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The Year in Cardiology 2018: Heart Failure

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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 over (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 (i.e.: 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 haematpoiesis 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 suggest 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](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](https://clinicaltrials.gov/ct2/show/NCT02861534)) and a smaller trial of HfPEF ([https://clinicaltrials.gov/ct2/show/NCT03547583](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 ≥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 ≤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)**

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-valsalartan, 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-valsalartan 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 If 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](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](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](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 after 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: Therapy withdrawal in Recovered DCM 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: Tafamidis 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


Central Illustration

# a patient may have more than one phenotype
Figure 1
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. 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
- Hazard ratio, 0.62 (95% CI, 0.43–0.87)
- P=0.007 by Cox regression
- P=0.006 by log-rank test

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
- Hazard ratio, 0.53 (95% CI, 0.32–0.86)
- P=0.01 by Cox regression
- P=0.009 by log-rank test

No. at Risk
Ablation: 179, 154, 130, 94, 71, 27
Medical therapy: 184, 168, 138, 97, 63, 19
Figure 5
Figure 6

No. at Risk
Centrifugal-flow pump  190  161  141  122  111
Axial-flow pump  176  134  114  90  75

Hazard ratio, 0.46 (95% CI, 0.31–0.69) P<0.001 by log-rank test

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 stroke 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.