

# DIALOGUES IN CARDIOVASCULAR MEDICINE

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**YEAR** in cardiology

**2016**

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# Dialogues in Cardiovascular Medicine

## Aims & Scope

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

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## Editors in Chief

### Roberto Ferrari

(Editorial Assistant: Ms Juliet Verri)  
Chair of Cardiology  
Azienda Ospedaliero - Universitaria di Ferrara  
Ospedale di Cona - 2/C/3° piano - Room 3:13:03  
Via Aldo Moro 8 - 44124 Cona (Ferrara) - ITALY  
Tel: +39 (0)532 239882  
E-mail: editor.dcvm@gmail.com

### Kim Fox

(Editorial Assistant: Ms Deborah Curcher)  
National Heart and Lung Institute  
Institute of Cardiovascular Medicine and Science  
Royal Brompton Hospital  
London SW7 2AZ - UK  
Tel: +44 (0)20 7351 8626  
E-mail: D.Curcher@rbht.nhs.uk

## Editorial Offices

### Director of Publication

Philippe Gonnard, MD

### Scientific coordinator

Sophie Nisse-Durgeat, PharmD  
E-mail: sophie.nisse-durgeat@servier.com

### Manager, Journal publications

Catriona Donagh, BAppSc  
E-mail: catriona.donagh@servier.com

## Production Editor

Sherri S. Smith, PhD  
50 rue Carnot  
92284 Suresnes Cedex - FRANCE  
Tel: +33 (0)1 55 72 38 37  
E-mail: sherri.smith@servier.com

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Institut La Conférence Hippocrate (AICH)  
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92284 Suresnes Cedex  
FRANCE  
Tel: +33 (0)1 55 72 60 00

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Tel: +33 (0)1 55 72 38 37  
E-mail: sherri.smith@servier.com

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## Editors in Chief

**Roberto Ferrari**, MD, PhD

Chair of Cardiology

University Hospital of Ferrara, Cona (Ferrara), Italy

**Kim Fox**, MD, FRCP

National Heart and Lung Institute

Institute of Cardiovascular Medicine and Science

Royal Brompton Hospital, London, UK

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## EDITORIAL

*Dialogues in Cardiovascular Medicine* was launched in 1996 by the Editors in Chief David Hearse and Roberto Ferrari. In 2013, David Hearse retired, and Kim Fox stepped in to become the next co-Editor in Chief. Each issue explored, in concise detail, a single, clinically relevant, cardiovascular topic, with topics that ranged from the origins and management of ischemic heart disease to HIV, genetics, stroke, Olympic athlete challenges, and even the brokenhearted. The project's success was made possible through the help of distinguished and world-renowned cardiovascular experts. Roberto Bolli's excellent discussion on myocardial stunning and Lionel Opie's outstanding review on cardiac metabolism for the first and second issues marked the beginning of what would become eighty-two very successful issues.

*Dialogues* is distributed to approximately 700 cardiologists and physicians worldwide, and both the International Society for Heart Research and the European Society of Cardiology have asked the publishers to distribute copies to a selected number of their members. The journal's success can be attributed to the fact that *Dialogues* was exactly what it promised to be: (i) a monothematic general review of emerging topics, which was enriched with three in-depth answers to the most eminent questions on the topic as well as summaries of the ten most pivotal publications; (ii) the selection of topics; and, most importantly, (iii) the esteemed writers. Consequently, *Dialogues* became an excellent teaching resource for students and postgraduates and an ideal source to use when preparing for a scientific presentation or writing a scientific article on a particular subject. All of this success, of course, was due to the great teamwork between the editors, authors, reviewers, and publishers.

In 2006, with the help of our dear friend Arnold Katz, who is sadly no longer with us, we published the 10-year anniversary issue, which summarized the advances and landmarks that had shaped cardiology over the previous 10 years. In Arnold's article "Blossoms on the tree of cardiology: some predictions for the coming decade," he made predictions for what would happen in 2016. However, what Arnold could not have predicted is that 2016 would be the year that *Dialogues* would make a pragmatic transformational change. After 20 successful years in its current format, the editors of *Dialogues* have been inspired by the multitude of scientific and medical forums and meetings to transform *Dialogues* into this new version, which is to serve as a "dialogue" between a selection of key opinion leaders and readers about the topics, guidelines, and registries that have impressed and captivated them at various meetings and congresses throughout the year.

This issue, the *Year in Cardiology 2016*, provides you with the latest information and advances in cardiology as presented at five of the top international congresses and meetings worldwide, including the American College of Cardiology meeting, the World Congress of Cardiology & Cardiovascular Health congress, the Heart Failure Association congress, the European Society of Cardiology congress, and the American Heart Association Scientific Sessions. In addition, this first issue introduces a new article, Cardiology Snapshot of the Year, which presents short summaries on each cardiology paper published in the *New England Journal of Medicine* and the *Lancet*, two of the world's most prominent scientific publications. Briefly, the Year in Cardiology will tell you what has happened in cardiology throughout the year in a simple, direct, and unbiased way.

Subsequent issues in 2017 will focus on the Heart Failure Association congress and the European Society of Cardiology congress.

Along with the new version of the journal, our website will be changing to reflect the redesign and to facilitate an open "dialogue" among all members of the cardiology community worldwide.

We invite you to visit [www.dialogues-cvm.com](http://www.dialogues-cvm.com) to discover the new site and updated contents.

We hope our readers (old and new) will enjoy this modernized version of *Dialogues*.

**ROBERTO FERRARI & KIM FOX**

Cardiology  
Snapshot of the Year



# CARDIOLOGY SNAPSHOT OF THE YEAR

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

*These articles were taken from the New England Journal of Medicine and the Lancet between January 1, 2016 and December 31, 2016. All research articles on cardiology were included; reviews and guidelines were excluded.*

## **GENERAL CARDIOLOGY**

**Khatib R, McKee M, Shannon H, et al; PURE Study Investigators. Availability and affordability of cardiovascular disease medicines and their effect on use in high-income, middle-income, and low-income countries: an analysis of the PURE study data. *Lancet*. 2016;387(10013):61-69.**

The PURE study showed that the secondary prevention medicines (aspirin,  $\beta$ -blockers, angiotensin-converting enzyme inhibitors, and statins) are unavailable and unaffordable for a large proportion of communities and households in upper middle-income, lower middle-income, and low-income countries, where the use of these medicines is very low.

**Prandoni P, Lensing AW, Prins MH, et al; PESIT Investigators. Prevalence of pulmonary embolism among patients hospitalized for syncope. *N Engl J Med*. 2016;375(16): 1524-1531.**

The PESIT investigators performed a systematic workup for pulmonary embolism in patients admitted to the hospital for a first episode of syncope, and they identified a pulmonary embolism in nearly one out of every six patients hospitalized for a first episode of syncope.

## **ARRHYTHMIA**

**Bagnall RD, Weintraub RG, Ingles J, et al. A prospective study of sudden cardiac**

**death among children and young adults. *N Engl J Med*. 2016;374(25):2441-2452.**

This prospective, population-based, clinical, and genetic study analyzed the causes of sudden cardiac death among children and young adults. Genetic testing was able to determine the likely cause of death in 27% of the cases of unexplained sudden cardiac death, showing that adding genetic testing to autopsy investigations helps determine the cause of death.

**Gillinov AM, Bagiella E, Moskowitz AJ, et al; CTSN. Rate control versus rhythm control for atrial fibrillation after cardiac surgery. *N Engl J Med*. 2016;374(20):1911-1921.**

The best initial treatment for atrial fibrillation after cardiac surgery—heart rate control vs rhythm control—remains controversial. The AFFIRM trial showed that neither treatment was superior to the other in terms of length of hospital stay, complication rates, and rates of persistent atrial fibrillation.

**Goette A, Merino JL, Ezekowitz MD, et al; ENSURE-AF Investigators. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. *Lancet*. 2016;388(10055): 1995-2003.**

The ENSURE-AF study, the largest randomized clinical trial of anticoagulation

for cardioversion in patients with atrial fibrillation, showed that edoxaban, an oral factor Xa inhibitor, is noninferior for the prevention of stroke and systemic embolism, and it is associated with less bleeding than well-controlled warfarin therapy.

---

**Healey JS, Oldgren J, Ezekowitz M, et al; RE-LY Atrial Fibrillation Registry and Cohort Study Investigators. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. *Lancet*. 2016;388(10050):1161-1169.**

The RE-LY Atrial Fibrillation Registry and Cohort Study showed that there were significant interregional variations in the occurrence of stroke, heart failure, and death among patients presenting to an emergency department with atrial fibrillation. While stroke continues to be a major problem globally, heart failure is by far the most common cause of death for patients with atrial fibrillation.

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**Kudenchuk PJ, Brown SP, Daya M, et al; Resuscitation Outcomes Consortium Investigators. Amiodarone, lidocaine, or placebo in out-of-hospital cardiac arrest. *N Engl J Med*. 2016;374(18):1711-1722.**

This randomized, double-blind trial compared the effects of a saline placebo and two antiarrhythmic drugs—amiodarone and lidocaine—on survival to hospital discharge after out-of-hospital cardiac arrest due to shock-refractory ventricular fibrillation or pulseless ventricular tachycardia. Overall, neither amiodarone nor lidocaine resulted in a significantly higher rate of survival or favorable neurologic outcomes than placebo.

**Kuck KH, Brugada J, Fürnkranz A, et al; FIRE AND ICE Investigators. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med*. 2016;374(23):2235-2245.**

The FIRE AND ICE investigators showed that, for drug-refractory paroxysmal atrial fibrillation, cryoballoon ablation was noninferior to radiofrequency ablation concerning both its efficacy and overall safety.

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**Reynolds D, Duray GZ, Omar R, et al; Micra Transcatheter Pacing Study Group. A leadless intracardiac transcatheter pacing system. *N Engl J Med*. 2016;374(6):533-541.**

In patients who had guideline-based indications for ventricular pacing, a newly designed leadless intracardiac transcatheter pacing system was implanted and met the prespecified safety and efficacy goals; it had a safety profile similar to that of a transvenous system, while providing low and stable pacing thresholds.

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**Sapp JL, Wells GA, Parkash R, et al. Ventricular tachycardia ablation versus escalation of antiarrhythmic drugs. *N Engl J Med*. 2016;375(2):111-121.**

In the VANISH trial, patients with ischemic cardiomyopathy and an implantable cardioverter-defibrillator who had ventricular tachycardia despite the use of antiarrhythmic drugs had a significantly lower rate of the composite primary outcome of death, ventricular tachycardia storm, or appropriate implantable cardioverter-defibrillator shock after catheter ablation than among those patients receiving an escalation of their antiarrhythmic drug therapy.

## HEART FAILURE

**Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB; CHAMPION Trial Study Group. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomised trial. *Lancet*. 2016;387(10017):453-461.**

In the CHAMPION trial follow-up, the rates of hospital admissions for heart failure were reduced in the treatment group vs the control group, which were further reduced after pulmonary artery pressure information became available to guide therapy during open access, showing that home transmission of pulmonary artery pressure has a significant long-term benefit on the hospital admission rates for heart failure.

**Filion KB, Azoulay L, Platt RW, et al; CNODES Investigators. A multicenter observational study of incretin-based drugs and heart failure. *N Engl J Med*. 2016;374(12):1145-1154.**

The CNODES investigators analyzed large cohorts of patients with diabetes, and they showed that the use of incretin-based drugs, including dipeptidyl peptidase 4 inhibitors and glucagon-like peptide 1 analogs, were not associated with an increased risk of hospitalization for heart failure compared with commonly used combinations of oral antidiabetic drugs.

**Greenberg B, Butler J, Felker GM, et al. Calcium upregulation by percutaneous administration of gene therapy in patients with cardiac disease (CUPID 2): a randomised, multinational, double-blind,**

**placebo-controlled, phase 2b trial. *Lancet*. 2016;387(10024):1178-1186.**

The CUPID 2 trial investigated the clinical benefits and safety of gene therapy through the infusion of adeno-associated virus 1 (AAV1) sarco(endo)plasmic reticulum Ca<sup>2+</sup> ATPase (SERCA2a) in patients with heart failure with reduced ejection fraction. However, despite the promising results obtained in previous studies, treatment with AAV1/SERCA2a, at the dose tested, did not improve the clinical course of these patients.

**Hasenfuß G, Hayward C, Burkhoff D, et al; REDUCE LAP-HF Study Investigators. A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial. *Lancet*. 2016;387(10025):1298-1304.**

The REDUCE LAP-HF study showed that the implantation of an interatrial shunt device is feasible, seems to be safe, reduces left atrial pressure during exercise, and could be a new strategy for the management of heart failure with preserved ejection fraction.

**Køber L, Thune JJ, Nielsen JC, et al; DANISH Investigators. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med*. 2016;375(13):1221-1230.**

The DANISH trial showed that prophylactic use of an implantable cardioverter-defibrillator in patients with symptomatic systolic heart failure, which was not caused by coronary artery disease, did not result in a significantly lower long-term rate of death from any cause vs usual clinical care.

**McMurray JJ, Krum H, Abraham WT, et al; ATMOSPHERE Committees Investigators. Aliskiren, enalapril, or aliskiren and enalapril in heart failure. *N Engl J Med.* 2016;374(16):1521-1532.**

The ATMOSPHERE study showed that, in patients with chronic heart failure, the addition of the renin inhibitor aliskiren to the angiotensin-converting enzyme inhibitor enalapril resulted in more adverse events than angiotensin-converting enzyme inhibitors alone, but no additional benefits.

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**Patel AN, Henry TD, Quyyumi AA, et al; ix-CELL-DCM Investigators. Ixmyelocel-T for patients with ischaemic heart failure: a prospective randomised double-blind trial. *Lancet.* 2016;387(10036):2412-2421.**

In patients with heart failure with reduced ejection fraction due to ischemic dilated cardiomyopathy, a catheter-based transcatheter injection of ixmyelocel-T, an expanded, multicellular therapy produced from a patient's own bone marrow, significantly reduced overall all-cause death and cardiovascular hospital admissions vs placebo, which improved patient outcomes.

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**Ware JS, Li J, Mazaika E, Yasso CM, et al; IMAC-2 and IPAC Investigators. Shared genetic predisposition in peripartum and dilated cardiomyopathies. *N Engl J Med.* 2016;374(3):233-241.**

Peripartum cardiomyopathy shares some clinical features with idiopathic dilated cardiomyopathy, a disorder caused by mutations in more than 40 genes, including TTN, which encodes the sarcomere protein titin. In a clinically well-characterized cohort of women with peripartum cardio-

myopathy, the presence of TTN truncating variants was significantly correlated with a lower ejection fraction at the 1-year follow-up.

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## **CORONARY ARTERY DISEASE**

**Buchholz EM, Butala NM, Ma S, Normand ST, Krumholz HM. Life expectancy after myocardial infarction, according to hospital performance. *N Engl J Med.* 2016;375(14):1332-1342.**

This study showed that, in both the short and long term, patients admitted to high-performing hospitals after an acute myocardial infarction had longer life expectancies than did patients treated in low-performing hospitals.

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**Cayla G, Cuisset T, Silvain J, et al; ANTARCTIC Investigators. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. *Lancet.* 2016;388(10055):2015-2022.**

The ANTARCTIC study showed that platelet function monitoring with treatment adjustment in elderly patients stented for an acute coronary syndrome did not improve the clinical outcome of elderly patients. Platelet function testing is still being used in many centers, and international guidelines still recommend platelet function testing in high-risk situations; however, this study does not support this practice or these recommendations.

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**Dewey FE, Gusarova V, O'Dushlaine C, et al. Inactivating variants in ANGPTL4 and risk**

**of coronary artery disease. *N Engl J Med.* 2016;374(12):1123-1133.**

Activation of the lipoprotein lipase, an enzyme that is inhibited by angiopoietin-like 4, reduces the levels of circulating triglycerides. Carriers of the missense E40K variant of angiopoietin-like 4 had lower triglycerides levels and a lower risk of coronary artery disease than did noncarriers.

**Jolly SS, Cairns JA, Yusuf S, et al; TOTAL Investigators. Outcomes after thrombus aspiration for ST elevation myocardial infarction: 1-year follow-up of the prospective randomised TOTAL trial. *Lancet.* 2016;387(10014):127-135.**

The TOTAL trial compared routine manual thrombectomy plus percutaneous coronary intervention with percutaneous coronary intervention alone in patients with ST-segment elevation myocardial infarction. Due to the possible increase in stroke and the lack of benefit for reduced long-term clinical outcomes, routine manual thrombectomy can no longer be recommended as a routine strategy for patients with ST-segment elevation myocardial infarction.

**Kaufman JD, Adar SD, Barr RG, et al. Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study. *Lancet.* 2016;388(10045):696-704.**

The MESA Air study demonstrated an association between long-term exposure to ambient air pollutant concentrations and the progression of coronary artery calci-

um and mean carotid artery intima-media thickness. The study results support the idea that reducing pollution may aid in the prevention of cardiovascular disease.

**Myles PS, Smith JA, Forbes A, et al; ATACAS Investigators of the ANZCA Clinical Trials Network. Stopping vs. continuing aspirin before coronary artery surgery. *N Engl J Med.* 2016;374(8):728-737.**

Most patients with coronary artery disease receive aspirin for the primary or secondary prevention of myocardial infarction, stroke, and death. To assess whether aspirin should be stopped before coronary artery surgery, patients were randomized to either aspirin or placebo preoperatively. The administration of preoperative aspirin, compared with placebo, did not result in a higher risk of bleeding or a lower risk of death or thrombotic complications.

**NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet.* 2016;387(10027):1513-1530.**

Since 1980, the prevalence of age-standardized diabetes in adults has increased, or, at best, has remained unchanged, in every country. One of the global targets for noncommunicable diseases is to stop, by 2025, the rise in the age-standardized adult prevalence of diabetes at its 2010 levels. However, if the post-2000 trends continue, the probability of meeting this global target is <1% for men and ≈1% for women.

