascular Risk in Patients With Stable Coronary Artery Disease. Circulation. 2007;116:2687-2693
104. Nagata M, Ninomiya T, Kiyohara Y, Murakami Y, Irie F et al. for the EPOCH-JAPAN Research Group, Prediction of Cardiovascular Disease Mortality by Proteinuria and Reduced Kidney Function: Pooled Analysis of 39,000 Individuals From 7 Cohort Studies in Japan, Am J Epidem 2013:178(1): 1-11
105. Weir MR. Microalbuminuria and cardiovascular disease. Clin J Am Soc Nephrol. 2007 May;2(3):581-90
106. Silverberg, D., Wexler, D., Blum, M., Schwartz, D., & Iaina, A. The association between congestive heart failure and chronic renal disease. Current Opinion in Nephrology and Hypertension 2004:13(2), 163-170.
107. Kottgen A, Russell S.D.,,Loehr L.R.,et al. Reduced kidney function as a risk factor for incident heart failure: the Atherosclerosis Risk in Communities (ARIC) study. J Am Soc Nephrol. 2007; 18: 1307-1315
108. Kloner RA, Rezkalla SH. To drink or not to drink? That is the question. Circulation. 2007;116:1306-1317.
109. Li X, Xue Q, Wang M, Zhou T, Ma T, Heianza Y, Qi L.Adherence to a Healthy Sleep Pattern and Incident Heart Failure.A Prospective Study of 408 802 UK Biobank Participants. Circulation. 2021;143:97-99
110. Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O et al. National Sleep Foundation's sleep time duration recommendations: methodology and results summary. Sleep Health. 2015 Mar;1(1):40-43.
111. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease. Am J Respir Crit Care Med. 2001; 163: 19-25.
112. Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Töpfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients.Eur J Heart Fail. 2007; 9:251-257
113. Alenghat, F. The Prevalence of Atherosclerosis in Those with Inflammatory Connective Tissue Disease by Race, Age and Traditional Risk Factors. Sci Rep 2016: 6, 20303.

114. Rosenkranz S, Howard LS, Gomberg-Maitland M, Hoeper MM. Systemic Consequences of Pulmonary Hypertension and Right-Sided Heart Failure. Circulation. 2020;141:678-693
115. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet 1997;350: 757-64.
116. Kostis JB, Davis BR, Cutler J, et al. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension: SHEP Cooperative Research Group. JAMA 1997;278:212-16
117. Beckett NS, Peters R, Fletcher AE, et al for the HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008;358:1887-98.
118. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure-lowering treatment. 6. Prevention of heart failure and new-onset heart failure-metaanalyses of randomized trials. J Hypertens. 2016;34:373-384.
119. Upadhya B, Rocco M, Lewis CE, et al; SPRINT Research Group. Effect of intensive blood pressure treatment on heart failure events in the Systolic Blood Pressure Reduction Intervention Trial. Circ Heart Fail 2017;10(4). pii: e003613.
120. Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S, Selby JV. Glycemic control and heart failure among adult patients with diabetes. Circulation. 2001; 103:2668-2673.
121. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. Diabetes Care. 2004;27:1879-1884
122. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015; 373:2117-2128.
123. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377:644-657.
124. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380:347-357.
125. Cannon CP, Pratley R, Dagogo-Jack S, et al., for the VERTIS CV Investigators. Cardiovascular Outcomes With Ertugliflozin in Type 2 Diabetes. N Engl J Med 2020;383:1425-35.
126. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2018; 393:31-39.
127. Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, Norhammar A, Birkeland KI, Jorgensen ME, Thuresson M, Arya N, Bodegard J, Hammar N, Fenici P. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). Circulation. 2017; 136:249-259.
128. Suskin N, Sheth T, Negassa A, Yusuf S. Relationship of current and past smoking to mortality and morbidity in patients with left ventricular dysfunction. J Am Coll Cardiol 2001;37:1677-82.
129. Ahmed AA, Patel K, Nyaku MA, Kheirbek RE, Bittner V et al. Risk of Heart Failure and Death After Prolonged Smoking Cessation.Role of Amount and Duration of Prior Smoking. Circulation: Heart Failure. 2015;8:694-701
130. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies. Eur Heart J 2021: 42: 3227-3337.
131. Ministry of Health. Clinical Practice Guidelines on Management of Dyslipidemia, 5th Ed [Internet]. 2017. Available from: www.acadmed.com.my
132. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al.; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation. 2018Mar;137(12):e67-492.
133. Djouss´e L, Driver JA, Gaziano JM. Relation between modifiable lifestyle factors and lifetime risk of heart failure. Physicians Health Study 1. JAMA 2009;302:4:394-400.
134. Kliger AS, Foley RN, Goldfarb DS, Goldstein SL, Johansen K, Singh A, et al. KDOQI US commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD. Am J Kidney Dis. 2013 Nov. 62 (5):849-59.
135. Bradley TD, Logan AG, Kimoff RJ, et al; CANPAP Investigators. Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med 2005;353:2025-33.
136. McEvoy RD, Antic NA, Heeley E, et al; SAVE Investigators and Coordinators. CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med 2016;375:919-31.
137. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med 2015;373:1095-105.
138. C.M. O'Connor, D.J. Whellan, M. Fiuzat, et al.Cardiovascular outcomes with minute ventilation-targeted adaptive servo-ventilation therapy in heart failure.J Am Coll Cardiol 2017: 69:1577-1587
139. R.D. McEvoy, N.A. Antic, E. Heeley, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med 2016:375: 919-931
140. Cowie MR, Gallagher AM. Sleep Disordered Breathing and Heart Failure: What Does the Future Hold? JACC: Heart Failure 2017: 5:715-723
141. Ministry of Health Malaysia. Malaysian Clinical Practice Guidelines on Prevention of Cardiovascular Disease. 1st Ed, 2018. Available at www.acadmed.org
142. Del Gobbo LC, Kalantarian S, Imamura F, Lemaitre R, Siscovick DS, Psaty BM, Mozaffarian D. Contribution of Major Lifestyle Risk Factors for Incident Heart Failure in Older Adults: The Cardiovascular Health Study. JACC Heart Fail. 2015 Jul;3(7):520-528.

143. Siscovick DS, Barringer TA, Fretts AM, Wu JHU et al. and On behalf of the American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Epidemiology and Prevention; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Omega-3 Polyunsaturated Fatty Acid (Fish Oil) Supplementation and the Prevention of Clinical Cardiovascular Disease. A Science Advisory From the American Heart Association. Circulation. 2017;135:e867-e884.
144. Ministry of Health. Clinical Practice Guidelines on Management of NON-ST Elevation Myocardial Infarction. 3RD Ed [Internet]. 2021. Available from: www.acadmed.gov.my
145. Ministry of Health. Clinical Practice Guidelines on Management of ST Elevation Myocardial Infarction. 4th Ed [Internet]. 2019. Available from: www.acadmed.gov.my
146. Ministry of Health. Clinical Practice Guidelines on Management of Stable Coronary artery Disease. 2nd Ed [Internet]. 2018. Available from: www.acadmed.gov.my
147. Ministry of Health. Clinical Practice Guidelines on Management of Hypertension. 5thd Ed [Internet]. 2018. Available from: www.acadmed.gov.my
148. Larstorp AC, Okin PM, Devereux RB, et al. Regression of ECG-LVH is associated with lower risk of new-onset heart failure and mortality in patients with isolated systolic hypertension; The LIFE study. Am J Hypertens. 2012 ;25(10):1101-9.
149. The SOLVD Investigator. Effect of Enalapril on Mortality and the Development of Heart Failure in Asymptomatic Patients with Reduced Left Ventricular Ejection Fractions. N Engl J Med 1992; 327:685-691
150. Jong P, Yusuf S, Rousseau MF, Ahn SA, Bangdiwala SI. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. Lancet. 2003 May 31;361(9372):1843-8
151. Arnold JMO, Yusuf S, Young J, et al. Prevention of heart failure in patients without known left ventricular dysfunction: the Heart Outcomes Prevention Evaluation (HOPE) study. Circulation. 2003; 107: 1284-1290.
152. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet. 2001 May 5;357(9266):1385-90.
153. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. JAMA Cardiol. 2021;6(2):148-158.
154. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. The Lancet. 2020;396(10254):819-29.
155. McDonagh T.A., Metra M., Adamo M., et al. "2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC". Eur Heart J 2021;42:36: 3599-3726
156. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145:e895-e1032
157. Pizga, A., Karatzanos, E., Tsikrika, S., Gioni, V., Vasileiadis, I., Nanas, S. and Kordoutis, P. Psychosocial Interventions to Enhance Treatment Adherence to Lifestyle Changes in Cardiovascular Disease: A Review of the Literature 2011-2021. Eur J Environ Public Health 2022, 6(1), em0102.
158. Jaarsma T, Hill L, Bayes-Genis A, La Rocca HPB, Castiello T et al. Self-care of heart failure patients: practical management recommendations from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2021: 23: 157-174
159. Inglis SC, Clark RA, McAlister FA, Ball J, Lewinter C, Cullington D, Stewart S, Cleland JG. Structured telephone support or telemonitoring programmes for patients with chronic heart failure. Cochrane Database Syst Rev. 2010 Aug 4;(8):CD007228. doi: 10.1002/14651858.CD007228.pub2.
160. Inglis SC, Clark RA, Dierckx R Structured telephone support or non invasive telemonitoring for patients with heart failure. Review. Cochrane Database of Systematic Reviews 2015, Issue 10. Art. No. CD007228.
161. Zhu Y, Gu X, Xu C. Effectiveness of telemedicine systems for adults with heart failure: a meta-analysis of randomized ontrolled trials. Heart Fail Rev. 2020 Mar;25(2):231-243.
162. Gensini GF, Alderighi C, Rasoini R, Mazzanti M, Casolo G. Value of Telemonitoring and Telemedicine in Heart Failure Management. Card Fail Rev. 2017 Nov;3(2):116-121.
163. Taylor R, Long L, Mordi I, et al. Exercise-Based Rehabilitation for Heart Failure. J Am Coll Cardiol HF. 2019 Aug, 7 (8) 691-705.
164. Long L, Mordi IR, Bridges C, Sagar VA, Davies EJ, Coats AJ, Dalal H, Rees K, Singh SJ, Taylor RS. Exercise-based cardiac rehabilitation for adults with heart failure. Cochrane Database Syst Rev. 2019 Jan 29;1(1):CD003331.
165. Taylor RS, S. Walker, N.A. Smart, et al. Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalization: an individual patient data meta-analysis of randomized trials. Eur J Heart Fail, 2018:20: 1735-1743
166. Taylor RS, Sagar VA, Davies EJ Briscoe S, Coats AJ, Dalal H, Lough F, Rees K, Singh S. Exercise-based rehabilitation for heart failure. Cochrane Database Syst Rev. 2014. p. CD003331.
167. Sagar VA, Davies EJ, Briscoe S et al. Exercise-based rehabilitation for heart failure: systematic review and meta-analysis. Open Heart. 2015;2:e000163.
168. Buckley BJR, Harrison SL, Fazio-Eynullayeva E, Underhill P, Sankaranarayanan R et al. Cardiac rehabilitation and all-cause mortality in patients with heart failure: a retrospective cohort study, Eur J Preventive Cardiol 2021: 28(15):1704-1710,
169. Pandey A, Parashar A, Kumbhani D et al. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. Circ Heart Fail. 2015;8:33-40.
170. Chan E, Giallauria F, Vigorito C, Smart NA. Exercise training in heart failure patients with preserved ejection fraction: a systematic review and meta-analysis. Monaldi Arch Chest Dis. 2016 Oct 14;86(1-2):759.

171. Chen YM, Li ZB, Zhu M, Cao YM. Effects of exercise training on left ventricular remodelling in heart failure patients: an updated meta-analysis of randomised controlled trials. Int J Clin Pract. 2012 : 66(8):782-791
172. Bozkurt B, Fonarow GC, Goldberg LR, Guglin M, Josephson RA et al. Cardiac Rehabilitation for Patients With Heart Failure. JACC Expert Panel. J Am Coll Cardiol 2021;77:1454-69
173. Mueller S, Winzer EB, Duvinage A, et al. Effect of High-Intensity Interval Training, Moderate Continuous Training, or Guideline-Based Physical Activity Advice on Peak Oxygen Consumption in Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial. JAMA. 2021;325(6):542-551.
174. Doukky R, Avery E, Mangla A, Collado FM, Ibrahim Z, Poulin MF, Richardson D, Powell LH. Impact of Dietary Sodium Restriction on Heart Failure Outcomes. JACC Heart Fail. 2016 Jan;4(1):24-35.
175. Ezekowitz JA, Colin-Ramirez E, Ross H, Escobedo J, Macdonald on behalf of the SODIUM-HF Investigators. Reduction of dietary sodium to less than 100 mmol in heart failure (SODIUM-HF): an international, open-label, randomised, controlled trial. Lancet 2022: 399:10333:1391-1400
176. Aliti GB, Rabelo ER, Clausell N, Rohde LE, Biolo A, Beck-da Silva. Aggressive fluid and sodium restriction in acute decompensated heart failure: a randomized clinical trial. JAMA Intern Med. 2013 Jun 24;173(12):1058-64.
177. von Haehling S, Anker SD. Prevalence, incidence and clinical impact of cachexia: facts and numbers-update 2014. J Cachexia Sarcopenia Muscle. 2014;5(4):261-263
178. Habaybeh D, de Moraes MB, Slee A, Avgerinou C. Nutritional interventions for heart failure patients who are malnourished or at risk of malnutrition or cachexia: a systematic review and meta-analysis. Heart Failure Reviews 2021: 26:1103-1118
179. Billingsley HE, Hummel SL, Carbone S. The Role of Diet and Nutrition in Heart Failure: A State-of-the-Art Narrative Review.Prog Cardiovasc Dis. 2020 Sep-Oct; 63(5): 538-551.
180. Vest AR, Chan M, Deswal A, Givertz MM, Lekavich C et al. Nutrition, obesity,and cachexia in patients with heart failure: a consensus statement from the Heart Failure Society of America Scientific Statements Committee. J Card Fail 2019;25:380-400.
181. Jaarsma T, Hill L, Bayes-Genis A, La Rocca HPB, Castiello T et al. Self-care of heart failure patients: practical management recommendations from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2021: 23: 157-174
182. Johansson P, van der Wal MH, Stromberg A, Waldreus N, Jaarsma T. Fluid restriction in patients with heart failure: how should we think? Eur J Cardiovasc Nurs 2016;15:301-304.
183. Padwal R, McAlister FA, McMurray JJV, Cowie MR, Rich M, Pocock S. Meta-Analysis Global Group In Chronic Heart Failure (MAGGIC). The obesity paradox in heart failure patients with preserved versus reduced ejection fraction: a meta-analysis of individual patient data. Int J Obes Relat Metab Disord 2014;38:1110-4.
184. Klatsky AL. Alcohol and cardiovascular diseases: where do we stand today? J Intern Med. 2015 Sep;278(3):238-50.
185. Laonigro I, Correale M, Di Biase M, Altomare E. Alcohol abuse and heart failure. Eur J Heart Fail 2009;11:453-62.
186. Son YJ, Lee HJ. Association between persistent smoking after a diagnosis of heart failure and adverse health outcomes: A systematic review and meta-analysis. Tob Induc Dis. 2020 Jan 20;18:
187. Jaarsma T. Sexual function of patients with heart failure: facts and numbers. ESC Heart Fail. 2017 Feb;4(1):3-7
188. Steinke E, Jaarsma T. Sexual counseling and cardiovascular disease - Practical approaches. Asian J Androl 2015;17:32-9.
189. Jaarsma T, Steinke E, Gianotten W. Sexual problems in cardiac patients. How to assess, when to refer. J Cardiovasc Nurs 2010;25(2):159-64.
190. Van Driel AG, De Hosson MJ, Gamel C. Sexuality of patients with chronic heart failure and their spouses and the need for information regarding sexuality. Eur J Cardiovasc Nurs 2014;13(3):227-34.
191. Oakley CM, Child A, Lung B, et al. Expert consensus document on management of cardiovascular diseases during pregnancy. The Task Force on the Management of Cardivascular Diseases during Pregnancy of the European Society of Cardiology. Eur Heart J 2003:24;761-81.
192. Ministry of Health Malaysia. Clinical Practice Guidelines on Heart Disease in Pregnancy, 2nd Ed, 2016. Available at www.acadmed.gov.my
193. Roos-Hesselink JW, Cornette J, Sliwa K, Pieper PG, Veldtman GR, Johnson MR. Contraception and cardiovascular disease. Eur Heart J 2015;36(27):1728-34.
194. Lindley KJ, Bairey Merz CN, Davis MB, Madden T, Park K, Bello , and on behalf of the American College of Cardiology Cardiovascular Disease in Women Committee and the Cardio-Obstetrics Work Group. Contraception and Reproductive Planning for Women With Cardiovascular Disease: JACC Focus Seminar. J Am Coll Cardiol. 2021 : 77 (14): 1823-1834
195. Cowie M, Linz D, Redline S, et al. Sleep Disordered Breathing and Cardiovascular Disease. J Am Coll Cardiol. 2021 Aug, 78 (6) 608-624.
196. Parati, G., Lombardi, C., Castagna, F. et al. Heart failure and sleep disorders. Nat Rev Cardiol 2016:13, 389-403
197. Constanzo MR, Khayat R, Ponikowski P, et al. Mechanisms and clinical consequences of untreated central sleep apnea in heart failure. J Am Coll Cardiol 2015;65(1):72-84.
198. McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med. 2016;375: 919-931.
199. Peker Y, Glantz H, Eulenburg C, et al. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with non-sleepy obstructive sleep apnea. The RICCADSA randomised controlled trial. Am J Resp Crit Care Med. 2016;194:613-620.
200. Sanchez-de-la-Torre M, Sanchez-de-la-Torre A, Bertran S, et al. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the presence of cardiovascular events in patients with acute coronary syndrome (ISAAC study): a randomised controlled trial. Lancet Respir Med. 2020;8:359-367.

