

DIALOGUES IN CARDIOVASCULAR MEDICINE

JUNE 2018

VOLUME 23 #2



Heart Failure Vienna

2018

www.dialogues-cvm.com

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.

Indexed in

EMBASE; Scopus

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Subscriptions

Orders can be placed directly with the publisher

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Next Issue

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Design: Creafirst
Layout: Bleu Banquise

Printed in France by: / Imprimé en France par:
Imprimerie Dridé
Zone Industrielle des Chanoux
49, rue des Frères-Lumière
93334 Neuilly-sur-Marne Cedex

ISSN 1272-9949

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Heart Failure Vienna

2018

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EDITORIAL

Hear failure remains the major cause of death and disability worldwide; in its most severe form (NYHA class III-IV), the outcome resembles that of metastatic cancer, and, in its milder form (NYHA class II-III), it adversely affects quality of life equal to that seen in patients with severe chronic obstructive airways disease. Hopefully as our understanding, prevention, and treatment of ischemic heart disease and dilated cardiomyopathy improve, so will heart failure become less and less of a medical challenge. The treatment and prevention of ST-segment elevation myocardial infarction is slowly beginning to change the epidemiology of heart failure, and, with a much earlier diagnosis and initiation of appropriate treatment, it has now become possible to interrupt the natural history of the disease. This issue of *Dialogues in Cardiovascular Medicine* focuses on the current state of knowledge of heart failure in 2018 through the eyes of the HFA congress.

In this issue, one section is devoted to the prevention and treatment of heart failure. **Massimo F. Piepoli** addresses the important role of prevention to reduce the burden of heart failure, as the cost of treating heart failure is becoming unsustainable. While many primary and secondary prevention methods are known and highlighted in the guidelines, implementation is often not easy and it may be more problematic for secondary prevention than for primary prevention. **Michael Böhm** discusses that, to treat heart failure successfully, an understanding of the pathophysiology is required, especially in the case of heart failure with preserved ejection fraction. Comorbidities are common in patients with heart failure, and, in this issue, two outstanding articles discuss the importance of treating comorbid conditions, with a focus on atrial fibrillation and diabetes. **Edoardo Bertero** and **Christoph Maack** discuss the effectiveness of catheter ablation in patients with atrial fibrillation and heart failure. Atrial fibrillation remains a huge problem in these patients, and, although there are new trial results available, the management of atrial fibrillation remains an open question. **Giuseppe M. C. Rosano** and **Cristiana Vitale** examine the management of patients with diabetes and heart failure, showing that the overall clinical status must be the target when treating patients with diabetes and heart failure. As cardiotoxicity is a problem following oncology treatment, two sessions of the HFA congress were dedicated to the underlying mechanisms of this cardiotoxicity, which are summarized by **Sara Hadzibegovic**, **Alessia Lena**, and **Markus S. Anker**. The prevention and treatment section of this issue is rounded out by **John Parissis** and **Vasiliki Bistola** who discuss the new guideline-recommended clinical classification, diagnosis, and treatment of patients with acute heart failure.

The introduction and development of more specific devices for the management of heart failure and its complications have resulted in a paradigm shift. Technology continues to develop and play an increasingly important role in heart failure management not only by improving the speed with which an accurate diagnosis is made, but also by improving long-term management. Moreover, the financial burden of heart failure in an increasingly elderly population will necessitate a greater emphasis on precision and personalized medicine if treatments are to be both effective and affordable. It is likely that technology will be the vanguard in this respect. Therefore, another section of this issue is dedicated to the advances in technology over the past year. **Jelena Čelutkienė** presents the new imaging techniques available for heart failure, showing that global longitudinal strain has superior reproducibility, precision, and sensitivity for diagnosing subclinical ventricular dysfunction than left ventricular ejection fraction, which will be especially important for monitoring myocardial damage in cancer patients during treatment. In addition, hybrid imaging protocols are increasingly being implemented in clinical workflows, as they provide complementary data from multiple sources in a single examination. Digital health care is an ever-increasing area of development. **Martin R. Cowie**, in his article on telemonitoring, presents e-health action plans, as well as digital advancements in mobile health, personalized health, implantable hemodynamic monitors, and ultrasound technologies. As a complement to the article by Cowie, **Gerd Hasenfuß** shows that digital medicine will influence future heart failure care and research, as patient self-measurements will not only be useful in supporting treatment adherence and lifestyle modifications, but will also be useful in providing the patient with relevant treatment recommendations. Finally, there is little point in making these huge advances if there are insufficient doctors and heart failure nurses to implement the latest treatments and technologies appropriately and successfully. Appropriate training is essential, and, as **Pascal Guéret** highlights, this training can be facilitated by simulation-based technology.

The implementation of these advances in heart failure treatment, monitoring, and technology in daily practice is not as simple as waving a magic wand, but rather, requires data from trials, registries, and meta-analyses. This information, in turn, is analyzed thoroughly and presented in the guidelines. This year's HFA congress did not disappoint, as our authors have demonstrated with their exciting recaps of the congress. **Andrew J. S. Coats** presents the results of late-breaking clinical trials. In addition to the article by Coats, **Petar M. Seferovic** provides an update on data from late-breaking clinical trials and the debates surrounding the pros and cons of certain trial results. The new HFA consensus definition of advanced heart failure was discussed by two articles—one by

Marisa G. Crespo-Leiro and one by Francesco Orso and Aldo P. Maggioni. Yuri M. Lopatin presents a new initiative called the European heart failure ATLAS, an initiative that will help realize the HFA mission to improve the quality of life and longevity of patients with heart failure.

We hope you enjoy reading this issue of *Dialogues in Cardiovascular Medicine*. ■

ROBERTO FERRARI & KIM FOX

Heart Failure
Snapshot of the Year



HEART FAILURE SNAPSHOT OF THE YEAR

ROBERTO FERRARI, MD, PhD, AND KIM FOX, MD, FRCP

These articles were taken from the European Heart Journal and the Journal of the American College of Cardiology between May 1, 2017 and April 30, 2018. All research articles on heart failure were included; reviews and guidelines were excluded.

MAY 2017

Carr H, Cnattingius S, Granath F, Ludvigsson JF, Edstedt Bonamy AK. Preterm birth and risk of heart failure up to early adulthood. *J Am Coll Cardiol.* 2017;69(21):2634-2642.

This register-based cohort study showed that preterm birth (<32 weeks) was strongly associated with heart failure in childhood and young adulthood. Although the absolute risk of heart failure is low at these ages, the findings indicate that preterm birth may be a previously unknown risk factor for heart failure.

Desai AS, Bhimaraj A, Bharmi R, et al. Ambulatory hemodynamic monitoring reduces heart failure hospitalizations in “real-world” clinical practice. *J Am Coll Cardiol.* 2017;69(19):2357-2365.

The CHAMPION trial showed that heart failure hospitalization rates and comprehensive heart failure costs are lower in patients with an implantable pulmonary artery pressure sensor compared with usual care.

Hall PS, Nah G, Howard BV, et al. Reproductive factors and incidence of heart failure hospitalization in the women’s health initiative. *J Am Coll Cardiol.* 2017;69(20):2517-2526.

Postmenopausal women who had a shorter total reproductive duration had a higher risk of incident heart failure, whereas nulliparous women had a higher risk for incident heart failure with preserved ejection fraction.

JUNE 2017

Dondo TB, Hall M, West RM, et al. β -Blockers and mortality after acute myocardial infarction in patients without heart failure or ventricular dysfunction. *J Am Coll Cardiol.* 2017;69(22):2710-2720.

Among survivors of hospitalization for an acute myocardial infarction who did not have heart failure or left ventricular systolic dysfunction, β -blockers did not lower the risk of death at any point in 1 year.

Greene SJ, Hernandez AF, Dunning A, et al. Hospitalization for recently diagnosed versus worsening chronic heart failure: from the ASCEND-HF trial. *J Am Coll Cardiol.* 2017;69(25):3029-3039.

The ASCEND-HF trial showed that there was a greater dyspnea relief and an improved postdischarge survival for patients when the diagnosis of heart failure was made ≤ 1 month before hospitalization than for patients with chronic heart failure.

Kotecha D, Flather MD, Altman DG, et al; Beta-Blockers in Heart Failure Collaborative Group. Heart rate and rhythm and the benefit of beta-blockers in patients with heart failure. *J Am Coll Cardiol.* 2017;69(24):2885-2896.

The Beta-Blockers in Heart Failure Collaborative Group showed that, in patients with heart failure with reduced ejection fraction and in sinus rhythm, β -blockers reduce mortality regardless of the patients’ pretreatment heart rate.

Matsue Y, Damman K, Voors AA, et al. Time-to-furosemide treatment and mortality in patients hospitalized with acute heart failure. *J Am Coll Cardiol.* 2017;69(25):3042-3051.

The REALITY-AHF trial showed that an early treatment with intravenous loop diuretics was associated with lower in-hospital mortality in patients presenting to the emergency department with acute heart failure.

Ouwkerk W, Voors AA, Anker SD, et al. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. *Eur Heart J.* 2017;38(24):1883-1890.

The BIostat-CHF study showed that, in patients with heart failure with reduced ejection fraction, only 22% and 12% achieved the recommended treatment dose for angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and β -blockers, respectively.

JULY 2017

Farris SD, Don C, Helterline D, et al. Cell-specific pathways supporting persistent fibrosis in heart failure. *J Am Coll Cardiol.* 2017;70(3):344-354.

Despite robust cardiac unloading, capillary density and fibrosis are unchanged in myocardium obtained from patients with end-stage heart failure compared with loaded hearts. In addition, fibroblast-specific collagen expression was decreased.

Reddy YNV, Andersen MJ, Obokata M, et al. Arterial stiffening with exercise in patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol.* 2017;70(2):136-148.

Abnormal pulsatile aortic loading during exercise occurs in patients with heart failure with preserved ejection fraction in-

dependent of hypertension. Inorganic nitrite mitigates arterial stiffening with exercise and improves hemodynamics.

Rogers JG, Patel CB, Mentz RJ, et al. Palliative care in heart failure: the PAL-HF randomized, controlled clinical trial. *J Am Coll Cardiol.* 2017;70(3):331-341.

The PAL-HF trial showed that, in advanced heart failure, an interdisciplinary palliative care intervention provided greater benefits in quality of life, anxiety, depression, and spiritual well-being compared with usual care alone.

AUGUST 2017

Morgan JM, Kitt S, Gill J, et al. Remote management of heart failure using implantable electronic devices. *Eur Heart J.* 2017;38(30):2352-2360.

Among patients with heart failure and an implanted cardiac electronic device, remote monitoring using weekly downloads and a formalized follow-up approach did not improve outcomes.

Pang PS, Butler J, Collins SP, et al. Biased ligand of the angiotensin II type 1 receptor in patients with acute heart failure: a randomized, double-blind, placebo-controlled, phase IIB, dose ranging trial (BLAST-AHF). *Eur Heart J.* 2017;38(30):2364-2373.

The BLAST-AHF trial showed that TRV027, a novel "biased" ligand of the angiotensin II type 1 receptor that selectively antagonizes the negative effects of angiotensin II, did not improve clinical status through the 30-day follow-up vs placebo.

Scuffham PA, Ball J, Horowitz JD, et al; WHICH? II Trial Investigators. Standard vs. intensified management of heart failure to reduce healthcare costs: results of a mul-

ticentre, randomized controlled trial. *Eur Heart J.* 2017;38(30):2340-2348.

During a 12-month follow-up, the WHICH? II trial showed that an intensified heart failure management program (INT-HF-MP) based on individual profiling did not reduce health care costs or improve health outcomes vs standard heart failure management.

Travers JG, Kamal FA, Valiente-Alandi I, et al. Pharmacological and activated fibroblast targeting of Gβγ-grk2 after myocardial ischemia attenuates heart failure progression. *J Am Coll Cardiol.* 2017;70(8):958-971.

Inhibition of the small molecule G protein βγ-G protein-coupled receptor kinase 2 (Gβγ-GRK2) was cardioprotective in the ischemia/reperfusion model of chronic heart failure, which included the preservation of cardiac contractility and reduction in cardiac fibrotic remodeling. In addition, Gβγ-GRK2 inhibition significantly attenuated the activation characteristics of failing human cardiac fibroblasts isolated from patients with end-stage heart failure.

Zittermann A, Ernst JB, Prokop S, et al. Effect of vitamin D on all-cause mortality in heart failure (EVITA): a 3-year randomized clinical trial with 4000 IU vitamin D daily. *Eur Heart J.* 2017;38(29):2279-2286.

In patients with advanced heart failure, a daily vitamin D dose of 4000 IU did not reduce mortality, but it was associated with a greater need for mechanical circulatory support implants.

SEPTEMBER 2017

Bonnet D, Berger F, Jokinen E, Kantor PF, Daubeney PEF. Ivabradine in children with dilated cardiomyopathy and symptomatic chronic heart failure. *J Am Coll Cardiol.* 2017;70(10):1262-1272.

In children with chronic heart failure and dilated cardiomyopathy, ivabradine safely reduced the resting heart rate. In addition, ivabradine improved left ventricular ejection fraction, and it showed favorable trends in improving clinical status and quality of life.

Emdin M, Mirizzi G, Giannoni A, et al. Prognostic significance of central apneas throughout a 24-hour period in patients with heart failure. *J Am Coll Cardiol.* 2017;70(11):1351-1364.

In patients with systolic heart failure, central apneas occurred throughout a 24-hour period, which were associated with a neurohormonal activation, ventricular arrhythmic burden, and a worse prognosis.

OCTOBER 2017

Aldahl M, Jensen AC, Davidsen L, et al. Associations of serum potassium levels with mortality in chronic heart failure patients. *Eur Heart J.* 2017;38(38):2890-2896.

Among patients with chronic heart failure, serum potassium levels within the lower and upper levels of the normal range (3.5-4.1 mmol/L and 4.8-5.0 mmol/L, respectively) were associated with a significant increase in short-term risk of death, as were potassium levels below 3.5 mmol/L and above 5.0 mmol/L.

Bayes-Genis A, Núñez J, Zannad F, et al. The PCSK9-LDL receptor axis and outcomes in heart failure: BIostat-CHF subanalysis. *J Am Coll Cardiol.* 2017;70(17):2128-2136.

The BIostat-CHF study showed that, in patients with worsening HF signs and/or symptoms, there was a positive linear association between proprotein convertase subtilisin/kexin type 9 levels and the risk of mortality and a negative association between low-density lipoprotein receptor and the risk of mortality.

Chen S, Dykes JC, McElhinney DB, et al. Haemodynamic profiles of children with end-stage heart failure. *Eur Heart J*. 2017;38(38):2900-2909.

In children <18 years old with end-stage heart failure, congestion was more common than low cardiac output, which correlates with New York Heart Association/Ross classification and end-organ dysfunction. Children with both congestion and low cardiac output have the highest risk of death or clinical deterioration.

Givertz MM, Stevenson LW, Costanzo MR, et al; CHAMPION Trial Investigators. Pulmonary artery pressure-guided management of patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol*. 2017;70(15):1875-1886.

The CHAMPION trial showed that pulmonary artery pressure-guided heart failure management reduces morbidity and mortality in patients with heart failure and reduced ejection fraction on guideline-directed medical therapy.

Lam PH, Dooley DJ, Deedwania P, et al. Heart rate and outcomes in hospitalized patients with heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2017;70(15):1861-1871.

Among the hospitalized patients with heart failure with preserved ejection fraction (ejection fraction $\geq 50\%$) in the OPTIMIZE-HF registry, a lower discharge heart rate was independently associated with a lower risk of all-cause mortality, but not readmission.

Polhemus DJ, Trivedi RK, Gao J, et al. Renal sympathetic denervation protects the failing heart via inhibition of neprilysin activity in the kidney. *J Am Coll Cardiol*. 2017;70(17):2139-2153.

This study shows that radiofrequency renal nerve denervation attenuates renal neprilysin activity, augments circulating natriuretic peptide levels, reduces myocardial fibrosis, and improves left ventricular function in the setting of heart failure.

Watanabe S, Ishikawa K, Fish K, et al. Protein phosphatase inhibitor-1 gene therapy in a swine model of nonischemic heart failure. *J Am Coll Cardiol*. 2017;70(14):1744-1756.

By inducing severe mitral regurgitation, Yorkshire swine developed volume-overload heart failure as evidenced by increased left ventricular end-diastolic pressure and left ventricular volume indexes. Intracoronary delivery of BNP116.I-1c, a reengineered adeno-associated viral vector carrying I-1c, was shown to be safe, and it improved both left ventricular and left atrial ejection fractions.

NOVEMBER 2017

Mogensen UM, Jhund PS, Abraham WT, et al; PARADIGM-HF and ATMOSPHERE Investigators and Committees. Type of atrial fibrillation and outcomes in patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol*. 2017;70(20):2490-2500.

Among patients with heart failure who have a history of atrial fibrillation, those with paroxysmal atrial fibrillation were at a greater risk of heart failure hospitalization and stroke than were patients with persistent or permanent atrial fibrillation.

Shah KS, Xu H, Matsouaka RA, et al. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. *J Am Coll Cardiol*. 2017;70(20):2476-2486.

Patients hospitalized with heart failure, regardless of the ejection fraction (ie, reduced, midrange, or preserved), have a similarly poor 5-year survival with an elevated risk of cardiovascular and heart failure hospital admissions.

van Vark LC, Lesman-Leegte I, Baart SJ, et al; TRIUMPH Investigators. Prognostic value of serial ST2 measurements in patients with acute heart failure. *J Am Coll Cardiol*. 2017;70(19):2378-2388.

The TRIUMPH study showed that repeated ST2 measurements appeared to be a strong predictor of outcome in patients with acute heart failure, independent of repeatedly measured N-terminal pro-brain natriuretic peptide levels.

DECEMBER 2017

Tsujimoto T, Kajio H. Abdominal obesity is associated with an increased risk of all-cause mortality in patients with HFpEF. *J Am Coll Cardiol*. 2017;70(22):2739-2749.

Data from the TOPCAT study showed that the risk of all-cause mortality was significantly higher in patients with heart failure with preserved ejection fraction and abdominal obesity than in those without abdominal obesity.

JANUARY 2018

Cleland JGF, Bunting KV, Flather MD, et al; Beta-blockers in Heart Failure Collaborative Group. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J*. 2018;39(1):26-35.

β -Blockers improved the left ventricular ejection fraction and prognosis for patients with heart failure in sinus rhythm with a reduced left ventricular ejection fraction. While the data are strongest for patients with a left ventricular ejection fraction <40%, similar benefits were observed in the subgroup of patients with a left ventricular ejection fraction between 40% and 49%.

Goliasch G, Bartko PE, Pavo N, et al. Refining the prognostic impact of functional mitral regurgitation in chronic heart failure. *Eur Heart J*. 2018;39(1):39-46.

