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The year in cardiology: heart failure

The year in cardiology 2019

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Preamble

The past year has brought many new concepts and an abundance of new data on the nature, management, and outcome of heart failure. The pace of change is accelerating. We look forward to an exciting new decade of research. The prognosis of cardiovascular disease is determined to a large extent by the ability to delay or prevent the development and progression of heart failure.[1] Accordingly, attention is shifting to earlier diagnosis of and intervention for heart failure. Patients with type-2 diabetes mellitus (T2DM)[2] or coronary artery disease (CAD)[3] have a relatively good prognosis unless plasma concentrations of natriuretic peptides are increased, indicating important cardiac or renal dysfunction. Adoption of a simple 'Universal Definition' of heart failure based on natriuretic peptides would facilitate early diagnosis and treatment but lead to an enormous increase in its prevalence and demand upon medical services.[4] We need to prepare for the impending shock.

Epidemiology and prevention

In cardiology, the term prevention is often used to mean delaying the onset of disease; in other words, procrastination. Failure to appreciate the difference between prevention and procrastination leads to problems in projecting future healthcare needs and costs. Older people have more co-morbid conditions that complicate management but may also offer more opportunities for intervention; consequently, more time and resources are required to manage older patients well.

A detailed report on heart failure in the UK shows that the median age of onset has risen to about 80 years, consistent with improvements in the treatment of hypertension and other risk factors for atherosclerosis and better management of myocardial infarction.[5] Unfortunately, data on left ventricular ejection fraction (LVEF) were not available for this report. Analyses of the diagnostic pathway in primary care in the UK suggest that key investigations are often not done.[6–8] Similar data from other countries are urgently required. Several large epidemiological surveys[9,10] and analyses of large trials[11,12] have recently been published that allow the demographics, aetiology, and management of heart failure to be compared internationally.

Mineralocorticoid receptor antagonists (MRAs) are effective anti-hypertensive agents that also improve the prognosis of patients with heart failure and a reduced (HFrEF) and possibly preserved (HFpEF) LVEF.[13] Whether MRAs have specific effects on reducing other potential drivers of the progression to heart failure such as inflammation and fibrosis is currently under investigation.[14,15]

Genetic propensity to greater body fat was associated with the risk of developing heart failure in an analysis on 367 703 UK Biobank participants.[16] However, the incidence of heart failure was only 1% (4803 patients), the diagnostic criteria were not robust, and the increase in risk was modest (odds ratio 1.22; 95% CI 1.06–1.41). Further analyses on this population showed a strong relationship between cardio-respiratory fitness and grip strength and future incidence of heart failure.[17] A study of 4403 people considered for bariatric surgery in Sweden and followed for 22 years, found that 188 (9%) of the 2003 who had surgery (25–35 kg weight loss; BMI 1 year after surgery 32 kg/m^2) developed heart failure compared with 266 (13%) of 2030 who did not (BMI after 1 year observation 40 kg/m^2).[18] Although these data suggest links between obesity and the risk of developing heart failure, it is possible that obesity just provokes similar symptoms. Once heart failure has developed, obesity is associated with a lower mortality, but this may also reflect earlier diagnosis

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rather than a protective effect.[19] Randomized controlled trials (RCTs) of effective interventions for obesity are required to demonstrate whether weight loss improves symptoms (likely) and clinical outcomes (less certain).

A report from 'the Atherosclerosis Risk in Communities' (ARIC) study confirmed the association between influenza epidemics and hospitalizations for heart failure, reinforcing guideline-recommendations for vaccination[20]; an RCT is underway.[21] Extended follow-up (median 18.9 years) of the Women's Health Initiative Hormone Therapy trials, which randomized 27 347 women to various hormone replacement regimens, showed that they had no effect on the incidence of HFrEF or pEF.[22]

The ISCHEMIA trial (presented at the American Heart Association 2019) compared strategies of early coronary revascularization, predominantly percutaneous, with conservative management for stable CAD, some of whom had mild symptoms of heart failure and/or a reduced LVEF. Revascularization did not reduce the risk of myocardial infarction or death but increased the risk of stroke almost four-fold and did not reduce new-onset heart failure over the following 4 years.

Diagnosis

The Heart Failure Association of the European Society of Cardiology has proposed a new scoring system for the diagnosis of HFpEF.[23] Its practical utility awaits confirmation.[24] Simpler approaches may be preferred.[4]

Congestion

Congestion lies at the heart of failure.[25–27] Imaging has long been used to identify dilation of the atria and venous system, which might be termed haemodynamic congestion, for which natriuretic peptides are a useful biomarker.[25] More recently imaging has been used to identify accumulation of fluid in tissues (tissue congestion),[25,28–32] which may be associated with increases in the biomarker, (bio)-adrenomedullin.[33] Imaging and biomarkers in combination are both sensitive and specific for detecting a failing heart, a useful guide to the severity of congestion and prognosis and a potential therapeutic target indicating successful management. Imaging remains the preferred method for identifying the cause of heart failure. If congestion is central to the management of heart failure, then better monitoring[34] and more effective (diuretic) interventions (perhaps acetazolamide?[35]) should improve outcome (*Take home figure*).

Age and prognosis

Analysis of a large primary care database suggested that the cardiovascular (CV) prognosis of new-onset heart failure improved substantially between 2002 and 2014 [hazard ratio (HR): 0.73; 95% CI 0.68–0.80] for patients above and below the age of 80 years.[5] However, in those aged >80 years, the fall in CV mortality was entirely offset by non-CV mortality. In other words, treatment changed the way that elderly patients died but not overall mortality (*Figure 1*). Unfortunately, information on LVEF was not available; many patients will have had HFpEF and, therefore, caution should be exercised in

