

DIALOGUES IN CARDIOVASCULAR MEDICINE

OCTOBER 2017

VOLUME 22 #3



ESC Barcelona

2017



www.dialogues-cvm.com

Editors in Chief

Ferrari R, MD, PhD
Chair of Cardiology
University Hospital of Ferrara, Cona (Ferrara), Italy

Fox K, MD, FRCP
National Heart and Lung Institute
Institute of Cardiovascular Medicine and Science
Royal Brompton Hospital, London, UK

Consulting Editors

Anand I, MD
La Jolla, CA, USA

Avkiran M, PhD
The Rayne Institute
St Thomas' Hospital
London, UK

Bertrand ME, MD
Hôpital Cardiologique
Lille, France

Böhm M, MD
Saarland University Hospital
Homburg/Saar, Germany

Borer JS, MD
University of New York
Downstate Medical Center
New York, NY, USA

Erol C, MD
Ankara University
Ankara, Turkey

Coats A, MD
University of Sydney
Sydney, Australia

Cowie M, MD, PhD
National Heart & Lung Institute
London, UK

Danchin N, MD
Hôpital Européen Georges-
Pompidou
Paris, France

Dargie HJ, MD
Western Infirmary
Glasgow, UK

Fox KA, MD
University of Edinburgh
Edinburgh, UK

Fuster V, MD, PhD
Mount Sinai Medical Center
New York, NY, USA

Gowdak L, MD, PhD
Heart institute
São Paulo, Brazil

Hasenfuss G, MD
Georg-August Universität
Göttingen, Germany

Heusch G, MD, PhD
Institute for Pathophysiology
University of Essen Medical
School
Essen, Germany

Hu D, MD
Heart Institute Intervention
Center
People Hospital of Pekin
University
Beijing, China

Kaski JC, MD
St George's
University of London
London, UK

Komajda M, MD
Hôpital Pitié-Salpêtrière
Paris, France

Libby P, MD
Brigham & Women's Hospital
Boston, MA, USA

Lopatin Y, MD, PhD
Volgograd State Medical
University
Volgograd, Russian Federation

Lopez-Sendon JL, MD
Hospital University
Gregorio Maranon
Madrid, Spain

Lüscher T, MD
University Heart Center
University Hospital
Zürich, Switzerland

Magaña A, MD
Mexican Institute of Social
Security
Mexico DF, Mexico

Maggioni AP, MD
ANMC Research Center
Florence, Italy

Marber MS, MD, PhD
The Rayne Institute
St Thomas' Hospital
London, UK

Marzili M, MD, PhD
University of Pisa
Pisa, Italy

Oto A, MD
University School of Medicine
Ankara, Turkey

Patrono C, MD
University La Sapienza
Rome, Italy

Pepine CJ, MD
University of Florida
Gainesville, FL, USA

Pfeffer MA, MD, PhD
Brigham and Women's
Hospital
Boston, MA, USA

Pinto F, MD
Universidade de Lisboa
Lisbon, Portugal

Rapezzi C, MD
University of Bologna
Bologna, Italy

Rosano G, MD, PhD
St George's Hospital Medical
School
London, UK

Rosen MR, MD
Columbia University College
of Physicians & Surgeons
New York, NY, USA

Ryden L, MD, PhD
Karolinska University
Hospital Solna
Stockholm, Sweden

Seabra-Gomes RJ, MD
Instituto do Coracao
Hospital Santa Cruz
Carnaxide, Portugal

Shah A, MD
James Black Centre
British Heart Foundation
Centre of Excellence
King's College London
London, UK

Simoons ML, MD
Thoraxcenter
Erasmus University
Medical Center
Rotterdam, The Netherlands

Sipido K, MD, PhD
Katholieke Universiteit
Leuven
Leuven, Belgium

Steg PG, MD
Hôpital Bichat-Claude
Bernard
Paris, France

Swedberg K, MD, PhD
Sahlgrenska University
Hospital Ostra
Göteborg, Sweden

Tardif JC, MD
Montreal Heart Institute
Québec, Canada

Tavazzi L, MD
Policlinico San Matteo IRCCS
Pavia, Italy

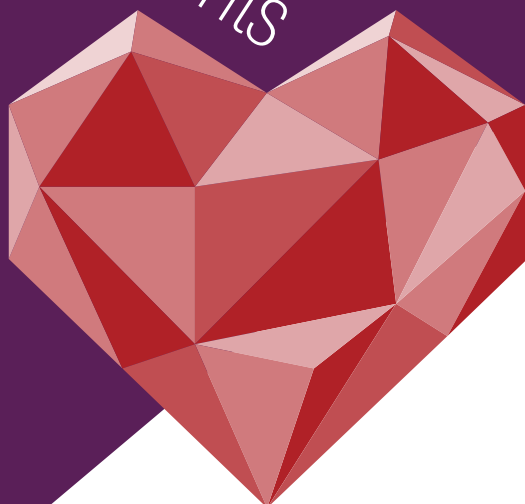
Tendera M, MD
Silesian School of Medicine
Katowice, Poland

Widimsky P, MD, PhD
Vinohrady Cardiocenter
Charles University Hospital
Prague, Czech Republic

Wijns WC, MD
OLV Hospital
Aalst, Belgium

Zamorano JL, MD
University Francisco de
Vitoria
Hospital Ramón y Cajal
Madrid, Spain

Contents



<i>Editorial</i> - Fausto J. Pinto (Portugal)	4
<i>Snapshot in cardiology</i> - Kim Fox (UK)	6
<i>Expert opinions</i>	12
Heart failure highlights: 2017 updates - Michael Böhm (Germany)	
Advances in basic science for cardiology - Lina Badimon (Spain)	
News for the management of coronary artery disease - Giuseppe M. C. Rosano (UK)	
Severe secondary mitral regurgitation in heart failure: a holistic approach Patrizio Lancellotti (Belgium)	
Hot topics in cardiac rehabilitation - Ana Abreu (Portugal)	
What is new in ischemic stroke? - Petr Widimsky (Czech Republic)	
Digital health comes of age - Martin R. Cowie (UK)	
Cardiotoxicity in cancer treatment: a congress report from the 2017 ESC congress Markus S. Anker & Stefan D. Anker (Germany)	
<i>Late-Breaking Science</i>	31
Late-breaking updates in heart failure - Michel Komajda (France)	
Late-breaking science in imaging - Victoria Delgado (The Netherlands)	
ESC registry results - Aldo P. Maggioni (Italy)	
<i>Hotlines</i>	39
Registry hotlines - Nicolas Danchin (France)	
Late-breaking trials: atrial fibrillation - Reza Wakili & Dobromir Dobrev (Germany)	
Late-breaking clinical trials: prevention and outcomes in coronary artery disease Filippo Crea (Italy)	
<i>Abbreviations and acronyms</i>	47
<i>Instructions for authors</i>	49

EDITORIAL

Barcelona once again welcomed the ESC congress. Despite the terrible events that occurred in the city just 1 week before the start of the congress, the medical community demonstrated an enormous sense of unity and responsibility toward the future, which is the only way that we should respond to such disgraceful situations.

The ESC congress is currently the largest meeting of the cardiovascular community worldwide. This year, 32 000 delegates came to Barcelona and experienced one of the most successful meetings ever organized. Certainly, every person that attended the meeting left Barcelona more enriched scientifically, with a few more answers to some of the clinical problems we face every day as cardiologists, as well as answers to some of the questions we still have regarding pathophysiology, mechanisms of disease, and new modalities for diagnosis and treatment of cardiovascular diseases. An enormous and beautifully organized exhibition provided the opportunity for everyone to enjoy the latest news coming from the industry, both pharmaceutical and devices.

One of the main features of the ESC congress is to provide delegates from around the world with the opportunity to present new science. This year, more than 11 000 abstracts were submitted and more than 4000 were selected for presentations. Japan was once again the leader in abstract submissions and acceptance. The ESC congress was comprised of 796 sessions, including the highly anticipated hotlines, clinical trial updates, registries, guidelines, abstract-based program, as well as a large number of symposiums, joint sessions, and many others. It was organized into nine villages, each one representing a major field in cardiovascular medicine:

Basic science; Hypertension; Cardiac imaging; Prevention; Arrhythmias; Interventions; Valvular disease; Coronary artery disease; Heart failure (chronic and acute).

This year, the spotlight was on the 40th anniversary of coronary angioplasty; therefore, percutaneous coronary interventions were the focus. During the 5 days of the congress, a space was dedicated to percutaneous coronary interventions, including a whole set of different presentations, including “Live in a Box” sessions that featured clinical cases and interventional procedures from leading cardiovascular centers to illustrate the new advancements in percutaneous coronary interventions.

Four new guidelines were presented at this year’s congress, including guidelines for (i) ST-segment elevation myocardial infarction; (ii) valvular heart disease; (iii) peripheral artery disease; and (iv) the use of dual antiplatelet therapy.

In this issue of *Dialogues in Cardiovascular Medicine*, you will have the opportunity to read short texts from experts in the different fields of cardiovascular medicine who summarized the main novelties and practical clinical implications that were presented at the 2017 ESC congress. Kim Fox provides a snapshot of all cardiology research articles published this year between January 1st and June 30th in the two most prestigious medical journals, the *Lancet* and the *New England Journal of Medicine*. A whole series of Expert Opinions follows, which are written by leaders in the respective fields. This section will be followed by summaries of late-breaking science in heart failure, imaging, and ESC registries. This issue will close with a series of hotlines on registries, atrial fibrillation, and the prevention and outcomes in coronary artery disease. Altogether, several important messages came out of the ESC congress in Barcelona in these different fields.

During the congress, many trial results were discussed, and some of those presented will likely have an impact on clinical practice. The following list contains just a few examples of what will be discussed in the different articles:

- The COMPASS trial showed that, in patients with a history of coronary artery disease and peripheral artery disease, intensifying therapy by adding rivaroxaban to aspirin provides a net clinical benefit.
- The CANTOS trial showed that, in patients after an acute myocardial infarction, canakinumab, an anti-IL-1 β agent, reduced the overall major adverse cardiac events by 15% and, surprising, death from any cancer by 51%.
- The Re-DUAL PCI trial showed that, when compared with triple therapy, dual therapy with dabigatran and a P2Y12 inhibitor is superior regarding the risk reduction in bleeding and noninferior regarding thromboembolic events.
- The GLAGOV trial showed that, when added to a statin, evolocumab, a PCSK-9 inhibitor, induces plaque regression, but does not change the composition of the plaque.
- The PURE study, a prospective cohort study, which analyzed a general population of over 135 000 people from 18 different countries, showed that dietary fats are protective and carbohydrates are harmful; the results of which are challenging the current guideline recommendations on the intake of saturated fat and carbohydrates.
- The CLARIFY registry of 32 703 patients with stable coronary artery disease and hypertension showed a J curve, where patients had a 40% to 50% increase in their cardiovascular risk with a systolic blood pressure <120 mm Hg and a diastolic blood pressure <70 mm Hg.

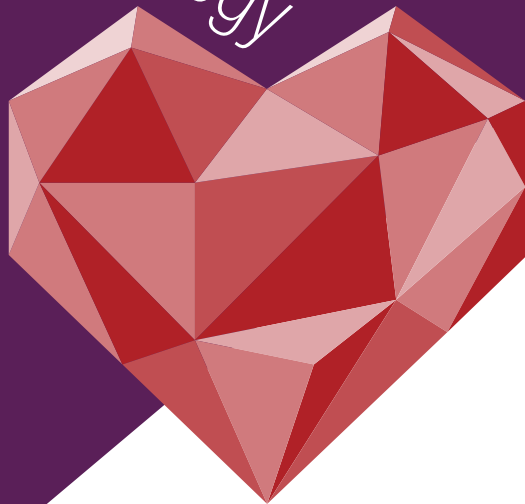
We really hope you will enjoy reading the different contributions from colleagues around the world, leaders in their field of expertise. We are looking forward to seeing you next year in Munich, Germany for another successful ESC congress. ■

FAUSTO J. PINTO, FESC, FACC

Immediate Past President of the ESC

Head of Cardiology, University Hospital Sta Maria, Universidade de Lisboa, Lisboa, Portugal

Snapshot in cardiology



SNAPSHOT IN CARDIOLOGY

KIM FOX, MD, FRCP

These articles were taken from the Lancet and the New England Journal of Medicine between January 1, 2017 and June 30, 2017. All research articles on cardiology were included; reviews and guidelines were excluded.

JANUARY

Fitzgerald K, White S, Borodovsky A, et al. A highly durable RNAi therapeutic inhibitor of PCSK9. *N Engl J Med.* 2017;376(1):41-51.

In this phase 1 trial, inclisiran, a long-acting RNA interference therapeutic agent that inhibits the synthesis of proprotein convertase subtilisin-kexin type 9 (PCSK9), a target to lower low-density lipoprotein cholesterol, did not result in serious adverse events, and doses ≥ 300 mg significantly reduced levels of PCSK9 and low-density lipoprotein cholesterol for at least 6 months.

Hiatt WR, Fowkes FG, Heizer G, et al; EUCLID Trial Steering Committee and Investigators. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med.* 2017;376(1):32-40.

Peripheral artery disease is considered a manifestation of systemic atherosclerosis with associated adverse cardiovascular and limb events. When compared with clopidogrel, ticagrelor was not shown to be superior in patients with symptomatic peripheral artery disease for the reduction in cardiovascular events.

Moler FW, Silverstein FS, Holubkov R, et al; THAPCA Trial Investigators. Therapeutic hypothermia after in-hospital cardiac arrest in children. *N Engl J Med.* 2017;376(4):318-329.

While targeted temperature management is recommended for comatose adults and children after out-of-hospital cardiac arrest, data on in-hospital cardiac arrest is limited. This study showed that therapeutic hypothermia, as compared with therapeutic normothermia, did not provide a significant survival benefit.

Myles PS, Smith JA, Forbes A, et al; ATACAS Investigators. Tranexamic acid in patients undergoing coronary-artery surgery. *N Engl J Med.* 2017;376(2):136-148.

Among patients undergoing coronary artery surgery, tranexamic acid had a lower risk of bleeding than did the placebo, without a higher risk of death or thrombotic complications within 30 days after surgery; however, there was a higher risk of postoperative seizures.

NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet.* 2017;389(10064):37-55.

This analysis shows that, during the last 40 years, the highest worldwide blood pressure levels have shifted from high-income countries to low-income countries in south Asia and sub-Saharan Africa, while blood pressure has been persistently high in Central and Eastern Europe.

FEBRUARY

Hanley DF, Lane K, McBee N, et al; CLEAR III Investigators. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. *Lancet.* 2017;389(10069):603-611.

In patients with a routinely placed extraventricular drain and an intraventricular hemorrhage obstructing the 3rd or 4th ventricles, alteplase irrigation did not substantially improve functional outcomes compared with saline irrigation.

Mehra MR, Naka Y, Uriel N, et al; MOMENTUM 3 Investigators. A fully magnetically levitated circulatory pump for advanced heart failure. *N Engl J Med.* 2017;376(5):440-450.

Among patients with advanced heart failure, a fully magnetically levitated centrifugal-flow left ventricular assist pump resulted in fewer reoperations for pump malfunction and fewer pump thrombosis at 6 months than did an axial-flow left ventricular assist pump.

Resnic FS, Majithia A, Marinac-Dabic D, et al. Registry-based prospective, active surveillance of medical-device safety. *N Engl J Med.* 2017;376(6):526-535.

The Mynx device, an implantable vascular-closure device, was associated with a significantly greater risk of any vascular complication than were alternative vascular-closure devices; there was also a significantly greater risk of access-site bleeding and transfusion. Among the recipients of a Mynx device after a percutaneous coronary intervention, a prospective and active surveillance of a clinical registry identified potential safety signals rapidly, with the initial alerts occurring within the first 12 months of monitoring.

Rogers JG, Pagani FD, Tatrooles AJ, et al. Intrapericardial left ventricular assist device for advanced heart failure. *N Engl J Med.* 2017;376(5):451-460.

In patients with advanced heart failure who were ineligible for heart transplantation, a small, intrapericardial, centrifugal-flow left ventricular assist device (LVAD) design was found to be noninferior to an axial-flow LVAD with respect to survival free from disabling stroke or device removal for malfunction or failure.

Russo RJ, Costa HS, Silva PD, et al. Assessing the risks associated with MRI in patients with a pacemaker or defibrillator. *N Engl J Med.* 2017;376(8):755-764.

This study showed that, in any patient with a non-MRI-conditional pacemaker (ie, not approved by the Food and Drug Administration for MRI scanning) or implantable cardioverter-defibrillator, device or lead failure did not occur during a clinically indicated nonthoracic MRI at 1.5 tesla.

Tawakol A, Ishai A, Takx RA, et al. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. *Lancet.* 2017;389(10071):834-845.

Emotional stress is associated with an increased risk of cardiovascular disease, and this study showed that activity in the amygdala, a region of the brain involved in stress, independently and robustly predicted cardiovascular disease events. Amygdalar activity is involved partly via a pathway that includes increased bone-marrow activity and arterial inflammation.

MARCH

Chow CK, Thakkar J, Bennett A, et al. Quarter-dose quadruple combination therapy for initial treatment of hypertension: placebo-controlled, crossover, randomised trial and systematic review. *Lancet.* 2017;389(10073):1035-1042.

The data from the small proof-of-concept study Quadpill suggest that a single capsule containing four blood pressure-lowering drugs each at a quarter dose (irbesartan 37.5 mg, amlodipine 1.25 mg, hydrochlorothiazide 6.25 mg, and atenolol 12.5 mg) could be additive across classes and might provide a clinically important reduction in blood pressure.

Costa F, van Klaveren D, James S, et al; PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet.* 2017;389(10073):1025-1034.

While dual antiplatelet therapy with aspirin plus a P2Y₁₂ inhibitor prevents ischemic events after coronary stenting, it increases bleeding. Therefore, the PRECISE-DAPT score, a simple five-item risk score based on age, creatinine clearance, hemoglobin, white blood cell count, and previous spontaneous bleeding, was generated to help predict out-of-hospital bleeding during dual antiplatelet therapy.

Smits PC, Abdel-Wahab M, Neumann FJ, et al; Compare-Acute Investigators. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. *N Engl J Med.* 2017;376(13):1234-1244.

In patients with ST-segment elevation myocardial infarction and multivessel disease who underwent primary percutaneous coronary intervention of an infarct-related artery, adding fractional flow reserve-guided complete revascularization of noninfarct-related arteries in an acute setting reduced the risk of the composite cardiovascular outcome.

Weitz JI, Lensing AWA, Prins MH, et al; EINSTEIN CHOICE Investigators. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med.* 2017;376(13):1211-1222.

The EINSTEIN CHOICE study showed that, among patients with venous thromboembolism in equipoise for continued anticoagulation, the risk of a recurrent event was significantly lower with rivaroxaban at either a treatment dose (20 mg) or a prophylactic dose (10 mg) than with aspirin, without a significant increase in the rate of bleeding.

APRIL

Bangalore S, Fayyad R, Laskey R, DeMicco DA, Messerli FH, Waters DD. Body-weight fluctuations and outcomes in coronary disease. *N Engl J Med.* 2017;376(14):1332-1340.

In patients with coronary artery disease, body weight variability (measured according to average successive variability and used as a time-dependent covariate) was associated with an increase in the risk of any coronary event, any cardiovascular event, and death.

INFANT Collaborative Group. Computerised interpretation of fetal heart rate during labour (INFANT): a randomised controlled trial. *Lancet*. 2017;389(10080):1719-1729.

In women in labor receiving continuous electronic fetal monitoring, the use of decision support with the INFANT system vs no decision support did not improve clinical outcomes for mothers or babies.

Kaplan H, Thompson RC, Trumble BC, et al. Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. *Lancet*. 2017;389(10080):1730-1739.

The results of the study on the Tsimane, a Bolivian population with a subsistence lifestyle of hunting, gathering, fishing, and farming with few cardiovascular risk factors, but a high infectious inflammatory burden, suggest that coronary atherosclerosis can be avoided by achieving a lifetime with very low levels of low-density lipoprotein cholesterol, low blood pressure, low glucose, normal body-mass index, no smoking, and plenty of physical activity.

Rawshani A, Rawshani A, Franzén S, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med*. 2017;376(15):1407-1418.

In Sweden, from 1998 through 2014, mortality and the incidence of cardiovascular outcomes declined substantially among patients with either type 1 diabetes or type 2 diabetes, although there was a lower decline in fatal outcomes among patients with type 2 diabetes than among controls and type 1 diabetes.

Ray KK, Landmesser U, Leiter LA, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. *N Engl J Med*. 2017;376(15):1430-1440.

In patients with a high risk of cardiovascular disease and elevated low-density lipoprotein cholesterol, inclisiran provided dose-dependent reductions in both proprotein convertase subtilisin-kexin type 9 and low-density lipoprotein cholesterol.

Reardon MJ, Van Mieghem NM, Popma JJ, et al; SURTAVI Investigators. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2017;376(14):1321-1331.

The SURTAVI study showed that, in patients with severe aortic stenosis who are at an intermediate surgical risk, transcatheter aortic-valve replacement was a nonin-

ferior alternative to surgery, with a different pattern of adverse events associated with each procedure.

Ridker PM, Revkin J, Amarenco P, et al; SPIRE Cardiovascular Outcome Investigators. Cardiovascular efficacy and safety of bococizumab in high-risk patients. *N Engl J Med*. 2017;376(16):1527-1539.