201. Da-Silva-Paulitsch F, Zhang L. Continuous positive airway pressure for adults with obstructive sleep apnea and cardiovascular disease: a meta-analysis of randomized trials. Sleep Med. 2019;54:28-34.
202. Ghosh, R. K., Ball, S., Prasad, V., & Gupta, A. (2016). Depression in heart failure: Intricate relationship, pathophysiology and most updated evidence of interventions from recent clinical studies. International Journal of Cardiology, 224, 170-177.
203. Moser, D. K., Dracup, K., Evangelista, L. S., Zambroski, C. H., Lennie, T. A., Chung, M. L., Doering, L. V., Westlake, C., & Heo, S. (2010). Comparison of prevalence of symptoms of depression, anxiety, and hostility in elderly patients with heart failure, myocardial infarction, and a coronary artery bypass graft. Heart and Lung, 39(5), 378-385.
204. Chamberlain AM, McNallan SM, Dunlay SM, et al. Physical health status measures predict all-cause mortality in patients with heart failure. Circ Heart Fail 2013;6:669-75.
205. Hoekstra T, Jaarsma T, van Veldhuisen DJ, et al. Quality of life and survival in patients with heart failure. Eur J Heart Fail 2013;15:94-102
206. Remme WJ, McMurray JV, Rauch B, et al. Public awareness of heart failure in Europe: first results from SHAPE. Eur Heart J 2005;26:2413-21.
207. Fang, J., Mensah, G. A., Croft, J. B., & Keenan, N. L. Heart failure related hospitalisation in the US 1979 to 2004. J Am Coll Cardiol 2008: 52(6): 428-434.
208. Maru S., Byrnes J., Carrington M., Chan Y., Thompson R.D., Stewart S., Scuffham A.P. Cost effectiveness of home versus clinic based management of chronic heart failure: Extended follow-up of pragmatic, multicentre randomised trial cohort - The WHICH? Study (which heart failure intervention is most cost-effective & consumer friendly in reducing hospital care). Int J Cardiol 2015: 15(201), 368-375.
209. Butt JH, Fosbøl EL, Gerds TA, Andersson C, McMurray JJV et al. Readmission and death in patients admitted with new-onset versus worsening of chronic heart failure: insights from a nationwide cohort. Eur J Heart Fail. 2020 Oct;22(10):1777-1785
210. Tavazzi L, Senni M, Metra M, Gorini M, Cacciatore G, Chinaglia A, Di Lenarda A, Mortara A, Oliva F, Maggioni AP; IN-HF (Italian Network on Heart Failure) Outcome Investigators. Multicenter prospective observational study on acute and chronic heart failure: one-year follow-up results of IN-HF (Italian Network on Heart Failure) outcome registry. Circ Heart Fail. 2013 May;6(3):473-81.
211. Shahar E, Lee S, Kim J, Duval S, Barber C, Luepker RV. Hospitalized heart failure: rates and long-term mortality. J Card Fail. 2004 Oct;10(5):374-9.
212. Okumura N, Jhund PS, Gong J, Lefkowitz MP, Rizkala AR et al PARADIGM-HF Investigators and Committees. Importance of Clinical Worsening of Heart Failure Treated in the Outpatient Setting.Evidence From the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF). Circulation. 2016;133:2254-2262.
213. Ferreira JP, Metra M, Mordi I, Gregson J, ter Maaten JM et al. Heart failure in the outpatient versus inpatient setting: findings from the BIOSTAT-CHF study. Eur J Heart Fail 2019: 21:112-120
214. Skali H, Dwyer EM, Goldstein R, Haigney M, Krone R et al. Prognosis and response to therapy of first inpatient and outpatient heart failure event in a heart failure clinical trial: MADIT-CRT. Eur J Heart Fail 2014;16 : 560-565
215. Sameer Kurmani, Iain Squires. Acute heart failure: definition, classification and epidemiology. Curr Heart Fail Rep 2017;14:385-392.
216. Gheorghiade M, Braunwald E. A proposed model for initial assessment and management of acute heart failure. JAMA 2011;Vol 305(16):1702-1703
217. Beusekamp JC, Ouwerkerk W, van der Meer P, Cleland JGF et al. Regional differences in precipitating factors of hospitalization for acute heart failure: insights from the REPORT-HF registry. Eur J Heart Fail. 2022 Apr;24(4):645-652.
218. United Kingdom. National Heart failure Audit 2020. Available at : https://www.nicor.org.uk/wp-content/up loads/2020 /12/National-Heart-Failure-Audit-2020-FINAL.pdf
219. Ponikowski P, Voors AA, Anker SD et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. EHJ 2016;37(27):2129-2200.
220. Chioncel O, Mebazaa A, Maggioni AP, Harjola V-P, Rosano G on behalf of the ESC-EORP-HFA Heart Failure Long-Term Registry Investigators. Acute heart failure congestion and perfusion status - impact of the clinical classification on in-hospital and long-term outcomes; insights from the ESC-EORP-HFA Heart Failure Long-Term Registry.Eur J Heart Fail 2019; 21(11):1338-1352
221. Collins SP, Lindsell CJ, Storrow AB, Abraham WT. Prevalence of negative chest radiography results in the emergency department patient with decompensated heart failure.Ann Emerg Med2006;47:13-18.
222. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1-39.e
223. Pellicori P, Platz E, Dauw J, ter Maaten JM, Martens P et al. Ultrasound imaging of congestion in heart failure: examinations beyond the heart. Eur J Heart Fail. 2021 May ; 23(5): 703-712
224. Maw AM, Hassanin A, Ho PM, et al. Diagnostic Accuracy of Point-of-Care Lung Ultrasonography and Chest Radiography in Adults With Symptoms Suggestive of Acute Decompensated Heart Failure: A Systematic Review and Meta-analysis. JAMA Netw Open. 2019;2(3):e190703.
225. Hernandez GA, Lenor A, Blumer V et al. Trends and outcomes of PAC in HF with and without cardiogenic shock. J of Card Fail 2019(25)5:364-371.
226. Binanay C, Califf RM, Hasselblad V, et al; ESCAPE Investigators and ESCAPE Study Coordinators. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. JAMA 2005;294(13):1625-33.
227. Shah MR, Hasselblad V, Stevenson LW, et al. Impact of the pulmonary artery catheter in critically ill patients: meta-analysis of randomized clinical trials. JAMA 2005;294(13):1664-70.
228. Stub D, Smith K, Bernard S, et al for the AVOID Investigators. Air versus oxygen in ST-segment- elevation myocardial infarction. Circulation 2015;131:2143-50.

229. Cabello JB, Burls A, Emparanza JI, Bayliss SE, Quinn T. Oxygen therapy for acute myocardial infarction (Review). Cochrane Database Syst Rev 2016;12:CD007160.
230. Hofmann R, James SK, Jernberg T, et al for the DETO2X-SWEDEHEART Investigators. Oxygen therapy in suspected acute myocardial infarction. N Engl J Med 2017;377:1240-9.
231. Sjöberg F, Singer M. The medical use of oxygen: a time for critical reappraisal. J Intern Med 2013;274(6):505-28.
232. Park JH, Balmain S, Berry C, Morton JJ, McMurray JJ. Potentially detrimental cardiovascular effects of oxygen in patients with chronic left ventricular systolic dysfunction. Heart 2010;96(7):533-8.
233. Shuvy M, Atar D, Steg PG, Halvorsen S, Jolly S, Yusuf S, Lotan C. Oxygen therapy in acute coronary syndrome: are the benefits worth the risk? Eur Heart J 2013:34: 1630-5.
234. Sepehrvand N, Ezekowitz JA. Oxygen Therapy in Patients With Acute Heart Failure: Friend or Foe? JACC Heart Fail. 2016 Oct;4(10):783-790
235. Yu, Y., Yao, RQ., Zhang, YF. et al. Is oxygen therapy beneficial for normoxemic patients with acute heart failure? A propensity score matched study. Military Med Res 2021: 8: 38
236. O'Driscoll BR,Howard LS, Davison AG on behalf of the British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. Thorax 2008;63(Suppl VI):vi1-vi68.
237. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J; Nicholl J for the 3CPO Trialists. Noninvasive ventilation in acute cardiogenic pulmonary edema. N Engl J Med 2008;359:142-151.
238. Masip J, Peacock WF, Price S, Cullen L, Martin-Sanchez FJ et al. Indications and practical approach to non-invasive ventilation in acute heart failure. Eur Heart J 2018: 39: 17-25.
239. Masip J, Roque M, Sanchz B, Fernandez R, Subirana M, Exposito JA. Non invasive ventilation in acute cardiogenic pulmonary edema: systemic review and meta-analysis. JAMA 2005;294(24):3124-30.
240. Helviz Y, Einav S. A systematic review of the high-flow nasal cannula for adult patients. Crit Care 2018;22:71.
241. Ni YN, Luo J, Yu H, et al. Can high-flow nasal cannula reduce the rate of endotracheal intubation in adult patients with acute respiratory failure compared with conventional oxygen therapy and noninvasive positive pressure ventilation? A systematic review and meta-analysis. Chest 2017;151:764-75.
242. Ko DR, Beom J, Lee HS, You JS, Chung HS et al. Benefits of High-Flow Nasal Cannula Therapy for Acute Pulmonary Edema in Patients with Heart Failure in the Emergency Department: A Prospective Multi-Center Randomized Controlled Trial. J Clin Med. 2020 Jun; 9(6): 1937.
243. Ho KM, Wong K. A comparison of continuous and bi-level positive airway pressure non-invasive ventilation in patients with acute cardiogenic pulmonary oedema: a meta-analysis. Crit Care 2006;10:R49.
244. Li H, Hu C, Xia J, et al. A comparison of bilevel and continuous positive airway pressure noninvasive ventilation in acute cardiogenic pulmonary edema. Am J Emerg Med 2013;31:1322-7.
245. Matsue Y, Damman K, Voors AA, Kagiyama N, Yamaguchi T et al. Time-to-Furosemide Treatment and Mortality in Patients Hospitalized With Acute Heart Failure. J Am Coll Cardiol. 2017 Jun 27;69(25):3042-3051
246. Miró Ò, Harjola P, Rossello X, Gil V, Jacob J et al. ICA-SEMES Research Group. The FAST-FURO study: effect of very early administration of intravenous furosemide in the prehospital setting to patients with acute heart failure attending the emergency department. Eur Heart J Acute Cardiovasc Care. 2021 Jun 30;10(5):487-496
247. Felker GM, Ellison DH, Mullens W, Cox ZL,Testani JM. Diuretic Therapy for Patients With Heart Failure: JACC State-of-the-Art Review. J Am Coll Cardiol 2020: 75: 1178-1195.
248. K.F. Adams Jr., G.C. Fonarow, C.L. Emerman, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE).Am Heart J, 149 (2005), pp. 209-216
249. Ng KT, Yap JLL. Continuous infusion vs. intermittent bolus injection of furosemide in acute decompensated heart failure: systematic review and meta-analysis of randomised controlled trials. Anaesthesia 2018;73(2):238-47.
250. Salvador DR, Rey NR, Ramos GC, Punzalan FE. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. Cochrane Database Syst Rev 2004;(1):CD003178.
251. Ng KT, Velayit A, Khoo DKY, Mohd Ismail A, Mansor M. Continuous infusion versus intermittent bolus injection of furosemide in critically ill patients: a systematic review and meta-analysis. J Cardiothorac Vasc Anesth 2018;32(5): 2303-10.
252. Triposkiadis FK, Butler J, Karayannis G, et al. Efficacy and safety of high dose versus low dose furosemide with or without dopamine infusion: the Dopamine in Acute Decompensated Heart Failure II (DAD-HF II) trial. Int J Cardiol 2014;172(1):115-21.
253. Giamouzis G, Butler J, Starling RC, et al. Impact of dopamine infusion on renal function in hospitalized heart failure patients: results of the Dopamine in Acute Decompensated Heart Failure (DAD-HF) Trial. J Card Fail 2010;16(12):922-30.
254. Brater DC, Day B, Burdette A, Anderson S. Bumetanide and furosemide in heart failure. Kidney International 1984: 26(2):183-189
255. Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. J Am Coll Cardiol. 2010;56(19):1527-1534.
256. Kissling KT, Pickworth KK. Comparison of the effects of combination diuretic therapy with oral hydrochlorothiazide or intravenous chlorothiazide in patients receiving intravenous furosemide therapy for the treatment of heart failure. Pharmacotherapy 2014;34(8):882-7.
257. Cox ZL, Hung R, Lenihan DJ, Testani JM. Diuretic Strategies for Loop Diuretic Resistance in Acute Heart Failure: The 3T Trial. JACC: Heart Failure 2020: 8: (3): 157-168
258. Wollam GL, Tarazi RC, Bravo EL, Dustan HP. Diuretic potency of combined hydrochlorothiazide and furosemide therapy in patients with azotemia. Am J Med 1982;72(6):929.
259. Fliser D, Schröter M, Neubeck M, Ritz E. Coadministration of thiazides increases the efficacy of loop diuretics even in patients with advanced renal failure. Kidney Int 1994;46(2):482.

260. Brisco-Bacik MA, Ter Maaten JM, Houser SR, et al. Outcomes Associated With a Strategy of Adjuvant Metolazone or High-Dose Loop Diuretics in Acute Decompensated Heart Failure: A Propensity Analysis. Journal of the American Heart Association. 2018;7(18):e009149.
261. Rosenberg J, Gustafsson F, Galatius S, Hildebrandt PR. Combination therapy with metolazone and loop diuretics in outpatients with refractory heart failure: an observational study and review of the literature. Cardiovasc Drugs Ther 2005;19(4):301-6.
262. Moranville MP, Choi S, Hogg J, Anderson AS, Rich JD. Comparison of metolazone versus chlorothiazide in acute decompensated heart failure with diuretic resistance. Cardiovasc Ther 2015;33(2):42-9.
263. Cheng, H.W.B., Sham, MK., Chan, KY. et al. Combination therapy with low-dose metolazone and furosemide: a "needleless" approach in managing refractory fluid overload in elderly renal failure patients under palliative care. Int Urol Nephrol 2014: 46:1809–1813.
264. Konstam MA, Kiernan M, Chandler A, Dhingra R, Mody FV, Eisen H, Haught WH, Wagoner L, Gupta D, Patten R, Gordon P, Korr K, Fileccia R, Pressler SJ, Gregory D, Wedge P, Dowling D, Romeling M, Konstam JM, Massaro JM, Udelson JE; SECRET of CHF Investigators, Coordinators, and Committee Members. Short-Term Effects of Tolvaptan in Patients With Acute Heart Failure and Volume Overload. J Am Coll Cardiol. 2017 ; 69(11):1409-1419.
265. Felker GM, Mentz RJ, Cole RT, Adams KF, Egnaczyk GF, Fiuzat M, Patel CB, Echols M, Khouri MG, Tauras JM, Gupta D, Monds P, Roberts R, O'Connor CM. Efficacy and Safety of Tolvaptan in Patients Hospitalized With Acute Heart Failure. J Am Coll Cardiol. 2017;69(11):1399-1406
266. Ma G, Ma X, Wang G, Teng W, Hui X. Effects of tolvaptan add-on therapy in patients with acute heart failure: meta-analysis on randomised controlled trials. BMJ Open 2019;9:e025537
267. O'Connor CM, et al. Effect of Nesiritide in Patients with Acute Decompensated Heart Failure. N Engl J Med 2011;365(1):32-43
268. Chen HH, Anstrom KJ, Givertz MM, Stevenson LW, Semigran MJ et al.for the NHLBI Heart Failure Clinical Research Network. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. JAMA. 2013 Dec 18;310(23):2533-43.
269. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P et al. for the ADVOR Study Group. Acetazolamide in Acute Decompensated Heart Failure with Volume Overload. N Eng J Med. 2022;387(13):1185-1195.
270. Publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. JAMA 2002;287(12):1531-40.
271. Wakai A, McCabe A, Kidney R, et al. Nitrates for acute heart failure syndromes. Cochrane Database Syst Rev 2013;(8):CD005151.
272. Kozhuharov N, Goudeva A, Flores D et al. Effect of a strategy of comprehensive vasodilator therapy versus usual care on mortality and heart failure hospitalization across patient in acute heart failure. The GALACTIC randomized controlled trial. JAMA 2019;322:2291-2302.
273. Freund Y, Cachanado M, Delannoy Q, Laribi S, Yordanov Y et al. Effect of an emergency department care bundle on 30-day hospital discharge and survival among elderly patients with acute heart failure: the ELISABETH randomized clinical trial. JAMA 2020;324:1948-1956.
274. Curfman G. Vasodilator Therapy in Acute Heart Failure. JAMA. 2019 ; 322(23): 2288-2289.
275. Miró Ò, Llorens P, Freund Y, Davison B, Takagi K et al EAHFE Research Group. Early intravenous nitroglycerin use in prehospital setting and in the emergency department to treat patients with acute heart failure: Insights from the EAHFE Spanish registry. Int J Cardiol. 2021 Dec 01; 344:127-134.
276. De Backer D, Biston P,Devriendt J, et al for the SOAP II Investigators. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 2010; 362:779-89.
277. Rui Q, Jiang Y, Chen M, Zhang N, Yang H, Zhou Y. Dopamine versus norepinephrine in the treatment of cardiogenic shock. A PRISMA-compliant meta-analysis. Medicine (Baltimore). 2017; 96(43):e8402.
278. Levy B, Perez P, Perny J, Thivilier C, Gerard A. Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. Crit Care Med 2011;39(3):450-5.
279. Leopold V, Gayat E, Pirracchio R, Spinar J, Parenica Jet al. Epinephrine and short-term survival in cardiogenic shock: an individual data meta-analysis of 2583 patients. Intensive Care Med 2018;44:847-856.
280. Elkayam U, Ng TMH, Hatamizadeh P, Janmohamed M, Mehra A. Renal Vasodilatory Action of Dopamine in Patients With Heart Failure. Magnitude of Effect and Site of Action. Circulation. 2008;117:200-205.
281. Lauschke A, Teichgräber UKM, Frei U, Eckardt K-U. 'Low-dose' dopamine worsens renal perfusion in patients with acute renal failure. Kidney Int 2006: 69: 1669-1674.
282. Tacon CL, McCaffrey J, Delaney A. Dobutamine for patients with severe heart failure - a systematic review and meta-analysis of randomised controlled trials. Intensive Care Med 2012;38(3):359–67.
283. Wang XC, Zhu DM, Shan YX. Dobutamine Therapy is Associated with Worse Clinical Outcomes Compared with Nesiritide Therapy for Acute Decompensated Heart Failure: A Systematic Review and Meta-Analysis. Am J Cardiovasc Drugs. 2015 Dec;15(6):429-37
284. Sosnowski MA. Review article: Lack of effect of opiates on the treatment of acute cardiogenic pulmonary edema. Emerg Med Australasia 2008;20:384-90.
285. Peacock WF, Hollander JE, Diercks DB, Lopatin M, Fonarow G, Emerman CL. Morphine and outcomes in acute decompensated heart failure: an ADHERE analysis. Emerg Med J 2008;25(4):205-9.
286. Domínguez-Rodríguez A, Suero-Mendez C, Burillo-Putze G, Gil V, Calvo-Rodriguez R et al for the MIMO (MIdazolam versus MOrphine) Trial Investigators. Midazolam versus morphine in acute cardiogenic pulmonary oedema: results of a multicentre, open-label, randomized controlled trial. Eur J Heart Failure .Available at https://doi.org/10.1002/ejhf.2602

287. Baldetti L, Pagnesi M, Gramegna M, Belletti A, Beneduce A et al. Intra-Aortic Balloon Pumping in Acute Decompensated Heart Failure With Hypoperfusion: From Pathophysiology to Clinical Practice. Circulation: Heart Failure. 2021;14
288. G.A.B Boros, V.S.C Bellini, D Fatori, C Bernoche, M.F Macatrao-Costa, L.N.G.D Lopes, F Bacal, W Hueb, L Kopel, S.G Lage, Intra-aortic balloon pump as a bridge therapy to heart transplant in refractory heart failure, Eur Heart J 2020: 41(Suppl 2), ehaa946.1234,
289. Morici N, Marini C, Sacco A, Tavazzi G, Saia F, Palazzini M, Oliva F, Ferrari GM, Colombo PC, Kapur NK, Garan AR, Pappalardo F. Intra-aortic Balloon Pump for Acute-on-Chronic Heart Failure Complicated by Cardiogenic Shock. J Card Fail. 2022 : 28(7):1202-1216.
290. Thiele H, Zeymer U, Neumann FJ, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock.N Engl J Med 2012;367(14):1287-96.
291. Thiele H, Zeymer U, Neumann F-J, et al. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised,open-label trial. Lancet 2013;382:1638-45.
292. Ohman EM, Nanas J, Stomel RJ, Leesar MA, Nielsen DW, O'Dea D, Rogers FJ, Harber D, Hudson MP, Fraulo E, et al.; TACTICS Trial. Thrombolysis and counterpulsation to improve survival in myocardial infarction complicated by hypotension and suspected cardiogenic shock or heart failure: results of the TACTICS Trial.J Thromb Thrombolysis. 2005; 19:33-39.
293. Romeo F, Acconcia MC, Sergi D, Romeo A, Muscoli S et al. The outcome of intra-aortic balloon pump support in acute myocardial infarction complicated by cardiogenic shock according to the type of revascularization: a comprehensive meta-analysis.Am Heart J. 2013; 165:679-692.
294. Marialisa Nesta, Federico Cammertoni, Piergiorgio Bruno, Massimo Massetti, Implantable ventricular assistance systems (VAD) as a bridge to transplant or as 'destination therapy', European Heart Journal Supplements, Volume 23, Issue Supplement_E, October 2021, Pages E99-E102
295. Cavallazzi R, Nair A, Vasu T, Marik PE. Natriuretic peptides in acute pulmonary embolism: a systematic review. Intensive Care Med. 2008 Dec;34(12):2147-56
296. Ronco C, McCullough P, Anker SD, et al for the Acute Dialysis Quality Initiative (ADQI) consensus group. Cardio-renal syndromes: report from the consensus conference of the Acute Dialysis Quality Initiative. Eur Heart J 2010;31(6):703-11.
297. Rosano GMC, Moura B, Metra M, Böhm M, Bauersachs J et al. Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2021 Jun;23(6):872-881.
298. Hammarlund MM, Paalzow LK, Odlind B. Pharmacokinetics of furosemide in man after intravenous and oral administration. Application of moment analysis. Eur J Clin Pharmacol 1984;26(2):197-207.
299. Lala A, McNulty SE, Mentz RJ, Dunlay SM, Vader JM et al. Relief and recurrence of con-gestion during and after hospitalization for acute heart failure: insights fromDiuretic Optimization Strategy Evaluation in Acute Decompensated Heart Fail-ure (DOSE-AHF) and Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF). Circ Heart Fail2015;8:741-748
300. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC et al. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial . Eur Heart J 2013: 34 (11): 835-0843,
301. Testani JM, Brisco MA, Kociol RD, Jacoby D, Bellumkonda L et al. Substantial discrepancy between fluid and weight loss during acute decompensated heart failure treatment. Am J Med 2015;128:776-783.
302. Pitt B, Zannad F, Remme WJ, et al. for the Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709-17.
303. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309-21.
304. Zannad F, McMurray JJV, Krum H, et al for the EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364:11-21.
305. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA 1995;273:1450-6.
306. Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet 2000;355:1575-81.
307. Packer M, Coats ASS, Fowler MB, et al. Effect of carvediolol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651-8.
308. The CAPRICORN Investigators. Effect of carvedilol on outcomes after myocardial infarction in patients with left ventricular dysfunction: the CAPRICORN randomized trial. Lancet 2001;357:1385-90.
309. Australia-New Zealand Heart failure Research Collaborative Group. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischemic heart disease. Lancet 1997;349:375-80.
310. Willenheimer R, van Veldhuisen DJ, Silke B, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence. Results of the Randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation 2005;112:2426-35.
311. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001-7.
312. Poole- Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with CHF in the Carvedilol Or Metoprolol European Trail (COMET): randomised controlled trial. Lancet 2003;362:7-13.
313. CIBIS-II Investigators and Committees The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353(9146):9-13

