> "In patients with heart failure, the highest mortality is observed shortly after discharge following an acute decompensation treated in the hospital. About 4% of patients die during the acute decompensation phase in the hospital. A quality of care reflected by the accessibility to the emergency department and well-equipped hospitals can deal with the care of acutely decompensated patients."

Latest trials and new perspectives in heart failure

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The following review summarizes new reports on acute and chronic heart failure, which were published during the last year.

Diagnosis of heart failure

Diagnostic methods in heart failure are described in detail in the Guidelines of the European Society of Cardiology.[1] Echocardiography has a predominant role in characterizing and following up left ventricular function. Biomarkers, like N-terminal pro-brain natriuretic peptide (NT-proBNP), have a high negative predictive value and can exclude clinically relevant heart failure in patients with dyspnea, signs, symptoms, and dyspnea on exertion or peripheral edema. A new development addresses the question of how acute pulmonary congestion can be diagnosed in an acutely decompensated patient. NT-proBNP integrates information about kidney function, wall stress, and the degree of volume overload. Echocardiographic data might not reflect acute decompensation, the degree of congestion, and does not allow clues on the severity of congestion. During the last years, pulmonary ultrasound has entered the clinical stage.[2] Recent studies have provided evidence that, in acutely worsened heart failure, ultrasonographically-detected B-lines correlate closely with NT-proBNP and radiological signs of congestion.[2] Meanwhile, there are more data providing evidence that this method is able to reliably quantify pulmonary congestion and, in particular, pulmonary edema.[3] B-lines are the results of fluid accumulation in interlobular septal spaces and reflect an enhanced fluid content of the lungs. In recent work, it has been shown that patients who are not congested at rest (as evidenced by the lack of B-lines on pulmonary ultrasound) get congestion during physical exercise.[4] The increase in echocardiographic signs of congestion on ultrasound was closely correlated with exercise-induced increases in pulmonary-arterial pressures and the degree of mitral incompetence during exercise. In turn, there was an inverse relationship with left ventricular ejection fraction. In extension to these studies, there was a close association of the rate of hospitalization and cardiovascular death[4] with these signs of congestion on ultrasound. Therefore, pulmonary ultrasound could be regarded as a valid add-on diagnostic test in heart failure patients with volume overload in future clinical practice.[5] A recent position paper of the ESC classifies pulmonary ultrasound as a valid and recommended tool for patient characterization when it is performed under standardized conditions.[6]

Acute heart failure

◆ *Structural problems of care*

In patients with heart failure, the highest mortality is observed shortly after discharge following an acute decompensation treated in the hospital. About 4% of patients die

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during the acute decompensation phase in the hospital. A quality of care reflected by the accessibility to the emergency department and well-equipped hospitals can deal with the care of acutely decompensated patients. A study from Germany shows that, in a country like Germany, there is a huge gradient in the accessibility to hospitals and cardiology care facilities, which is closely associated with the prevalence as well as the morbidity and mortality of heart failure patients.[7] In this study, about 87% of care reality was captured. Accessibility to care facilities can differ up to 40%. In those underequipped regions, the accessibility of care and the mortality of heart failure is closely associated.[7] Other European regions should be investigated to detect care deficiencies simply due to structural problems.