Although the trials were stopped early, in patients with a high cardiovascular risk, bococizumab, a humanized monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 and reduces levels of low-density lipoprotein cholesterol, had a significant benefit with respect to major adverse cardiovascular events.

Ridker PM, Tardif JC, Amarenco P, et al; SPIRE Investigators. Lipid-reduction variability and anti-drug-antibody formation with bococizumab. *N Engl J Med*. 2017;376(16):1517-1526.

In six multinational trials evaluating bococizumab, a substantial proportion of patients developed antidrug antibodies, which significantly attenuated the lowering of low-density lipoprotein cholesterol. In patients who did not develop antidrug antibodies, there was a wide variation in the relative reduction in cholesterol.

van den Berg LA, Dijkgraaf MG, Berkhemer OA, et al; MR CLEAN Investigators. Two-year outcome after endovascular treatment for acute ischemic stroke. *N Engl J Med*. 2017;376(14):1341-1349.

The extended follow-up of the MR CLEAN trial showed that, in patients with acute ischemic stroke, the beneficial effect of endovascular treatment on functional outcome at 2 years was similar to that reported at 90 days in the original trial.

MAY

Davies JE, Sen S, Dehbi HM, et al. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. *N Engl J Med*. 2017;376(19):1824-1834.

In patients with coronary artery disease, coronary revascularization guided by instantaneous wave-free ratio (iFR) was noninferior to revascularization guided by fractional flow reserve (FFR) with respect to the risk of major adverse cardiac events at 1 year. The rate of adverse procedural signs and symptoms was lower and the procedural time was shorter with iFR than with FFR.

Götberg M, Christiansen EH, Gudmundsdottir IJ, et al; iFR-SWEDEHEART Investigators. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *N Engl J Med.* 2017;376(19):1813-1823.

Among patients with stable angina or an acute coronary syndrome, an instantaneous wave-free ratio (iFR)-guided revascularization strategy was noninferior to an fractional flow reserve (FFR)-guided revascularization strategy with respect to the rate of major adverse cardiac events at 1 year.

Kragholm K, Wissenberg M, Mortensen RN, et al. Bystander efforts and 1-year outcomes in out-of-hospital cardiac arrest. *N Engl J Med.* 2017 4;376(18):1737-1747.

Among patients who survived to day 30 after an out-of-hospital cardiac arrest, bystander cardiopulmonary resuscitation and defibrillation were associated with a significantly lower risk of brain damage or nursing home admission, a lower risk of death from any cause, and a lower risk of the composite end point of brain damage, nursing home admission, or death than that associated with no bystander resuscitation.

Landoni G, Lomivorotov VV, Alvaro G, et al; CHEETAH Study Group. Levosimendan for hemodynamic support after cardiac surgery. *N Engl J Med.* 2017;376(21):2021-2031.

This study showed that, in patients who needed perioperative hemodynamic support after cardiac surgery, low-dose levosimendan in addition to standard care did not result in a lower 30-day mortality rate vs placebo.

Lincoff AM, Nicholls SJ, Riesmeyer JS, et al; ACCELERATE Investigators. Evacetrapib and cardiovascular outcomes in high-risk vascular disease. *N Engl J Med.* 2017;376(20):1933-1942.

In patients with high-risk vascular disease (ie, an acute coronary syndrome within the previous 30 to 365 days, cerebrovascular atherosclerotic disease, peripheral vascular arterial disease, or diabetes mellitus with coronary artery disease), evacetrapib in addition to standard medical therapy did not lower the rate of cardiovascular events vs placebo.

Mehta RH, Leimberger JD, van Diepen S, et al; LEVO-CTS Investigators. Levosimendan in patients with left ventricular dysfunction undergoing cardiac surgery. *N Engl J Med.* 2017;376(21):2032-2042.

In patients with a reduced left ventricular ejection fraction who were undergoing cardiac surgery with the use of cardiopulmonary bypass, levosimendan, an inotropic agent, did not reduce the rate of the short-term composite end point of death, renal-replacement therapy, perioperative myocardial infarction, or the use of a mechanical cardiac assist device to a rate that was lower than that obtained with placebo.

Ohman EM, Roe MT, Steg PG, et al. Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial. *Lancet.* 2017;389(10081):1799-1808.

In the treatment of patients with acute coronary syndromes, a dual pathway antithrombotic therapy approach combining low-dose rivaroxaban with a P2Y12 inhibitor had a similar risk of clinically significant bleeding as did the combination of aspirin and a P2Y12 inhibitor.

Packer M, O'Connor C, McMurray JJV, et al; TRUE-AHF Investigators. Effect of ularitide on cardiovascular mortality in acute heart failure. *N Engl J Med.* 2017;376(20):1956-1964.

In patients with acute heart failure, an early intervention with ularitide exerted favorable physiological effects without affecting cardiac troponin levels, but short-term treatment did not affect the clinical composite end point or reduce long-term cardiovascular mortality

Sabatine MS, Giugliano RP, Keech AC, et al; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med.* 2017;376(18):1713-1722.

In patients with atherosclerotic cardiovascular disease and low-density lipoprotein cholesterol levels ≥ 70 mg per deciliter who were receiving statin therapy, evolocumab plus statin therapy lowered low-density lipoprotein cholesterol levels to a median of 30 mg per deciliter and reduced the risk of cardiovascular events.

JUNE

Anderson CS, Arima H, Lavados P, et al; HeadPoST Investigators and Coordinators. Cluster-randomized, crossover trial of head positioning in acute stroke. *N Engl J Med.* 2017;376(25):2437-2447.

There were no significant differences in the 90-day disability outcomes between patients after an acute ischemic stroke who were assigned to either a fully supine position (ie, with the back horizontal and the face upwards) for 24 hours or a sitting-up position (ie, with the head elevated to at least 30 degrees) for 24 hours.

Böhm M, Schumacher H, Teo KK, et al. Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. *Lancet.* 2017;389(10085):2226-2237.

For high-risk patients, achieving a mean systolic blood pressure <120 mm Hg during treatment was associated with an increased risk of cardiovascular outcomes (except for myocardial infarction and stroke), and achieving a very low blood pressure was associated with increased risks of several cardiovascular disease events.

Chakravarty T, Søndergaard L, Friedman J, et al; RESOLVE; SAVORY Investigators. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet.* 2017;389(10087):2383-2392.

Patients receiving a transcatheter valve replacement had a higher frequency of subclinical leaflet thrombosis than did patients receiving a surgical aortic valve replacement. Anticoagulation (both nonsteroidal anti-inflammatory drugs and warfarin), but not dual antiplatelet therapy, was effective in preventing or treating subclinical leaflet thrombosis.

Chan FKL, Ching JYL, Tse YK, et al. Gastrointestinal safety of celecoxib versus naproxen in patients with cardiothrombotic diseases and arthritis after upper gastrointestinal bleeding (CONCERN): an industry-independent, double-blind, double-dummy, randomised trial. *Lancet.* 2017;389(10087):2375-2382.

In patients at high risk of both cardiovascular and gastrointestinal events who require concomitant aspirin and a nonsteroidal anti-inflammatory drug, celecoxib plus a proton-pump inhibitor is superior to naproxen in reducing the risk of recurrent upper gastrointestinal bleeding.

Gupta A, Thompson D, Whitehouse A, et al; ASCOT Investigators. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. *Lancet.* 2017;389(10088):2473-2481.

This analysis of the ASCOT-LLA trial demonstrates the so-called nocebo effect. There was an excess rate of muscle-related adverse events reported only when patients and their doctors were aware that statin therapy was being used and not when its use was blinded.

Paterno E, Huybrechts KF, Bateman BT, et al. Lithium use in pregnancy and the risk of cardiac malformations. *N Engl J Med.* 2017;376(23):2245-2254.

Infants exposed to lithium during the first trimester had an increased risk of cardiac malformations, including Ebstein's anomaly (a right ventricular outflow tract obstruction defect); however, the magnitude of this effect was smaller than had been previously postulated.

Wykrzykowska JJ, Kraak RP, Hofma SH, et al; AIDA Investigators. Bioresorbable scaffolds versus metallic stents in routine PCI. *N Engl J Med.* 2017;376(24):2319-2328.

In patients undergoing a percutaneous coronary intervention, no significant differences were observed in the rate of target-vessel failure between patients who received a bioresorbable scaffold and those who received a metallic stent. However, the bioresorbable scaffold was associated with a higher incidence of device thrombosis than was the metallic stent. ■

Expert opinions



HEART FAILURE HIGHLIGHTS: 2017 UPDATES

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; β -blocker; exergaming; SWEDEHEART registry

β -BLOCKERS, HEART RATE, AND ATRIAL FIBRILLATION

A single, individual retrospective analysis of β -blocker trials has shown that β -blockers act only in sinus rhythm, and not in atrial fibrillation. This finding was reevaluated in the ESC-HF Registry, and presented by Krzysztof Ozieranski (PL). In patients with heart failure and atrial fibrillation, heart rate was only associated with an increased risk at a heart rate >110 bpm, but heart rates below this level did not alter the outcomes. β -Blockers reduced cardiovascular death and the composite of cardiovascular death and heart failure hospitalizations in an unadjusted analysis. However, atrial fibrillation was associated with poorer outcomes in sinus rhythm. After careful adjustment, the effect of β -blockers remained significant (HR, 0.52; 95% CI, 0.31–0.89; $P=0.02$). The combined outcome of death and heart failure hospitalizations was not significantly different, indicating that β -blockers, in real-life conditions, tend to have beneficial effects, although these effects are less pronounced than the effects of β -blockers in heart failure patients in sinus rhythm. Since the controlled trials were conducted in populations where 20% of the patients had atrial fibrillation, the results do not present an argument against the general use of β -blockers.

One analysis from the SWEDEHEART registry, presented by Liyew Desta (SE), showed that adherence to β -blocker treatment after a first myocardial infarction reduced the risk of heart failure or death (HR, 0.79; 95% CI, 0.73–0.85). These effects were more prominent in patients with HFREF than in patients with HFPEF. These findings argue in favor of the differential effects of β -blockers at different levels of ejection fraction. Kotecha et al (UK) discussed an individual patient analysis from β -blocker trials and the effect of β -blockers at different ejection fractions both in patients in sinus rhythm and patients with atrial fibrillation. The association of outcome with ejection fraction at baseline was more prominent in patients in sinus rhythm (HR, 1.24; 95% CI, 1.21–1.28; $P<0.0001$) than in patients with atrial fibrillation (HR, 1.09; 95% CI, 1.03–1.15; $P=0.002$). In sinus rhythm, β -blocker treatment reduced all-cause mortality and cardiovascular death from ejection fractions $<20\%$ to 40% – 49% , but there was no effect at an ejection fraction $>50\%$. In patients with atrial fibrillation, there were no positive effects of β -blockers at any level of ejection fraction, indicating that, in patients in sinus rhythm, including the patients

with HFMEF, β -blockers reduced mortality, while such an effect was not observed in patients with atrial fibrillation.

In patients on β -blockers with a heart rate >70 bpm in sinus rhythm, ivabradine has been shown to reduce cardiovascular death and heart failure hospitalizations (SHIFT study). Cleland et al (UK) reinvestigated a subgroup of patients from the SHIFT trial, mainly patients who cannot tolerate or are not willing to take a β -blocker. In the patients not taking a β -blocker, there was a significant reduction in the primary end point with ivabradine alone (HR, 0.69; 95% CI, 0.52–0.88; $P=0.031$), with similar results being obtained for heart failure hospitalizations. The patients not taking β -blockers were older, had more comorbidities, such as COPD, or had higher classes of heart failure (NYHA classes III to IV); they also had higher heart rates. In adjusted analyses, there was a trend for a greater effect for patients not taking a β -blocker or taking a lower dose of a β -blocker ($<25\%$ of target dose) compared with those on higher doses. These findings suggest that ivabradine reduces morbidity and mortality in patients unwilling or unable to take a β -blocker and reinforces its use for patients who cannot tolerate β -blockers.

MINERALOCORTICOID RECEPTOR ANTAGONISTS

Ida Löfman (SE) presented an analysis from the SWEDEHEART registry, showing that, in 70508 patients with heart failure and an acute myocardial infarction, there was a trend for a reduction in morbidity and mortality in those receiving an MRA after hospital discharge ($n=5251$). The overall results were not statistically significant, although significant effects were observed in the subgroup of patients with chronic kidney disease and low ejection fraction. These data show that particular high-risk patients who are usually undertreated or not treated in daily clinical practice benefit more from treatment with MRAs. Undertreatment might result from a fear of hyperkalemia, which directly translates into poorer outcomes for these patients. The UK database from 2006–2015, presented by Qin et al (US), showed that a nadir for heart failure patients for the lowest risk was a potassium level between 4.5 and 5.0 mmol/L. When potassium levels rise to 6 mmol/L, the risk increases to a hazard ratio of 3.54. The same holds true for main cardiovascular events, such as cardiovascular death and heart failure hospitaliza-

tions. In agreement with and extension of these findings, a Danish population-based cohort study, presented by Marianne Thomsen (DK), showed that the hazard ratio of patients undergoing an episode of hyperkalemia was 3- to 5-fold higher vs the 6 months preceding the event, indicating that hyperkalemia might have a direct impact on subsequent events after its resolution.

DIABETES AND SGLT2 INHIBITORS

The EMPEROR study recently showed that patients with diabetes receiving an SGLT2 inhibitor had a significant reduction in heart failure hospitalizations; a further subanalysis of heart failure patients has confirmed this finding. However, the mechanisms of SGLT2 inhibition are completely unclear. An analysis of the EMPEROR study, presented by David Fitchett (CA), showed that the risk reduction was not affected by adjusting the data to the decrease in blood pressure and to the improvement in LDL cholesterol or HbA_{1c}. Therefore, there was no influence of these vascular risk factors as mechanistic contributors to improving the risk in these patients. Two ongoing, prospective, randomized trials are exploring the effects of SGLT2 inhibition in heart failure patients (presented by Javed Butler [US]).

EXERGAMING

Exergaming is a comprehensive approach of testing and training neuronal networks in chronically ill patients, including patients with heart failure. Tiny Jaarsma (SE) presented a pilot and feasibility study on 486 patients using a training program of physical exercise in combination with intellectually challenging video games in patients with heart failure. This study showed that a combined training approach for 3 months with exergaming resulted in a significant improvement in exercise tolerance, as demonstrated by the 33 meter improvement in the 6-minute walk test ($P=0.004$). This program trains the patients in multitasking, coordination, exercise tolerance, and, potentially, neurocognition. This novel approach might be useful for chronically ill patients and heart failure patients to improve their daily activities, quality of life, and, potentially, adherence to medical treatments.

TAKE-HOME MESSAGES

- Atrial fibrillation affects patient outcomes, with the effects of β -blockers being heterogeneous. An association of heart rate with risk is only observed at high heart rates (>110 bpm) in patients with atrial fibrillation and heart failure.
- β -Blockers prevent cardiac mortality in patients in sinus rhythm more prominently than in patients with atrial fibrillation. Protective β -blocker effects are seen in patients with HFMEF. In case of intolerance to β -blockers, ivabradine is a suitable alternative in β -blocker-naïve patients.
- In patients with ischemic cardiomyopathy and heart failure, MRAs are associated with better long-term survival, particularly in patients at high risk with chronic kidney disease and a low ejection fraction. In these patient groups, new potassium levels might facilitate or enable the treatment with MRAs.
- SGLT2 inhibitors will be tested in patients with heart failure. Their effects in a diabetes study might not relate to an improvement in LDL, blood pressure, and HbA_{1c}, while other mechanisms still need to be explored.
- Exergaming is a new approach to improve exercise tolerance, coordination, and quality of life in heart failure patients. Further studies are needed to analyze its effect on long-term outcomes. ■

ADVANCES IN BASIC SCIENCE FOR CARDIOLOGY

LINA BADIMON, BSc, PharmD, PhD, FESC, FAHA

Author affiliations: Cardiovascular Sciences Institute, CIBER CV, IIB Sant Pau, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Address for correspondence: Lina Badimon, Cardiovascular Research Center (CSIC-ICCC), CIBERCV, and Biomedical Research Institute Sant Pau (IIB-Sant Pau), c/Sant Antoni M Claret 167, 08025 Barcelona, Spain (email: lbadimon@csic-iccc.org)

Keywords: biomarker; cardioprotection; hypertrophic cardiomyopathy; stem cell biology; transcription factor; vascular remodeling

The Basic Science track, an area that has been expanding in the ESC congresses since the creation of the Basic Science Council, had a diversity of high-quality symposia and more than 400 abstracts selected for oral or poster presentations. In recent years, more and more basic research abstracts are coming from Japan, Singapore, China, and the US, satisfactorily complementing the submissions from the European countries and the ESC-associated countries. Newly reported results range from developmental biology and fundamental discoveries to those that have clear implications for clinical diagnosis or treatment. Both clinicians and scientists are deeply interested in uncovering mechanisms of disease and developing targeted and innovative pathophysiology-based treatments. The Basic Science track covers all areas of cardiology and it is organized into three topic areas, including cardiac, vascular, and integrative science from a basic, translational, and preclinical approach. The present chair of the Council on Basic Cardiovascular Sciences, Jeremy Pearson (UK) was greatly satisfied with this year's program as he reported in the Highlights Session on the last morning of our 2017 ESC meeting.

STEM CELL RESEARCH

The stem cell research area was widely represented by special tracks devoted to both the therapeutic use of cells and cell-based products and the basic concepts of stem cell biology to understand cellular function. The use of pluripotent stem cells to define pathways of disease and strategies to correct them was explored and presented by different groups. Xinru Ran (HK) discussed the generation of induced pluripotent stem cells (iPSC) from patients with hypertrophic cardiomyopathy with a defined mutation in the troponin I3 gene, which were differentiated into cardiomyocytes in culture. In contrast to control cells, patient-derived cells reproduced the in vivo phenotype with hypertrophy, disordered sarcomere protein structure, and severe disturbances in Ca²⁺ handling. Therefore, these cells serve as a model to study, in detail, the altered molecular pathways that have been linked with the transcription factor NFATc4. Similarly, iPSC-derived cardiomyocytes have been generated from a patient with Wolff-Parkinson-White syndrome, which is caused by a mutation in a subunit of the enzyme AMP-activated protein kinase. These cells have a prolonged and more highly variable beating rate in culture as well as other characteristic features of cardiomyocyte functional disturbance in Wolff-Parkinson-White syndrome. Ronen Ben Jehuda (IL) showed that the specific correc-

tion of the mutation using CRISPR/Cas-9 gene editing substantially shortened and reduced the beat rate variability.

The latest results from various clinical studies have discouraged the initial hype on stem cell therapy to regenerate the heart after a myocardial infarction. The ESC General Assembly, as proposed by the ESC board, has approved the creation of a new ESC Working Group on Cardiovascular Regeneration and Repair (CARE), which has the mission of promoting basic and translational science into the clinics. Underlying research needs to understand the shortcomings of the current approaches to be able to overcome them. Interestingly, initiatives to engineer cardiac tissue were presented. Hidetoshi Masumoto (JP) discussed how the in vitro combination of human iPSC-derived cardiomyocytes, endothelial cells, and vascular smooth muscle cells produces patches that have been shown to improve the efficacy of functional recovery and myocardial regeneration after a myocardial infarction; pilot studies with heart engraftment in rodents and pigs are underway.

CARDIAC RESEARCH

Significant advances in cardiac areas requiring research were presented. Mutations in the transcription factor TBX5 are known to cause serious congenital heart defects, and, as shown by Franziska Sophie Rathjens (DE), TBX5 is not only essential for normal heart development, but its loss in heart failure also leads to important defects in cardiac conduction, suggesting that it could be a novel target for therapy in heart failure. In addition, Can Tepekoylu (AT) showed that toll-like receptor 3 has been identified as an effective target for the pharmacological prevention of valve calcification and valvular heart disease. Stuart Alexander Cook (UK) showed that IL-11 is a profibrotic molecule in human cardiac fibrosis samples, making it a potential target for therapy. Interestingly, Javier Larrasa-Alonso (ES) showed that the loss of the serine- and arginine-rich splicing factor (SRSF4) in cardiomyocytes induces hypertrophy, diastolic dysfunction, and the risk of sudden death. Han-Bin Cooz Lin (CA) showed that nod1/rip2 signaling interacts with the mitochondrial danger activator during the cardiac hypertrophic response.

An area with unmet medical needs is cardioprotection; however, interesting new results were presented at this year's congress. Laura Valls-Lacalle (ES) showed that

the inhibition of succinate dehydrogenase (complex II) by mevalonate in mice reduces infarct size. Two presentations by Guiomar Mendieta (ES) and Gemma Vilahur (ES) showed that the comorbidities in patients requiring cardioprotection might have a say in the low translation of basic science results to the clinical arena, as demonstrated by the abrogation of the effects of high-density lipoprotein cholesterol in the presence of dyslipidemia in a swine preclinical model. Rabea Hinkel (DE) showed that locked nucleic acid (LNA)-based miR92a inhibition can achieve therapeutic neovascularization in pigs with chronic myocardial ischemia. New targets may have to be uncovered in this complicated area: Naoya Otake (JN) described how myonectin (CTRP15) protects against ischemia / reperfusion, Judit Cubedo (ES) how targeting protein deglycase DJ-1 reduces infarct size during myocardial infarction, and Fatih Arslan (NL) how targeting an alternatively spliced fibronectin (fn) variant containing extradomain A (fnEDA) with an antibody prevents adverse remodeling in mice.

