Heart Failure Pathway

Definition

- Divided into heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF)
- HFrEF and HFpEF present with similar symptoms

Background

- In India, burden of HF is high
  - Estimate from 2010, 1.3-4.6 million
  - Likely higher now
- 1 year mortality from HF in India is 23%
- IHD is the leading cause of mortality in India
- Burden not just directly from IHD, but the sequelae of cardiac ischemia, including heart failure

Links to other pathways

- This pathway should be considered in conjunction with (mostly to be written)
  - Risk factor modification pathway
  - HTN pathway
  - Diabetes pathway
  - Chest pain pathway
  - IHD pathway
  - Others?

Questions for contextualisation

- How do we treat HF at CSA partner sites?
- What are the barriers to HF management in India?
  - Financial
  - Can these be overcome?
- "The best adapted solution to the problem at hand"

Outpatient management of HFrEF

Establish diagnosis

- Clinical signs suggestive of HF
- ECG may show LV hypertrophy, evidence or previous ischaemia
- Echocardiogram with LVEF < 40% consistent with HFrEF
  - This will likely require referral to nearest district hospital
  - **Echocardiogram ability of partner locations to be determined**
- Pregnant patients require pregnancy specific management – this pathway cannot be used

Assessment of severity

- See appendix (NYHA Class)

Assess and manage comorbid conditions

- Ischaemic heart disease
  - HF is common sequelae of coronary artery disease
  - Risk reduction and symptomatic management as per **CSA IHD pathway (TBD)**
- Hypertension
  - Manage as per **CSA hypertension pathway (TBD)**
- Diabetes
- Arrythmias
  - Particularly AF
- Valvular disease
  - Refer to specialist
- Cardiomyopathy
- Anaemia
- Smoking

Symptomatic management

- Diuretic
- furosemide 20-40mg once or twice a day
  - Morning and midday dosing to avoid nocturnal diuresis
  - Monitor renal function once a week
  - Titrate to minimum dose required to eliminate evidence of fluid retention
  - Can provide a weigh scale to facilitate this

If HFrEF

Disease modifying management

- Drug from each of the below classes should be initiated at time of diagnosis
  - Dosages and sequence of initiation in Appendix I
  - See below if specific therapies unavailable at CSA partner site
- Angiotensin receptor-neprilysin inhibitor (**ARNI**), angiotensin converting enzyme (**ACE**) inhibitor, or angiotensin receptor blocker (**ARB**)
  - ARNI: Sacubitril-Valsartan
    - Preference for ARNI if possible – however, significant barriers due to cost
  - ACE inhibitor: Captopril, enalapril, lisinopril, ramipril
    - Lisinopril and ramipril and once daily dosing, which may be preferable
  - ARB
    - Candesartan, losartan, valsartan
  - The use of ARNI/ACE/ARB in patients with eGFR < 30 is not contraindicated, but caution should be exercised
- **Beta blocker**
  - Evidence based beta-blockers: Bisoprolol, carvedilol, metoprolol XR
- Mineralocorticoid receptor antagonists (**MRA**)
  - Spironolactone or eplerenone
  - Monitor serum potassium, down titrate or discontinue if serum potassium elevated

- Contraindications: eGFR < 30 or potassium > 5

- **SGLT2 inhibitor**
  - Dapagliflozin or empagliflozin
  - Contraindications: T1DM, symptomatic hypotension, frequent UTI, risk factors for foot amputation, eGFR < 30 (dapafliglozin), eGFR < 20 (empagliflozin)
- Monitor blood pressure and electrolytes post initiation
- Ensure SBP > 100

Alternative treatment regimens

- On the basis of current evidence, combination therapy with an ARNI, BB, MRA and SGLT2 inhibitor has the greatest mortality benefit for patients with HFrEF, and is the CSA preferred regimen
- However, some of these drugs may not be available at CSA partner sites, due to location or cost
- If the above medications are not available, the below alternative regimens can be considered (Appendix II)
- If ARNI unavailable
  - Replace ARNI with ACEI (e.g. ramipril) or ARB (e.g. valsartan)

