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Dialogues in Cardiovascular Medicine

Aims & Scope

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

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Next Issue

Heart Failure Vienna 2018

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EDITORIAL

It is hard to believe that a year has already passed since we announced the new format for *Dialogues in Cardiovascular Medicine*. We are pleased that it has been such a success so far, having received letters of appreciation, especially for the sections dedicated to “Snapshots in Cardiology” and the “Hot Topics.” The website (www.dialogues-cvm.org) is also proving to be popular with over 200 visits per month. We are continuing to evolve and the format will change again slightly in 2018, adding the option to store the issues in an online library. We remain ambitious and hope to continue providing a good record of what has happened over the past year by reporting from the most prestigious cardiovascular congresses and journals.

The year 2017 was particularly full of important news, with preventive cardiology and coronary artery disease being at the forefront. We learned about several large trials that delivered new and unexpected results. Could we ever imagine that a medical trial could involve 135 000 individuals from 667 urban and rural communities in 18 countries and conclude that dietary fats are protective and carbohydrates are harmful? The PURE trial (Prospective Urban Rural Epidemiology) certainly gave us surprising results. Results are of course important, but their interpretation is even more important and challenging. Salim Yusuf and his team have certainly made us rethink and challenge the current guideline recommendations when an increased consumption of saturated fats decreases overall mortality. Medicine is a continuous evolution and we keep this innovative momentum.

Equally, the scientific community learned about the extraordinary reduction in low-density lipoprotein achieved by inhibiting PCSK-9. PCSK-9 inhibition gave good results on outcomes and showed an effective reduction in atheroma volume, as demonstrated by plaque regression, without any changes in plaque composition. This result is indeed another challenge: a positive result that deserves further explanation.

Perhaps the most unexpected result is related to cardiovascular disease and inflammation. What is not totally unexpected is that canakinumab, an inhibitor of interleukin 6 and therefore of inflammation, reduced the cardiovascular end point in the CANTOS trial. What was totally unexpected, however, was the benefit on cancer mortality, particularly lung cancer. Of course, a single study is not enough to draw a firm conclusion, but Paul Ridker and his team have pointed us in another direction regarding inflammation and coronary artery disease, even if the costs are currently prohibitive.

On the subject of cost, we should consider the recent anticancer drugs that have been approved with an equally prohibitive cost, with the understanding that their mechanism of action, aimed at a specific target, confirmed significant benefits. However, an analysis of drugs approved by European Medicines Agency between 2019 and 2013 shows that 49% of the 68 approved drugs do not show any survival benefit. Out of the 35 drugs that did show a survival benefit, a clinically meaningful benefit was only found with 11 of them. All 68 approved drugs are reimbursed throughout Europe, each at an annual cost higher than that of the full treatment of nearly 50 patients with coronary artery disease and heart failure, which tells us that we are missing adequate advocacy mastered by patient groups at national and European Union levels to support anticancer drugs. The mortality rate for cancer and cardiovascular disease is similar, but cardiology has managed to prolong life by nearly 7 years and, yet, when there is innovation, such as with canakinumab, we consider the cost prohibitive. We are certainly victims of our own success.

Still on the subject of costs, something quite interesting came about related to the guidelines for the symptomatic treatment of chronic ischemic heart disease. As you know, the guidelines recommend first- and second-line treatments with dated drugs: ie, β -blockers, calcium channel blockers, and short-acting nitrates being first-line recommendations and the others, such as ivabradine, ranolazine, and trimetazidine, being only second-line recommendations. They all have similar, if not identical, antianginal efficacy; unfortunately, none have improve outcomes. They are becoming generic, meaning that there is no longer a cost issue. Yet, habit is labeling them as either first- or second-line treatments, which is another example of how authorities and cardiologists are stifling instead of supporting innovation.

Interestingly, a newly proposed strategy, the “Diamond Approach,” suggests putting all antianginal drugs at the same level and providing a more personalized pharmacological approach to angina based on patient characteristics, pathophysiology, and comorbidities.

Of course, there have been many other interesting and challenging results presented in 2017, which have been highlighted and discussed by experts in this issue of *Dialogues in Cardiovascular Medicine*. We hope that you enjoy this user-friendly format that gives you up-to-date information. ■

ROBERTO FERRARI & KIM FOX

Snapshot in Cardiology



SNAPSHOT IN CARDIOLOGY

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

These articles were taken from the Lancet and the New England Journal of Medicine between January 1, 2017 and December 22, 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 I 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 thromboses 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, Tatoes 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 a 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 a 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 an 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 patient with 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 noninferior 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 antidrug-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.

Göteborg 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–guided revascularization strategy was noninferior to a fractional flow reserve–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 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 anti-thrombotic 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, the 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/dL who were receiving statin therapy, evolocumab plus statin therapy lowered low-density lipoprotein cholesterol levels to a median of 30 mg/dL 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 cardioprotective 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.

Patorno 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.

Ulug P, Sweeting MJ, von Allmen RS, Thompson SG, Powell JT; SWAN collaborators. Morphological suitability for endovascular repair, non-intervention rates, and operative mortality in women and men assessed for intact abdominal aortic aneurysm repair: systematic reviews with meta-analysis. *Lancet.* 2017;389(10088):2482-2491.

This analysis showed that, compared with men, a smaller proportion of women are eligible for endovascular repair, a higher proportion of women are not offered intervention, and operative mortality is much higher in women for both endovascular repair and open repair.

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.

JULY

Dewey FE, Gusarova V, Dunbar RL, et al. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. *N Engl J Med.* 2017;377(3):211-221.

In the DiscovEHR study, participants with heterozygous loss-of-function variants in the angiopoietin-like 3 gene had significantly lower serum levels of triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol than did the participants without these variants.

Graham MJ, Lee RG, Brandt TA, et al. Cardiovascular and metabolic effects of ANGPTL3 antisense oligonucleotides. *N Engl J Med.* 2017;377(3):222-232.

After 6 weeks of treatment with an antisense oligonucleotide targeting angiopoietin-like 3, the people in the multiple-dose group had reductions in the levels of the angiopoietin-like 3 protein, triglycerides, low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, apolipoprotein B, and apolipoprotein C-III.

Jaiswal S, Natarajan P, Silver AJ, et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. *N Engl J Med.* 2017;377(2):111-121.

The risk of coronary heart disease in humans nearly doubled when clonal hematopoiesis of indeterminate potential was present in peripheral-blood cells. Clonal he-

matopoiesis of indeterminate potential also accelerated atherosclerosis in mice.

Li L, Geraghty OC, Mehta Z, Rothwell PM; Oxford Vascular Study. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. *Lancet.* 2017;390(10093):490-499.

The long-term risk of major bleeding is higher and more sustained in older patients who are receiving aspirin-based antiplatelet treatment without the routine use of proton-pump inhibitors; in addition, there is a substantial risk of disabling or fatal upper gastrointestinal bleeding.

Rutty GN, Morgan B, Robinson C, et al. Diagnostic accuracy of post-mortem CT with targeted coronary angiography versus autopsy for coroner-requested post-mortem investigations: a prospective, masked, comparison study. *Lancet.* 2017;390(10090):145-154.

England and Wales have one of the highest frequencies of autopsies in the world. For most sudden natural adult deaths investigated by Her Majesty's Coroners, targeted coronary angiography could be used to avoid an invasive autopsy.

Shen L, Jhund PS, Petrie MC, et al. Declining risk of sudden death in heart failure. *N Engl J Med.* 2017;377(1):41-51.

Among ambulatory patients with heart failure with reduced ejection fraction who were enrolled in clinical trials, the rates of sudden death declined substantially over time, which is consistent with a cumulative benefit of evidence-based medications.

van der Hulle T, Cheung WY, Kooij S, et al; YEARS Study Group. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospec-

ive, multicentre, cohort study. *Lancet.* 2017;390(10091):289-297.

This prospective, multicenter, cohort study showed that, in patients with a suspected pulmonary embolism, the YEARS diagnostic algorithm could be used to safely exclude a pulmonary embolism. The YEARS algorithm decreased the number of computed tomography pulmonary angiography examinations in all ages and across several relevant subgroups by 14% for patients with a suspected pulmonary embolism.

AUGUST

Ali ZA, Serruys PW, Kimura T, et al. 2-year outcomes with the Absorb bioresorbable scaffold for treatment of coronary artery disease: a systematic review and meta-analysis of seven randomised trials with an individual patient data substudy. *Lancet.* 2017;390(10096):760-772.

A meta-analysis of seven studies comparing bioresorbable vascular scaffolds with everolimus-eluting stents showed that bioresorbable vascular scaffolds increased the rates of composite device-oriented adverse events and device thrombosis.

ATTEND Collaborative Group. Family-led rehabilitation after stroke in India (ATTEND): a randomised controlled trial. *Lancet.* 2017;390(10094):588-599.

Most people with stroke in India have no access to organized rehabilitation services. The ATTEND trial results do not support investing in new stroke rehabilitation services that shift tasks to family caregivers, unless new evidence emerges.

Berlowitz DR, Foy CG, Kazis LE, et al; SPRINT Research Group. Effect of intensive blood-pressure treatment on patient-reported outcomes. *N Engl J Med.* 2017;377(8):733-744.

An analysis of the SPRINT trial showed that the patient-reported outcomes were similar among participants who received intensive blood pressure-lowering treatment (target systolic blood pressure <120 mm Hg) to those who received standard treatment (target systolic blood pressure <140 mm Hg).

Giugliano RP, Mach F, Zavitz K, et al; EBBINGHAUS Investigators. Cognitive function in a randomized trial of evolocumab. *N Engl J Med.* 2017;377(7):633-643.

Cognitive function was prospectively assessed in a subgroup of patients from a randomized, placebo-controlled trial comparing evolocumab or placebo in addition to statin therapy, using the Cambridge Neuropsychological Test Automated Battery. This assessment showed no significant between-group difference in cognitive function over a median of 19 months.

Jinatongthai P, Kongwatharapong J, Foo CY, et al. Comparative efficacy and safety of reperfusion therapy with fibrinolytic agents in patients with ST-segment elevation myocardial infarction: a systematic review and network meta-analysis. *Lancet.* 2017;390(10096):747-759.

In settings where health care resources are scarce, fibrinolytic therapy is an alternative to mechanical reperfusion for ST-segment elevation myocardial infarction; however, significant differences exist among the various regimens. Alteplase (accelerated infusion), tenecteplase, and reteplase should be considered over streptokinase and a non-accelerated infusion of alteplase, and the addition of glycoprotein IIb or IIIa inhibitors to fibrinolytic therapy should be discouraged.

Jobs A, Mehta SR, Montalescot G, et al. Optimal timing of an invasive strategy in patients with non-ST-elevation acute coronary syndrome: a meta-analysis of randomised trials. *Lancet.* 2017;390(10096):737-746.

While a routine invasive strategy is recommended for patients with non-ST-segment elevation acute coronary syndromes, an early strategy does not reduce mortality compared with a delayed invasive strategy; however, in high-risk patients, an early strategy might reduce mortality.

Khanna A, English SW, Wang XS, et al; ATHOS-3 Investigators. Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med.* 2017;377(5):419-430.

An infusion of angiotensin II significantly increased blood pressure in patients with vasodilatory shock who did not respond to high doses of conventional vasopressors.

Marso SP, McGuire DK, Zinman B, et al; DEVOTE Study Group. Efficacy and safety of degludec versus glargine in type 2 diabetes. *N Engl J Med.* 2017;377(8):723-732.

The DEVOTE trial showed that, among patients with type 2 diabetes at high risk for cardiovascular events, degludec was non-inferior to glargine with respect to the incidence of major cardiovascular events.

Mundle S, Bracken H, Khedikar V, et al. Foley catheterisation versus oral misoprostol for induction of labour in hypertensive women in India (INFORM): a multicentre, open-label, randomised controlled trial. *Lancet.* 2017;390(10095):669-680.

The INFORM trial showed that, in women ≥18 years old who required delivery due to pre-eclampsia or hypertension, oral misoprostol was more effective than transcervical Foley catheterization for inducing labor.

Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017;377(7):644-657.

The CANVAS program showed that, in patients with type 2 diabetes and an elevated risk of cardiovascular disease, canagliflozin, a sodium-glucose cotransporter 2 inhibitor, lowered the risk of cardiovascular events vs placebo; however, it increased the risk of amputation.

Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal - full cohort analysis. *N Engl J Med.* 2017;377(5):431-441.

In emergency situations, idarucizumab, a monoclonal antibody fragment, rapidly, durably, and safely reversed the anticoagulant effect of dabigatran in patients who had uncontrolled bleeding or who were about to undergo an urgent procedure.

Praz F, Spargias K, Chrissoheris M, et al. Compassionate use of the PASCAL transcatheter mitral valve repair system for patients with severe mitral regurgitation: a multicentre, prospective, observational, first-in-man study. *Lancet.* 2017;390(10096):773-780.

This multicenter, prospective, observational, first-in-man study, showed that the Edwards PASCAL transcatheter mitral valve repair system is feasible with a high rate of technical success and a reduction in mitral regurgitation severity.

Shroyer AL, Hattler B, Wagner TH, et al; Veterans Affairs ROOBY-FS Group. Five-Year outcomes after on-pump and off-pump coronary-artery bypass. *N Engl J Med.* 2017;377(7):623-632.

The 5-year clinical outcomes for patients who had been included in the Veterans Affairs trial showed that off-pump coronary artery bypass grafting resulted in lower rates of 5-year and event-free survival than did on-pump coronary artery bypass grafting.

SEPTEMBER

Bowman L, Hopewell JC, Chen F, et al; HPS3/TIMI55-REVEAL Collaborative Group. Effects of anacetrapib in patients with atherosclerotic vascular disease. *N Engl J Med.* 2017;377(13):1217-1227.

Among patients with atherosclerotic vascular disease who were receiving intensive statin therapy, anacetrapib increased high-density lipoprotein cholesterol and lowered low-density lipoprotein cholesterol, which resulted in a lower incidence of major coronary events than that observed in patients receiving placebo.

Erlinge D, Omerovic E, Fröbert O, et al. Bivalirudin versus heparin monotherapy in myocardial infarction. *N Engl J Med.* 2017;377(12):1132-1142.

Treatment with bivalirudin lowered the rate of the composite of death from any cause, myocardial infarction, or major bleeding in patients with either STEMI or NSTEMI who were undergoing a percutaneous coronary intervention and receiving treatment with a potent P2Y12 inhibitor vs heparin monotherapy.

Hofmann R, James SK, Jernberg T, et al; DETO2X-SWEDEHEART Investigators. Oxygen therapy in suspected acute myocardial infarction. *N Engl J Med.* 2017;377(13):1240-1249.

The DETO2X-SWEDEHEART trial showed that, in patients with a suspected acute myocardial infarction who do not have hypoxemia at baseline, the routine use of supplemental oxygen did not reduce 1-year all-cause mortality.

Holman RR, Bethel MA, Mentz RJ, et al; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2017;377(13):1228-1239.

Among patients with type 2 diabetes with or without previous cardiovascular disease, exenatide did not result in any significant difference in the incidence of major adverse cardiovascular events vs placebo.

Mas JL, Derumeaux G, Guillon B, et al; CLOSE Investigators. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med.* 2017;377(11):1011-1021.

The CLOSE trial showed that, among patients with a recent cryptogenic stroke attributed to a patent foramen ovale, the rate of stroke recurrence was lower in those patients assigned to patent foramen ovale closure combined with antiplatelet therapy than among those assigned to antiplatelet therapy alone.

Ridker PM, Everett BM, Thuren T, et al; CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med.* 2017;377(12):1119-1131.

In patients with a previous myocardial infarction and a high-sensitivity C-reactive protein level ≥ 2 mg/L, treatment with canakinumab, an anti-inflammatory therapy targeting the interleukin-1 β pathway, at a dose of 150 mg every 3 months, significantly lowered the rate of recurrent cardiovascular events vs placebo, which was independent of the level of lipid lowering.

Saver JL, Carroll JD, Thaler DE, et al; RESPECT Investigators. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med.* 2017;377(11):1022-1032.

The RESPECT trial showed that, among adults with a cryptogenic ischemic stroke, closure of a patent foramen ovale resulted in a lower rate of recurrent ischemic strokes than did medical therapy alone during extended follow-up.

Søndergaard L, Kasner SE, Rhodes JF, et al; Gore REDUCE Clinical Study Investigators. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med.* 2017;377(11):1033-1042.

The Gore REDUCE trial showed that, among patients with a patent foramen ovale who had had a cryptogenic stroke, the risk of a subsequent ischemic stroke was lower in those assigned to patent foramen ovale closure combined with antiplatelet therapy than among those assigned to antiplatelet therapy alone.

OCTOBER

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;377(16):1513-1524.

The RE-DUAL PCI trial showed that, in patients with atrial fibrillation who had undergone a percutaneous coronary intervention, the risk of bleeding was lower among those who received dual therapy with dabigatran and a P2Y12 inhibitor than among those who received triple therapy with warfarin, a P2Y12 inhibitor, and aspirin.

Eikelboom JW, Connolly SJ, Bosch J, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med.* 2017;377(14):1319-1330.

In patients with stable atherosclerotic vascular disease, rivaroxaban (2.5 mg twice daily) plus aspirin resulted in better cardiovascular outcomes, but more major bleeding events vs aspirin alone. However, rivaroxaban (5 mg twice daily) alone did not result in better cardiovascular outcomes and it resulted in more major bleeding events vs aspirin alone.

Giugliano RP, Pedersen TR, Park JG, et al; FOURIER Investigators. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. *Lancet*. 2017;390(10106):1962-1971.

This prespecified secondary analysis of the FOURIER trial, showed that there was a monotonic relationship between achieved low-density lipoprotein cholesterol and major cardiovascular outcomes down to low-density lipoprotein cholesterol concentrations <0.2 mmol/L.

Kandzari DE, Mauri L, Koolen JJ, et al; BIOFLOW V Investigators. Ultrathin, bioresorbable polymer sirolimus-eluting stents versus thin, durable polymer everolimus-eluting stents in patients undergoing coronary revascularisation (BIOFLOW V): a randomised trial. *Lancet*. 2017;390(10105):1843-1852.