314. Prins KW, Neill JM, Tyler JO et al. Effect of beta blocker withdrawal in acute decompensated heart failure, A systematic review and meta analysis. JACC HF 2015;3:647-653
315. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP et al for the PIONEER-HF Investigators. Angiotensin -Neprilysin Inhibition in Acute Decompensated Heart Failure. N Engl J Med 2019; 380:539-548
316. Greene SJ, Choi S, Lippmann SJ, Mentz RJ, Greiner MA et al. Clinical Effectiveness of Sacubitril/Valsartan Among Patients Hospitalized for Heart Failure With Reduced Ejection Fraction. J Am Heart Assoc. 2021 Aug 17;10(16):e021459
317. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA et al SOLOIST-WHF Trial Investigators. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med. 2021: 384(2):117-128
318. Voors AA, Angermann CE, Teerlink JR et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nature Med 2022:28:568-574
319. Brunner-La Rocca HR, Knackstedt C, Eurlings L et al. Impact of worsening renal function related to medication in heart failure. Eur J Heart Fail 2015;17:159-168
320. Cohen AT, Spiro TE, Buller HR et al. Rivaroxaban for thromboprophylaxis in acute ill medical patients. NEJM 2013:368;512-523.
321. Kleber FX, Witt C, Vogel E et al. Randomized comparison of enoxaparin with unfractionated heparin for the prevention of venous thromboembolism in medical patients with heart failure or severe respiratory disorder. Am J Cardiol 2003;145:614-621.
322. Malaysian Clinical Practice Guidelines on Type 2 Diabetes Mellitus 2020. 6Th Ed. Available at www.acadmed.org. my
323. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America.Circulation. 2017; 136:e137-e161.
324. Ponikowski P, Kirwan BA, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomized, controlled trial. Lancet 2020;369:1895-1904.
325. Sawicki KT, Ardehali H. Intravenous Iron Therapy in Heart Failure With Reduced Ejection Fraction: Tackling the Deficiency. Circulation. 2021;144:253-255
326. WA, Ali MS, Kader SKA, Ross NT, Ramli AW et al for the MYHF Investigators'. Abstract 12125: Baseline Analysis of National Malaysian Heart Failure Registry Indicates Hospitalization as a Key Opportunity to Initiate GDMT in HF Patients. Circulation 2021; 144: A12125
327. Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. Lancet. Published on line 7th November 2022.DOI:https://doi.org/10.1016/S0140-6736(22)02076-1
328. Lucas C, Johnson W, Hamilton MA, Fonarow GC, Woo MA et al. Freedom from congestion predicts good survival despite previous class IV symptoms of heart failure. American heart journal. 2000; 140:840-847
329. The Consensus Trial Study Group. Effects of Enalapril on Mortality in Severe Congestive Heart Failure. N Engl J Med 1987; 316:1429-1435
330. The SOLVD Investigators. Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure. N Engl J Med 1991; 325:293-302
331. Pfeffer MA, McMurray JJ, Velazquez EJ, et al for the Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril or both in myocardial infarction complicated by heart failure, left-ventricular dysfunction or both. N Engl J Med 2003; 349:1893-906.
332. Yusuf S, Teo K, Anderson C, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet 2008;372(9644):1174-1183.
333. Maggioni AP, Anand I, Gottlieb SO, et al; Val-HeFT Investigators (Valsartan Heart Failure Trial). Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. J Am Coll Cardiol. 2002; 40: 1414-1421.
334. Caldeira D, David C, Sampaio C. Tolerability of angiotensin-receptor blockers in patients with intolerance to angiotensin-converting enzyme inhibitors: a systematic review and meta-analysis. Am J Cardiovasc Drugs 2012;12(4):263-77.
335. McMurray JJ, Packer M, Desai AS, et al; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.
336. Fitchett D., Zinman B., Wanner C., et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME trial. European Heart Journal.2016;37(19):1526-1534.
337. Kato E. T., Silverman M. G., Mosenzon O., et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation. 2019;139(22):2528-2536
338. Bhatt D. L., Szarek M., Steg P. G., et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. New England Journal of Medicine. 2021;384(2):117-128
339. Rådholm K., Figtree G., Perkovic V., et al. Canagliflozin and heart failure in type 2 diabetes mellitus. Circulation. 2018;138(5):458-468.
340. Anker S. D., Butler J., Filippatos G., et al. Effect of empagliflozin on cardiovascular and renal outcomes in patients with heart failure by baseline diabetes status. Circulation. 2021;143(4):337-349.
341. McMurray J. J. V., Solomon S. D., Inzucchi S. E, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. New England Journal of Medicine. 2019;381:1995-2008.
342. Santos-Gallego C. G., Vargas-Delgado A. P., Requena J. A., et al. Randomized trial of empagliflozin in non-diabetic patients with heart failure and reduced ejection fraction. Journal of the American College of Cardiology. 2020;77(3)
343. Seo Y., Yamamoto M., Machino-Ohtsuka T., Ishizu T., Aonuma K. Effects and safety of sodium glucose cotransporter 2 inhibitors in diabetes patients with drug-refractory advanced heart failure. Circulation Journal. 2018;82(7):1959-1962

344. Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. Int J Cardiol. 2002;82(2):149-158.
345. Elhassan MG, Chao PW, Curiel A. The Conundrum of Volume Status Assessment: Revisiting Current and Future Tools Available for Physicians at the Bedside. Cureus. 2021 May 26;13(5):e15253
346. Kalantari K, Chang JN, Ronco C, Rosner MH. Assessment of intravascular volume status and volume responsiveness in critically ill patients. Kidney International 2013: 83:1017-1028
347. Ely EW, Smith AC, Chiles C et al. Radiologic determination of intravascular volume status using portable, digital chest radiography: a prospective investigation in 100 patients. Crit Care Med 2001; 29 :1502-1512
348. Rivas-Lasarte M, Álvarez-García J, Fernández-Martínez J, Maestro A, López-López L, Solé-González E, Pirla MJ, Mesado N, Mirabet S, Fluvià P, Brossa V, Sionis A, Roig E, Cinca J. Lung ultrasound-guided treatment in ambulatory patients with heart failure: a randomized controlled clinical trial (LUS-HF study). Eur J Heart Fail. 2019 Dec;21(12): 1605-1613
349. Martens P, Verbrugge FH, Boonen L, Nijst P, Dupont M, Mullens W. Value of routine investigations to predict loop diuretic down-titration success in stable heart failure. Int J Cardiol 2018;250:171-175.
350. Vardeny O, Claggett B, Kachadourian J, et al. Reduced loop diuretic use in patients taking sacubitril/valsartan compared with enalapril: the PARADIGM-HF trial. Eur J Heart Fail. 2019;21(3):337-341.
351. Delanaye P, Scheen AJ. The diuretic effects of SGLT2 inhibitors: A comprehensive review of their specificities and their role in renal protection. Diabetes Metab. 2021 Nov;47(6):101285
352. Verma A, Patel AB, Waikar SS. SGLT2 Inhibitor: Not a Traditional Diuretic for Heart Failure. Cell Metabolism 2020: 32 (1): 13-14
353. Schulze PC, Bogoviku J, Westphal J, Aftanski P, Haertel F et al. Effects of Early Empagliflozin Initiation on Diuresis and Kidney Function in Patients With Acute Decompensated Heart Failure (EMPAG-HF). Circulation. 2022;146:289-298
354. Rohde LE, Rover MM, Figueiredo Neto JA, et al. Short-term diuretic withdrawal in stable outpatients with mild heart failure and no fluid retention receiving optimal therapy: a double-blind, multicentre, randomized trial. Eur Heart J. 2019;40(44):3605-3612.
355. Lee VC, Rhew DC, Dylan M, et al. Meta-analysis: angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction. Ann Intern Med 2004;141:693-704.
356. Heran BS, Musini VM, Bassett K, Taylor RS, Wright JM. Angiotensin receptor blockers for heart failure. Cochrane Database of Systematic Reviews 2012, Issue 4. Art. No.: CD003040.
357. Tai C, Gan T, Zou L, Sun Y, Zhang Y et al. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on cardiovascular events in patients with heart failure: a meta-analysis of randomized controlled trials. BMC Cardiovascular Disorders (2017) 17:257
358. Kostis WJ, Sargsyan D, Mekkaoui C, Moreyra AE, Cabrera J et al. Association of orthostatic hypertension with mortality in the Systolic Hypertension in the Elderly Program. J Hum Hypertens. 2019 Oct;33(10):735-740.
359. Bakris GL, Weir MR. Angiotensin converting enzyme inhibitor associated elevations in serum creatinine. Is this a cause for concern? Arch Intern Med 2000;160:685-93.
360. Pereira ANP, Júnior RA, Macedo CRB, Teixeira RRDN, Magalhães IR, et al. Angiotensin-Converting Enzyme Inhibitor-Induced Cough Prevalence in Refractory Hypertensive Patients. J Hypertens Manag 2016: 2:015
361. Banerji A, Blumenthal KG, Lai KH, Zhou L. Epidemiology and Incidence of ACE Inhibitor Angioedema Utilizing a Large Electronic Health Record. J Allergy Clin Immunol Pract. 2017 ; 5(3): 744–749
362. Brown T, Gonzalez J, Monteleone C. Angiotensin-converting enzyme inhibitor–induced angioedema: A review of the literature. J Clin Hyper 2017: 19 : 1377-1382
363. Caldeira D, David C, Sampaio C. Tolerability of angiotensin-receptor blockers in patients with intolerance to angiotensin-converting enzyme inhibitors: a systematic review and meta-analysis. Am J Cardiovasc Drugs. 2012;12:263-277.
364. Knecht SE, Dunn SP, Macaulay TE. Angioedema related to angiotensin inhibitors. J Pharm Pract. 2014;27:461-465.
365. Yusuf S; Teo KK; Pogue J; Dyal L; Copland I; Schumacher H; Dagenais G; Sleight P; Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events.N Engl J Med. 2008; 358(15):1547-59
366. Okumura N, Jhund PS, Gong I, et al on behalf of the PARADIGM-HF Investigators and Committees. Effects of sacubitril/valsartan in the PARADIGM-HF Trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) according to background therapy. Circ Heart Fail 2016;9:e003212.
367. Zheng C, Dai H, Huang J, Lin M, Zheng Q et al. The efficacy and safety of Sacubitril/Valsartan in the treatment of chronic heart failure: a meta-analysis. Am J Transl Res 2021;13(11):12114-12128
368. Pfeffer MA, Claggett B, Lewis EF, Granger CB, Køber L et al for the PARADISE-MI Investigators and Committees. Angiotensin Receptor–Neprilysin Inhibition in Acute Myocardial Infarction. N Engl J Med 2021;385:1845-55
369. Mohebi R, Liu Y, Piña IL, Prescott MF, Butler J et al. Dose-Response to Sacubitril/Valsartan in Patients With Heart Failure and Reduced Ejection Fraction. J Am Coll Cardiol 2022;80:1529–1541
370. The RESOLVD Investigators. Effects of metoprolol CR in patients with ischemic and dilated cardiomyopathy. Circulation 2000;101:378-84.
371. Foody JM, Farrell MH, Krumholz HM. Beta-blocker therapy in heart failure: scientific review. JAMA 2002;287:883-9.
372. van Veldhuisen DJ, Cohen-Solal A, Bohm M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: data from SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). J Am Coll Cardiol 2009;53:2150-8.
373. Cooper LB, Lippmann SJ, Greiner MA, Sharma A, Kelly JP et al. Use of Mineralocorticoid Receptor Antagonists in Patients With Heart Failure and Comorbid Diabetes Mellitus or Chronic Kidney Disease. JAHA 2017;6:e006540.
374. Ferreira JP, Rossello X, Eschalier R, McMurray JJV, Pocock S et al. MRAs in Elderly HF Patients: Individual Patient-Data Meta-Analysis of RALES, EMPHASIS-HF, and TOPCAT. JACC Heart Fail. 2019;7(12):1012-1021

375. Filippatos G, Anker SD, Pitt B, Rossing P, Joseph A et al. Finerenone and Heart Failure Outcomes by Kidney Function/Albuminuria in Chronic Kidney Disease and Diabetes. J Am Coll Cardiol HF. 2022 Nov, 10 (11) 860-870
376. Pitt B., Filippatos G., Agarwal R., et al. "Cardiovascular events with finerenone in kidney disease and type 2 diabetes". N Engl J Med 2021;385:24: 2252-2263.
377. Filippatos G., Anker S.D., Agarwal R., et al. "Finerenone reduces risk of incident heart failure in patients with chronic kidney disease and type 2 diabetes: analyses from the FIGARO-DKD trial". Circulation 2022;145:6: 437-447.
378. Agarwal R., Filippatos G., Pitt B., et al. "Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis". Eur Heart J 2022;43:6: 474-484.
379. Kosiborod MN, Jhund PS, Docherty KF, et al. Effects of Dapagliflozin on Symptoms, Function, and Quality of Life in Patients With Heart Failure and Reduced Ejection Fraction: Results From the DAPA-HF Trial. Circulation. 2020;141 (2):90-99.
380. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;383(15):1413-1424.
381. Butler J, Anker SD, Filippatos G, et al. Empagliflozin and health-related quality of life outcomes in patients with heart failure with reduced ejection fraction: the EMPEROR-Reduced trial. Eur Heart J. 2021;42(13):1203-1212.
382. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T et al. for the DAPA-CKD Trial Committees and Investigators. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2020; 383:1436-1446
383. Abdelnabi M, Ahmed A, Almaghraby A, Saleh Y, Badran H. Ivabradine and AF: Coincidence, Correlation or a New Treatment? Arrhythm Electrophysiol Rev. 2020 Feb 12;8(4):300-303.
384. Martin RIR, Pogoryelova O, Koref MS, Bourke JP, Teare MD, Keavney BD. Atrial fibrillation associated with ivabradine treatment: meta-analysis of randomised controlled trials. Heart 2014;100:1506-1510
385. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376(9744):875-885.
386. Swedberg K, Komajda M, Böhm M, et al. Effects on outcomes of heart rate reduction by ivabradine in patients with congestive heart failure: is there an influence of beta-blocker dose?: findings from the SHIFT (Systolic Heart failure treatment with the I(f) inhibitor ivabradine Trial) study. J Am Coll Cardiol. 2012;59(22):1938-1945.
387. Böhm M, Borer J, Ford I, et al. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. Clin Res Cardiol. 2013;102(1):11-22.
388. Fox K, Ford I, Steg PG, et al. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:807
389. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2020;382(20):1883-1893.
390. Thadani U. Challenges with nitrate therapy and nitrate tolerance: prevalence, prevention, and clinical relevance. Am J Cardiovasc Drugs. 2014;14(4):287-301.
391. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. N Engl J Med. 1986;314(24):1547-1552.
392. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med. 2004;351(20):2049-2057.
393. The Digitalis Investigation Group. The Effect of Digoxin on Mortality and Morbidity in Patients with Heart Failure. N Engl J Med. 1997;336(8):525-533.
394. Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. PROVED Investigative Group. J Am Coll Cardiol. 1993;22(4):955-962.
395. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. N Engl J Med. 1993;329(1):1-7.
396. Fauchier L, Grimard C, Pierre B, et al. Comparison of beta blocker and digoxin alone and in combination for management of patients with atrial fibrillation and heart failure. Am J Cardiol. 2009;103(2):248-254.
397. Kotecha D, Bunting KV, Gill SK, et al; for the Rate Control Therapy Evaluation in Permanent Atrial Fibrillation (RATE-AF) Team. Effect of digoxin vs bisoprolol for heart rate control in atrial fibrillation on patient-reported quality of life: the RATE-AF randomized clinical trial. JAMA. JAMA. 2020;324(24):2497-2508.
398. Fauchier L, Laborie G, Clementy N, Babuty D. Beta-blockers or Digoxin for Atrial Fibrillation and Heart Failure? Card Fail Rev. 2016 May;2(1):35-39
399. Kim D, Yang PS, You SC. Treatment timing and the effects of rhythm control strategy in patients with atrial fibrillation: nationwide cohort study. BMJ. 2021;373:n991.
400. Bavishi, C., Khan, A. R., & Ather, S. Digoxin in patients with atrial fibrillation and heart failure: A meta-analysis. Int J Cardiol 2015: 188: 99-101.
401. Lopes RD, Rordorf R, De Ferrari GM, et al. Digoxin and Mortality in Patients With Atrial Fibrillation. J Am Coll Cardiol. 2018;71(10):1063-1074
402. Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA. 2003;289(7):871-878.
403. Adams KF, Jr., Patterson JH, Gattis WA, et al. Relationship of serum digoxin concentration to mortality and morbidity in women in the digitalis investigation group trial: a retrospective analysis. J Am Coll Cardiol. 2005;46(3):497-504.
404. Madelaire C, Gislason G, Kristensen SL, et al. Low-Dose Aspirin in Heart Failure Not Complicated by Atrial Fibrillation: A Nationwide Propensity-Matched Study. JACC Heart Fail. 2018;6(2):156-167.
405. Cokkinos DV, Haralabopoulos GC, Kostis JB, Toutouzas PK. Efficacy of antithrombotic therapy in chronic heart failure: the HELAS study. Eur J Heart Fail. 2006;8(4):428-432.
406. Cleland JG, Findlay I, Jafri S, et al. The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. Am Heart J. 2004;148(1):157-164.

