2017 HFA Congress

Heart Failure Association

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PEER-REVIEWED CONFERENCE REPORT

Late Breaking Trials
Results from the multicentre RELAX-AHF-2 trial: no significant safety concerns using serelaxin. The trial showed encouraging data, particularly on troponin release and the impact on worsening of heart failure in the hospital.

read more on PAGE 3

Heart Failure and Diabetes
It is important to choose the right anti-diabetic in patients with acute and chronic heart failure, because not all anti-diabetics are heart-friendly.

read more on PAGE 8

Biomarkers in Acute Heart Failure
Biomarkers become the corner-stone in the diagnosis and prognostication of heart failure, they are indispensable for the daily clinical practice.

read more on PAGE 12

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Editor Prof. dr. Rudolf de Boer, University of Groningen, the Netherlands

Contents

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Letter from the Editor

Prof. dr. Rudolf de Boer

Dear Reader,

This years' ESC HF congress was hosted by the City of Light, Paris. The congress is one of the flagships of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC), welcoming well over 5,000 attendants.

The congress kicked off with two major trials: the RELAX-AHF 2 (serelaxin) and TRUE-HF (ularitide), which were simultaneously published in the New England Journal of Medicine. Another major focus of the congress was the implementation of the 2016 heart failure guidelines, featuring several sessions with lively discussions. Further, the growing epidemic of heart failure with preserved ejection fraction was discussed, and experts from other fields such as diabetes and atrial fibrillation discussed their importance. A growing and successful track is the basic and translational track, in which working mechanisms of old and new drugs, of cardiomyopathies and other aspects of HF are addressed in more detail.

Paris was a fantastic venue, the Palais de Congrès being centrally located within walking distance of l'Arc de Triomphe, les Champs-Elysées, and la Tour Eiffel.
ESC HF 2017 turned out to be a wonderful "rendez-vous with the future" and next years' congress will be in another historical and vibrant city, Vienna, with the theme: "classical repertoire, modern instruments".
I sincerely hope to meet all of you again!

With my warmest regards,
Rudolf de Boer

Cardiologist, UMC Groningen, the Netherlands
Fellow of the European Society of Cardiology (FESC)
Fellow of the Heart Failure Association (FHFA)
HFA Board member

Biography

Rudolf de Boer (1972, Gouda, the Netherlands) is a Clinical Cardiologist and a Full Professor of (Translational) Cardiology at the University Medical Center Groningen. He studied medicine in Groningen and completed a post-doctoral fellowship at Harvard Medical School, Boston, USA.
His basic research focuses on cardiac remodeling, fibrosis, metabolic changes and diabetes. He connects mechanisms with clinical data e.g. from the LifeLines study, of which he was a founding member the scientific committee. His clinical interests span from inherited cardiomyopathies to end-stage heart failure.
Dr. de Boer has authored and co-authored over 250 articles in peer reviewed journals and wrote over 10 book chapters. He was appointed a Fellow of the European Society of Cardiology (ESC) in 2010, is the current the president of the Heart Failure Working Group of the Dutch Society of Cardiology and Board Member and Chair of the Basic Section of the Heart Failure Association (HFA) of the ESC.

Interview with

Prof. dr. Frank Ruschitzka

University Hospital Zürich (Switzerland), president of the Heart Failure Association (HFA)

Interview by Dr. Susanne Kammerer

Heart failure is moving truly towards centre stage within cardiology

What are the highlights of this year's Heart Failure convention?

First of all, we had some exciting new trials being presented in the field of acute heart failure which well, in a way, were a bit sobering, though. Thus, the RELAX-HF trial with 6,600 patients in acute heart failure assessing the hormone serelaxin was presented. Physiologically, this hormone prepares the expecting mother for the hemodynamic challenges of pregnancy, thus providing the rationale for testing this hormone in patients with acute heart failure. Unfortunately, it showed us that short term infusion for 48 hours doesn't improve outcomes six months later. It is a daunting proposition to think that the short-term infusion would change outcomes after six months. There were some encouraging data with this drug presented, though, particularly on troponin release and the impact on worsening of heart failure in the hospital.

We also heard the results of the TRUE-AHF trial that I was involved in. In this trial patients were treated with ularitide, the chemically synthesized form of the human natriuretic peptide urodilatin. Similar to RELAX-AHF, TRUE-AHF was neutral on the primary outcome. Interestingly, Milton Packer presented results from a post hoc analysis that only included eligible patients. In this post-hoc analysis, ularitide provided at least some symptom relief. This comes with all the cautionary remarks of a post-hoc analysis, though.

Taken together, it`s now about time to rethink how we will be designing trials in acute heart failure in the future. In contrast to acute coronary syndromes, there is not one key plaque rupture or thrombus formation equivalent in acute heart failure. There is an obvious need to better understand the enemy. At the time, the patient is admitted to the hospital, the ship may have already sailed. As such, in the future we may want to intervene and infuse vasodilators, if at all, earlier and longer or both.

We have had a lot of other, great trials and great science presented here at Heart Failure 2017. The annual HFA congress is the premier heart failure event in the world, by far. This year, we had more than 5,000 healthcare professionals from over 100 countries. It's not only the size that matters, the energy, the positive vibe at this congress was literally palpable – the rooms were packed throughout the congress.

If you are looking for networking, for science, for education, or if you want to get an update on the latest developments in heart failure, this is the place to go. Heart failure is the one speciality within cardiology that is moving truly towards centre stage.

Regarding acute heart failure, do you think there are any new biomarkers which could allow us to identify patients earlier?

Biomarkers remain surrogates, surrogates of outcome. There was to some extent a disconnection between biomarkers and clinically relevant outcomes in TRUE-AHF and RELAX-AHF. Indeed, serelaxin reduced troponin and didn't impact the outcome. On the other hand, ularatide did not reduce troponin levels, but was associated with lower N-terminal pro-brain natriuretic peptide levels.

Are there any new features integrated in this years' congress?

We have lots of new features in this year´s meeting. For example, how do I translate guidelines into practice? The major hurdle in guideline implementation is that the doctors, in the end, they don't practice it. We need to be even more hands on, more practical, more translational. Simple top-down listening you can do online.

But here you learn and people tell a little bit off-the-record what they do. For example, this year we introduced the so called grand debates on important topics or controversies in heart failure. First, an expert presents the clinical case and provides the rationale and thereby setting the stage for a debate between two discussants. We try to modify the concept of debate sessions to where we put more emphasis on someone giving guidance first, being a referee and a moderator, and then really breaking it down to chewable bits, that people in the end go out there and say that's how we should do it.

Late-Breaking Trials

Late-breaking trials I: Focus on acute heart failure

The first late-breaking session features what meeting organisers called a „deep dive" into 2 major studies of IV vasodilators for acute decompensated heart failure (ADHF).

Ularitide: no influence on cardiovascular mortality at 36 months

The vasodilator ularitide failed to show long-term benefits in the TRUE-AHF trial and there were no favourable effects on a hierarchical clinical composite endpoint at 48 hours (which included moderate or marked improvement in symptoms at 6, 24, and 48 hours without in-hospital worsening heart failure or death) [1-2].

In this trial, 2,157 patients with AHF were randomised to a continuous intravenous infusion of ularitide (15 ng/kg/min) or placebo for 48 hours. Dr. Milton Packer said that he was "puzzled by the lack of benefit with ularitide for the hierarchical clinical composite endpoint, because the drug exerted its expected haemodynamic benefits, such as reducing BP and cardiac wall stress and promoting haemoconcentration". Dr. Packer subsequently discovered that 17% of patients in the study were ineligible according to the study's original protocol—largely because of the concomitant use of prohibited intravenous medication. This may be an important issue: ularitide significantly improved dyspnoea in the 83% of patients, who had been eligible for the trial. In contrast, in the 17% of patients identified as ineligible, the infusion was associated with adverse outcomes.

"What is absolutely amazing is that the drug was significantly better in eligible patients and significantly worse than placebo in ineligible patients. So not only did the two groups respond differently, they responded in opposite directions", said Dr. Packer. Importantly, this finding was post-hoc and therefore merely hypothesis-generating. Dr. Packer discussed that it may be possible for a drug to potentially work, but for a trial not to find it. It is possible for a trial design that the inclusion criteria are followed, However, safety still has to be guaranteed for patients having IV treatment.

Serelaxin fails to show long-term benefit

The much-awaited results of the multicentre RELAX-AHF-2 trial enrolling approximately 6,600 patients hospitalised for acute heart failure came as a surprise: the trial met neither of its two primary endpoints "cardiovascular mortality at 180 days" (8.7% and 8.9% for serelaxin and placebo respectively) and "worsening heart failure through day five" (6.9% and 7.7%, respectively, P=0.97) [3].

In RELAX-AHF-2, patients were randomised within 16 hours from presentation to 48-hour intravenous infusions of serelaxin (30 µg/kg/day), a bioengineered version of the human hormone relaxin 2, or placebo, both in addition to standard of care.

