The Year in Cardiology 2018: Heart Failure

John GF Cleland #

Dirk J van Veldhuisen @

Piotr Ponikowski ##

Robertson Centre for Biostatistics & Clinical Trials, University of Glasgow and National Heart & Lung Institute, Royal Brompton & Harefield Hospitals, Imperial College, London. UK.

@ Department of Cardiology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

Department of Heart Diseases, Wroclaw Medical University, Centre for Heart Diseases, Military Hospital, ul.Weigla 5, 50-981 Wroclaw, Poland,

Introduction

"Doctors pour drugs of which they know little, to cure diseases of which they know less, into patients of whom they know nothing." Jean-Baptiste Poquelin (aka Molière) 1622-1673.

This article summarises some of the research highlights on heart failure published in the previous year. Hopefully, it will show that Moliere's perception of doctors is no longer quite as true as it once may have been. A key emerging theme in the science and medicine of heart failure is the need to identify and target specific causes of heart failure, defined by phenotype or genotype, that will respond to a particular intervention (Central Illustration). QRS duration (a marker of cardiac dyssynchrony) (1, 2), mitral regurgitation (3, 4), iron deficiency (5, 6) and amyloidosis (7) each identifies groups of patients that will respond to a specific intervention. Just as for that other large cluster of malignant diseases called cancer, the 'war' on heart failure will be won one 'battle' at a time.

The outcome of many large clinical trials is determined neither by universal failure nor universal success but rather the proportions of patients that obtained benefit or harm compared to those for whom the intervention had little effect. For instance, the success of trials of beta-blockers may be because they did not enrol too many patients that respond poorly to these agents, including those with atrial fibrillation, a pacemaker or with a left ventricular ejection fraction (LVEF) >50% (8, 9). Had the trials been less selective they might have been neutral. Had they been more selective, the trials would have been smaller and shown an even larger benefit. Conversely, many interventions for heart failure with a preserved LVEF (≥50%; HFpEF) probably benefited some patients within this phenotype but not a large enough proportion to drive the overall result. We should take care that we do not reject effective treatments due to misunderstanding the results of trials that required a huge investment from patients, clinicians, academics, clinical research organisations and funders. Of course, a phenotype only really matters to a patient and a clinician when it informs management. This last year has seen an explosion of data on a variety of "therapeutic phenotypes" that matter.

Epidemiology

There is a paucity of contemporary data on the incidence and prevalence of heart failure, with few new useful sources of data. Conrad et al, using administrative data from both primary and secondary care health records of four million adults in England & Wales, provide some estimates and trends show that the age-adjusted incidence of heart failure is declining but the overall incidence and prevalence are increasing due to the growing proportion of the population aged >70 years (Figure 1) (10). More affluent regions had a lower age-adjusted incidence of heart failure, implying that we already have the means to modify risk. Most patients had three or more co-morbid conditions, most commonly hypertension, ischaemic heart disease and osteoarthritis but 25% also had cancer. The National Audit of Heart Failure in England & Wales is now probably the world's largest, with >500,000 individual patients now enrolled (11). This shows a steady increase in hospital admissions with a primary diagnosis of heart failure over the last decade. The median age at admission is 80 years, with men being on average 4 years younger than women. Most patients are not breathless at rest, at least when sitting upright, at the time of admission. For those aged <75 years, the in-patient mortality is about 5% and the three-year mortality of those surviving to discharge about 30%. For those aged >75 years, in-patient is 12% and 3-year mortality about 60%.

Overall, in-patient mortality appears to be much higher in the UK than in the USA. However, after correcting for risk profile, mortality appears similar suggesting a lower threshold for admission in the USA rather than better treatment (12, 13). The prognosis of patients admitted with heart failure in Japan is better than for either the UK or USA and is only partially explained by differences in risk profile or plasma concentrations of natriuretic peptides (14). Heart failure aetiology, phenotype, presentation and outcome varies by world region as shown by global registries (REPORT-HF: https://clinicaltrials.gov/ct2/show/NCT02595814) and a growing number of reports from sub-Saharan Africa, China and South-East Asia (15-18).

There is a growing interest in prevention of heart failure. Cohort studies show that the common risk factors are, predictably, the presence of cardiovascular disease and risk-factors, including age (19). There have already been notable therapeutic successes with thiazide-like diuretics and ACE inhibitors for older patients with hypertension (20) and, more recently and tentatively, sodium/glucose cotransporter-2 (SGLT2) inhibitors for Type-2 Diabetes Mellitus (T2DM) (21).

A key problem with epidemiological research in heart failure is the lack of criteria that are both sensitive and specific (22). Too often, sensitivity is sacrificed for specificity, which may lead to a

serious underestimate of the disease burden associated with heart failure not only epidemiologically but also as endpoints in clinical trials. For instance, for every admission due primarily to heart failure there are probably 3-4 admissions for other reasons that are complicated or prolonged by heart failure (23). These patients have a poorer prognosis than patients with a primary diagnosis of heart failure (24) but are no less in need of expert review; an opportunity that hospitalisation provides.

Diagnosis & Phenotypes

Personalised medicine is about delivering the right intervention, in the right "dose", to the right patient at the right time. This is what medical science, good clinicians, patients, carers and most health-care systems already strive to achieve and perhaps always have.

During the 20th Century, heart failure medicine adopted a one-treatment for all approach. However, just as oncologists now focus on precise mutations and molecular targets for treating cancers, heart failure specialists are now paying more attention to diverse phenotypes that may require very different treatments. The classification of heart failure with an LVEF of 40-49% as mid-range (HFmrEF) has stimulated re-analyses of landmark trials. The results suggest that treatments that are effective for patients with an LVEF <40% (HFrEF) are similarly effective for those with HFmrEF (40-49%) (8, 25, 26), leading some to suggest that HFrEF should be re-defined as an LVEF <50% (27). There are many other phenotypes that may influence choice of therapy for heart failure including valve disease, heart rhythm, QRS duration, aetiology of ventricular dysfunction and myocardial scar, to name but a few. New phenotypes, such as coronary microvascular dysfunction (28) or pulmonary hypertension (29-31), provide new potential therapeutic targets.

Phenotypic labelling can be misleading with serious consequences. Probably the most important example is acute heart failure. For many clinicians, this implies a requirement for emergency care for the treatment of severe breathlessness requiring oxygen and urgent intravenous diuretics. However, in clinical trials as few as 20% of patients enrolled were transferred to hospital by ambulance (32) and in clinical practice fewer than 50% of people admitted may be breathless at rest at the time of presentation (24, 33). Many patients labelled as acute heart failure present with gradually worsening symptoms over several weeks, signs of fluid overload, orthopnoea and exertional breathlessness but are not breathless at rest sitting up. A 48-hour intervention with an intravenous agent may be highly appropriate for a patient whom is acutely breathless but is unlikely to alter the 6-month outcome of patients admitted for peripheral oedema that has developed over a period of weeks. Patients with

peripheral rather than pulmonary oedema have less need of urgent care but a poorer long-term prognosis (33).

Progress is also being made on genetic contributions to the development of heart failure. Pathological variants in several genes, most notably titin, have been identified, which may directly cause a dilated cardiomyopathy or increase the heart's susceptibility to injury (34-36). No specific treatment for titin cardiomyopathy is currently available but many patients respond well to standard treatments for HFrEF and its effect on long-term outcome is uncertain. Specific treatments are available for some other genetic causes of heart failure (7, 37). Although a negative genetic test is reassuring for an individual and their children, the highly variable penetrance and uncertain value of intervening before the clinical onset of disease often render positive tests less satisfactory. There is growing interest in heart failure as a polygenic disease (38); whether this will provide useful additional insights into the causes and prevention of heart failure is uncertain but so-called Mendelian randomisation (perhaps more accurately termed Mendelian sorting) may identify new disease associations and therapeutic targets (39).

These traditional methods of classifying patients can now be complemented by phenomics using a vast range of biological signals obtained from bodily fluids or tissues, including the proteome, metabolome, transcriptome and inflammasome and their sub-domains (40). Systems biology and other new approaches to data-analysis are creating new hypotheses about causal associations and therapeutic targets that still, however, need to be tested and verified by conventional methods, such as randomised trials (40-42).

The increasing diversity of investigations and therapeutic targets makes heart failure more complex to manage but may also help tailor treatment more effectively for the individual patient and potentially reduce the therapeutic burden of unnecessary treatments. This may be facilitated by computer-based, decision-support tools that can help spread expertise in the management of heart failure and many other conditions.

Biomarkers & Monitoring

Trials investigating the utility of a biomarker guided approach to the management of heart failure have generally failed to demonstrate benefit; the GUIDE-IT trial, which was stopped for futility, was no exception (43). However, some would consider the lack of difference in achieved plasma concentration of NT-proBNP as evidence that the biomarker strategy has not been adequately

tested. Another biomarker of congestion, cancer antigen-125 (CA-125), has met with some success for guiding diuretic management of congestion but the results need to be replicated (44). A problem with the design of biomarker-guided strategy trials is that they selectively enrol patients who are at high risk of events and not already on optimal treatment, many of whom were unable to tolerate guideline-recommended therapy. Consequently, treatment often differed little between strategies. Indeed, once guideline-recommendations have been implemented in full, what more should be done? Is the biomarker just being used as a reminder to ensure that all guideline-recommended treatments have been considered and, if appropriate, implemented? If so, a mobile-app might be simpler, more effective and less expensive (45). Should guideline-recommended treatment be withheld if the biomarker is normalised? We have very little evidence to support this possibility (46).

The CHAMPION trial (n = 550) showed that daily monitoring of pulmonary artery pressures and treating to pre-specified targets (systolic 15-35 mmHg, diastolic 8-20 mmHg and mean 10-25 mmHg; modified if necessary for individual patients) reduced hospitalisation for heart failure (47, 48). A larger (n = 3,600) complex trial including both randomised and observational arms is now underway (GUIDE-HF; https://clinicaltrials.gov/ct2/show/NCT03387813) to confirm whether treating according to pulmonary artery pressure will reduce heart failure morbidity and all-cause mortality over the following 12 months for patients in functional NYHA Class II-IV and HFrEF with an NT-proBNP ≥1,000ng/L or HFmrEF/HFpEF with an NTproBNP ≥700ng/L (thresholds for NT-proBNP are not modified according to heart rhythm).

The reluctance of the cardiology community to adopt home telemonitoring despite the evidence of benefit is disappointing (49). A Cochrane Systematic Review demonstrated high patient acceptance, improved quality of life, reductions in heart failure hospitalisations and all-cause mortality (50). These findings were recently reinforced by the TIM-HF-2 trial, a randomised trial of 1,571 patients with predominantly NYHA Class II/III HFrEF or HFmrEF that showed reductions in mortality and hospital length of stay for heart failure (51-53). It is likely that telemonitoring will provide the foundation of good care for many chronic diseases once systematically implemented (54). A clear distinction between a policy of ‘health maintenance’ rather than ‘crisis management’, should improve both patient-experience and outcomes (55). Intelligent use of telemonitoring engages the patient as part of the healthcare workforce and should not be neglected (53).

Recovered Heart Failure (Figure 2) (295 words)

There is a growing evidence that left ventricular systolic dysfunction can resolve, either spontaneously or with treatment, especially beta-blockers and cardiac resynchronisation therapy) leading to remission of disease (56). This is most likely to occur in younger patients with dilated cardiomyopathy who do not have myocardial scar or QRS prolongation. There are some special circumstances where remission is sometimes permanent (ie:- resolved or cured) provided the cause of myocardial dysfunction is removed. This includes cardiomyopathy associated with pregnancy, persistent tachycardia, excess alcohol consumption or treatment with herceptin.

When the heart recovers, physicians often wonder, and patients often ask, whether they need to stay on treatment long-term. In the TRED-HF trial, 51 patients with recovered DCM were randomised to treatment withdrawal or continuation for 6 months (followed by attempted withdrawal of therapy for all patients thereafter) (57). A high proportion (40%) of patients relapsed after treatment withdrawal and a further 10% had to have treatment reinstated due to hypertension or atrial fibrillation. Treatment withdrawal was associated with an average increase in heart rate of 15bpm. Greater age, those on more treatment for heart failure, higher plasma NT-proBNP (median [interquartile range]: 72 [44-147]ng/L) and worse global longitudinal strain predicted a greater propensity to relapse but pathological variants in the titin gene did not. This small trial suggests that treatment should generally not be withdrawn after recovery of LV function. If the patient insists on treatment being withdrawn or the clinician decides to do so, the patients should be monitored carefully and indefinitely. Further research may identify better predictors of durable recovery or relapse, measured either at baseline or soon after treatment withdrawal, which may identify patients who can safely stop treatment. It is also possible that only some treatments, such as beta-blockers, might need to be continued.

Association between Heart Failure and Cancer (211 words)

Predicting, preventing and managing chemo- and radio-therapy related cardiac toxicity amongst cancer patients is becoming a specialty in its own right. Several reports also suggest that cancer may cause cardiac dysfunction and that the incidence and prevalence of cancer may be increased in heart failure (58, 59). These associations may reflect common environmental risk factors, such as age and smoking history, common genetic predisposition or that heart failure is itself oncogenic, possibly mediated through neuro-endocrine and cytokine pathways(60, 61). In a mouse-model, the induction of heart failure was associated with enhanced tumor growth, possibly related to heart-derived

proteins, the plasma concentrations of which are known to be elevated in humans with heart failure (62). However, an analysis of the US Physicians study, which included only men, found no association between the development of heart failure and cancer (63). Another possible link between cardiovascular disease and cancer is clonal haematpoeisis of indeterminate potential (CHIP) (64-66). Ageing is associated with the development of an increasing number of clones of haematopoetic cells, the development of some clonal lines increases inflammatory cytokines and the risk of developing atherosclerosis and also possibly heart failure (66, 67). People who develop multiple clones may not only be at greater risk of developing heart failure but also of leukaemia.

Palliative Care & Euthanasia

For many patients with recalcitrant heart failure complicated by other problems that preclude heart transplantation or implantation of left ventricular assist devices, palliative care may provide symptom relief, prevent hospitalisation and allow the patient the choice of place of death (68, 69) (70, 71). However, given the option, some, perhaps many, would choose euthanasia rather than face the indignity, loss of independence and social isolation caused by recalcitrant severe heart failure. This is already an option in parts of Europe and North America, where euthanasia is responsible for >5% of all deaths (72). Many patients and the public consider the "right to die" an important issue, which should not be ignored by those involved in managing severe heart failure.

Treatment of Heart Failure

Diet and Exercise (167 words)

For many decades, guidelines have suggested that patients should restrict their dietary sodium intake, but many clinicians and patients do not follow this advice. Systematic review demonstrates there is little evidence to support this recommendation(73). Salt restriction may aggravate hyponatraemia and renal dysfunction whilst diuretics may be more effective when dietary sodium is increased. It seems wise to educate patients to avoid excessive sodium intake, but the exact threshold is uncertain.

Guidelines generally recommend patients to take more exercise. Training improves exercise capacity, health-related quality of life (HRQoL) and symptoms (74) but there is little evidence that it improves cardiac function or rates of decompensation, hospitalisation or death (75, 76). Moreover, the evidence that frail elderly patients benefit, other than perhaps from the companionship that a rehabilitation class gives, is scant (77). If exercise had a marked effect on wellbeing, why do so many patients stop taking exercise once the training programme is over? Perhaps better methods of delivering rehabilitation at home may provide a solution (74).

Anti-thrombotic and Anti-inflammatory Therapies for Coronary Artery Disease

Many patients with HFrEF have coronary artery disease (CAD). Myocardial infarction, stunning and hibernation undoubtedly contribute to LV systolic dysfunction and therefore it is reasonable to think that interventions to protect the myocardium from ischaemia and to reduce coronary events should improve outcome. However, the evidence in support of this hypothesis is inconsistent. Beta-blockers certainly improve ventricular function and outcome for patients with CAD by restoring function to stunned or hibernating myocardium (78). Evidence for revascularisation of patients with CAD and HFrEF is conflicting (79-81). The benefits of revascularisation may be offset by the substantial peri-operative mortality associated with coronary artery bypass surgery (CABG) for patients with HFrEF (81). Percutaneous coronary intervention (PCI) might be associated with a lower peri-procedural mortality for patients with HFrEF but propensity-matched observational analyses have not shown that PCI reduces mortality overall compared to CABG (82). A randomised trial is investigating whether PCI, in addition to guideline-recommended pharmacological therapy, improves outcome for patients with HFrEF (82). The efficacy and safety of aspirin in patients with CAD and HFrEF is also in doubt although warfarin does reduce the risk of stroke; a relatively uncommon event in these trials (83, 84). Trials of statins have also been neutral, although post-hoc analyses suggests that patients with symptomatically milder heart failure might benefit (85).

The COMPASS trial enrolled patients with stable atherosclerotic vascular disease, excluding those with a known LVEF <30% or in NYHA class III/IV. Compared to aspirin alone, rivaroxaban 2.5mg bd with aspirin 100mg/day reduced the primary composite of myocardial infarction, stroke or cardiovascular mortality, largely driven by reductions in stroke and mortality (86). This did not translate into a reduction in hospitalisations for heart failure. However, compared to patients without heart failure, those with heart failure (n = 5,902), predominantly HFmrEF/HFpEF, had a greater benefit and were also at lower risk of bleeding with combination therapy, perhaps reflecting greater activation of pro-thrombotic pathways (87). The COMPASS trial suggests that patients with stable CAD with mild-to-moderate symptoms of heart failure benefit from treatment with rivaroxaban; custom dictates that this will usually be in addition to low-dose aspirin (88). In COMPASS, rivaroxaban 5mg bd alone was neither clearly superior to aspirin alone nor clearly inferior to the combination but was associated with a slightly higher rate of intra-cranial bleeding. Data on rivaroxaban alone in the subset of patients with heart failure has not been presented. The efficacy and safety of rivaroxaban 2.5mg bd as a sole anti-thrombotic agent is unclear.

