Dialogues in Cardiovascular Medicine

Aims & Scope

Dialogues in Cardiovascular Medicine is published three times a year, and it is a journal for cardiologists and physicians who have an interest in cardiology. The aims are to provide up-to-date information on specific areas of cardiovascular medicine and to encourage an open dialogue between key opinion leaders and readers about the topics, guidelines, registries, etc, that have impressed and captivated them at various meetings and congresses throughout the year. One issue will be devoted to the Heart Failure congress and another to the European Society of Cardiology congress. The third issue, “The Year in Cardiology,” will provide an overview of the most important events and information that occurred in cardiology throughout the year. Dialogues is indexed in EMBASE and Scopus and is part of the continuing medical education program of several major international cardiological societies.

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ESC Congress 2017

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Abbreviations and acronyms

Instructions for authors
Dialogues in Cardiovascular Medicine comes of age in 2017 (it was launched 21 years ago in 1996 by David Hearse and Roberto Ferrari), and it is great that we can celebrate in style. This issue is published to coincide with the annual meeting of the Heart Failure Association of the European Society of Cardiology, which was held in Paris in the month of May! To make it even more special, this issue focuses on heart failure, the only cardiovascular disorder that is ever growing in prevalence and impact, even as we continue to succeed in finding and implementing both preventive and treatment approaches. The aging population carries with it the clinical manifestations of the ravages of years, of accumulated fibrosis in the heart, the strain of hypertension, and the aging of the coronary and large arteries. Despite our treatment successes, all of these manifestations promote more heart failure, especially the type with a preserved ejection fraction—HFPEF.

In this issue, we have a sharp review – a snapshot – on heart failure written by our editors-in-chief, Roberto Ferrari and Kim Fox, and two very topical updates on the basic science in heart failure research by Christoph Maack and on clinical research in the field by Massimo Piepoli. It has only been 12 months since the influential heart failure guidelines were issued at last year’s heart failure conference in Florence, Italy, and, since then, much has been spoken about the guidelines. Guidelines are of ever-increasing importance in both treatment choices and implementation; now they set the standard for what doctors should and should not do. Who better to review the past 12 months since the release of the influential European guidelines for heart failure than the chair of the guidelines, Piotr Ponikowski? How have we fared during these eventful 12 months? Has the new concept of heart failure with midrange ejection fraction (HFMEF) taken hold? It is too early to know because one of the main purposes of this new classification was to promote further clinical trials in this difficult-to-classify group, and, as we all know, major clinical trials are many years in the planning and execution.

What have we discovered in the last 12 months? In heart failure itself, we have had a relatively quiet year on the major trials front, with the only major mortality and morbidity trial to report (RELAX-AHF-2) being neutral, with no added benefit of serelaxin in acute heart failure. These results are an ongoing disappointment as we try to find effective treatments for acute decompensated heart failure. Other aspects of heart failure management, especially the influence of common comorbidities, are attracting increasing attention. For diabetes, following a run of newer agents with a demonstrated potential to worsen heart failure, the guidelines went back to the past to recommend metformin as a first-line hypoglycemic therapy in heart failure patients with coincident diabetes. However, the good news is that empagliflozin, an agent from a new class of drugs known as SGLT2 inhibitors or “gliflozins,” has major cardiovascular benefits in patients with high cardiovascular risk. The EMPA-REG OUTCOME trial demonstrated reduced cardiovascular death when empagliflozin was given to patients with type 2 diabetes and cardiovascular disease. It also showed a significant reduction in new-onset heart failure. The upcoming two EMPEROR HF clinical trials—EMPEROR-Preserved [NCT03057951] in HFPEF and EMPEROR-Reduced [NCT03057977] in HFREF—are planned to explore these findings in specific heart failure patient populations. In the recent LEADER study, another agent from a different class, the GLP-1 receptor agonist liraglutide, showed an overall benefit on cardiovascular mortality, but no effect on fatal, nonfatal, or silent myocardial infarction or stroke and no effect on heart failure hospitalizations.

Other topical areas are reviewed by experts, including Patrick Jourdain’s discussion on telemedicine and telemonitoring. This topic is of prime importance for heart failure, yet the clinical trial results in this area are seldom as clear-cut as they are in pharmacological trials. In drug trials, the active agents are given in standard doses and a virtually identical fashion. In trials on disease management strategies, the local procedures, provision of information, staffing levels, and even changes in the devices themselves as they undergo generational or algorithm changes mean that positive trials may be followed by less posi-
tive trials or that background clinical care is so different as to make previous results less clear. We value the expert advice to guide us through this complexity. Cardio-oncology is reviewed by Markus Anker and Stefan Anker. This issue is very important as newer chemotherapeutic agents, such as anthracyclines, trastuzumab, and tyrosine kinase inhibitors, are developed with the potential to improve cancers, but which may damage the heart in the process. The article also covers the potential of cancer itself to affect the heart in ways that we are only just beginning to unravel. The enigmatic condition of HFPEF is reviewed by Michel Komajda as we wait patiently for any major trial to show a positive result in this common illness. All we can say to date is that symptomatic fluid retention should be treated with diuretics, and cardiovascular risk factors, such as high blood pressure, should be controlled, especially by agents that are well tolerated in heart failure, such as β-blockers and ACE inhibitors. We urgently need more trials on HFPEF.

Newer pharmacological agents on the horizon for heart failure are reviewed by Giuseppe Rosano. The clinically crucial issue of how best to manage the aging and frail heart failure patient is one that is too often ignored, and one that is elegantly covered by Cristiana Vitale. Lastly, Eugene Reyes describes the Optimize Heart Failure Care Program in the Philippines.

I hope you enjoy reading this issue of Dialogues as much as I have.

ANDREW J. S. COATS
Heart Failure
Snapshot of the Year

Of the patients diagnosed with hypertrophic cardiomyopathy, only 5% have hereditary transthyretin-related familial amyloid cardiomyopathy. Transthyretin genetic screening should be done for elderly patients with increased left ventricular wall thickness, especially in patients of African descent with neuropathy, carpal tunnel syndrome, low voltage ECG, or late gadolinium enhancement.


In patients with type 2 diabetes and high cardiovascular risk, empagliflozin, a drug approved for the treatment of diabetes, which inhibits sodium glucose cotransporter-2, reduced heart failure hospitalizations and cardiovascular death, regardless of whether or not the patients had baseline heart failure. Empagliflozin also reduced hospitalization for or death from heart failure, and it was associated with a reduction in all-cause hospitalizations.


While contemporary adjuvant treatment for early breast cancer improves survival, it increases the risk of cardiac toxicity and cardiac dysfunction. The PRADA trial showed that concomitant treatment with candesartan protects against the decline in left ventricular ejection fraction caused by anthracycline-containing regimens with or without trastuzumab and radiation.


Sleep-disordered breathing and nocturnal hypoxemia are highly prevalent in patients with chronic and stable heart failure with reduced ejection fraction. This study showed that the nocturnal hypoxemic burden was a robust and independent predictor of all-cause mortality in these patients; however, further studies are needed to determine whether treating nocturnal hypoxemia reduced the mortality in these patients.


The Gutenberg Health Study showed that there are distinct alterations in the end-diastolic pressure–volume relationship between patients with heart failure with reduced ejection fraction and patients with heart failure with preserved ejection fraction. In patients without heart failure, cardiovascular risk factors for heart failure were linked with an increased stiffness coefficient β, and the end-diastolic pressure–volume relationship shifted left with age and female sex, but right with all other risk factors.


This analysis of the SICA-HF study showed that cardiac cachexia was associated with intestinal congestion irrespective of heart failure stage and cardiac function. Possible mechanisms by which intestinal congestion triggers cardiac cachexia include gastrointestinal discomfort, appetite loss, and proinflammatory activation.


In patients with heart failure with preserved ejection fraction, factors, such as age, body mass index, N-terminal pro–brain natriuretic peptide levels, early mitral inflow velocity/mitral peak velocity of late filling, and diastolic pulmonary artery pressure, were independently associated with NYHA classes III and IV.

These articles were taken from the European Heart Journal and the Journal of the American College of Cardiology between May 1, 2016 and April 30, 2017. All research articles on heart failure were included; reviews and guidelines were excluded.

In patients undergoing pulmonary artery catheterization, there was a weak, but significant, inverse correlation between cardiac index and estimated glomerular filtration rate; however, cardiac index was not associated with blood urea nitrogen, the blood urea nitrogen to creatinine ratio, or better renal function across multiple subgroups.


Light-chain amyloidosis with cardiac involvement carries a poor prognosis. This study evaluated the triple therapy of bortezomib, dexamethasone, and an alkylating agent (BDex+AA) as a first-line treatment strategy to reduce mortality in patients with symptomatic heart failure from light-chain cardiac amyloidosis. After adjusting for clinical variables, the use of BDex+AA in patients presenting with symptomatic heart failure improves survival.

**JULY 2016**


The PARADIGM-HF trial showed that, compared with heart failure patients receiving enalapril, heart failure patients receiving the sacubitril/valsartan (LCZ696) combination had fewer 30-day readmissions for any cause following discharge from the hospital.


The ARTS-HF study showed that, in patients with worsening heart failure, reduced ejection fraction, chronic kidney disease, and/or diabetes mellitus, the nonsteroidal mineralocorticoid receptor antagonist finerenone was well tolerated, and it reduced the levels of N-terminal pro-brain natriuretic peptide by ≥30%.

**SEPTEMBER 2016**


The INOVATE-HF trial showed that, among patients with heart failure with reduced ejection fraction, vagal nerve stimulation did not reduce all-cause death or heart failure events. However, this technique favorably improved the quality of life, New York Heart Association functional class, and 6-minute walking distance.


In 1081 patients with a prior myocardial infarction, 228 developed heart failure and 98 developed cancer (excluding nonmelanoma skin cancer). The incidence density rates for cancer diagnosis (per 1000 person-years) were 33.7 for patients with heart failure and 15.6 for patients without heart failure, showing that patients who develop heart failure after a myocardial infarction have an increased risk of cancer.

**AUGUST 2016**


Among the 67 161 patients identified with new-onset heart failure during an inpatient hospitalization, only 17.5% underwent testing for ischemic coronary artery disease during the index hospitalization. Heart failure patients with a baseline diagnosis of coronary artery disease had a greater probability of undergoing noninvasive and invasive ischemic testing at the index hospitalization than those without baseline coronary artery disease.


High-output heart failure is an unusual cause of cardiac failure that is related to excessive vasodilation, and the common causes include obesity, liver disease, arteriovenous shunts, lung disease, and myeloproliferative disorders. Given the high mortality and increasing prevalence of these comorbidities in Western countries, high-output heart failure must be considered in the differential diagnosis of patients presenting with dyspnea, congestion, and a normal ejection fraction.

**SEPTEMBER 2016**


Among 35 163 heart failure patients, ischemic heart disease occurred in 62% of patients with type 2 diabetes mellitus in ischemic and nonischemic heart failure.
and 47% of those without type 2 diabetes, of whom 53% and 48%, respectively, had previously undergone revascularization. Ischemic heart disease in patients with type 2 diabetes had an especially negative influence on mortality, an impact that was beneficially influenced by a previous revascularization.


The AKINESIS trial showed that neutrophil gelatinase-associated lipocalin, a novel renal biomarker, is not superior to creatinine for predicting worsening renal function or adverse in-hospital events; therefore, it is not recommended to use neutrophil gelatinase-associated lipocalin levels in the diagnosis of acute kidney injury in patients with acute heart failure.


This study identifies a novel regulatory pathway to inhibit cardiac hypertrophy and heart failure. MicroRNA-223, a positive regulator of cardiac hypertrophy, is inhibited by heart-related circular RNA. This inhibition increases the levels of the apoptosis repressor with a caspase recruitment domain that is decreased in the failing heart. Therefore, modulating this pathway provides an attractive treatment target for cardiac hypertrophy and heart failure.


In patients with heart failure with preserved ejection fraction and an abnormal diastolic response to exertion, spironolactone improved exercise capacity, anaerobic threshold, and O₂ uptake efficiency, and it reduced the exercise-induced increase in the ratio between early mitral inflow velocity and mitral annular early diastolic velocity.


Myocardial structure, systolic function, and diastolic function improved substantially in 5% and 21% of patients with ischemic and nonischemic cardiomyopathy, respectively, who were supported by a left ventricular assist device for 6 months.


The OptiLink HF study showed that, among patients with advanced heart failure and an implantable cardioverter defibrillator, automated fluid status alert notification via telemedicine did not improve patient outcomes significantly.

Borlaug BA, Kane GC, Melenovsky V, Olson TP. Abnormal right ventricular-pulmonary artery coupling with exercise in heart failure with preserved ejection fraction. Eur Heart J. 2016;37(43):3293-3302.

During exercise, patients with heart failure and preserved ejection fraction had a lower increase in stroke volume, heart rate, and cardiac output. In addition, there is an impaired right ventricular reserve during exercise, which is associated with high filling pressures and inadequate cardiac output responses.


