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The year in cardiology 2017: heart failure

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Preamble

The 2016 European Society of Cardiology (ESC) heart failure (HF) guidelines brought to the fore new recommendations for the management of HF with reduced ejection fraction (HFrEF; EF <40%); introduced a new term: HF with mid-range EF (HFmrEF) for the previously denoted 'grey area' corresponding to EF 40–49%; highlighted the continued lack of evidence based interventions in HFmrEF and HF with preserved EF (HFpEF; EF ≥40%); and introduced the concept of early intervention in acute HF (AHF). Here we summarize data from autumn 2016 to autumn 2017 that analyses implementation and utilization of existing proven therapy in HFrEF; additional neutral trials in HFpEF but detailed characterization of and potential efficacy of therapy in HFmrEF; further disappointing trials in AHF; and growing evidence in favour of treating comorbidities.

Heart failure with reduced ejection fraction treatment: implementation and optimal utilization of existing therapy

Drug therapy

The last 30 years have seen a remarkable series of successful randomized trials in HFrEF, which have brought to clinical use multiple interventions that improve symptoms and quality of life and reduce HF hospitalization and/or mortality (1, 2). While success of even large-scale outcome trials often depend on a small number of events and has been traditionally defined by statistical P-values, a novel measure of the robustness (or fragility) of the results of a clinical trial has been recently introduced. The fragility index (FI) describes the number of non-events that need to become events in order to render a trial result non-significant thus indicating how many patients would be required to convert a trial from being statistically significant to not significant. In a humbling analysis of 25 randomized controlled trials (RCT) with median sample size 2331 and primary events 688, the median FI was 26, and it was less than 10 in one-third of trials (3), suggesting they may be less robust than we commonly assume.

Nevertheless, a greater concern is that existing therapy is not optimally utilized in the real world. Although angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARBs) and β-blockers appear to be used in 80–90% of patients with HFrEF even in real-world settings, dosing is sub-optimal, which is associated with higher mortality and HF hospitalization (4). Recent data from the ESC HF Long-Term Registry (selected European sites) suggest that mineralocorticoid receptor antagonists (MRAs) are used in only two-third of patients with HFrEF (5, 6) and in the non-selective Swedish HF Registry, in less than one-third (7). Chronic kidney disease and hyperkalaemia are common in HF (8) and reasons for MRA under-use appear to be perceived risk of or actual hyperkalaemia and worsening renal function (9). More novel drugs such as ivabradine and sacubitril/valsartan may be deferred due to clinician inertia, even though they have demonstrated benefit regardless of HF duration (10) and very early after initiation (11).

How can appropriate utilization be improved? One appealing strategy is monitoring. However, intensified management using home visits and structured telephone support did not reduce recurrent hospitalization, mortality or costs (12). In the large and much anticipated Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) trial a strategy of aiming for an NT-proBNP <1000 ng/L vs. usual care did not reduce cardiovascular (CV) death or first or total HF hospitalizations, or even NT-proBNP levels (13). In Remote Management of Heart Failure Using Implantable Electronic Devices (REM-HF), remote monitoring using implantable devices did not improve

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outcomes (14). In the MultiSENSE study, the HeartLogic algorithm using implantable device data predicted HF decompensation (15) but has still to be shown to improve outcomes.

Another strategy concerns improving the organization and prioritization of care. The use of devices is highly variable but overall underutilized (7). Although, cardiac resynchronization therapy (CRT) benefit does not appear compromised by comorbidity burden (16), it is conceivable that older and comorbid patients are less prioritized. In Sweden, non-use appears due to poor access to cardiology specialists rather than clinical variables (17). In the international QUALIFY registry, guideline adherence was associated with improved outcomes (18). A large Swedish study showed that enrolment vs. non-enrolment in the non-selective but voluntary Swedish Heart Failure Registry was associated with a 35% lower risk of death, and that the strongest explanatory factor was greater use of HF and CV medications in patients enrolled in the registry (19).

Cardiac rhythm management devices

Implantable cardioverter-defibrillators (ICDs) and CRT improve outcomes in selected patients with HFrEF in multiple randomized clinical trials. These recent successes notwithstanding, a substantial number of patients receiving an ICD and/or CRTs do not benefit from the device thus highlighting the need for improvement in patient selection. Longer QRS duration, left bundle branch block morphology, and lower LVEF remain the most important independent predictor of response to CRT (20, 21). In the RESPOND-CRT trial, non-response was ameliorated by an echo-guided optimization of atrioventricular (AV) and ventriculoventricular (VV) intervals (22). Multimodality cardiac imaging strategies for lead placement, and possibly, left ventricular-only pacing, may increase CRT response (23–25). But given the many factors involved in CRT response and outcomes, predicting CRT response remains elusive and the potential for larger multi parametric big-data approaches should be considered for future trials (26, 27).