In addition, serelaxin had no beneficial effect on the secondary endpoints of all-cause mortality at 180 days, length of initial hospital stay or the combined endpoint of cardiovascular death or rehospitalisations due to heart/renal failure through day 180. The 180-day curves for these secondary end points were almost superimposable. There were no significant safety concerns with serelaxin. "In RELAX-AHF-2 we continued to show that serelaxin was safe, but unfortunately, we did not find that it was also efficacious," said co-principal investigator Professor Marco Metra. "It is concerning that the findings of this trial should be so disparate from the prior RELAX-AHF trial."

In the smaller RELAX-AHF trial, serelaxin met its primary endpoint of improving dyspnoea through day five in patients admitted for AHF (P=0.007), a result was driven almost exclusively by an improvement in worsening heart failure. Compared to placebo, serelaxin also reduced worsening heart failure by 47% through day five and both all-cause and cardiovascular mortality by 37% through day 180 [4].

Regarding the results of both the TRUE-AHF and the RELAX-AHF-2 trials Dr. Frank Ruschitzka commented. "We were misled by our analogy with acute coronary syndromes. It was to start with, I think, always a daunting proposition to believe that a short-term infusion, no matter what, 24 or 48 hours, would have an effect after 6 months".

Women with peripartum cardiomyopathy may benefit from bromocriptine

The use of bromocriptine to treat peripartum cardiomyopathy (PPCM) appears to be associated with significantly improved left ventricular (LV) recovery and low morbidity [5]. Only 1 week of bromocriptine treatment seems to be sufficient in most patients.

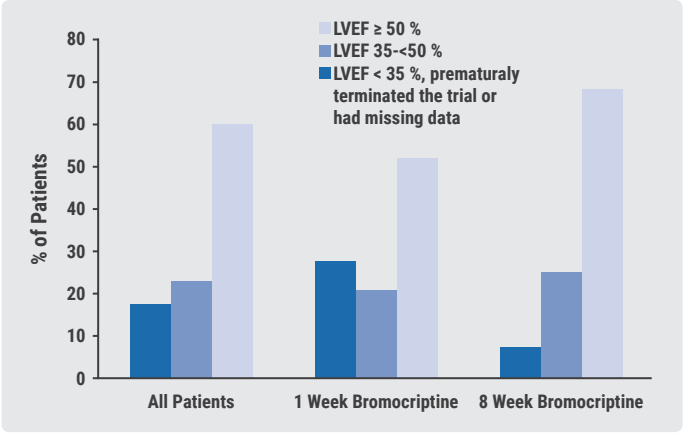
The multicentre proof-of-concept study randomly assigned

63 postpartum PPCM patients with LV ejection fraction (LVEF) ≤35% to short-term (bromocriptine, 2.5 mg for 7 days) or long-term bromocriptine (8 weeks: 5 mg for 2 weeks, followed with 2.5 mg for 6 weeks) treatment, in addition to standard heart failure therapy. The primary endpoint was LVEF change (delta) from baseline to 6 months, assessed by magnetic resonance imaging. Secondary endpoints were hospitalisation for heart failure, cardiac transplantation, LVAD implantation, and death. In a previous study, patients not treated with bromocriptine fully recovered in 37%, whereas 37% remained in severe heart failure, 19% needed a heart transplant and/or an LVAD, and mortality was 15%. In the presented bromocriptine study, 62% of patients fully recovered, 3% remained in severe heart failure, and no patient needed a heart transplant, required an LVAD or died (Figure 1).

Prof. Denise Hilfiker-Kleiner and Johann Bauersachs concluded that the therapy was safe in PPCM for one- and eight-week treatment. Furthermore, they found that it was associated with significantly improved LV recovery with no difference between groups. Comparisons with prospective patient cohorts not treated with bromocriptine indicate beneficial effects of the addition of bromocriptine for at least one week to standard heart failure treatment.

"Currently, patients with PPCM obtain standard therapy for heart failure. But so far, no therapy exists that particularly addresses the pathophysiology of PPCM, for which more and more evidence is accumulating that prolactin and specifically its cleaved angiostatic form of 16 kDa prolactin, plays a role." Both investigators told that more data are required to confirm the effect of bromocriptine "although our study included 63 patients and is the largest randomised study so far in this relatively rare disease".

Figure 1 Treatment with bromocriptine for 8 weeks was associated with higher number of patients displaying full recovery after 6 months follow-up compared to the 1-week treatment



The worldwide PPCM registry organised by the EURObservational Research Programme from the HFA/ESC will provide more data.

"It also appears, that a short low-dose bromocriptine therapy is sufficient in most forms of PPCM. However, our own experience suggests that critically ill patients (that is, those with a baseline LVEF <25% and cardiogenic shock) may profit from a prolonged treatment with a higher initial dosage of bromocriptine", told the investigators. However, this hypothesis needs to be tested in a prospective randomised outcome trial.

IGF-1: promising new kid on the block?

Insulin-like growth factor 1 (IGF-1) at very low doses in the nanogram range showed to improve survival in large animal models of acute myocardial infarction. Its cytoprotective effects in the infarct/border zone prevented infarct expansion and LV remodelling. In a small trial, safety and efficacy of 2 low doses of intracoronary IGF-1 were assessed in patients with myocardial infarction with ST elevation (STEMI) with reduced LV function [6]. As Prof. Noel Caplice pointed out, IGF had no influence on the change in global LVEF from baseline to 8 weeks (primary endpoint). However, the agent was safe and significantly improved LV remodelling changes at 2 months post-therapy. Further studies of this remodelling effect are warranted.

Late-breaking trials II: Chronic heart failure

Highlights of the second late-breaking sessions were an analysis of the EMPA-REG Outcome trial: the choice of the antidiabetic drug empagliflozin might be able to slow decline in kidney function.

Empagliflozin preserves kidney function in type 2 diabetes

Short-term treatment with the sodium-glucose co-transporter-2 (SGLT2) inhibitor empagliflozin attenuated renal hyperfiltration in type 1 diabetes, likely by affecting tubular-glomerular feedback mechanisms [7]. "This trial and several other mechanistic studies were highly promising and suggested that empagliflozin has renoprotective effects," explained Professor Alfred Cheung. These data for empagliflozin led to the prespecified renal endpoints in the EMPA-REG OUTCOME trial—which, overall, found that empagliflozin significantly reduced cardiovascular outcomes in patients with type 2 diabetes with or without heart failure at baseline. In this present analysis, Cheung further examined the renal endpoint results of the EMPA-REG OUTCOME trial.

In the EMPA-REG OUTCOME trial, 7,020 patients with type 2 diabetes, established cardiovascular disease (but not necessarily heart failure) and an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73 m^2 were randomised to receive empagliflozin 10 mg or 25 mg or equivalent placebo. The drug caused an initial acute reduction, but was followed by a long-term stabilisation in eGFR in patients with type 2 diabetes independent of whether or not patients had heart failure at baseline.

"The potential renal effects of empagliflozin should be further investigated in studies specifically targeting various populations, such as that of patients with chronic kidney disease", suggested Prof. Cheung. Two such studies, both part of the EMPEROR HF trial programme, have already been initiated. In addition to cardiovascular endpoints, EMPEROR-Reduced will evaluate the kidney effects of empagliflozin in patients with heart failure and HFrEF (with or without type 2 diabetes) while EMPEROR-Preserved will examine the drug in this context in patients with preserved ejection fraction (again, with and without type 2 diabetes). Another drug in this class, dapagliflozin, will be tested in patients with heart failure and renal failure, in the DAPA-HF and DAPA-CKD trials, respectively, both of which are currently recruiting.

CHARM-trial demonstrates benefit of candesartan regardless of ejection fraction

New results from the CHARM trial indicate that candesartan provides a similar benefit in patients with mid-range ejection fraction heart failure (HFmrEF) as it does in patients with HFrEF [8]. As Prof. Lars H. Lund pointed out, patients with HFmrEF—according to the 2016 European Society of Cardiology definition—have "symptoms and signs of heart failure, elevated levels of natriuretic peptides and some evidence of structural or functional heart disease". He added that the category of HFrEF (40–49% ejection fraction) sits between HFrEF (ejection fraction <40%) and heart failure with preserved ejection (ejection fraction ≥50%). The original CHARM trial programme only divided patients into HFrEF and HFpEF.

Therefore, the aim of the present study was to evaluate the use of candesartan in patients who come under this novel category of HFmrEf.

Patients included in the original CHARM study were aged 18 or older, were in New York Health Association (NYHA) class II–IV heart failure symptoms of at least four weeks' duration and had a history of hospital admission for a cardiac reason. Of the 7,598 patients who participated in the trial, 1,322 (17%) were in the HFmrEF category and they were intermediate between HFrEF (n=4,323; 57%) and HFpEF (n=1,953; 26%) in terms of their history of hypertension, NYHA class and body mass index. However, HFmrEF patients resembled HFrEF patients in regard to most other characteristics, including age, systolic BP, gender, previous myocardial infarction and atrial fibrillation.

Over a mean follow-up of 2.9 years, the effect of candesartan on the primary outcome of CHARM (time to composite of cardiovascular death or first hospitalisation for heart failure) in the HFmrEF range was similar to that in the HFrEF range. The results were consistent for time to first and for recurrent heart failure hospitalisation. These data therefore suggest that patients with HFmrEF might benefit from evidence based therapies that work for patients with HFrEF, while they appear ineffective for patients with HFpEF.

