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1 Heart Failure Drug Treatment

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22

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24 **Abstract**

25 Heart failure (HF) is the most common cardiovascular reason for hospital admission over the age
26 of 60. There are few areas in medicine where progress has been as remarkable as that observed
27 with HF therapy over the last three decades. However, progress has been consistent only for
28 chronic HF with reduced ejection fraction (HFrEF). In acutely decompensated HF and HF with
29 preserved ejection fraction (HFpEF), none of the therapies tested to date have been definitively
30 proven to improve survival. Delaying or preventing HF has become increasingly important in
31 HF-prone patients. It is also of paramount importance to prevent worsening chronic HF and
32 hospitalisations for acute decompensation. The objective of this review article is to provide
33 concise and practical summary of the current state of HF drug therapy. We support the
34 implementation of the international guidelines. Where gaps in evidence are present, we offer
35 views based on personal experience. The best possible evidence based drug therapy is useful
36 only when optimally implemented. However, implementation may be challenging. We believe
37 that disease management programmes may be helpful in providing a multidisciplinary, holistic
38 approach to the delivery of optimal medical care.

39

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41

42 Key Words:

43 Heart failure – medical therapeutics- disease management programmes- reduced ejection

44 fraction- preserved ejection fraction - narrative review

45 **Introduction**

46 Heart failure (HF) is the most common cardiovascular reason for hospital admission among
47 individuals over the age of 60.¹ The prevalence of HF is increasing worldwide because of an
48 increasing incidence related to population aging, rising prevalence of poorly controlled risk
49 factors (i.e., hypertension, diabetes mellitus, and obesity), and prolonged survival of patients
50 with HF due to implementation of evidence-based therapies.² It is a clinical syndrome
51 characterised by fatigue and dyspnoea, induced by left (or global) ventricular dysfunction, often
52 with signs of congestion. The New York Heart Association (NYHA) classification is used to
53 describe symptom severity (Figure 1 and Short panel). Heart failure carries a poor prognosis.
54 Thirty day all-cause readmission rates of 19% have been reported in the United States.³ One-year
55 all-cause mortality rates for acute HF and stable/ambulatory HF patients were 17% and 7%,
56 respectively, and the 12-month hospitalisation rates were 44% for hospitalised patients and 32%
57 for ambulatory patients, respectively, in recent observational data from Europe.⁴ Similar data
58 have been reported in the ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry;
59 19.2% of patients died or were hospitalized for HF within 1 year.⁵ The THESUS-HF (Sub-
60 Saharan Africa Survey of Heart Failure) reported an estimated 6-month mortality of 17.8%.⁶
61 The International Congestive Heart Failure (INTER-CHF) study, representing Africa, China,
62 India, the Middle East, southeast Asia, and South America, reported an overall 1-year mortality
63 of 16.5%, with substantial variation by region (Africa 34%, India 23%, southeast Asia 15%,
64 South America 9%, Middle East 9%, and China 7%).⁷

65 In most patients, abnormalities of systolic and diastolic function coexist, irrespective of the
66 ejection fraction (EF), which in clinical trials was the most used classifier to define either heart
67 failure with reduced EF (HFrEF) if $EF < 40\%$, or heart failure with preserved EF (HFpEF).

68 In a recent European survey, mortality at 1 year was 8.8% and 6.3% in HFrEF and HFpEF,
69 respectively.⁸ The HFrEF subtype has been the most well studied, yielding a robust body of
70 evidence to support clinical practice guidelines.^{9,10}

71 The objective of this review article is to provide concise and practical summary of the current
72 state of HF drug therapy. We support the implementation of the available international
73 guidelines. These may differ in some occasional respects, and there are persistent gaps in
74 evidence, in which cases we offer views based on our personal expertise.

75 Priorities for future research in terms of unmet needs and evidence gaps are also identified.

76

77 **Search strategy and selection criteria**

78 Data for this narrative review were identified by searches of MEDLINE and PubMed, and
79 references from relevant articles, in addition to the most recent European Society of Cardiology
80 (ESC) and American College of Cardiology/American Heart Association (ACC/AHA)
81 guidelines.⁹⁻¹¹

82

83

84 **Diuretic and sodium management**

85 Regardless of EF, heart failure symptoms are mostly related to congestion,¹² and congestion is
86 one of the main predictors of poor patient outcome.¹³ Despite the lack of large randomised
87 outcome trials, loop diuretics are strongly (Grade 1^{9,10}) recommended for decongestion, albeit
88 with a lower level of evidence (B⁹ or C¹⁰) by the ESC and ACC/AHA guidelines to improve
89 symptoms in chronic and acutely decompensated HF. Diuretic dosing is largely empiric. Diuretic
90 doses should be titrated according to the decongestion target. The use of inappropriately low

91 doses of diuretics may result in persistent congestion. Conversely, the use of inappropriately high
92 doses of loop diuretics may trigger hypokalaemia and hypovolaemia with a related risk of
93 hypotension and worsening renal function,¹⁰ which may lead to down titration of life- saving
94 drugs (ACEI, MRA). Furthermore, this may further stimulate the RAAS, which may worsen HF.
95 Once optimal decongestion has been achieved, the lowest dose that maintains euvolaemia should
96 be prescribed, and some heart failure centers educate appropriately selected patients to manage
97 symptoms with “as needed” diuretics. Candidate patients might be those not requiring daily
98 diuretic who can be educated to follow the strategy and will contact clinical staff quickly if
99 symptoms worsen, although it is acknowledged that this strategy has not been well studied.
100 However, determination of optimal decongestion and early detection of a re-congestion is
101 challenging. Indeed, although numerous clinical scores, imaging and hemodynamic tools, and
102 biological tests are available to assist physicians in ascertaining and quantifying congestion, not
103 all are appropriate for use along the course of the disease and across all settings of patient
104 presentations (pre-admission, admission to the emergency department, in-hospital management,
105 and lastly, discharge and continued monitoring in the community).¹³ For instance, weight loss
106 lacks sensitivity. Imaging (i.e., chest x-ray, B-mode lung ultrasound, inferior vena cava and other
107 echocardiography measures) may be helpful.¹⁴ Clinical trials of chronic optimisation of therapy
108 guided by natriuretic peptide levels, have led to conflicting results.^{15,16}
109 Diuretic resistance may occur in the most severe patients. In this setting, specific
110 pharmacological algorithms encompassing loop diuretic dose adjustments, inotropes, and the
111 addition of thiazide-like diuretics may be proposed as an alternative to extracorporeal
112 ultrafiltration in hospitalized patients, while the efficacy of either approaches in outcome trials
113 are lacking.¹⁷ Neurohormonal imbalances created by HF lead to an inability to excrete sodium