◆ *New studies*

In acute heart failure, the majority of studies fail to show the superiority of novel treatment approaches compared with standard care. A novel approach of treating acute heart failure with serelaxin was tested, serelexin is a recombinant form of the pregnancy hormone relaxin. Phase 2 studies provided evidence that the rate of decompensation can be accelerated with a small signal in the improvement in cardiovascular mortality.[8-11] Definite clinical evidence was hoped to be provided by the RELAX-HF study, the results of which have been recently published.[11] After treatment of patients with serelaxin within 48 hours, there was no evidence for an improvement in cardiovascular death or subsequent heart failure hospitalization after 6 months.[11] The concept of rapidly unloading the left ventricle to improve congestion and maintain myocardial performance is usually accompanied by a blood pressure reduction in the treated patients. It is important to know that, as the majority of these drugs strongly reduce blood pressure, inclusion criteria start from high levels of blood pressure, whereas patients with low pressure, as present in most heart failure patients, are frequently excluded. This principle of safety was also appreciated in the RELAX-HF study, resulting, however, in an inclusion of patients with an average blood pressure above 142 mm Hg. Therefore, this study and previous studies were performed in a highly selected patient population with relatively high blood pressure, which is usually rarely observed in patients with acutely decompensated heart failure in daily clinical practice.[11] Moreover, it might be argued that the concept of early and pathophysiologically based recompensation resulting in an improvement in death and hospitalization months after the acute decompensation was too optimistic. Development of a long-acting serelaxin derivate given on a regular basis to improve outcomes in chronic heart failure patients, even after an acute decompensation, appears worthwhile and is meanwhile under development.

News in medical treatment

◆ *When to start after an acute decompensation?*

After hospitalization due to decompensated heart failure, about 30% to 50% of patients die within the first 60 days after discharge. Furthermore, a majority of patients are rehospitalized; this is the most precise predictor of death in the following year. The reasons are unclear, but may involve incomplete initiation of guideline-recommended medical therapies after discharge, nonadherence to medications due to intolerance, or inertia of physicians to explain to the patient the importance of drug intake. Moreover, these patients are frail, have low blood pressure and a high level of neuroendocrine activation, which renders many treatments intolerable for patients with more advanced heart failure. Several analyses from registries have shown that many applications of drugs in the hospital facilitate persistence after discharge and are associated with improved outcomes. This has been shown for β-blockers as well as inhibitors of the renin-angiotensin-aldosterone system in a European Registry.[12] In the OPTIMIZE-HF registry[13] and in the IMPACT-HF registry,[14] the application of β-blockers in the hospital before discharge let to increased rates of treatment at 8 or 12 months after discharge, with 93.3% who were still on β-blockers 3 months after discharge, while only 30% took a β-blocker at the same time when they were discharged without a β-blocker.[13] Therefore, the question arose whether the quality of treatment in the hospital is associated with better outcomes thereafter. In the PIONEER-HF study,[15] patients were treated shortly after decompensation with either enalapril or sacubitril/valsartan. As a primary efficacy end point, the drop in NT-proBNP was more pronounced in patients treated with sacubitril/valsartan than with enalapril. The exploratory analysis suggested a 46% reduction in the composite of clinical outcomes, such as all-cause death, heart failure death, and heart failure rehospitalization, as well as a necessity for implantation of a left ventricular assist device or listing for heart transplantation.[15] The number needed to treat was only 13 to prevent 1 clinical outcome 6 weeks after discharge.[15] Interestingly, these effects were observed in patients not only with acute and chronic decompensated heart failure, but also patients with de novo heart failure. Associated with this, these patients were only at 50% of an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB). Therefore, PIONEER-HF demonstrated for the first time that, in patients naive to treatment with RAS inhibitors, sacubitril/valsartan treatment is safe and even provides benefit in these patients. Although sacubitril-valsartan therapy was initiated at a low dose among patients with lower systolic blood pressure and the dose was adjusted according to a prespecified algorithm, approximately 20% of the patients in each treatment group had discontinued treatment by 8 weeks, in most cases because of an adverse event.