This long-term observational study demonstrates the prognostic significance of functional mitral regurgitation, showing an increasing prevalence of functional mitral regurgitation with increasing severity of heart failure in a patient cohort under optimal medical therapy.

Nägele MP, Barthelmes J, Ludovici V, et al. Retinal microvascular dysfunction in heart failure. *Eur Heart J*. 2018;39(1):47-56.

Patients with compensated chronic heart failure have impaired retinal microvascular dilatation in response to flicker light; however, retinal vessel analysis, may be a new and noninvasive method to monitor microvascular abnormalities without using radiation.

Ouwerkerk W, Zwinderman AH, Ng LL, et al. Biomarker-guided versus guideline-based treatment of patients with heart failure: results from BIOSTAT-CHF. *J Am Coll Cardiol*. 2018;71(4):386-398.

The BIOSTAT-CHF study showed that the use of biomarker values to determine which patients should receive an uptitration of the guideline-recommended heart failure treatments might result in fewer deaths or hospitalizations.

Qureshi WT, Zhang ZM, Chang PP, et al. Silent myocardial infarction and long-term risk of heart failure: the ARIC study. *J Am Coll Cardiol*. 2018;71(1):1-8.

This analysis of the ARIC study showed that a silent myocardial infarction was associated with an increased risk of heart failure.

FEBRUARY 2018

Fitchett D, Butler J, van de Borne P, et al; EMPA-REG OUTCOME Trial Investigators. Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME® trial. *Eur Heart J.* 2018;39(5):363-370.

Many patients with type 2 diabetes and established cardiovascular disease, but no heart failure at baseline, have a high or very high risk of heart failure outcomes. The EMPA-REG OUTCOME® trial showed that empagliflozin consistently improved heart failure outcomes both in patients with either a low or a high risk of heart failure.

Sano S, Oshima K, Wang Y, et al. Tet2-mediated clonal hematopoiesis accelerates heart failure through a mechanism involving the IL-1 β /NLRP3 inflammasome. *J Am Coll Cardiol.* 2018;71(8):875-886.

In murine models of heart failure, a deficiency in the epigenetic regulator TET2 in hematopoietic cells is associated with greater cardiac dysfunction due to an elevation in IL-1 β signaling, suggesting that individuals with TET2-mediated clonal hematopoiesis may be at a greater risk of developing heart failure and may respond better to IL-1 β -NLRP3 inflammasome inhibition.

MARCH 2018

Taqueti VR, Solomon SD, Shah AM, et al. Coronary microvascular dysfunction and future risk of heart failure with

preserved ejection fraction. *Eur Heart J.* 2018;39(10):840-849.

In patients undergoing evaluation for suspected coronary artery disease, impaired coronary flow reserve was independently associated with diastolic dysfunction and adverse events, especially hospitalization for patients with heart failure with preserved ejection fraction (HFPEF). Patients with both coronary microvascular and diastolic dysfunctions had a markedly higher risk of HFPEF events.

Tayal B, Gorgsan J 3rd, Bax JJ, et al. Cardiac resynchronization therapy in patients with heart failure and narrow QRS complexes. *J Am Coll Cardiol.* 2018;71(12):1325-1333.

In patients with a narrow QRS treated with cardiac resynchronization therapy who were enrolled in the EchoCRT trial, an absence of delayed mechanical activation by cross correlation analysis using tissue Doppler imaging was significantly associated with poor outcomes.

APRIL 2018

Selvaraj S, Bhatt DL, Claggett B, et al. Lack of association between heart failure and incident cancer. *J Am Coll Cardiol.* 2018;71(14):1501-1510.

An analysis of a cohort of patients from the Physicians' Health Studies I and II showed that there was no association between heart failure and either site-specific cancer incidence or cancer-specific mortality after multivariable adjustment. ■

Advances in
Technology



NOVEL IMAGING TECHNIQUES FOR HEART FAILURE

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Keywords: cardiovascular imaging; diastolic stress test; heart failure; hybrid imaging; myocardial strain

STRAIN IS BECOMING A MANDATORY MARKER OF MYOCARDIAL PERFORMANCE

The value of LVEF is markedly overrated among practitioners, despite the fact that this marker of volume change is useless for half of the patients with HF and hypertrophic remodeling.¹ The inability to increase cardiac output during exercise has been observed across all types of HF regardless of the LV volume. LVEF should not be erroneously interpreted as a measure of myocardial contractility or exercise tolerance, but rather should be used for the estimation of stroke volume. Like most echocardiographic parameters, LVEF is load dependent; an interobserver variability of up to 10% has been reported.²

Deformation imaging helps detect impairment in myocardial mechanics across the entire spectrum of LVEF. In the HFPEF population of the RELAX trial, the median global longitudinal strain was -14.6% (25th percentile, -17.0%; 75th percentile, -11.9%). Patients in the tertile with the worst myocardial deformation had significantly higher levels of N-terminal pro-brain natriuretic peptide and collagen III N-terminal propeptide compared with the tertile with the best global longitudinal strain.³

Global longitudinal strain has demonstrated superior reproducibility, precision,⁴⁻⁶ and sensitivity for the early diagnosis of subclinical ventricular dysfunction compared with LVEF.⁷ Monitoring patients during cytotoxic cancer treatment is one of the areas demanding a sensitive imaging tool for the timely detection of myocardial damage and possible pharmacological intervention. According to a growing body of evidence, global myocardial longitudinal strain seems to be superior to the marker of volume change for this purpose.⁸ In 52 women with breast cancer, global longitudinal strain decreased from -17.7 to -16.3% ($P < 0.01$) with 48% of the global measurements reduced by >10% after chemotherapy; meanwhile, no reduction in LVEF >10% was observed.⁹ A more recent study of 100 consecutive patients with breast cancer demonstrated that anthracycline treatment significantly reduced longitudinal, circumferential, radial, and area strain, which was not the case for two-dimensional LVEF.¹⁰ The position paper of the ESC on cancer treatment and cardiovascular toxicity suggests that a relative reduction >15% in global longitudinal strain should be used as a marker of cardiotoxicity.¹¹ In a single-center series

of 86 patients with Hodgkin disease, non-Hodgkin lymphoma, or acute leukemia, a global longitudinal strain $>-17.5\%$ obtained after 150 mg/m^2 of anthracycline therapy showed a high specificity for predicting future anthracycline-induced cardiotoxicity.¹² The ongoing SUCCOUR trial is testing whether global longitudinal strain can be used to guide the initiation of cardioprotective therapy and improve clinical outcomes.¹³

Global longitudinal strain, a robust parameter of myocardial shortening from base to apex, showed a stronger association with adverse events than did LVEF. The additive value of global longitudinal strain for the outcome prognostication was particularly important in the group of patients with an LVEF $>35\%$, as demonstrated in the large cohort of consecutive patients undergoing echocardiography.¹⁴ In this study, a global longitudinal strain $\geq-12\%$ was equivalent to an LVEF $\leq 35\%$ for predicting prognosis. Notably, LV systolic dysfunction, which was determined using a global longitudinal strain cut-off of -14.7% , appeared to be a powerful and independent predictor of cardiovascular events in patients with a normal LVEF in the community-based prospective Northern Manhattan Study.¹⁵ The prevalence of an abnormal LVEF in this cohort was 4.2% , whereas the prevalence of an impaired global longitudinal strain in patients with a normal LVEF was 16.8% (mean LVEF, 63.7% ; mean global longitudinal strain, -12.8%).

In a large cohort ($n=4172$) of patients with acute HF,¹⁶ the mean global longitudinal strain was 10.8% . Each 1% increase in global longitudinal strain was associated with a 5% decreased risk for mortality. Given that the prognostic value of global longitudinal strain is greater than that of LVEF, the authors consider that global longitudinal strain should become the standard measurement in all patients with HF. A recently performed comparison of segmental strain measurements between 7 different systems and 2 independent software packages showed a substantial test-retest and inter-vendor variability, suggesting that, for clinical decision-making, more reliance should be placed on analyzing the segmental strain curve shape and regional pattern.⁷ A novel attractive possibility is to perform a simultaneous assessment of longitudinal strain in all four cardiac chambers in the same cardiac cycle.¹⁷ The imaging of left atrial deformation provides insights into three components of left atrial function: reservoir, conduit, and booster pump, which are related to left atrial stiffness.¹⁸ Speckle tracking modality is also being intensively examined to characterize right ventricular and right atrial failure.

DIASTOLIC STRESS TESTING TO DIAGNOSE HFPEF

The differential diagnosis of HFPEF remains a challenge in daily clinical practice. A recent invasive echocardiographic study showed that, at rest, the current guidelines criteria,¹⁹ although specific, have poor sensitivity (34% to 60%).²⁰ Many ambulatory patients with HFPEF present with normal LV filling pressure at rest;

moreover, normal resting E/e' does not exclude an elevated filling pressure when measured invasively. Therefore, according to the disease pathophysiology, it is recommended to utilize a stress test to demonstrate an inadequate rise of LV filling pressure during exercise. The gold standard would be an invasive exercise testing; however, this test requires special expertise and equipment and it poses an increased risk to the patient. Using an exercise echocardiography threshold for stress $E/e' >14$ increased the sensitivity of the HFPEF diagnosis up to 90%, but decreased the specificity, suggesting that the major value of ultrasound diastolic stress test is for ruling out HFPEF in patients with unexplained dyspnea. It seems most useful to employ this kind of examination in patients with an intermediate pretest probability of the disease.

HYBRID IMAGING IDENTIFIES THE MORPHOLOGY AND PATHOGENIC PROCESS

In the last few years, hybrid imaging protocols have been increasingly implemented in clinical workflows, providing complementary data from multiple modalities in a single examination. Surprisingly, only 17.5% of patients with new-onset HF undergo a diagnostic workflow for obstructive coronary artery disease.²¹ The EVINCI study showed that matched cases of hybrid imaging of computed tomography/myocardial perfusion imaging improved specificity and accuracy vs single modalities.²² A unique advantage of hybrid imaging is a more reliable individual allocation of hypoperfused myocardial segments to the culprit coronary arteries. Physiological or molecular processes, such as apoptosis, necrosis, fibrosis, and inflammation, can be targeted with novel radiotracers, given suitable uptake in the area of interest. Hybrid ^{18}F -FDG PET/MRI imaging has promise for the diagnosis of active cardiac sarcoidosis, providing incremental information about both the pattern of injury and disease activity in a single scan.²³ Combining late gadolinium enhancement with ^{18}F -FDG uptake helps identify patients with active disease who are likely to benefit from anti-inflammatory therapy.

A multi-imaging approach incorporating CT and PET scans demonstrated an excellent sensitivity in diagnosing infective endocarditis after transcatheter valve replacement by precisely identifying abscesses, pseudoaneurysms, fistulae, vegetations and leaflet thickening, and ^{18}F -FDG uptake on the valve.²⁴ A recent meta-analysis of 11 single-center studies with a pooled number of 331 patients showed high accuracy (AUC 0.952) with ^{18}F -FDG PET/CT imaging for the diagnosis of cardiac electronic device infections.²⁵ In patients with continuous-flow LV assist devices, a series of 61 quantitative ^{18}F -FDG PET/CT examinations demonstrated optimal discriminator power in detecting superficial and deep driveline infections.²⁶

A completely novel concept integrates echocardiography with computed tomography for grading of mitral regurgitation.²⁷ An integrated parameter of mitral regurgitant volume was developed that combines the true largest cross-sectional

mitral regurgitant orifice area assessed with 320-slice multidetector computed tomography using planimetry with flow data from echocardiography. A significant reclassification of the severity of mitral regurgitation (both upgraded and downgraded) was achieved. ■

Conflicts of interest: The author has received honoraria from Novartis, Servier, Orivas, and a research grant from NordForsk.

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TELEMONITORING TECHNOLOGIES AND NOVEL DEVICES IN HEART FAILURE

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Keywords: health care technology; m-health; p-health

Two sessions at the 2018 HFA meeting in Vienna, Austria were focused on emerging imaging and monitoring technologies for heart failure. Such technologies hold the promise of not only speeding up the diagnosis of heart failure, but also improving the long-term management of the syndrome. This promise must be seen within the context of a rapidly aging population, with more comorbidities, limited health care budgets and fixed numbers of health care professionals, and politicians who view digital technologies as the answer to delivering more and better care at a lower cost. It is not only health care professionals who struggle to keep up with the technological advances or the legal and data privacy issues, but also the policy makers, regulators, and reimbursement authorities are finding it difficult to navigate through the rapid changes that are taking place. However, the European Commission is fully behind the digital “transformation,” believing it will empower citizens and build a healthier society. On April 25, 2018, the European Commission issued a communication on further enabling such transformation in the Digital Single Market,¹ building on its earlier e-health action plans.²

Safe, rapid, and secure data transfer from a patient to a health care professional is the key to maximizing the value of digital technologies. The increasing connectedness of technologies (including the “internet of things”) and the ability to store and access data from anywhere (“the cloud”) are vital to the success of many digital developments. The introduction of a new data protection law in the European Union on May 25, 2018, the most important tightening of previous legislation in over 20 years, may have serious consequences for digital technologies. The European Society of Cardiology has recognized the need for cardiologists to become more involved in the stakeholder discussions about digital transformation/disruption, and it has set up a Digital Committee to help catalyze activity across the Society and its associations in terms of education, teaching, research, and advocacy. It is my great pleasure to chair this committee. Please look out for new initiatives, including the likely launch of a new virtual multimedia journal on Digital Cardiology and a stand-alone Digital Health meeting in 2019.

MOBILE HEALTH

m-Health (mobile health) is an area of huge interest to policy makers, citizens, and health care professionals. Dr Koehler (Berlin, Germany), a world leader in remote monitoring of patients with heart failure using nonimplantable technologies, briefly reviewed the many apps now available for heart failure. These apps range from relatively simple educational tools to medication reminders to apps that can connect via Bluetooth™ (and other such technologies) to blood pressure machines and weighing scales. With the aid of decision-support software, patients can be assisted to make better and more informed choices about their lifestyle and diuretic doses. Such apps can send data directly to a nominated health care professional or the patient can choose to send a data download at a specific point in time. Regulatory oversight and reimbursement decisions are struggling to cope with this rapidly developing field.

PERSONALIZED HEALTH

Dr Amir (Poria, Israel) educated the audience about the exciting area of wearable technologies (sometimes called p-health or personalized health). Many of us are already aware of various watch-like devices (such as FitBit™ or JawBone™) that can collect information on heart rate, activity, and position/location. Wearable fabric can have circuitry sewn into it that can collect information on a range of physiological variables, such as temperature, sodium content, physical activity, and position. New imaging and auditory technologies can collect information that may indicate deterioration in patients with heart failure merely from the sound of a patient's voice or the variation in skin temperature on the face. Connecting all of the data sources together is now straightforward, and it is possible to access the data from anywhere in the world. The difficult thing is managing the potential "tsunami" of data, and making sense out of all of the noise in the signals. Integrating new data flows into our current models or pathways of care is not straightforward, and this issue was discussed frequently at the conference.

ULTRASOUND AND HEART FAILURE

Ultrasound has long been used to image the heart and vascular system; it is central to the diagnosis of heart failure. Dr Stankovic (Belgrade, Serbia) reminded us of the recent guidelines that suggest using a shorter, more focused echocardiographic examination (possibly with an ultrasound probe that can be connected to a smartphone) in settings where a full echocardiographic examination may be difficult or often delayed, such as in the emergency room.³ With appropriate training of the operator and education around the limits of such an examination, this technique shows promise in increasing the speed of detection of serious underlying cardiovascular pathologies, particularly outside the usual working hours of an echocardiographic laboratory.

Dr Platz (Brookline, MA, US) reviewed the value of an ultrasound in the detection of pulmonary congestion. B-lines can be used to determine whether a patient's breathlessness is likely to be cardiac in origin, and it can be used to monitor the degree of decongestion that is occurring during hospitalization.⁴ The latter may be of considerable value, particularly as there is evidence that many patients leave the hospital still in a congested state, with the consequent risk of early readmission for worsening symptoms.

IMPLANTABLE HEMODYNAMIC MONITORS

Dr Abraham (Columbus, OH, US) updated the conference on the real-world evidence that physicians can use data from the implantable CardioMEMS™ system to manage pulmonary artery pressure, driving this down with greater use of diuretics or vasodilators, but also “backing off” treatment if pressures dive too low. Surprisingly, in day-to-day practice, physicians and their teams appear to manage pulmonary artery pressure more effectively than they did in the randomized CHAMPION trial, which may explain the very positive real-world reports of a substantially decreased risk of hospitalization in such patients.⁵ Other implantable hemodynamic monitors are being developed and assessed in trials, but are not yet ready for day-to-day practice. Other approaches that use multiparametric monitoring of cardiac implantable electronic devices (such as CRT-D or ICD systems) were also discussed at the conference, with one example being the HeartLogic™ system, which is currently being examined in the MANAGE-HF trial, an FDA-approved randomized trial (NCT03237858).

CONCLUDING REMARKS

The challenge for health care professionals is to keep up with the high speed of innovation in the digital space. Many approaches will fail to find a use or be too cumbersome to be practical, but many technologies will be potentially useful, be popular with patients and their families, and be integrated into self-monitoring, self-management, and more traditional health care practices. It is clear that the role of a cardiologist will change rapidly in the coming decades. Technology, rather than disrupting care in a destructive way, is likely to support evolutionary change and improvement, allowing patients and their families to access expertise remotely. Citizens will no longer be limited by their geography, rather modern information and communication technology, coupled with better sensors and decision-support systems, should enable us to improve the outcome and experience of the care of patients with heart failure across the world. Undoubtedly, we will make mistakes, but now is a very exciting time for health care.

The ESC plans to be firmly at the center of all of these creative tensions, making sure cardiologists and other health care professionals are part of the conversation

in society about digital “transformation.” We, as a professional community, require evidence that technologies improve the outcome or experience of care and are safe, but once convinced, we move quickly, within the relevant privacy and legal constraints. Reimbursement is often the thing that is lacking, but it can be used as a tool to foster innovation and implementation and discourage us from doing what does not work.

Finally, do come and see the Digital Area at the European Society of Cardiology meeting in Munich, Germany in August 2018. You will be sure to see even more examples of technologies that may change the way we practice cardiology in the near future.⁶ ■

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SIMULATION-BASED TRAINING FOR CARDIOLOGISTS

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Keywords: patient simulator; procedure simulator; simulation training

There are numerous different teaching methods used for simulation training, but they ultimately all come under the general principle of “never for the first time on the patient” or, more accurately, “never for the first times on the patient” because it usually takes more than a single attempt to master a procedure or process. Therefore, this form of training has an ethical dimension. Nevertheless, its state of development varies greatly from one country to another, and even between medical specialties. How is it being used for cardiologists in 2018?