The ATLAS-ACS trial suggested that, compared to placebo, adding low-dose rivaroxaban to dual antiplatelet therapy in patients with an acute coronary syndrome reduced mortality with a greater effect amongst those with heart failure (89). This trial stimulated the design of COMMANDER-HF, which enrolled patients with HFrEF, CAD and in sinus rhythm who had recently been discharged after a hospitalisation for heart failure. Patients were randomised to rivaroxaban 2.5mg bd or placebo in addition to background anti-platelet therapy. The trial was neutral for its composite primary endpoint of myocardial infarction, stroke and all-cause mortality, nor did it reduce worsening fatal or non-fatal heart failure events. However, in a post-hoc analysis, it appeared that rivaroxaban did reduce a composite of potential thrombotic events, including stroke, myocardial infarction and sudden death. This suggests that rivaroxaban may retain efficacy throughout the spectrum of severity of heart failure but, when the heart failure is sufficiently severe, the benefit is swamped by heart failure events driven by myocardial dysfunction rather than any anti-thrombotic or anti-inflammatory effect rivaroxaban might have.

In the CANTOS trial, inhibition of interleukin-1β by canakinumab, in patients with a prior myocardial infarction (including 21.6% of patients with a history of heart failure) reduced markers of inflammation such as high-sensitivity C-reactive protein and interleukin-6 and at higher doses this led to a reduction in the primary composite outcome of myocardial infarction, stroke or cardiovascular death (90-92) and, in a substudy on just 15 patients,possible improvements in exercise capacity and ventricular function (93) . Subsequent analyses suggested an extraordinarily low rate of hospitalisation for heart failure regardless of randomised group but with some evidence that it was even lower for patients assigned to canakinumab after some years of treatment (94). Whilst the very low rate of events questions the validity of the analysis, it does provide some evidence to support a role for inflammation in the progression of heart failure. In the CORONA trial, rosuvastatin was associated with a similar reduction in hsCRP (from 5.5 to 3.8mg/L; $p<0.0001$) as canakinumab (4.15 to 1.80mg/L; $p<0.001$) in patients with an elevated baseline hsCRP but had no clear benefit overall in patients with coronary disease and HFrEF (90, 95-97). Whether these differences reflect the play of chance or differences in the intervention or the trial populations is uncertain.

Better Diuretics?

Diuretics are one of the most valuable and least researched class of agents for heart failure. A recent cohort study suggested that intensification of loop diuretic dose may be a better strategy than using a combination of thiazide and loop diuretics albeit in a patients who probably had low rates of

treatment with mineralo-corticoid receptor antagonists (98). Whether furosemide or torasemide is the better diuretic agent is the question posed in the TRANSFORM-HF trial [https://clinicaltrials.gov/ct2/show/NCT03296813].

In patients with T2DM, SGLT2 inhibitors cause a rapid but modest reduction in weight, haemoconcentration and reduce blood pressure, consistent with a diuretic effect that could improve congestion regardless of LV phenotype (21, 99). Others believe that SGLT-2 inhibitors cause blood ketones to rise and that these may be a superior myocardial energy substrate leading to improved cardiac function (100-102). Three large clinical trials conducted in patients with T2DM, mostly without heart failure and excluding those with a known LVEF <30%, have shown reductions in hospitalisations for heart failure and improvements in renal function but only one showed a reduction in mortality (21) and none showed a reduction in myocardial infarction, a potential cause of new-onset or worsening heart failure (21). The effect of on heart failure hospitalisation although substantial in relative terms is very modest when considered in terms of absolute rate. For instance in EMPA-REG the rate declined from 1.45% to 0.94% per year; an absolute reduction of about one event for every 200 patient-years of follow-up. Several large trials of SGLT2 inhibitors (EMPEROR-Reduced and Preserved, DAPA-HF, DELIVER and SOLOIST) enrolling patients with HFmrEF/HFpEF and HFrEF with and without T2DM are underway. The effects of SGLT2 inhibitors on heart failure events contrasts with the lack of effect or harm caused by agents from most other classes (103, 104) with perhaps the exception of metformin, which is also the subject of a substantial trial in patients with heart failure [DANHEART: https://clinicaltrials.gov/ct2/show/NCT03514108]

Iron

Iron deficiency is associated with more severe cardiac dysfunction, worse symptoms and poorer exercise capacity regardless of LV phenotype. Several medium-size randomized trials have shown the benefits of intravenous ferric carboxymaltose on symptoms and exercise capacity for patients with HFrEF and iron deficiency (5, 6, 105). However, these trials are too small to provide robust evidence for a reduction in morbidity and mortality or for safety. Three larger outcome trials in chronic HFrEF are well underway and have, combined, already enrolled more patients than in all of the previous randomised trials. (https://clinicaltrials.gov/ct2/show/NCT03036462; https://clinicaltrials.gov/ct2/show/NCT02642562; https://clinicaltrials.gov/ct2/show/NCT03037931). In addition , substantial trials in acute HFrEF/HFmrEF (https://clinicaltrials.gov/ct2/show/NCT02937454) and HFpEF (https://clinicaltrials.gov/ct2/show/NCT03074591) have been initiated. One small trial that enrolled patients in whom the evidence of iron deficiency was questionable, suggested that oral iron may be less

effective than intravenous iron (106). Although there is no doubt that intravenous iron will replete iron stores more quickly, there is no proof that oral iron is ineffective when given for longer or for the prevention (of recurrent) of iron deficiency.

What Else is in the Pharmacological Pipeline?

Phase II trials of a cardiac myosin activator, Omecamtiv Mecarbil, showed promise for patients with HFrEF (107); a large Phase III trial should report in 2020. (https://clinicaltrials.gov/ct2/show/NCT02929329). Although the results of Phase II trials of vericiguat, a soluble guanylate cyclase stimulator, were equivocal (108-110), a Phase III trial in HFrEF (https://clinicaltrials.gov/ct2/show/NCT02861534) and a smaller trial of HFpEF (https://clinicaltrials.gov/ct2/show/NCT03547583) are underway.

Valve Disease (Figure 3)

Valve disease is the primary or important contributory cause of many cases of heart failure. In Europe and North America, the most common primary valve problems are calcific aortic stenosis or degenerative mitral regurgitation. Patients with valve disease often do well until they develop heart failure but the combination is deadly. Functional mitral and tricuspid regurgitation are also common in patients with heart failure, causing additional volume loading and an increase in atrial pressures leading to pulmonary hypertension, an increased risk of atrial fibrillation and worsening symptoms and signs. Functional mitral and tricuspid regurgitation are key mechanisms underlying the development and progression of bi-ventricular failure (3, 111).

The risks of conventional surgery for aortic stenosis and mitral regurgitation are substantial for patients with heart failure and therefore many patients are not referred. The advent of transcutaneous approaches for both degenerative aortic and mitral disease is transforming clinical practice, provided there is access to skilled operators and adequate finance (3, 4, 112). For functional mitral regurgitation associated with HFrEF, recent trials of a percutaneous device (MitraClip) designed to reduce mitral regurgitation appear to provide conflicting results. One, conducted in France (MITRA.fr), enrolled 304 patients but demonstrated no benefit on symptoms, morbidity or mortality after one year (4). Another, conducted in North America (COAPT), enrolled 614 patients and demonstrated substantial improvements in symptoms and reductions in both hospitalisation for heart failure and all-cause mortality (3). Mortality at one year was similar in the control group of each study (22% in MITRA.fr and 23% in COAPT); the difference between trials was due to a lower mortality for those assigned to the MitraClip intervention in COAPT. Both trials showed that the device reduced regurgitant volume although the reduction was greater in COAPT.

The patients and their management appeared similar in most respects, but those in COAPT may have had more severe mitral regurgitation and less severe left ventricular dilatation. This ratio may be of key importance; correcting functional mitral regurgitation may only help when it is disproportionate to the severity of left ventricular dysfunction. The clinical and academic community should be cautious about over-interpreting these trials as there is at least one substantial trial still underway [https://clinicaltrials.gov/ct2/show/NCT02444338]. However, these data do suggest that carefully selected patients with severe functional mitral regurgitation should be considered for the MitraClip device. A trial of a mitral annuloplasty device (REDUCE-FMR; n = 163) has also been reported, showing promising results, albeit with a relatively high rate of severe implant-related complications (2% mortality and 3.5% myocardial infarction) [https://clinicaltrials.gov/ct2/show/NCT02325830].

In the meantime, the effect of cardiac resynchronisation (CRT) and pharmacological therapy on functional mitral regurgitation should not be forgotten (113).

Atrial Fibrillation (Figure 4)

Atrial fibrillation has a large impact on the efficacy and choice of therapy. Patients with heart failure and atrial fibrillation, regardless of ventricular phenotype, should generally receive an anticoagulant; guidelines generally recommend a direct-acting agent rather than warfarin (114). An individual patient-data meta-analysis suggests that beta-blockers improve ventricular function for patients with HFrEF/HFmrEF and are safe but do not improve outcome and are of no benefit when LVEF is $\geq$50% (8). In contrast to patients in sinus rhythm, reduction in ventricular rate below a range of 70-90bpm at rest may be harmful for patients in atrial fibrillation. For patients with atrial fibrillation, ivabradine is not thought to be effective and there is little evidence to support CRT (115-117).

The debate on whether rate or rhythm control is the better strategy for managing atrial fibrillation complicating heart failure continues. Anticoagulants should be continued even if sinus rhythm is restored, at least until atrial contraction is both restored and maintained for a protracted period. An optimal rate-control strategy must avoid excessive heart rate reduction as well as toxic anti-arrhythmic agents, potentially including digoxin and amiodarone (9). A modest dose of beta-blocker may be the safest option for rate-control in patients with atrial fibrillation, even if beta-blockers do not appear to improve outcome when titrated to conventional target doses (9). A rate control strategy for persistent atrial fibrillation avoids the need for procedures and potentially toxic drugs and the problems that relapse into atrial fibrillation cause (118). For those with paroxysmal atrial fibrillation and heart failure there is a stronger rationale for a rhythm control strategy, either

pulmonary vein ablation or His-bundle ablation followed by CRT. The CASTLE-HF trial assessed 3,103 patients in 33 centres over a period of 8 years for a trial comparing pharmacological rate or rhythm control with pulmonary vein ablation (119). Finally, 363 patients with atrial fibrillation, heart failure, an LVEF $\leq$35% and an ICD or CRT-D device were randomised. Neither patients nor investigators were blind to assigned management strategy and 33 patients were lost to follow-up. The trial was positive for its primary composite endpoint of death from any cause or hospitalization for worsening heart failure. After 3-years of follow-up, at which time there were slightly less than 100 patients in each group, a difference in mortality began to appear, which became statistically significant (24 deaths with ablation versus 46 deaths in the control group). Another large trial of atrial fibrillation in a broad range of patients most of whom did not have heart failure (CABANA (120)) has been presented but not yet published; it was neutral [https://clinicaltrials.gov/ct2/show/NCT00911508]. A meta-analysis of older trials reported 18 deaths amongst patients assigned to control compared to 9 assigned to ablation (121). The data suggesting that a rhythm control strategy might be superior is not robust, the trials were not blinded and the population in the trials was highly selected. Further trials are required.

Therapy of Heart Failure with a Left Ventricular Ejection Fraction >40% (HFmrEF / HFpEF) (1,209 words)

There is much speculation about the pathophysiology of HFpEF generated by research on animal models and patient-cohorts (101, 122). Well-designed randomised trials of therapeutic interventions targeting specific mechanisms can provide important evidence of the validity and therapeutic importance of hypotheses generated by observational research.

So far, trials of HFpEF have met with little success in convincingly improving symptoms, functional capacity, morbidity or mortality (123). This may be due to a lack of efficacy of the agents studied so far or problems with trial concept and design. A major problem with older trials of HFpEF was the lack of robust diagnostic criteria for HFpEF, which probably allowed many people who did not have heart failure to be enrolled. Diagnostic uncertainty also forced the exclusion of co-morbid conditions that could cause symptoms and signs of heart failure (such as lung and renal disease) that are also important drivers of adverse outcomes. This led to trials with much lower than anticipated event rates. When plasma concentrations of natriuretic peptides are not elevated, either the patient does not have heart failure or they have responded well to treatment and have a good prognosis. Such patients are unlikely to benefit from a new intervention for heart failure but may still be prone to side effects. Requiring a combination of physician diagnosis of heart failure, treatment with diuretics

for the treatment of congestion, elevated plasma concentrations of natriuretic peptides and a dilated left atrium provides robust evidence of HFpEF, which then allows higher-risk patients with co-morbid conditions to be enrolled. However, markedly elevated plasma concentrations of natriuretic peptides may indicate greater risk but might also indicate a poorer response to treatment. The concept of a therapeutic sweet-spot, focussing on patients who are neither too well nor too sick to respond to a particular intervention, appears valid for many phenotypes of and interventions for heart failure (124). A trial of irbesartan in HFmrEF/HFpEF (I-PRESERVE) showed a progressive increase in morbidity and mortality with increasing plasma concentrations of NT-proBNP. Irbesartan did not improve prognosis overall but appeared to do so amongst lower-risk patients with below median NT-proBNP (339ng/L) (125). Similarly, in TOPCAT, higher NT-proBNP was associated with a worse prognosis but the treatment benefit was greatest in the lowest-risk tertile (<682ng/L) (126).

Hypertension is a key determinant of the development of HFpEF. A combination of ACE inhibitors and thiazide-like diuretics reduces the incidence of heart failure in older people with hypertension in the HYVET trial, patients at high risk of HFpEF who also have very similar rates of myocardial infarction stroke and death to patients labelled as HFpEF (127). Although patients in HYVET had lower rates of hospitalisation for heart failure than in I-PRESERVE, given the lack of difference in mortality rates, this may reflect reporting-bias rather than a real difference (128). Sacubitril-valsartan, an agent that also reduces blood pressure, improved cardiac function and symptoms (129) and is now the subject of a large, well-designed Phase III trial (PARAGON) (130). The PARAGON trial will be the first to analyse prospectively whether an intervention is similarly effective for both HFpEF and HFmrEF. If PARAGON is as positive as PARADIGM (131), sacubitril-valsartan will be the first agent shown to improve outcomes regardless of left ventricular phenotype.

Congestion is a potential therapeutic target for all heart failure phenotypes. Re-analysis of the TOPCAT trial suggested that spironolactone, an agent that also causes a natriuresis as well as lowering blood pressure, reduced morbidity and mortality for patients with HFmrEF (25). Further trials of MRA in HFmrEF/HFpEF are underway to confirm or refute these observations [https://clinicaltrials.gov/ct2/show/NCT02901184]. Trials of SGLT2 inhibitors will further test the hypothesis that lowering blood pressure and better control of congestion improves outcomes for HFpEF (see above).

Trials of nitrates and nitrites in HFpEF have been neutral (132, 133). This may not augur well for trials of soluble guanylate cyclase inhibitors in HFpEF. The EDIFY trial failed to demonstrate that heart rate reduction with an I_f channel inhibitor improved outcome (134). Nor did beta-blockers improve outcome for patients with HFpEF in an individual patient-data meta-analysis of landmark trials in heart failure, although patients with HFmrEF did appear to benefit provided they were in sinus rhythm (8).

A pathognomonic feature of HFpEF is the exaggerated increase in left atrial pressure with exercise, as also occurs with mitral stenosis. In Lutembacher's syndrome, an atrial septal defect associated with mitral stenosis, the symptoms of mitral stenosis are delayed and/or less prominent due to off-loading of left atrial pressure into the right atrium. An inter-atrial septal device (IASD) has been developed to create a moderate-sized ASD to attenuate the rise in left atrial pressure during exercise but avoid a substantial left to right shunt that might provoke pulmonary hypertension and right ventricular failure (135). The REDUCE-LAP-HF-1 trial randomly assigned 44 patients with an LVEF >40% (median 60%) to have an IASD implanted or a sham procedure. Patients were blind to assigned group. At one-month, atrial pressures were lower during exercise in those assigned to the IASD (136). At one year, shunts were patent but there were too few events to provide evidence of safety or efficacy but the trends were sufficiently favourable to justify initiating a Phase III trial investigating the effect of treatment on morbidity and mortality (137).

Obesity exacerbates the symptoms of heart failure and might also contribute to disease development and progression, especially for HFpEF (138, 139). Although a causal role for obesity in the development of HFpEF in not yet clear, the association with inflammation may be important (140). Visceral (including epicardial) and perivascular fat is increased in patients with HFpEF and may be a source of inflammatory cytokines in close proximity to the myocardium and coronary arteries, which could be important in the pathophysiology of HFpEF (141-143).

The greatest therapeutic success for HFpEF in 2018 was for transthyretin (TTR) amyloidosis (144). Observational studies of HFpEF and of elderly patients with calcific aortic stenosis suggest that 15-20% have cardiac uptake of radiolabelled agents conventionally used for bone scans suggesting cardiac TTR rather than amyloid light-chain (AL) amyloidosis (145-147). The ATTR-ACT trial enrolled 441 patients with hereditary or acquired TTR amyloidosis and randomly assigned them to placebo or tafamadis, a selective TTR stabilizer that prevents further amyloid production (7). Over the next 30 months, patients assigned to tafamadis had a substantially slower rate of deterioration in quality of

life and 6-minute walk distance and fewer cardiovascular hospitalisations and deaths. Tafamadis was similarly effective for acquired and hereditary TTR amyloidosis even though patients with the acquired form are generally 10-15 years older than those with hereditary disease. Patients with milder disease obtained greater benefit, suggesting that screening and early treatment of asymptomatic cases is warranted. Although tafamadis is highly effective, it is unlikely to gain widespread use until its cost is reduced. Two injectable agents that interfere with the hepatic production of TTR, inotersen (148) and patisiran (149) have been developed for treating hereditary TTR amyloidosis but might also be effective for the acquired form. In trials, both agents retarded the progression of neurological problems and patisiran retarded progression of cardiac dysfunction but there were too few deaths to evaluate effects on mortality. Whether greater benefit and/or reversal of established disease can be obtained by combining these agents with tafamadis is uncertain.