114 and water. Therefore, conventional wisdom has advised limiting sodium and fluid intake.¹⁸
115 Major HF guidelines lack consensus on recommendations for dietary sodium (and fluid)
116 restriction. Currently, 4 trials are ongoing (NCT02467296, NCT02148679, NCT01733017,
117 NCT02012179) targeting sodium restriction in HF, including one large trial evaluating clinical
118 outcome endpoints.¹⁹
119 Altogether, we believe it is possible that detection, dynamic monitoring, and management of
120 congestion/decongestion could help improve HF management. However, we acknowledge that
121 evidence from robust randomized outcome trials are lacking. One possible exception is a single
122 trial using a remote monitoring of pulmonary artery diastolic pressures with an implanted
123 device.²⁰ In a randomised clinical trial that enrolled over 500 patients with HFrEF and HFpEF,
124 monitoring and managing patients demonstrated improved clinical outcomes including
125 hospitalisation for HF. Of note, one limitation of the trial is that the control group did not have a
126 systematic form of disease management practiced, so that one might question whether the trial
127 truly showed benefit of the invasive technology over and above non-invasive disease
128 management. In addition, the reduction in HF hospitalization with the implanted device
129 appeared to be associated with increased use of diuretics and vasodilators; to what extent this
130 increase in doses may have contributed to the better outcomes remains an open question.

131

132 **Chronic heart failure with reduced ejection fraction medical treatment**

133 The primary pathophysiological cardiac abnormalities in HFrEF are cardiac chamber
134 enlargement due to cardiac remodelling, weak contraction (deficient inotropism), elevated filling
135 pressures (preload), and increased peripheral resistance (afterload), leading to an inability to
136 provide adequate cardiac output at rest or with exercise. These elevated intracardiac pressures

137 may also cause lung and peripheral congestion. Myocyte number and function decline and are
138 replaced by myocardial interstitial fibrosis, which stiffens the heart and creates the anatomical
139 substrate basis for lethal arrhythmias. The disease is increasingly viewed as a syndrome with
140 multiple systemic mechanisms potentially involving inflammation and disorders of
141 neurohormonal systems, involving the renin angiotensin aldosterone (RAAS), the autonomic
142 nervous, the endothelium, the natriuretic peptide (NP), and the vasopressin systems. Other
143 potential pathophysiologic mechanisms include elevated heart rate, atrial fibrillation, and
144 abnormalities of ventricular-vascular coupling, and complex cardiorenal interactions (i.e.
145 “cardiorenal syndrome”).²¹

146 Better management of acute coronary syndromes has resulted in less frequent progression to
147 post-MI HFrEF.²² Non-ischaemic aetiologies account for up to 30% of HFrEF and include
148 valvular heart disease,²³⁻²⁵ familial cardiomyopathy, and secondary cardiomyopathies (e.g.,
149 inflammatory, cardiotoxic [alcohol, chemotherapy induced], infectious).

150 Current treatment guidelines are based on robust evidence stemming from well-designed
151 randomised outcome trials.^{9,10} Inhibitors of the RAAS (i.e. ACE-inhibitors or angiotensin
152 receptor blockers), mineralocorticoid receptor antagonists (MRA), and beta-blockers are strongly
153 recommended (Class IA) for improving survival, decreasing sudden death, and preventing HF
154 hospitalisations.⁹ Based on the results of the PARADIGM HF trial (Prospective Comparison of
155 ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–
156 Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure),
157 sacubutril-valsartan is recommended to replace ACE-inhibitors to further reduce the risk of HF
158 hospitalisation and death in ambulatory patients with HFrEF who remain symptomatic despite
159 optimal treatment. Unless contraindicated, all symptomatic HFrEF patients should receive the

160 above-mentioned medications in combination, preferably at target maximally tolerated doses.^{9,11}
161 The combined optimal use of these class IA therapies in clinical trials has led to a decline in
162 mortality among patients with severe as well as mild-moderate HFrEF (Figure 2).²⁶ Furthermore,
163 a recent network meta-analysis of 58 trials dominated by 15 large-scale trials with 1984 to 18898
164 patient-years of follow-up showed that combining evidence-based drugs may produce
165 cumulative reduction in all-cause mortality up to 60% and in all-cause hospitalizations with
166 reductions up to 40%, on average.- Concomitantly, in patients enrolled in clinical trials, the
167 annual rate of sudden cardiac death has declined below 5%.²⁷
168 International registry data showed that physician's adherence to guideline recommended
169 medications in HFrEF was associated with better outcomes.²⁸ Unfortunately, current guidelines
170 are not being optimally implemented, both in terms of overall use as well as under-dosing,²⁹
171 most often because of excessive concern about adverse events.⁴ Hypotension, hyperkalemia and
172 worsening renal function are the most frequently cited reasons for under-dosing, underuse, and
173 discontinuation of RAAS inhibitors and MRAs⁴. In a large US database including more than
174 20,000 HF patients, nearly 60% who discontinued RAASi after an hyperkalaemic episode
175 experienced an adverse outcome or mortality compared with 52% of patients on RAASi
176 submaximal doses and 44% of patients on maximum doses (all comparisons $P < .05$). Patients on
177 submaximal dose or who discontinued RAASi died twice as frequently as patients on maximum
178 dose.³⁰ Beta blocker use may be hampered by concerns about hypotension, fatigue, and
179 bradycardia. However, most of these adverse events are predictable, reversible, and manageable.
180 Most importantly, occurrence of these events does not diminish survival benefits.³¹ Thus, in our
181 opinion, concerns about adverse events may be excessive in some cases, and it should be
182 recognized that this has the potential to deprive patients of life-saving therapies. Hypotension if

183 symptomatic can often be managed by discontinuing unnecessary vasodilators (e.g., calcium
184 channel antagonists, alpha-blockers, nitrates), or by reducing diuretic doses to the lowest dose
185 that maintains euvolaemia, and ultimately by staggering doses of RAAS inhibitors and beta-
186 blockers. Frequent monitoring (within 3 days of initiation or dose adjustments and every 4
187 months once stable) of eGFR, serum potassium and blood pressure, slow up-titration, and
188 avoidance of other concomitant, non-essential, interacting drugs (e.g., non-steroidal anti-
189 inflammatory drugs, potassium supplements, dietary potassium, other blood pressure-lowering
190 drugs, excessive diuretic doses) are strategies to achieve optimal use of these therapies. Down-
191 titration of doses or discontinuation of RAAS inhibitors may be warranted temporarily for
192 persistent or severe hyperkalemia, hypotension, or worsening renal function. However, this
193 should not prevent attempts at re-initiation or up-titration of therapy as soon as safely possible.
194 The use of potassium binders may facilitate up-titration in patients prone to in hyperkalemia,³²
195 although whether this may prevent cardiovascular outcome occurrence needs to be demonstrated
196 in a dedicated outcome trial. It should be acknowledged that patients with HFrEF are
197 increasingly older and have multiple comorbidities. Clinical trials have generally excluded these
198 types of patients, and as a result, their response to HF therapy and the best approaches for
199 managing comorbid conditions and concomitant drug therapies that may have pharmacodynamic
200 or pharmacokinetic interactions with the HF regimen is less certain. However, there is no
201 evidence that such patients would not benefit from standard HF therapy,³³ and guidelines should
202 also be followed in these patients, with individual adjustments in dose or monitoring as clinically
203 indicated according to comorbidity or interacting medications.