- If SGLT2 unavailable
  - No comparative alternative

Drugs to use with caution

- Digoxin is commonly used for the treatment of heart failure in India
  - Robust evidence to support the use of digoxin in HFrEF is lacking
  - Digoxin use does not appear to reduce mortality, but may reduce hospitalisations
  - This should be balanced against the risks of digoxin therapy (i.e. digoxin toxicity), and difficulty with monitoring drug levels in the rural Indian setting
- In general, we do not recommend the use of digoxin in heart failure, especially if any of the above therapies are available
- If digoxin is to be used (not evidence based), starting dose:
  - 0.125mg daily if eGFR ≥ 30
  - 0.125mg every second day or 0.0625mg daily if eGFR < 30, or elderly, or low body weight
  - Check electrolytes (particularly potassium) prior to initiation
- Exercise particular caution if digoxin used in conjunction with drugs that suppress heart rate (e.g. beta blockers), or increase digoxin concentration (e.g. furosemide)
- Have a high index of suspicion for digoxin toxicity (e.g. vomiting/nausea, visual disturbances, arrhythmias)

Other considerations

- Patients with recent myocardial infarction and HFrEF
  - Major studies of HFrEF have excluded patients with recent myocardial infarction
  - ACEI/ARB, beta blockers and MRAs have been shown to be beneficial in these patients

    - ARNI is not superior to ACEI in the setting of recent myocardial infarction
    - The impact of SGLT2 in the post-MI period still being studied
- Lifestyle modifications (see CSA risk factor/lifestyle modification pathway)
- Cardiac rehab
    - Refer to physiotherapist/local cardiac rehab program
    - Can give education materials for home cardiac rehab
- Vaccinations
    - Pneumococcal, influenza, COVID
- Smoking cessation

Indications for referral to specialist cardiology services (adapted from Maddox et al, 2021)

- Heart failure refractory to therapy
- Persistent hypotension
- Renal failure
- Heart failure with atrial fibrillation
- 2+ issues of decompensation in previous 12 months
- Valvular or structural heart disease
- Inability to tolerate medical therapy for heart failure
- Diagnostic uncertainty
- Patients who are potential candidates for device-based therapies

Outpatient management of HFpEF

- The diagnosis of heart failure with preserved ejection fraction requires an echocardiogram
- Unlike HFrEF, there are limited therapeutic options in HFpEF
- If HFpEF confirmed:
    - Manage comorbid conditions
        - Hypertension, AF, CAD risk management, AD, hyperlipidaemia, obesity, anaemia, diabetes, CKD, OSA
- If fluid overload, diuretics
    - Titrate to euvolaemia
    - furosemide 20-40mg as starting dose
- If HFpEF
    - Consider SGLT2 inhibitor as first line
- If HFpEF with elevated BNP
    - Consider SGLT2 inhibitor and MRA
- Avoid the following drugs unless prescribed for other conditions such as hypertension:
    - ARNI, ACEI, ARB, calcium channel blocker, digoxin
    - None of the above classes of drugs have been shown to improve clinical outcomes in HFpEF

Appendices

Appendix I

Sequence of Initiation and Starting and Target doses of Pharmacotherapies for HFrEF (adapted from Maddox et al, 2021)

Starting and Target Doses of Pharmacotherapies for HFrEF		
	Starting Dose	**Target Dose**
Beta-Blockers		
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25 mg twice daily for weight <85 kg and 50 mg twice daily for weight ≥85 kg
Metoprolol succinate	12.5–25 mg daily	200 mg daily
ARNIs		
Sacubitril/valsartan	24/26 mg–49/51 mg twice daily	97/103 mg twice daily
ACEIs		
Captopril	6.25 mg 3× daily	50 mg 3× daily
Enalapril	2.5 mg twice daily	10–20 mg twice daily
Lisinopril	2.5–5 mg daily	20–40 mg daily
Ramipril	1.25 mg daily	10 mg daily
ARBs		
Candesartan	4–8 mg daily	32 mg daily
Losartan	25–50 mg daily	150 mg daily
Valsartan	40 mg twice daily	160 mg twice daily
Aldosterone antagonists		
Eplerenone	25 mg daily	50 mg daily
Spironolactone	12.5–25 mg daily	25–50 mg daily
SGLT2 inhibitors		
Dapagliflozin	10 mg daily	10 mg daily
Empagliflozin	10 mg daily	10 mg daily

Sequence of initiation

- For all patients commencing pharmacotherapy, monitor:
  - Blood pressure
  - Electrolytes
  - Renal function
  - Potassium
- ARNI or ACEI/ARB **AND**
  - If starting ARNI, ensure no history of angioedema
  - Commence starting dose, then assess tolerability every 2 weeks. If dose is tolerated, then double dose every 2 weeks until target dose
  - Tolerability defined as SBP > 100, lack of symptomatic hypotension
- Beta Blocker **AND**