VASCULAR RESEARCH

At a vascular level, Jiangning Yang (SE) reported that erythrocytes from patients with type 2 diabetes induce vascular endothelial dysfunction via vascular arginase I and reactive oxygen species; interestingly, in a human proteomic study, a time-dependent systemic change in heme-related proteins after STEMI has been associated with the release of free hemoglobin upon erythrocyte activation in highly occlusive thrombotic masses. Judit Cubedo (ES) showed that the early increase in circulating levels of haptoglobin appears to be an endogenous response to quench the damaging effects of free hemoglobin with a potential impact on the evolution of the disease.

Teresa Padro (ES) presented new data on the role of perilipin (TIP47) in the extracellular matrix of human atherosclerotic plaques. Jochen Dutzmann (DE) presented data on how adventitial cells do not seem to contribute to neointimal formation, although their cytokine production is critical for negative vascular remodeling. Byambasuren Vanchin (NL) showed that microRNA-374b contributes to coronary artery stenosis through the induction of an endothelial-mesenchymal transition by targeting MAPK7 signaling. Two new areas of research were presented: Constance Emannueli (UK) discussed the role of exosomes as crosstalk mediators in cellular function, and Malashicheva (RU) discussed the mechanisms of smooth muscle cell differentiation in aneurysms.

INTEGRATIVE RESEARCH

Research in the area of biomarkers to predict cardiovascular risk is needed, and the results presented during the congress provided a new dimension to the potential candidates. Different strategies have been proposed from phenotypical characterization of microvesicles for the identification of damaged parental cells, to exomirs, to circulating noncoding RNAs and new proteins. Lina Badimon (ES) showed that specific subsets of platelet and leukocyte-derived microvesicles have been associated with clinical outcomes months later in asymptomatic patients with familial hypercholesterolemia. Gemma Chiva-Blanch (ES) presented a study showing that, by using proteomic approaches, platelets from patients with diabetes have increased levels of peroxiredoxin-2 (PRDX2) and heat shock cognate 71 kDa (HSPA8), which are two possible, but tentative, targets and/or biomarkers for diabetes.

Inflammation was highlighted in this year's meeting with the results of the CANTOS clinical trial, but it has been a recurrent theme in the basic science arena of atherosclerosis. New data, presented in two talks by Kazuyuki Nishimura (JP) and Julian Merz (DE), showed that a P2X7 deficiency blocks lesion inflammasome activity and ameliorates atherosclerosis in mice. In addition, Florian Willecke (DE) showed that targeting CD40-induced TRAF6 signaling in macrophages affects atherosclerosis in mice.

Research into the effects beyond the initial targets of existing drugs was presented in the research corner with two paradigmatic case studies. Using cardiac magnetic resonance imaging in pigs, Guiomar Mendieta (ES) demonstrated that, beyond platelet inhibition, ticagrelor has effects on myocardial remodeling and cardiac function. Marina Camera (IT) showed that PCSK-9 enhances platelet activation and aggregation; therefore, circulating PCSK-9 may contribute to the hyperreactivity of platelets, which points to possible unrecognized benefits of PCSK-9 inhibition that are unrelated to lowering LDL cholesterol.

CONCLUDING REMARKS

In conclusion, both bench to bedside and bedside to bench questions have been broadly analyzed and responded to in the basic science corner of the 2017 ESC congress in Barcelona. What is now debated in the clinical arena was years ago discussed in the basic science corner. That is why the ESC should be proud to host more basic science from around the world every year. By promoting this platform, the ESC stimulates interaction, innovation, and translation in cardiology and facilitates an earlier future for advances in clinical medicine. ■

REFERENCES

ESC 365: <http://congress365.escardio.org>

NEWS FOR THE MANAGEMENT OF CORONARY ARTERY DISEASE

GIUSEPPE M. C. ROSANO^{1,2}, MD, PhD, MSC, FESC, FHFA

Author affiliations: ¹Cardiovascular Clinical Academic Group, St George's Hospitals NHS Trust University of London;

²IRCCS San Raffaele, Roma, Italy

Address for correspondence: Giuseppe M.C. Rosano, St George's Hospitals NHS Trust University of London, Cranmer Terrace, London SW17 0RE, UK (email: grosano@sgul.ac.uk)

Keywords: anacetrapib; dual antiplatelet therapy; ivabradine; percutaneous coronary intervention; rivaroxaban; trimetazidine

One of the most important new items for the management of coronary artery disease at the 2017 ESC congress has been the ESC focused update on DAPT in coronary artery disease. DAPT reduces the risk of acute and late stent thrombosis, but the risk of bleeding in patients on DAPT is proportionally related to its duration. The benefits of prolonged DAPT, especially on mortality, depend on the patient's risk profile. The new document advocates an individualized approach based on ischemic vs bleeding risks and recommends the use of prediction models to estimate the on-DAPT bleeding risk. The task force recommendations are that, for patients with acute coronary syndromes, the default DAPT duration should be 12 months, while 6 months of DAPT should be considered in patients with a high risk of bleeding. Therapy longer than 12 months may be considered in patients who have tolerated DAPT without any bleeding complications. The duration of DAPT in patients with stable coronary artery disease treated with a percutaneous coronary intervention should be, irrespective of the type of stent implanted, from 1 to 6 months according to the risk of bleeding. However, a longer duration of DAPT may be considered for those patients whose ischemic risk is greater than the risk of bleeding. It is well known that the addition of DAPT to oral anticoagulation therapy increases the risk of bleeding complications and the duration of triple therapy (DAPT plus oral anticoagulation) should be limited to 6 months or discontinued after hospital discharge depending on the risk of ischemia and bleeding. The recommended duration of DAPT therapy is similar for male and female patients and for patients with and without diabetes mellitus.

REVEAL-2

The REVEAL-2 study¹ showed that anacetrapib, an inhibitor of cholesteryl ester transfer protein activity, lowers the risk of myocardial infarction and cardiovascular complications in patients receiving intensive statin treatment. The results of this study add relevant information on the importance of cholesterol metabolism in patients with vascular disease because anacetrapib increases HDL cholesterol and reduces LDL cholesterol. Until now, it was unclear whether increasing HDL cholesterol in patients already receiving a statin translated into fewer cardiovascular events. Some hints had been suggested by the FIELD and ACCORD study with fenofibrate, but the

REVEAL-2 confirmed that HDL cholesterol modulation is important for patients with vascular disease.

REVEAL-2 assessed the efficacy of adding anacetrapib vs placebo to atorvastatin in 30 449 patients with cardiovascular disease for an average of 4 years. The addition of atorvastatin therapy reduced LDL cholesterol levels by at least 20% and doubled the level of HDL cholesterol. The study showed that the addition of anacetrapib to intensive statin treatment produced a significant 9% reduction in the incidence of the primary outcome compared with placebo (risk ratio [RR], 0.91; 95% CI, 0.85-0.97; $P=0.004$). Anacetrapib was also effective in reducing the composite outcome of coronary death or myocardial infarction as well as coronary revascularization. The findings of the REVEAL-2 study are in contrast to the disappointing results of previous trials with other cholesteryl ester transfer protein inhibitors, which were stopped because of an increased risk or apparent lack of efficacy.

COMPASS

Important findings for patients with coronary artery disease come from the COMPASS study,² which tested whether rivaroxaban alone or in combination with aspirin was effective in reducing the occurrence of myocardial infarction and stroke in patients with stable coronary or peripheral artery disease. The trial randomized 27 395 patients to rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily or rivaroxaban 5 mg twice daily, each of which were compared with the standard therapy of aspirin 100 mg once daily. The primary end point was a composite of cardiovascular death, stroke, or myocardial infarction. The study was stopped early, as recommended by the Data Safety Monitoring Board, because of a clear superiority of the combination of rivaroxaban plus aspirin vs aspirin alone. The results showed that the addition of rivaroxaban to aspirin, compared with aspirin alone, reduced cardiovascular death, stroke, or myocardial infarction by 24% and improved survival by 18%. The results are believed to be due to the synergistic effect of rivaroxaban and aspirin because rivaroxaban alone was not superior to aspirin alone. However, the addition of rivaroxaban to aspirin increased bleeding, mostly intestinal, while there was no significant increase in fatal or brain bleeding. The results indicate that, for every 1000

patients treated for an average of 23 months, rivaroxaban plus aspirin prevents 13 myocardial infarctions, strokes, or cardiovascular deaths and 7 deaths from any cause, at a cost of 12 major bleeds, most of which were readily treatable. The 1.3% percent reduction in the composite end point translates to a number needed to treat of 76. The results, therefore, should be taken with caution and rivaroxaban should be considered only in selected patients with coronary artery disease.

FIXED-DOSE COMBINATION THERAPY: IVABRADINE PLUS β -BLOCKERS

Fixed-dose combination therapy is used in many cardiovascular conditions, but, until now, it has not been implemented in patients with coronary artery disease. Both ivabradine and β -blockers have been shown to be effective treatments for patients with angina. However, data on the use of fixed-dose combination therapy with these drugs is lacking. An important study that evaluated the effectiveness and tolerability of the fixed-dose combination of ivabradine and metoprolol in clinical practice was presented at the congress.³ The study included 747 outpatients with stable angina pectoris in a prospective, multicenter, observational cohort study. Patients received a fixed-dose combination of ivabradine and metoprolol (bid) for 4 months in addition to the standard cardiovascular therapy. The study showed that 86% of all patients were already treated with a free combination of ivabradine and a β -blocker at baseline. At the 4-month follow-up, the switch from a free combination to a fixed-dose combination was associated with a significant 10 bpm reduction in mean heart rate, with a significant reduction in the episodes of angina per week (from 38% to 7%), which was mirrored by a reduction in nitrate use. Complete adherence to medications was achieved in 58% of patients compared with 34% at baseline. The study showed the importance of fixed-dose combinations of antianginal medications for the treatment of patients with coronary artery disease because this treatment was effective in reducing angina symptoms and improving both exercise capacity and adherence to medications.

TRIMETAZIDINE

Trimetazidine is a drug that is living a second life after the confirmation of its benefits for angina by the European Medicines Agency. Trimetazidine is effective at improving angina, effort-induced myocardial ischemia, and quality of life. It also has significant and relevant benefits in heart failure, and, for this reason, it has been included in the 2016 ESC/HFA guidelines on heart failure. Previous studies have demonstrated that a 1-year treatment with trimetazidine modified release reduced the rate of ischemia-driven revascularization and repeat hospitalizations in postmyocardial infarction patients with multivessel disease that underwent incomplete revascularization. A study presented in Barcelona assessed whether these positive effects were sustained with chronic treatment in 100 postmyocardial infarction patients with multivessel disease and incomplete revascularization. Trimetazidine modified release significantly reduced ischemia-driven revascularizations or repeat hospitalizations (RR, 0.53; 95% CI, 0.34–0.85; $P < 0.005$) vs the conventional treatment. The study also showed a very significant reduction in the rate of repeat hospitalizations with trimetazidine modified release vs the control group (20% vs 50%; $P < 0.03$).⁴

CONCLUSIONS

Data presented at the 2017 ESC congress has shown the efficacy of newer therapies in patients with vascular disease and has confirmed the efficacy of already established drugs in new formulations or in fixed-dose combinations for the treatment of patients with angina. ■

REFERENCES

1. HPS3/TIMI55-REVEAL Collaborative Group. Effects of anacetrapib in patients with atherosclerotic vascular disease. *N Engl J Med*. 2017 Aug 28. Epub ahead of print.
2. Eikelboom JW, Connolly SJ, Bosch J, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017 Aug 27. Epub ahead of print.
3. Divchev D. Angina treatment with a new fixed-dose combination of ivabradine and metoprolol: first clinical data from a large prospective observational cohort. ESC 2017 (P884).
4. Lopatin Y. Trimetazidine modified release therapy in post-myocardial infarction patients with multivessel disease having undergone incomplete revascularization: results of two years of follow up. ESC 2017 (P4293).

SEVERE SECONDARY MITRAL REGURGITATION IN HEART FAILURE: A HOLISTIC APPROACH

PATRIZIO LANCELLOTTI^{1,2}, MD, PhD, FESC

Author affiliations: ¹University of Liège hospital, GIGA Cardiovascular Science, Heart Valve Clinic, Imaging Cardiology, Belgium;

²Gruppo Villa Maria Care and Research, Anthea Hospital, Bari, Italy

Address for correspondence: Patrizio Lancellotti, Heart Valve Clinic Echo Department, Intensive Care Unit, University Of Liège, University Hospital Sart Tilman B45, 4000 Liège, Belgium (email: plancellotti@chu.ulg.ac.be)

Keywords: echocardiography; left ventricular dilation; mitral regurgitation; mitral valve

During the 2017 ESC annual congress in Barcelona, a session was dedicated to severe secondary mitral regurgitation in heart failure. Secondary mitral regurgitation is a common and insidious complication of heart failure patients with ischemic or idiopathic systolic left ventricular dysfunction. Its incidence and clinical importance are largely underestimated, partly because a physical examination is not sufficient. When present, secondary mitral regurgitation may exhibit a broad range of severity. Any degree of secondary mitral regurgitation in patients with left ventricular dysfunction conveys an adverse prognosis, with a graded relationship between the severity of regurgitation and reduced survival.¹

Secondary mitral regurgitation results from an imbalance between tethering forces—annular dilatation, left ventricular dilatation, papillary muscle displacement, and left ventricular sphericity—and closing forces—reduction in left ventricular contractility, global left ventricular dyssynchrony, papillary muscle asynchrony, and altered mitral systolic annular contraction. Chronic secondary mitral regurgitation is categorized as type IIIb according to Carpentier's classification, given that leaflet restriction leading to mitral regurgitation only occurs during systole. Two main patterns of mitral valve geometry alteration have been described: (i) the symmetric pattern, generally caused by global left ventricular remodeling with spherical left ventricular enlargement, which involves tethering of both the anterior and posterior leaflets, and mainly creates a central mitral regurgitation jet; and (ii) the asymmetric pattern, which is more often caused by local inferior wall remodeling with a predominantly posterior leaflet restriction, an asymmetric leaflet apposition, and a posteriorly directed mitral regurgitation jet.

ASSESSING MITRAL REGURGITATION

2D echocardiography plays an essential role in the assessment of mitral regurgitation etiology, severity, consequences, and the likelihood of mitral valve repair.² Several echocardiographic methods allow an exact quantification of the degree of mitral regurgitation. Qualitatively, color-flow imaging is the most common way to assess mitral regurgitation severity. Semi-quantitatively, a vena contracta <3mm indicates mild mitral regurgitation, whereas a width ≥7mm defines severe mitral regurgitation.

The flow convergence method is the most recommended quantitative approach whenever feasible.

In the 2017 ESC guidelines, primary mitral regurgitation is considered severe if the effective regurgitant orifice area is ≥40mm² and the regurgitant volume is ≥60mL. In secondary mitral regurgitation, the corresponding thresholds of severity, which are of prognostic value, are 20mm² and 30mL, respectively. In the 2017 American Heart Association / American College of Cardiology focused update guidelines, on the basis of the criteria used for the determination of severe mitral regurgitation in randomized controlled trials on surgical interventions, both primary and secondary mitral regurgitation are considered severe if the effective regurgitant orifice area is ≥40mm², the regurgitant volume is ≥60mL, and the regurgitant fraction is ≥50%. These differences in the definition of severe secondary mitral regurgitation are generating considerable controversy within the cardiology community. The reasons for the controversy include single-frame measurements of effective regurgitant orifice area using the proximal isovelocity surface area (PISA) method, which may not reflect the dynamic changes during systole; the use of a formula that assumes a round orifice geometry when the orifice is crescent-shaped in secondary mitral regurgitation; dynamic changes in mitral regurgitation with loading conditions, ischemia, or dyssynchrony; and the squaring of small errors in measurement.

Although echocardiography can underestimate mitral regurgitation severity, it has a general tendency to overestimate it, as shown in a recent comparison of echocardiography with either cardiac magnetic resonance imaging or 3D echocardiography. The assessment of mitral regurgitation using 3D echocardiography is reasonable to provide additional information on severity, especially in measurements of effective regurgitant orifice area and regurgitant volume. A 3D-derived vena contracta area has been shown to correlate more closely with Doppler-derived effective regurgitant orifice area than the 2D vena contracta diameter. A vena contracta area ≥0.41cm² seems to be indicative of severe mitral regurgitation, although further validation of this cut-off is necessary given that the comparison standards have been conventional 2D estimates of mitral regurgitation severity. In practice, it is likely that the true threshold depends on the severity of left ventricular dysfunction/dilatation,

since the relationship between mitral regurgitation and left ventricular volume is influenced by the mean systolic pressure gradient between the left ventricle and the left atria, with higher effective regurgitant orifice area values in decompensated heart failure patients with hypotension and elevated left atrial pressure compared with hypertensive patients with normal left atrial pressure.³

Secondary mitral regurgitation is characteristically dynamic during exercise.⁴ The magnitude of exercise-induced changes in mitral regurgitation severity is unrelated to the degree of mitral regurgitation at rest. An increase in mitral regurgitation by one grade during exercise is observed in about one-third of patients with moderate secondary mitral regurgitation. Such an increase in mitral regurgitation during dynamic exercise identifies a subgroup of patients at high risk for cardiac events (mortality, acute pulmonary edema, acute heart failure worsening). However, the guidelines do not address how to approach the dynamic nature of secondary mitral regurgitation. Therefore, it seems prudent not to label patients as having severe mitral regurgitation until they are on optimally tolerated doses of guideline-directed medical therapy, and, if clinically indicated, have undergone revascularization and/or cardiac resynchronization therapy.

MANAGEMENT OF SECONDARY MITRAL REGURGITATION

The management of patients with chronic secondary mitral regurgitation remains challenging. Medical therapy is limited in its efficacy.⁵ A combination of angiotensin-converting enzyme inhibitors and β -blockade can limit the negative left ventricular remodeling process, yet a decrease in the incidence or severity of mitral regurgitation and its dynamic component has not been demonstrated by this approach. Cardiac resynchronization therapy has been shown to improve clinical status, quality of life, and exercise capacity, promote reverse left ventricular remodeling, and prolong survival of selected heart failure patients with intraventricular conduction delay. Responses to cardiac resynchronization therapy largely depend on the extent of left ventricular dyssynchrony and the severity of

secondary mitral regurgitation. Cardiac resynchronization therapy acutely reduces secondary mitral regurgitation by increasing closing forces with an improvement in left ventricular dP/dt and by improving coordinated timing of the mechanical activation of papillary muscle insertion sites. This benefit appeared to be dependent on continued pacing because withholding pacing resulted in an immediate loss of effect and recurrence of mitral regurgitation. The expected attenuation of exercise-induced secondary mitral regurgitation is about 30%. However, cardiac resynchronization therapy reduces the amount of increase in secondary mitral regurgitation, but does not avoid the development of at least some dynamic component in most patients. In this situation, combining a percutaneous mitral valve approach with cardiac resynchronization therapy might be of interest.

CONCLUSION

Secondary mitral regurgitation is associated with poor outcomes, but whether its correction reverses the underlying left ventricular pathology or improves the prognosis remains controversial. The major determinants for a lack of survival benefit after surgical mitral repair include: (i) the risk of the procedure; (ii) the fact that the problem is the ventricle, not the valve; and (iii) the issue related to recurrent mitral regurgitation and the need for a late reintervention. Therefore, surgery for secondary mitral regurgitation is only reserved for patients with an acceptable operative risk. Moderate secondary mitral regurgitation should be left untreated at the time of coronary bypass grafting. For severe mitral regurgitation, repair is the optimal treatment when it is expected to be durable, otherwise valve replacement should be carried out. With advancements in technology, it is likely that, in the near future, surgery for secondary mitral regurgitation will be carried out only if percutaneous methods are contraindicated. To date, the interventional edge-to-edge repair technique, ie, MitraClip, has been established as a reliable method, which is associated with: (i) durable mitral regurgitation reduction; (ii) clinical improvements; and (iii) a signal for improved survival over optimized medical treatment. However, the efficacy of this therapy might be limited in patients with severe biventricular heart failure due to a high 1-year mortality rate. ■

REFERENCES

1. Lancellotti P, Fattouch K, La Canna G. Therapeutic decision-making for patients with fluctuating mitral regurgitation. *Nat Rev Cardiol*. 2015;12(4):212-219.
2. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2013;14(7):611-644.
3. Grayburn PA, Carabello B, Hung J, et al. Defining "severe" secondary mitral regurgitation: emphasizing an integrated approach. *J Am Coll Cardiol*. 2014;64(25):2792-2801.
4. Piérard LA, Lancellotti P. The role of ischemic mitral regurgitation in the pathogenesis of acute pulmonary edema. *N Engl J Med*. 2004;351(16):1627-1634.
5. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J*. 2012;33(19):2451-2496.

HOT TOPICS IN CARDIAC REHABILITATION

ANA ABREU, MD, PhD

Author affiliations: Cardiology Department, Hospital Santa Marta, Centro Hospitalar Lisboa Centro, CHLC, Lisboa, Portugal

Address for correspondence: Ana Abreu, Hospital Santa Marta, R. de Santa Marta, 1169-024 Lisboa, Portugal (email: ananabreu@hotmail.com)

Keywords: cardiac rehabilitation; coronary heart disease; exercise; telerehabilitation

Cardiac rehabilitation (CR) started out as a “fictional” treatment almost like an “alternative” treatment in medicine. Progressively, the demonstration of benefits has been growing and CR is finally considered to be a consistent reality in the treatment of cardiovascular patients. A steep evolution has taken us from exercise-based CR, consisting of straight exercise protocols for patients after myocardial infarction or coronary surgery, to comprehensive multidisciplinary programs that include other components besides exercise for a larger scope of cardiac patients. Flexible and tailored protocols, home-based CR with telemedicine tools, psychological interventions for adherence and motivation, and targeted risk factor education are nowadays employed without exit.