204 Ivabradine or digoxin may prevent HF hospitalisation in patients with sinus rhythm, after
205 attempts to optimise beta-blocker therapy if heart rate remains above 75 beats per minute.⁹ Beta-

206 blockers and digoxin may help control ventricular response in patients with atrial fibrillation
207 (AF), although with no demonstrated outcome benefit. There is no consensus about an optimal
208 target heart rate in patients with AF and HF, with recommended targets varying between 60 bpm
209 to 110 bpm.^{9,34} Because of safety concerns, amiodarone is not preferred as first line for rate
210 control. Rhythm control using electrical or pharmacological conversion may be considered to
211 improve symptoms in patients with persisting symptoms and/or signs of HF, despite optimal
212 medical therapy and adequate control of ventricular rate. Anticoagulation, preferably with direct
213 oral anticoagulants, should be offered to patients with HF and AF, recognizing that bleeding
214 rates may be higher than in non-HF patients, since HF is a component of the CHADS2VASC2
215 score.³⁵

216 Furthermore, even in the absence of AF, based on the underlying pathophysiologic hypothesis
217 that thrombin could play a key role in worsening chronic HF, the ongoing COMMANDER HF
218 trial is exploring the efficacy and safety of rivaroxaban 2.5 mg bid compared with placebo (with
219 standard care) after an exacerbation of HF in patients HFrEF and documented coronary artery
220 disease and sinus rhythm.³⁶

221 Intravenous iron may be used for improving functional capacity and quality of life in patients
222 with iron deficiency (serum ferritin <100 mg/L or ferritin between 100 and 299 mg/L and
223 transferrin saturation <20%).^{9,37,38} However long-term data on the cardiovascular efficacy and
224 on safety are lacking so far.

225

226 **Heart failure with preserved ejection fraction medical treatment**

227 First recognised in the 1980s and initially termed “diastolic HF,” HFpEF accounts for
228 approximately half of all hospital admissions for HF, is associated with substantial morbidity and

229 mortality, and is increasing in prevalence.³⁹ The definition, pathophysiology, and aetiology of
230 HFpEF have been subject to controversy and debate, and consensus among experts is still rare.
231 Nevertheless, most current guidelines agree that the minimum requirements for the diagnosis of
232 HFpEF are signs and symptoms of HF and a relatively preserved EF.⁹ What constitutes
233 “preserved” has evolved, and initially encompassed the entire EF range above the reduced range,
234 generally considered an LVEF of $\leq 40\%$.

235 Patients with HFpEF tend to be older than those with HFrEF, and the prevalence of this disorder
236 is increasing as the population ages.⁴⁰ Moreover, HFpEF is associated with more comorbidities
237 than those with HFrEF,⁴¹ including hypertension, diabetes, atrial fibrillation, anaemia and
238 chronic obstructive pulmonary disease, and the attributable risk associated with these
239 comorbidities increases as EF rises.⁴² The high prevalence of comorbidities in HFpEF has
240 contributed to the notion that HFpEF may not exist as an independent entity, but may simply be a
241 collection of comorbidities. The concept is countered by the substantially higher event rates in
242 patients with HFpEF than in patients with these comorbidities but without HF.⁴³ While
243 ambulatory patients with HFpEF have substantially lower morbidity and mortality than patients
244 with HFrEF,⁴⁴ the subsequent hospitalisation and mortality rates in hospitalised patients with
245 HFpEF is comparable to that in patients with HFrEF.⁴⁵

246 The primary pathophysiologic abnormality in HFpEF is generally considered to be an inability to
247 provide adequate cardiac output at rest or with exercise or to do so only in the setting of elevated
248 filling pressures,⁴⁶ as is the case with HFrEF. Indeed, elevation in left sided filling pressure is
249 thought to be the sine qua non of HFpEF and has traditionally been thought secondary to
250 abnormalities of diastolic function. However, it has become increasingly recognised that
251 abnormalities of diastolic function are common in the elderly and present in many individuals

252 without HF.⁴⁷ Moreover, abnormalities of systolic function are prevalent in and related to
253 outcomes in patients with HFpEF.^{48,49} Some patients with HFpEF have either rest or exercise
254 induced elevation in pulmonary pressures.⁵⁰ Other pathophysiologic mechanisms that have been
255 implicated include chronotropic incompetence,⁵¹ abnormalities of ventricular-vascular
256 coupling,⁵² and abnormalities of renal function.⁵³

257 Several aetiologic molecular mechanisms have been postulated in HFpEF.⁵⁴ Diseases like
258 hypertension and diabetes, known precursors of HFpEF, are associated with myocardial
259 intracellular fibrosis and increased collagen deposition and turnover.⁵⁵ Abnormal
260 phosphorylation of the spring-like titin protein, responsible for restoring the sarcomere to its
261 resting state, has been implicated.⁵⁶ It has recently been shown that patients with obesity-related
262 HFpEF display unique pathophysiological features, including greater biventricular remodeling,
263 volume overload, more right ventricular dysfunction, greater ventricular interaction and
264 pericardial restraint, worse exercise capacity, more profound hemodynamic derangements, and
265 impaired pulmonary vasodilation. These distinctions suggest that obesity may be considered as a
266 specific HFpEF phenotype.⁵⁷ Interestingly, a randomized trial comparing exercise only, diet
267 only, combined exercise and diet, to a control group for 20 weeks, in 100 older obese HFpEF
268 patients showed that caloric restriction diet or aerobic exercise training increased peak oxygen
269 consumption..⁵⁸ Increased adiposity also contributed to worse NYHA functional class in
270 HFpEF.^{59,60} Initially healthy subjects with elevated waist circumference have a higher long-term
271 diastolic dysfunction risk.⁶¹ Several laboratories have suggested obesity (and comorbidities such
272 as chronic kidney disease) lead to a systemic pro-inflammatory state, and generation of reactive
273 oxygen species limits nitric oxide availability to myocytes, resulting in reduced cGMP
274 production and ultimately decreasing protein kinase G activity which may result in hypertrophy