Therapy of Heart Failure with Reduced Left Ventricular Ejection Fraction (HFrEF)

Sacubitril-Valsartan

The PARADIGM-HF trial compared the effects of the angiotensin receptor neprilysin inhibitor (ARNI), sacubitril-valsartan, to enalapril in 8,442 patients with stable and predominantly mild symptoms of heart failure (20% of whom did not even require treatment with diuretics) who had tolerated target doses of both agents (150). Patients assigned to sacubitril-valsartan fared better than those assigned to enalapril in terms of symptoms, quality of life, hospitalisations and mortality. Although these differences were highly statistically significant and substantial, the results were treated with caution because it was a single trial with little other supporting data and the selection criteria were designed to address regulatory concerns rather than reflect clinical practice. The PIONEER-HF trial was designed to address some of these concerns, in particular the safety of pre-discharge initiation of sacubitril-valsartan in patients recovering from an episode of decompensated heart failure (151). The 881 patients enrolled were relatively young (median age 62 years), 36% were African-Americans and 34% had new-onset heart failure, which accounted, in-part, for the low use of disease-modifying therapies at baseline. Plasma concentrations of NT-proBNP were grossly elevated (median [IQR] 4812 [3050 to 8745] ng/L). Most patients received loop diuretics prior to randomisation but only 10% of patients received an MRA. Treatment at discharge was not reported. The primary endpoint was the decline in plasma concentrations of NT-proBNP with sacubitril-valsartan compared to enalapril after 8 weeks of treatment and this was met. Patients assigned to sacubitril-valsartan also had a greater fall in troponin and reductions in serious clinical events, predominantly hospitalisation

for heart failure. PIONEER-HF suggests that it is safe to initiate sacubitril-valsartan in the recovery phase of decompensated heart failure. However, by 8 weeks about 20% of patients had discontinued each agent. Only 55% were receiving the target dose of sacubitril-valsartan and 61% the target dose of enalapril. More research is required to understand why even those patients who volunteer to participate in trials don't persist with treatments that otherwise appear to approve symptoms and outcomes and whether this is similar, worse or better than in clinical practice

Levosimendan (136 words)

The management of advanced heart failure when mechanical circulatory support or heart transplantation is inappropriate or unavailable remains a major challenge. Levosimendan is a vasodilator and inotropic agent that is available in some countries but has not substantially improved outcomes compared either to placebo or dobutamine in the setting of acute heart failure (152, 153) or after cardiac surgery (154-156). For patients with advanced but relatively stable chronic heart failure the trial evidence is less certain, although a substantial trial of an oral form did not improve outcome (157). In the LIONHEART trial, repetitive dosing with levosimendan over 12 weeks for 69 patients with severe HFrEF reduced plasma concentrations of NT-proBNP, worsening of health-related quality of life and hospitalisation for heart failure (158). A meta-analysis including 319 patients supports the argument for a larger trial (159).

Cell-Based Therapies (123 words)

Cardiac stem-cell research has long been tainted by exaggerated claims, leading to growing scepticism amongst cardiologists about this approach (160). The NIH funded CONCERT-HF trial, investigating a combination of mesenchymal and c-Kit+ cardiac stem cells (https://clinicaltrials.gov/ct2/show/NCT02501811), was recently suspended due to concerns about possible falsification of the data on which its scientific rationale was based. The results of substantial trials of stem-cells in post-infarction ventricular dysfunction are awaited, such as REPEAT (https://clinicaltrials.gov/ct2/show/record/NCT01693042; n = 676; minimum two-year follow-up; report due 2022) and BAMI (https://clinicaltrials.gov/ct2/show/record/NCT01693042; n = 350; report due 2019). More recently, the realisation that many cell types, including cardiomyocytes, shed particles containing highly organised information, called exosomes, that can home-in on similar cells and perhaps promote repair offers a new approach (161).

Devices & Transplantation (700 words)

Trials of vagal stimulation were neutral, perhaps because of inadequate vagal stimulation (162, 163). Trials of cardiac contractility modulation did not provide sufficiently convincing results to obtain a guideline-recommendation but a new trial of 160 patients with NYHA Class III/IV heart failure, an LVEF of 25-45% and QRS duration <130msec suggested improvement in symptoms, quality of life and peak oxygen uptake during exercise as well as a reduction in hospitalisations for heart failure over 24 weeks (164, 165). Unfortunately, the trial was not blinded, which may create bias. BeAT-HF, an open-label randomised trial of baroreceptor stimulator implanted (or not). Recruitment was stopped afetr an interim analysis indicated that a reduction in morbidity or mortality was unlikely although functional capacity and quality of life may have improved; follow-up of enrolled patients continues [https://clinicaltrials.gov/ct2/show/NCT02627196]. Research into phrenic nerve pacing to improve sleep apnoea (166) and diaphragmatic pacing to improve cardiac function shows some promise (167).

The role of implantable cardioverter defibrillators for the management of heart failure remains problematic. Rates of sudden death in trials of heart failure are declining (168). The benefits of adding a defibrillator function to CRT are uncertain, especially for older patients and those without CAD (169, 170). Few patients with heart failure aged >70 years or with LVEF >30% have been randomised in trials of ICD (171). It appears that ICDs are most effective for younger patients with mild symptoms who, nonetheless, have severe LV dysfunction and/or myocardial scar (172, 173). The benefits of ICDs need to be reassessed in the light of the progress in the management of heart failure and the demographic change in the population being treated. For patients with recurrent ventricular tachycardia, ablation [invasive (174) or non-invasive (175)] may reduce the rate of painful ICD interventions although this does not seem to lead to a substantial improvement in quality of life (176). Most ICD interventions that are either inappropriate (ie:- not for ventricular tachycardia) or unnecessary (ie:- for non-sustained, self-terminating ventricular tachycardia) can be prevented by conservative device programming (177).

New, “intelligent” algorithms and technologies may improve on standard CRT programming (178-180). There has been a great deal of speculation about why women appear to obtain greater benefit from CRT. An individual patient-data meta-analysis shows that shorter people obtain greater benefit from CRT which explains the apparent difference in effect between sexes (1). Shorter people, when healthy, may have intrinsically narrower QRS complexes. Perhaps correcting QRS duration for height may be appropriate when selecting patients for CRT. A prolonged PR interval may predict a better response to CRT (181) perhaps because this allows greater shortening of atrio-ventricular delay

leading to increased left ventricular pre-load and improved contractility through the Frank-Starling mechanism (182). The importance of synchronous atrial contraction may explain the paucity of evidence that CRT is effective for patients with HFrEF who have atrial fibrillation. Brignole et al showed that bi-ventricular pacing was superior to right ventricular pacing after His-bundle ablation for patients with atrial fibrillation but this outcome may reflect a deleterious effect of right ventricular pacing rather than benefit from bi-ventricular pacing (116). A further trial randomised 102 patients with a narrow QRS complex to ablation and bi-ventricular pacing or pharmacological treatment (115). Twenty patients assigned to pharmacological treatment and 10 assigned to ablation and pacing had a heart failure event (heart failure related death, hospitalisation or worsening) which was statistically significant; quality of life also improved in the ablate and pace group (115). New algorithms may help deliver bi-ventricular pacing more effectively in patients with atrial fibrillation (183). However, CRT is more than just bi-ventricular pacing. Coordinated atrial function may be responsible for much of its benefit, in which case restoration of electrical and mechanical sinus rhythm might be essential (117, 182). The ESC CRT-II survey shows that large variations in clinical practice exist in countries belonging to the European Society of Cardiology (184).

Trials of left ventricular assist devices show that safety and outcomes continue to improve with reductions in drive-line infections and thrombosis (185) (Figure 5). Hopefully, the next great breakthrough will be completely implantable systems with an extended, safe power supply. Meanwhile, the development of deceased-donor programmes is breathing new life into heart transplant programmes (186).

Conclusion

There has been remarkable progress in the science of medicine of heart failure during 2018. The greatest successes have come from trials focussing on specific mechanisms and phenotypes, including atrial fibrillation, mitral regurgitation and TTR amyloidosis. So-called, precision medicine is perhaps a misnomer, since care should be accurate and not just precise. Accurate medicine may make therapeutic decisions more complex for clinicians but increase the therapeutic response and reduce the therapeutic burden on patients. Computer technologies are becoming ever more important for both health professionals and patients, offering therapeutic choices, helping make management decisions, ensuring that things are not forgotten, monitoring the health of patients and the performance of clinicians and, throughout this process, analysing practice, learning and teaching. Computer-assisted care will help ensure that the right patient, receives the right intervention at the

right dose at the right time and as such, may become the greatest health-care revolution so far. We have no doubt that 2019 will bring equally exciting news.

Legends to Figures

Central Illustration

Heart failure, classified by 'therapeutic' phenotypes (highlighted in blue) with their relevant treatment (highlighted in purple) and most recent or relevant randomised trial (highlighted in red).

Figure 1

Title: Changing Prevalence of Heart Failure in the United Kingdom

Change in the prevalence of heart failure between 2002 and 2014 obtained from a primary-care population of 4 million people aged >16 years in the United Kingdom and extrapolated to the whole population (approximately 66 million). The increase in prevalence is largely explained by ageing population demographics but changes in rates of diagnosis and greater longevity with heart failure may also contribute.

[Adapted from Supplementary Figure 1; reference 11].

Figure 2

Title: Withdrawal of Medication from Recovered Dilated Cardiomyopathy (TRED-HF)

Effect of withdrawing medications from patients with recovered dilated cardiomyopathy. Of 50 patients who attempted withdrawal of therapy (see flow-diagram), 20 relapsed within 6 months and a further four required re-initiation of therapy for hypertension or recurrent atrial fibrillation. Older age, use of mineralo-corticoid antagonists or ≥3 heart failure medications, higher NT-proBNP concentrations and decreased global radial strain were associated with a higher rate of relapse. (TRED-HF: **T**herapy withdrawal in **Re**covered **D**CM and Heart Failure)

[Adapted from reference 43]

Figure 3

Title: MITRA.fr and COAPT Trials for Functional Mitral Regurgitation

Outcome of two randomised trials of the MitraClip device for the treatment of functional mitral regurgitation. CV = cardiovascular. HF Hosp. = heart failure hospitalisation. LV = left ventricular. MR = mitral regurgitation

MITRA-FR: Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation
COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation

[Adapted from references 3 and 4]

Figure 4

Title: CASTLE-AF Trial of pulmonary vein ablation for atrial fibrillation in patients with heart failure

Effect of pulmonary vein ablation for atrial fibrillation in patients with a left ventricular ejection fraction ≤35% and either an implanted defibrillator (72%) or cardiac resynchronisation therapy (28%) device. Note that there was less than 100 patients per group followed for three or more years (only after which the survival curves really begin to separate) and that 33 patients were lost to follow-up and that 37 further patients were excluded after randomisation (although prior to baseline evaluation). Of 179 patients assigned to ablation, 28 did not have the procedure.

CASTLE-AF: Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation

[Adapted from reference 94].

Figure 5

Title:- Tafamdis for Transthyretin Amyloid Cardiomyopathy (ATTR-ACT)

Results of the ATTR-ACT trial of tafamadis for patients with heart failure due to transthyretin amyloid cardiomyopathy.

ATTR-ACT: The Transthyretin Amyloidosis Cardiomyopathy Clinical Trial
[Adapted from references 7 and 118].

Figure 6

Title:- MOMENTUM-3: A Trial of Centrifugal compared to Axial Flow Left Ventricular Assist Devices

The primary endpoint of MOMENTUM-3 comparing centrifugal with axial flow left ventricular assist devices was survival free of disabling stroke or surgery to repair or replace the device. Benefits in terms of improved symptoms, quality of life and exercise capacity were similar for each device.

MOMENTUM-2: Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3

[Adapted from Figure 1 and supplementary Figure 7 of reference 142].

Reference List

1. Linde C, Cleland JGF, Gold MR, Claude DJ, Tang ASL, Young JB, Sherfesee L, Abraham WT. The interaction of sex, height, and QRS duration on the effects of cardiac resynchronization therapy on morbidity and mortality: an individual-patient data meta-analysis. *Eur J Heart Fail* 2018;**20**(4):780-791.

2. Cleland JG, Abraham WT, Linde C, Gold MR, Young JB, Claude DJ, Sherfesee L, Wells GA, Tang AS. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. *Eur Heart J* 2013;**34**(46):3547-3556.

3. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopal V, Sarembock IJ, Brieke A, Marx SO, Cohen DJ, Weissman NJ, Mack MJ. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. *N ENGL J MED* 2018.

4. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, Lefevre T, Piot C, Rouleau F, Carrie D, Nejjari M, Ohlmann P, Leclercq F, Saint EC, Teiger E, Leroux L, Karam N, Michel N, Gilard M, Donal E, Trochu JN, Cormier B, Armoiry X, Boutitie F, Maucort-Boulch D, Barnel C, Samson G, Guerin P, Vahanian A, Mewton N. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. *N ENGL J MED* 2018.

5. Van Veldhuisen DJ, Ponikowski P, van der Meer P, Metra M, Bohm M, Doletsky A, Voors AA, Macdougall IC, Anker SD, Roubert B, Zakin L, Cohen-Solal A. Effect of Ferric Carboxymaltose on Exercise Capacity in Patients with Chronic Heart Failure and Iron Deficiency. *Circulation* 2017.

6. Cleland JG, Zhang J, Pellicori P, Dicken B, Dierckx R, Shoaib A, Wong K, Rigby A, Goode K, Clark AL. Prevalence and Outcomes of Anemia and Hematinic Deficiencies in Patients With Chronic Heart Failure. *JAMA Cardiol* 2016;**1**(5):539-547.

7. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. *N ENGL J MED* 2018;**379**(11):1007-1016.

8. Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, Manzano L, McMurray JJV, Ruschitzka F, Van Veldhuisen DJ, von Lueder TG, Bohm M, Andersson B, Kjekshus J, Packer M, Rigby AS, Rosano G, Wedel H, Hjalmarson A, Wikstrand J, Kotecha D. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J* 2018;**39**(1):26-35.

9. Kotecha D, Flather MD, Altman DG, Holmes J, Rosano G, Wikstrand J, Packer M, Coats AJS, Manzano L, Bohm M, Van Veldhuisen DJ, Andersson B, Wedel H, von Lueder TG, Rigby AS, Hjalmarson A, Kjekshus J, Cleland JGF. Heart Rate and Rhythm and the Benefit of Beta-Blockers in Patients With Heart Failure. *J Am Coll Cardiol* 2017;**69**(24):2885-2896.

10. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, Allison M, Hemingway H, Cleland JG, McMurray JJV, Rahimi K. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet* 2018;**391**(10120):572-580.

11. National Heart Failure Audit. April 2015 - March 2016.http://www.ucl.ac.uk/nicor/audits/heartfailure/documents/annualreports/annual-report-2015-6-v8.pdf: 2017.

12. Nagai T, Sundaram V, Rothnie K, Quint JK, Shoaib A, Shiraishi Y, Kohsaka S, Piper S, McDonagh TA, Hardman SMC, Goda A, Mizuno A, Kohno T, Rigby AS, Yoshikawa T, Clark AL, Anzai T, Cleland JGF. Mortality after admission for heart failure in the UK compared with Japan. *Open Heart* 2018;**5**(2):e000811.

13. Nagai T, Sundaram V, Shoaib A, Shiraishi Y, Kohsaka S, Rothnie KJ, Piper S, McDonagh TA, Hardman SMC, Goda A, Mizuno A, Sawano M, Rigby AS, Quint JK, Yoshikawa T, Clark AL, Anzai T, Cleland JGF. Validation of U.S. mortality prediction models for hospitalized heart failure in the United Kingdom and Japan. *Eur J Heart Fail* 2018;**20**(8):1179-1190.

14. Shiraishi Y, Nagai T, Kohsaka S, Goda A, Nagatomo Y, Mizuno A, Kohno T, Rigby A, Fukuda K, Yoshikawa T, Clark AL, Cleland JGF. Outcome of hospitalised heart failure in Japan and the United Kingdom stratified by plasma N-terminal pro-B-type natriuretic peptide. *Clin Res Cardiol* 2018.

15. Malamba-Lez D, Ngoy-Nkulu D, Steels P, Tshala-Katumbay D, Mullens W. Heart Failure Etiologies and Challenges to Care in the Developing World: An Observational Study in the Democratic Republic of Congo. *J Card Fail* 2018.

16. Tromp J, Teng TH, Tay WT, Hung CL, Narasimhan C, Shimizu W, Park SW, Liew HB, Ngarmukos T, Reyes EB, Siswanto BB, Yu CM, Zhang S, Yap J, MacDonald M, Ling LH, Leineweber K, Richards AM, Zile MR, Anand IS, Lam CSP. Heart failure with preserved ejection fraction in Asia. *Eur J Heart Fail* 2018.

17. Teng TK, Tromp J, Tay WT, Anand I, Ouwerkerk W, Chopra V, Wander GS, Yap JJ, MacDonald MR, Xu CF, Chia YM, Shimizu W, Richards AM, Voors A, Lam CS. Prescribing patterns of evidence-based heart failure pharmacotherapy and outcomes in the ASIAN-HF registry: a cohort study. *Lancet Glob Health* 2018;**6**(9):e1008-e1018.

18. Lam CSP, Gamble GD, Ling LH, Sim D, Leong KTG, Yeo PSD, Ong HY, Jaufeerally F, Ng TP, Cameron VA, Poppe K, Lund M, Devlin G, Troughton R, Richards AM, Doughty RN. Mortality associated with heart failure with preserved vs. reduced ejection fraction in a prospective international multi-ethnic cohort study. *Eur Heart J* 2018;**39**(20):1770-1780.

19. Jacobs L, Efremov L, Ferreira JP, Thijs L, Yang WY, Zhang ZY, Latini R, Masson S, Agabiti N, Sever P, Delles C, Sattar N, Butler J, Cleland JGF, Kuznetsova T, Staessen JA, Zannad F. Risk for Incident Heart Failure: A Subject-Level Meta-Analysis From the Heart "OMics" in AGEing (HOMAGE) Study. *J Am Heart Assoc* 2017;**6**(5).

20. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008;**358**(18):1887-1898.

21. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2018.

22. Taylor KS, Verbakel JY, Feakins BG, Price CP, Perera R, Bankhead C, Pluddemann A. Diagnostic accuracy of point-of-care natriuretic peptide testing for chronic heart failure in ambulatory care: systematic review and meta-analysis. *BMJ* 2018;**361**:k1450.

23. Cleland JGF, McDonagh T, Rigby AS, Yassin A, Whittaker T, Dargie HJ, on behalf of the National Heart Failure Audit Team for England and Wales. The National Heart Failure Audit for England and Wales 2008-2009. *Heart* 2011;**97**(11):876-886.

24. Shoaib A, Farag M, Nolan J, Rigby A, Patwala A, Rashid M, Kwok CS, Perveen R, Clark AL, Komajda M, Cleland JGF. Mode of presentation and mortality amongst patients hospitalized with heart failure? A report from the First Euro Heart Failure Survey. *Clin Res Cardiol* 2018.

25. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, O'Meara E, Shah SJ, McKinlay S, Fleg JL, Sopko G, Pitt B, Pfeffer MA. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J* 2016;**37**(5):455-462.

26. Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, Swedberg K, Yusuf S, Granger CB, Pfeffer MA, McMurray JJV, Solomon SD. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. *Eur J Heart Fail* 2018;**20**(8):1230-1239.

27. Atherton JJ, Sindone A, De Pasquale CG, Driscoll A, Macdonald PS, Hopper I, Kistler PM, Briffa T, Wong J, Abhayaratna W, Thomas L, Audehm R, Newton P, O'Loughlin J, Branagan M, Connell C. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018. *Heart Lung Circ* 2018;**27**(10):1123-1208.

28. Shah SJ, Lam CSP, Svedlund S, Saraste A, Hage C, Tan RS, Beussink-Nelson L, Fermer ML, Broberg MA, Gan LM, Lund LH. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. *Eur Heart J* 2018;**39**(37):3439-3450.

29. Damy T, Hobkirk J, WALTERS M, Ciobanu A, Rigby AS, Kallvikbacka-Bennett A, Guellich A, Dubois-Rande JL, Hittinger L, Clark AL, Cleland JG. Development of a Human Model for the Study of Effects of Hypoxia, Exercise and Sildenafil on Cardiac and Vascular Function in Chronic Heart Failure. *J Cardiovasc Pharmacol* 2015.

30. Damy T, Goode KM, Kallvikbacka-Bennett A, Lewinter C, Hobkirk J, Nikitin NP, Dubois-Rande JL, Hittinger L, Clark AL, Cleland JG. Determinants and prognostic value of pulmonary arterial pressure in patients with chronic heart failure. *Eur Heart J* 2010;**31**(18):2280-2290.

31. Damy T, Kallvikbacka-Bennett A, Goode K, Khaleva O, Lewinter C, Hobkirk J, Nikitin NP, Dubois-Rande JL, Hittinger L, Clark AL, Cleland JG. Prevalence of, associations with, and prognostic value of tricuspid annular plane systolic excursion (TAPSE) among out-patients referred for the evaluation of heart failure. *J Card Fail* 2012;**18**(3):216-225.

32. Ezekowitz JA, Podder M, Hernandez AF, Armstrong PW, Starling RC, O'Connor CM, Califf RM. Arrival by ambulance in acute heart failure: insights into the mode of presentation from Acute Studies of Nesiritide in Decompensated Heart Failure (ASCEND-HF). *BMJ Open* 2016;**6**(3):e010201.

33. Shoaib A, Waleed M, Khan S, Raza A, Zuhair M, Kassianides X, Djahit A, Goode K, Wong K, Rigby A, Clark A, Cleland J. Breathlessness at rest is not the dominant presentation of patients admitted with heart failure. *Eur J Heart Fail* 2014;**16**(12):1283-1291.

34. Ware JS, Amor-Salamanca A, Tayal U, Govind R, Serrano I, Salazar-Mendiguchia J, Garcia-Pinilla JM, Pascual-Figal DA, Nunez J, Guzzo-Merello G, Gonzalez-Vioque E, Bardaji A, Manito N, Lopez-Garrido MA, Padron-Barthe L, Edwards E, Whiffin N, Walsh R, Buchan RJ, Midwinter W, Wilk A, Prasad S, Pantazis A, Baski J, O'Regan DP, Alonso-Pulpon L, Cook SA, Lara-Pezzi E, Barton PJ, Garcia-Pavia P. Genetic Etiology for Alcohol-Induced Cardiac Toxicity. *J Am Coll Cardiol* 2018;**71**(20):2293-2302.

35. Tayal U, Newsome S, Buchan R, Whiffin N, Halliday B, Lota A, Roberts A, Baksi AJ, Voges I, Midwinter W, Wilk A, Govind R, Walsh R, Daubeney P, Jarman JWE, Baruah R, Frenneaux M, Barton PJ, Pennell D, Ware JS, Prasad SK, Cook SA. Phenotype and Clinical Outcomes of Titin Cardiomyopathy. *J Am Coll Cardiol* 2017;**70**(18):2264-2274.

36. Ware JS, Li J, Mazaika E, Yasso CM, DeSouza T, Cappola TP, Tsai EJ, Hilfiker-Kleiner D, Kamiya CA, Mazzarotto F, Cook SA, Halder I, Prasad SK, Pisarcik J, Hanley-Yanez K, Alharethi R, Damp J, Hsich E, Elkayam U, Sheppard R, Kealey A, Alexis J, Ramani G, Safirstein J, Boehmer J, Pauly DF, Wittstein IS, Thohan V, Zucker MJ, Liu P, Gorcsan J, III, McNamara DM, Seidman CE, Seidman JG, Arany Z. Shared Genetic Predisposition in Peripartum and Dilated Cardiomyopathies. *N ENGL J MED* 2016;**374**(3):233-241.

37. Liu D, Oder D, Salinger T, Hu K, Muntze J, Weidemann F, Herrmann S, Ertl G, Wanner C, Frantz S, Stork S, Nordbeck P. Association and diagnostic utility of diastolic dysfunction and myocardial fibrosis in patients with Fabry disease. *Open Heart* 2018;**5**(2):e000803.

38. Lindgren MP, PirouziFard M, Smith JG, Sundquist J, Sundquist K, Zoller B. A Swedish Nationwide Adoption Study of the Heritability of Heart Failure. *JAMA Cardiol* 2018;**3**(8):703-710.

39. Finan C, Gaulton A, Kruger FA, Lumbers RT, Shah T, Engmann J, Galver L, Kelley R, Karlsson A, Santos R, Overington JP, Hingorani AD, Casas JP. The druggable genome and support for target identification and validation in drug development. *Sci Transl Med* 2017;**9**(383).

40. Tromp J, Westenbrink BD, Ouwerkerk W, Van Veldhuisen DJ, Samani NJ, Ponikowski P, Metra M, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Lang CC, Ng LL, Zannad F, Zwinderman AH, Hillege HL, van der Meer P, Voors AA. Identifying Pathophysiological Mechanisms in Heart Failure With Reduced Versus Preserved Ejection Fraction. *J Am Coll Cardiol* 2018;**72**(10):1081-1090.

41. Sharma A, Demissei BG, Tromp J, Hillege HL, Cleland JG, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Davison BA, Givertz MM, Bloomfield DM, Dittrich H, Van Veldhuisen DJ, Cotter G, Ezekowitz JA, Khan MAF, Voors AA. A network analysis to compare biomarker profiles in patients with and without diabetes mellitus in acute heart failure. *Eur J Heart Fail* 2017;**19**(10):1310-1320.

42. Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Hillege HL, Lang CC, Ter Maaten JM, Ng L, Ponikowski P, Samani NJ, Van Veldhuisen DJ, Zannad F, Zwinderman AH, Metra M. A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure: rationale, design, and baseline characteristics of BIOSTAT-CHF. *Eur J Heart Fail* 2016;**18**(6):716-726.

43. Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, Januzzi JL, Jr., Mark DB, Pina IL, Passmore G, Whellan DJ, Yang H, Cooper LS, Leifer ES, Desvigne-Nickens P, O'Connor CM. Effect of Natriuretic Peptide-Guided Therapy on Hospitalization or Cardiovascular Mortality in High-Risk Patients With Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. *JAMA* 2017;**318**(8):713-720.

44. Nunez J, Llacer P, Bertomeu-Gonzalez V, Bosch MJ, Merlos P, Garcia-Blas S, Montagud V, Bodi V, Bertomeu-Martinez V, Pedrosa V, Mendizabal A, Cordero A, Gallego J, Palau P, Minana G, Santas E, Morell S, Llacer A, Chorro FJ, Sanchis J, Facila L. Carbohydrate Antigen-125-Guided Therapy in Acute Heart Failure: CHANCE-HF: A Randomized Study. *JACC Heart Fail* 2016;**4**(11):833-843.

45. Coorey GM, Neubeck L, Mulley J, Redfern J. Effectiveness, acceptability and usefulness of mobile applications for cardiovascular disease self-management: Systematic review with meta-synthesis of quantitative and qualitative data. *Eur J Prev Cardiol* 2018;**25**(5):505-521.

46. Pellicori P, Urbinati A, Shah P, MacNamara A, Kazmi S, Dierckx R, Zhang J, Cleland JGF, Clark AL. What proportion of patients with chronic heart failure are eligible for sacubitril-valsartan? *Eur J Heart Fail* 2017;**19**(6):768-778.

47. Adamson PB, Abraham WT, Aaron M, Aranda JM, Jr., Bourge RC, Smith A, Stevenson LW, Bauman JG, Yadav JS. CHAMPION trial rationale and design: the long-term safety and clinical efficacy of a wireless pulmonary artery pressure monitoring system. *J Card Fail* 2011;**17**(1):3-10.

48. Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomised trial. *Lancet* 2016;**387**(10017):453-461.

49. Cleland JFG, Clark RA. Telehealth: delivering high-quality care for heart failure. *Lancet* 2018;**392**(10152):990-991.

50. Inglis SC, Clark RA, Dierckx R, Prieto-Merino D, Cleland JG. Structured telephone support or non-invasive telemonitoring for patients with heart failure. *Cochrane Database Syst Rev* 2015;(10):CD007228.

51. Koehler F, Koehler K, Deckwart O, Prescher S, Wegscheider K, Kirwan BA, Winkler S, Vettorazzi E, Bruch L, Oeff M, Zugck C, Doerr G, Naegele H, Stork S, Butter C, Sechtem U, Angermann C, Gola G, Prondzinsky R, Edelmann F, Spethmann S, Schellong SM, Schulze PC, Bauersachs J, Wellge B, Schoebel C, Tajsic M, Dreger H, Anker SD, Stangl K. Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): a randomised, controlled, parallel-group, unmasked trial. *Lancet* 2018;**392**(10152):1047-1057.

52. Koehler F, Koehler K, Deckwart O, Prescher S, Wegscheider K, Kirwan BA, Winkler S, et al. Efficacy of Telemedical Interventional Management in Heart Failure Patients II (TIM-HF2): a randomised controlled trial. *Lancet* 2018.

53. Cleland JFG, Clark RA. Telehealth: delivering high-quality care for heart failure. *Lancet* 2018;**392**(10152):990-991.

54. Cleland JGF, Pellicori P, Clark AL, Petrie MC. Time to Take the Failure Out of Heart Failure: The Importance of Optimism. *JACC Heart Fail* 2017;**5**(7):538-540.

55. Cleland JG, Antony R. It makes SENSE to take a safer road. *Eur Heart J* 2011;**32**(18):2225-2227.

56. Kalogeropoulos AP, Fonarow GC, Georgiopoulou V, Burkman G, Siwamogsatham S, Patel A, Li S, Papadimitriou L, Butler J. Characteristics and Outcomes of Adult Outpatients With Heart Failure and Improved or Recovered Ejection Fraction. *JAMA Cardiol* 2016;**1**(5):510-518.

57. Halliday BP, Wassall R, Lota AS, Khalique Z, Gregson J, Newsome S, Jackson R, Rahneva T, Wage R, Smith G, Venneri L, Tayal U, Auger D, Midwinter W, Whiffin N, Rajani R, Dungu JN, Pantazis A, Cook SA, Ware JS, Baksi AJ, Pennell DJ, Rosen SD, Cowie MR, Cleland JGF, Prasad SK. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet* 2018.

58. Banke A, Schou M, Videbaek L, Moller JE, Torp-Pedersen C, Gustafsson F, Dahl JS, Kober L, Hildebrandt PR, Gislason GH. Incidence of cancer in patients with chronic heart failure: a long-term follow-up study. *Eur J Heart Fail* 2016;**18**(3):260-266.

59. Hasin T, Gerber Y, McNallan SM, Weston SA, Kushwaha SS, Nelson TJ, Cerhan JR, Roger VL. Patients with heart failure have an increased risk of incident cancer. *J Am Coll Cardiol* 2013;**62**(10):881-886.

60. Bertero E, Canepa M, Maack C, Ameri P. Linking Heart Failure to Cancer. *Circulation* 2018;**138**(7):735-742.

61. Kitsis RN, Riquelme JA, Lavandero S. Heart Disease and Cancer. *Circulation* 2018;**138**(7):692-695.

62. Meijers WC, Maglione M, Bakker SJL, Oberhuber R, Kieneker LM, de JS, Haubner BJ, Nagengast WB, Lyon AR, van d, V, Van Veldhuisen DJ, Westenbrink BD, van der Meer P, Sillje HHW, de Boer RA. Heart Failure Stimulates Tumor Growth by Circulating Factors. *Circulation* 2018;**138**(7):678-691.

63. Selvaraj S, Bhatt DL, Claggett B, Djousse L, Shah SJ, Chen J, Imran TF, Qazi S, Sesso HD, Gaziano JM, Schrag D. Lack of Association Between Heart Failure and Incident Cancer. *J Am Coll Cardiol* 2018;**71**(14):1501-1510.

64. Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, Mar BG, Lindsley RC, Mermel CH, Burtt N, Chavez A, Higgins JM, Moltchanov V, Kuo FC, Kluk MJ, Henderson B, Kinnunen L, Koistinen HA, Ladenvall C, Getz G, Correa A, Banahan BF, Gabriel S, Kathiresan S, Stringham HM, McCarthy MI, Boehnke M, Tuomilehto J, Haiman C, Groop L, Atzmon G, Wilson JG, Neuberg D, Altshuler D, Ebert BL. Age-related clonal hematopoiesis associated with adverse outcomes. *N ENGL J MED* 2014;**371**(26):2488-2498.

65. Jaiswal S, Natarajan P, Silver AJ, Gibson CJ, Bick AG, Shvartz E, McConkey M, Gupta N, Gabriel S, Ardissino D, Baber U, Mehran R, Fuster V, Danesh J, Frossard P, Saleheen D, Melander O, Sukhova GK, Neuberg D, Libby P, Kathiresan S, Ebert BL. Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease. *N ENGL J MED* 2017;**377**(2):111-121.

66. Dorsheimer L, Assmus B, Rasper T, Ortmann CA, Ecke A, Abou-El-Ardat K, Schmid T, Brune B, Wagner S, Serve H, Hoffmann J, Seeger F, Dimmeler S, Zeiher AM, Rieger MA. Association of Mutations Contributing to Clonal Hematopoiesis With Prognosis in Chronic Ischemic Heart Failure. *JAMA Cardiol* 2018.

67. Sano S, Oshima K, Wang Y, MacLauchlan S, Katanasaka Y, Sano M, Zuriaga MA, Yoshiyama M, Goukassian D, Cooper MA, Fuster JJ, Walsh K. Tet2-Mediated Clonal Hematopoiesis Accelerates Heart Failure Through a Mechanism Involving the IL-1beta/NLRP3 Inflammasome. *J Am Coll Cardiol* 2018;**71**(8):875-886.

68. Warraich HJ, Rogers JG, Dunlay SM, Hummel E, Mentz RJ. Top Ten Tips for Palliative Care Clinicians Caring for Heart Failure Patients. *J Palliat Med* 2018;**21**(11):1646-1650.

69. Kernick LA, Hogg KJ, Millerick Y, Murtagh FEM, Djahit A, Johnson M. Does advance care planning in addition to usual care reduce hospitalisation for patients with advanced heart failure: A systematic review and narrative synthesis. *Palliat Med* 2018;**32**(10):1539-1551.

70. Maessen M, Veldink JH, van den Berg LH, Schouten HJ, van der Wal G, Onwuteaka-Philipsen BD. Requests for euthanasia: origin of suffering in ALS, heart failure, and cancer patients. *J Neurol* 2010;**257**(7):1192-1198.

71. Henson KE, Brock R, Charnock J, Wickramasinghe B, Will O, Pitman A. Risk of Suicide After Cancer Diagnosis in England. *JAMA Psychiatry* 2018.

72. Dierickx S, Deliens L, Cohen J, Chambaere K. Comparison of the Expression and Granting of Requests for Euthanasia in Belgium in 2007 vs 2013. *JAMA Intern Med* 2015;**175**(10):1703-1706.

73. Mahtani KR, Heneghan C, Onakpoya I, Tierney S, Aronson JK, Roberts N, Hobbs FDR, Nunan D. Reduced Salt Intake for Heart Failure: A Systematic Review. *JAMA Intern Med* 2018.

74. Dalal HM, Taylor RS, Jolly K, Davis RC, Doherty P, Miles J, Van LR, Warren FC, Green C, Wingham J, Greaves C, Sadler S, Hillsdon M, Abraham C, Britten N, Frost J, Singh S, Hayward C, Eyre V, Paul K, Lang CC, Smith K. The effects and costs of home-based rehabilitation for heart failure with reduced ejection fraction: The REACH-HF multicentre randomized controlled trial. *Eur J Prev Cardiol* 2018;2047487318806358.

75. Taylor RS, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O, O'Connor C, Whellan D, Keteyian SJ, Coats A, Davos CH, Dalal HM, Dracup K, Evangelista L, Jolly K, Myers J, McKelvie RS, Nilsson BB, Passino C, Witham MD, Yeh GY, Zwisler AO. Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation: an individual patient data meta-analysis of randomised trials. *Eur J Heart Fail* 2018.