407. Lip GY, Shantsila E. Anticoagulation versus placebo for heart failure in sinus rhythm. Cochrane Database Syst Rev. 2014;2014(3):Cd003336.
408. Zannad F, Anker SD, Byra WM, et al. Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease. N Engl J Med. 2018;379(14):1332-1342
409. Homma S, Thompson JL, Pullicino PM, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med. 2012;366(20):1859-1869.
410. Massie BM, Collins JF, Ammon SE, et al. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. Circulation. 2009;119(12):1616-1624.
411. Mehra MR, Vaduganathan M, Fu M, et al. A comprehensive analysis of the effects of rivaroxaban on stroke or transient ischaemic attack in patients with heart failure, coronary artery disease, and sinus rhythm: the COMMAND ER HF trial. Eur Heart J. 2019;40(44):3593-3602.
412. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2019;74(1):104-132.
413. Shantsila E, Lip GYH. Antiplatelet versus anticoagulation treatment for patients with heart failure in sinus rhythm. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD003333.
414. Steffel J, Collins R, Antz M, et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vita min K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace. 2021;23(10):1612-1676.
415. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955-962.
416. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J.2021;42(5):373-498.
417. Lattuca B, Bouziri N, Kerneis M, et al., on behalf of the ACTION Study Group. Antithrombotic Therapy for Patients With Left Ventricular Mural Thrombus. J Am Coll Cardiol 2020;75:1676-1685.
418. Ali, Z., Isom, N., Dalia, T. et al. Direct oral anticoagulant use in left ventricular thrombus.2020: Thrombosis J :18: 29
419. Dalia, T., Lahan, S., Ranka, S. et al. Warfarin versus direct oral anticoagulants for treating left ventricular thrombus: a systematic review and meta-analysis. Thrombosis J 2021: 19: 7
420. Camaj A, Fuster V, Giustino G, Bienstock SW, Sternheim D, Mehran R, Dangas GD, Kini A, Sharma SK, Halperin J, Dweck MR, Goldman ME. Left Ventricular Thrombus Following Acute Myocardial Infarction: JACC State-of-the-Art Review. J Am Coll Cardiol. 2022 Mar 15;79(10):1010-1022
421. Swedberg K, Olsson LG, Charlesworth A, et al. Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET. Eur Heart J. 2005;26(13):1303-1308.
422. Mogensen UM, Jhund PS, Abraham WT, et al. Type of Atrial Fibrillation and Outcomes in Patients With Heart Failure and Reduced Ejection Fraction. J Am Coll Cardiol. 2017;70(20):2490-2500.
423. Smit MD, Moes ML, Maass AH, et al. The importance of whether atrial fibrillation or heart failure develops first. Eur J Heart Fail. 2012;14(9):1030-1040.
424. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation. 2003;107(23):2920-2925.
425. Kirchhof, P, Camm, AJ, Goette, A, . EAST-AFNET 4 Trial Investigators. Early rhythm-control therapy in patients with atrial fibrillation. N Engl J Med. 2020;383:1305-1316
426. Olshansky B, Rosenfeld CE, Warner AL, et al. The Atrial Fibrillation Follow Up Investigation of Rhythm Management (AFFIRM) Study; Approaches to control rate in atrial fibrillation. J Am Col Cardiol 2004;43:1201-8.
427. Van Gelder IC, Wyse DG, Chandler ML, Cooper HA, Olshansky B et al. RACE and AFFIRM Investigators. Does intensity of rate-control influence outcome in atrial fibrillation? An analysis of pooled data from the RACE and AFFIRM studies. Europace 2006;8:935942.
428. Nikolaidou T, Channer KS. Chronic atrial fibrillation: a systematic review of medical heart rate control management. Postgrad Med J. 2009;85(1004):303-312.
429. Kotecha D, Holmes J, Krum H, et al. Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. Lancet. 2014;384(9961):2235-2243.
430. Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I, Cleland JG. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? J Am Coll Cardiol. 2003;42(11):1944-1951.
431. Ziff OJ, Lane DA, Samra M, et al. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. BMJ. 2015;351:h4451.
432. Mulder BA, Van Veldhuisen DJ, Crijns HJ, et al. Digoxin in patients with permanent atrial fibrillation: data from the RACE II study. Heart Rhythm. 2014;11(9):1543-1550.
433. Hofmann R, Steinwender C, Kammler J, Kypta A, Leisch F. Effects of a high dose intravenous bolus amiodarone in patients with atrial fibrillation and a rapid ventricular rate. Int J Cardiol 2006;110:27-32.
434. Hofmann R, Wimmer G, Leisch F. Intravenous amiodarone bolus immediately controls heart rate in patients with atrial fibrillation accompanied by severe congestive heart failure. Heart 2000;84:635.
435. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med. 2008;358(25):2667-2677.
436. Parkash R, Wells GA, Rouleau J, Talajic M, Essebag V et al. Randomized Ablation-Based Rhythm-Control Versus Rate-Control Trial in Patients With Heart Failure and Atrial Fibrillation: Results from the RAFT-AF trial. Circulation. 2022;145:1693-1704

437. K.M. Trulock, S.M. Narayan, J.P. Piccini.Rhythm control in heart failure patients with atrial fibrillation: contemporary challenges including the role of ablation.J Am Coll Cardiol 2014: 64: 710-721
438. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med. 1991;324(12):781-788.
439. Hayashi M, Shimizu W, Albert CM. The spectrum of epidemiology underlying sudden cardiac death. Circ Res. 2015;116(12):1887-1906.
440. Wellens HJ, Schwartz PJ, Lindemans FW, et al. Risk stratification for sudden cardiac death: current status and challenges for the future. Eur Heart J. 2014;35(25):1642-1651.
441. Luu M, Stevenson WG, Stevenson LW, Baron K, Walden J. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. Circulation. 1989;80(6):1675-1680.
442. Wang YS, Scheinman MM, Chien WW, Cohen TJ, Lesh MD, Griffin JC. Patients with supraventricular tachycardia presenting with aborted sudden death: incidence, mechanism and long-term follow-up. J Am Coll Cardiol.1991;18(7): 1711-1719.
443. Al-Gobari M, El Khatib C, Pillon F, Gueyffier F. β-Blockers for the prevention of sudden cardiac death in heart failure patients: a meta-analysis of randomized controlled trials. BMC Cardiovasc Disord. 2013;13:52.
444. Domanski MJ, Exner DV, Borkowf CB, Geller NL, Rosenberg Y, Pfeffer MA. Effect of angiotensin converting enzyme inhibition on sudden cardiac death in patients following acute myocardial infarction. A meta-analysis of randomized clinical trials. J Am Coll Cardiol. 1999;33(3):598-604.
445. Cleland JG, Erhardt L, Murray G, Hall AS, Ball SG. Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure. A report from the AIRE Study Investigators. Eur Heart J. 1997;18(1):41-51.
446. Teo KK, Mitchell LB, Pogue J, Bosch J, Dagenais G, Yusuf S. Effect of ramipril in reducing sudden deaths and nonfatal cardiac arrests in high-risk individuals without heart failure or left ventricular dysfunction. Circulation. 2004;110(11):1413-1417.
447. Solomon SD, Wang D, Finn P, et al. Effect of candesartan on cause-specific mortality in heart failure patients: the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) program. Circulation. 2004;110(15):2180-2183.
448. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial--the Losartan Heart Failure Survival Study ELITE II. Lancet. 2000;355(9215):1582-1587.
449. Naccarella F, Naccarelli GV, Maranga SS, et al. Do ACE inhibitors or angiotensin II antagonists reduce total mortality and arrhythmic mortality? A critical review of controlled clinical trials. Curr Opin Cardiol. 2002;17(1):6-18.
450. Rohde LE, Chatterjee NA, Vaduganathan M, et al. Sacubitril/Valsartan and Sudden Cardiac Death According to Implantable Cardioverter-Defibrillator Use and Heart Failure Cause: A PARADIGM-HF Analysis. JACC Heart Fail. 2020;8(10):844-855.
451. Desai AS, McMurray JJ, Packer M, et al. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. Eur Heart J. 2015;36(30):1990-1997.
452. Bapoje SR, Bahia A, Hokanson JE, et al. Effects of mineralocorticoid receptor antagonists on the risk of sudden cardiac death in patients with left ventricular systolic dysfunction: a meta-analysis of randomized controlled trials. Circ Heart Fail. 2013;6(2):166-173.
453. Rossello X, Ariti C, Pocock SJ, et al. Impact of mineralocorticoid receptor antagonists on the risk of sudden cardiac death in patients with heart failure and left-ventricular systolic dysfunction: an individual patient-level meta-analysis of three randomized-controlled trials. Clin Res Cardiol. 2019;108(5):477-486.
454. Al-Gobari M, Le H-H, Fall M, Gueyffier F, Burnand B. No benefits of statins for sudden cardiac death prevention in patients with heart failure and reduced ejection fraction: A meta-analysis of randomized controlled trials. PLoS One. 2017;12(2):e0171168-e0171168.
455. Rahimi K, Majoni W, Merhi A, Emberson J. Effect of statins on ventricular tachyarrhythmia, cardiac arrest, and sudden cardiac death: a meta-analysis of published and unpublished evidence from randomized trials. Eur Heart J. 2012;33(13):1571-1581.
456. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER et al. ESC Scientific Document Group, 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Developed by the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC) Endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC), Eur Heart J 2022: 43(40): 3997-4126,
457. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. Eur Heart J 2000;21: 2071-2078.
458. Schrage B, Uijl A, Benson L, Westermann D, Ståhlberg M, Stolfo D, et al. Association between use of primary-pre vention implantable cardioverter-defibrillators and mortality in patients with heart failure: a prospective propensity score-matched analysis from the Swedish Heart Failure Registry. Circulation 2019;140:1530-1539
459. Zabel M, Willems R, Lubinski A, Bauer A, Brugada J, Conen D, et al. Clinical effectiveness of primary prevention implantable cardioverter-defibrillators: results of the EU-CERT-ICD controlled multicentre cohort study. Eur Heart J 2020;41:3437-3447.
460. Poole JE, Olshansky B, Mark DB, et al. Long-Term Outcomes of Implantable Cardioverter-Defibrillator Therapy in the SCD-HeFT. J Am Coll Cardiol. 2020;76(4):405-415.
461. Steinberg JS, Martins J, Sadanandan S, et al. Antiarrhythmic drug use in the implantable defibrillator arm of the Antiarrhythmics Versus Implantable Defibrillators (AVID) Study. Am Heart J. 2001;142(3):520-529.

462. Santangeli P, Muser D, Maeda S, et al. Comparative effectiveness of antiarrhythmic drugs and catheter ablation for the prevention of recurrent ventricular tachycardia in patients with implantable cardioverter-defibrillators: A systematic review and meta-analysis of randomized controlled trials. Heart Rhythm. 2016;13(7):1552-1559.
463. Vergara P, Tung R, Vaseghi M, Brombin C, Frankel DS, Di Biase L, et al. Successful ventricular tachycardia ablation in patients with electrical storm reduces recurrences and improves survival. Heart Rhythm 2018;15:48-55
464. Elkayam U, Amin J, Mehra A, Vasquez J, Weber L, Rahimtoola SH. A prospective, randomized, double-blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy with that of isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. Circulation. 1990;82(6):1954-1961.
465. Littler WA, Sheridan DJ. Placebo controlled trial of felodipine in patients with mild to moderate heart failure. UK Study Group. Br Heart J. 1995;73(5):428-433.
466. Goldstein RE, Boccuzzi SJ, Cruess D, Nattel S. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. The Adverse Experience Committee; and the Multicenter Diltiazem Postinfarction Research Group. Circulation. 1991;83(1):52-60.
467. Danish Study Group on Verapamil in Myocardial Infarction. Effect of verapamil on mortality and major events after acute myocardial infarction (The Danish Verapamil Infarction Trial II-DAVIT II). Am J Cardiol. 1990;66(10):779-785.
468. Packer M, O'Connor CM, Ghali JK, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group. N Engl J Med. 1996;335(15):1107-1114.
469. Packer M, Carson P, Elkayam U, et al. Effect of amlodipine on the survival of patients with severe chronic heart failure due to a nonischemic cardiomyopathy: results of the PRAISE-2 study (prospective randomized amlodipine survival evaluation 2). JACC Heart Fail. 2013;1(4):308-314.
470. Cohn JN, Ziesche S, Smith R, et al. Effect of the calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril: V-HeFT III. Vasodilator-Heart Failure Trial (V-HeFT) Study Group. Circulation. 1997;96(3):856-863.
471. Chapman N, Dobson J, Wilson S, Dahlöf B, Sever PS et al. on behalf of the Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Effect of Spironolactone on Blood Pressure in Subjects With Resistant Hypertension. Hypertension. 2007;49:839-845
472. Kotecha D, Flather MD, Altman DG, et al. Heart Rate and Rhythm and the Benefit of Beta-Blockers in Patients With Heart Failure. J Am Coll Cardiol. 2017;69(24):2885-2896.
473. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845-53.
474. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140-50.
475. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539-49.
476. Goldenberg I, Kutyifa V, Moss AJ. Survival with cardiac-resynchronization therapy. N Engl J Med 2014;371:477-478.
477. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329-38.
478. Abraham WT, Young JB, Leon AR, et al. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. Circulation 2004;110:2864-8.
479. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: Developed by the Task Force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC) With the special contribution of the European Heart Rhythm Association (EHRA). Eur Heart J. 2021;42(35):3427-3520.
480. Birnie DH, Ha A, Higginson L, Sidhu K, Green M, Philippon F, Thibault B, Wells G, Tang A. Impact of QRS morphology and duration on outcomes after cardiac resynchronization therapy: results from the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT). Circ Heart Fail 2013;6:1190-1198.
481. Linde C, Leclercq C, Rex S, Garrigue S, Lavergne T et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. J Am Coll Cardiol 2002;40:111-118.
482. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol 2008;52:1834-43.
483. Auricchio A, Stellbrink C, Butter C, Sack S, Vogt Jet al. Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. J Am Coll Cardiol 2003;42:2109-2116.
484. Tang A, Wells G, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010;363:2385-95.
485. Ruschitzka F, Abraham WT, Singh JP, et al for the EchoCRT Study Group. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med 2013;369:1395-405.
486. Beshai JF, Grimm RA, Nagueh SF, et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. N Engl J Med 2007;357(24):2461-71.
487. Donahue T, Niazi I, Leon A, et al. One year follow-up of CRT in narrow QRS patients with mechanical dyssynchronie. Circulation 2008:118:949
488. Gasparini M, Auricchio A, Metra M, et al. Long-term survival in patients undergoing cardiac resynchronization therapy: the importance of performing atrio-ventricular junction ablation in patients with permanent atrial fibrillation. Eur Heart J 2008;29:1644-52.

489. Khadjooi K, Foley PW, Chalil S, et al. Long-term effects of cardiac resynchronisation therapy in patients with atrial fibrillation. Heart 2008;94:879-83.
490. Brignole M, Pokushalov E, Pentimalli F, et al; APAF-CRT Investigators. A randomized controlled trial of atrioventricular junction ablation and cardiac resynchronization therapy in patients with permanent atrial fibrillation and narrow QRS. Eur Heart J 2018:39:3999-4008.
491. Padala SK, Master VM, Terricabras M, et al. Initial experience, safety, and feasibility of left bundle branch area pacing: a multicenter prospective study. JACC Clin Electrophysiol. 2020;6(14):1773-1782
492. Vijayaraman P, Ponnusamy S, Cano Ó, et al. Left bundle branch area pacing for cardiac resynchronization therapy: results from the International LBBAP Collaborative Study Group. J Am Coll Cardiol EP. 2021;7(2):135-147
493. Pujol-Lopez M, Jiménez-Arjona R, Garre P, Guasch E, Borràs R et al. Conduction System Pacing vs Biventricular Pacing in Heart Failure and Wide QRS Patients: LEVEL-AT Trial. J Am Coll Cardiol EP. 2022 Nov, 8 (11) 1431-1445
494. Vijayaraman P, Zalavadia D, Haseeb A, Dye C, Madan N et al. Clinical outcomes of conduction system pacing compared to biventricular pacing in patients requiring cardiac resynchronization therapy. Heart Rhythm 2022: 19: 1263-1271
495. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002; 346:877-83.
496. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225-37.
497. Kadish A, Dyer A, Daubert JP, et al for the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 2004;350:2151-8.
498. Desai AS, Fang JC, Maisel WH, Baughman KL. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. JAMA 2004;292:2874-9.
499. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G et al. STICH Investigators. Coronary-artery bypass surgery in patients with left ventricular dysfunction. N Engl J Med 2011;364:1607-1616.
500. Velazquez EJ, Lee KL, Jones RH, et al for the STICH Investigators. Coronary artery bypass surgery in patients with ischemic cardiomyopathy. N Engl J Med 2016;374:1511-20.
501. Perera D, Clayton T, O'Kane PD, Greenwood JP, Weerackody R eat al for the REVIVED-BCIS2 Investigators. Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction. DOI: 10.1056/NEJMoa2206606
502. Jones RH, Velazquez EJ, Michler RE, et al. Coronary bypass surgery with or without surgical ventricular reconstruction. N Engl J Med. 2009;360(17):1705-17.
503. Dor V, Civaia F, Alexandrescu C, et al. Favorable effects of left ventricular reconstruction in patients excluded from the Surgical Treatments for Ischemic Heart Failure (STICH) trial. J Thorac Cardiovasc Surg. 2011;141:905-916, 916e1-4.
504. Holley CT, Harvey L, John R. Left ventricular assist devices as a bridge to cardiac transplantation. J Thorac Dis. 2014;6(8):1110-1119.
505. Jakovljevic DG, Yacoub MH, Schueler S, et al. Left Ventricular assist device as a bridge to recovery for patients with advanced heart failure. J Am Coll Cardiol. 2017;69:1924-1933.
506. Rogers JG, Butler J, Lansman SL, et al. Chronic mechanical circulatory support for inotrope-dependent heart failure patients who are not transplant candidates: results of the INTrEPID Trial. J Am Coll Cardiol. 2007;50:741-747.
507. Baras Shreibati J, Goldhaber-Fiebert JD, Banerjee D, Owens DK, Hlatky MA. Cost-Effectiveness of Left Ventricular Assist Devices in Ambulatory Patients With Advanced Heart Failure. JACC Heart Fail. 2017 Feb;5(2):110-119.
508. Starling RC, Estep JD, Horstmanshof DA, et al. Risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients: the ROADMAP study 2-year results. J Am Coll Cardiol HF. 2017;5:518-527.
509. Health Quality Ontario. Left Ventricular Assist Devices for Destination Therapy: A Health Technology Assessment. Ont Health Technol Assess Ser. 2016 Feb 8;16(3):1-60. PMID: 27026798; PMCID: PMC4761917.
510. Tsuji K, Sabata Y, Nochioka K et al. Characterization of heart failure patients with mid-range left ventricular function - a report from the CHART-2 study. EJHF 2017:19;1258-69.
511. Packer M, Butler J, Zannad F et al. Effect of Empagliflozin on worsening heart failure in patients with heart failure and preserved ejection fraction: the EMPEROR-Preserved Trial. Circ 2021:144;1284-1294
512. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E et al . Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021; 385:1451-1461
513. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D et al for the DELIVER Trial Committees and Investigators. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. Published on line 27th August 2022. N Engl J Med 2022: DOI: 10.1056/NEJMoa2206286
514. Ellison DH, Felker GM. Diuretics treatment in heart failure. NEJM 2017:377;1964-1975.
515. Faselis C, Arundel C, Patel S et al. Loop diuretic prescription and 30-day outcomes in older patients with heart failure. JACC 2020:76;669-679.
516. Cleland JGF, Bunting KV, Flather MD et al. Beta blockers for heart failure with reduced, mid-range and preserved HF: an individual patient level analysis of double-blind randomized trial. Eur Heart J. 2018;39:26-35.
517. Solomon SD, McMurray JJV, Anand IS et al, Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. NEJM 2019:381;1609-1620.
518. Lund L. Heart failure with mid-range ejection fraction. Lessons from CHARM. Card Fail Rev 2018:4(2);70-72.
519. Savarese G, Stolfo D, Sinagra G et al. Heart failure with mid-range or mildly reduced ejection fraction. Nature Rev Card 2022:19:100-116.
520. Wilcox JE, Fang JC, Margulies KB et al. Heart failure with recovered left ventricular ejection fraction: JACC scientific Expert Panel. JACC 2020:70:719-734.