275 and myocyte stiffness.⁶² More specifically, obesity may lead to the accumulation and
276 inflammation of epicardial adipose tissue, which may impair the electrophysiological properties
277 and distensibility of the myocardium. It has recently been hypothesized that epicardial adipose
278 tissue is a transducer which could be targeted by therapeutic interventions aimed at decreasing its
279 accumulation and inflammation (e.g. statins, metformin, SGLT-2 inhibitors, mineralocorticoid
280 receptor antagonists).⁶³ Despite strong support for several hypotheses, the aetiologic factors
281 responsible for HFpEF are likely to be multifactorial and more precise etiologic phenotyping is
282 essential for the identification of novel therapies. Indeed, because of phenotypic diversity in
283 HFpEF, personalized therapeutic strategies are proposed, which may be adapted to combinations
284 of clinical presentations and risk predispositions⁶⁴.

285 Both treatment of HFpEF and the ability to test new therapies in HFpEF requires accurate
286 diagnosis of the disorder. In addition to signs and symptoms of HF and documentation of a
287 preserved EF, most guidelines and consensus documents recommend that other diagnostic
288 criteria be incorporated when considering this disorder, including echocardiographic evidence of
289 diastolic abnormalities or elevation in NP.⁶⁵ Both of these increase the likelihood that patients
290 truly have HF, yet neither are sufficient for the diagnosis and can be abnormal in patients without
291 HF.

292 Several clinical outcomes trials have been performed in patients with HFpEF yet none have met
293 their primary endpoint (Table 1).⁶⁶⁻⁷⁰ All of these trials have thus far assessed inhibitors of the
294 RAAS, either ACE Inhibitors,⁶⁷ angiotensin receptor blockers,^{66,68} or MRAs.⁶⁹ In CHARM
295 (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity)-Preserved,⁶⁶
296 candesartan was associated with a 11% non-significant reduction in cardiovascular death or HF
297 hospitalisation, although post-hoc analyses suggested a significant reduction in total

298 hospitalisations.⁷¹ The TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure
299 with an Aldosterone Antagonist) comparing spironolactone to placebo, based on the success of
300 MRAs in HFrEF and the likelihood that myocardial fibrosis plays a role in the pathophysiology
301 of HFpEF, failed to meet its primary endpoint, with an 11% non-significant reduction in
302 cardiovascular death or HF hospitalisation. Nevertheless, after unblinding it was noted that
303 patients enrolled in one specific region (Russia and Republic of Georgia) had substantially lower
304 event rates than those enrolled in United States, Canada, Argentina and Brazil, suggesting that
305 many patients in that region may not have had HF.⁷² The 18% nominally significant risk
306 reduction of the primary outcome in the remaining regions has encouraged some to believe that
307 if properly tested, spironolactone would improve outcomes in HFpEF. For instance, the latest
308 US guidelines state that “In appropriately selected patients with HFpEF (with EF \geq 45%, elevated
309 BNP levels or HF admission within 1 year, estimated glomerular filtration rate $>$ 30 mL/min,
310 creatinine $<$ 2.5 mg/dL, potassium $<$ 5.0 mEq/L), aldosterone receptor antagonists might be
311 considered to decrease hospitalization”¹¹.

312 Therapeutic approaches other than RAAS inhibition have been tested in HFpEF, including
313 several that have targeted the nitric oxide pathway but did not show any benefit.⁷³⁻⁷⁵ Despite
314 data suggesting the importance of cGMP in HFpEF and a relative reduction in intracellular
315 cGMP, the soluble guanylate cyclase stimulator vericiguat was ineffective in lowering NT-
316 proBNP or improving left atrial size in HFpEF,⁷⁶ although there were significant improvements
317 in quality of life measures. However, data from cardiovascular outcome trials data are lacking. In
318 the only positive phase 2 trial in HFpEF, sacubitril/valsartan was superior to valsartan in
319 reducing NT-proBNP, improving left atrial size and NYHA class.⁷⁷ These findings provided the
320 rationale for the ongoing PARAGON-HF (Efficacy and Safety of LCZ696 Compared to

321 Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection
322 Fraction, NCT01920711) outcomes trial comparing sacubitril/valsartan to valsartan in 4822
323 patients with HFpEF, defined as LVEF \geq 45%, elevation in NP and evidence of structural heart
324 disease, which is expected to report in 2019.⁷⁰ More recently, the results of EMPA-REG and
325 CANVAS (Canagliflozin Cardiovascular Assessment Study) provided the rationale for an
326 outcomes trial in HFpEF with the SGLT-2 inhibitor empagliflozin (Table 1).^{78,79} Finally,
327 spironolactone for HFpEF is being retested in two separate trials (NCT02901184 and SPIRIT-
328 DHF [Spironolactone in the treatment for diastolic heart failure]).

329 It is obviously of paramount importance to rule out other causes of symptoms, including
330 ischaemic heart disease, overt lung disease, hypertrophic cardiomyopathy, or infiltrative
331 cardiomyopathies that could mimic signs and symptoms of HFpEF but which may have specific
332 alternative therapies. In the absence of evidence-based therapy, treatment of HFpEF remains
333 empiric and based on management of symptoms and comorbidities.⁸⁰ Although the benefits of
334 diuretic use in HFpEF has not been rigorously proven in clinical trials, treatment of congestion
335 with diuretics remains the mainstay of therapy (as described above) and appears to improve
336 symptoms. It also appears prudent to control ventricular rates in patients with AF, particularly
337 because elevated heart rates are associated with reduced ventricular filling time, but whether
338 rhythm control is beneficial in HFpEF remains unclear. Finally, as mentioned above, current US
339 guidelines recommend consideration of spironolactone.¹¹ Recognizing the challenges and
340 uncertainty in establishing a definitive diagnosis in many cases, probability score-based
341 diagnostic algorithms have most recently been proposed, where patients are assessed for the
342 probability of having HFpEF based on routine clinical and echocardiographic features.⁸¹
343

344 **Acutely decompensated heart failure treatment**

345 Acute HF is a common cause of hospitalisation among individuals >65 years of age globally.⁸²⁻⁸⁵

346 These acute events are associated with poor short and long-term prognosis in terms of survival

347 and rehospitalisation.⁸⁶⁻⁸⁹ The pathophysiology of AHF is multifactorial, with many potential