**Nioi P, Sigurdsson A, Thorleifsson G, et al. Variant ASGR1 associated with a reduced**

**risk of coronary artery disease. *N Engl J Med.* 2016;374(22):2131-2141.**

ASGR1 is a gene that encodes a subunit of the asialoglycoprotein receptor, a lectin that plays a role in the homeostasis of circulating glycoproteins was identified in a population of Icelanders. This study showed that ASGR1 haploinsufficiency was associated with reduced levels of non-high-density lipoprotein cholesterol and a reduced risk of coronary artery disease.

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**Stitzel NO, Stirrups KE, Masca NG, et al. Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators. Coding variation in ANGPTL4, LPL, and SVEP1 and the risk of coronary disease. *N Engl J Med.* 2016;374(12):1134-1144.**

This study showed that carriers of loss-of-function mutations in the gene coding for angiopoietin-like 4 had lower triglyceride levels than did noncarriers. In addition, these mutations were associated with protection from coronary artery disease.

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**Tegn N, Abdelnoor M, Aaberge L, et al; After Eighty Study Investigators. Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): an open-label randomised controlled trial. *Lancet.* 2016;387(10023):1057-1065.**

Non-ST-segment myocardial infarction and unstable angina pectoris are frequent causes of hospital admission for the elderly ( $\geq 80$  years old). The After Eighty study showed that, in these patients, an invasive strategy is superior to a conservative strategy in the reduction of composite events.

**Twig G, Yaniv G, Levine H, et al. Body-mass index in 2.3 million adolescents and cardiovascular death in adulthood. *N Engl J Med.* 2016;374(25):2430-2440.**

This study examined the association between body mass index in late adolescence and death from cardiovascular causes in adulthood. There was a graded increase in the risk of cardiovascular and all-cause mortality among the group with a body mass index in the 50th to 74th percentiles during adolescence.

---

**Velazquez EJ, Lee KL, Jones RH, et al; STICHES Investigators. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med.* 2016;374(16):1511-1520.**

The effect of adding coronary artery bypass grafting to guideline-directed medical therapy vs medical therapy alone on survival was tested in patients with an ejection fraction  $\leq 35\%$  and coronary artery disease amenable to coronary artery bypass grafting. This procedure significantly reduced death from any cause, death from cardiovascular causes, and death from any cause or hospitalization for cardiovascular causes in patients with ischemic cardiomyopathy.

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**Vestbo J, Anderson JA, Brook RD, et al; SUMMIT Investigators. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet.* 2016;387(10030):1817-1826.**

The SUMMIT trial showed that, in patients with moderate chronic obstructive

pulmonary disease and a heightened cardiovascular risk, the combination treatment of the corticosteroid fluticasone furoate and the long-acting  $\beta$ -agonist vilanterol did not affect all-cause mortality or cardiovascular outcomes. In addition, there were no reported excess risks of pneumonia or adverse cardiac events in the treatment groups.

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**Vidal-Petiot E, Ford I, Greenlaw N, et al; CLARIFY Investigators. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. *Lancet.* 2016;388(10056):2142-2152.**

The CLARIFY registry shows that, in patients with hypertension and coronary artery disease, systolic blood pressure <120 mm Hg and diastolic blood pressure <70 mm Hg were each associated with adverse cardiovascular outcomes, including mortality.

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**Wallentin L, Lindhagen L, Årnström E, et al; FRISC-II Study Group. Early invasive versus non-invasive treatment in patients with non-ST-elevation acute coronary syndrome (FRISC-II): 15 year follow-up of a prospective, randomised, multicentre study. *Lancet.* 2016;388(10054):1903-1911.**

The 15-year follow-up of the FRISC-II trial showed that, in patients with non-ST-segment elevation acute coronary syndrome, an early invasive treatment strategy postponed the occurrence of death, the next myocardial infarction, and readmission to the hospital for ischemic heart disease.

**Yusuf S, Bosch J, Dagenais G, et al; HOPE-3 Investigators. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med.* 2016;374(21):2021-2031.**

While statins have been shown to lower cholesterol, it is not known whether statins can provide the same benefits to an intermediate-risk, ethnically diverse population without cardiovascular disease. The HOPE-3 trial shows that treating patients in this intermediate-risk category with rosuvastatin resulted in a significantly lower risk of cardiovascular events than did placebo.

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**Yusuf S, Lonn E, Pais P, et al; HOPE-3 Investigators. Blood-pressure and cholesterol lowering in persons without cardiovascular disease. *N Engl J Med.* 2016;374(21):2032-2043.**

The HOPE-3 trial evaluated the effects of rosuvastatin vs placebo, candesartan plus hydrochlorothiazide vs placebo, and the combination of both treatments vs dual placebo on the prevention of major cardiovascular events. The trial showed that the combination of rosuvastatin, candesartan, and hydrochlorothiazide significantly lowered the rate of cardiovascular events vs dual placebo among patients who were at an intermediate risk for cardiovascular disease.

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**Zheng Z, Jayaram R, Jiang L, et al. Perioperative rosuvastatin in cardiac surgery. *N Engl J Med.* 2016;374(18):1744-1753.**

Perioperative statin therapy with rosuvastatin lowered the concentrations of low-density lipoprotein cholesterol and

C-reactive protein after elective cardiac surgery; however, the treatment did not prevent postoperative atrial fibrillation or perioperative myocardial damage in patients undergoing elective cardiac surgery.

## **STRUCTURAL HEART DISEASE**

**Goldstein D, Moskowitz AJ, Gelijns AC, et al; CTSN. Two-year outcomes of surgical treatment of severe ischemic mitral regurgitation. *N Engl J Med.* 2016;374(4):344-353.**

The 2-year follow-up of the randomized trial comparing mitral-valve repair with mitral-valve replacement in patients with severe ischemic mitral regurgitation show no significant between-group differences in left ventricular reverse remodeling or survival. Mitral regurgitation recurred more frequently in the repair group, resulting in more heart failure-related adverse events and cardiovascular admissions.

**Michler RE, Smith PK, Parides MK, et al; CTSN. Two-year outcomes of surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med.* 2016;374(20):1932-1941.**

The 2-year outcomes from the trial comparing coronary artery bypass grafting alone with coronary artery bypass grafting plus mitral valve repair in patients with moderate ischemic mitral regurgitation showed that mitral valve repair, in addition to coronary artery bypass grafting, did not improve survival or reduce overall adverse events, and it was associated with an early hazard of increased neurologic events and supraventricular arrhythmias.

## **INTERVENTIONAL CARDIOLOGY**

**Ali ZA, Maehara A, Généreux P, et al; ILUMIEN III: OPTIMIZE PCI Investigators. Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (ILUMIEN III: OPTIMIZE PCI): a randomised controlled trial. *Lancet.* 2016;388(10060):2618-2628.**

The ILUMIEN III: OPTIMIZE PCI trial, the first randomized controlled trial to compare optical coherence tomography-guided, intravascular ultrasound-guided, and angiography-guided percutaneous coronary interventions, showed that imaging guidance provides advantages compared with angiography guidance alone and that optical coherence tomography guidance is noninferior to intravascular ultrasound guidance for achieving acute procedural success.

**Bønaa KH, Mannsverk J, Wiseth R, et al; NORSTENT Investigators. Drug-eluting or bare-metal stents for coronary artery disease. *N Engl J Med.* 2016;375(13):1242-1252.**

The NORSTENT trial showed that, in patients undergoing percutaneous coronary interventions, no significant differences between drug-eluting stents and bare-metal stents occurred for the composite outcome of death from any cause and nonfatal spontaneous myocardial infarction; however, the rates of repeat revascularizations were lower with drug-eluting stents.

**Cassese S, Byrne RA, Ndrepepa G, et al. Everolimus-eluting bioresorbable vascular scaffolds versus everolimus-eluting metallic**

**stents: a meta-analysis of randomised controlled trials.** *Lancet.* 2016;387(10018):537-544.

This meta-analysis showed that, in patients undergoing percutaneous coronary interventions, everolimus-eluting bioreabsorbable vascular scaffolds had similar rates of repeat revascularizations at the 1-year follow-up as did everolimus-eluting metallic stents, but there was an increased risk of subacute stent thrombosis.

**Haude M, Ince H, Abizaid A, et al. Safety and performance of the second-generation drug-eluting absorbable metal scaffold in patients with de-novo coronary artery lesions (BIOSOLVE-II): 6 month results of a prospective, multicentre, non-randomised, first-in-man trial.** *Lancet.* 2016;387(10013):31-39.

The BIOSOLVE-II study showed that the implantation of a novel second-generation drug-eluting absorbable metal scaffold (DREAMS 2G) in patients with de-novo coronary artery lesions is feasible, with favorable safety and performance outcomes at 6 months, thus providing an alternative to absorbable polymeric scaffolds for the treatment of obstructive coronary disease.

**Kelbæk H, Høfsten DE, Køber L, et al. Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (DANAMI 3-DEFER): an open-label, randomised controlled trial.** *Lancet.* 2016;387(10034):2199-2206.

The DANAMI 3-DEFER trial showed that, in patients with ST-segment elevation myocardial infarction, routine deferred stent implantation did not reduce the

occurrence of death, heart failure, myocardial infarction, or repeat revascularization compared with conventional percutaneous coronary interventions.

**Leon MB, Smith CR, Mack MJ, et al; PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients.** *N Engl J Med.* 2016;374(17):1609-1620.

In intermediate-risk patients with severe aortic stenosis, transcatheter aortic-valve replacement was tested for noninferiority vs surgical aortic-valve replacement. The rate of death from any cause or disabling stroke was similar in both groups. Transcatheter aortic-valve replacement resulted in larger aortic-valve areas than did surgery, and it resulted in lower rates of acute kidney injury, severe bleeding, and new-onset atrial fibrillation; surgery resulted in fewer major vascular complications and less paravalvular aortic regurgitations.

**Lincoff AM, Mehran R, Povsic TJ, et al; REGULATE-PCI Investigators. Effect of the REG1 anticoagulation system versus bivalirudin on outcomes after percutaneous coronary intervention (REGULATE-PCI): a randomised clinical trial.** *Lancet.* 2016;387(10016):349-356.

Although the REGULATE-PCI trial was terminated early, REG1—the novel anticoagulation system consisting of pegnivacogin, an RNA aptamer inhibitor of coagulation factor IXa, and anivamersen, a complementary sequence reversal oligonucleotide—showed no evidence for a reduction in ischemic events or bleeding compared with bivalirudin.

**Sabaté M, Brugaletta S, Cequier A, et al. Clinical outcomes in patients with ST-segment elevation myocardial infarction treated with everolimus-eluting stents versus bare-metal stents (EXAMINATION): 5-year results of a randomised trial. *Lancet*. 2016;387(10016):357-366.**

The 5-year outcomes of the EXAMINATION trial, which compared everolimus-eluting stents with bare-metal stents in an all-comer population with ST-segment elevation myocardial infarction, showed that patients allocated to receive an everolimus-eluting stent had a reduction in both the combined patient-oriented and device-oriented end points.

**Serruys PW, Chevalier B, Sotomi Y, et al. Comparison of an everolimus-eluting bioresorbable scaffold with an everolimus-eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II): a 3 year, randomised, controlled, single-blind, multicentre clinical trial. *Lancet*. 2016;388(10059):2479-2491.**

The ABSORB II trial compared the Absorb bioresorbable scaffold with the Xience metallic stent to analyze whether bioresorbable scaffolds resulted in increased luminal dimensions due to recovered vasomotion in the scaffolded vessel. However, the trial did not meet its coprimary end points of superior vasomotor reactivity and noninferior late luminal loss for the Absorb bioresorbable scaffold.

**Stone GW, Gao R, Kimura T, et al. 1-year outcomes with the Absorb bioresorbable scaffold in patients with coronary artery disease: a patient-level, pooled meta-analysis. *Lancet*. 2016;387(10025): 1277-1289.**

The 1-year relative rates of patient-oriented and device-oriented composite end points were similar between the everolimus-eluting Absorb bioresorbable vascular scaffold and the Xience cobalt-chromium everolimus-eluting stent. However, target vessel-related myocardial infarction increased with the bioresorbable vascular scaffold compared with cobalt-chromium everolimus-eluting stent.

**von Birgelen C, Kok MM, van der Heijden LC, et al. Very thin strut biodegradable polymer everolimus-eluting and sirolimus-eluting stents versus durable polymer zotarolimus-eluting stents in allcomers with coronary artery disease (BIO-RESORT): a three-arm, randomised, non-inferiority trial. *Lancet*. 2016;388(10060):2607-2617.**

The BIO-RESORT trial analyzed the safety and efficacy of three drug eluting stents—everolimus, sirolimus, or Zotarolimus—in all-comers who needed a percutaneous coronary intervention and a drug-eluting stent implantation. While both the everolimus- and sirolimus-eluting stents were noninferior to the Zotarolimus-eluting stent at the 12-month follow-up, the absence of a loss of 1-year safety and efficacy is a prerequisite before assessing their potential longer-term benefits.

**Weisz G, Génèreux P, Iñiguez A, et al; RIVER-PCI Investigators. Ranolazine in patients with incomplete revascularisation after percutaneous coronary intervention (RIVER-PCI): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*. 2016;387(10014):136-145.**

The RIVER-PCI trial showed that adjunctive anti-ischemic pharmacotherapy with ranolazine did not reduce the composite rate of ischemia-driven revascularization or hospitalization without revascularization in patients with a history of chronic angina and an incomplete revascularization after a percutaneous coronary intervention.

## **HYPERTENSION**

**Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet.* 2016;387(10022):957-967.**

This meta-analysis showed that every 10 mm Hg reduction in systolic blood pressure significantly reduced the risk of major cardiovascular disease events, coronary heart disease, stroke, and heart failure, which led to a significant 13% reduction in all-cause mortality. The results strongly support lowering systolic blood pressure to less than 130 mm Hg.

**Lonn EM, Bosch J, López-Jaramillo P, et al; HOPE-3 Investigators. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med.* 2016;374(21):2009-2020.**

The HOPE-3 trial evaluated the effects of candesartan plus hydrochlorothiazide vs placebo in patients without cardiovascular disease, but who were at an intermediate risk. The trial showed that the treatment was not associated with a lower rate of major cardiovascular events than the placebo.

**Mente A, O'Donnell M, Rangarajan S, et al; PURE, EPIDREAM, ONTARGET/TRANSCEND Investigators. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies. *Lancet.* 2016;388(10043):465-475.**

This study showed that increased sodium intake was associated with an increased risk of cardiovascular events and death in hypertensive populations (no association in normotensive populations), while low sodium intake was associated with an increased risk of cardiovascular events and death in patients with or without hypertension.

**Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet.* 2016;387(10017):435-443.**

As recent hypertension guidelines have reversed previous recommendations for lower blood pressure targets in high-risk patients, this study assessed the efficacy and safety of intensive blood pressure-lowering strategies. This meta-analysis showed that intensive blood pressure lowering provided greater vascular protection than standard regimens, and that the net absolute benefits of intensive blood pressure lowering in high-risk individuals are substantial.

## **STROKE**

**Baharoglu MI, Cordonnier C, Al-Shahi Salman R, et al; PATCH Investigators. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with an-**

**tiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial.** *Lancet.* 2016;387(10038):2605-2613.

The randomized, open-label, phase 3 PATCH trial showed that, due to the increased odds of death or dependence and the higher number of serious adverse events during the patients' hospital stay, platelet transfusion plus standard care is inferior to standard care alone.

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**Goyal M, Menon BK, van Zwam WH, et al; HERMES Collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials.** *Lancet.* 2016;387(10029):1723-1731.

The HERMES collaboration conducted a meta-analysis to test whether endovascular thrombectomy was efficacious for the diverse patient populations included in five randomized trials. Their analysis showed that endovascular thrombectomy benefits most patients with acute ischemic stroke caused by occlusion of the proximal anterior circulation, irrespective of patient characteristics or geographical location.

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**Howard G, Roubin GS, Jansen O, et al; Carotid Stenting Trialists' Collaboration. Association between age and risk of stroke or death from carotid endarterectomy and carotid stenting: a meta-analysis of pooled patient data from four randomised trials.** *Lancet.* 2016;387(10025):1305-1311.

The Carotid Stenosis Trialists' Collaboration showed that carotid endarterectomy was superior to carotid artery stenting in patients aged 70-74 years and older. Carotid artery stenting increases the risk of

periprocedural stroke in older patients. However, age had little effect on the post-procedural risk after either procedure or on the periprocedural risk of carotid endarterectomy.

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**Qureshi AI, Palesch YY, Barsan WG, et al; ATACH-2 Trial Investigators and the Neurological Emergency Treatment Trials Network. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage.** *N Engl J Med.* 2016;375(11):1033-1043.

The ATACH-2 trial showed that treating patients with an intracerebral hemorrhage with intensive blood pressure-lowering therapy to achieve a target systolic blood pressure between 110 and 139 mm Hg did not result in a lower rate of death or disability than the standard blood pressure reduction to a target between 140 and 179 mm Hg.

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**Rothwell PM, Algra A, Chen Z, Diener HC, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials.** *Lancet.* 2016;388(10042):365-375.

This analysis shows that aspirin reduces the early risk of all stroke, ischemic stroke, and acute myocardial infarction; in addition, aspirin reduces the severity of early recurrent ischemic stroke, resulting in an 80% to 90% reduction in the early risk of disabling or fatal recurrent ischemic stroke. ■

Expert Opinions



# HOT NEW DRUGS FOR SYSTOLIC HEART FAILURE: BE CAREFUL WHAT YOU WISH FOR

Summary of the 2016 American College of Cardiology Meeting

**JEFFREY S. BORER, MD**

**Author affiliations:** State University of New York Downstate Medical Center, Brooklyn and New York, NY, USA

**Address for correspondence:** Jeffrey S. Borer, MD, 47 East 88th Street, New York, NY 10128, USA  
(email: jsborer1@gmail.com)

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In 2015, the US Food and Drug Administration approved both ivabradine and the sacubitril-valsartan combination for use in patients with chronic systolic HF. In the US, these drugs were the first in almost 9 years to be approved for this purpose. In April 2016, the American College of Cardiology sponsored a symposium at its annual scientific session to present current data regarding these drugs. This article summarizes the information presented at this symposium.