The 2016 ESC guidelines recommend primary prevention ICD in both ischaemic and non-ischaemic cardiomyopathy (1). This was called into doubt by DANISH (28), where primary prevention ICD in non-ischaemic cardiomyopathy reduced sudden cardiac death but not all-cause death. In a secondary analysis, the association between ICD and survival decreased with age, and a cut-off of 70 years was suggested to yield the highest survival for the population as a whole (29). Furthermore, inappropriate ICD therapy appears more likely in patients with more severe HF (30). At the same time, in the last year, several meta-analyses point to a distinct reduction in both sudden and all-cause death (31–34). Patients in these meta-analyses may have had less effective medical therapy than contemporary patients. Indeed, a large analysis form 12 clinical trials suggested that the rates of sudden death have declined over time *(Figure 1)* (35), which would be consistent with potentially lower benefit of primary prevention ICD in patients with contemporary treatment. Furthermore, benefits may differ substantially depending on e.g. age (28) and concomitant use of CRT, and in several recent studies multivariable

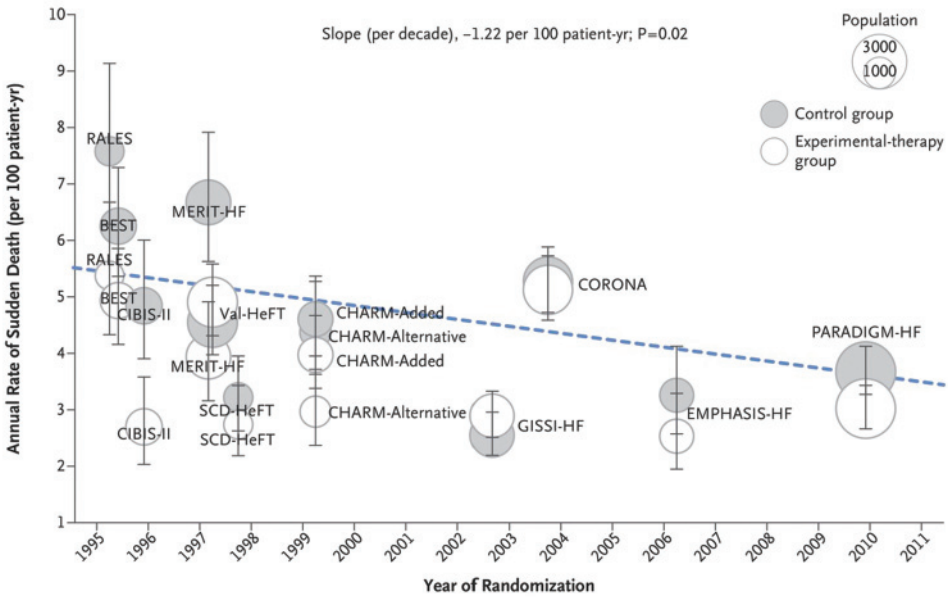

FIGURE 1. Rates of sudden death per 100 patient-years in heart failure with reduced ejection fraction trials. From: The year in cardiology 2017: heart failure

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prediction models were used to refine sudden death risk prediction and ICD benefit (36–38).

Heart failure with preserved ejection fraction

Controversy remains as to whether HFpEF is a variant of HFrEF, a distinct entity, or merely a consequence of ageing and related comorbidities. It is associated with lower CV risk than HFrEF but it is indisputable that in the real world, it has the same overall mortality as HFrEF and is increasing more rapidly in prevalence (1). Previous trials of ACEi, ARBs, and nitrates have been disappointing (1). Recently, in EDIFY, ivabradine did not improve 6MWT, NT-proBNP, or E/e' (39). In Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT), spironolactone was overall not effective (40) but regional analyses suggested a potential effect in North and South America (41). Perhaps more importantly, in the pre-specified stratum including patients based on NT-proBNP levels, consistent with confirmed HF, spironolactone was effective (42). Interestingly, in both TOPCAT and I-PRESERVE, treatment was more effective in patients with lower natriuretic peptide levels (43–45). So as we struggle in HFpEF trial design to ensure presence of HF and to enrich for HF events by requiring elevated NPs, as NPs go too high, the syndrome may be less amenable to intervention. Now, MRAs will be reassessed in a large pragmatic trial including patients with both HFpEF and HFmrEF (46).