76. Ciani O, Piepoli M, Smart N, Uddin J, Walker S, Warren FC, Zwisler AD, Davos CH, Taylor RS. Validation of Exercise Capacity as a Surrogate Endpoint in Exercise-Based Rehabilitation for Heart Failure: A Meta-Analysis of Randomized Controlled Trials. *JACC Heart Fail* 2018;**6**(7):596-604.

77. Lang CC, Smith K, Wingham J, Eyre V, Greaves CJ, Warren FC, Green C, Jolly K, Davis RC, Doherty PJ, Miles J, Britten N, Abraham C, Van LR, Singh SJ, Paul K, Hillsdon M, Sadler S, Hayward C, Dalal HM, Taylor RS. A randomised controlled trial of a facilitated home-based rehabilitation intervention in patients with heart failure with preserved ejection fraction and their caregivers: the REACH-HFpEF Pilot Study. *BMJ Open* 2018;**8**(4):e019649.

78. Cleland JGF, Pennell DJ, Ray SG, Coats AJ, MacFarlane PW, Murray GD, Dalle Mule J, Vered Z, Lahiri A, on behalf of the CHRISTMAS (carvedilol hibernating reversible ischaemia trial: marker of success) investigators. Myocardial viability as a determinant of the ejection fraction response to carvedilol in patients with heart failure (CHRISTMAS trial): randomised controlled trial. *Lancet* 2003;**362**:14-21.

79. Cleland JG, Calvert M, Freemantle N, Arrow Y, Ball SG, Bonser RS, Chattopadhyay S, Norell MS, Pennell DJ, Senior R. The Heart Failure Revascularisation Trial (HEART). *Eur J Heart Fail* 2011;**13**(2):227-233.

80. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A, Ali IS, Pohost G, Gradinac S, Abraham WT, Yii M, Prabhakaran D, Szwed H, Ferrazzi P, Petrie MC, O'Connor CM, Panchavinnin P, She L, Bonow RO, Rankin GR, Jones RH, Rouleau JL. Coronary-Artery Bypass Surgery in Patients with Left Ventricular Dysfunction. *N Engl J Med* 2011.

81. Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, Michler RE, Bonow RO, Doenst T, Petrie MC, Oh JK, She L, Moore VL, Desvigne-Nickens P, Sopko G, Rouleau JL. Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. *N ENGL J MED* 2016;**374**(16):1511-1520.

82. Perera D, Clayton T, Petrie MC, Greenwood JP, O'Kane PD, Evans R, Sculpher M, McDonagh T, Gershlick A, de BM, Redwood S, Carr-White G, Marber M. Percutaneous Revascularization for Ischemic Ventricular Dysfunction: Rationale and Design of the REVIVED-BCIS2 Trial: Percutaneous Coronary Intervention for Ischemic Cardiomyopathy. *JACC Heart Fail* 2018;**6**(6):517-526.

83. Zannad F, Anker SD, Byra WM, Cleland JGF, Fu M, Gheorghiade M, Lam CSP, Mehra MR, Neaton JD, Nessel CC, Spiro TE, Van Veldhuisen DJ, Greenberg B. Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease. *N ENGL J MED* 2018;**379**(14):1332-1342.

84. Ferreira JP, Girerd N, Alshalash S, Konstam MA, Zannad F. Antithrombotic therapy in heart failure patients with and without atrial fibrillation: update and future challenges. *Eur Heart J* 2016;**37**(31):2455-2464.

85. Cleland JG, McMurray JJ, Kjekshus J, Cornel JH, Dunselman P, Fonseca C, Hjalmarson A, Korewicki J, Lindberg M, Ranjith N, Van Veldhuisen DJ, Waagstein F, Wedel H, Wikstrand J. Plasma concentration of amino-terminal pro-brain natriuretic peptide in chronic heart failure: prediction of cardiovascular events and interaction with the effects of rosuvastatin: a report from CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure). *J Am Coll Cardiol* 2009;**54**(20):1850-1859.

86. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, Widimsky P, Hori M, Avezum A, Piegas LS, Branch KRH, Probstfield J, Bhatt DL, Zhu J, Liang Y, Maggioni AP, Lopez-Jaramillo P, O'Donnell M, Kakkar AK, Fox KAA, Parkhomenko AN, Ertl G, Stork S, Keltai M, Ryden L, Pogosova N, Dans AL, Lanas F, Commerford PJ, Torp-Pedersen C, Guzik TJ, Verhamme PB, Vinereanu D, Kim JH, Tonkin AM, Lewis BS, Felix C, Yusoff K, Steg PG, Metsarinne KP, Cook BN, Misselwitz F, Chen E, Leong D, Yusuf S. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *N ENGL J MED* 2017;**377**(14):1319-1330.

87. Connolly SJ, Eikelboom JW, Bosch J, Dagenais G, Dyal L, Lanas F, Metsarinne K, O'Donnell M, Dans AL, Ha JW, Parkhomenko AN, Avezum AA, Lonn E, Lisheng L, Torp-Pedersen C, Widimsky P, Maggioni AP, Felix C, Keltai K, Hori M, Yusoff K, Guzik TJ, Bhatt DL, Branch KRH, Cook BN, Berkowitz SD, Anand SS, Varigos JD, Fox KAA, Yusuf S. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2018;**391**(10117):205-218.

88. Cleland JG. Is aspirin useful in primary prevention? *Eur Heart J* 2013;**34**(44):3412-3418.

89. Korjian S, Braunwald E, Daaboul Y, Mi M, Bhatt DL, Verheugt FWA, Cohen M, Bode C, Burton P, Plotnikov AN, Gibson CM. Usefulness of Rivaroxaban for Secondary Prevention of Acute Coronary Syndrome in Patients With History of Congestive Heart Failure (from the ATLAS-ACS-2 TIMI-51 Trial). *Am J Cardiol* 2018;**122**(11):1896-1901.

90. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N ENGL J MED* 2017;**377**(12):1119-1131.

91. Ridker PM, Libby P, MacFadyen JG, Thuren T, Ballantyne C, Fonseca F, Koenig W, Shimokawa H, Everett BM, Glynn RJ. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). *Eur Heart J* 2018;**39**(38):3499-3507.

92. Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. *Lancet* 2018;**391**(10118):319-328.

93. Trankle CR, Canada JM, Cei L, Abouzaki N, Oddi-Erdle C, Kadariya D, Christopher S, Viscusi M, Del BM, Kontos MC, Arena R, Van TB, Abbate A. Usefulness of Canakinumab to Improve Exercise Capacity in Patients With Long-Term Systolic Heart Failure and Elevated C-Reactive Protein. *Am J Cardiol* 2018;**122**(8):1366-1370.

94. Everett BM, Cornel J, Lainscak M, Anker SD, Abbate A, Thuren T, Libby P, Glynn RJ, Ridker PM. Anti-Inflammatory Therapy with Canakinumab for the Prevention of Hospitalization for Heart Failure. *Circulation* 2018.

95. Kjekshus J, Apetrei E, Barrios V, Bohm M, Cleland J.G.F., Cornel JH, Dunselman P, Fonseca C, Goudev A, Grande P, Gullestad L, Hjalmarson A, Hradec J, Janosi A, Kamensky G, Komajda M, Korewicki J, Kuusi T, Mach F, Mareev V, McMurray JJ, Ranjith N, Schaufelberger M, Vanhaecke J, Van Veldhuisen D, Waagstein F, Wedel H, Wikstrand J, CORONA Group. Rosuvastatin in Older Patients with Systolic Heart Failure. *New Engl J Med* 2007;**357**(22):2248-2261.

96. McMurray JJ, Kjekshus J, Gullestad L, Dunselman P, Hjalmarson A, Wedel H, Lindberg M, Waagstein F, Grande P, Hradec J, Kamensky G, Korewicki J, Juusi T, Mach F, Ranjith N, Wikstrand J, CORONA Study Group. Effects of statin therapy according to plasma high sensitivity C-reactive protein concentration in the Controlled rosuvastatin Multinational Trial in Heart Failure (CORONA): a retrospective analysis. *Circulation* 2009;**120**(22 Dec 1):2188-2196.

97. McMurray JJ, Kjekshus J, Gullestad L, Dunselman P, Hjalmarson A, Wedel H, Lindberg M, Waagstein F, Grande P, Hradec J, Kamensky G, Korewicki J, Kuusi T, Mach F, Ranjith N, Wikstrand J. Effects of statin therapy according to plasma high-sensitivity C-reactive protein concentration in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA): a retrospective analysis. *Circulation* 2009;**120**(22):2188-2196.

98. Brisco-Bacik MA, Ter Maaten JM, Houser SR, Vedage NA, Rao V, Ahmad T, Wilson FP, Testani JM. Outcomes Associated With a Strategy of Adjuvant Metolazone or High-Dose Loop Diuretics in Acute Decompensated Heart Failure: A Propensity Analysis. *J Am Heart Assoc* 2018;**7**(18):e009149.

99. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N ENGL J MED* 2018.

100. Packer M, Anker SD, Butler J, Filippatos G, Zannad F. Effects of Sodium-Glucose Cotransporter 2 Inhibitors for the Treatment of Patients With Heart Failure: Proposal of a Novel Mechanism of Action. *JAMA Cardiol* 2017;**2**(9):1025-1029.

101. Packer M, Kitzman DW. Obesity-Related Heart Failure With a Preserved Ejection Fraction: The Mechanistic Rationale for Combining Inhibitors of Aldosterone, Neprilysin, and Sodium-Glucose Cotransporter-2. *JACC Heart Fail* 2018;**6**(8):633-639.

102. Zelniker TA, Braunwald E. Cardiac and Renal Effects of Sodium-Glucose Co-Transporter 2 Inhibitors in Diabetes: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2018;**72**(15):1845-1855.

103. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. *Lancet* 2007;**370**(9593):1129-1136.

104. Bethel MA, Patel RA, Merrill P, Lokhnygina Y, Buse JB, Mentz RJ, Pagidipati NJ, Chan JC, Gustavson SM, Iqbal N, Maggioni AP, Ohman P, Poulter NR, Ramachandran A, Zinman B, Hernandez AF, Holman RR. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. *Lancet Diabetes Endocrinol* 2018;**6**(2):105-113.

105. Anker SD, Kirwan BA, Van Veldhuisen DJ, Filippatos G, Comin-Colet J, Ruschitzka F, Luscher TF, Arutyunov GP, Motro M, Mori C, Roubert B, Pocock SJ, Ponikowski P. Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. *Eur J Heart Fail* 2017.

106. Lewis GD, Malhotra R, Hernandez AF, McNulty SE, Smith A, Felker GM, Tang WHW, LaRue SJ, Redfield MM, Semigran MJ, Givertz MM, Van BP, Whellan D, Anstrom KJ, Shah MR, Desvigne-Nickens P, Butler J, Braunwald E. Effect of Oral Iron Repletion on Exercise Capacity in Patients With Heart Failure With Reduced Ejection Fraction and Iron Deficiency: The IRONOUT HF Randomized Clinical Trial. *JAMA* 2017;**317**(19):1958-1966.

107. Teerlink JR, Felker GM, McMurray JJ, Solomon SD, Adams KF, Jr., Cleland JG, Ezekowitz JA, Goudev A, Macdonald P, Metra M, Mitrovic V, Ponikowski P, Serpytis P, Spinar J, Tomcsanyi J, Vandekerckhove HJ, Voors AA, Monsalvo ML, Johnston J, Malik FI, Honarpour N. Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): a

phase 2, pharmacokinetic, randomised, placebo-controlled trial. *Lancet* 2016;**388**(10062):2895-2903.

108. Pieske B, Maggioni AP, Lam CSP, Pieske-Kraigher E, Filippatos G, Butler J, Ponikowski P, Shah SJ, Solomon SD, Scalise AV, Mueller K, Roessig L, Gheorghiade M. Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: results of the SOluble guanylate Cyclase stimulatoR in heArT failurE patientS with PRESERVED EF (SOCRATES-PRESERVED) study. *Eur Heart J* 2017;**38**(15):1119-1127.

109. Gheorghiade M, Greene SJ, Butler J, Filippatos G, Lam CS, Maggioni AP, Ponikowski P, Shah SJ, Solomon SD, Kraigher-Krainer E, Samano ET, Muller K, Roessig L, Pieske B. Effect of Vericiguat, a Soluble Guanylate Cyclase Stimulator, on Natriuretic Peptide Levels in Patients With Worsening Chronic Heart Failure and Reduced Ejection Fraction: The SOCRATES-REDUCED Randomized Trial. *JAMA* 2015;**314**(21):2251-2262.

110. Filippatos G, Maggioni AP, Lam CSP, Pieske-Kraigher E, Butler J, Spertus J, Ponikowski P, Shah SJ, Solomon SD, Scalise AV, Mueller K, Roessig L, Bamber L, Gheorghiade M, Pieske B. Patient-reported outcomes in the SOluble guanylate Cyclase stimulatoR in heArT failurE patientS with PRESERVED ejection fraction (SOCRATES-PRESERVED) study. *Eur J Heart Fail* 2017;**19**(6):782-791.

111. Prihadi EA, van der Bijl P, Gursoy E, Abou R, Mara VE, Hahn RT, Stone GW, Leon MB, Ajmone MN, Delgado V, Bax JJ. Development of significant tricuspid regurgitation over time and prognostic implications: new insights into natural history. *Eur Heart J* 2018;**39**(39):3574-3581.

112. Wendler O, Schymik G, Treede H, Baumgartner H, Dumonteil N, Neumann FJ, Tarantini G, Zamorano JL, Vahanian A. SOURCE 3: 1-year outcomes post-transcatheter aortic valve implantation using the latest generation of the balloon-expandable transcatheter heart valve. *Eur Heart J* 2017;**38**(36):2717-2726.

113. Ghio S, Freemantle N, Scelsi L, Serio A, Magrini G, Pasotti M, Shankar A, Cleland JGF, Tavazzi L. Long term left ventricular reverse remodelling with cardiac resynchronization therapy. Results from the CARE-HF trial. *Eur J Heart Failure* 2009;**11**(5):480-488.

114. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**(27):2129-2200.

115. Brignole M, Pokushalov E, Pentimalli F, Palmisano P, Chieffo E, Occhetta E, Quartieri F, Calo L, Ungar A, Mont L. A randomized controlled trial of atrioventricular junction ablation and cardiac resynchronization therapy in patients with permanent atrial fibrillation and narrow QRS. *Eur Heart J* 2018.

116. Brignole M, Botto G, Mont L, Iacopino S, De MG, Oddone D, Luzi M, Tolosana JM, Navazio A, Menozzi C. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. *Eur Heart J* 2011;**32**(19):2420-2429.

117. Cleland JG, Keshavarzi F, Pellicori P, Dicken B. Case selection for cardiac resynchronization in atrial fibrillation. *Heart Fail Clin* 2013;**9**(4):461-74, ix.

118. Chatterjee S, Sardar P, Lichstein E, Mukherjee D, Aikat S. Pharmacologic rate versus rhythm-control strategies in atrial fibrillation: an updated comprehensive review and meta-analysis. *Pacing Clin Electrophysiol* 2013;**36**(1):122-133.

119. Marrouche NF, Brachmann J. Catheter ablation versus standard conventional treatment in patients with left ventricular dysfunction and atrial fibrillation (CASTLE-AF) - study design. *Pacing Clin Electrophysiol* 2009;**32**(8):987-994.

120. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Moretz K, Poole JE, Mascette A, Rosenberg Y, Jeffries N, Al-Khalidi HR, Lee KL. Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) Trial: Study Rationale and Design. *AM HEART J* 2018;**199**:192-199.

121. Chen C, Zhou X, Zhu M, Chen S, Chen J, Cai H, Dai J, Xu X, Mao W. Catheter ablation versus medical therapy for patients with persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomized controlled trials. *J Interv Card Electrophysiol* 2018;**52**(1):9-18.

122. Gorter TM, Obokata M, Reddy YNV, Melenovsky V, Borlaug BA. Exercise unmasks distinct pathophysiologic features in heart failure with preserved ejection fraction and pulmonary vascular disease. *Eur Heart J* 2018;**39**(30):2825-2835.

123. Martin N, Manoharan K, Thomas J, Davies C, Lumbers RT. Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction. *Cochrane Database Syst Rev* 2018;**6**:CD012721.

124. Cleland JG, Tavazzi L, Daubert J-C, Tageldien A, Freemantle N. Cardiac Resynchronization Therapy. Are Modern Myths Preventing Appropriate Use? *J Am Coll Cardiol* 2009;**53**(7):608-611.

125. Anand IS, Rector TS, Cleland JG, Kuskowski M, McKelvie RS, Persson H, McMurray JJ, Zile MR, Komajda M, Massie BM, Carson PE. Prognostic value of baseline plasma amino-terminal pro-brain natriuretic peptide and its interactions with irbesartan treatment effects in patients with heart failure and preserved ejection fraction: findings from the I-PRESERVE trial. *Circ Heart Fail* 2011;**4**(5):569-577.

126. Anand IS, Claggett B, Liu J, Shah AM, Rector TS, Shah SJ, Desai AS, O'Meara E, Fleg JL, Pfeffer MA, Pitt B, Solomon SD. Interaction Between Spironolactone and Natriuretic Peptides in Patients With Heart Failure and Preserved Ejection Fraction: From the TOPCAT Trial. *JACC Heart Fail* 2017;**5**(4):241-252.

127. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008;**358**(18):1887-1898.

128. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A. Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction. *N ENGL J MED* 2008.

129. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJ. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet* 2012;**380**(9851):1387-1395.

130. Solomon SD, Rizkala AR, Gong J, Wang W, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, Van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Shi VC, Lefkowitz MP, McMurray JJV. Angiotensin Receptor Neprilysin Inhibition in Heart Failure With Preserved Ejection Fraction: Rationale and Design of the PARAGON-HF Trial. *JACC Heart Fail* 2017;**5**(7):471-482.

131. McMurray JJ, Packer M, Solomon SD. Neprilysin inhibition for heart failure. *N Engl J Med* 2014;**371**(24):2336-2337.