The PARADIGM-HF trial showed that, after adjustment for prognostic variables (relative to North America), the risk of cardiovascular death was higher in Latin America and the Asia-Pacific region, and the risk of hospitalization for heart failure was lower in Western Europe. Despite these geographical differences in age, symptoms, comorbidities, background treatment, and the rate of events, the benefits of the sacubitril/valsartan combination was consistent across regions.


Across Asia, the majority of patients had two or more comorbid conditions, such as hypertension, coronary artery disease, or diabetes. Compared with the Chinese, the Malaysians and Indians had a higher odds ratio for coronary artery disease, whereas the Koreans and Japanese had a lower odds ratio. The prevalence of hypertension and diabetes was highest in Southeast Asia and high-income regions. These data highlight the significant heterogeneity among Asian patients with stable heart failure and the important influence of both ethnicity and regional income on patient characteristics.

The PARADIGM-HF trial showed that a reduction in N-terminal pro-B-type natriuretic peptides (NT-proBNP) was associated with a decrease in heart failure hospitalizations and cardiovascular mortality in patients with heart failure with reduced ejection fraction. The sacubitril/valsartan combination was nearly twice as likely as enalapril to reduce NT-proBNP to values ≤1000 pg/mL.


The Great Network study showed that, in patients with acute heart failure, proenkephalin A (PENK) levels independently predicted worsening renal function, mortality at 1 year, death and/or heart failure at 1 year, outcomes at 3 or 6 months, and in-hospital mortality.


In human and murine failing myocardia, the NOD1 pathway is upregulated. Compared with wild type mice, Nod1 knockout mice had increased cardiac function and attenuated structural remodeling, which was associated with the prevention of the Ca\(^{2+}\) dynamic impairment that is linked to heart failure. Therefore, NOD1 may emerge as a new target for heart failure therapy.


Plasma angiotensin (Ang) peptides are altered in heart failure and in response to recombinant human angiotensin-converting enzyme 2 (ACE2). ACE inhibitors increase plasma Ang-(1-7) levels, whereas acute heart failure reduces Ang-(1-7) levels and suppresses the Ang-(1-7)/Ang II ratio, which is associated with worsening heart failure symptoms. Recombinant human ACE2 normalizes elevated Ang II and increases Ang-(1-7) and Ang-(1-9) levels.


Due to concerns about relying on arbitrary threshold \(P\) values to report results as statistically significant, the fragility index has been proposed as an additional measure of the robustness of trial findings. This study shows that the fragility index is an additional, easy-to-understand metric that helps interpret the robustness of the results of randomized controlled trials.


After a myocardial infarction, mice with a cardiomyocyte-targeted deletion of irp1 and irp2, two mRNA-binding iron-regulatory proteins, developed more severe left ventricular dysfunction with increased heart failure mortality. While iron deficiency in cardiomyocytes impairs mitochondrial respiration and adaptation to acute and chronic increases in workload, iron supplementation restores cardiac energy reserve and function in iron-deficient hearts.


Among heart failure patients (n=59 202), influenza vaccination was associated with a lower risk of hospitalization due to cardiovascular disease, with more modest effects for hospitalization due to respiratory infections, and all-cause hospitalizations.


\(\beta\)-Adrenergic receptor autoantibodies (\(\beta\)AR-AAbs) belonging to the immunoglobulin G3 (IgG3) subclass were independent predictors of left ventricular ejection fraction at 6 months and change in left ventricular ejection fraction over 6 months in patients with recent-onset cardiomyopathy.

Patients with heart failure with preserved ejection fraction (HFPEF) without atrial fibrillation had a lower risk of stroke compared with HFPEF patients with atrial fibrillation. However, approximately one-third of the patients with HFPEF without atrial fibrillation belong to a high-risk subset of patients, and they have a risk of stroke similar to HFPEF patients with atrial fibrillation.


In preliminary efficacy studies, cardiopoietic cells, which are produced through cardiogenic conditioning of patients' mesenchymal stem cells, have shown promise; therefore, the CHART-1 trial tested this cardiopoiesis-based biotherapy in a larger heart failure cohort. The primary end point—a Finkelstein-Schoenfeld hierarchical composite—was neutral, with safety demonstrated across the cohort.


This EchoCRT subanalysis showed that low left ventricular global longitudinal strain is associated with poor outcomes in heart failure patients with a QRS width <130 ms, which is independent of whether or not the patient received cardiac resynchronization therapy. However, cardiac resynchronization therapy may be detrimental in the group of patients in the lowest quartile of left ventricular global longitudinal strain.


The RESPOND-CRT study investigated the safety and efficacy of the contractility sensor system, SonR, in heart failure patients undergoing cardiac resynchronization therapy. Automatic atrioventricular and interventricular optimization using the contractility sensor was safe and as effective as echo-guided atrioventricular and interventricular optimization in increasing the response to cardiac resynchronization therapy.


In patients hospitalized with acute heart failure, dyspnea, and congestion, the TACTICS-HF study showed that the addition of tolvaptan to a furosemide regimen did not improve dyspnea, despite resulting in greater weight loss and net fluid loss compared with placebo. In addition, tolvaptan-treated patients were more likely to experience worsening renal function during treatment.


While the addition of tolvaptan to a background diuretic resulted in rapid and persistent weight loss, tolvaptan did not result in an early improvement in dyspnea in acute heart failure patients. However, patients without elevated jugular venous pressure and patients without ascites showed directional favorability of tolvaptan vs placebo.


There is an increased risk of heart failure in patients with rheumatoid arthritis, but this risk is independent of these patients’ increased risk of ischemic heart disease. However, the increased risk of nonischemic heart failure occurred early, and it was associated with rheumatoid arthritis severity.


This study showed that there was a dose-dependent association between higher leisure-time physical activity, lower body mass index, and overall heart failure risk, meaning that, among HF subtypes, higher leisure-time physical activity and lower body mass index were more consistently associated with a lower risk of heart failure with preserved ejection fraction compared with heart failure with reduced ejection fraction.

The CAT-HF trial showed that, in hospitalized heart failure patients with moderate-to-severe sleep apnea, adding adaptive servo-ventilation to optimal medical therapy did not improve the 6-month cardiovascular outcomes; however, additional studies are needed in this population.

APRIL 2017


In the PARADIGM-HF trial, heart failure patients with lower systolic blood pressure at randomization had a higher risk for both all-cause and cardiovascular mortality. In addition, the benefits of the sacubitril/valsartan combination over enalapril were similar across all baseline systolic blood pressure values.


In many patients who underwent a left ventricular assist device bridge-to-recovery protocol, who recovered sufficiently to allow explantation of their left ventricular assist device, can achieve cardiac and physical functional capacities nearly equivalent to those of healthy controls.


The HF-ACTION study showed that, in patients with chronic heart failure, atrial fibrillation was associated with older age, reduced exercise capacity at baseline, and a higher overall rate of clinical events, but it was not associated with a differential response to exercise training for clinical outcomes or changes in exercise capacity.


The SOCRATES-PRESERVED study showed that, in patients with chronic heart failure and a preserved ejection fraction (ejection fraction ≥45%), vericiguat, a soluble guanylate cyclase stimulator, did not change N-terminal pro-B-type natriuretic peptide levels and left atrial volume at 12 weeks compared with placebo, and it was associated with improvements in quality of life.
Highlights
At this year’s Heart Failure Congress in Paris, France, the basic and translational research track was further expanded compared with the previous years based on the growing interest, also from clinicians, for mechanistic insights into the pathophysiology and treatments of HF. This year’s focus was on (among other topics) cardiomyopathies, metabolic aspects of HF, two HF comorbidities (ie, diabetes and cancer), iron metabolism, and arrhythmias. The track was rounded up by a session in which the results of the past three workshops held by the Committee of Translational Research of the HFA were presented, and this session was introduced by a special lecture given by the famous cardiologist Eugene Braunwald.

**CARDIOMYOPATHIES**

Two sessions were dedicated to the pathophysiology and treatment of cardiomyopathies. Denise Hilfiker-Kleiner (DE) reported on recent developments in peripartum cardiomyopathy (PPCM). In her previous seminal work, she had discovered that, in patients with PPCM, an aberrant cleavage of the nursing hormone prolactin into a 16 kDa peptide induces maladaptive cardiac remodeling and HF. Formation of this 16 kDa prolactin is prevented by inhibiting the production of the full-length prolactin using bromocriptine. Several smaller clinical studies revealed that bromocriptine improves LVEF and the outcome of patients with PPCM. Data from more recent mechanistic studies revealed that, in addition to the 16 kDa peptide, the PAI-1/uPAR signaling pathway contributes to microvascular dysfunction in patients with PPCM, a key driver of the cardiomyopathy phenotype. She presented data from a randomized multicenter trial on 57 patients with PPCM, revealing that both prolonged (8 weeks) and short-term (1 week) treatment with bromocriptine improved LVEF by 21% and 24%, respectively. After the 8-week treatment, more patients displayed full recovery of LVEF than after a 1-week treatment. Overall, the results further support a potential benefit of bromocriptine in addition to standard guideline-recommended HF therapy in patients with PPCM, suggesting that, overall, 1 week of bromocriptine treatment is sufficient to promote healing in patients with PPCM, although critically ill patients with an LVEF <30% may benefit from prolonged treatment.

In recent years, the Takotsubo syndrome has moved to the focus of extensive clinical and preclinical research. Elmir Omerovic (SE) reported on the progress in both fields. Although it is widely accepted that a catecholamine surge may play an important pathophysiological role, the exact downstream signaling pathways (ie, which adrenergic receptors and associated signaling cascades and consequences are involved) are still incompletely understood. The development of animal models of Takotsubo syndrome, which recapitulate the phenotype, will presumably shed important new insights into the underlying mechanisms in the coming years.

Hypertrophic cardiomyopathy (HCM) is the most common monogenetic cardiac disorder that is frequently caused by mutations in genes that encode sarcomeric proteins. A common mutual mechanism of various mutations is that the affinity of the myofilaments to calcium is increased, which implies that, at any given cytosolic calcium concentration, more myofilaments are activated in HCM than in normal hearts. Based on the results from two different animal models of HCM, Christoph Maack (DE) reported a novel concept that, through this increase in myofilament calcium sensitivity, a mismatch in the mitochondrial redox state occurs, which leads to oxidative stress that underlies the commonly observed arrhythmias in HCM and potentially the induction of left ventricular hypertrophy. Consequently, targeting this energy mismatch and mitochondrial ROS production reduced arrhythmias, which could resemble a novel therapeutic strategy for patients with HCM.

**METABOLIC ASPECTS OF HEART FAILURE**

Several lines of evidence have shown that metabolism is substantially affected in patients with HFREF and HFPEF. Reduced cardiac phosphocreatine predicts an adverse outcome in patients with HFREF, coined the idea of the failing heart as an “engine out of fuel.” In the past 20 years, tremendous effort has been devoted to finding the underlying mechanisms and determining how to treat this energy deficit; one important aspect of this is substrate metabolism. The normal heart is an omnivore that uses both carbohydrates and fats for energy, whereas the failing heart as a “stove out of fuel.” In HF, cardiac substrate metabolism is altered. In diabetes, metabolism is shifted from glucose to fatty acid utilization, which reduces the metabolic flexibility of the heart, and, by activating uncoupling proteins, metabolic efficacy is decreased, while the formation of ROS is increased. In HF, cardiac uptake of fatty acids and glucose into the cytosol are increased, while their oxidation in the mitochondria is impaired. This provokes accumulation of metabolic intermediates in the cytosol that can induce (partly mal-
adaptive) signaling in their own right. Drugs that inhibit fatty acid oxidation, such as perhexiline or trimetazidine, can increase glucose oxidation and, thereby, presumably shift metabolism toward glucose utilization. Although smaller trials suggested benefits, the evidence that such drugs improve the outcome of patients with HF is still lacking.

A recent observation is that, in this situation of reduced fatty acid and glucose oxidation, the failing heart relies more on alternative fuels, such as ketone bodies. Kieran Clarke (UK) gave a deeper insight into ketone body metabolism. She and her colleagues have developed a highly energetic ketone body diet called ΔG®, which increases maximal endurance in top athletes. Whether this is related to improving the endurance capacity of the heart or skeletal muscles or both and whether such a diet would be beneficial in patients with HF is currently unresolved. Recently, empagliflozin, an inhibitor of the renal sodium-glucose transporter that lowers blood glucose levels, has reduced the risk of hospitalization and death due to HF. While one likely underlying mechanism is the drug’s diuretic and blood pressure–lowering effect, it has alternatively been suggested that, by elevating ketone bodies, empagliflozin provides a “super fuel” for the heart (the so-called “thrifty substrate hypothesis”). This hypothesis, however, has been questioned by Clarke since the elevations of ketone bodies in these patients, which resemble elevations occurring in normal humans after 12 to 24 hours of fasting, may not be sufficient to account for a relevant improvement in cardiac function. Similar concerns have been raised previously by Lopaschuk and Verma.