521. Shah SJ, Katz DH, Deo RC. Phenotypic spectrum of heart failure with preserved ejection fraction. Heart Fail Clin. 2014;10(3):407-418.
522. Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA, Paulus WJ. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap.Circulation. 2016; 134:73-90
523. Roh J, Hill JA, Singh A, Valero-Muñoz M, Sam F. Heart Failure With Preserved Ejection Fraction: Heterogeneous Syndrome, Diverse Preclinical Models. Circulation Research. 2022;130:1906-1925
524. Mentz RJ, Kelly JP, von Lueder TG, et al. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. J Am Coll Cardiol. 2014;64: 2281-2293.
525. Tromp J, Teng TH, Tay WT, Hung CL, Narasimhan C, Shimizu W, et al. Heart failure with preserved ejection fraction in Asia. Eur J Heart Fail 2019;21:23-36.
526. Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251
527. Wehner GJ, Jing L, Haggerty CM, Suever JD, Leader JB, Hartzel DN, Kirchner HL, Manus JNA, James N, Ayar Z, Gladding P, Good CW, Cleland JGF, Fornwalt BK. Routinely reported ejection fraction and mortality in clinical practice: where does the nadir of risk lie? Eur Heart J 2020;41:12491257.
528. Stewart S, Playford D, Scalia GM, Currie P, Celermajer DS, Prior D, Codde J, Strange G, NEDA Investigators. Ejection fraction and mortality: a nationwide register-based cohort study of 499 153 women and men. Eur J Heart Fail 2021;23:406-416.
529. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. Nat Rev Cardiol 2020;17:559-573
530. Henry, A., C. Y. Lee, W. Y. Haniff, W. Isa, et al. "Malaysian Heart Failure (MYHF) Registry Substantiates High Burden of Comorbidities across the Continuum of Ejection Fraction in Malaysian HF Patients." Int J Cardiology 2021: 345 : 12. Available at : https://doi.org/10.1016/j.ijcard.2021.10.055
531. Borlaug BA, Kane GC, Melenovsky V, Olson TP. Abnormal right ventricular-pulmonary artery coupling with exercise in heart failure with preserved ejection fraction.Eur Heart J. 2016; 37:3293-3302
532. Iwanaga Y, Nishi I, Furuichi S, Noguchi T, Sase K, Kihara Y, Goto Y, Nonogi H. B-type natriuretic peptide strongly reflects diastolic wall stress in patients with chronic heart failure: comparison between systolic and diastolic heart failure. J Am Coll Cardiol. 2006;47:742-748
533. Buckley LF, Canada JM, Del Buono MG, Carbone S, Trankle CR, Billingsley H, Kadariya D, Arena R, Van Tassell BW, Abbate A. Low NT-proBNP levels in overweight and obese patients do not rule out a diagnosis of heart failure with preserved ejection fraction. ESC Heart Fail. 2018 Apr;5(2):372-378.
534. Meijers WC, Hoekstra T, Jaarsma T, van Veldhuisen DJ, de Boer RA. Patients with heart failure with preserved ejection fraction and low levels of natriuretic peptides. Neth Heart J. 2016 Apr;24(4):287-95.
535. Richards M, Di Somma S, Mueller C, Nowak R, Peacock WF, Ponikowski P, Möckel M, Hogan C, Wu AH, Clopton P, Filippatos GS, Anand I, Ng L, Daniels LB, Neath SX, Shah K, Christenson R, Hartmann O, Anker SD, Maisel A. Atrial fibrillation impairs the diagnostic performance of cardiac natriuretic peptides in dyspneic patients. JACC Heart Fail 2013;1:192-199
536. Pieske B, Tschöpe C, De Boer RA, Fraser AG, Anker SD, Donal E, et al. How to diagnose heart failure with preserved ejection fraction: The HFA-PEFF diagnostic algorithm: A consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J 2019;40:3297-3317
537. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. Circulation. 2018;138:861-870
538. Sanders-van Wijk S, Barandiarán Aizpurua A, Brunner-La Rocca HP, Henkens MTHM, Weerts J, Knackstedt C, Uszko-Lencer N, Heymans S, van Empel V. The HFA-PEFF and H2 FPEF scores largely disagree in classifying patients with suspected heart failure with preserved ejection fraction. Eur J Heart Fail. 2021 May;23(5):838-840.
539. Adamczak, D.M., Oduah, MT., Kiebalo, T. et al. Heart Failure with Preserved Ejection Fraction-a Concise Review. Curr Cardiol Rep 200: 22: 82
540. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, et al. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the Framingham Heart Study of the National Heart, Lung, and Blood Institute. Circulation. 2009;119:3070-7.
541. Maréchaux S, Six-Carpentier MM, Bouabdallaoui N, Montaigne D, Bauchart JJ, Mouquet F, Auffray JL, Le Tourneau T, Asseman P, LeJemtel TH, Ennezat PV. Prognostic importance of comorbidities in heart failure with preserved left ventricular ejection fraction. Heart Vessels. 2011 May;26(3):313-20
542. CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC, Committee ASA, et al. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol. 2006;47:76-84
543. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006;355(3):251-9
544. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007;50(8):768-77
545. Tadic M, Cuspidi C. Obesity and heart failure with preserved ejection fraction: a paradox or something else? Heart Fail Rev. 2019 May;24(3):379-385
546. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, et al. Relation of Disease Pathogenesis and Risk Factors to Heart Failure With Preserved or Reduced Ejection Fraction: Insights From the Framingham Heart Study of the National Heart, Lung, and Blood Institute. Circulation. 2009;119(24):3070-7

547. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, Eggebeen J, Nicklas BJ. Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial. JAMA. 2016;315:36-46.
548. Kitzman DW, Brubaker PH, Morgan TM, Stewart KP, Little WC. Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. Circ Heart Fail. 2010;3:659-67.
549. W.R. Miranda, J.A. Batsis, M.G. Sarr, et al.Impact of bariatric surgery on quality of life, functional capacity, and symptoms in patients with heart failure. Obes Surg, 2013:23: 1011-1015
550. Y.J. Shimada, Y. Tsugawa, D.F. Brown, K. Hasegawa. Bariatric surgery and emergency department visits and hospitalizations for heart failure exacerbation: population-based, self-controlled series. J Am Coll Cardiol, 2016: 67 : 895-903
551. Fukuta H, Goto T, Wakami K, et al. Effects of drug and exercise intervention on functional capacity and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. Eur J Prev Cardiol 2016;23:78-85.
552. Taylor RS, Davies EJ, Dalal HM, Davis R, Doherty P, Cooper C, Holland DJ, Jolly K, Smart NA. Effects of exercise training for heart failure with preserved ejection fraction: a systematic review and meta-analysis of comparative studies. Int J Cardiol. 2012 Dec 15;162(1):6-13.
553. Xie X, Atkins E, Lv J, Bennett A, Neal B, Ninomiya T, Woodward M, MacMahon S, Turnbull F, Hillis GS, Chalmers J, Mant J, Salam A, Rahimi K, Perkovic V, Rodgers A. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet. 2016 Jan 30;387(10017):435-43.
554. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387:957-967.
555. Piller LB, Baraniuk S, Simpson LM, et al. Long-term follow-up of participants with heart failure in the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). Circulation. 2011;124: 1811-1818.
556. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged >75 years: a randomized clinical trial. JAMA. 2016;315: 2673-2682.
557. SPRINT Research Group, Wright JT Jr, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373:2103-2116.
558. Bavishi C, Chatterjee S, Ather S, Patel D, Messerli FH. Beta-blockers in heart failure with preserved ejection fraction: a meta-analysis. Heart Fail Rev. 2015 Mar;20(2):193-201.
559. Gevaert AB, Kataria R, Zannad F, et al. Heart failure with preserved ejection fraction: recent concepts in diagnosis, mechanisms and management. Heart 2022;Jan 12
560. Palau P, Seller J, Domínguez E, Sastre C, Ramón JM et al. Effect of β-Blocker Withdrawal on Functional Capacity in Heart Failure and Preserved Ejection Fraction. J Am Coll Cardiol. 2021 Nov, 78 (21) 2042-2056
561. Lumbers RT, Martin N, Manoharan K, et al. Do beta-blockers and inhibitors of the renin-angiotensin aldosterone system improve outcomes in patients with heart failure and left ventricular ejection fraction > 40%. Heart. 2019;105 :1533-1535.
562. Martin N, Manoharan K, Davies C, Lumbers RT. Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction. Cochrane Database Syst Rev. 2021 May 22;5(5): CD012721.
563. Yusuf S,Pfeffer MA , Swedberg K et al. Effects of candesartan in patients with CHF and preserved left-ventricular ejection fraction: the CHARM – Preserved Trial.Lancet 2003; 362 : 777-81.
564. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J, PEP-CHF Investigators. The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study. Eur Heart J 2006;27(19):2338-45
565. Solomon SD, McMurray JJV, et al. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. N Eng J Med 2019;381:1609-20.
566. McMurray JJV, Jackson AM, Lam CSP, et al. Effects of sacubitril-valsartan versus valsartan in women compared with men with heart failure and preserved ejection fraction: insights from PARAGON-HF. Circulation. 2020;141:338-351.
567. Edelmann F, Wachter R, Schmidt AG, et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. JAMA. 2013;309:781-791
568. Pitt B, Pfeffer MA, Assmann SF, et al. TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383-92.
569. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation
570. Cohen JB, Schrauben SJ, Zhao L, Basso MD, Cvijic ME, Li Z, Yarde M, Wang Z, Bhattacharya PT, Chirinos DA, Prenner S, Zamani P, Seiffert DA, Car BD, Gordon DA, Margulies K, Cappola T, Chirinos JA. Clinical Phenogroups in Heart Failure With Preserved Ejection Fraction: Detailed Phenotypes, Prognosis, and Response to Spironolactone. JACC Heart Fail. 2020 Mar;8(3):172-184
571. MacDonald MR, Petrie MC, Hawkins NM, Petrie JR, Fisher M et al. Diabetes, left ventricular systolic dysfunction, and chronic heart failure. Eur Heart J. 2008 May;29(10):1224-40.
572. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. Diabetes Care . 2004;27:1879-1884.
573. Andersson C, Norgaard ML, Hansen PR, et al. Heart failure severity, as determined by loop diuretic dosages, predicts the risk of developing diabetes after myocardial infarction: a nationwide cohort study. Eur J Heart Fail 2010;12:1333-8.
574. Kristensen SL, Jhund PS, Lee MMY, Kober L, Solomon SD et al for the CHARM Investigators and Committees. Prevalence of prediabetes and undiagnosed diabetes in patients with HFpEF and HFrEF and associated clinical outcomes. Cardiovasc Drugs Ther 2017;31:545-549.

575. Vermes E, Ducharme A, Bourassa MG, Lessard M, White M et al. Enalapril reduces the incidence of diabetes in patients with chronic heart failure: insight from the studies of left ventricular dysfunction (SOLVD). Circulation 2003;107:1291-1296.
576. Yusuf S, Ostergren JB, Gerstein HC, Pfeffer MA, Swedberg K et al. Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity Program Investigators. Effects of candesartan on the development of a new diagnosis of diabetes mellitus in patients with heart failure. Circulation. 2005 Jul 5;112(1):48-53.
577. Demant MN, Gislason GH, Kober L, Vaag A, Torp-Pedersen C, Andersson C. Association of heart failure severity with risk of diabetes: a Danish nationwide cohort study. Diabetologia 2014;57:1595-1600.
578. Preiss D, Zetterstrand S, McMurray JJ, Ostergren J, Michelson EL et al. Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity Investigators. Predictors of development of diabetes in patients with chronic heart failure in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program. Diabetes Care. 2009;32:915-920
579. Preiss D, van Veldhuisen DJ, Sattar N, Krum H, Swedberg K et al. Eplerenone and new-onset diabetes in patients with mild heart failure: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHA- SIS-HF). Eur J Heart Fail. 2012;14:909-915.
580. Torp-Pedersen C, Metra M, Charlesworth A, Spark P, Lukas MA et al. COMET Investigators. Effects of metoprolol and carvedilol on pre-existing and new onset diabetes in patients with chronic heart failure: data from the Carvedilol Or Metoprolol European Trial (COMET). Heart. 2007;93:968-973.
581. Tenenbaum A, Motro M, Fisman EZ, Leor J, Freimark D et al. Functional class in patients with heart failure is associated with the development of diabetes. Am J Med. 2003;114:271-275
582. McMurray JJ, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. Lancet Diabetes Endocrinol 2014;2:843-51.
583. Birkeland KI, Bodegard J, Eriksson JW, Norhammar A, Haller H et al. Heart failure and chronic kidney disease manifestation and mortality risk associations in type 2 diabetes: a large multinational cohort study. Diabetes Obes Metab. 2020;22(9):1607-18.
584. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41(2):255-323.
585. Cai X, Liu X, Sun L, He Y, Zheng S, Zhang Y, et al. Prediabetes and the risk of heart failure: A meta-analysis. Diabetes Obes Metab. 2021;23(8):1746-53.
586. Ohkuma T, Komorita Y, Peters SAE, Woodward M. Diabetes as a risk factor for heart failure in women and men: a systematic review and meta-analysis of 47 cohorts including 12 million individuals. Diabetologia. 2019;62(9):1550-1560.
587. Wang Y, Negishi T, Negishi K, Marwick TH. Prediction of heart failure in patients with type 2 diabetes mellitus - a systematic review and meta-analysis. Diabetes Res Clin Pract 2015;108:55-66.
588. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. Diabetes Care. 2004 ; 27(8):1879-84
589. Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL et al. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. Diabetes Care. 2004; 27(3):699-703
590. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G et al. Heart Failure Association (HFA) of the European Society of Cardiology. 1-year follow-up outcomes and differences across regions. Eur J Heart Fail 2016;18:613-625.
591. Dauriz M, Targher G, Laroche C, Temporelli PL, Ferrari R et al. for the ESC-HFA Heart Failure Long-Term Registry. Association between diabetes and 1-year adverse clinical outcomes in a multinational cohort of ambulatory patients with chronic heart failure: results from the ESC-HFA Heart Failure Long-Term Registry. Diabetes Care. 2017;40:671-678.
592. Johansson I, Dahlström U, Edner M, Näsman P, Rydén L, Norhammar A. Prognostic implications of type 2 diabetes mellitus in ischemic and non- ischemic heart failure. J Am Coll Cardiol. 2016;68:1404-1416.
593. Targher G, Dauriz M, Laroche C, Temporelli PL, Hassanein M et al. on behalf of the ESC-HFA HF Long-Term Registry Investigators. In-hospital and 1-year mortality as- sociated with diabetes in patients with acute heart failure: results from the ESC-HFA Heart Failure Long-Term Registry. Eur J Heart Fail. 2017;19:54-65.
594. Sandesara PB, O'Neal WT, Kelli HM, et al. The prognostic significance of diabetes and microvascular complications in patients with heart failure with preserved ejection fraction. Diabetes Care 2018;41:150-15.
595. Lawson CA, Jones PW, Teece L, Dunbar SB, Seferovic PM et al. Association between type 2 diabetes and all-cause hospitalization and mortality in the UK general heart failure population: stratification by diabetic glycemic control and medication intensification. JACC Heart Fail. 2018;6:18-26.
596. Cavender MA, Steg PG, Smith SC Jr, Eagle K, Ohman EM, Goto S, Kuder J, Im K, Wilson PW, Bhatt DL; REACH REGISTRY Investigators. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the Reduction of Atherothrombosis for Continued Health (REACH) Registry. Circulation 2015;132:923-931.
597. McAllister DA, Read SH, Kerssens J, et al. Incidence of hospitalization for heart failure and case-fatality among 3.25 million people with and without diabetes mellitus. Circulation 2018;138: 2774-2786
598. Kong MG, Jang SY, Jang J, Cho HJ, Lee S et al. Impact of diabetes mellitus on mortality in patients with acute heart failure: a prospective cohort study. Cardiovasc Diabetol. 2020;19(1):49.
599. Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers . JP et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009;52:2288-2298.
600. Krumholz HM, Chen YT, Wang Y, et al., Predictors of readmission among elderly survivors of admission with heart failure. Am Heart J 2000;139:72-7.
601. Shindler DM, Kostis JB, Yusuf S, et al. Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry, Am J Cardiol 1996;77:1017-20.
602. Kishimoto I, Makino H, Ohata Y, et al., Hemoglobin A1c predicts heart failure hospitalization independent of baseline cardiac function or B-type natriuretic peptide level, Diabetes Res Clin Pract 2014;104(2):257-65.

603. Wang Y, Negishi T, Negishi K, Marwick TH. Prediction of heart failure in patients with type 2 diabetes mellitus - a systematic review and meta-analysis. Diabetes Res Clin Pract 2015;108:55-66.
604. Rawshani A, Rawshani A, Franzén S, Sattar N, Eliasson B et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2018;379(7):633-44
605. Dunlay SM, Givertz MM, Aguilar D, Allen LA, Chan M et al. American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; and the Heart Failure Society of America. Type 2 Diabetes Mellitus and Heart Failure: A Scientific Statement From the American Heart Association and the Heart Failure Society of America: This statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update. Circulation. 2019 Aug 13;140(7):e294-e324.
606. Jia G, Hill MA, Sowers JR. Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity. Circ Res. 2018;122(4):624-38.
607. Zaveri MP, Perry JC, Schuetz TM, Memon MD, Faiz S, Cancarevic I. Diabetic cardiomyopathy as a clinical entity: is it a myth? Cureus.2020;12(10):e11100.
608. Pandey A, Patel KV, Bahnson JL, et al.; Look AHEAD Research Group. Association of intensive lifestyle intervention, fitness, and body mass index with risk of heart failure in overweight or obese adults with type 2 diabetes mellitus: an analysis from the Look AHEAD trial. Circulation 2020;141:1295-1306
609. Sabuncu T, Sonmez A, Eren MA, Sahin I, Çorapçioğlu D et al. Characteristics of patients with hypertension in a population with type 2 diabetes mellitus. Results from the Turkish Nationwide SurvEy of Glycemic and Other Metabolic Parameters of Patients with Diabetes Mellitus (TEMD Hypertension Study). Primary Care Diabetes. 2021;15(2):332-9.
610. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of intensive glucose lowering treatment on all-cause mortality, cardiovascular death, and microvascular events in type 2 diabetes:meta-analysis of randomised controlled trials. BMJ 2011;343:d4169.
611. Elder DH, Singh JS, Levin D, et al. Mean HbA1c and mortality in diabetic individuals with heart failure: a population cohort study. Eur J Heart Fail 2016;18:94-102.
612. Gerstein HC, Miller ME, Genuth S, et al. for the ACCORD Study Group. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med 2011;364:818-28.
613. Ukena C, Dobre D, Mahfoud F, et al. Hypo- and hyperglycemia predict outcome in patients with left ventricular dysfunction after acute myocardial infarction: data from EPHESUS. J Card Fail 2012;18:439-45.
614. Ceriello, A., Lucisano, G., Prattichizzo, F. et al. HbA1c variability predicts cardiovascular complications in type 2 diabetes regardless of being at glycemic target. Cardiovasc Diabetol 2022: 21, 13
615. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. JAMA Cardiol. 2021;6(2):148-158. doi:10.1001/jamacardio.2020.4511
616. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. The Lancet. 2020;396 (10254):819-29.
617. American Diabetes Association. Standards of Medical Care in Diabetes-2020 Abridged for Primary Care Providers. Clin Diabetes. 2020 Jan;38(1):10-38
618. Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S et al.. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol. 2021 Oct;9(10):653-662.
619. Kristensen SL, Rorth R, Jhund PS, Docherty KF, Sattar N et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinology. 2019;7(10):776-85.
620. Gerstein HC, Sattar N, Rosenstock J, et al.; AMPLITUDE-O Trial Investigators. Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. N Engl J Med 2021;385:896-907
621. Ceriello A, Prattichizzo F, Phillip M, Hirsch IB, Mathieu C, Battelino T. Glycaemic management in diabetes: old and new approaches. Lancet Diabetes Endocrinol. 2022 Jan;10(1):75-84.
622. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA et al. SAVOR-TIMI 53 Steering Committee and Investigators*. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation. 2014 Oct 28;130(18):1579-88
623. Eurich DT, Majumdar SR, McAlister FA, Tsuyuki RT, Johnson JA. Improved clinical outcomes associated with metformin in patients with diabetes and heart failure. Diabetes Care 2005;28:2345-2351
624. Richardson TL Jr, Hackstadt AJ, Hung AM, Greevy RA, Grijalva CG et al. Hospitalization for Heart Failure Among Patients With Diabetes Mellitus and Reduced Kidney Function Treated With Metformin Versus Sulfonylureas: A Retrospective Cohort Study. J Am Heart Assoc. 2021 Apr 6;10(8):e019211
625. Chu PY, Hackstadt AJ, Chipman J, et al. Hospitalization for lactic acidosis among patients with reduced kidney function treated with metformin or sulfonylureas. Diabetes Care 2020;43:1462-1470
626. Khan MS, Solomon N, DeVore A, Sharma A, Felker GM et al. Clinical Outcomes With Metformin and Sulfonylurea Therapies Among Patients With Heart Failure and Diabetes. Clinical Research. J Am Coll Cardiol HF. 2022 Mar, 10 (3) 198-210.
627. U.S. Food and Drug Administration. FDA drug safety communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function, 2016. Accessed 10 June 2022. Available from https://www.fda.gov/media/96771/download
628. Packer M. Are physicians neglecting the risk of heart failure in diabetic patients who are receiving sulfonylureas? Lessons from the TOSCA.IT trial. European Journal of Heart Failure (2018) 20, 49-51.