The BIOFLOW V trial showed that, in patients undergoing elective and urgent percutaneous coronary intervention, the ultrathin, bioresorbable polymer sirolimus-eluting stent outperformed the durable polymer everolimus-eluting stent.

Sibbing D, Aradi D, Jacobshagen C, et al; TROPICAL-ACS Investigators. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. *Lancet*. 2017;390(10104):174-175.

The TROPICAL-ACS trial showed that an early de-escalation of antiplatelet treatment from prasugrel to clopidogrel guided by platelet function testing was noninferior at 1 year in net clinical benefit to the standard treatment with prasugrel after a percutaneous coronary intervention.

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;390(10104):1737-1746.

In patients with atrial fibrillation who were at risk for a stroke, the IMPACT-AF trial showed that the use of oral anticoagulants could be significantly improved using a multifaceted and multilevel educational intervention.

NOVEMBER

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;390(10107):2050-2062.

The PURE study showed that a higher carbohydrate intake was associated with an increased risk of total mortality. Total fat and types of fat were not associated with cardiovascular disease, myocardial infarction, or cardiovascular disease mortality, whereas saturated fat had an inverse association with stroke.

Goldstone AB, Chiu P, Baiocchi M, et al. Mechanical or biologic prostheses for aortic-valve and mitral-valve replacement. *N Engl J Med*. 2017;377(19):1847-1857.

In patients undergoing aortic valve or mitral valve replacement, a mechanical prosthesis was associated with a long-term mortality benefit, as compared with a biologic prosthesis, that persisted until age 70 among patients undergoing mitral valve replacement and until age 55 among those undergoing aortic valve replacement.

Landry CH, Allan KS, Connelly KA, Cunningham K, Morrison LJ, Dorian P; Rescu Investigators. Sudden cardiac arrest during

participation in competitive sports. *N Engl J Med.* 2017;377(20):1943-1953.

Based on data from the Rescu Epistry cardiac arrest database, this retrospective study showed that the incidence of sudden cardiac arrest during participation in competitive sports was 0.76 cases per 100 000 athlete-years, but occurrence of sudden cardiac arrest due to structural heart disease was uncommon.

Lindholt JS, Sogaard R. Population screening and intervention for vascular disease in Danish men (VIVA): a randomised controlled trial. *Lancet.* 2017;390(10109):2256-2265.

The VIVA trial showed that screening for abdominal aortic aneurysm, peripheral arterial disease, and hypertension in men 65 to 74 years old living in the Central Denmark Region resulted in significant hazard ratio of 0.93 (95% CI, 0.88-0.98; $P=0.01$) and an absolute risk reduction of 0.006 (95% CI, 0.001-0.011).

Marcovecchio ML, Chiesa ST, Bond S, et al; AddIT Study Group. ACE inhibitors and statins in adolescents with type 1 diabetes. *N Engl J Med.* 2017;377(18):1733-1745.

Among adolescents with type 1 diabetes, rapid increases in albumin excretion during puberty precede the development of microalbuminuria and macroalbuminuria; however, the use of an angiotensin-converting enzyme inhibitor and a statin did not change the albumin-to-creatinine ratio over time.

Mazer CD, Whitlock RP, Fergusson DA, et al; TRICS Investigators and Perioperative Anesthesia Clinical Trials Group. Restrictive or liberal red-cell transfusion for cardiac surgery. *N Engl J Med.* 2017;377(22):2133-2144.

The TRICS III study showed that, in patients undergoing cardiac surgery who

were at moderate-to-high risk for death (ie, EuroSCORE ≥ 6), a restrictive strategy regarding red-cell transfusion was noninferior to a liberal strategy regarding the composite outcome of death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis.

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;390(10107):2037-2049.

The PURE study showed that fruit intake was associated with a lower risk of cardiovascular, noncardiovascular, and total mortality; legume intake was inversely associated with noncardiovascular death and total mortality (in fully adjusted models); raw vegetable intake was strongly associated with a lower risk of total mortality; and cooked vegetable intake showed a modest benefit against mortality.

Townsend RR, Mahfoud F, Kandzari DE, et al; SPYRAL HTN-OFF MED Trial Investigators. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. *Lancet.* 2017;390(10108):2160-2170.

The SPYRAL HTN-OFF MED trial showed that, in patients who were drug naive or who had discontinued their antihypertensive medications, renal denervation reduced office and 24-hour ambulatory blood pressure significantly, whereas no significant changes were seen in the sham-control group.

DECEMBER

Cuculich PS, Schill MR, Kashani R, et al. **Noninvasive Cardiac radiation for ablation of ventricular tachycardia.** *N Engl J Med.* 2017;377(24):2325-2336.

In five patients with high-risk, refractory ventricular tachycardia, catheter-free, electrophysiology-guided, noninvasive cardiac radioablation markedly reduced the burden of ventricular tachycardia.

Lear SA, Hu W, Rangarajan S, et al. **The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study.** *Lancet.* 2017;390(10113):2643-2654.

This prospective cohort study, showed that higher recreational and nonrecreational physical activity was associated with a lower risk of mortality and cardiovascular disease events in individuals from low-income, middle-income, and high-income countries.

Lu J, Lu Y, Wang X, et al. **Prevalence, awareness, treatment, and control of hypertension in China: data from 1.7 million adults in a population-based screening study (China PEACE Million Persons Project).** *Lancet.* 2017;390(10112):2549-2558.

Data from the China PEACE (Patient-Centered Evaluative Assessment of Cardiac Events) Million Persons Project showed that, among Chinese adults aged 35-75 years, nearly one-half have hypertension, less than one-third are being treated, and less than one-twelfth have control of their blood pressure.

Spiering W, Williams B, Van der Heyden J, et al; CALM-FIM_EUR investigators. **Endovascular baroreflex amplification for resistant hypertension: a safety and proof-of-principle clinical study.** *Lancet.* 2017;390(10113):2655-2661.

The CALM-FIM_EUR study showed that, in patients with resistant hypertension, the novel endovascular baroreceptor amplification device, MobiusH, substantially lowered blood pressure with an acceptable safety profile.

Su M, Zhang Q, Bai X, et al. **Availability, cost, and prescription patterns of antihypertensive medications in primary health care in China: a nationwide cross-sectional survey.** *Lancet.* 2017;390(10112):2559-2568.

Data from the China PEACE Million Persons Project primary health care survey, a nationwide cross-sectional survey, showed that China has marked deficiencies in the availability, cost, and prescription of antihypertensive medications.

Thiele H, Akin I, Sandri M, et al; CULPRIT-SHOCK Investigators. **PCI strategies in patients with acute myocardial infarction and cardiogenic shock.** *N Engl J Med.* 2017;377(25):2419-2432.

The CULPRIT-SHOCK trial showed that, in patients with multivessel disease, acute myocardial infarction, and cardiogenic shock, the 30-day risk of a composite of death or severe renal failure leading to renal-replacement therapy was lower among those who initially underwent a percutaneous coronary intervention of the culprit lesion only than among those who underwent an immediate multivessel percutaneous coronary intervention.

Vedantham S, Goldhaber SZ, Julian JA, et al; ATTRACT Trial Investigators. **Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis.** *N Engl J Med.* 2017;377(23):2240-2252.

In patients with acute proximal deep vein thrombosis, the ATTRACT trial showed that, while the addition of pharmacomechanical catheter-directed thrombolysis to anticoagulation did not lower the risk of a postthrombotic syndrome, it did not increase the risk of major bleeding. ■

*New Therapies
& Technologies*



SCIENTIFIC ADVANCES IN ATRIAL FIBRILLATION AND ARRHYTHMIAS

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In June 2017, 6200 participants from 90 countries gathered to attend the Europace – Cardiostim congress in Vienna, Austria. The program of this major scientific event included 156 sessions covering the following main topics: (i) atrial fibrillation; (ii) devices and syncope; (iii) cardiac resynchronization therapies; (iv) basic science and genetics; (v) catheter ablation; and (vi) innovative products and techniques. This review will discuss the main scientific presentations related to atrial fibrillation, devices and smartphone applications for detecting arrhythmias, and ablation for patients with arrhythmias.

ATRIAL FIBRILLATION

GLORIA-AF registry

The GLORIA-AF registry was a prospective registry program that included 56000 patients from 44 countries worldwide. The study was designed to obtain real-world data on the characteristics of patients who were newly diagnosed (<3 months from the baseline visit) with nonvalvular atrial fibrillation, on changes in treatment patterns, and on the outcomes of anticoagulation therapy in a broad patient population outside of randomized clinical trials. The phase 2 part of GLORIA-AF began after the approval of dabigatran, the first NOAC, and collected, among other things, data on the safety and effectiveness of dabigatran. Steffen Christow (DE) presented the main findings, showing that about two-thirds of the patients in Western Europe with newly diagnosed nonvalvular atrial fibrillation were asymptomatic or minimally symptomatic. In addition, the rate of previous stroke in these patients was more than twice as high as in symptomatic patients, despite observing no differences in the CHA₂DS₂-VASc score, which may be explained by a longer, but hidden, and therefore, undiagnosed atrial fibrillation history.

Thoroscopic ligation of the left atrial appendage

Kent Nilsson (US) presented the results from a study that included a consecutive cohort of 20 patients with absolute contraindications for anticoagulation who underwent thoroscopic left atrial appendage ligation with the AtriClip, there-

by eliminating the need for periprocedural anticoagulation. The patients had a CHA₂DS₂-VASc score of 4.5±1, a HASBLED score of 3.3±0.78, and a mean age of 73.1±6.4 years. The investigators reported an acute procedural occlusion of 100%, with no leaks. Additional studies are needed to define the efficacy of this technique.

Systematic screening for atrial fibrillation: the ACE 1950 study

Trygve Berge (NO) presented the ACE 1950 study, which was designed to investigate the yield of screening for atrial fibrillation in 65-year-old individuals from the general population in Norway who had risk factors for stroke. All people who were invited to undergo atrial fibrillation screening had a CHA₂DS₂-VASc score ≥2 for men or ≥3 for women and no history of atrial fibrillation (n=1601). The screening was performed using a portable handheld ECG recorder to collect 2-week intermittent ECG recordings. The screening revealed undiagnosed atrial fibrillation in 0.9% of participants included in the trial. The total prevalence of atrial fibrillation was 7.6 per 1000 and the mean CHA₂DS₂-VASc score was 2.8±0.8 in the screened population. Arterial hypertension and diabetes mellitus were the most prevalent risk factors.

DEVICES AND SMARTPHONE APPLICATIONS FOR ARRHYTHMIAS

Indications and outcomes in patients with wearable cardioverter-defibrillators

Tanja Odeneg (AT) presented the results from the Austrian wearable cardioverter-defibrillator registry. This study included 720 patients from 56 centers who received a wearable cardioverter-defibrillator between 2010 and 2017. The median duration for wearing the device was 48 days (range, 1-436). The most common patients using the wearable cardioverter-defibrillator were patients after an acute myocardial infarction with a significantly reduced ejection fraction (≤35%) and patients with nonischemic cardiomyopathies (18% and 20% of patients, respectively). Of those patients treated with a wearable cardioverter-defibrillator, 25 (3.8%) were appropriately shocked due to ventricular tachycardia / ventricular fibrillation events, while 4 (0.4%) were inappropriately shocked.

Subcutaneous ICD cohort: long-term complications

Anne-Floor Quast (NL) presented the 6-year follow-up analysis of the Dutch cohort who received a subcutaneous ICD, showing that the 30-day complication rate was 3% (95% CI, 0% to 6%), while the long-term complication rate was 12% (95% CI, 6% to 18%). The annual complication rate was 2%.

A matched comparison of subcutaneous and transvenous ICD therapy

In this propensity-score matching analysis of the SIMPLE and EFFORTLESS studies, a large number of matched patients with subcutaneous ICDs were followed for 60 months and compared with a similar group of patients who had a trans-

venous ICD. Tom Brouwer (NL) presented data showing that, in the subcutaneous ICD group, the complication-free rate was 91.1% vs 92.7% in the transvenous ICD group ($P=0.38$), the device implantation pouch was free of problems in 96.6% vs 98.0% ($P=0.25$), the electrodes were free of problems in 99.1% vs 97.5% ($P=0.055$), the infection-free rate was 97.8% vs 99.5% ($P=0.04$), and there were no inappropriate shocks in 99.3% vs 99.2% of the patients. Together, these results show that both approaches for ICD devices have comparable results during a long-term follow-up.

Detecting atrial fibrillation using smartphone applications

Two different smartphone applications for atrial fibrillation detection were compared and their sensitivity and specificity were evaluated. The first application (BeatScanner) utilized the smartphone's accelerometer and gyroscopic sensors, while the second (Preventicus) utilized the smartphone's camera function. Karim Nabeela (UK) presented data showing that the sensitivity and specificity for the identification of atrial fibrillation was 89% (95% CI, 79% to 95%) and 67% (95% CI, 55% to 78%) with BeatScanner compared with 94% (95% CI, 86% to 98%) and 96% (95% CI, 88% to 99%) for Preventicus. Finally, the user preference was 37% for BeatScanner and 63% for Preventicus.

ABLATION IN PATIENTS WITH ARRHYTHMIAS

Second-generation cryoballoon ablation in patients with paroxysmal atrial fibrillation

Robert Hokanson (US) presented the results of the 24-month safety and efficacy follow-up of the STOP-AF postapproval study. This study was the largest prospective, multicenter FDA study in North America to assess the long-term safety and effectiveness of the Arctic Front Advance Cryoballoon system in patients with drug-refractory recurrent symptomatic paroxysmal atrial fibrillation. Acute procedural pulmonary vein isolation was achieved in 342 of the 344 enrolled patients (99.4%). In 89% of the procedures, a 28-mm balloon was used exclusively; each patient received 9.1 ± 2.7 applications. The mean balloon temperatures for the 28-mm and 23-mm balloons were -47.5°C and -53.1°C , respectively. There were 20 patients (5.8%) with major procedure-related events and 11 patients (3.2%) with phrenic nerve injury that was unresolved before hospital discharge. No device- or procedure-related deaths were reported. Concerning the efficacy of the technique, the results showed that 82% of the patients were free from atrial fibrillation at 1 year and 75.3% at 2 years. Freedom from atrial fibrillation and symptomatic atrial flutter / atrial tachycardia was 79.5% at 1 year and 72.3% at 2 years.

CONCLUSION

The new diagnostic and therapeutic modalities for arrhythmias are evolving at a steady pace, although for pacing there is a relative stagnation if leadless pacing is excluded. In contrast, there is a continuing evolution of wearable and implantable devices related to rhythm monitoring because digital health – and especially telehealth – is increasingly becoming the domain with extremely promising prospects. Finally, for ICDs, subcutaneously implanted devices are becoming established as a reliable technique with a particularly promising future that will deal more effectively with one of the most lethal mistakes of nature, namely ventricular fibrillation. ■

INNOVATIONS IN CORONARY ARTERY DISEASE: A BENCH-TO-BEDSIDE APPROACH

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Keywords: angina pectoris; coronary artery disease; interventional therapy; pharmacotherapy

The 2017 Innovations in Coronary Artery Disease (ICCAD) meeting in Venice, Italy brought together scientists, physicians, and surgeons from 55 countries around the world, who were able to interact and expound on a broad range of new advances and new directions in the field of coronary artery disease. This bench-to-bedside approach allowed for a comprehensive overview of innovations in coronary artery disease.

BASIC SCIENCE AND MOLECULAR BIOLOGY

The basic science sessions focused on three main areas: (i) advances in stem cell science; (ii) studies on cell death, mitochondria, and autophagy; and (iii) novel strategies for protection against ischemia-reperfusion injury. Discussions included stem cell exosomes, iPS-derived extracellular vesicles, and bone marrow cell therapy to repair the failing heart. In the field of ischemia and reperfusion, mTOR signaling and cardioprotection may be important for patients with diabetes, while the role of microRNA, nitric oxide and nitrite pathways, and mitochondrial redox function need further evaluation.

ANGINA PECTORIS: THE ANGINA AWARENESS INITIATIVE

A global angina awareness program was launched at ICCAD 2017 to refocus attention on angina pectoris. Angina pectoris, once a central theme in patient management, has been largely neglected in the era of reperfusion and revascularization.¹ However, angina remains a frequent and disabling condition, affecting 20 000 to 40 000 cases per million European inhabitants, has increasing prevalence in the aging population, and is the initial presentation in approximately 50% of patients with angiographically proven coronary artery disease. Angina is costly, with an estimate that it accounts for 2.6% of overall health care expenditures in the European Union, with a staggering annual bill of more than €40 000 million.

The REACH registry highlighted the risk of cardiovascular events in patients with stable coronary artery disease.² The 1-year cardiovascular event rates (cardiovascular

death, nonfatal myocardial infarction, stroke, and/or hospitalization) increased as a function of the number of symptomatic disease locations. More than 25% of patients with disease in ≥ 3 locations had a cardiovascular event at 1 year. The REACH registry also showed that, in the long term, patients with angina at baseline had higher rates of future cardiovascular events, including later heart failure, cardiovascular hospitalization, and coronary revascularization.³

One-third of patients with chronic stable angina remain symptomatic.⁴ Moreover, under-recognition of angina is common in routine clinical practice. The APPEAR study, which involved 155 cardiologists and 1257 outpatients with coronary artery disease, showed that, in 43% of cases, angina was under-recognized by the treating physician.⁵ Under-recognition of angina was associated with a lower chance of treatment optimization, resulting in poorer angina control. In addition, angina is an important predictor of events in patients with stable coronary artery disease.

OPTIMAL MEDICAL THERAPY FOR ANGINA

What, then, should be the medical management in patients with stable coronary artery disease? The ESC stable angina guidelines divide angina management into two clear areas: management of anginal symptoms and management of outcome events using appropriate therapy according to measures of event prediction.⁶ The management of angina symptoms is based mainly on short-acting nitrates, β -blockers, and calcium antagonists, while second-line therapy includes ivabradine, long-acting nitrates, ranolazine, and trimetazidine. Second-line drugs may be switched to first-line in certain patients (eg, ivabradine in patients for whom β -blockers are contraindicated).⁷ Importantly, angiography and revascularization by PCI or bypass surgery should always be considered, depending on the age and clinical state of the patient.