## **IVABRADINE**

### **Pharmacological effects**

The pharmacological effects of ivabradine were discussed by Edo Birati (US). Ivabradine blocks the  $I_f$  current, a small current created by the flow of sodium and potassium ions in opposite directions across an HCN channel. This event is unusual ( $f$ ="funny") because most currents are activated by depolarization rather than hyperpolarization and are carried by a single ion moving in a single direction through any single channel. The HCN channel is found in sinoatrial nodal cells; however, under physiological conditions, it is largely absent from the remainder of the heart and, if present, it appears to be nonfunctional. The drug does not affect repolarization or contractility.

Michael Böhm (DE) discussed the mechanistic relationship between systolic HF and heart rate. There is an imbalance between myocardial oxygen supply and demand as heart rate increases, which leads to myocardial dysfunction. He stated that the failing myocardium responds to increases in heart rate very differently from normal myocardium. In experimental preparations, normal myocardium increases its contractile force as the electrical stimulation rate increases, while the failing myocardium almost immediately loses contractile force when the electrical stimulation rate increases, regaining the lost function quickly when the electrical stimulation rate slows again.

### **SHIFT study data**

Results of clinical trials were discussed. These data were drawn from the SHIFT study, which involved more than 6500 patients with moderate to severe symptoms (NYHA II to

IV), LVEF  $\leq 35\%$ , in sinus rhythm, heart rate  $\geq 70$  bpm, and who had been admitted to the hospital during the preceding 12 months for worsening HF. SHIFT was designed to test the hypothesis that slowing the heart rate with ivabradine improves cardiovascular outcomes in patients who met the trial's inclusion criteria. All patients were randomized to ivabradine or placebo on a background of standard pharmacological therapy for HFREF (ie,  $\beta$ -blockers, ACE inhibitors or ARBs, MRAs, and diuretics, plus devices or other drugs, such as digoxin, when deemed appropriate). However, an important feature of SHIFT, which was not employed in the PARADIGM-HF trial, was the intense effort to maximize  $\beta$ -blocker use before adding either placebo or ivabradine. For this purpose, each time a patient was not receiving the guideline-based target  $\beta$ -blocker doses, the investigators completed a special case report form to explain why the dose was lower than the target. Therefore, considerable information became available from SHIFT about the adverse effects of  $\beta$ -blockers in patients with moderate-to-severe HFREF.

When randomized to ivabradine, patients in SHIFT experienced an 18% lower primary outcome event rate than patients who received the placebo.<sup>1</sup> This result was primarily driven by a 26% reduction in the rate of the first hospitalizations for HF. The mortality rate was 9% lower with ivabradine vs placebo, but this difference did not reach statistical significance. However, the protocol carried a requirement for a secondary analysis based on the median heart rate at entry (77 bpm), which showed that patients with a heart rate greater than the median had a significant reduction in mortality. Indeed, a significant benefit was seen when the heart rate was segregated at 75 bpm, leading to the approval of ivabradine for reducing mortality in HF patients in Europe, but not in the US. The reduction in hospitalizations for HF, which is the indication for ivabradine in the US, was maintained throughout the trial. When all hospitalizations were considered throughout the 3.5-year maximum trial duration, twice as many total hospitalizations occurred as first hospitalizations, and the reduction in the total hospitalization rate was 25%.<sup>2</sup> In addition, prespecified analyses revealed a significant improvement in HRQOL and left ventricular systolic function.

### **SIGNIFY trial data**

A potential concern regarding the SHIFT data was raised after publication of the SIGNIFY trial, even though the overall results from SIGNIFY were neutral.<sup>3</sup> Following the SIGNIFY publication, a post hoc study was performed that included SHIFT patients divided according to the presence or absence of angina at randomization, which showed similar results between SHIFT patients with angina, those without angina, and the entire SHIFT population, suggesting no loss of the benefits observed in SHIFT if the patients had angina. Moreover, when SIGNIFY end points were considered, patients with HF plus angina manifested numerical improvements in outcomes with ivabradine, unlike the SIGNIFY population. These results abrogate the concerns raised in SIGNIFY when applied to patients with HFREF.

### **Eligible patients for ivabradine**

This portion of the symposium concluded with a debate between Michael Givertz (US) and Maria Rosa Costanzo (US) about appropriate patients for ivabradine. Reinterpreting

subset data from SHIFT and thus ignoring the protocol-mandated analyses, Givertz advocated limited application to HF patients with NYHA class II-III, LVEF  $\leq$ 35%, nonischemic etiology, heart rate  $>$ 80 bpm, in sinus rhythm, at low risk for atrial fibrillation and QT prolongation, and who are receiving guideline-directed medical therapy, including target doses of  $\beta$ -blockers with proven HF survival benefit. Costanzo countered these assertions by noting that the benefits of ivabradine on mortality or HF hospitalizations were achieved in the entire study population and across multiple prespecified subgroups, that all ivabradine trials have consistently shown the drug to be acceptably safe for the intended use, and that the benefits of ivabradine are clearly additive to and independent from those afforded by  $\beta$ -blockers. She concluded by stating that ivabradine should be added to the regimen of all patients who meet the criteria for use indicated on the drug's labeling.

## **SACUBITRIL-VALSARTAN COMBINATION**

### **Pharmacological effects and mechanism of action**

Biykem Bozkurt (US)<sup>4</sup> discussed the pharmacological effects and putative mechanism of action of the combination. Sacubitril-valsartan is a prototype of drugs called ARNI. Valsartan results in peripheral vasodilatation with a possible reduction in myocardial collagen formation (fibrosis), without inhibiting the metabolism of bradykinin, another physiological vasodilator. The neprilysin inhibitor prevents the enzymatic cleavage of several physiological peptides, including bradykinin and natriuretic peptides that help mitigate the volume overload in HF.

### **Clinical results in patients with HFREF**

Akshay Desai (US)<sup>5</sup> presented the results of clinical trials on sacubitril-valsartan in patients with systolic HF, now commonly called HFREF as opposed to HFPEF. The primary source of information is the PARADIGM-HF trial,<sup>6,7</sup> in which sacubitril-valsartan was compared with enalapril on a background of other drugs considered appropriate for HFREF, including  $\beta$ -blockers, diuretics, and MRAs. The purpose of the trial was to evaluate replacing ACE inhibitors or ARB with sacubitril-valsartan as a primary therapy for patients with HFREF. The trial involved more than 8000 HFREF patients in NYHA class II-IV.

Before randomization, patients underwent a single-blind run-in period to assure that the target doses of enalapril or sacubitril-valsartan could be tolerated. At the time of randomization, the patients were taking either an ACE inhibitor or an ARB, and they were able to tolerate stable doses equivalent to at least 10 mg enalapril daily (guideline target is  $\geq$ 20 mg daily) for at least 4 weeks. In addition, the patients were receiving guideline-recommended  $\beta$ -blockers and MRAs. These patients each had an LVEF  $\leq$ 40%, a BNP blood concentration  $\geq$ 150 pg/mL (or NT-proBNP  $\geq$ 600 pg/mL; both BNP and NT-proBNP levels were reduced by one-third if hospitalized for HF within 12 months), systolic blood pressure  $\geq$ 95 mm Hg, eGFR  $\geq$ 30 mL/min/1.73 m<sup>2</sup>, and serum potassium  $\leq$ 5.4 mEq/L (valsartan can increase potassium to potentially dangerous concentrations).

The primary outcome of PARADIGM-HF was cardiovascular death or hospitalization for HF. Baseline characteristics were evenly distributed among the two treatment groups. However, compared with enalapril plus standard therapy, sacubitril-valsartan was associated with a reduction in the rate of primary outcome events (-20%), cardiovascular death (-20%), and first hospitalizations for HF (-21%). HRQOL, which was determined using the Kansas City Cardiomyopathy Questionnaire, improved with sacubitril-valsartan vs enalapril, although the magnitude of the difference fell below the accepted standard for clinical perceptibility. The incidence of new-onset atrial fibrillation was indistinguishable between the two treatment strategies, but increased hyperkalemia, increased creatinine levels, and discontinuation for renal impairment occurred significantly more frequently with enalapril than with sacubitril-valsartan. Angioedema was numerically, but not significantly, more frequent with sacubitril-valsartan.

### Eligible patients

Following the discussion about the clinical results, a debate about appropriate patients to receive the new combination drug occurred between Marvin Konstam (US) and Lynne Stevenson (US). Konstam argued that sacubitril-valsartan should be administered to all patients with HFREF who met the PARADIGM entry criteria. He pointed out that, while questions remained about individual applications, post hoc assessment of all subgroups of interest support benefit with the combination drug compared with enalapril. In addition, adverse events were more common with enalapril. Konstam concluded by saying that there is no basis for withholding the combination. Stevenson countered by stating that some caution should be exercised until more knowledge is obtained from regular use of sacubitril-valsartan in clinical practice. Many of the nonmetabolized peptides due to the neprilysin inhibitor may be vasodilatory or  $\beta$ -blocking, requiring dose adjustments of the remaining drugs. In addition, natriuresis that is caused by nonmetabolized natriuretic peptides may alter the appropriate doses of diuretics. The trial also had a paucity of African-Americans and patients in NYHA class IV. Stevenson concluded by stating that amyloid proteins involved in Alzheimer's disease have the potential to remain nonmetabolized, which are a potential detriment for cognitive function. ■

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# THE NEW GUIDELINES FOR THE MANAGEMENT OF HEART FAILURE: HOW TO INTEGRATE NEWER DRUGS IN THE THERAPEUTIC ALGORITHM

Summary of the 2016 Heart Failure Congress

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

**Author affiliations:** St George's Hospital Medical School, London, UK

**Address for correspondence:** Giuseppe M. C. Rosano, MD, PhD, Cardiovascular and Cell Sciences Institute, St George's Hospital Medical School, Cranmer Terrace, London SW170RE, UK (email: grosano@sgul.ac.uk)

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The Heart Failure Congress is the annual meeting of the HFA of the ESC, and it is the largest and most important scientific event in the field of HF worldwide. The 2016 Heart Failure Congress took place in Florence, Italy in May. The meeting was attended by 6142 delegates from 277 faculties and 38 countries, and there were 108 scientific sessions. The congress confirmed that the HFA is the leading HF association worldwide. Therefore, the HFA guidelines for the diagnosis and treatment of acute and chronic HF released at the congress have a significant relevance and applicability to clinical practice worldwide.<sup>1</sup>

The guidelines on HF have featured several important changes, including the diagnosis and treatment algorithms for the management of HF, new indications for the use of cardiac resynchronization therapy, and the inclusion of new devices for the management of chronic HF patients. However, the most sought after news of the 2016 guidelines was the algorithm on the management of chronic HF. The first change in the chronic HF algorithm was the indication for the use of diuretics, which should now be adjusted according to the patient's condition and needs. No major change occurred in the first classes of drugs with a level IA indication for the treatment of chronic HF. ACE inhibitors and  $\beta$ -blockers can now be initiated together; however,  $\beta$ -blockers should not be started before an ACE inhibitor has been started. Mineralocorticoid receptor antagonists should be used as a second step.

The most important news from the guidelines came from the third step of the treatment algorithm. Here, ivabradine and LCZ696 feature at the same level with a suggestion that these two drugs can be combined when indicated, which is an extremely important and practical suggestion. While ivabradine is very safe, effective, and it has a neutral effect on blood pressure in patients in sinus rhythm, it is also recognized that LCZ696 can significantly reduce blood pressure. Adjusting the background therapy with  $\beta$ -blockers may lead to an increase in heart rate, which can benefit from adding ivabradine.<sup>1</sup> The benefits of ivabradine and LCZ696 on cardiovascular mortality and hospitalizations are similar, especially when patients with a heart rate >75 bpm are considered. While ivabradine can be used at any stage in the treatment of patients with chronic HF, LCZ696 should currently only be used in ambulatory patients.

Several analyses of the pivotal ivabradine studies, which were presented at the congress, have corroborated the evidence that ivabradine can be used safely and efficiently in the vulnerable phase of HF, which is the phase of HF when patients are at an increased risk of death or rehospitalization for HF. Notwithstanding the higher risk for mortality and readmissions, the vulnerable phase represents a window of opportunity because, if sufficiently managed, patients who survive this phase and who are managed adequately are expected to have a good long-term prognosis. Management of patients in the vulnerable phase should be well planned before discharge to provide clinical stabilization and reduce the risk of short- and medium-term complications. Ideally, patients should be discharged when they have been hemodynamically stable for at least 24 to 48 hours on oral therapy. Often preexisting treatment is discontinued or reduced during the acute phase; therefore, it will be important to implement  $\beta$ -blockers and ACE inhibitors appropriately, although their uptitration is often hampered by borderline low blood pressure.

The 2016 ESC/HFA guidelines state that, after an acute episode of decompensation, patients should be discharged when clinical parameters are stable and after an individualized education program about self-care has been implemented. The use of ACE inhibitors (or ARBs, only if ACE inhibitors are not tolerated) at the full therapeutic dose is indicated, and  $\beta$ -blockers should be initiated or restarted before discharge.<sup>2-4</sup> In addition, these guidelines suggest that, for the management of patients with HF, patients should be visited by their general practitioner within 1 week of discharge, while the HF team should follow-up the patients within 2 weeks of discharge, if possible. In this early phase, elevated heart rate and low blood pressure are frequent. Therefore, if the patient's heart rate is still high despite therapy with  $\beta$ -blockers, which cannot be implemented further because of the low blood pressure, the addition of ivabradine is the best approach to improve prognosis, symptoms, and functional capacity.

Previous studies have shown that administration of ivabradine in the acute phase of HF is safe and leads to an improved left ventricular ejection fraction.<sup>5</sup> Other studies have also suggested that, in patients with a recent hospitalization for HF, the association of ivabradine with  $\beta$ -blockers leads to a greater number of patients with target heart rate control and improved functional capacity than  $\beta$ -blockers alone at the maximum dose.<sup>6</sup> A recent randomized study, which was presented at the congress (abstract P1634),<sup>7</sup> found that the early coadministration of ivabradine and  $\beta$ -blockers (24 hours after hospital admission) in acute patients hospitalized with HFREF was safer and more efficacious at reducing heart rate after hospital discharge than treatment with  $\beta$ -blockers alone.<sup>8</sup> The authors also observed a significantly greater improvement in ejection fraction in the ivabradine plus  $\beta$ -blocker group. These findings are consistent with the results from the SHIFT trial.<sup>9</sup>

Therefore, for the optimal management of the vulnerable phase and an early improvement in functional capacity, ivabradine should be added to  $\beta$ -blockers, whenever indicated, early during hospitalization or in the immediate postdischarge phase. ■

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# RESPONDING TO THE UNMET NEEDS IN CARDIOVASCULAR MEDICINE

Summary of the 2016 World Congress of Cardiology and Cardiovascular Health

## ANTONIO MAGAÑA SERRANO, MD, FACC, PCHF

**Author affiliations:** Head of the Division of Heart Failure and Cardiac Transplantation, Cardiology Hospital, National Medical Centre, Mexican Institute of Social Security, Mexico

**Address for correspondence:** Antonio Magaña Serrano, MD, FACC, PCHF, Head of the Division of Heart Failure and Cardiac Transplantation, Cardiology Hospital, National Medical Centre, Mexican Institute of Social Security, Mexico (email: ams03mx@hotmail.com)

**Keywords:** Chagas disease; rheumatic fever; SII program

In 1962, the 4<sup>th</sup> WCC was held in Mexico City, Mexico. Fifty-four years later, in June 2016, the WCC returned to the capital of the second largest country in Latin America and the twelfth largest city in the world. The WCC was once again organized by the World Heart Federation and a local committee involving cardiology associations from the host country, ie, the Mexican Society of Cardiology and the National Association of Cardiologists of Mexico.

Unlike other large cardiology congresses (ie, European Society of Cardiology, American College of Cardiology, and American Heart Association), the WCC aims to bring together representatives in the field of cardiology from around the world, including countries and world regions that are often underrepresented at other congresses in this specialty. In addition, the purpose of this event goes beyond the presentation of the results of new clinical trials or clinical guidelines. The primary objective of the WCC is to present global cardiovascular problems, as well as highlighting the positions and the new health care policies on the prevention and treatment of cardiovascular diseases. The WCC involves the active participation of international organizations that work together to share the best clinical practices that respond to unmet needs in cardiovascular medicine.

The WCC included almost 5000 delegates, 120 scientific activities (conferences, symposium, workshops) with 36 thematic categories, 550 foreign and local faculty, 200 hours of academic activities, 41 discussion panels on contemporary cardiology problems, and around 1000 posters. The leading topics in the WCC included: (i) local health, political advocacy, and Latin American cardiology; (ii) coronary artery disease; (iii) arrhythmias; (iv) imaging and technology; (v) heart failure; (vi) preventive cardiology; (vii) other cardiac diseases, such as rheumatic fever and Chagas disease; and (viii) epidemiology, public health, and health systems.

## CARDIOVASCULAR DISEASE IN UNDERDEVELOPPED COUNTRIES

The most relevant topics in terms of importance and magnitude were the epidemiological changes in underdeveloped countries, particularly the significant increase in the prevalence of diabetes, hypertension, dyslipidemia, smoking, and obesity; all of which

are associated with the development of coronary artery disease. Today, this issue is of particular importance because countries with more vulnerable economies face these diseases as well as having a specific weight regarding mortality and morbidity that represent catastrophic expenditures for health care systems. Therefore, during academic and scientific activities of the congress, the importance of generating concrete short-, medium-, and long-term action plans for the primary and secondary prevention of these conditions was reiterated. In addition, the importance of the joint participation of governments, medical associations, the pharmaceutical industry, and civil society was also highlighted, since it is impossible for a single actor to have a decisive impact on these serious problems of population health. However, despite sociodemographic changes and epidemiological transition in many countries, there are still diseases that are considered linked to underdevelopment. These diseases continue to claim lives and represent a challenge for many countries, with the two most important diseases being rheumatic heart disease and Chagas disease.