Johannes Backs (DE) reported on the connection between epigenetics and metabolism. He and his colleagues found that the consequence of diabetes on the heart depends on preexisting epigenetic alterations secondary to other cardiovascular risk factors (unpublished data). In other words, if preexisting neuroendocrine activation has altered epigenetic regulation through histone deacetylase 4, diabetes may aggravate the cardiac phenotype, while, in otherwise healthy subjects with normal nuclear histone deacetylase 4 localization, diabetes may even exert cardioprotective effects.

To summarize, metabolic alterations in HF are likely contributing to maladaptive cardiac remodeling and the energetic deficit of the failing heart. The advent of metabolomic profiling (and other techniques) has deepened our understanding of substrate utilization in recent years; however, further research will be necessary to design the right interventions to improve metabolic defects in patients with HREF and HFPEF.

**CANCER AND THE HEART**

Alexander Lyon (UK) gave a brilliant introduction to the topic. Over the past decades, the median survival from any cancer has increased, which is why we are now seeing more patients with chemotherapy-induced cardiac dysfunction or HF. When treating cancer, signaling pathways that induce cell survival (of the cancer cell) are often targeted, which means that the survival of cardiac and noncardiac myocytes are also negatively affected by chemotherapies. Lyon reported data from various studies addressing cardiovascular outcomes in response to cancer treatments, with a special focus on trastuzumab–induced cardiotoxicity. He highlighted the importance of a dose dependency of such effects and the potential use of biomarkers to identify patients at risk for cardiotoxicity.

Heinrich Taegtmeyer (US) highlighted similarities between heart and cancer cells regarding metabolism. The “Warburg effect” of cancer cells is characterized by a shift of isoforms of PKM from an adult (PKM1) to a fetal isoform (PKM2). In failing human hearts, such a shift can be observed, which may highlight the similarities in metabolism in failing heart cells and cancer cells. Furthermore, during cancer, so-called oncometabolites accumulate due to changes in cancer cell metabolism. One of these oncometabolites, D-2-hydroxyglutarate, impairs the functioning of the Krebs cycle, which may induce contractile dysfunction, resembling a metabolic cause of HF development during cancer (independent of chemotherapy).

Catherine Vergely (FR) and her team recently discovered from epidemiological studies that obesity is a risk factor for anthracycline and trastuzumab cardiotoxicity in patients with breast cancer. She also discussed the results of preclinical studies and the potential mechanisms that underlie the obesity-induced sensitivity of patients toward chemotherapies. Some of these factors involved elevated levels of leptin and cytokines, such as IL6, TNF-α, or PAI-1, and decreased levels of adiponectin and omentin, which may converge onto decreased prosurvival signaling within cardiac myocytes and impaired metabolism and oxidative stress in the mitochondria.

Kari Alitalo (FI) rounded up this interesting session by suggesting that gene therapy with VEGF-B could protect hearts from doxorubicin-induced cardiotoxicity. Based on a preclinical mouse model, he revealed that such an intervention reduces doxorubicin–induced cardiac atrophy, protected endothelial cells from apoptosis, and preserved the myocardial capillary network. Furthermore, the doxorubicin–induced whole body wasting (cachexia), which impairs the quality of life and increases the drug toxicity in patients to decrease their survival, was inhibited by VEGF-B treatment in doxorubicin–treated mice. For the potential continued development of VEGF-B gene therapy, further preclinical and clinical research is required.

**IRON METABOLISM**

In patients with HF, iron deficiency is associated with adverse outcomes, and restoring iron levels in these patients with intravenous infusions of iron improves morbidity and symptoms, but not survival. Ewa Jankowska (PL) introduced these clinical aspects, highlighted the evidence from randomized clinical trials, and discussed diagnostic dilemmas and future therapeutic perspectives of iron deficiency and treatment. Tibor Kempf (DE) presented preclinical data that, in myocardial infarction, genetically-induced iron deficiency impairs mortality and cardiac function and that intravenous iron supplementation could rescue these deficits. In their model, iron deficiency was associated with decreased activity of respiratory chain complex I and subsequently respiration. These results suggest that
iron supplementation restores cardiac energy reserve and function in iron-deficient hearts.

Hossein Ardehali (US) delivered some counterpoints to this line of evidence. He highlighted that iron overload, which occurs in various diseases, such as hemochromatosis, thalassemia, sickle cell disease, or Friedreich’s ataxia, causes mitochondrial damage by excessive formation of ROS, which is fostered by the Fenton or Haber-Weiss reactions in which iron catalyzes the formation of the highly toxic hydroxyl radical. He also presented preclinical evidence that, in myocardial ischemia/reperfusion injury and doxorubicin-induced cardiotoxicity, mitochondrial iron depletion is protective, whereas iron overload is harmful. He concluded that, for the long-term treatment of patients with HF without iron deficiency, iron chelation might be beneficial, whereas, in patients with HF and iron deficiency, iron supplementation would be useful.

ARRHYTHMIAS

Up to 50% of patients with HF die by sudden cardiac death, and arrhythmias are mostly related to scar formation and/or disturbed calcium handling in cardiac myocytes. A second problem in HF is that, by structural and electrical cardiac remodeling, asynchronous contraction of the left ventricle reduces the efficacy of cardiac ejection of blood. This session focused on the implications of the cardiac myocytes’ transversal (t) tubular system for calcium handling and, consequently, for contractility and the risk for arrhythmias.

William Louch (NO) presented interesting data on how an increase in transmural wall stress (as occurs in HF) disturbs the t-tubular system in cardiac myocytes, which disturbs calcium handling. Such disturbances were also associated with a reduced expression of junctophilin-2, an important protein that guides the well-coordinated calcium-induced calcium release from the sarcoplasmic reticulum. Overall, the structural remodeling of cardiac myocytes by itself can induce contractile deficit and possibly arrhythmias.

Jean-Pierre Benitah (FR) explained how hyperaldosteronism, a common feature in patients with hypertension and/or HF, could disturb excitation-contraction coupling and induce hypertrophy that involves transient receptor potential channels. These mechanisms may underlie the beneficial effects of aldosterone antagonism in the treatment of patients with HF. Julia Gorelik (UK) presented data provided by cutting-edge microscopy in which they identified differences in receptor and calcium signaling in the t-tubuli and the rests (ie, the areas between the t-tubuli on the surface of the cell). They observed that, during HF, t-tubular remodeling disturbs calcium and cAMP handling in cardiac myocytes, which may all predispose a patient to contractile dysfunction and arrhythmias. Finally, Frank B. Sachse (US) presented insights from studies on models and patients with dysynchronous HF; he also discussed how cardiac dyssynchronicity induces t-tubular remodeling and defects in calcium handling, while CRT can reverse some of these maladaptive changes. These data provide insight on how CRT in patients with HF improves cardiac function acutely, induces reverse cardiac remodeling, and lowers the risk of (sudden cardiac) death.

CONCLUSIONS

Together, the basic and translational science program once again highlighted how important it is to understand the underlying mechanisms of HF and its comorbidities to design rationale therapies directed against the progression of the syndrome.
LATE BREAKING TRIALS IN CLINICAL SCIENCE: HIGHLIGHTS FROM THE HEART FAILURE MEETING, PARIS 2017

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FOCUS ON ACUTE HEART FAILURE

Bromocriptine for the treatment of peripartum cardiomyopathy - multicenter proof-of-concept study

PPCM is a poorly understood, rare disorder in which LV systolic dysfunction and symptoms of HF occur between the last month of pregnancy and the first 5 months postpartum. Recent data suggest that uncontrolled oxidative stress leads to the activation of the prolactin cleaving enzyme cathepsin D, which, in turn, leads to an increase in a cleaved 16 kDa prolactin, which is angiostatic and proapoptotic and appears to drive PPCM by adversely impacting the endothelium and cardiomyocytes. Bromocriptine reduces prolactin production by dopamine agonists, which may improve outcomes in PPCM patients, by eliminating the cleaved form of prolactin. In a small, multicenter trial, presented by Denise Hilfiker-Kleiner (DE), bromocriptine associated with prophylactic anticoagulation using LMWH was associated with better outcomes in morbidity, mortality, and functional recovery and less VAD or heart transplantation. A total of 63 PPCM patients with a LVEF <35% were randomly assigned to short-term (2.5 mg for 7 days) or long-term (8 weeks, 5 mg for 2 weeks followed by 2.5 mg for 6 weeks) bromocriptine treatment, in addition to standard HF therapy. This is the largest RCT so far in PPCM.

Safety and efficacy of low-dose intracoronary IGF-1 to prevent HF following PCI for acute MI (RESUS-AMI)

In an MI, there is blockage of a coronary artery supplying oxygen to the heart muscle, which may weaken, causing HF. The body naturally makes a protein called IGF-1, which may prevent the cardiomyocyte death and HF, or lessen the damage. In this study, MI patients were given either a dose of mecasermin (a recombinant IGF-1) or a placebo (inactive treatment) after stenting of their coronary artery. This therapy was assessed in terms of safety and its capacity to prevent or lessen HF using a cardiac MRI one day and eight weeks after the MI. Of the 473 patients originally screened, 47 were randomized to low-or high-dose IGF-1 or placebo. Noel Caplice (IE) reported that there were no safety issues, but there were no differences between the treatment arms and the placebo arms, and only the low-dose IGF-1 treatment improved LV remodeling.

Relationship between baseline SBP and long-term outcomes in patients with acute HF treated with TRV027: an exploratory subgroup analysis of the BLAST-AHF trial

TRV027 is a novel “biased” ligand of the angiotensin-2 type 1 receptor that antagonizes angiotensin-stimulated G-protein activation while stimulating β-arrestin. In animal models, these effects reduce afterload while increasing cardiac performance and maintaining stroke volume. In the initial human studies, TRV027 appeared to be hemodynamically active primarily in patients with activation of the RAAS, a potentially attractive profile in acute HF therapy. BLAST-AHF is an international, prospective, randomized, phase 2b, dose-ranging study in over 600 patients with acute HF and SBP values between 120 and 200 mm Hg within 24 hours of the initial presentation. Patients were randomized to 1 of 3 doses of intravenous TRV027 (1, 5, or 25 mg/hour) or matching placebo (1:1:1:1) for at least 48 hours and up to 96 hours. The primary end point was a composite of five clinical end points (dyspnea, worsening HF, length of hospital stay, 30-day rehospitalization, and 30-day mortality). Gadi Cotter (US) reported no effect on the clinical end points and identified two typical scenarios in acute HF: a 60-year-old with low LVEF and BP, in contrast to 70 to 80 year old patients with high LVEF and BP. He highlighted the inefficacy of a standardized approach and the need for a more tailored therapy.

Deep-dive results of the TRUE-AHF trial

TRUE-AHF is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of ularitide as an IV infusion in addition to conventional therapy in patients with acute HF. In the presentation at the last AHA meeting, early IV treatment with a synthetic natriuretic peptide decongested patients with acute decompensated HF and made them feel better in the first 48 hours, but did nothing to improve long-term survival or protect the myocardium from damage, as measured by troponin levels, which was an important prospective end point. Milton Parker (US) reported that a short-term infusion of ularitide reduced SBP, BNP, and cardiac decompression, but not troponin levels, hospitalization, or death. However, there was an issue with eligibility: 17% of the recruited patients did not meet the prespecified enrollment criteria (such as stability, prohibition of confounding drugs, or BP instability). In the 1799 eligible patients, ularitide did better, but this did not affect mortality. Therefore, in the “deep-dive” analysis,
the 48-hour infusion may benefit eligible patients, but it is associated with adverse outcomes in ineligible patients. This result may have led to the “neutral” finding of the overall TRUE-AHF trial (relating to the hierarchical clinical composite end point). There was also a geographical issue: the majority of the ineligible patients were recruited in some specific areas and countries.

**RELAX-AHF-2: serelaxin in acute HF**

Serelaxin, the first-in-class recombinant form of human hormone relaxin 2, improved symptoms and outcomes in the RELAX-AHF trial. However, it failed to meet its primary end points in acute HF in RELAX-AHF-2. An update of the phase 3 data presented by John R. Teerlink (US) and Marco Metra (IT) confirmed that serelaxin did not significantly reduce the rate of CV death through day 180 or worsening HF through day 5 in patients with acute HF when added to standard therapy. The RELAX-AHF-2 study involved >6600 patients from >550 sites in 34 countries: 3298 patients were allocated to serelaxin and 3271 to placebo. There was no safety issues or effect of serelaxin on CV death.

**FOCUS ON CHRONIC HEART FAILURE**

Which HF intervention is most cost-effective in reducing the length of the hospital stay?

The WHICH study is investigating the cost-effective application of chronic HF management programs to reduce the negative impact on individuals and the wider community. Simon Stewart (AU) presented the WHICH II trial, which compared two interventions. The first was a standard, postdischarge chronic HF management program, incorporating a combination of at least one home visit and hospital outpatient clinics for metropolitan-dwelling patients and structured telephone support for patients in remote areas. The second was a more intensive program of management targeting those most at risk of recurrent and costly hospital stays. The two programs were compared in a population of 809 patients (mean age, 74; two-thirds had HFREF, mainly NYHA class II). There were no differences between the two interventions in health care cost or clinical end points, such as CV events or mortality.