LIMITATIONS OF TRADITIONAL TEACHING METHODS

Medical training (for doctors, nurses, dentists, physiotherapists, psychologists, radiologic technicians, etc) usually involves some form of mentoring. The more experienced practitioner teaches the student by showing him or her how to perform a particular procedure. These “procedures” come in a wide range of forms, such as a simple or complex technical intervention, ranging from intramuscular injections to highly advanced surgery, but also techniques for bedside manner, such as how to inform family members about a death or give a serious diagnosis. Once the theory has been mastered, the student progresses to practical learning. Having been told about the correct method and learned about the risks and how to avoid them, the day finally comes when a student, without the benefit of any simulation training, must “take the plunge” and perform the procedure for the first time in a real patient. The rate of adverse events and accidents, of varying degrees, whether obvious or hidden, immediate or delayed, depends on several factors, such as the complexity of the procedure, the skills shown by the student, the teaching abilities of the mentor, etc.

REDUCING MEDICAL ERROR

There are several reasons behind the rapid development of simulation methods as teaching tools; for example, the perfectly legitimate aim of reducing adverse events and complications; the rise of a “claims culture” among patients who are nowadays better informed, exposing professionals to complaints and court actions with sometimes serious consequences; and the considerable advances in technology, especially computers. First and foremost, the goal is to reduce medical error and thus improve patient care, but also to reduce costs and thus make the system more efficient in both medical terms and economically.

SIMULATION TRAINING METHODS

Based on the experiences of numerous high-risk professions, such as aeronautics, the merchant navy, the armed forces, and security, a wide range of simulation methods have been developed for the medical sector. Some have not changed much from these original applications, whereas others are more specific to the teaching of medical sciences. However, they all share the same educational pattern, namely the acquisition of knowledge, followed by skills, and finally behaviors and attitudes.

There are many types of simulation. The most common type is the use of manikins. Numerous models have been developed with endless uses designed for doctors and carers, from very simple devices (defibrillators; sites and methods for subcutaneous, intramuscular, or intravenous injections) to the more sophisticated (eg, models that reproduce all clinical signs of shock, including skin color and reaction to treatments). The manikins may replicate only part of the body (forearm, chest, head, and neck for learning orotracheal intubation or tracheotomy, also known as “procedure simulators”) or a whole body (“patient simulators”). Certain models may be entirely computer-controlled (known as “high-fidelity” manikins).

However, simulation training may also involve the use of standardized patients, virtual reality, electronic case studies, serious games (a fun way of approaching serious topics), laboratory animals, cadavers, or even human anatomical specimens, which have been used for a long time in surgical schools.

Every method must be adapted to the aim pursued and the specific situation, in particular depending on whether it is for an emergency setting (eg, cardiac arrest, organ damage, surgery, or incident during coronary angioplasty) or otherwise (announcing a diagnosis). One of the main benefits is the chance to practice in a safe environment because nothing is real, which offers security for the student who can repeatedly practice the techniques in reproducible conditions. This does not mean that the facts, events, technical conditions, and even the sights and sounds cannot be as realistic as possible (eg, reproduction of the noises present in a public location, which could prevent heart sounds or the alarms on monitoring devices from being heard properly). Scenarios should always be based on situations and conditions that are authentic or as real as possible (eg, prehospital care, realistic appearance of natural or artificial tissues used for learning how to suture or remove organs), and those situations should evolve in a way that echoes real life.

PRECISE TEACHING METHODS

The development of a simulation program is a rigorous process and must go through each of the following stages: (i) identify the educational goals and topics of the program; (ii) consider available techniques and select which resources are best for

achieving the chosen goal; and (iii) then implement the program in three successive stages of “briefing” (presentation of the context, environment, equipment used), “action” (the scenario is played out), and “debriefing” (for analyzing and summarizing what occurred), this last step being fairly characteristic of these teaching by simulation methods and an absolutely essential part of simulation training.

Depending on the goals pursued and their content, the training may be provided at simulation centers that usually have the simulators and human resources required, or even in situ at the student’s place of work (eg, at a hospital’s critical care unit). It may also be provided during external simulation workshops, involving role-playing games or animal studies, or even virtual reality software and computer-controlled “serious games.”

TARGET AUDIENCE

What all these different simulation methods have in common is their multidisciplinary and multiprofessional nature: most situations to which a student will be exposed require the involvement of many different health care professionals (usually doctors, surgeons, and nurses, but sometimes psychologists or other specialists) whose roles may be similar (learning how to communicate a treatment-related adverse event) or complementary. Each participant has their own predefined role, for example treating a cardiac arrest, emergency treatment for a complication during an interventional cardiology procedure, such as cardiac tamponade, serious arrhythmia during a stress echocardiography, or withdrawing extracorporeal circulation during cardiac surgery.

Medical simulation training is therefore appropriate for every health care professional at any stage of their career, whether initial training for students or continuing medical education or recertification for professionals.

CONFERENCES, SPECIALIST JOURNALS, AND SIMULATION RESEARCH

There is currently a lot of active research into the field of simulation. Numerous national and international conferences and meetings are held on this topic. Each month, several international journals specializing in simulation publish articles in the field. For example, over the past 10 years, there has been a two-fold increase in the number of articles discussing simulation in the main critical care and anesthesiology journals.

SIMULATION TRAINING FOR CARDIOLOGISTS

However, there are still relatively few programs specifically designed for cardiology training, and this field is definitely lagging behind, especially when compared with critical care and anesthesiology. Some companies are offering specialist ed-

educational tools, such as manikins for teaching transthoracic or transesophageal echocardiography, procedure simulators for interventional cardiology (coronary, structural, or arrhythmias), and serious games for teaching atrial fibrillation, for instance. However, it is also possible to share some of the educational solutions developed by other disciplines, such as how to treat a cardiac arrest or perform cardiopulmonary resuscitation.

CONCLUSIONS

Although on-the-job mentoring still has its uses, simulation offers many advantages, such as increased patient safety, which is the ultimate goal, the ability to repeat the procedure as many times as necessary, the ability to learn from mistakes without the student being held accountable, and the multitude of different interactions between teacher/student. We are therefore talking about a paradigm shift in terms of teaching culture and program content, the way in which that content is incorporated into educational programs, and the variety of methods available. The number of structured programs available for cardiology training is increasing, with multiple applications since students have become very demanding when it comes to this type of learning, and both patients and their families are better informed and are very anxious about the way in which medical procedures are carried out. ■

DIGITAL HEALTH STRATEGIES IN HEART FAILURE

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Keywords: digital clinic; Lab-on-a-chip; mobile health; smartphone; smartwatch

Digital medicine is a topic that has gained tremendous interest over the last couple of years. Various stakeholders have completely different expectations of digital medicine, including improving the quality of health care, compensating for the lack of physicians, improving health care economics, and enabling new research strategies. Digital medicine covers a spectrum ranging from (i) digital clinics, including clinical workflows, big data, and computer-aided diagnostics to (ii) mobile health (telemedicine), including wearable and smartphone-based devices, sensors, Lab-on-a-chip, handheld imaging, and app-based evaluations of medication compliance to (iii) robotics.¹ The importance of digital medicine or e-health for cardiovascular research and patient care has recently be highlighted in a position paper of the European Society of Cardiology.²

This year's Heart Failure Association congress included a number of presentations focusing on e-health in cardiovascular medicine and in heart failure research. Based on these presentations, the present article develops a scenario of how digital medicine may influence heart failure medicine during the coming years, with a particular focus on mobile health.

Mobile health is defined by the application of portable devices to support medicine.¹ Current mobile health strategies include a number of wearable devices specifically designed for recording biophysical data, and mobile data can be collected by conventional smartphone and smartwatches together with specific apps. One such system is the cardio patient monitoring platform (CPMP), which has been developed by Medopad (London, UK) and the Clinic for Cardiology and Pneumology (University of Göttingen, Germany). This system is composed of a smartphone and a smartwatch. The patient enters self-measured data (eg, blood pressure and body weight), confirms medication intake, and enters symptoms into the smartphone. The system measures heart rate and daily steps, and assists the patient in executing a 6-minute walk test. The app-based system ensures transfer of the patient's information via a safe data transfer automatically from the patient's device to the tablet at the site of the physician. Of course, the patient is able to monitor his data. The feasibility of CPMP has been demonstrated, and the system is currently being evaluated for telemonitoring of patients with heart

failure. Moreover, using machine-based learning, a parameter combination will be optimized to predict morbidity/mortality. Accordingly, the system may be used for the care of patients with heart failure and for clinical trials, which may include new surrogate end points.

In the future, other smartphone- and smartwatch-based analyses may be available. Potential smartphone and smartwatch applications for the care of patients with heart failure could include: (i) a patient voice to estimate dyspnea; (ii) an app-based sleep apnea analysis; (iii) app-based analysis of cognitive function; (iv) an app-based electronic stethoscope for artificial intelligence-based patient follow-up; and (v) an app-based evaluation of medication compliance with ingestible sensors.

With improving quality and reliability of heart rhythm analysis through smartphones and smartwatches, arrhythmias will be detected early in patients with a high-risk profile. Considering the broad availability of these devices in the future, atrial fibrillation will no longer go undetected, which would allow for a completely new strategy in the primary prevention of cardioembolic strokes.

Algorithms have to be developed to restrict data transfer to only the data relevant for patient safety and care and to avoid data floods to the telemonitoring centers. An excellent example of sensor-based telemedicine was presented in the CHAMPION trial. Pulmonary artery pressure was detected by a sensor implanted in the pulmonary artery and the data was transmitted wirelessly. The data were used to adjust therapy. The system was evaluated for HFPEF and HFREF, showing an impressive improvement in heart failure hospitalizations.³

A number of apps are available for therapeutic application in depression and neurological/psychiatric disorders. A systematic review and meta-analysis of guided internet-based vs face-to-face cognitive behavior therapy for psychiatric and somatic disorders showed equivalence of the app-based approach to conventional face-to-face practice, suggesting that medication adherence and lifestyle modification interventions may be successfully performed with an app-based telemedicine approach.

For heart failure care, it would also be important to obtain laboratory parameters, such as biomarkers and creatinine and potassium levels, through a telemedicine approach, which is indeed close to clinical realization based on the so-called Lab-on-a-chip. Lab-on-a-chip refers to a device that integrates one or several laboratory functions on a single chip that is only millimeters to a few square centimeters in size. A typical Lab-on-a-chip device contains microchannels, which allow liquid samples to flow inside the chip, and it integrates measuring and sensing. Lab-on-a-chip technology will allow for a patient self-test, where a droplet of blood spread on the chip will be enough for a number of measurements. An

analysis can be done using smartphone technology and transmitted to the physician for evaluation. Moreover, the chips may be small enough for subcutaneous implantation. Lab-on-a-chip exhibits a high sensitivity, and it has recently been shown that this system would allow identification of a single leukemia cell from blood in a high-density microfluidic trapping array.⁴

Lab-on-a-chip technology is developing rapidly, including further miniaturization (minimizing sample volume), new types of sampling and sensing (breathing air, optics) to reduce invasiveness, increased speed to real-time data availability, improved connectivity for telemedicine applications, reduced costs due to advanced manufacturing technology, and improved usability for less skilled people.

CONCLUSIONS

In summary, digital medicine will have a tremendous influence on future heart failure care and research. Patient self-measurements based on portable technologies may represent a core component of heart failure diagnostics, treatment, and research (Figure 1). The patient’s self-measurements will be available for patient interpretation, supporting medication adherence and lifestyle modification. Patient measurements will be transferred via the internet to health care practitioners, heart failure clinics, and heart failure research units. This process will be modified by machine-based learning to control data transfer and prevent health care providers from overwhelming amounts of data for analysis. The health care practitioner interprets the filtered data relevant for patient treatment and gives treatment recommendations to the patient. Also, patient self-measurements will

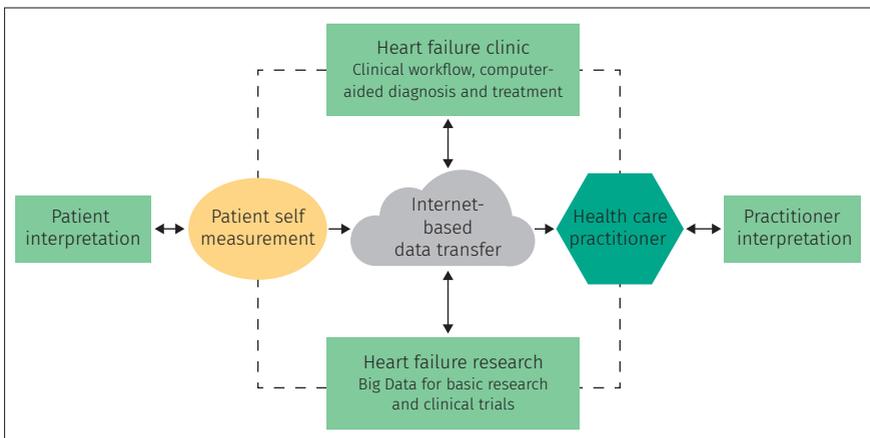


Figure 1. Digital heart failure care and research.

be integrated into clinical workflow systems of heart failure clinics. Computer-aided diagnosis and treatment will be developed and derived from these data. Moreover, in case of patient hospitalization, this information will be available directly. Patient self-measurements will also be available to the heart failure research units. Heart failure research units will use this “big data” for various types of basic research and clinical trials. The realization of this scenario requires a close interaction of patients, engineers, computer specialists, and data protection specialists. No doubt, the tremendous opportunities for heart failure care and research associated with mobile health justify any effort in this direction. ■

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Prevention & Treatment



TIME FOR ELECTROPHYSIOLOGISTS TO MOVE FROM A CASTLE TO A CABANA?

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Keywords: anticoagulation therapy; atrial fibrillation; catheter ablation; heart failure

The annual congress of the Heart Failure Association of the European Society of Cardiology took place in Vienna, Austria from May 26 to 29, 2018. With almost 6000 participants from all over the world, this meeting has now established its name as the premier global forum for cardiology specialists to exchange ideas and keep updated on novel therapeutic approaches to treat HF. During the four days of the congress, several sessions highlighted the importance of aggressively treating comorbid diseases affecting the management and clinical course of HF. In fact, many promising therapeutic strategies for patients with HF involve the treatment of comorbidities, such as obesity, diabetes, and iron deficiency.

This recurring theme set the framework for the intense “Grand Debate” session, which addressed the important and yet unresolved question about whether catheter ablation (ie, pulmonary vein isolation) lowers morbidity and mortality compared with medical therapy in patients with AF and HF. Up to one-third of patients with new-onset AF have HF, and the co-occurrence of AF and HF portends an increased risk of stroke, hospitalization, and death compared with patients with HF without AF. In spite of the well-established overlap between the two conditions, strong evidence supporting a recommendation for either pharmacological or interventional therapy is missing, and studies addressing this gap in knowledge have so far been inconclusive due to the small number of patients enrolled, an open-label design, and high numbers of missing data.²⁻⁴

A CASTLE WITH SHAKY FOUNDATIONS

During the “Grand Debate,” session, Nassir Marrouche (US) spoke in favor of catheter ablation based on the results of the CASTLE-AF⁵ and CABANA trials, whereas the counterpoint was given by Milton Packer (US), who ruthlessly exposed the methodological and analytical flaws of these studies.

In the CASTLE-AF trial, patients with AF, NYHA class II, III, or IV, and HFREF (EF <35%) were randomized to receive either catheter ablation or pharmacological treatment for AF.⁵ In this study, ablation was associated with a significantly lower rate of the primary end point (a composite of death for any cause or HF-related hospitalizations). Given the strength of these end points and the number of patients

enrolled ($n=397$, which is substantially higher than previous studies addressing the same question), these findings support a paradigm shift in favor of catheter ablation in patients with HF with concomitant AF. However, these results should be interpreted cautiously in light of the important limitations of the study. First, the comparison between medical- and device-based therapies is flawed by the study's open-label design. Furthermore, the trial was stopped before reaching its planned enrollment target, which means it was underpowered to test its hypothesis. Finally, a significant number of randomized patients were either excluded from the primary intention-to-treat (ITT) analysis or lost to follow-up, and the vast majority of these patients belonged to the ablation group. Therefore, as pointed out by Packer during the debate, a more careful scrutiny of the trial questions the validity of CASTLE-AF results.

On this basis, a more conclusive answer to this question was expected from the CABANA trial, the results of which were recently presented at the Heart Rhythm Society meeting in Boston, MA, US. The CABANA trial enrolled 2204 patients worldwide; therefore, it is the largest randomized trial conducted so far comparing catheter ablation with drug therapy. In contrast to CASTLE-AF, these patients did not have HF or HFREF as an inclusion criterion. After 5 years of follow-up, an analysis performed according to ITT failed to show a significant impact on the primary outcome of the trial (a composite of death, disabling stroke, serious bleeding, or cardiac arrest) (HR, 0.86; $P=0.3$). However, catheter ablation markedly reduced the risk of hospitalization for cardiovascular causes and AF recurrence. The trial was characterized (as expected) by a high rate of crossover, ie, almost one-third of patients randomized to receive medical therapy eventually underwent catheter ablation. On this basis, a great emphasis was put on the results of the per-protocol analysis, in which patients were not analyzed according to the assigned group, but rather on the treatment that they eventually received. In striking contrast with the ITT analysis, "on-treatment" analysis revealed a substantial advantage (33% risk reduction in the primary end point) of catheter ablation vs pharmacological therapy. The validity of this alternative analysis is questionable, since it has the obvious consequence of altering the integrity of the randomization process, thereby converting a clinical trial into an observational study.

Therefore, in spite of the large number of patients enrolled, the CABANA trial does not provide a conclusive answer to the question of whether catheter ablation has a higher impact on mortality compared with medical therapy, particularly for patients with HF. However, it does provide strong evidence regarding the safety of pulmonary vein isolation and its higher effectiveness in reducing the risk of AF recurrence and HF-related hospitalization compared with anti-arrhythmic drugs, which are burdened by important side effects and a high rate of AF recurrence.

ANTICOAGULATION IN HF WITH AND WITHOUT AF

The co-occurrence of AF and HF is characterized by an increased risk of stroke compared with patients with AF, but not HF. Interestingly, a recent study analyzing the impact of different types of AF in patients with HFREF observed that only patients with new-onset or paroxysmal AF, but not persistent or permanent AF, are subjected to an increased risk of stroke and HF hospitalization.⁷ This finding might explain why catheter ablation did not influence the risk of stroke in the CABANA trial, and suggests that other strategies should be adopted to detect episodes of asymptomatic AF. A viable approach may be represented by the evaluation of the burden of subclinical AF in patients with a cardiac implantable electronic device, who now account for almost 25% of all patients with HF.⁶ In these patients, regular device interrogation may favor the early detection of asymptomatic AF. However, no recommendation exists regarding device interrogation in this setting, and the anticoagulation strategy to be pursued in patients with episodes of AF detected using a cardiac implantable electronic device is still a matter of debate.