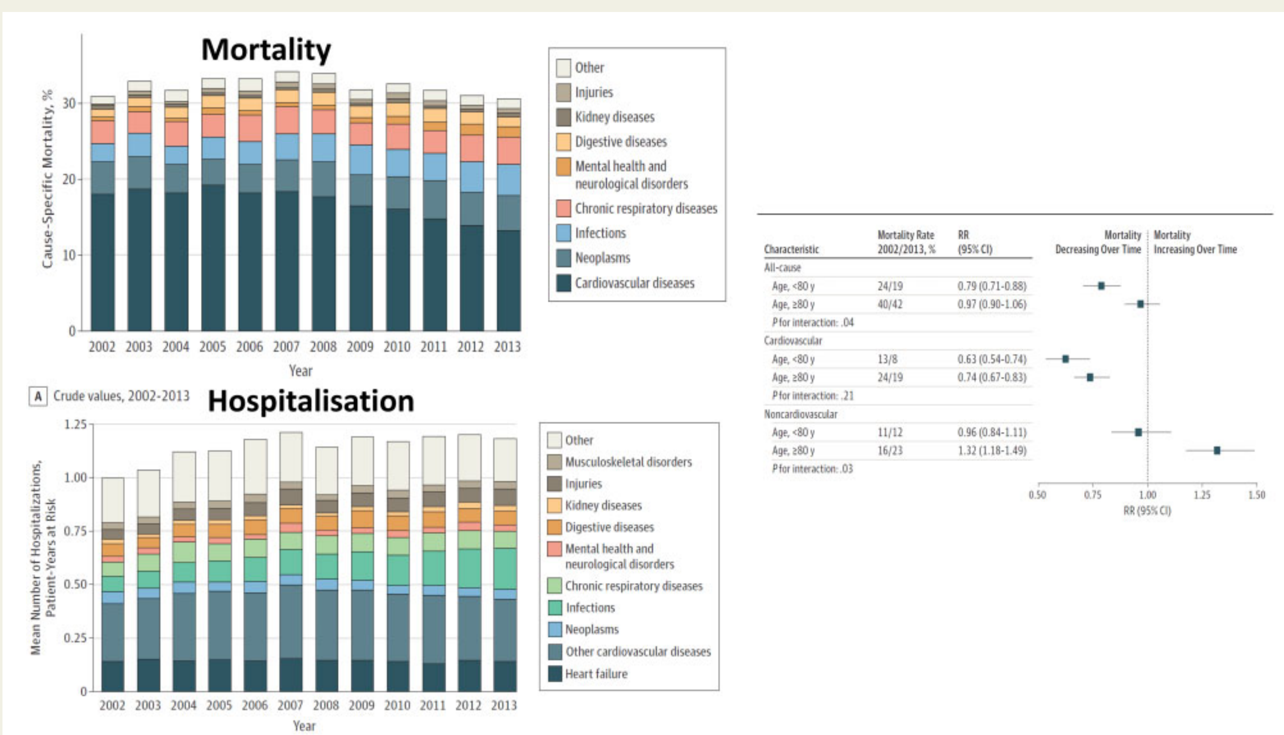


Figure 1 Changes in cause-specific mortality and hospitalizations for patients with incident heart failure in the UK between 2002 and 2013. Reproduced with permission from ref.[5]

attributing the reduction in CV mortality to treatment of heart failure. A systematic review of survey and registry data also suggested that the prognosis of heart failure had improved; important determinants of outcome were age and cardiology input to management.[36] Frailty, which might be considered a biological rather than chronological measure of age, may be an even more powerful predictor of disability and death.[37]

Guideline-recommendations for the treatment of HFrEF do not discriminate by age. The Swedish Heart Failure Registry found that prescription of ACE inhibitors or beta-blockers to patients with HFrEF aged >80 years was associated with a lower mortality.[38,39] However, observational associations have many explanations other than a therapeutic effect.[40] An individual patient-data meta-analysis of three RCTs of MRA (RALES, EMPHASIS, and TOPCAT-Americas)[13] suggested that MRAs exerted a similar reductions in mortality (by about ∼25%) for patients with HFrEF above and below age 75 years but benefit was less certain for HFpEF.

The diversity of heart failure phenotypes

Precision-medicine, which should also be accurate, requires patients to be classified in a way that informs management. For oncology, this has focused on the genetic cause, tumour location, and spread. For heart failure, a multi-system disorder, it is much more complex.[41–47]

Current, therapeutically relevant classifications of heart failure include the severity of congestion (based on symptoms, signs, blood biomarkers, and imaging), CAD, heart rate and rhythm and QRS duration, blood pressure, serum potassium, renal function, indices of iron deficiency, mitral regurgitation, infiltrative myocardial disease (e.g. amyloid), and ventricular phenotype.[41,48] Optimal management of heart failure, with a few rare exceptions, requires only a modest amount of information but this still creates many thousands of patient-subgroups or clusters that might have different therapeutic needs.[45,46] Such subgroups will increase exponentially with the introduction of each new class of treatment. Despite this heterogeneity of substrate and wealth of interventions, precision-medicine is in its infancy in heart failure.

One therapeutically relevant classification of heart failure is by LVEF, a surrogate for left ventricular (LV) dilation. Prior to the 1980s, imaging of cardiac function was available only in expert centres. Clinical trials relied on the chest X-ray rather than the echocardiogram to support a diagnosis of heart failure. The success of trials such as SOLVD, MERIT, and CHARM, which all had a reduced LVEF as an inclusion criterion, led to the adoption of LVEF <40% as the European Society of Cardiology (ESC) Guideline definition for HFrEF.[49] Values ≥40% were termed HFpEF, comprising patients with a mid-range or mildly-reduced (HFmrEF), normal (HFnEF) and, perhaps, supra-normal (HFsnEF) LVEF.[50] Analyses of >350 000 routinely collected echocardiograms suggested that the nadir of risk, whether or not the patient has a diagnosis of heart failure, lies in the range 60–65% both for men and women. Interestingly, an LVEF of >70% was associated with similar risk as an LVEF of 30–40% (*Figure 2*).[50]

The ESC Guidelines of 2016 introduced the concept of HFmrEF, for two main reasons. Firstly, because of imprecision, an echocardiographic measurement could not reliably distinguish between two measurements of LVEF within 10% of each other. Creating a buffer-zone between HFrEF and HFnEF meant that misclassification was less likely. This innovation meant that a trial of HFpEF could not claim benefit for all patients with an LVEF >40% based solely on an effect in those with an LVEF 40–49%. Secondly, the introduction of HFmrEF challenged the convention that an LVEF <40% was the correct threshold for HFrEF. Some analyses subsequent to the ESC 2016 Guideline suggest that patients with an LVEF <50% may respond to treatment similarly to those with an LVEF <40%.[51] However, this interpretation could reflect confirmation-bias amongst enthusiastic proponents of HFmrEF (*Table 1*). The evidence is not so consistent when looked at in its entirety, especially if mortality is considered a key outcome. In the future, many trials will probably include both HFrEF and HFmrEF, others will include HFmrEF, HFnEF, and HFsnEF, but NT-proBNP should be used routinely to stratify risk and potentially exclude low-risk patients who have little to gain from yet another 'pill'. Assuming we continue to use LVEF to classify patients, which seems likely since we cannot undo the past, then the major issue is where to set thresholds. For HFrEF, these have ranged from <25% in COPERNICUS, <30% in MADIT-II, and RAFT to <35–40% for the bulk of other trials.[51] For HFpEF, LVEF has generally been set at >40% or >45% with no upper limit. Analyses of recent trials have led some to suggest that, for patients with an elevated NT-proBNP, the upper limit of LVEF for HFmrEF should be increased to 55% or even 60% but this seems premature until consistency is demonstrated across multiple interventions and end-points and measurement precision for LVEF improves.

In a substantial observational study of patients with HFpEF and pulmonary hypertension, progression of right rather than left ventricular

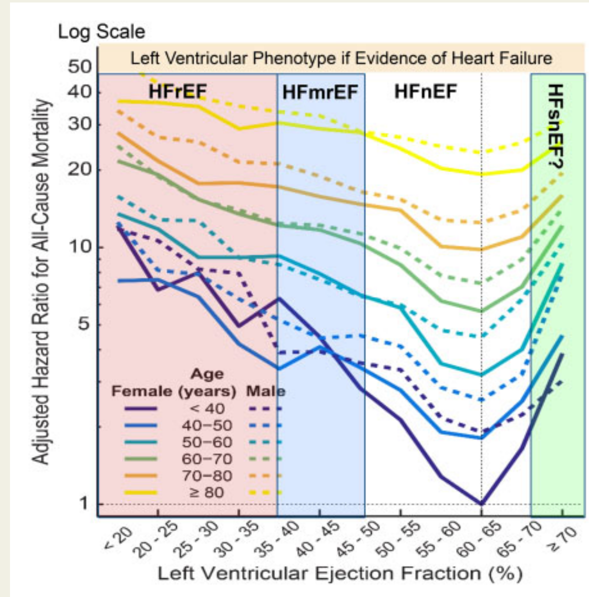


Figure 2 All-cause mortality according to left ventricular ejection fraction reported on >350 000 routine echocardiograms stratified by age and sex. HFmrEF, heart failure with mildly reduced ejection fraction; HFnEF, heart failure with normal ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFsnEF, heart failure with supra-normal ejection fraction. Reproduced with permission from ref.[50]