Another negative HFpEF trial

Heart rate reduction with ivabradine does not improve outcomes in patients with HFpEF: this was the disappointing result of the randomised placebo-controlled EDIFY trial, which assessed whether heart rate reduction with ivabradine improves diastolic function, exercise capacity, and plasma levels of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) in patients with HFpEF [9]. "The rationale for testing ivabradine in HFpEF is that the left ventricle is abnormally stiff in this condition, which leads to an impaired LV filling and an increase in pressures in the left atrium and upstream. Slowing down the heart rate would be expected to improve LV filling and therefore, cardiac function", explained Prof. Michel Komajda.

In the trial, a total of 171 patients were studied (at 8 centres) and were split into 2 groups: 1 group (87 patients) received ivabradine (titrated to a target dose of 7.5 mg twice daily) and the other (84 patients) received equivalent placebo. Patients were enrolled if they were in NYHA class II–III, in sinus rhythm, had a heart rate of ≥70 bpm, NTproBNP of ≥220 ng/mL (or BNP of 80 pg/mL), and preserved LV ejection fraction (LVEF ≥45%).

Ivabradine was associated with a significant reduction in heart rate compared with placebo but was not associated with significant improvements in diastolic function, exercise capacity or NT-proBNP. "Our trial does not suggest any benefit of heart rate reduction in HFpEF" concluded Prof. Komajda.

Africa and India: problem kids regarding HF mortality

Death in patients with heart failure is inversely related to the wealth of the country they live in, according to results from the INTERCHF study [10]. Death rates in India and Africa were 3 to 4 times higher than those documented in Western countries (Figure 2).

"Our study was conducted to fill large gaps in knowledge about congestive heart failure in non-Western countries", said Dr. Hisham Dokainish.

The INTERCHF study was an observational cohort study that enrolled 5,823 patients with heart failure in 16 countries grouped into 6 regions: Africa, China, India, the Middle East, Southeast Asia, and South America.

Data on each patient was collected at baseline, 6 months and 1 year and entered into the electronic data management system at the public health research institute centre.

At 6 months and 1 year data was collected on the frequency and cause of any hospitalisations in the previous 6 months. Information was also recorded on death and cause of death. The investigators calculated death rates in each region and adjusted for 20 variables which included demographic, clinical and socioeconomic factors, medications and cause of heart failure.

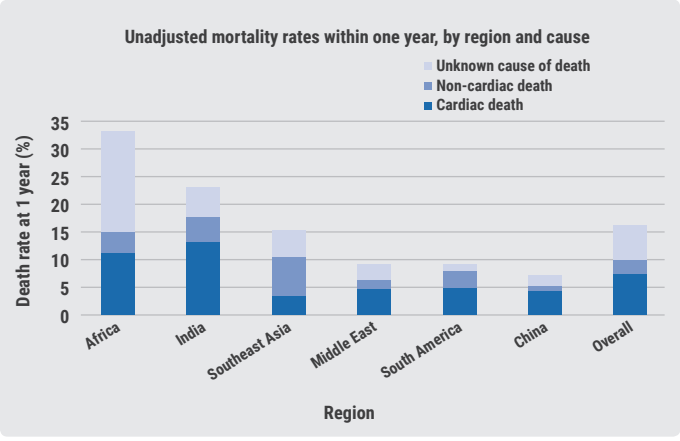
The overall all-cause mortality rate for the entire study population was 17%. It was highest in Africa (34%) and India (23%), intermediate in Southeast Asia (15%), and lowest in the Middle East (9%), South America (9%) and China (7%; Figure 2).

Dr. Dokainish said: "Mortality in patients with heart failure was inversely related to the wealth of the country. The poorer the country, the higher the mortality and the richer the country, the lower the mortality".

Late-breaking trials III: Innovative and device therapies

This session allowed a glimpse of the future: will high-risk patients be monitored with the help of implantable devices? After a couple of drawbacks in previous studies, cardiac stem cells seem to play a role in patients with ischaemic heart failure.

Figure 2 Unadjusted mortality rates within one year, by region and cause [1]



Multisensor device identifies patients at highest risk for HF events

The MultiSENSE trial showed that a multisensor cardiac implanted device accurately identifies an increased risk of worsening heart failure and thus can help triage resources more effectively for those at greatest risk [11].

Dr. Roy Gardner found that the device alerts identified periods of time with an elevated risk of heart failure events, independent of baseline clinical predictors. A positive alert was associated with a 10-fold risk for heart failure events, even after adjusting for baseline clinical predictors such as NT-proBNP. They concluded that dynamic assessment using the alerts can automatically identify periods of time in which patients are at significantly increased risk of worsening heart failure, and help better triage resources to this vulnerable patient population.

The multicentre trial enrolled 900 ambulatory heart failure patients implanted with the multisensory device that was able to collect data for up to one year from North America, Europe and Asia. The non-randomised feasibility, significant risk investigational device exemption study used the chronic ambulatory data collected from multiple sensors to develop an algorithm for early detection of worsening heart failure. Heart failure events were defined as either heart failure admissions or unscheduled visits with augmented intravenous heart failure treatment and were independently adjudicated.

"The device is comprised of a diverse set of implanted sensors built into a cardiac resynchronisation therapy-defibrillator device that has been designed to identify different pathophysiological changes associated with common signs and symptoms of heart failure", explained Dr. Gardner. These sensors include heart sounds, respiration rate, volume, thoracic impedance, night heart rate and daily activity. Multiple changes from these sensors are aggregated and given a weight based on an individual's daily risk of worsening heart failure to create a composite index. This index is updated daily and an alert is issued when the index crosses a user-definable threshold.

Advantageous in patients that need cardiac resynchronisation therapy

Thus, with the inbuilt sensors, data can be collected non-invasively in patients that need a cardiac resynchronisation therapy-defibrillator device therapy. In contrast, biomarkers such as BNP or NT-proBNP are known to be highly predictive of death or heart failure events, but are clinically invasive as they require a blood draw. Recently, multivariate models

have been developed on the heels of large clinical trial data, but they require numerous clinical variables, many of which are also dependent on a blood sample.

The advantage of the new device is its non-invasive prediction of heart failure in at-risk patients. "While this device shows promising performance and has been validated, using data from the MultiSENSE study with high sensitivity, weeks of advance notice, and a low burden rate, future studies are needed to understand if intervening in response to an alert from this device can mitigate the risk of impending heart failure events and thus improve outcomes", concluded Dr. Gardner.

Can cardiopoietic stem cell injections reverse left ventricular remodelling?

In the CHART-1 trial, endomyocardial injections of cardiopoietic stem cells were associated with beneficial effects on LV remodelling in patients with ischaemic heart failure. The greatest effect was seen in patients receiving fewer than 20 injections [12].

Multiple stem cell studies have already evaluated various cell types for the treatment of HF. However, most of the previous results have been relatively disappointing. The reasons for this relative failure are manifold, but may include improperly selected patient population, ineffective cell therapy, inefficient delivery system, poor cell retention and limited sample sizes of the studies. The strategy employed in CHART-1 relied on guided cardiopoiesis using the patient's own mesenchymal stem cells as the basis for a reparative response. "Early proof-of-concept studies and the C-CURE clinical study suggested that this strategy holds promise," said Prof. John Teerlink.

In this study, 271 patients with advanced chronic heart failure, secondary to ischaemic disease, and LV ejection fraction <35% were randomised to receive up to 600 x 106 bone marrow-derived, lineage-directed autologous cardiopoietic stem cells (n=120) or a sham procedure (n=151). Changes in LV structural and functional measures were reviewed at 26, 39 and 52 weeks. Endomyocardial cardiopoietic stem cell injection was associated with mean improvements in LV end diastolic volume and LV end-systolic volume.

Long-term treatment benefit

At 52 weeks, LV end systolic volume decreased by 12.8 mL from the baseline 172.6 mL, which was more in cardiopoietic stem cell treatment patients compared to controls (P=0.017) and the LV end-diastolic volume decreased by 17 mL from the baseline 239.9 mL, which was more in cardiopoietic stem cell treated patients compared with controls (P=0.06).

The benefit of the injections at 52 weeks on LV end diastolic volume was maintained after multivariate adjustment for age, history of myocardial infarction, systolic BP, and baseline LV ejection fraction and LV ejection end-diastolic volume.

Of note, patients receiving ≤16 injections had larger mean improvements in LV dimensions than patients receiving ≥20 injections.

Possible explanations for this finding include local myocardial damage from the multiple injections, compression from the volume injected and the number of cells delivered.

"These exciting data from CHART-1 provide a path forward for identifying a patient population more likely to benefit from this therapy and offer guidance for the optimal administration", concluded Prof. Teerlink.