132. Borlaug BA, Anstrom KJ, Lewis GD, Shah SJ, Levine JA, Koepp GA, Givertz MM, Felker GM, LeWinter MM, Mann DL, Margulies KB, Smith AL, Tang WHW, Whellan DJ, Chen HH, Davila-Roman VG, McNulty S, Desvigne-Nickens P, Hernandez AF, Braunwald E, Redfield MM. Effect of Inorganic Nitrite vs Placebo on Exercise Capacity Among Patients With Heart Failure With Preserved Ejection Fraction: The INDIE-HFpEF Randomized Clinical Trial. *JAMA* 2018;**320**(17):1764-1773.

133. Redfield MM, Anstrom KJ, Levine JA, Koepp GA, Borlaug BA, Chen HH, LeWinter MM, Joseph SM, Shah SJ, Semigran MJ, Felker GM, Cole RT, Reeves GR, Tedford RJ, Tang WH, McNulty SE, Velazquez EJ, Shah MR, Braunwald E. Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction. *N ENGL J MED* 2015;**373**(24):2314-2324.

134. Komajda M, Isnard R, Cohen-Solal A, Metra M, Pieske B, Ponikowski P, Voors AA, Dominjon F, Henon-Goburdhun C, Pannaux M, Bohm M. Effect of ivabradine in patients with heart failure with preserved ejection fraction: the EDIFY randomized placebo-controlled trial. *Eur J Heart Fail* 2017.

135. Hasenfuss G, Hayward C, Burkhoff D, Silvestry FE, McKenzie S, Gustafsson F, Malek F, Van der Heyden J, Lang I, Petrie MC, Cleland JG, Leon M, Kaye DM. A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial. *Lancet* 2016;**387**(10025):1298-1304.

136. Feldman T, Mauri L, Kahwash R, Litwin S, Ricciardi MJ, van der Harst P, Penicka M, Fail PS, Kaye DM, Petrie MC, Basuray A, Hummel SL, Forde-McLean R, Nielsen CD, Lilly S, Massaro JM, Burkhoff D, Shah SJ. Transcatheter Interatrial Shunt Device for the Treatment of Heart Failure With Preserved Ejection Fraction (REDUCE LAP-HF I [Reduce Elevated Left Atrial Pressure in Patients With Heart Failure]): A Phase 2, Randomized, Sham-Controlled Trial. *Circulation* 2018;**137**(4):364-375.

137. Shah SJ, Feldman T, Ricciardi MJ, Kahwash R, Lilly S, Litwin S, Nielsen CD, van der Harst P, Hoendermis E, Penicka M, Bartunek J, Fail PS, Kaye DM, Walton A, Petrie MC, Walker N, Basuray A, Yakubov S, Hummel SL, Chetcuti S, Forde-McLean R, Herrmann HC, Burkhoff D, Massaro JM, Cleland JGF, Mauri L. One-Year Safety and Clinical Outcomes of a Transcatheter Interatrial Shunt Device for the Treatment of Heart Failure With Preserved Ejection Fraction in the Reduce Elevated Left Atrial Pressure in Patients With Heart Failure (REDUCE LAP-HF I) Trial: A Randomized Clinical Trial. *JAMA Cardiol* 2018;**3**(10):968-977.

138. Streng KW, Voors AA, Hillege HL, Anker SD, Cleland JG, Dickstein K, Filippatos G, Metra M, Ng LL, Ponikowski P, Samani NJ, Van Veldhuisen DJ, Zwinderman AH, Zannad F, Damman K, van der Meer P, Lang CC. Waist-to-hip ratio and mortality in heart failure. *Eur J Heart Fail* 2018;**20**(9):1269-1277.

139. Rao VN, Zhao D, Allison MA, Guallar E, Sharma K, Criqui MH, Cushman M, Blumenthal RS, Michos ED. Adiposity and Incident Heart Failure and its Subtypes: MESA (Multi-Ethnic Study of Atherosclerosis). *JACC Heart Fail* 2018;**6**(12):999-1007.

140. Lam CSP, Voors AA, de Boer RA, Solomon SD, Van Veldhuisen DJ. Heart failure with preserved ejection fraction: from mechanisms to therapies. *Eur Heart J* 2018;**39**(30):2780-2792.

141. van WG, Gorter TM, Westenbrink BD, Willems TP, Van Veldhuisen DJ, Rienstra M. Epicardial fat in heart failure patients with mid-range and preserved ejection fraction. *Eur J Heart Fail* 2018;**20**(11):1559-1566.

142. Ansaldo AM, Montecucco F, Sahebkar A, Dallegri F, Carbone F. Epicardial adipose tissue and cardiovascular diseases. *INT J CARDIOL* 2018.

143. Packer M. The epicardial adipose inflammatory triad: coronary atherosclerosis, atrial fibrillation, and heart failure with a preserved ejection fraction. *Eur J Heart Fail* 2018;**20**(11):1567-1569.

144. Sperry BW, Tang WHW. Amyloid heart disease: genetics translated into disease-modifying therapy. *Heart* 2017;**103**(11):812-817.

145. Castano A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, Rubin J, Chiuzan C, Nazif T, Vahl T, George I, Kodali S, Leon MB, Hahn R, Bokhari S, Maurer MS. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J* 2017;**38**(38):2879-2887.

146. Gonzalez-Lopez E, Gagliardi C, Dominguez F, Quarta CC, de Haro-Del Moral FJ, Milandri A, Salas C, Cinelli M, Cobo-Marcos M, Lorenzini M, Lara-Pezzi E, Foffi S, Alonso-Pulpon L, Rapezzi C, Garcia-Pavia P. Clinical characteristics of wild-type transthyretin cardiac amyloidosis: disproving myths. *Eur Heart J* 2017;**38**(24):1895-1904.

147. Gonzalez-Lopez E, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C, Bornstein B, Salas C, Lara-Pezzi E, Alonso-Pulpon L, Garcia-Pavia P. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J* 2015;**36**(38):2585-2594.

148. Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK, Plante-Bordeneuve V, Barroso FA, Merlini G, Obici L, Scheinberg M, Brannagan TH, III, Litchy WJ, Whelan C, Drachman BM, Adams D, Heitner SB, Conceicao I, Schmidt HH, Vita G, Campistol JM, Gamez J, Gorevic PD, Gane E, Shah AM, Solomon SD, Monia BP, Hughes SG, Kwoh TJ, McEvoy BW, Jung SW, Baker BF, Ackermann EJ, Gertz MA, Coelho T. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. *N ENGL J MED* 2018;**379**(1):22-31.

149. Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, Tournev I, Schmidt HH, Coelho T, Berk JL, Lin KP, Vita G, Attarian S, Plante-Bordeneuve V, Mezei MM, Campistol JM, Buades J, Brannagan TH, III, Kim BJ, Oh J, Parman Y, Sekijima Y, Hawkins PN,

Solomon SD, Polydefkis M, Dyck PJ, Gandhi PJ, Goyal S, Chen J, Strahs AL, Nochur SV, Sweetser MT, Garg PP, Vaishnaw AK, Gollob JA, Suhr OB. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. *N ENGL J MED* 2018;**379**(1):11-21.

150. McMurray J, Packer M, Desai A, Gong J, Greenlaw N, Lefkowitz M, Rizkala A, Shi V, Rouleau J, Solomon S, Swedberg K, Zile MR, Andersen K, Arango JL, Arnold M, Belohlavek J, Bohm M, Boytsov S, Burgess L, Cabrera W, Chen CH, Erglis A, Fu M, Gomez E, Gonzalez A, Hagege AA, Katova T, Kiatchoosakun S, Kim KS, Bayram E, Martinez F, Merkely B, Mendoza I, Mosterd A, Negrusz-Kawecka M, Peuhkurinen K, Ramires F, Refsgaard J, Senni M, Sibulo AS, Jr., Silva-Cardoso J, Squire I, Starling RC, Vinereanu D, Teerlink JR, Wong R. A putative placebo analysis of the effects of LCZ696 on clinical outcomes in heart failure. *Eur Heart J* 2015;**36**(7):434-439.

151. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, Rocha R, Braunwald E. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. *N ENGL J MED* 2018.

152. Packer M, Colucci W, Fisher L, Massie BM, Teerlink JR, Young J, Padley RJ, Thakkar R, Delgado-Herrera L, Salon J, Garratt C, Huang B, Sarapohja T. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. *JACC Heart Fail* 2013;**1**(2):103-111.

153. Mebazaa A, Nieminen MS, Filippatos GS, Cleland JG, Salon JE, Thakkar R, Padley RJ, Huang B, Cohen-Solal A. Levosimendan vs. dobutamine: outcomes for acute heart failure patients on beta-blockers in SURVIVE. *Eur J Heart Fail* 2009;**11**(3):304-311.

154. Cholley B, Caruba T, Grosjean S, Amour J, Ouattara A, Villacorta J, Miguet B, Guinet P, Levy F, Squara P, Ait HN, Carillion A, Boyer J, Boughenou MF, Rosier S, Robin E, Radutoiu M, Durand M, Guidon C, Desebbe O, Charles-Nelson A, Menasche P, Rozec B, Girard C, Fellahi JL, Pirracchio R, Chatellier G. Effect of Levosimendan on Low Cardiac Output Syndrome in Patients With Low Ejection Fraction Undergoing Coronary Artery Bypass Grafting With Cardiopulmonary Bypass: The LICORN Randomized Clinical Trial. *JAMA* 2017;**318**(6):548-556.

155. Landoni G, Lomivorotov VV, Alvaro G, Lobreglio R, Pisano A, Guarracino F, Calabro MG, Grigoryev EV, Likhvantsev VV, Salgado-Filho MF, Bianchi A, Pasyuga VV, Baiocchi M, Pappalardo F, Monaco F, Boboshko VA, Abubakirov MN, Amantea B, Lembo R, Brazzi L, Verniero L, Bertini P, Scandroglio AM, Bove T, Belletti A, Michienzi MG, Shukevich DL, Zabelina TS, Bellomo R, Zangrillo A. Levosimendan for Hemodynamic Support after Cardiac Surgery. *N ENGL J MED* 2017;**376**(21):2021-2031.

156. Mehta RH, Leimberger JD, van DS, Meza J, Wang A, Jankowich R, Harrison RW, Hay D, Fremes S, Duncan A, Soltesz EG, Luber J, Park S, Argenziano M, Murphy E, Marcel R, Kalavrouziotis D, Nagpal D, Bozinovski J, Toller W, Heringlake M, Goodman SG, Levy JH, Harrington RA, Anstrom KJ, Alexander JH. Levosimendan in Patients with Left Ventricular Dysfunction Undergoing Cardiac Surgery. *N ENGL J MED* 2017;**376**(21):2032-2042.

157. Nieminen MS, Cleland JG, Eha J, Belenkov Y, Kivikko M, Poder P, Sarapohja T. Oral levosimendan in patients with severe chronic heart failure --the PERSIST study. *Eur J Heart Fail* 2008;**10**(12):1246-1254.

158. Comin-Colet J, Manito N, Segovia-Cubero J, Delgado J, Garcia Pinilla JM, Almenar L, Crespo-Leiro MG, Sionis A, Blasco T, Pascual-Figal D, Gonzalez-Vilchez F, Lambert-Rodriguez JL, Grau

M, Bruguera J. Efficacy and safety of intermittent intravenous outpatient administration of levosimendan in patients with advanced heart failure: the LION-HEART multicentre randomised trial. *Eur J Heart Fail* 2018;**20**(7):1128-1136.

159. Silvetti S, Belletti A, Fontana A, Pollesello P. Rehospitalization after intermittent levosimendan treatment in advanced heart failure patients: a meta-analysis of randomized trials. *ESC Heart Fail* 2017;**4**(4):595-604.

160. Mielewczik M, Cole GD, Nowbar AN, Schilling R, Whinnett ZI, Bordachar P, Wilmshurst P, Chambers JC, Olshansky B, Morgan J, Israel C, Sethi AS, van HM, Cleland JG, Schmidt G, Francis DP. The C-CURE Randomized Clinical Trial (Cardiopoietic stem Cell therapy in heart failURE). *J AM COLL CARDIOL* 2013;**62**(25):2453.

161. Sluijter JPG, Davidson SM, Boulanger CM, Buzas EI, de Kleijn DPV, Engel FB, Giricz Z, Hausenloy DJ, Kishore R, Lecour S, Leor J, Madonna R, Perrino C, Prunier F, Sahoo S, Schiffelers RM, Schulz R, Van Laake LW, Ytrehus K, Ferdinandy P. Extracellular vesicles in diagnostics and therapy of the ischaemic heart: Position Paper from the Working Group on Cellular Biology of the Heart of the European Society of Cardiology. *CARDIOVASC RES* 2018;**114**(1):19-34.

162. De Ferrari GM, Stolen C, Tuinenburg AE, Wright DJ, Brugada J, Butter C, Klein H, Neuzil P, Botman C, Castel MA, D'Onofrio A, de Borst GJ, Solomon S, Stein KM, Schubert B, Stalsberg K, Wold N, Ruble S, Zannad F. Long-term vagal stimulation for heart failure: Eighteen month results from the NEural Cardiac TherApy foR Heart Failure (NECTAR-HF) trial. *INT J CARDIOL* 2017;**244**:229-234.

163. Gold MR, Van Veldhuisen DJ, Hauptman PJ, Borggrefe M, Kubo SH, Lieberman RA, Milasinovic G, Berman BJ, Djordjevic S, Neelagaru S, Schwartz PJ, Starling RC, Mann DL. Vagus Nerve Stimulation for the Treatment of Heart Failure: The INOVATE-HF Trial. *J Am Coll Cardiol* 2016;**68**(2):149-158.

164. Abraham WT, Kuck KH, Goldsmith RL, Lindenfeld J, Reddy VY, Carson PE, Mann DL, Saville B, Parise H, Chan R, Wiegn P, Hastings JL, Kaplan AJ, Edelmann F, Luthje L, Kahwash R, Tomassoni GF, Gutterman DD, Stagg A, Burkhoff D, Hasenfuss G. A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation. *JACC Heart Fail* 2018;**6**(10):874-883.

165. Tschope C, Kherad B, Klein O, Lipp A, Blaschke F, Gutterman D, Burkhoff D, Hamdani N, Spillmann F, Van LS. Cardiac contractility modulation: mechanisms of action in heart failure with reduced ejection fraction and beyond. *Eur J Heart Fail* 2018.

166. Costanzo MR, Ponikowski P, Coats A, Javaheri S, Augostini R, Goldberg LR, Holcomb R, Kao A, Khayat RN, Oldenburg O, Stellbrink C, McKane S, Abraham WT. Phrenic nerve stimulation to treat patients with central sleep apnoea and heart failure. *Eur J Heart Fail* 2018.

167. Beeler R, Schoenenberger AW, Bauer P, Kobza R, Bergner M, Mueller X, Schlaepfer R, Zuber M, Erne S, Erne P. Improvement of cardiac function with device-based diaphragmatic stimulation in chronic heart failure patients: the randomized, open-label, crossover Epiphrenic II Pilot Trial. *Eur J Heart Fail* 2014;**16**(3):342-349.

168. Shen L, Jhund PS, Petrie MC, Claggett BL, Barlera S, Cleland JGF, Dargie HJ, Granger CB, Kjekshus J, Kober L, Latini R, Maggioni AP, Packer M, Pitt B, Solomon SD, Swedberg K, Tavazzi

L, Wikstrand J, Zannad F, Zile MR, McMurray JJV. Declining Risk of Sudden Death in Heart Failure. *N ENGL J MED* 2017;**377**(1):41-51.

169. Beggs SAS, Jhund PS, Jackson CE, McMurray JJV, Gardner RS. Non-ischaemic cardiomyopathy, sudden death and implantable defibrillators: a review and meta-analysis. *Heart* 2018;**104**(2):144-150.

170. Marijon E, Leclercq C, Narayanan K, Boveda S, Klug D, Lacaze-Gadonneix J, Defaye P, Jacob S, Piot O, Deharo JC, Perier MC, Mulak G, Hermida JS, Milliez P, Gras D, Cesari O, Hidden-Lucet F, Anselme F, Chevalier P, Maury P, Sadoul N, Bordachar P, Cazeau S, Chauvin M, Empana JP, Jouven X, Daubert JC, Le Heuzey JY. Causes-of-death analysis of patients with cardiac resynchronization therapy: an analysis of the CeRtiTuDe cohort study. *EUR HEART J* 2015;**36**(41):2767-2776.

171. Al-Khatib SM, Hellkamp AS, Fonarow GC, Mark DB, Curtis LH, Hernandez AF, Anstrom KJ, Peterson ED, Sanders GD, Al-Khalidi HR, Hammill BG, Heidenreich PA, Hammill SC. Association between prophylactic implantable cardioverter-defibrillators and survival in patients with left ventricular ejection fraction between 30% and 35%. *JAMA* 2014;**311**(21):2209-2215.

172. Halliday BP, Gulati A, Ali A, Guha K, Newsome S, Arzanauskaite M, Vassiliou VS, Lota A, Izgi C, Tayal U, Khalique Z, Stirrat C, Auger D, Pareek N, Ismail TF, Rosen SD, Vazir A, Alpendurada F, Gregson J, Frenneaux MP, Cowie MR, Cleland JGF, Cook SA, Pennell DJ, Prasad SK. Association Between Midwall Late Gadolinium Enhancement and Sudden Cardiac Death in Patients With Dilated Cardiomyopathy and Mild and Moderate Left Ventricular Systolic Dysfunction. *Circulation* 2017;**135**(22):2106-2115.

173. Gulati A, Japp AG, Raza S, Halliday BP, Jones DA, Newsome S, Ismail NA, Morarji K, Khwaja J, Spath N, Shakespeare C, Kalra PR, Lloyd G, Mathur A, Cleland JGF, Cowie MR, Assomull RG, Pennell DJ, Ismail TF, Prasad SK. Absence of Myocardial Fibrosis Predicts Favorable Long-Term Survival in New-Onset Heart Failure. *Circ Cardiovasc Imaging* 2018;**11**(9):e007722.