### **Rheumatic heart disease**

Rheumatic heart disease results from an inflammatory process associated with infections due to  $\beta$ -hemolytic streptococcus bacteria. In the acute phase, this disease conditions a pancarditis that can evolve chronically to cause valvular heart disease and heart failure. The main valve affected is the mitral valve, but the aortic valve and the tricuspid are also frequently affected. This disease remains one of the leading causes of heart valve disease in several underdeveloped countries (eg, certain countries in Africa) above congenital or degenerative causes. Affected patients are usually young, meaning that the impact of this disease is devastating because patients are often economically active and become handicapped when they are suffering from the disease.

As drug treatment is frequently insufficient, the best treatment option is either management by an interventional cardiology team or cardiac surgery; however, these options are expensive and require an advanced medical infrastructure that is difficult to put in place in many countries where the disease is endemic. Therefore, it is important to target primary prevention measures through campaigns to eradicate streptococcal infections, especially during childhood, which requires health policies from the care implemented by primary care physicians, and a better education on the proper management of these infections for patients and families. However, due to globalization and migration of people from countries where rheumatic fever is endemic to developed countries, it is likely that if we do not contain this disease in the countries of origin, the condition will be imported into countries that had hitherto considered the disease eradicated. It is for this reason that this condition remains one of the most important challenges in contemporary cardiology and demands an urgent call to action.

### **Chagas disease**

Chagas disease continues to be one of the leading causes of heart failure in certain countries of the world, such as Brazil, and it produces a particular type of dilated car-

diomyopathy that is difficult to treat. Patients are particularly susceptible to the adverse effects of drugs that are considered first-line agents because patients often present with low blood pressure, and most of the medications, such as ACE inhibitors,  $\beta$ -blockers, aldosterone antagonists, and diuretics, affect blood pressure. Heart transplantation is an option for patients in advanced stages; however, this alternative is very expensive and difficult to carry out for large populations. Therefore, early detection and monitoring of seropositive patients are necessary. Chagas disease reflects the significant gaps in the development of countries because it is particularly associated with poverty. So, once again, the joint participation of the government at every level in conjunction with the medical community, civil society, and industry is necessary to reduce the magnitude of the problem.

### **THERAPEUTIC COMPLIANCE**

Another important aspect considered was the imperative need for therapeutic compliance to achieve control targets for the primary and secondary prevention of cardiovascular disease. Therefore, world-class opinion leaders, such as Valentin Fuster, stressed the importance of cardiovascular prevention programs starting from early childhood through multidisciplinary interventions in both children 3 to 5 years old (SII Program<sup>1</sup>), adults (50/50 Program<sup>2</sup>), and incorporating the polypill as part of the most important actions for the secondary prevention of cardiovascular diseases. The latter measure is in the process of being adopted by health care institutions, such as the Mexican Institute of Social Security, which is the largest organization of public health in Mexico with about 70 million affiliates. By now, the institute has developed local clinical trials with the aim of incorporating the polypill into their global strategy called “A todo Corazón,” which promotes prevention throughout the cardiovascular continuum.

### **CONCLUSIONS**

The highlight of the WCC activities was the signing of the “The Mexico Declaration for Circulatory Health.” This document was designed and signed by the leaders of the most important cardiology organizations worldwide. The commitments include: (i) reducing tobacco consumption and smoking; (ii) detecting and controlling arterial hypertension early; (iii) improving the actions for the secondary prevention of cardiovascular diseases; (iv) promoting healthy lifestyles; and (v) implementing regional and local (“a la carte”) guidelines and plans according to the reality of each region and country. Thus, the WCC became a platform that leverages the actions to be taken to achieve the 25x25 goal of the World Health Organization (reducing the cardiovascular morbidity and mortality by 25% by the year 2025) and the most appropriate forum to give voice to those who have had no voice until now. ■

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# ALL CARDIOLOGY ROADS LED TO ROME

Summary of the 2016 European Society of Cardiology Congress

**MICHEL KOMAJDA, MD**

**Author affiliations:** University Pierre & Marie Curie and Pitié Salpêtrière Hospital, Paris, France

**Address for correspondence:** Michel Komajda, Department of Cardiology Hospital Saint Joseph, 185 rue Raymond Losserand, 75014 Paris, France (email: mkomajda@hpsj.fr)

**Keywords:** heart failure; implantable cardioverter defibrillator; telemonitoring

The 2016 ESC congress took place in Rome, Italy and convened more than 33 000 participants, reaching an unprecedented record of participation to confirm that this meeting is the largest cardiovascular forum worldwide. In addition, this meeting had the honor to welcome His Holiness Pope Francis who strongly encouraged the professionals to continue their efforts to reduce the burden of cardiovascular diseases in the world and heal the people who are affected by these diseases. In the area of HF, several important studies were presented.

## TELEMONITORING IN HF: DISAPPOINTING RESULTS

Two implant-based telemonitoring studies were presented. Martin Cowie (UK) presented the results from the REM-HF trial,<sup>1</sup> which included 1650 patients with mild-to-moderate HF from nine centers in the UK. The trial compared usual care with usual care plus weekly transmission of data through an implantable cardiac defibrillator or a pacemaker. The primary outcome (all-cause mortality or cardiovascular hospitalization) and its components were unchanged in the telemonitoring group although transmission of information led to action in ≈70% of the patients.

Similarly, the MORE-CARE trial,<sup>2</sup> which was presented by Giuseppe Boriani (IT), enrolled just over 900 patients before recruitment was stopped due to a low enrollment rate. Patients were randomized to in-office follow-ups alone or remote monitoring plus in-office follow-ups. No significant differences were found in the primary end point (composite of death and cardiovascular and device-related hospitalizations) or its components. However, there was a modest reduction in health care resource utilization with the remotely monitored patients, which was mainly due to a reduction in scheduled cardiovascular in-office visits.

These results raised some questions about the potential interest of telemonitoring for HF since they do not show a reduction in hospitalizations. Previous studies of implant-based monitoring have provided mixed results. The IN-TIME study<sup>3</sup> used a call center 24/24 hours and 7/7 days, and the data showed a significant reduction in the primary outcome, which was entirely driven by a decrease in mortality. However, the thoracic impedance-based system used in the OPTILINK study was not associated with any benefit.<sup>4</sup>

Several explanations can be put forward, including the fact that patients from several studies had mild HF and/or were optimally treated, which may have limited the impact of potential medical interventions or the need to change medications. Other limiting factors include the large amounts of information to be analyzed, the patients' adherence to the system, and the reactivity of health care professionals, ie, the actions taken after receiving a warning signal. In any case, these two new studies, REF-HF and MORE-CARE, cast doubt on the interest of implant-based telemonitoring systems as a substitute for the standard of care in the management of chronic HF.

### **IMPLANTATION OF A DEFIBRILLATOR IN NONISCHEMIC CARDIOMYOPATHY**

The current indications of an ICD in patients with HFREF are stronger in ischemic HF due to the results of the MADIT<sup>5</sup> and SCD-HeFT<sup>6</sup> trials than in dilated cardiomyopathy where only one trial—DINAMIT<sup>7</sup>—suggested benefit.

Recently, the DANISH trial<sup>8</sup> enrolled more than 1100 patients with dilated cardiomyopathy to evaluate the potential benefit of an ICD with or without cardiac resynchronization compared with standard of care with or without cardiac resynchronization. The primary outcome was total mortality, but there was only a nonsignificant trend in favor of the ICD group. In contrast, there was a significant 50% reduction in the secondary end point (sudden cardiac death). The authors also performed subgroup analyses and found that, in the younger patients (lower tertile <68 years), there was a 36% relative risk reduction in the primary outcome in favor of the ICD group. One important implication of this trial is that an individual decision should be made regarding ICD implantation for dilated cardiomyopathy and that the potential benefit was higher in younger patients.

### **HF IN THE COMMUNITY: A HUGE BURDEN TO COME**

Several epidemiological studies were presented during the meeting. Ragnar Danielsen (Iceland) presented the results from the AGES-Reykjavík study,<sup>9,10</sup> which included 5706 randomly selected elderly participants who were representative of the population of Iceland. The study assessed the prevalence of HF in elderly people; the prevalence was 1.9% in patients <69 years old and increased to 6% in patients >80 years old. Importantly, based on the predicted age distribution and the increase in the number of elderly people >70 years old, the study forecasts that the number of patients with HF will have increased 2.9 times by the year 2060.

Rahul Potluri (UK) presented another study, ACALM,<sup>11</sup> which enrolled 457 000 patients hospitalized in the Midlands, UK from 2000 to 2014, 13 416 of whom were diagnosed with HF. The study assessed the number of readmissions within 5 years and recorded the vital status. The study confirmed that recurrent readmissions are the hallmark of HF: 42% of the studied population had 0-3 readmissions, 29% had 4-7 readmissions, and 14% had 8-11 readmissions. The study also calculated the risk of death associated with rehospitalizations and concluded that each readmission significantly increased the mortality risk by 2%.

Pardeep Jhund (UK) presented the results from a study that assessed the mortality and morbidity in a cohort of 14 546 patients with HF from Scotland.<sup>12</sup> He observed that death was 15 per 100 patient-years and that cardiovascular hospitalizations were highly prevalent (31 per 100 patient-years), where half of these hospitalizations were related to HF. The median length of stay was 8 days. Noncardiovascular hospitalizations were also highly prevalent (49 per 100 patient-years), the most common specified causes being respiratory or gastrointestinal. Finally, the investigators looked at the rate of prescriptions for recommended medications, which was suboptimal, particularly for  $\beta$ -blockers and MRAs (56% and 25% respectively in the subgroup with left ventricular dysfunction). Only a minority of patients were receiving the target doses recommended by the international guidelines (41% for ACE inhibitors, 19% for ARBs, and 20% for  $\beta$ -blockers).

These results highlight the facts that HF is a growing health care burden with increased prevalence, coexistent comorbidities, high mortality, and a high rate of recurrent hospitalizations and that the pharmacological management of patients with HF remains suboptimal. These findings should prompt governmental initiatives to anticipate the epidemic of HF, which is forecast due to the aging population in Western countries. In addition, these results should lead to specific studies to analyze the reasons why patients with HF do not receive recommended therapies and remain at low dosage of these treatments when prescribed.

## **NEW GUIDELINES ON THE MANAGEMENT OF HF**

The updated version of the ESC guidelines on the diagnosis and the management of HF have been extensively discussed during the meeting. Several important changes have been introduced in the new version, including:

- A new algorithm for the diagnosis of nonacute-onset HF, which is based on an a priori probability, and that is determined using simple diagnostic tools (clinical history, signs, symptoms, and electrocardiograms) and then using natriuretic peptides and echocardiography or echocardiography directly if the dosage of natriuretic peptide levels are not routinely available.
- A new category for HF has been included that is based on the determination of ejection fraction: HFMEF. HFMEF is defined by an ejection fraction between 40% and 49%, signs and/or symptoms, and elevated natriuretic peptides or evidence of structural cardiac abnormalities or diastolic dysfunction. The rationale for introducing this intermediate category is that the level of 40% to 49% already suggests that there is an alteration in systolic dysfunction, which may be a transitional phase from HFPEF to HFREF or conversely a transition from documented HFREF toward normal HF, but it can be argued that, in this “gray zone,” there is no evidence to guide treatment.
- A new algorithm for the management of HFREF: ACE inhibitors (or ARBs if not tolerated),  $\beta$ -blockers, and MRAs are the first steps of the pharmacological management. Then, three different options are proposed if the patients remain symptomatic: (i)

ARNi (sacubitril-valsartan combination) in patients tolerating ACE inhibitors or ARBs; (ii) ivabradine in patients with increased heart rate >70 bpm and in sinus rhythm; or (iii) cardiac resynchronization therapy in patients with a QRS >130 msec and in sinus rhythm. The new guidelines state that these three different options are not exclusive.

## **CONCLUSION**

At the end of the 2016 ESC congress, it was evident that substantial progress has been made in the management of HF. However, there are important areas where the situation remains suboptimal due to gaps in the evidence or to unmet medical needs, such as high rehospitalization rates, low titration of recommended medications, HFPEF, and acute HF. In particular, acute HF remains a major concern for patients and physicians, and health care systems will be under strain if no action is taken to reduce the burden of this condition. ■

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# BIOMARKERS FOR THE PERSONALIZATION OF CARDIOVASCULAR MEDICINE

Summary of the 2016 American Heart Association Scientific Sessions

**ANICK DUBOIS, PhD<sup>1,3</sup>; MARIE-PIERRE DUBÉ, PhD<sup>1,2,3</sup>; JEAN-CLAUDE TARDIF, MD<sup>1,2,3</sup>**

**Author affiliations:** <sup>1</sup>Montreal Heart Institute, 5000 Belanger Street, Montreal, Quebec, Canada

<sup>2</sup>Faculty of Medicine, Université de Montréal, Montreal, Quebec, Canada

<sup>3</sup>Université de Montréal Beaulieu-Saucier Pharmacogenomics Centre, Montreal, Quebec, Canada

**Address for correspondence:** Jean-Claude Tardif, MD, Montreal Heart Institute, 5000 Belanger Street, Montreal, Quebec, Canada, H1T 1C8 (email: jean-claude.tardif@icm-mhi.org)

**Keywords:** biomarker; cardiovascular disease; dalcetrapib; pharmacogenomics; precision medicine

Cardiovascular diseases remain the leading cause of death and hospitalization worldwide, representing a serious economic burden with the highest direct health care costs. This burden is predicted to increase greatly over the next few years, in part because of the epidemics of obesity, metabolic syndrome, and diabetes, as well as an aging population. Many drugs are available to treat cardiovascular diseases, but these are not effective for a large proportion of individuals, and the need for innovative, safe, and effective treatments remains very high for this indication. Despite this, over the past two decades, the number of new cardiovascular drugs approved and the investments in cardiovascular drug development have declined, and are relatively lower when compared with other therapeutic areas.<sup>1</sup> Between the years 2000 and 2012, the field of oncology had the highest number of new molecular entity applications (n=61) at the FDA Center for Drug Evaluation and Research and the highest rate of first-cycle approvals of all therapeutic classes (72%). In contrast, cardiovascular drugs had considerably fewer new molecular entity applications (n=21) and a much lower rate of first-cycle approvals (32%).<sup>1,2</sup>

One of the causes for this cutback in investments throughout the years is the relatively high cost of conducting cardiovascular outcome trials, which require a direct assessment of clinically relevant cardiovascular benefits.<sup>1,2</sup> In addition to the complicated nature of cardiovascular diseases and the rising costs and time necessary to develop new cardiovascular drugs, the burdensome institutional and regulatory requirements are increasingly challenging. By using genetics and biomarkers to stratify patients at enrollment and monitor therapy during the studies, precision medicine and adaptive design trials, can reduce the size and cost of clinical trials, lead to more efficient outcomes trials, and provide valuable evidence of efficacy and safety to regulatory agencies. Precision medicine has the potential to facilitate the development of new drugs and reposition existing drugs for responder populations.<sup>2</sup>

Based on a 2015 study from the Tufts Center for the Study of Drug Development, 42% of the development programs for new drugs in the pipeline now involve biomarkers, showing that the pharmaceutical industry has progressively embraced precision medicine. A growing share of the industry's resources is directed toward the development of

precision medicine with investments increasing by 87% over the past 5 years, which is expected to increase by another 33% over the next 5 years.

## **ARE WE THERE YET IN THE CARDIOVASCULAR FIELD?**

According to the Personalized Medicine Coalition, the number of novel drugs approved by the FDA and classified as personalized medication (ie, with biomarker information on their labels to guide decisions and procedures) has increased from 0% in 2010 to 22% (9 out of 41 novel drugs) in 2014 and to 28% in 2015 (13 out of 45 novel drugs), hitting a new record.<sup>3</sup> Five of the 13 precision drugs approved last year were for oncology. In contrast, precision medicine is still at an embryonic stage for cardiovascular indications. Only 2 of the 13 precision drugs approved were for cardiovascular indications (ie, evolocumab and alirocumab).<sup>3</sup> Evolocumab and alirocumab are monoclonal antibodies that target PCSK9, and they are indicated for the treatment of patients with heterozygous or homozygous familial hypercholesterolemia or atherosclerotic heart disease that requires additional lowering of low-density lipoprotein cholesterol. In some lists of personalized drugs approved in 2015 (eg, GenomeWeb list), these two medications are not classified as personalized, setting the number of precision cardiovascular drugs to zero.

One discovery that may pave the way for a new era in precision cardiovascular medicine pertains to the pharmacogenomics of dalcetrapib. Developed by Hoffmann-La Roche, dalcetrapib inhibits the cholesteryl ester transfer protein that increases high-density lipoprotein cholesterol in the plasma. Dalcetrapib is an investigational drug that has already been evaluated in several large clinical trials, most notably dal-OUTCOMES, a study of more than 15 000 patients. The dal-OUTCOMES study was designed to evaluate the effect of dalcetrapib in patients with a recent acute coronary syndrome; however, the study was stopped after a median of 2.6 years of follow-up for futility because dalcetrapib, when compared with placebo, did not alter the risk of cardiovascular morbidity and mortality, despite a 30% increase in high-density lipoprotein cholesterol. Still, the study demonstrated the safety and tolerability of dalcetrapib in this population.