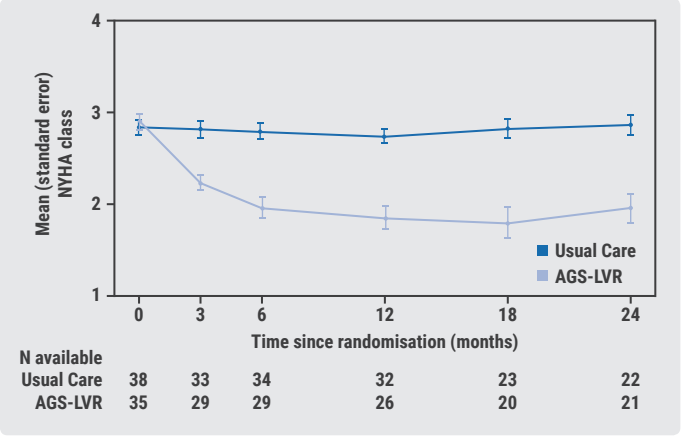
Positive 24 months outcome after injection of alginate hydrogel

Another fascinating new treatment modality is Algisyl® (AGS), a device comprised of a sodium-calcium alginate hydrogel.

This was shown in the 24 months follow-up results from Augment-HF, presented by Prof. Andrew Coats [13]. They showed that AGS combined with standard medical therapy (SMT) provided sustained improvements in NYHA Class (Figure 3), patient global assessment and quality of life compared to patients on SMT alone.

The multicentre prospective randomised AUGMENT-HF trial included 78 patients with severe heart failure that were treated with the AGS implant procedure plus SMT (n=38) or SMT alone. Previously it has already been shown that AGS injections can be administered safely, with a superior peak VO^2 increase from baseline.

Figure 3 Change in NYHA function class over time after AGS procedure [13]



Permanent implant gel strength similar to myocardium

The AGS device contains two components that cross-link and gel within 1 hour of admixture forming a permanent implant with a gel strength similar to that of the myocardium. Initially, the method of administration was a trans-epicardial injection via a limited thoracotomy.

However, larger prospective randomised controlled trials are needed to evaluate clinical outcomes such as HF hospitalisations and CV mortality. In addition, there is a new Myo Tec percutaneous delivery system for AGS implantation that should be assessed.

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Heart Failure and Diabetes – A Dangerous Liaison

This year´s inaugural lecture dealt with the intertwining of heart failure and diabetes. Antidiabetic therapy can have a dramatic effect on cardiovascular outcomes, as could be demonstrated in the landmark EMPA-REG outcome trial.

The title of this year's inaugural lecture was a nod to the famous French novel by Pierre Choderlos de Laclos "Les liaisons dangereuses". Prof. Michel Komajda chose this title as a metaphor for the relationship between heart failure and diabetes. "I think the fact that diabetes mellitus is one of the major risk factors for heart failure has been largely ignored," said Prof. Komajda. Until today, heart failure is a common and underestimated complication of diabetes mellitus—with the condition being observed in 30–40% of patients that have heart failure. Patients with both heart failure and diabetes have a worse prognosis [1].

Diabetic patients have a 2.5 higher risk to develop HF: in 2012 the first epidemiological study was performed that provided exact prevalence estimates of heart failure and LV dysfunction in a representative sample of patients with type 2 diabetes [2]. This trial showed that 28% of patients with type 2 diabetes have undiagnosed heart failure. According to the authors, it is really important to unmask these patients as this will have an influence on the management.

Accelerated atherosclerosis

Diabetic patients have a higher risk of heart failure due to associated comorbidities and accelerated and more extensive atherosclerosis. Cardiovascular risk is greatest, when both diabetes and chronic kidney disease are present. Among patients with diabetes and chronic kidney disease, the rate of cardiovascular events is more than twice that among patients with diabetes only [3]. Previous trials have shown

that intensive glycaemic control reduces microvascular but not macrovascular outcomes [4]. In a follow-up of this trial, the intensive control conferred also significant benefit for end-stage renal disease [5].

On the other hand, HF patients have also an elevated risk to develop diabetes, which has a couple of reasons. "They lead a sedentary life style and have a loss of skeletal muscle mass. In addition, there is a hypoperfusion of the pancreas and a chronic neuro-endocrine activation", said Prof. Komajda.

Effective management of type 2 diabetes in patients with heart failure has been challenging, since previously there has been no evidence showing improved HF outcomes with intensive glucose control using existing glucose-lowering medications. This situation changed with the EMPA-REG Outcome trial [6].

EMPA-REG OUTCOME trial: a game changer

"In the large EMPA-REG OUTCOME trial, empagliflozin was associated with not only a benefit for most of the outcomes but also—importantly for those who are specialists in heart failure—with a significant decline in the rate of heart failure hospitalisations. It was so spectacular that the drug is going to be tested in heart failure with or without diabetes", said Prof. Komajda. Empagliflozin inhibits the SGLT2, which leads to increased urinary glucose excretion and improved hyperglycemia, without affecting ß-cell function and insulin resistance. Potentially, empagliflozin may become the treatment of choice for patients with heart failure and diabetes.

The results of EMPA-REG trial were also presented in a lecture by Prof. Per-Henrik Groop. This trial examined the long-term effects of empagliflozin in addition to standard care vs placebo on cardiovascular morbidity and mortality in over 7,000 patients with type 2 diabetes and high risk of cardiovascular events. All included patients had established cardiovascular disease (e.g. prior myocardial infarction, coronary artery disease, stroke, unstable angina or occlusive peripheral arterial disease).

A third less heart failure hospitalisations

The primary outcome was a 3-point Major Adverse Cardiovascular Event, consisting of time to the first occurrence of CV death, non-fatal myocardial infarction or non-fatal stroke. Patients treated with empagliflozin had a 14% risk reduction for this combined endpoint. The hospitalisation for heart failure or cardiovascular death was even lowered by 34% (HR 0.66, P<0.001). The benefit of the therapy was evident very early after starting the therapy. The benefit of empagliflozin was independent of age, eGFR or presence of heart failure or medication at baseline. "It is very astonishing to see this dramatic effect", said Prof. Groop.

In addition, a new analysis of the data shows that new onset or worsening diabetic kidney disease was reduced by 39% (Figure 4) [7]. "I think, SGLT2-inhibition may be an as important innovation as renin angiotensin aldosterone system inhibition", concluded Prof. Groop.

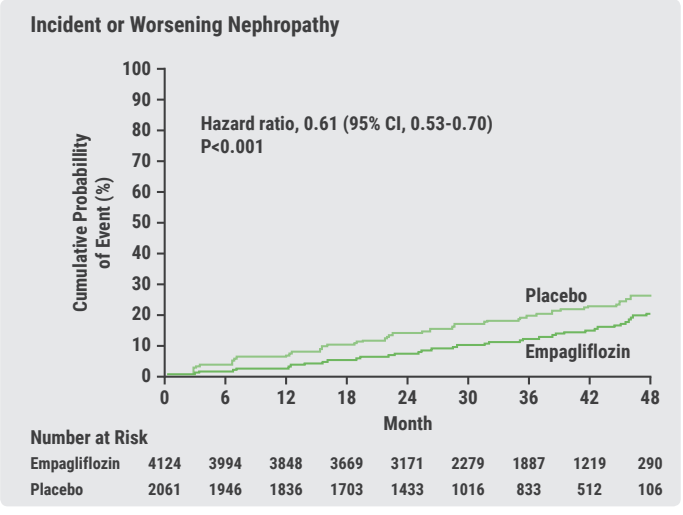
Not all antidiabetics are heart-friendly

As John McMurray pointed out, antidiabetic medications can be harmful, as could be demonstrated for sulfonylurea [8]. Another class of agents, the thiazolidinediones, have shown to increase the risk of heart failure [9]. A higher risk of heart failure could also be demonstrated in the RECORD trial for rosiglitazone [10]. In the SAVOR TIMI 53 trial, patients treated with the dipeptidyl peptidase 4 inhibitor saxagliptin had a significantly elevated risk for heart failure hospitalisations [11]. Furthermore, GLP-1 analogues [glucagon-like peptide-1 receptor agonists], such as liraglutide, failed to show greater post-hospitalistion clinical stability in patients with established heart failure and reduced LVEF who were recently hospitalised [12].

Choosing the right antidiabetic in HF

According to the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, metformin is the treatment of choice in patients with HF [13]. Sulphonylureas should be used with caution and thiazolidinediones are not recommended. Insulin may also exacerbate fluid retention, leading to HF worsening. Regarding the SGLT2 inhibitors, the guidelines emphasise that empagliflozin reduced the risk of HF hospitalisation, however the efficacy in HFpEF and HFrEF patients still requires elucidation.

Figure 4 Empagliflozin reduces the likelihood of new onset or worsening diabetic kidney disease by 39% [7].



According to Prof. McMurray, the positive effects seen in the EMPA-REG trial could be due to the 'glycosuria' and 'natriuresis,' leading to amelioration of systemic glycemic homoeostasis and potential cardio-renal protection. However, the precise mechanisms by which SGLT2 inhibitors affect benefits on the CV systems are yet to be fully elucidated [14]. Further trials will shed light on other groups of heart failure patients. In the EMPEROR-Preserved trial, the efficacy of empagliflozin will be assessed in 4,126 patients with symptomatic HF, but an EF of >40% and NTproBNP levels of >300 pg/ml. The primary endpoint of this trial is cardiovascular death or HF hospitalisation.