174. Sapp JL, Wells GA, Parkash R, Stevenson WG, Blier L, Sarrazin JF, Thibault B, Rivard L, Gula L, Leong-Sit P, Essebag V, Nery PB, Tung SK, Raymond JM, Sterns LD, Veenhuyzen GD, Healey JS, Redfearn D, Roux JF, Tang AS. Ventricular Tachycardia Ablation versus Escalation of Antiarrhythmic Drugs. *N ENGL J MED* 2016;**375**(2):111-121.

175. Cuculich PS, Robinson CG. Noninvasive Ablation of Ventricular Tachycardia. *N ENGL J MED* 2018;**378**(17):1651-1652.

176. Gula LJ, Doucette S, Leong-Sit P, Tang ASL, Parkash R, Sarrazin JF, Thibault B, Essebag V, Tung SK, Deyell MW, Raymond JM, Lane C, Nery PB, Veenhuyzen GD, Redfearn DP, Healey JS, Roux JF, Giddens K, Sapp JL. Quality of life with ablation or medical therapy for ventricular arrhythmias: A substudy of VANISH. *J Cardiovasc Electrophysiol* 2018;**29**(3):421-434.

177. Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, Estes NA, III, Greenberg H, Hall WJ, Huang DT, Kautzner J, Klein H, McNitt S, Olshansky B, Shoda M, Wilber D, Zareba W. Reduction in inappropriate therapy and mortality through ICD programming. *N Engl J Med* 2012;**367**(24):2275-2283.

178. Martin DO, Lemke B, Birnie D, Krum H, Lee KL, Aonuma K, Gasparini M, Starling RC, Milasinovic G, Rogers T, Sambelashvili A, Gorcsan J, III, Houmsse M. Investigation of a novel algorithm for synchronized left-ventricular pacing and ambulatory optimization of cardiac

resynchronization therapy: results of the adaptive CRT trial. *Heart Rhythm* 2012;**9**(11):1807-1814.

179. Brugada J, Delnoy PP, Brachmann J, Reynolds D, Padeletti L, Noelker G, Kantipudi C, Rubin Lopez JM, Dichtl W, Borri-Brunetto A, Verhees L, Ritter P, Singh JP. Contractility sensor-guided optimization of cardiac resynchronization therapy: results from the RESPOND-CRT trial. *EUR HEART J* 2016.

180. Whinnett ZI, Sohaib SMA, Mason M, Duncan E, Tanner M, Lefroy D, Al-Obaidi M, Ellery S, Leyva-Leon F, Betts T, Dayer M, Foley P, Swinburn J, Thomas M, Khiani R, Wong T, Yousef Z, Rogers D, Kalra PR, Dhileepan V, March K, Howard J, Kyriacou A, Mayet j, Kanagaratnam P, Frenneaux M, Hughes AD, Francis DP. Multicenter Randomized Controlled Crossover Trial Comparing Hemodynamic Optimization Against Echocardiographic Optimization of AV and VV Delay of Cardiac Resynchronization Therapy: The BRAVO Trial. *JACC Cardiovasc Imaging* 2018.

181. Olshansky B, Day JD, Sullivan RM, Yong P, Galle E, Steinberg JS. Does cardiac resynchronization therapy provide unrecognized benefit in patients with prolonged PR intervals? The impact of restoring atrioventricular synchrony: an analysis from the COMPANION Trial. *Heart Rhythm* 2012;**9**(1):34-39.

182. Jones S, Lumens J, Sohaib SMA, Finegold JA, Kanagaratnam P, Tanner M, Duncan E, Moore P, Leyva F, Frenneaux M, Mason M, Hughes AD, Francis DP, Whinnett ZI. Cardiac resynchronization therapy: mechanisms of action and scope for further improvement in cardiac function. *Europace* 2017;**19**(7):1178-1186.

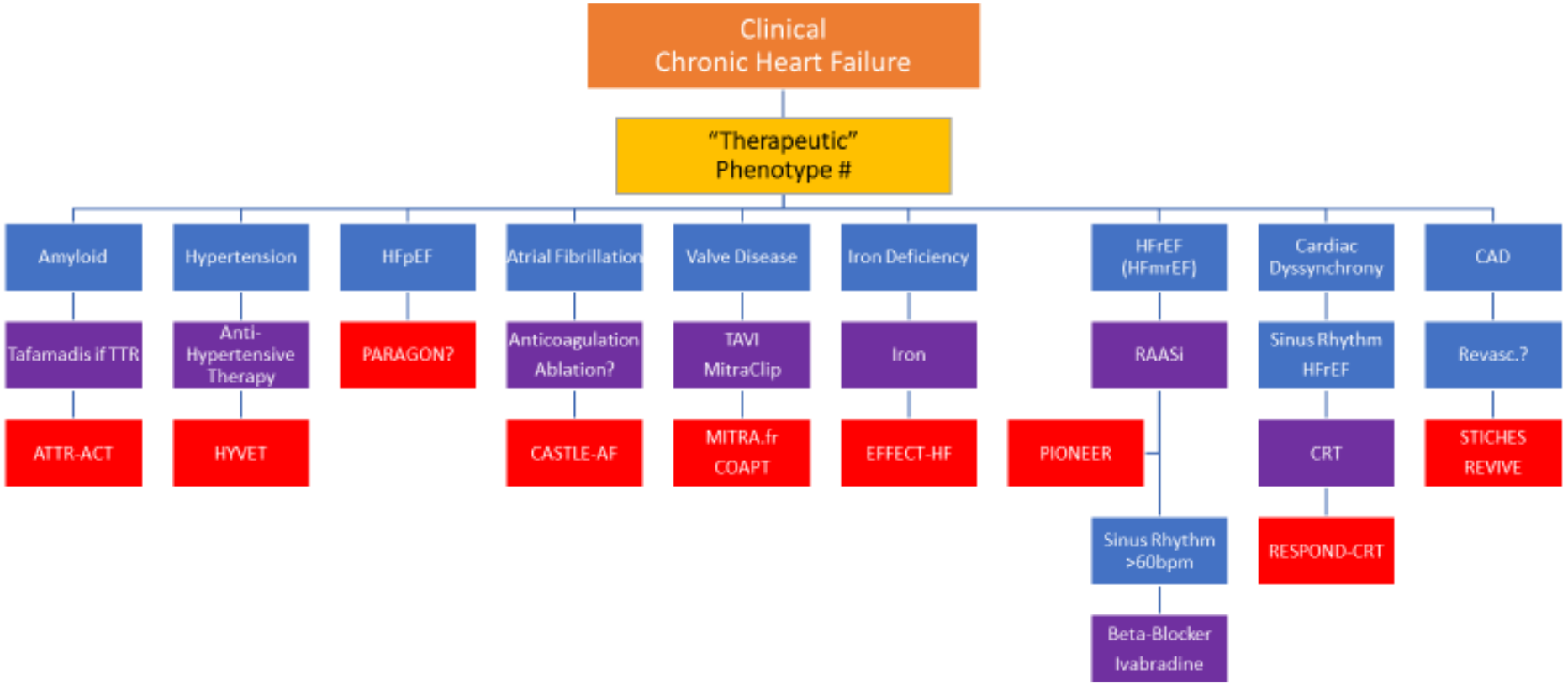
183. Plummer CJ, Frank CM, Bari Z, Al Hebaishi YS, Klepfer RN, Stadler RW, Ghosh S, Liu S, Mittal S. A novel algorithm increases the delivery of effective cardiac resynchronization therapy during atrial fibrillation: The CRTee randomized crossover trial. *Heart Rhythm* 2018;**15**(3):369-375.

184. Dickstein K, Normand C, Auricchio A, Bogale N, Cleland JG, Gitt AK, Stellbrink C, Anker SD, Filippatos G, Gasparini M, Hindricks G, Blomstrom LC, Ponikowski P, Ruschitzka F, Botto GL, Bulava A, Duray G, Israel C, Leclercq C, Margitfalvi P, Cano O, Plummer C, Sarigul NU, Sterlinski M, Linde C. CRT Survey II: a European Society of Cardiology survey of cardiac resynchronisation therapy in 11 088 patients-who is doing what to whom and how? *Eur J Heart Fail* 2018;**20**(6):1039-1051.

185. Mehra MR, Goldstein DJ, Uriel N, Cleveland JC, Jr., Yuzefpolskaya M, Salerno C, Walsh MN, Milano CA, Patel CB, Ewald GA, Itoh A, Dean D, Krishnamoorthy A, Cotts WG, Tatooles AJ, Jorde UP, Bruckner BA, Estep JD, Jeevanandam V, Sayer G, Horstmanshof D, Long JW, Gulati S, Skipper ER, O'Connell JB, Heatley G, Sood P, Naka Y. Two-Year Outcomes with a Magnetically Levitated Cardiac Pump in Heart Failure. *N ENGL J MED* 2018;**378**(15):1386-1395.

186. Beuth J, Falter F, Pinto Ribeiro RV, Badiwala M, Meineri M. New Strategies to Expand and Optimize Heart Donor Pool: Ex Vivo Heart Perfusion and Donation After Circulatory Death: A Review of Current Research and Future Trends. *Anesth Analg* 2018.

Central Illustration



a patient may have more than one phenotype

Figure 1

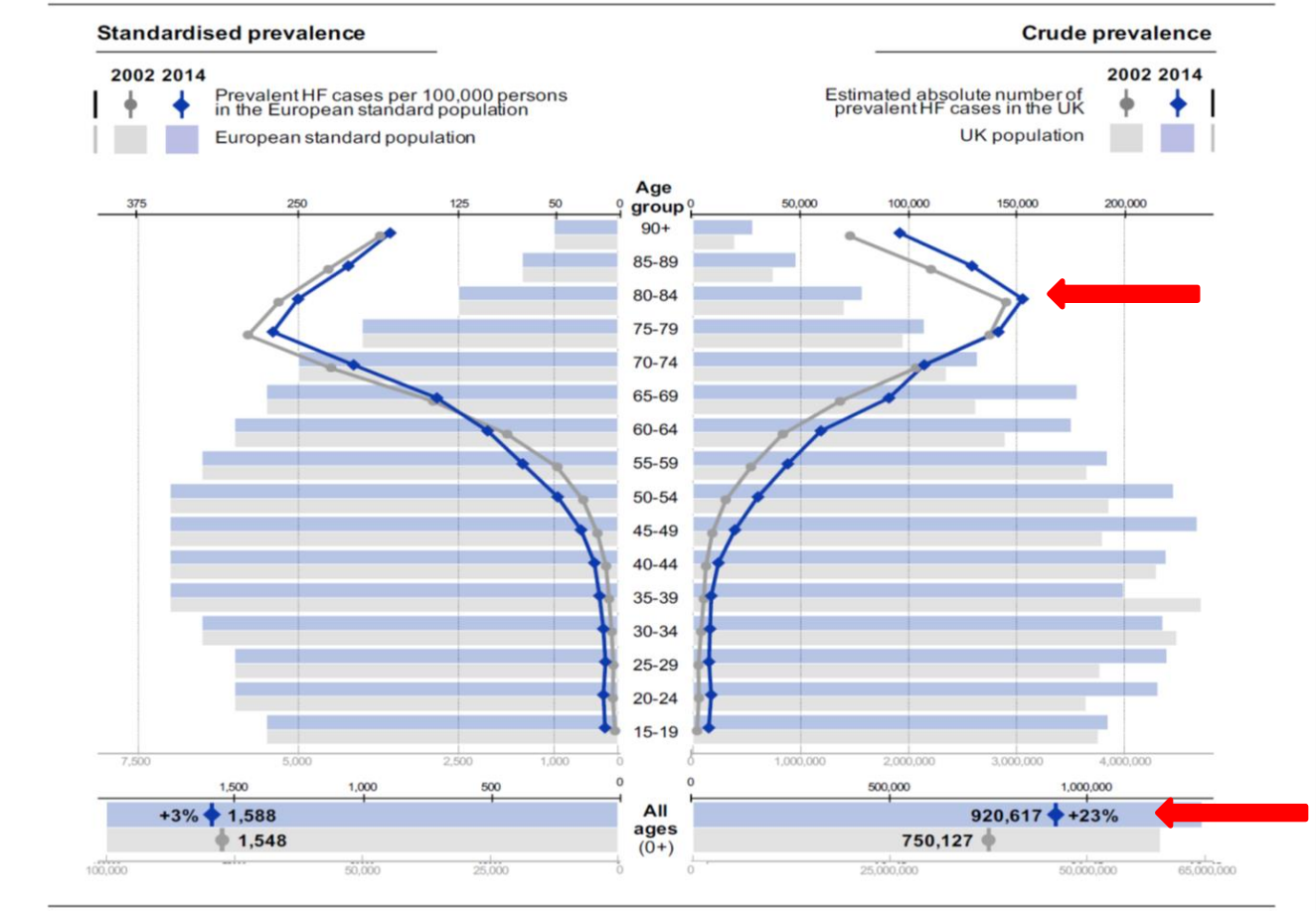
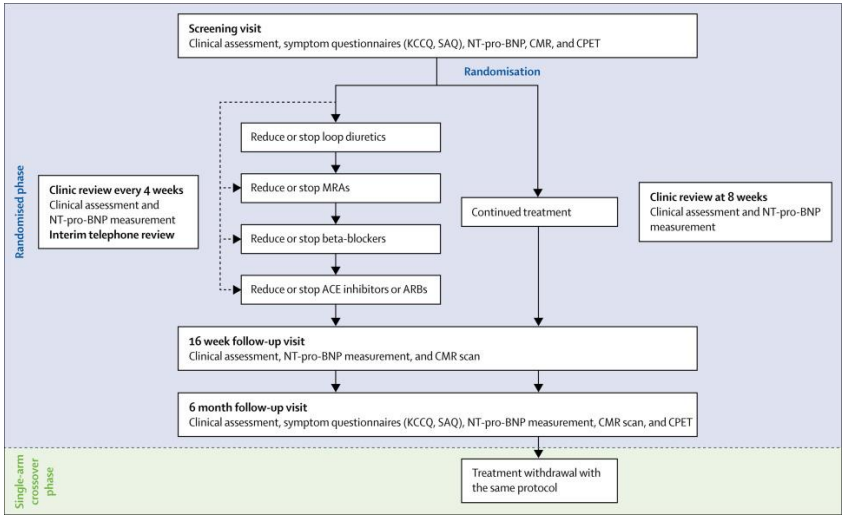

Standardised prevalence
Crude prevalence
2002 2014
Prevalent HF cases per 100,000 persons in the European standard population
European standard population
Estimated absolute number of prevalent HF cases in the UK
UK population
Age group
90+
85-89
80-84
75-79
70-74
65-69
60-64
55-59
50-54
45-49
40-44
35-39
30-34
25-29
20-24
15-19
+3% 1,588
1,548
All ages (0+)
920,617 +23%
750,127

Figure 2



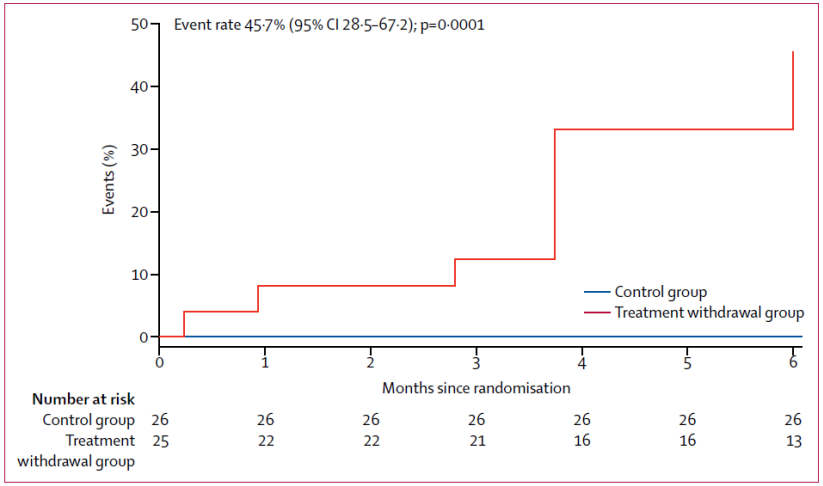


Figure 3: **Kaplan-Meier curve of time to primary endpoint in randomised phase, according to treatment group**
One patient dropped out at 7 days.