Medical therapy for angina should be optimized on an individual basis for proper symptom control. In a contemporary, multicenter study of US outpatients, 44% of patients were on suboptimal antianginal pharmacologic therapy and there was a wide variability across the sites.⁸ The CADENCE study in Australia⁴ found that only 54% of angina patients were treated with either a β -blocker or a nitrate. A cross-sectional, multicenter study in Spain reported that nearly half (49.7%) of the patients reported frequent angina symptoms.

Simplifying the medication regimen improves symptom control and patient treatment satisfaction.⁹ Optimizing treatment can lead to major improvements in patient satisfaction and the Seattle Angina Questionnaire score.

RECENT AND ONGOING CLINICAL TRIALS

During the ICCAD session with the ESC Working Group on Cardiovascular Pharmacotherapy, the recent advances and ongoing news from clinical trials were presented. The COMPASS trial data present perhaps more questions than answers regarding when to use combination antiplatelet-anticoagulant therapy for the secondary prevention of coronary artery disease. Treatment individualization seems to be prudent when considering efficacy and safety issues. Importantly, the findings are clearer for patients with peripheral artery disease. We now have a pharmacotherapy that reduces acute limb ischemic events and the need for limb amputations. The antithrombotic management of patients with both atrial fibrillation and acute coronary syndrome or PCI was examined in the REDUAL-PCI trial. This trial showed that dual therapy with dabigatran and a P2Y₁₂ inhibitor was associated with less bleeding than triple therapy using aspirin, a P2Y₁₂ inhibitor, and warfarin. However, caution must be urged regarding the use of the lower dose of dabigatran (110 mg twice a day) in patients undergoing PCI, since there was a numerically greater incidence of stent thrombosis and ischemic events with this dose. In 2018, we expect the results of the AUGUSTUS trial, which is comparing, in a 2 X 2 factorial design, apixaban with warfarin in combination with a P2Y₁₂ inhibitor, with or without the addition of a third antithrombotic drug (aspirin).

Lipidology outcome trials are breaking new ground almost daily. Is an LDL-C value of ≤ 50 mg/dL the new target or should it be ≤ 30 mg/dL? We await further analyses from FOURIER and, in 2018, from ODYSSEY to define the population that will benefit the most from PCSK-9 inhibitors. The ORION program is examining the inhibition of PCSK-9 synthesis by inclisiran, a long-acting inhibitor of mRNA that is administered once or twice every six months. Another new strategy is targeting ANGPTL3 (an inhibitor of lipoprotein lipase), and, in preliminary studies, evinacumab significantly reduces LDL in patients with familial hypercholesterolemia. Apolipoprotein-A1 infusions post-MI are the subject of the AEGIS program and we are waiting to see whether this strategy decreases recurrent cardiovascular events. The PROMINENT study is examining the new SPPARM- α drug pemafibrate on triglyceride levels and outcome in diabetic patients with hypertriglyceridemia. BETonMACE is targeting epigenetics and testing whether apabetalone improves outcome in patients with diabetes and recent acute coronary syndrome.

Recent diabetes trials have shown that SGLT2 inhibitors reduce outcome events; further results are expected regarding dapagliflozin in 2018 and ertugliflozin in 2019. The GLP-1 analogs also carry survival benefit, although it is not clear whether this benefit is confined to drugs administered by daily injection. What is clear is that, in patients with cardiovascular disease, diabetes should now be treated by the cardiologist, just as it is the cardiologist who prescribes statins for lipid management.

In the field of heart failure, the most recent clinical trials have been disappointing, probably reflecting our lack of understanding of the pathophysiology. Despite the success of the PARADIGM trial in selected heart failure patients, the clinical applicability of sacubitril is still not clear in the general heart failure population.

INTERVENTIONAL CARDIOLOGY, VALVE INTERVENTIONS, AND CARDIAC SURGERY

The areas of interventional cardiology and surgery are beyond the scope of the present discussion. Many patients undergoing revascularization are elderly; therefore, additional issues regarding valve disease must be addressed. Cost-benefit studies are starting to show the advantage of transcatheter aortic valve replacement over surgical aortic valve replacement in selected populations.

CONCLUSION

ICCAD 2017 presented new information regarding stem cells and basic cellular mechanisms and discussed how this information may be translated into clinical use in future research. The angina awareness initiative was launched to remind the modern cardiologist about optimizing medical treatment in the clinical arena and about the importance of recognizing patients with angina who are at an increased risk of future cardiac events. Clinical cardiovascular trials have provided compelling new information that has improved outcomes considerably. Finally, the interventional arena now presents a holistic approach to patients with coronary artery disease, including the management of patients with accompanying valve disease and other comorbidities. ■

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CARDIAC REHABILITATION: WHAT ARE THE LATEST ADVANCES?

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2016 EUROPEAN GUIDELINES

Cardiac rehabilitation is a complex intervention offered to patients diagnosed with heart disease, and it includes components of health education, advice on cardiovascular risk reduction, physical activity, and stress management. There is increasing evidence that cardiac rehabilitation reduces mortality, morbidity, and unplanned hospital admissions and improves exercise capacity, quality of life, and psychological well-being, and it is now highly recommended for both patients after an acute coronary event or revascularization and patients with heart failure, as clearly stated in the European guidelines.¹ Unfortunately, referral to and participation in cardiac rehabilitation programs varies widely across countries. Many cardiac rehabilitation programs do not include unstable patients, patients with heart failure, devices, or peripheral artery disease, and the referral and retention of both women and older, higher risk patients remain suboptimal. The guidelines recommend referrals to be increased through electronic prompts or automatic referrals, while patient uptake may be improved with a structured follow-up by nurses or therapists and early entry into cardiac rehabilitation programs after discharge (Table 1).¹

NEW EVIDENCE FROM META-ANALYSES AND REGISTRIES

The CROS meta-analysis² evaluated the effectiveness of cardiac rehabilitation on total mortality and other clinical end points after an acute coronary event, but it considered only clinical studies performed during and after 1995. These strict criteria were chosen to evaluate the role of this intervention in the era of contemporary optimized treatment. The included studies involved mostly patients with stable coronary artery disease (158 781 patients), patients after an acute coronary syndrome (46 338 patients), and patients after a coronary artery bypass graft (14 583 patients), and it involved 219 702 patients in total. CROS demonstrated that cardiac rehabilitation reduced total mortality in all populations, but not hospital readmissions and nonfatal cardiovascular events. However, the meta-analysis had several inherent limitations. In several studies, the information on cardiac

rehabilitation protocols, content, and the processes used to form the groups was scarce, with different implemented exercise programs and very heterogeneous populations. Furthermore, the distribution and combination of secondary outcomes differed in every study, with a large variation in the statistical methods used. Therefore, it was not possible to perform any subgroup analyses.

Poffley et al published a systematic review on all available cardiac rehabilitation registries at both national and international levels³; it was based on a search of four databases conducted in July 2016. Finally, eleven articles were included that comprised seven national registries and one international registry (of twelve European countries). Data were most often provided to the registry by a web-based application, and the data collected included individual-level data, such as sociodemographic characteristics, medical history, and clinical measurements). This review showed that there was a large heterogeneity in the registries, mainly due to the differences in cardiac rehabilitation structure, legislation, funding, and national guidelines. Follow-up data were missing and the evaluation of cardiac rehabilitation outcomes limited.

EuroCaReD,⁴ a multinational cardiac rehabilitation registry in European countries, was created as a platform for putting together information on the clinical status of cardiac rehabilitation across Europe. Although EuroCaReD is one of the first international registries, its preliminary findings showed almost the same disappointing results (in terms of heterogeneity, reliability, and representativeness) as the rest of the registries presented by Poffley et al.

To overcome problems and challenges in developing cardiovascular disease registries in Europe, the creation of specific recommendations by scientific associations and countries, which have a long experience in maintaining cardiac rehabilitation registries, is an emerging need.⁵

EMERGING PATIENT GROUP: FRAIL SUBJECTS

The interest of the cardiac rehabilitation experts has been recently focused on frail patients. Frailty is a geriatric syndrome characterized by a vulnerability status associated with declining function in multiple physiological systems and the loss of physiological reserves. It correlates to medical outcomes in the elderly, and it has been shown to have prognostic value for patients in different clinical settings, such as in patients with coronary artery disease, patients after cardiac surgery or transvalvular aortic valve replacement, patients with chronic heart failure, or patients after implantation of a left ventricular assist device. The prevalence, clinical relevance, and prognostic relevance of frailty in a cardiac rehabilitation program has not yet been well characterized despite the increasing frequency of elderly patients in this setting, where frailty is likely to influence the onset, type, and

intensity of the exercise training program as well as the design of tailored rehabilitation interventions⁶. Therefore, the need to start looking for frailty in elderly patients entering cardiac rehabilitation programs is emerging, as is the need to have a better understanding of whether exercise-based cardiac rehabilitation may change the course and prognosis of frailty in cardiovascular patients.

NEW CARDIAC REHABILITATION SETTINGS

The European guidelines have considered alternative modes of cardiac rehabilitation, such as home-based rehabilitation and telerehabilitation, ie, the use of electronic communication and information technologies to provide and support remote clinical care after an acute cardiovascular event.¹ In a prospective evaluation, home-based cardiac rehabilitation was tested in frail patients awaiting an elective coronary artery bypass graft or valve surgery.⁷ No adverse events or cardiac symptoms were reported and there were significant improvements in the clinical frailty score, the 6-minute walking test distance, and the short physical performance battery total score. A large randomized controlled study is required to reveal the potential beneficial effects of home-based cardiac rehabilitation in this patient population.

MOBILE TECHNOLOGY

In the last years, the implementation of mobile computing and communication technologies for health service and information (ie, mHealth) has increased patient engagement while reducing health care costs and improving patient outcomes.⁸ A major concern is that the development of mHealth has not been driven by the needs and expectations of health care professionals and patients, but mainly by the technical possibility of the devices. However, little is known about the use of and interest in mobile technology by cardiac patients, particularly for health reasons, or about whether the usage of mobile technology varies across patient demographics.⁹

A study was conducted to describe cardiac patients' use of mobile technology and determine variations between age groups after adjusting for education, employment, and confidence with using mobile technology.¹⁰ Cardiac patients eligible for attending cardiac rehabilitation (mainly after percutaneous coronary intervention [33.3%, 94/282] and myocardial infarction [22.7%, 64/282]) were recruited from nine hospitals and community sites across metropolitan and rural settings in New South Wales, Australia. The participants showed an unexpectedly high interest and confidence with using mobile technology, willingness and interest in learning, and health-related use. The majority (91.1%) used at least one type of technology device, 70.9% used mobile technology (mobile phone/tablet), and 31.9% used all types. Technology was used by 54% for health care purposes, most often to access

information on health conditions (41%) and medications (34.8%). Age, school education, and areas of living had an important independent association with the use of mobile technology after adjusting for education, employment, and confidence. The youngest group (<56 years) was over 4 times more likely to use any mobile technology, 5 times more likely to use mobile apps, and 3 times more likely to use technology for health-related reasons than those in the oldest group (>69 years). Participants who had completed high school were twice as likely to use mobile technology apps and mobile technology for health-related reasons as those who had not completed high school.

TELEREHABILITATION

Finding innovative and cost-effective care strategies that induce long-term health benefits in cardiac patients constitutes a big challenge today. The feasibility and efficacy of a 4-month integrated telerehabilitation home-based program (Telereab-HBP) was evaluated in 112 patients with combined heart failure and lung disease. Telereab-HBP included remote monitoring of cardiorespiratory parameters, weekly phone calls by the nurse, an exercise program, and weekly monitoring by the physiotherapist. After 4 months, the intervention group showed improvements in exercise capacity (Δ 6-min walk test, +60), time free from hospitalization, dyspnea index, physical activity profile, disability (Barthel), and quality of life compared with the control group. At 6 months, these benefits, regarding outcomes, were maintained.¹¹

The aim of the Telerehab III follow-up study was to assess whether a 6-month cardiac telerehabilitation program could induce long-term health benefits and remain cost-effective after the teleintervention ended.¹² In 126 cardiac patients, 2 years after completing a multicenter, randomized controlled telerehabilitation trial, exercise tolerance fell significantly in the intervention group at year 2 vs year 1 (24 ± 8 mL/min*kg at year 1 vs 22 ± 6 mL/min*kg at year 2; $P\leq 0.001$), but it remained significantly higher than the control group ($P=0.032$). Dividing the incremental cost (€878/patient) by the differential incremental quality-adjusted life years (0.22 quality-adjusted life years) yielded an incremental cost-effectiveness ratio of €3993/quality-adjusted life year, demonstrating a cost-effectiveness up to 2 years after the end of the intervention. ■

Recommendations	Class of recommendation	Level of evidence
Participation in a cardiac rehabilitation program for both patients hospitalized for an acute coronary event or revascularization and patients with heart failure is recommended to improve patient outcomes	I	A
Methods to increase referral to and uptake of cardiac rehabilitation should be considered, such as electronic prompts or automatic referrals, referral and liaison visits, structured follow-up by physicians, nurses, or therapists, and starting a program soon after discharge	IIa	B
Programs led by nurses and allied health care professionals should be considered to provide cardiovascular disease prevention across health care settings	IIa	B

Table I. Recommendations for specialized prevention programs.

From reference 1. Piepoli et al. Eur J Prev Cardiol. 2016;23(11):NP1-NP96.

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DIGITAL HEALTH: HYPE OR HOPE?

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Digital is the new normal. Digital technologies allow us to access information (sometimes of variable quality) almost instantly, trigger actions remotely (such as transferring money to anywhere in the world), and even communicate with a huge audience of people that we have never met (Twitter™ and other social media platforms). Where do health care and health care professionals sit in all of this? At times, it looks like health care is the one area of human activity that is the most resistant to change.

The term “eHealth” or “digital health” covers the use of information and communication technologies and services in health. These technologies may be used by health care institutions, health care professionals, and, of course, patients/citizens. mHealth is a relatively new subdomain of eHealth that involves mobile phones as well as the more complex applications (apps) that are available for smartphones. It is a rapidly expanding field: an estimated 2.3 billion people worldwide own a smartphone,¹ and half of these people are using health or lifestyle/wellbeing apps. The distinction between health, medical, lifestyle, and fitness information is becoming increasingly blurred, and it is difficult for health care professionals, regulators, and policy makers to keep up with the rapid changes happening all around us.

As cardiologists, we are generally early adopters of new technologies, but, in our day-to-day practice, we often struggle to know what to do when a patient shows us an app on their smartphone that has collected data on them since the last clinical visit. Can we trust the data? How do we import the data into the patient’s electronic medical record even if we do trust the data? And, what happens if a lawyer challenges our use of the data if we make a decision that ends in an adverse event? Often there is little guidance to help us. Politicians strongly believe that digital transformation (or “disruption”) will ensure a better and more efficient health (care) system. A previous European Commission Vice President, Neelie Kroes, is quoted as stating in 2014 that “mHealth will reduce costly visits to hospitals, help citizens take charge of their own health and wellbeing, and move toward prevention rather than cure.”² Not coincidentally, she also highlighted the economic benefits of supporting the “booming app economy and entrepreneurs.”

Although we might be somewhat more critical of the rush to adopt new technologies than the politicians might be, it is clear that there are many potential benefits to digital transformation. Easier access to health information should improve health literacy, increase the chances of healthier lifestyle choices, and improve self-monitoring and self-care. Empowering or “activating” patients should lead to better outcomes and more shared decision-making processes. Those living in remote or underserved areas may be able to access better care and advice. Digital technologies may also enable older people to live more safely in their own homes for longer, with fall detection and remote monitoring already available, which trigger carer visits if something is detected, or even just sending medication and medical appointment reminders. Many people do not like the concept of “Big Brother” watching, while others find this reassuring, particularly if they live far from their families.

Digital technologies can enable us to interact remotely with patients (teleconsultations on mobile phones or smartphones using platforms, such as Skype™ or FaceTime™) and other professionals (virtual multidisciplinary teams, second opinions, etc). Already, an app has been developed that is more accurate at diagnosing skin cancer than a dermatologist; and imaging interpretation, more generally, is an obvious target for expert advisory systems and machine learning.

The massive increase in recorded data may allow systems to increase the safety and consistency of medical care. In theory, there should at least be better organizational monitoring of effectiveness and efficiency and a more tailored approach to an individual’s needs and care provision. Big data approaches are often discussed at conferences, where huge volumes of rapidly changing data collected from a wide range of sources can be used to provide new insights into disease and health outcomes. Many universities and global information technology companies are investing heavily in this area.

The World Health Organization has recently reviewed the progress of implementing eHealth solutions in the European area.³ On a positive note, the report identified clear evidence that there was an increased appetite for eHealth, with tangible progress in many countries. The majority of European countries had national strategies or policies for eHealth and national health information systems. However, the report sounded a warning that eHealth requires far more than just the acquisition of technology and that initiatives were often derailed by the changes required on organizational processes and structures, staff roles, education, reimbursement, and culture. Also, a lack of a legal framework has often slowed progress down, and many projects have failed to convert from pilots to large-scale implementation.

Therefore, there is much promise. Maybe even hype. However, what might be some of the downsides? There is concern among regulators about data security, and among health care professionals about the legal issues: when new data becomes available 24/7, what happens if action is not immediately triggered? Who will look at the tsunami of data potentially available? Will we ever be allowed to “switch off?” How can we incorporate patient-generated data into our medical records and decision-making processes? How can we be sure that these data are valid and reliable? Which apps (if any) should we recommend or prescribe to our patients?