Another important observation is that there is no clear temporal relationship between asymptomatic AF and thromboembolic events. In fact, although the duration of episodes of asymptomatic AF is correlated to the risk of stroke, two studies reported that only a minority of patients suffering from a thromboembolic event had a significant AF burden in the 30 days preceding the event.^{7,8} This result suggests that, in this setting, AF may represent a marker for comorbid diseases rather than the mechanism underlying thrombus formation. In addition, HFREF is associated with a hypercoagulable state⁹ and portends a heightened thromboembolic risk, even in the absence of AF. On this basis, several studies have been conducted to assess the efficacy of oral anticoagulants in patients with HF in sinus rhythm, but their results (reviewed in reference 10) have led to the conclusion that anticoagulation therapy improves neither mortality nor vascular events in this group of patients. Recently, however, experimental evidence pinpointed the important role played by thrombin in mediating the cross talk between several procoagulation pathways that may underlie the increased risk of thrombosis in HF.¹¹ This “thrombin hypothesis” provided the rationale for a double-blind, randomized controlled trial (COMMANDER HF) that is investigating the effects of direct thrombin inhibition with rivaroxaban in patients with HF and significant coronary artery disease following an episode of decompensated HF; the rationale and design were presented at the HFA congress.¹²

CONCLUSIONS

In conclusion, several gaps in evidence regarding the role of anticoagulation therapy in patients with HF and asymptomatic AF or without AF remain to be addressed by future studies. ■

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HEART FAILURE WITH PRESERVED EJECTION FRACTION: DILEMMAS AND CURRENT MEDICAL TREATMENTS

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Keywords: cardiovascular outcome; heart rate; HFPEF; HFREF

DILEMMAS

Chronic heart failure is a growing health problem and typically refers to patients with a reduced ejection fraction. In 2001, a report on 38 patients showed that patients can develop signs of acute heart failure in the presence of a normal ejection fraction and “small hearts.”¹ Since then, HFPEF came into focus and it is now appreciated as a serious condition with similar outcomes. About half of the patients with HFPEF are suffering from similar symptoms as those with HFREF.² While the pathophysiological distinction between contractile defects in HFREF and defective filling in HFPEF provides a clear pathophysiological description, the symptoms overlap, which might be partly due to the fact that, in clinical practice, systolic and diastolic dysfunction in both conditions are usually present and rarely occur alone. An intermediate form of heart failure, HFMEF, has been recently defined by the European Society of Cardiology guidelines.³

Since HFPEF can develop into HFMEF and HFREF can improve to HFMEF, it is clear that this whole group of patients with heart failure is quite heterogeneous concerning ventricular mechanics and pathophysiology, which may potentially explain the difference in outcomes and treatment effects.⁴ The diversity in the clinical appearance is further complicated by a high comorbidity burden as well as the high variability in the extent and interindividual distribution in patients with HFPEF.⁵ It might have a large impact on outcomes in these patient populations⁶ by contributing to a high mortality rate, which is not much different from patients with HFREF.⁷ Finally, the cellular mechanisms of HFPEF are incompletely understood and specific cellular targets of disease-modifying therapies need to be clearly defined.

Until now, the heart failure guidelines have clearly stated that no treatments are available to improve morbidity and mortality. The majority of trials have been neutral or inconclusive. Although the pathophysiological rationale was often convincingly raised in experimental studies, showing a reduction in hypertrophy, fibrosis, and heart rate, many of these concepts have failed to show efficacy in clinical trials.

MEDICAL TREATMENTS

ACE inhibitors and AT1 antagonists

The ACE inhibitor perindopril had no effect on outcomes in patients with HFPEF. As AT1 receptors have been shown to mediate maladaptive responses, such as hypertrophy, fibrosis, and finally heart failure, ARBs were evaluated in outcome trials, which showed that they improved diastolic function, reduced myocardial hypertrophy, and improved diastolic dysfunction. The I-PRESERVE trial showed that, in patients with HFPEF, irbesartan neither improved mortality nor hospitalization rates with clearly superimposable Kaplan-Meier curves over 50 months. The CHARM-PRESERVED study showed that candesartan, while it had some effect on hospitalization rates, it had no effect on cardiovascular death. In the VALIDD study, valsartan improved diastolic dysfunction somewhat, which was closely related to blood pressure control. Therefore, due to the lack of outcome data in HFPEF, ACE inhibitors or ARBs are not recommended beyond blood pressure control.³

Mineralocorticoid receptor antagonists

Convincing data show that aldosterone mediates myocardial fibrosis, providing the rationale that fibrosis leading to myocardial stiffness and filling abnormalities might be a target for MRAs. In the ALDO-DHF trial, spironolactone improved diastolic dysfunction (E/e' reduction), decreased left ventricular hypertrophy, and concomitantly reduced NT-proBNP levels, which did not translate into an improvement in exercise tolerance. However, spironolactone had neutral effects on cardiovascular outcomes in the TOPCAT study, which, according to a secondary analysis, might be accounted for by regional differences because, in the American population, there was a reduction in cardiovascular death and cardiovascular hospitalization, but not in Russia and Georgia, where patients were at a much lower risk and most likely were not in heart failure and did not take the drugs properly. The neutral results of TOPCAT might also have been due to a dilution effect of patients not suitable for such treatment. Future studies will try to clarify this uncertainty. The prospective outcome trial SPIRIT-HF in Germany will put particular emphasis on patient characterization and selection. Novel MRAs, such as nonsteroidal aldosterone antagonists, will also be tested.

β -Blockers and ivabradine

High heart rate is associated with an increased outcome risk for patients with HFPEF,⁸ which could only be verified in patients in sinus rhythm, but not in atrial fibrillation. Therefore, β -blockers might maintain sinus rhythm and provide a better heart rate control during exercise in patients with high heart rates. The first evidence was generated in a subgroup analysis of the SENIORS trial. The β -blocker nebivolol had a slight effect on cardiovascular outcomes, but only in the subgroup

with an ejection fraction >40%. The ELANDD study showed that nebivolol reduced heart rate and improved oxygen consumption; however, the NYHA status did not change. Registry data provided some evidence for an improvement in mortality,⁹ while the OPTIMIZE-HF study showed no effect. Therefore, widespread use of β -blockers in HFPEF is not recommended.³ However, class differences, such as that observed with carvedilol, might be present, with carvedilol improving ejection fraction, outcomes, and exercise tolerance in a small underpowered trial.

In patients with HFPEF, reducing heart rate increases the length of diastole and might improve diastolic filling. Animal models show that β -receptor-independent heart rate reduction with the I_f inhibitor ivabradine improves vascular stiffness and left ventricular systolic and diastolic function in a mouse model of HFPEF. However, the EDIFY study showed no difference in E/e' , exercise tolerance, and NT-proBNP levels despite a 30% reduction in heart rate. Thus, reducing heart rate per se does not improve outcomes and provides evidence that the pathophysiological concept of prolonging diastole is not applicable in patients with HFPEF.

Calcium channel blockers

Calcium channel blockers do not improve outcomes regardless of the class. In addition, only small trials have been performed, indicating that they have no role beyond blood pressure control.³

Ranolazine (late sodium current inhibitors)

Ischemia and hypoperfusion are reported to occur in patients with HFPEF¹⁰ and are involved in the pathophysiology of heart failure by worsening the diastolic function and involving the late sodium current. Ranolazine inhibition of this current has been tested in the RALI-DHF study; however, the drug was largely ineffective with neither a decline in NT-proBNP levels nor an improvement in ventricular mechanics.

Cardiac glycosides

A subgroup of the DIG study on 980 patients with an ejection fraction >45% showed a trend toward a reduction in cardiovascular hospitalizations without any other beneficial effects. Therefore, there might be a role for cardiac glycosides, but only for controlling tachyarrhythmias.³

Statins

The GISSI-HF study and the CORONA study did not show a positive effect of statins in patients with heart failure in general. In agreement with meta-analyses, some small studies provided evidence for lower mortality with statins.¹¹ Since statins have not been studied in this particular condition in randomized controlled trials, there is no general recommendation.

NOVEL THERAPIES

Phosphodiesterase-5 inhibitors

The PDE5 inhibitor sildenafil prevents cardiac myocyte remodeling. However, a prospective trial in 216 stable patients with HFPEF failed to detect any improvement in exercise tolerance or clinical status after 24 weeks of treatment. Organic nitrates had no effect on quality of life, but a novel endothelial nitric oxide synthase enhancer (AVE3085) will be studied. However, until now, only experimental data are available.

Soluble guanylyl cyclase stimulators and activators

Phase 2 clinical studies have analyzed vericiguat and riociguat in patients with heart failure. Recently, the SOCRATES-PRESERVED study showed that vericiguat led to a nonsignificant change in NT-proBNP and an improvement in quality of life. Outcome studies are underway.

Sodium glucose cotransporter 2 inhibitors

In the recent EMPEROR outcome study, the SGLT2 inhibitor empagliflozin reduced cardiovascular mortality and, surprisingly, cardiovascular hospitalization (-35%), which was associated with a reduction in all-cause death (-32%). Randomized controlled studies are planned for patients with HFPEF (EMPEROR-HFPEF and EMPEROR-HFREF). Interestingly, these trials will also include patients without diabetes. Myocardial hypertrophy and HFPEF are supposed to be energy depleted due to mitochondrial electron transporter change defects. The mechanisms of SGLT2 inhibition are unclear and under discussion.

Mitochondrial stabilizers

Myocardial energy balance can be restored experimentally with so-called “Szeto-Schiller peptides (SS peptides),” such as elamipretide, which binds to the phospholipid cardiolipin in the mitochondria and stabilizes electron transport and ATP generation. There are favorable experimental data available, but the EMBRACE-STEMI study showed that SS peptides had no effect on infarct size. New results are awaited.

Novel interventions

Atrial septal stent generation, which mimics the Lutembacher syndrome, with atrial shunt devices are promising. However, long-term studies are needed, but are underway. Other techniques, such as renal denervation, cardiac contractility modulation, carotid body ablation, and baroreflex activation, are awaiting controlled studies. One option in heart failure therapy might be exercise and diet, thereby reducing the risk of HFPEF by controlling blood pressure and weight. Performing regular exercise is at the forefront of symptomatic therapies.

WHAT IS LEFT?

Diuretics

In patients with HFPEF, a total volume expansion occurs that is comparable to patients with HFREF; therefore, diuretic treatment as in decompensated HFREF is a cornerstone of symptomatic improvement in patients with HFPEF.³ It was shown that, after optimal treatment with diuretics, the addition of ACE inhibitors or ARBs had no additional effect on quality of life, exercise capacity, or myocardial function. The latter highlights the importance of optimal fluid management in patients with HFPEF. Overtreatment may be a problem because stiff hearts may depend on an adequate filling pressure, which has not been rigorously examined.

SUMMARY

The management of HFPEF is a challenge because no outcome data are available, which should not hamper efforts to develop disease-modifying strategies. Interesting ongoing studies, like those with SGLT2 inhibitors, might improve the medical treatment of heart failure. Device therapy with an atrial left ventricular shunt is promising, but safety needs to be confirmed. The ongoing PARAGON study will improve our knowledge in HFPEF after LCZ696 was tested in the phase 2 PARAMOUNT trial. The results from PARAGON are optimistically awaited. Currently, only symptomatic treatments have been shown to improve quality of life, leaving the field open for interventional techniques that reduce neuroendocrine activation and facilitate ventricular filling by improving diastolic function. Further research is eagerly awaited in order to improve the treatment of the challenging condition of HFPEF. ■

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CANCER TREATMENTS AND CARDIOTOXICITY: HIGHLIGHTS FROM THE 2018 HFA CONGRESS

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Keywords: cancer; cardiotoxicity; chemotherapy; heart failure; immunotherapy

An important translational research topic that has gained a lot of interest in recent years is that of cardio-oncology.¹ Therefore, this year, the 2018 Heart Failure Association congress, including the World Congress on Acute Heart Failure, was held in Vienna from May 26, 2018 until May 29, 2018 and was attended by close to 6000 participants with more than 300 faculty members. Two sessions were solely dedicated to underlying mechanisms and possible new therapies in cardio-oncology. The purpose of the first session was to give practical tips for clinicians on managing cancer patients with possible cardiotoxicity. The second session focused on the mechanisms of cardiotoxicity and the prevalence of cardiac dysfunction in cancer patients.

CARDIOTOXICITY: DETECTION AND TREATMENT

Cardiotoxicity is a great problem in modern-day oncology treatments.¹ Many chemotherapeutic, immune modulating, and targeted therapies can cause cardiotoxicity, which is defined as a decrease in left ventricular ejection fraction by >10 percentage points and below the lower limit of normality.¹ Cardiotoxicity most frequently occurs in patients who are at a high risk of cardiovascular diseases. Teresa López-Fernández (ES), in her congress presentation, identified important risk factors for developing cardiotoxicity: age >65 years or pediatric patients (<18 years), chronic kidney disease, previous radiation therapy, concomitant chemotherapy with other potential cardiotoxic agents, and known cardiovascular disease; hence, it is important to stratify the cardiotoxic risk for cancer patients before initiating chemotherapy treatment.¹ She pointed out that echocardiography is the first choice to detect heart failure and to control patients before, during, and after cancer treatment.¹ Besides a reduction in left ventricular ejection fraction, a relative percentage decrease in global longitudinal strain by >15% from baseline and/or elevated troponin T levels during chemotherapy administration can help identify patients with a greater risk of left ventricular dysfunction.¹ In addition, Cardinale et al² showed that, in 2625 patients with anthracycline chemotherapy, 98% of car-

diotoxicity occurred within the first year of treatment. This result emphasizes that, especially in the first year after the initiation of anticancer therapy, patients should be monitored for cardiac dysfunction. Furthermore, when cardiotoxicity occurred in the aforementioned study,² ACE inhibitor and β -blocker therapy were initiated and uptitrated to the maximum tolerated dose. Under this therapy, 82% of patients had at least a partial recovery of the left ventricular ejection fraction (>50%), but clearly randomized controlled trials are urgently needed to confirm this benefit.

Alain Cohen-Solal (FR) discussed different diagnostic approaches on how to detect early systolic dysfunction and identified troponin T as a biomarker for patients with high-dose anthracycline chemotherapy.³ Patients who had elevated troponin values after initiation of chemotherapy benefited from the implementation of therapy with enalapril.³ Of note, the International CardioOncology Society-one trial (ICOS-ONE),⁴ which was recently published, assessed the benefit of enalapril treatment in 273 adult cancer patients with low cardiovascular risk receiving low cumulative doses of anthracyclines. Patients were randomized to receive enalapril in a preventive strategy before and during chemotherapy administration or only if the troponin levels increased during chemotherapy cycles. Both treatment strategies resulted in similar results concerning the occurrence of cardiotoxicity. The authors therefore concluded that administering enalapril to this low cardiovascular risk group with low-dose anthracycline therapy might be more convenient if only done in patients with elevated troponin levels.

Thomas Suter (CH) discussed other options for preventing cardiotoxicity. In patients with a high risk of cardiotoxicity, nonanthracycline-containing chemotherapy could be an option sometimes. These other agents are often associated with a smaller likelihood of cardiotoxicity.¹ Other options include using concomitant dexrazoxane or a liposomal doxorubicin, which may decrease the occurrence of cardiotoxicity and left ventricular dysfunction in selected patients.¹

WHERE DOES CARDIOLOGY MEET ONCOLOGY?

In this session, Rudolf De Boer (NL) pointed out that an increased risk of developing cancer has been reported previously in patients with heart failure and that patients with cancer and heart failure have a worse prognosis.⁵ Markers of chronic cardiovascular disease (hypertension, tachycardia, high total cholesterol) and markers of other chronic diseases (eg, chronic kidney disease, diabetes) have been shown to be predictors of cancer and the risk is even higher if heart failure and other chronic diseases are present.⁶

Jochen Springer (DE) discussed the relatively high prevalence of heart failure in cancer patients, which is often associated with anticancer therapy.⁷ However, this

might not be the only factor, as preclinical studies have shown that tumor-induced factors cause cardiac muscle wasting by interfering with cardiomyocyte metabolism.⁸ A multivariate survival analysis showed that cancer patients with an elevated resting heart rate, representing a possible activation of the sympathetic nervous system, also have higher mortality.⁹ These observations demand more clinical research to have a better understanding of the systemic effects that cancer has on cardiovascular function.

Javid Moslehi (US) emphasized the importance of understanding the underlying cardiotoxic mechanisms of classic and new antineoplastic therapies. Besides the anthracycline dose- and age-dependent effects of therapy on the heart, plenty of other antineoplastic drugs and targeted therapies (eg, trastuzumab and tyrosine kinase inhibitors) are also associated with cardiac alterations. In particular, rare, but clinically significant, myocarditis has been recently associated with immune checkpoint inhibitors.¹⁰

CONCLUSIONS

This year's cardio-oncology sessions during the heart failure association congress confirmed the importance of this growing field. The congress focused on the importance of understanding the underlying mechanisms of cardiotoxicity and recognizing it as early as possible in the clinical setting. Nevertheless, further studies about early detection and management of cardiotoxicity are needed. ■

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PREVENTING HEART FAILURE: A MAJOR CHALLENGE

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Hear failure is a growing problem, both in terms of the number of individuals affected and the implications for national health services. The increasing size of the elderly population means that this issue is only going to get worse in the coming years, with the cost of treating patient risks becoming unupportable. In order to reduce hospital readmissions and the clinical and economic burdens of heart failure, preventing the development of heart failure in the general population and preventing recurrences and deterioration in patients with established heart failure are key issues in modern cardiovascular medicine. This article focuses on these issues to provide practical indications that are based on the most recent ESC guidelines.

PREVENTING HEART FAILURE IN THE GENERAL POPULATION

We all know the important risk factors for the development of cardiovascular diseases and heart failure in particular, such as hypertension, smoking, obesity, diabetes, sleep apnea, a sedentary lifestyle, and a poor diet. However, we also know that persuading at-risk individuals to adopt and adhere to a healthier lifestyle and to comply with treatment is easier said than done. For example, even among individuals experiencing an acute coronary event, half of those who smoked prior to the event will continue to smoke after it, against the strong advice of health care professionals. Moreover, some behavioral risk factors are increasing due to pervasive aspects of economic transition, rapid urbanization, and 21st-century lifestyles (in particular tobacco use, an unhealthy diet, insufficient physical activity, and the harmful use of alcohol). The greatest effects of these risk factors fall increasingly on low- and middle-income countries and on poorer people within all countries. A major reduction in the burden of cardiovascular events will come from population-wide interventions that are cost-effective. One of the most reliable ways to ensure this success is by educating clinicians and health care providers. However, at the end of the day, we should recognize that much depends on the motivation of the individual patient and the responsibility they take for their own health. We need to train doctors to help patients understand that, by making the right lifestyle choices, they can reduce their risk of developing this life-limiting condition.