Heart failure with mid-range ejection fraction

The 2016 ESC guidelines introduced a new term HFmrEF, corresponding to the previously denoted "grey area" EF 40–49% (1). However, EF is not an ideal marker to classify HF, and EF may change with treatment and time (47). A recent study suggested that 17-34% of patients with HFrEF or HFmrEF improve to a higher category, and that this, as expected, was more common in the absence of ischaemic heart disease (48). Other modalities may refine characterization of HF, such as global longitudinal strain (49, 50) but their impact in clinical routine remains to be seen. Given the heterogeneity of HF and difficulty characterizing HF, in particular with preserved EF, multimarker personalized approaches to HF, as occurs in oncology, may improve characterization and classification in HF (27, 51).

But EF remains the most commonly used classifier and the fact remains: EF 40–49% is not normal but there is no evidence based therapy, and further research is needed in this group (1), comprising more than 20% of patients with HF (52, 53). Extensive work during the last year suggest that although HFmrEF may be intermediate regarding some characteristics (54–57), it resembles HFrEF regarding age, preponderance of male sex, greater prevalence of ischaemic heart disease (48) and greater prognostic impact of chronic kidney disease (52). Recent studies also suggest that standard HF therapy may be effective in HFmrEF. In an individual patient-level meta-analysis from RCTs, β-blockers were not effective in atrial fibrillation (AF), but in sinus rhythm, they reduced all-cause and CV mortality in HFrEF and HFmrEF but not HFpEF *(Figure 2)* (58). Similarly, in a posthoc analysis from Candesartan in Heart failure – Assessment of moRtality and Morbidity (CHARM), candesartan reduced the composite of CV death and HF hospitalization in HFrEF (where 57% received concomitant ACEi), and HFmrEF (27% ACEi) but not HFpEF (16% ACEi) (59). Currently, drugs recommended in HFrEF are not recommended in HFmrEF, but these data suggest that they may be effective, and novel pragmatic trials should test this hypothesis (46).

Comorbidities

In diabetes mellitus, SGLT2 inhibitors modestly lower HbA1c. But in EMPA-REG (10% HF at baseline), empagliflozin reduced HF hospitalization by 35% (60) and in CANVAS (14% HF at baseline), canagliflozin reduced HF hospitalization by 33% (61). This has generated considerable interest in SGLT2 and also SGLT2/1 inhibition in HF (62, 63) and several trial programs are underway (64) to address whether SGLT2/1 inhibitors in combination with diuretics can improve outcomes in prevalent HF, with HFrEF, HFmrEF, and/or HFpEF, and with and without diabetes.

Recent real-world data suggest that AF is more common in HF than previously believed, at 53% in HFrEF, 60% in HFmrEF and 63% in HFpEF in one generalizable study (54). In CASTLE-AF, catheter ablation in patients with HFrEF (EF <35%) and paroxysmal or persistent AF appeared to reduce combined HF hospitalization and all-cause mortality (65) although these result have not yet been published. In RACE 3, in patients with HF and persistent AF who underwent electrical cardioversion, a concomitant strategy of cardiac rehabilitation, statins, an ACEi or ARB, and an MRA, resulted in maintained sinus rhythm at 1 year in 75% of patients, compared with 63% in the usual care group (66).

Iron deficiency affects as many as half of patients with HFrEF, irrespective of anaemia (67), and recent animal studies suggest that this occurs through impaired cardiomyocyte mitochondrial respiration and adaptation to increases in workload (68). Intravenous iron treatment results in considerable improvements in 6MWT and quality of life, and a meta-analysis suggest that it also reduced HF hospitalization (69). It would be appealing to treat with oral rather than intravenous iron, but bioavailability is low and the large IRONOUT-HF trial showed that oral iron did not improve peak VO2, 6MWT, KCCQ score, or NT-proBNP levels (70).