Taken together, these considerations suggest that the initiation of any neurohormonal agent in this population should be performed cautiously. According to these data, a recent position paper of the European Heart Failure Association recommended treatment in the acutely decompensated patient naive to any treatment in order to not lose time and to avoid the occurrence of early outcomes.[16]

Heart failure with preserved ejection fraction

◆ *PARAGON study*

In patients with preserved ejection fraction, there is evidence that sacubitril/valsartan reduces remodeling. In addition, the PARADIGM-HF study[17] has shown a 20% reduction in cardiovascular death and heart failure hospitalizations. Therefore, it was tempting to speculate that these similar effects might also occur in patients with heart failure with preserved ejection fraction (HFPEF). The PARAGON study compared the effects of sacubitril/valsartan with the effects of valsartan alone in a randomized, controlled, and well-powered study. The primary end point was all hospitalizations for heart failure and death due to cardiovascular causes. There was no significant effect of sacubitril/valsartan compared with valsartan on the primary end point. This not only holds true for the primary end point, but also for the individual components of it. Significance for the relative risk reduction of 13% with a confidence interval of 0.87 (0.75-1.01) was missed very narrowly (*P*=0.06) with a numerical consequence that only 7 events were missing on valsartan to render the trial a statistically positive one. Therefore, PARAGON[18] provided data again showing no significant improvement in HFPEF treatment. Among others, the following three mechanisms are discussed.

1. Is the pathophysiological hypothesis correct?
2. Is the comparator valsartan not neutral?
3. Is patient selection by study design influenced precluding to detect any differences?

◆ *Pathophysiological hypotheses*

In patients with heart failure and reduced ejection fraction (HFREF), the amount of circulating neprilysin is associated with poor outcomes (cardiovascular death and cardiovascular death plus heart failure hospitalization). In patients with a neprilysin concentration above the median, there was a 20% increase in outcomes.[19] In patients with HFPEF, there was no association between neprilysin concentrations and cardiovascular outcomes.[20] It was concluded that the elevated concentrations of neprilysin might be of inferior importance in HFPEF compared with HFREF and might not represent a modifiable risk factor or treatment target.

◆ *Effect of valsartan*

The effect of valsartan was possibly not completely neutral. In a previous study, valsartan provided evidence that, in patients with elevated blood pressure and diastolic dysfunction, there is an improvement in diastolic dysfunction when patients have a drop in blood pressure >10 mm Hg.[21] In PARAGON, about 90% to 96% of the patients had a history of hypertension.[18] The median for systolic blood pressure was 137 mm Hg. Accordingly, approximately 60% to 70% of patients had uncontrolled blood pressure. Sacubitril/valsartan reduces blood pressure approximately twice as strong as valsartan alone.[22] Thus, it is important to evaluate blood pressure values and their association with outcomes on treatment. In addition, a nominal reduction in outcomes of 11% was observed in CHARM-Preserved[23] with, however, a neutral *P* value of 0.118.[23] In this respect, there was no great difference between PARAGON and CHARM-Preserved.

◆ *Patient selection and subgroups*

In the nonadjusted analysis of subgroups in PARAGON, as shown in the forest plots, there were some heterogeneity.[18] In patients with an ejection fraction above the median (EF >57%), there was no effect, while, in patients below the median, the risk reduction for all-cause death and heart failure hospitalization was minus 22%. In a recently published secondary analysis on the pooled data of PARAGON and PARADIGM, it was shown that below an ejection fraction of approximately 55%, sacubitril/valsartan provided significant effects on cardiovascular death and heart failure hospitalization compared with valsartan or placebo. It is noteworthy that both trials did not have the same comparator. However, this is in agreement with the recent secondary analysis from CHARM, where similar effects as in PARAGON, namely a risk reduction at an ejection fraction <49%, was observed.[25] Interestingly, similar effects on outcomes below 55% were recently observed in individual patient-based analysis from β-blocker trials.[26]

◆ *Patient selection*

A recent position paper of the European Heart Failure Association summarized diagnostic measures and reasons for heart failure with preserved ejection fraction. In a large list of causes for HFPEF (about 50 causes) many specific cardiomyopathies, such as storage diseases, sarcoidosis, and, in particular, amyloidosis can be found.[27] Thus, it cannot be excluded that, in this trial where the selection was simply based on simple echocardiographic diastolic parameters as well as dilation of the atria, some of the specific cardiomyopathies have been included, which are resistant to a therapy with neuroendocrine antagonists. These cases might have diluted the treatment effect in the remaining population, where, in the overall population, no significant therapeutic effect was detected.

