Heart Failure 2018

Heart Failure Association

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PEER-REVIEWED CONFERENCE REPORT

Late-Breaking Trials

The greater splanchnic nerve could be a new target in the treatment of heart failure as redistribution of fluid volume rather than volume overload is often responsible for decompensation.

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Diabetes and the Heart – a Global Challenge

Choice of heart-friendly antidiabetics, such as SGLT-2 inhibitors, have a distinct cardioprotective effect in diabetics. Whether heart failure patients without diabetes will also benefit from this treatment is to be discovered in future trials.

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Novel Drugs in Heart Failure

There is a high medical need for new heart failure therapy: Agonists of soluble guanylate cyclase could have beneficial effects by preventing the progression of, or even reversing, ventricular hypertrophy and fibrosis.

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Editor Prof. Marc Peter Bonaca, Harvard Medical School, USA

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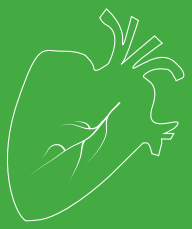

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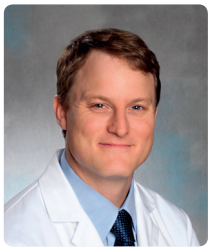


Prof. Marc Peter Bonaca

Marc P. Bonaca, MD, MPH is an Associate Physician in Cardiovascular Medicine at Brigham and Women's Hospital, an Assistant Professor of Medicine at Harvard Medical School and an investigator at the TIMI Study Group. Dr Bonaca earned his medical degree (M.D.) from University of Connecticut School of Medicine and a Master of Public Health (M.P.H.) from the Harvard School of Public Health. He completed his internal medicine residency, fellowship in cardiovascular medicine, and fellowship in vascular medicine at Brigham and Women's Hospital, and is board certified in internal medicine and cardiology.

Dr Bonaca's research interests include characterisation and prediction of cardiovascular risk in patients with atherosclerotic vascular disease, as well as investigation of therapies to reduce that risk. Specific disease states of interest include peripheral artery disease, stable coronary artery disease, and aortic disease. He is an active investigator in clinical trials investigating novel therapies including antithrombotic agents for the reduction of cardiovascular risk in patients with symptomatic peripheral artery disease and stable coronary disease. In addition, he is actively involved in the evaluation of established and novel biomarkers as well as clinical characteristics for risk prediction in specific patient populations. In addition to scientific investigation and clinical trial work, Dr Bonaca leads the TIMI Safety Desk which includes 20 staff members and which is responsible for the monitoring and processing of safety data for multiple large international clinical trials. In addition to his scientific, clinical trial, and safety responsibilities, Dr Bonaca is an active member of the clinical staff at Brigham and Women's hospital and attends on the inpatient cardiology and cardiology/vascular medicine consult services. He maintains a regular clinic and is the Medical Director of the the Brigham and Women's Aortic Center.

Fight Against Heart Failure: HFA Goes Global

Interview with Heart Failure 2018 Congress Chair
Prof. Mitja Lainscak PhD, FESC, FHFA
conducted in June 2018 in Los Angeles by Kirsten Westphal
Faculty of Medicine, University of Ljubljana, Slovenia
Department of Internal Medicine, General Hospital Murska Sobota
Heart Failure Association, Executive Committee Member

Reflecting on Heart Failure 2018 and his time as Congress Chair, Prof. Mitja Lainscak shares his top priorities and how they have influenced the Heart Failure Association, as well as his hopes for the future.

Professor Lainscak, what do you consider the highlights of this year's ESC Heart Failure 2018 congress?

"In line with the main theme 'Heart Failure: classical repertoire, modern instruments', the HFA has transformed itself to broaden its understanding of heart failure and its treatment, and that is how Heart Failure 2018 differs from previous congresses. We have to consider heart failure in the context of cardiovascular disease as a whole in order to see the bigger picture. There are some established therapies that we might change, and some new strategies will need to be introduced. The congress focussed on a range of devices and interventions that improve patient outcomes. There was also a great emphasis on novel drugs or drugs in development. Although very few studies have been published in the last ten years, there has been much progress. These studies have not yet reached the stage of outcome trials, but we need to embrace these scientific findings as it is necessary to show what is happening in the course of heart failure. Also, we put much emphasis on patient management because we should focus on more than just symptoms. We have to take care that the quality of life is adequate in the years patients gain due to therapy."

Why is it so important to increase the awareness for chronic heart failure?

"Awareness for heart failure is relatively low. We don't have ambassadors like breast cancer has, for example. Usually, heart disease is seen as a disease of elderly people, which is one reason for the low awareness. Another reason is that the general perception and the perception among decision makers remains that having a malignant disease is dreadful and deadly, and that it is going to kill you in a matter of time. Whereas the impact of other diseases on your life and quality of life is not perceived as equally severe. We know this is definitely not true, and the HFA sees it therefore as our task to change these perceptions. The message is that heart failure is common and has poor outcomes, but that it can be managed."

How common is chronic heart failure, and what are the main underlying conditions?

"Over the years, the underlying conditions have stayed more or less the same, with ischaemic heart disease and arterial hypertension being the two main drivers around the globe. Knowledge about prevalence is another issue. We still 'preach' that prevalence of heart failure is 1-2 percent, but this insight comes from older studies. There have only been a handful of well-designed studies that have looked at prevalence. Since then, the population has aged, diagnostic criteria have changed, and we have introduced another phenotype in heart failure. We lack insight into incidence and prevalence numbers and need to do more epidemiology, because without numbers we cannot adequately discuss anything."

Why is it so difficult to make an early diagnosis?

"As I said earlier, the typical heart failure patient is an elderly person. We all have some shortness of breath in older age, like oedema or early fatigue. These symptoms are shared with other diseases or perceived as symptoms of old age. Moreover, if subjects are experiencing difficulties in daily life, they often adjust their daily activities to avoid them. They subsequently forget about the symptoms, which allows the disease to progress. Often, hospitalisation is the first mark indicating heart failure. This shouldn't happen. We should be able to detect the disease much earlier on. Unfortunately, we currently don't have any well-designed programmes in Europe, and this needs to change. We can only do this with strong support on a political level. With that support we can start defining screening strategies. The two main questions are: how will we do the screening, and who will do it?"

Where will the future path of heart failure therapy lead?

"There are some exciting on-going studies that include patients with preserved ejection fraction (HFpEF). For these patients, we still don't have any therapies that will be approved as lifesaving. This is definitely an unmet need. Then, over the years, we have been able to enrich our armamentarium of therapies for heart failure with reduced ejection fraction (HFrEF). In patients that survive longer, we are confronted with new complications and new consequences of the disease, which need to be addressed. Currently, an exciting pharmacotherapeutic path is focusing on patients with HFpEF, and there are additional promising strategies with new devices and

operative interventions, which focus on both sides of the heart. Where we still don't have any large, randomised, controlled trials is the HFm-recEF, the 'middle child' with ejection fraction 40 to 50. Here, we still don't know which way to go. There is some emerging data from registries and trials that suggests that managing HFm-recEF should not be too different from the management of HFrEF."

Which area of heart failure has made the most progress in recent years?

"We have witnessed some progress in every single area – basic research, diagnostics, and therapy. Unfortunately, we haven't have seen any ground-breaking trials in recent years. The last ground-breaking trail was the PARADIGM-HF in 2014 with sacubitril/valsartan taking drug therapy for HFrEF to the next level. Understandably, it took some years to make that drug available for clinical practice. Since then, we haven't seen trials of a similar magnitude. Though we have seen some recently published studies in terms of interventions."

What do you consider the most important issues in treatment heart failure today? How does Heart Failure 2018 help to push these forward?

"We have to acknowledge the need to improve strategies for early detection of heart failure, and we need proper diagnostics to see what the cardiac function is and which other diseases are present to be more precise with comprehensive management. We know that many patients who are labelled with heart failure don't actually have heart failure and that many patients with heart failure remain undiagnosed."

What would you like your legacy as chairman of Heart Failure 2018 to be?

"The most important thing is that the people were excited and happy with the congress. The delegate number exceeded 5,000. This is a respectable number and likely a result of the first-class programme put together by the Scientific Committees. Personally, I am excited about the increased focus on devices and multidisciplinary interventions at this year's meeting. We have moved on from the days when drugs were the mainstay of heart failure treatment. Now, specialists also use a range of devices and interventions to improve patient outcomes. I really hope that there were remarkable sessions for everybody with impact on clinical practice, maybe even affecting some change in routine in clinical or scientific aspects."

How has this congress expanded the HFA's educational mission worldwide?

"The HFA wants to invest in the future by supporting young investigators and encouraging them to present research at this meeting, the largest heart failure congress in the world. To make this congress accessible to as many members as possible, the HFA has once again made travel grants available to young specialists – Heart Failure Specialists of Tomorrow – who are first authors on an accepted abstract or clinical case and who have difficulty obtaining funding from other sources. For Heart Failure 2018, an incredible 150 travel grants have been awarded. The HFA is going global."

Do you have something you would like to share with your fellow cardiologists?

"Yes, we need to stay strong in our clinical practice and in our research activities. We need to increase awareness of heart failure, and we need to be very, very clear that heart failure can be approached, treated, and managed. Therefore, we have to be conclusive in the diagnostic part and then embrace patients as a whole with all their comorbidities in a comprehensive manner."

Late-Breaking Trials

Late-breaking trials I: Acute heart failure

The first late-breaking session presented at Heart Failure 2018 covered acute heart failure. One is a promising pilot study that hints at a more effective way of enhancing diuresis in congestion.