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Acute Heart Failure and the Quest for the Ideal Therapy

"Better treatment of patients with AHF remains a major unmet clinical need", said Professor Marco Metra and this summarised the common grounds for the great amount of ongoing research fairly well. A special session updated about new approaches to treat AHF and their different stages of development from animal model to phase 3 studies.

Myosin activation-the way to go?

The pathophysiology of AHF combines a primary cause e.g. structural heart disease or chronic HF that can be triggered by various factors like infections, arrhythmias, hypertension or non-adherence. Response from the myocardial, renal, vascular or neurohormonal system acts as an amplifying mechanism leading to congestion and dysfunction of end organs.

A new drugs bearing high hopes for the future is omecamtiv mecabil (OM) a novel, selective cardiac myosin activator. Prof. John R. Teerlink explained that their concept with OM was to primarily look at the heart itself assuming that improving the heart function will have an effect on the other mechanisms. A drawback of currently used inotropes and inodilators is that they all increase intracellular calcium, correlating to an increase in heart rate, oxygen demand and arrhythmias, while also lowering BP and cardiac efficiency.

Most of us use drugs like dobutamine and milrinone, because we have to. This is despite the knowledge that they can cause bad outcomes. It would be nice to use something that worked a little better. OM is one of the few agents specifically designed for HF. It improves energy utilisation by increasing the likelihood of interaction between active myosin and actin, thereby leading to force production. This results in a longer systole and a bigger stroke volume without causing more calcium in the myocyte nor augmenting myocardial oxygen demand or changing contractility (dP/dt_{max}). Results of early trials were very suggestive of overall improved cardiac performance. "In HF patients with HFrEF on OM essentially normalises the systolic ejection time", explained Teerlink. The phase 2 ATOMIC-AHF RCT randomised over

600 hospitalised AHF-patients with EF ≤40%, dyspnea and elevated natriuretic peptides to 48h IV administration of OM or placebo in 3 sequential, escalating-dose cohorts [1]. The primary endpoint of "dyspnea relief through 48 hours was not met, but a dose to concentration response in terms of LV ejection time was significant in further analyses. Adverse events, especially arrhythmias were not different comparing OM to placebo. Overall the influence of OM on systolic ejection time was consistent and it was encouraging to see that we had a drug that was predictable in its effects. OM has also been investigated as oral agent for chronic HF in COSMIC-HF, where it significantly improved cardiac function [2]. Currently, the phase 3 GALACTIC-HF with over 8,000 patients is enrolling HF patients with HFrEF to evaluate if OM can improve outcomes in chronic HF.

HNO-the right inotrope for AHF?

"Nitroxyl (HNO) has demonstrated its vasodilating effects already in 1992 and influence on cardiac inotropy in 2003", said Prof. Javed Butler.

It is studied through the use of a prodrug, a so-called HNO donor. Abnormalities of calcium handling in myocytes can lead to a negative influence on contractility as well as relaxation of the myocardium. This is where HNO shows the effect in changing multiple parts of the calcium cycle: it makes more calcium available thereby improving contractility, but also accounts for more calcium being taken back out of the cell, thus enhancing relaxation. Moreover, HNO increases calcium sensitivity of the myofilament and acts positive inotropic. In contrast to nitric oxide, HNO is not dependent on oxygen and non-enzymatically reversible. HNO has a much broader pharmacological effect than nitric oxide and generates its influence on the heart without changing the net increase of intracellular calcium. As it works differently from legacy inotropes it should in theory not lead to a higher risk of cardiac death.

Improvements of contractility and relaxation were first shown in animals without a drop in heart rate and lowering of myocardial oxygen consumption. A dose finding study in humans showed a significant reduction in pulmonary capillary wedge pressure. This result was encouraging enough to initiate the presently ongoing phase 2b trial to evaluate safety and efficacy of 48h IV HNO donor vs placebo in about 300 hospitalised patients with AHF and LVEF ≤40%. The study primarily assesses the dose related effects on clinically relevant hypotension, but secondarily also parameters like NT-proBNP and dyspnea. "Do we need yet another short term non-specific AHF study and do we need another study with a vasodilating property, which is given in the hospital over 48 hours, looking at a potential development program in the long run for outcome improvement?" was the critical question of Prof Butler also referring to the TRUE-AHF and the RELAX-AHF2 study results. He foresaw a lot of discussions that may be needed to e.g. define different phenotypes for HF treatments or rethinking changes in treatment plans in order to advance research.

Mitochondria- a promising treatment target?

"The drug that I am going to talk about is different than everything you have heard of as it specifically targets mitochondria and in doing so, in the setting of HF, modifies myocardial energetics", said Prof. Hani N. Sabbah. In HF structural, dynamic and functional mitochondrial abnormalities were proven in heart, skeleton muscle and also the kidney. From these mitochondrial changes result reduced ATP (adenosine triphosphate) production and increased ROS (reactive oxygen species) causing more damage. Cardiolipin is a lipid only present in mitochondria and forming the inner part of its membrane that holds on to the electron transport chain components. It plays a key role in the structure and function of the mitochondria. In HF, ROS oxidises the lipid accompanied by an unfolding of the membrane leading to increased insufficiency of electron transfer. Also, organelle size, numbers and biogenesis of mitochondria are reduced while break up of mitochondrial (fission) increases. "Elamipretide is a small molecule that enters the cell and the mitochondria in the cell and localises itself at the inner mitochondrial membrane where cardiolipin is present, the only lipid it associates with", explained Prof. Sabbah. The presumption is that the tetrapeptide thus normalises the mitochondrial function. First studies with HFrEF dogs treated over 90 days with elamipretide found, at least partial, reversal of mitochondrial abnormalities with significant changes in cardiac output and LV ejection fraction, but without changes in heart rate, BP and de novo arrhythmias. In a small study with older patients (60-85 years) without HF, ATP rose after elamipretide as well as skeleton muscle function. There are 3 ongoing phase 2 trials with elamipretide at the moment comprising about 400 patients with HFpEF and HFrEF. Pre-clinical and early clinical experience with elamipretide back the potential for a first in class drug targeting MC in HF. "The bottom line is a drug that has hope and promise for treating HF patients and patients with other MC diseases as well", Prof. Sabbah concluded [3].

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Biomarkers in Acute Heart Failure

Introduction by Prof. dr. Carolyn S.P. Lam

Biomarkers: an important diagnostic tool in acute heart failure

In a brief interview, Prof. dr. Carolyn S.P. Lam highlights new research regarding biomarkers in acute heart failure. Interview taken on 1 May 2017 by Dr. Suzanne Kammerer.

What is the role of biomarkers in acute heart failure?
Biomarkers have become a cornerstone in the diagnosis and prognostication of heart failure. The natriuretic peptides and troponins, for example, are indispensable for our daily clinical practice in the management of acutely breathless patients.

What are in your eyes the new interesting kids on the block with respect to acute heart failure?
There were a number of new kids on the block highlighted by the speakers in this symposium. Prof. Alan Maisel highlighted ST-2, a marker of fibrosis that gives complementary information to the natriuretic peptides in the acute situation. I appreciated Dr. Tousoulis' point that it is important to have a biomarker that allows us to exclude coexistent conditions in the acute situation such as pneumonia, and procalcitonin was brought up in this context. Dr. Müller gave an excellent talk on high-sensitivity troponin T, convincingly showing that its measurement makes a big difference and should become standard of care in the acute situation. In addition, we discussed cases where there might be confusion regarding the interpretation of high-sensitivity troponin T levels. Finally, Dr. di Somma emphasised the importance to treat the kidney in the acute situation. His emerging data using cystatin C are really impressive.

Do you think, we should already use biomarkers that are not in the guidelines yet – as recommended by one of the speakers?
This is a tricky question. As a clinician researcher, I am deeply interested in understanding these biomarkers better. We really need to understand what we are measuring before we use biomarkers for clinical decisions.

Biomarkers in acute heart failure

Prof. Alan Maisel made a passionate plea for the extensive use of biomarkers in acute heart failure. "If we treat a person for acute HF and this diagnosis is wrong, it can be deadly – therefore, we have to use all we can", said Prof. Maisel. Congestion often does not translate in signs/symptoms. Biomarkers are extremely helpful in finding the right diagnosis, particularly BNP. Used in conjunction with other clinical information, rapid measurement of BNP is useful in establishing or excluding the diagnosis of congestive heart failure in patients with acute dyspnea and are more accurate than physical findings [1]. This is also true in HF patients with preserved ejection fraction: BNP levels are not as high as in patients with HFrEF, but they are still elevated.

"We should really monitor the BNP-levels of our patients and they should be low at discharge", recommended Prof. Maisel. The REDHOT study showed a direct correlation between high BNP values and mortality [2]. Therefore, BNP levels can predict future outcomes and thus may aid physicians in decisions about whether to admit or discharge patients.
In addition, monitoring patients with biomarkers is cost effective and a lot cheaper than X-rays and echo. "A new biomarker I use in addition to BNP is ST-2, which opens the fibrotic pathway", said Prof. Maisel. BNP levels together with ST-2 give synergistic information regarding treatment outcome. Among dyspneic patients with and without acute HF, ST-2 concentrations are strongly predictive of mortality at 1 year [3]. "I do serial ST-2/BNP measurement to guide my therapeutic decisions, although at current it must be emphasized that we have no prospective trial data to support this behaviour, nor to provide insights as to how exactly treat patients differently based on markers", said Prof. Maisel. However, he added that according to Dr. Maisel, it makes no sense to wait for another 10 years until these markers made their way into the guidelines.