348 precipitating factors (e.g., acute coronary syndrome, arrhythmia, hypertension, renal impairment,

349 infection, non-adherence), some of them (acute coronary syndrome or infection) being associated

350 with an increased mortality.⁹⁰

351 Treatment approaches are aimed at treating the underlying cause (which is often not known) and

352 relieving symptoms. Despite intensive investigation in prospective, randomised trials, no

353 therapies for acute HF have been shown to improve clinical outcomes.⁹¹ In the absence of

354 therapies that prolong survival or reduce morbidity, the goal of initial therapy is to stabilise the

355 patient and decrease congestion to produce symptomatic relief and to decrease the potential for

356 organ impairment secondary to congestion.⁹² Specific therapies depend on the individual

357 patient's clinical presentation. Most patients present with evidence of congestion and normal or

358 elevated systolic blood pressure ("wet and warm") and are treated with intravenous diuretics and

359 vasodilators.^{9,89,93} A smaller proportion present with hypoperfusion where inotropes or

360 vasopressors may be considered in patients with systolic blood pressure <90 mmHg.⁹ Once the

361 patient is stable, the most important long-term intervention for patients with AHF may be to

362 optimise medical management prior to discharge⁹⁴ and plan for early post-discharge follow-up,

363 ideally in a HF disease management programme if available.⁹⁵

364 Many factors have been proposed to explain the lack of efficacy of acutely administered

365 therapies on clinical outcome in patients with AHF, including patient heterogeneity, multiple

366 pathophysiologic mechanisms, generally rapid response to standard care (i.e., diuretics) in most

367 patients, and the low likelihood that short-term administration of a therapy can impact long-term
368 outcomes.^{91,96} Future trials should apply the lessons learned from past trials to design study
369 protocols, select candidate therapies, and identify target patient populations.⁹⁷

370

371 **New drugs in research and development**

372 Promising agents are now in phase 3 outcome trials (Table 2), and many new compounds, most
373 targeting new molecular mechanisms, are currently in early clinical development (Table 3).

374

375 **Enabling life saving pharmacological therapy with multidisciplinary management.**

376 It is recommended that optimisation of available symptom-alleviating and life- saving HF rEF
377 pharmacological treatments should be pursued when patients are discharged. Observational
378 studies show however that this is simply not the case and that prescriptions filled upon discharge
379 have the highest chance of being unchanged, months after discharge. Therefore, unfortunately,
380 evidence-based therapies are not being optimally implemented within the current health care
381 systems resulting in life-saving drugs under-prescription and under-dosing in HF rEF. The
382 monitoring of creatinine and potassium after an MRA prescription is also poor both in the US⁹⁸
383 and in EU.⁹⁹

384 More broadly, the recognition of HF as a complex disorder with multiple co-morbidities and
385 different strategies for improving health, multidisciplinary management has become a foundation
386 of care (Figure 3). Systems of care that include multidisciplinary management have been shown
387 to reduce HF hospitalisation and improve survival in patients discharged from the hospital.^{100,101}
388 In France, a regional HF-disease management programme (DMP) (ICALOR programme) was
389 established in 2006 in Lorraine,^{102,103} applying all major components of recommended DMPs as

390 per European Society of Cardiology guidelines. The ICALOR programme was proven to
391 decrease cost-effectively both HF hospitalizations and all-cause mortality stabilizing HF
392 hospitalization rate progression in Lorraine,^{102,103} whereas those observed overall in France
393 progressed continually. This benefit stopped right after the unfortunate programme
394 interruption.¹⁰¹

395 To deliver successful programs, it is important to have close collaboration and a team-oriented
396 approach to HF care across the different domains of a health care system. Cardiologists and HF
397 nurses need to coordinate with general practitioners and primary care physicians. The HF team
398 should include clinical pharmacists who review and focus on complex pharmacological
399 treatments that may have important drug-drug or drug-disease interactions to consider. Dieticians
400 and exercise physiologists counsel patients on establishing everyday habits that support a healthy
401 lifestyle for HF and other preventive care strategies. Social workers are also critical team
402 members and ensure patients have appropriate access to resources. Psychologists can guide
403 patients through anxiety or depression, which are common in patients with HF. This integrated
404 care team approach shifts clinical management towards a proactive system as opposed to a
405 reactive system.

406 A key focus of multidisciplinary teams is to prevent readmission after a HF hospitalisation.
407 Patients enter a vulnerable period early post-discharge. Throughout the hospitalisation, a
408 multidisciplinary team should address potential aetiologies of the worsening HF event, develop
409 preventive strategies for future events, and coordinate post-discharge care. Systems with early
410 physician follow-up after discharge are associated with lower 30-day readmission rates.¹⁰⁴

411 Heart failure is a life-long condition, monitoring strategies for patients with HF continue to shift
412 towards a more proactive care model. By continuously monitoring a patient's condition, early

413 identification of worsening HF may be possible and followed by targeted interventions. In
414 addition, monitoring strategies can identify potential problems that need to be addressed such as
415 potassium management (hyper or hypokalemia)¹⁰⁵ a major hurdle toward RAASi implementation
416 in HFrEF, as described above.

417 Telemedicine programs that remotely monitor symptoms and other parameters such as weight
418 have had variable results.¹⁰⁶ While meta-analysis suggests clinical benefits,¹⁰⁷ large clinical trials
419 have not shown consistently demonstrated benefits. Some of the neutral trials failed to couple the
420 monitoring effort with a structured disease management practice which could systematically
421 review and respond to the monitored data. Others have pointed out that there is limited value to
422 monitoring alone, without a well-conceptualized, systematic process of integrating and acting
423 upon the information. As new technology evolves integrating multiple sensors, patient self-
424 reported health status, and seamless home to clinic monitoring systems, it is possible that more
425 consistent benefits may be achieved.¹⁰⁸ Implantable devices with integrated physiological signals
426 and sensors designed to alert when patients are higher risk for hospitalisation for HF may
427 provide actionable data for future telemedicine programs.¹⁰⁹ Ongoing trials are testing whether
428 alert management with specific treatment protocols may achieve improved outcomes. Priorities
429 for research to continue advancement of lifestyle interventions such as exercise and application
430 of monitoring technologies for patients with HF are outlined in Box 1.