629. Tzoulaki I, Molokhia M, Curcin V, Little MP, Millett CJ et al. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. BMJ 2009;339:b4731.
630. Varas-Lorenzo C, Margulis AV, Pladevall M, Riera-Guardia N et al. The risk of heart failure associated with the use of noninsulin blood glucose-lowering drugs: systematic review and meta-analysis of published observational studies. BMC Cardiovasc Disord 2014;14:129.
631. McAlister FA, Eurich DT, Majumdar SR, Johnson JA. The risk of heart failure in patients with type 2 diabetes treated with oral agent monotherapy. Eur J Heart Fail 2008;10:7035-708.
632. Jeon WK, Kang J, Kim HS, Park KW. Cardiovascular Outcomes Comparison of Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylurea as Add-on Therapy for Type 2 Diabetes Mellitus: a Meta-Analysis. J Lipid Atheroscler. 2021 May;10(2):210-222.
633. Bazo-Alvarez, J.C., Pal, K., Pham, T.M. et al. Cardiovascular outcomes of type 2 diabetic patients treated with DPP-4 inhibitors versus sulphonylureas as add-on to metformin in clinical practice. Sci Rep 2021: 11, 23826
634. Rosenstock J, Kahn SE, Johansen OE et al. Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes. The CAROLINA Randomized Clinical Trial. JAMA. 2019;322(12): 1155-1166
635. He W, Yuan G, Han Y, Yan Y, Li G et al. Glimepiride Use is Associated with Reduced Cardiovascular Mortality in Patients with Type 2 Diabetes and Chronic Heart Failure: A Prospective Cohort Study. Eur J Prev Cardiol. 2022 Dec 27:zwac312.
636. Cosmi F, Shen L, Magnoli M, Abraham WT, Anand IS et al. Treatment with insulin is associated with worse outcome in patients with chronic heart failure and diabetes. Eur J Heart Fail. 2018 May;20(5):888-895
637. Jang, S.Y., Jang, J., Yang, D.H. et al. Impact of insulin therapy on the mortality of acute heart failure patients with diabetes mellitus. Cardiovasc Diabetol 2021: 20, 180
638. Hernandez AV, Usmani A, Rajamanickam A, Moheet A. Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus: a meta-analysis and meta-regression analysis of placebo-controlled randomized clinical trials. Am J Cardiovasc Drugs 2011;11:115-128.
639. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ; RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet 2009;373:2125-2135.
640. Foo JH, Chong WL , Abdullah MA , Yen CH et al. Rheumatic heart diseases screening in Bornean Malaysia: a pilot echocardiography study. Eur Heart J 2019: 40 (Supplement), 1899
641. Vahanian, A., Beyersdorf, F., Praz, F., Milojevic, M., Baldus, S.et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2022; 43(7), 561-632.
642. Otto CM. Timing of surgery in mitral regurgitation. Heart 2003;89(1):100-5.
643. Fattouch K, Guccione F, Sampognaro R, et al. Efficacy of adding mitral valve restrictive annuloplasty to coronary artery bypass grafting in patients with moderate ischemic mitral valve regurgitation: a randomized trial. J Thorac Cardiovasc Surg 2009;138:278-85.
644. Chan KMJ, Punjabi PP, Flather M, et al for the RIME Investigators. Coronary artery bypass surgery with or without mitral valve annuloplasty in moderate functional ischemic mitral regurgitation. Final results of the Randomized Ischemic Mitral Evaluation (RIME) Trial. Circulation 2012;126:2502–10.
645. Stone GW, Lindenfeld J, Abraham WT, et al for the COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med 2018 379:2307 18.
646. Marmagkiolis K, Hakeem A, Ebersole DG, Iliescu C, Ates I, Cilingiroglu M. Clinical outcomes of percutaneous mitral valve repair with MitraClip for the management of functional mitral regurgitation. Catheter Cardiovasc Interv. 2019 Nov 15;94(6):820-826
647. Gorav Ailawadi G, Lim DS, Mack MJ, Trento A, Kar S et al.On behalf of the EVEREST II Investigators. One-Year Outcomes After MitraClip for Functional Mitral Regurgitation. Circulation. 2019;139:37-47
648. Giustino G, Camaj A, Kapadia SR, et al. Hospitalizations and Mortality in Patients With Secondary Mitral Regurgitation and Heart Failure: COAPT Trial. J Am Coll Ca.rdiol 2022;80:1857-68
649. Oh NA, Kampaktsis PN, Gallo M, Guariento A et al. An updated meta-analysis of MitraClip versus surgery for mitral regurgitation. Ann Cardiothoracic Surgery 2021; 10: 1
650. Obadia J-F, Messika-Zeitoun D, Leurent G, et al for the MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med 2018;379:2297-306.
651. Leurent G, Auffret V; Donal E; Corbineau H, Grinberg D et al. Delayed hospitalisation for heart failure after transcatheter repair or medical treatment for secondary mitral regurgitation: a landmark analysis of the MITRA-FR trial. EuroIntervention 2022;18:514-523
652. GentryJ. L, Phelan D, Desai MY, Griffin B P. The Role of Stress Echocardiography in Valvular Heart Disease: A Current Appraisal. Cardiology 2017: 137(3), 137-150.
653. Leon MB , Mack MJ, Hahn RT, Thourani VH, Makkar R et al. PARTNER 3 Investigators. Outcomes 2 years after transcatheter aortic valve replacement in patients at low surgical risk. J Am Coll Cardiol2021;77:1149-1161.
654. Makkar RR, Thourani VH, Mack MJ, Kodali SK et al.for the PARTNER 2 Investigators* Five-Year Outcomes of Transcatheter or Surgical Aortic-Valve Replacement. N Engl J Med 2020; 382:799-809
655. Chakos A, Wilson-Smith A, Arora S, Nguyen TC, Dhoble A, Tarantini G, Thielmann M, Vavalle JP, Wendt D, Yan TD, Tian DH. Long term outcomes of transcatheter aortic valve implantation (TAVI): a systematic review of 5-year survival and beyond. Ann Cardiothorac Surg. 2017 Sep;6(5):432-443
656. Popma JJ , Deeb GM, Yakubov SJ, Mumtaz M, Gada H et al. Evolut Low Risk Trial Investigators. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med2019;380:1706-1715.

657. The UK TAVI Trial Investigators. Effect of Transcatheter Aortic Valve Implantation vs Surgical Aortic Valve Replacement on All-Cause Mortality in Patients With Aortic Stenosis: A Randomized Clinical Trial. JAMA. 2022;327(19):1875-1887.
658. Siontis GCM , Overtchouk P, Cahill TJ, Modine T, Prendergast B et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. Eur Heart J2019;40:3143-3153.
659. Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A et al. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2016;37:1850-1858
660. Arbustini E, Narula N, Dec GW, Reddy KS, Greenberg B et al. The MOGE(S) classification for a phenotypegenotype nomenclature of cardiomyopathy: endorsed by the World Heart Federation. J Am Coll Cardiol 2013;62:20462072. 893.
661. Hazebroek MR, Kemna MJ, Schalla S, Sanders-van Wijk S, Gerretsen SC et al. Prevalence and prognostic relevance of cardiac involvement in ANCA-associated vasculitis: eosinophilic granulomatosis with polyangiitis and granulomatosis with polyangiitis. Int J Cardiol 2015;199:170179. 894.
662. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ et al. MB. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. Circulation 2016;133:e38-e360.
663. Richardson P, McKenna W, Bristow M, Maisch B, Mautner B et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies. Circulation 1996;93:841-842.
664. Jefferies JL, Towbin JA. Dilated cardiomyopathy. Lancet 2010;375:752 -762
665. Japp AG, Gulati A, Cook SA, Cowie MR, Prasad SK. The diagnosis and evaluation of dilated cardiomyopathy. J Am Coll Cardiol 2016;67:2996-3010.
666. Wilcox JE, Fonarow GC, Ardehali H, Bonow RO, Butler J et al.'Targeting the Heart' in heart failure: myocardial recovery in heart failure with reduced ejection fraction. JACC Heart Fail 2015;3:661-669.
667. Thorvaldsen T, Benson L, Dahlstrom U, Edner M, Lund LH. Use of evidence-based therapy and survival in heart failure in Sweden 2003–2012. Eur J Heart Fail 2016;18:503-511.
668. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the diagnosis and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2733-2779
669. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F et al. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2008;29:270-276.
670. Maron BJ, Rowin EJ, Udelson JE, Maron MS. Clinical spectrum and management of heart failure in hypertrophic cardiomyopathy. JACC Heart Fail 2018;6:353-363
671. Maron BJ, Desai MY, Nishimura RA, Spirito P, Rakowski H et al. Management of Hypertrophic Cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2022 : 79 (4): 390-414
672. Ommen S.R., Maron B.J., Olivotto I., et al. "Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy". J Am Coll Cardiol 2005;46:470-476.
673. Melacini P, Basso C, Angelini A, Calore C, Bobbo F et al. Clinicopathological profiles of progressive heart failure in hypertrophic cardiomyopathy. Eur Heart J 2010;31:2111-2123.
674. Olivotto I, Cecchi F, Poggesi C, Yacoub MH. Patterns of disease progression in hypertrophic cardiomyopathy: an individualized approach to clinical staging. Circ Heart Fail 2012;5:535-546.
675. Thaman R, Gimeno JR, Murphy RT, Kubo T, Sachdev B et al. Prevalence and clinical significance of systolic impairment in hypertrophic cardiomyopathy. Heart 2005;91:920-925.
676. Harris KM, Spirito P, Maron MS, Zenovich AG, Formisano F et al. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. Circulation 2006;114:216 - 225.
677. Ommen SR, Mital S, Burke MA, Day SM, Deswal A et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy. A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2020;142:e558-e631
678. Maron B.J., Shen W.-K., Link M.S., et al. "Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy". N Engl J Med 2000;342:365-373.
679. Olivotto I, Oreziak A, Barriales-Villa R, Abraham TP, Masri A et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2020; 396 (10253): 759-769
680. Spertus JA, Fine JT, Elliott P, Ho CY, Olivotto I et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): health status analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2021: 397(10293); 2467-2475
681. Geske JB, Anavekar NS, Nishimura RA, Oh JK, Gersh BJ. Differentiation of constriction and restriction: complex cardiovascular hemodynamics. J Am Coll Cardiol 2016;68:2329-2347.
682. Charron P, Elliott PM, Gimeno JR, Caforio AL, Kaski JP et al. The cardiomyopathy registry of the EURObservational Research Programme of the European Society of Cardiology: baseline data and contemporary management of adult patients with cardiomyopathies. Eur Heart J 2018;39:1784-1793.
683. Pereira NL, Grogan M, Dec GW. Spectrum of restrictive and infiltrative car- diomyopathies: Part 1 of a 2-Part Series. J Am Coll Cardiol 2018;71:1130-1148. 187.
684. Murphy CJ, Oudit GY. Iron-overload cardiomyopathy: pathophysiology, diagnosis, and treatment. J Card Fail 2010;16:888-900.
685. Maurer MS, Elliott P, Comenzo R, Semigran M, Rapezzi C. Addressing common questions encountered in the diagnosis and management of cardiac amyloidosis. Circulation 2017;135:1357-1377
686. Mogensen J, Arbustini E. Restrictive cardiomyopathy. Curr Opin Cardiol 2009;24:214-220.

687. Huizar JF, Ellenbogen KA, Tan AY, Kaszala K. Arrhythmia-Induced Cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019 May, 73 (18) 2328-2344
688. Bozkurt B., Colvin M., Cook J.et al. Current diagnostic and treatment strategies for specific dilated cardiomyopa thies: a scientific statement from the American Heart Association". Circulation 2016; 134: e579.
689. Watanabe H., Okamura K., Chinushi M.et al. : "Clinical characteristics, treatment, and outcome of tachycardia induced cardiomyopathy". Int Heart J 2008; 49: 39.
690. Medi C., Kalman J.M., Haqqani H.et al. : "Tachycardia-mediated cardiomyopathy secondary to focal atrial tachycardia: long-term outcome after catheter ablation". J Am Coll Cardiol 2009; 53: 1791
691. Steven A. Lubitz et al. Atrial Fibrillation in Congestive Heart Failure. Heart Fail Clin. 2010 Apr; 6(2): 187-200.
692. Rillig A, Magnussen C, Ozga AK, Suling A, Brandes A, Breithardt G, Camm AJ, Crijns HJGM, Eckardt L, Elvan A, Goette A, Gulizia M, Haegeli L, Heidbuchel H, Kuck KH, Ng A, Szumowski L, van Gelder I, Wegscheider K, Kirchhof P. Early Rhythm Control Therapy in Patients With Atrial Fibrillation and Heart Failure. Circulation. 2021 Sep 14;144(11):845-858
693. Nassir F. Marrouche et al. Catheter Ablation for Atrial Fibrillation with Heart Failure. N Engl J Med 2018;378:417-427.
694. Al-Khatib SM, Stevenson WG, Ackerman MJ et al 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. Circulation. 2018;138:e272-e391
695. Callans DJ. Premature Ventricular Contraction-induced Cardiomyopathy. Arrhythm Electrophysiol Rev. 2017 Dec;6(4):153-155
696. Baman TS, Lange DC, Ilg KJ, et al. Relationship between burden of premature ventricular complexes and left ventricular function. Heart Rhythm, 2010; 7: 865-869
697. Hasdemir, C. Ulucan, O. Yavuzgil, et al. Tachycardia-induced cardiomyopathy in patients with idiopathic ventricular arrhythmias: the incidence, clinical and electrophysiologic characteristics, and the predictors.J Cardiovasc Electrophysiol 2011: 22: 663-668
698. Huizar F, Fisher SG, Kaszala,F et al. Amiodarone is an effective treatment of PVC-cardiomyopathy in the veteran population (abstr). Circulation, 136 (Suppl 1) (2017), p. 14667
699. Latchamsetty R. et al. Multicenter Outcomes for Catheter Ablation of Idiopathic Premature Ventricular Complexes. JACC Clin Electrophysiol. 2015 Jun;1(3):116-123.
700. Yokokawa M et al. Recovery from left ventricular dysfunction after ablation of frequent premature ventricular complexes. Heart Rhythm. 2013 Feb;10(2):172-5
701. Khurshid S, Liang JJ, Owens A, et al. Longer paced QRS duration is associated with increased prevalence of right ventricular pacing-induced cardiomyopathy. J Cardiovasc Electrophysiol. 2016;27(10):1174-9
702. Dreger H, Maethner K, Bondke H, et al. Pacing-induced cardiomyopathy in patients with right ventricular stimulation for >15 years. Europace. 2012;14(2):238-242
703. Cicchitti V, Radico F, Bianco F, Gallina S, Tonti G, De Caterina R. Heart failure due to right ventricular apical pacing: the importance of flow patterns. EP Europace, 2016: 18: 1679-1688,
704. Sharma AD, Rizo-Patron C, Hallstrom AP, O'Neill GP, Rothbart S et al. DAVID Investigators. Percent right ventricular pacing predicts outcomes in the DAVID trial. Heart Rhythm. 2005 Aug;2(8):830-4
705. Schwerg M, Dreger H, Stangl K, Leonhardt V, Melzer C. Prevalence of left ventricular systolic dysfunction in a typical outpatient pacemaker cohort. Herzschrittmachertherapie & Elektrophysiologie. 2020 Jun;31(2):219-223.
706. Tantengco MV, Thomas RL, Karpawich PP, Left ventricular dysfunction after long-term right ventricular apical pacing in the young , J Am Coll Cardiol (2001);37(8): pp. 2093-2100.
707. McGavigan AD, Mond HG, Selective site ventricular pacing , Curr Opin Cardiol (2006);21(1): pp. 7-14.
708. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, Kutalek SP, Sharma A; Dual Chamber and VVI Implantable Defibrillator Trial Investigators. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. JAMA. 2002 Dec 25;288(24):3115-23.
709. Wilkoff BL, Kudenchuk PJ, Buxton AE, Sharma A, Cook JR, Bhandari AK, Biehl M, Tomassoni G, Leonen A, Klevan LR, Hallstrom AP; DAVID II Investigators. The DAVID (Dual Chamber and VVI Implantable Defibrillator) II trial. J Am Coll Cardiol. 2009 Mar 10;53(10):872-80
710. Curtis AB, Worley SJ, Chung ES, Li P, Christman SA, St John Sutton M. Improvement in Clinical Outcomes With Biventricular Versus Right Ventricular Pacing: The BLOCK HF Study. J Am Coll Cardiol. 2016 May 0;67(18):2148-2157
711. Shakir DK, Rasul KI. Chemotherapy induced cardiomyopathy: pathogenesis, monitoring and management. J Clin Med Res 2009:1(1), 8-12.
712. Albini A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncology prevention. J Natl Cancer Inst 2010:102(1):14-25.
713. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 2003:97:2869-79.
714. Fraley C, Milgrom SA, Kondapalli L et al. Mechanism and insights for the development of heart failure associated with cancer therapy. Children 2021,8,829.
715. Zamorano JL, Lancellotti P, Rodriguez-Munoz D et al. 2016 ESC Position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for practice guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC), EHJ 2016;37:2768-2801.
716. Lyon AR, Dent S, Stanway S et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the cardio-oncology study group of the heart failure association of the European society of cardiology in collaboration with the international cardio-oncology society. EJHF 2020;22(11):1945-1960
717. Curigliano G, Cardinale D, Suter T, et al. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. Vol. 23. Suppl 7: 2012. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. pp. vii155-16

718. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol. 2002;20(5):1215-1221
719. Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. Journal of the American College of Cardiology. 2010;55:213-220
720. Ewer MS, Vooletich MT, Durand JB et al. Reversibility of Trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. J Clin Oncol 2005:23:7820-6.
721. Braveman AC, Antin JH, Plappert MT, Plappert MT, Cook EF, Lee RT. Cyclophosphamide cardiotoxicity in bone marrow transplantation: a prospective evaluation of new dosing regimens. J Clin Oncol 1991;9:1215-23.
722. Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of Trop I in cardiac risk stratification of cancer patients undergoing high dose chemotherapy. Circ 2004;109:2749-54.
723. Cardinale D, Sandri MT, Martinoni A, et al. Myocardial injury revealed by plasma troponin I in breast cancer treated with high dose chemotherapy. Ann Oncol 2002;13:710-5.
724. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2014;27(9):911-39.
725. Armenian SH, Laccheti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancer: American Society of Clinical Oncology Clinical Practice Guidelines. J Clin Oncol 2017;35:893-911.
726. Yeh ET, Tong AT, Lenihan DJ, Yusuf SW, Swafford J et al. Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. Circulation. 2004 Jun 29;109(25):3122-31.
727. Thavendiranathan P, Grant AD, Negishi T et al. Reproducibility of echocardiography techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. JACC 2013;61(1):77-84.
728. Thavendiranathan P. Poullin F, Lim KD et al. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systemic review. JACC 2014;63:2751-68.
729. Semeraro GC, Cipolla CM, Cardinale DM. Role of cardiac biomarkers in cancer patients. Cancers 2021,13, 5426
730. Cardinale DM, Colombo A, Sandri MT et al. Prevention of high dose chemotherapy induced cardiotoxicity in high risk patients by angiotensin converting enzyme inhibition. Circulation 2006;114(23):2474-81.
731. Gulati G, Heck SL, Ree AH et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): A 2x2 factorial, randomized, placebo-controlled, double blind clinical trial of candesartan and metoprolol. EHJ 2016;37:1671-80.
732. Boekhout AH, Gietama JA, Milojkovic KB et al. Angiotensin II-receptor inhibition with candesartan to prevent trastuzumab related cardiotoxic effects in patients with early breast cancer: A randomized clinical trial. JAMA Oncol 2016;2:1030-7,
733. Cardinale DM, Colombo A, Bacchini G et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation 2015;131:1981-8.
734. Tromp J, Tay WT, Ouwerkerk W, et al for ASIAN-HF authors. Correction: Multimorbidity in patients with heart failure from 11 Asian regions: a prospective cohort study using the ASIAN-HF registry. PloS Med 2018;15(5):e1002583.
735. Heywood JT, Fonarow GC, Costanzo MR, et al. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. J Card Fail 2007;13:422-30.
736. Ronco C, McCullough P, Anker SD, et al for the Acute Dialysis Quality Initiative (ADQI) consensus group. Cardio-renal syndromes: report from the consensus conference of the Acute Dialysis Quality Initiative. Eur Heart J 2010;31(6):703-11.
737. Forman DE, Butler J, Wang Y, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. J Am Coll Cardiol 2004:43(1):61-7.
738. Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 2009;53:589-96.
739. Haynes R, Judge PK, Staplin N, Herrington WG, Storey BC et al. Effects of Sacubitril/Valsartan Versus Irbesartan in Patients With Chronic Kidney Disease. Circulation. 2018 :138(15):1505-1514
740. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene Tet al DAPA-CKD Trial Committees and Investigators. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020;383(15):1436-1446
741. The EMPA-KIDNEY Collaborative Group. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2023; 388:117-127
742. Kidney Disease Improving Outcomes (KDIGO) CKD Work Group.KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl.2013;3(1):134-5)
743. Testani JM, Kimmel SE, Dries DL, Coca SG. Prognostic importance of early worsening renal function following initiation of angiotensin converting enzyme inhibitor therapy in patients with cardiac dysfunction. Circ Heart Fail 2011;4(6):685-91.
744. Metra M, Davison B, Bettari L, et al. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. Circ Heart Fail 2012;5:54-62.
745. Greene SJ, Gheorghiade M, Vaduganathan M, et al. Hemoconcentration, renal function, and post-discharge outcomes among patients hospitalized for heart failure with reduced ejection fraction: insights from the EVEREST trial. Eur J Heart Fail 2013;15:1401-11.
746. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation 2010;122:265-72.
747. Ezekowitz JA, O'Meara E, McDonald AM, et al. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Can J Cardiol 2017;33:1342-433.
748. Dormans TP, Gerlag PG, Russel FG, et al. Combination diuretic therapy in severe congestive cardiac failure. Drugs 1998;55:165-72.

