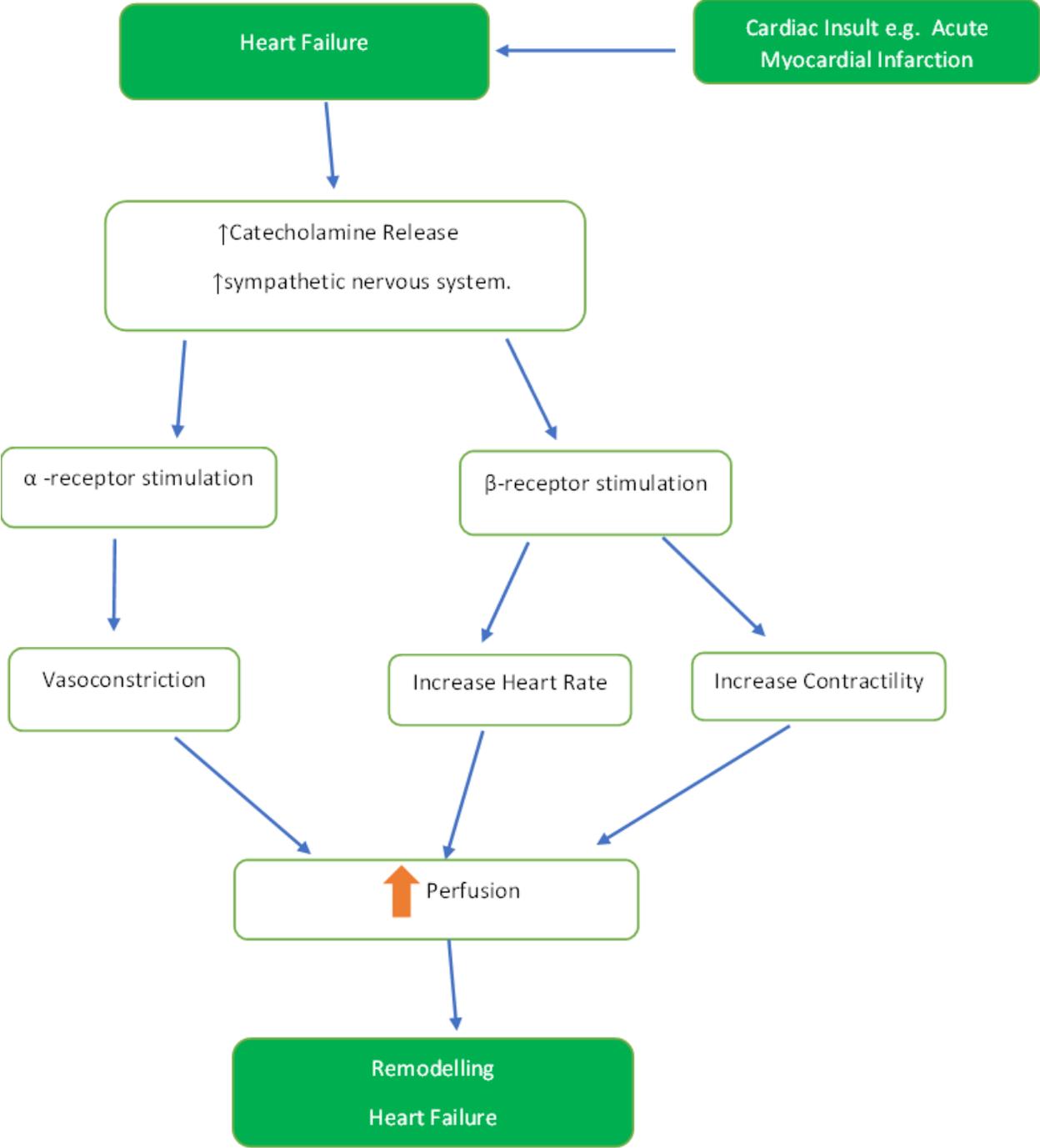


**Supplementary Figure 1:** The mechanism of the sympathetic activation in heart failure



**Supplementary Table 1:** Common symptoms and signs of heart failure

Symptoms	Signs
Shortness of breath	Raised JVP
Fatigue	Displaced apex beat laterally/downward.
Orthopnoea	Fine chest crepitations
Paroxysmal nocturnal dyspnoea	S3 gallop
Bendopnoea	Pedal oedema