IS CARDIAC REHABILITATION STILL WORTHWHILE?

As the beneficial effects of CR were mostly demonstrated before statins and percutaneous coronary interventions, some skeptics and opponents of CR considered it to be a matter of the past; however, this hypothesis was disproved recently and it can now be completely discarded. A 2016 Cochrane systematic review and meta-analysis on exercise-based CR for coronary heart disease, which included old and recent study data, demonstrated a significant reduction in cardiovascular mortality and hospital readmission, but not in total cardiovascular mortality.¹ A posterior meta-analysis showed that the benefit was also extended to total mortality.²

CROS study

The CROS study, a methodological and very rigorous meta-analysis analyzing patients with coronary artery disease, demonstrated, without a doubt, a significant reduction in total mortality after CR.² The aim of this study was to evaluate the effectiveness of CR on the clinical prognosis after a recent cardiac event in the modern era of statin therapy and acute revascularization for acute coronary syndromes, including only CR studies conducted after 1995. Patients hospitalized for acute coronary syndromes or coronary artery bypass grafting and patients with mixed coronary artery disease, from retrospective and prospective controlled cohort studies and from one trial, the RAMIT trial, were included.

The intervention was a CR program starting up to 3 months after discharge from the hospital or treatment of the index event (acute coronary syndromes or coronary

artery bypass grafting). The control group included patients with an index event, who did not participate in CR. The program was structured as a multicomponent program with exercise training at least twice a week, and CR was performed in either an outpatient or an inpatient setting. The outcome was total mortality during a follow-up of at least 6 months. In 218524 patients from 25 controlled cohort studies in 9 countries, total mortality was reduced by 36% to 80% after sudden cardiac arrest, 38% to 88% after coronary artery bypass grafting, and 33% to 44% in mixed coronary artery disease populations. CR was associated with a reduction in total mortality after an acute coronary event, even in the era of statins and acute revascularization. CROS was the first study to demonstrate a benefit of CR in all groups of patients with coronary artery disease.

An important issue to highlight in this study is that the controlled cohort studies, which in reality are more representative of clinical practice, exhibited large heterogeneity due to the different CR protocols, study designs, and statistical analyses. This important meta-analysis highlights the urgent need to define international minimal standards for CR by specifying certain aspects, such as early referral, structured and supervised exercise at least twice a week, education sessions, psychosocial interventions, and a multidisciplinary team of skilled health care professionals.

TAILORED CARDIAC REHABILITATION PROGRAMS

Due to the growing complexity of the patients and the possibility of using different exercise protocols, exercise prescription may not be simple. Aortic stenosis patients who need a transcatheter aortic valve implantation are a specific subset of patients who are old or very old and present with multiple geriatric problems, several comorbidities, cognitive disorders, incapacity, and frailty. It is easy to understand that the aim of treating these patients is more to reduce the symptoms and incapacity and improve their quality of life than to reduce mortality. Implanting a new valve is not enough. Sometimes the valve is working well, but the patient is still not completely treated. Their management needs to start with a comprehensive multidimensional evaluation using specific geriatric tools.³ Independence and quality of life should be the target of the rehabilitation program.

An interesting review of CR in transcatheter aortic valve implantation and surgical aortic valve patients shows

that CR improves their quality of life and functioning.⁴ In addition to these benefits, other studies have recently demonstrated an improvement in frailty and anxiety. The cost-effectiveness of CR in these patients has been challenged; however, the benefits to their health are so obvious that the essential discussion needs to focus on the choice of the most cost-effective program for transcatheter aortic valve implantation patients.^{5,6} Awareness needs to be raised regarding the specificities of the training program for these patients.⁷ The exercise protocol needs to be well tailored to the individual patient. Aerobic training is important, but resistance, balance, and coordination training may be even more important in this very old population.⁸ Treating the comorbidities, frailty, disability, and psychological/cognitive disorders are no less important than training, and it is an important part of the rehabilitation process of a transcatheter aortic valve implantation patient.⁹

IS HIGH-INTENSITY INTERVAL TRAINING BETTER THAN MODERATE CONTINUOUS TRAINING?

Aerobic moderate continuous exercise training has been used for a long time with demonstrated benefits in cardiac patients. This modality has been challenged by high-intensity interval training, and the discussion in heart failure patients is ongoing. The recently published SMARTEX-HF study,¹⁰ a randomized, multicenter trial, tested the hypothesis that high-intensity interval training would yield superior effects vs moderate continuous exercise training. The conclusion shows that high-intensity interval training is not superior to moderate continuous exercise training regarding aerobic capacity and left ventricular remodeling in patients with heart failure. According to the authors, until a mortality trial is finished, both interventions can be initiated, but due to the larger number of patients already assessed by moderate continuous exercise training, this may still be the preferred intervention for patients with HFREF. These results and conclusions cannot be directly extrapolated to the subset of patients with HFPEF. For this reason, the OptimEX CLIN study,¹¹ a trial to evaluate high-intensity interval training vs moderate continuous exercise training in HFPEF is currently underway.

EXERCISE PRESCRIPTION: THE EXPERT FLOWCHART

Exercise prescription raises several problems, especially at an individual level, and they cannot be resolved completely using the general indications of the guidelines. The prescription can be very different according to the prescribing doctors, and there are many reasons for this situation, which involve patients being older, more complex, having more comorbidities, and more severe and heterogeneous cardiovascular disease. The guidelines and position papers indicate the general lines of prescription; however, if the patient has a combination

of several risk factors, several comorbidities, and one or even two cardiovascular diseases, the prescription will need to be tailored. Therefore, the Expert Flowchart¹² project developed a very complete digital tool, which “plays” with the diagnosis, risk factors, comorbidities, and other aspects to achieve the best prescription for the patient. This may be a very practical tool to help doctors determine the best individualized exercise prescription, and it will be available soon.

TELEREHABILITATION AND HOME-BASED CARDIAC REHABILITATION: PRESENT AND FUTURE ADVANCES

Today, new advances in telerehabilitation have been achieved. The need for home-based CR stimulated the development of telerehabilitation techniques and now the advances in telerehabilitation are promoting the improved use of home-based CR. According to the Telehealth exercise-based CR study,¹³ a systematic review and meta-analysis, home-based telerehabilitation compared with center-based rehabilitation was more effective for enhancing physical activity and exercise adherence, controlling diastolic blood pressure and LDL cholesterol levels, and as effective for maximal aerobic exercise capacity and an improvement in modifiable risk factors.

A Cochrane meta-analysis on home-based vs center-based CR shows a similar effectiveness in improving clinical and health-related quality of life outcomes in patients after a myocardial infarction or revascularization or in patients with heart failure.¹⁴ The choice may reflect local availability and consider the preference of the individual patient. Further data are needed to determine whether the effects of home- and center-based rehabilitation in the short term can be confirmed in the long term.

FIT@Home study

A recent study compared the clinical cost-effectiveness of home-based CR with conventional center-based CR based on the results of the FIT@Home study.¹⁵ The study showed that home-based training with telemonitoring guidance was associated with higher patient satisfaction, and it appeared to be more cost-effective, despite no differences regarding center-based training on physical fitness, physical activity level, or health-related quality of life. It is important to understand the longer-term effects of home-based exercise interventions on exercise capacity and physical activity in patients with coronary artery disease. A systematic review and meta-analysis on this topic shows that home-based exercise is slightly more effective than center-based CR in terms of maintaining exercise capacity and physical activity behavior, which is the ultimate goal of CR. This meta-analysis highlights the urgent need for randomized controlled trials to evaluate the long-term effectiveness of well-designed, home-based interventions and shows that there is a lack of data on how to implement home-based rehabilitation optimally.¹⁶

Cardiac rehabilitation for women

Home-based rehabilitation may be a tool to overcome the barriers associated with CR, particularly in several patient subsets, such as women and old patients. A systematic review study from the Mayo Clinic evaluated the barriers and solutions in CR for women.¹⁷ The study shows that a lower education level, multiple comorbid conditions, non-English native language, lack of social support, and high burden of family responsibilities were the main barriers for women, meaning that, in addition to the use of automatic referral, assisted enrollment, and incentive-based strategies, home-based programs are a solution for improving attendance and completion rates.

Digital medicine

Digital medicine is rapidly growing with exciting advances in programs, tools, and devices. A smartphone-based home-care model for CR was studied in a recent randomized controlled trial that submitted 120 patients to 6 weeks of CR followed by a 6-month maintenance period with health and exercise monitoring, motivational and educational material, and weekly mentoring consultations.¹⁸ The study showed that, in postmyocardial infarction patients, telerehabilitation improved uptake, adherence, and completion with a similar effectiveness as traditional center-based CR regarding the improvement in physiological and psychological health outcomes. An internet-based telerehabilitation study,¹⁹ where 140 patients with coronary artery disease and/or heart failure performed 6 weeks of regular CR, demonstrated the impact of telerehabilitation or usual care on quality of life, with a greater impact on physical, emotional, and global health-related quality of life with telerehabilitation vs usual care.

Ongoing projects in telerehabilitation

TELEREH-HF, a multicenter, randomized controlled study in heart failure, is applying telemedicine technologies in a novel model of organizing and implementing comprehensive CR in heart failure patients (LVEF <40%). The main end point is days alive without hospitalization.

Telerehab III,¹⁹ a multicenter, randomized controlled trial, is investigating the long-term effectiveness of a comprehensive cardiac telerehabilitation program by evaluating the long-term effectiveness of patient-tailored, internet- and home-based CR. This study involves not only the exercise component, but also all other components of CR.

A personalized patient-centered web application, based on the protocol for the SmartCare-CAD randomized controlled trial, is based on the hypothesis that cardiac telerehabilitation using evidence-based behavioral changes, modern communication methods, and on-demand coaching will result in improved self-management skills and sustainable behavioral changes, which translates to higher physical activity levels in a cost-effective way. These investigators think that telerehabilitation may overcome

the barriers of CR; however, the superiority of telerehabilitation has not been convincingly demonstrated yet, which may be due to an insufficient focus on changing behaviors and developing self-management skills.

CONCLUSION

Cardiac rehabilitation is unquestionably still beneficial and important for patients with coronary artery disease. CR is being used more in different subsets of patients who are older with more complex and diverse pathologies and comorbidities that need carefully tailored and individualized programs. Different exercise programs for heart failure are being evaluated regarding benefits and cost-effectiveness. CR delivery is heterogeneous and needs standardization. New techniques, including telemedicine tools, are evolving and might help in program prescription and breaking CR barriers. Delivery of good quality CR to all cardiac patients, assuring motivation and adherence, are presently our main goals. ■

REFERENCES

- Andersen L, Oldridge N, Thompson DR, et al. Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane Systematic Review and Meta-Analysis. *J Am Coll Cardiol*. 2016;67(1):1-12.
- Rauch B, Davos CH, Doherty P, et al. The prognostic effect of cardiac rehabilitation in the era of acute revascularization and statin therapy: a systematic review and meta-analysis of randomized and non-randomized studies – The Cardiac Rehabilitation Outcome Study (CROS). *Eur Prev Cardiol*. 2016;23(18):1914-1939.
- Eichler S, Salzwedel A, Reibis R, et al. Multicomponent cardiac rehabilitation in patients after transcatheter aortic valve implantation: predictors of functional and psychocognitive recovery. *Eur J Prev Cardiol*. 2017;24(3):257-264.
- Ribeiro GS, Melo RD, Deresz LF, Dal Lago P, Pontes MR, Karsten M. Cardiac rehabilitation programme after transcatheter aortic valve implantation versus surgical aortic valve replacement: systematic review and meta-analysis. *Eur Prev Cardiol*. 2017;24(7):688-697.
- Hansen B, Zwisler AD, Berg SK, et al. Cost-utility analysis of cardiac rehabilitation after conventional heart valve surgery versus usual care. *Eur J Prev Cardiol*. 2017;24(7):698-707.
- Abreu A. Cardiac rehabilitation in cardiac valve surgery patients: beyond cost-effectiveness. *Eur J Prev Cardiol*. 2017;24(11):1145-1147.
- Piepoli MF, Corrà U, Benzer W, et al. Secondary prevention through cardiac rehabilitation: from knowledge to implementation. *Eur J Cardiovasc Prev Rehabil*. 2010;17(1):1-17.
- Eichler S, Völler H. Advances in cardiac rehabilitation: cardiac rehabilitation after transcatheter aortic valve implantation. *Monaldi Arch Chest Dis*. 2016;86(1-2):758.
- Vigorito C, Abreu A, Ambrosetti M, et al. Frailty and cardiac rehabilitation: a call to action from the EAPC Cardiac Rehabilitation Section. *Eur J Prev Cardiol*. 2017;24(6):577-590.
- Støylen A, Conraads V, Halle M, Linke A, Prescott E, Ellingsen Ø. Controlled study of myocardial recovery after interval training in heart failure: SMART-EX-HF--rationale and design. *Eur J Prev Cardiol*. 2012;19(4):813-21.
- Suchy C, Massen L, Rognmo O, et al. Optimising exercise training in prevention and treatment of diastolic heart failure (OptimEx-CLIN): rationale and design of a prospective, randomised, controlled trial. *Eur J Prev Cardiol*. 2014;21(suppl 2):18-25.
- Hansen D, Dendale P, Coninx K, et al. The European Association of Preventive Cardiology Exercise Prescription in Everyday Practice and Rehabilitative Training (EXPERT) tool: a digital training and decision support system for optimized exercise prescription in cardiovascular disease. Concept, definitions and construction methodology. *Eur J Prev Cardiol*. 2017;24(10):1017-1031.
- Rawstorn JC, Gant N, Direito A, Beckmann C, Maddison R. Telehealth exercise-based cardiac rehabilitation: a systematic review and meta-analysis. *Heart*. 2016;102(15):1183-1192.
- Andersen I, Sharp GA, Norton RJ, et al. Home-based versus centre-based cardiac rehabilitation. *Cochrane Database Syst Rev*. 2017;6:CD007130.
- Kraal JJ, Van den Akker-Van Marle ME, Abu-Hanna A, et al. Clinical and cost-effectiveness of home-based cardiac rehabilitation compared to conventional centre-based cardiac rehabilitation: results from the FIT@HOME study. *Eur J Prev Cardiol*. 2017;24(12):1260-1273.
- Claes J, Buys R, Budts W, Smart N, Cornelissen VA. Longer-term effects of home-based exercise interventions on exercise capacity and physical activity in coronary artery disease patients: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2017;24(3):244-256.
- Supervia M, Medina-Inojosa JR, Yeung C, et al. Cardiac rehabilitation for women: a systematic review of barriers and solutions. *Mayo Clin Proc*. 2017 Mar 13. Epub ahead of print.
- Varnfield M, Karunanithi M, Lee CK, et al. Smartphone-based home care model improved use of cardiac rehabilitation in postmyocardial infarction patients: results from a randomized controlled trial. *Heart*. 2014;100(22):1770-1779.
- Frederix I, Hansen D, Coninx K, et al. Medium-term effectiveness of comprehensive internet-based and patient-specific telerehabilitation program with text messaging support for cardiac patients: randomized controlled trial. *J Med Internet Res*. 2015;23:17(7):e185.

WHAT IS NEW IN ISCHEMIC STROKE?

PETR WIDIMSKY, MD

Author affiliations: Third Faculty of Medicine, Cardiocenter, Charles University, University Hospital Kralovske Vinohrady, Srobařova 50, 100 00 Prague, Czech Republic

Address for correspondence: Petr Widimsky, Cardiocenter, Third Faculty of Medicine, Charles University, Prague, Czech Republic (email: petr.widimsky@fnkv.cz)

Keywords: antithrombotic drug; atrial fibrillation; endovascular treatment; European Society of Cardiology; interventional cardiology; secondary prevention; stroke; transient ischemic attack

The ESC, in recognition of the importance of stroke for cardiac patients and for cardiology in general, decided to create a new constituent body—the ESC Council on Stroke—during the 2016 congress. The council was actively involved in preparing the stroke track for the 2017 ESC congress. This article summarizes some of the most interesting information concerning stroke that was presented during this congress.

WHAT DO CARDIOLOGISTS NEED TO KNOW ABOUT STROKE?

This section was prepared by the ESC Council on Stroke and all presenters are members of this council, except for the first keynote lecture “Stroke types and their diagnosis” presented by the ESO president-elect Bart van der Worp (NL). Marta Rubiera (ES) summarized the data on embolic stroke of unknown source, which is a recently established classification of strokes that includes those strokes where all diagnostic tests (vascular ultrasound, echocardiography, ECG monitoring) were made, but failed to reveal the source of the embolic stroke. Embolic stroke of unknown source is a subgroup of cryptogenic strokes, which also includes strokes without a diagnostic workup and strokes with multiple possible etiologies. Robert Storey (UK) presented the recent data on anti-thrombotic drugs in stroke prevention. Mikael Mazighi (FR) commented on the European recommendations for acute stroke intervention (EUROICAS). Endovascular (catheter-based) thrombectomy is currently a class IA indication, and it is the best possible therapy for an acute ischemic stroke. Whenever indicated, it can be preceded by intravenous thrombolysis, but doctors should never delay the intervention by waiting for the effect of the thrombolytic drugs. John Camm (UK) discussed whether atrial ablation procedures could prevent a stroke. Petr Widimsky (CZ) summarized the data concerning percutaneous left atrial appendage closure and patent foramen ovale closure. The latest evidence from the CLOSE and GORE REDUCE trials clearly supports routine patent foramen ovale closure in secondary stroke prevention (when patent foramen ovale is detected in patients after a stroke or transient ischemic attack). The left atrial appendage closure is still only a class IIb/C indication according to the European guidelines, but this may change in the future after ongoing trials finish (eg, PRAGUE-17).

ETIOLOGIC APPROACH TO STROKE PREVENTION AND TREATMENT

This joint session, which was prepared by the ESC Council on Stroke and the European Stroke Organization, demonstrated the diversity of stroke causes. Bart van der Worp presented the noncardiac causes of stroke, while Wolfram Doehner (DE) presented the cardiac causes of ischemic stroke. Hans Christoph Diener (DE) discussed antithrombotic therapy that is tailored to the stroke etiology and showed that antiplatelet treatment is optimal for the prevention of a vascular stroke (eg, carotid lesions), while anticoagulation is better for the prevention of an embolic stroke. Mikael Mazighi summarized the current evidence on the endovascular treatment of an acute stroke and Alison Halliday (UK) presented the data and guidelines on carotid revascularization.

COMPASS TRIAL

The COMPASS trial¹ demonstrated that adding low-dose rivaroxaban (2.5mg twice daily) to aspirin (100mg once daily) significantly decreased the combined cardiovascular end point (ie, cardiovascular death, myocardial infarction, and stroke), and it is likely to become the standard of care for the secondary prevention in patients with coronary artery disease and/or peripheral artery disease. Interestingly, the most impressive benefit was the 50% relative risk reduction in stroke, whereas the relative risk reduction in myocardial infarction was only 14%. Furthermore, the benefits of the rivaroxaban-aspirin combination were slightly greater in the subgroup of patients with peripheral artery disease; the benefit on limb salvage was especially impressive. The hypothetical explanation for these observations is that antiplatelet treatment may be sufficient for coronary atherosclerosis, while anticoagulant treatment is important for stroke prevention, as may be the case for critical limb ischemia. The key message from the COMPASS trial is that the combination of a low-dose antiplatelet agent with a low-dose oral anticoagulant is beneficial for the entire vascular tree, ie, coronary arteries, cerebral arteries, and peripheral arteries. Thus, COMPASS is a landmark trial, shifting secondary prevention to a new level.

CANTOS TRIAL

The CANTOS trial showed that the interleukin antibody canakinumab, which inhibits chronic inflammation, decreased the combined end point (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death).² However, the benefit was almost exclusively on lowering the rates of revascularization as there was no effect on mortality (including cardiovascular death) or stroke. Thus, the real clinical benefits on hard end points remain to be established in future trials.

CASTLE-AF TRIAL

In the CASTLE-AF trial, catheter ablation of atrial fibrillation in patients with heart failure improved all-cause mortality and decreased hospital admissions for worsening heart failure compared with the conventional standard of care. In addition, there was a nonsignificant trend for fewer strokes (3.9%) in the ablation arm versus the control arm (6.7%).

CAAM TRIAL

The CAAM trial compared bag-mask ventilation versus endotracheal intubation in patients resuscitated for out-of-hospital cardiac arrest. There was a nonsignificant trend showing better results with intubation. Survival with a good neurologic outcome at 28 days was only 5%.

EMANATE STUDY

The EMANATE study randomized patients before elective cardioversion for atrial fibrillation to either apixaban or heparin/vitamin K antagonist anticoagulation. There were six strokes in the heparin/vitamin K antagonist arm and no strokes in the apixaban arm, showing that apixaban is safe for cardioversion.