The European Society of Cardiology is increasingly active in the digital health space. It has published a position statement and identified a roadmap for the organization.⁴ A digital committee has been set up to help accelerate and coordinate activities across its members and affiliated groups. At the Annual Scientific Meeting in Barcelona in August 2017, there was a “Digital Village” (in partnership with 4 years from Now [4YFN], a program of the Mobile World Capital Barcelona) where delegates could view start-up technologies from key digital health pioneers. The key words were digital empowerment, digital transformation, and digital care innovation. Examples of such innovation included atrial fibrillation diagnostic technologies (ranging from wearables to apps), internet-based digital health data depositories, new remote monitoring systems, rehabilitation gaming systems, automatic echocardiogram reading software, and decision support technologies for doctors and patients.

Cardiologists strongly embrace evidence-based medicine, and they are most comfortable with large randomized trials that clearly demonstrate improvements in survival, reductions in hospitalization rates, and/or improvements in quality of life. Such robust assessments ensure that we adopt innovations that truly make a difference, but the pathway from idea to implementation is long and very expensive. Digital solutions do not fit easily into this framework, and many of the key stakeholders (doctors, regulators, reimbursement authorities) struggle with how to value digital innovation. Some things are likely to happen without robust evidence (increased electronic medical records and e-prescribing across borders) and some things are likely to be pushed into practice by popular demand (home-based monitoring of blood sugar, blood pressure, remote consultation), but other technologies do require robust evaluation (eg, artificial intelligence–based image recognition software for diagnostic purposes, implantable monitoring technologies, decision support technologies, app-based triage replacing the general practitioner assessment). In recognition of these challenges, the Food and Drug Administration Center for Devices and Radiological Health in the US has set up a Digital Health Program, which “seeks to better protect and promote public health and provide continued regulatory clarity by fostering collaborations with digital health customers and developing and implementing regulatory strategies and

policies for digital health technologies.”⁵ Other areas of the world are likely to follow shortly.

What is clear is that cardiologists cannot always just say “no” to disruption coming from digital innovation. We need to be part of the conversation, not only by supporting innovation to address unmet needs and improving outcomes and patient experience and convenience, but also by demanding robust evidence and a regulatory/legal framework that clarifies what role these technologies should have in clinical practice. We need to work with all of the key stakeholders to navigate through these potentially choppy waters together.

The future is hopefully bright and undoubtedly more digital! ■

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NEW CARDIOVASCULAR DISEASE THERAPIES: LIFE PROLONGATION, BUT AT WHAT COST?

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Keywords: antianginal drug; anticoagulant; antiplatelet; coronary artery disease; cost; mortality, quality of life

Each year, after a congress, we have new challenges to tackle, which is also true after the 2017 ESC congress, especially in the field of chronic coronary artery disease. What shall we propose to our patients when talking about new therapies? Should we talk about survival or should we talk about quality of life? Once more, at this year's ESC congress, new clinical trial data was presented. Of them, I recall three trials that might be adequate to this discussion—COMPASS, PEGASUS TIMI 54, and CANTOS.

COMPASS

The COMPASS trial¹ investigators tested the hypothesis of noninferiority of three strategies in 27395 patients with chronic coronary artery disease: (i) rivaroxaban (2.5 mg twice a day) plus aspirin; (ii) aspirin alone (100 mg once a day); and (iii) rivaroxaban alone (5 mg twice a day). The primary end point was a combination of cardiovascular death, stroke, or myocardial infarction. The results showed that the combination of rivaroxaban 2.5 mg twice a day plus aspirin had the best results; however, to achieve a 0.7% absolute reduction in death, 143 patients need to be treated to save one life, and, to reduce major adverse cardiovascular events, 77 patients need to be treated, with an almost similar risk of a major bleeding event. Based on this data, we must determine whether it is necessary to conduct a cost-efficacy study before implementing this treatment.

PEGASUS TIMI 54

PEGASUS TIMI 54, another trial similar to COMPASS, included patients with coronary artery disease who had a previous myocardial infarction 1 to 3 years before randomization. PEGASUS TIMI 54² compared three treatments: (i) ticagrelor (90 mg twice a day) plus aspirin; (ii) ticagrelor (60 mg twice a day) plus aspirin; and (iii) aspirin alone with the same primary end point as the COMPASS trial. Compared with aspirin alone, a benefit was observed with both ticagrelor 90 mg twice a day plus aspirin and ticagrelor 60 mg twice a day. While the benefit was similar between the two treatments, ticagrelor 90 mg twice a day plus aspirin resulted in more major bleeding events.

These results mean that 188 patients need to be treated to prevent 1 cardiovascular death and 79 patients need to be treated to avoid 1 primary end point event, but with a cost of one major bleeding event with this dual antiplatelet treatment.

The trial results from both COMPASS and PEGASUS TIMI 54 support using a double antiplatelet or a non-vitamin K-antagonist oral anticoagulant plus aspirin regimen to reduce cardiovascular events and death; however, as expected, these treatments result in a higher number bleeding events. As such, we need to determine which treatment to choose, if any, and if a treatment is chosen, when it should be given.

CANTOS

Another trial—CANTOS—tested a new treatment strategy to reduce atherosclerosis progression, ie, targeting inflammation using an anti-inflammatory drug. The trial³ included 10 061 patients who had all been previously treated with statins to lower cholesterol levels, but who still an excess of inflammation as indicated by a high-sensitivity C-reactive protein level >2.0 mg/L. CANTOS analyzed three doses of canakinumab (50, 150, and 300 mg), a monoclonal antibody against interleukin-1 β , given subcutaneously every 3 months vs placebo for 48 months. The results showed a reduction in major cardiovascular events (3.8% vs 4.5%) with the 150-mg dose vs placebo. In addition, patients in the active treatment arm also had a higher incidence of fatal infections. Considering that 158 patients need to be treated with canakinumab to obtain the reduction in cardiovascular events, but with no reduction in the number deaths, and a cost that is estimated to be \$40 000 per year, is this treatment really cost-effective?

COST-BENEFIT ANALYSIS OF TREATMENTS

In addition to the three trials previously discussed, another trial—FOURIER—showed a reduction in cardiovascular events when treating patients with an antibody against the PCSK-9 proprotein. The FOURIER trial was published in March 2017 and presented at the ESC congress in August. The trial provided data about prespecified safety concerns and showed no problems with the very low levels of LDL cholesterol achieved with the treatment.⁴ Based on data from studies with the PCSK-9 proprotein antibody, Arieta A et al⁵ conducted a cost-benefit analysis showing that the cost for an additional quality-adjusted life year was \$337 729.

When we see the net effect in all trials, they are near a 0.8% to 1.8% absolute reduction for all events. For example, in the COMPASS trial, almost 150 patients needed to be treated to save one life, which is similar to the results from the PEGASUS trial (NNT=188). So, can we afford these costs? Or should we think about these results differently? The best way to determine which treatment to prescribe would not include thinking about money, but, unfortunately, to have a longer life and/or an improved quality of life someone must pay the costs.

Cost-effectiveness is calculated by health care systems to determine whether they will or will not spend money for a treatment. Obviously, there are many possibilities, which vary by country depending on the available resources in each country or health care system. However, there is no calculation for cost-effectiveness that considers quality of life and well-being instead of available resources, even if we consider that medicines or actions improve people's lives. While some studies have compared interventions (eg, CABG) with angioplasty and clinical treatment or renal transplantation or on-pump CABG with off-pump CABG in terms of cost-effectiveness, other studies have compared an intervention with no intervention in terms of quality of life. However, in chronic coronary artery disease, no study has calculated the cost-effectiveness of the combination of drugs that prolongs life with the necessity and costs of the drugs that alleviate the symptoms of angina, in other words, quality of life, even though drugs are available that improve quality of life by decreasing angina attacks at a relatively low cost (eg, trimetazidine [especially], ivabradine, ranolazine, and β -blockers).

If we could find a way to calculate the cost-benefit ratio of a longer lifespan together with quality of life, then we could have a better decision-making tool because, for many patients who suffer from a disease, a longer life may mean a lower quality of life. New therapeutic strategies must be developed with this concept in mind because more often we will see a very small decrease in mortality in clinical trials, but at a much higher cost. ■

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Treatment Adherence



HOW TO ASSESS AND IMPROVE PATIENT ADHERENCE TO HYPERTENSION TREATMENT?

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Keywords: adherence; antihypertensive treatment; cardiovascular outcome; compliance; hypertension; single-pill combination

Despite the clear-cut benefits of modern cardiovascular pharmacotherapy, the majority of patients remain undertreated. Blood pressure control is poor even when hypertension is detected and treated. There is growing evidence that low adherence to treatment is the most important cause of apparently resistant hypertension. Several recent reports focused on detection, predisposing factors, and consequences of treatment nonadherence, and these reports suggested different methods to improve treatment adherence.

ASSESSING PATIENT ADHERENCE TO TREATMENT

There is no gold standard in the assessment of patient adherence to treatment, and several methods probably must be combined to improve diagnostic precision. In general, a physician's prediction regarding their patients' treatment adherence is poor.¹ However, technological progress has provided novel insights into the assessment and management of treatment nonadherence. Ultraperformance liquid chromatography–tandem mass spectrometry became an accurate and practical tool to monitor treatment adherence in both research and clinical settings.¹ Studies based on this method have shown that low adherence to the prescribed medications can affect up to 50% of patients with apparently resistant hypertension.² A substantial proportion of these patients are completely noncoherent. There is a clear association between the degree of treatment nonadherence and both office and ambulatory blood pressure values. Importantly, the results of direct nonadherence tests do not overlap with self-reported adherence questionnaires,³ indicating a poor reliability of nondirect methods.

TREATMENT NONADHERENCE AND A HIGH RISK OF CARDIOVASCULAR EVENTS

Nonadherence to antihypertensive treatment has been constantly linked to a higher risk of cardiovascular events.⁴ A meta-analysis that included nearly 2 million participants has shown that high treatment adherence is associated with a 29% relative risk reduction in all-cause mortality.⁵ Thus, the benefits reported in clinical trials are reproduced in real-life patients only when there is treatment compliance.

FACTORS ASSOCIATED WITH LOW TREATMENT ADHERENCE

Both previous and recent studies identified several factors associated with poor treatment adherence. Patient-related predictors include young age, early phase of treatment, female sex, low educational level, low income, unemployment, and comorbidities, such as depression.¹ Nonadherence is also strongly affected by treatment-related factors, such as the choice of drug class and the dosing regimen. In a recent study based on mass spectroscopy measurements, the prevalence of nonadherence to blood pressure–lowering treatment was directly related to the number of antihypertensive pills.⁶ While treatment nonadherence among those who were prescribed one antihypertensive drug was minimal, its prevalence increased to more than 40% among patients who were prescribed three or more drugs. This phenomenon was observed independently of basic demographics and the classes of prescribed antihypertensive drugs, thus supporting the need for treatment simplification.

IMPROVING PATIENT ADHERENCE TO TREATMENT

Patient adherence can be improved by using an appropriate treatment and follow-up regimen,⁷ which might be achieved by: (i) choosing effective drugs with a favorable safety profile and monitoring possible drug-related adverse events; (ii) avoiding complex dosing schedules; (iii) using single-pill combinations when combination therapy is required; (iv) self-monitoring of blood pressure, including electronic transmission of recorded home values; and (v) using motivational interviewing and coaching. Interestingly, repeated screenings for treatment nonadherence based on direct methods might have a therapeutic value per se. Such an approach might improve treatment adherence and blood pressure control.⁸

CONCLUSION

The role of treatment nonadherence as a potential cause of poor blood pressure control is clearly underestimated. Recent evidence suggests that true resistant hypertension is much less frequent than previously thought. Therefore, an evaluation of treatment adherence should become an integral part of the assessment of all patients with difficult-to-manage hypertension.⁹ Whenever we face a patient with apparently resistant hypertension, we should always pose a key question: is it treatment resistance or treatment nonadherence? Importantly, early recognition of poor treatment adherence might reduce the number of costly investigations and procedures, including interventional treatments.¹⁰ Hopefully, the assessment of treatment adherence will be improved further with cheaper and more reliable methods that could be applied in daily practice. Further research is needed to improve our understanding of the psychological and social mechanisms that underlie treatment nonadherence. Finally, we have to develop structured programs

for patients who are nonadherent to their treatment. Such an approach, which is focused on understanding the practical difficulties and perceptions affecting the motivation to adhere, might help physicians achieve target blood pressure values.⁸ Whether such interventions improve cardiovascular outcomes remains to be tested in clinical trials. ■

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IMPACT OF ADHERENCE ON ANGINA CONTROL

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Keywords: antianginal therapy; compliance; ischemic heart disease; stable angina; treatment adherence

Stable angina is a common and potentially life-threatening disease process. Therefore, its recognition and appropriate management are very important to lower its risks. Current guidelines include pharmacological as well as mechanical treatment with PCI for symptom relief when there is significant narrowing of the epicardial coronary arteries.¹ Several studies have shown the multifactorial nature of myocardial ischemia and the need to develop a more tailored approach related to the underlying mechanism of ischemia. This result has been further emphasized in the recently published ORBITA trial, the only blinded, randomized, placebo-controlled trial on PCI. The ORBITA trial showed, in a small group of patients with single vessel disease, that even with severe coronary stenosis, exercise capacity and symptoms are not improved significantly with PCI vs a placebo intervention.²

Different drugs are currently used in the management of angina, meaning that the medical treatment strategies must be correctly implemented. Compliance (or adherence) as it relates to health care is the extent to which a person's behavior coincides with medical or health advice provided by a health care professional. No medicine can be effective if a patient does not take it as prescribed. Consequently, the adherence of patients with stable angina to antianginal therapy is a key factor for controlling the disease. It is known that, among patients with chronic illnesses, approximately 50% do not take medications as prescribed.³ This poor adherence to medication leads to increased morbidity and death, and it is estimated to incur costs of approximately \$100 billion per year.⁴ The adherence of patients with stable angina to antianginal therapy is the key factor for controlling the disease. It is estimated that the level of adherence to prescribed medication in patients with stable angina follows the same pattern as other chronic illnesses; therefore, up to 50% of the patients will drop some of the medication up to 1 year after they have been put on the drugs.

Therefore, noncompliance is a very serious problem for the long-term treatment of patients with stable angina. There are several reasons for noncompliance, which may change from individual to individual and needs to be taken into account by the doctor when managing patients with angina. Some of these factors include:

1. Lack of communication by the doctor on the advantages of being on a certain medication at the time of the prescription.
2. Development of undesirable side effects, such as headache, nausea, tinnitus, sexual dysfunction, etc, that will lead to withdrawal of medication by the patient (many times the side effects are more limiting than the symptoms resultant from the disease process itself).
3. Educational level of the patient.
4. Cost issues.

Accurate assessment of adherence behavior is necessary for an effective and efficient treatment plan and for ensuring that changes in health outcomes can be attributed to the recommended regimen. In addition, decisions to change recommendations, medications, and/or communication style to promote patient participation depend on a valid and reliable measurement of the adherence. Indisputably, there is no “gold standard” for measuring adherence behavior.⁵ A variety of strategies have been reported in the literature. Although objective strategies may initially appear to be an improvement over subjective approaches, each has drawbacks in the assessment of adherence behaviors. There are methods that can be used to monitor compliance, such as using prescription reminders and asking patients to take note of the pills taken each day. Some patients, for instance, like to use pill boxes, which can help improve compliance. Remaining dosage units (eg, tablets) can be counted at clinical visits; however, counting inaccuracies are common and typically result in overestimation of adherence behavior, and important information (eg, timing of dosage and patterns of missed dosages) is not captured using this strategy. Another method that has been tested is the electronic monitoring device (medication event monitoring system), which records the time and date when a medication container was opened, thus better describing the way patients take their medications.⁶

Patient nonadherence to prescribed antianginal therapies has several potential consequences that can be summarized by two major aspects: (i) the patient is not obtaining the proven benefits regarding symptom relief (ie, better quality of life and better outcomes) that translates into a prolonged event-free survival; and (ii) the chances of having an event increases, which may have major consequences for the patient (including life-threatening conditions) and an increase in the economic burden of the disease process for society as a whole. Poor adherence compounds the challenges of improving health in poor populations, resulting in waste and underutilization of already limited treatment resources.

To improve medication adherence, the multifactorial causes of decreased adherence must be understood. The WHO classifies these factors into five categories: (i) socioeconomic factors; (ii) factors associated with the health care team and

system in place; (iii) disease-related factors; (iv) therapy-related factors; and (v) patient-related factors. In broader terms, these factors fall into the categories of patient-related factors, physician-related factors, and health care system/team building-related factors. Other factors may influence noncompliance in patients with angina, some are related to the individual patient, such as age, mental status, socioeconomic condition, and literacy, while others are related to the clinical condition of the patient, such as the presence of other comorbidities (eg, renal failure) or the concomitant ingestion of multiple medications, which will affect the ability of the patient to keep taking the prescribed medication regularly.

One study, which included 870 patients, assessed the relationship between adherence to treatment with trimetazidine modified release (MR) by patients with stable angina and the frequency (risk) of emergency medical care.⁷ They consistently included patients with stable angina in primary health care. The results of treatment for 16 weeks were assessed according to number of patients with angina attacks three times per week or more, the use of short-acting nitrates, and treatment with generic trimetazidine. To strengthen the antianginal therapy, generic trimetazidine was replaced with the original trimetazidine MR. Adherence was considered relatively high if the patients were taking 80% to 120% of the recommended dose of the drug (70 mg/day). The effectiveness of treatment was evaluated by the frequency of emergency hospitalizations and/or ambulance calls due to pain, discomfort, tightness in the chest, or ischemic changes on the electrocardiogram. The study showed that replacing generic trimetazidine with original trimetazidine MR in patients with a high frequency of angina attacks could achieve a significant antianginal effect.⁷

Education is essential to provide the most complete information to the patient about the underlying disease condition and the different treatment options available. The rational, objectives, and potential side effects of a certain medication must also be explained very well because these are the main reasons why many patients stop their medication.

One of the most recognized solutions to improve compliance to recommended therapies relies on the use of a single pill containing associated drugs because this reduces the number of pills the individual patient has to take, which improves compliance. This method is particularly relevant in the elderly patient population with other disease conditions who consequently need to take other medications. It is also important to reduce, as much as possible, the number of times the patient needs to take the medication; once a day medications will improve compliance.