**HFMEF in CHARM: characteristics, outcomes, and effects of candesartan across the entire EF spectrum.**

An LVEF of 40% to 49% was recently defined as HFMEF by the 2016 ESC guidelines. In the CHARM program, a unimodal, bell-shaped distribution was observed across the range of EFs, indicating a substantial proportion of patients (17%) in the “middle band” of EFs (40% to 50%). Among patients with chronic stable HFMEF, Lars Lund (SE) reported a graded relationship between a lower EF and a higher risk of events, with increased risk beginning at an EF <50%. Above an EF of >45%, all-cause mortality, CV death, and all components of CV death remained relatively stable with increasing EF values. These data suggest that, in terms of outcomes, chronic stable HFMEF has characteristics intermediate between HFREF and HFHF. The beneficial treatment effect of candesartan was significant and similar in HFMEF and HFREF. A limitation of the CHARM program is that it was published in 2003, and it used a patient population with a low-percentage use of β-blockade (55%) and MRAs (17%).

**Empagliflozin decreases the risk of kidney function decline in patients with type 2 diabetes**

EMPA-REG OUTCOME, the first type 2 diabetes trial to demonstrate improved CV outcomes in high-risk patients, involved 7020 patients with type 2 diabetes, established CVD (but not necessarily HF), and an eGFR of at least 30 mL/min/1.73m², randomized to receive empagliflozin 10 mg or 25 mg or equivalent placebo. The SGLT2 inhibitor empagliflozin significantly reduced deaths among individuals with type 2 diabetes and established CVD when compared with placebo. In patients with type 1 diabetes, short-term treatment with empagliflozin attenuated renal hyperfiltration, likely by affecting tubular-glomerular feedback mechanisms. Alfred Cheung (US) reported that empagliflozin caused an initial acute reduction in eGFR, followed by a long-term stabilization of eGFR in patients with type 2 diabetes, independently of the concomitant presence of HF.

**Targeting heart rate to improve mortality in patients with HFREF: a comparison of sinus rhythm and AF**

AF and HF often coexist, causing substantial CV morbidity and mortality. Although β-blockers are indicated in patients with symptomatic HFREF, their efficacy in patients with concomitant AF is uncertain. John Cleland (UK) reported the individual patient data meta-analysis of the efficacy of β blockers in 8254 patients with HF in sinus rhythm (13 946; 76%) vs those with AF (3066; 17%). β-Blocker therapy significantly reduced all-cause mortality in patients in sinus rhythm (HR, 0.73), but not in patients with AF (HR, 0.97), with a significant P value (0.002) for interaction of baseline rhythm. In patients in sinus rhythm, β-blockers reduced heart rate and mortality, but, in patients with AF, this heart rate reduction did not affect mortality.

**Does the duration of chronic HF affect patient outcomes?**

The SHIFT trial showed that, in patients with chronic systolic HF and in sinus rhythm, ivabradine reduces the composite of CV death and HF hospitalization; however, it is unknown whether the duration of HF affects the outcomes. Therefore, Michael Böhmer et al (DE) examined the outcomes and treatment effects of ivabradine vs placebo in patients with systolic HF, who had a short (<1.5 years), medium (1.5 to <4 years), or long (>4 years) HF duration before randomization. Patients with a longer duration of HF were older, had greater disease severity (NYHA III/IV), and had more comorbidities compared with patients with a more recent diagnosis of HF. The longer duration of HF was also associated with poorer outcomes. Böhmer et al showed that the heart rate reduction achieved with ivabradine improved clinical outcomes in chronic systolic HF independent of HF duration, including patients with recent-onset HF. Therefore, ivabradine treatment should be initiated early.

**Physicians’ guideline adherence is associated with better prognosis in outpatients with HFREF: the QUALIFY international registry**

QUALIFY, an international, prospective, observational, longitudinal survey, recruited 6669 outpatients with HFREF between 1 and 15 months after HF hospitalization in 36 countries. In the Registry Hotline session, Michel Komajda et al (FR) reported the results from their evaluation of the impact of physicians’ adherence to guideline-recommend-
ed medications for HREF on clinical outcomes at a 6-month follow-up visit. The authors showed that good adherence to the pharmacologic treatment guidelines, as determined by the prescription of ACE inhibitors, ARBs, β-blockers, MRAs, and ivabradine, in dosages that are at least 50% of those recommended, is associated with better clinical outcomes.

FOCUS ON INNOVATIVE AND DEVICE THERAPIES

Do the patients with acute HF who secrete relaxin-2 at pregnancy concentrations have longer survival rates?

Oscar Miro et al (ES) enrolled around 500 patients with acute HF, of whom 10 fulfilled the criteria for elevated relaxin-2 secretion (>1000 pg/dL, ie, at pregnancy concentrations). This group did not differ from the remaining population or show differences in outcomes.

The HeartLogic multisensor algorithm as an automatic predictor of HF events: results from the MultiSENSE trial

Roy S. Gardner (UK) reported that, in the MultiSENSE trial in around 900 CRT-D patients, the HeartLogic alert had an observed sensitivity of 70% and a low explained alert rate (alerts not followed by an HF event) of 1.47 per patient per year. The HeartLogic alert successfully notified clinicians of an associated HF event—defined as hospitalization with HF as the primary diagnosis and HF outpatient treatment with intravenous therapy—with a 34-day median alert window. This algorithm, which mimics the activity and analysis of a clinician by combining multiple measurements evaluating different aspects of heart physiology, may be a better predictor of HF events than natriuretic peptide concentration.

Cardiopoietic stem cell therapy improved LV remodeling: longitudinal results from the CHART-1 study

John R. Teerlink (US) reported that therapy using bone marrow–derived stem cells to promote heart repair did not significantly improve the primary outcome over a sham procedure among patients with congestive HF. Cardiopoietic stem cell therapy involves isolating mesenchymal stem cells from a patient’s own bone marrow, exposing these cells to a “cardiogenic cocktail” that turns them into cardiopoietic cells, and injecting these cardiopoietic cells into damaged heart tissue. The CHART-1 study randomized patients with symptomatic ischemic HF to either a sham procedure (n=151) or cardiopoietic cells (n=120). At 39 weeks, there were no significant between-group differences in the primary efficacy end point, which was a composite of all-cause mortality, worsening HF events, Minnesota Living with Heart Failure Questionnaire total score, 6-minute walk distance, LVEDV, and ejection fraction. However, a subgroup analysis of patients with severe heart enlargement at baseline (LVEDV between 200 and 370 mL) suggested a positive effect of the cell treatment over sham. Data at 1 year showed reductions in LVEDV and LVEF, but these reductions may have been influenced by treatment modification. The benefit was related to the number of injections.

CRT survey: a comparison of CRT survey I and II

Camilla Normand (NO) reported that a comparison between 13 Western European countries involved in 2 surveys showed that a substantial percentage of patients underwent CRT implantation in the absence of evidence-based medicine data (ie, 23% with AF, 2% with NYHA class I, 31% older than 75).

Two-year follow-up results from the AUGMENT-HF trial

AUGMENT-HF, an international, multicenter, prospective, open-label, randomized, controlled evaluation, tested the hypothesis that Algisyl (an injectable calcium alginate hydrogel) is superior to standard medical therapy for improving functional capacity and clinical outcomes in patients with advanced HF. Andrew Coats (UK) reported that, after a 12-month follow-up, there was a significant improvement in exercise tolerance and quality of life indices in 78 patients with advanced HF; patients were randomized 1:1 to Algisyl plus standard medical therapy or standard medical therapy alone as previously reported. The patient inclusion criteria were an LVEF ≤35%, peak VO2 between 9.0 and 14.5 mL/min/kg, and an LVEDD index between 30 and 40 mm/m². During a 12-month follow-up, there were 4 deaths (10.5%) in the control group and 9 in the Algisyl group (22.5%). The 2-year extended follow-up data confirmed the benefit on quality of life. However, exercise tolerance data are missing and the lack of evidence concerning cardiac hemodynamics requires further investigation.

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CURRENT THINKING IN CARDIO-ONCLOGY

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Keywords: cancer; cardio-oncology; cardiotoxicity; heart failure

This article will highlight preclinical and clinical studies as well as new basic science models in cardio-oncology that were presented at this year’s “Heart Failure 2017 and 4th World Congress on Acute Heart Failure,” which was held in Paris, France from April 29, 2017 to May 2, 2017 and attended by over 5000 participants from about 100 countries. Two symposium sessions during the congress were dedicated to the field of cardio-oncology. In addition, 27 posters on this topic were presented. The congress provided a good forum for cardio-oncologists to share their newest research and exchange ideas. In order to understand the underlying mechanisms in cardio-oncology better, new preclinical models were presented at the congress. Due to the growing prevalence of cardiovascular and oncology disease in the industrialized world, cardio-oncology is of great interest.

Important findings at this year’s congress included a meta-analysis associating obesity with increased cardiotoxicity and a new mechanistic understanding of the receptor tyrosine-protein kinase erbB-2 and the oncometabolite d-2-hydroxyglutarate. Chemotherapies (like anthracyclines and trastuzumab) are associated with the development of heart failure, which is currently being studied extensively. Further emphasis was placed on the development of cardio-oncology clinical services and the associated hurdles, challenges, and opportunities. When heart failure during oncology treatment occurs, adequate treatment regimens by cardiologists and oncologists are needed to treat both heart failure and tumors at the same time. The overall message of the congress was that even more collaborative approaches between cardiologists and oncologists are needed to investigate new diagnostic and research options further for these patients.

BASIC SCIENCE

Many basic researchers are currently investigating the underlying mechanisms of chemotherapy- or radiation-induced cardiotoxicity. Today, there are many different approaches. Alexander Lyon (UK) discussed data by de Korte et al.⁴ on the receptor tyrosine-protein kinase erbB-2, which is associated with cardiac injury. After four cycles of doxorubicin chemotherapy, these receptors were upregulated in cardiomyocytes due to stress on the myocardium, demonstrating that anthracyclines (namely doxorubicin) have cardiotoxic effects. Heinrich Taegtmeyer (US) displayed new data from his group showing that mutant leukemic cells affected cardiomyocytes. They administered the oncometabolite d-2-hydroxyglutarate, which is produced by isocitrate dehydrogenase 2 mutant leukemic cells, to rodents for 5 weeks, which induced contractile dysfunction in the heart.² Taegtmeyer proposed that cardiac dysfunction is promoted by d-2-hydroxyglutarate by inducing histone modifications through higher ATP citrate lyase activity and disrupting the function of a-ketoglutarate dehydrogenase. In another rodent model demonstrated by Kari Alitalo (FI), VEGF-B was able to prevent cardiac atrophy after administration of doxorubicin, while preventing loss of body weight at the same time.⁵ The antineoplastic effects of the chemotherapy were unchanged under the administration of VEGF-B; therefore, this treatment might be of further interest in the future.

In an effort to understand the underlying mechanisms in cardio-oncology further, a talk by Catherine Vergely (FR) focused on the role of obesity. In a rodent model with obese rats, obesity was associated with increased mortality. In one arm of the study, the rats were on a normal diet, and, in the other arm, the rats were on a high-fat diet. After 43 days, the rats on the high-fat diet gained 30% more in body weight than did the rats on the normal diet, and a sublethal dose (LD10) of doxorubicin was injected in both groups. In the normal weight group, 10% of the animals died within 25 days, but, in the overweight group, 80% died. In addition, in the overweight group, cardiac biomarkers, such as troponin and creatine kinase-MB, were significantly elevated within 2 days of administering doxorubicin. In alignment with this data is a recent meta-analysis by Guenancia et al.,⁶ which included 35 studies and 8745 patients with breast cancer. The meta-analysis found an increased odds ratio for cardiotoxicity related to anthracycline and trastuzumab therapy in obese and overweight patients (BMI >25 kg/m²; OR, 1.38; 95% CI, 1.06-1.80). Therefore, their group proposed potential influences of adipocytokines on cardiomyocytes or mitochondria.

CHEMOTHERAPY-ASSOCIATED HEART FAILURE

Many large-scale trials have shown that heart failure is associated with cardiotoxic chemotherapy. Accordingly, a study by Erin et al.⁷ was highlighted, which included 12500 patients with breast cancer. Depending on the chemotherapy used, the 5-year incidence of heart failure significantly differed. It was elevated in patients receiving only anthracyclines (adjusted HR vs patients without che-
motherapy, 1.40; 95% CI, 1.11-1.76) or trastuzumab (adjusted HR, 4.12; 95% CI, 2.30-7.42) and highest in patients receiving both anthracyclines and trastuzumab (adjusted HR, 7.19; 95% CI, 5.00-10.35). Furthermore, Alexander Lyon talked about the Persephone trial by Earl et al, which evaluated the frequency of cardiac events with 6 months vs 12 months of adjuvant trastuzumab treatment in 2500 female patients with confirmed HER2-positive, early-stage breast cancer. Of these patients, 93% were treated with anthracyclines, and, of these, 49% additionally received taxanes. In the 6-month group, significantly fewer cardiac events (defined by the alteration or introduction of new chronic heart failure medications or symptoms and/or signs of congestive heart failure) occurred. From a cardiologist’s point of view, the 6-month arm might be preferred, but the overall survival data has to be considered once published. The trial additionally identified risk factors for cardiac events and dysfunction when patients received cardiotoxic chemotherapy, including LVEF <55%, prior use of cardiac medications, >3 cycles of anthracyclines, and patients >70 years old.