Table 1 Evidence supporting or refuting the benefits of treatments for heart failure with a left ventricular ejection fraction in the "mid-range" (HFmrEF: 40–49%)

	LVEF	Symptoms	Hospitalization for heart failure[a]	CV death or HFH[a]	CV mortality	All-cause mortality
Diuretics						
Perindopril		Improved		**0.38 (0.19–0.75)**[b]		
Candesartan		Improved	**0.72 (0.55–0.95)**∏	**0.76 (0.61–0.96)**	0.81 (0.60–1.11)	0.79 (0.60–1.04)
Irbesartan				0.98 (0.85–1.12)Δ		
ARNI (Sac/Val) vs. Val[c]		Improved	0.77 (0.58–1.02)	0.81 (0.64–1.03)	0.94 (0.69–1.28)	NYR
MRA (overall)[c]			0.76 (0.46–1.27)	0.72 (0.50–1.05)	0.69 (0.43–1.12)	0.73 (0.49–1.10)
MRA (Americas)[c]			0.60 (0.32–1.10)	**0.55 (0.33–0.91)**	**0.46 (0.23–0.94)**	**0.58 (0.34–0.99)**
ß-Blocker (SR)	Improved		0.95 (0.68–1.32)	0.83 (0.60–1.13)	**0.48 (0.24–0.97)**	0.59 (0.34–1.03)
ß-Blocker (AF)	Improved		1.15 (0.57–2.32)	1.06 (0.58–1.94)	0.86 (0.36–2.03)	1.30 (0.63–2.67)
Ivabradine						
Digoxin			0.80 (0.63–1.03)	0.96 (0.79–1.17)	1.24 (0.94–1.64)	1.08 (0.85–1.37)
Rivaroxaban vs. aspirin			0.65 (0.40–1.05)			0.75 (0.53–1.06)
Rivaroxaban+Aspirin vs. aspirin			0.87 (0.56–1.35)			**0.63 (0.44–0.90)**
CRT						
ICD						
BNP-guided therapy				Reduction from 67% to 44% patients with an event		

Statistically significant results are shown in bold on a blue background. Blank cells indicate no relevant information reported. Other data shown are not significant, although may not be heterogeneous with the effect in patients with a reduced left ventricular ejection fraction (HFrEF). Data for sacubitril/valsartan taken from reference for LVEF >42.5% to 52.5%.[98]

AF, atrial fibrillation; ARNI, angiotensin receptor-neprilysin inhibitors; BNP, brain natriuretic peptide; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, Mineralocorticoid receptor antagonist; SR, sinus rhythm.

[a]Recurrent event analyses used when available.

[b]The PEP-CHF trial specified inclusion of patients with LVEF 40–49% as was LVEF >49% but did not report effects in this subgroup. However, it did report effects in patients with a prior myocardial infarction who were more likely to have HFmrEF.

[c]Stronger effect in women.

dysfunction was observed and was associated with an increased risk of atrial fibrillation (AF) and death.[52] Although right ventricular (RV) dysfunction is a powerful prognostic marker, remarkably few trials focusing on RV dysfunction have been done (SERENADE: https://clinicaltrials.gov/ct2/show/NCT03153111).

Atrial fibrillation

About a third of outpatients, perhaps more for those with HFpEF,[53] and more than half of those admitted with heart failure will be in AF, which is associated with an adverse prognosis even after correcting for age and other risk factors.[54] Controversy continues over whether medical management focused on rate control or restoration of sinus rhythm is the better strategy for AF and heart failure. In practice, the strategy needs to be tailored to the patient. When AF is the driver of symptoms and worsening cardiac function, restoration of sinus rhythm might be appropriate but when AF reflects the progression of underlying cardiac dysfunction, it may not.[55] For new-onset or paroxysmal AF associated with a clear deterioration in symptoms, restoration of sinus rhythm may be warranted to improve symptoms. For long-standing AF and heart failure with markedly dilated atria, sustained restoration of sinus rhythm and atrial contraction is less likely. Optimal pharmacological management includes anticoagulation, avoiding toxic anti-arrhythmic agents and lenient ventricular rate control. Beta-blockers are the agent of choice for rate control, a resting day-time ventricular rate of 70–90 b.p.m. is preferred,[49] which may require only modest doses; digoxin should be used sparingly, if at all. Unfortunately, RCTs of rate vs. rhythm control for AF have failed to optimize the rate control strategy in the above fashion.

A meta-analysis of RCTs of rate vs. rhythm control included four trials ($n = 2486$) comparing pharmacological rhythm to rate control found no difference in mortality or thromboembolic events but an increase in hospitalizations, often due to recurrent AF, in the rhythm control group.[56] Six trials ($n = 1112$) comparing AF ablation with rate control reported reductions in mortality (0.51; 95% CI 0.36–0.74), hospitalizations (0.44; 95% CI 0.26–0.76), and stroke (0.59: 95% CI 0.23–1.51) and an improved quality of life.[56] However, none of the trials individually had a robust result, patients were highly selected and the rate control strategy was not optimal. As such, this meta-analysis should be considered hypothesis generating. Further trials are required with greater involvement of heart failure physicians.

Implanted electrical devices

The controversy over the role of high-energy devices for heart failure continues. Long-term follow-up of cardiac resynchronization therapy

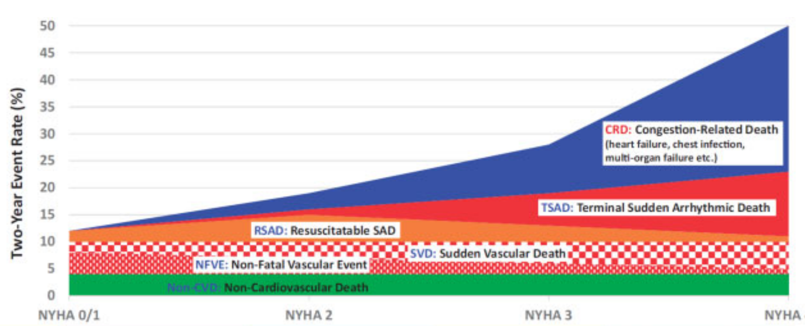
(CRT) in a French Registry showed a low rate of sudden death amongst patients who received CRT-Pacing (without a defibrillator).[57–59] A systematic review of observational studies and RCTs reported that differences in the rate of sudden death with CRT-Pacing and CRT-D were narrowing.[58] RCTs comparing CRT-Pacing and CRT-D are underway[59] (*Take home figure*). Whether myocardial scar found on cardiac magnetic resonance imaging identifies patients with more to gain from an implantable cardioverter defibrillator (ICD) is also under investigation[60] (CMR_GUIDE; https://clinicaltrials.gov/ct2/show/NCT01918215). Retrospective analysis of SCD-HeFT found that patients with T2DM did not benefit from an ICD.[61] An individual patient-data meta-analysis confirmed a reduction in sudden death with MRA.[62] A systematic review identified 22 studies with post-mortem interrogation of ICDs; the analysis suggested that 24% of sudden deaths were not arrhythmic.[63] A substantial multi-point pacing trial failed, so far, to show improvements in the clinical or echocardiographic response to CRT.[64]

Mitral regurgitation

COAPT suggested that a percutaneously delivered mitral clip could reduce functional (secondary) regurgitation with a subsequent substantial improvement in morbidity and mortality that was moderately cost-effective in a US healthcare context (US$40 361 per life-year gained and $55 600 per quality-adjusted life year).[65–68] Two-year follow-up of MITRA.fr suggested no benefit.[69] A possible explanation for the apparent discrepancy could be the ratio of the severity of LV dysfunction to the severity of mitral regurgitation. When regurgitation is disproportionate to the severity of LV dysfunction it may drive disease progression and correction may improve outcome.[70,71] When regurgitation is proportionate to the severity of LV dysfunction, fixing the mitral regurgitation may be less useful because myocardial dysfunction drives disease progression. The concept is simple and plausible but application in practice may be difficult. Mitral regurgitation offloads the LV and may mask dysfunction. It is also likely that there is a spectrum of primary and secondary mitral regurgitation, with some patients having a mixed picture. More experience and further data from RCTs may improve patient selection (RESHAPE-HF2: https://clinicaltrials.gov/ct2/show/NCT02444338). However, optimizing guideline-recommended therapy, including diuretic dose, may cause mitral regurgitation secondary to dilation of the LV and mitral ring to improve or resolve. Other technologies for secondary mitral[72] and tricuspid regurgitation[73,74] are being developed.