IMPACT-EU trial shows no advantage of biomarker-guided antibiotic therapy

A surprising result from the IMPACT-EU trial indicates that procalcitonin-guided antibiotic therapy, a recommended procedure in the 2016 European Society of Cardiology (ESC) guidelines, does not improve mortality rates in patients with dyspnoea and suspected acute heart failure (AHF) [1]. The ESC guidelines' recommendation is based on the observational BACH study [2]. In this trial, procalcitonin levels improved the accuracy of pneumonia diagnoses among patients with shortness of breath (SOB). Adequate antibiotic use is important in patients with AHF: In the BACH trial, patients with an elevated procalcitonin concentration (>0.21 ng/mL) had a worse outcome if not treated with antibiotics (P=0.046), while patients with low procalcitonin values (<0.05 ng/mL) had a better outcome, if they did not receive antibiotic therapy (P=0.049).

According to Prof. Martin Möckel (Charité Universitätsmedizin Berlin, Germany), the current IMPACT-BIC-18 study set out to proof the value of procalcitonin-guided antibiotic initiation in a randomised setting [3]. This multicentre trial included patients presenting to emergency departments of 16 centres with SOB and increased natriuretic peptide levels. They either received standard treatment, which means that initiation of antibiotics was guided by fever and/or leukocytosis, or additional procalcitonin levels with the same cut-off level used in the BACH trial (0.2 ng/ml). Primary endpoint of the trial was the 90-day mortality rate. The study ended prematurely after assessment of a data safety and review committee due to futility. There was no significant difference between the groups regarding the primary endpoint and the 30-day mortality rate. Remarkably, the IMPACT-EU study showed very low 90-day mortality rates in an AHF study population. This is probably due to clinical trial selection criteria, which resulted in the exclusion of patients with a higher mortality risk. In addition, the study population had generally low procalcitonin levels with a mean value of 0.07 ng/ml. Only 16.4% of patients had concentrations above 0.2 ng/mL, the value used in this study for the diagnosis of concomitant infection. "The lack of benefit of a procalcitonin-guided antibiotic initiation strategy may reflect the relatively low risk of death and very low infectious burden of our patient population," concluded Prof. Möckel. In addition, there was a 16.8% protocol deviation in the procalcitonin-guided group vs 2% in the standard group.

Despite the neutral trial results, Prof. Möckel thinks that the ESC recommendation of antibiotic therapy administration according to procalcitonin levels is still justified, as the concept of natriuretic peptides and procalcitonin for the very early diagnosis of complicated AHF is biologically plausible. The current findings do raise some questions about this concept, but may be explained by patient selection with relatively low mortality. Prof. Marco Metra (University of Brescia, Italy), a discussant of the trial, shared this opinion: "The patient population was less sick than predicted, and only 16% had elevated procalcitonin levels. If we move to a less selected milieu this may magnify the beneficial effects of biomarker guided treatments," concluded Prof. Metra. Therefore, more studies including HF patients with a higher mortality risk are needed to assess the value of procalcitonin-guided antibiotic initiation.

Triggers of acute heart failure vary globally

Triggers and management of patients with AHF vary around the world, suggests the REPORT-HF registry [4]. Prior AHF registries were either country-specific or region-specific, and none had simultaneous global enrolment. This was the rationale for the REPORT-HF registry, a global, prospective registry in 44 countries comparing regional differences in causes of AHF, AHF therapies, time to treatment, and outcomes. All participating countries used the same protocol, allowing for a direct comparison of how AHF patients are managed around the world. Worldwide, 18,805 adult patients were hospitalised with AHF; either as a new diagnosis or a decompensation of previously diagnosed chronic heart failure. A first analysis of the registry was presented at the Heart Failure 2018 congress. The analysis evaluated the initial hospital admission of patients in 358 hospitals over 32 months in 44 countries. A total of 3,661 patients were

admitted in Western Europe, 2,810 patients in Eastern Europe, 2,265 in the Eastern Mediterranean and Africa, 1,622 in North America, 2,686 in Central and South America, 2,369 in Southeast Asia, and 3,392 in the Western Pacific. The median age of patients was 67 years, 61% were men, 52% were Caucasian, 31% were Asian, and 5% were Black.

In Western Europe, patients were considerably older than in the other regions (median age 75 years compared to 61 years in South East Asia, for example). In Western Europe, 70% showed dyspnoea at rest, 39% had ischaemic heart disease/decompensated chronic HF, and only 4% of cases were caused by nonadherence to diet and medication. In contrast, nonadherence to diet and medication was the most frequent cause of admission affecting 19% of cases in North America. A distinct regional difference was observed regarding patients with uncontrolled hypertension: only 48% in South East Asia had uncontrolled hypertension compared to 63% in Western Europe, 77% in the US, and a staggering 80% in Eastern Europe. In Southeast Asia, the main reasons for admission were ischaemic events (26%), and dyspnoea at rest (88%). In this region, there were more de novo cases compared to Europe and the US (79% vs 37% and 20%, respectively).

In addition, the time between contacting medical services and receiving intravenous (IV) diuretics was longer in North America compared to other regions – a median of 3.5 hours vs just over one hour. A reason for the delay in treatment in the US might be that patients in North America had less dyspnoea at rest at presentation (72% compared to 91% in the Eastern Mediterranean and Africa) and may have been perceived to be less ill. Further, the majority of patients worldwide were treated with an IV therapy with diuretics only, followed by therapy with vasodilators and nitrates with or without diuretics. Inotropic agents were used three times more often in Southeast Asia, Western Pacific, and Eastern Europe (11.3–13.5%) compared to Western Europe and North America (3.1–4.3%).

The analysis also showed that older age, a valvular etiology of HF, signs of congestion on chest X-ray, and a creatinine concentration >2.75 mg/dl had a significant negative impact on mortality. Age, systolic blood pressure <115 mmHg, signs of congestion on chest X-ray, impaired kidney function and cause of AHF were associated with a longer hospital stay.

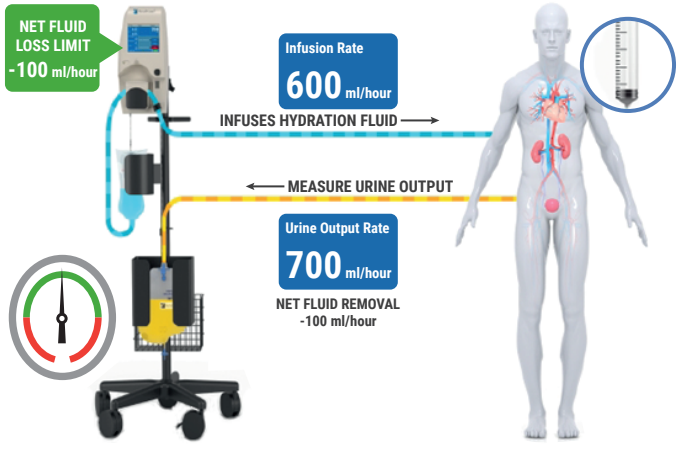
As Prof. Sean Collins (Vanderbilt University Medical Center, USA) pointed out, the REPORT-HF registry shows for the first time that the causes and treatment of AHF differ by region. This might identify opportunities to improve care and inform future clinical trial design. Patients enrolled in REPORT-HF will be followed-up for three years after hospital discharge to collect information on treatment, rehospitalisation, and death.

Device-guided diuretic might improve outcome of diuresis in AHF patients

A preliminary proof of concept trial in nine patients demonstrated the safety and efficacy of a novel automated, controlled fluid replacement for guided diuretic dosing that avoids over-diuresis leading to adverse events [5]. Congestion is the major cause of acute decompensation of chronic HF. A relief of congestion is therefore a major determinant of a good prognosis, and an effective and safe decongestion is a major objective of therapy. As Prof. Piotr Ponikowski (Wroclaw Medical University, Poland) pointed out, a controllable decongestive therapy is needed that enables the optimal guideline-recommended dose of diuretic, which allows both hemodynamic (intravascular and extravascular fluid) and clinical decongestion resulting in a resolution of symptoms.

The new device allows clinicians to titrate IV diuretic administration to a preset urine-output target. The device was originally designed to minimise contrast-induced nephropathy after angiography. It constantly measures urine output and can be set to infuse replacement fluid of the total or a percentage of urine output (Figure 1). To accomplish this, patients need both a peripheral IV for infusion of replacement solution and a Foley catheter to measure urine output.

Figure 1 The device-guided diuretic doses system allows controlled fluid removal as it enables physicians to titrate IV diuretic administration to a preset urine-output target [5]



The prospective TARGET trial tested the ability of this system to enable controlled fluid removal in patients with acute decompensation in 9 patients who served as their own controls [5]. All patients completed at least 24 hours of standard diuretic therapy followed by 27 approx. 3-hour diuretic therapy with this new system. Signs and symptoms of HF were assessed, including dyspnoea, rales, a positive jugular venous pulse, and peripheral oedema. As Prof. Ponikowski pointed out, no adverse events, such as symptomatic hypotension, hypovolemia or hypervolemia, electrolyte imbalance or renal dysfunction, were related to diuresis with or without the device-guided system. Following the device-guided diuretic therapy, all patients reported significant improvement in dyspnoea and HF signs. Diuretic efficiency improved significantly in the 24 hours after the device-guided system (from 998 ml urine/40 mg furosemide to 1650 mg urine/40 mg furosemide with the system). "In our small study, we have shown that this system increases urine production in a safe and efficient way in congested patients. This is a promising first step toward developing a new treatment therapy for patients with acute decompensation. Of course, more studies will have to follow," concluded Prof. Ponikowski.

Late-breaking trials II: Chronic heart failure

One of the highlights of the second late-breaking session was the trial that suggests exergaming is an efficient way to improve fitness and quality of life (QOL) in HF patients.