431

432 **Heart failure prevention**

433 Prevention is likely the best mechanism to combat HF and its associated clinical and societal
434 burdens.² Heart failure is often a preventable cardiovascular syndrome. Reducing blood pressure

435 lowers the risk of 'new onset' HF by as much as 40%, similar to the effect of lowering blood
436 pressure on stroke and greater than the effect of lowering blood pressure on the risk of MI.^{110,111}
437 Diabetes mellitus may contribute to HF development, although glycaemic control or choice of
438 glucose lowering therapy in patients with type 2 diabetes mellitus has not until recently been
439 associated with HF prevention, and may have actually led to worsening heart failure (e.g. with
440 glitazones). However, beyond glycaemic control, some inhibitors of sodium-glucose co-
441 transporter 2 (SGLT-2) improve clinical outcomes, including hospitalisation for HF, in patients
442 with type 2 diabetes and pre-existing cardiovascular disease or cardiovascular risk factors.¹¹²⁻¹¹⁴
443 In primary and secondary cardiovascular prevention trials, statins may reduce the rate of HF
444 hospitalisation¹¹⁵. Smoking, excessive alcohol consumption, sedentary lifestyle, and obesity are
445 all associated with the development of cardiovascular disease. Moreover, adherence to healthy
446 lifestyle factors, no smoking, regular exercise, normal weight, moderate alcohol intake, and
447 consumption of breakfast cereal and fruits and vegetables was found associated with a lower risk
448 of developing HF in a database from 20,900 men from the Physicians' Health Study who were
449 apparently healthy at baseline.¹¹⁶ Furthermore, recent observational data in 11,351 participants
450 in the ARIC (Atherosclerosis in the Community) study showed that maintaining recommended
451 activity levels was associated with the lowest HF risk, while initiating and increasing physical
452 activity, even in late middle age, were also linked to lower HF risk. The authors concluded that
453 "augmenting physical activity may be an important component of strategies to prevent HF".¹¹⁷
454 However, HF prevention in these observational data may be the result of better control of risk
455 factors and prevention of ischemic heart disease. In patients with ischaemic heart disease,
456 angiotensin converting enzyme (ACE) inhibitors delay the onset of HF and reduce
457 cardiovascular mortality.¹¹⁸

458 Identification of mechanistic therapeutic targets (e.g., cardiac remodelling, inflammation,
459 fibrosis, diastolic dysfunction, vascular dysfunction) may be a more effective approach for HF
460 prevention in the future. Mechanistic bioprofiling of patients (i.e., selecting subgroups of patients
461 based on biomarker profiles indicative of underlying mechanisms associated with HF risk) and
462 subsequently matching prevention strategies to mechanistic biotargets may be a promising
463 approach to the development of specific HF prevention strategies.¹¹⁹

464

465 **Conclusion**

466 There are few areas in medicine where progress has been as remarkable as that observed with
467 drug therapy of chronic HFrEF over the last three decades. Unfortunately, no such evidence basis
468 exists for HFpEF or acute heart failure, beyond management of cardiovascular risk factors.
469 Therefore, notwithstanding improving outcome in prevalent HF, delaying or preventing HF has
470 become increasingly important in patients at-risk for HF and should be prioritised in future
471 research programmes. It is also of paramount importance to prevent chronic HF from worsening
472 and necessitating hospital admission for acute HF. Implementation of disease management
473 programmes possibly including modern monitoring technology may in our opinion help achieve
474 this objective.

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482

483 **Declaration of Interests**

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502 Cardiovascular Clinical Trialists (CVCT) and of CardioRenal

503

504 **Figure Legends**

505

506 Figure 1. Heart Failure Presentation at a Glance, depicting the spectrum of HF patient population
507 presentation

508 Figure 2. Decrement of mortality associated with mild to moderate and severe HFrEF in major
509 outcome trials

510 Results of random effect network meta-analysis for all-cause mortality: hazard ratios for
511 intervention versus placebo for all-cause mortality and 95% credible intervals. ACEI indicates
512 angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNI,
513 angiotensin receptor-neprilysin inhibitor; BB, beta blocker; and MRA, mineralocorticoid
514 receptor antagonist.

515 Reprinted with permission from: Burnett H, Earley A, Voors AA, Senni M, McMurray JJV,
516 Deschaseaux C, Cope S. Thirty years of evidence on the efficacy of drug treatments for chronic
517 heart failure with reduced ejection fraction. A network meta-analysis. *Circulation Heart Failure*
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519

520 Figure 3. Heart failure multidisciplinary and multi-technology enabled care

521 Heart failure care is evolving into a more patient-centered, multidisciplinary and multi-
522 technology management program. Patients will have more personalised health recommendations
523 based on their underlying condition, comorbidities and social environment. Continuous
524 monitoring will be enabled by remote, wireless technology at the home to detect early signals of
525 worsening of heart failure as well as to reinforce self-management of heart failure. When early
526 signals detect a potential worsening, remote management can alter care and/or have rapid in-

527 clinic treatment. As a last step, patients can come into the hospital for more intensive
528 management with the plans to have early follow-up after discharge to ensure stability.

529

530

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894 Short Panel:

895 **Heart failure presentation**

- 896 • Patients at high risk for HF (i.e., those with hypertension, diabetes mellitus,
897 atherosclerotic disease, obesity) but without structural heart disease or HF symptoms are
898 considered Stage A in the development of HF.¹²⁰
- 899 • Stage B describes the development of asymptomatic structural heart disease (i.e. previous
900 myocardial infarction [MI], left ventricular remodeling, left ventricular hypertrophy,
901 reduced EF, asymptomatic valvular disease).¹²⁰
- 902 • Stage C HF reflects symptomatic patients who should receive optimal medical therapy
903 unless contraindicated.^{9,10,120} Symptoms are non-specific and dominated by shortness of
904 breath and fatigue, leading to reduced functional capacity assessed by clinical scores
905 (NYHA classification I to IV) and 6-minute walk distance or other ergometric tests. The
906 most common signs of HF are related to congestion, whether vascular or interstitial,
907 pulmonary (e.g., rales, pleural effusion) or peripheral (e.g. leg oedema, jugular vein
908 dilatation, and, in more severe cases, liver enlargement and ascites). ~~Stage C patients may~~
909 ~~be relatively stable on GDMT, but ultimately progression of the disease is marked by~~
910 ~~episodes of acute decompensation, which can be precipitated by several cardiovascular~~
911 ~~and non-cardiovascular factors.~~
- 912 • Acute decompensation is accompanied by distressing symptoms of congestion and the
913 potential for end-organ (i.e., cardiac, liver, kidney) damage.¹³ Hospitalisations for HF
914 carry a poor prognosis. Among patients hospitalised in the United States for HF from
915 2008 to 2010, 67·4% experienced a readmission and 35·8% died within one year of the
916 index hospitalisation.¹²¹ Data from Europe show consistent results.¹²²

917 • Patients with refractory symptoms despite optimal implementation of best medical care
918 are considered Stage D.¹²⁰ These patients should be considered for additional
919 interventions (e.g., mechanical circulatory support, transplant evaluation), but these
920 therapies are beyond the scope of this review.