Coronary artery disease

In COMPASS (n = 27 395), 5902 with CAD, in sinus rhythm and with a diagnosis of heart failure (predominantly HFpEF) were randomly assigned them to aspirin 100 mg/day, rivaroxaban 5 mg bd or aspirin and rivaroxaban 2.5 mg bd.[75,76] The study was stopped early for benefit on the primary endpoint (a composite of CV death, stroke, or myocardial infarction) with the combination compared with aspirin alone. Further analysis suggested a reduction in all-cause mortality for patients with heart failure, especially HFpEF, assigned to combination therapy (HR: 0.63; 0.44–0.90) or rivaroxaban alone (HR: 0.75; 0.53–1.06) with an estimated 4% absolute difference at 2 years; rather similar to the magnitude of effect in HFrEF for sacubitril-valsartan[77] or dapagliflozin[78] (*Figure 3*). This suggests that coronary events might be



	NYHA 0/1		NYHA 2		NYHA 3		NYHA 4	
	Absolute Rate	% of Events	Absolute Rate	% of Events	Absolute Rate	% of Events	Absolute Rate	% of Events
CRD	0%	0%	3%	16%	9%	32%	27%	54%
TSAD	<1%	<1%	1%	5%	6%	21%	12%	24%
RSAD	2%	17%	5%	26%	3%	11%	1%	2%
SVD	2%	17%	3%	16%	4%	14%	5%	10%
NFVE	4%	33%	3%	16%	2%	7%	1%	2%
Non-CVD	4%	33%	4%	21%	4%	14%	4%	8%

Take home figure Two-year cause-specific mortality and non-fatal vascular events for patients with cardiovascular disease according to New York Heart Association (NYHA) class. Numbers and proportions are a conceptual representation of absolute and relative risk and are not strictly evidence-based. Note that for patients in NYHA Class 4, interventions for sudden arrhythmic death may be ineffective or fail to lead to a meaningful prolongation of life because the patient is likely soon to die of worsening heart failure. CRD, congestion-related death, otherwise called death due to worsening heart failure; NFVE, non-fatal vascular event (e.g. myocardial infarction and stroke; note that events are more likely to be suddenly fatal as heart failure progresses); non-CVD, non-cardiovascular death; RSAD, resuscitatable sudden arrhythmic death; SVD, sudden vascular death; TSAD, terminal (non-resucitatable) sudden arrhythmic death. Reproduced with permission from ref.[59]

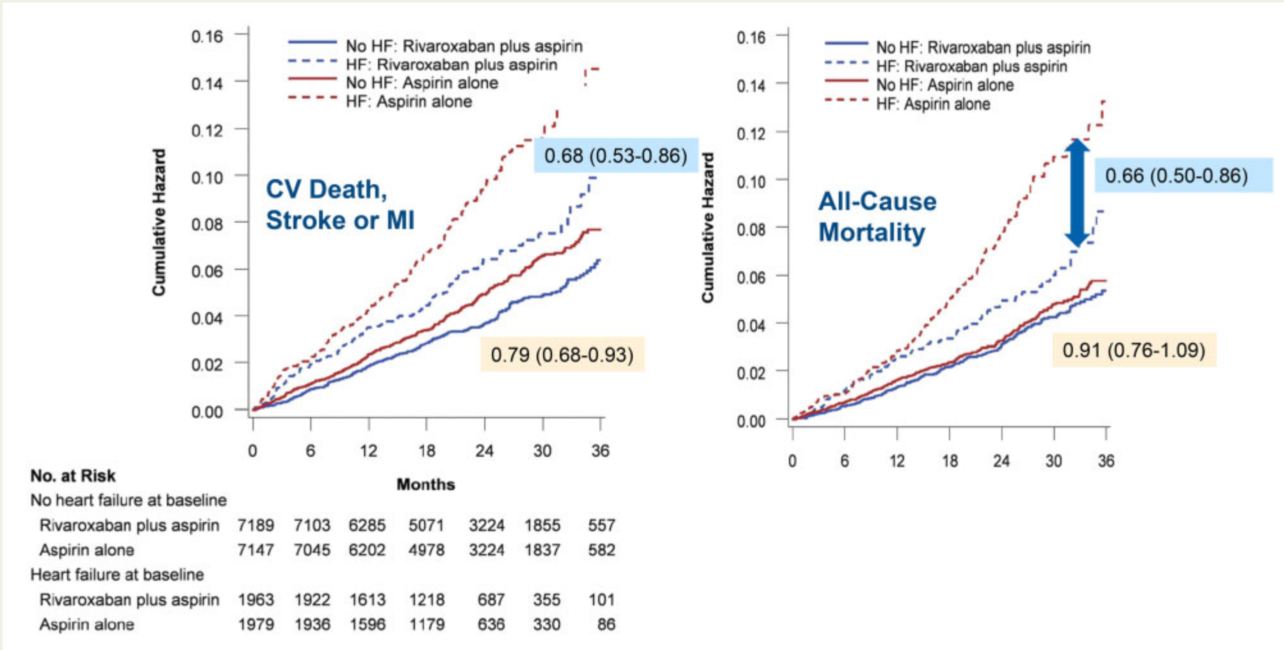


Figure 3 Effect of rivaroxaban 2.5 mg bd and aspirin 100 mg/day compared with aspirin alone for stable CAD, sinus rhythm and heart failure (predominantly heart failure with preserved ejection fraction) in COMPASS-HF. Reproduced with permission from ref.[75]

an important driver of death in HFpEF (*Take home figure*), although effects of rivaroxaban on endothelial function, inflammation, and fibrosis should not be discounted. The analysis also suggests that those who do not have heart failure have little to gain from additional treatment with rivaroxaban.

However, for patients with HFrEF, CAD in sinus rhythm with a recent hospital discharge for worsening heart failure, addition of rivaroxaban 2.5 mg bd to background anti-platelet therapy did not improve overall prognosis, although a composite of vascular outcomes (stroke, myocardial infarction, and sudden death) was reduced, driven mainly by a reduction in stroke.[79,80] This suggests that for patients with stable CAD and more advanced heart failure, hospitalizations, and deaths due to worsening heart failure are not greatly influenced by anti-thrombotic therapy (*Take home figure*).