    - Commence at starting dose, doubling every 2 weeks until target dose
    - Only bisoprolol, carvedilol and metoprolol have demonstrated mortality benefits in HFrEF – avoid other beta blockers
- Diuretics **AND**
- Aldosterone antagonist **AND**
    - Commence starting dose, then assess tolerability. Dose can be doubled every 2 weeks until target dose
    - Check electrolytes/potassium and renal function 2-3 days post initiation, then 7 days after initiation, and then at least every 3 months thereafter
- SGLT2 inhibitor **AND**
    - Commence at starting dose, no titration is required
    - Ensure eGFR ≥ 30ml/min for dapagliflozin
    - Ensure eGFR ≥ 20ml/min for empagliflozin

Appendix II
Sample treatment regimens for HFrEF

CSA preferred regimen
- Based on recent clinical trials, and in accordance with most updated global guidelines
- Sacubitril/Valsartan AND beta blocker (e.g. bisoprolol) AND MRA (e.g. spironolactone or eplerenone) AND SGLT2 inhibitor (dapagliflozin or empagliflozin)
- **Approx annual cost of this regimen: ₹77k**

If sacubitril/valsartan unavailable
- E.g. due to cost, then use:
- ACEI (e.g. ramipril) or ARB (e.g. valsartan) AND beta blocker (e.g. bisoprolol) AND MRA (e.g. spironolactone) AND SGLT2 inhibitor (e.g. dapagliflozin)
- **Approx annual cost: ₹10k**

If sacubitril/valsartan AND SGLT2 inhibitors unavailable
- E.g. due to cost, then use:
- ACEI (e.g. ramipril) or ARB (e.g. valsartan) AND beta blocker (e.g. bisoprolol) AND MRA (e.g. spironolactone)
- There are no alternative agents for SGLT2 inhibitors
- **Approx annual cost: ₹3k**

Sample Treatment Regimens

Regimen	RAAS	BB	MRA	SGLT2	Diuretic	Monitoring
CSA Preferred	Sacubitril-Valsartan	Bisoprolol *	Eplerenone	Dapagliflozin	furosemide	Electrolytes Renal Function

Alternate #1	Ramipril or Valsartan **	Bisoprolol *	Spironolactone	Dapagliflozin	furosemide	Electrolytes Renal Function
Alternate #2	Ramipril or Valsartan **	Bisoprolol *	Spironolactone	None	furosemide	Electrolytes Renal Function

*Bisoprolol can be replaced with carvedilol or metoprolol XR
** Ramipril can be replaced with alternate ACE inhibitor, valsartan can be replaced with alternate angiotensin receptor blocker

Appendix III

Key Evidence Summaries

- PARADIGM study (2014)
  - 8442 patients with NYHA Class II-IV HFrEF (EF < 40%) randomized to sacubitril-valsartan vs enalapril, in addition to regular therapy
  - Sacubitril-valsartan reduced risk of death and hospitalisation compared to enalapril
- EMPEROR-reduced (2020)
  - 3730 patients with NYHA Class II-IV HFrEF (EF < 40%) randomized to empagliflozin or placebo, in addition to recommended therapy
  - Empagliflozin reduced risk of cardiovascular death or hospitalization for heart failure compared to placebo, regardless of diabetes status
- DAPA-HF (2019)
  - 4744 patients with NYHA Class II-IV HFrEF (EF < 40%) randomized to dapafliflozin vs placebo, in addition to recommended therapy
  - Dapagliflozin reduced risk of worsening heart failure or death from cardiovascular causes compared to placebo
- EMPHASIS study 2011
  - 2737 patients with NYHA Class II HFrEF (EF < 35%) randomized to eplerenone vs placebo, in addition to regular therapy
  - Eplerenone reduced risk of death and hospitalisation compared to placebo
- Estimated lifetime benefits of comprehensive disease-modifying medical therapies in HFrEF (Vaduganathan 2020)
  - Treatment with ARNI + MRA + SGLT2 inhibitor superior to conventional therapy with ACEi/ARB and BB
  - Estimate magnitude of benefit for comprehensive disease-modifying therapy: between 2.7 additional years (for an 80-year-old) to 8.3 additional years (for a 55-year-old) before cardiovascular death or first hospital admission for heart failure to 1.4 additional years (for an 80-year-old) to 6.3 additional years (for a 55-year-old) of survival compared to conventional therapy