749. Mullens W, Martens P, Testani JM, et tal. Renal effects of guideline-directed medical therapies in heart faiure: a consensus document from the Heart Failure Association of the European Society of Cardiology. European J of Heart Failure 2022;24: 603-619
750. Malaysian Clinical Practice Guidelines. 2nd Ed Management of Chronic Kidney Disease .2018. Available at www.acadmed.org
751. Bhandari S, Ives N, Brettell EA, et al. Multicentre randomized controlled trial of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker withdrawal in advanced renal disease: the STOP-ACEi trial. Nephrol Dial Transplant 2016;31(2):255-61.
752. Bhandari S, Mehta S, Khwaja A et al . Renin-Angiotensin System Inhibition in Advanced Chronic Kidney Disease. N Engl J Med 2022 : 387(22):2021-2032)
753. Constanzo MR, Ronco C, Abraham WT, et al. Extracorporeal ultrafiltration for fluid overload in heart failure: current status and prospects for further research. J Am Coll Cardiol 2017;69(19):2428-45.
754. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. The Task Force for the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J 2018:39:3165-241.
755. Ruys TP, Roos-Hesselink JW, Hall R, Subirana-Domènech MT, Grando-Ting J, Estensen M, Crepaz R, Fesslova V, Gurvitz M, De Backer J, Johnson MR, Pieper PG. Heart failure in pregnant women with cardiac disease: data from t he ROPAC. Heart. 2014; 100:231-238
756. Maternal mortality ratio in Malaysia 2011- 2020: Published by Statista Research Department, Oct 5, 2022.Available at//www.statista.com/statistics/642032/malaysia-maternal-mortality-ratio. Accessed on 13th December 2022.
757. Billebeau G, Etienne M, Cheikh-Khelifa R, et al. Pregnancy in women with a cardiomyopathy: outcomes and predictors from a retrospective cohort. Arch Cardiovasc Dis. 2018;111:199-209.
758. Lima F, Nie L, Yang J, et al. Postpartum cardiovascular outcomes among women with heart disease from a nation wide study. Am J Cardiol. 2019;123: 2006-2014.
759. Krul SP, van der Smagt JJ, van den Berg MP, et al. Systematic review of pregnancy in women with inherited cardiomyopathies. Eur J Heart Fail. 2011;13: 584-594.
760. Ng AT, Duan L, Win T, et al. Maternal and fetal outcomes in pregnant women with heart failure. Heart. 2018;104:1949-1954.
761. Elkayam U, Goland S, Pieper PG, et al. High-risk cardiac disease in pregnancy: part I. J Am Coll Cardiol. 2016;68:396-410.
762. Roos-Hesselink JW, Ruys TP, Stein JI, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. Eur Heart J. 2013;34:657-665.
763. Ruys TP, Roos-Hesselink JW, Hall R, et al. Heart failure in pregnant women with cardiac disease: data from the ROPAC. Heart. 2014;100:231-238
764. Sliwa K, van der Meer P, Petrie MC, Frogoudaki A, Johnson MR et al.Risk stratification and management of women with cardiomyopathy/heart failure planning pregnancy or presenting during/after pregnancy: a position statement from the Heart Failure Association of the European Society of Cardiology Study Group on Peripartum Cardiomyopathy. Eur J Heart Fail 2021;23:527-540
765. van Spaendonck-Zwarts KY, Posafalvi A, van den Berg MP, et al. Titin gene mutations are common in families with both peripartum cardiomyopathy and dilated cardiomyopathy. Eur Heart J 2014;35:2165-73.
766. van Spaendonck-Zwarts KY, van Tintelen JP, van Veldhuisen DJ, et al. Peripartum cardiomyopathy as a part of familial dilated cardiomyopathy. Circulation 2010;121:2169-75.
767. van Tintelen JP, Pieper PG, van Spaendonck-Zwarts KY, van den Berg MP. Pregnancy, cardiomyopathies and genetics. Cardiovasc Res 2014;101:571-8.
768. Silversides CK, Grewal J, Mason J, et al. Pregnancy outcomes in women with heart disease. The CARPREG II Study. J Am Coll Cardiol 2018;71:2419-30.
769. Hilfiker-Kleiner D, Sliwa K. Pathophysiology and epidemiology of peripartum cardiomyopathy. Nat Rev Cardiol 2014;11:364-70.
770. Sliwa K, Fett J, Elkayam U. Peripartum cardiomyopathy. Lancet 2006;368:687-93.
771. Sliwa K, Hilfiker-Kleiner D, Petrie MC, et al. Current state of knowledge on etiology, diagnosis, management, and therapy of peripartum cardiomyopathy: A Position Statement from the Heart Failure Association of the European Society of Cardiology Working Group on Peripartum Cardiomyopathy. Eur J Heart Fail 2010;12:767-78.
772. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation 2001;104(5):515-21.
773. National Library of Medicine. Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD). Accessed October 2, 2020. https:// wwwncbinlmnihgov/books/NBK501922
774. National Health Service, UK . Pregnancy, breastfeeding and fertility while taking metoprolol. Available at https://ww w.nhs.uk/medicines/metoprolol/pregnancy-breastfeeding-and-fertility-while-taking-metoprolol/
775. Halpern DG, Weinberg CR, Pinnelas R, et al. Use of medication for cardiovascular disease during pregnancy: JACC state-of-the-art review. J Am Coll Cardiol. 2019;73:457-476
776. Kearney L, Wright P, Fhadil S, Thomas M. Postpartum Cardiomyopathy and Considerations for Breastfeeding. Card Fail Rev. 2018 Aug;4(2):112-118.
777. Kampman MA, Balci A, van Veldhuisen DJ, et al. N terminal pro-B-type natriuretic peptide predicts cardiovascular complications in pregnant women with congenital heart disease. Eur Heart J. 2014;35:708-715.
778. Tanous D, Siu SC, Mason J, et al. B-type natriuretic peptide in pregnant women with heart disease. J Am Coll Cardiol. 2010;56:1247-1253.
779. Sliwa K, Petrie MC, van der Meer P, Mebazaa A, Hilfiker-Kleiner D et al. Clinical presentation, management, and 6-month outcomes in women with peripartum cardiomyopathy: an ESC EORP registry. Eur Heart J 2020;41:3787-3797.
780. Davis MB, Arany Z, McNamara DM, Goland S, Elkayam U. Peripartum cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol 2020;75:207- 221

781. McNamara DM, Elkayam U, Alharethi R, et al. Clinical outcomes for peripartum cardiomyopathy in North America: results of the IPAC study (Investigations of Pregnancy-Associated Cardiomyopathy). J Am Coll Cardiol. 2015;66:905-914
782. Elkayam U. "Risk of subsequent pregnancy in women with a history of peripartum cardiomyopathy". J Am Coll Cardiol 2014;64:1629-1636.
783. Ahmad WA, Khanom M, Yaakob ZH. Heart failure in pregnancy: an overview. Int J Clin Pract 2011;65(8):848-51.
784. John KJ, Mishra AK, Ramasamy C, George AA, Selvaraj V, Lal A. Heart failure in COVID-19 patients: Critical care experience. World J Virol. 2022 Jan 25;11(1):1-19.
785. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med 2020: 382(25):e102.
786. Zhou F, Yu T, Du R, Fan G, Liu Y et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020: 395(10229):1054-1062.
787. Bader F, Manla Y, Atallah B, Starling RC. Heart failure and COVID-19. Heart Fail Rev. 2021 Jan;26(1):1-10.
788. Writing Committee, Gluckman TJ, Bhave NM, Allen LA, Chung EH, Spatz ES, et al. 2022 ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults: Myocarditis and Other Myocardial Involvement, Post-Acute Sequelae of SARS-CoV-2 Infection, and Return to Play: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2022 May 3;79(17):1717-1756
789. Italia L, Tomasoni D, Bisegna S, Pancaldi E, Stretti L et al. COVID-19 and Heart Failure: From Epidemiology During the Pandemic to Myocardial Injury, Myocarditis, and Heart Failure Sequelae. Front Cardiovasc. Med., 10 August 2021.Sec. General Cardiovascular Medicine https://doi.org/10.3389/fcvm.2021.713560
790. Block JP, Boehmer TK, Forrest CB, et al. Cardiac Complications After SARS-CoV-2 Infection and mRNA COVID-19 Vaccination - PCORnet, United States, January 2021-January 2022. MMWR Morb Mortal Wkly Rep 2022;71:517-523.
791. Ammirati E, Lupi L, Palazzini M, Hendren NS, Grodin JL et al. Prevalence, Characteristics, and Outcomes of COVID-19-Associated Acute Myocarditis. Circulation. 2022 Apr 12;145(15):1123-1139Ammirat et al, Prevalence, Characteristics, and Outcomes of COVID-19–Associated Acute Myocarditis. Circulation. 2022;145:1123-1139
792. Lai FTT, Chan EWW, Huang L, Cheung CL et al. Prognosis of Myocarditis Developing After mRNA COVID-19 Vaccination Compared With Viral Myocarditis. J Am Coll Cardiol. 2022:80: 2255-2265
793. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. Nat Med. 2022 Mar;28(3):583-590.
794. T. van der Bom, B.J. Bouma, F.J. Meijboom, et al., The prevalence of adult congenital heart disease, results from a systematic review and evidence based calculation, Am. Heart J. 164 (4) (2012) 568-575.
795. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. Circulation. 2014;130(9):749-56.
796. Stout KK, Broberg CS, Book WM, et al., American Heart Association Council on Clinical Cardiology CoFG, Translational B, council on cardiovascular R and imaging. Chronic heart failure in congenital heart disease: a scientific statement from the American Heart Association. Circulation 2016;133: 770-801
797. Book WM, Gerardin J, Saraf A, Marie Valente A, Rodriguez F 3rd. Clinical Phenotypes of Fontan Failure: Implications for Management. Congenit Heart Dis. 2016 Jul;11(4):296-308. doi: 10.1111/chd.12368.
798. Gilljam T, Mandalenakis Z, Dellborg M, Lappas G, Eriksson P, Skoglund K, Rosengren A. Development of heart failure in young patients with congenital heart disease: A nation-wide cohort study. Open Hear 2019; 6: e000858.
799. Arnaert S, De Meester P, Troost E, Droogne W, Van Aelst L, Van Cleemput J, Voros G, Gewillig M, Cools B, Moons P, Rega F, Meyns B, Zhang Z, Budts W, Van De Bruaene A. Heart failure related to adult congenital heart disease: prevalence, outcome and risk factors. ESC Heart Fail. 2021 Aug;8(4):2940-2950..
800. Yu C, Moore BM, Kotchetkova I, et al. Causes of death in a contemporary adult congenital heart disease cohort. Heart. 2018;104(20):1678-1682.
801. Oechslin EN, Harrison DA, Connelly MS, et al. Mode of death in adults with congenital heart disease. Am J Cardiol. 2000 Sep 15;86 (10):1111-1116.
802. Verheugt CL, Uiterwaal CSPM, van der Velde ET, et al. Mortality in adult congenital heart disease. Eur Heart J 2010;31(10):1220-9.
803. Diller GP, Kempny A, Alonso-Gonzalez R, et al. Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary centre. Circulation. 2015 Dec 1;132(22): 2118-2125.
804. Zomer AC, Vaartjes I, Uiterwaal CSPM, et al. Circumstances of death in adult congenital heart disease. Int J Cardiol. 2012 Jan 26;154 (2):168-172.
805. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease. A report of the American College of Cardiology/American Heart Association TaskForce on Clinical Practice Guidelines. J Am Coll Cardiolo 2019;73(12):e81-192.
806. Rodriguez Iii FH, Moodie DS, Parekh DR, et al. Outcomes of heart failure–related hospitalization in adults with congenital heart dis- ease in the United States. Congenit Heart Dis. 2013;8(6):513-0519. 19.
807. Agarwal S, Sud K, Menon V. Nationwide hospitalization trends in adult congenital heart disease across 2003-2012. J Am Heart Assoc. 2016;5(1):e002330
808. Zomer AC, Vaartjes I, van der Velde ET, et al. Heart failure admissions in adults with congenital heart disease; risk factors and prognosis. Int J Cardiol. 2013;168(3):2487-93.
809. Budts W, Roos-Hesselink J, Radle-Hurst T, Eicken A, McDonagh TA et al. Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology. Eur Heart J 2016;37:1419-1427.
810. Brida M, Lovrić D, Griselli M, Riesgo Gil F, Gatzoulis MA. Heart failure in adults with congenital heart disease. Int J Cardiol. 2022 Jun 15;357:39-45
811. Gratz A, Hess J, Hager A. Self-estimated physical functioning poorly predicts actual exercise capacity in adolescents and adults with congenital heart disease, Eur. Heart J. 2009:30;) 497-504.

812. Leusveld EM, Kauling RM, Geenen LW, Roos-Hesselink JW. Heart failure in congenital heart disease: management options and clinical challenges, Expert Review of Cardiovascular Therapy 2020: 18:8, 503-516
813. Negishi J, Ohuchi H, Miyazaki A, et al. Clinical characteristics of adult patients with congenital heart disease hospitalized for acute heart failure. Circ J. 2018;82(3):840-846
814. Perrin N, Dore A, van de Bruaene A, Mongeon FP, Mondésert B, Poirier N, Miró J, Khairy P, Ibrahim R, Chaix MA. The Fontan Circulation: From Ideal to Failing Hemodynamics and Drug Therapies for Optimization. Can J Cardiol. 2022 Jul;38(7):1059-1071
815. Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, et al., 2020 ESC Guidelines for the management of adult congenital heart disease, Eur. Heart J. 2021; 42 (6) (2021) 563-645.
816. Cunningham JW, Nathan AS, Rhodes J, Shafer K, Landzberg MJ, Opotowsky AR. Decline in peak oxygen consumption over time predicts death or transplantation in adults with a Fontan circulation. Am Heart J. 2017: 189:184-192
817. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV et al., Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication, Circulation 2005: 112 (6) : 828-835.
818. Menachem JN, Reza N, Mazurek JA, Burstein D, Birati EY, et al . Cardiopulmonary exercise testing-a valuable tool, not gatekeeper when referring patients with adult congenital heart disease for transplant evaluation. World J Pediatr Congenit Heart Surg. 2019;10(3):286-291
819. Dimopoulos K, Okonko DO, Diller GP, Broberg CS, Salukhe TV et al Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. Circulation. 2006:113(24):2796-2802
820. Suradi HS, Hijazi ZM. Adult Congenital Interventions in Heart Failure. Interv Cardiol Clin. 2017 Jul;6(3):427-443..
821. Bouchardy J, Therrien J, Pilote L, et al. Atrial arrhythmias in adults with congenital heart disease. Circulation 2009;120:1679-86.
822. Konstam MA, Kiernan MS, Bernstein D, Bozkurt B, Jacob M . Evaluation and Management of Right-Sided Heart Failure: a scientific statement from the American Heart Association, Circulation 2018: 137 (20): e578-e622.
823. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, et al ESC/ERS Scientific Document Group. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2023 Jan 6;61(1): 2200879.
824. Dos L, Pujadas S, Estruch M, Mas A, Ferreira-González I, Pijuan A, Serra R, Ordóñez-Llanos J, Subirana M, Pons-Lladó G, Marsal JR, García-Dorado D, Casaldàliga J. Eplerenone in systemic right ventricle: double blind randomized clinical trial. The evedes study. Int J Cardiol. 2013 Oct 15;168(6):5167-73
825. Ladouceur M, Segura de la Cal T, Gaye B, Valentin E, Ly R, Iserin L, Legendre A, Mousseaux E, Li W, Rafiq I, Kempny A, Barradas-Pires A, Babu-Narayan SV, Gatzoulis MA, Dimopoulos K. Effect of medical treatment on heart failure incidence in patients with a systemic right ventricle. Heart. 2021 Sep;107(17):1384-1389.
826. Perrin N, Dore A, van de Bruaene A, Mongeon FP, Mondésert B, Poirier N, Miró J, Khairy P, Ibrahim R, Chaix MA. The Fontan Circulation: From Ideal to Failing Hemodynamics and Drug Therapies for Optimization. Can J Cardiol. 2022 Jul;38(7):1059-1071.
827. Rychik, J., Atz, A. M., Celermajer, D. S., Deal, B. J., Gatzoulis, M. A et al. American Heart Association Council on Cardiovascular Disease in the Young and Council on Cardiovascular and Stroke Nursing. Evaluation and management of the child and adult with Fontan circulation: a scientific statement from the American Heart Association. Circulation 2019;, 140(6), e234-e284.
828. Cheung YF, Penny DJ, Redington AN. Serial assessment of left ventricular diastolic function after Fontan procedure. Heart Br Card Soc 2000:3:420-424.
829. Hern´andez-Madrid A, Paul T, Abrams D, Aziz PF , Blom NA Chen, et al., Arrhythmias in congenital heart disease: a position paper of the European Heart Rhythm Association (EHRA), Association for European Paediatric and Congenital Cardiology (AEPC), and the European Society of Cardiology (ESC) Working Group on Grown-up Congenital heart disease, endorsed by HRS, PACES, APHRS, and SOLAECE, Europace 2018: 20 (11): 1719-1753.
830. Khairy P, Van Hare GF, Balaji S, et al. PACES/HRS expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS).Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology (ACC), theAmerican Heart Association (AHA), the European Heart Rhythm Association (EHRA), the Canadian Heart Rhythm Society (CHRS), and the International Society for Adult Congenital Heart Disease (ISACHD). Can J Cardiol 2014;30(10):e1-63.
831. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for devicebased therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society Circulation 2013;127:e283-352.
832. Chubb H, O'Neill M, Rosenthal E. Pacing and defibrillators in complex congenital heart disease. Arrhythm Electrophysiol Rev. 2016 5;May(1):57-64. PubMed PMID: 27403295.
833. Dubin, A. M., Janousek, J., Rhee, E., Strieper, M. J., Cecchin, Fet al. Resynchronization Therapy in Pediatric and Congenital Heart Disease Patients. J Am Coll Cardio 2005: 46(12), 2277-2283.
834. Janousek J, Gebauer A. Cardiac Resynchronization Therapy in Pediatric and Congenital Heart Disease. Pacing and Clinical Electrophysiology 2008: 31, S21-S23. doi:10.1111/j.1540-8159.2008.00949
835. Givertz MM, DeFilippis EM, Landzberg MJ, Pinney SP, Woods RK, Valente AM. Advanced Heart Failure Therapies for Adults With Congenital Heart Disease: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019 Nov 5;74(18):2295-2312.
836. Menachem JN, Schlendorf KH, Mazurek JA, Bichell DP, Brinkley DM et al.. Advanced Heart Failure in Adults With Congenital Heart Disease. JACC Heart Fail. 2020 Feb;8(2):87-99.
837. Ministry of Health Malaysia. Malaysian Clinical Practice Guidelines for Prevention, Diagnosis and Management of Infective Endocarditis,1st Ed 2017 (Internet).Available at www.acadmed.org.my