Angiotensin receptor-neprilysin inhibitors

Heart failure with reduced ejection fraction

As experience in the implementation of angiotensin receptor-neprilysin inhibitors (ARNIs) grows, both in clinical trials and in clinical practice, there is a strong argument to consider them as first-line agents, rather than angiotensin converting-enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), for the treatment of HFrEF. In PIONEER-HF,[81] 881 patients with an LVEF ≤40% who were hospitalized for worsening heart failure were randomly assigned, without a run-in period, to sacubitril/valsartan or enalapril prior to discharge and followed for 8 weeks to determine the effect on plasma concentrations of NT-proBNP; about one-third had new-onset heart failure. Sacubitril-valsartan exerted a greater reduction in NT-proBNP. Reductions in markers of myocardial injury or stress, high-sensitivity cardiac troponin-T and soluble ST2, were also observed. These effects appeared early after randomization (within 1–4 weeks). Moreover, patients assigned to sacubitril/valsartan were less likely to experience adverse outcomes within the first 8 weeks. TRANSITION[82] randomly assigned 1002 patients to pre- or post-discharge initiation of sacubitril/valsartan, showing no adverse consequences to earlier administration.

EVALUATE[83] compared the effects of sacubitril/valsartan and enalapril on aortic stiffness in HFrEF most of whom were already chronically treated with an ACEi or ARB. After 24 weeks treatment, no differences in aortic stiffness were observed but slightly greater reductions in LV end-diastolic and systolic volumes were observed with sacubitril/valsartan compared with enalapril, although changes in LVEF were similar. Mitral E-velocity and left atrial volume declined, consistent with a fall in left atrial pressure. PROVE-HF,[84] an observational study, had similar findings and showed that most of the decline in NT-proBNP occurred within 14 days consistent with the rapid onset of clinical benefit observed with sacubitril/valsartan in trials and clinical practice. PRIME[85] was an RCT ($n = 118$) comparing the effects of sacubitril/valsartan or valsartan on functional mitral regurgitation in patients with an LVEF between 25% and 49% who were already receiving an ACEi or ARB. Those assigned to sacubitril/valsartan had greater reductions in mitral regurgitation and LV end-diastolic and left atrial volumes but LVEF increased by a similar small amount in each group (about 2.5%).

Further reports from PARADIGM-HF suggest that, compared with enalapril, sacubitril/valsartan may improve markers of collagen

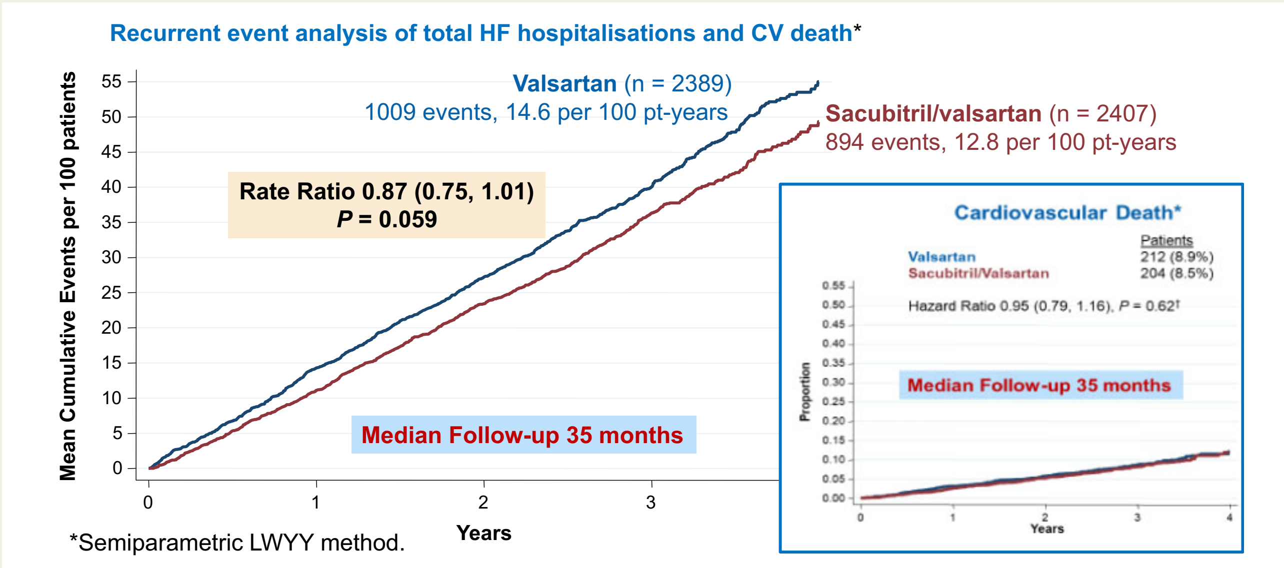


Figure 4 Effect of sacubitril/valsartan compared with valsartan for heart failure with preserved ejection fraction in PARAGON-HF. Reproduced with permission from ref.[91]

metabolism, in particular, decreasing synthesis of type-I collagen, which makes an important contribution to myocardial stiffness.[86] In I-PRESERVE, irbesartan (an ARB) did not affect collagen biomarkers compared with placebo.[87]

Heart failure with preserved ejection fraction

PARAGON-HF investigated the effect of sacubitril/valsartan compared to valsartan alone on morbidity and mortality in patients with HFpEF (defined as an LVEF >45%).[88] It was the first RCT since PEP-CHF[89] to require patients to be treated with diuretics, the first-line treatment for the relief of symptoms and signs of congestion, and to have echocardiographic evidence of cardiac dysfunction. It was also the first large trial of HFpEF to require all patients to have raised plasma concentrations of natriuretic peptides, the most powerful, widely available prognostic marker in HFpEF. Sacubitril/valsartan was compared with valsartan rather than placebo because many patients eligible for PARAGON-HF had indications for ACE inhibitors and ARBs such as hypertension and CAD. The only trial comparing valsartan to placebo in HFpEF was of modest size and neutral.[90] Previous RCTs of other ARBs, including candesartan (CHARM-Preserved) and irbesartan (I-PRESERVE) failed to show substantial benefit for HFpEF.[88] Patients had to tolerate, sequentially, both valsartan and sacubitril/valsartan at half the intended target dose before randomization. This simulates clinical practice (doctors do not usually prescribe medicines to patients unwilling or unable to take them) and reduces the risk of a neutral trial-outcome due to low adherence. Of 10 539 patients screened, 4822 were randomized.

PARAGON-HF was neutral for its primary endpoint (CV death or the total number of recurrent hospitalizations for heart failure[91]; *Figure 4*). Some have argued that the *P*-value was very close to 0.05 and that it was 'almost' positive. This misses the point. The trial shows that the size of the potential benefit of sacubitril/valsartan for HFpEF is modest, regardless of the *P*-value and that the treatment is, overall, unlikely to be cost-effective. Accordingly, we should look for more effective treatments or, more controversially, subgroups that obtain greater benefit. After a median follow-up of 35 months, 23% of patients experienced a primary event but the annual incidence of CV and all-cause mortality were, respectively, only about 3% and 5%, which is similar to those for previous trials of HFpEF and for elderly patients with resistant hypertension assigned to placebo in HYVET.[92] Although <3% of patients were reported to have heart failure in HYVET, a combination of indapamide and perindopril reduced all-cause mortality and cut the incidence of heart failure by >50%. Many of these patients probably had undiagnosed HFpEF prior to randomization. Higher rates of hospitalization for heart failure in trials of HFpEF compared to hypertension may well reflect ascertainment bias, as clinicians who are interested or expert in the management of heart failure are more likely to diagnose or report heart failure events. Overall, these trials suggest that the mortality rate and possibly the rates of cardiovascular and all-cause hospitalization may be similar in patients with and without a diagnosis of HFpEF, if they have a similar burden of co-morbidities. However, it is also likely that many patients with hypertension, CAD and T2DM have undiagnosed heart failure.