HF-Wii shows: exercising with video games improves QOL in HF patients

Playing video games that involve physical exertion, so-called exergaming, can improve QOL in patients with heart failure (HF) [6]. The randomised HF-Wii study is the largest study in exergaming and HF, involving patients from 10 international centres. It assessed whether exergaming, for example, playing virtual tennis in front of a television, improves exercise capacity and other outcomes in patients with HF [7]. In this trial, 605 patients with HF were randomised to the exergame or standard exercise advice. Patients in the exergame group had the game installed at home, received a tutorial on how to play, and were advised to play for 30 minutes a day. Patients in the standard exercise group were advised to be physically active for 30 minutes a day. Primary endpoint of the trial was exercise capacity at 3 months as measured by the 6-minute walk test. "In last year's primary analysis, we saw that exergaming significantly improved the 6-minute walk test of patients with HF compared with the standard approach of offering advice on physical activity," said principal investigator of the study Prof. Tiny Jaarsma (Linköping University, Sweden). At the start of the study, no difference in exercise capacity was measured between the groups. After three months, patients in the exergame group could walk significantly farther – 33 metres more on average – than those in the standard exercise group.

At the Heart Failure meeting, results were presented on the impact of exergaming on QOL, anxiety, and depression. Impact was measured by validated questionnaires at the start of the study and at 3 months [6]. "Our current analysis showed that exergaming significantly improved QOL," said Prof. Jaarsma. The researchers also wanted to investigate whether the amount of time spent exergaming, which varied widely between patients, had an impact on physical benefit. "We found an association between duration and exercise capacity improvement," said Prof. Jaarsma, "although we cannot specify the minimum duration of exergaming required for a positive effect." Differences in anxiety and depression failed statistical significance, but playing the exergame did not increase anxiety. According to the investigators, QOL improved because patients were able to walk further and do more activities around the house. In addition, they felt more included socially because they play the game with friends or family. An advantage of exergaming is that there is no age limit: the exergaming group even included patients in their 90s. In addition, the investigators saw no adverse effects of exergaming in any of the patients included in the study.

"We know exergaming will not suit everyone," concluded Prof. Jaarsma. "Some patients really enjoy it while others prefer to exercise in other ways, for example, in groups or outdoors. But this is precisely why exergaming is so useful; it provides HF patients with another effective option to help them improve their physical and emotional well-being." The group is currently working with the Swedish Heart and Lung Association and other patient associations to try to determine the best way to integrate exergaming into clinical practice.

Obese diabetics with HF have less benefit from ß-blocker therapy

Analysis of a large data set showed that ß-blocker treatment lowers the risk for all-cause mortality in both diabetics and non-diabetics without obesity, thus giving a clear impetus to prescribe guideline-recommended therapy [7]. However,

obesity reduces the prognostic impact of ß-blockers, particularly in patients with diabetes. Diabetes in HF is associated with increased mortality. HF patients with obesity seem to have a less poor prognosis across numerous studies and different cardiovascular (CV) diseases; a fact that is commonly referred to as the "obesity paradox". The prognostic impact of having both diabetes and obesity in HF is unknown to date and was the rationale for the analysis presented by Dr Dipak Kotecha (University of Birmingham, Great Britain) [8].

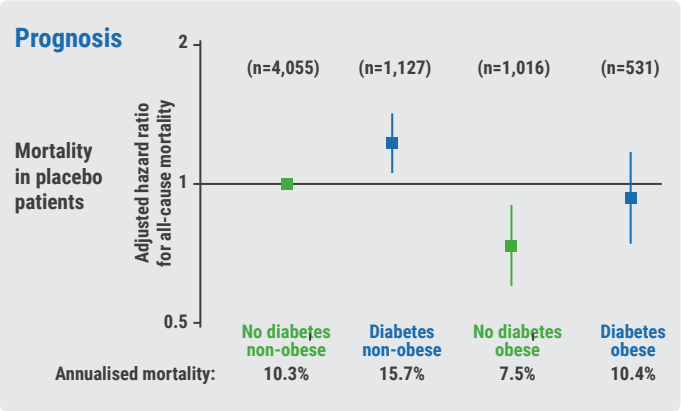
Dr Kotecha and his colleagues investigated the prognostic impact of diabetes and obesity, and the effects of ß-blockers on reduced mortality in 13,859 patients with HF and reduced ejection fraction (median age 65 years; 75% male). The analysis comprised patients from 9 large, mortality-endpoint, randomised, double-blinded, controlled trials. Of these subjects, 8,298 had neither diabetes nor obesity; 2,331 had diabetes but were not obese; 2,121 were obese but did not have diabetes; and 1,109 had both diabetes and obesity. Mean follow-up in the 11 included studies was 1.4 years.

Taking the no diabetes, non-obese patients as a reference (annualised mortality: 10.3%), the adjusted mortality risk was increased for those who are non-obese but have diabetes (15.7%), while it was lower in obese patients without diabetes (7.3%). In patients with diabetes and obesity, it was comparable to the reference group (10.4%). Thus, the two factors obesity and diabetes contradict each other: patients with obesity and diabetes showed a hazard risk similar to that of patients without diabetes or obesity.

In patients without diabetes, ß-blockers significantly lowered all-cause mortality (HR: 0.68, 95%CI: 0.61-0.75, P<0.001) and CV death (HR: 0.67, 95%CI: 0.59-0.75, P<0.001). The same was true for diabetics, and the treatment effect was also less pronounced. In addition, non-obese patients had a significant positive treatment effect regarding all-cause mortality and CV mortality (both P<0.001). In contrast, ß-blocker treatment did not significantly lower all-cause mortality or CV mortality in obese patients.

"In the diabetic and non-diabetic patients, there is significant reduction in death, as long as they are not obese," Dr Kotecha summarised. The obesity paradox was confirmed in this trial: diabetics that were not obese had the highest rate of mortality (Figure 2). For patients with obesity, the benefits of ß-blockers are much less certain, with marked attenuation

Figure 2 Non-obese diabetes patients have the highest annual mortality, confirming the obesity paradox [8]



of their prognostic impact, in particular for patients who also have diabetes. "Our novel finding is that we think obesity might be the interacting factor here, which has not been explored before in diabetic patients with HF," concluded Dr Kotecha.

Although the large sample size is certainly a strength of this analysis, one should keep in mind that this data is exploratory. The mechanisms of the observed effect modification cannot be explained by this observation. Therefore, further prospective trials are urgently needed to elucidate this mechanism and confirm the results of this analysis.

Gene therapy in HF: Lessons learned from SERCA-LVAD

According to Dr Alexander Lyon (Royal Brompton Hospital and Imperial College London, UK), the prematurely terminated SERCA-LVAD trial allows a glimpse in the future of gene therapy in HF [9]. "Down-regulation of the SERCA2a protein affects cardiomyocyte calcium cycling and is a common feature of HF," says Dr Lyon. Cardiomyocyte Ca2+ is critical for normal excitation-contraction coupling and ventricular function. Sarcoplasmic/endoplasmic reticulum Ca2+ ATPase 2a (SERCA2a) transfers Ca2+ from the cytoplasm back into the sarcoplasmic reticulum during diastole. "Restoring SERCA2a levels, in this case by cardiac delivery of an adeno-associated virus 1 vector containing the human SERCA2a gene (AAV1/SERCA2a), could improve cardiac muscle strength and stabilise rhythm based on the results from many preclinical studies," explained Dr Lyon. This approach also proved to be successful in animal models of chronic heart failure (CHF). The previously published CUPID 1 trial assessed 4 doses of AAV1/SERCA2a in patients with advanced HF and reported benefits in the highest dose

studied [10]. Therefore, 3 clinical trials (CUPID 2, AGENT-HF, and SERCA-LVAD) were performed with this dose in different HF populations. SERCA-LVAD included patients with HF and a left ventricular assist device. Unfortunately, when the CUPID 2 trial failed to show a positive treatment effect of the gene therapy, it was considered unethical to continue with SERCA-LVAD, and recruitment was halted after only 5 patients had been randomised and treated. The 5 intracoronary infusions could be performed safely. "We learned some very useful information from these patients. There were no major adverse events or signs of virus-related cardiac inflammation. And in the 1 patient with neutralising antibodies, there was no evidence of an adverse reaction to gene therapy, suggesting that these antibodies may not be a contraindication to treatment from a safety perspective," said Dr Lyon. Two of the five patients underwent cardiac transplant, and their myocardial tissue could be examined. Dr Lyon added that "viral DNA was detected in cardiac tissue but at very low levels—with DNA copy number detected being 25-250-times lower than in animal models—confirming findings from the CUPID studies. This strongly suggests that the doses delivered in CUPID 2 and SERCA-LVAD were too low to impact on the underlying pathophysiology and it indicates that we need to find new ways to achieve delivery of clinically effective doses."

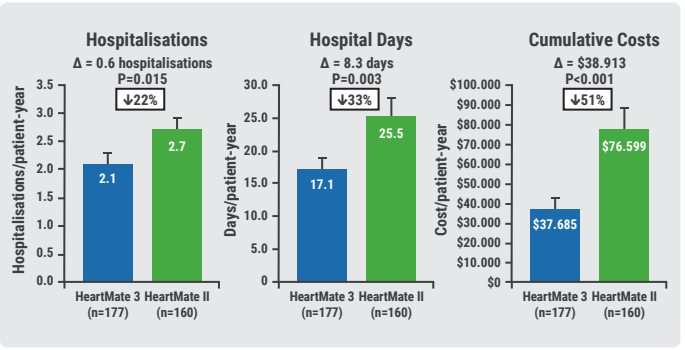
Late-breaking trials III: Innovative and device therapy

An analysis presented during the third late-breaking session showed that the HeartMate 3 system does not only improve survival, but is also cost effective.