PRIMARY PREVENTION RECOMMENDATIONS

There are many avenues for preventing the onset of heart failure, including both healthy lifestyle behavior and proper medical treatment for conditions that predispose people to heart failure. Regular physical activity (exercising >5 days per week) and maintaining a healthy body weight are key ingredients to preventing heart failure. Other healthy behaviors also lower the risk of developing heart failure, including not smoking, eating fruits and vegetables (4 servings per day), and moderate alcohol intake (1 drink per day). On the other hand, heavy alcohol consumption, binge drinking, and cocaine and amphetamine abuse can lead to heart failure and other health problems, which should therefore be avoided. Lastly, eating fish and drinking a moderate amount of coffee (>4 cups per day) have also been linked to lowering the risk of heart failure.

Hypertension (high blood pressure) is a major risk factor for the development of heart failure. In some people known to be at a higher risk for heart disease, lowering blood pressure to an optimal level (<140/90 mm Hg and probably even lower in high-risk individuals) can significantly reduce their risk. Specific medicines that lower blood pressure and are effective in lowering the risk of heart failure include diuretics, ACE inhibitors, ARBs, and β -blockers. Type 2 diabetes (high blood glucose) predisposes people to the development of heart failure, and treating diabetes to lower blood glucose with diet, exercise, and certain antidiabetic medications under the care of a physician can significantly lower the risk of heart failure.

Cholesterol build up in the arteries that supply blood to the heart, also known as atherosclerotic coronary artery disease, can result in heart attacks that damage and weaken the heart muscle, which is another leading cause of heart failure. Under the care of a cardiologist, treatment of risk factors can effectively reduce the risk of heart attacks and heart failure with drugs, such as statins and aspirin; however, diet and exercise are also important. Genetics also plays a role in many forms of heart failure; therefore, if a family member has heart failure, relatives should consult their doctor to consider heart failure screening and, eventually, genetic testing.

SECONDARY PREVENTION

Secondary prevention may be even more problematic than primary prevention. Traditionally, our medical training focuses on treatment, but this needs to change by switching doctors to thinking about how they can help patients avoid developing heart failure. Societies and associations, such as the HFA of the ESC, are taking a leading role in changing the culture and putting prevention center stage. Both the 2016 ESC guidelines for the diagnosis and treatment of heart failure¹ and the 2016 European guidelines on cardiovascular disease prevention,² which were introduced at the 2016 HFA meeting, dedicated a chapter to heart failure prevention.

The HFA also promotes the message through various activities, such as those of the Exercise Physiology and Training Committee, including a biennial training course “Rehabilitation and long-term management of heart failure patients,” the latest of which took place in Pisa, Italy earlier this year. This message needs to be spread beyond heart failure specialists to the wider cardiology and general medical community. Technology may be able to offer some help. The use of telemedicine devices will enable doctors to monitor how well patients are implementing healthier lifestyles, and smartphone apps can help patients manage their exercise and medication regimes. The data already obtained from the use of these approaches are encouraging.

It is often difficult to initiate these types of programs due to a lack of infrastructure and investments; however, investment in prevention is unavoidable and there is no shortcut to success. Cardiovascular prevention in patients with heart failure should start as soon as possible, but it requires a multifaceted, integrated tactic. Since discharge is a vulnerable transition phase, a comprehensive discharge plan should be organized, according to the ESC guideline recommendations.

Patients with heart failure are at high risk; therefore, they deserve special attention by using a multifaceted and multidisciplinary intervention that should be started as soon as possible during and after hospital admission to develop a life-long structured prevention course. In the hospital, clinical management and risk assessment are decisive; however, for patients, secondary cardiovascular prevention extends from optimized pharmacological treatment to physical activity counseling, psychological support, and patient/caregiver management education. Recommendations for preventive measures for the general population are different from those for patients with heart failure because the clinical stage may have an impact on the recommendations; for example, advanced heart failure might be associated with a low blood pressure and lipid profile, concomitant disease (eg, cachexia, renal dysfunction, and so on), and may require future strategies (heart transplantation and mechanical circulatory support), which advocates for specialized interventions.

Although congestion management is critical for improving symptoms and reducing the risk of readmission, management extends beyond diuresis alone, and preventing adverse cardiovascular events requires reducing cardiac injury, inhibiting maladaptive systemic responses, and controlling relevant comorbidities. Although the patient’s condition and clinical progress are informative, monitoring systems that rely less on patient input are attractive. Since most readmissions for heart failure exacerbations are attributable, at least in part, to poor self-care, non-adherence to medications and dietary advice, and failure to act upon escalating symptoms, effective self-care is essential for cardiovascular prevention.

Before leaving the hospital, several issues should be considered and discussed with the patient and carers. A discharge plan should be organized to build an appropriate management strategy aimed at preventing cardiovascular readmissions: congestion should be resolved and a stable oral diuretic regimen established for at least 48 hours. Long-term disease-modifying therapy should be optimized as much as possible and appropriate education provided to the patient and family/caregivers. Pre- and postdischarge management should follow the standards of care and goals of treatment suggested by the ESC guidelines.

SECONDARY PREVENTION RECOMMENDATIONS

Table 1 summarizes the recommendations for secondary prevention, in particular, it is essential to control risk factors and optimize pharmacological treatments, which should include β -adrenergic blockers, renin-angiotensin-receptor blockers, and mineralocorticoid antagonists. The most recent armamentarium should consider using ivabradine and/or the sacubitril/valsartan combination, when appropriate. The indication for devices, such as implantable cardioverter defibrillators and/or cardiac resynchronization, should be also taken into consideration.

Exercise training is usually prescribed to outpatients, but it is a fundamental preventive action in patients with stable heart failure. Since patients experience exercise intolerance due to several maladaptive changes, even when on optimal medical therapy, exercise training dominates symptoms and affects outcomes. However, adherence is crucial and exercise intensity should be a balance between efficacy and safety. Exercise protocols can vary, even though moderate-

- Assess and stabilize the patient
- Optimize the pharmacological therapy
- Help patients understand the indications and aims of device implantation
- Manage and control the risk factors (eg, smoking cessation)
- Control weight and manage cachexia and obesity
- Provide dietary and nutritional counseling
- Promote physical activity and recommend an exercise-training program
- Provide psychosocial support
- Educate patients about self-care management
- Institute home-based care monitoring

Table 1. Recommendations for secondary prevention.^{1,2}

to-vigorous intensity exercise is frequently employed. A “high-intensity interval training” program may yield even greater improvements in peak VO_2 . Before commencing any exercise program, clinical stability and functional evaluations are warranted.

Finally, the recommendations for prevention and intervention modalities are similar for both patients with HFPEF and patients with HFREF; however, the data are limited. ■

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ACUTE HEART FAILURE: WHAT IS NEW?

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Keywords: acute HF; biomarker; dyspnea; imaging; management

Acute HF is a complex and often life-threatening clinical condition.¹ Existing and new therapeutic approaches have failed to reduce the risk for recurrent hospitalizations and mortality in this condition, possibly because they treat similar patients with different clinical profiles and underlying pathophysiology.¹ The necessary steps for the optimal evaluation and treatment of patients with acute HF include: (i) making a firm diagnosis (using biomarkers, echocardiography, thoracic ultrasound, and an invasive evaluation); (ii) classifying and evaluating the patient for specific etiologies and determining the underlying pathophysiology (CHAMP evaluation for acute de novo heart failure: four clinical scenarios based on clinical evaluation for acutely decompensated heart failure); (iii) treating the acute phase according to the underlying pathophysiology and clinical profiles; (iv) providing specific instructions for chronic disease-modifying medications after clinical stabilization; and (v) creating a discharge plan and managing significant comorbidities.² This review summarizes some new aspects regarding the classification, diagnosis, and therapy of acute HF syndromes.

NEW GUIDELINE-RECOMMENDED CLINICAL CLASSIFICATION

The initial clinical evaluation aims to classify patients with acute HF into four different clinical profiles according to the presence of congestion (wet or dry patient) and/or peripheral hypoperfusion (warm or cold patient). *Table 1* describes the new ESC HF guideline-recommended clinical classification of acute HF, clinical profile-associated in-hospital mortality, and recommended management according to each clinical scenario.^{2,3}

DIAGNOSTIC PROCESS AND TOOLS

Upon emergency department admission, the current diagnostic algorithm initially recommends a comprehensive investigation for the detection of severe hemodynamic instability/cardiogenic shock and/or respiratory failure requiring support with invasive or noninvasive mechanical ventilation.² After excluding these severe entities, the next diagnostic step is to assess the potential specific causes of acute symptoms, such as acute coronary syndromes, hypertension emergencies, arrhythmias, mechanical factors (eg, acute valve regurgitation, septal rupture, aortic dissection), or pulmonary embolism (CHAMP diagnostic approach for acute de

novo heart failure).² Confirmation of the diagnosis of acute HF typically requires additional diagnostic tests after the initial comprehensive clinical evaluations, which mainly consist of imaging modalities and biomarkers.

IMAGING MODALITIES

Echocardiography

In patients with hemodynamic instability or frank cardiogenic shock, immediate echocardiography is mandatory. Early echocardiography, preferably within the first 48 hours after presentation is required in cases of new-onset acute HF and in all cases with no previously documented assessment of cardiac function. Pocket-sized portable echocardiography may provide a reliable initial assessment of left ventricular systolic function and it can be used as part of the clinical evaluation of the patient in the emergency room.²

Thoracic ultrasound

With appropriate expertise, bedside thoracic ultrasound can be useful for the detection of interstitial lung edema and pleural effusion. Interstitial lung edema is detected by the presence of comet-like vertical reverberation artifacts caused

Clinical phenotype	Pathophysiology	In-hospital mortality*	Management
Warm and dry	No congestion No hypoperfusion	1.7%	Dyspnea of noncardiac cause: manage accordingly
Warm and wet	Pulmonary and/or peripheral congestion No hypoperfusion	4.1%	CPAP IV diuretics and vasodilators Ultrafiltration
		Acute hypertensive pulmonary edema, 2.6%	
Cold and dry	Hypoperfusion and hypovolemia Excessive use of diuretics	13.6%	Exclude noncardiac causes Fluid administration, inotropes
Cold and wet	Congestion Hypoperfusion	16.5%	Inotropes IV diuretics Mechanical support Ultrafiltration
		Cardiogenic shock, 36.1%	

Table I. New ESC heart failure guideline-recommended clinical classification of acute heart failure, clinical profile-associated in-hospital mortality, and recommended management.

**Mortality rates according to the ESC Long-term heart failure registry.³*

by extravascular lung water accumulation, which are called B-lines. Detection of B-lines has been shown to have 94% sensitivity and 92% specificity for the differential diagnosis of acute HF from noncardiac causes of acute dyspnea.⁴ However, the specificity of B-lines is compromised in patients with alveolar consolidations due to infectious, infiltrative, or traumatic lung diseases or in cases with fibrotic pleural abnormalities, such as in systemic sclerosis.⁴

BIOMARKERS

Natriuretic peptides

Natriuretic peptides are useful tools in differentiating dyspnea of cardiac etiology from dyspnea of noncardiac etiology and are recommended in all patients with suspected acute HF. Their diagnostic value lies predominantly in the exclusion of acute HF in patients with normal natriuretic peptide levels, as they show a high negative predictive value of 94% to 98% (upper normal values: BNP <100 pg/mL, NT-proBNP <300 pg/mL, MR-proANP <120 pg/mL).² However, increased natriuretic peptide levels do not confirm the diagnosis of acute HF, as they may become elevated in a wide variety of cardiac (eg, atrial fibrillation, pulmonary embolism, etc) and noncardiac diseases (eg, renal dysfunction, sepsis, stroke, etc).²

Procalcitonin

The assessment of procalcitonin may be considered in patients with acute HF and suspected infection for the differential diagnosis of pneumonia and to guide antibiotic therapy in these patients. A procalcitonin level of 0.1 ng/mL excludes pneumonia in patients with acute dyspnea, while a procalcitonin level >0.21 ng/mL identifies patients with acute HF with pneumonia in need of antibiotic therapy.⁵

Soluble ST2

The soluble ST2 factor is increased in acute HF vs dyspnea of noncardiac etiology, with an optimal cut-off value of 0.20 ng/mL. However, its clinical utility is best as a prognostic biomarker in acute HF. In patients with acute HF, increased ST2 levels both at admission and at discharge have been associated with an increased risk of all-cause and cardiovascular mortality, and an increased discharge ST2 is associated with an risk of rehospitalization.⁶

MANAGEMENT

Diuretics and vasodilators

Diuretics are the mainstay therapy for the treatment of congestion in acute HF and they should be administered early after the diagnosis of acute HF. Dosing of intravenous diuretics should be 20 to 40 mg furosemide (or equivalent) initially in patients not previously on diuretic therapy, while patients previously treated with

diuretics should receive an initial intravenous dose that is at least equivalent to their previously administered oral dosing.²

Intravenous vasodilators (nitrates, nitroprusside, and nesiritide) provide symptom relief and they should be considered in patients with cardiac-type acute HF whose systolic blood pressure is >90 mm Hg in combination with diuretics. In patients with vascular-type acute HF, vasodilators should be considered as initial therapy to improve symptoms and reduce congestion.² Newer vasodilators, including ularitide and serelaxin, have failed to show a reduction in mortality and morbidity risk in recent randomized controlled trials.²

Inotropes and vasopressors

Intravenous inotropes may be considered as short-term therapy for patients with hypotension and peripheral hypoperfusion despite adequate filling status to increase cardiac output and blood pressure and maintain end-organ function. Due to an increase in myocardial oxygen consumption, inotropes may aggravate myocardial ischemia and induce tachyarrhythmias, contributing to increased medium- and long-term mortality. Levosimendan is an inodilator that was developed as an alternative to classical β -agonists for the treatment of low cardiac output acute HF. Levosimendan may be preferred over β -agonist inotropes in patients with acute HF previously treated with β -blockers, as its mechanism of action is independent of the β -adrenergic receptor pathway.²

Vasopressors may be considered in patients with cardiogenic shock, who remain hypotensive/hypoperfused despite treatment with another inotrope to increase arterial blood pressure and maintain end-organ perfusion.² Recently published data demonstrated that epinephrine use in cardiogenic shock has been associated with increased short-term mortality (30-day mortality is up to 4.7-fold higher with epinephrine vs other vasopressors, including norepinephrine and dopamine).⁷ Therefore, epinephrine should be avoided and norepinephrine should be the preferred vasopressor in cardiogenic shock.²

Chronic life-saving medications

In patients with previously diagnosed HFREF who are on chronic therapy with life-saving medications, it is recommended to continue these therapies during hospitalization for acute HF unless a contraindication exists, including hypotension, bradycardia, or hypoperfusion (β -blockers); worsening renal function and hyperkalemia (ACE inhibitors/ARBs/mineralocorticoid receptor antagonists).² In this case, doses might be reduced or drugs temporarily discontinued until the patient stabilizes. Regarding sacubitril/valsartan, an ongoing study will examine the feasibility and safety of starting sacubitril/valsartan in the hospital, early after hemodynamic stabilization vs postdischarge initiation in patients with HFREF

hospitalized for acute HF. A previous study confirmed the safety and feasibility of initiating ivabradine plus β -blockers vs β -blockers alone in hospitalized patients with HFREF. The study showed that ivabradine plus β -blockers improved heart rate during the postdischarge period.⁸

Existing therapies for acute HF, with the respective class of recommendation according to the most recent ESC HF guidelines, are presented in *Table II*.

Treatment	Class of recommendation and level of evidence
Diuretics	IC
Vasodilators	IIaB
Inotropes (short-term)	IIbC
Vasopressors (norepinephrine)	IIbB
Opiates	IIbB
Noninvasive ventilation (CPAP/BiPAP in respiratory distress)	IIaB
Ultrafiltration	IIbB
IABP (routine use)	III
Short-term mechanical circulatory support	IIbC
Chronic HFREF medications (continuation in decompensated chronic HFREF and initiation in de novo acute HF in the absence of contraindications)	IC

Table II. Currently available pharmacological and device therapies in acute heart failure and corresponding class of recommendation according to the ESC heart failure guidelines.

NEW DRUGS

Vericiguat

Vericiguat is a direct, oral, soluble guanylate cyclase (sGC) stimulator that enhances sGC sensitivity to endogenous nitric oxide. In a phase 2 study, vericiguat reduced the natriuretic peptide levels, while being safe and tolerable in patients with chronic HFREF.⁹ Currently, an ongoing trial is testing the efficacy of vericiguat vs placebo added to standard therapy to reduce cardiovascular mortality and HF hospitalizations in patients with HFREF and a previous hospitalization due to worsening HF.

Nitroxyl donors

Nitroxyl donors are pharmacological agents that release nitroxyl (HNO), a reactive nitrogen species with unique biochemical and pharmacological actions from NO.¹⁰ A phase 2a trial has confirmed the positive inotropic and vasodilatory effects of a pure HNO donor (CXL-1020) in hospitalized patients with HFREF, while an ongoing phase 2b trial is testing the safety and the clinical efficacy of CXL-1020 in reducing natriuretic peptide levels and improving dyspnea in patients with acute HF.

Omecamtiv mecarbil

Omecamtiv mecarbil is a selective cardiac myosin activator that enhances cardiomyocyte contraction by promoting the transition of actin-myosin complexes from a weakly to a strongly bound state and inhibiting nonproductive degradation of ATP. The phase 2 ATOMIC-AHF trial compared intravenous infusion of omecamtiv mecarbil with placebo in patients with acute HF and reduced left ventricular ejection fraction. Although the primary efficacy end point of dyspnea relief was not met in the pooled cohort, omecamtiv mecarbil reduced dyspnea at 48 hours and through 5 days in the high-dose cohort, with concomitant increases in left ventricular systolic ejection time and decreases in end-systolic left ventricular diameter.¹¹ An ongoing phase 3 trial is testing the efficacy of oral omecamtiv mecarbil in reducing cardiovascular mortality and HF hospitalizations in patients with HFREF and a recent acute decompensation.

SUMMARY

Optimal management of acute HF remains an unresolved issue in daily clinical practice. For de novo acute HF, early recognition and correction of the cause is the gold-standard practice for in-hospital management. For acutely decompensated chronic heart failure, current therapeutic strategies have failed to improve cardiovascular outcomes as patients continue to exhibit high short- and long-term morbidity and mortality. Long-term adverse cardiovascular events are more likely to be decreased by adhering to evidence-based life-saving medications for chronic heart failure as well as optimal management of comorbidities in order to prevent heart failure exacerbations. Until new effective therapies become available, individualized treatment with existing drugs and devices according to the underlying pathophysiology appears the most suitable strategy for the management of acute HF. ■

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DIABETES AND HEART FAILURE

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Keywords: diabetes; heart failure; hospitalization; mortality

Diabetes mellitus is one of the major risk factors for heart failure, and patients with the two conditions have a higher risk of mortality compared with patients without diabetes or heart failure.¹ The increased risk of developing heart failure among patients with diabetes is multifactorial and includes the abnormal cardiac handling of glucose and free fatty acids, the effect of the metabolic derangements of diabetes on the cardiovascular system, and the development of coronary artery disease. Furthermore, the metabolic risk of diabetes in heart failure is heightened by the negative effect of most antidiabetic medications.