Given the enormous complexities involved in medication adherence, research on improving adherence has been challenging and generally focused on single-

disease states. A recent Cochrane review of 78 randomized trials showed that no simple intervention and relatively few complex ones were effective at improving long-term medication adherence and health outcomes,⁸ highlighting the difficulty in improving medication adherence. The multifactorial nature of poor medication adherence implies that only a sustained, coordinated effort will ensure optimal medication adherence and realization of the full benefits of current therapies. Current recognition of the importance of medication adherence has resulted in the development of many useful internet-based resources.

In conclusion, adherence to therapy is an essential component in the management of angina, and the implementation of different strategies that can help improve adherence is of the utmost importance, which will certainly provide better health care for these patients. ■

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Guidelines, Trials,
& Registries



HEART FAILURE: TRIAL RESULTS, GUIDELINES, AND MORE

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Keywords: bromocriptine; empagliflozin; heart failure; mineralocorticoid receptor antagonist; sacubitril/valsartan combination; serelaxin

The 2017 Heart Failure Congress and the 4th World Congress on Acute Heart Failure took place in Paris, France. The congress was a unique forum where heart failure professionals from around the world met and exchanged ideas and information. The congress was attended by 5024 participants from 121 countries, with a large faculty of 287 international experts. The record number of abstracts (1704; up by 151 from the previous year) and case study submissions (253; up by 36 from the previous year) has established the 2017 Heart Failure Congress as the largest and most influential heart failure meeting in the world. Besides its attractive core program, this year's congress had several distinct and attractive features, including three late-breaking trial sessions, a guidelines into practice track, HFA championships, HFA grand debates, and off-the-record sessions.

INAUGURAL SESSION

Two named lectures, the HFA Eugene Braunwald lecture and the HFA Philip Poole Wilson lecture, were delivered by the world-leading scientists Michel Komajda (FR) and Faiez Zannad (FR), respectively. Komajda addressed the common and underestimated relationship between heart failure and diabetes, stressing that diabetes is a major risk factor for heart failure and the combination is associated with poor outcomes. He emphasized the importance of selecting the appropriate antidiabetic drugs, highlighting the clinical advantages of the SGLT2 inhibitor empagliflozin. Zannad discussed MRAs in the treatment of heart failure. MRAs have demonstrated a reverse translational track, showing how clinical science can influence basic research. The discovery of aldosterone and MRAs almost 40 years ago had little influence on heart failure treatment until the positive findings of the RALES trial¹ revived the basic science interest in the topic. He stated that MRAs are at the beginning of their evolution and that the development of newer drugs that are tolerated better is needed.

LATE-BREAKING TRIALS

Among the late-breaking trials, the results of RELAX-AHF-2² and TRUE-AHF³ were eagerly anticipated. RELAX-AHF-2 was an event-driven, phase 3 trial involving 6600 patients hospitalized for acute heart failure, who received the relaxin receptor antagonist, serelaxin. Although the use of serelaxin was safe, the study did not meet the primary end points, with no difference in cardiovascular mortality at 180 days and a reduction in worsening heart failure. The secondary end points (all-cause mortality at 180 days, length of initial hospital stay, or the combined end point of cardiovascular death or rehospitalizations) were also not met. TRUE-AHF demonstrated that a 48-hour infusion of ularitide, given an average of 6 hours after heart failure presentation, did not reduce cardiovascular mortality at 36 months, nor did it improve the symptoms at 6, 24, or 48 hours; however, it was shown to be safe, improve hemodynamics, and decrease blood pressure and cardiac wall stress.

EDIFY,⁴ another late-breaking trial, investigated the use of ivabradine in patients with HFPEF. The results demonstrated that ivabradine significantly reduced heart rate compared with placebo, but had no effect on diastolic function, exercise capacity, or NTproBNP levels.

Another study, a multicenter, proof-of-concept study, investigated the short- or long-term use of low- vs high-dose bromocriptine for the treatment of peripartum cardiomyopathy. This therapy was safe for both short- and long-term use and it was associated with a significant improvement in LVEF, with no between-group differences. The results show that short-term, low-dose bromocriptine is sufficient in most cases and that critically ill patients may benefit from prolonged treatment with high-dose bromocriptine.

GUIDELINES IN DAILY PRACTICE

The 2016 ESC/HFA guidelines for the diagnosis and treatment of acute and chronic heart failure were reviewed in the new “guidelines in daily practice” session. The session was focused on the patient; it was based on the analysis of two cases and presented by the top experts involved in developing the guidelines. They described the optimal treatment related to the case and explained where the relevant information, tables, and algorithms can be found in the guidelines. This session was highly interactive because the delegates were given the opportunity to send questions via the Heart Failure 2017 app.

An exciting new initiative was the HFA Championships, the competition for the best clinical case among the teams from Japan, Poland, and France. The teams were composed of four health care professionals who presented a case, followed by discussion and questions from the chairpersons. This session was also based on the ESC guidelines, and the teams had the opportunity to ask “trick” ques-

tions and to use two “jokers,” which increased the tension and expectations of the competition. After a fierce, but fair, battle, Fausto Pinto, the president of the ESC, awarded the trophy to the French team.

GRAND DEBATES

The Grand Debate sessions attracted a lot of attention. In one session, the first debate focused on the use of sacubitril/valsartan as a first-line therapy in chronic heart failure, while the second discussed the role of vasodilators in acute heart failure. The arguments for the use of sacubitril/valsartan as a first-line therapy in chronic heart failure are based on the PARADIGM-HF trial⁵ and it included the reduction in mortality and rehospitalization as well as the improvement in the biomarker profile, renal function, and symptoms/quality of life. However, it can be disputed that all of these beneficial findings are based on only one trial, which was done on the stable, outpatient population who were already taking ACE inhibitors or ARBs. In addition, due to the run-in design of the PARADIGM trial, the use of sacubitril/valsartan as a first-line therapy was not really tested. The second debate, which highlighted the role of vasodilators in acute heart failure in the years to come, concluded that, after the failure of two major clinical trials on promising drugs, a future strategy needs to be determined. It was felt that the targets in acute heart failure trials should be redefined and that the joint efforts from both sides of the Atlantic Ocean are needed for innovative study designs.

In another Grand Debate session, the first debate focused on the benefit of treating nonischemic heart failure with an ICD. In light of the Danish study, which demonstrated that only nonischemic heart failure patients under the age of 68, but not older, benefited from ICD implantation, the discussion focused on the best indications. It was felt that the expense and uncertainty of the response to ICD therapy requires a more individualized strategy to avoid unnecessary procedures. The second debate during the session discussed surgical revascularization in heart failure patients based on the long-term results from the STICH trial,⁶ which demonstrated a 10-year improvement with CABG in comparison with optimal medical therapy. The 2014 ESC/EACTS guidelines on myocardial revascularization recommend CABG for a subgroup of patients with significant left main and proximal left anterior descending coronary artery stenosis, a group that was excluded from STICH. Since improved blood flow and viable myocardium after revascularization are the most important factors for a long-term benefit, it was felt that the treatment should be individualized.

BEST HEART FAILURE PAPERS IN 2016

A special session featured the best heart failure papers of 2016, which was extremely well received. Marco Metra (IT), editor-in-chief of the *European Journal*

of *Heart Failure*, acknowledged that the best paper published in this journal was the paper on the 2016 ESC/HFA guidelines for the diagnosis and treatment of acute and chronic heart failure, which was the most downloaded article in 2016, with the highest number of citations. Thomas Luscher (CH), editor-in-chief of the *European Heart Journal*, considered the paper on the results of the EMPA-REG OUTCOME trial⁷ to be the best, since it is the most cited paper in this journal. The EMPA-REG OUTCOME trial demonstrated that empagliflozin reduced heart failure hospitalization and cardiovascular death in both patients with and without heart failure and type 2 diabetes. Stephan von Haehling (DE), the deputy editor of the *ESC Heart Failure*, an open-access journal, believed that the best paper was the article on the use of the CHAD₂DS₂-VASC score to predict the mortality of heart failure patients with or without atrial fibrillation. This manuscript concluded that the CHAD₂DS₂-VASC score was a predictor of all-cause mortality in both groups, and may help identify high-risk heart failure patients.

THE GOLDEN ANNIVERSARY OF THE FIRST HUMAN HEART TRANSPLANT

One session of the congress was dedicated to the golden anniversary of the world's first human heart transplant. Heart transplantation is considered the breakthrough treatment for end-stage heart failure; it is the most successful therapeutic modality for these patients, with a mean life expectancy of 6 to 12 years. The progress in organ preservation and immunosuppression are important advancements, while the limited number of organs available remains a major obstacle. A total artificial heart needs further improvement, but it will be a viable option in the future.

CHART-1 TRIAL

The session on endomyocardial injection of cardiopoietic stem cells used for the treatment of ischemic heart failure reviewed the results of the CHART-1 clinical trial.⁸ In this investigation, the patient's own mesenchymal stem cells were used as a basis for the reparatory response. The results revealed that a stem cell injection was associated with benefits in left ventricular remodeling, including an improvement in left ventricular end-systolic and end-diastolic volume after 52 weeks. The patients receiving fewer injections (<16) had a greater improvement in left ventricular dimensions than did patients receiving more injections.

CONCLUSION

The 2017 Heart Failure congress was an extraordinary scientific event, which confirmed heart failure as a new, emerging specialty in cardiology, and it gave the latest updates on the recent developments in the field, reflecting the continuing success and leading place of the Heart Failure Association. ■

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TOP CARDIOVASCULAR RESEARCH IN 2017

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Keywords: atherosclerosis; coronary artery disease; inflammation; lipid; peripheral artery disease

The 2017 annual meeting of the European Society of Cardiology took place in Barcelona, Spain, and, despite the terrible events that transpired less than 2 weeks before the congress in La Rambla, one of the most famous points in the city connecting Plaça de Catalunya in the center with the Christopher Columbus Monument at Port Vell, it did not prevent almost 32 000 people from gathering in the Fira Gran Via to renew their commitment to foster science for the benefit of those afflicted by, or at risk of, cardiovascular disease. As usual, the congress was the place for breakthrough clinical trials to be presented, some of which are highlighted in this paper.

CARDIOVASCULAR ATHEROSCLEROTIC DISEASE

Atherosclerosis is a complex, multifactorial pathogenic process affecting millions worldwide with clinical manifestations related to the main arterial territories involved (ie, the brain, the heart, and/or the inferior limbs). This year, the science presented at the ESC offered exciting news on how we can decrease cardiovascular risk further by effectively targeting inflammation and by using a strategy of dual anti-thrombotic therapy. Moreover, the always controversial/debatable issue on how low LDL-C levels can go and remain safe was addressed. Taken together, these data may indeed affect future guidelines on cardiovascular prevention.

FROM BENCH TO BEDSIDE: A TALE OF SUCCESS FROM CANTOS

As much as our understanding of atherosclerosis being an inflammatory disease has deepened, it has yet to be proven whether targeting the inflammation cascade directly would affect both the inflammatory mediators and, more importantly, the clinical outcomes. The CANTOS trial¹ tested the hypothesis that canakinumab, a human IL-1 β -targeted monoclonal antibody that lowers systemic inflammation by reducing the plasma levels of IL-6, could reduce cardiovascular events in patients with stable coronary artery disease and a residual inflammatory risk, defined as an hsCRP level of at least 2 mg/dL.

CANTOS was a large trial that included 10 061 patients who were randomized to placebo or 1 of 3 different doses of canakinumab (300 mg, 150 mg, or 50 mg) given

subcutaneously once every 3 months. The primary end point was a composite of the first occurrence of a nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. The study population was comprised mainly of middle-aged men with a median LDL-C level of 82 mg/dL and an hsCRP level of 4.1 mg/dL. Patients were on optimal medical therapy, which included the use of lipid-lowering agents (93%) and an oral antithrombotic drug (95%). The results of the trial showed that canakinumab, at a median follow-up of 3.7 years, led to a significant 15% risk reduction in the primary end point in the group receiving 150 mg of canakinumab, with no discernible effect on LDL-C or HDL-C levels. Other findings of the trial included a significantly higher incidence of fatal infections and sepsis with canakinumab than with placebo and a reduction in platelet counts with no corresponding increase in the risk of bleeding. On the other hand, cancer mortality was significantly lower among treated patients (0.45/100 person-years) compared with placebo (0.64/100 person-years).

In an era in which patients are already on medical therapy that has been proven to lower overall cardiovascular risk, the findings of the CANTOS trial are welcome, showing that, by understanding the underlying mechanisms of the disease better, new opportunities for better therapeutic strategies may arise. Nevertheless, the price of a single 150 mg dose of canakinumab, which is estimated to be around \$16000,² may be prohibitive for its widespread use, considering the target population of the drug.

DUAL ANTITHROMBOTIC THERAPY IN PATIENTS WITH ATHEROSCLEROSIS: ARE WE HEADED IN A NEW DIRECTION?

One of the main pillars in the treatment of all forms of atherosclerotic disease (cerebrovascular, coronary, and/or peripheral) is the use of an antithrombotic agent, such as aspirin. In patients after an acute coronary event or who are undergoing a PCI, the current guidelines recommend dual antiplatelet therapy for different periods of time afterward. A more complex scenario arises in patients who have another preexisting prothrombotic condition, such as atrial fibrillation, which must also be specifically managed. In the latter, effective anticoagulation should be offered to lower the risk of a cardioembolic event. The role of NOACs (rivaroxaban and dabigatran) were put to the test in two trials (ie, COMPASS and RE-DUAL PCI), which were presented in Barcelona, and new light was shed on how safely and effectively we can manage antithrombotic strategies in different clinical, but sometimes challenging, scenarios.

Based on the positive results of the ATLAS ACS 2-TIMI 51 trial in patients with an acute coronary syndrome,³ investigators from McMaster University in Hamilton, Canada, tested, in the COMPASS trial, the hypothesis that low doses of rivaroxaban, a selective direct factor Xa inhibitor, alone or in combination with aspirin,

could further reduce the incidence of cardiovascular events (cardiovascular death, stroke, or myocardial infarction) relative to aspirin alone in patients with stable coronary artery disease or peripheral artery disease. In this international, multicenter trial, 27395 high-risk patients were included and randomized to receive rivaroxaban 2.5 mg twice a day + aspirin 100 mg once a day, rivaroxaban 5 mg twice a day, or aspirin 100 mg daily.⁴ The study population included mostly men with a mean age of 68 years; 91% had coronary artery disease and 27% peripheral artery disease. After a mean follow-up of only 23 months, the trial had to be stopped prematurely due to a significant efficacy favoring the combination of rivaroxaban + aspirin. The dual antithrombotic therapy significantly reduced the composite rate of cardiovascular death, stroke, and myocardial infarction by 24%. As expected, both rivaroxaban treatment arms resulted in more major bleeds than aspirin alone. In the combination arm, major bleeding was increased by 70%, although there was no increase in fatal bleeding or intracranial hemorrhage. In conclusion, the COMPASS trial showed that, in high-risk patients with coronary and/or peripheral artery disease, a dual antithrombotic strategy of low dose rivaroxaban + aspirin reduces cardiovascular events, at the expense of an increase in nonfatal major bleeding.

In patients with atrial fibrillation undergoing a PCI, triple antithrombotic therapy (warfarin + DAPT) is considered the usual care, although this strategy carries a higher risk of bleeding complications. NOACs have consistently shown efficacy and good tolerability in patients with atrial fibrillation compared with warfarin. In the RE-DUAL PCI trial,⁵ investigators assessed the efficacy and safety of dual therapy with dabigatran + a P2Y12 inhibitor (ticagrelor or clopidogrel) vs triple therapy (warfarin + DAPT) in 2725 patients with atrial fibrillation who had undergone a PCI. The results of the trial revealed that the dual therapy (dabigatran 110 mg + a P2Y12 inhibitor) cut the incidence of major or clinically relevant nonmajor bleeding at 14 months by almost 50%; the dual therapy with dabigatran 150 mg yielded a significant 5.5% absolute risk reduction in bleeding complications. Regarding the rates of thrombotic events, dual therapy was noninferior to triple therapy for the incidence of death, thromboembolic events, or unplanned revascularization (13.7% vs 13.4%, respectively). These data could provide another treatment strategy for patients with atrial fibrillation who need a PCI. Maybe now we have an answer for the old riddle: “what is not enough for one, just right for two, and too much for three?”

DIMINISHING LDL-C VALUES: HOW LOW CAN WE GO?

It is irrefutable that lower LDL-C levels are associated with a lower incidence of cardiovascular events across different populations at risk for cardiovascular disease. As strategies, beyond statins, that are more effective at lowering LDL-C hit the market, a growing concern is that maybe we have just gone too far.

In the FOURIER trial,⁶ evolocumab, a PCSK-9 inhibitor, demonstrated a 59% reduction in LDL-C, which was accompanied by significant reductions in cardiovascular outcomes. In a prespecified subanalysis of FOURIER, the safety and efficacy of achieving progressively lower LDL-C levels were assessed in 25 982 patients with stable cardiovascular disease.⁷ The overall results of the trial showed a significant and progressive relationship between lower LDL-C levels and a reduction in cardiovascular outcomes (cardiovascular death, myocardial infarction, unstable angina, coronary revascularization, or stroke). No safety flags were raised in any patient subgroup, including liver or muscle toxicity, neurocognitive decline, cancer, or new cases of diabetes mellitus. Of note, one-third of patients achieved an LDL-C level between 20 mg/dL and 50 mg/dL, and 10% achieved an LDL-C level <20 mg/dL. Once again, future guidelines will have to deal with the new information provided by FOURIER, considering that extremely low levels of LDL-C are usually only achieved by a combination of lipid-lowering strategies.