In addition, new data was discussed in one of the sessions about the association of radiotherapy with the development of heart failure. Recently, in a case-control study on 59 breast cancer patients with radiotherapy-associated HFPEF, Saiki et al showed that HFPEF could be diagnosed after a median follow-up time of 6 years after the radiation therapy was initiated. Further, higher radiation doses were associated with a more frequent occurrence of HFPEF.

Nevertheless, cardiac biomarkers have also gained more interest. In the last years, studies have shown that they are important and useful in identifying patients at a higher risk of cardiac dysfunction. A study on 452 patients with breast cancer receiving trastuzumab by Zardavas et al was highlighted, which found evidence that elevated baseline levels of troponins I and T were significantly associated with cardiac dysfunction during therapy.

CONCLUSION

This year’s symposium sessions on cardio-oncology and the increasing amount of posters submitted to the Heart Failure Association congress show the importance of this still young field of research. The 2017 Heart Failure Association annual congress provided an excellent opportunity for researchers to exchange ideas and learn from each other on how to treat patients with simultaneous heart failure and cancer.

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TELEMEDICINE AND HEART FAILURE: HYPE OR HOPE?

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Keywords: heart failure; teleassistance; telexpertise; telemedicine; telemonitoring

Telemedicine is like the two faces of the Roman god Janus. On one side, telemedicine seems to promise to open up new dimensions in medicine by giving doctors the possibility of overcoming the inconvenience of distance and the opportunity of bringing expertise into every medical office. On the other side, telemedicine may imply and/or require huge investments, which could increase the numeric fracture between high- and low-income populations.

WHAT IS TELEMEDICINE?

The definition of telemedicine varies depending on the country and culture. Etymologically, telemedicine could be defined as a medical act between two people (and at least one health professional) located in different places using communication or digital technologies. Telemedicine is included in e-health, but it is only a small part of it. The main difference between connected tools and telemedicine is the link between measurements and medical decisions. A connected tool could provide good measurements, which could be interesting for coaching patients or giving healthy lifestyle advice, but it is not clearly associated with medical adjustments. A connected tool is associated with wellness rather than a well-defined patient pathway; therefore, it is mainly paid for by the patients. However, telemedicine is integrated into medical practice to optimize a patient’s medical management, and it is primarily associated with public funding. In a patient’s life, the needs will change progressively from coaching and prevention to telemonitoring; therefore, connected tools and telemedicine could be associated, alternate, or they could be more interesting for some specific settings or at different disease stages.

Four telemedicine types

1. Teleconsultation is a telemedicine act between a patient and a health care professional.
2. Telexpertise is a telemedicine act between two health care professionals, such as a general practitioner and a specialist.
3. Telemonitoring is a follow-up of medical signs or symptoms at a patient’s home using alerts that are generated and transmitted to the doctor with or without the interface or an algorithm and/or nurses.
4. Teleassistance is a telemedicine act performed to help isolated health care professionals perform a technical act (thrombolysis, echocardiography, etc).

TELEMEDICINE AND HF: A PROMISING TARGET?

HF is a polymorphic chronic disease that causes significant patient disability and a high rehospitalization rate. In most epidemiological studies, the prevalence of HF is between 10% and 15% in patients older than 75 years. HF is associated with a degradation in a patient’s quality of life and a high mortality rate and numerous days spent at the hospital that are directly or indirectly related to HF. HF costs are mainly related to hospitalizations, and they increase every year. Certain HF specificities are promising for telemedicine considering that: (i) many rehospitalizations could be prevented with early treatment optimization because the first month after discharge is the most critical period; (ii) more than 50% of patients present with clinical signs of deterioration 5 days before rehospitalization; and (iii) some patients do not have any medical appointments after discharge from the hospital (eg, elderly patients).

The use of telemedicine for patients with HF is sometimes complex, especially for telemonitoring, because most patients are elderly and rarely use electronic devices. Telemedicine in chronic HF has numerous applications. Some programs focus on teleconsultation after discharge using early, remote medical appointments with a general practitioner or cardiologist to optimize diuretic therapy and patient self-management. Some programs focus on telexpertise to help general practitioners increase the use of ACE inhibitors or β-blockers according to the guidelines. However, most telemedicine programs focus on telemonitoring.

Telemonitoring programs could be divided into two models: (i) implanted devices and (ii) external devices. These two models can also be mixed. In most cases, the difference is based more on the sensors used to measure the clinical parameters than on the transmitter. For defibrillators and pacemaker-based systems, such as CardioMEMS®, which continuously measures pulmonary arterial pressure, all sensors are implanted, but the transmitter is external, and transmits the data through a specific connection made by the patient or during the night. In the second model, all of the sensors are external, and they are linked with a transmitter by Bluetooth, Wi-Fi, or a USB cable! In the first model, patient implication and compliance is low, and, in the second model, patient adherence is mandatory to have a significant impact. In the two models, the ability of the system to trigger a medical decision (eg, therapy adaptation, quick medical appointment, low-salt regimen adaptation) with a good accuracy is key to creating a powerful system. It is difficult to optimize the balance between high sensitivity for identifying early decompensation (with a high rate of false positive alerts) and high specificity (with a low
Teleconsultation and teleexpertise are based on the use of communication technologies; therefore, they do not really change the medical strategies. Instead, they bring medical expertise close to the patient, especially in rural areas and areas with a low medical density. Therefore, the studies published emphasized the improvement in the patient pathway and the conformity of care to the guidelines. While evidence for a specific medical impact is scarce, this does not limit the extent of use for these types of telemedicine, as there is an increase in remote medical appointments, with a reasonable percentage of necessary secondary office visits.

The impact of telemonitoring has been analyzed in numerous studies. Some studies, such as CHAMPION,\(^2\) have shown promising results with a significant reduction in morbidity or mortality with some implantable monitoring systems. However, most of the large randomized studies on external sensors have not yet successfully demonstrated significant positive results. Cochrane-based meta-analyses have shown a slight positive impact of telemedicine, but the heterogeneity of studies leads to practically inconclusive results. However, some real-life or cluster-randomized studies have shown promising results according to health policies.

The Whole System Demonstrator cluster randomized trial focused on the effect of telehealth on the use of secondary care and mortality.\(^3\) A total of 238 practices were randomized to control or intervention groups, and the different sites recruited 1625 control patients and 1605 intervention patients from 179 general practices. More than 30% of the patients were older than 75, and 33% had HF. During the 12 months of the trial, 42.9% of the patients in the intervention group were admitted to the hospital vs 48.2% in the control group. These proportions corresponded to an unadjusted odds ratio of 0.82 (95% CI, 0.70–0.97; \(P=0.017\)). During the trial, fewer participants died in the intervention group than in the control group (4.6% vs 8.3%; unadjusted odds ratio, 0.54; 95% CI, 0.39–0.75; \(P=0.001\)). Participants in the intervention group visited emergency departments 0.64 times per person during the trial compared with 0.75 for the control group. This difference was significant in the adjusted estimates only (incidence rate ratio, 0.85; 95% CI, 0.73–1.00; \(P=0.044\)). The intervention and control groups spent an average of 4.87 and 5.68 days in the hospital, respectively; \(P=0.023\).

The national costs of hospital activity to commissioners of care were £188 per person lower for intervention participants than for controls. More recently, a German regional insurance agency analysis of the impact of a telemedicine system (Cordiva® system) in a 2-year prospective study demonstrated a significant reduction in all-cause mortality in patients with HF using a system associating weight/symptoms with structured telephone support for patients, which was done by specifically trained nurses.\(^4\) These real-life studies are complementary to randomized studies, especially when studying process and pathways rather than therapies; this is especially true for telemedicine, a process of patient follow-up where efficacy is driven by medical reactivity and patient willingness. Therefore, in 2017, the French national health ministry launched a national experiment on telemedicine, ETAPEs, focusing on chronic diseases, especially chronic HF, with a national plan for private practices and hospitals to analyze the impact of standardized telemonitoring in real life.

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HEART FAILURE WITH PRESERVED EJECTION FRACTION: CAN WE SUCCEED?

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Keywords: clinical trial; heart failure; pharmacology; preserved ejection fraction; treatment

THE CONTEXT

Heart failure (HF) is a growing health care problem, because of its increasing prevalence, complexity in patients with multiple comorbidities, high mortality, and as a cause of repeated hospitalizations. A general trend observed everywhere is the growing proportion of patients with so-called “preserved” ejection fraction, i.e., an ejection fraction within the normal range.

Observational studies conducted in different geographic regions concur on the fact that HFPEF has a prevalence of approximately 30% to 40% in HF patients at large, and, according to some studies, is more common than the “usual” HFREF and dilated heart.

Although the cutoff value separating normal from subnormal is arbitrary, there is a general agreement that an ejection fraction >45% or 50% is necessary (but not sufficient) to define HFPEF. The recently published guidelines of the European Society of Cardiology highlight the fact that diagnosis requires other components beyond a normal ejection fraction: (1) signs or symptoms of HF; (2) increased levels of plasma natriuretic peptides and one additional factor, including either evidence of structural abnormalities of the heart (left ventricular hypertrophy or left atrium enlargement) or indices of diastolic dysfunction (in particular, an increased E/é ratio on Doppler echocardiography suggesting increased filling pressure of the left ventricle).

Due to the complexity of HFPEF, its diagnosis is often challenging in clinical practice, particularly with respect to measuring diastolic function, which requires good echocardiographic skills, and to the fact that patients with HFPEF are frequently elderly with poor echogenicity or have comorbidities, such as obesity or chronic pulmonary disease, which can mimic HF symptoms or make Doppler echocardiography technically difficult.

There is no consensus that HFPEF is a totally distinct entity from HFREF, but some arguments are in favor of a distinct pathophysiology where chronic inflammation, endothelial dysfunction, and reduced nitric oxide bioavailability play a central role. Clinically, there are important differences in the general profile of HFPEF patients compared with HFREF patients: they tend to be older, more often female, with a higher prevalence of hypertension and conversely a lower prevalence of ischemic heart disease.

CLINICAL TRIALS IN HFPEF: A SUCCESSION OF FAILURES

No drug has yet been shown convincingly to reduce morbidity and mortality in HFPEF patients. Despite several attempts based on different pathophysiological hypotheses, large outcome clinical trials and several proof-of-concept trials have invariably failed to show any benefit in terms of the primary outcomes or surrogate end points.

OUTCOME TRIALS

Four trials used a RAAS blocker (see review in ref 4). The rationale was based on the potential beneficial effects of RAAS system blockade on left ventricular hypertrophy, fibrosis, and sympathetic nervous system stimulation, among other mechanisms.

Using the ACE inhibitor perindopril in an elderly population of 850 patients, the PEP-CHF trial found no improvement in the primary end point, a composite of all-cause death or HF hospitalization. The CHARM-Preserved trial tested the ARB candesartan in 3023 patients and the I-PRESERVE trial tested irbesartan, another ARB, in an elderly population of 4128 patients. The primary outcome (cardiovascular death or HF hospitalization) was not met in CHARM-Preserved, but there was a reduction in HF hospitalization of borderline significance. In I-PRESERVE, there was no change in any of the outcomes, including the primary outcome of all-cause death or cardiovascular hospitalizations.

The TOPCAT study tested the potential benefit of the mineralocorticoid receptor antagonist spironolactone in a large HFPEF population and showed a nonsignificant reduction in the primary composite end point of all-cause mortality, HF hospitalization, or aborted cardiac arrest, whereas HF hospitalizations alone were significantly reduced. However, this trial showed huge geographic heterogeneity in the rate of clinical events and was therefore criticized.

The strategy of adding the ARB olmesartan to existing therapies was tested in the Japanese trial SUPPORT. Unfortunately, the addition of olmesartan did not improve clinical outcomes, and it was associated with more renal deterioration, whereas patients receiving both an ARB and an ACE inhibitor or an ARB and a β-blocker had more cardiovascular events.
The dual ARNi LCZ 696 was tested in 266 patients with HFPEF in the PARAMOUNT trial. Compared with valsartan, LCZ 696 significantly reduced plasma NT-proBNP and the size of the left atrium. LCZ 696 is currently being tested in the large outcome trial PARAGON.