HeartMate 3: Less costs due to a reduction in hospitalisations

Continuous-flow Left Ventricular Assist Systems (LVAS) improve survival and quality of life in patients with advanced HF refractory to medical therapy [11,12]. Earlier this year, the MOMENTUM 3 trial showed that the newer magnetically levitated, centrifugal continuous-flow, circulatory pump HeartMate 3 is superior to the older-generation, mechanical-bearing, axial continuous-flow pump HeartMate 2. Patients with advanced HF who got the new device were more likely to survive 2 years free of a disabling stroke or the need to remove or replace the pump than those who received the older-generation HeartMate 2 (79.5% vs 60.2%; P<0.001) [12]. The question whether this new device is also cost effective was addressed by the principle investigator of the MOMENTUM 3 trial, Dr Mandeep Mehra (Brigham and Women's Hospital,

Figure 3 Cumulative costs, hospitalisations, and hospital days [13]



Difference shown is for HeartMate II - HeartMate 3. P values derived from bootstrap simulation (x1500)

USA), in a healthcare use analysis of the MOMENTUM data [13]. In the analysis, costs of re-hospitalisation for device attributable events and device-unrelated events were compared. The relative cost differences between the HeartMate 3 and HeartMate 2 LVAS groups were determined, irrespective of intended goal of therapy. Average payer costs were based on billing data retrieved from 2 US databases. Compared to HeartMate 2 those treated with the HeartMate 3 device had 22% less hospitalisations and 33% fewer days in hospital. Cumulative hospital costs were lowered by 51% (Figure 3). There were 8.3 fewer hospital days per patient-year. There was no cost difference per patient-year depending on gender, intended use, or insurance type. As Dr Mehra pointed out, these savings were driven by more expensive hospitalisation for device attributable events in the HeartMate 2 arm.

Cardiac contractility modulation: a promising option for patients with moderately reduced ejection fraction

Cardiac contractility modulation (CCM) therapy successfully improved exercise tolerance and mortality in patients with left ventricular ejection fractions between 35% and 45% under real-life conditions [14]. This was the main result of the registry data presented by Prof. Gerd Hasenfuß (University Hospital Göttingen, Germany).

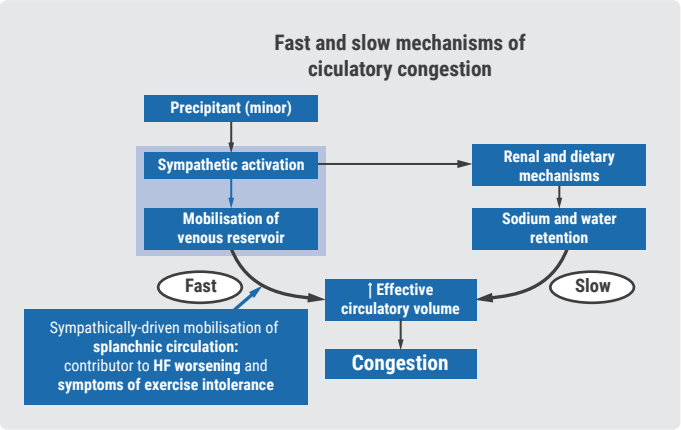
CCM is a new, rechargeable, therapeutic device that delivers a signal to the right ventricular (RV) septum during the absolute refractory period via standard pacing leads. The signals affect the biology of failing myocardium (genes, proteins, and phosphorylation) and, thus, might improve function of the failing heart. This system proved to be effective in the prospective randomised FIX-HF-5C study that was designed to confirm the hypothesis that CCM

improves exercise tolerance in patients with HF and an ejection fraction (EF) of 25-45%. Indeed, in the FIX-HF-5C trial CCM significantly improved exercise capacity, with a statistically significant difference between groups at 24 weeks of 0.84 mlO2/kg/min. In addition, QOL and functional status was improved in the patients. A subgroup analysis showed that clinical effects are greater in patients with an EF of 35-45%. "We share the hypothesis that this device will work better in patients with EF of 35-45% because they have less scar tissue," explained Prof. Hasenfuß. He assessed the efficacy of CCM in 140 patients with 35% ≤ LVEF ≤ 45% and compared it with patients with an EF of 25-45%. The data is derived from a European prospective registry involving 31 sites that is aimed to assess the longer-term impact of CCM on hospitalisations and mortality in a real-world setting, but in the same population as patients in the FIX-HF-5C trial. The patients in the registry were followed for up to 2 years for hospitalisations, Minnesota Living with Heart Failure Questionnaire (MLHFQ), and New York Heart Association (NYHA), and followed up to 3 years for mortality. Reported mortality was compared with the predicted mortality rate by the Seattle Heart Failure Model (SHFM) and the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC). Compared to optimal medical therapy, the cohort with an EF of 35-45% had a significantly lower 3-year mortality rate than predicted with these models, where the whole cohort EF 25-47% had a similar mortality to prediction. CV and HF hospitalisation decreased by 75%. All patients treated with CCM had a significant improvement in QOL, NYHA-class, and left ventricular EF. "Our subgroup analysis confirmed that patients with EF 35-45% saw larger clinical effects than those with a lower EF," concluded Prof. Hasenfuß.

Greater splanchnic nerve ablation: A new treatment paradigm for HF?

The greater splanchnic nerve (GNS) could be a new target in the treatment of HF patients. GNS ablation showed to be tolerable and effective in a proof-of-concept trial [15]. As Prof. Piotr Ponikowski (Wroclaw Medical University, Poland) pointed out, the rationale behind this novel concept is that HF may be caused by inappropriate fluid shifts or fluid redistribution in some patients rather than fluid accumulation. This concept leads to a different clinical presentation and requires different therapeutic consequences. According to the conventional concept, renal and dietary mechanisms lead to sodium and water retention and a higher effective circulatory volume. These mechanisms occur relatively slowly over a period of days to weeks. In addition, sympathetically driven

Figure 4 The rationale behind splanchnic nerve ablation in HF: sodium and water retention is not the sole cause of volume overload. Adapted from Fallick et al. [16]



mobilisation of splanchnic circulation is a dynamic process that can occur rapidly and is an important contributor to HF worsening and to symptoms of exercise intolerance [16]. The consequence of this process is a shift of volume from the capacitance vessels into the systemic circulation, increasing effective circulatory volume and causing congestions (Figure 4).

The splanchnic circulation is the body´s major blood volume reservoir: it receives about 25% of cardiac output and contains 20-50% of the total blood volume. Controlling the amount of blood stored in the splanchnic vessels would allow one to affect the pressure in the heart and lungs [17]. As Prof. Ponikowski pointed out, HF patients with preserved ejection fraction (HFpEF) have congestion as an intermittent phenomenon, and no persistent hypervolemia: they suffer from inappropriate fluid redistribution, caused by the splanchnic circulation, which therefore might be a target of intervention, in particular in HFpEF patients.

To test this hypothesis, Prof. Ponikowksi and colleagues performed a first proof-of-concept study in 10 humans, in which right-sided GSN ablation was performed via video-assisted thoracoscopic surgery. The GSN was only done on the right side to retain some ability for the sympathetic nerve system to effect splanchnic bed vascular function in an emergency such as hypotension or haemorrhage. All patients had guideline-defined HFpEF class III/IV (EF > 40% on optimal medical therapy), and a history of exertion-related dyspnoea in the last 3 months, but no evidence of clinically significant peripheral oedema/fluid overload. The primary safety endpoint was the safety of the procedure through 3

months. The primary efficacy endpoint was a delay in the rise of the pulmonary capillary wedge pressure (PCWP) during exercise.

After the procedure, there were no adverse events (AEs) related to the absence of the right-side GSN. However, there were three AEs related to the surgical procedure: one haematoma requiring transfusion, one infection, and one prolonged hospitalisation following surgery. The procedure led to a significant decrease of resting, as well as exercise PCWP. In addition to these haemodynamic improvements, patients also had a clinical benefit: all patients had NYHA-III at the procedure; after six months, 9 patients were in NYHA class 2 and one in class 1. In addition, exercise capacity and tolerance improved significantly. "Therefore, we propose right-side GSN ablation for the treatment of HFpEF, but we certainly need larger randomised-control trials to better understand the magnitude of effect in HFpEF patients," concluded Prof. Ponikowski.

Late-breaking trials IV: Registries

The last late-breaking session featured new data on registries, an indispensable research tool to judge the value of a treatment in real-life conditions.

CHAMP-HF registry shows: HF patients benefit from sacubitril/valsartan

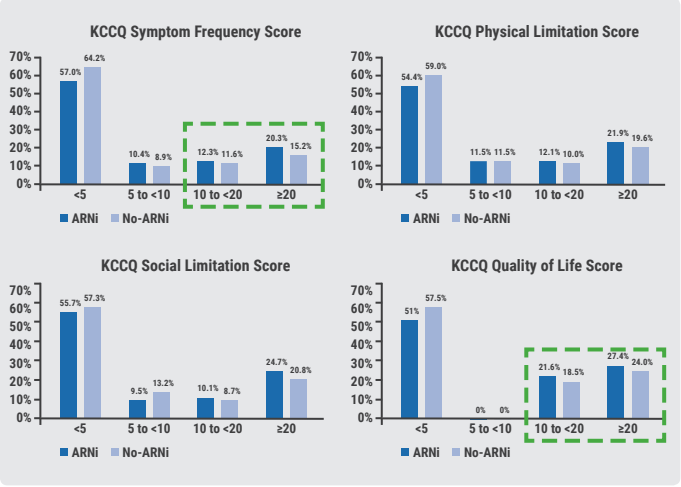
The angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan improved all endpoints and quality of life in the randomised clinical trial PARADIGM-HF. "However, we needed data from a registry to truly understand the short-term health benefit of ARNI vs no-ARNI and whether these benefits are also evident in a real-life scenario," said Dr Yevgeniy Khariton (Saint Luke´s Mid-America Heart Institute, University of Missouri-Kansas City, USA) during the presentation of a pre-specified analysis of an interim data cut from the registry Change the Management of Patients with Heart Failure (CHAMP-HF) [18]. In this registry, patients with CHF and reduced ejection fraction with sacubitril/valsartan therapy were compared to patients not taking an ARNI. Patients treated with an ARNI reported early, statistically significant improvement in health status, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ-12) overall summary score (KCCQ-OS).