Finally, inclisiran, the “new kid on the block” for lowering lipid levels, targets the PCSK-9 messenger RNA, which produces dose-dependent reductions in LDL-C. The ORION-1 trial⁸ enrolled 501 patients on statin therapy with or at a high risk of atherosclerotic cardiovascular disease with LDL-C levels >70 mg/dL or >100 mg/dL, respectively. The comparison of different regimens of inclisiran with placebo revealed that the best regimen was inclisiran 300 mg given subcutaneously at days 1 and 90, with a maintenance dose of 300 mg at day 270, and then every 6 months. With this regimen, a 46% time-averaged reduction in LDL-C levels over 12 months could be achieved. The safety profile was good with only 5% of the patients presenting injection-site reactions. Clinical outcomes were not assessed in ORION-1 and they are eagerly awaited.

CONCLUSION

Cardiovascular research is unstoppable. Clinical investigators, along with basic scientists, work in tandem to bring new discoveries from the laboratory, which may open the door for new therapies in the clinical arena. The 2017 ESC congress was packed with science at the highest level, so that physicians and health care providers alike, on their way back home after the meeting, had a lot on their minds. We learned about the first trial designed to look at inflammation as a potential therapeutic target in atherosclerotic cardiovascular disease, which successfully affected clinical outcomes, although its high cost may hamper a more far-reaching use. Different antithrombotic strategies were also presented, with many safe and effective options to deal with high-risk patients, and “the lower, the better” theory behind LDL-C seems to remain unchallenged. New evidence is paving the way to a change in clinical practice.

As we left Barcelona, our minds had already turned to Munich 2018 with great expectation for what will be in store for us during the next ESC meeting.

Adiós, Barcelona. Hallo, München. ■

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IS THE DEVIL IN THE DETAIL? AUTOPSIES OF NEUTRAL HEART FAILURE TRIALS

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Keywords: adherence; enrollment; heart failure; population; procedure

The 14th Global CardioVascular Clinical Trialists Forum was attended by representatives from academia, industry, regulatory authorities, and patients to discuss contemporary cardiovascular outcome trials. In a session titled “Positive signals from recent neutral heart failure trials: time for an autopsy,” which was chaired by Mona Fiuzat (US) and Christopher O’Connor (US), investigators from several of the most discussed HF trials in recent years gave their viewpoints on why the trials did not render a positive result. The lessons learned encompassed most aspects of a clinical trial and the absolute necessity of complete control and oversight of the trial to avoid disappointments further down the line was emphasized.

DEFINE THE RIGHT STUDY POPULATION AND AVOID DISCREPANCIES IN ENROLLMENT

The predefined inclusion and exclusion criteria of a clinical trial serve to ensure that the included patients are those presumed to benefit the most from the studied therapy and to establish adequate safety. In RELAX-AHF2, patients with acute HF were randomized to treatment with the vasodilator serelaxin or placebo. The primary end point, a composite of cardiovascular death at 6 months and worsening HF within 5 days, was not met. Michael Felker (US), one of the investigators, stated that, while the intended population as defined in the protocol was the one actually enrolled, safety considerations regarding potential study treatment effects on blood pressure had prompted an inclusion criteria of a blood pressure ≥ 125 mm Hg before randomization in the study. It is well known that, in acute HF, patients with higher blood pressure fare considerably better than those who are hypotensive, which is, in part, a reflection of different degrees of hemodynamic impairment and disease severity. Thus, the relatively high blood pressure cut-off will result in a study population with a relatively good prognosis and in whom a treatment effect is more difficult to establish. This assumption was also confirmed by the relatively low event rates in the study (8.7% vs 8.9% cardiovascular mortality at 180 days in the serelaxin vs placebo group, respectively).

In TOPCAT, 3445 patients with HFPEF were randomized to treatment with spironolactone or placebo. In the overall population, the primary end point of cardiovascular death, HF hospitalization, and aborted cardiac arrest was not met. However, in a post hoc analysis on regional differences, the investigators found a 4-fold difference in event rates between patients in the Americas (the US, Canada, Argentina, and Brazil) compared with patients in Russia/Georgia. Patients in Russia/Georgia had low mortality rates – close to that of the general population and much lower than observed in HF – whereas patients in the Americas had high event rates, as expected in the enrolled HF population. This, in combination with the observed lower levels of canrenone, a metabolite of spironolactone, at the 12-month study visit in patients from Russia compared with the US and Canada, led the investigators to believe that a significant proportion of patients from Russia/Georgia did not actually have HF and further, may not actually have taken the study drug.

The subgroup findings from TOPCAT have been known for quite some time, but the presentation by the primary investigator Bertram Pitt (US) nevertheless sparked a lot of discussion and further explanation of the observations. For instance, while the regional differences were indeed considerable, on closer inspection, the underlying problem appeared more related to site than to strict geographic disparities, with many sites in Russia/Georgia displaying similar patient characteristics and outcomes as those in the rest of the world, but a few sites with very high recruitment producing the differences. Pitt stated that, while we are careful to ascertain and adjudicate HF-related outcomes in our trials, perhaps we should take more care to adjudicate the baseline diagnosis itself.

In TOPCAT, enrolled patients were stratified based on the inclusion criterion of either a previous HF hospitalization or elevated levels of natriuretic peptides. The majority of those enrolled in Russia/Georgia were included based on the criterion of a prior HF hospitalization, often without information about natriuretic peptide levels, and consequently with a presumably less reliable HF diagnosis. Further, in an additional remark by Nancy Geller (US), director of biostatistics at NHLBI, the importance of equal costs attributed to different strata was highlighted. In the example of TOPCAT, a higher cost associated with the measurement of NT-proBNP could have been a factor in the low proportion of patients included based on this criterion in Russia/Georgia, which, in turn, could have contributed to the unfortunate discrepancy in enrollment.

ENSURE ADHERENCE TO STUDY PROTOCOLS AND PROCEDURES

Equally important to selecting and enrolling the right study population is the ensuing study conduct and appropriate delivery of the intervention for the success of a trial. The possible consequences of diverging from the specific instructions for the study intervention were reflected upon by Milton Packer (US), primary

investigator in TRUE-AHF. In the study, patients admitted with acute HF were randomized to a 48-hour infusion with ularitide or placebo, but the study was neutral with respect to the coprimary end point, which consisted of cardiovascular death throughout the trial and a complex measure of clinical status in the first 48 hours after the intervention. In an effort to avoid ambiguity as to the effects of the study intervention vis-à-vis other aspects of acute HF management, investigators were specifically instructed to refrain from making any changes to other treatments in the 2 hours before and 4 hours after the study drug administration. However, in 17% of patients, these predefined stability criteria were not met. In a subsequent analysis, ularitide was found to be superior among the remaining 83% in whom the stability criteria were satisfied, although the overall trial result was neutral. Packer pointed out that a significant proportion of the study population (772 out of 2157 patients) were recruited from a few high recruitment sites and that it was among these sites that the protocol deviation was most common.

In SOCRATES-PRESERVED, a safety and dose-finding study that evaluated vericiguat (1.25 mg, 2.5 mg, 5 mg, and 10 mg daily) vs placebo, the primary end point of change in NT-proBNP and left atrial volume at 12 weeks was not met. Javed Butler (US) gave one explanation that could have contributed to a neutral result by reducing the study's statistical power. An erroneous software update in the drug dispensation system during the study resulted in 48 patients, who were randomized to the two highest doses, receiving lower doses than intended and they were consequently excluded from the final analysis. Therefore, the potential effects of the higher doses of vericiguat could have been more difficult to detect.

AVOID ERRONEOUS HYPOTHESES, MISMATCHED END POINTS, AND INCOMPLETE PATHOPHYSIOLOGICAL UNDERSTANDING

Many neutral outcomes in trials, however, do not arise from flawed patient selection, enrollment, or protocol adherence, but are the fundamental result of an incorrect hypothesis. Unfounded assumptions, unrealistic effect size projections, failures of logic, and insufficient pathophysiological understanding are not uncommon in contemporary clinical trials and were discussed by the investigators.

BLAST-AHF was designed to determine the optimal dose and safety of an IV infusion of TRV027, a selective angiotensin II type 1 receptor-biased ligand, in acute HF. Although the treatment appeared safe, there was no effect on the primary end point. Peter Pang (US), primary investigator in BLAST-AHF, questioned whether the hypothesis that provided the rationale for the study might not have been adequate, namely that neurohormonal activation is as viable a treatment target in acute HF as it has proven to be in chronic HF. Another example came from SERVE-HF, in which the concept of adaptive servoventilation for central sleep apnea in HFREF was tested based on previous observations of associations between

central sleep apnea and an adverse prognosis. The primary end point was not met and there was even an increase in cardiovascular and all-cause mortality in the treatment arm, which has since resulted in extensive discussion and further research. Faiez Zannad (FR) highlighted the need for more detailed pathophysiological knowledge and better founded hypotheses in general when embarking on new large-scale clinical trials, mere associations rarely suffice.

Even if studied treatments may indeed have potential and a plausible rationale, beneficial effects could go undetected if the primary end point is disproportionate to what the treatment can be expected to achieve. In the case of RELAX-AHF2 and TRUE-AHF, both testing a 48-hour infusion, there were evident hemodynamic effects, which, however, diminished after the infusion was stopped. Both studies used coprimary end points that included cardiovascular death at 6 months or throughout the trial, which may have been far too ambitious. In other cases, new pathophysiological knowledge may come to light during or after the trial that, had it been known earlier, could possibly have altered the course of the trial. Michael Bristow (US) recounted an example from the somewhat older BEST trial that tested the β -blocker bucindolol vs placebo in advanced HF. No overall effect on the primary end point was observed, but there was an apparent interaction effect for race and treatment reflecting a lack of benefit in black patients. Later research suggested that genetic polymorphisms in black patients could explain the interaction and had this been known at the time of the trial, a different outcome may have been achieved.

CHALLENGING INTERVENTIONS

In some trials, the design itself, or, more specifically, the handling of the intervention and the comparator, may prove most challenging. Michael Felker (US) emphasized the difficulty of running a strategy trial, in which the intervention is a disease-management strategy rather than a pharmacological or device intervention. In GUIDE-IT, HF patients were randomized to either NT-proBNP-guided therapy or usual care with a primary composite end point of cardiovascular mortality or HF hospitalization. Felker stated that, in the trial, both the intervention and comparator group received excellent care and, although the NT-proBNP arm received a few more pharmacological interventions, this did not amount to any differences in outcomes. Patients in a clinical trial are generally well taken care of with respect to treatment and follow-up, which can make extraordinary demands with respect to the power of the intervention if any benefit is to be demonstrated. Another example of a challenging strategy trial was made by Dave Whellan (US), primary investigator in ACTION-HF. The trial set out to evaluate the efficacy and safety of aerobic training among 2331 stable HF outpatients. The intervention was both complex and ambitious, consisting of an initial supervised 36 sessions

followed by home-based exercise. In the primary protocol-specified analysis, the intervention did not achieve a statistically significant reduction in the primary composite end point of all-cause mortality and hospitalization. In a supplementary prespecified analysis adjusting for highly prognostic baseline characteristics, the intervention did achieve a modest risk reduction. Whellan proposed that one explanation for the modest result could have been the difficulty of transitioning patients from the supervised to the home-based exercise phase. In the home-based phase, adherence to the training program decreased considerably, which could have lessened the impact of the intervention on outcomes, ultimately signaling that the trial and, more specifically, the intervention, may have been too ambitious.

ADMITTING DEFEAT AND GOING FORWARD

During the session, only one of the trialists on the panel conceded head-on defeat. Karl Swedberg (SE), primary investigator in RED-HF, a trial testing darbepoetin alpha vs placebo in anemic HF patients, said that the trial was well designed and that there were no other apparent reasons for its neutral outcome than the treatment simply being ineffective. As disappointing as a neutral result can be, Swedberg pointed out that such a result is equally important and that burying one concept will allow us to move on to others that show promise. Finally, in the discussion between the panelists and the audience, a few key learning points recurred several times over the course of the session. Both Pitt and Packer emphasized the importance of a close relationship between the trial steering committee, the involved contract research organizations, the data safety monitoring committee, and the sponsor. In the cases of TOPCAT and TRUE-HF, both investigators concluded that a more efficient communication between the trial stakeholders could perhaps have allowed for a swift intervention correcting ongoing mistakes in trial inclusion and conduct. In parallel, effective and close monitoring of sites to ensure the quality of the data was stressed by several investigators and that a rapid enrollment clearly can compromise quality. Felker proposed a solution to the problem and called for a system change with more focus on sites providing high-quality data rather than only incentivizing patient enrollment. ■

THE FIRST RESULTS FROM THE OPTIMIZE HEART FAILURE CARE PROGRAM

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Keywords: heart failure; HFMEF; ivabradine; Optimize Program; prescription rate

Hear failure (HF), as one of the leading causes of death and disability, is an important problem for health care systems around the world. Due to the high rates of hospitalization, readmission, and outpatient visits, the disease continues to remain a costly condition; the management of which requires many human and economic resources. In this regard, the search for strategies to optimize the management of the HF patients is particularly relevant.

At the 2017 HFA congress in Paris, the first results of the Optimize Heart Failure Care Program (Optimize Program; www.optimize-hf.com) were presented. The Optimize Program, a global initiative that currently covers 45 countries, is devoted to improving the outcomes following HF hospitalization by using patient education, engagement, and postdischarge planning. All participating hospitals were provided with examples of best practice protocols developed for optimizing HF management based on the latest recommendations from the ESC HF guidelines, pre- and post-discharge checklists, a patient HF passport, and a smartphone application to improve the patients' understanding of HF and encourage their involvement in HF care and treatment adherence.

THE OPTIMIZE PROGRAM IN HOSPITALS WITHOUT A MULTIDISCIPLINARY HF PROGRAM

Saldarriaga et al¹ described the impact of implementing the Optimize Program in hospitals without a multidisciplinary HF program. Of the 436 HF patients included in this study, 192 and 244 were recruited from hospitals with and without a multidisciplinary HF program, respectively. Thirty days after discharge from the hospital, the composite outcome of decompensation plus hospitalization was 2.2% vs 3.3% ($P=0.530$) in hospitals with and without a multidisciplinary HF program, respectively. The authors concluded that, in hospitals without a multidisciplinary HF program, the implementation of the Optimize Program improved the short-term prognosis in patients with HF, and it is a good strategy to standardize the management approach in all types of hospitals as part of a quality-improvement initiative.

PRESCRIPTION RATES FOR GUIDELINE-RECOMMENDED HF TREATMENT

The inclusion of eight post-Soviet countries (Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Russia, Ukraine, and Uzbekistan) in the Optimize Program allowed, for the first time in this region, the prescription rates for guideline-recommended medications for HF treatments (ie, ACE inhibitors/ARBs, β -blockers, MRAs, and ivabradine) to be analyzed.² A total of 800 patients from the participating countries who were hospitalized due to worsening HF were included in the study (mean age, 62.4 ± 0.4 ; 69.6% male; NYHA class II-IV; 78.7% in sinus rhythm). At discharge from the hospital, the prescription rates for ACE inhibitors/ARBs, β -blockers, MRAs, and ivabradine were 91.2%, 90.4%, 92.3%, and 29.0%, respectively. The prescription rates for these agents remained high throughout the 12-month follow-up. Diuretics and digoxin were used in 72.2% and 7.2% of patients with HF, respectively. However, the proportion of patients receiving the target doses and $\geq 50\%$ of the target dose was low (25.4% and 43.5% for ACE inhibitors/ARBs, 21.1% and 47.2% for β -blockers, and 5.1% and 26.2% for ivabradine). Moreover, patients with HF who were treated with $\leq 50\%$ of the target doses of ACE inhibitors/ARBs and β -blockers had a high rate of hospital readmission for worsening HF compared with the patients receiving the target doses (38% vs 35.1% and 19.3% vs 20.3%, respectively; $P < 0.05$ for both). Despite the fact that the prescription rates for these HF medications were satisfactory and comparable with the data from other countries, additional efforts are needed to improve the implementation of the HF guidelines in clinical practice.

INITIATION OF IVABRADINE IN THE VULNERABLE PHASE OF HF

Several groups participating in the Optimize Program demonstrated that the early initiation of ivabradine therapy during the vulnerable phase of HF improved the NYHA functional class, LV systolic function, and, most importantly, the outcomes following the HF hospitalization. Within the scope of the Optimize Program in Colombia, the efficacy of an early initiation of ivabradine therapy in patients with HF was studied.³ Among 436 HF patients (68% male; mean age, 66 years; mean LVEF, 32%; 94% were on β -blockers), 61.4% were followed up in an outpatient service 30 days after discharge from the hospital. Ivabradine therapy, which was started in HF patients ($n=131$) during the vulnerable phase, improved LVEF (+5% vs 0% in the group without ivabradine; $P=0.005$) and NYHA functional class by at least one class (42% vs 12%; $P=0.0001$), and it reduced the composite end point of decompensation plus HF hospitalization (1.53% vs 8.57%; $P=0.009$).

EFFECTS OF β -BLOCKERS AND IVABRADINE ON HF HOSPITALIZATIONS

The effect of a β -blocker and ivabradine combination vs β -blockers alone in patients in sinus rhythm hospitalized due to worsening HF was analyzed.⁴ This analysis included data collected over 12 months from 414 patients in sinus rhythm

hospitalized due to worsening HF (mean age, 61.8±0.9; 74.6% male; NYHA classes II-IV; LVEF <40% [mean, 28.7%±0.5%]). In total, 37.2% of hospitalized HF patients received a β-blocker and ivabradine combination and 62.8% received β-blocker therapy alone. There were no differences regarding age, sex, NYHA functional class, and LVEF between the two groups of patients; however, the baseline heart rate in HF patients on a β-blocker and ivabradine combination was significantly higher than in the patients on β-blockers alone (88.9±1.3 bpm vs 78.6±0.9 bpm; $P<0.05$). After a 12-month follow-up, the rate of repeat hospitalizations due to worsening HF was significantly lower in the patients receiving a β-blocker and ivabradine combination compared with β-blocker therapy alone (9.1% vs 30.4%; $P<0.01$).