The detrimental effect of some antidiabetic medications in patients with heart failure may be dependent upon a direct effect of the glucose-lowering molecules on the cardiovascular system (ie, sodium retention by insulin) and/or upon the negative effect of excessive glucose lowering. In the past, there have been doubts about the safety of several antidiabetic medications in patients with cardiovascular disease. Unexpectedly, however, two new classes of drugs have been shown to reduce heart failure hospitalizations and mortality in patients with diabetes and proven cardiovascular disease, opening a new dawn for the treatment of both heart failure and diabetes.²

MANAGEMENT OF PATIENTS WITH DIABETES AND HEART FAILURE

The management of patients with diabetes and heart failure was an important topic at the 2018 HFA congress. Several speakers discussed the important topic of identifying the sweet spot for glucose lowering when treating patients with heart failure.³⁻⁵ Despite the aggressive approach of most diabetologists who prefer to reduce HbA_{1c} as much as possible, cumulating evidence from clinical trials seems to suggest that a lenient glycemic control (HbA_{1c}, 7.5% to 8%) is preferable in patients with diabetes and heart failure, especially in the older patients.

Since discovering that there is an increased risk of cardiovascular events with glucose-lowering medications, the regulatory agencies (EMA and FDA) have requested cardiovascular event-driven clinical trials for newer molecules to treat diabetes mellitus. Although initially only linked to ischemic heart disease, the negative effect of glucose-lowering agents on heart failure has become evident after rosiglitazone was withdrawn from the EU market because of the increased risk

of cardiovascular events. Despite the initial focus of regulatory agencies on the risk of coronary events, it was evident, even from the rosiglitazone clinical data, that the most significant risk with the use of this drug was related to heart failure.

NEWER ANTIDIABETIC MEDICATIONS

The new regulations for the registration of glucose-lowering agents have led to a proliferation of clinical trials in the area and have helped elucidate the risks and benefits of the newer antidiabetic medications in patients at an increased risk of developing heart failure.

Dipeptidylpeptidase-4 inhibitors

While initial studies questioned the safety of dipeptidylpeptidase-4 inhibitors in patients with heart failure due to an increased risk of heart failure hospitalizations, recent data suggest that they may be safe to use in patients without heart failure. However, given their limited clinical benefit and the lack of clear safety data in patients with heart failure, their use is not recommended except under exceptional circumstances and under strict cardiology supervision.

GLP-1 receptor agonists

Recently, in the LEADER trial, liraglutide, a GLP-1 receptor agonist, showed a significant reduction in the composite primary outcome of the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, but no effect on heart failure end points. This effect does not seem to be shared by lixisenatide. However, given the paucity of detailed data in patients with heart failure, the use of GLP-1 receptor agonists should be implemented only under strict cardiology supervision.

SGLT2 inhibitors

SGLT2 inhibitors enhance glucose control by increasing the urinary excretion of glucose. Recently, the EMPA-REG OUTCOME study showed that the SGLT2 inhibitor empagliflozin significantly reduced the rates of death from cardiovascular causes, hospitalizations for heart failure (35% relative risk reduction), and death from any cause (32% relative risk reduction). Empagliflozin reduced the cumulative endpoint of hospitalizations or death from heart failure by 39%. These results do not seem to be unique for empagliflozin, as similar results were obtained from a recent FDA meta-analysis of clinical trials with dapagliflozin and the CANVAS study with canagliflozin.

Prompted by these positive results, SGLT2 inhibitors are currently being tested in patients with heart failure. The designs of four, ongoing, event-driven clinical trials with SGLT2 inhibitors in patients with heart failure—EMPEROR-Preserved, EMPEROR-Reduced (both with empagliflozin), Dapa-HF (with dapagliflozin), and

SOLOIST-WHF (with sotagliflozin)—were presented during an ad-hoc session on diabetes at the 2018 HFA congress. Empagliflozin is also being tested in the IMPERIAL trial aimed at assessing the effect of this molecule on exercise capacity in patients with heart failure.

DELAYING THE ONSET OF DIABETES

Apart from the effect of antidiabetic medications in heart failure, cumulating evidence suggest that cardiovascular drugs may have a positive effect on delaying the onset of diabetes. The clinical significance of these effects is still to be fully understood. Valsartan reduced the incidence of diabetes by 14% in the NAVIGATOR trial, but failed to show any effect on cardiovascular outcomes. Ramipril improved glucose tolerance in patients with impaired fasting glucose or impaired glucose tolerance in the DREAM trial. LCZ696 and the metabolic modulators trimetazidine and ranolazine improved glucose tolerance in patients with diabetes and heart failure by an extent similar to that of the newer antidiabetic drugs.

CONCLUSIONS

Diabetes mellitus was a focus at the 2018 HFA congress. It is clear that heart failure and diabetes often coexist in a bidirectional relationship, and, when combined, they lead to high rates of morbidity and mortality. The treatment of patients with diabetes and heart failure must target the overall clinical status, as an aggressive treatment of diabetes can decompensate heart failure. Novel glucose-lowering agents are under investigation in patients with heart failure, raising hopes for the future. ■

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Guidelines,
Registries, & Trials



LATE-BREAKING CLINICAL TRIAL HIGHLIGHTS

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Keywords: cardiac contractility modulation; exergaming; gene therapy; heart failure; rivaroxaban; peak VO₂

For those readers who were fortunate enough to attend the 2018 HFA annual scientific conference in Vienna, Austria, I need not tell you that we had such a wonderful congress with fantastic weather in the beautiful city of Vienna, Austria. Many people must have felt this as nearly 6000 people attended, making it the second largest ever HF-specific conference, second only to the 2016 HFA annual scientific conference in Florence, Italy when the ESC guidelines were launched. For those readers who were not so fortunate to attend in person, we can still summarize the excellent science and research that was presented at this year's meeting. Since the 2016 ESC/HFA guidelines¹ for the diagnosis and treatment of acute and chronic HF were launched at the same HFA meeting in Florence, Italy just 2 years previously, new information has emerged in the area of treatments, both drug and device, in the new classification that includes HF with mid-range ejection fraction, and in the importance of the common comorbidities of HF, such as the fact that the HF population is getting older.

This meeting also saw the baton passed on from Professor Frank Ruschitzka (Zurich, Switzerland) to the incoming HFA President, Professor Petar M. Seferović (Belgrade University Medical Center, Serbia). Professor Seferović sees the HFA as the leading HF association for its members and patients with HF throughout the world, as well as a leading force with the ESC, using the five strategic ESC pillars of congresses, education, research, advocacy, and membership. This mission will be achieved by working closely with the national societies of the ESC family and their HF divisions, where 48 countries are now actively participating in activities led by the HFA. Professor Seferović predicts that major advances are possible using three fundamental axes: (i) the European HFA Atlas (HFA Atlas), (ii) Heart Failure Centers of Excellence, and (iii) increased active participation of the HFA members. The HFA Atlas will detail HF-specific variables (eg, disease and population demographics), information from HF centers (eg, their facilities and detailed information concerning procedures performed, patient care episodes delivered, and outcomes). The HFA Atlas has the potential to be a major source of information for cardiologists, HF specialists, health care systems, and anyone interested in the future of HF care. The Heart Failure Centers of Excellence, based in part on data generated by the HFA Atlas project, will help identify expert HF centers across Europe to improve patient care by sharing best practices. All this and the success of the conference

itself depend on active and engaged HFA members, particularly younger members, through the association's Heart Failure Specialists of Tomorrow (HoT) initiative.

LATE-BREAKING CLINICAL TRIAL RESULTS

COMPASS trial

One of the highlights of the HF meeting is the new research presented from late-breaking clinical trials, often for the first time publically. One such trial was a substudy report from the COMPASS trial,² in which Dr Kelley Branch (University of Washington, Seattle, Washington, US) reported that a combination of rivaroxaban and aspirin reduced the risk of MACE in patients with CAD and/or PAD and HF. He described how patients with HF have both an enhanced absolute risk, and, importantly, a greater absolute benefit from combination therapy with rivaroxaban plus aspirin compared with patients without HF. The main COMPASS trial had earlier reported that MACE (cardiovascular death, stroke, or myocardial infarction) were significantly lower in over 27 000 patients with stable CAD and/or PAD compared with standard treatment with aspirin alone. In an important HF cohort of 22% of these patients (>5000 HF patients), with a median follow-up of just under 2 years, the rates of MACE increased on the background of HF irrespective of treatment allocation, and, importantly, the combination of rivaroxaban and aspirin reduced the absolute risk of MACE more in the HF cohort (2.4%) vs the overall patient population (1.0%). These results indicate that as few as 42 patients need to be treated with combination therapy vs aspirin monotherapy to prevent major adverse CV outcomes. Results are awaited from studies, such as the COMMANDER HF trial, that are looking at the combination of rivaroxaban and aspirin in patients with ischemic HFREF.

Cardiac contractility modulation

New research was also presented on cardiac contractility modulation, which is occasionally described loosely, if inaccurately, as a form of electrical device stimulation of the heart that aims to be the "CRT" for patients with HF without a prolonged QRS duration. It actually delivers accurately timed stimulation to cardiac muscle cells during their absolute refractory period, which induces enhanced cardiac contractility by beneficially changing cardiac gene expression. Professor Gerd Hasenfuß (Universitätsmedizin Göttingen, Germany) reported on the long-term benefits of cardiac contractility modulation based on results from a 24-week study (n=160 patients with HF) that evaluated exercise performance with peak Vo_2 and a single-center registry (n=140 patients with HF) with 3 years of follow-up. The focus was on patients with a mild-to-moderate reduction in systolic function, ie, LVEF between 25% and 45% and a QRS duration <130 msec. Professor Hasenfuß presented results that showed a significant and clinically relevant 0.84 mL O_2 /kg/min

increase in peak Vo_2 , along with improved Minnesota Living with Heart Failure Questionnaire results, improved NYHA class, and an increase in the 6-minute walk distance. Although not powered for such outcomes, a 75% reduction in hospitalization rates was reported, going from 1.2 per patient-year in the year before device implantation to 0.35 per patient-year following implantation ($P < 0.0001$). At year 2, there was a significant improvement in LVEF; in addition, compared with risk score predictions, mortality appears lower, which is a finding that, of course, would need a powered randomized controlled trial to prove conclusively.

SERCA-LVAD trial

At the more experimental end of HF therapeutics, Professor Alexander Lyon (Royal Brompton Hospital and Imperial College London, UK) reported on 5 patients in the SERCA-LVAD trial concerning gene therapy for HF, the first trial to evaluate gene therapy for patients with HF and a LVAD. This trial was designed to show whether the downregulation of the SERCA2a protein, which adversely affects cardiomyocyte calcium cycling and is common in HF, could be restored by cardiac delivery of an adeno-associated virus 1 vector containing the human SERCA2a gene (AAV1/SERCA2a). Although the CUPID-2 trial³ failed to show a benefit of AAV1/SERCA2a, there were no safety issues in the SERCA-LVAD trial and no evidence of virus-related cardiac inflammation. Viral DNA was detected in cardiac tissue from two patients, but only at very low levels, indicating, according to Professor Lyon, that the doses delivered in both the CUPID-2 and SERCA-LVAD trial were too low for benefit to be seen, meaning that new gene technologies are required for clinically effective doses of the gene to be delivered.

IMPACT - BIC - 18 study

Heart failure is not a specialty in isolation. Patients have other conditions, such as septic shock and chest infections, both of which can present diagnostic difficulties. Professor Martin Möckel (Charité Universitätsmedizin, Berlin, Germany) presented the IMPACT – BIC - 18 study, reporting that, when added into the diagnostic and treatment pathway, procalcitonin-guided antibiotic therapy, despite showing considerable promise, did not improve mortality in patients with shortness of breath, acute HF, and a suspected infection. The earlier observational BACH study⁴ had suggested that procalcitonin levels could improve the accuracy of diagnosing pneumonia and that antibiotics used after such an evaluation were beneficial for patients with high procalcitonin levels. However, the study was stopped by the Data Safety and Review Committee after 75% recruitment for presumed futility in assessing the primary end point of 90-day mortality, even though the trial confirmed the prognostic value of procalcitonin.

Exergaming

Professor Tiny Jaarsma (Linköping University, Norrköping, Sweden) reported on one of the more appealing HF treatment approaches, ie, exergaming and its effects on physical capacity and quality of life in older patients with HF. In an update from the HF Wii study,⁵ which showed that exergaming improved the 6-minute corridor walk test distance in patients with HF, Professor Jaarsma also reported that exergaming significantly improved QOL and the patients' expectations for future wellbeing. She also showed that the time spent exergaming was crucial for the ultimate improvement in functional capacity achieved, and summarized that exergaming provides patients with HF an effective option that may lead to better compliance with regular exercise recommendations, as it can be incorporated into daily life more easily and can help with social interaction if done together with friends or relatives. No adverse effects were seen in any of the 600 patients studied.

Network meta-analysis

Professor Michel Komajda (Hôpital Saint Joseph, Paris, France) reported on the incremental benefit of drug therapies for patients with chronic HFREF. On behalf of colleagues, he presented a network meta-analysis that assessed the efficacy of all guideline-recommended drug classes on all-cause mortality, CV mortality, all-cause hospitalizations, and hospitalizations for HF. A systematic literature review identified 58 randomized controlled trials testing ACE inhibitors, ARBs, β -blockers, MRAs, ivabradine, and the sacubitril-valsartan combination in patients with chronic HFREF (LVEF <45%) and analyzed the efficacy results by combining individual trials using a Bayesian network meta-analysis with a random-effects model to consider the relative efficacy of each treatment class or combination of classes on the rates of major outcomes. Professor Komajda argued that the combination of ACE inhibitors, ARBs, β -blockers, MRAs, ivabradine, and ARNI resulted in a progressive improvement in mortality and hospitalization outcomes in HFREF over the last 30 years and that the two most effective combinations were (i) ARNI + β -blockers + MRAs and (ii) ACE inhibitors + β -blockers + MRAs + ivabradine, stressing the need to combine multiple disease-modifying therapies as recommended in the major contemporary HFREF treatment guidelines.

EUGENE BRAUNWALD AND PHILIP POOLE-WILSON AWARDS

A major highlight from the 2018 HFA meeting was the return of the father of heart failure (and arguably all cardiology), Professor Eugene Braunwald, to his birthplace. Over the years, Professor Braunwald has given his time to help and mentor young cardiologists. This year, he awarded the Eugene Braunwald award to a former pupil, Professor Marc Pfeffer who gave a wonderful award speech concentrating on the area cited as one of the major advances in cardiology of the last

30 years—the ability to devise and develop drugs that limit the size of myocardial infarctions following coronary occlusion. Limiting infarct size at the time of a myocardial infarction and preventing further late cardiac remodeling has led to major clinical benefits. Professor Walter Paulus, the Philip Poole-Wilson award winner, presented his lifelong work on assessing and defining diastolic function and on what is now called HFPEF. These two talks were the real highlights of this year's HFA meeting and a credit to the depth and achievements of HF research over the last few decades since subspecialties came of age. ■

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ADVANCED HEART FAILURE: THE NEW HFA CONSENSUS DEFINITION

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Keywords: advanced heart failure; heart transplantation; mechanical circulatory support devices

In a special session during the 2018 HFA congress, which took place in Vienna from May 26 to 29, 2018, a new definition of advanced heart failure was presented. Concomitantly, the HFA-ESC position statement on advanced heart failure was published in the *European Journal of Heart Failure*.¹

Patients with advanced heart failure comprise an estimated 1% to 10% of the overall heart failure population. They are patients with severe symptoms despite optimal management, according to the guidelines of clinical practice, and they are at high risk of death. Advanced heart failure does not depend on ejection fraction, but on the patient's symptoms, prognostic markers, presence of end-organ damage, and goals for therapy.

A thorough definition of advanced heart failure is mandatory to facilitate appropriate application of advanced treatments, such as heart transplantation or long-term mechanical circulatory support devices. Heart transplantation remains the treatment of choice in patients without contraindications and long-term mechanical circulatory support devices can support patients either as a bridge to heart transplantation or as destination therapy. Finally, some patients will not be candidates for advanced heart failure therapies. Often a general cardiologist is responsible for directing patients to advanced heart failure resources and helping patients navigate the next steps in their care. Thus, clinicians need to be appropriately equipped to identify patients that might be candidates for advanced heart failure therapies and to recognize the optimal time for referral.

The goals of this document are to (i) describe the clinical characteristics of patients with advanced heart failure; (ii) inform physicians about markers of poor prognosis that indicate an advanced stage of disease; (iii) educate physicians on optimal short-term management strategies for these patients to improve their candidacy for heart transplantation or mechanical circulatory support; (iv) enable physicians to recognize the optimal time and processes for referring patients to advanced heart failure centers; and (v) ensure collaboration between advanced heart failure, palliative, or symptom-focused care, including end-of-life care events.

In the last few years, there have been several definitions of advanced heart failure,^{2,3} including the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles aimed at describing the clinical parameters and characteristics of patients to be considered for a long-term mechanical circulatory support implantation.⁴ In this new definition, the criteria suggested in the 2007 HFA-ESC position statement⁵ have been updated.

UPDATED HFA-ESC CRITERIA FOR DEFINING ADVANCED HEART FAILURE

Advanced heart failure is defined by the presence of all of the following criteria despite optimal guideline-directed treatments:

1. Severe and persistent symptoms of heart failure (NYHA class III [advanced] or IV).
2. Severe cardiac dysfunction defined by a reduced LVEF ($\leq 30\%$), isolated RV failure (eg, ARVC), or nonoperable severe valve abnormalities or congenital abnormalities, or persistently high (or increasing) BNP or NT-proBNP values, and data of severe diastolic dysfunction or LV structural abnormalities according to the ESC definition of HFPEF and HFMEF.⁶
3. Episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low-output requiring inotropes or vasoactive drugs, or malignant arrhythmias causing >1 unplanned visit or hospitalization in the last 12 months.
4. Severe impairment in exercise capacity with an inability to exercise or a low 6-minute walk test distance (<300 m) or pV_{O_2} (<12 - 14 mL/kg/min), estimated to be of cardiac origin.