All participants had HF with an ejection fraction of ≤ 40% in 12 months prior to enrolment and were treated with at least one oral HF pharmacotherapy. They were followed for 24 months or until death or study withdrawal. Efficacy was measured by change in the KCCQ-12 at different time points. This questionnaire assesses four domains, i.e. physical limitation, symptoms, social limitation, and QOL, which are combined into an overall summary score. It is an established research tool to represent the patients´ perspective of HF with higher scores meaning better health status. Dr Khariton explained: "5, 10, and 20 points changes represent small, moderate and large clinical changes".

Distinct symptom improvement

Patients taking sacubitril/valsartan had statistically significant improvement in health status, as measured by the mean group difference in the KCCQ-OS compared to those not taking the agent (6.01±19 vs 3.55±17). This improvement in the KCCQ score was seen early with a median follow-up of 32 days reported. Patients on the ARNI scored numerically higher on all domains compared to patients not taking the agent, but the improvement in the KCCQ-OS score was especially driven by statistically significant improvements in two domains: symptom frequency (5.07 vs 1.60) and QOL (7.53 vs 4.09). Figure 5 shows the percentage of patients who gain small, moderate, and large differences in the KCCQ. The proportion of patients with a large improvement in overall score (defined as a >20-point improvement from baseline) was 21.4% (78 out of 365 patients) for those taking sacubitril/valsartan vs 12.5% (91 out of 730 patients) for those not taking the agent. "On an individual basis it was even more evident that ARNI patients had less symptoms: we only need to treat 10 patients to experience relevant health status changes," concluded Dr Khariton. He pointed

Figure 5 Distribution of change in KCCQ [18]



KCCQ change: 5 to < 10 points = small, 10 to < 20 points 0 moderate, ≥ 20 points = large
KCCQ = Kansas City Cardiomyopathy Questionnaire

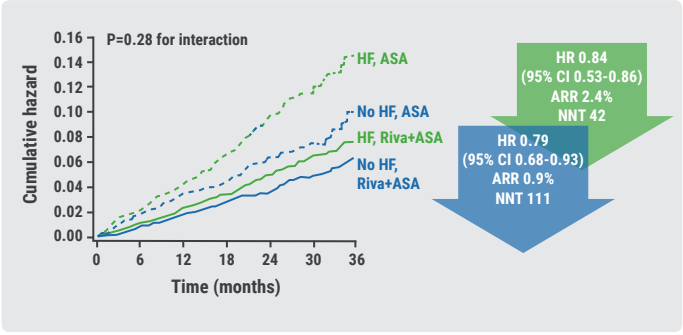
out that further studies are needed to describe long-term health status trajectories in patients prescribed ARNI.

COMPASS substudy: Greater CV benefit with rivaroxaban plus aspirin vs monotherapy

In the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, published in 2017, researchers examined whether patients with stable atherosclerotic disease treated with rivaroxaban plus aspirin have better CV outcomes compared to those treated with monotherapy (either aspirin or rivaroxaban) after a median follow-up of 23 months [19]. Indeed, the combination of rivaroxaban and ASA vs ASA alone led to a reduction of the primary composite endpoint of cardiovascular death, stroke, and myocardial infarction by 24%. Although major bleeding events were more frequent in the combination group, the COMPASS trial was stopped due to superiority of the rivaroxaban plus aspirin combination group after a mean follow-up period of 23 months.

HF patients with atherosclerotic coronary artery disease (CAD) and/or peripheral artery disease (PAD) have a higher risk of increased CV events compared to those without CAD or PAD [20]. Therefore, patients with HF could have an even greater benefit from the combination. A substudy assessed the endpoints depending on the HF status of participants of the COMPASS trial at the beginning of the trial [21]. Dr Kelley Branch, (University of Washington Medical Center, USA) presented the result of the substudy on behalf of the COMPASS steering committee and investigators. In general, patients with HF had higher event rates than those without HF. "Although there was no significant interaction for the benefit of rivaroxaban between the two groups, we observed a difference in absolute risk reduction in patients with HF," said Dr Branch. The absolute risk was reduced by 2.4% in the HF group compared to 0.9% in the patients without HF at baseline. Accordingly, 42 patients with HF have to be treated to prevent one event compared to 111 patients without HF (Figure 6).

Figure 6 COMPASS HF substudy: Primary MACE outcome by HF status[21]



In accordance with the main trial, major bleeding events were more pronounced in patients treated with the combination. In addition, the net clinical benefit, a composite endpoint of primary outcome plus severe bleeding events, of patients with HF and no HF were consistent with the overall trial. Although there was a higher absolute risk reduction for patients with HF.

Prof. Faiez Zannad (Vandoeuvre-lés-Nancy, France) was the discussant of this study. His one point of criticism was that patients with HF in the COMPASS trial were – unexpectedly – younger than patients without HF: this might have resulted in the safety of the combination being judged too good because bleeding events occur more frequently in an elderly population. Another point of interest is whether there are differences in HFrEF or HFpEF patients. As Dr Branch pointed out, the upcoming COMMANDER HF trial will look at a similar dose in HFrEF patients and coronary artery disease and will shed more light on potential differences between HFrEF and HFpEF.

BNP-concentration can identify patients that benefit from early targeted intervention

Estimating the risk of future CV events using traditional risk factors, such as age, gender, smoking, diabetes, hyperlipidaemia, and hypertension, is well accepted in the medical field. These estimates are based on a number of robust observational studies, including the original Framingham study. While these methods apply reasonably well on a population level, their application to the individual patients is not always straightforward. Risk charts may underestimate risk in certain groups, notably diabetics and patients of Indo-Asian background, whilst overestimating risk in others. The Alternative Risk Markers in Coronary Artery Disease (ARM-CAD) study aimed to assess several known and a few novel risk factors, including heart rate variability, pulse wave analysis, high-sensitivity C-reactive protein (CRP), and B-type natriuretic peptide (BNP), in a prospective cohort of patients prior to planned elective coronary angiography (cross-sectional analysis) [22]. The trial included 526 Australian, unselected patients referred for elective coronary angiography. All-risk markers were assessed prior to angiography. Clinicians were blinded to risk markers throughout the follow-up time of 5 years.

Over 5 years, 15.6% of patients underwent coronary artery bypass grafting (CABG), and 29.9% had at least one percutaneous coronary intervention (PCI) procedure (drug-eluting stents were used in 55%). In this period, 9% of patients died, 8% had a myocardial infarction (MI), and 4% a stroke. There was a lower MI rate but higher mortality than expected. Markers that proved not to be useful in predicting the outcomes were the CRP concentration and the pulse wave analysis. Regarding both parameters, no difference was observed between patients in the lower, middle, and upper tertile. "We had some disappointments here," said Dr Dipak Kotecha (University of Birmingham, UK). Heart rate variability, a promising risk factor according to previous trials, was only predictive over the first 2 years, but no long-term difference was observed between the tertiles. In addition, conventional risk factors only had a limited use in predicting the risk. In a multivariate analysis, age was the only conventional risk factor independently associated with outcome. In contrast, there was a dramatic difference in the number of events between the groups according to BNP concentration, independent of overt ventricular dysfunction and revascularisation. Patients with a BNP value >100 pg/ml had an almost twofold increase of events and all-cause mortality compared to those with BNP concentrations of ≤100 pg/ml.

In this population, conventional risk factors, including inflammation and vascular properties, seem no longer important. "In contrast, BNP is a great marker of more subtle ventricular dysfunction than we can see overtly. A cut-off value of >100 pg/ml is particularly useful to identify patients that need extra attention and that could benefit from early, targeted and individualised management," concluded Dr Kotecha.

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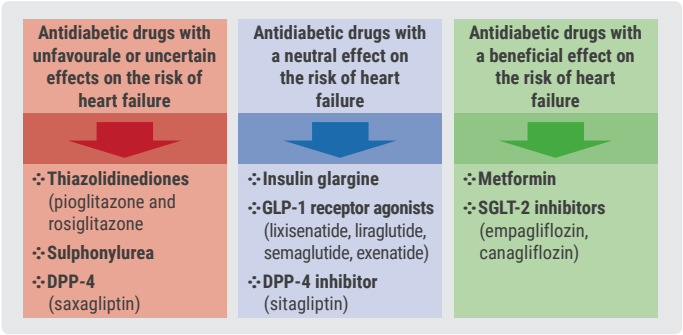
Diabetes and the Heart – a Global Challenge

The cardiovascular (CV) safety of antidiabetic drugs are assessed in many trials. Sodium-glucose cotransporter 2 (SGLT2) inhibitors might even have a cardioprotective effect in patients without type 2 diabetes.

"Until 2008, there were hardly any trials with regard to cardiovascular safety of diabetic drugs, which is remarkable considering that heart disease is the number one cause of death in diabetics," said Prof. John McMurray (University of Glasgow & Queen Elisabeth University Hospital, Scotland) [1]. Since the inception of mandatory CV safety outcome trials by the US Food and Drug Association (FDA) in 2008, many trials have assessed the CV risk of antidiabetic drugs (Figure 7).