HEART FAILURE WITH MIDRANGE EJECTION FRACTION

Kurlianskaya et al⁵ investigated the effects of pharmacological treatments and patient education on the rate of hospitalization due to worsening HF in patients with HFMEF. The study included 93 HF patients with NYHA classes I-IV and an LVEF of 40% to 49%. The average number of rehospitalizations due to worsening HF in patients who started a coadministration of β-blockers and ivabradine before discharge from the hospital was lower compared with the patients on β-blockers alone (0.8 and 9.0, respectively; $P=0.028$), especially among patients classified as possessing a high learning capacity. The authors concluded that both a dynamic education of patients with HF and pharmacological treatments that included ivabradine positively affected the course of the disease, as evidenced by the significant decrease in the rate of hospital readmission for HF within the 12-month follow-up.

CONCLUSION

The first results of the Optimize Program have clearly demonstrated the benefits of simple clinician- and patient-focused tools, which are raising awareness about HF and improving the current approaches to the management of HF patients. For the first time, it was shown that optimizing HF management, particularly heart rate-lowering therapies during the vulnerable phase of HF, reduces the rate of death and rehospitalizations. Further results, which will be obtained during the implementation of the Optimize Program in different parts of the world, may provide the basis for the development of new tools and strategies for the management of patients with HF. ■

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UPDATE ON THE ESC EUROBSERVATIONAL RESEARCH PROGRAMME REGISTRIES

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Keywords: cardiomyopathy; chronic ischemic cardiovascular disease; EORP; ESC congress; registry; valvular heart disease

At the 2017 ESC congress, one entire session titled “Valuable lessons on frequent diseases – insights from ESC registries” was dedicated to the EURObservational Research Programme (EORP).¹

Alec Vahanian (FR), the EORP Oversight Committee chairman, presented the EORP, which was started in 2009 by the ESC to obtain epidemiological, diagnostic, and therapeutic data to improve the understanding of cardiovascular diseases and facilitate adherence to the guidelines. There are 20 registries that constitute EORP, which are categorized as general registries (Heart Failure, Atrial Fibrillation General, Chronic Ischemic Cardiovascular Disease, Acute Coronary Syndrome STEMI), sentinel registries (Atrial Fibrillation Ablation, TransCatheter Valve Treatment, European Lead Extraction ConTRolled, Epicardial/Hybrid Atrial Fibrillation Ablation Registry, Valvular Heart Disease II), special registries (Registry Of Pregnancy And Cardiac Disease, PeriPartum CardioMyopathy, Cardiomyopathy and Myocarditis, Cardiac Oncology Toxicity, European Infective Endocarditis Registry), and prevention registries (EuroAspire IV and EuroAspire V). Currently, 100 000 patients from more than 2200 centers have been enrolled in the EORP registries.^{1,2}

VALVULAR HEART DISEASE II REGISTRY

Bernard Lung (FR) presented the objectives and design of the Valvular Heart Disease II registry, as well as some preliminary data. The main aims of the registry are to analyze the current clinical practice for the management of patients with valvular heart disease, to evaluate adherence to the ESC guidelines in this setting, and to assess the changes in practice following the previous survey in 2001 and in the 6-month outcomes (mortality and morbidity) after study enrollment according to the management strategy. Until August 2017, 7 090 patients (47% female; median age, 71 years) have been enrolled; 62% were inpatients and the most common reason for hospital referral/consultation was a diagnostic evaluation (33%). Native left-sided and native isolated right-sided valvular heart disease was reported in

71% and 3% of the patients, respectively, with 26% who had previously undergone a valve intervention. The most frequently reported left-sided valvular heart disease was aortic stenosis (54%), followed by mitral regurgitation (31%). For patients with left-sided valvular heart disease, 73% were single-valve diseases. Among patients with a previous valve intervention (28%), 82% had a valve replacement and 18% a valve repair. Inpatients were more likely to have undergone a valve intervention (41%) or to have an intervention scheduled (24%) vs outpatients (7% and 21%, respectively). These data represent a detailed overview of valvular heart disease in Europe; however, more data on the clinical characteristics of patients with valvular heart disease and additional data on the concordance with the guidelines and on the outcomes are expected to be available soon.¹

CHRONIC ISCHEMIC CARDIOVASCULAR DISEASE REGISTRY

Michael Komajda (FR) presented the 6-month follow-up data from the chronic ischemic cardiovascular disease registry. The 2420 patients (31% female; median age, 67 years) who were included in the registry were divided into 4 cohorts: (i) patients with chronic CAD and NSTEMI-ACS who were revascularized within 72 hours after symptom onset (ACS PCI group); (ii) patients with chronic stable CAD who had undergone an elective PCI (elective PCI group); (iii) patients with stable CAD who were not revascularized (stable CAD group); and (iv) patients with peripheral artery disease who were revascularized (PAD group). At 6 months, 23.7% of the population reported all-cause death or hospitalization, and 1514 of the 1579 clinical events (death/hospitalization) were cardiovascular events. The composite of all-cause and cardiovascular death/hospitalization were more frequently reported in the ACS PCI group and the PAD group vs the elective PCI group. No differences were observed in the outcomes between the stable CAD group and elective PCI group.

Predictors of any death/hospitalization included higher age, having CAD and NSTEMI-ACS with an urgent revascularization, living in Eastern vs Southern countries, a higher heart rate, previous peripheral revascularization, chronic kidney disease, and chronic obstructive pulmonary disease (univariate analysis). All of these factors, with the exception of chronic kidney disease, were also associated with the risk of cardiovascular death/hospitalization risk. The Chronic Ischemic Cardiovascular Disease registry is expected to provide data on the comparison between real-world clinical practice and guideline-recommended management of patients with chronic ischemic cardiovascular disease and to assess both the geographical differences in outcomes and the long-term prognosis for these patients.¹

CARDIOMYOPATHY AND MYOCARDITIS REGISTRY

Philippe Charron (FR) discussed data from the Cardiomyopathy and Myocarditis registry. In the long-term phase of the program, 3109 patients from 23 countries were enrolled, of whom 75% had adult cardiomyopathy, 13% had pediatric cardiomyopathy, and 12% had myocarditis. In particular, among those with adult cardiomyopathy, 51% had hypertrophic cardiomyopathy (HCM), 43% dilated cardiomyopathy (DCM), 4% arrhythmogenic right ventricular cardiomyopathy (ARVC), and 2% restrictive cardiomyopathy (RCM).

Data from the long-term phase of the program have been pooled with those from the previous pilot phase to provide a better comparison of the characteristics of patients with different cardiomyopathies.³ In particular, a familial involvement was more frequent in patients with HCM (48.5%), followed by patients with ARVC (40.6%), RCM (30%), and DCM (25.2%). More patients with RCM had a history of atrial fibrillation (48.5%), followed by patients with DCM (28.3%), HCM (26.6%), and ARVC (14%); whereas, more patients with ARVC had a history of sustained ventricular tachycardia (39.2%), followed by patients with DCM (13.6%), HCM (7.7%), and RCM (1.5%). The diagnosis was performed earlier in ARVC (mean age, 40.2±15.5 years) and later in RCM (52.4±19.6).

Regarding diagnostic tests, magnetic resonance imaging was performed in 51%, 36.4%, 33.8%, and 20.6% of patients with ARVC, RCM, HCM, and DCM, respectively, and genetic testing was performed in 54.6%, 46.4%, 42.9%, and 17.9% of patients with ARVC, HCM, RCM and DCM, respectively. An implantable cardioverter-defibrillator was implanted in 56.6%, 31.7%, 19.9%, and 9.1% of patients with ARVC, DCM, HCM, and RCM, respectively. Cardiac ablation was performed mainly in patients with ARVC (11.2%). There were geographical differences observed for several clinical characteristics, diagnostic tests, and treatments used. The data from this registry provide a contemporary overview of cardiomyopathies and a useful platform for guideline implementation. In 2018, data on pediatric cardiomyopathies and myocarditis are expected to be released.²

CONCLUSION

As reported by Aldo Maggioni (IT), the EORP scientific coordinator, the EORP activities are a rich source of knowledge for cardiovascular diseases. Thus, the EORP registries represent an incredible tool to understand the unmet needs in cardiovascular disease, which may contribute significantly to improving daily clinical practice. ■

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Perspectives



HEART FAILURE: WHAT'S NEW IN 2017?

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The 2017 annual Scientific Sessions of the American College of Cardiology in Washington, D.C. reviewed the updates in cardiology from 2016, with a specific focus on heart failure.

PRACTICE GUIDELINES FOR HEART FAILURE: AN UPDATE

Clyde Yancey (US) presented the 2016 focused update of the ACC/AHA practice guidelines for heart failure, which included new epidemiological data. The prevalence of heart failure was 6.5 million between 2011 and 2014, which was a 14% increase from the data obtained between 2009 and 2012. However, the age- and sex-adjusted incidence decreased by 37.5%. The 5-year survival from heart failure post-MI improved by 7% in the 2001 to 2010 interval versus the 1990 to 2000 interval (61% from 54%). While the lifetime risk of heart failure has diminished, hospitalizations have increased (34%), although these hospitalizations were due predominantly to noncardiac causes (63%). The risk of cardiovascular death was lower for HFPEF than for HFREF, but it was the same as the risk of noncardiovascular death.

The updated guidelines emphasize the need to respond with evidence-based therapies for natural history improvement. These therapies all are supported by RCTs and now include an ACE inhibitor or ARB, which can be replaced with an ARNI in appropriate patients, supplemented by an MRA, a β -blocker, and, in appropriately selected patients in whom the heart rate is not adequately controlled with a β -blocker alone, by the addition of ivabradine. In addition, in African-American patients who remain symptomatic on these therapies (despite an adjunctive diuretic), a combination of hydralazine and isosorbide dinitrate is valuable. Evidence indicates that, at recommended doses, treating between 7 and 26 patients (depending on the drug) can be expected to reduce mortality and/or heart failure hospitalizations by one event. Finally, in patients with HFREF, a biomarker response (specifically BNP) may predict the best outcomes, although this has not yet been rigorously demonstrated.

The changes in recommended therapies since the last update to the guidelines all relate to chronic stable HFREF, and, in appropriately defined patients, include replacing the ACE inhibitor or ARB with an ARNI, administering ARNI in conjunction with β -blockers and adding ivabradine to ACE inhibitors or ARBs plus a β -blocker.

DOSE SELECTION

Tracy E. Macaulay (US) discussed dose selection, responding to the question, “how much is too much?” She illustrated her concerns with the effects of therapy on BP, where the issues are the clearest. Macauley cited three trials (MOCHA, HF-ACTION, and CIBIS-ELD) that demonstrated dose-related improvements in outcomes to support slow titration of β -blockers to the peak doses achieved in the trials. Support for a similar strategy with ACE inhibitors/ARBs/ARNIs was inferred from the results of the ATLAS, HEAAL, NETWORK, and PARADIGM-HF trials, but these can be interpreted as supporting preferential titration of β -blocker therapy first. However, the potential downside of dose titration to the maximal targets includes adverse drug effects; thus, this strategy requires more frequent patient monitoring. Hypotension, hyperkalemia, and fluid imbalance are among the most prominent adverse effects. In addition, polypharmacy, defined as taking six or more concurrent medications, makes it likely that at least one of the drugs is inappropriate, though selecting the inappropriate drug might be insolubly challenging. Finally, complicated regimens that involve high pill burden and costs can decrease adherence to the prescribed, evidence-based regimen, resulting in sub-optimal outcomes. Indeed, patients receiving two drugs or less are twice as likely to be adherent than are patients on six or more.

The potential for an overdose and achieving less than optimal outcomes is best illustrated with relation to the effects of drugs on BP. In large RCTs for heart failure, patients with severe heart failure, low BP, and a low heart rate were largely excluded from evaluation and many dose combinations were not studied. Nonetheless, several trials suggest that outcomes can be adversely affected if the BP is reduced below a certain level. In the LIFE trial, among patients with hypertension and left ventricular hypertrophy, a systolic BP <130 mm Hg increased the risk of death (HR, 1.29) compared with subjects with a systolic BP \geq 130 mm Hg. Similarly, among patients with HFREF in the DIG trial, an LVEF <30% increased cardiovascular and heart failure mortality as the BP decreased (HR, 1.15 and 1.30, respectively). Consistent with these observations, the BEST study showed that, in patients with severe HFREF, a systolic BP <120 mm Hg was an independent predictor of poor outcomes (HR, 1.33). To minimize the adverse effects, Macauley suggested: first, assembling a complete medication list (over the counter and herbal medications, inhalers, etc); second, assessing adherence to the prescribed regimen (eg, the Morisky scale for drug adherence); third, identifying and remedying adherence

barriers (eg, using relatively longer acting drugs to reduce daily pill burden); and fourth, engaging the patient in their treatment through education. The resulting Comprehensive Medication Management Plan must include the patient's primary physician and other specialists to ensure that there is an agreement on minimal therapy, individualized therapy, and monitoring based on the patient's goals, preferences, and other disease states, and to provide patients and caregivers with an updated medication list after each visit. Macauley suggests using slow and diligent dose titration, increasing monitoring frequency in high-risk patients, and recognizing that not all patients will tolerate maximum or target doses. The best results are likely to be obtained if the clinician discusses the possible adverse drug effects and titration schedules that may be expected.

THERAPEUTIC ROLE OF LOWERING HEART RATE

Finn Gustafsson (DK) discussed the therapeutic role of lowering heart rate, focusing on data from studies using ivabradine, a pure heart rate–lowering drug with no direct effects on vascular tone, inotropy, or electrolyte and fluid metabolism. The pharmacological effect of ivabradine involves blocking the hyperpolarization-activated cyclic nucleotide–gated channels in the sinoatrial node. Ivabradine was approved in the US in 2015 specifically to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic, chronic heart failure with an LVEF $\leq 35\%$, who are in sinus rhythm with a resting heart rate ≥ 70 bpm while taking maximally tolerated doses of β -blockers or for whom β -blockers are contraindicated. The drug had been approved previously in Europe and elsewhere for patients with heart failure to reduce mortality or heart failure hospitalizations.

After discussing the pharmacological effect of ivabradine, Gustafsson presented the results of the BEAUTIFUL trial (which included patients with chronic, stable, coronary artery disease, many of whom had symptoms suggesting heart failure, usually mild, and an LVEF $\leq 40\%$) and the SHIFT study (which included patients with NYHA class II to IV heart failure, ischemic or nonischemic etiology, with an LVEF $\leq 35\%$, and a heart rate ≥ 70 bpm in sinus rhythm, with a documented hospitalization for worsening heart failure < 12 months prior to inclusion). Although one analysis of the SHIFT trial supported the European labeling for reducing mortality and/or heart failure hospitalizations, this analysis only included the subset of patients with a heart rate ≥ 75 bpm at study entry. He emphasized that the ivabradine-associated benefits in SHIFT were obtained from the population who were already receiving β -blockers; therefore, he concluded that ivabradine should be used when β -blockers alone cannot lower heart rate below < 70 bpm.

TRANSITIONING TO SACUBITRIL/VALSARTAN

Matthew Konerman (US) discussed in whom, when, and how a transition should be made from ACE inhibitors or ARBs to sacubitril/valsartan. First, he noted that sacubitril/valsartan was studied in stable patients with mild-to-moderate HFREF who were tolerating ACE inhibitor/ARB therapy. Their systolic BP was ≥ 100 mm Hg, renal dysfunction, if present, was no more than moderate (GFR ≥ 30), hyperkalemia was not present ($K \leq 5.2$ mmol/L), and there was no history of angioedema. Applying the drug to patients outside of this patient population may introduce unforeseen hazards and may limit the benefits. Indeed, during the run-in phase of PARADIGM-HF, 977 patients on sacubitril/valsartan (approximately 10% of the patients screened for the study) were discontinued from therapy because of symptomatic hypotension, unacceptable renal dysfunction, or hyperkalemia. Thus, little experience was compiled among patients outside the stated population. For context, after the publication of the RALES trial and the consequent widespread application of spironolactone for heart failure, the rate of hyperkalemia more than doubled compared with pre-RALES values in patients treated with the new preferred drug combination, suggesting that trial-related inclusion and exclusion criteria were not being rigorously followed after the release of the data. Next, he suggested that initiation should occur before patients deteriorate; the PARADIGM-HF data indicate that the reduction in mortality and heart failure hospitalizations occurred throughout the study population, including those with a relatively low risk of heart failure sequelae. Therefore, the combination should be applied as soon as possible. Nonetheless, data on the results of inpatient initiation are largely lacking. Therefore, initiation should occur in stable outpatients, never in decompensated patients and always after a 36-hour washout from ACE inhibition. Further, noting the titration schedule used in PARADIGM-HF, Konerman suggested that there should be a “low and slow” dose titration.

SUMMARY STATEMENT

In summary, in 2017, several issues were clarified with new data, leading, it is hoped, to therapies that are more effective for patients with heart failure. ■

LEFT VENTRICULAR FILLING PRESSURE, DIASTOLIC FUNCTION, AND HEART RATE

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Keywords: heart failure with preserved ejection fraction; heart rate; left ventricular end-diastolic pressure; left ventricular filling pressure

EVALUATION OF DIASTOLIC FUNCTION AND LV FILLING PRESSURE

Elevated LV filling pressure is a major determinant of cardiac symptoms and prognosis in patients with chronic heart failure, regardless of LVEF.¹ The invasive estimation of LV filling pressure may be done either by right heart catheterization, which allows PCWP to be measured as an indirect, though accurate, estimate of left atrial pressure, or by direct sampling of the LV cavity during left heart catheterization.^{1,2} In clinical practice, measuring PCWP with right heart catheterization has been established as a surrogate measurement that has largely replaced direct measurements of LVEDP. However, a recent patient series showed a poor agreement between the two methods.^{3,4} In patients with HFPEF and elevated left atrial pressure, it has been shown that there is a relevant pressure drop between PCWP and the left atrium due to an increase in pulmonary venous resistance. In a recent study on patients with HFPEF, it was reported that PCWP measurements were more closely related to outcome than those of LVEDP.³ It was then speculated that both the low diffusion capacity of carbon monoxide and the pressure gradient between PCWP and LVEDP reflect thickening of the alveolocapillary membrane due to chronic congestion.³ Both parameters are associated with disease severity and should be addressed in future large-scale studies.