Subgroup analysis suggested that the effect of sacubitril/valsartan on the primary endpoint was greater for patients with an LVEF below the median (57%), but this was driven almost entirely by an effect on hospitalization for heart failure rather than on CV death.[93] The effect of sacubitril/valsartan on the primary endpoint was also greater for women and this was true throughout the studied range of LVEF, but again this was driven by a difference in hospitalization for heart failure and not CV mortality.[94] Reductions in NT-proBNP were similar for each sex. Sacubitril/valsartan appeared to have a favourable effect on quality of life for men but not for women. Patients with a recent heart failure hospitalization may also have benefited more.[95] These observations should be interpreted in the light of a trial that was neutral for its primary endpoint. No effect was observed on mortality and the benefits of treatment on quality of life and hospitalizations for heart failure according to sex were inconsistent. In PARADIGM-HF, no difference in treatment effect according to sex was observed. A further sizeable RCT in HFpEF, PARALLAX-HF, investigating the effects of sacubitril/valsartan on quality of life and exercise capacity will provide more evidence in 2020 (https://clinicaltrials.gov/ct2/show/NCT03066804).

Do women and men respond differently to treatment?

An analysis of 12 058 patients with HFrEF in two large trials found that women had more severe symptoms, similar LVEF but a substantially better prognosis than men, even after adjusting for key prognostic variables including aetiology and NT-proBNP (HR: 0.68; 0.62–0.89).[96] A combined analysis of PARAGON-HF and PARADIGM-HF suggested that patients with HFrEF and HFpEF had similarly impaired quality of life but that women generally reported a worse quality of life than men.[97] In an observational analysis of patients with HFrEF, the BIOSTAT survey also found that women generally had a better prognosis than men despite being prescribed lower doses of beta-blockers and ACE inhibitors.[98] Interestingly, men and women had the same heart rate, the pharmacodynamic marker of beta-blocker dose. For patients with HFpEF in the TOPCAT trial, reductions in mortality, but not hospitalizations for heart failure, were greater for women, although the interaction was statistically significant only for all-cause mortality.[99] In the PARAGON-HF trial (HFpEF), women obtained greater benefit than men throughout the studied range of LVEF but the difference was driven by differences in the rate of hospitalization for heart failure rather than mortality.[94] One obvious difference between men and women, on average, is size. Cardiac resynchronization therapy is reputed to be more effective in women than men, but differences disappear once adjusted for height.[100] Many medicines are cleared by the kidney. Estimated glomerular filtration rate (eGFR) is indexed to body surface area (BSA) but doses of treatment are usually not. A woman (or small man) weighing 64 kg and 160 cm tall has BSA of 1.67 m^2 using the Dubois formula and a man (or large woman) weighing 85 kg and 180 cm tall has a BSA 2.05 m^2. If both have an eGFR of 60 mL/kg/m^2, then the woman (or small man) has an un-indexed eGFR of 100 mL/min and the man (or large woman) has an un-indexed eGFR of 123 mL/min. If a medicine is cleared by the kidney then perhaps smaller people require lower doses to achieve the same plasma therapeutic concentration and clinical benefit?

Sodium-glucose cotransporter-2 inhibitors

Sodium-glucose cotransporter protein-2 (SGLT2) is found mainly in the proximal renal tubule and to a lesser extent in other organs. SGLT1 is abundant in the intestine and myocardium. SGLT2 inhibitors (SGLT2i) cause glycosuria, improving glycaemia, which led to their development for the treatment of T2DM, and an osmotic diuresis, leading to a contraction of plasma volume.[101,102] SGLT1 inhibitors reduce intestinal glucose absorption, which can cause diarrhoea but might have favourable effects on myocardial energy-utilization.[103] Most SGLT2i are highly selective, including dapagliflozin and empagliflozin, but sotagliflozin is less selective.[103]

EMPA-REG enrolled 7020 patients with T2DM, about 10% of whom had heart failure (LVEF was not measured) and showed that empagliflozin reduced the risk of hospitalization for heart failure and mortality.[104] Within a few weeks of initiating empagliflozin, body weight, and blood pressure fell and haematocrit rose, consistent with a diuretic effect. Subsequent RCTs of other SGLT2i in T2DM had similar findings. Meta-analyses suggested that SGLT2i were the hypoglycaemic agents most likely to reduce incident heart failure,[105–107] whilst observational data raises concerns about insulin therapy.[108] A meta-analysis of RCTs of empagliflozin, canagliflozin, and dapagliflozin for T2DM, including >30 000 patients, showed benefit, at least for those with established CV disease.[109] For the outcome of hospitalization for heart failure or CV death, the annual rate was about 0.6% for the 13 672 patients with multiple risk factors but without established CV disease, about 3% for the 20 650 patients with established atherosclerotic disease and about 6% for 3891 patients with heart failure at baseline; the relative risk reductions with SGLT2i in these populations were 16%, 24%, and 29%, respectively, without evidence of heterogeneity amongst agents. The largest of these trials, DECLARE,[110] included 17 160 patients of whom 671 had HFrEF and 1316 had HFpEF or an unspecified LVEF. In a subgroup analysis,[111] dapagliflozin reduced hospitalizations for heart failure and CV mortality for HFrEF but not for other patient-groups (*Figure 5*).

DAPA-HF[78,112] enrolled 4744 patients and followed them for a median of 18.3 months, demonstrating that addition of dapagliflozin to guideline-recommended therapy for HFrEF-reduced hospitalizations for heart failure by 30% and mortality (mainly cardiovascular) by 18%, preventing 3–5 hospitalizations and 1–2 deaths per 100 patients treated per year (*Figure 6*). Patients were somewhat less likely to experience serious adverse events, especially renal, with dapagliflozin compared with placebo. The benefits appeared consistent across subgroups, although patients with evidence of more severe congestion (worse NYHA class or higher NT-proBNP) may have received less benefit. Importantly, benefits were similar for those with and without T2DM and regardless of age.[113] Dapagliflozin also improved quality of life,[114] an effect that was confirmed in a smaller RCT (DEFINE)[115] that followed 263 patients for 12 weeks; about one in six patients got a meaningful benefit, either prevention of worsening or an improvement in symptoms, compared with placebo.

In DAPA-HF, the placebo-corrected decline in weight between baseline and 8 months was 0.87 kg and this was associated with a small fall in NT-proBNP and systolic blood pressure and a small increase in haematocrit and serum creatinine. These findings are again consistent with the belief that SGLT2i exert at least some of their benefits by enhancing diuresis, either through an osmotic effect of glycosuria or by interfering with sodium-hydrogen exchange in the nephron.[116] The effects of SGLT2i appear early, consistent with an immediate haemodynamic effect. However, alternative or additional explanations for the effect of SGLT2i have been proposed. A small RCT suggested that empagliflozin stimulated production of erythropoietin leading to a rise in haematocrit and a fall in ferritin, a marker