Estimation of relative treatment effects of comprehensive disease-modifying pharmacological therapy on key cardiovascular events (from Vaduganathan 2020)

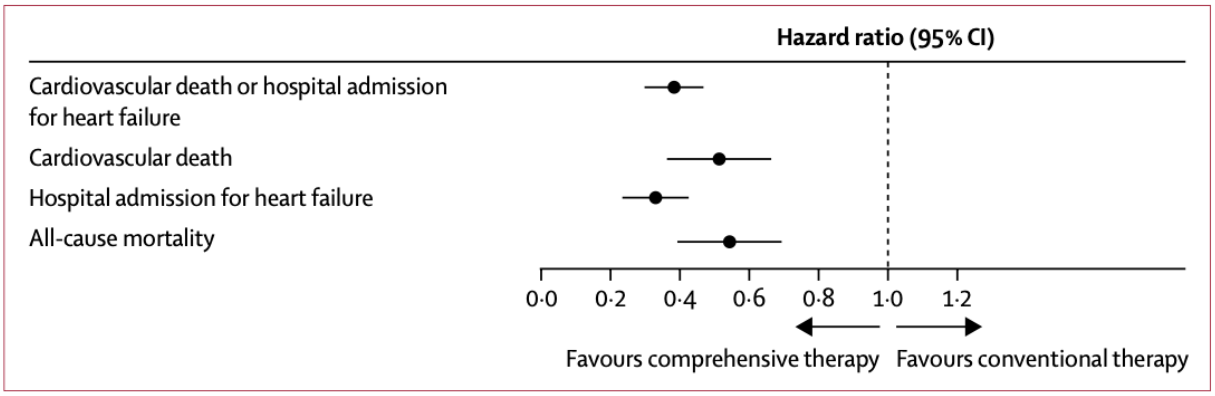

Figure 1: **Estimation of relative treatment effects of comprehensive disease-modifying pharmacological therapy on key cardiovascular events**

Comprehensive therapy consisted of an ARNI, β blocker, MRA, and SGLT2 inhibitor; conventional therapy consisted of an ACE inhibitor or ARB and β blocker. ACE inhibitor=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor–neprilysin inhibitor. MRA=mineralocorticoid receptor antagonist. SGLT2 inhibitor=sodium/glucose cotransporter 2 inhibitor.