**Supplementary Table 2:** Randomised controlled trials of beta blockers.

Study (Date)	Study arms (n)	Crude Mortality	RRR (%)	ARR (%)	Clinical Class (NYHA)	All-cause mortality reduction % (p-value)
US Carvedilol Program <sup>1</sup>	Carvedilol 696 Placebo 398	22 (3.2%) 31 (7.8%)	41	3.2	NYHA II-IV EF ≤35%	65% (0.0001)
CIBIS II (1998) <sup>2</sup>	Bisoprolol 1327 Placebo 1320	156 (12%) 228(17.2%)	42	3.7	NYHA III-IV EF ≤ 35%	34% (<0.001)
MERIT-HF (1999) <sup>3</sup>	Metoprolol 1990 Placebo 2001	641(32%) <sup>a</sup> 767(38%) <sup>a</sup>	16	6.1	NYHA II-IV EF ≤34%	34% (0.0062)
COPERNICUS (2001) <sup>4</sup>	Carvedilol 1156 Placebo 1133	140 (12.1%) 190 (17%)	27.7	4.6	NYHA NA EF < 25%	35% (0.00013)

<sup>a</sup> Combined all-cause mortality and hospitalisation

**Supplementary Table 3:** Randomised controlled trials of ACE-I/ARNI/ARBs with improvements in the primary heart failure endpoints.

Study (date)	Study arms (n)	Crude Mortality	RRR (%)	ARR (%)	Heart Failure Class	Other effects
Consensus <sup>5</sup> (1987)	Enalapril 127 Placebo 126	33 (26%) 55 (44%)	40	18	NYHA IV EF ≤40%	Improved heart failure symptoms
SOLVD-T (1991) <sup>6</sup>	Enalapril 1285 Placebo 1284	452 (35.2%) 510 (39.7%)	16	4.5	NYHA II-III EF ≤35%	26% reduction of HFH
SOLVD-Prevention (1991) <sup>7</sup>	Enalapril 2111 Placebo 2117	313 (14.8%) 334 (15.8%)	8	1	NYHA I EF ≤35%	20% RRR in death or HFH
Val-HeFT (2001) <sup>8</sup>	Valsartan 2511 Placebo 2499	98 (39%) 96 (38%)	11.45 combine mortality and morbidity reduction	3.3 combined mortality and morbidity reduction	NYHA II – IV EF ≤40%	24% RRR in HFH 9.7% RRR combined mortality and morbidity. No difference in mortality alone
CHARM-Alternative (2003) <sup>9</sup>	Candesartan 1013 Placebo 1015	164 (16%) 200 (20%)	25	7	NYHA II-IV EF ≤ 40%	33% reduction in HFH
CHARM-Added (2003) <sup>10</sup>	Candesartan 1276 Placebo 1272	251 (20%) 278 (22%)	12	2.2	NYHA II-IV EF ≤ 40%	
PARADIGM-HF (2014) <sup>11</sup>	Sacubitril/Valsartan 4187 Enalapril 4212	84 (2%) 99 (2.4%)	14.1	2.8	NYHA II-IV EF ≤40%	21% reduction in HFH 17.7% RRR for composite of death or HFH

HFH = Heart failure hospitalisation

Note: Mortality is all cause mortality and or heart failure mortality where data is available. Where both are available, all-cause mortality is used.