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924 BOX: Research priorities

925 • Randomized evidence that lifestyle modifications delay per se the onset of HF and reduce
926 cardiovascular mortality

927 • Identification of mechanistic therapeutic targets to prevent and treat HFrEF and HFpEF

928 • Defining the best monitoring strategies to monitor decongestion/re-congestion

929 • Identification of the most effective components of disease management programs

930 • The incorporation of digital self-management tools and patient facing applications for heart
931 failure management

932 • The use of external (wearables) and internal sensors to identify early signals of worsening
933 heart failure including remote imaging and the protocols for managing heart failure with
934 worsening signals

935 • Understanding whether virtualisation of clinical management of heart failure may be
936 automated and the benefits or risks for medication titration or alteration based on multiple,
937 integrated electronic data streams from home and clinic

938 • Understanding whether population management systems can be used for managing and
939 monitoring patients with heart failure using new data science methods such as machine
940 learning

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Table 1. Completed and ongoing outcomes trials in heart failure with preserved ejection fraction

Trial	N	Treatment arms	Key Inclusion criteria	Primary Endpoint	Findings
CHARM-Preserved ⁶⁶	3023	Candesartan vs. placebo	NYHA class II-IV, prior CV hospitalisation	Time to first cardiovascular death or heart failure hospitalisation	Primary outcome HR 0.89 (0.77, 1.03), p = 0.12
PEP-CHF ⁶⁷	850	Perindopril vs. placebo	Clinical diagnosis of DHF with ≥signs/symptoms of HF, ≥2 of the following: Left atrial enlargement/LVH/Impaired LV filling/Atrial fibrillation	Time to first all-cause death or heart failure hospitalisation	Primary outcome HR 0.92 (0.70, 1.21), p = 0.55
I-PRESERVE ⁶⁸	4128	Irbesartan vs. placebo	NYHA class II-IV + any corroborating evidence (e.g., HF sign), LVH or	Time to first all-cause death or cardiovascular hospitalisation	Primary outcome HR 0.95 (0.86, 1.05), p = 0.35

Table 1. Completed and ongoing outcomes trials in heart failure with preserved ejection fraction (continued)

Trial	N	Treatment arms	Key Inclusion criteria	Primary Endpoint	Findings
			LAE considered optional corroborating evidence, HFH required unless in NYHA class III-IV		
TOPCAT⁶⁹	3445	Spirolactone vs. placebo	Signs and symptoms of HF, elevated NP, or HFH	Time to first cardiovascular death, heart failure hospitalisation or resuscitated sudden death	Primary outcome HR 0·89 (0·77, 1·04), p = 0·14
PARAGON-HF⁷⁰	~4800	Sacubitril/valsartan vs. valsartan	NYHA class II-IV, elevated NT-proBNP (depending on timing of prior heart failure hospitalisation and atrial fibrillation status),	Cardiovascular death or total heart failure hospitalisation (first and recurrent)	Ongoing, fully recruited

Table 1. Completed and ongoing outcomes trials in heart failure with preserved ejection fraction (continued)

Trial	N	Treatment arms	Key Inclusion criteria	Primary Endpoint	Findings
			structural heart disease (left atrial enlargement or left ventricular hypertrophy)		
EMPEROR-Preserved (NCT03057951)	~4126	Empagliflozin vs. placebo	NYHA class II-IV heart failure, EF > 40%, elevated NT-proBNP (depending on atrial fibrillation status), structural heart disease (left atrial enlargement or LVH) or documented HF hospitalisation	Time to first cardiovascular death or heart failure hospitalisation	Ongoing

CHARM, Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity; CV, cardiovascular; DHF, diastolic heart failure; EF, ejection fraction; EMPEROR, Empagliflozin outcome trial in patients with chronic heart failure with reduced

Table 1. Completed and ongoing outcomes trials in heart failure with preserved ejection fraction (continued)

ejection fraction; HF, heart failure; HFH, heart failure hospitalisation; HR, hazard ratio; I-PRESERVE, Irbesartan in Heart Failure with Preserved Ejection Fraction Study; LV, left ventricular; LVH, left ventricular hypertrophy; NP, natriuretic peptides; NT-proBNP, N-terminal B-type natriuretic peptide; NYHA, New York Heart Association; PARAGON-HF, Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction; PEP-CHF, Perindopril for Elderly People with Heart Failure; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist

Table 2. Ongoing Heart Failure with Reduced Ejection Fraction Outcome Trials

Trial	Number of patients	Treatments	Key inclusion criteria	Primary endpoint
COMMANDER HF (NCT01877915)	5070	Rivaroxaban vs. placebo (in addition to standard of care for HF and CAD)	Symptomatic HF, episode of decompensated HF within 30 days, LVEF \leq 40%, evidence of significant CAD, BNP \geq 200 pg/mL or NT-proBNP \geq 800 pg/mL	Major acute cardiovascular events (all-cause mortality, MI, stroke)
GALACTIC HF (NCT02929329)	8000	Omecamtiv mecarbil vs. placebo	History of chronic HF, LVEF \leq 35%, NYHA class II-IV, current hospitalisation for HF or within previous year, elevated BNP or NT-proBNP	Time to CV death or first HF event
FAIR-HF2 NCT03036462	1200	Intravenous iron (ferric	Chronic HF, confirmed presence of iron deficiency,	Combined rate of recurrent hospitalisations for HF and CV death

Table 2. Ongoing Heart Failure with Reduced Ejection Fraction Outcome Trials (continued)

Trial	Number of patients	Treatments	Key inclusion criteria	Primary endpoint
		carboxymaltose) vs. placebo	serum haemoglobin 9.5 to 14.0 g/dL	
HEART-FID NCT03037931	3014	Ferric carboxymaltose vs. placebo	Stable HF on maximal tolerated background therapy, LVEF $\leq 35\%$, haemoglobin >9.0 g/dL and <13.5 g/dL (females) or <15.0 (males), serum ferritin <100 ng/mL or 100-300 ng/mL with TSAT $<20\%$, hospitalisation for HF within 12 months or screening NT-proBNP >600 pg/mL or BNP >200 pg/mL (sinus rhythm) or NT-proBNP >1000 pg/mL or	All-cause mortality or HF hospitalisation at 1 year; change in 6-minute walk distance