REDUAL PCI TRIAL

The REDUAL PCI trial compared dual antithrombotic therapy (dabigatran + P2Y12 inhibitor) with triple antithrombotic therapy (warfarin + P2Y12 inhibitor + aspirin) in patients with atrial fibrillation undergoing PCI with stent implantation. The study showed that dual therapy was safer with less bleeding, including fewer intracranial hemorrhages (0.2% vs 1.0%) than triple therapy. There was no difference in the rate of ischemic stroke between the two groups.

IMPACT-AF TRIAL

The IMPACT-AF trial demonstrated that regular contact between the patient and the physician, including written information about atrial fibrillation and anticoagulation, decreased the risk of stroke by 48%.

LAACS STUDY

The small Danish study LAACS randomized patients undergoing open-heart surgery to either surgical closure of the left atrial appendage or no closure. The results are promising as the risk of stroke with surgical closure decreased from 7% to 2%.

THE ROLE OF CARDIOLOGISTS IN STROKE PREVENTION AND TREATMENT

In general, the stroke track at the 2017 ESC congress was extremely interesting; attendance was higher compared with the previous year. More cardiologists are realizing the impact that strokes have for their cardiac patients. The ESC Council on Stroke published its first position paper³ in the *European Heart Journal*, which provides an excellent basis for future developments in this field, maybe pointing to a new subspecialty of “neurocardiology.” ■

REFERENCES

1. Eikelboom JW, Connolly SJ, Bosch J, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017 Aug 27. Epub ahead of print.
2. Ridker PM, Everett BM, Thuren T, et al; CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017 Aug 27. Epub ahead of print.
3. Widimsky P, Doehner W, Diener HC, Van Gelder IC, Halliday A, Mazighion M; ESC Council on Stroke. The role of cardiologists in stroke prevention and treatment: position paper of the European Society of Cardiology Council on stroke. *Eur Heart J*. 2017 Aug 28. Epub ahead of print.

DIGITAL HEALTH COMES OF AGE

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, Dovehouse Street, London SW3 6LY, UK (email: m.cowie@imperial.ac.uk)

Keywords: Big Data; digital health; e-health; social media; telemonitoring

Digital health was a major focus of the 2017 ESC meeting held in Barcelona, Spain in August 2017, which was entirely appropriate, as not only are digital approaches to health and health care increasingly changing the way cardiologists work and interact with each other and their patients, but Barcelona is also one of the most digitally advanced cities in Europe.

DIGITAL INNOVATION

The ESC partnered with 4 Years From Now (4YFN), a program of Mobile World Capital Barcelona, to bring delegates the “Digital Health Area” – a space where delegates could view start-up technologies from key digital health pioneers. Mobile World Capital Barcelona is an initiative aiming to drive the mobile and digital transformation of society, while helping to improve people’s lives globally. Its mission can be summarized as Digital Empowerment, Digital Transformation, and Digital Innovation. The ESC was delighted to partner with 4YFN to showcase digital innovation to the delegates in Barcelona, such as atrial fibrillation diagnostic technologies (ranging from wearables to apps [smart phone-based applications]), internet-based health information depositories, new remote monitoring technologies, rehabilitation gaming systems, automatic echocardiogram reading software, and decision support technologies for doctors and patients.

I was delighted to announce the winner of the 2017 ESC digital technologies prize for an app that can be prescribed by a doctor to detect atrial fibrillation when you press your fingertip onto the camera of your smartphone for 60 seconds. The app sends the information to the prescribing doctor; it already has a European CE mark (Fibrichck™ from Belgium; www.fibrichck.com)

BIG DATA

The inaugural address at the congress was given by Eric Topol (US), where he highlighted the disruption that digital technologies are bringing to traditional medicine and health care systems. Everything is now “Big”: Big Data, Big Technology, Big Promise, but he emphasized the importance of maintaining the interpersonal skills required for good communication between physicians and their patients: “Big Empathy.” The role of doctors and other health care professionals in the future will be very different

from in the past, with us relying more on remotely collected information, artificial intelligence, and automated decision support for patients and physicians. Patients may only need to have face-to-face interactions when they require physical proximity to a cardiologist for a specific technical diagnostic or therapeutic intervention. Even traditional clinic-based face-to-face interactions will increasingly be done remotely using technologies, such as Skype™, Facetime™, etc. However, the need to understand patients’ values and anxieties and to provide reassurance and the “human touch” will mean a good doctor or nurse will still have plenty of interaction with their patients, either remotely or face-to-face.

The 2017 ESC meeting received a lot of news coverage, but, for the first time, there was massive coverage on social media. There were more than 274 million reactions to 44 309 tweets, covering not only the results of new trials, with links to the published papers, but also the opinions of those who were tweeting and retweeting. This has accelerated the collective understanding of new data from clinical trials, and highlighted what gets cardiologists interested (and what does not!). There are, of course, pitfalls to instant communication, and several sessions focused on the best use of social media for cardiologists.

Big Data for Dummies was a very popular session. Big Data, a large-scale integration and analysis of heterogeneous data sources, usually of high volume, velocity, and variety, was explained, and some examples of the new insights it can provide were showcased. The benefits of being able to link health data with lifestyle data seem obvious, provided concerns around data security are addressed. Undoubtedly, there will be more on this topic in future meetings: arguably, it is modern epidemiology at a lower cost and a faster speed, provided data quality is good.

SMARTPHONE APPLICATIONS FOR CARDIOLOGY

Most cardiologists will be aware of the smartphone-based single-lead ECG system Kardia™ (Alivecor™). A patient can record an ECG by pressing the device to their chest or by holding the device between their thumbs. This has allowed detection of atrial fibrillation at the patient’s convenience with very reasonable specificity and sensitivity. It was interesting to hear about two large studies using this device. At the Late-Breaking Registries session, Ngai-yin Chan (HK) showed that volunteers could be trained to use the Kardia™ device and work in community

centers to screen people who might never go to see a doctor. After screening more than 11 500 citizens in the AFinder Programme, 74 newly diagnosed cases of atrial fibrillation were identified (number needed to screen =145), but when this information was sent to the relevant general practitioner, few of them acted on this information, with only 17 participants starting an anticoagulant despite high CHA₂DS₂VASc scores. This shows that technology is only part of the answer, it has to be embedded in a pathway of care and the key stakeholders primed to act appropriately on the data collected.

Another study, the REHEARSE-AF study, was presented by Julian Halcox (UK) at one of the Late-Breaking Clinical Trials sessions.¹ In a randomized trial that compared the use of Kardia™ twice-weekly with usual care in 1000 patients, there was a 4-fold increase in the diagnosis of the arrhythmia. The downside was the cost of the devices and the staff time to deal with the data and the necessary actions, meaning that the cost per new diagnosis of atrial fibrillation was around €9000. Further trials, with streamlined data management, should help confirm the place of this new technology in strategies to reduce atrial fibrillation-related strokes.

The ESC produces guidelines on clinical topics that are extremely influential in clinical practice across many countries. Recently, the guidelines have been made available in a smartphone applicable format and the new ESC Pocket Guideline app can be downloaded from the App Store or Google Play. During an ESC TV session, Larissa Fabritz (UK) highlighted two new atrial fibrillation apps—one for patients (My AF) and one for physicians (AF Manager)—that were developed by the CATCH ME consortium, which brings together the expertise of leading academic institutes and professional societies (including the ESC) to improve the care of patients with atrial fibrillation. It has been funded by the European Union's Horizon 2020 research and innovation program. Both apps are available for download from the App Store and Google Play.

E-CARDIOLOGY

The working group on e-cardiology was extremely active during the congress; they organized many sessions and identified key speakers. They will be holding the 4th European Congress on e-Cardiology and e-Health in Berlin on November 8-10, 2017, where many of these topics will be covered in more detail (<http://www.e-cardiohealth.com>). The tagline for their conference is “connecting clinicians and technology to implement e-health in daily practice,” which is something that the 2017 ESC congress also did very effectively.

The ESC has published its e-health strategy,² identifying how important it is for the ESC and its members to get involved in discussions on the different domains of e-health: electronic health records; e-prescribing and e-appointments; decision support tools; internet-based technologies and services; telemedicine and telecare; and m-health. The board will be discussing this topic before the end of 2017, further strengthening the visibility of the ESC and its members in this blossoming field. Many companies, including the traditional pharmaceutical and device companies, are rapidly moving into e-health, and they are joined by information and communication technology companies, mobile operators, thousands of start-ups, in addition to the giants that are Google, Microsoft, Apple, and Amazon. The European Commission is targeting digital technologies in health care as an area in which to support research and development, particularly during the Estonian Presidency of the European Union – Estonia, like Catalonia, is a country at the forefront of the digital transformation in Europe.

CONCLUSION

At the 2017 ESC congress, it was difficult to miss digital technology, and, undoubtedly, future meetings of the society will emphasize how important this transformation is for cardiologists. Yes, there was some hype around the topic, but there was also much hope that this can lead to better care and cardiovascular health, delivered at greater convenience for the patient or citizen, and at a sustainable cost. ■

REFERENCES

1. Halcox JPI, Wareham K, Cardew A, et al. Assessment of remote heart rhythm sampling using the AliveCor heart monitor to screen for atrial fibrillation: the REHEARSE-AF study. *Circulation*. 2017 Aug 28. Epub ahead of print.
2. Cowie MR, Bax J, Bruining N, et al. e-health: a position statement of the European Society of Cardiology. *Eur Heart J*. 2016;37(1):63-66.

CARDIOTOXICITY IN CANCER TREATMENT: A CONGRESS REPORT FROM THE 2017 ESC CONGRESS

MARKUS S. ANKER^{1,2}; STEFAN D. ANKER², MD, PhD

Author affiliations: ¹Charité - Campus Benjamin Franklin (CBF), Department of Cardiology, Berlin, Germany

²Division of Cardiology and Metabolism - Heart Failure, Cachexia & Sarcopenia; Department of Internal Medicine & Cardiology; and Berlin-Brandenburg Center for Regenerative Therapies (BCRT), at Charité University Medicine, Berlin, Germany

Address for correspondence: Markus S. Anker, Charité - Campus Benjamin Franklin, Hindenburgdamm 30, 12200 Berlin, Germany (email: ankerms@aol.com)

Keywords: arterial blood pressure; cardiotoxicity; chemotherapy; heart failure

This article will focus on the latest clinical studies and basic science models that were discussed at this year's ESC congress. Two symposia were solely dedicated to cardio-oncology, focusing on the cardiotoxic effects of chemotherapy and on blood pressure management in cancer patients. A special emphasis was placed on the prevention of myocarditis under dual checkpoint inhibition, a rather new and successful treatment. This year's ESC congress provided a good forum for clinicians to share treatment strategies and promote the ongoing research in this rapidly growing field due to the high prevalence of cancer and cardiovascular disease.

CARDIOTOXICITY: MECHANISMS IN CANCER DRUG THERAPY

The 2017 ESC congress focused on how cancer drugs interact with the heart and thereby result in cardiovascular disease. Alexander Lyon (UK) highlighted two mechanisms that are now believed to cause anthracycline (doxorubicin)-induced cardiotoxicity. Zhang et al¹ showed that cardiac-specific topoisomerase II β knockout mice were protected against morphological and functional cardiotoxicity, suggesting that topoisomerase II β is crucial in developing doxorubicin-induced cardiotoxicity in cardiomyocytes. Ichikawa et al² demonstrated that there is a second independent mechanism. In mice after anthracycline treatment, doxorubicin accumulated in cardiomyocytes, thus inhibiting mitochondrial proteins, such as ABCB8, that are required for iron export from the mitochondria. Consequently, iron accumulates in the cardiac mitochondria causing an increase in intracellular reactive oxygen species and finally cardiomyocyte apoptosis. When ABCB8 was overexpressed in both in vitro and in vivo mice models, mitochondrial iron decreased and intracellular reactive oxygen species declined and thereby protected against doxorubicin-induced cardiomyopathy. When cardiomyocytes from patients with anthracycline-induced cardiomyopathy were examined, similar results were attained with markedly increased iron levels in cardiomyocytes when compared with biopsies from patients with other cardiomyopathies or healthy hearts. Therefore, there are now two independent models, which are probably both partly responsible for anthracycline-induced cardiotoxicity.

The effects of doxorubicin on the heart are dose dependent,³ whereas age, with a cut-off of 65 to 70 years, is an important risk factor for developing congestive heart failure. A study by Erin et al⁴ showed that, in 12 500 women with breast cancer, the 5-year incidence of heart failure significantly differed depending on the chemotherapy used. The 5-year heart failure incidence increased in patients receiving only trastuzumab (adjusted HR, 4.1; 95% CI, 2.3-7.4) or anthracyclines (adjusted HR vs patients without chemotherapy, 1.4; 95% CI, 1.1-1.8), and it was strongly elevated in patients receiving a combination of trastuzumab and anthracyclines (adjusted HR, 7.2; 95% CI, 5.0-10.4). These results show that there is a synergy in amplifying toxicity when cardiotoxic drug therapies are combined.

In addition to the underlying mechanisms of cardiovascular damage, Alexander Lyon also stated that underlying comorbidities have to be considered. Risk factors that were identified included diabetes, obesity, ischemic heart disease, and hypertension. Another already mentioned factor is age, showing a J-shaped association. Very young and elderly patients are likewise prone to develop cardiac damage. Using another mouse model, Duran et al⁵ tested how mice that were receiving treatment with or without sorafenib, a multikinase inhibitor, reacted to a myocardial infarction. In mice treated with sorafenib, due to cardiotoxic effects, the mortality after myocardial infarction increased. At the same time, their group showed that rodents treated with additional β -blockers in the same model had a lower mortality rate.

Very interesting new data, published by Johnson et al,⁶ concerning two cases of fulminant myocarditis after a combination immune checkpoint blockade was discussed. These treatments are used, for example, in melanoma patients, and they are associated with improved survival; however, until recently, there was only limited data on how often myocarditis occurred during or after such therapies. The authors noted that, until recently, immunotherapy trials did not routinely monitor for cardiac adverse effects with regular electrocardiograms and troponin level assessments. Currently, these cases of myocarditis are predominantly treated with high-dose glucocorticoids, but therapy guidelines are not available yet. Therefore, it is even more important to watch out for such side effects during or after immune checkpoint blockade.

OVERSEEING CARDIOTOXICITY

Another internationally renowned speaker in the ESC symposia, Daniela Cardinale (IT), discussed the management of cardiotoxicity. First, it is important to identify patients in collaboration with oncologists that are at an increased risk before the start of any treatment. All patients that are scheduled for potential cardiotoxic treatments need a baseline echocardiogram. If possible, cardiovascular risk factors should be clinically controlled or corrected, and, if cardiovascular disease is already present, the existing therapy should be optimized. Daniela Cardinale recommended starting a pharmacological primary prevention treatment in high-risk patients before the initiation of the cancer therapy.

During drug or radiation treatment for cancer, it is important to watch the patients closely. Preferably, biomarkers, such as troponin, and strain echo (if not available, left ventricular ejection fraction) should be used to identify and screen patients for worsening heart function. If pre-clinical or clinical signs of cardiotoxicity are identified, cardioprotective therapies should be implemented. In a study by Cardinale et al,⁷ 114 patients with increased troponin I levels after high-dose chemotherapy treatment were randomized to receive enalapril or placebo for 1 year. In the enalapril group, no patient had a decrease in the left ventricular ejection fraction that was more than 10%, whereas this was the case in 43% of the patients receiving placebo. Daniela Cardinale also presented the preliminary results from the ICOS-ONE trial,⁸ which evaluated primary vs secondary implementation of enalapril after troponin increase; both arms were associated with only small decreases in left ventricular ejection fraction.

Maria Lorenza (IT) and Thomas Suter (CH) discussed the significance of the early detection of arterial hypertension during cancer drug treatment. Hypertension is often associated with vascular endothelial growth factor inhibitor treatment (bevacizumab, sorafenib, sunitinib, etc). New hypertension or worsening blood pressure control is observed in 11% to 45% of patients.⁹ In 2% to 20% of cancer patients, severe hypertension is identified. Here, the current ESC position paper points out that the preferred drugs in such cases are β -blockers, ACE inhibitors or ARBs, and dihydropyridine calcium channel blockers. Adequate blood pressure management is important to ensure the continuation of vascular endothelial growth factor inhibitors.

After anticancer therapy is completed, cardiac function should be rigorously observed to identify patients with worsening parameters. Daniela Cardinale concluded that patients with even a small decrease in ejection fraction will most likely benefit from the initiation of a therapy consisting of ACE inhibitors and β -blockers. It is important to identify patients before the clinical signs of congestive heart failure appear. Once heart failure symptoms occur, it is much less likely to be reversed,¹⁰ and the adverse effects may be permanent.

CONCLUSION

This year's cardio-oncology symposia sessions during the ESC congress showed the importance of this still young, but growing field. The congress focused on the importance of recognizing cardiotoxicity as early as possible and on how to treat our patients in a real-world setting. The congress provided an excellent forum for basic scientists and clinicians to meet and exchange ideas on current studies in this rapidly growing field. ■

REFERENCES

1. Zhang S, Liu X, Bawa-Khalfe T, et al. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. *Nat Med*. 2012;18(11):1639-1642.
2. Ichikawa Y, Ghanefar M, Bayeva M, et al. Cardiotoxicity of doxorubicin is mediated through mitochondrial iron accumulation. *J Clin Invest*. 2014;124(2):617-630.
3. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer*. 2003;97(11):2869-2879.
4. Bowles EJ, Wellman R, Feigelson HS, et al. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. *J Natl Cancer Inst*. 2012;104(17):1293-1305.
5. Duran JM, Makarewich CA, Trapanese D, et al. Sorafenib cardiotoxicity increases mortality after myocardial infarction. *Circ Res*. 2014;114(11):1700-1712.
6. Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med*. 2016;375(18):1749-1755.
7. Cardinale D, Colombo A, Sandri MT, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation*. 2006;114(23):2474-2481.
8. Cardinale D. Managing cardiotoxicity: the "top ten" of practical advice. ESC congress 2017 (FP Nr. 918).
9. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines. *Eur Heart J*. 2016;37(36):2768-2801.
10. Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol*. 2010;55(3):213-220.

Late-breaking science



LATE-BREAKING UPDATES IN HEART FAILURE

MICHEL KOMAJDA, MD

Author affiliations: Department of Cardiology Hospital Saint Joseph, 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: adherence; diabetes; guidelines; heart failure; SGLT inhibitor

PHYSICIANS' ADHERENCE TO THE GUIDELINES IMPACTS CLINICAL OUTCOMES

Several studies suggest that prescribing the recommended heart failure therapies favorably influence short-term outcomes in chronic heart failure. QUALIFY, a large international registry, recently demonstrated that a physician's adherence to the guidelines was associated with a significant improvement in all-cause, cardiovascular, and heart failure mortality at 6 months, whereas there was a favorable trend for a reduction in heart failure hospitalizations.¹ This registry enrolled more than 7000 outpatients with chronic HFREF from 36 countries worldwide and the adherence score was based on the prescription of ACE inhibitors (or ARBs in case of intolerance to ACE inhibitors), β -blockers, MRAs, and ivabradine (if indicated), but it also took the dosage of these disease-modifying medications into consideration. A dosage of at least 50% of the target recommended dose was considered as an index of good adherence. The adherence score included three categories: good, intermediate, and poor; \approx 55% of this population was in the good adherence group.

In Barcelona, the longer-term 18-month follow-up data were presented by Michel Komajda (FR).² The results are consistent with the 6-month data and show that good adherence is associated with a lower rate of cardiovascular and heart failure mortality, which is in the range of 50%. A benefit is also observed on heart failure hospitalizations, which are \approx 20% lower in the good adherence group vs the intermediate and low adherence groups. These results emphasize the importance of implementing evidenced-based, guideline-recommended medications in chronic heart failure in order to reduce mortality and hospitalizations during the patient's heart failure journey. Several factors can influence a physician's adherence to the guidelines, including patient factors (frailty, comorbidity, intolerance), physician factors (lack of knowledge on the objectives of the treatment, reluctance to uptitrate medications, postdischarge inertia), and, of course, economic factors (access to health care and medications). However, the 18-month findings of QUALIFY should prompt doctors to implement guidelines not only in terms of classes of medications, but also in terms of dosage, and efforts should be made to reach the highest tolerated dose of heart failure medications.

MANAGEMENT OF ATRIAL FIBRILLATION IN PATIENTS WITH HEART FAILURE

The debate between rate control and rhythm control in patients with heart failure and atrial fibrillation was clarified a few years ago when the atrial fibrillation in congestive heart failure trial compared the two strategies and showed that there was no benefit on mortality and an increase in hospitalizations due to repeated cardioversion in the rhythm control arm. These results led to the conclusion that rate control was appropriate and that trying, by any means, to keep patients with heart failure in sinus rhythm did not bring any significant clinical benefits.

In this context, the CASTLE-AF trial presented by Nassir Marrouche (US) compared two strategies—conventional therapy (n=179) vs ablation (n=165)—in patients with HFREF (NYHA II or more) and already implanted with a defibrillator or cardiac resynchronization therapy with home monitoring capabilities.³ These patients had symptomatic paroxysmal or persistent atrial fibrillation and had received at least one antiarrhythmic drug that had either failed or was poorly tolerated. The atrial burden during the course of the trial was significantly lower in the ablation group. There was also a highly significant relative risk reduction of 38% for the primary composite end point (all-cause mortality or heart failure hospitalizations), 47% for all-cause mortality, and 51% for cardiovascular mortality in the group treated with ablation after a 5-year follow-up. Although the population enrolled in this trial was of a limited size and there were some crossovers, these findings suggest that aggressive treatment of atrial fibrillation by early ablation in patients with HFREF is beneficial on clinical outcomes, and a larger trial comparing these two strategies in patients with HFREF should be considered.