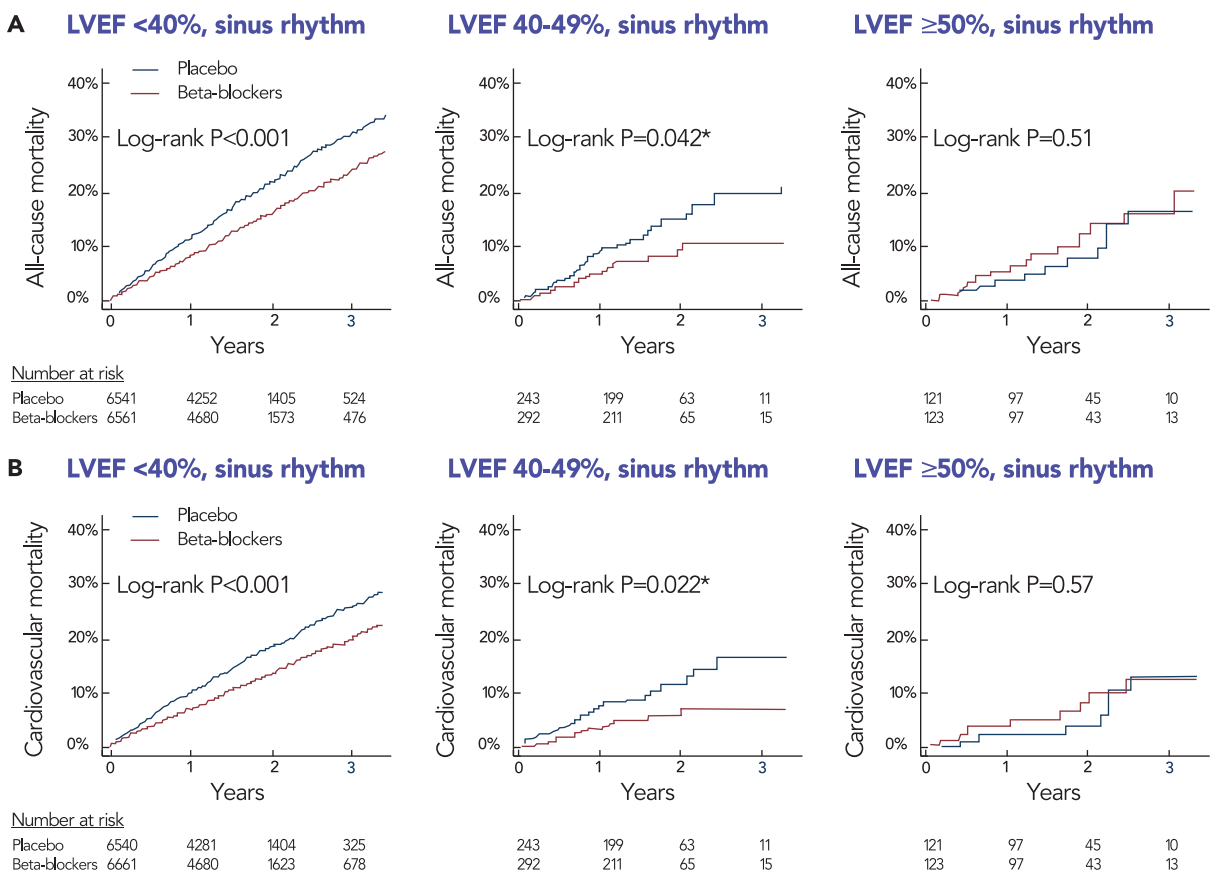

FIGURE 2. All-cause mortality (A) and cardiovascular mortality (B) in patients with sinus rhythm and heart failure with different ejection fraction categories treated with ß-blockers vs. placebo. From an individual patient-level analysis of double-blind randomized trials (58)

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Acute heart failure

On the basis of the ACS concept of "time is muscle" (1), the initial presentation of acutely decompensated HF may represent a period of substantial myocardial vulnerability (71). As such, the early intervention with an intravenous vasodilator has been proposed as a therapeutic goal to reduce cardiac-wall stress and myocardial injury, and ultimately long-term prognosis in patients with AHF (71).

In the TRUE-AHF trial, a randomized, double-blind, parallel-group, placebo-controlled, event-driven trial, however, ularitide given at a median of 6 h after evaluation did not reduce the composite endpoint of 48 h clinical course and 15 month CV mortality (72). Similarly, early administration of serelaxin did not improve the composite endpoint of worsening HF at 5 days or CV death at 6 months in RELAX-AHF2 (73). Interestingly, an observational study suggested that treatment with intravenous loop diuretic within 1-h of presentation to the emergency department was associated with lower in-hospital mortality (74), but the observational nature of this study precludes any conclusions regarding optimal type or timing of AHF interventions.