Based on the hypothesis of a dysfunctioning nitric oxide pathway, two proof-of-concept trials have been conducted. RELAX tested the benefit of sildenafil, a phosphodiesterase-5 inhibitor, which plays a key role in the degradation of cGMP, the intracellular messenger of the nitric oxide pathway. No significant change in any of the end points tested was observed. Based on the idea that the pathophysiologic defect would be an insufficient production rather than an increased degradation of cGMP, the SOCRATES-PRESERVED study tested different regimens of the once-daily, oral, soluble guanylate cyclase stimulator vericiguat in 477 patients with HFPEF. After 12 weeks of exposure, no benefit was seen in terms of plasma NT-proBNP levels or left atrial volume.

Recently, the EDIFY study tested the heart rate-lowering agent ivabradine, an I
current inhibitor, titrated to 75 mg bid in 179 patients with HFPEF in sinus rhythm and used three coprimary end points: change in plasma NT-pro-BNP, 6 minute walking distance, and E/e ratio on Doppler echocardiography, together with various echo-Doppler indices. The recruitment of patients was stopped prematurely because of a high rate of screening failures resulting in a low rate of enrollment, and the trial did not reach the target of 400 patients. After 8 months of exposure to ivabradine, there was no change in any of the three coprimary end points. One potential explanation is that patients with advanced HFPEF develop extensive myocardial fibrosis with predominant restriction and no or little stroke volume reserve, thus making cardiac output entirely dependent on heart rate. Another explanation is that, unlike what is commonly believed, prolonging left ventricular filling through heart rate reduction in a stiff left ventricle with a normal ejection fraction may not work. Whatever the explanation, EDIFY does not support the use of ivabradine in HFPEF, and further studies are needed to evaluate the potential of heart rate reduction in some subgroups of patients with HFPEF.

HFPEF remains a clinical dilemma in 2017 due to a lack of evidence-based therapies. The causes of failure to demonstrate benefit are probably multifactorial: identification of HFPEF is challenging, particularly in elderly patients with advanced HF and in patients with comorbidities. It is therefore possible that some patients enrolled in the trials cited above did not have HF, but only symptoms related to a noncardiac cause, such as chronic pulmonary disease or obesity, or they had cardiac amyloidosis. Another potential explanation is the heterogeneity of the patients enrolled in clinical trials: age, ejection fraction threshold, and baseline plasma natriuretic peptide levels vary significantly from one trial to another and may reflect the fact that the patients enrolled are at different stages of the disease.

Finally, trial-related factors may play a role: several clinical trials have experienced a high rate of screening failures or a low rate of enrollment resulting in a prolonged recruitment time and crossover issues. Therefore, we follow empirical recommendations, ie, prevention of factors that may lead to HFPEF, such as hypertension, treatment of arrhythmias, which are often poorly tolerated due to the shortening of diastole in a stiff ventricle, and prevention of congestion or pulmonary edema by means of diuretic agents, whereas the role of β-blockers and calcium channel antagonists remains uncertain.

In summary, the situation is worrisome given the high prevalence of HFPEF. The underlying pathophysiology is imperfectly understood and we need to go back to experimental studies in order to test new hypotheses. In clinical trials, a better phenotypic characterization individualizing different categories may be necessary since the “one size fits all” approach has been unsuccessful so far. Therefore, there is a need to combine expertise from scientists, HF specialists, and geriatricians in order to understand HFPEF better and identify new therapies that will improve quality of life and reduce mortality and the rate of rehospitalization.

REFERENCES
ONE YEAR AFTER THE PRESENTATION OF THE 2016 ESC HEART FAILURE GUIDELINES: NEW STUDIES WITH IMPLICATIONS FOR EVERYDAY CLINICAL PRACTICE

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Keywords: algorithm; comorbidity; heart failure guidelines; HFMEF

It was last year in May 2016, during the annual meeting of the ESC Heart Failure Association, when we presented the new 2016 ESC HF guidelines.1 In these guidelines, we proposed the following new aspects related to the comprehensive management of chronic and acute HF:

1. A new algorithm for the diagnosis of HF in the non-acute setting based on three elements: (i) an initial evaluation of the clinical probability of the disease, including a history of coronary artery disease, arterial hypertension, exposure to cardiotoxic drugs, use of diuretics, symptoms of orthopnea/paroxysmal nocturnal dyspnea; (ii) a careful physical examination; and (iii) a resting ECG. In cases where any of the three criteria are abnormal, plasma levels of natriuretic peptide should be assessed (if available) to identify patients who need a transthoracic echocardiography; however, if natriuretic peptide levels cannot be assessed, a direct echocardiography assessment is indicated.

2. A new classification of HF across the whole spectrum of LVEF, with the introduction of a new term—HFMEF—to identify patients with HF and an LVEF between 40% and 49%. We believe that identifying HFMEF as a separate group will stimulate research into the underlying characteristics, pathophysiology, and treatment of this patient population.

3. A new therapeutic algorithm for HF patients with reduced LVEF (HFREF) that contains indications for the use of the sacubitril/valsartan combination, the first ARNi combination (based on the results of the PARADIGM-HF trial2), and modified indications for cardiac resynchronization therapy (based on the results of the EchoCRT trial3).

4. Updated recommendations on the management of comorbidities that often complicate the natural course of the disease, with new data on diabetes mellitus, iron deficiency, sleep disordered breathing, and hyperkalemia.

5. A modified approach to the management of acute HF including (i) a concept to shorten all diagnostic and therapeutic decisions in the initial phase; (ii) the need to identify coexisting, life-threatening, clinical conditions and/or precipitants immediately (according to the CHAMP criteria) to introduce a specific guideline-recommended management; (iii) a therapeutic algorithm based on clinical profiles to evaluate the presence and/or absence of congestion and peripheral hypoperfusion.

Since the presentation of the 2016 ESC HF guidelines, additional evidence has become available, which may affect everyday practice and possibly form a background for new recommendations and guidelines in the near future. Some of these studies will be summarized below.

IMPORTANCE OF ADHERING TO THE GUIDELINES: RESULTS FROM THE QUALIFY REGISTRY

Although it is taken for granted that good adherence to the HF treatment guidelines would translate into better outcomes; surprisingly, only a few studies have properly addressed this problem. It is particularly important in the context of guideline-recommended disease-modifying treatments that these treatments be applied at optimal target doses. The aim of QUALIFY, a recent international, prospective, longitudinal survey, was to evaluate adherence to five classes of medications recommended by the ESC guidelines as standard disease-modifying therapies for HFREF: ACE inhibitors (or ARBs), β-blockers, MRAs, and ivabradine.4 A global adherence to the guidelines score was developed for the prescription of these drugs and their dosages. From September 2013 to December 2014, 6669 outpatients with HFREF were recruited between 1 and 15 months after HF hospitalization in 36 countries and followed-up at 6 months. The baseline global adherence score was good in 23%, moderate in 55%, and poor in 22% of the patients. At the 6-month follow-up, both poor and moderate adherence were associated with significantly higher overall cardiovascular and HF mortality vs good adherence. There was also a strong trend between poor adherence and a higher risk of HF hospitalizations. The results of the study confirm the necessity for a global use of educational initiatives and disease management programs to facilitate the implementation of guideline-recommended disease-modifying HF therapies (at evidence-based target doses) into everyday clinical practice.
The ESC HF Long-Term (ESC-HF-LT) registry is the largest pan-European cohort, which provides a detailed description of the real-world population of patients with chronic HF from all regions of Europe and the Mediterranean countries. As mentioned previously, the new 2016 ESC guidelines proposed a new HF classification, introducing the term HFMEF. There are neither evidence-based characteristics nor any specific therapeutic recommendations for this group of patients. The recent analysis from ESC-HF-LT provides a unique piece of information on the clinical epidemiology, treatment patterns, and long-term outcomes in HFMEF vs the remaining HF patients. Among 9134 ambulatory HF patients with information on LVEF available, 59.8% were classified as HFREF, 24.2% as HFMEF, and 16% as HFPEF (ie, LVEF >50%). HFMEF was the most prevalent in North African countries (45.5% of all HF patients) and resembled the HFREF group in features, such as age, sex, and ischemic etiology, but had less left ventricular and atrial dilation. The use of guideline-directed medical therapies was similar in the HFMEF and HFREF groups; however, ACE inhibitors/ARBs and β-blockers were used in more than 90% of HFREF/HFMEF patients, whereas MRAs were used in less than 70% and ivabradine in less than 10% of these patients.

Devices were implanted at much lower rates in HFMEF vs HFREF patients. CRT in 8.4% (vs 18.3%) and ICD in 13.4% (vs 34.8%). Mortality rates at 1 year were 8.8% in patients with HFREF, 7.6% in patients with HFMEF, and 6.4% in patients with HFPEF. By pairwise comparison, all-cause mortality in HFMEF did not differ significantly from mortality in HFREF or HFPEF. Interestingly, the percentage of patients hospitalized for HF was 8.7% in HFMEF, which was lower than in HFREF (14.6%), but similar to HFPEF (9.7%). The authors concluded that HF patients stratified according to different LVEF categories represent diverse phenotypes of demography, clinical presentation, etiology, and outcomes. Further studies are urgently needed to explore the effects of treatments, which are commonly applied in clinical practice, on the outcomes of patients with HFMEF.

Iron deficiency frequently occurs with HF, and it is associated with poor exercise capacity, impaired quality of life, and a high risk of mortality and morbidity. The 2016 HF guidelines recommended that all HF patients be screened for iron deficiency (based on the assessment of serum ferritin and transferrin) and that patients with HFREF who have an iron deficiency receive intravenous ferric carboxymaltose to alleviate symptoms and improve exercise capacity and quality of life. However, it remains unknown whether correcting iron deficiencies with intravenous iron would improve the outcomes. Anker et al presented the individual patient data meta-analysis from four randomized clinical trials comparing ferric carboxymaltose with placebo in patients with HFREF and an iron deficiency on recurrent hospitalizations and mortality.

Patients randomized to ferric carboxymaltose had lower rates of recurrent cardiovascular/HF hospitalizations and cardiovascular/all-cause mortality (vs placebo), and these effects were independent of the baseline hemoglobin levels. Clinical trials are now set up to confirm these findings.

In the EMPA-REG OUTCOME trial, treatment with empagliflozin (an SGLT2 inhibitor), added to the standard of care in patients with type 2 diabetes and a high cardiovascular risk, reduced the risk of the primary composite outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke and the overall risk of mortality. Fitchett et al recently reported the results of additional analyses of the EMPA-REG OUTCOME trial with respect to HF outcomes, where they found that HF hospitalization or cardiovascular death occurred in a significantly lower percentage of patients treated with empagliflozin vs placebo (HR, 0.66). Consistent benefits of empagliflozin were observed across subgroups defined by baseline characteristics, including patients with or without HF. Empagliflozin improved other HF outcomes, including hospitalization for or death from HF, and it was associated with a reduction in all-cause hospitalizations. There are still uncertainties concerning the mechanisms underlying the favorable effect of this drug in terms of early prevention of cardiovascular death and HF hospitalizations.

The guidelines recommend using an ICD to reduce the risk of sudden cardiac death and all-cause mortality in patients with symptomatic HF (NYHA class II-III) and an LVEF ≤35% despite optimal medical therapy. However, the evidence on the benefits of an ICD is much stronger for patients with ischemic cardiomyopathy than for those with HF from other etiologies. Given the limited evidence of a benefit from the implantation of an ICD in patients with chronic, nonischemic HF, the DANISH trial recruited patients with symptomatic HFREF (LVEF ≤35%) not caused by coronary artery disease, who were then assigned either an ICD or usual clinical care (control group). The primary outcome of the trial was death from any cause. After a median follow-up period of 67.6 months, the primary outcome had occurred in 21.6% in the ICD group vs 23.4% in the control group (HR, 0.87; P=0.28). However, there was a significant 50% reduction in the risk of sudden cardiac death in the ICD group (4.3% vs 8.2% in the ICD vs controls, respectively, P=0.005). The authors concluded that the use of an ICD for primary prevention in patients with HFREF (not caused by coronary artery disease) did not reduce the rate of long-term all-cause mortality. The results raised an interest and started a widespread discussion in the context of both guidelines recommendations and clinical practice.

The interpretation of these findings is still a matter of debate, but this may be because contemporary pharmacological and nonpharmacological treatments for patients with nonischemic HFREF result in a much better outcome, particularly the relatively low rate of sudden cardiac death (which is favorably affected by an ICD). On
the other hand, as ICDs do not reduce the risk of death due to pump failure or death due to noncardiovascular causes, it explains the lack of effect on all-cause mortality. The results of the DANISH trial justify the need for a careful and optimal selection of candidates who would benefit from an ICD.