838. Budts W, Börjesson M, Chessa M, et al. Physical activity in adolescents and adults with congenital heart defects: individualized exercise prescription. Eur Heart J 2013;34:3669-74.
839. Sarno LA, Misra A, Siddeek H, et al. Cardiac rehabilitation for adults and adolescents with congenital heart disease: extending beyond the typical patient population. J Cardiopulm Rehabil Prev. 2020;40 (1):E1-E4.
840. Troost, E., Roggen, L., Goossens, E., Moons, P., De Meester, P.et al. Advanced care planning in adult congenital heart disease: Transitioning from repair to palliation and end-of-life care. Int J Cardiol 2019; 279:57-61
841. Kovacs AH, Kaufman TM, Broberg CS. Cardiac rehabilitation for adults with congenital heart disease: physical and psychosocial considerations.Can J Cardiol. 2018 Oct 01;34(10, Supplement 2):S270-S277.
842. Khush KK, Cherikh WS, Chambers DC, Goldfarb S, Hayes D, Kucheryavaya AY, Levvey BJ, Meiser B, Rossano JW, Stehlik J. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-fifth adult heart transplantation report-2018; focus theme: multiorgan transplantation.J Heart Lung Transplant. 2018; 37:1155-1168
843. Crespo-Leiro MG, Costanzo MR, Gustafsson F, Khush KK, Macdonald PS, Potena L, Stehlik J, Zuckermann A, Mehra MR. Heart transplantation: focus on donor recovery strategies, left ventricular assist devices, and novel therapies. Eur Heart J. 2022 Jun 14;43(23):2237-2246.
844. Goldstein DJ, Naka Y, Horstmanshof D, et al. Association of Clinical Outcomes With Left Ventricular Assist Device Use by Bridge to Transplant or Destination Therapy Intent.The Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3 (MOMENTUM 3) Randomized Clinical Trial. JAMA Cardiol. 2020;5(4):411-419
845. Patel S, Nicholson L, Cassidy CJ, Wong K Y-K. Left ventricular assist device: a bridge to transplant or destination therapy? . Postgrad Med J 2016;92:271-281
846. Estep JD, Starling RC, Horstmanshof DA, et al; ROADMAP Study Investigators. Risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients: Results from the ROADMAP study. J Am Coll Cardiol 2015;66:1747-61.
847. Pagani FD, Milano CA, Tatooles AJ, et al. HeartWare HVAD for the treatment of patients with advanced heart failure ineligible for cardiac transplantation: results of the ENDURANCE destination therapy trial. J Heart Lung Transplant 2015;34:S9.
848. Health Quality Ontario. Left ventricular assist devices for destination therapy: a health technology assessment. Ont Health Technol Assess Ser 2016;16(3):1-60.
849. Adler ED, Goldfinger JZ, Kalman J, et al. Palliative care in the treatment of advanced heart failure. Circulation 2009; 120(25): 2597-606.
850. Jaarsma T, Beattie JM, Ryder M, et al for the Advanced Heart Failure Study Group of the HFA of the ESC. Palliative care in heart failure: a position statement from the palliative care workshop of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2009;11:433-43.
851. Chang YK, Allen LA, McClung JA, et al. Criteria for Referral of Patients With Advanced Heart Failure for Specialized Palliative Care. J Am Coll Cardiol 2022; 80(4): 332-344.
852. Whellan DJ, Goodlin SJ, Dickinson MG, et al for Quality of Care Committee, Heart Failure Society of America. End-of-life care in patients with heart failure. J Card Fail 2013;20:121-34.
853. Sobanski PZ, Alt-Epping B, Currow DC, et al. Palliative care for people living with heart failure: European Association for Palliative Care Task Force expert position statement. Cardiovasc Res 2020 ;116(1): 12-27.
854. Gililan R, Puchalski C. Spiritual issues in heart failure. In: Supportive Care in Heart Failure, Beattie J, Goodlin S (Eds), Oxford University Press, Oxford 2008. p.299.
855. Stewart S, Carrington MJ, Marwick TH, et al. The WHICH trial: Impact of home versus clinic-based management of chronic heart failure. JACC 2012;60(14):1239-48.
856. Sunnerhagen KS, C. A., Schaufelberger M, Hedberg M, Grimby G. Muscular performance in heart failure. J Card Fail 1998: 4(2): 97-104.
857. Wilson JR, M. D. Factors contributing to the exercise limitation of heart failure. J Am Coll Cardiol 1993: 22(4 Suppl A): 93A-98A.
858. Piña IL, A. C., Balady GJ, Belardinelli R, Chaitman BR, Duscha BD et al. American Heart Association Committee on exercise, rehabilitation, and prevention. Exercise and heart failure: A statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. Circulation 2003:107(8): 1210-1225.
859. Belardinelli R, G. D., Cianci G, Purcaro A. 10-year exercise training in chronic heart failure: a randomized controlled trial. J Am Coll Cardiol 2012: 60(16): 1521-1528.
860. Leggio M. F. A., Loreti C, Limongelli G, Bendini MG, Mazza A et al. Effects of exercise training in heart failure with preserved ejection fraction: an updated systematic literature review. Heart Fail Rev 2020: 25(5): 703-711.
861. Edwards, J. J., O'Driscoll, J.M. Exercise Training in Heart failure with Preserved and Reduced Ejection Fraction: A Systematic Review and Meta-Analysis. Sports Med 2022: Open 8(76).
862. Piepoli MF, C. V., Corrà U, Dickstein K, Francis DP, Jaarsma T et al. Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. Eur J Heart Fail 2011; 13(4): 347-357.
863. O'Connor CM, W. D., Lee KL, Keteyian SJ, Cooper LS, Ellis SJ et al. HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009: 301(14): 1439-1450.
864. Long L, M. I., Bridges C, Sagar VA, Davies EJ, Coats AJ et al.Exercise-based cardiac rehabilitation for adults with heart failure. Cochrane Database 2019; Syst Rev. 1(1): CD003331.
865. Bjarnason-Wehrens B, N. R., Jensen K, Hackbusch M, Grilli M, Gielen S et al. German Society of Cardiovascular Prevention and Rehabilitation (DGPR). Exercise-based cardiac rehabilitation in patients with reduced left ventricular ejection fraction: The Cardiac Rehabilitation Outcome Study in Heart Failure (CROS-HF): A systematic review and meta-analysis. ." Eur J Prev Cardiol. 2020; 27(9): 929-952.

866. Forman DE, S. B., Josephson RA, Raikhelkar J, Bittner V; American College of Cardiology's Prevention of Cardiovascular Disease Section. Heart Failure as a Newly Approved Diagnosis for Cardiac Rehabilitation: Challenges and Opportunities. J Am Coll Cardiol 2015: 65. 2652-2659.
867. Meng Y, Z. W., Huang H, Zhang T, Ge X. The effects of early exercise on cardiac rehabilitation-related outcome in acute heart failure patients: A systematic review and meta-analysis. . Int J Nurs Stud 2022: 130(104237).
868. Izawa H, Yoshida T, Ikegame T, Izawa KP, Ito Y et al. Japanese Association of Cardiac Rehabilitation Standard Cardiac Rehabilitation Program Planning Committee. Standard Cardiac Rehabilitation Program for Heart Failure. Circ J. 2019 Nov 25;83(12):2394-2398.
869. Adsett JA, M. A., Morris N, Kuys S, Paratz JD. Aquatic exercise training and stable heart failure: A systematic review and meta-analysis. Int J Cardiol 2015:186: 22-28.
870. Cornelis J, B. P., Taeymans J, Vrints C, Vissers D. Comparing exercise training modalities in heart failure: A systematic review and meta-analysis. Int J Cardiol 2016: 221: 867-876.
871. Palmer K, B. K., Paton M, Jepson M, Lane R. Chronic Heart Failure and Exercise Rehabilitation: A Systematic Review and Meta-Analysis. Arch Phys Med Rehabil. 2018: 99(12): 2570-2582.
872. Chun, K-H., Kang S-M. Cardiac Rehabilitation in Heart Failure. Int J Heart Fail 2021: 3(1): 1-14.
873. Nichols S, M. G., Breckon J, Ingle L. Current Insights into Exercise-based Cardiac Rehabilitation in Patients with Coronary Heart Disease and Chronic Heart Failure. Int J Sports Med 2021: 42(1): 19-26.
874. Tegegne TK, R. J., Nourse RA, Kibret KT, Ahmed KY, Maddison R. Effects of exercise-based cardiac rehabilitation delivery modes on exercise capacity and health-related quality of life in heart failure: a systematic review and network meta-analysis. Open Heart 2022: 9(1): e001949.
875. Imran HM, B. M., Erqou S, Taveira TH, Shah NR, Morrison A et al. Home-Based Cardiac Rehabilitation Alone and Hybrid With Center-Based Cardiac Rehabilitation in Heart Failure: A Systematic Review and Meta-Analysis. J Am Heart Assoc 2019: 8(16): e012779.
876. Indraratna P, T. D., Yu J, Delbaere K, Brodie M, Lovell N, Ooi SY. Mobile Phone Technologies in the Management of Ischemic Heart Disease, Heart Failure, and Hypertension: Systematic Review and Meta-Analysis. JMIR Mhealth Uhealth 2020: 8(7): e16695.
877. Velayati F, A. H., Hemmat M. A Systematic Review of the Effectiveness of Telerehabilitation Interventions for Therapeutic Purposes in the Elderly. Methods Inf Med 2020; 59(2-03): 104-109.
878. Cavalheiro AH, S. C. J., Rocha A, Moreira E, Azevedo LF. Effectiveness of Tele-rehabilitation Programs in Heart Failure: A Systematic Review and Meta-analysis. Health Serv Insights 2021: 14: 11786329211021668.
879. Chen, Z. B., Fan, L. B., Liu, Y. J., & Zheng, Y. R. Meta-Analysis of the Effects of Cardiac Rehabilitation on Exercise Tolerance and Cardiac Function in Heart Failure Patients Undergoing Cardiac Resynchronization Therapy. Biomed Res Int. 2019: 3202838.
880. Ye LF, W. S., Wang LH. Efficacy and Safety of Exercise Rehabilitation for Heart Failure Patients With Cardiac Resynchronization Therapy: A Systematic Review and Meta-Analysis. Front Physiol 2020: 21(11): 980.
881. Guo R, W. Y., Xu Y, Jia R, Zou S, Lu S et al. The impact of exercise training for chronic heart failure patients with cardiac resynchronization therapy: A systematic review and meta-analysis. Medicine (Baltimore) 2021: 100(13): e25128.
882. Pandey A, S. M., Singh S, Reeves GR, O'Connor C, Piña I et al. Frailty Status Modifies the Efficacy of Exercise Training Among Patients With Chronic Heart Failure and Reduced Ejection Fraction: An Analysis From the HF-ACTION Trial. ." Circulation 2022: 146(2): 80-90.
883. Aili SR, Lo P, Villanueva JE, Joshi Y, Emmanuel S, Macdonald PS. Prevention and Reversal of Frailty in Heart Failure - A Systematic Review. Circ J. 2021 Dec 24;86(1):14-22
884. Daw, P., Withers, T.M., van Zanten, J.J.C.S.V. et al. A systematic review of provider-and system-level factors influencing the delivery of cardiac rehabilitation for heart failure. BMC Health Serv Res 2021: 21, 1267
885. McAlister FA, Stewart S, Ferrua S, McMurray JJ. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. J Am Coll Cardiol 2004;44:810-19.
886. Feltner C, Jones CD, Cené CW, et al. Transitional care interventions to prevent readmissions for persons with heart failure: a systematic review and meta-analysis. Ann Intern Med 2014;160:774-84.
887. Hauptman PJ, Rich MW, Heidenreich PA, et al; Heart Failure Society of America. The Heart Failure Clinic: a consensus statement of the Heart Failure Society of America. J Card Fail 2008;14:801-15.
888. Gustafsson F, J. Arnold MO. Heart failure clinics and outpatient management: review of the evidence and call for quality assurance. Eur Heart J 2004;25:1596-1604.
889. Ministry of Health Malaysia (Pharmacy Practice and Development Division). Protocol Medication Therapy Adherence Clinic (MTAC): Heart Failure 2018, 1st Ed.
890. Pufulete M, Maishman R, Dabner L, et al. B-type natriuretic peptide-guided therapy for heart failure (HF): a systematic review and meta-analysis of individual participant data (IPD) and aggregate data. Systematic Reviews. 2018:7:112.
891. Mark DB, Cowper PA, Anstrom KJ, et al. Economic and quality of life outcomes as natriuretic peptide guided therapy for heart failure. J Am Coll Cardiol. 2018; 72:2551-2562.
892. Tersalvi G, Winterton D, Cioffi GM, Ghidini S, Roberto M et al.Telemedicine in Heart Failure During COVID-19: A Step Into the Future. Frontiers in Cardiovascular Medicine. 2020: Vol 7, Article 612818
893. Soran O, Kennard ED, Kfoury AG, Kelsey SF,IEPR Investigators Two year clinical outcomes after Enhanced External Counterpulsation (EECP) therapy in patients with refractory angina pectoris and left ventricular dysfunction (report from the international EECP Patient Registry). Am J Cardiol 2006; 97: 17-20.
894. McKenna C, McDaid C, Suekarran S, Hawkins N, Claxton K, Light K, Chester M, Cleland J, Woolacott N, Sculpher M. Enhanced external counterpulsation for the treatment of stable angina and heart failure: a systematic review and economic analysis. Health Technol Assess. 2009 Apr;13(24):iii-iv, ix-xi, 1-90.
895. Tecson KM, Silver MA, Brune SD, et al. Impact of EECP on heart failure rehospitalization in patients with ischemic cardiomyopathy. Am J Cardiol 2016;117:901-5.

896. Zhou ZF, Wang Dj, Li XM, Zhang CL, Wu CY. Effects of enhanced external counterpulsation on exercise capacity and quality of life in patients with chronic heart failure: A meta-analysis. Medicine. 2021;100:27(e26536).
897. Feldman AM, Silver MA, Francis GS, et al.. Enhanced external counterpulsation improves exercise tolerance in patients with chronic heart failure. J Am Coll Cardiol 2006;48:1198-205
898. Lawson WE, Kennard ED, Holubkov R, et al; IEPR investigators. Benefit and safety of enhanced external counterpulsation in treating coronary artery disease patients with a history of congestive heart failure. Cardiology 2001;96:78-84.
899. Madonna R, Van Laake LW, Davidson SM, et al. Position Paper of the European Society of Cardiology Working Group Cellular Biology of the Heart: cell-based therapies for myocardial repair and regeneration in ischemic heart disease and heart failure. Eur Heart J. 2016;37(23):1789-1798.505.
900. Fernandez-Aviles F, Sanz-Ruiz R, Climent AM, et al for TACTICS (Transnational Alliance for Regenerative Therapies in Cardiovascular Syndromes) Writing Group; Authors/Task Force Members. Chairpersons; Basic Research Subcommittee; Translational Research Subcommittee; Challenges of Cardiovascular Regenerative Medicine Subcommittee; Tissue Engineering Subcommittee; Delivery, Navigation, Tracking and Assessment Subcommittee; Clinical Trials Subcommittee; Regulatory and funding strategies subcommittee; Delivery, Navigation, Tracking and Assessment Subcommittee. Global position paper on cardiovascular regenerative medicine. Eur Heart J 2017;38:2532-46.
901. Rheault-Henry M, White I, Grover D, Atoui R. Stem cell therapy for heart failure: Medical breakthrough, or dead end? World J Stem Cells. 2021 Apr 26;13(4):236-259.
902. Tavazzi L, Maggioni AP, Marchioli R, et al; Gissi-HF Investigators. Effect of n3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF Trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1223-30.
903. Siscovick DS, Barringer TA, Fretts AM, et al. Omega-3 polyunsaturated fatty acid (fish oil) supplementation and the prevention of cardiovascular disease. A Science Advisory From the American Heart Association. Circulation 2017;135:(15):e867-84.
904. Abdelhamid AS, Brown TJ, Brainard JS, Biswas P, Thorpe GC et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2020, Issue 3. Art. No.: CD003177. DOI: 10.1002/14651858.CD003177.pub5
905. Kojuri J, Ostovan MA, Rezaian GR, Archin Dialameh P, Zamiri N et al. Effect of omega-3 on brain natriuretic peptide and echocardiographic findings in heart failure: Double-blind placebo-controlled randomized trial. J Cardiovasc Dis Res. 2013 Mar;4(1):20-4
906. Djoussé L, Cook NR, Kim E, Walter J, Al-Ramady OT et al. Diabetes Mellitus, Race, and Effects of Omega-3 Fatty Acids on Incidence of Heart Failure Hospitalization. JACC: Heart Failure 2022; 10 (4): 235-237
907. Block RC, Liu L, Herrington DM, Huang S, Tsai MY et al. Predicting Risk for Incident Heart Failure With Omega-3 Fatty Acids: From MESA. J Am Coll Cardiol HF. 2019 Aug, 7 (8) 651-661
908. Al Saadi T, Assaf Y, Farwati M, Turkmani K, Al-Mouakeh A et al. Coenzyme Q10 for heart failure. Cochrane Database of Systematic Reviews 2021, Issue 1. Art. No.: CD008684. DOI: 10.1002/14651858.CD008684.pub3.
909. Di Lorenzo A, Iannuzzo G, Parlato A, Cuomo G, Testa C et al. Clinical Evidence for Q10 Coenzyme Supplementation in Heart Failure: From Energetics to Functional Improvement. J Clin Med. 2020 Apr 27;9(5):1266
910. Raizner AE, Quiñones MA. Coenzyme Q10 for Patients With Cardiovascular Disease: JACC Focus Seminar. J Am Coll Cardiol 2021: 77 (5): 609-619
911. Yeh GY, McCarthy EP, Wayne PM, Stevenson LW, Wood MJ, Forman D, Davis RB, Phillips RS. Tai chi exercise in patients with chronic heart failure: a randomized clinical trial. Arch Intern Med. 2011: 171(8):750-7
912. Gu Q, Wu SJ, Zheng Y, et al. Tai Chi exercise for patients with chronic heart failure. Am J Phys Med Rehabil 2017;96(10):706-16.
913. Ren X, Li Y, Yang X, Li J, Li H, Yuan Z, Sun Y, Shang H, Xing Y, Gao Y. The Effects of Tai Chi Training in Patients with Heart Failure: A Systematic Review and Meta-Analysis. Front Physiol. 2017 Dec 7;8:989.
914. Chen X, Savarese G, Cai Y, Ma L, Lundborg CS et al. Tai Chi and Qigong Practices for Chronic Heart Failure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Hindawi Volume 2020 | Article ID 2034625 | https://doi.org/10.1155/2020/2034625
915. Gomes-Neto M, Rodrigues ES Jr, Silva WM Jr, Carvalho VO. Effects of Yoga in Patients with Chronic Heart Failure: A Meta-Analysis. Arq Bras Cardiol. 2014 Nov;103(5):433-439.
916. Guddeti, Raviteja R. MD; Dang, Geetanjali MD; Williams, Mark A. PhD; Alla, Venkata Mahesh MD. Role of Yoga in Cardiac Disease and Rehabilitation. Journal of Cardiopulmonary Rehabilitation and Prevention 2019; 39(3):p 146-152.
917. Fonarow GC, Albert NM, Curtis AB, et al. Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). Circulation 2010;122:585-96.
918. Nakaoab K, Yasudaac S, Noguchia T, Sumitaa Y, Nakao YM et al. Association of hospital performance measures with readmissions for patients with heart failure: A report from JROAD-DPC study. Int J Cardiology 2021: 340 : 48-54.
919. Nakano A, Vinter N, Egstrup K, Svendsen ML, Schjødt I et al. Association between process performance measures and 1-year mortality among patients with incident heart failure: a Danish nationwide study, European Heart Journal - Quality of Care and Clinical Outcomes, Volume 5, Issue 1, January 2019, Pages 28-34

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