An analysis of the RECORD trial, showed that rosiglitazone doubles the relative risk for heart failure (HF) [2]. HF is therefore a CV outcome in diabetes that can no longer be ignored. Another trial that showed a negative impact of an antidiabetic on CV outcomes was the SAVOR-TIMI53 trial. In this trial, therapy with the dipeptidyl peptidase-4 (DPP-4)

Figure 7 Antidiabetic drugs and the risk of HF [7]



inhibitor saxagliptin was associated with an increased risk for HF [3]. In contrast, both the glucagon-like peptide 1 (GLP-1) agonist liraglutide in the LEADER trial and the semaglutide in the SUSTAIN-6 trial demonstrated superiority in reducing the three-point major adverse CV event primary outcome (i.e. CV mortality, non-fatal myocardial infarction, and non-fatal stroke). Yet, can GLP-1 receptor agonists also be safely used in patients with established HF? The SUSTAIN-6 trial showed that GLP-1 receptor agonists elevate heart rate, which is probably detrimental for patients with HF. The effect of therapy with liraglutide on clinical stability in patients with advanced HF was assessed in the trial Functional impact of GLP-1 for Heart Failure Treatment (FIGHT) [4]. For 180 days, 300 patients with HF and reduced EF were treated. The use of liraglutide did not lead to greater posthospitalisation clinical stability in this trial.

New approaches to reduce blood glucose are the SGLT2 inhibitors. These agents lead to increased urinary glucose excretion and improved hyperglycaemia, without affecting ß-cell function and insulin resistance. Thus, SGLT2 inhibitors cause diuresis and natriuresis, lower blood pressure, and reduce weight. A breakthrough was the EMPA-REG OUTCOME trial, which included 7,020 patients with diabetes and CV disease. This large trial assessed the long-term effects of empagliflozin in addition to standard care vs placebo on CV morbidity and mortality in over 7,000 patients with type 2 diabetes and high risk of CV events [5]. All included patients had established CV disease, including CVD (prior to myocardial infarction), CAD, stroke, unstable angina, and occlusive peripheral arterial disease. The primary endpoint was 3-point MACE, consisting of time to first occurrence of CV death, non-fatal myocardial infarction, and non-fatal stroke. Patients treated with empagliflozin had a 14% risk reduction for this combined endpoint. The hospitalisation for HF or CV death was even lowered by 34% (HR 0.66; P<0.001). The benefit of the therapy was already evident soon after starting the therapy. Another positive trial was the Canagliflozin Cardiovascular Assessment Study (CANVAS) [6], which showed that canagliflozin led to a significant reduction in HF hospitalisation.

According to Prof. McMurry, some key questions remain unsolved with regard to SGLT2 inhibitors. For example, what their mechanisms of benefit are, what types of HF they prevent, and whether they can be used to treat established (prevalent) HF. Numerous ongoing trials with SGLT2 inhibitors in individuals with type 2 diabetes are currently trying to provide answers to these important questions.

Paradigm shift with regard to SGLT2 inhibitors

"With regard to SGLT2 inhibitors, we might see a paradigm shift from a beneficial effect for prevention of HF in diabetics to a beneficial effect for the treatment of HF even in patients without diabetes," said Prof. Petar Seferovic (Belgrade University School of Medicine, Serbia) [7]. This the topic of two upcoming trials: the EMPEROR-preserved trial will investigate the safety and efficacy of empagliflozin in patients with chronic HF with HFpEF, and the EMPEROR-Reduced trial in patients with chronic HF with reduced ejection fraction. In both trials, patients with and without type 2 diabetes will be included.

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Cardiomyopathy: High risk in Cancer Survivors

Peripartum cardiomyopathy (PPCM) is a rare heart disease occurring in the last months of pregnancy or in the first 6 months after delivery. Clinically, PPCM resembles a dilated cardiomyopathy (DCM) but the left ventricle may not always be dilated. The ejection fraction is nearly always reduced below 45%. This condition occurs in about 1 in 1,000 pregnant women worldwide [1]. Its incidence is rising in Western societies, probably due to socio-economic changes (e.g. rising maternal age, fertility-assisted treatments, and multifetal pregnancies), better diagnostic tools, and increasing awareness [1]. New studies observe links between PPCM and cancer. Women who survived cancer early in life have a higher risk of developing peripartum cardiomyopathy when pregnant later in life. In addition, patients with this rare heart disease have elevated cancer markers, according to a data analysis of a German registry.

"It is suspected, without having real data, that cardiotoxic anticancer treatment injures the heart, and that years later a second stress on the heart, like pregnancy, induces cardiomyopathy," said Prof. Hilfiker-Kleiner (Hannover Medical School, Germany) during the presentation of the results that suggest links between cancer and PPCM [2]. In part one of the study, the 10-year prevalence of cancer, which occurred before or after PPCM in 207 women, was compared to the 10-year cancer prevalence in the general population of women aged 0–49 years in Germany.

Thirteen of the 207 women with PPCM had cancer during the 10-year period – a prevalence of 6.3%. Of the 14 cancer diagnoses, 9 occurred before PPCM and 5 after PPCM. The 10-year cancer prevalence in the general population of women in Germany aged 0–49 years was only 0.59%. Thus, women with PPCM had ten times more cancer, either before or after their heart failure, than the general population. About two-thirds of cancers occurred in children or young adults who then developed PPCM later in life (3 lymphoma, 2 breast carcinoma, 2 osteosarcoma, 1 melanoma, and 1 prolactinoma), while one-third were diagnosed two to three years after PPCM (3 breast carcinoma, 1 colorectal carcinoma, and 1 acute myeloid leukaemia). "We think there may be genetic or epigenetic factors that make women more prone to both diseases. This is on top of the long-term cardiotoxic effects of anticancer therapies," concluded Prof. Hilfiker-Kleiner.

Elevated cancer markers in patients with PPCM

In part two of the study, the researchers analysed time since pregnancy and plasma levels of 61 markers in 47 women with PPCM and 29 healthy women of the same age to look for possible associations. Some plasma markers potentially associated with cancer (i.e. HER2/neu, PAI-1, sIL-6Ra, osteopontin) were significantly elevated at baseline and at a follow-up at 6 months ($P<0.05$) in patients with PPCM compared to healthy controls. Human epidermal growth factor receptor 2 (HER2) is a protein that is elevated in around 20% of breast cancer patients. These markers returned to a normal level after a long-term follow-up period of 11 months to 7.5 years. A comparison between the subgroups of patients with PPCM according to their LVEF revealed significantly elevated baseline levels of HER2/neu ($P=0.0024$) and sIL-6Ra ($P=0.0435$) in patients with persistently reduced cardiac function (LVEF=34%) compared to patients with cardiac recovery (LVEF=50%). Cancer markers were elevated during the study in women with PPCM regardless of whether or not they had previous or subsequent cancer.

"Our finding that cancer and peripartum cardiomyopathy share some biological markers in the blood suggests that there is a physiological connection between these diseases," said Prof. Hilfiker-Kleiner. PPCM is associated with a high morbidity and mortality, and previous studies have shown that diagnosis is often delayed [3]. Therefore, young female cancer survivors should be warned of this pregnancy-associated HF so that they can be closely monitored. "These are high-risk pregnancies and women need close monitoring of their hearts for any sign of heart failure. We need more data so that we can tell pregnant women with a history of

cancer how high their risk of developing a second deadly disease is," concluded Prof. Hilfiker-Kleiner.

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Novel Drugs in Heart Failure

Heart failure remains a deadly and significant problem despite advances in treatment. Therefore, it is imperative to explore new targets in the treatment of chronic HF.

A feature in the pathophysiology of chronic HF is that systolic function decreases. "Therefore, we still pursue inotropes, although we know that current inotropes have negative effect,s" said Prof. John Teerlink (University of California San Francisco, USA) [1]. None of the approved inotropes, such as dobutamine, amrinone, and milrinone, are pure inotropic acting agents; they are more like inodilators. They work through an indirect mechanism of improving contractility by elevating calcium in the sarcoplasmic reticulum. Unfortunately, this mechanism has inherent negative effects: it increases heart rate, decreases blood pressure, increases oxygen demand, and decreases cardiac efficiency. These agents therefore contribute to arrhythmia and death. However, there are many mechanisms of inotropy; some of which do not affect calcium concentrations.

New inotropes improve the energetic status of the heart

An emerging new pharmacotherapeutic for acute HF is nitroxyl (HNO). This agent is not only a potent vasodilator, but also improves the energetic status of the heart. Its mechanism of action is not mediated by cyclic adenosine monophosphate (cAMP), and it does not increase myocardial oxygen consumption or heart rate. It is currently being tested in a phase 2b study in patients with acute decompensated HF.

Neladenoson is a partial adenosine A1 receptor agonist, which has an inotrope activity by energetic modulation. It improves mitochondrial function and is able to reverse ventricular remodelling. In addition, it has anti-ischaemic cardioprotective effects, improves Ca2+ handling, and protects the heart from calcium overload. Thus, it could simultaneously improve cardiomyocyte energetics, calcium homeostasis, and cardiac structure and function [2]. Neladenoson was safe in two small pilot studies, and no atrioventricular conduction disorders were observed [3]. In the phase 2 PANTHEON trial, the agent will be assessed in 427 patients with chronic HF, and the results are expected later this year. Another phase 2 trial is the PANACHE trial, which plans to study Neladenoson in HFpEF patients.

Another inotropic agent discussed at Heart Failure 2018 is omecamtiv mecarbil, a cardiac myosin activator. It accelerates the transition of myosin into the force-generating state without affecting cardiac myocyte calcium homeostasis [4]. As Prof. Teerlink pointed out, this mode of action avoids the deleterious effect of conventional inotropes, such as the increase in myocardial O2 demand. In a dose-ranging phase 2 trial, the agent improved cardiac function in patients with left ventricular dysfunction with an impressively effect size. The infusions were also well tolerated [5].