Inflammation: a key factor in heart failure

Inflammation is not only important in plaque rupture, but also in the pathogenesis of heart failure: a vicious circle between cell death and inflammation fuels the progression of heart failure. Proinflammatory biomarkers in acute HF are metalloproteinases, cytokines, chemokines, adipokines and cyclo oxygenase 2.
Proinflammatory cytokines activate monocytes that impair myocardial function. Levels of TNF-α are related to higher mortality in heart failure [4].

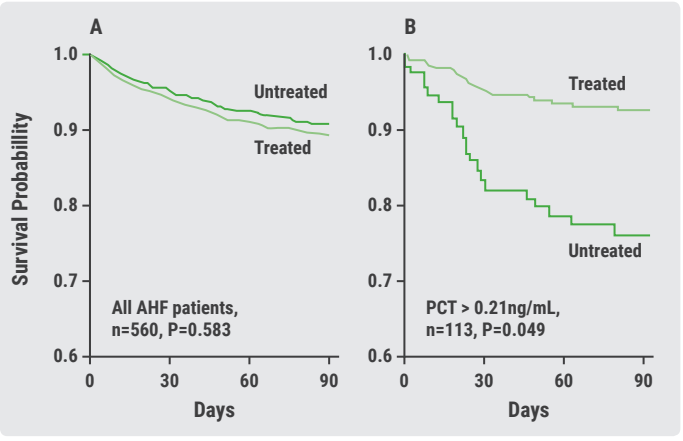
In the critically ill patient, it is often difficult to determine, if symptoms of the systemic inflammatory response are due to underlying infection or other aetiologies. Procalcitonin may be a useful marker of bacterial infection, because procalcitonin expression in parenchymal tissue is induced by bacterial infection. One study has retrospectively shown that patients might benefit from antibiotics, when procalcitonin levels are higher than 0,21 ng/mL (Figure 5; [5]).

Despite being strongly linked to spontaneous (Type I) acute myocardial infarction concentrations of circulating troponins above the 99th percentile of a normal population are also common in the context of both acute and chronic HF", said Prof. Christian Müller. Non-coronary triggers, such as cellular necrosis, apoptosis, or autophagy in the context of wall stress may explain the troponin release in HF, as can toxic effects of circulating neurohormones, toxins, inflammation, and infiltrative processes, among others. In general, when troponin elevation occurs, independent of mechanism, it is strongly predictive of an adverse outcome [6]. "All patients with acute HF should get their troponin values measured", recommended Prof. Müller.
However, one should think of AHF plus myocardial infarction in patients with very high troponin levels and typical ischemic chest pain or new ST elevation.

Do not forget the kidney

"Acute Kidney Injury (AKI) is prevalent in about 20% of patients with acute decompensated HF. Therefore, we should never forget to take a look at the kidney in these patients", recommended Prof. Salvatore die Somma. Biomarkers of AKI would be useful for early management and development of new therapeutic strategies. However, studies with new biomarkers had conflicting results: cystatin C is a marker of glomerular function. "Unfortunately, it does not seem to be of additive value to creatinine in AKI", sad Prof. di Somma. In a trial, the predictive value of serial assessment of cystatin C was not superior to serum creatinine and GFR in distinguishing AKI from non-AKI [7].
Neutrophil Gelatinase-associated Lipocalin, a new biomarker of tubular function also failed. In a trial, plasma neutrophil gelatinase-associated lipocalin was not superior to creatinine for the prediction of worsening renal failure or adverse in hospital outcomes. Therefore, its use cannot be recommended to diagnose acute kidney injury in AHF [8].

Figure 5 Patients with acute heart failure benefit from antibiotic treatment, when their procalcitonin levels are >0.21 ng/ml [6]



AHF= acute heart failure, PCT= procalcitonin

As Prof. di Somma pointed out, proenkephalin is a really interesting new biomarker that could be the light at the end of the tunnel. In a trial that will be published this year, high admission proenkaphalin predicted future increase of creatinine (within 72 h), and low admission proenkaphalin predicted future decrease of creatinine in patients coming to the emergency department [9]. In addition, proenkaphalin predicts renal function and outcome in ambulatory heart failure patients [10].

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Grand Debate:
Vasodilators under the Spotlight

The first Grand Debate, a new feature in this year´s heart failure congress, dealt with the question, whether the novel drug LCZ696 is "ready for prime time".

Prof. John McMurray took a clear position in favour of first-line therapy with neprilysin on top of standard treatment. "In the PARADIGM-HF trial, we saw a significant risk reduction within 30 days, when we gave the drug combination sacubitril/valsartan. We did not see any signs of cognitive signals", said Prof. McMurray. As a consequence, the drug got both a first line recommendation of the FDA and ESC.
The cornerstone of treatment for heart failure with HFrEF is to use a combination of drugs: an angiotensin converting enzyme (ACE) inhibitor (or angiotensin receptor blocker, ARB, for those intolerant to ACE inhibitors), a beta-blocker, and a mineralocorticoid receptor antagonist (MRA). Prof. McMurray said: "We know with a great deal of certainty that if you add a neprilysin inhibitor to an ARB, patients will do much better than if they just get conventional treatment. They will be less likely to die, less likely to be admitted to the hospital, and less likely to show deterioration in their quality of life over time". He said the results from the PARADIGM-HF trial support this view. "This trial had more than 8,400 patients and it showed a strong statistically significant benefit of adding neprilysin inhibition to conventional treatment, compared to conventional treatment alone. Not only that but also all the other data in the trial were incredibly consistent. "No matter what we looked at, people did better, if they received a neprilysin inhibitor than if they didn't biomarkers, renal function, symptoms, quality of life; it was all better. It was overwhelmingly clear, that neprilysin inhibition added substantially to conventional therapy", concluded Prof. McMurray.
Prof. Mariell Jessup provided the "contra" side to this view. "There were many beneficial findings in the PARADIGM-HF trial using this new class of agent, but there has only been one trial. It was done on stable outpatients who were already on either an ACE inhibitor or an ARB", said Prof. Jessup. Moreover, because of the run-in trial design, patients who were randomised were able to tolerate 10 mg twice daily of enalapril and the target dose of the angiotensin II receptor blocker neprilysin inhibitor (ARNI). "So, truly, the terrific results of the trial were not obtained as 'first-line therapy'", said Prof. Jessup. In her view, sacubitril/valsartan is only suitable for a limited number of patients and there is no evidence to support its role as first-line therapy. She thinks that only after clinicians have developed significant clinical experience with the ARNI drug, and the costs of the drug are clear to clinicians and patients alike, there may be very stable outpatients with newly discovered heart failure with HFrEF who could be initiated on ARNI first before an ACE inhibitor is tried. "However, this is not typically how HFrEF patients present with initial symptoms; they present as decompensated hospitalised patients instead", said Prof. Jessup. "Just because in that patient population it looks good, we do not know what happens to patient with class IV HF. If you expand the population of patients you give the drug, you do not know what happens", concluded Prof. Jessup.

However, Prof. McMurray disagrees, commenting that ARNI use is contraindicated in only a few patients. He added that neprilysin inhibition is always used in conjunction with a renin angiotensin system (RAS) blocker. "The RAS blocking part of the treatment is the main barrier to its use," he explained, adding: "Patients with a very low BP, patients with significant renal impairment, patients with hyperkalaemia, and patients with a history of angioedema shouldn't be given an ACE inhibitor or the combination of a neprilysin inhibitor and a RAS blocker." Prof. McMurray and Jessup both agree that further trials are needed. Prof. Jessup said: "We need to see more investigation into the possible cognitive effects of neprilysin inhibition. I do not think we need another HFrEF trial, but we all need to have more clinical experience with the drug class."
Neprilysin is an enzyme that breaks down the Aβ peptide that forms amyloid plaques in the brain. Therefore, there have been concerns regarding the cognitive effects of the drug. Previous trials did not formally measure cognition, but did include reports of dementia as adverse events and saw no difference between treatment groups
"Until we have other trials I think we have to stick to the facts and stick to the guidelines", concluded Prof. Jessup [1].

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What are the most fascinating innovation in the field of intervention?

We are a specialty that now blends drugs, devices and multidisciplinary interventions. You will note that we added this year more sessions on new percutaneous valvular interventions and particularly on devices, e.g. for CRT (cardiac resynchronisation therapy) and ventricular assist devices. Since this year we celebrate the fiftieth-year anniversary of heart transplantation, we had a great session with Prof. Eugene Braunwald on the future of advanced heart failure therapies.

What is the role of heart failure specialists in the heart team?

The soul of the heart team approach is patient centred care. We put the patient in the middle and we bring the doctors around them. The heart failure doctor works with the other specialists, he is the bridge builder between other members of a multidisciplinary heart team, so we live the heart team. Think about valvular interventions. Valvular disease is also a myocardial disease. Valvular disease, particularly mitral and tricuspid, are often secondary to the underlying ventricular dilatation. As such, if you plan an intervention then you better work with a heart failure doctor on board. They have now become the integral part of most heart teams. In heart failure, we have lived the team approach before the now so fashionable word heart team was coined.