New approaches

◆ *SGLT2 inhibitors (DAPA-HF)*

Early data from the Framingham study suggested that diabetes mellitus is closely associated with incident heart failure.[28] A safety study with empagliflozin showed that the primary end point of cardiovascular death and vascular end points (major adverse cardiovascular events [MACE]), such as stroke, myocardial infarction, and cardiovascular death, was significantly reduced. Interestingly, the exploratory end point of heart failure hospitalization was reduced by 36% (EMPA-REG study).[29] Similar data were observed with the SGLT2 inhibitor dapagliflozin (DECLARE study).[30] These studies attracted interest to explore the effect of SGLT2 inhibitors in patients with chronic heart failure. The first randomized controlled outcome trial (DAPA-HF) was published recently.[31] DAPA-HF compared dapagliflozin against placebo on top of an optimal back-

ground guideline-directed therapy. The primary end point was cardiovascular death, heart failure hospitalization, or urgent heart failure presentation with the necessity of applying IV diuretics. The primary end point was reduced by 26% with dapagliflozin, resulting in a number needed to treat of 21.[31] A risk reduction of 30% was observed for heart failure hospitalizations, 18% for cardiovascular death, and 17% for all-cause death. All the primary and secondary end points were homogenously reduced in the same direction.[30,31] Meanwhile, the first secondary analysis was published. Interestingly, the effect in heart failure patients with or without diabetes was similar.[31] The event rate in patients with diabetes was higher than in patients without diabetes resulting in a lower number needed to treat. Interestingly, the treatment effect was not affected by different glycated hemoglobin (HbA_{1c}) concentrations.[32] The quality of life was significantly improved on dapagliflozin or patients deteriorated on placebo as shown in a secondary analysis presented recently.[33] Furthermore, there was no interaction for treatment effects with age.[34] Further studies addressing exercise tolerance with dapagliflozin (DETERMINE) and empagliflozin (EMPERIAL) will be published shortly. Another trial program (EMPEROR-Preserved, EMPEROR-Reduced) has finished recruitment. In patients with HFREF, the EMPEROR-Preserved and the DELIVER studies are ongoing. Finally, in patients after an acute decompensation, the SOLOIST-WHF study will investigate the mixed SGLT1 and SGLT2 inhibitor sotagliflozin also in post-acute heart failure patients.

What is new?

◆ *Clonal hematopoiesis*

"Clonal hematopoiesis of indeterminate potential" (CHIP) describes polymorphisms observed in bone marrow precursor cells, which develop into a macrophage phenotype characterized by an elevated proinflammatory activity. These cell types have been suggested to be important in accelerated atherogenesis.[35] In heart failure after myocardial infarction, it was recently shown that, with increasing age, there is a higher prevalence of these polymorphisms.[36] After 50 years of age, the likelihood to get CHIP mutations increases, which affects, in particular, TET2 mutations, which are accompanied by a particularly elevated mortality rate and elevated rates of cardiovascular death and heart failure hospitalizations.[36]

◆ *Guanylate cyclase modulators*

In patients with chronic heart failure, there is a guanylate cyclase deficiency. This enzyme is potentially modified by oxidative stress leading to its reduced activity. The oxidatively modified form cannot be stimulated, but needs to be activated by direct guanylate cyclase activators with compounds, such as cinaciguat. The guanylate cyclase SGC activator (BAY 58-2667-cinaciguat) directly activates the soluble form of guanylate cyclase.[37] In a recent press release, the sponsors of the VICTORIA trial announced that this trial met its primary end point, which was a reduction in heart failure hospitalization and cardiovascular death. There are no published data, but the data will be presented at the 2020 American College of Cardiology congress.