Omecamtiv mecarbil was also tested in patients with acute decompensated HF in the ATOMIC-AHF trial [6]. The primary endpoint was the dyspnoea response through 48h, assessed with the Likert Scale. In this trial, the agent did not meet the primary endpoint of dyspnoea improvement, but it was generally well tolerated, it increased systolic ejection time, and therapy resulted in greater dyspnoea relief at 48h (placebo 37% vs OM 51%; P=0.034) and through 5 days (P=0.038) in the high-dose cohort.

In the COSMIC AF trial, omecamtiv mecarbil is tested in chronic HF with LVEF ≤ 40% [7]. After 24 weeks, the agent improved cardiac function and decreased ventricular diameter. "In another analysis of the COSMIC AF trial, we could show that patients feel better after therapy with omecamtiv

mecarbil", said Prof. Teerlink. Over time, there is no evidence of tachyphylaxis. "We saw a consistent improvement in stroke volume, and, consistent with the concept of reverse remodelling, we saw a progressive decrease in end-diastolic volume," said Prof. Teerlink. In addition, there was a continuous decrease in NT-proBNP concentrations up to four weeks after drug discontinuation.

Lastly, the GALACTIC-HF trial is a double-blinded, randomised, placebo-controlled, multicentre phase 3 trial with chronic HF patients on standard of care therapy and a reduced ejection fraction. Primary endpoint of this trial is CV death and HF hospitalisation within 12 months. "At the end of this trial we will know whether the improvement of cardiac function by omecamtiv mecarbil translates into clinical outcomes," concluded Prof. Teerlink.

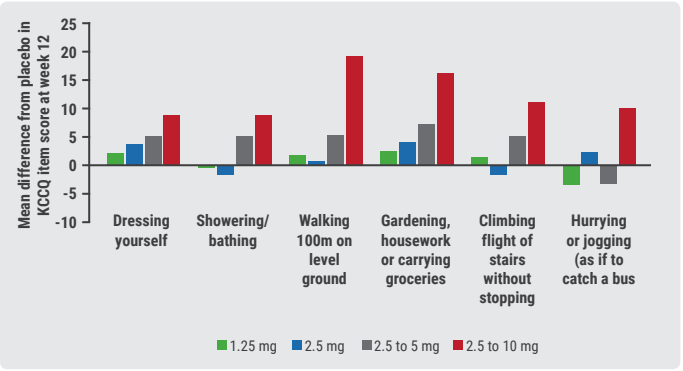
Soluble guanylate cyclase: another novel target in HF

As Prof. Christopher O´Connor (Duke University, USA) pointed out, soluble guanylate cyclase (sGC), a key enzyme of the nitric oxide (NO) signalling pathway, is increasingly attracting interest as a therapeutic target in cardiopulmonary disease [8]. Upon binding of NO to a prosthetic haeme group on sGC, the enzyme catalyses synthesis of the second messenger cyclic guanosine monophosphate (cGMP), which produces vasorelaxation and inhibits smooth muscle proliferation, leukocyte recruitment, and platelet aggregation through a number of downstream mechanisms [9]. "We had experience with NO-donors but had to face challenges like tachyphylaxis. So, there was an intensive investigation to look for an NO independent way of stimulating sGC," explained Prof. O´Connor. In his view, sGC modulation is an exciting new class of medication. Agonists of sGC could have beneficial effects in HF by preventing the progression of, or even reversing, ventricular hypertrophy and fibrosis. In addition, sGC agonists may have acute beneficial effects by decreasing right and left ventricular afterload through vasodilatation of both the pulmonary and systemic circulation. This holds true in particular for oxidised sGC stimulation. "This is the type of stimulation HF patients are probably in chronically, which makes it so important," said Prof. O´Connor.

Riociguat was the first sGC stimulator to receive FDA approval for the treatment of pulmonary hypertension and chronic thromboembolic hypertension. Another agent in this class, vericiguat has a dual mode of action and might therefore be more interesting to treat HF patients. It stimulates sGC directly, but also makes the enzyme more sensitive to NO. Vericiguat was tested in patients with worsening CHF and reduced EF in the SOCRATES-REDUCED trial [10]. In this dose-finding phase 2b trial, the primary endpoint of a reduction of NT-proBNP from baseline to week 12 was not met. However, a pre-specified exploratory analysis suggest that, compared to placebo, the highest dose (10 mg) decreased NT-proBNP. In addition, reduction in NT-proBNP in the highest-dose arm was associated with improved LVEF and trends toward fewer clinical events at 12 weeks. Currently under way is the VICTORIA trial, a phase 3 trial with classical endpoint, i.e. time to first occurrence of the composite of CV death and HF hospitalisation after a follow-up duration of about 18 months [11].

Vericiguat was also tested in HFpEF patients in the phase 2b study SOCRATES-PRESERVED [12]. "The HFpEF condition is one in which there is systemic inflammation. Vericiguat may have unique effects as it is able to reduce inflammation, dilate vessels, and reduce fibrosis," explained Prof. O´Connor. In the main study, vericiguat was well tolerated but did not change NT-proBNP and left atrial volume at 12 weeks compared with placebo [12]. However, in an analysis evaluating patient-reported outcomes of this trial, vericiguat was associated with clinically important improvements in patients' health status, as assessed by the disease-specific KCCQ and the generic health-related quality of life measure EQ-5D (Figure 8) [13]. "I think there is still an opportunity. Therapy with vericiguat led to a dramatic improvement in the quality of life across all sorts of activity," said Prof. O´Connor. Hence, the new VITALITY-HFpEF trial. In this trial, an incremental increase of the dose is assessed, because applied doses might have been too low. Primary endpoint of this trial will be a change in the 6-minute walk test. "This unique new target may even hold greater promise," concluded Prof. O´Connor.

Figure 8 Vericiguat improved all domains in the KCCQ item analysis compared to placebo [13]



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Prevention of Heart Failure – the Only Sustainable Long-term Option

Educating clinicians is of key importance to develop effective preventive strategies. Especially high-risk populations, such as hypertensive or cancer patients, benefit from early intervention.

"Heart failure is a growing problem in terms both of the number of individuals affected and the implications for national health services," said Prof. Massimo Piepoli (Guglielmo da Saliceto Polichirurgico Hospital, Italy). "The increasing size of the elderly population means that this issue is only going to get worse in the coming years and the cost of treating patients risks becoming unsupportable."

Prof. Piepoli, who held a lecture on prevention of HF in patients with hypertension, is aware that prevention is not easy [1]. "We all know the important risk factors—hypertension, smoking, obesity, diabetes, sleep apnoea, a sedentary lifestyle, and poor diet. But we also know that persuading individuals at risk to adopt—and adhere to—a healthier lifestyle and to comply with treatment is easier said than done". This is despite the recommendation of lifestyle modification in both the 2016 ESC Guidelines for the diagnosis and treatment of HF, and the 2016 European Guidelines on cardiovascular (CV) disease prevention, and the evidence that these modifications are effective in reducing risk factors such as hypertension (Table 1) [2,3]. Effective antihypertensive therapy does not only reduce the risk of HF by 52%, but also the risk of fatal/nonfatal stroke, fatal/nonfatal coronary artery disease, and vascular death [4,5].

Table 1 Lifestyle modification and their influence on blood pressure [1]

Modification	Approximate SBP
Weight reduction	5-20 mm Hg/10 kg weight loss
Adopt DASH[1] eating plan	8-14 mm Hg
Dietary sodium reduction	2-8 mm Hg
Physical activity	4-9 mm Hg
Moderation of alcohol consumption	2-4 mm HG

SBP = systolic blood pressure
[1]DASH eating plan is a programme supported by the National Heart, Lung and Blood Institute to reduce blood pressure. The programme is low in saturated fat, cholesterol, and total fat and emphasises fruits, vegetables, and fat-free or low-fat milk and milk products

According to Prof. Piepoli, investment in prevention is unavoidable. One of the most reliable ways to ensure this success is by educating clinicians. "Traditionally, our medical training focuses on treatment. We need to change this and get doctors to think about how we can help patients to avoid developing heart failure. Societies and associations, like the Heart Failure Association, must take a leading role in changing the culture and putting prevention centre stage," said Prof. Piepoli. He believes that new technology like the use of telemedicine devices will enable doctors to monitor how well patients are implementing healthier lifestyles, and smartphone apps can help patients to manage their exercise and medication. However, much depends on the motivation of the individual and the responsibility they take for their own health.

Cancer patients: a high-risk group for development of HF

Cancer patients are at a high risk to develop HF. Different classes of anticancer drugs, such as anthracyclines and alkylating agents but also newer biologics such as the

monoclonal antibody trastuzumab, elevate the risk for left ventricular dysfunction [6]. There are many ways in which cancer drugs can damage the heart: cisplatin causes myocardial ischaemia, VEGF inhibitors arterial hypertension, immune checkpoint inhibitor myocarditis, and alkylating agents arrhythmias. In addition, cancer patients and HF patients share common risk factors such as aging, smoking, drugs, alcohol, obesity, physical inactivity, and a poor diet [7]. "It is important to see patients early, before left ventricular dysfunction develops," said Dr Dimitrios Farmakis (National and Kapodistrian University of Athens, Greece) [8]. Different strategies exist to combat HF in cancer patients. Primordial prevention, for example, is prevention before cancer therapy, in absence of any abnormality. In this respect, topoisomerase (Top) 2β was recently revealed as the key mediator of anthracycline-induced cardiotoxicity. Top2 inhibition by anthracycline causes double-stranded breaks in DNA, which can lead to cardiomyocyte death [9]. By measuring Top2ß concentration in peripheral blood, anthracycline-sensitive patients can be detected.