Based on the hypothesis that the response to dalcetrapib may vary according to the genetic profile of patients (because of previous research demonstrating the cardioprotective properties of high-density lipoprotein and the paradoxical increase in C-reactive protein in the dal-OUTCOMES trial), the Beaulieu-Saucier Pharmacogenomics Centre at the Montreal Heart Institute conducted a pharmacogenomic study on 5749 patients from dal-OUTCOMES.<sup>4</sup> A strong association was found between the effects of dalcetrapib on cardiovascular outcomes and the ADCY9 gene on chromosome 16, specifically the rs1967309 genetic variant. In patients with the AA genetic profile at position rs1967309, a 39% reduction in the combination of cardiovascular events (ie, cardiovascular death, myocardial infarction, stroke, unstable angina, and coronary revascularization) was observed with dalcetrapib compared with placebo (HR, 0.61; 95% CI, 0.41-0.92).<sup>4</sup> Approximately 1 in 5 patients studied had this genetic variant, and these patients also benefited from a reduction in the amount of atherosclerosis in their carotid vessels as observed in

the imaging study dal-PLAQUE-2. The dal-PLAQUE-2 study demonstrated a reduction in intima-media thickness of the carotid artery in patients with the AA genotype treated with dalcetrapib compared with placebo. In patients with the GG genotype (found in roughly 2 in 5 patients), an increase in cardiovascular events (27%) and atherosclerosis progression were observed with dalcetrapib vs placebo.

Additional findings, which have been recently published,<sup>5</sup> support dalcetrapib's pharmacogenomic effects and offer insights into the molecular mechanisms linking genomic variations at the ADCY9 locus and the cardiovascular effects of dalcetrapib. The results indicate that genotype-dependent effects on the inflammation biomarker hs-CRP and the serum cholesterol efflux capacity are supportive of dalcetrapib benefits on atherosclerotic cardiovascular outcomes in patients with the AA genotype at polymorphism rs1967309 in the ADCY9 gene. The dal-OUTCOMES study demonstrated that treatment with dalcetrapib resulted in an 18.1% ( $P=0.0009$ ) and 18.7% ( $P=0.00001$ ) placebo-adjusted geometric mean percent increase in hs-CRP from baseline to the end of the trial in patients with the GG and AG genotypes, respectively, but the change was -1.0% ( $P=0.89$ ) in patients with the protective AA genotype, with an interaction  $P$  value of 0.02 for the interaction term between the treatment and the genotype effects. Furthermore, while the mean change over time in cholesterol efflux in dal-PLAQUE2 was similar among study arms in patients with the GG genotype (mean, 7.8% and 7.4%), there was a 22.3% and 3.5% increase with dalcetrapib and placebo, respectively, for patients with the AA genotype ( $P=0.004$ ). There was a significant genetic effect on the change in efflux for dalcetrapib ( $P=0.02$ ), but not with placebo.<sup>5</sup>

This breakthrough association between the ADCY9 gene and responses to dalcetrapib in terms of clinical outcomes, atherosclerosis imaging, cholesterol efflux, and inflammation provided support to conduct the 5000-patient, prospective, phase 3, multicenter trial called dal-GenE (NCT02525939), which will examine the effects of dalcetrapib in subjects recently hospitalized for an acute coronary syndrome and who have the appropriate genetic profile. This trial represents the first late-stage personalized medicine initiative directed toward reducing the risk of cardiovascular morbidity and mortality in a population at a high risk for future events. If successful, dalcetrapib will be the first cardiovascular medication to be approved with a companion diagnostic. It is likely that other drugs that failed in phase 2 or 3 trial could be developed for a subgroup of responders. Several developed cardiovascular drugs may be currently misclassified as ineffective because they were not tested with the appropriate genetic/biomarker analyses.

## **CONCLUSION**

To eliminate the increasing global burden of cardiovascular diseases on individuals, families, health care systems, and public health, the innovative combination of pharmacogenomics, other omics/biomarkers, and imaging with artificial intelligence may radically transform the landscape of cardiovascular drug development as it did successfully for the dalcetrapib discovery. There is a strong need to develop cardiovascular drugs with reduced

toxicity and major health benefits for the population of patients for which the current therapies are not optimal. With the recent advances in precision medicine, investigators in the field of cardiovascular disease can now work with a new set of unique tools to enable novel and more powerful prevention and treatment strategies for cardiovascular diseases. ■

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*Key Abstract Presentations*



# COMORBIDITIES AND HEART FAILURE OUTCOMES

Recent highlights from the 2016 American College of Cardiology Meeting

## MICHAEL BÖHM, MD

**Author affiliations:** Universitätsklinikum des Saarlandes, Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Kirrberger Str. 1, DE 66424 Homburg/Saar, Germany

**Address for correspondence:** Michael Böhm, Universitätsklinikum des Saarlandes, Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Kirrberger Str. 1, DE 66424 Homburg/Saar, Germany (email: michael.boehm@uks.eu)

**Keywords:** atrial fibrillation; depression; heart failure; pulmonary function; renal dysfunction

Chronic HF is still associated with a poor prognosis. The incidence is not only increasing in the developed Western world, but also in the middle- and low-income countries. The increasing incidence of HF is due to the increased life expectancy of our populations, with a higher number of elderly individuals being affected by the disease. Treatment for HF includes neuroendocrine antagonists and diuretics, and they have reduced the mortality and hospitalizations for HF patients. In parallel with age, there is an increase in comorbidities in HF patients, which contributes significantly to the poor outcomes. Current scientific literature increasingly addresses this phenomenon, and provocative hypotheses and questions have been brought forward, such as the question “has the epidemic of heart failure been replaced by a Tsunami of comorbidities?”<sup>1</sup> At the 2016 American College of Cardiology meeting in Chicago, IL, USA, several interesting studies on comorbidities, such as depression, chronic pulmonary diseases, and renal dysfunction, were presented.

## DEPRESSION

Depression is associated with poor clinical outcomes in patients with chronic HF. In particular, when arrhythmias coincide with HF, outcomes might be particularly poor in depressive patients. This hypothesis was addressed in a study by Lima et al (US).<sup>2</sup> The study investigators enrolled 471 HF patients with suspected depression from Pittsburgh-area hospitals and, of these, 41% had AF. The demographic characteristics were similar to patients in sinus rhythm. According to scores from the validated PHQ-9, all HF-AF patients had increased depressive symptoms. In association with depressive symptoms, the mortality rate increased when dividing the PHQ-9 scores into tertiles. This association was robust after adjustment for other demographic confounders or characteristics of HF. This contribution by Lima et al provides insight on the association between depression, mortality, and comorbidities in HF patients. AF, a frequent comorbidity in HF, was associated with the add-on effect of depression and an increase in mortality. This study provides evidence that both independent cardiac and noncardiac comorbidities in HF patients act in concert to increase mortality.

## LUNG DISEASE

Lung disease and other pulmonary diseases are associated with an increased incidence of HF. In turn, many HF patients have a concomitant pulmonary disease. This is related to the common “soil” of risk factors,<sup>3</sup> such as smoking and oxidative stress, in pulmonary disease, coronary artery disease, and subsequent HF. Furthermore, there might be a direct interrelationship between pulmonary function and myocardial function and vice versa. Silvestre et al (US) investigated the patient population in the ARIC study without HF, but a rapid decline in pulmonary function after a 2.9-year follow-up. Pulmonary function was measured by spirometry, which was then examined to determine if there was a correlation between pulmonary function and the incidence of HF or the outcomes of HF.<sup>4</sup> Patients with a rapid decline in pulmonary function had worse outcomes and increased incident HF events, even when adjusted for height, body mass index, heart rate, hypertension, and cardiovascular risk factors, such as LDL-C, smoking, diabetes, and preexisting pulmonary disease. The rapid decline of pulmonary function was highly predictive of incident HF. This study sheds an interesting light on the interaction between pulmonary comorbidities and HF, and it lends itself to the hypothesis that interfering with pulmonary function can halt new-onset HF in high-risk patients.<sup>4</sup>

## RENAL FUNCTION

Renal dysfunction occurs in almost 50% of patients with HF, and it is associated with poor outcomes. In turn, high doses of diuretics, particularly loop diuretics, can aggravate renal dysfunction, leading to diuretic resistance, which is also related to poor outcomes in HF. ter Maaten et al (US and NL) studied possible mechanisms for loop diuretic-induced resistance.<sup>5</sup> These investigators differentiated between global diuretic resistance and diuretic resistance due to tubular dysfunction. In a population with acute HF, they associated the effect of intravenous bumetanide on 6-hour urine collection for sodium and bumetanide clearance. Interestingly, tubular dysfunction was responsible for diuretic resistance in 71% of the population. Tubular defects are substantially more important than reduced diuretic delivery in HF patients after acute decompensation. Global renal dysfunction, as determined by estimated glomerular filtration rates (eGFR), might not be the only, or even the right, tool to study diuretic resistance in general.

The presented contributions show that, beyond the simple association of comorbidities and outcome in HF, specific intervention possibilities that target comorbidities are available to help improve outcomes in HF. Future studies will have to show whether directly targeting comorbidities affect the outcomes of patients suffering from HF. ■

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# IS IT TIME TO OPTIMIZE HEART RATE—LOWERING THERAPY IN HOSPITALIZED PATIENTS WITH HEART FAILURE?

Recent highlights from the 2016 Heart Failure Congress

**YURY M. LOPATIN, MD, PhD, FHFA**

**Author affiliations:** Volgograd State Medical University, Cardiology Centre, Russian Federation

**Address for correspondence:** Yury Lopatin, Head of Department of Cardiology, Volgograd State Medical University, Cardiology Centre, 106, Universitetsky prospect, Volgograd, 400008, Russian Federation (email: yu.lopatin@gmail.com)

**Keywords:**  $\beta$ -blocker; heart failure; heart rate-reducing therapy; ivabradine

**H**eat failure is a common, chronic, and progressive disease that is characterized by frequent hospital admissions and high mortality rates. Despite the recent advances in the management of chronic and acute heart failure, it continues to be a growing financial burden on health care systems. The enormous costs associated with mortality and hospitalizations in patients with decompensated chronic heart failure require new effective solutions to optimize the management of heart failure.

Key strategies to manage symptomatic patients with heart failure in sinus rhythm include heart rate-lowering therapies, ie,  $\beta$ -blockers, the  $I_f$  inhibitor ivabradine, and  $\beta$ -blockers plus ivabradine. The current indication for ivabradine in heart failure is based on the results of the SHIFT trial that included patients with stable symptomatic chronic heart failure with a duration of at least 4 weeks, who had been hospitalized for heart failure within the previous 12 months.<sup>1</sup> However, data obtained in recent European or national studies show that the number of heart failure patients with a heart rate  $\geq 70$  bpm (including patients before discharge from the hospital<sup>2</sup>) remains high and that these patients have the worst 1-year outcomes.<sup>3-6</sup> This issue raises questions about the optimization of the heart rate-lowering therapy with ivabradine before discharging heart failure patients from the hospital. Several interesting studies on this topic were presented at the 2016 Heart Failure Congress in Florence, Italy.

## ELIGIBILITY FOR IVABRADINE AFTER HOSPITALIZATION FOR ACUTE HEART FAILURE

Ammirati et al (IT) investigated the number of patients eligible for ivabradine treatment after hospitalization for acute decompensated heart failure and at the first outpatient appointment.<sup>7</sup> Eligibility for ivabradine was defined as patients with an LVEF  $\leq 35\%$ , sinus heart rate  $\geq 70$  bpm, and NYHA class II-IV. This retrospective analysis included 309 consecutive patients who were discharged from three specialized heart failure centers in Italy. At discharge, 23.0% of patients with heart failure were eligible for ivabradine; however, most of these patients (19.1%) did not receive ivabradine. Patients with heart failure who did not receive ivabradine therapy at discharge had the following characteristics:

age, 65±14 years; female, 32%; ischemic etiology, 35.6%; median LVEF, 28%; de novo cases, 40.7%; NYHA class III-IV, 32.2%; mean systolic blood pressure, 109±18 mm Hg; median heart rate, 75 bpm; and a previous episode of atrial fibrillation, 32.2%.

β-Blockers were used in 86.4% of the patients with heart failure, and the average doses of bisoprolol and carvedilol were 2.5 mg/day and 15.6 mg/day, respectively. At the first outpatient appointment (after a median time of 3 months), only 9.1% of the patients with heart failure were still eligible for ivabradine, which was started in only 5 patients (2%), leaving 7.8% of heart failure patients without proper heart rate control. The authors concluded that, even in specialized heart failure centers, every fifth patient discharged after acute decompensated heart failure was not on ivabradine even though they were suitable for this treatment. They hypothesized that a more rapid achievement of the target heart rate could reduce early events after an episode of acute decompensated heart failure; however, this hypothesis needs to be tested.

### **HEART RATE-LOWERING THERAPY: OUTCOMES IN PATIENTS WITH HF**

Lesmes et al (ES) investigated the effect of the early administration of ivabradine added to β-blockers (ivabradine + β-blocker) vs β-blockers alone on heart rate and outcomes in hospitalized patients with systolic heart failure.<sup>8</sup> The primary end point of this comparative, randomized study was heart rate at 28-days postdischarge. Heart rate, LVEF, NYHA class, BNP levels, and clinical outcomes at 1 year were also analyzed. The study included 62 consecutive patients with heart failure (30 in the ivabradine + β-blocker group and 32 in the β-blocker alone group). Both groups were homogeneous in terms of age, sex, blood pressure, heart rate at admission, BNP levels, renal function, and therapy with guideline-recommended drugs.

In the ivabradine + β-blocker group, ivabradine was started 24 hours after admission. The dosage at discharge was 5 mg twice daily in 18 patients and 7.5 mg twice daily in 12 patients. The β-blocker dosage at discharge and the 1-year follow-up was similar in both groups. The primary end point was significantly lower in the ivabradine + β-blocker group when compared with the β-blocker alone group (64.3±7.5 bpm vs 70.3±9.3 bpm;  $P=0.01$ ). Heart rate remained lower at 1 year in the ivabradine + β-blocker group (61.8±5.5 bpm vs 68.5±9.3 bpm;  $P=0.01$ ). At discharge, LVEF was similar in both groups of patients with heart failure, but at 1 year, LVEF was significantly higher in the ivabradine + β-blocker group (48.2±17.2% vs 41.8±10.2%;  $P=0.002$ ). At 1 year, there were no differences in BNP levels, the number of patients in NYHA class III or IV, or clinical events (rehospitalizations or death). No severe adverse effects related to the drugs were noted.

The authors concluded that coadministration of ivabradine and a β-blocker early after admission to the hospital for patients with systolic heart failure, sinus rhythm, and heart rate >70 bpm is feasible, safe, and significantly decreases heart rate 28-days postdischarge compared with β-blockers alone. In addition, heart rate at 1-year postdischarge decreased and systolic function improved with this drug protocol without differences in β-blocker doses.

Thus, the early coadministration of ivabradine and  $\beta$ -blockers before discharge from the hospital may be considered as a new option to optimize heart rate-lowering therapy in hospitalized heart failure patients. However, a longer period of follow-up and a larger number of patients with heart failure are needed to determine whether these results translate into improved prognosis in terms of reducing long-term events. ■

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# NEW CLINICAL APPLICATIONS FOR IVABRADINE

Recent highlights from the 2016 World Congress of Cardiology & Cardiovascular Health

**LUIS H. W. GOWDAK, MD, PhD**

**Author affiliations:** Heart and Lung Disease, Heart Institute (InCor-HCFMUSP), São Paulo, Brazil

**Address for correspondence:** Heart Institute (InCor), Hospital das Clínicas, University of São Paulo Medical School, Av. Doutor Enéas de Carvalho Aguiar, 44, São Paulo 05403-000, Brazil (email: luis.gowdak@incor.usp.br)

**Keywords:** aortic stenosis; heart failure;  $I_f$  current; ivabradine

In 1994, Thollon et al<sup>1</sup> first described the electrophysiological effects of the new molecule ivabradine, a sinoatrial node modulator, on rabbit and guinea pig cardiac preparations. The study showed that ivabradine could inhibit the  $I_f$  current, thus reducing heart rate. Later on, ivabradine was shown to exert a dose-dependent bradycardic effect in healthy volunteers.<sup>2</sup> For the past two decades, the clinical benefits of ivabradine have been documented in different scenarios in cardiovascular medicine, especially in the field of coronary artery disease and HF. In the latter, ivabradine was not only able to improve symptoms and functional capacity, but also to reduce the risk of death due to HF.<sup>3</sup> As a result, ivabradine has been incorporated into international guidelines for the management of HF patients. In addition to the common indication for patients with stable, symptomatic coronary artery disease and/or HF who are already on optimal medical therapy, recent data presented at the 2016 WCC held in Mexico in June showed new, still investigational clinical applications for ivabradine, which are briefly summarized in this article.

## **PATIENTS WITH AORTIC STENOSIS AND STABLE CORONARY ARTERY DISEASE**

Aortic stenosis is the most common valvular heart disease in Europe that usually requires invasive procedures for symptom and prognosis improvement in severe cases. As many as one-third of patients with aortic stenosis may have angina, half of which are over 75 years old with concomitant coronary artery disease, leading many clinicians to prescribe  $\beta$ -blockers for patients with severe aortic stenosis and deny invasive treatment. Previously, Quiroga et al<sup>4</sup> (ES) performed an interesting exploratory study to compare the hemodynamic and clinical effects of  $\beta$ -blocker treatment and ivabradine in this patient population. The study included patients with symptomatic, severe aortic stenosis who dismissed invasive treatments. All of the patients had angina or a known coronary artery disease, were in sinus rhythm, and had an LVEF >55%. Clinical, functional, and hemodynamic assessments were performed at baseline while patients were on  $\beta$ -blockers. Patients were reassessed after  $\beta$ -blockers had been replaced with ivabradine for 1 month. Although no significant changes in heart rate could be detected between treatments, heart performance improved after ivabradine treatment with significant increases in LVEF (69% vs 73%), systolic volume (87.4 mL vs 95.8 mL), cardiac output (5.2 L/min vs 5.7 L/min), and 6-min walking distances (251 m vs 333 m). The authors concluded that treatment with ivabradine was safe, and it may be more appropriate than  $\beta$ -blockers in this population. Certainly, new studies with a larger number of patients and a longer follow-up should confirm these initial findings.