In addition to the above, extra-cardiac organ dysfunction due to HF (eg, cardiac cachexia, liver, or kidney dysfunction) or type 2 pulmonary hypertension may be present, but are not required. Criteria 1 and 4 can be met in patients who have cardiac dysfunction (as described in criterion #2), but who also have substantial limitations due to other conditions (eg, severe pulmonary disease, noncardiac cirrhosis, or most commonly by renal disease with mixed etiology). These patients still have limited quality of life and survival due to advanced disease and warrant the same intensity of evaluation as someone in whom the only disease is cardiac, but the therapeutic options for these patients are usually more limited.

In comparison with the 2007 criteria,⁵ in the current version, criteria 2 and 3 have been updated. Criterion 2 is now based completely on the 2016 ESC guidelines.⁶ Using the ESC criteria for cardiac dysfunction gives the same importance to all patients with heart failure, independently of LVEF. Criterion 3 now includes heart failure hospitalization, unplanned visits for heart failure, and malignant arrhyth-

mias. Acute events leading to one or more unplanned visits or hospitalizations within 12 months are the hallmark of advanced heart failure, independent of treatment, emphasizing the instability of the clinical course and resource utilization.

PROGNOSTIC STRATIFICATION

Accurate prognostic stratification is especially important to identify the proper time for referral to an advanced heart failure center, to convey expectations to patients and families, and to plan treatment and follow-up strategies. This is a complex and difficult process. Numerous single-risk markers and composite risk scores have been derived, validated, and made available as interactive online tools. However, there are limitations for use in clinical settings and no single variable can account for all prognostic dimensions.

There are some suggestions to trigger referral based on clinical, laboratory, imaging, and risk core data. Cardiopulmonary exercise testing is objective and reproducible and provides relevant information about cardiovascular reserve and prognosis. Guidelines for listing elective patients for heart transplantation state that a $pV_{O_2} \leq 12$ mL/kg/min is a potential indication for heart transplantation (≤ 14 mL/kg/min if β -blocker intolerant) after ensuring that peak values have been achieved (respiratory exchange rate >1.05).

MANAGEMENT STRATEGIES FOR PATIENTS WITH ADVANCED HEART FAILURE

Advanced heart failure therapies refer to heart transplantation or long-term mechanical circulatory support devices. However, in situations where the patient's clinical condition deteriorates or end-organ damage occurs, short-term therapies until mechanical circulatory support can be implanted or used while the patient is on the transplant waiting list.

- Management strategies include different therapies (nonexclusive):
- Intravenous vasoactive drugs;
- Management of congestion (including loop diuretics or combinations of diuretics, ultrafiltration, or peritoneal dialysis);
- Short-term mechanical circulatory support: intra-aortic balloon pump, extracorporeal membrane oxygenation, TandemHeart, Impella® ventricular support systems, CentriMag™ acute circulatory support systems, etc;
- Conventional cardiac surgery;
- Heart transplantation in patients who are capable of complying with the intensive treatment required postoperatively, motivated, well informed, emotionally stable, and without contraindications; and

- Long-term mechanical circulatory support devices for those advanced heart failure patients that are inotrope-dependent (bridge to transplantation), those with relative contraindications for heart transplantation (bridge to candidacy), or in patients with contraindications for heart transplantation (destination therapy). Careful selection is mandatory for achieving satisfactory results.

PALLIATIVE CARE

Optimal care of patients with advanced heart failure includes palliative care at their end-of-life period, when conventional therapy (cardiology therapeutic approach) is not enough to reduce patient suffering and maximize quality of life. Successful palliative care must involve shared care through a multidisciplinary approach (patient's caregivers, primary care, specialist palliative care, and advanced heart failure service) according to the resources of each center.

ORGANIZATIONAL ISSUES FOR PATIENT REFERRAL TO ADVANCED HEART FAILURE CENTERS: HUB AND SPOKE NETWORK

The broad spectrum of heart failure ranges from patients in early stages largely managed by primary care physicians and secondary care cardiologists to those who progress to more advanced stages and require advanced therapies (tertiary care centers). Ideally, secondary care centers without advanced heart failure therapies (spoke centers) should liaise with a tertiary center (hub center) to develop a strong working relationship. Heart failure patients are then managed within this "hub and spoke" continuum of care, both to send patients in a safe and timely manner and to share follow-up information after the heart transplant or the implantation of a long-term mechanical circulatory support. Tertiary hub centers must provide education on advanced heart failure therapies and share their experience with the spoke center.

CONCLUSIONS

Advanced heart failure is a major clinical challenge. Changes in the clinical characteristics, clinical practices, and greater opportunities for these patients have made it necessary to develop the present update of the original HFA-ESC criteria for the definition of advanced heart failure. Standard therapy is insufficient. Inotropic therapy may be used as a bridge strategy, but it is only a palliative measure. Major progress has occurred with short-term mechanical circulatory support for immediate management of cardiogenic shock and long-term mechanical circulatory support as a bridge to heart transplantation or destination therapy. Heart transplantation is the treatment of choice in patients without contraindications. However, for those patients who are not candidates for advanced therapies, symptomatic therapy for increased quality of life is the required therapy. However, we

must recognize that no therapy in advanced heart failure is based on reliable prospective studies; therefore, there is an urgent need to develop evidence-based algorithms to prolong life, increase quality of life, and reduce the burden of hospitalizations in this vulnerable patient population. ■

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THE EUROPEAN HEART FAILURE ATLAS

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Keywords: demographics; heart failure; initiatives; national societies

One global health problem is heart failure, the management of which requires significant human and economic resources. The HFA of the ESC, the leading professional association in this area in the world, declared that its mission is to improve the quality of life and longevity of patients with heart failure through better prevention, diagnosis, and treatment of heart failure, including the establishment of networks for disease management, education, and research. One of the ways to undertake this mission is to develop better policies aimed at improving the efficacy and effectiveness of heart failure care. However, to create such policies, robust data on the economic, political, and administrative aspects of heart failure care are required, which is why the HFA together with the ESC Atlas Group decided to develop a new initiative called the European heart failure ATLAS.

The HFA already has experience analyzing real-life demographic data and heart failure statistics, as well as organizing major activities of the national heart failure societies and working groups in ESC member countries. A few years ago, data from 33 countries were collected from the presidents and representatives of the national heart failure societies during the first HFA summit of national heart failure societies in Belgrade, Serbia on October 29, 2011. The main result from this heart failure survey was the understanding that there is significant heterogeneity in the organization of heart failure management and the activities of national heart failure societies and working groups. It was noted that almost all countries already had organizations dealing specifically with heart failure. Most national heart failure societies participate in the organization of European Heart Failure Awareness Days. However, most countries are using national or translated ESC heart failure guidelines, lack a national heart failure registry, and have differences in the availability of natriuretic peptide and echocardiographic measurements between developed and developing countries. From today's perspective, this heart failure survey looks like a pioneering idea, as it is analyzing real-life information on heart failure across Europe.

OBJECTIVES OF THE EUROPEAN HEART FAILURE ATLAS

The objective of the European heart failure ATLAS is to highlight gaps and disparities in heart failure care systems across Europe and to identify and uncover

resources for changing heart failure care systems for the better. The European heart failure ATLAS contains 46 variables and 4 sections, and includes information about the country's population, health care system, heart failure epidemiology, management, and organization, as well as including the major activities of the national heart failure societies. The list of variables was developed and finalized by experts and members of the task force of the ESC ATLAS group and the HFA board of the ESC. The first two sections of the European heart failure ATLAS will be focused on each country's population and health care system. The following variables will be analyzed: country population, number of inhabitants who are 65 years of age and older, mean life expectancy for women and men, number of physicians, cardiologists, general practitioners, and hospitals per 1 million inhabitants, top three fatal diseases, type of health care system, and availability of general health statistics.

The third section of the European heart failure ATLAS will be devoted to heart failure epidemiology and management statistics. The list of variables in this section includes the incidence and prevalence of heart failure, mortality due to heart failure, the number of hospitals with dedicated heart failure clinics, heart failure units, heart failure nurses, the number of heart failure-related hospital admissions, and the average number of days spent in the hospital due to heart failure. In addition, the survey will analyze the number of hospitals: (i) with BNP (NT-proBNP) or echocardiography testing available in the emergency rooms for acute dyspnea or suspected acute heart failure; (ii) performing spirometry; (iii) with a heart failure management exercise program; and (iv) with the capability of providing ICD remote control or other remote monitoring systems. Special attention will be paid to the number of centers with interventional cardiology and cardiac surgery, the number of hospitals performing transcatheter mitral valve repair (MitraClip) and implanting left ventricular assist devices, as well as the total number of LVADs implanted in the last 2 years. Close attention will also be given to the use of guideline-recommended heart failure medications (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β -blockers, mineralocorticoid receptor antagonists, and diuretics) and to the availability of more innovative agents (ivabradine, angiotensin receptor-neprilysin inhibitor, and novel oral anticoagulants).

The final section of the European heart failure ATLAS will include a description of the organization and major activities of national heart failure societies. This section will cover data on the number of members in each national society, the participation of other health care professionals (nurses, general practitioners, geriatricians) in the national heart failure society, existence of annual or regular heart failure meetings, heart failure patient organizations, and heart failure patient education (videos, online lectures, websites). Special attention will be given to the

participation of national heart failure societies in HFA registries, the existence of a national heart failure registry or survey, implementation of ESC/HFA guidelines, the existence of a heart failure screening program in the country, existence of certification for heart failure cardiologists and heart failure nurses, use of the website Heartfailurematters.org, and help in the organization of the Heart Failure Awareness Days.

DATA SOURCES

The above-mentioned data will be gathered from various sources, including government websites and institutes, ministries of health, official statistics services, and academic institutions. Information from ad hoc publications, payers, and databases and registries of the national heart failure societies will also be used. Since the European heart failure ATLAS is intended as a long-term project, a constant quality control of collected data will be needed. The participation of 37 ESC member countries is being considered at present. All collected country data will be reviewed and approved by corresponding national heart failure societies. Thereafter, all country data will be peer-reviewed by experts not involved in the project.

Periodically updated data in the European heart failure ATLAS will allow trends, disparities, and gaps in heart failure management to be identified at the country level and to allow for a comparison between countries. This information will be useful not only for the ESC member countries, but also for other countries around the world.

CONCLUSIONS

Data from the European heart failure ATLAS will be in demand in the ESC, the HFA, or national heart failure societies, and at the level of policy and governmental agencies, academic, research, financial institutions, the technology industry, public or private insurance agencies, and other parties that are interested in optimizing the management of patients with heart failure. Currently, the HFA considers the European heart failure ATLAS as a key initiative that will help realize the HFA mission to improve the quality of life and longevity of patients with heart failure. ■

THE NEW DEFINITION OF ADVANCED HEART FAILURE

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Keywords: criterion; advanced heart failure; prognosis

Patients with severe heart failure represent a growing percentage among the whole cohort of patients with heart failure and these patients have a poor prognosis and quality of life.¹⁻³ Advanced heart failure encompasses patients who remain severely symptomatic despite optimal guideline-directed management regardless of LVEF, including patients who remain ambulatory, but are in the NYHA class IV. A correct definition of patients with advanced heart failure is therefore important in order to select patients that could undergo evaluation for heart transplantation or long-term mechanical circulatory support devices.

During the 2018 Heart Failure Association congress, the position paper on the new definition of advanced heart failure was presented and, at the same time, published online in the *European Journal of Heart Failure*.⁴ The task force led by Professors Marisa Crespo-Leiro and Marco Metra extensively revised the previous document published in 2007.⁵ The relevance of the new definition of advanced heart failure should also be considered in the context of the largely improved outcomes of patients treated with modern circulatory support devices or who underwent a heart transplant. The importance of screening and referring patients with suspect advanced heart failure has been repeatedly highlighted in order to identify the most appropriate time for indicating more aggressive and costly interventions. An updated definition could help clinicians guide their screening activities of patients with heart failure with any level of LVEF.

The criteria suggested in 2007⁵ identified a stage where conventional treatments are insufficient to control the patient's symptoms, and advanced therapies (eg, cardiac transplantation, mechanical circulatory support) or palliative therapies (eg, inotropic infusions, ultrafiltration or peritoneal dialysis to control volume, or end-of-life comfort care) are needed. Compared with the former definition of advanced heart failure, two criteria—2 and 3—have been mainly revised (*Table 1*).

MAJOR UPDATES TO THE CRITERIA FOR DIAGNOSING ADVANCED HEART FAILURE

Criterion 2, which defines cardiac dysfunction, is now based on the most recent ESC heart failure guidelines.² The ESC criteria are sufficient to define cardiac dys-

2007 HFA–ESC criteria ⁴	2018 Updated HFA–ESC criteria for defining advanced heart failure ³
<p>Characterized by the presence of all of the following:</p> <ol style="list-style-type: none"> 1. Severe symptoms of HF with dyspnea and/or fatigue at rest or with minimal exertion <ol style="list-style-type: none"> a) NYHA functional class III or IV 2. Episodes of fluid retention (pulmonary and/or systemic congestion, peripheral edema) and/or of reduced cardiac output at rest (peripheral hypoperfusion) 3. Objective evidence of severe cardiac dysfunction, shown by at least one of the following: <ol style="list-style-type: none"> a) A low LVEF (<30%) b) A severe abnormality of cardiac function on Doppler echocardiography with a pseudonormal or restrictive mitral inflow pattern c) High LV filling pressures <ol style="list-style-type: none"> i. Mean PCWP >16 mm Hg and/or mean RAP >12 mm Hg by pulmonary artery catheterization d) High BNP or NTproBNP plasma levels, in the absence of noncardiac causes 4. Severe impairment of functional capacity shown by one of the following: <ol style="list-style-type: none"> a) Inability to exercise b) 6-min walk test distance ≤300 m in females and/or patients ≥75 years old c) Peak Vo_2 <12–14 mL/kg/min 5. History of one or more HF hospitalizations in the past 6 months. 6. Presence of all the previous features despite “attempts to optimize” therapy, including diuretics, RAAS inhibitors, and β-blockers, unless these are poorly tolerated or contraindicated, and CRT, when indicated 	<p>All the following criteria must be present despite optimal guideline-directed treatment:</p> <ol style="list-style-type: none"> 1. <u>Severe and persistent symptoms of heart failure</u> <ol style="list-style-type: none"> a) NYHA class III (advanced) or IV 2. <u>Severe cardiac dysfunction</u> <ol style="list-style-type: none"> a) Reduced LVEF ≤30%, isolated RV failure (eg, ARVC) or nonoperable severe valve abnormalities or congenital abnormalities or persistently high (or increasing) BNP or NTproBNP values and data of severe diastolic dysfunction or LV structural abnormalities according to the ESC definition of HFPEF and HFMEF 3. <u>Episodes of pulmonary or systemic congestion</u> requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing more than one unplanned visit or hospitalization in the last 12 months 4. <u>Severe impairment of exercise capacity</u> with an inability to exercise or a low 6-min walk test distance (<300 m) or Vo_2 (<12–14 mL/kg/min), estimated to be of cardiac origin <p>In addition to the above, extracardiac organ dysfunction due to heart failure (eg, cardiac cachexia, liver, or kidney dysfunction) or type 2 pulmonary hypertension may be present, but are not required</p> <p>Criteria 1 and 4 can be met in patients who have cardiac dysfunction (as described in criterion #2), but who also have substantial limitations due to other conditions (eg, severe pulmonary disease, noncardiac cirrhosis, or most commonly by renal disease with mixed etiology). These patients still have limited quality of life and survival due to advanced disease and warrant the same intensity of evaluation as someone in whom the only disease is cardiac, but the therapeutic options for these patients are usually more limited.</p>

Table I. The new criteria for advanced heart failure.

function, and they can be used for the definition of advanced heart failure when accompanied by other criteria that characterize patient severity. Using the ESC criteria for cardiac dysfunction gives the same importance to all patients with heart failure, independent from LVEF. With a few exceptions, such as patients with hypertrophic cardiomyopathy or restrictive cardiomyopathy,⁵ the vast majority of patients with an indication for heart transplantation or mechanical circulatory support have a reduced LVEF. However, almost 50% of patients hospitalized for acute heart failure have a preserved LVEF, and these patients may be considered advanced provided that the other criteria outlined in the definition are present. In the previous definition, advanced symptoms in the setting of HFPEF were not sufficiently emphasized and it is important to raise awareness about the fact that advanced heart failure does not depend on LVEF, but rather on the patient's symptoms, prognostic markers, presence of end-organ damage, and goals for therapy. In addition, the INTERMACS classification describes patient profiles with severe heart failure, but includes only patients with HFREF, whereas the definition of advanced heart failure should be applicable to all ejection fraction categories.⁶

Criterion 3 acknowledges that acute events, leading to one or more unplanned visits or hospitalizations within 12 months, are the hallmark of advanced heart failure, independent from treatment, with emphasis placed on the instability of the clinical course and resource utilization. Unplanned visits for heart failure have been added and have the same value as a heart failure hospitalization. Outpatient visits with intravenous administration of loop diuretics and/or other vasoactive medications are increasingly replacing hospitalizations for heart failure.⁷ Thus, both unplanned outpatient visits and hospitalizations for worsening symptoms of heart failure must be considered among the criteria for the diagnosis of advanced heart failure to reflect evolving clinical practice. In this context, malignant arrhythmias have been added as a major cause of acute events.

Major emphasis has also been given to comorbidities, which often complicate the evaluation of patients with advanced heart failure, and may influence the candidacy for mechanical circulatory support or heart transplantation. Severe kidney or liver dysfunction and pulmonary hypertension may be a consequence of acute congestion and/or a low-output state, but it may be difficult to distinguish primary and secondary dysfunction or to predict reversibility.⁸ An early recognition and treatment of these clinical conditions, which frequently complicate the course of heart failure, specifically when heart failure is advanced, could further improve quality of life and survival of patients with advanced heart failure. Having increased the attention on the aspect of relevant and invalidating comorbidities further enhances the concept that a multidisciplinary approach is mandatory to manage patients with heart failure appropriately, especially those with an advanced condition.

CONCLUSIONS

Now that the updated definition is available, it is necessary to see how this definition will be accepted by cardiologists dealing with patients with heart failure and implemented in real clinical practice. The heart failure registry of the ESC is designed to collect data in patients with acute and chronic heart failure in different countries and it is likely the ideal setting to evaluate: (i) how many patients with advanced heart failure are observed in daily practice using the updated definition; (ii) how these patients are treated; and (iii) whether a gap exists between the recommendations of the updated document and the management of these patients in the real world. ■

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HEART FAILURE: GUIDELINES, CONSENSUS STATEMENTS, TRIAL RESULTS, AND MORE

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Keywords: *atrial fibrillation; catheter ablation; comorbidities; heart failure; revascularization*

The 2018 Heart Failure and the 5th World Congress on Acute Heart Failure took place from May 26 to May 29, 2018 in the Exhibition and Congress Center in Vienna, Austria. The congress was organized by the HFA of the ESC. This congress is a unique forum where HF professionals worldwide meet and exchange ideas and information. The congress was attended by 5881 participants, with a large faculty of over 300 international experts. The record number of abstracts (2010 [up by 306 compared with the previous year]) and case studies submissions, has established the 2018 HFA congress as the largest and most influential HF meeting in the world.