Table 2. Ongoing Heart Failure with Reduced Ejection Fraction Outcome Trials (continued)

Trial	Number of patients	Treatments	Key inclusion criteria	Primary endpoint
			BNP >400 pg/mL (atrial fibrillation)	
EMPEROR Reduced (NCT03057977)	2850	Empagliflozin vs. placebo	Chronic HFrEF, NYHA class II-IV, elevated NT-proBNP or BNP (at various levels depending on LVEF and cardiac rhythm)	Time to first adjudicated CV death or HF hospitalisation
DAPA-HF (NCT03036124)	4500	Dapagliflozin vs. placebo	HFrEF, LVEF \leq 40%, elevated NT-proBNP, eGFR \geq 30 ml/min/1.73 m ²	Time to first CV death, hospitalisation for HF, or urgent HF visit
VICTORIA (NCT02861534)	4872	Vericiguat vs. placebo	Chronic HFrEF, NYHA class II-IV, HF hospitalisation within 6 months or intravenous diuretics within 3 months;	Time to first CV death or HF hospitalisation

Table 2. Ongoing Heart Failure with Reduced Ejection Fraction Outcome Trials (continued)

Trial	Number of patients	Treatments	Key inclusion criteria	Primary endpoint
			elevated BNP or NT-proBNP (specific levels dependent on cardiac rhythm) LVEF <45%	

For all trials, all patients on standard background therapy for HF

BNP, B-type natriuretic peptide; CAD, coronary artery disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association

Table 3. Candidate drugs under early clinical development in chronic heart failure

Mechanism of action	Drugs
Adenosine A1 partial agonists	Neladenoson dalanate
<u>Aminopeptidase A (APA) inhibitor.</u>	QCG001
<u>Antidiabetics</u>	GLP-1 agonists, SGLT2 inhbitors
Apelin	Apelin, CLR325
Atrial natriuretic peptides	Cenderitide (CD-NP), ANX-042, PL-3994 (NPR-A agonist)
AT1R biased ligands	TVR120027
β 3-agonists	Mirabegron
Cardiac ion channels modulator	Ranolazine (I_{NaL}), GSK2193874, (TRPV4)
IL-1 β recept antagonists	Anakinra
Mitochondrial targeting peptide	MTP-131 (elamipretide), Perhexilene
Mineralocorticoid receptor antagonists	Finerenone, BR-4628109, CS-3150, LY-2623091, MT-3995
Neuregulin-1	GGF (rhNR-1)
Phosphodiesterase inhibitors	ITI-214, CRD-733
Probiotics (GUT microbiome)	Rifaxamin

Table 1. Completed and ongoing outcomes trials in heart failure with preserved ejection fraction(continued)

Mechanism of action	Drugs
sGC stimulator	Riociguat
Selective androgen receptor modulators	GSK2849466
Vasodilators	Urocortins 2 and 3
Vasopressin receptor antagonists	Tolvaptan, Ribuvaptan
Xanthine-oxidase inhibitors	Febuxostat
Uricosurics	Probenecid
Drugs targeting Epigenetics	DNA methyltransferase inhibitors. HDAC inhibitors

Figure 1.

Chronic

Acutely

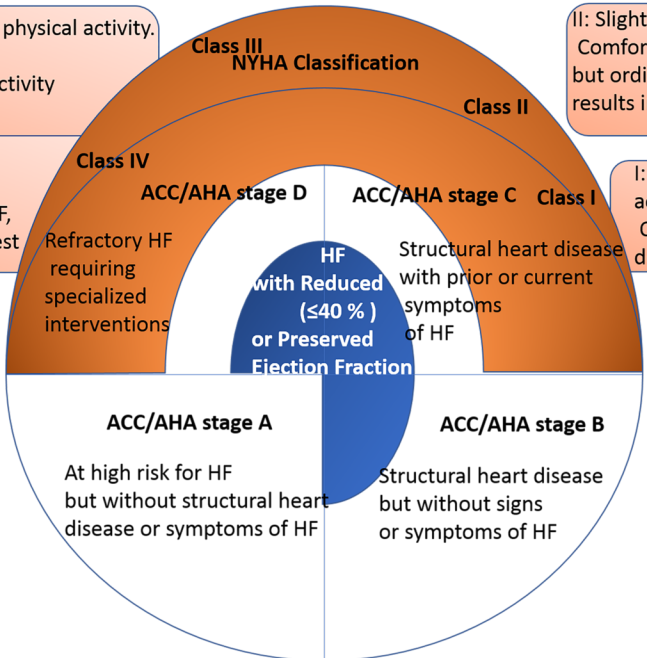
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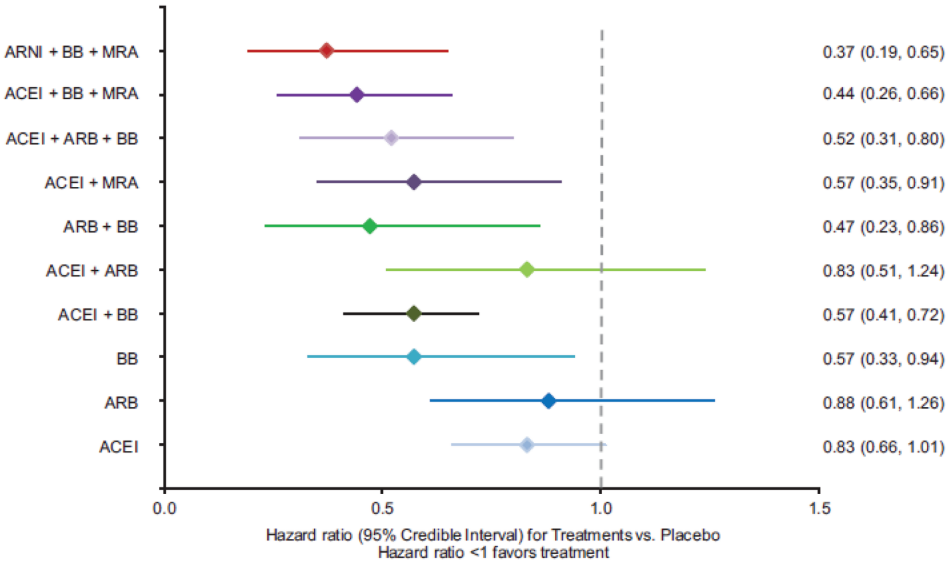
III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF

IV: Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest

II: Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF

I: No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF





Personalized Health Plan



Remote Monitoring and Management



Enhanced Clinic Support with Rapid Access



Emergency and Hospital Care