In the 2016 WCC, the same group of investigators showed the effect of reducing heart rate on the mid-term clinical outcomes in patients with severe aortic stenosis. There was an absolute 8.3% and 11.8% decrease in mortality in patients receiving ivabradine at 12 and 18 months, respectively, compared with  $\beta$ -blockers. The authors concluded that treatment with ivabradine was not only safe, but also that it may be more appropriate than  $\beta$ -blockers in this patient population. These results are in line with the results presented at the 2014 WCC. Certainly, new studies with larger patient numbers and a longer follow-up should confirm these initial findings.

### **IVABRADINE IN PATIENTS WITH ACS**

Patients with ACS are at a high risk for future cardiovascular events, including in-hospital mortality and LV dysfunction if they are not treated aggressively; moreover, elevated heart rate has been recognized as a risk marker that is linked to worse outcomes. Despite an increase in the rate of primary PCI in this setting, optimal medical therapy is a key player in further improving prognosis in this population. Reyes et al (MX)<sup>5</sup> sought to investigate the role of ivabradine in 20 patients with non-ST-segment elevation ACS as an add-on therapy after successful PCI. Ivabradine was well tolerated and led to an improvement in the NYHA functional class compared with baseline, and all patients remained free of angina. Echocardiography, performed after 2 months, revealed a significant increase in LVEF from 47% to 59%. No cardiovascular events occurred during a 2-year follow-up.

In the same field, Eissa et al (EG)<sup>6</sup> presented their work on the effect of ivabradine on infarct size and remodeling in 57 patients with ST-segment elevation ACS undergoing PCI. Patients were randomized to receive optimal medical therapy with ivabradine +  $\beta$ -blockers or  $\beta$ -blockers alone. In patients with diabetes and a heart rate >100 bpm at baseline, adding ivabradine to standard therapy significantly reduced LV end-diastolic volume with an absolute gain of 14% in LVEF in the first 3 weeks post-ACS.

Taking those two studies together, ivabradine was shown to be safe in patients with ACS and may have helped improve prognosis. These findings warrant further research on the role of ivabradine in patients with ACS.

### **CONCLUSION**

It is fascinating to observe that clinical demand has led to new scenarios in which ivabradine may be useful. This reflects the nature of clinical scientists who are always looking for an opportunity, based on a solid rationale, to do something different that does not expose patients to unnecessary risks. In the studies selected from the 2016 WCC, researchers did just that, and they found that the clinical use of ivabradine in patients with severe aortic stenosis or with acute coronary syndromes has clinical benefits. For their initiative and contribution to clinical science, they should be congratulated. We must now eagerly await new studies in the field that have sufficient patient numbers and an adequate follow-up. ■

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# REMOTE MONITORING MOVES ON

Recent highlights from the 2016 European Society of Cardiology Congress

**MARTIN R. COWIE, MD, MSc, FRCP, FRCP (Ed), FESC**

**Author affiliations:** Imperial College London (Royal Brompton Hospital), London, UK

**Address for correspondence:** Professor Martin R. Cowie, National Heart and Lung Institute, Imperial College London, Dovehouse Street, London, SW36LY, UK (email: m.cowie@imperial.ac.uk)

**Keywords:** cardiac resynchronization therapy; heart failure; remote monitoring

Health care systems are facing the dual challenges of an aging population with both an increasing number of comorbidities and rising expectations for care and little to no increases in budgets. Digital technologies are often proposed as a potential solution. In theory, remotely collected data can be used to tailor the care a patient receives and to allow decision making to be done from a distance. Although this solution is appealing to patients and politicians, providing evidence that remote monitoring has a meaningful impact on outcomes has proven more challenging.

## IMPLANTED ELECTRONIC DEVICES

At the ESC meeting in Rome in August 2016, two new randomized trials on the remote monitoring of patients with heart failure and cardiac implantable electronic devices were presented—REM-HF and MORE-CARE. Neither trial showed differences in outcomes compared with usual care, although one trial suggested that there might be marginal cost-saving benefits for the health care system.

The REM-HF trial, the world's largest randomized trial in this area to date, randomized 1650 patients from 9 English hospitals to usual care or usual care plus a weekly review of the remotely transmitted data obtained from the implanted devices (eg, CRT-P or ICD): Specially trained staff reviewed the data and used a protocol to determine whether additional actions were needed, ie, calling the patient, arranging a clinic or general practitioner review, or changing medications. Over a median follow-up of 2.8 years, there was no difference in the primary end point of all-cause mortality or urgent hospitalization for cardiovascular reasons (HR, 1.01; 95% CI, 0.87-1.18;  $P=0.87$ ). There was also no difference in a wide range of secondary end points or the individual components of the primary end point. A subgroup analysis of the events could not identify a particular group of patients who benefited from weekly remote monitoring.

The MORE-CARE trial enrolled 918 patients from 64 study sites in 9 countries within 8 weeks of implanting a CRT-D system. The patients were randomized to either remote monitoring that alternated with in-office follow-ups ("remote" arm) or in-office follow-ups alone ("standard" arm).<sup>2</sup> Over a median 24-month follow-up, no significant differences were found in either the primary end point of all-cause death or cardiovascular and device-related hospitalizations (HR, 1.02; 95% CI, 0.80-1.30;  $P=0.89$ ) or the individual components of the primary end point. In-office visits were lower in the remote monitoring

arm, which was likely to decrease health care costs modestly by approximately €29 per patient over 2 years. From the patient's perspective, there was also a cost-saving benefit with an estimated cost of €373 for traveling to the clinic for their in-office visits in the remote arm and €518 in the standard arm over the 2-year period.

There was much discussion concerning the results of these two studies at the ESC meeting. The findings from REM-HF and MORE-CARE add to the evidence base that it is not straightforward to use remote monitoring with either stand-alone or implanted systems to improve patient outcomes. Although patients are often enthusiastic about information being collected at home, and the fact that the heart failure teams are looking at the data, it would not appear sensible to redesign services to collect data very frequently, especially considering that, with the current state of the art, it is difficult to ensure that any action taken in response to large amounts of data will improve outcomes. Remote monitoring is disruptive, and it is organizationally complex to redesign services to cope with remotely collected data. If there is no improvement in identifying when patients should have their therapy changed, more monitoring just means more activity without any reward for the patient or the health care system.

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## **IMPLANTED HEMODYNAMIC MONITORING**

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The situation with implanted hemodynamic monitoring may be different. The CardioMEMS device has been the subject of one randomized controlled trial in the USA, which showed a 30% reduction in the risk of heart failure hospitalization in patients with NYHA class III when physicians acted on pulmonary pressure collected daily from the patients at home. Extension of the data collection period suggested that the effect was likely to be sustainable. Confirmation in a non-USA setting is awaited.

Another hemodynamic monitoring system that collects data from the left atrium has been developed. The pivotal LAPTOP-HF study<sup>3,4</sup> results were presented at the Heart Failure Society of America several weeks after the ESC meeting. This randomized trial was stopped early by the Data Safety and Monitoring Board due to concern regarding the risk of implanting the left atrial pressure sensor across the interatrial septum. Consequently, the now underpowered study failed to show a difference in the primary end point of heart failure and heart failure-related hospitalizations (RR, 0.91;  $P=0.49$ ). In an analysis using the CHAMPION trial end point of heart failure hospitalization alone, data at 12 months suggested that there may be a similar reduction in the HF hospitalization risk when using pulmonary artery pressure monitoring (HR, 0.57;  $P=0.003$ ; 0.40 events per patient year for the treatment group vs 0.70 for controls), but this requires prospective confirmation.<sup>5</sup>

The field of remote monitoring is maturing, but recent results suggest that we need to learn more about integrating the technology into health care decision-making. A new generation of technologies enabling a better identification of patients who require a specific change to their therapy or providing a new therapeutic target, such as pulmonary artery pressure, show promise, but we are some distance away from the disruptive changes in health care delivery that have been promised for so long. ■

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# THE PRECISION AND TRUE-AHF TRIALS

Recent highlights from the 2016 American Heart Association Scientific Sessions

## FRANK RUSCHITZKA, MD, FRCP

**Author affiliations:** University Heart Center, Zurich, Switzerland

**Address for correspondence:** Frank Ruschitzka, MD, FRCP, Professor of Cardiology, University Heart Center, CH-8091 Zurich, Switzerland (email: frank.ruschitzka@usz.ch)

**Keywords:** acute heart failure; celecoxib; nonsteroidal anti-inflammatory drug; ularitide

## THE PRECISION TRIAL

Hundreds of millions of patients with arthritis worldwide require pain-relieving therapy to maintain an acceptable quality of life. However, the ongoing uncertainty concerning the cardiovascular safety of NSAIDs, including conventional and COX-2 selective inhibitors, leaves practitioners and patients with difficult management decisions. As such, evidence from adequately powered, independently run, randomized clinical trials prospectively designed to capture cardiovascular outcomes was urgently needed. Therefore, PRECISION,<sup>1,2</sup> a double-blind, triple-dummy, randomized, 3-arm parallel group design, multicenter, cardiovascular safety trial was designed to test the cardiovascular safety of the COX-2 selective inhibitor celecoxib in patients with osteoarthritis and rheumatoid arthritis and an overt or high risk of developing cardiovascular disease in comparison with two commonly prescribed nonselective NSAIDs—ibuprofen and naproxen. Ibuprofen is the most widely used nonselective NSAID, and naproxen is used commonly in arthritis patients, and it was hitherto believed to have the lowest cardiovascular toxicity.

Patients received celecoxib 200 to 400 mg daily (100 to 200 mg twice daily), ibuprofen 1600 to 2400 mg daily (600 to 800 mg three times daily) or naproxen 750 to 1000 mg daily (375 to 500 mg twice daily) in addition to the usual standard of care treatment for their cardiovascular disease. The allowed doses of celecoxib, naproxen, and ibuprofen were given in accordance with approved labeling in the countries where the study was conducted. The primary end point was the first occurrence of the composite end point that consisted of cardiovascular death, nonfatal MI, or nonfatal stroke, as defined by the Antiplatelet Trialists' Collaboration composite end point.<sup>3</sup>

In the PRECISION trial, 24 081 patients were randomly assigned to celecoxib, naproxen, or ibuprofen for a mean treatment duration of 20.3±16.0 months and a mean follow-up period of 34.1±13.4 months. In the intention-to-treat analyses, a primary outcome event occurred in 188 patients in the celecoxib group, 201 patients in the naproxen group, and 218 patients in the ibuprofen group (HR for celecoxib vs naproxen, 0.93; 95% CI, 0.76-1.13; HR for celecoxib vs ibuprofen, 0.85; 95% CI, 0.70-1.04;  $P<0.001$  for noninferiority in both comparisons). In the on-treatment analysis, a primary outcome event occurred in 134 patients in the celecoxib group, 144 patients in the naproxen group, and 155 patients in the ibuprofen group (HR for celecoxib vs naproxen, 0.90; 95% CI, 0.71-1.15; HR for celecoxib vs ibuprofen, 0.81; 95% CI, 0.65-1.02;  $P<0.001$  for noninferiority in both comparisons). As

expected, the risk of gastrointestinal events was significantly lower with celecoxib than naproxen ( $P=0.01$ ) or ibuprofen ( $P=0.002$ ). Intriguingly, the risk of renal events was significantly lower with celecoxib than with ibuprofen ( $P=0.004$ ). Thus, PRECISION clearly demonstrates that celecoxib is noninferior to ibuprofen or naproxen regarding cardiovascular safety.

PRECISION provides further insight that the NSAIDs and COX-2 selective inhibitors are not as homogenous as previously thought, which might reflect differences in chemical structure, pharmacokinetic properties, and subsequent metabolism, resulting in clinically relevant differential effects, particularly on blood pressure.

### **THE TRUE-AHF TRIAL**

Hospitalizations for acute heart failure syndromes account for  $\approx 1$  million admissions annually in both Europe and the US, and this value continues to increase. The high morbidity, mortality, and economic costs of acute heart failure are explicable, in part, by the lack of safe and effective therapies. To date, the management of patients with acute heart failure remains empirical and highly variable across institutions. Unfortunately, efforts to develop new drugs and interventions have largely been proven ineffective in changing the short-term course of the disease. Therefore, the TRUE-AHF trial<sup>4</sup> was designed to delineate whether administering a vasodilator within the first 6 hours following an initial clinical evaluation and in doses sufficient to improve myocardial wall stress and clinical stability rapidly would reduce the long-term risk of cardiovascular death in patients hospitalized for acute heart failure.

In TRUE-AHF, 2157 patients hospitalized for acute heart failure were randomized to receive either placebo ( $n=1069$ ) or the natriuretic peptide ularitide ( $n=1088$ ) at a dose of 15 ng/kg/hr for 48 hours. Ularitide is a chemically synthesized analog of urodilatin. Urodilatin is synthesized in renal tubular cells, and it is secreted lumenally to act downstream at distal segments of the nephron. Intravenous administration of urodilatin leads to both systemic and renal vasodilation, diuresis and natriuresis, and renin-angiotensin system inhibition in animal models of heart failure, in healthy volunteers, and in patients with heart failure. The primary outcomes of TRUE-AHF were death from cardiovascular causes during a follow-up period of up to 34 months and a hierarchical composite end point that evaluated each patient's initial 48-hour clinical course.

While ularitide exerted the expected hemodynamic effects of reducing blood pressure and NT-proBNP levels and resulted in fewer episodes of in-hospital worsening heart failure during the infusion, no long-term benefits were demonstrated. In particular, death from cardiovascular causes occurred in 225 patients in the placebo group and 236 patients in the ularitide group (HR, 1.03; 95% CI, 0.85-1.25;  $P=0.75$ ). In addition, no differences between the two groups for the hierarchical composite end point or other measures of death or hospitalization were reported.

The TRUE-AHF findings indicate that ularitide can exert favorable short-term physiological effects, but these benefits do not appear to change the natural disease history for these patients. A definitive answer as to whether it will remain worthwhile to continue pursuing the early injury hypothesis should be provided by the eagerly awaited results of the RELAX-AHF2 trial that is testing the effects of the vasodilatory peptide hormone serelaxin on the primary end point of cardiovascular mortality. ■

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Short Reports



# CONTROVERSIES IN HYPERTENSION MANAGEMENT: WHAT IS THE OPTIMAL TARGET BLOOD PRESSURE?

**KRZYSZTOF NARKIEWICZ, MD, PhD**

**Author affiliations:** Medical University of Gdansk, Gdansk, Poland

**Address for correspondence:** Krzysztof Narkiewicz, MD, PhD, Department of Hypertension and Diabetology, Medical University of Gdansk, Debinki 7c, 80-952 Gdansk, Poland (email: knark@gumed.edu.pl)

**Keywords:** blood pressure target; clinical trial; guidelines; hypertension

**A**lthough hypertension is the leading risk factor for cardiovascular disease, there is a continuous debate regarding the optimal target BP. This controversy has been recently fuelled by the SPRINT trial! The trial enrolled more than 9300 participants aged 50 years and older without diabetes or a previous stroke. The patients were randomized to either a standard treatment group that received an average of two antihypertensive drugs to achieve a SBP target <140 mm Hg or to an intensive treatment group that received on average three drugs to achieve an SBP target <120 mm Hg. A target SBP <120 mm Hg was associated with a 25% reduction in the rate of the composite primary outcome (myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes) and a 27% reduction in the risk of all-cause mortality vs an SBP target <140 mm Hg. However, it remains controversial whether the results of the SPRINT study can be implemented directly into the hypertension guidelines to aim for a lower SBP target than the currently recommended target <140 mm Hg. Several aspects should be taken into account when assessing the implications of the SPRINT trial for clinical practice.

First, the intensive treatment did not reduce the risk of myocardial infarction or stroke, and the positive outcome of the trial was primarily driven by a reduction in the incidence of heart failure. It should be noted that the majority (over 90%) of the patients were treated before randomization, and many of them had an SBP slightly above 130 mm Hg. In a substantial proportion of the patients randomized to an SBP target <140 mm Hg, the previous pharmacotherapy (including diuretics, which were recommended to adjust the treatment) was downtitrated. The opposite happened in the intensive group, suggesting that possible differences in the use of diuretics may have unmasked latent heart failure to drive the difference in mortality favoring the intensive arm.<sup>2</sup>

Second, achieving an SBP <120 mm Hg may reduce the DBP to levels that could compromise myocardial perfusion. Indeed, a recent analysis of the ARIC cohort<sup>3</sup> showed that a low DBP, especially in subjects with an SBP close to 120 mm Hg, might harm the myocardium, and it is associated with subsequent coronary artery disease.

Third, there is growing concern regarding the adverse outcomes of the SPRINT trial. Controversy remains as to whether the potential benefits of intensive blood pressure exceed the risk of harm<sup>4,5</sup> because the patients in the intensive treatment group of the SPRINT trial had more hypotension, syncope, electrolyte disturbances, acute renal injury, and acute renal failure. An analysis of the SPRINT-MIND trial, a SPRINT substudy, will evaluate the effects of reducing SBP on cognitive function and all-cause dementia, and it should provide novel insights into the overall benefits of intensive BP lowering.