PREVENTION OF HEART FAILURE IN DIABETES MELLITUS

Diabetes mellitus is associated with a high risk of heart failure, and meta-analyses suggest that the risk of developing heart failure is increased by 20% for each point increase in HbA_{1c}. An unexpected finding of the EMPA-REG OUTCOME trial, which was conducted in patients with type 2 diabetes and a high cardiovascular risk, was the

highly significant 38% reduction in the risk of heart failure hospitalizations in patients treated with the SGLT2 inhibitor empagliflozin. These favorable results have recently been confirmed with canagliflozin, another SGLT2 inhibitor, in the CANVAS trial, a large outcome trial that also enrolled patients with type 2 diabetes and a high cardiovascular risk. These findings generated several hypotheses to explain the benefit, including the role of reduced blood pressure, arterial stiffness, body weight, sodium depletion, reduction in oxidative stress, or a more efficient cardiac metabolism. David Fitchett (CA)⁴ presented a subanalysis of the EMPA-REG OUTCOME trial in which the outcome data were adjusted for control of blood pressure, LDL cholesterol, and HbA_{1c}. After adjustment, the observed reduction in heart failure hospitalizations was similar to that observed in the primary analysis (39% relative risk reduction), suggesting that other mechanisms are involved.

In an experimental mouse model of heart failure induced by doxorubicin (selected as a “best poster”), Jolanda Sabatino (IT) showed that exposure to empagliflozin protected the animals against this well-known complication of doxorubicin therapy, suggesting a direct myocardial effect of the drug.⁵

Additional studies are needed to elucidate the mechanism by which SGLT2 inhibitors protect patients with diabetes from developing heart failure. These mechanistic studies are even more important because several large outcome trials are going to test the potential of SGLT inhibitors in patients with heart failure (both reduced and preserved) with or without diabetes mellitus. ■

REFERENCES

1. Komajda M, Cowie MR, Tavazzi L, et al. Physicians' guideline adherence is associated with better prognosis in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. *Eur J Heart Fail*. 2017 Apr 30. Epub ahead of print.
2. Komajda M. Physicians guideline adherence is associated with better long-term in outpatients with heart failure with reduced ejection fraction (HFrEF): the prospective international QUALIFY registry. Late-Breaking ESC registry Results, ESC 2017 (FP 1060).
3. Marrouche N. Catheter ablation versus standard conventional treatment in patients with left ventricular dysfunction and atrial fibrillation: the CASTLE-AF trial. Late-Breaking Clinical Trials 1, ESC 2017 (FP 1148).
4. Fitchett D, McKnight J, Lee J, et al. Empagliflozin reduces heart failure irrespective of control of blood pressure, low density lipoprotein cholesterol and HbA_{1c}. Moderated posters, ESC 2017 (FP4903).
5. Sabatino J, Yasuda M, De Rosa S, et al. Empagliflozin reduces the doxorubicine-induced myocardial dysfunction. Best Posters, ESC 2017 (FP 4230).

LATE-BREAKING SCIENCE IN IMAGING

VICTORIA DELGADO, MD, PhD

Author affiliations: Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

Address for correspondence: Victoria Delgado, Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands (email: v.delgado@lumc.nl)

Keywords: abdominal aortic aneurysm; cardiovascular magnetic resonance; computed tomography; coronary artery disease; myocardial scar; speckle-tracking echocardiography

At the 2017 ESC congress, several late-breaking trials on cardiovascular imaging were presented, including, but not limited to, the PROMISE trial, the ICONIC study, the BSCMR Valve Consortium multicenter registry, and the Akershus Cardiac Examination 1950 study. This article will review the results of some of the late-breaking trials presented during the congress.

COMPUTED TOMOGRAPHY FOR CORONARY ARTERY DISEASE

Several trials focused on the use of computed tomography to evaluate patients with suspected coronary artery disease.^{1,2} A substudy from the PROMISE trial compared CAC testing with functional testing to predict the occurrence of all-cause mortality, myocardial infarction, or hospitalization for unstable angina.³ Patients with stable chest pain and an intermediate pretest probability for obstructive coronary artery disease were randomized to an anatomic evaluation (including CAC testing and coronary computed tomography angiography) or functional testing (exercise electrocardiogram, stress echocardiography, or myocardial perfusion scintigraphy). A total of 4209 patients underwent CAC testing as part of the anatomic evaluation, whereas 4602 patients underwent functional testing. A normal functional testing was reported in 78% of the patients, whereas mildly, moderately, and severely abnormal test results were observed in 9.4%, 4.7%, and 7.9%, respectively. In contrast, the CAC scores were normal in only 34.6% of patients, and 31.8%, 18.3%, and 15.2% of patients presented with mildly, moderately, and severely abnormal CAC scores. These results confirm previous results, indicating that the CAC score is a mere marker of atherosclerosis burden, but it does not provide information on the presence of flow-limiting coronary artery stenosis.

During a median follow-up of 26 months, 131 patients in the anatomic evaluation arm presented with an event (all-cause mortality, myocardial infarction, or hospitalization for unstable angina) compared with 132 in the functional testing arm. Interestingly, in the anatomic evaluation arm, 84% of the events occurred in patients with any positive CAC score (CAC >0), whereas 43% of the events occurred in patients with any abnormal functional test. Therefore, abnormal functional tests were more specific than CAC scores to predict an event during follow-up (78.6% vs 43%; $P < 0.001$). The discriminatory ability

of both the CAC score and abnormal functional testing for predicting the occurrence of an event was modest (0.59 vs 0.60, respectively).

David Newby put these findings into clinical perspective in his editorial in *Circulation* where the strengths of each test are highlighted, which may help make the selection of a diagnostic test clearer.³ For low-risk individuals in whom we want to rule out coronary artery disease to avoid unnecessary treatments and further testing, CAC testing would seem appropriate; however, for high-risk patients who may benefit from revascularization, functional testing would be better.

In contrast to CAC testing, coronary computed tomography angiography enables a quantitative evaluation of atherosclerotic plaque characteristics in stable patients with suspected coronary artery disease. The ICONIC registry included 26 123 consecutive patients without known coronary artery disease who underwent coronary computed tomography angiography and a subsequent 3.2-year follow-up to look for the occurrence of acute coronary syndromes. Based on this registry, the ICONIC study, a nested case-controlled study, was performed.² A total of 234 patients who presented during follow-up with an acute coronary syndrome were matched with 234 patients without an acute coronary syndrome by a propensity score accounting for age, sex, coronary artery disease risk factors, and angiographic coronary artery disease and severity. A quantitative analysis of the atherosclerotic plaques for all coronary arteries and their branches was performed, including the angiographic stenosis and plaque volume by composition (calcified, fibrous, fibrofatty, and necrotic core).

During the follow-up period, 234 acute coronary syndromes were recorded, and the mean percentage of coronary artery stenosis was <50% in all patients (44% in patients with acute coronary syndromes vs 34% in patients without; $P < 0.001$). Among patients with acute coronary syndromes, 78% had no coronary stenosis (defined as stenosis >70%) and 48% had no stenosis (defined as >50%). Interestingly, patients with acute coronary syndromes showed greater fibrofatty and necrotic core plaque volume than did patients without an acute coronary syndrome. Fibrofatty and necrotic core plaque volumes were independently associated with the occurrence of acute coronary syndromes after correcting for the percentage of coronary stenosis. However, total or calcified plaque volumes were not associated with the

occurrence of acute coronary syndromes. These results suggest that fibrofatty and necrotic core plaque volumes are precursors of acute coronary syndromes, and they can be assessed for the early identification of patients at risk before the coronary artery stenosis is >70%.

BSCMR VALVE CONSORTIUM

In the field of cardiovascular magnetic resonance, the BSCMR Valve Consortium presented the results of a multicenter registry on the prognostic implications of myocardial scar assessed with LGE CMR in patients with severe aortic stenosis.⁴ A total of 703 patients (mean age, 73 years; 63% male) with severe aortic stenosis who underwent echocardiography and LGE CMR as part of a workup for aortic valve replacement were recruited in 6 cardiothoracic centers in the UK. Myocardial scar on LGE CMR was classified as either infarct pattern (when the scar followed the distribution of the coronary artery supply) or non-infarct pattern.

Myocardial scar was present in 51% of patients (17% with an infarct pattern; 34% with a non-infarct pattern). During a median follow-up of 3.6 years, 24% died after aortic valve replacement. Every 1% increase in left ventricular myocardial scar was independently associated with an increase in all-cause mortality (HR, 1.10; 95% CI, 1.04-1.16; $P<0.001$) and cardiovascular mortality (HR, 1.09; 95% CI, 1.01-1.17; $P=0.029$). Myocardial scar was independently associated with all-cause mortality independent from the type of intervention (transcatheter or surgical aortic valve replacement) and type of scar (infarct or non-infarct pattern).

Currently, in patients with symptomatic severe aortic stenosis, LGE CMR will not have an impact on the indication of aortic valve replacement. However, in asymptomatic patients with severe aortic stenosis, LGE CMR may help identify the patients who will benefit from an early intervention. Additional studies are needed to demonstrate that, in asymptomatic severe aortic stenosis, the presence of left ventricular myocardial scar is associated with worse prognosis if medically treated.

EARLY DETECTION OF AN ABDOMINAL AORTIC ANEURYSM

The use of ^{18}F -NaF positron emission tomography (PET)-computed tomography can help in the early detection of patients with an abdominal aortic aneurysm who may be at risk of rupture.⁵ Previous studies have demonstrated that ^{18}F -NaF binds to areas of microcalcification, and, in patients with carotid and coronary atherosclerosis, the uptake of ^{18}F -NaF correlates with necrotic core inflammation and plaque rupture. Forsythe et al compared the uptake of ^{18}F -NaF in normal and aneurysmal aortae between 20 control volunteers and 20 patients

with an abdominal aortic aneurysm; the subjects were prospectively followed-up to look for the occurrence of the composite end point of aortic aneurysm repair or rupture.⁵ Patients with an abdominal aortic aneurysm compared with controls had a higher uptake of ^{18}F -NaF within the aneurysm and within the nonaneurysmal regions of the abdominal aorta, indicating that there is higher inflammatory and microcalcification activity. During the mean follow-up of 510 days, 19 patients underwent aortic aneurysm repair and 3 patients presented with an aneurysm rupture. When dividing the patients according to the tertile of ^{18}F -NaF uptake, patients within the highest tertile showed 2.5 times the growth rate of the aneurysm than did patients within the lowest tertile. This study demonstrated, for the first time, that ^{18}F -NaF uptake was associated with an increased risk of abdominal aortic aneurysm repair or rupture after correcting for age, sex, blood pressure, body mass index, and aneurysm diameter.

MEASURING MYOCARDIAL PERFORMANCE

Finally, speckle-tracking echocardiography is an advanced technique that enables the quantification of myocardial shortening and thickening as a measure of myocardial performance. Left ventricular global longitudinal strain is a measure of left ventricular systolic function. This measurement has demonstrated superior prognostic value compared with left ventricular ejection fraction.⁶ Based on the standard deviation of time to peak longitudinal strain of 16-17 segments of the left ventricle, the mechanical dispersion of the left ventricle can be calculated. A prolonged left ventricular mechanical dispersion has been associated with all-cause mortality and ventricular arrhythmias in patients with heart failure and ischemic heart disease.^{7,8} However, little is known about the value in the general population.

The Akershus Cardiac Examination 1950 study, which included 3706 men and women born in 1950, provided further insight into the distribution of left ventricular mechanical values in the general population.⁹ The assessment of left ventricular mechanical dispersion with speckle-tracking echocardiography was feasible in 2525 individuals. The median left ventricular mechanical dispersion was 38 ms. Patients with a left ventricular mechanical dispersion >38 ms had more cardiovascular risk factors, coronary artery disease, renal dysfunction, obesity, and diabetes. This study provides information on the associations with increased left ventricular mechanical dispersion. However, the prognostic implications of these findings need further evaluation. ■

REFERENCES

1. Budoff MJ, Mayrhofer T, Ferencik M, et al; PROMISE Investigators. The prognostic value of coronary artery calcium in the PROMISE study. *Circulation*. 2017 Aug 28. Epub ahead of print.
2. Min JK. Coronary atherosclerotic precursors of acute coronary syndromes: results from the ICONIC (Incident COroNary Syndromes Identified by Computed Tomography). ESC 2017 (3146).
3. Newby DE. Computed tomography or functional stress testing for the prediction of risk: can I have my cake and eat it? *Circulation*. 2017 Aug 28. Epub ahead of print.
4. Treibel TA. Myocardial scar predicts mortality in severe aortic stenosis: data from the BSCMR Valve Consortium. ESC 2017 (3144).
5. Forsythe RO, Dweck MR, Vesey AT, et al. 18F-Sodium fluoride is a novel independent predictor of abdominal aortic aneurysm growth and clinical outcome. ESC 2017 (4148).
6. Kalam K, Otahal P, Marwick TH. Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. *Heart*. 2014;100(21):1673-1680.
7. Ersbøll M, Valeur N, Andersen MJ, et al. Early echocardiographic deformation analysis for the prediction of sudden cardiac death and life-threatening arrhythmias after myocardial infarction. *JACC Cardiovasc Imaging*. 2013;6(8):851-860.
8. Van Der Bijl P, Khidir M, Leung M, et al. Left ventricular mechanical dispersion after cardiac resynchronisation therapy: prognostic implications. ESC 2017 (103).
9. Aagaard EN, Kvisvik B, Pervez MO, et al Left ventricular mechanical dispersion, a novel marker for ventricular arrhythmic events, is increased in conditions with enhanced risk for cardiovascular disease. Data from the ACE 1950 study. ESC 2017 (P1441).

ESC REGISTRY RESULTS

ALDO P. MAGGIONI, MD, FESC, FHFA

Author affiliations: ANMCO Research Center, Florence, Italy

Address for correspondence: Aldo P. Maggioni, ANMCO Research Center, Via La Marmora 34, 50121 Florence, Italy (email: maggioni@anmco.it)

Keywords: atrial fibrillation; cardiomyopathy; chronic ischemic cardiovascular disease; observational research; oral anticoagulant

Each year during the ESC congress, the evidence provided by the registries of the EurObservational Research Program are presented. This tradition continued this year in Barcelona with the presentation of the results from three registries: (i) the 6-month follow-up of the Chronic Ischemic Cardiovascular Disease pilot registry; (ii) the baseline characteristics of patients enrolled in the cardiomyopathy registry; and (iii) the contemporary stroke prevention strategies adopted in the patients enrolled in the Atrial Fibrillation General Long-Term registry, together with a comparison of the management of atrial fibrillation between the recent Atrial Fibrillation General Long-Term registry and the Euro Heart Survey on Atrial Fibrillation that was conducted more than 10 years ago.

CHRONIC ISCHEMIC CARDIOVASCULAR DISEASE PILOT REGISTRY: THE 6-MONTH FOLLOW-UP RESULTS

The purpose of the Chronic Ischemic Cardiovascular Disease registry¹ was to collect contemporary data on the clinical epidemiology of the enrolled patients across ESC member countries. The 6-month follow-up and the clinical outcomes of this registry were reported by Michel Komajda (FR), chairman of the registry. The pilot survey was conducted in 100 centers in 10 ESC countries. Patients were stratified into the following cohorts: (i) patients with chronic coronary artery disease and non-ST-segment elevation acute coronary syndrome undergoing a percutaneous coronary intervention (cohort 1); (ii) patients with chronic stable coronary artery disease undergoing an elective coronary intervention (cohort 2); (iii) patients with stable coronary artery disease enrolled in general hospitals or clinics without interventional and cardiovascular surgery facilities (cohort 3); and (iv) patients with peripheral artery disease interventions (cohort 4).

The results from this registry show that the rate of prescription of ACE inhibitors or ARBs, β -blockers, and aspirin declined from baseline to 6 months, while no reduction in the prescription of statins was observed, which was attributed mainly to the suboptimal cooperation between in-hospital and territory health care professionals, the cost of medications, and access to health care in some participating countries. During this 6-month follow-up, there was a high rate of clinical events, where 2.6% of the patients died from any cause, nearly 25% either died

or were rehospitalized, confirming that these patients had a very high cardiovascular risk and that they should be more carefully followed. Important variations were observed in the event rates across the four cohorts of patients and across geographic regions, as the events occurred more frequently in cohorts 1 and 4 than in cohorts 2 and 3. Further, events were almost twice as frequent in the Western region than in the Southern countries. The authors also showed that, after a multivariable analysis, six independent clinical factors were predictive of the primary outcome (all-cause death or all-cause rehospitalizations): age, region, heart rate, previous peripheral revascularization, chronic kidney disease, and chronic obstructive pulmonary disease.

In conclusion, this contemporary European registry of patients with chronic ischemic cardiovascular disease showed that the rate of clinical events at 6 months is high, variable across regions, and influenced by age and comorbidities. The medical management of this condition is suboptimal. These observations confirm the data obtained from another large registry conducted in this clinical field.²

CARDIOMYOPATHY REGISTRY

Philippe Charron (FR) presented data from an adult population with a cardiomyopathy, combining pilot and long-term registry phases.³ Patients with one of four major cardiomyopathy subtypes, including hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and restrictive cardiomyopathy, were eligible for the study. Familial/genetic forms and non-familial/non-genetic forms were included. Sixty-nine centers from 18 countries participated in the study and included 3208 patients. The most common diagnosis was hypertrophic cardiomyopathy (54.2%), followed by dilated cardiomyopathy (39.3%), arrhythmogenic right ventricular cardiomyopathy (4.4%), and restrictive cardiomyopathy (2.1%). A history of familial disease was observed in 38.9% of the total population, with significant differences according to the cardiomyopathy subtype: the rate was higher for hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy (48.5% and 40.6%, respectively), and it was lower for restrictive cardiomyopathy and dilated cardiomyopathy (30.0% and 25.2%, respectively).

All cardiomyopathies increased the odds of life-threatening arrhythmias, as ventricular arrhythmias or implantable cardioverter defibrillator implantation were most frequently reported in arrhythmogenic right ventricular cardiomyopathy, while atrial fibrillation was the dominant rhythm issue in restrictive cardiomyopathy. The study also showed the different frequencies of diagnostic and therapeutic approaches adopted in the participating centers/countries.

The authors concluded that the registry provided a unique picture of the contemporary management of adult patients with cardiomyopathy. The results emphasize the complexity of the services and expertise required for the management of patients with a cardiomyopathy, suggesting the need for dedicated, expert, multidisciplinary teams.

ATRIAL FIBRILLATION GENERAL LONG-TERM REGISTRY

Following the publication of the data from the pilot study,⁴ Giuseppe Boriani (IT), chairman of the Atrial Fibrillation General Long-Term registry, presented contemporary data regarding atrial fibrillation management and the current use of oral anticoagulants for stroke prevention. From October 2013 to September 2016, 11 096 patients with a median age of 71 years were enrolled in 250 centers from 27 participating ESC countries. Patients with permanent atrial fibrillation had the highest thromboembolic risk and bleeding risk compared with patients with other atrial fibrillation subtypes.

In most patients (84.9%), an oral anticoagulant was used, which was less likely to be prescribed in patients with paroxysmal atrial fibrillation and newly detected atrial fibrillation. Antiplatelet drugs were prescribed in 20.0% of the patients, with the majority receiving aspirin, mostly in patients with newly detected atrial fibrillation or paroxysmal atrial fibrillation. Of the patients on oral anticoagulants, half were treated with a vitamin K

antagonist, especially those with permanent atrial fibrillation. Conversely, a novel oral anticoagulant was used in 34.8% of patients, mostly for newly detected and persistent atrial fibrillation. Among patients treated with an oral anticoagulant, a small proportion was treated with concomitant antiplatelet drugs (14.5%), mostly in patients with newly detected atrial fibrillation. The authors showed that the patients prescribed an oral anticoagulant were older and had more prevalent cardiovascular risk factors (such as diabetes mellitus or lipid disorders), hypertension, and previous thromboembolic events and stroke. Conversely, those patients not prescribed oral anticoagulants were more likely to be affected by coronary artery disease, peripheral vascular disease, and chronic kidney disease. The patients prescribed novel oral anticoagulants were younger with fewer risk factors and comorbidities than were patients who were prescribed a vitamin K antagonist. This study also highlighted a large variability in the use of novel oral anticoagulants across the European regions, probably due to the heterogeneity in the health care systems and differences in affordability, prices, and compensations.