**OPTIMIZATION OF LONG-TERM THERAPY FOR PATIENTS HOSPITALIZED FOR ACUTE HF: NEW ANALYSIS FROM THE SHIFT TRIAL**

Patients discharged from the hospital after an episode of acute HF decompensation are at a very high risk of death and/or readmission in the first weeks following hospital discharge. Within this vulnerable period, the ESC guidelines recommend setting up a plan for a careful patient follow-up, optimally with the first visit occurring 1 to 2 weeks after discharge as well as enrollment in a disease management program. Although reducing the burden of rehospitalization during the vulnerable phase is of critical clinical importance, in practice, there is a lack of evidence-based protocols for the optimization of pharmacological, disease-modifying therapies. In this context, there is an interesting, recent analysis from the SHIFT trial that evaluated the effects of chronic exposure to ivabradine vs placebo on hospital readmissions occurring up to 3 months after a hospitalization for worsening HF. Among patients who experienced hospitalization due to acute HF during the study, 28% were rehospitalized within 3 months after discharge, mostly for cardiovascular causes (86%), including HF (61%). The use of ivabradine was associated with fewer all-cause hospitalizations at 1, 2, and 3 months (incidence rate ratios, 0.70-0.79), and, additionally, a trend for a reduction in cardiovascular and HF hospitalizations was observed in ivabradine-treated patients. The results form a background for future studies to investigate whether in-hospital or early postdischarge initiation of ivabradine could be useful to improve early outcomes in hospitalized HF patients.

We stated in the HF guidelines that “in the year 2016, by applying all evidence-based discoveries, heart failure is becoming a preventable and treatable disease.” We are all eagerly awaiting new data from ongoing studies, which will form the background of the new ESC guidelines.

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HEART FAILURE BURDEN

The increase in the incidence of heart failure has escalated into epidemic proportions in the last decade. The actual national data are unknown; however, at least two hospital reports showed that there was a dramatic increase in the incidence of emergency room consults and hospital admissions and readmissions. The estimated prevalence across the Asia-Pacific regions ranged from 1% to as high as 12%. In the Philippines, the rough estimate is between 1% and 2% or between 700,000 and 1.3 million Filipinos. Those patients with asymptomatic left ventricular dysfunction were not included in this estimate because many were undiagnosed and not seen by health care personnel. The most common cause of heart failure is coronary artery disease, especially after a myocardial infarction, followed by hypertension and diabetes mellitus.

POOR OUTCOMES

The prognosis of heart failure remains poor even with the availability of newer drugs. The mortality rate remains high, ranging from 3% to 10% in the early in-hospital phase. Health expenditures are high. The rehospitalization rates are high, and they are estimated to be 10% in the first 30 days after the initial hospitalization. Comorbidities are very common, and they may influence the outcome of treatment and the overall prognosis. Polypharmacy is the general rule with the number of drugs ranging from 4 to 12 depending on the number of comorbidities.

INEFFECTIVE PREVENTIVE MEASURES

The government health sector’s thrust is primary prevention through a healthy lifestyle. This idea is obviously ineffective because there is a rising incidence of chronic heart disease events and heart failure itself. Risk factors, such as hypertension, dyslipidemia, obesity, and diabetes, all had rising trends in all clinical surveys of the National Nutrition and Health Surveys and private sectors, and these risk factors are known determinants of heart failure.

LOW UTILIZATION RATE OF CLASS A HEART FAILURE DRUGS

In all registries and when performance measures in heart failure were monitored, the quality of care indices for the pharmacological management of heart failure before discharge were low. In a 2004 report, the utilization rate of β-blockers and renin-angiotensin-aldosterone blockers was 38% and 70%, respectively, before hospital discharge. More than 10 years later, the utilization rate of these drugs were 49% and 74%, and the utilization rate of mineralocorticoid receptor antagonists was 21%. This small increase in the utilization rates may have a significant impact on the outcomes, but this remains to be seen, and there is room for improvement.

SIMILARITY IN BURDEN ACROSS ASIA AND THE WORLD

In 2014, in an initiative from Servier that was chaired by Martin Cowie in Paris, France, a group of Asian experts from 9 countries (Hong Kong, Indonesia, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand, and Vietnam) met and contributed the most recently available data on heart failure care from their countries, which was obtained by using what they considered to be the best available sources. These data were nationally published data from local or regional registries or audit projects. The data were mostly on heart failure with reduced ejection fraction and its etiologies. The mean age at admission was young, ie, ≤60 years, compared with the ≥70 years in the US and the European Union. Hypertension and diabetes have been significant causes of and risk factors for heart failure. The in-hospital mortality rate is between 3% and 7%, and the 30-day mortality rate is between 1% and 17%.

DIFFERENCES IN HEALTH CARE ACROSS ASIA

The pathophysiology of heart failure is the same in all regions. The experts agree that the differences observed in the heart failure epidemiology were due to differences in the prevalence of risk factors for heart failure, and the outcome is dependent on the health care system in each country. This difference has been attributed to country-specific economies. For example, the health care system in Singapore is highly supported by the...
government, where almost 100% of hospitalizations, pharmacological therapies, and even device therapies are shouldered by a finance system. In the Philippines, the health care system is an “out of pocket” system, and the overall outcome may somehow be dependent on the socioeconomic state and the health care system at the time of risk-factor prevention or at the time the heart failure event happened.

OPTIMIZE HEART FAILURE CARE PROGRAM

With the growing burden of heart failure, the need to offer the best standard of care to patients became the priority of cardiologists and major stakeholders. Planning is imperative, and execution is of utmost importance. In 2014, the Optimize Heart Failure Care program was started. This initiative was supported by the Philippine Heart Association, the national organization of cardiologists in the country. Small as it may seem, the impact in certain areas was felt. Several key people participated in this program, and, of note, the Council on Heart Failure of the Philippine Heart Association and the different training officers from nine training institutions in metropolitan Manila.

The Optimize Heart Failure Care Program has a four-pronged approach that is composed of education, guidance, research, and indicator identification (Table I). The education arm was aimed at educating specialists, general practitioners, cardiology fellows in training, nurses, and patients, and it focused on how to maximize the benefits of heart failure therapies. The education program was initiated by both the Philippine Heart Association Continuing Education Program Committee and the Council on Heart Failure. The guidance arm involved using checklists, booklets, and smartphone applications, with the goal of guiding clinicians in adjusting drugs and monitoring patients for signs of decompensation. The research arm included the Philippine Heart Association registry on heart failure and fostering research on performance measures. The indicator identification arm included quality of care indices and hard outcomes, such as those reported in hospital statistics. This program contains the “optimize before discharge” concept because many people believe that the best time to optimize medical therapy for heart failure is during hospital admission. This concept is somehow linked to early decompensation and rehospitalization following discharge, where the highest rates of decompensation and rehospitalization were observed in the first 30 days following discharge. The reason for this is the poor optimization of Class A drugs for heart failure. There may be reasons for the failure to optimize these drugs, but most of these reasons can be counterbalanced by careful titration and persistence. Nevertheless, there are situations where optimization is not possible; however, there are now drugs and strategies available that can be used to address these limitations. Examples of new drugs and strategies include: (i) using ultra-low doses of ACE inhibitors in hypotensive patients with heart failure without deferral orders; (ii) using ivabradine in hypotensive patients with tachycardia, where β-blockers and ACE inhibitors cannot be initiated; and (iii) using a combination of low-dose β-blockers and ivabradine in patients with elevated HR and marginal blood pressure. These options are just some of the innovative ways to address the limitations in the usual drugs used for heart failure.

KEY MESSAGES

1. Optimize drugs before discharge.
2. Optimize drugs by achieving the target doses or at least half of the target doses of β-blockers, ACE inhibitors, or mineralocorticoid receptor antagonists.
3. Provide an early follow-up after discharge, ideally within 7 days postdischarge.
4. Include lifelong monitoring of heart rate, blood pressure, weight, and NYHA class.
5. Drugs are available that can further reduce the risk of heart failure hospitalizations and death (ivabradine for patients with an elevated HR).
6. Continual improvement and education are necessary to address the gaps in heart failure management.

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Table I. Four-pronged approach to the Optimize Heart Failure Care program in the Philippines.
NEW THERAPIES FOR HEART FAILURE

GIUSEPPE M. C. ROSANO, MD, PhD, MSC, FESC, FHFA

Heart failure is a fatal condition where only 50% of patients are alive 5 years after the diagnosis. The disease affects millions of people around the world, with 15 million affected in Europe alone. Its incidence is predicted to rise sharply in the next two decades. In the past 20 years, ACE inhibitors, β-blockers, diuretics, and mineralocorticoid receptor antagonists have been instrumental in extending the survival of patients with heart failure. More recently, ivabradine and LCZ696 have been shown to reduce mortality and morbidity in patients with chronic heart failure, and they now play a central role in the treatment of heart failure.

The treatment of heart failure has been transformed by ivabradine and LCZ696 due to the strength of their outcome data, although the full potential of their combined use has not yet been fully explored. Both drugs have been shown to be effective in reducing not only mortality, but also the recurrence of hospitalizations for heart failure, which represents an important clinical and economic burden. However, even when prescribed ivabradine and/ or LCZ696 and implanted with an ICD or a cardiac re-synchronization pacemaker, patients with heart failure are still at a high risk of mortality and rehospitalizations. Therefore, the advent of new pharmacological therapies that are effective in reducing mortality and morbidity further are pivotal to reduce the future social burden of heart failure.

Furthermore, while there has been progress in treating chronic heart failure, little has been achieved for acute heart failure and HFPEF, and no treatments have been tested for HFMEF or in patients in the vulnerable phase, i.e., in the first few months after a hospitalization for heart failure. This lack of progress means that more than half of the overall patients with heart failure have a dismal prognosis with no effective treatment options.

NEW HEART FAILURE DRUGS IN THE PIPELINE

Despite a market access that penalizes drugs for heart failure more than drugs for diabetes, cancer, or neurological disease and a regulatory framework that makes it difficult to develop heart failure drugs compared with the other above-mentioned conditions, several drugs for heart failure are coming through the research pipelines.

Omecamtiv mecarbil

The drug that is more advanced in the development program is omecamtiv mecarbil, an activator of cardiac myosin, which is designed to increase the duration of cardiac muscle contractility and improve cardiac muscle performance. Cardiac myosin, the cytoskeletal motor protein in the cardiomyocyte that is directly responsible for cardiomyocyte contraction, converts the chemical energy stored in ATP into a mechanical force that shortens the sarcomere. Omecamtiv mecarbil shifts the enzymatic cycle to favor a force-producing state.

Preclinical studies have shown that omecamtiv mecarbil increases cardiac contractility without altering the intracellular calcium levels in cardiomyocytes, and early phase clinical studies have shown that the effect observed in the preclinical models also applies to humans. Omecamtiv mecarbil has completed the dose-finding phase 2 clinical trials, and it is currently being tested in GALACTIC-HF, a phase 3 clinical trial. If positive, omecamtiv mecarbil may change the treatment paradigm for patients with heart failure. GALACTIC-HF is based on the positive results of the COSMIC-HF study, which evaluated the treatment in patients with chronic heart failure.

The chronic dosing trial of omecamtiv mecarbil, presented at the 2017 Congress of the Heart Failure Association in Paris, France, met its primary pharmacokinetic objective and demonstrated a significant improvement in all pre-specified secondary measures of cardiac function in the treatment group employing a pharmacokinetic-based dose titration.

Other heart failure drug candidates

Other candidate drugs in mid-stage testing include the natriuretic peptide receptor agonist cenderitide; the small molecule elamipretide, which enhances electron transport in the mitochondria favoring energy production; and perhexiline, a look-a-like of the well-known drug trimetazidine, but it has a significant and problematic safety profile.

Finerenone, a mineralocorticoid receptor antagonist, which was to be developed for heart failure as a safer replacement for older drugs in the class, such as eplerenone and spironolactone, has been shifted, for marketing reasons, from heart failure to renal impairment. The intravenous nitroxyl donor CXL-1427 and its oral follow-up CXL-1036 are currently being tested in patients with heart failure, while the sodium zirconium cyclosilicate ZS9 and patiromer are in the late phases of the regulatory approval process to start phase 3 studies aimed at improving efficacy in improving the use of adequate treatments with renin-angiotensin-aldosterone system inhibitors, which are often withheld because of elevated potassium levels. After showing stunning results in reducing mortality and hospitalizations for heart failure in patients with diabe-
tes, the sodium glucose cotransporter 2 empagliflozin is currently being tested in patients with heart failure with or without diabetes, and it is probable that other drugs from the same class will follow suit.

**Gene and stem cell therapy**

Gene and stem cell therapies currently seem to hold most of the hopes for reversing heart failure progression. The non-viral gene therapy JVS-100, which expresses stromal cell-derived factor-1 and activates the body’s tissue repair pathways, has started phase 2b studies, while the gene therapy Mydicar, which consists of an adeno-associated virus carrying the gene for the enzyme SERCA2a, failed to show any benefit in the CUPID 2 trial. Stem cell therapy is currently being tested using the muscle stem cell therapy Myocell (phase 3 trial), the allogenic mesenchymal stem cell therapy Neofuse, and the autologous cardiac stem cell therapy C-Cure.