Fourth, the trial did not include patients with diabetes mellitus, a history of stroke, or institutionalized elderly subjects, which limits the generalizability of the results.<sup>6</sup> Importantly, the HOPE-3 trial showed that BP-lowering therapy was not beneficial in the intermediate-risk patients with baseline SBP levels <130 mm Hg.<sup>7</sup>

Finally, the most important aspect differentiating SPRINT from all other trials is the method of BP assessment, which was based on unattended automated office measurements.<sup>8</sup> The manual of operations and central training called for the study personnel to leave the room, and the device was set to 5 minutes before starting the measurement. Consequently, the SPRINT investigators were able to avoid the alert reaction or so-called “white coat” effect. However, previous studies in treated hypertensive patients have shown that unattended automated office SBP is comparable with or even lower than daytime ambulatory SBP, and it is up to 20 mm Hg lower than conventional in-office SBP measurements.<sup>9</sup> A very recent study carried out in more than 300 treated hypertensive patient showed a difference of 16 mm Hg.<sup>10</sup> Therefore, the BP measured in the SPRINT trial cannot be directly compared with the BP measurements from other trials. In fact, the intensive treatment arm of the SPRINT trial may correspond to an office SBP <136 mm Hg, which is not very different from the SBP <140 mm Hg recommended by the current ESH/ESC hypertension guidelines.

In conclusion, the SPRINT trial has limited implications for clinical practice. The in-office blood pressure target <140/90 mm Hg recommended by the current European guidelines seems sufficient for most patients; however, this target should be reached soon and controlled over time.<sup>11</sup> We should use well-tolerated antihypertensive drugs tested in clinical trials. Our efforts must focus on the improvements in patient compliance to obtain every benefit from the current effective therapeutic strategies. The growing spectrum of fixed-dose double and triple combinations can clearly facilitate this task. ■

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# EDUCATION IN CARDIAC REHABILITATION: THE FORGOTTEN COMPONENT!

MIGUEL MENDES, MD, FACC

**Author affiliations:** Hospital de Santa Cruz, Centro Hospitalar de Lisboa Ocidental, Carnaxide/Lisboa, Portugal  
**Address for correspondence:** Miguel Mendes, MD, Cardiology Department, Hospital de Santa Cruz, Centro Hospitalar de Lisboa Ocidental, Rua Professor Reinaldo dos Santos, 2794-035 Carnaxide, Portugal (email: miguel.mendes.md@gmail.com)

**Keywords:** andragogy; behavior change; cardiac rehabilitation; risk factor

The 2016 ESC guidelines on cardiovascular prevention in clinical practice considered cardiac rehabilitation as a class I (level of evidence A) intervention for patients hospitalized for an acute coronary event or revascularization and for patients with heart failure to improve their clinical outcomes.<sup>1</sup> Beyond its clinical benefits, it is recognized that cardiac rehabilitation is a cost-effective treatment. The cardiac rehabilitation section of the European Association of Cardiovascular Prevention and Rehabilitation defined nine components in a cardiac rehabilitation program: patient assessment, physical activity counseling, nutrition counseling, weight control, lipid management, blood pressure monitoring, smoking cessation, and psychosocial management.<sup>2</sup>

Although cardiac rehabilitation is either a comprehensive secondary prevention program for most coronary artery disease patients (noncomplicated acute coronary syndrome or after coronary angioplasty and stenting) or a physical recovery intervention that is necessary to provide a better and faster recovery (after a complicated acute cardiac event, cardiac surgery, or heart failure episode), it is perceived by many health care professionals as an adapted exercise program for cardiac patients. This view is indeed a very restrictive perspective, since a cardiac rehabilitation program is much more than an exercise program. It integrates several interventions to help the patient resume their place in society by themselves and to delay or reduce the occurrence of new cardiovascular events in the future.

The goal of cardiac rehabilitation is for patients to adopt a long-term healthy lifestyle, where regular physical activity is only one part of the proposed change. Besides this, for a patient with heart failure or coronary artery disease, it is crucial to understand that they must make important changes in their diet and others areas, such as to stop smoking, respect a complex medication regime, and reduce psychological stress.

## CARDIAC REHABILITATION BEYOND EXERCISE

Cardiac rehabilitation is more than just an exercise prescription; it is mainly a program oriented to changing a patient's previous unhealthy behaviors. Although these changes have already been demonstrated to be important over a lifetime, many patients are reluctant to or have difficulties in making the necessary changes. Changing behaviors that have been followed for decades, even after a hospital stay for a cardiac event, is par-

ticularly problematic, especially for patients in their 70s or 80s, because many of them do not understand why they must do it or have problems adopting the changes in both the short and long term. The cardiac rehabilitation program is starting to address these needs and difficulties, a component that is not usually discussed in scientific meetings, although good results have been recognized with several techniques.

To assist in changing unhealthy behaviors, it is necessary to inform the patients and their partners or caregivers about the disease etiology, risk factors, clinical manifestations, drug regime, recommended lifestyle, how to act in emergencies, and stress and anxiety management. This information is usually provided through lectures performed by the multidisciplinary cardiac rehabilitation program staff, but these lectures have produced limited results. Adults do not learn well by pedagogy, the classic teaching method used for children, even if some modern supports, such as audiovisual presentations, are used. This methodology has questionable results in children, but it is clearly unsuitable for older adults. For this population, andragogy is the appropriate teaching methodology, where the person responsible for the learning session provides the necessary information and promotes a direct discussion and interaction between the audience and the different participants.<sup>3</sup>

Adults need to be motivated to change, and this is not difficult to achieve as long as they are provided with adequate information and if they understand that the acute cardiac event or their illness is a consequence of an unhealthy lifestyle or unfavorable genetics, which can be managed by adhering to a healthy lifestyle and the prescribed drug regime. The first hours or days in the hospital, the so-called “golden hours or days,” are the perfect moments to increase patient awareness. Besides motivation, adult learning must be self-directed, problem-oriented, and involve direct or indirect experiences that the changes produce positive outcomes. That is why patients must be informed upon entering the cardiac rehabilitation program about their personal targets for blood pressure, hemoglobin A1C, LDL, HDL, triglycerides, weight, diet, physical activity, and stress and anxiety management.

Adults may change their behaviors by listening to other group members in the same situation and by sharing and discussing difficulties and strategies to overcome the barriers. If the session coordinator can promote a group commitment to change unhealthy behaviors, the results are even better.<sup>3</sup> It is also crucial to involve the patient in a positive environment for lifestyle changes, where their partners and caring doctors (cardiologist and general practitioner) are supportive of the program's proposals.<sup>4</sup>

## **INDIVIDUAL APPROACH**

Besides the group-teaching program, each patient must be approached individually to identify the risk factors present specifically and the new behaviors that need to be adopted. The situation at program entry must be registered, and both the mid-term and final goals need to be negotiated and fixed with the patients, while considering their needs and desires to improve their lifestyle. A written contract can be used to define

the targets and the agreed-upon strategy to reach these targets. This agreement is not usually enough: it is mandatory to monitor and assess the changes during the program phase, but especially over the long term.

The 5 A methodology (Ask, Advise, Assess, Assist, and Arrange) may be used for each behavior that needs to be changed, which also considers where the patient is within the stage of change regarding each risk factor or every unhealthy behavior present. This methodology is anchored in the Prochaska and DiClemente's Stages of Change Model, a 6-stage process designated by precontemplation, contemplation, preparation, action, maintenance, and relapse.<sup>5</sup> In each stage, defined techniques drive the patient to move in the direction of change. In this model, it is clear that the patient will only be able to adopt a new behavior after reaching the preparation stage. Many patients never leave the precontemplation or contemplation stages, even if they were provided with the scientific information and a positive environment to support the change. Patients only move in the direction of change after both a balanced decision is made that considers that the value of the health gains provided by the changes is superior to the personal losses by keeping the unhealthy behavior and if they believe that they are capable of sustaining the change in the long term.

The 2014 Cochrane collaboration's review on cardiac rehabilitation for low-risk cardiac disease analyzed 148 randomized controlled studies (n=>98 000 participants) and demonstrated that psychological and education based–programs only improved the health-related quality of life score.<sup>6</sup>

## **CONCLUSION**

Cardiac rehabilitation is a comprehensive intervention that can be considered as the sum of the behavioral changes, which aims for patients to adhere to the following for life: a healthy lifestyle, risk factor control, and drug regime. This major challenge is attainable for many patients, but demands the input of a clearly targeted cardiac rehabilitation program that is provided by a dedicated multidisciplinary team. Fighting a sedentary lifestyle by regular physical activity is a specific target of the program in itself, which may be a promoter of healthy changes in the other program components. ■

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# MY PERSONAL VIEW ON THE 2016 EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINES

JOSÉ L. ZAMORANO, MD, FESC

**Author affiliations:** Head of Cardiology, University Hospital La Zarzuela & Ramón y Cajal, Madrid

**Address for correspondence:** José L. Zamorano, Head of Cardiology, University Hospital La Zarzuela & Ramón y Cajal, Carretera De Colmenar Km 9.100, 28034, Madrid, Spain (email: zamorano@secardiologia.es)

**Keywords:** atrial fibrillation; cardiovascular prevention; dyslipidemia; guidelines; heart failure

There is no doubt that every year many physicians wait for the release of the new guidelines that, in the end, will not only provide an update on the knowledge of specific diseases, but also help diagnose and treat our patients. During 2016, four new guidelines were released by the ESC for heart failure, cardiovascular prevention, dyslipidemia, and AF.

## HEART FAILURE GUIDELINES

The Task Force of the ESC for the diagnosis and treatment of acute and chronic heart failure, with the special contribution of the HFA of the ESC, presented new guidelines<sup>1</sup> containing significant changes and adaptations compared with the previous version published in 2012.

Now, there is a new classification for patients with heart failure, including the new subcategory of HFMEF. In my view, the main reason for this addition was the gray area where patients with heart failure had an LVEF between 40% and 49%. In addition, the guidelines contain a diagnostic algorithm that includes the diagnostic criteria for HFMEF. This algorithm requires the presence of symptoms and signs of heart failure, an LVEF between 40% and 49%, elevated levels of NPs, and evidence of other cardiac functional or structural alterations, such as LAE, LV hypertrophy, or diastolic dysfunction.

### Heart failure treatment

For the pharmacological treatment of HFREF, ACE inhibitors,  $\beta$ -blockers, and MRA maintain their recommendations. Diuretics are recommended to improve symptoms and exercise capacity, and they should be considered for reducing the risk of heart failure hospitalizations in patients with signs and/or symptoms of congestion.

Ivabradine should be considered for patients in sinus rhythm if their heart rate is  $\geq 70$  bpm despite optimal medical therapy or in patients who cannot receive  $\beta$ -blockers. ARBs are recommended when ACE inhibitors are contraindicated or in patients who remain symptomatic despite using ACE inhibitors and  $\beta$ -blockers and who are unable to tolerate MRAs. A new compound—LCZ696—has been added to the pharmacological treatment of symptomatic HFREF. LCZ696 combines valsartan and the neprilysin inhibitor

sacubitril. The PARADIGM-HF trial showed that LCZ696 is superior to enalapril in reducing the risk of death and hospitalization for heart failure. Therefore, LCZ696 is recommended to replace ACE inhibitors in ambulatory HFREF patients who remain symptomatic despite optimal medical therapy.

In patients with an LVEF  $\leq 35\%$  despite receiving optimal medical therapy, CRT should be considered. The CRT recommendations focus on symptomatic patients despite optimal medical therapy who are in sinus rhythm, and the recommendation does not differ between NYHA classes. CRT is contraindicated in patients with a QRS duration  $< 130$  msec, and it is recommended in case of LBBB and a QRS duration  $\geq 130$  msec. In the event of non-LBBB, CRT is recommended with a QRS duration  $\geq 150$  msec, and it should be considered if the QRS duration is between 130 and 150 msec. In patients with AF and NYHA class III-IV, CRT should be considered if a strategy to ensure biventricular pacing is put in place. CRT rather than right ventricular pacing is also recommended for HFREF patients who have an indication for ventricular pacing.

## **CARDIOVASCULAR PREVENTION AND DYSLIPIDEMIA GUIDELINES**

Cardiovascular prevention and dyslipidemia are two guidelines that highlighted the importance of prevention in cardiology.<sup>2,3</sup> The guidelines recommend assessing cardiovascular risk. Prevention of CVD in a given person should be adapted to their total cardiovascular risk: the higher the risk, the more intense the action should be. The ESC recommends using the SCORE chart to calculate cardiovascular risk. One of the advantages of the SCORE system is that it can be recalibrated for use in different countries/populations by adjusting for secular changes in CVD mortality and risk factor prevalence.

Some factors can modify the SCORE risk, including social deprivation, which is at the root of many of the causes of CVD; obesity as measured by BMI; physical inactivity; psychosocial stress; family history of premature CVD; autoimmune and other inflammatory disorders; major psychiatric disorders; treatment for HIV; AF; and left ventricular hypertrophy. Of these factors, AF and left ventricular hypertrophy are the most relevant. Also, in those patients at an intermediate risk, other factors, including metabolic factors, such as increased Lp[a], triglycerides, apoB, or increased high-sensitivity C-reactive protein, or the presence of albuminuria, may improve risk classification. Many other biomarkers are also associated with an increased risk for CVD, although few of these have been shown to be related to appreciable reclassification.

Total cardiovascular risk will also be higher than indicated in the SCORE charts in asymptomatic people with abnormal markers of subclinical atherosclerotic vascular damage detected by CAC, ankle-brachial index, pulse-wave velocity, or carotid ultrasonography. In studies comparing these markers, CAC had the best reclassification ability. Patients who need reclassification belong to the intermediate cardiovascular risk group. Therefore, the use of methods to detect these markers should be of interest in that group. The cut-off values that should be used when considering these markers as modifiers of total cardiovascular risk are a CAC score  $> 400$  Agatston units, ankle-brachial (blood pressure)

index  $<0.9$  or  $>1.40$ , aortic pulse wave velocity of 10 m/s, and the presence of plaques on carotid ultrasonography. Some factors, such as elevated HDL-C or apoA1 and a family history of longevity, can reduce the CVD risk.

Nevertheless, who are the patients at risk? Patients can be defined as having a very high, high, moderate, or low risk. Patients at very high risk are patients with any of the following:

- Documented CVD, clinical or unequivocal on imaging. Documented CVD includes previous myocardial infarction, acute coronary syndrome, coronary revascularization (percutaneous coronary intervention, coronary artery bypass grafting), other arterial revascularization procedures, stroke, transient ischemic attack, and peripheral artery disease. Unequivocally documented CVD on imaging is what strongly predisposes a patient to clinical events, such as significant plaque on coronary angiography or carotid ultrasound.
- Diabetes with target organ damage, such as proteinuria, or a major risk factor, such as smoking, hypertension, or dyslipidemia.
- Severe chronic kidney disease (GFR  $<30$  mL/min/1.73 m<sup>2</sup>).
- A calculated SCORE value  $\geq 10\%$  for the 10-year risk of fatal CVD.

Patients at high risk are those with:

- Markedly elevated single risk factors, such as familial dyslipidemia and severe hypertension.
- Most people with diabetes (some young people with type 1 diabetes may be at a low or moderate risk).
- Moderate chronic kidney disease (GFR 30-59 mL/min/1.73 m<sup>2</sup>).
- A calculated SCORE value  $\geq 5\%$  and  $<10\%$  for the 10-year risk of fatal CVD.

Patients at moderate risk have a SCORE value that is between 1% and 5% at 10 years. Many middle-aged subjects belong to this risk category. The risk level is often modified by factors not included in SCORE. Finally, low risk applies to patients with a SCORE value  $<1\%$ .

### Treatment targets

LDL remains the main treatment target for patients with dyslipidemia. Non-HDL-C is used as an estimation of the total amount of atherogenic lipoproteins in the plasma (VLDL, VLDL-remnants, IDL, LDL, Lp[a]), and relates well to apoB levels. Non-HDL-C is easily calculated from total cholesterol minus HDL-C. Since all trials use LDL-C, ESC guidelines still recommend using this value as the primary treatment target. However, non-HDL-C should be utilized as a secondary target to reach when the LDL target is reached. Targets for non-HDL-C are easily calculated as LDL-C targets plus 0.8 mmol/L.

In patients at a very high cardiovascular risk, an LDL-C goal  $<1.8$  mmol/L (70 mg/dL) or at least a 50% reduction if the baseline LDL-C is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended. In patients at high cardiovascular risk, an LDL-C goal  $<2.6$  mmol/L (100 mg/dL) or at least a 50% reduction if the baseline LDL-C is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended. In patients at a low or moderate risk, an LDL-C goal  $<3.0$  mmol/L ( $<115$  mg/dL) is recommended. The non-HDL-C secondary targets should be 2.6, 3.4, and 3.8 mmol/L (100, 130, and 145 mg/dL) for very high-, high- and moderate-risk patients, respectively.

## **ATRIAL FIBRILLATION GUIDELINES**

Finally, in 2016, the ESC also released the AF guidelines.<sup>4</sup> It is a comprehensive document for the diagnosis and treatment of this disease, and it highlights the importance of the problem. AF increases mortality, especially cardiovascular mortality due to sudden death, heart failure, or stroke. Therefore, for AF, opportunistic screening by measuring pulse or using ECG rhythm strips in patients  $>65$  years of age is recommended. For patients with a transient ischemic attack or ischemic stroke, screening for AF is recommended using short-term ECG recordings followed by continuous ECG monitoring for at least 72 hours.

There are different types of AF—paroxysmal, persistent, long-standing persistent, and permanent. Paroxysmal AF is self-terminating, and, in most cases, it terminates within 48 hours. However, some AF paroxysms may continue for up to 7 days. In addition, AF episodes that are cardioverted within 7 days should be considered paroxysmal. Persistent AF lasts longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or by direct current cardioversion after 7 days or more. AF is categorized as long-standing persistent AF when continuous AF lasts for  $\geq 1$  year and when a decision has been made to adopt a rhythm control strategy. Permanent AF is AF that is accepted by the patient (and physician); therefore, rhythm control interventions are, by definition, not pursued in patients with permanent AF. Should a rhythm control strategy be adopted, the arrhythmia would be reclassified as “long-standing persistent AF.”