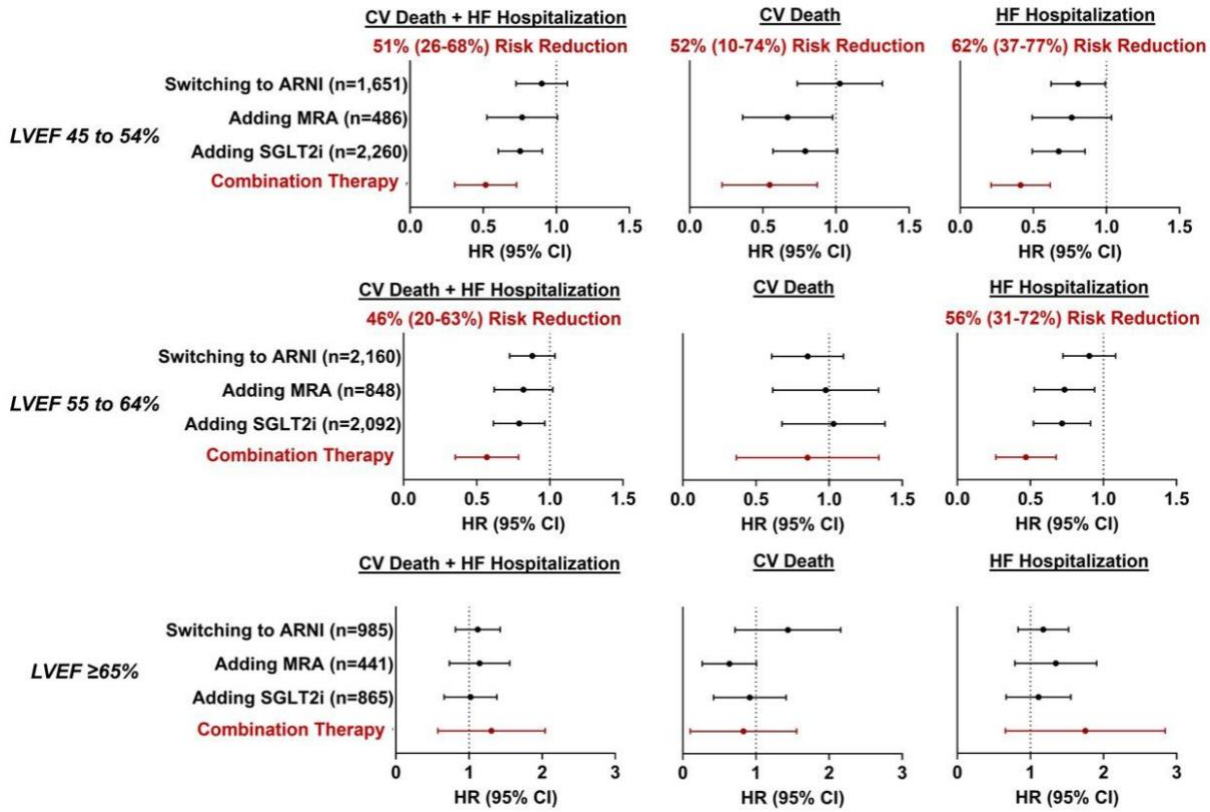

Figure: Risk reduction with combination therapy for HFrEF

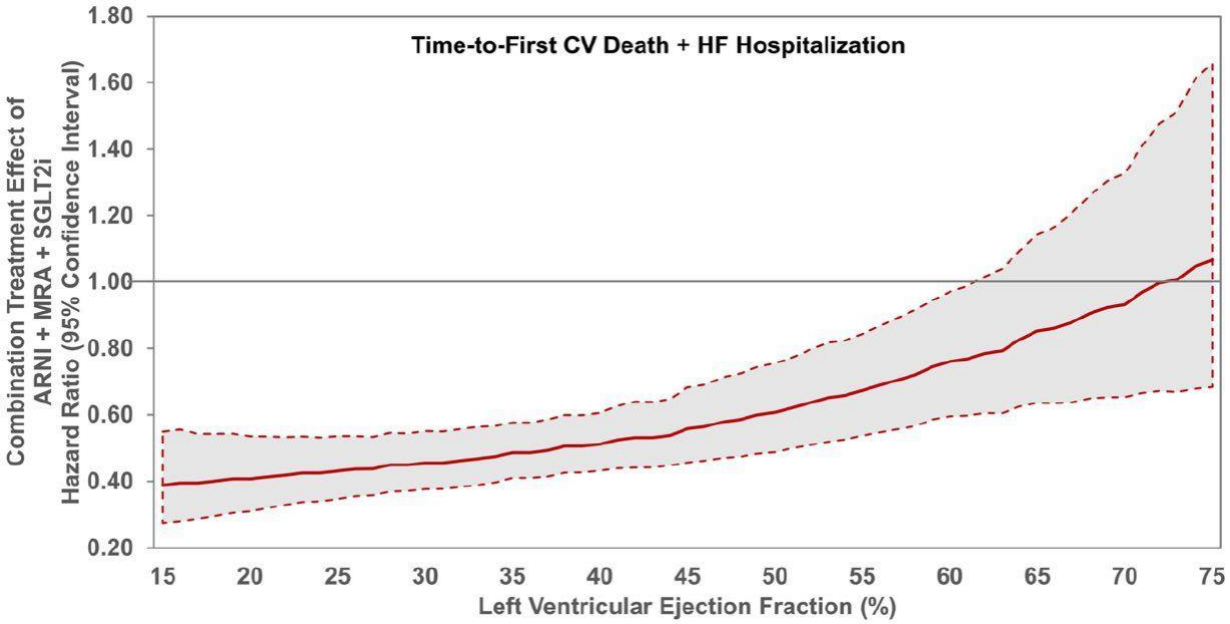

Figure: Impact on combination therapy for HFrEF on cardiovascular outcomes stratified by LVEF

Appendix IV – Assessment of Heart Failure Severity

NYHA Functional Classification

Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Appendix V
Challenges to be addressed (for innovation workstream)

- Cost of medications for HF
- Can HF drugs be added to the government essential drug list?
- **How do we integrate POC electrolytes into our treatment pathways?**