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**CONCLUSION**

Therefore, despite the regulatory and market access hurdles, there is a new wave of drugs currently being tested in heart failure. The past 20 years have witnessed many successes and several failures, for example, serelaxin and ularitide in acute heart failure. The mistakes made in the early years with drugs, such as amrinone, ibopamine, and flosequinan, are now avoided due to more structured development plans. The lessons from the past with drugs, such as omapatrilat, have been learned, which have resulted in many successes. However, it is time to move to a more pragmatic and tailored approach to clinical trial designs to address the needs of specific patients with heart failure who still have a poor quality of life and prognosis.
HOW TO APPROACH HEART FAILURE DISEASE IN FRAIL PATIENTS

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In industrialized countries, populations are rapidly aging, and it is expected that the global population of people aged 65 years or more will rise to around 2 billion by 2050. This continuous aging of the global population is due to the progressive improvement in life conditions and the availability of more effective treatments for previously untreatable diseases. The improved outcomes after acute morbid events have been changing the epidemiology of cardiovascular disease in older people, and, among people 65 years of age or older, heart failure has become a major public health problem and the leading cause of morbidity, hospitalization, and mortality.

Although the definition of elderly people is mainly based on chronological age (≥65 years), it is now clear that age thresholds are arbitrary and unable to reflect all the disease- and non-disease-related variables that impact biological aging. Indeed, the progressive “physiological” changes that occur with aging in all organ systems are influenced by disease-related variables, such as the presence of several concomitant and chronic diseases (both cardiac and noncardiac), the level of functional capacity, and the cognitive status of patients. The interaction between disease- and non-disease-related variables, such as socio-demographic factors (poverty, malnutrition, living alone, low physical activity), leads to different phenotypes of aging, independent of chronological age.

Among people over 65 years old, 30% do not suffer from any major pathology (robust phenotype), 20% report a chronic disease with no major impact on physical and cognitive function, and 50% have multiple chronic morbidities, resulting in mobility problems or difficulties in undertaking daily life activities (frail phenotype). The high prevalence of such frail phenotypes has led to the common misconceptions that advanced age is inevitably associated with the phenotype of the frail elderly and that frailty is synonymous with advanced age. However, several studies have confirmed that, although the prevalence of frailty increases with age, frailty is not necessarily an inevitable part of aging nor is it exclusive to the elderly. Frailty is a multidimensional syndrome defined as a state of decreased reserve (physical and/or psychological) and resistance to stressors resulting from cumulative declines across multiple physiological systems, which results in an increased risk of vulnerability to adverse health outcomes.

The relationship between frailty and heart failure is bidirectional, and frail older adults are at an increased risk of developing heart failure. Patients with heart failure are up to six times more likely to be frail, and frail patients have a significantly increased risk of developing new-onset heart failure. Frailty affects almost half of the patients with heart failure independently of age or NYHA functional classification, and its prevalence is significantly higher than the one seen among community-dwelling elderly people (from 3.2% in people 65 to 70 years old to 25.7% in those aged 85 to 90 years old in the Cardiovascular Health Study). Frailty predisposes patients to the progression of heart failure and reduces the resistance to stressors, such as myocardial ischemia, pressure and volume overload, and arrhythmias. Therefore, the presence of frailty in patients with heart failure interferes with prognosis since the lack of physiological reserve allows acute stressors to cause decompensation and rapid functional deterioration and disability. Patients with heart failure and frailty have been shown to have a higher risk of mortality at 1 year (17% vs 5%), heart failure hospitalizations (21% vs 13%) with longer lengths of stay in the hospital, impaired quality of life, and a lower probability of surviving more than 10 years (6% vs 31%) compared with heart failure patients without frailty. Frail heart failure patients also have an impaired quality of life because the presence of frailty accelerates the risk of developing a disability and therefore dependency in performing activities needed for independent living or self-care and other activities important for a person’s quality of life (basic activities of daily living [ADL] or instrumental activities of daily living [IADL]). However, while most disabled older people are frail, not all frail people are disabled.

A dysregulation of inflammatory processes, the presence of increased oxidative stress, mitochondrial dysfunction, and cellular senescence, the hormonal and metabolic derangement resulting in an anabolic-catabolic imbalance, and skeletal muscle dysfunction can be found in both frailty and heart failure, and they have been proposed as underlying pathogenic mechanisms for disease progression. The global imbalance between the anabolic and catabolic state, which is typical of frail people, may lead to muscle wasting and loss (sarcopenia) and, eventually, to cachexia, which are common syndromes in heart failure patients. Sarcopenia is defined as having a lean body mass that is two standard deviations below the sex-specific mean in a young healthy sample, while cachexia, typical in the advanced stages of heart failure, is a complex metabolic syndrome associated with an underlying illness that is characterized by a 5% weight loss in ≤12 months or a body mass index <20, in addition to...
at least 3 of the following 5 criteria: (i) decreased muscle strength; (ii) fatigue; (iii) anorexia; (iv) low fat-free mass index; or (v) abnormal biochemistry (inflammation, anemia, or low serum sodium).

Although frailty has been increasingly recognized as a critical health problem in older adults, especially in those with heart failure, a universally accepted frailty model is still lacking. Several methods have been proposed to assess frailty, and more than 60 instruments are available in the literature for its assessment: from short, fast, and crude frailty screening instruments to sophisticated, time-consuming measurements. The two most widely used instruments to assess frailty are the Fried’s phenotypic definition of frailty1 and the frailty index.

The Fried’s frailty phenotype is defined by five key domains that are focused on the physical aspects of frailty: (i) weakness (dominant knee extension strength); (ii) low energy (or exhaustion measured with three questions: “Did you feel worn out?” “Did you feel tired?” “Did you have a lot of energy?”); (iii) slowed walking speed (6-meter fast gait speed test); (iv) low physical activity (self-reported time spent doing light, moderate, and vigorous activities on weekdays and during the weekend); and (v) unintentional weight loss (≥4.5 kg in the past 6 months or a BMI <18.5 kg/m²). The number of criteria presented by the individual determines the condition of frailty (ie, ≥3), pre-frailty (ie, 1 or 2), and robustness (ie, none). The main limitation of this instrument is that it does not include the psychosocial and social components of frailty.

The frailty index has been proposed as a way to incorporate the multidimensional nature of frailty into an operational definition. Originally, 92 baseline variables, consisting of signs, symptoms, disability, and laboratory values, were used to define frailty, and then, a simplified 30-item bedside assessment tool was developed without loss of predictive validity. This index is generated as the ratio between the number of deficits the individual presents divided by the total number of deficits considered in the computation.

Alternatives to these two frailty scales are instruments based on the assessment of single performance measures, such as gait speed, Timed Get up and Go, chair stand test, or hand grip strength, or based on auto-questionnaires, such as gait speed, Timed Get up and Go, chair stand test, or the PRISMA-7 (Program on Research for Integrating Services for the Maintenance of Autonomy) questionnaires. The latter is based on seven items, including demographic data and self-reported answers to questions focused on health status, functional autonomy, and the need for help, and it is used by the British Geriatrics Society in the Fit for Frail consensus as the best practice guidance for the care of community-dwelling older people. The Study of Osteoporotic Fractures index is also used frequently, and it is based on three criteria: (i) involuntary weight loss; (ii) inability to rise from a chair; and (iii) reduced energy levels. Although these alternative instruments may have a role as screening tests due to their easy use, they are not able to evaluate the multidimensional components (eg, physical, psychological, and sociological components) of frailty due to their focus on the physical and disease-related aspects of frailty, and they are not “specific” due to their influence by clinical conditions (ie, cognitive state) and/or sociocultural factors.

To date, a gold-standard method that would be simple to apply, yet simultaneously able to accurately identify frailty and reliably predict adverse clinical outcomes is still lacking in both research and clinical practice.

The comprehensive geriatric assessment is a multidimensional, interdisciplinary diagnostic process used in geriatric medicine to determine the medical, psychological, and functional capabilities and the social circumstances of a frail elderly person. Its purpose is to develop and implement a coordinated and integrated plan for treatment, rehabilitation, support, and long-term follow-up. In elderly patients with heart failure and frailty, the comprehensive geriatric assessment remains the central and most reliable instrument able to assess the whole patient in its complexity and not just the part that it is perceived to be more relevant.

Elderly patients with heart failure frequently develop frailty that further impairs their prognosis. Since frailty is a dynamic and potentially reversible state, it is important to identify the individual needs and goals in order to plan an individualized and tailored health care program for each patient that may be helpful in preventing the ”cascade to dependency” that often results in institutionalization and negative outcomes. The personalized approach is also important in improving health-related quality of life and overall wellbeing in this complex patient population. Therefore, a multidimensional assessment is pivotal to developing and implementing a coordinated and integrated plan for treatment, rehabilitation, support, and palliative care in elderly patients with heart failure and frailty.

REFERENCES

Abbreviations and acronyms
ACE  angiotensin-converting enzyme
ADL  activities of daily living
AHA  American Heart Association
ARB  angiotensin receptor blocker
ARNi angiotensin receptor-neprilysin inhibitor
AUGMENT-HF evaluation of Algisyl-LVR™ as a method of left ventricular AUGMENTation for Heart Failure
BLAST-AHF Biased Ligand of the Angiotensin receptor Study in Acute Heart Failure [trial]
BNP brain natriuretic peptide
BP  blood pressure
CHARM Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity
CHARM-Preserved CHARM-patients with Preserved left ventricular function
CHART-1 Congestive Heart failure Cardiopoietic Regenerative Therapy
COSMIC-HF Chronic Oral Study of Myosin activation to Increase Contractility in Heart Failure
CRT cardiac resynchronization therapy
cRT-D cardiac resynchronization therapy defibrillator
CUPID2 Calcium Upregulation by Percutaneous administration of gene therapy in cardiac Disease phase 2b
CV cardiovascular
EchoCRT Echocardiography-guided Cardiac Resynchronization Therapy
EDIFY preServe0 left ventricular ejection fraction chronic heart failure with ivabradine study
eGFR estimated glomerular filtration rate
EMPA-REG OUTCOME Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes [trial]
EMPEROR EMPagliflozin outcomE Trial in patients with chronic heart failure
ESC European Society of Cardiology
FRAIL Fatigue, reduced Resistance, Aerobic deficit, Illnesses, and Loss of weight
GALACTIC-HF Goal directed AfterLoad reduction in Acute Congestive Cardiac decompensation [study]
HCM hypertrophic cardiomyopathy
HF  heart failure
HFA Heart Failure Association
HFMEF heart failure with midrange ejection fraction
HFPEF heart failure with preserved ejection fraction
HFREF heart failure with reduced ejection fraction
IADL instrumental activities of daily living
IGF-1 insulin-like growth factor 1
IL6 interleukin 6
I-PRESERVE Irbesartan in heart failure with PRESERVED systolic function [trial]
IV intravenous
LEADER Liraglutide Effect and Action in Diabetes: Evaluation of CV outcome Results
LV  left ventricle
LVEDD  left ventricular end-diastolic diameter
LVEDV  left ventricular end-diastolic volume
LVEF left ventricular ejection fraction
LVESV  left ventricular end-systolic volume
MI  myocardial infarction
MRA mineralocorticoid receptor antagonist
MultiSENSE MultiSENSOR chronic Evaluations in ambulatory heart failure patients
NT-proBNP N-terminal pro-brain natriuretic peptide
NYHA New York Heart Association
PAI plasminogen activator inhibitor
PARADIGM-HF Prospective comparison of Angiotensin Receptor-neprilysin inhibitor with an Angiotensin-converting enzyme inhibitor to Determine Impact on Global mortality and Morbidity in Heart Failure [trial]
PARAGON-HF Prospective comparison of ARNi with ARB Global Outcomes in heart failure with preserved ejection fraction
PARAMOUNT Prospective Comparison of ARNi With ARB on Management of Heart Failure With Preserved Ejection Fraction
PCI percutaneous coronary intervention
PEP-CHF Perindopril in Elderly People with Chronic Heart Failure
PKM pyruvate kinase
PPCM peripartum cardiomyopathy
PRISMA-7 Program on Research for Integrating Services for the Maintenance of Autonomy
RAAS renin-angiotensin-aldosterone system
RCT randomized controlled trial
RELAX phosphodiesterase-5 inhibition to improve clinical status and exercise capacity in diastolic heart failure
RELAX-AHF RELAXin in Acute Heart Failure
RESUS-AMI safety and efficacy of a single low dose of intracoronary IGF-1 following PCI for ST-elevation AMI
ROS reactive oxygen species
SBP systolic blood pressure
SERCA2a sarco(endo)plasmic Ca\(^{2+}\) ATPase type 2
SGLT-2 sodium glucose cotransporter 2
SHIFT Systolic Heart failure treatment with the \(I_i\) inhibitor ivabradine Trial
SOCRATES-PRESERVED SOluble guanylate Cyclase stimulator in heART failure patients with PRESERVED ejection fraction
TNF-α tumor necrosis factor α
TRUE-AHF Trial of Ularitide Efficacy and Safety in Acute Heart Failure
uPAR urokinase-type plasminogen activator receptor
VEGF-B vascular endothelial growth factor B
WHICH Which Heart failure Intervention is most Cost-effective & consumer friendly in reducing Hospital care [trial]
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