In BLAST-AHF, a biased ligand of the angiotensin II type 1 receptor did not reduce dyspnoea, worsening HF or hospital length of stay (75). Another concept is early aldosterone inhibition, but in ATHENA-HF, 100 mg of spironolactone compared to placebo did not improve natriuretic peptides or clinical measures (76). Thus by end of 2017, numerous interventional strategies in AHF have failed, including continuous diuretics infusion, ultrafiltration, vasodilators and inotropes.

Advanced heart failure

In patients with severe refractory symptoms despite optimal medical management, quality of life and prognosis are dismal. The remaining options include heart transplantation (HTx), durable mechanical circulatory support (MCS), and palliation. After 30 years of remarkable success of HFrEF drug trials (1, 2), it is notable that In 2017 we celebrate 50 years since the first HTx performed in

1967, and indeed the establishment of HTx as an option paved way for the worldwide HF referral centres and research programs that brought us the subsequent advances in HF pharmacotherapy.

Similarly, implantable left ventricular assist devices (LVADs) were introduced already in the 1960s. In recent years, outcomes with HTx (77) and with LVAD both as bridge to transplantation and as destination therapy (78) have improved worldwide. However, HTx is associated with complications and studies are suggesting immunosuppression should be more individualized (79). The number of HTx procedures performed are stagnant (77) and LVAD use is increasing only modestly (78). Despite remarkable effect on mortality, LVADs are still limited by complications. Modern small centrifugal continuous flow LVADs appear to reduce the risk of thrombosis in the device (80) but concerns over stroke and bleeding, right ventricular failure and infection through the external driveline remain. In the PAL-HF trial, interdisciplinary palliative care compared with usual care showed benefits in quality of life, anxiety, depression, and spiritual well-being (81). It is increasingly recognized that the scarcity of donor organs and the still high cost and complications with durable MCS demand especially careful selection, considering both indications and benefits as well as contraindications and risks.

Novel interventional strategies

As much as we need to focus on optimal utilization of existing therapy, HF remains a chronic, incurable, generally irreversible, and still debilitating syndrome, and novel inventive approaches have continued appeal. A new myosin activator which improves impaired contractility, omecamtiv mecarbil, was studied in the phase II study COSMIC-HF (82). Titration guided by pharmacokinetics resulted in improved cardiac function and decreased NT-proBNP (82). A Phase III trial is ongoing. Stem cell therapy has generally proven disappointing, but in the exploratory REGENERATE-IHD and CHART-1, intramyocardial injection of autologous bone-marrow derived cells in ischaemic cardiomyopathy appeared safe and improved EF, New York Heart Association (NYHA) class and NT-proBNP, and left ventricular (LV) end-systolic and diastolic volumes (83–85). Novel radiocarbon (14C) techniques allow assessment of cardiomyocyte turnover dynamics and may provide a future foundation for regenerative strategies (86). The ESC Task Force for stem cells in myocardial infarction and HF (87) and a global position statement on cardiovascular regenerative medicine (88) outline challenges for the stem cell field, and standardization of animal models, clinical trials and regulatory procedures are put forth as necessary for future success. Gene 'editing' targeting Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) is a promising technique with broad applications that has been used e.g. to edit hypertrophic cardiomyopathy causing genes in human embryos (89).

Conclusions

This has been another year with many new trials reporting in HF. However, none of them will change clinical practice at present. A major challenge for the practising physician is to make sure that eligible patients with HFrEF receive guideline recommended care, and a major challenge for the HF community is to develop effective interventions in HFpEF and AHF.

Conflict of interest

L.H.L. reports grants and/or personal fees from Novartis, AstraZeneca, ViforPharma, Bayer, Sanofi, Relypsa, Amgen L.K. reports grants and other from Novartis, grants and other from AstraZeneca, outside the submitted work. F.R. reports grants and personal fees from SJM, personal fees from Servier, personal fees from Zoll, personal fees from AstraZeneca, personal fees from Sanofi, personal fees from Cardiorentis, grants and personal fees from Novartis, personal fees from Amgen, personal fees from BMS, personal fees from Pfizer, personal fees from Fresenius, personal fees from Vifor, personal fees from Roche, personal fees from Bayer, personal fees from Abbott, outside the submitted work. K.S. has received personal fees from Amgen, Astrazeneca, Novartis, Servier and Vifor Pharma.

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