During the 2017 ESC congress, a comparison between the current data from the Atrial Fibrillation General Long-Term registry and the old Euro Heart Survey on Atrial Fibrillation,⁵ which was conducted more than 10 years ago, was presented. The authors found that the proportion of elderly patients significantly increased over time and that patients enrolled in the Atrial Fibrillation General Long-Term registry had a higher prevalence of cardiovascular comorbidities (ie, previous myocardial infarction, chronic heart failure, cardiomyopathy, peripheral artery disease). The clinical management of patients with atrial fibrillation was mostly unchanged for 10 years, with a significant increase only seen with catheter ablation therapy. The overall thromboembolic risk was increased compared with 10 years ago, with a marked increase in the use of oral anticoagulants. Finally, there was a significant decrease in the rates of both thromboembolic events and major cardiovascular events, but a significant increase in all-cause and cardiovascular mortality. ■

REFERENCES

1. Komajda M, Weidinger F, Kerneis M, et al. EURObservational Research Programme: the Chronic Ischaemic Cardiovascular Disease Registry: pilot phase (CICD-PILOT). *Eur Heart J*. 2016;37:152-160.
2. Steg PG, Bhatt DL, Wilson PW, et al; REACH Registry Investigators. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA*. 2007;297:1197-1206.
3. Elliott P, Charron P, Blanes JR, et al; EORP Cardiomyopathy Registry Pilot Investigators. European cardiomyopathy pilot registry: EURObservational Research Programme of the European Society of Cardiology. *Eur Heart J*. 2016;37(2):164-173.
4. Lip GY, Laroche C, Dan GA, et al. A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. *Europace*. 2014;16:308-319.
5. Nieuwlaat R, Capucci A, Camm AJ, et al. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J*. 2005;26:2422-2434.

Hotlines



REGISTRY HOTLINES

NICOLAS DANCHIN, MD

Author affiliations: Hôpital européen Georges-Pompidou and Université Paris Descartes, Paris, France

Address for correspondence: Nicolas Danchin, Département de Cardiologie, Hôpital européen Georges-Pompidou, 20 rue Leblanc, 75015 Paris, France (email: nicolasdanchin@yahoo.fr)

Keywords: acute myocardial infarction; epidemiology; lifestyle; nutrition; registry

Besides randomized trials, registries now constitute a well-recognized source of information, often filling the gaps left by clinical trials. Recently, registries have also been used to implement randomized trials that are closer to “real-world” situations. Several important studies were presented at the 2017 ESC congress in Barcelona.

ACUTE MYOCARDIAL INFARCTION

Trends in STEMI characteristics, management, and outcomes in the SWEDEHEART registry from 1995 to 2014

The SWEDEHEART registry represents a common effort of all Swedish institutions, which collect data on all patients admitted for acute myocardial infarction; the data from the index hospitalizations are then cross-linked with the Swedish hospitalization database and municipal registers to ensure adequate follow-up.¹ Data collection began in the 1990s, and, since the early 2000s, all Swedish institutions now participate. More than 105 000 patients with STEMI were included in the current analysis. Over this 20-year period, the median age decreased from 71 years to 69 years; fewer patients had a history of acute myocardial infarction before the index episode, while more patients had a history of PCI; fewer patients had a history of congestive heart failure (20.5% in 1995 vs 15% in 2014); reperfusion therapy increased from 66% to 82%, with a concomitant increase in the use of primary PCI (4.5% to 78%) and a decrease in intravenous fibrinolytic treatment (62% to 4%); secondary prevention medication also increased considerably: dual antiplatelet therapy from 0% to 90%, statins from 14% to 94%, β -blockers from 78% to 91%, and ACE inhibitors or ARBs from 41% to 85%. The 1-year mortality decreased from 20% to 14%. Improvement in survival over the 20-year period was no longer significant when adjusted for changes in initial management, suggesting that most, if not all, of the improvements in outcomes were related to the changes in the initial management of the patients. Interestingly, however, there has been no further improvement in early and 1-year mortality since 2005; 1-year death was 14.6% in 2005, 13.7% in 2009, and 14.1% in 2013-2014.

Trends in STEMI and NSTEMI characteristics, management, and outcomes in the FAST-MI program from 1995 to 2015

The French FAST-MI program consists of 1-month nationwide surveys implemented every 5 years in all French

institutions wishing to participate (approximately 75% of all institutions taking care of patients with acute myocardial infarction in France).² The snapshot methodology of the study allows the collection of a considerable number of items, and therefore, the characterization of the population is extremely detailed. The five surveys from 1995 to 2015 included over 14 000 patients.

In patients with STEMI, the mean age decreased from 66 to 63 years, with similar trends to those in the SWEDEHEART registry regarding previous history of acute myocardial infarction, PCI, and heart failure. Reperfusion therapy increased from 49% to 82%, with an increase in primary PCI from 12% to 76%. Antiplatelet therapy, statins, β -blockers, and ACE inhibitors or ARBs increased considerably from 1995 to 2010, but slightly decreased in 2015 compared with 2010. The 6-month mortality decreased from 17.2% in 1995 to 5.3% in 2015, reflecting a continuous trend from one survey to another. Standardized mortality (ie, mortality in the initial surveys if the populations had the same baseline characteristics as the 2015 population) showed concordant figures (a decrease from 15.4% to 5.3%).

In patients with NSTEMI, the mean age remained stable (68 years), the history of heart failure before the index episode also decreased markedly, and the use of early PCI (≤ 72 hours from admission) increased from 9% to 60%. In addition, the recommended secondary prevention medications from the early stage to discharge showed the same pattern as the patients with STEMI: a regular increase from 1995 to 2010, followed by a slight decrease in 2015. The 6-month mortality decreased from 17.2% to 6.3%. Contrary to the patients with STEMI, the mortality stabilized in patients with NSTEMI after 2010, with standardized mortality rates of 6.2% in 2010 and 6.3% in 2015.

Overall, the results of SWEDEHEART and FAST-MI appear encouraging: the implementation of recommended strategies was associated with improved outcomes and reduced mortality. In Sweden, however, no further improvement in survival in patients with STEMI has been observed for the last 8 years, while, in France, mortality had continued to decline until 2015; in contrast, NSTEMI mortality has remained stable since 2010. In the French registries, a worrying trend (slight decrease) in the use of recommended medications has been noted since 2010; also, the increasing proportion of young women among the STEMI population (among women with STEMI, 13.7% were ≤ 60 years in 1995 vs 29.4% in 2015) should deserve specific attention.

Impact of pretreatment with P2Y12 inhibitors in patients with STEMI: the SCAAR registry

The optimal timing of P2Y12 administration in patients with STEMI undergoing primary PCI is a subject of debate. From a population of nearly 45 000 patients with primary PCI included in SCAAR, 84% received P2Y12 inhibitors before coronary angiography (pretreatment). The 30-day mortality was 5.2% in patients receiving pretreatment vs 7.6% in those not pretreated. However, after adjustment for differences in the baseline characteristics, pretreatment was no longer associated with lower mortality (OR, 1.07; 95% CI, 0.94-1.22). There was also no difference in stent thrombosis. Propensity score matching yielded similar results. Overall, these results from a large cohort of patients suggest that outcomes are similar in patients with STEMI when P2Y12 inhibitors are administered in the catheterization laboratory or before.

CARDIOVASCULAR DISEASE PREVENTION: LIFESTYLE, MORTALITY, AND CARDIOVASCULAR EVENTS

PURE study: association of fruit, vegetable, and legume consumption with cardiovascular disease and death

The PURE study included 135 335 people from 18 countries, aged 35 to 70 years, and without known cardiovascular disease at baseline.³ Validated food questionnaires were used and the median follow-up was 7.4 years. Mortality was associated with total fruit, vegetable, and legume intake; compared with <1 serving/day, the risk of mortality decreased by approximately 20% in people with ≥3 servings per day, with little difference from 3 servings (HR, 0.78; 95% CI, 0.69-0.88) to >8 servings (HR, 0.81; 95% CI, 0.68-0.96). There was, however, no significant association with the risk of major cardiovascular disease. Fruit was associated with a lower risk of death, but it had no

definite association with major cardiovascular disease or myocardial infarction. Vegetable consumption was associated with a borderline reduction in mortality, but not with cardiovascular disease or myocardial infarction; cooked vegetables were not associated with lower risks, while raw vegetables (>2 servings per day) were associated with a reduction in mortality and a borderline reduction in major cardiovascular disease. Legume intake was associated with a reduction in mortality and a borderline effect on stroke in people consuming 1 to 12 servings per month.

PURE study: association of fat and carbohydrate consumption with cardiovascular disease and death

Using the same population described above, the association between fat and carbohydrate consumption was investigated.⁴ High carbohydrate consumption was associated with an increased risk of mortality (quintile 5 vs quintile 1; HR, 1.28; 95% CI, 1.12-1.46), but not with the risk of cardiovascular mortality or major cardiovascular disease. Higher fat consumption was associated with a lower risk of mortality (quintile 5 vs quintile 1; HR, 0.77; 95% CI, 0.67-0.87); there was little difference regarding the type of fat, although polyunsaturated fat had a lower HR (0.80) than saturated fat (HR, 0.86). Fat and fat types were not associated with cardiovascular mortality or the risk of myocardial infarction, while a high intake of saturated fat was associated with a borderline reduction in the risk of stroke.

These results from a large cohort of adults recruited from different regions of the world, including developing countries, document an association between nutritional habits and mortality. Somewhat surprisingly, the association between food intake and cardiovascular disease and cardiovascular mortality is virtually nonexistent. These findings emphasize the difficulty of documenting the impact of lifestyle on health, particularly cardiovascular health. The results of epidemiologic studies in this field should probably be taken with a pinch of salt. ■

REFERENCES

1. Szummer K, Erlinge D, Wallentin L, et al. Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: experiences from the SWEDEHEART registry 1995-2014. *Eur Heart J*. 2017 Aug 29. Epub ahead of print.
2. Puymirat E, Simon T, Cayla G, et al; USIK, USIC 2000, and FAST-MI Investigators. Acute myocardial infarction: changes in patient characteristics, management, and 6-month outcomes over a period of 20 years in the FAST-MI program (French registry of acute ST-elevation or non-ST-elevation myocardial infarction) 1995 to 2015. *Circulation*. 2017 Aug 27. Epub ahead of print.
3. Miller V, Mente A, Dehghan M, et al; PURE Study Investigators. Fruit, vegetable, and legume intake, and cardiovascular disease and deaths in 18 countries (PURE): a prospective cohort study. *Lancet*. 2017 Aug 28. Epub ahead of print.
4. Dehghan M, Mente A, Zhang X, et al; PURE Study Investigators. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. *Lancet*. 2017 Aug 28. Epub ahead of print.

LATE-BREAKING TRIALS: ATRIAL FIBRILLATION

REZA WAKILI¹, MD; DOBROMIR DOBREV², MD

Authors affiliations: ¹Department of Cardiology and Vascular Medicine, West-German Heart and Vascular Center Essen, University of Essen Medical School, University Duisburg-Essen, Essen, Germany

²Institute for Pharmacology, West German Heart and Vascular Center, University Duisburg-Essen, Essen, Germany

Address for correspondence: Dobromir Dobrev, MD, Hufelandstr. 55, 45122 Essen, Germany (email: dobromir.dobrev@uk-essen.de)

Keywords: ablation; anticoagulation; atrial fibrillation; therapy

FOCUS ON ANTICOAGULATION

RE-DUAL PCI trial

The dilemma of finding the best antithrombotic regimen in patients with AF undergoing a PCI is still under debate and investigation. On one hand, oral anticoagulation is needed to prevent a stroke, but, on the other hand, dual antiplatelet therapy is required to prevent stent thrombosis. Nevertheless, so-called triple therapy bears a very high risk of bleeding. The RE-DUAL PCI trial,¹ presented by Christopher Cannon (US), addressed the use of dabigatran (110 mg or 150 mg bid), a non-VKA oral anticoagulant, vs a VKA; and the omission of acetylsalicylic acid from the guideline-recommended triple antithrombotic regimen (ie, a VKA, a P2Y12 inhibitor, and acetylsalicylic acid). The primary end point included major bleeding events and bleeding events requiring medical attention. The trial design consisted of three groups: (i) dabigatran 150 mg + P2Y12 inhibitor; (ii) dabigatran 110 mg + P2Y12 inhibitor; and (iii) control. Both experimental arms, dabigatran 110 and dabigatran 150, were superior in reducing bleeding events. In addition, this is the first triple therapy trial to date to show a benefit on the secondary end point of major bleeding (both experimental arms). This trial provides important insights for guiding therapy of patients with AF undergoing a PCI.

EMANATE trial

In the EMANATE trial, anticoagulation-naïve patients with AF (<48 hours of parenteral and/or oral anticoagulation) indicated for cardioversion were prospectively randomized to either the apixaban arm or the heparin/VKA arm prior to cardioversion and investigated with respect to the composite primary end point of stroke and systemic embolism for 30 to 90 days. The safety end point included major bleeding and clinically relevant nonmajor bleeding. The trial enrolled 1500 patients, who were equally distributed between both arms. While six events occurred in the heparin/VKA group (5 ischemic, 1 hemorrhagic stroke, 0 systemic embolic events), no event was detected in the apixaban group, which translated into a significant benefit of apixaban vs heparin/VKA regarding the primary end point ($P=0.0164$). Despite the fact that this trial was underpowered for the primary end point, the outcome still highlights the low event rate in such a cohort and the feasibility and safety of using apixaban prior to cardioversion.

IMPACT-AF trial

The IMPACT-AF trial, a cluster-randomized trial performed in Argentina, Brazil, China, India, and Romania, specifically investigated the effect of “multifaceted patient and provider education with data monitoring and feedback” on the primary outcome, ie, changes in the proportion of patients treated with oral anticoagulation from baseline to 1 year. Secondary clinical outcomes were death, stroke, and bleeding. The main inclusion criteria were AF not due to reversible causes and a CHA₂DS₂-VASC score ≥ 2 (or rheumatic valvular disease). The intervention sites scheduled in-clinic visits at 6 and 12 months and telephone calls or visits at 1, 3, 6, 9, and 12 months, while the control sites only scheduled visits for clinical event assessment at 6 and 12 months. The interventions included education, clinical monographs, 3 background webinars, monthly site calls with the national coordinating center, and regular data evaluation and feedback. An analysis of the primary end point showed an oral anticoagulation rate of 80% in the intervention group vs 67% in the control group, which translated into an improvement in anticoagulation treatment in the intervention group ($P=0.0002$ vs control). Furthermore, the secondary analysis revealed an additional benefit on stroke rate in the intervention vs the control group (1% vs 2%; HR, 0.48; 95% CI, 0.23-0.99; $P=0.043$). These results show the potential of a focused education and feedback program on therapy initiation, adherence, and clinical end points.²

FOCUS ON ABLATION

CASTLE-AF trial

The CASTLE-AF trial, presented by Nassir Marrouche (US), was a highlight of the ESC meeting from an electrophysiological point of view, since it is the first multicenter, randomized controlled trial to show a benefit of catheter ablation therapy vs conventional standard treatment on hard clinical end points. The composite primary end point was mortality and hospitalizations due to heart failure progression in patients with AF and concomitant heart failure. The studied cohort was represented by the specific inclusion criteria: symptomatic paroxysmal or persistent AF; failure or intolerance to ≥ 1 (or unwillingness to take) antiarrhythmic drugs; left ventricular ejection fraction $\leq 35\%$; NYHA class $\geq II$; ICD/CRT-D device with home monitoring capabilities. The patients were followed for 60 months and monitored continuously using the implantable device and home monitoring. Overall, 397 patients

were randomized 1:1 to catheter ablation therapy or conventional standard treatment. The primary end point was met, showing a 38% relative risk reduction with catheter ablation therapy. Furthermore, catheter ablation therapy reduced all-cause mortality by 47% and cardiovascular mortality by 51%. The results were highlighted by an analysis of the continuous rhythm monitoring, showing a significant reduction in AF burden (>60% of patients treated with catheter ablation therapy were in sinus rhythm vs <40% with conventional standard treatment) after the 60-month follow-up period. This trial provides strong evidence for the use of catheter ablation therapy in patients with AF and heart failure, with important prognostic implications for the patient.

CAPTAF trial

The CAPTAF trial assessed the effect of catheter ablation therapy on quality of life. In this study, catheter ablation therapy was compared with optimized drug therapy for AF. The CAPTAF trial, presented by Carina Blomström-Lundqvist (SE), was a randomized multicenter study that used implantable cardiac monitoring. The primary end point included changes in quality of life with respect to general health, and it was assessed using the short form 36-item health survey (scores, 0 to 100). After 12 months of follow-up, catheter ablation therapy significantly improved quality of life in patients with paroxysmal and persistent AF vs optimized drug therapy (+11.0 vs +3.1; $P=0.0084$). This improvement was accompanied by a reduction in AF burden in the catheter ablation therapy group. These results highlight that the main goal of symptomatic AF therapy, ie, relief of symptoms for the patient, could be achieved by catheter ablation therapy and that this effect is associated with a reduced AF burden. In addition, the data demonstrated that implantable cardiac monitoring could be used reliably to assess rhythm control vs quality of life.

MISCELLANEOUS

RACE-3 trial

Isabelle Van Gelder (NL) presented this trial on behalf of the RACE-3 investigators. This study tested the hypothesis that upstream risk factor therapy in addition to routine

care would improve the efficacy of rhythm control in patients with an early stage of AF and heart failure. The upstream therapy group also received MRAs, statins, and ACE inhibitors or ARBs. Furthermore, cardiac rehabilitation was addressed by aiming for physical activity, dietary restrictions, and patient counseling. The primary end point was the presence of sinus rhythm, defined as sinus rhythm for at least six-sevenths of the assessable time, at 1 year. Between 2009 and 2015, 245 patients were enrolled and randomized 1:1 to upstream therapy or routine care. The primary end point was met for superiority of upstream therapy, showing that 75% of patients were in sinus rhythm at 1 year vs 63% in the routine care group ($P=0.021$). These results point toward a potential benefit of upstream therapy in the selected group of patients. However, the long enrollment period for this relatively low number of patients, in combination with the moderate decrease in AF burden, is an important limitation of the study.

REHEARSE-AF trial

One focus of this year's ESC meeting was the role of e-health and the variety of electronic devices available to improve patient care. In this context, the REHEARSE-AF trial investigated the potential of a mobile-phone- or handheld-analog-based ECG tool (AliveCor Kardia Mobile) to improve the detection of AF vs routine care over a period of 1 year in a representative broad group of patients at a certain risk of AF (≥ 65 years old with a CHA₂DS₂-VASc score ≥ 2). Of the 1272 individuals who volunteered to participate, 1004 were randomized 1:1 to either AliveCor with ECG recording by a single-lead ECG device twice weekly for 52 weeks (iECG) or to routine care, defined as usual routine clinical care with a local medical practitioner. In the AliveCor group, 60 440 iECGs were recorded and transmitted for 500 iECG participants. The primary end point, detection of AF during the 1-year follow-up, was significantly different between the groups (HR, 3.9; 95% CI, 1.4-10.4; $P=0.007$). This is almost a 4-fold increase in the detection of AF over the course of a year, costing \approx €9000 per AF diagnosis. Despite the fact that these data are promising, the questions of if and how these screening tools will be implicated in general routine health care needs further evaluation in subsequent trials addressing hard clinical end points. ■

REFERENCES

1. Cannon CP, Bhatt DL, Oldgren J, et al; RE-DUAL PCI Steering Committee and Investigators. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med*. 2017 Aug 27. Epub ahead of print.
2. Vinereanu D, Lopes RD, Bahit MC, et al; IMPACT-AF Investigators. A multifaceted intervention to improve treatment with oral anticoagulants in atrial fibrillation (IMPACT-AF): an international, cluster-randomised trial. *Lancet*. 2017 Aug 25. Epub ahead of print.
3. Grayburn PA, Carabello B, Hung J, et al. Defining "severe" secondary mitral regurgitation: emphasizing an integrated approach. *J Am Coll Cardiol*. 2014;64(25):2792-2801.
4. Piérard LA, Lancellotti P. The role of ischemic mitral regurgitation in the pathogenesis of acute pulmonary edema. *N Engl J Med*. 2004;351(16):1627-1634.
5. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J*. 2012;33(19):2451-2496.

LATE-BREAKING CLINICAL TRIALS: PREVENTION AND OUTCOMES IN CORONARY ARTERY DISEASE

FILIPPO CREA, MD

Author affiliations: Department of Cardiovascular and Thoracic Sciences, Fondazione Policlinico Universitario A. Gemelli - Catholic University, Roma, Italy

Address for correspondence: Filippo Crea, MD, Professor of Cardiology, Director, Department of Cardiovascular and Thoracic Sciences, Fondazione Policlinico Universitario A. Gemelli, Catholic University of the Sacred Heart, L.go Vito 1, 00168 Roma, Italy (email: filippo.crea@unicatt.it)

Keywords: atherosclerosis; canakinumab; coronary artery disease; hsCRP; inflammation; rivaroxaban; small interfering RNA

Among the several exciting late-breaking clinical trials on prevention and outcomes presented at the 2017 ESC congress, I will focus on CANTOS, COMPASS, ORION-1, and HPS3/TIMI55–REVEAL.

CANTOS

Inflammatory mechanisms participate in all phases of atherothrombosis and elevated plasma levels of the inflammatory biomarker hsCRP can be used to identify high-risk patients for both first and recurrent vascular events. CANTOS is the first randomized, double-blind, placebo-controlled, event-driven, phase 3 study designed to formally address the “inflammatory hypothesis of atherosclerosis” by evaluating if the inhibition of inflammation per se lowers vascular event rates, especially in patients with persistent evidence of inflammation despite usual therapies.¹

The drug tested in CANTOS was canakinumab, a human monoclonal antibody that selectively inhibits IL-1 β , which produces a rapid and sustained inhibition of the acute phase response with only marginal effects on lipid levels. CANTOS enrolled 10 061 patients with a previous acute myocardial infarction and evidence of persistent systemic inflammation (hsCRP >2 mg/L) despite contemporary secondary prevention strategies. Patients were randomly allocated to either placebo or canakinumab at doses of 50, 150, or 300 mg administered subcutaneously once every 3 months. All participants were followed up for 3.7 years.