So you think the future is bright for cardiology?

It could not be brighter! This year is the 40-year anniversary of the percutaneous coronary intervention. The last decades were the decades of intervention and then came electrophysiology. The future as it is now, the future of the next decade or two is heart failure. Heart failure is a booming specialty in cardiology, and I anticipate that we will see further exciting therapeutic advances in the treatment of heart failure. Advances in treatment have led to an upsurge of doctors wanting to specialise in heart failure. Specialising in heart failure is becoming more and more popular among young doctors. Heart failure remains the most prevalent, deadly and costly of all heart disease – and we can do something about it! We have now 8 life-saving therapies available, ACE inhibitors, beta blockers, MRAs, ARNI, ICD, CRT, transplant and VAD and there is more to come. It is an exciting time to be a heart failure doctor.

Poster Sessions 2017

In the moderated poster sessions, particularly interesting posters were presented and discussed with the audience. Enclosed a selection of the presented data.

New predictors of left ventricular hypertrophy: Insights from an epidemiologic survey

Left ventricular hypertrophy (LVH) is a major cause of heart failure with HFpEF. LVH is associated with older age, higher BP and body weight. On the other hand, effects of volume overload due to dietary sodium intake, as well as arterial stiffness and BP variability rarely have been evaluated as predictors of LVH and HFpEF in population-based studies. Against this background, this study focused on detecting new predictors of LVH in normotensive adults with preserved EF enrolled in the so-called SEPHAR III survey [1].

In adult patients enrolled in SEPHAR III, 2 study visits were performed. The examinations included anthropometric measurements, 3 sitting BP measurements per visit according to ESC-ESH guidelines, arterial stiffness measurements (with an oscillometric device), volemia measurements by transthoracic bioimpedance, laboratory workup (lipids, fasting plasma glucose, HbA1c, and an estimation of 24 h sodium excretion from morning spot urine sample) and standard echocardiography. Normal BP was defined as BP below 140/90 mmHg and lack of hypertension history or treatment. LVH was defined as indexed left ventricular mass > 95g/m^2 in females and > 115 g/m^2 in males).

Out of a total of 1,970 subjects, 828 normotensive subjects with preserved EF were identified (mean age 42.7 ± 16.8 years, 57% females). LVH was shown in 11.4% of the patients (10.4% in males and 12.1% in females). Binary logistic regression adjusted for age and mean arterial pressure confirmed several independent predictors for LVH. The used model had 83.7% accuracy of predicting the presence of LVH in normotensive subjects. Besides well-known determinants of LVH as age, BP values and obesity, also increased arterial stiffness, central BP parameters, visit-to-visit BP variability and hypervolemia independently emerged as independent predictors of LVH onset in normotensive adults.
These results stress the need of adequate preventing strategies. Moreover, the finding of volume overload being independently associated with the manifestation of LVH urges the reduction of dietary sodium intake for preventing new onset of HFpEF.

Similar comorbidities in heart failure with reduced or preserved ejection fraction

Comorbidities are an important issue in HF patients. Traditionally, it is thought that they are more relevant in HF with HFpEF than in HF with HFrEF, though both are present in HF patients. In this study, the prevalence of comorbidities in HF patients according to LVEF was evaluated in Spain, a country with a population of 46.77 million people [2].

All the discharges from Spanish hospitals from 2012 to 2013 with a primary diagnosis of HF were analysed. Altogether, 400,861 hospital admissions because of HF were documented. In 77,652 patients, HF was the primary diagnosis. This analysis exclusively focused on patients with HFrEF (n=4,241) and HFpEF (n=1,752). Demographic characteristics such as age and gender and the main comorbidities are shown in Table 1. According to the results of this Spanish administrative database, patients with HFrEF as well as patients with HFpEF show a broad spectrum of comorbidities. The comorbidity profiles were rather similar, showing only slight differences not considered to be clinically relevant. However, the diagnosis heart failure was often poorly coded at discharge. This obviously limits the significance of these results.

Table 1 Distribution of comorbidities (%) according to ventricular ejection fraction

Parameter	HFrEF	HFpEF
Age	74.1	78.5
Men	65.7	36.7
Ischemic heart disease	36.7	20.5
Arterial Hypertension	59.1	64.6
Diabetes mellitus	38.5	41.3
Stroke	0.4	0.2
Chronic kidney disease	32.5	30.6
COPD	17.3	15.9
Malnutrition	0.9	1.2
Dementia and senility	14.0	17.4
Functional disability	3.0	2.9
Peripheral arterial disease	66.9	76.3
Advanced cancer	1.2	1.7
Trauma in the last year	2.4	2.7

Higher cardiovascular risk in carriers of non-O blood groups

A few studies have shown an association between blood group alleles and vascular disease, including atherosclerosis. It has been suggested that carriers of non-O blood groups (ABO groups A, B, and AB) have an elevated CV risk, including a higher risk of myocardial infarction, stroke, heart failure and CV death. However, this assumption is mainly based on case-control studies [3]. An increased mortality, particularly due to cardiovascular diseases, of non-O blood groups has also been found in a large cohort study including data from 50,045 patients in the age of 40-60 [4]. According to the authors, the elevated risk may be due to the effect of blood group alleles on blood biochemistry or their effect on von Willebrand factor and factor VIII levels.

To clarify the influence of blood group alleles on cardiovascular outcomes, Dr. Tessa Kole performed a meta-analysis of prospective studies reporting on blood group and CV events, which was presented as a poster during the meeting [5].

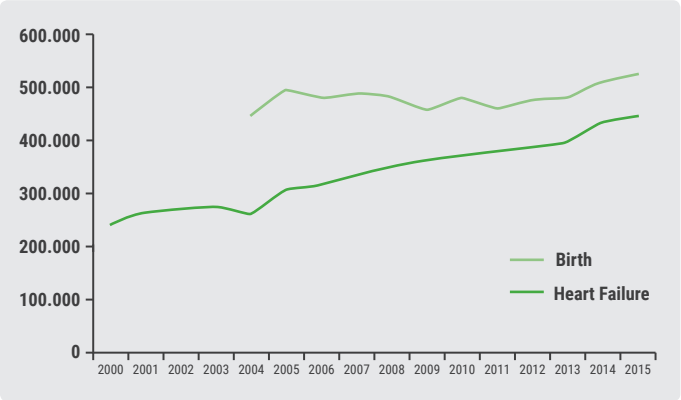
The total number of subjects included in all studies was 1,362,569, and they experienced 23,154 CV events. The odds ratio's (OR, with 95% Confidence Intervals, CI) for subjects having non-O blood groups compared to O blood group for fatal coronary events, all coronary events and combined CV events were 1.00 (CI 0.85-1.18; P=0.98), 1.09 (CI 1.06-1.13; P<0.00001) and 1.09 (CI 1.06-1.11; P=0.006), respectively.

This meta-analysis confirmed previous data that subjects carrying non-O blood group have an increased risk of (nonfatal) CV events, especially myocardial infarction. Underlying mechanisms may be multifold, although this increased risk has been attributed to a higher concentration of von Willebrand factor and dyslipidemia in subjects with non-O blood group. According to the authors, further studies should address if the excess CV risk of non-O blood group is amenable to treatment.

Demographic change results in need for heart failure clinics

The demographic change typically seen in Western society, namely an increase in elderly people in the general population is also reflected by the two leading causes for hospitalisation in Germany, which are "Delivery/Birth" (Z38) and "Heart Failure" (I50) [6]. Prof. Stefan Störk, analysed data available from the German Federal Statistical Office for both diagnoses in the time period from 2000 to 2015. Their analysis was based upon publicly available databases for ICD-10-GM diagnoses in Germany. The researchers were available to collect data from 2000 to 2015 for heart failure and from 2004 to 2015 for birth. In this time period, hospitalisations due to delivery increased by 1.55%/year from 444,306 in 2004 to 526,437 in 2015, whereas

Figure 6 Trends in hospitalisation 2000-2015: HF versus birth (absolute numbers) [6]



hospitalisation for heart failure increased by 4.96%/year from 260,803 in 2004 to 444,632 in 2015 (Figure 6). Within this time period, heart failure became the most common cause for disease-related hospitalisation in Germany. Should these trends continue, there will be more hospitalisations for heart failure than for birth from 2020 onwards.

The demographic change in Germany will lead to a greater need for comprehensive heart failure care, while the number of hospitalisations for birth only mildly increased during the previous years.

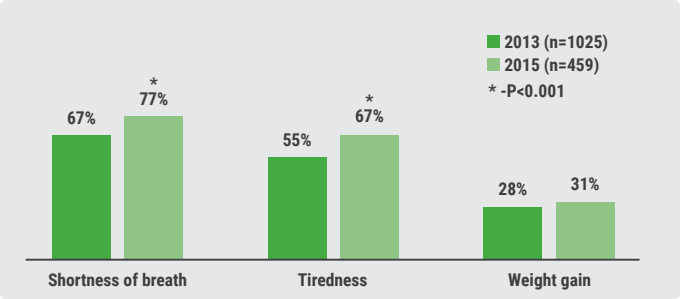
Public knowledge about heart failure is improving

Heart failure is a common and increasingly important cause of morbidity and mortality. However, previous trials have shown that the level of awareness in the lay public in Europe is unsatisfactory and important misconceptions remain [7].