◆ *Omecamtiv mecarbil*

A newly developed drug with a direct action on the myocardial cell was tested in phase 2 trials. Omecamtiv mecarbil is a myosin activator, which is classified as a myotropic agent according to a new nomenclature suggested by an expert consensus document.[38] Omecamtiv mecarbil directly activates myosin and leads to an energy-independent enhancement in contractility with a prolongation of contraction duration, which can be measured in patients in vivo as systolic ejection time.[39] It was already shown in the 1960s that one phenotype of chronic heart failure is a reduction in systolic ejection time, which is associated with the severity of heart failure and compromised ejection fraction.[40] In contrast, so called "calcitropica" agents, such as dobutamine (classic positive inotropic agents), led to an abbreviated contraction duration in vitro and to a reduction in systolic ejection time in patients with heart failure. As dobutamine is associated with poorer outcomes, Omecamtiv mecarbil, in contrast, specifically addresses this phenotype, which is shortening of systolic ejection time. Phase 2 studies have shown that neuroendocrine activation can be reversed with Omecamtiv mecarbil, along with a prolonged ejection time, reduced heart rate, and reduced NT-proBNP levels.[41] Recently, the GALACTIC-HF study has stopped recruitment and patients are in the follow-up phase. This trial will provide definite evidence for a clinical role of improvement in cardiac performance by activating the myosin-actin interaction, and it will be able to provide information of whether it improves clinical outcomes in patients with HFREF, in both inpatient and outpatient setting.[42] The results could be available by the end of 2020.

◆ *Importance of guideline adherence for drug therapy in chronic HFREF*

The incremental use of combinations of disease-modifying therapies has resulted in the progressive improvement in clinical outcomes for patients with HFREF. In a recent network analysis, the most effective combinations were ARNIs+β-blockers+MRAs and ACE inhibitors+β-blockers+MRAs+ivabradine, showing reductions in all-cause mortality (vs placebo) of 62% and 59%, respectively (hazard ratios, 0.38 [credible interval (CrI), 0.20-0.65] and 0.41 [CrI, 0.21-0.70) and reductions in all-cause hospitalizations of 42% for both combinations. These two combinations were also the most effective for the other outcomes studied.[43]

In QUALIFY (QUality of Adherence to guideline recommendations for LIFe-saving treatment in heart failure surveY), an international, prospective, observational, longitudinal survey, among 6669 outpatients with HFREF after a recent HF hospitalization, good adherence for treatment with ACE inibitors, ARBs, β-blockers, MRAs, and ivabradine, and with a prescrip-

tion of at least 50% of the recommended doses, was associated with better clinical outcomes during both the 6-month and 18-month follow-up visits.[44,45] Practical strategies should be established to improve physicians' adherence to guidelines."

Perspectives

Along the patient journey in heart failure, specific problems were addressed in the trials and publications during the last year. In acute heart failure, pulmonary ultrasound might provide important clues for the diagnosis and potentially treatment follow-up in patients with acute congestion, but also in stable patients during exercise. In several countries, a gradient and differential availability of care facilities for heart failure patients might importantly influence morbidity and mortality in heart failure. In patients after hospitalization for worsening heart failure, treatments should be started in the hospitals, doses adjusted for all treatments, and missing guideline-directed drugs added. All registries and observational studies have shown benefit in patients in whom treatment was started early. The PIONEER-HF study was the first randomized trial to compare two different treatment modalities immediately after recompensation of worsening of de novo and "acute on chronic" heart failure. In HFPEF, the PARAGON study provided overall neutral results, while some signs of effectiveness were provided in patients below 55% as did previous studies with AT1 antagonists and β-blockers. A novel approach was observed with SGLT2 inhibitors in a first study (DAPA-HF) and further trials will be published. Novel approaches represent guanylate cyclase activators like vericiguat (VICTORIA trial) and the selective cardiac myosin activator Omecamtiv mercarbil (GALACTIC-HF trial), which will be presented shortly. ■

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