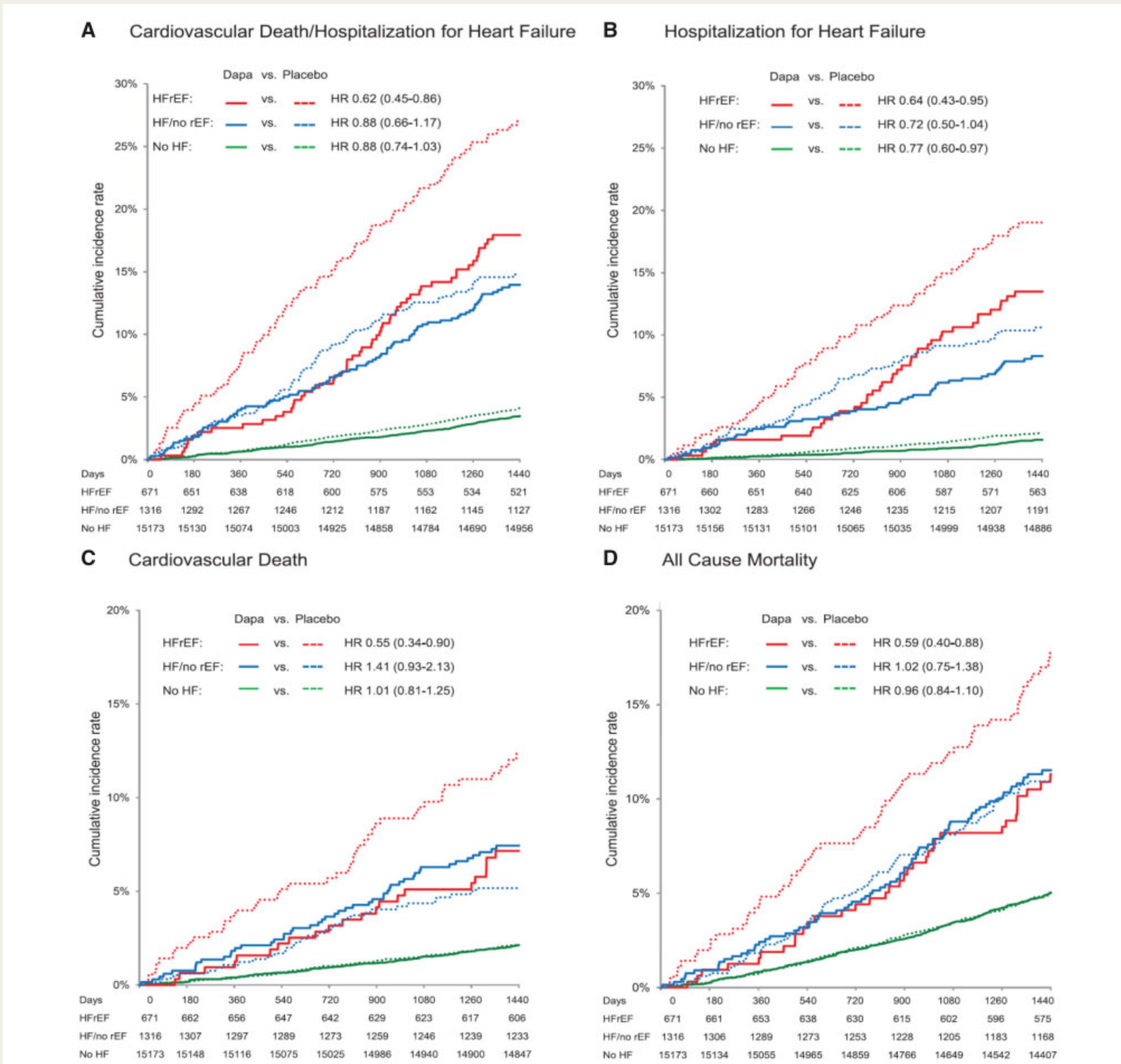


Figure 5 Effect of dapagliflozin compared with placebo in type-2 diabetes mellitus in patients with heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, or without heart failure in DECLARE. Reproduced with permission from ref.[111]

of inflammation and iron deficiency, although not transferrin saturation, a marker of iron deficiency alone.[117] However, administration of exogenous erythropoietin did not reduce morbidity or mortality in the RED-HF trial.[118] Others have suggested that SGLT2i increase the production of ketones, which may be a more efficient myocardial energy substrate, or block myocardial sodium–hydrogen exchanger-3, which may improve myocardial function and reduce fibrosis.[119,120] An RCT of empagliflozin in patients with T2DM but not heart failure[121] suggested little effect on cardiac function or remodelling; RCTs of the effects of SGLT2i on cardiac function in patients with HFrEF and HFpEF are awaited. Future trials will confirm whether the benefit observed in DAPA-HF is a class effect and whether they are effective for HFpEF or when congestion is severe.[122,123]

Acute heart failure

Two large RCTs of serelaxin failed to confirm the results of the original RELAX-AHF trial. RELAX-AHF-EU,[124] an open-label RCT ($n = 2688$), reported a similar and low rate for mortality (≤2%) and re-admissions for heart failure (<1%) at 14 days for patients assigned placebo or serelaxin, despite a reduction in worsening heart failure at day 5 [6.7–4.5% ($P < 0.008$)]. The RELAX-AHF-2 trial,[125] a double-blind RCT ($n = 6545$), reported that the rates of worsening heart failure in the first 5 days (about 7%) and 180-day mortality (about 11%) were similar for placebo and serelaxin. The failure of so many short-term interventions for AHF may reflect failed therapeutic concepts, ineffective interventions, or problems with trial design. RCTs of AHF are