In their study, Gerda Burneikaite et al. evaluated the changes in knowledge about HF of the general population in Lithuania from 2013 to 2015 [8]. Participants were asked to complete a questionnaire during European Heart Failure Awareness Day activities. A total of 1,025 attendees in 2013 and 459 attendees in 2015 participated in surveys: 15% of the participants in 2013 and 21.4% in 2015 worked in the medical area. The correct identification of typical complaints and symptoms of HF significantly improved from 2013 to 2015 (Figure 7).

The perception that HF is not a normal symptom of old age significantly increased from 31.8% in 2013 to 37.1% in 2015 (P<0.001). In the 2015 survey, significantly more participants knew that patients with HF should not avoid sports activities and that HF affects multiple organs (P<0.001 for each comparison). Knowledge about available HF treatment options was similar at both time points: respondents marked pharmacotherapy in 76.6% and 70.6%, pacemaker in 49.9% and 50.2%, and heart surgery in 47.7% and 47.5% of cases in 2013 and 2015, respectively.

Figure 7 Typical complaints and symptoms of heart failure [8]



Basic HF knowledge increased from 2013 to 2015, but there is still a lot of room for improvement. Therefore, further activities on education and awareness in the general population and in HF patients should be continued.

Similar biomarker profile in HFmrEF and HFrEF patients

Few data are available on the phenotype and prognosis of patients with mid-range HF according to the new ESC classification, because most HF studies and clinical trials included patients with EF below 35–40% or above 50% [9]. To better define this group of patients, Dr Pedro Moliner explored a panel of biomarkers in patients with HF based on the new HF classification and assessed whether they have different prognostic value in HFmrEF [10].

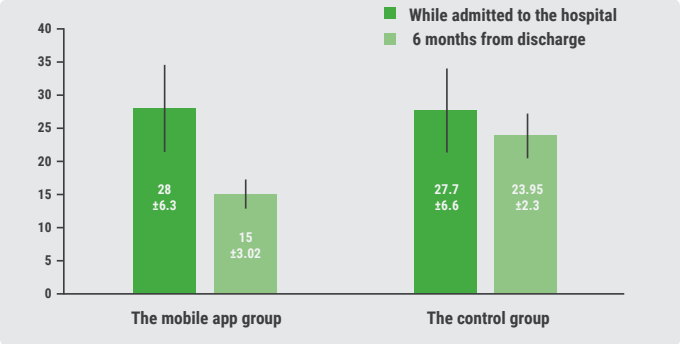
A total of 1,069 HF patients were included. Serum concentrations of NT-proBNP, high-sensitivity troponin T (hs-TnT), ST2, Galectin-3 high-sensitivity C reactive protein (hs-CRP), Cystatin-C (n=804), neprilysin and soluble transferrin receptor were measured in consecutive ambulatory HF patients followed during 4.9 ± 2.8 years.

NT-proBNP in HFmrEF patients was significantly lower than in HFrEF patients and was similar to those in HFpEF patients. In contrast, all the other biomarkers were similar between HFrEF and HFmrEF patients. From a multi biomarker point of view HFmrEF seems to be more similar to HFrEF with the exception of lower NT-proBNP levels.

Interactive smartphone application improves adherence in HF patients

Patient education and improvement of self-care are considered as key strategies for preventing further deterioration of HF. New data shows that an interactive smartphone application (app) based on the 9-item European Heart Failure Self-care Behaviour Scale (EHFScBS) improves self-care management in patients with heart failure, provides their continuous and persistent education and may be considered as a promising tool in the management of patients with heart failure [11].

Figure 8 Mean EHFScBS-9 scores [11]



In this study, the effectiveness of the Russian version of the interactive app was tested in 47 patients with decompensated HF. 95 patients who refused to use the smartphone app served as controls. Mean age of the patients was 59 ± 12 years, 63% were male and 61% had ischemic HF, the mean LVEF was 32 ± 7.0%. All patients were provided with general information about HF such as symptoms, principles of self-care, diet, medical therapy and physical activity according to the Russian HF guidelines. The smartphone support app was downloaded on the mobile phone before discharge of the hospital. There were no differences in demographic and clinical characteristics between the 2 groups.

On admission, the mean EHFScBS-9 score was similar in both groups. However, after 6 months of follow-up, a significant reduction of the mean EHFScBS-9 score was noted in the smartphone app group (–56.4%, P<0.05) but not in the control group (–13.7%, n.s.) (Figure 8). The smartphone app group demonstrated a higher adherence to daily weight control, contact with a physician or a nurse in case of increased dyspnea and adherence to medication. There were no readmissions because of HF in the smartphone app group, but 21% in the control group. The patients noted that the app was easy to use, and only 10.6% of patients needed the help of relatives.

Troponin increases in amateur marathon runners

Strenuous exercise such as marathon running might induce an increase of the blood concentrations of some cardiac biomarkers usually measured for diagnosis and prognosis prediction of heart diseases. This is confirmed by new data showing that cardiac biomarkers significantly increase in amateur runners reaching abnormal values for hs-TnT (high-sensitive troponin T) and ST-2. The increase of these cardiac biomarkers was significantly associated with worse athlete performance [12].

In this study, biomarkers of 79 subjects (72% men, mean age of 39 ± 6.2 years (71% ≥35 years) were tested 24h to 48h before the race, in the immediate hours after the race and 48h after the race. hs-TnT blood levels tended to be higher in women (P=0.07). Only NT-proBNP correlated with age (P=0.007). hs-TnT (P=0.01) correlated with weekly training hours and inversely

correlated with the real-time for completing the race (P=0.009). No biomarker correlated with the years of training. Blood levels of the 3 cardiac biomarkers significantly increased during the race. NT-proBNP and ST-2 decreased to similar pre-race values 48h after the race, while hs-TnT blood levels decreased but remained higher than pre-race (P<0.001). In women, increase of hs-TnT was higher than in men (P=0.03). There was no significant relationship between increase in the studied biomarkers and age or years of training. Between weekly training hours and ST-2 increase, there was an inverse relationship (P=0.007), and a direct relationship between race time and increases hs-TnT (P<0.001) and ST-2 (P=0.052). In multivariable linear regression analysis including age, sex and those variables with a P≤0.10 in the correlation analyses, race time remained independently associated with increases of ST-2 (P=0.031) and hs-TnT (P<0.001).

Brain natriuretic peptide improves risk stratification in cardiac surgery

Pre-operative testing BNP in combination with the EuroSCORE II improves risk stratification in cardiac surgery [13]. The combination was evaluated in a prospective cohort of 2,209 patients. Intrahospital mortality rate was 4.8%. However, there were significant differences between predicted and observed mortality (P<0.0001) (Figure 9). Elevated BNP (above 100 ng/L) emerged as an independent risk factor of intrahospital mortality (2.9% vs. 6.5%, P=0.008). BNP reclassified 1,180 (53.4%) patients. Moreover, BNP significantly improved risk stratification of EuroSCORE II with an NRI (net reclassification index) of 0.24 (95%-CI 0.11–0.38, P<0.001). The authors concluded that preoperative BNP enhances the predictive power of EuroSCORE II. Patients with elevated BNP had a theoretical risk multiplied by 1.8 regarding intrahospital mortality after cardiac surgery.

Discharge checklist for HF patients reduces readmission rates

Therapeutic improvements in AHF have significantly reduced in-hospital mortality of AHF patients. Rehospitalisation rates are a powerful predictor of mortality. AHF ESC guidelines recommend pre-discharge and long-term management to prevent early readmissions. In unselected patients hospitalised for AHF, the use of a standardised checklist reduced cardiovascular mortality at 6 months [14]. The use of the checklist also improved therapeutic strategies at discharge and increased systematic follow-up plan utilisation. The checklist was designed according to ESC recommendations in order to optimise treatment and the development of a care plan after discharge and evaluated in 103 patients hospitalised for AHF from July 2015 to January 2016. A total of 137 patients who were hospitalised before the introduction of the checklist (from June to December 2014) served as control group. The primary endpoint was cardiovascular death at 6-month. The mean age of the patients was 77 ± 12 years, 56% were male and 57% had heart failure with HFrEF. There was a significant reduction in cardiovascular death at 6 months in the checklist group (P=0.02). Disease management program was more often used in the checklist group (36% vs. 15%, P=0.0002). At discharge, 82% of the patients of the checklist group had a medical appointment within a month, compared to 33% of patients in the control group (P<0.0001). Therapeutic optimisation was better in the checklist group, especially for patients with HFrEF: ARB/ACE-Inhibitors and beta-blockers were more often prescribed or up-titrated according to ESC guidelines (P=0.016 and P=0.03, respectively) [14].

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Figure 9 Observed and predicted mortality (by EuroSCORE II alone and combined with preoperative BNP) across EuroSCORE II ranges [13]