The primary end point was the first occurrence of a nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. Canakinumab lowered hsCRP levels in a dose-dependent manner, as expected, without reducing lipid levels from baseline. At doses of 150 or 300 mg, canakinumab reduced the risk of cardiovascular events by 15% and 14%, respectively.

About safety, there was no significant difference between the canakinumab groups and the placebo group in all-cause mortality, even if canakinumab was associated with a higher incidence of infections vs placebo (approximately 1 in every 1000 patients had a potentially fatal infection). Interestingly, exploratory findings in CANTOS suggest that canakinumab might lower the risk of cancer.²

These fascinating results represent the first step toward anti-inflammatory strategies to reduce cardiovascular risk. Nevertheless, considering the cost of canakinumab and the associated risk of infection, it will be important to define the subset of patients susceptible to its beneficial effects better, probably those with very high levels of CRP. It will also be important to test other cheaper and safer anti-inflammatory drugs, such as low-dose methotrexate and drugs that modulate adaptive immunity.

COMPASS

Stable coronary and/or peripheral artery disease portends a significant risk of debilitating or fatal myocardial infarction and stroke, the leading cause of death and disability in the world. Aspirin is the single most used treatment for secondary prevention, but it is only modestly effective. COMPASS, a randomized, double-blind, placebo-controlled, event-driven, phase 3 trial, evaluated whether treatment with rivaroxaban 2.5 mg twice daily plus aspirin 100 mg or rivaroxaban 5 mg twice daily alone is better than aspirin 100 mg daily alone in the prevention of myocardial infarction, stroke, or cardiovascular death in high-risk patients.³ The trial enrolled 27 395 patients with stable coronary (90.6%) or peripheral (27.4%) artery disease. Patients who needed dual antiplatelet therapy, nonaspirin antiplatelet therapy, or oral anticoagulant therapy were excluded.

The primary end point was a composite of cardiovascular death, stroke, and myocardial infarction. The net clinical benefit outcome was a composite of the primary end point plus fatal bleeding or symptomatic bleeding into a critical organ. Rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily was superior to aspirin 100 mg once daily in reducing MACE by 4.1% (vs 5.4%), reducing cardiovascular death, stroke, or myocardial infarction by 24%, and improving survival by 18%. Rivaroxaban 5 mg twice daily also reduced MACE vs aspirin without achieving statistical significance. The net clinical benefit outcome rate was 20% lower with rivaroxaban plus aspirin than with aspirin alone.

Given these results, the independent Data Monitoring Committee recommended early discontinuation of the study for “overwhelming efficacy” of rivaroxaban plus as-

pirin after a mean follow-up of 23 months, but maybe this early stop may overestimate the real treatment effect. Concerning the safety outcomes, rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily increased the rate of major bleeding vs aspirin 100 mg once daily (3.1% vs 1.9) (most of which was into the gastrointestinal tract), but there was no significant between-group differences in the rate of fatal bleeding, intracranial bleeding, or symptomatic bleeding into a critical organ.

So far, secondary prevention has been based on aspirin administration and risk-factor control. The COMPASS results suggest that the outcomes can be further improved by intensifying the antithrombotic regimen. Low doses of a factor Xa inhibitor (not only rivaroxaban) plus other antiplatelet drugs (like P2Y₁₂ inhibitors) as well as dual antiplatelet treatment may represent other antithrombotic regimens to improve prevention strategies. The more potent antithrombotic regimens, however, increase the risk of bleeding. Further studies are needed to identify patients at a low risk of bleeding who may benefit from a more potent antithrombotic regimen without increasing the risk of bleeding.

Another interesting area of intervention is represented by dyslipidemia. Recent trials have shown that more intense lipid-lowering regimens might improve the outcome better than regimens that are based on statins only; a target LDL cholesterol <70 mg is perhaps too lenient. In this case, again, it is important to identify patient subsets in whom the risk of side effects, such as new-onset diabetes and intracranial hemorrhage, is acceptable.

ORION-1

ORION-1, a randomized, double-blind, placebo-controlled, phase 2, multicenter trial, evaluated the safety, tolerability, and efficacy of different doses of inclisiran in lowering LDL cholesterol. Inclisiran is a chemically synthesized small interfering RNA designed to silence PCSK-9 specific RNA by turning off its synthesis in the liver and promoting degradation of LDL. The study enrolled 501 patients with a high risk of cardiovascular events who were receiving the maximum possible dose of statins, but with suboptimal control of LDL cholesterol.⁴ Participants were randomized to receive placebo or inclisiran at doses of 200, 300, or 500 mg in one (at day 1) or two doses (at days 1 and 90).

The primary end point was the percentage change in LDL cholesterol from baseline to day 180. Inclisiran treatment significantly reduced LDL cholesterol and PCSK-9 levels vs placebo. The greatest reduction in LDL cholesterol (52.6%) was reached with two doses of inclisiran 300 mg; in this treatment arm, 48% of patients achieved an LDL cholesterol level below 50 mg/dL. At day 240, PCSK-9 and LDL cholesterol levels were 56.1% and 47.2% lower than at baseline, respectively, showing that a consistent reduc-

tion was maintained over time. No significant changes in hsCRP levels were observed. About safety, the rates of adverse events did not differ between the inclisiran and placebo groups.

Further studies with longer follow-up periods and clinical end points are warranted to establish the effectiveness and safety of this drug. It will also be important to compare the effects of inclisiran with those of a monoclonal antibody against PCSK-9. Indeed, production costs of RNA interfering drugs are much lower than the costs of monoclonal antibodies, which might favor the former in the presence of a similar clinical benefit.

HPS3/TIMI55-REVEAL

HPS3/TIMI55-REVEAL, a randomized, double-blind, placebo-controlled trial, evaluated the safety and clinical efficacy on improving cardiovascular outcomes of adding anacetrapib 100 mg daily vs placebo to intensive atorvastatin therapy in patients with atherosclerotic vascular disease. Anacetrapib inhibits the cholesteryl ester transfer protein, a molecule that facilitates the exchange of cholesteryl esters and triglycerides between HDL particles and atherogenic particles containing apolipoprotein B.⁵ The pharmacologic effect is an increase in HDL cholesterol with a reduction in non-HDL cholesterol (particularly LDL cholesterol). The trial involved 30 449 patients with atherosclerotic vascular disease who were receiving intensive atorvastatin therapy and who had well-controlled lipid levels at baseline. The median follow-up was 4.1 years.

The primary end point was the first major coronary event (a composite of coronary death, myocardial infarction, or coronary revascularization). In the group randomized to anacetrapib, the mean level of HDL cholesterol was 43 mg/dL higher, with a relative difference of 104%, while the mean non-HDL cholesterol level was 17 mg/dL lower, with a relative difference of -18% vs the placebo group. There was a significant between-group difference in the incidence of the primary end point with a greater risk reduction after the first year of treatment in the anacetrapib group vs the placebo group (10.8% vs 11.8%).

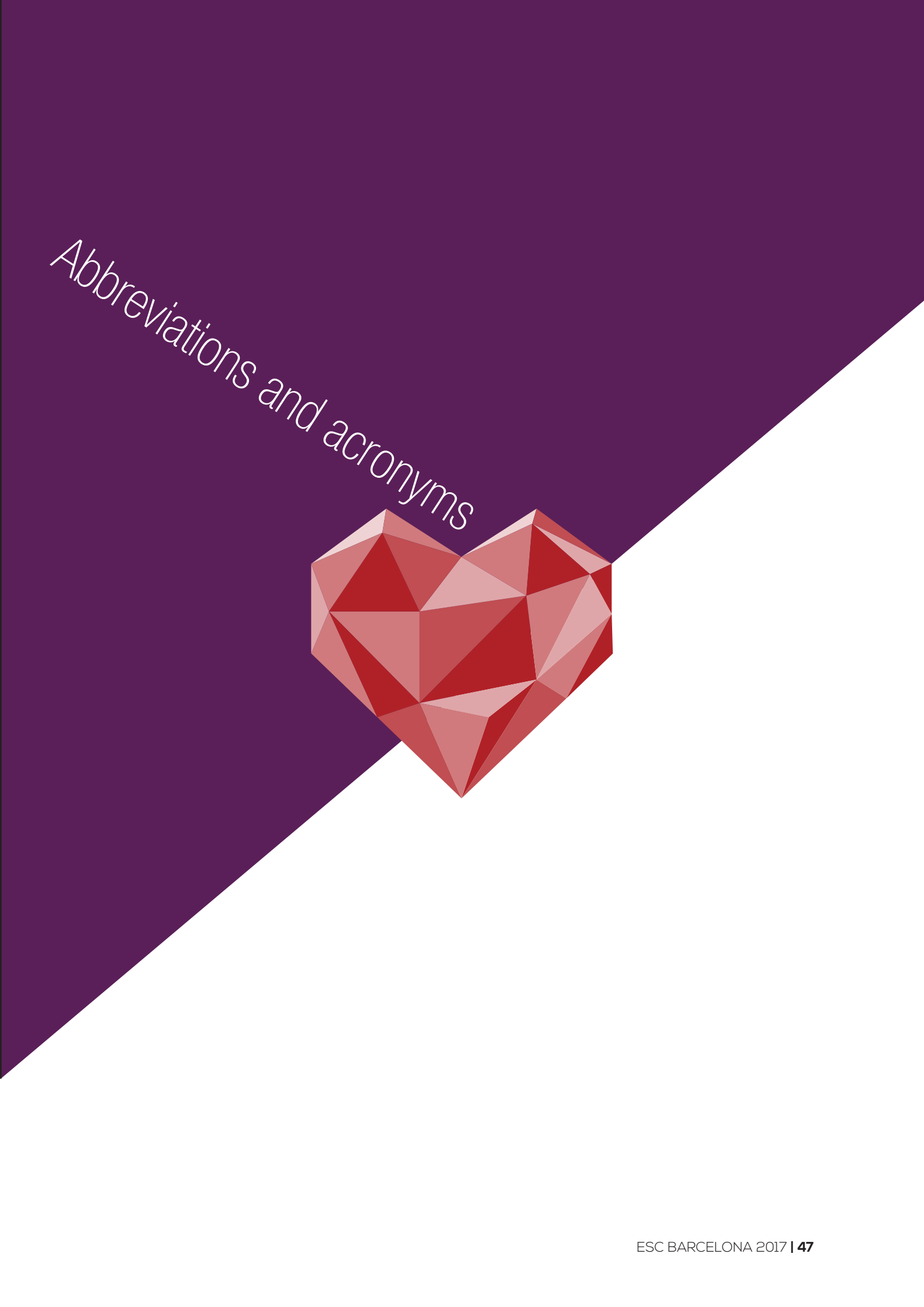
About the safety outcome, there were no significant between-group differences in the risk of death (both from cardiovascular and all noncardiovascular causes), cancer, liver muscle events, cognitive function, or other serious adverse events. In the anacetrapib group, there was a small increase in blood pressure and an estimated glomerular filtration rate <60 mL/min/1.73 m² of body surface area vs the placebo group, but this did not have an impact on the rates of hypertension-related or renal failure-related serious adverse events. While previous trials showed neutral or detrimental effects of cholesteryl ester transfer protein inhibitors, this trial showed a clinical benefit. It is worth mentioning, however, that the observed reduction in cardiovascular events is entirely consistent with that

expected by lowering non-HDL cholesterol by 17 mg/dL as was achieved in this study.

Mendelian randomization trials suggested that cholesteryl ester transfer protein is in the causal pathway leading to cardiovascular events; however, clinical trials have hitherto failed to prove the hypothesis that cholesteryl ester transfer protein inhibition improves outcomes in patients with atherosclerotic disease, which is probably because HDL particles are dysfunctional in this patient population. Thus, it is likely that cholesteryl ester transfer protein antagonists will never reach the clinical arena. ■

REFERENCES

1. Ridker PM, Everett BM, Thuren T, et al; CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017 Aug 27. Epub ahead of print.
2. Ridker PM, MacFadyen JG, Thuren T, Everett BM, Libby P, Glynn RJ; CANTOS Trial Group. Effect of interleukin-1 β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. *Lancet*. 2017 Aug 25. Epub ahead of print.
3. Eikelboom JW, Connolly SJ, Bosch J et al; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017 Aug 27. Epub ahead of print.
4. Ray KK, Landmesser U, Leiter LA, Kallend D, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. *N Engl J Med*. 2017;376(15):1430-1440.
5. HPS3/TIMI55-REVEAL Collaborative Group. Effects of anacetrapib in patients with atherosclerotic vascular disease. *N Engl J Med*. 2017 Aug 28. Epub ahead of print.



Abbreviations and acronyms

ACCORD	Action to Control Cardiovascular Risk in Diabetes	ICOS-ONE	prevention of anthracycline-induced cardiotoxicity
ACE	angiotensin-converting enzyme	IMPACT-AF	Integrated Management Program Advancing Community Treatment of Atrial Fibrillation
AF	atrial fibrillation	LAACS	Left Atrial Appendage Closure during open heart Surgery
ARB	angiotensin receptor blocker	LDL	low-density lipoprotein
BSCMR	British Society of Cardiovascular Magnetic Resonance	LGE CMR	late gadolinium contrast enhancement on cardiovascular magnetic resonance
CAAM	initial airway management in patients with out-of-hospital Cardiac Arrest: tracheal intubation vs bag-valve-Mask ventilation	MACE	major adverse cardiac events
CAC	coronary artery calcium	MRA	mineralocorticoid receptor antagonists
CAD	coronary artery disease	NSTEMI	non-ST-segment elevation myocardial infarction
CANTOS	Canakinumab Antiinflammatory Thrombosis Outcome Study	NYHA	New York Heart Association
CAPTAF	Catheter Ablation compared with optimized Pharmacological Therapy for Atrial Fibrillation	OptimEx Clin	Optimizing Exercise training in prevention and treatment of diastolic heart failure – Clinical study
CASTLE-AF	Catheter Ablation versus Standard conventional Treatment in patients with Left ventricular dysfunction and Atrial Fibrillation	ORION-1	evaluation of the effect Of inclisiran (ALN-PCSSc) tTreatment on low density lIpOprotein cholesterol
CLOSE	patent foramen ovale CLOSurE or anticoagulants versus antiplatelet therapy to prevent stroke recurrence	PCI	percutaneous coronary intervention
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation StrategieS	PCSK-9	proprotein convertase subtilisin/kexin type 9
COPD	chronic obstructive pulmonary disease	PISA	proximal isovelocity surface area
CROS	Cardiac Rehabilitation Outcome Study	PRAGUE-17	left atrial aPpendage closuRe vs novel AnticoaGulation agEnts in atrial fibrillation
CRT-D	cardiac resynchronization therapy–defibrillator	PROMISE	PROspective Multicenter Imaging Study for Evaluation of chest pain
DAPT	dual antiplatelet therapy	PURE	Prospective Urban Rural Epidemiology
EMANATE	Effectiveness of apixaban coMpared with usual care Anticoagulation in subjects with Non-valvular ATrial fibrillation undergoing cardiovErsion	QUALIFY	QUality of Adherence to guideline recommendations for LIfe-saving treatment in heart failure surveY
EMPA-REG OUTCOME	Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes	RACE-3	Routine versus Aggressive upstream rhythm Control for prevention of Early atrial fibrillation in heart failure
EMPEROR	EMPagliflozin outcomE tRial in patients with chrOnic heaRt failure	RAMIT	Rehabilitation After Myocardial Infarction Trial
ESC	European Society of Cardiology	RE-DUAL PCI	Evaluation of DUAL therapy with dabigatran vs. triple therapy with warfarin in patients with AF that undergo a PCI with stenting
ESO	European Stroke Organization	REHEARSE-AF	assessment of REmote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibrillation
FAST-MI	French registry of acute ST-elevation or non–ST-elevation myocardial infarction	REVEAL-2	Randomized Evaluation of the Effects of Anacetrapib through Lipid modification
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes	SCAAR	Swedish Coronary Angiography and Angioplasty Registry
GLAGOV	GLobal Assessment of plaque reGression with a PCSK-9 antibOdy as measured by intraVascular ultrasound	SGLT2	sodium glucose cotransporter 2
GORE REDUCE	GORE® HELEX® Septal Occluder / GORE® CARDIOFORM Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients With Patent Foramen Ovale	SHIFT	Systolic Heart failure treatment with the If inhibitor ivabradine Trial
HDL	high-density lipoprotein	SMARTX-HF	Study of MyocardiAl Recovery afTer EXercise training in Heart Failure
HFMEF	heart failure with midrange ejection fraction	STEMI	ST-segment elevation myocardial infarction
HFREF	heart failure with reduced ejection fraction	SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based bare in Heart disease Evaluated According to Recommended Therapies
hsCRP	high sensitivity C-reactive protein	VKA	vitamin K antagonist
ICD	implantable cardioverter defibrillator		
ICONIC	Incident COroNary Syndromes Identified by Computed tomography		

Instructions for authors



INSTRUCTIONS FOR AUTHORS

GENERAL INSTRUCTIONS

Submission

Manuscripts should be submitted as a Word file by email to Sophie Nisse-Durgeat (sophie.nisse-durgeat@servier.com).

Title Page

The title page should include a title, the full names of all the authors, the highest academic degrees of all authors (in country of origin language) as well as fellowship designations and honorary degrees, affiliations (names of department(s) and institution(s) at the time the work was done), 5 to 10 keywords, the corresponding author's complete mailing address, telephone, e-mail, and acknowledgements.

Text

All texts should be submitted in English. Authors who do not write fluently in English are strongly advised to have their article checked by a native or fluent English speaker before submission. Abbreviations should be used sparingly. The style of headings and subheadings should be consistent throughout the text. The editorial office reserves the right to modify, add or delete headings, and change their level when necessary. *Dialogues in Cardiovascular Medicine* uses SI units and generic names of drugs.

Disclosure/Acknowledgments

Full statements of funding acknowledgements and disclosures of conflicts of interest must be included at the end of the article.

COPYRIGHT

Permissions

Requests for permission to reproduce material published in *Dialogues in Cardiovascular Medicine* should be sent directly to the editorial office (sherri.smith@servier.com).

Transfer of copyright

Copyright of articles will be transferred to the publisher of *Dialogues in Cardiovascular Medicine*. The Copyright Transfer Agreement must be signed by all authors and returned to the publisher by post.

REFERENCES

The authors bear total responsibility for the accuracy and completeness of all references and for correct text citation.

Citation in text

All references should be cited in the text and numbered consecutively using superscript Arabic numerals.

Reference list

Presentation of the references should be AMA style:

- Author(s). Title. *Journal Name* [using National Library of Medicine abbreviations]. Year;vol:inclusive pages.
- Abbreviate and italicize journal names using National Library of Medicine abbreviations at <http://www.ncbi.nlm.nih.gov/nlmcatalog/journals>.
- List all authors unless there are more than six. If there are more than six, list the first three then use "et al."
- Use authors' last name followed by initials. No periods after initials. Separate names with commas.

Example of style for references

Journal articles

- Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation*. 2007;115:2689-2696.
- Connolly SJ, Camm AJ, Halperin JL, et al; PALLAS Investigators. Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med*. 2011;365:2268-2276.

Chapter in a book

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

Web-based material

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

EDITORIAL ASSESSMENT AND PROCESSING

Peer review

All contributions to *Dialogues in Cardiovascular Medicine* will be reviewed by the Editors and submitted to expert consultants for peer review. All contributions should be original review articles.

Editorial processing

All manuscripts are copyedited according to the guidelines of the latest online edition of the American Medical Association Manual of Style, Oxford University Press. The spelling used is American (reference dictionaries: latest editions of Merriam-Webster's Collegiate Dictionary, Stedman's Medical Dictionary, and Dorland's Illustrated Medical Dictionary).

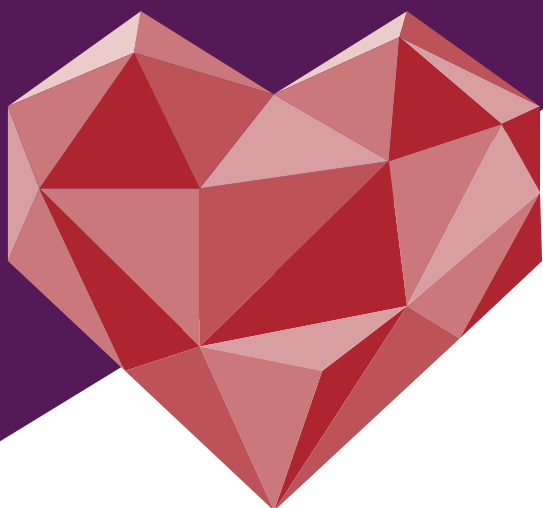
Duplicate content detection software

All manuscripts are run through iThenticate
<http://www.ithenticate.com>.

Proofs

Page proofs will be sent to the corresponding author for approval in PDF format by e-mail. Author corrections should be returned within the specified time by e-mail to Sherri Smith (sherri.smith@servier.com). If this deadline is not met, the editorial office will assume that the author accepts the proofs as they stand, including changes made by the editorial office. Authors are responsible for all statements made in their work, including changes made by the editorial office and authorized by the author.

DIALOGUES IN CARDIOVASCULAR MEDICINE



**Get the latest news
from the main cardiology meetings!**

The journal provides up-to-date information on specific areas of cardiovascular medicine and encourages dialogue between key opinion leaders and readers.

Read the latest issue online:
www.dialogues-cvm.com