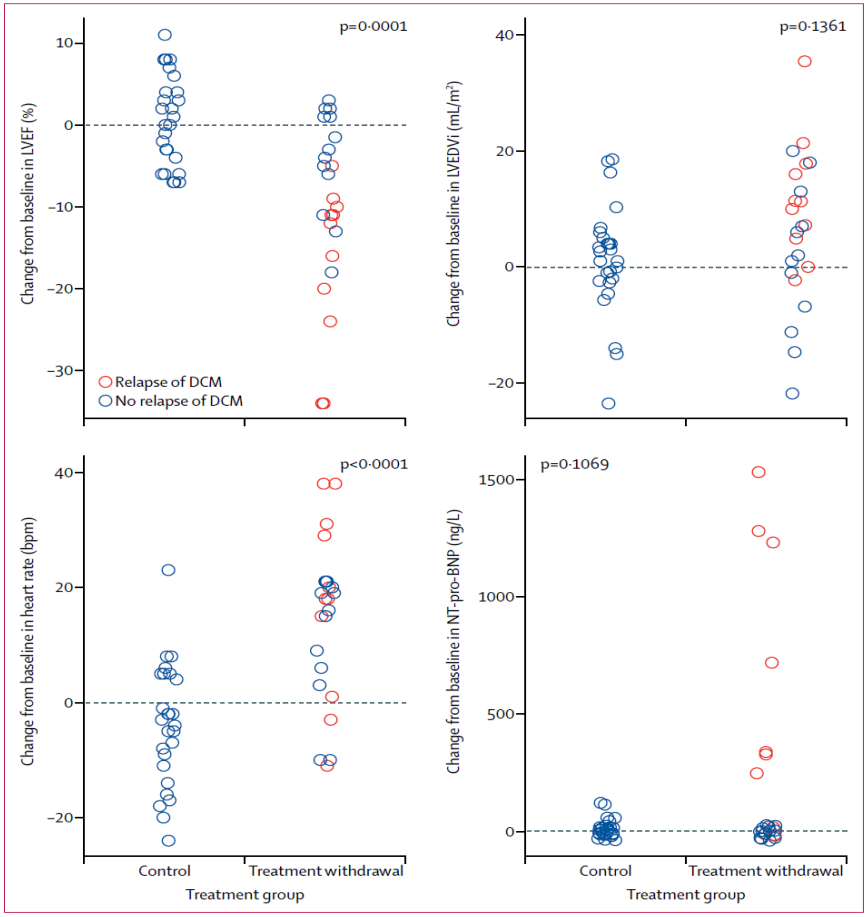
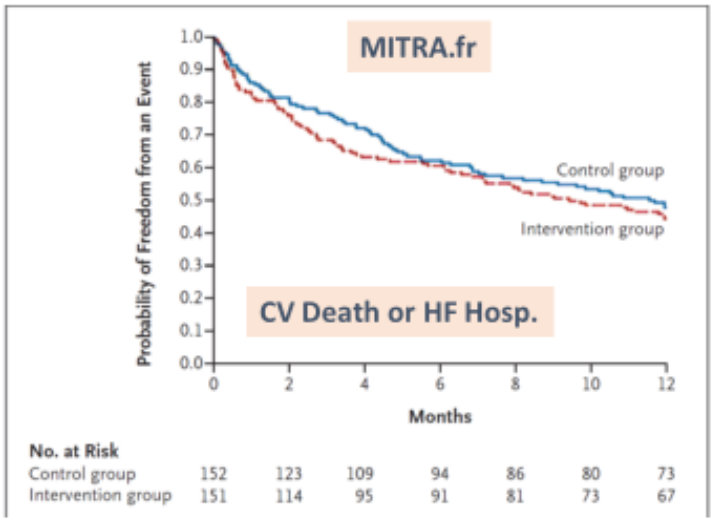


Figure 5: **Change in secondary endpoint variables between baseline and follow-up in the randomised phase of the study, based on treatment group**
Each circle represents one patient. bpm=beats per min. DCM=dilated cardiomyopathy. LVEDVi=left ventricular end-diastolic volume indexed to body surface area. LVEF=left ventricular ejection fraction. NT-pro-BNP=N-terminal pro-B-type natriuretic peptide.

Figure 3



- Are differences between trials real?
  - Duration of follow-up
  - Play of chance
- Ratio of severity of MR to severity of LV dilation may be important
- Differences in
  - Pharmacological treatment
  - Number of clips
  - Residual MR

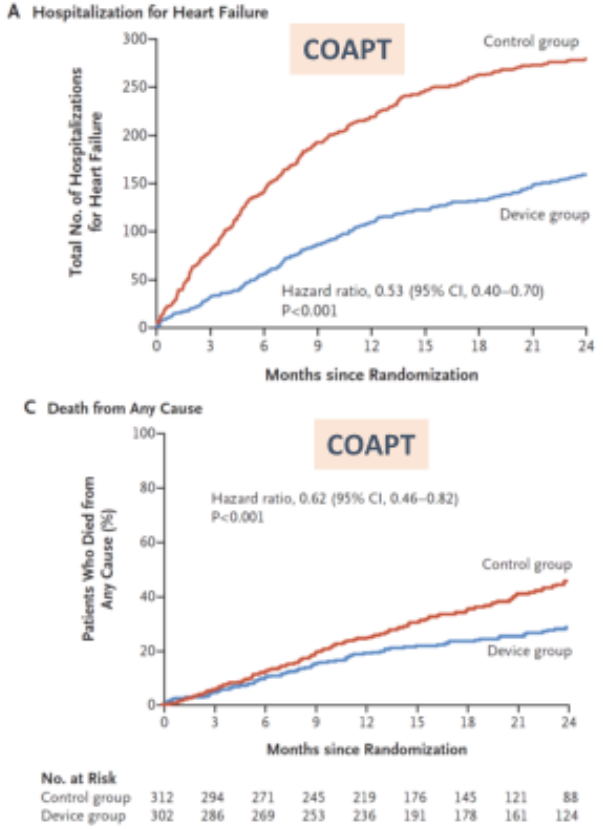
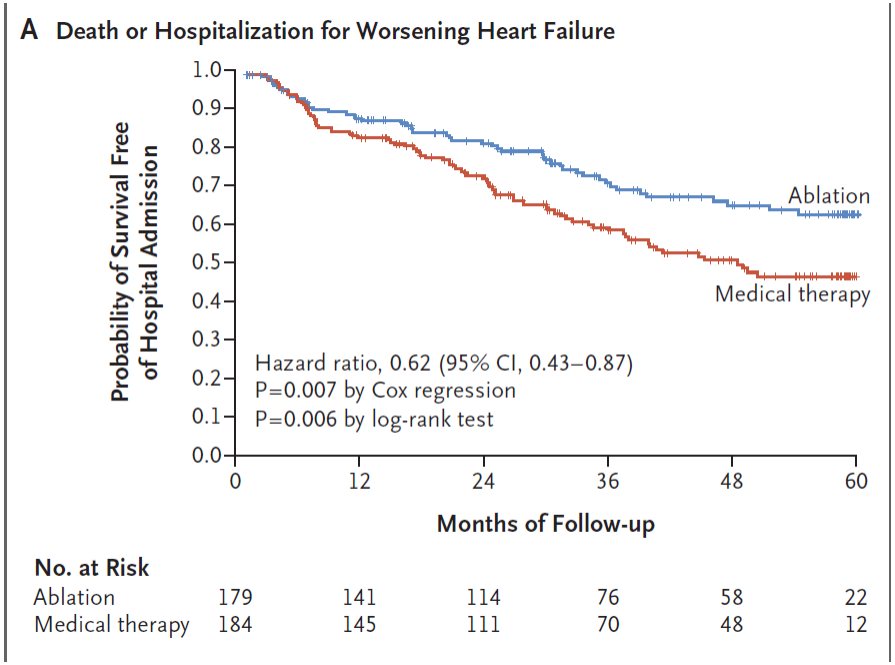


Figure 4


A Death or Hospitalization for Worsening Heart Failure
Probability of Survival Free of Hospital Admission
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
12
24
36
48
60
Ablation
Medical therapy
Hazard ratio, 0.62 (95% CI, 0.43–0.87)
P=0.007 by Cox regression
P=0.006 by log-rank test
Months of Follow-up
No. at Risk
Ablation 179 141 114 76 58 22
Medical therapy 184 145 111 70 48 12

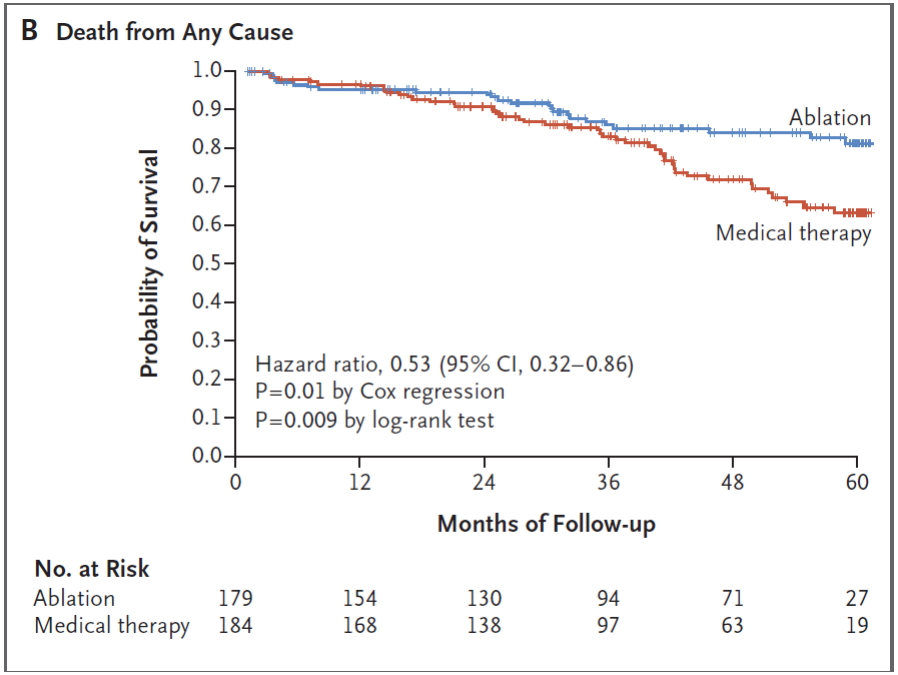
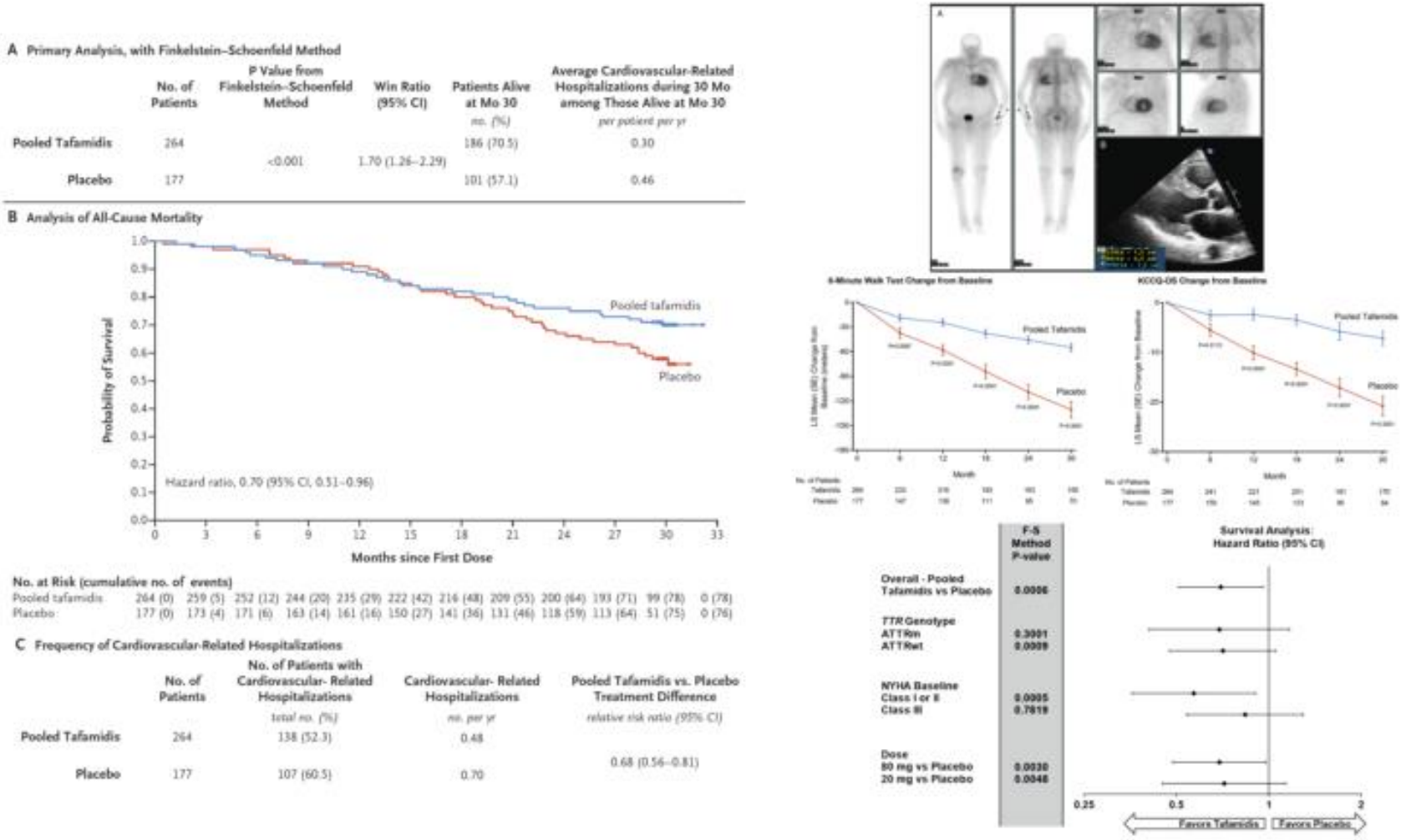

B Death from Any Cause
Probability of Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
12
24
36
48
60
Ablation
Medical therapy
Hazard ratio, 0.53 (95% CI, 0.32–0.86)
P=0.01 by Cox regression
P=0.009 by log-rank test
Months of Follow-up
No. at Risk
Ablation 179 154 130 94 71 27
Medical therapy 184 168 138 97 63 19

Figure 5



A Primary Analysis, with Finkelstein–Schoenfeld Method

	No. of Patients	P Value from Finkelstein–Schoenfeld Method	Win Ratio (95% CI)	Patients Alive at Mo 30	Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30
				no. (%)	*per patient per yr*
Pooled Tafamidis	264	<0.001	1.70 (1.26–2.29)	186 (70.5)	0.30
Placebo	177			101 (57.1)	0.46

B Analysis of All-Cause Mortality

No. at Risk (cumulative no. of events)

Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)	
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)	

C Frequency of Cardiovascular-Related Hospitalizations

	No. of Patients	No. of Patients with Cardiovascular- Related Hospitalizations	Cardiovascular- Related Hospitalizations	Pooled Tafamidis vs. Placebo Treatment Difference
		total no. (%)	*no. per yr*	*relative risk ratio (95% CI)*
Pooled Tafamidis	264	138 (52.3)	0.48	0.68 (0.56–0.81)
Placebo	177	107 (60.5)	0.70	

Figure 6

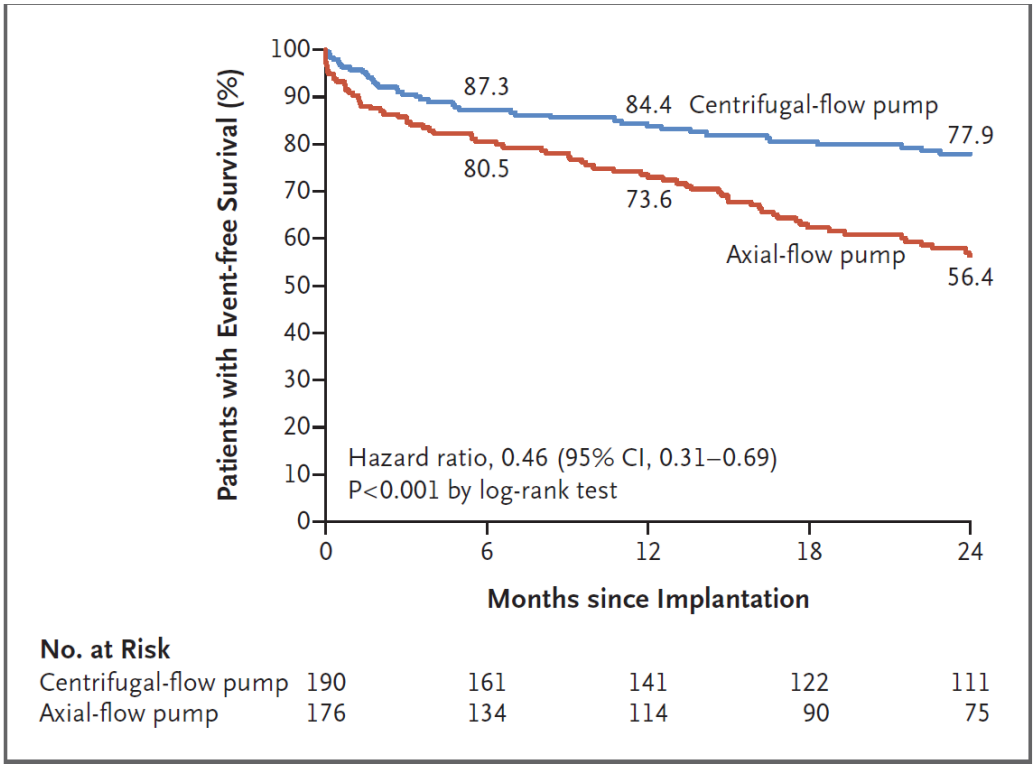
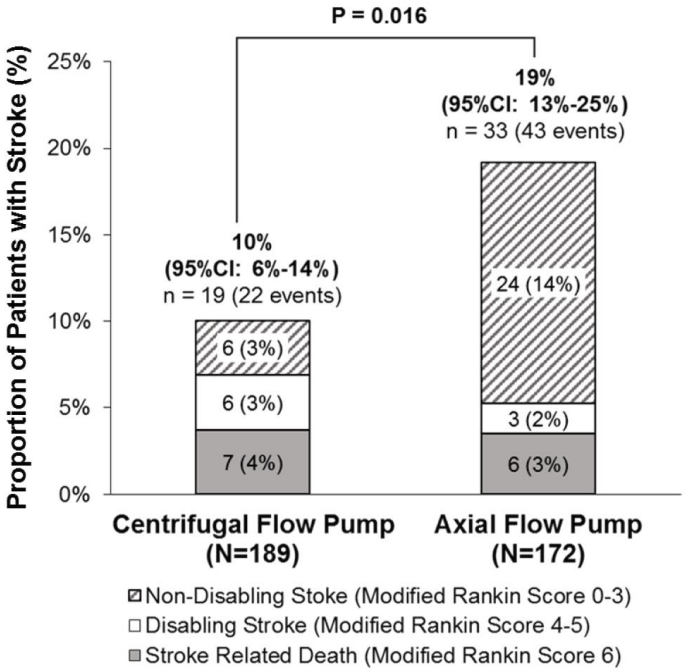


Figure S7. Stroke Events and Severity (Per Protocol Population)



Two centrifugal flow pump subjects and 9 axial flow pump subjects had >1 stroke. The score for the most severe stoke is shown. 1.6% of centrifugal flow pump subjects (n = 3) and 5.2% of axial-flow pump subjects (n = 9) had a modified Rankin score of 0 at 60 days post-stroke.