The theme of this year's congress was "Heart failure: classical repertoire, modern instruments," alluding to Vienna as the world's capital of classical music. Besides an attractive core program, the congress had several distinct and attractive features, including "Late-Breaking Trials," "Guidelines in Daily Practice," "HFA Championship," "HFA Grand Debates," and "Off the Record" sessions.

HFA LIFETIME ACHIEVEMENT AWARDS

During the Inaugural session, two leading HF scientists were awarded the HFA Lifetime Achievement Award: Walter Paulus for basic science and Marc Pfeffer for clinical research. Walter Paulus gave the Philippe Poole Wilson basic science lecture, which was titled "Fighting heart failure with preserved ejection fraction: the battle lines are shifting." During the talk, he discussed the challenges of treating HFPEF and highlighted some of the novel strategies that are being explored. There is a shift in the balance of HF phenotypes, such that HFPEF is becoming increasingly prevalent. He outlined that the major contributors to the growing burden of HFPEF include an increasing elderly population and the epidemic of obesity, metabolic syndrome, and diabetes. Marc Pfeffer, a former mentee of Eugene Braunwald, gave the HFA Eugene Braunwald lecture for clinical excellence, which was titled "Building on concepts." He talked about his life-long devotion to research in cardiovascular medicine, focusing on the interface

between high-risk patient characteristics and prognosis. He expressed his gratitude to Eugene Braunwald for his lifelong support and fruitful collaboration in scientific research.

LATE-BREAKING TRIALS

HF worldwide

Sean Collins presented the primary results from the worldwide prospective HF registry, REPORT-HF! This registry included 18 000 patients from 44 countries across the globe. The results showed some striking regional differences in acute HF characteristics, its precipitants, and initial care across the world that may have considerable implications for clinical practice and future research. There were interregional differences in the hospital entry points, comorbidities, and precipitants of acute HF. In addition, there were observed differences clustered within regions across the globe. This finding indicates that there are difficulties in implementing evidence-based patient care specific to counties and regions, which must be addressed.

β -Blockers in patients with HF

Dipak Kotecha reported on the effectiveness of β -blockers for reducing all-cause mortality in patients with HF depending on the presence of diabetes and obesity. These results were derived from an analysis made by the Beta-Blockers in HF Collaborative Group,² which included data on 8298 patients with HF without diabetes or obesity, 2331 nonobese patients with diabetes, 2121 obese patients without diabetes, and 1109 obese patients with diabetes. The results showed that β -blockers lowered the risk of all-cause mortality in both patients with diabetes without obesity and patients without diabetes or obesity, which provides further support for a wider implementation of the guideline-recommended use of β -blockers in patients with HF. Patients with diabetes and HF, but not obesity, have the highest mortality rate. In patients with both diabetes and obesity, the benefit with β -blockers is less certain, as obesity attenuates their effectiveness.

SERCA-LVAD trial

Alexander Lyon discussed findings from the SERCA-LVAD trial (NCT00534703). This trial is testing the hypothesis that restoring SERCA2a levels, which are downregulated in patients with HF, by cardiac delivery of an adenovirus vector containing the human SERCA2a gene, could improve outcomes. Although prematurely terminated for futility, this trial provides some valuable insights into gene therapy for HF. The viral DNA was detected in human hearts, but at a level too low to have an impact on physiological processes, which indicates that one of the biggest challenges for future research would be to improve gene delivery to the heart to achieve effective doses in the cells.

Cardiac resynchronization therapy

Cecilia Linde discussed findings from the ESC Cardiac Resynchronization Survey (CRT Survey II) on 11 088 patients with HF, concerning a comparison between upgrades from a previous device and de novo CRT implantation.³ It was stressed that, although patients in whom an upgrade was performed were older and with more severe comorbidities compared with de novo CRT recipients, there were no significant differences regarding the quality of the procedure or periprocedural complications.

Niraj Varma reported the results from the EchoCRT trial concerning the impact of left ventricular size on the effectiveness of CRT in patients with HF and a QRS duration <130 ms.⁴ This study showed that CRT had opposite effects on outcomes in patients with a narrow QRS depending on left ventricular size. Worse outcomes in terms of mortality and HF hospitalization were observed in patients with larger left ventricles. However, beneficial effects on outcomes were seen in those with smaller ventricles. This study gave a new perspective for CRT in patients with a narrow QRS.

GUIDELINES IN DAILY PRACTICE

The Guidelines in Daily Practice session reviewed the 2016 ESC/HFA guidelines for the diagnosis and treatment of acute and chronic HF, focusing on five important topics, ie, iron deficiency, acute heart failure, valvular disease, chronic heart failure, and HFPEF. These were patient-centered sessions that were based on the analysis of clinical cases, presented by top experts involved in the development of the guidelines. They described the optimal treatment related to the case and explained where in the guidelines the relevant information, tables, and algorithms could be found. This session was highly interactive because the delegates were given the opportunity to send questions via the Heart Failure 2018 mobile app.

HFA CHAMPIONSHIP

The HFA Championship, a competition for the best clinical case presentation, attracted a lot of attention among the teams from Korea, Austria, and the last year's winner, France. The teams consisted of four health care professionals who presented a case, followed by a discussion and questions from the chairpersons. This session was also based on the ESC guidelines, and the teams had the opportunity to ask "trick" questions and to use two "jokers," which increased the tension and expectations of the competition. After a fierce, but fair debate, the French team won and kept the trophy they had won in 2017.

GRAND DEBATES SESSIONS

Coronary revascularization

The first session focused on drugs or interventions. John Cleland and Eric Velazquez debated the pros and cons of the statement “Coronary revascularization provides no meaningful clinical benefit over optimal medical therapy (OMT) in patients with stable ischemic HF.” John Cleland stated that, in patients with HFREF and a previous myocardial infarction, it is important to weigh the risks and benefits of revascularization. Potential benefits include relieving angina, improving HF symptoms and left ventricular function, preventing new coronary events, and increasing longevity. Revascularization can also lead to procedural deaths and myocardial damage, or the procedure may be futile. He also stressed that there might be some discrepancies in the results of clinical trials on the benefits of revascularization in patients with HFREF.^{5,6} On the contrary, Eric Velazquez stated that evidence from observational studies and RCTs favors revascularization for appropriately indicated patients with HFREF. Moreover, he stated that no groups that are at risk of harm from revascularization have been identified in RCT subgroup analyses. There is also no age cut-off and there is no imaging prerequisite before performing revascularization. Thus, the trial results support revascularization in patients with HFREF, provided the right patients are selected.

Catheter ablation vs drug treatment for AF

The value of catheter ablation vs drug treatment for patients with AF and HF was also debated. Nassir Marrouche stated that catheter ablation is superior to drugs. He reviewed the results of the recent RCTs, including the CASTLE-AF⁷ and the much-anticipated CABANA (NCT00911508) trials, and concluded that the trial evidence shows that ablation improves ejection fraction, as well as AF burden, quality of life, hospitalization rate, and mortality. Milton Packer’s main criticism was that most conclusions on the effectiveness of ablation were based on the “on-treatment” analyses, rather than the “intention-to-treat” analysis of the RCT results, which could exaggerate the effectiveness of the procedure. He also stated that most of the trials were small and open-labeled, meaning that their results should be viewed as hypothesis-generating, rather than conclusive on the role of catheter ablation in patients with AF and HF.

Definition and management of HFMEF

In another very interesting session, Lars Lund and Scott Solomon debated the controversies in the definition and management of HFMEF. Lars Lund, basing his discussion on the CHARM trial, in which patient characteristics and outcomes were evaluated across the spectrum of echocardiographically assessed ejection fraction,⁸ pointed out that there are significant similarities between patients with

HFMEF and patients with HFREF, including the average age, the proportion of women, systolic blood pressure, the proportion of ischemic etiology, and AF. All of these traits in patients with HFMEF were more similar to HFREF than to HFPEF. In addition, the outcomes of patients with HFMEF, although milder than in patients with HFREF, were still more similar to HFREF than to HFPEF. On the contrary, Scott Solomon emphasized that the differences in patient characteristics and outcomes observed between HFREF, HFMEF, and HFPEF are so pronounced that there are unquestionably three distinct phenotypes. Thus, he concluded that it is hard to argue that HFMEF is the same as HFREF.

CONSENSUS PAPER ON DIAGNOSING HFPEF

One of the highlights of the congress was the session dedicated to the new HFA expert consensus paper regarding the diagnosis of HFPEF, which is based on a four-step diagnostic approach, and is due to be published in the *European Journal of Heart Failure* and the *European Heart Journal*. Burkert Pieske said that the first diagnostic step should occur at the point of the patient's first entry, and that this step could be conducted by doctors who do not need to be HF specialists. This step involves assessing the probability of HF based on a combined assessment of the patient's risk factors, medical history, ECG, and laboratory tests, including hemoglobin and natriuretic peptides. This step also includes a standard echocardiography exam to assess left ventricular ejection fraction and an exercise test. If the evidence points toward HFPEF, patients should proceed to the second step, which is the most innovative part of the consensus statement. In the second step, a sophisticated echocardiographic work-up in conjunction with natriuretic peptide levels (stratified by the presence or absence of AF) will result in an individual HFPEF likelihood score, which is meant to confirm or exclude HFPEF. According to this score, patients in the grey zone should proceed to the third step, where exercise testing in combination with echocardiography is used to confirm or exclude a HF diagnosis. The fourth step concerns assessing the underlying etiology and pathophysiology, and generally relies on magnetic resonance imaging, sophisticated laboratory measures, and/or myocardial scintigraphy or biopsy. This crucial information will enable HF specialists to tailor treatment to the patient.

HF COMORBIDITIES AND ADVERSE CARDIOVASCULAR EVENTS

The 2018 HFA congress also provided sessions focusing on the treatment of common comorbidities in patients with HF. Among the best attended were sessions dedicated to the treatment of patients with concomitant HF and diabetes. Besides reviewing clinical trial results on cardiovascular outcomes with novel antidiabetic medications, these sessions also highlighted that some of the novel drugs, such as the SGLT-2 inhibitors, demonstrated a significant reduction in the risk of ad-

verse HF outcomes among patients with diabetes. Based on these results, there are trials underway that assess the effectiveness of SGLT-2 inhibitors to reduce HF outcomes in patients with HFREF and HFPEF, with and without diabetes.

Kelly Branch presented the results of a substudy of the COMPASS trial⁹ that focused on the prevention of MACE in patients with HF and stable coronary and/or peripheral arterial disease. This analysis demonstrated that the risk of MACE was higher in patients with HF. Importantly, the combination of rivaroxaban and aspirin was more effective than aspirin alone for reducing MACE in patients with and without HF. However, due to a higher risk, patients with HF had an absolute risk reduction that was more than doubled with the rivaroxaban and aspirin combination (2.4%) compared with treatment with aspirin alone (1.0%).

OFF THE RECORD SESSIONS

This year's popular "Off the Record" sessions featured some of the most prominent scientists in the world of cardiology. In these interactive sessions, discussants and the audience had an opportunity to hear about the current advances in the treatment of HF with antidiabetic drugs from Eugene Braunwald, to share thoughts about the interpretation of clinical trial results with Marc Pfeffer, to get an in-depth view on the underlying mechanisms of AF and their relevance for the patient care with Barbara Casadei, and to discuss some of the future perspectives in HF treatment based on putative pathophysiological mechanisms with Walter Paulus.

CONCLUSIONS

In conclusion, the 2018 HFA congress again provided fireworks of new scientific data, blended with extraordinarily useful clinical information. Gathering both basic and clinical scientists at the same arena, the HFA proved its global leading position, setting a solid foundation for further breakthroughs and successes. ■

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Abbreviations & Acronyms



ACE	angiotensin-converting enzyme
AF	atrial fibrillation
ALDO-DHF	Aldosterone Receptor Blockade in Diastolic Heart Failure
ARB	angiotensin receptor blocker
ARVC	arrhythmogenic right ventricular cardiomyopathy
ASCEND-HF	Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure
ATMOSPHERE	Aliskiren Trial to Minimize OutcomeS in Patients with HEaRt FailurE
ATOMIC-AHF	Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure
BACH	Biomarkers in Acute Heart Failure
BIOSTAT-CHF	a systems BIOlogy Study to TAIlored Treatment in Chronic Heart Failure
BLAST-AHF	Biased Ligand of the Angiotensin receptor STudy in Acute Heart Failure
BNP	brain natriuretic peptide
CABANA	Catheter Ablation vs ANti-arrhythmic drug therapy for Atrial fibrillation
CAD	coronary artery disease
CANVAS	CANagliflozin cardioVascular Assessment Study
CASTLE-AF	Catheter Ablation versus Standard conventional Treatment in patients with LEft ventricular dysfunction and Atrial Fibrillation
CHAMPION	CardioMEMS Heart failure sensor Allows Monitoring of Pressures to Improve Outcomes in NYHA functional class III heart failure patients
CHARM	Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity
COMMANDER HF	COMparison of the efficacy and safety of rivaroxaban with placebo for reducing the risk of death, Myocardial infArctioN or stroke in subjects with heart failure and significant coronary artery Disease following an episode of decompensated Heart Failure

COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
CORONA	Controlled Rosuvastatin Multinational Trial in Heart Failure
CPMP	cardio patient monitoring platform
CRT	cardiac resynchronization therapy
CRT Survey II	Cardiac Resynchronization Survey
CRT-D	cardiac resynchronization therapy defibrillator
CUPID 2	Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease Phase 2b
Dapa-HF	Dapagliflozin on the incidence of worsening heart failure or cardiovascular death in patients with chronic Heart Failure
DIG	Digitalis Investigation Group
DREAM	Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication
EchoCRT	Echocardiography Guided Cardiac Resynchronization Therapy
EDIFY	prEserved left ventricular ejection fraction chronic heart Failure with ivabradine study
ELANDD study	Effects of Long-term Administration of Nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with Diastolic Dysfunction
EMA	European Medicines Agency
EMBRACE	Evaluation of Myocardial Effects of Bendavia for Reducing Reperfusion Injury in Patients With Acute Coronary Events
EMPA-REG OUTCOME	Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes
EMPERIAL-Preserved	Empagliflozin in Patients With Chronic Heart Failure With Preserved Ejection Fraction
EMPERIAL-Reduced	Empagliflozin in Patients With Chronic Heart Failure With Reduced Ejection Fraction
EMPEROR-Preserved	EMPagliflozin outcomE tRIal in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction

EMPEROR-Reduced	EMPagliflozin outcome tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction
ESC	European Society of Cardiology
EVINCI	EValuation of INtegrated Cardiac Imaging for the Detection and Characterization of Ischaemic Heart Disease
EVITA	Effect of Vitamin D on All-cause Mortality in heart failure patients
FDA	Federal Drug Administration
GISSI-HF	Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto miocardico Heart Failure
GLP-1	glucagon-like peptide 1
GRK2	G protein-coupled receptor kinase 2
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
HNO	nitroxyl
IABP	intra-aortic balloon pump
ICD	implantable cardioverter-defibrillator
ICOS-ONE	International CardioOncology Society-one trial
I_f	funny channel
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
INT-HF-MP	intensified heart failure management program
I-PRESERVE	Irbesartan in heart failure with PRESERVEd systolic function
LDL	low-density lipoprotein
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results
LV	left ventricle
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
MACE	major adverse cardiac events

MANAGE-HF	Multiple cArDiac seNsors for mAnaGEment of Heart Failure
MR-proANP NAVIGATOR	MR-pro-atrial natriuretic peptide Long-term Study of Nateglinide+Valsartan to Prevent or Delay Type II Diabetes Mellitus and Cardiovascular Complications
NT-proBNP NYHA	N-terminal pro-brain natriuretic peptide New York Heart Association
OMT	optical medical therapy
OPTIMIZE-HF	Organized Program To Initiate lifesaving treatMent In hospitaliZed patients with Heart Failure
PAD	pulmonary artery disease
PAL-HF	PALliative care in Heart Failure
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
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
PCSK-9	proprotein convertase subtilisin/kexin type 9
PDE5	phosphodiesterase-5
RALI-DHF	RANoLazIne for the Treatment of Diastolic Heart Failure
RCT	randomized controlled trial
REALITY-AHF	Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure
RELAX	PhosphdiesteRasE-5 Inhibition to Improve CLinical Status and EXercise Capacity in Diastolic Heart Failure
REPORT-HF	REgistry to assess medical Practice with lOngitudinal obseRvation for Treatment of Heart Failure
RV	right ventricle

SENIORS	Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure
SERCA2a	sarco(endo)plasmic Ca ²⁺ ATPase type 2a
SERCA-LVAD	investigation of the safety and feasibility of AAV1/ SERCA2a gene transfer in patients with chronic heart failure and a Left Ventricular Assist Device
sGC	soluble guanylate cyclase
SGLT2	sodium glucose cotransporter 2
SOCRATES-PRESERVED	SOluble guanylate Cyclase stimulatO in heArT failurE patientS with PRESERVED ejection fraction
SOLOIST-WHF	Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure
SPIRIT-HF	Sharing Patient Illness Representations to Increase Trust in Heart Failure
ST2	suppresion of tumorigenicity 2
STEMI	ST-segment elevation myocardial infarction
SUCCOUR	Strain sUrveillance during Chemotherapy for improving CardiOvascUlAR outcomes
TOPCAT	Treatment Of Preserved Cardiac function heart failure with an Aldosterone anTagonist
TRIUMPH	Translational Initiative on Unique and novel strategies for Management of Patients with Heart failure
VALIDD	ValSartan In Diastolic Dysfunction
WHICH	Which Heart failure Intervention is most Cost-effective & consumer friendly in reducing Hospital care

Instructions for Authors



INSTRUCTIONS FOR AUTHORS

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Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation*. 2007;115:2689-2696.

● Chapter in a book

Green J, Naylor L, George K, Dempsey J, Stickland M, Katayama K. Cardiovascular and pulmonary adaptations to endurance exercise. In: Taylor N, Groeller H, eds. *Physiological Bases of Human Performance During Work and Exercise*. Philadelphia, PA: Elsevier Ltd; 2008:49-70.

● Web-based material

American College of Cardiology. CardioSmart. <https://www.cardiosmart.org>. Accessed May 11, 2016.

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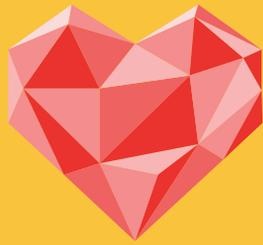
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Heart Failure Vienna 2018

This publication is supported by an unrestricted grant from
Institut La Conférence Hippocrate - Servier Group