**Supplementary Table 4:** Randomised clinical trials of MRAs.

Study (Year)	Arms of study (n)	Outcomes/End points	Crude Mortality	RRR (%)	ARR (%)	Clinical Class (EF)
RALES (1999) <sup>12</sup>	Spironolactone 822  Placebo 841	Deaths: 284  Deaths 386	345 (34.5%)  459 (45.9%)	25	11	Chronic Severe Heart Failure EF NYHA Class III-IV  30% reduction in death & 35% reduction in HFH
EPHESUS (2003) <sup>13</sup>	Eplerenone 3313  Placebo 3319	Death 478  Deaths 554	144 (14.4%)  167 (16.7%)	13.6	2.3	Heart Failure after MI EF ≤ 40%
EMPHASIS-HF (2011) <sup>14</sup>	Eplerenone 1364  Placebo 1373	Deaths 249  Deaths 356	183 (18.3%)  259 (25.9%)	30	7.7	Chronic HF with mild symptoms EF ≤ 35 NYHAC II 38% reduction in HFH

HFH = Heart failure hospitalisation

**Supplementary Table 5:** Randomised clinical trials of sodium glucose cotransporters 2 inhibitors (SGLT2-i)

Study (Date)	Study arms (n)	Crude Mortality	RRR (%)	ARR (%)	Clinical Class (EF)	Outcome(s)
DECLARE-TIMI 58 (2019) <sup>15</sup>	Dapagliflozin 8582 Placebo 8578	64 <sup>φ</sup>	7.2	0.48	NYHA* EF <45%	Reduced CV death 4.9% and HFH by 5.8% Improved CVRFs
DAPA-HF (2019) <sup>16</sup>	Dapagliflozin 2368 Placebo 2368	117 139	16	2.2	NYHA II-IV EF ≤ 40%	HFH reduced by 3.7%
EMPEROR Reduced (2020) <sup>17</sup>	Empagliflozin 1863 Placebo 1867	100 143	7.2	0.78	NYHA II-IV EF ≤ 40%	HFH reduced by 5.1%
EMPEROR Preserved (2021) <sup>18</sup>	Empagliflozin 2997 Placebo 2991	140.8 142.8	10.4	0.85	NYHA II-IV EF ≤ 40%	Reduced HFH by 3.2%
DELIVER (2022) <sup>19</sup>	Dapagliflozin 3131 Placebo 3132	163	5.58	0.92	NYHA II-IV EF > 40%	Reduced HFH by 2.7%
EMPULSE (2022) <sup>20</sup>	Empagliflozin 265  Placebo 265	41.5  83	50	4.6	NYHA (Acute decompensated HF) Spectrum of EF	Improved patient's performance, QoL and kidney function

\*Not available, Mortality is all-cause mortality, <sup>φ</sup>Composite of all-cause mortality and HFH, CVRFs= Cardiovascular risk factors

**Supplementary Table 6:** Rationale for use of heart failure treatment

Medication Category	Examples in this category	Benefits
Angiotensin Converting Enzyme-Inhibitor (ACE-I)	Enalapril <sup>a</sup> Ramipril	Reduces mortality and morbidity
Angiotensin Receptor Blocker (ARB)	Valsartan Candesartan Telmisartan	Reduces mortality and morbidity
Beta blockers	Bisoprolol Metoprolol Carvedilol Atenolol <sup>a, φ</sup>	Reduces mortality and morbidity.
Aldosterone antagonists	Spirolactone <sup>a</sup> Eplerenone	Reduces mortality and morbidity in moderate to severe heart failure
Sodium Glucose Transporter 2-Inhibitor (SGLT2-i)	Dapagliflozin Empagliflozin Canagliflozin Sotagliflozin	Reduces mortality, morbidity and improves QoL
ARB/Nepriylsin Inhibitor	Valsartan/Sacubitril	Reduces mortality and morbidity
Digitalis	Digoxin <sup>a</sup>	Improve symptom and reduce recurrent hospitalisation
Arteriodilator/Nitrates	Hydralazine/Nitrates <sup>a</sup>	Alternate to ACE-I/ARB Reduces morbidity and mortality in black population
Diuretics	Furosemide <sup>a</sup> Bumetanide Metolazone Thiazide <sup>a</sup>	Symptoms relieve. No mortality reduction

<sup>a</sup> Drugs available on the PNG Public Pharmaceutical Catalogue

<sup>φ</sup>Not evidenced based therapy (Atenolol has not been studied in a RCT but is available on the PPC)

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