The most severe complication of AF is the development of stroke. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score assessment is recommended for predicting the risk of stroke in patients with AF. To prevent thromboembolism, oral anticoagulation therapy is recommended for all male AF patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 or more. Special consideration should be given to females, and oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 3 or more. The guidelines have updated the recommendations for which anticoagulant to prescribe patients. When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (eg, apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is preferred to a vitamin K antagonist.  $\beta$ -Blockers, digoxin, diltiazem, or verapamil are recommended to control heart rate in AF patients with an LVEF  $\geq 40\%$ ; whereas,  $\beta$ -blockers and/or digoxin are recommended to control heart rate in AF patients with an LVEF  $<40\%$ . However, it must be stated that rhythm control therapy is indicated for symptom improvement in patients with AF, but

this therapy should not be used in patients with asymptomatic long-standing AF or patients with permanent AF.

In summary, the ESC has again provided excellent guidelines in 2016, and this year there is an emphasis on the prevalent diseases in our patients. These guidelines provide the best cutting-edge information for diagnosis and treatment. Now, it is time to implement these guidelines. ■

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# THE EUROBSERVATIONAL RESEARCH PROGRAMME EXPERIENCE

**ALDO P. MAGGIONI, MD, EORP SCIENTIFIC COORDINATOR**

**Author affiliations:** EURObservational Research Programme Department, European Society of Cardiology, Sophia Antipolis, France

**Address for correspondence:** Aldo P. Maggioni, EURObservational Research Programme Department, European Society of Cardiology, The European Heart House, 2035 Route des Colles-Les Templiers, 06903 Sophia Antipolis, France (email: [maggioni@anmco.it](mailto:maggioni@anmco.it))

**Keywords:** educational programs; epidemiology; guidelines; registries

Europe needs reliable data on cardiovascular diseases, and the ESC is the body that should provide such data. Registries are essential in the assessment of cardiovascular epidemiology, diagnostic/therapeutic processes, and adherence to current guidelines. In 2000, the ESC started the Euro Heart Survey program to assess adherence to the cardiology guidelines. In 2009, the EURObservational Research Programme (EORP) was launched to help understand European medical practices better, based on observational data collected using robust methodological procedures.

## EORP OBJECTIVES

Europe is a heterogeneous cluster of countries, the result of a millenary sequence of migrations, conflicts, and wars, with borders mostly established by force-related political reasons. It follows that, medically, Europe is a patchwork of different countries, with huge diversities in economic levels, political systems, and, as a consequence, health structures, as was recently documented by the ESC Atlas of Cardiology.<sup>1</sup> The ESC Atlas of Cardiology showed significant variations and inequalities within and between countries regarding financing (with health care expenditures ranging from 5% to 12% of the gross domestic product), organization, access, delivery, quality, and effectiveness of cardiac care among the ESC country members. For example, the number of physicians and cardiologists per million inhabitants ranges from 540 to 4550 and from 15 to 250, respectively.<sup>2</sup> Similarly, there are large variations in the epidemiological patterns, risk factors, and health care spending, which translates into huge and unacceptable differences in cardiovascular outcomes.

Updated information and a better knowledge of the epidemiological trends and health care scenarios are essential for reducing the heterogeneity of health care and governance across European countries. The ESC is the natural body for collecting, interpreting, and providing meaningful cardiovascular data to the European Health Authorities, which is one of the reasons why EORP was created. In essence, in Europe, like elsewhere, registries should continue to play an increasingly important role in measuring health care outcomes, appropriateness of care, and disparities in the delivery of care, and these registries could serve as the basis for clinical and comparative effectiveness research.

## **EORP CHARACTERISTICS**

### **Acquisition of data representative of Europe**

This task is one of the most difficult to achieve in observational research, considering the diversity that exists among European countries. The EORP is attempting to: (i) provide a balanced mix of participating countries located in northern, southern, western, and eastern Europe; (ii) obtain a predefined number of centers per million inhabitants; (iii) utilize a proportion of centers, according to their complexity (community hospitals, hospitals with interventional facilities, and hospitals with cardiovascular surgery); and (iv) produce a homogeneous enrollment setting and a consecutiveness of patient enrollment.

### **Conduct studies using ESC constituent bodies**

According to predefined criteria, the participating centers are selected by relevant national societies for country-based registries or associations and working groups for center-based registries.

### **Centralized management of all registries**

An ad-hoc professional team has been established in a specific department that operates at the ESC Heart House in Sophia Antipolis (Nice, France). The team has many responsibilities, including (i) communication between all stakeholders; (ii) formal commitments with local institutional review boards; (iii) administrative duties with hospitals; (iv) central quality data control; (v) local auditing and monitoring according to a monitoring risk approach; (vi) preparing electronic case report forms and on-line data collection; (vii) statistical analyses; and (viii) providing support for scientific presentations and publications.

### **Independent**

Although the EORP is supported by the ESC, the program is conducted in cooperation with, but independently from, drug/device industries. In practice, this principle requires that the EORP exclusively conducts and manages the registries and that companies who support EORP fund the whole program for 3 years rather than individual registries. This funding rule allows registries to be conducted on orphan diseases or clinical conditions (ie, the ongoing registries on peripartum cardiomyopathy, pregnancy in heart disease, cardiomyopathies, and endocarditis) for which industrial interest is frequently low; and (iii) the EORP and ESC own the databases, define the publication policy, and are responsible for all of the published results.

## **THE PORTFOLIO OF REGISTRIES**

Three main models of surveys/registries—general, sentinel, and specific topic—have been implemented for clinical cardiology, according to the topic under investigation. General

registries are country-based registries to assess the epidemiology and management of diseases with a major impact on public health; sentinel registries are center-based registries to evaluate the impact of interventional procedures, imaging techniques, and therapeutic tools; specific topic registries are center-based registries to assess epidemiology and management of rare, complex, costly, and demanding conditions. Finally, cardiovascular prevention is included as a fourth type of registry. Overall, 20 pilot and/or long-term registries have been put in place since 2010 involving more than 1400 centers, and, up to June 2016, they have collected clinical information on more than 100 000 patients.

## **SCIENTIFIC PRODUCTION**

After the initial period in which the main objective was to recruit countries, cardiologists, and patients in the EORP initiative, an intense scientific activity was started using the clinical information collected in the different registries. The collaboration with the Executive Committee members of the various registries in planning, drafting, and submitting of the papers produced with data from the EORP registries have resulted in a relevant increase in the number of papers published in peer-reviewed journals.

Regarding the contents of these manuscripts, one of the main topics of the EORP publications is the adherence of ESC cardiologists to the current guideline recommendations. This aspect was evaluated by describing the rate of use of evidence-based treatments and by identifying the reasons why treatments were not appropriately prescribed.

For heart failure, the adherence to the guidelines for atrial fibrillation treatment and cardiovascular prevention was investigated to identify the clinical variables, that may have an impact on the level of adherence to the guidelines. In EURASPIRE, the modifications over time with the pharmacological and nonpharmacological approaches to cardiovascular prevention were also investigated.<sup>3-5</sup> For heart failure, a further effort was made to include the possible causes of inappropriate prescriptions, such as clinical variables and descriptions of the health care organizations in the participating countries.<sup>6</sup> This approach is designed to understand if health care programs and structures in the different countries, together with economic descriptions, can play a relevant role in the delivery of better clinical care. This approach has been made possible with the active collaboration from the Organisation for Economic Cooperation and Development, which collects this kind of information systematically, and the project will be continued by using the data contained in the ESC ATLAS of Cardiology. The results of this work should be able to explain some of the inequalities in health care provisions across the ESC countries and help plan the delivery of recommendations to try to overcome these inequalities.

The model of EORP sponsorship offers the freedom to plan registries that are generally not in the interest of drug and/or device companies. The best example is probably the ROPAC registry,<sup>7</sup> where the data collected from thousands of pregnant women with structural heart disease resulted in the publication of several papers on how to improve the management of these high-risk patients.

## PERSPECTIVES

### Alignment of EORP registries with the guidelines

The consensus is that EORP registries should be aligned more with the development of guidelines and related educational programs, which is already a matter of fact for some registries, but it was never specifically planned. The possibility of including the most relevant topics identified by the guidelines in the case report forms will improve the possibility of evaluating how the guidelines are implemented in practice in the different ESC countries.

### Long-term registries for relevant epidemiological conditions (general registries) or the evaluation of the appropriateness of use and related outcomes of new technologies (sentinel registries)

The approach described above, even if essential for making the virtuous circle of optimized medical care as concrete as possible, is not sufficient to fulfill all of the objectives that a program of observational research of the ESC should achieve. The knowledge of the clinical epidemiology, use of resources, related costs, and outcomes of patients with frequent clinical conditions (eg, heart failure, atrial fibrillation, acute coronary syndromes, chronic ischemic disease) in many of the ESC countries, which are heterogeneous regarding patient characteristics and health care policies, could make the ESC data collection unique in the context of current observational research.

With respect to new technologies (drugs/devices), the development and a correct interpretation of more informative and complete data sets are essential for policy makers and for making clinical decisions for individuals, regulatory authorities, and populations. When, for example, issues with new medical technologies arise, they could potentially be detected and understood within the appropriate context just by collecting specific data on the phenotypes of patients for whom the technology is applied, the short- and long-term complications, and patient outcomes. ■

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# ISCHEMIC HEART DISEASE IS AT A CROSSROAD IN 2016

MARIO MARZILLI, MD, PhD

**Author affiliations:** Professor and Chairman, Cardiovascular Medicine Division, University of Pisa, Italy

**Address for correspondence:** Mario Marzilli, Professor and Chairman, Cardiovascular Medicine Division, University of Pisa Medical School, Via Paradisa, 2, 56124, Pisa, Italy (email: mario.marzilli@med.unipi.it)

**Keywords:** coronary atherosclerotic obstruction; ischemic heart disease; percutaneous coronary intervention

Scientific progress proceeds linearly until the accumulation of sufficient evidence forces the reexamination of underlying assumptions, and a new paradigm must be established.<sup>1</sup> For decades, ischemic heart disease has been perceived as the direct and consistent consequence of atherosclerotic obstructions of the coronary vessels. This concept has dictated both diagnostic strategies that have all searched for a “significant” stenosis and therapeutic strategies that have all focused on the mechanical and/or pharmacological removal of the stenosis. In addition, enormous resources have been invested in identifying and quantifying obstructive coronary artery disease, assuming that this condition underlies virtually all stable ischemic heart disease syndromes. However, a large body of evidence has accumulated in recent years that strongly challenges this concept of equating obstructive stenosis with stable ischemic heart disease, suggesting that it is time to rethink this scientific paradigm.<sup>2</sup>

The 2013 ESC guidelines eventually acknowledged that ischemic heart disease is a complex and multifactorial pathophysiological process that may be precipitated by a number of mechanisms, including microvascular dysfunction, coronary vasospasm, and fixed or dynamic stenosis. The guidelines also explained that these mechanisms might be active in the same patient at the same time or different moments in their medical history. The complexity of these pathogenetic mechanisms provides a possible explanation for the common observation that patients continue to suffer from angina attacks after a “successful” coronary revascularization procedure, and this complexity helps to understand the lack of prognostic benefits from elective revascularization procedures.

## A NEW DIAGNOSTIC AND THERAPEUTIC FOCUS

Based on available evidence, we recently suggested shifting the focus away from obstructive epicardial coronary atherosclerosis to the microvasculature and the cardiomyocytes, which is where the ischemia occurs. If cardiomyocytes are placed at the center of the model, all the possible pathological inputs can be considered, and strategies that protect cardiomyocytes from ischemic damage, regardless of the causative mechanism, can be developed.

This new concept of ischemic heart disease as a multifactorial syndrome, which was officially proposed more than 3 years ago, is still waiting for full implementation in clinical practice. According to the guidelines, invasive coronary angiography has lost its diagnos-

tic value, and it should no longer be performed for the sole purpose of ruling in (or out) ischemic heart disease. Obviously, this is not the case in most catheterization laboratories, where many patients, mostly female, are denied a diagnosis of angina pectoris if no obstruction is found at coronary angiography. Conversely, all chest pains are diagnosed as angina in patients that present at coronary angiography with some degree of coronary atherosclerotic obstruction.

This simplistic diagnostic approach is then translated into an even more simplistic treatment strategy, with all “significant” ( $\geq 70\%$ ) stenoses deemed worthy of a percutaneous coronary intervention and stenting. The guidelines again provide very strict recommendations, with a class 1 indication that revascularization is only for patients with suitable coronary anatomy and unacceptable angina despite guideline-dictated medical therapy. Unfortunately, many patients who are not taking an antianginal therapy are still referred for percutaneous coronary interventions and stenting without any objective evidence of myocardial ischemia.

The reluctance of many cardiologists to face the complexity of ischemic heart disease can be, to some extent, explained by the absence of validated diagnostic and therapeutic strategies consistent with the new concepts.

In fact, after challenging the diagnostic role of coronary angiography and the therapeutic role of percutaneous coronary interventions and stenting, a number of questions need to be addressed:

- How do we diagnose ischemic heart disease, without referring to invasive coronary angiography?
- How do we select patients that really need percutaneous coronary interventions?
- How do we treat ischemic heart disease without relying on stenosis removal?
- Is preventing coronary atherosclerosis still sufficient to prevent ischemic heart disease?

Moving to clinical practice, cardiologists who do wish to follow the current guidelines would like answers to a number of questions:

- How many patients qualify for invasive angiography who have angina that is refractory to guideline-dictated medical therapy?
- How many patients with refractory angina have a coronary anatomy suitable for a percutaneous coronary intervention?
- How many patients have persistent angina after a complete revascularization?

- Which drugs should be prescribed to patients with angina who have no coronary obstruction?
- Do the current guideline-dictated medical therapies have an impact on prognosis?

## CONCLUSION

In 2016, the cardiology community has had to confront a number of challenging questions that affect the management of the ischemic heart disease, which is still the number one killer in most countries worldwide. Determination and humility are needed to abandon the old, simplistic concepts (stenosis=ischemia, no stenosis=no ischemia) and face the frightening challenge of developing more effective diagnostic and therapeutic strategies that are consistent with the new understanding of the complex multifactorial pathogenesis of ischemic heart disease.

However, as Claude Bernard said:

“Quand le fait qu'on rencontre est en opposition avec une théorie régnante, il faut accepter le fait d'abandonner la théorie, lors même que celle-ci, soutenue par de grands noms, est généralement adoptée. (When we meet a fact that contradicts a prevailing theory, we must accept the fact and abandon the theory, even when the theory is supported by great names and generally accepted.)” ■

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# Abbreviations & Acronyms



<b>ACALM</b>	Algorithm for Comorbidities, Associations, Length of stay and Mortality
<b>ACE</b>	angiotensin-converting enzyme
<b>AGES-</b>	Age, Gene/Environment
<b>Reykjavík</b>	Susceptibility–Reykjavík
<b>ARB</b>	angiotensin receptor blocker
<b>ARIC</b>	Atherosclerosis Risk In Communities
<b>ARNi</b>	angiotensin receptor-neprilysin inhibitor
<b>BNP</b>	brain natriuretic peptide
<b>CAC</b>	coronary artery calcium
<b>CHAMPION</b>	CardioMEMS Heart failure sensor Allows Monitoring of Pressures to Improve Outcomes in NYHA functional class III heart failure patients
<b>CRT</b>	cardiac resynchronization therapy
<b>DANISH</b>	DANISH study to assess the efficacy of ICDs in patients with nonischemic systolic heart failure on mortality
<b>DINAMIT</b>	Defibrillator IN Acute Myocardial Infarction Trial
<b>ESC</b>	European Society of Cardiology
<b>HDL-C</b>	high-density lipoprotein cholesterol
<b>HF</b>	heart failure
<b>HFA</b>	Heart Failure Association
<b>HFMEF</b>	heart failure with midrange ejection fraction
<b>HFREF</b>	heart failure with reduced ejection fraction
<b>HOPE-3</b>	Heart Outcomes Prevention Evaluation
<b>HRPEF</b>	heart failure with preserved ejection fraction
<b>HRQOL</b>	health-related quality of life
<b>hs-CRP</b>	high sensitivity C-reactive protein
<b>ICD</b>	implantable cardioverter-defibrillator
<b><math>I_f</math></b>	funny channel

<b>IN-TIME</b>	Influence of home monitoring on mortality and morbidity in heart failure patients with impaired left ventricular function
<b>LAPTOP-HF</b>	Left Atrial Pressure monitoring to Optimize Heart Failure therapy
<b>LDL-C</b>	low-density lipoprotein cholesterol
<b>LVEF</b>	left ventricular ejection fraction
<b>MADIT</b>	Multicenter Automatic Defibrillator Implantation Trial
<b>MRA</b>	mineralocorticoid receptor antagonist
<b>NOAC</b>	non-vitamin K antagonist oral anticoagulant
<b>NSAID</b>	nonsteroidal anti-inflammatory drug
<b>NT-proBNP</b>	N-terminal pro-brain natriuretic peptide
<b>NYHA</b>	New York Heart Association
<b>OPTILINK</b>	Optimization of Heart Failure Management using OptiVol Fluid Status Monitoring and CareLink
<b>PARADIGM-HF</b>	Prospective comparison of Angiotensin Receptor–neprilysin inhibitor with an Angiotensin-converting enzyme inhibitor to Determine Impact on Global mortality and Morbidity in Heart Failure
<b>PHQ-9</b>	9-item patient health questionnaire
<b>PRECISION</b>	Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen
<b>RELAX-AHF</b>	seRELAXin in Acute HFPEF patients
<b>SCD-HeFT</b>	Sudden Cardiac Death in Heart Failure Trial
<b>SHIFT</b>	Systolic Heart failure treatment with the $I_f$ inhibitor ivabradine Trial
<b>SIGNIFY</b>	Study assessIng the morbidity-mortality benefits of the $I_f$ inhibitor ivabradine in patients with coronary artery disease
<b>SPRINT</b>	Systolic Blood Pressure Intervention Trial
<b>TRUE-AHF</b>	Trial of Ularitide's Efficacy and safety in patients with AHF
<b>WCC</b>	World Congress of Cardiology & Cardiovascular Health

*Instructions for Authors*



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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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