Biomarkers should also be assessed after chemotherapy. "High concentrations of troponin and NT-proBNP have shown to predict LVEF decline," said Dr Farmakis. In primary prevention, conflicting evidence exists regarding the use of the ß-blocker carvedilol and ACE inhibitors. According to some studies, therapy was effective in reducing LVEG decline, while other trials showed no effect for cancer patients treated with trastuzumab, but did show a protective effect for patients treated with an anthracycline [10,11]. In secondary prevention, both ACE inhibitors and ß-blockers showed to be effective in full or partial recovery of LVEF in patients treated for anthracycline cardiotoxicity [12,13]. This treatment is also recommended in an ESC position paper [14].

Heart failure patients benefit from high-protein intake

In secondary prevention, high-protein intake might be a way to protect HF patients. This was shown by a study presented at Heart Failure 2018. The BIOSTAT-CHF study, conducted in 11 European countries, investigated the association between protein intake and survival in 2,281 HF patients in the study [15]. One of the major threats to living independently is the loss of muscle mass, strength, and function that progressively occurs with aging [16]. Several studies have identified protein, especially the essential amino acids, as a key nutrient for muscle health in elderly adults. The requirement for a larger dose of protein to generate responses in elderly adults similar to the responses in younger adults provides the support for a beneficial effect of increased protein intake in older populations [16]. Until recent, little was known about the impact of low vs high protein intake in patients with HF. A total of 2,281 patients with an average age of 68 years were included in the analysis [15]. Daily protein intake was estimated from urine urea excretion, corrected for urine creatinine and body mass index (BMI) using a validated formula. Patients were divided into 4 groups according to the amount of protein they consumed. The median protein intake was 53 grams per day, ranging from 40 grams in the lowest quartile to 70 grams in the highest. Patients in the highest quartile of protein intake were more often male, had lower NTproBNP levels and had a higher BMI.

At the end of the median 21-month follow-up period, 31% of patients in the lowest quartile of protein intake (40 grams or less per day) had died compared to 18% of patients in the highest quartile of protein intake (70 grams or more per day) (P<0.001). After adjusting for multiple confounders including age and renal function, patients in the lowest quartile of protein intake still had a 46% higher risk of death than those in the highest quartile of protein intake (hazard ratio 1.46; 95% confidence interval 1.01–2.12; P=0.045). Dr Koen Streng (University Medical Centre Groningen, the Netherlands) said: "We observed that in patients with heart failure, a higher protein intake is independently associated with better survival. The study did not look at causes for this link, but it is likely that dietary protein builds muscle mass, which is beneficial for health in these patients." According to Streng, a randomised controlled trial is needed to determine a recommended amount of daily protein intake for patients with heart failure.

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Pearls of the Posters

Poster sessions and moderated poster sessions belonged to the highlights of the scientific programme at the HF meeting. In this chapter a selection of the most interesting topics.

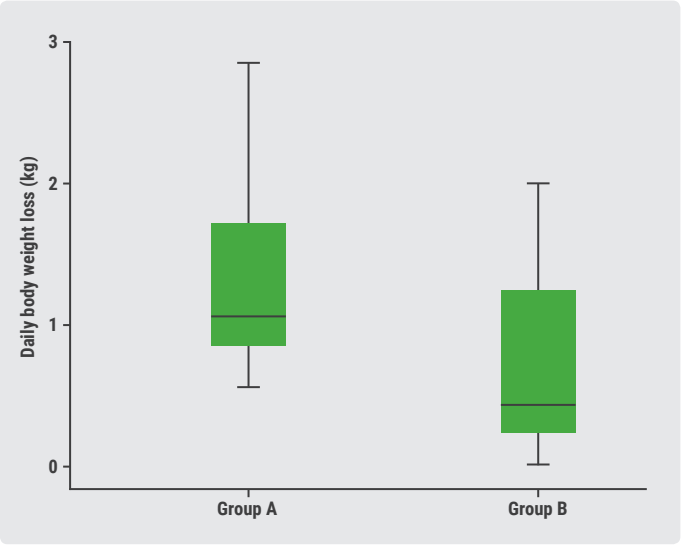
Higher myocardial infarction risk in frail patients

Elderly patients with acute coronary syndrome (ACS) can experience a wide spectrum of geriatric conditions that aggravate their prognosis [1]. Older age is universally considered a risk factor, but geriatric conditions are usually not evaluated in clinical practice. A Russian study assessed the prevalence of geriatric syndromes and its impact on clinical outcomes [2]. Physical disability (Barthel index), functional mobility, nutritional status (Mini Nutritional Assessment), and cognitive function (Mini Mental State Examination) were assessed in 130 patients with a mean age of 83.5 years. Frailty was revealed in 66% of participants. Patients with frailty were more likely women (72% vs 59%; P<0.05). More than half of the patients had malnutrition, and 74.6% had a physical disability of daily living. Nearly a third of the patients were cognitively impaired. Geriatric syndromes were associated with a higher rate of MI during index hospitalisation, a higher index of diabetes mellitus, and a higher risk of mortality and bleeding.

High-dose spironolactone improves decongestion in patients with acute heart failure

Intravenous (IV) loop diuretics induce a rapid diuresis that reduces congestion and dyspnoea [3]. Diuretics are the number one treatment choice for patients hospitalised with acute heart failure (AHF) presenting with signs and symptoms of volume overload. However, their effectiveness declines with repeated exposure [4]. In addition, AHF is a state of severe, secondary hyperaldosteronism. To overcome the inconsistent responsiveness to diuretic treatment, high doses of spironolactone have been proposed as a potential measure to increase diuresis in AHF with congestion; in particular in patients with diuretic resistance. This approach was tested in a Greek study of 20 patients who were hospitalised with AHF and received high doses of spironolactone (75-300 mg daily, group A) on top of standard of care therapy (group B) [5]. They were compared with 20 matched patients who received standard care treatment. Patients treated with high doses of spironolactone in addition to standard of care demonstrated significantly greater daily urine output (2.9 vs 2.2 l/day; P=0.009), daily weight loss (1.1 vs 0.4 kg/day; P=0.005; Figure 9), and total body weight loss (10.5 kg vs 3.8 kg; P<0,001) compared with patients on standard care therapy alone. Incidence of worsening renal function, hypokalaemia, and hyperkalaemia were similar between the two groups. In group A, 19 out of 20 patients were prescribed spironolactone at discharge as compared with 14 of 20 patients in group B. At a follow-up at three months, only 5% of patients in group A vs 25% patients in group B had been rehospitalised (P=0.077). The authors conclude that in patients with AHF with congestion, administration of high doses of spironolactone on top of standard of care treatment appears to be safe and is associated with significantly greater decongestion than standard of care alone.

Figure 9 Box plot analysis showing significant differences between the two study groups in favour of the spironolactone group regarding daily weight loss (P=0.005) [5]



Intravenous iron therapy: also beneficial in a real-life scenario

The double-blinded, placebo-controlled CONFIRM-HF trial has shown that patients with iron deficiency and chronic HF with reduced ejection benefit from long-term CV iron

supplementation [6]. In a Spanish study, the impact of this intervention on non-CV hospitalisation rates and emergency department (ED) visits was assessed in a cohort of patients with HF and iron deficiency [7]. Baseline characteristics and previous-year admission rates and ED visits were retrospectively collected. During the follow-up, hospitalisation rate and ED visits were registered and compared with previous-year rates.

IV iron therapy reduced all-cause hospitalisations and CV hospitalisation rates. In addition, there was a significant decline in ED visits (P<0.01). Benefits could be seen regardless of LEVF. Only CV hospitalisation rate was not influenced in patients with preserved ejection fraction. The authors conclude that their findings are consistent with the CONFIRM-HF trial in patients with LVEF ≤45%. Yet, also in patients with LVEF >45%, non-CV hospitalisation rate, and CV and all-cause ED visits can be reduced by IV iron supplementation.

Gut microbiota – a novel risk factor for cardiovascular disease?

Previous studies have shown that gut microbiota composition plays an essential role in immunology. However, is there also an association between gut microbiota and CV risk factors such as diabetes, hypertension, and obesity, or the prevalence of CAD? To answer this, the gut microbiota of apparently healthy individuals from Moscow were evaluated with the help of 16S rRNA sequencing (V3-V4 regions) [8]. Before the assessment, the presence of CVD risk factors was evaluated in all participants by means of clinical and laboratory evaluation (i.e. ECG, treadmill test, carotid ultrasound examination including intima-media thickness measurement). Mild hypertension was found in 37% of the participants, 25% were obese, 55% had abdominal obesity, and 23% diabetes. Obesity, abdominal obesity, and diabetes were all associated with a high abundance of the gram-negative opportunistic genera *Serratia* and *Prevotella* (Table 2). On the other hand, *Oscillospira* species were inversely correlated with abdominal obesity. This genus has shown to be an important component of gut microbiome, which reduces inflammation, and high concentrations are associated with leanness and high physical activity level.

Table 2: Microbiotaspecies and association with CV risk factors [8]

Genus	Features	Association
Blautia	Gram (+), activate the secretion of TNFa, cytokines	Arterial hypertension and diabetes mellitus
Serratia	Gram (-), opportunistic pathogens	Obesity, abdominal obesity, and diabetes mellitus
Prevotella	Gram (-), opportunistic pathogens	Obesity, abdominal obesity, and diabetes mellitus
Oscillospira	Gram (+), ferment carbohydrates, symbiont bacteria	Inverse association with abdominal obesity
Bifidobacterium	Gram (+), ferment carbohydrates, symbiont bacteria	High-fat diet

Interestingly, the *Blautia* genus was highly abundant in patients with hypertension and diabetes. In addition, a high-fat diet was associated with low representation of Bifidobacterium. This study suggests that gut microbiota composition shifts along with classical risk factors is associated with CVD risk factors. In particular, the combination of a high-fat diet together with abundance of the *Blautia* species may enhance the metabolic risk and pave the way for diabetes mellitus. Composition of gut microbiota might be an interesting novel marker of CV risk. Validation of these findings and whether gut microbiota play a causative role in CV risk is needed.

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