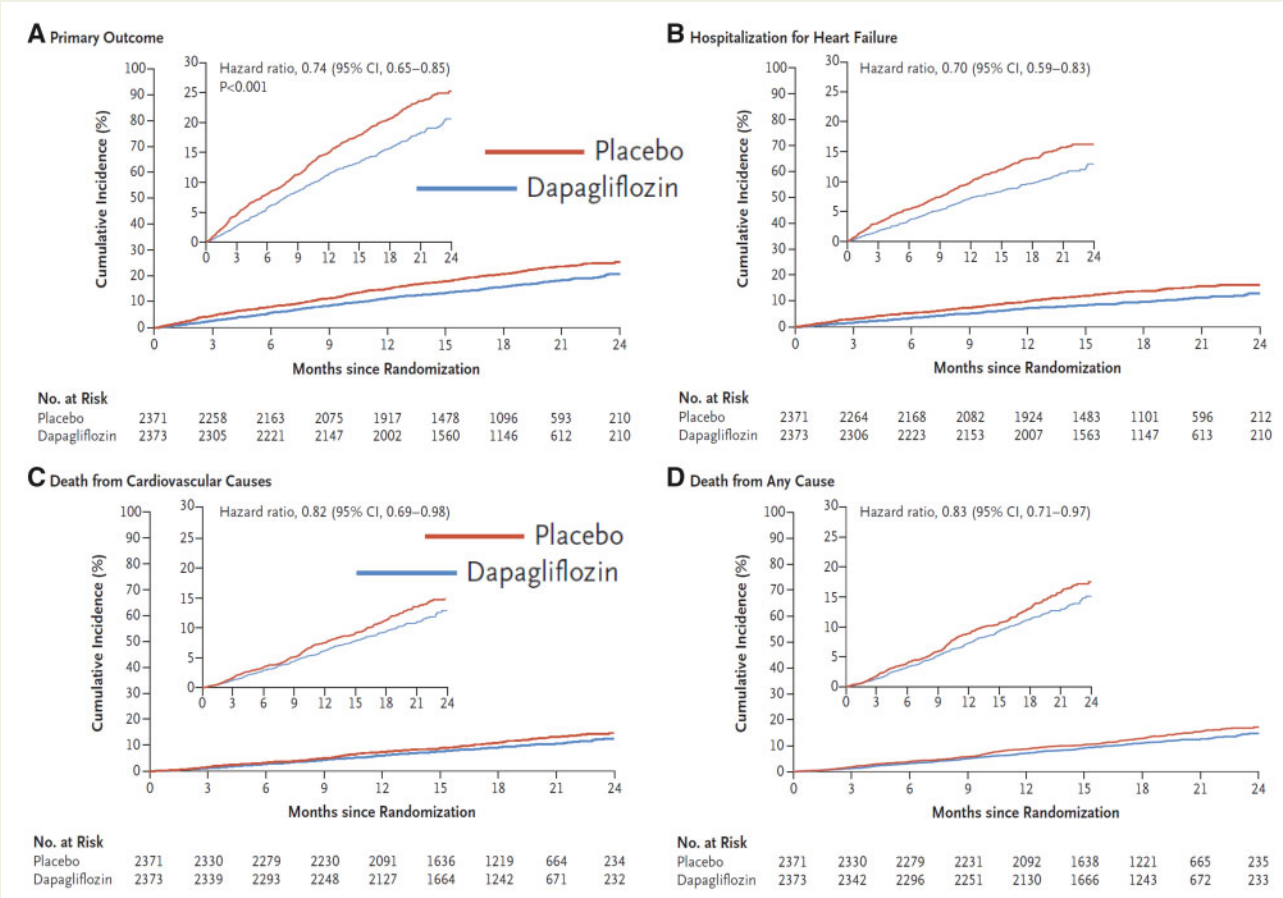


Figure 6 Effect of dapagliflozin compared with placebo in patients with heart failure with reduced ejection fraction, with or without type-2 diabetesmellitus in DAPA-HF. Reproduced with permission from ref.[78]

difficult to implement, especially if conducted double-blind. Indeed, GALACTIC, a trial of personalized, early intensive and sustained vasodilation with nitrates and hydralazine, also failed to show benefit, calling into question the concept of vasodilator therapy for the routine management of acute heart failure.[126] Many patients present with acute breathlessness in the middle of the night. It is difficult to have research staff available '24/7' when there is no 'gateway' similar to a coronary care unit or catheter laboratory. Compassionate investigators may also be unwilling to enrol frail elderly patients who are most at risk of adverse outcomes. Moreover, breathlessness usually responds to oxygen and diuretics within hours,[127] especially for patients with a systolic blood pressure ≥125 mmHg, as required in the serelaxin trials. On the other hand, patients with extensive peripheral oedema,[26] renal dysfunction, and a low blood pressure, who often do not constitute an acute emergency have a poor prognosis and an unmet need for more effective interventions; pharmacological, or device.[127,128]

Stem cell therapy

Intra-myocardial injection of stem cells failed to improve weaning from left ventricular assist devices.[130]

Heart failure in patients with cancer

Interest in cardio-oncology reflects increasing survival after treatment for cancer, growing awareness of the CV toxicity associated with both established and new treatments for cancer, and interest in personalized risk-profiling prior to chemotherapy. People with cardiomyopathy-related gene mutations may be more prone (7.5% of those with compared to 1.1% of those without a titin gene mutation) to develop ventricular dysfunction after the administration of chemotherapy.[131]

Interruption of trastuzumab is associated with a higher risk of cancer recurrence in women with early invasive HER2^{+ve} breast cancer; about 60% of interruptions are for cardiotoxicity.[132] An observational study showed that of 30 women receiving HER2-targeted therapies who developed an LVEF of 40–49% and were treated prospectively with beta-blockers and ACE inhibitors, only three went on to develop severe heart failure or a LVEF <35%.[133] Cardiac function rarely returned to normal after completion of treatment, challenging the view that trastuzumab-related LV dysfunction is usually reversible. A recent study reported high rates of CV events, especially heart failure, amongst patients with multiple myeloma receiving potent proteasome inhibitors, such as carfilzomib and bortezomib,[134] which were associated with much poorer survival. Risk factors for developing a CV event included elevated pre-treatment NT-proBNP or an increase during treatment. A systematic review of prophylactic use of renin–angiotensin–aldosterone antagonists and beta-blockers identified 22 relevant RCTs, of which the largest had only 206 patients,[135,136] but found no convincing evidence of clinical efficacy

Implementation of therapy

Analyses of administrative data from primary care in the UK suggest that implementation of therapy has improved substantially over the last decade, with 72% now prescribed a beta-blocker, although many patients remain on less than target doses.[6] Amongst hospital discharges in England and Wales, 89% of those with HFrEF were discharged on a beta-blocker (https://www.nicor.org.uk/wp-content/uploads/2019/09/Heart-Failure-2019-Report-final.pdf), which is very similar to that observed in patients with HFrEF selected for enrolment in the ESC-EURObservational Heart Failure Long-Term Registry.[137] However, an analysis of Medicare beneficiaries in the USA found that only 51% of patients with HFrEF were prescribed a beta-blocker after a first or recurrent hospitalization for heart failure and only 12% received at least ≥50% of the target dose by 1 year.[138] This suggests that the organization of care for HFrEF makes an important difference to treatment and, consequently, outcome. However, a cluster RCT ($n = 2494$) of service redesign aiming to improve hospital-to-home transition, which included self-care education, a structured hospital discharge summary, family physician follow-up within 1 week, and, for high-risk patients, home-visits, did not substantially improve patient well-being or outcome.[139] An RCT ($n = 110$) showed that frequent (several times per month) visits to participating community pharmacies could improve medication adherence and well-being.[140] An RCT of 450 patients found benefits of e-Health intervention on self-care behaviour and quality of life in the first 3 months after initiation but not thereafter,[141] with no effect on hospitalizations or mortality. There are many reasons why RCTs of complex interventions fail including inadequate power, suboptimal trial design, already excellent or unintended improvements in care for the control group, lack of long-term engagement and motivation of staff and patients, inclusion of patients for whom pharmacological intervention is largely ineffective (e.g. HFpEF) but sometimes we just have to admit that what should work does not. More evidence is required; learning from past experience.[142]

Rehabilitation

Systematic reviews suggest that exercise-based rehabilitation can improve patients' well-being and exercise capacity and reduce heart failure-related and all-cause hospitalization but may not reduce mortality, despite potentially improving adherence to treatment.[143–147] The best and most cost-effective service-model is a topic of active research.[148,149]

Palliative care

Morphine relieves chronic breathlessness in patients with chronic lung disease but data for heart failure are sparse. An RCT of 45 patients failed to demonstrate important clinical benefits of morphine administration to patients with HFrEF or HFpEF predominantly in NYHA functional class III.[150]

Withdrawing treatment for heart failure after recovery

Withdrawing treatment from patients with idiopathic or genetically determined dilated cardiomyopathy who have experienced full recovery of ventricular function should be done with great caution if at all.[151] Although patients with a recovered LVEF (HFrcEF) may have a better prognosis, it may still not be good.[152] Further research is required for peripartum and other specific types of cardiomyopathy. A recent report from an old trial (DIG), suggested that withdrawal of digoxin was associated with an increased risk of hospitalization for heart failure but did not affect mortality.[153] An RCT of 188 patients with stable heart failure from Brazil suggested that 75% of patients could be withdrawn from loop diuretics for at least 90 days without deterioration in symptoms, need for reinstitution of diuretic therapy, or a rise in plasma NT-proBNP.[154] This is in stark contrast to a smaller RCT from the UK, where withdrawal of diuretics and other therapies for 48 h led to a doubling of plasma concentrations of NT-proBNP, an increase in LV and left atrial volumes and worsening symptoms.[155]

Conclusion

Great progress in the understanding and management of heart failure has been made over the last year. New controversies and new evidence challenge many old assumptions. As ever, some will resist progress and others will embrace it. You, the reader, must help our professions and patients find the correct balance between reckless enthusiasm and diagnostic and therapeutic inertia.

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