A noninvasive estimation of LV filling pressure may be obtained using Doppler echocardiography.^{4,5} Mitral inflow, tissue Doppler annular velocities, tricuspid regurgitation velocity, and left atrial volume are the cornerstones of diastolic function evaluation. However, the fact that the various parameters used are subject to fundamental limitations and reflect different physiological aspects of diastole has led to substantial ambiguity in the diagnosis of LV diastolic dysfunction. Current recommendations encourage the use of pulsed tissue Doppler for calculating the ratio between the preload-dependent transmitral E velocity and the average of septal and lateral velocities of the earliest diastolic motion (e') of the mitral annulus for the estimation of LV filling pressure.¹ This average veloci-

ty may reflect the rate of myocardial relaxation, not depending on pressure flow gradients. In addition to being very feasible and widely available, the prognostic significance of the E/e' ratio is widely recognized in various cardiovascular diseases (eg, heart failure, myocardial infarction, arterial hypertension).⁴

Despite its wide use, the real utility of the E/e' ratio has been recently challenged in several studies, which led to a revision of the 2009 recommendations for the assessment of LV diastolic function and LV filling pressure.¹ To examine and validate the accuracy of these new recommendations, the European Association of Cardiovascular Imaging (EACVI) Research committee performed the EURO-FILLING study, a large multicenter prospective project with simultaneous assessment of invasive measurements and noninvasive estimates of LV filling pressure.^{4,5} A total of 159 patients were enrolled in 9 EACVI centers; 39 (25%) patients had a reduced LVEF (<50%), 77 (64%) had an NYHA class \geq II, 85 (53%) had coronary artery disease, and 64 (40%) had elevated LVEDP (\geq 15 mm Hg). Taken individually, all echocardiographic Doppler estimates of LV filling pressure (E/A , E/e' , left atrial volume, tricuspid regurgitation jet velocity) were marginally correlated with LVEDP.⁵ By using the 2016 recommendations, 65% of patients with a normal noninvasive estimate of LV filling pressure had a normal LVEDP, while 79% of those with an elevated noninvasive LV filling pressure had an elevated invasive LVEDP.

By using the 2009 recommendations, 68% of the patients with a normal noninvasive LV filling pressure had a normal LVEDP, while 55% of those with an elevated noninvasive LV filling pressure had an elevated LVEDP. The 2016 recommendations (sensitivity, 75%; specificity, 74%; positive predictive value, 39%; negative predictive value, 93%; AUC, 0.78) identified patients with an elevated invasive LVEDP (\geq 15 mm Hg) slightly better than the 2009 recommendations (sensitivity, 43%; specificity, 75%; positive predictive value, 49%; negative predictive value, 71%; AUC, 0.68). The authors of the EURO-FILLING study concluded that the new 2016 recommendations for noninvasively assessing LV filling pressure are fairly reliable, clinically useful, and superior to the 2009 recommendations in estimating invasive LVEDP. In a more recent study, Andersen et al showed a good correlation between the 2016 echocardiographic algorithm for the estimation of LV filling pressure and the invasive assessment of PCWP.⁶

IMPACT OF HEART RATE ON LV DIASTOLIC FUNCTION

Although previous works have considered changes in echocardiographically derived indexes as a function of HR, no HR-adjusting index has been proposed that incorporates the smooth and continuous increase in the rate of cardiac output as HR increases.⁷⁻⁹ Changes in HR in the context of shortening the R-R interval are primarily modulated by the duration of diastasis. The duration of the E wave and the A wave are roughly HR independent. Each shows a <15% to 20% decrease in

duration for a 100% increase in HR. Mitral deceleration time shows a mere 20% decrease for a 100% increase in HR. Moreover, HR is positively associated with peak velocity A and atrial filling fraction and inversely associated with peak velocity E, peak velocity E/A, and time velocity E/A.⁷ The relationship between relaxation and frequency shortens in response to increasing HR⁹; however, the slope of this relationship is significantly steeper in patients with heart failure compared with patients with normal LV function.

In heart failure, changes in HR affect early relaxation and diastolic compliance more than in control subjects. However, with sinus tachycardia, various degrees of merging of mitral E and A velocities are observed secondary to shortening of the diastolic filling period, adding complexity to the evaluation of filling dynamics and pressure.¹⁰ Nevertheless, the E/e' ratio can still be used to estimate PCWP with reasonable accuracy in sinus tachycardia, even with a complete merging of E and A velocities. Exercise-induced elevation of filling pressures limits exercise capacity, which may indicate diastolic dysfunction. In subjects with a normal myocardial relaxation, E and e' velocities increase proportionally, and the E/e' ratio remains either unchanged or reduced. However, in patients with impaired myocardial relaxation, the increase in e' with exercise is much less than that of the mitral E velocity, such that the E/e' ratio increases.¹¹ In this regard, the E/e' ratio was shown to relate significantly to LV filling pressure during exercise, when Doppler echocardiography was acquired simultaneously with cardiac catheterization.¹²

EFFECT OF REDUCING HR ON LV DIASTOLIC FUNCTION

Exertional dyspnea is a nonspecific symptom; therefore, concern is often expressed over the frequency of diastolic dysfunction leading to the overdiagnosis of HFPEF. In the early stages of HFPEF, while the primary problem relates to impaired LV relaxation (rather than impaired LV compliance or increased filling pressure at rest), a high HR during exercise may be particularly detrimental by reducing the time for diastolic filling and promoting an increased LV filling pressure, and exercise intolerance and dyspnea.¹³ The patients can be identified by assessing the increments of E/e' ratio with exercise. Therapeutic measures prolonging the LV filling phase may optimize transmitral flow, thereby reducing increased filling pressures and the resultant dyspnea.

During exercise, the marked increase in LV filling rate in early diastole mainly depends on the ability of the LV to relax rapidly and completely.¹ The physiological mechanisms allowing this adaptation involve an increase in both heart rate and contractility through adrenergic stimulation.¹⁴ As a consequence, β -blockers strongly alter the relaxation process as a result of the combination of their negative chronotropic and inotropic properties, both at rest and during exercise. For instance, atenolol alleviates the acceleration of LV pressure fall during exercise

and fails to decrease the LV relaxation rate during exercise in a dose-dependent manner. In contrast to atenolol, ivabradine, an inhibitor of the pacemaker I_f current, for a similar reduction in heart rate at rest and during exercise, does not exert any negative lusitropic effect.¹⁴ Ivabradine induces dose-dependent reductions in heart rate, is devoid of an intrinsic negative inotropic effect, and does not alter either global LV systolic function or coronary vasomotion.

Patients with HFPEF have inappropriate tachycardia during exercise, with higher heart rates at constant workloads than in subjects with normal LV filling, based on impaired stroke volume reserve and reliance on increasing heart rate to augment cardiac output. Interestingly, a selective HR reduction by ivabradine improves vascular stiffness, LV contractility, and diastolic function in patients with HFPEF.^{15,16} The mechanisms behind the favorable effect of ivabradine on LV diastolic function are not confined to a simple lengthening of diastolic filling time. Other benefits include acceleration of myocardial relaxation by enhancing the phosphorylation of phospholamban and subsequent stimulation of sarcoplasmic reticulum Ca^{2+} adenosine triphosphatase, increase in myocardial compliance by reducing the expression of the titin N2B isoform and myocardial collagen content, and improving arterial stiffness and endothelial function. Clinically, short-term treatment with ivabradine increases exercise capacity, with a contribution from improved LV filling pressure response to exercise as reflected by a better E/e' ratio at exercise.¹⁷ ■

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CARDIOVASCULAR DISEASE IN WOMEN: HOW WELL ARE WE DOING?

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Cardiovascular disease is the leading cause of death in developed countries and an increasing problem in low- and middle-income countries. According to the most recent report from the American Heart Association, cardiovascular disease was the most common underlying cause of death in the world in 2013, accounting for an estimated 17.3 million of the 54 million total deaths or 31.5% of all deaths worldwide. In Europe, each year cardiovascular disease causes an estimated 3.9 million deaths, accounting for 45% of all deaths.^{1,2}

During the last decades, mortality related to cardiovascular disease has significantly declined in most developed countries. However, despite the extraordinary advancements made in understanding the pathogenesis of atherosclerotic cardiovascular disease and the development of new therapeutic targets, the prevalence of traditional risk factors and established cardiovascular disease are growing. Currently, an estimated 92.1 million adults in the US have at least one type of cardiovascular disease, but, by 2030, 43.9% of the US adult population is projected to have some form of cardiovascular disease. Cardiovascular disease also appears as one of the main sources of health care spending and one of the principal determinants of disability. Cardiovascular disease and stroke accounted for 14% of total health expenditures in 2012 to 2013, which is more than any other major diagnostic group. The annual direct and indirect cost of cardiovascular disease and stroke in the US was an estimated \$316.1 billion in 2012 to 2013.

CARDIOVASCULAR DISEASE: WHAT ARE THE DIFFERENCES BETWEEN MEN AND WOMEN?

Traditionally, cardiovascular disease has been considered a “man’s disease,” but this myth has been debunked in recent years. Recent data show that cardiovascular disease is the leading cause of death in women in developed countries and most emerging economies, with the mortality attributed to cardiovascular disease being higher than the mortality caused by cancer, chronic lower respiratory disease, Alzheimer disease, and accidents combined. Cardiovascular disease in women was commonly neglected by physicians until the two decades ago. Various

studies that analyzed the management and outcomes of women with NSTEMI in the late 1990s suggested that treatment strategies for women with cardiovascular disease were less aggressive than for men. In recent years, substantial efforts have been made to increase prevention awareness and promote healthy lifestyles in women. These efforts have been successfully reflected in health surveys: in 1997, only 30% of women in the US surveyed were aware that cardiovascular disease was the primary cause of mortality in women; this percentage increased to 54% in 2009 and has subsequently stabilized when the last survey was conducted in 2012.

Sex-specific differences in the clinical presentation of ACS

The terminology of coronary artery disease, atherosclerotic disease limited to the epicardial coronary arteries, should not be used and should not be confused with ischemic heart disease because there are some differences in this pathology depending on the sex that should be highlighted. Data shows that there are sex-related differences in the clinical presentation, pathophysiology, evaluation, management, and outcomes in patients with cardiovascular disease and, more specifically, in patients with ACS. The clinical presentation of ACS differs between women and men. Women are more likely to present with angina as their first presentation of ischemic heart disease and they are less likely to develop an acute myocardial infarction compared with men. Among patients with ACS, fewer women present with STEMI and more present with unstable angina. An analysis of GUSTO IIb, a trial that included 12142 patients (30% women), showed that significantly fewer women than men presented with ST-segment elevation,³ and, in the patients with NSTEMI or unstable angina, women were more likely to have unstable angina than were men. The lower rate of STEMI in women was later confirmed in a large registry of 78254 patients included in the Get With The Guidelines–Coronary Artery Disease registry.⁴ Women are more likely to experience a wide range of atypical symptoms, such as fatigue, shortness of breath, weakness, nausea, right arm pain, intermammary pain, and epigastric pain, that might make their diagnosis and subsequent management challenging. However, crushing substernal chest pain is the most common presenting symptom, which is also a strong predictor of an acute coronary syndrome in both men and women.⁵

Many hypotheses have been generated regarding the reasons behind the sex-related presentation differences. Biological variances and cardiovascular system differences among women and men are the results of gene expression and the influence of sex hormones. These differences play a fundamental role in the pathophysiology and the disparity in the presentation of ischemic heart disease in women and men. Some cardiovascular conditions are predominant in women, such as those related to autonomic regulation of the arteries, eg, vasospastic disease, Raynaud's phenomenon, and another vasculitis. Women with ACS also present more frequently with nonobstructive coronary artery disease, whereas, in

men, the rupture of atherosclerotic plaque and microembolization is predominate.

Sex-specific differences in biomarkers

Although the hearts of men and women seem to be structurally similar, some sex-specific differences in the expression of biomarkers in ACS have been described; for example, the baseline concentrations of some biomarkers are different between women and men. The emergence of high-sensitivity assays for cardiac troponin has made the differences between women and men more clear. In a recent prospective cohort study, an assay for high-sensitivity troponin I significantly increased the diagnosis of ACS in women (from 11% to 22%; $P < 0.001$), but it had a minimal effect on the diagnosis in men (from 19% to 21%; $P = 0.002$).⁶ Additionally, it is more likely to observe an increase in CRP and BNP in women who present with ACS, which reflects a higher prevalence of heart failure and a higher risk profile at the moment of presentation. Other biomarkers, such as proneurotensin, have been shown to be sex-specific and related to incident cardiovascular disease only in women, which might improve the prediction of incident cardiovascular disease.

Regarding the management of cardiovascular disease and ACS, there is strong evidence confirming that medications and invasive procedures are similarly effective in men and women. However, different studies have reported that women are treated more conservatively and they receive fewer evidence-based medications. Accordingly, clinicians should be aware of these differences when diagnosing and managing patients to avoid sex-related bias.

Sex-related differences in mortality

A substantial body of evidence supports a sex-related difference in short-term mortality after an ACS, especially after STEMI. However, differences regarding long-term outcomes between men and women with ACS are conflicting. Current evidence suggests that age plays an important role in these observed differences in sex-related outcomes. Since the first study reported by Vaccarino et al⁷ and the subsequent confirmation by many other registries, women who suffer an acute myocardial infarction, either STEMI or NSTEMI, at a young age have a worse prognosis than men in the same age group, with a 22% higher risk of 30-day hospital readmission than young men. In contrast, in patients >65 years old, women appear to have better outcomes than men.⁷ Although many hypothesis have been proposed, the explanation of sex-related differences in young and middle-aged patients is still unclear.

CONCLUSION

In our opinion, the sex-related differences concerning the clinical presentation, management, treatment, and outcomes are obvious in patients presenting with an ACS. Despite the efforts made in recent years to develop new strategies for revas-

cularization and new therapeutic targets that have led to an overall reduction in mortality due to cardiovascular disease, there are still aspects for reflection and improvement. Undoubtedly, one aspect concerns the differences between men and women because women with cardiovascular disease have a persistent sub-optimal treatment pattern, higher mortality, and poorer cardiovascular disease outcomes compared with men.

Many aspects remain to be addressed. Are we promoting prevention awareness and healthy lifestyles regardless of sex? Why are women less likely to be treated with invasive strategies and to receive fewer evidence-based medications than are men? Are the disparities regarding clinical presentation only the result of differences in the pathophysiology or rather differences in the recognition or expression of symptoms between women and men? Compared with men, why do young and middle-aged women have a poor prognosis and more adverse outcomes after an ACS? To understand this complex issue better and to answer these crucial questions, we are in dire need of research efforts to reduce sex-related differences between women and men with cardiovascular disease and to improve the clinical management of women with cardiovascular disease. ■

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HEART FAILURE AND DIABETES MELLITUS: DANGEROUS LIASONS

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Diabetes mellitus and heart failure affect a significant proportion of the population worldwide. Estimates of the prevalence of heart failure vary between 1% and 2% of the general population, and the number of patients with heart failure continues to grow, particularly due to the increase in life expectancy and the resulting aging of the population. Similarly, diabetes mellitus is a matter of concern due to the epidemic of this condition worldwide, particularly in emerging countries due to changing lifestyles; current estimates show that diabetes affects 400 million people worldwide.¹ As a result, many patients with heart failure have diabetes mellitus, and, conversely, heart failure is an important complication for patients with diabetes mellitus. The objectives of this article are to review the epidemiological data, the clinical outcomes, and the management peculiarities of patients affected by both diabetes mellitus and heart failure.

EPIDEMIOLOGICAL DATA AND CLINICAL OUTCOMES

Recent clinical trials and observational studies show that, on average, 30% to 40% of the patients with heart failure have diabetes mellitus. The proportion is similar for patients with chronic heart failure, patients with acute heart failure, and patients with either HFREF or HFPEF; however, it may increase to more than 50% in some geographic areas, such as the Middle East.

Conversely, heart failure events are very common in patients with diabetes mellitus. In particular, the prevalence of heart failure hospitalizations has been largely underestimated; for example, in the control arm of some clinical trials that include people with type 2 diabetes mellitus, heart failure events are as common or even more frequent than coronary events. Data from large international registries suggest that the presence of diabetes is a strong predictor of future heart failure hospitalizations.² A recent meta-analysis pooling more than 70 000 people with diabetes mellitus shows that each one point increase in HbA_{1c} is associated with a 20% increase in the risk of heart failure hospitalizations.³

The coexistence of heart failure and diabetes mellitus is also associated with a significant increase in the risk of rehospitalizations for heart failure and in-hos-

pital or 1-year mortality. In particular, the level of glycemia at referral is a strong predictor of in-hospital mortality. Therefore, these data confirm that the association of heart failure with diabetes mellitus is deadly.

MANAGEMENT OF HEART FAILURE IN PATIENTS WITH DIABETES

There is no fundamental difference in the management of HFREF patients with or without diabetes mellitus. All classes of medications that showed benefit in HFREF patients are equally effective in patients with diabetes mellitus: this holds true for angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β -adrenergic blockers, mineralocorticoid receptor antagonists, ivabradine, and sacubitril/valsartan. The evidence is derived from subgroup analyses performed on the large outcome trials that were conducted with these classes of heart failure medications. The magnitude of the effect on clinical outcomes is similar to that observed in people without diabetes; however, since people with diabetes have a higher cardiovascular risk than those without diabetes, the absolute benefit is usually greater in people with diabetes.

The safety is also excellent, except for the increase in the risk of hyperkalemia or renal function deterioration observed with renin-angiotensin-aldosterone system blockers. This observation derives from subanalyses of the CHARM trial with candesartan, the EPHEsus trial with eplerenone, and observational studies. As a result, regular monitoring of renal function and kalemia is recommended after the initiation or during the uptitration of renin-angiotensin-aldosterone system inhibitors in patients with both diabetes mellitus and heart failure.

MANAGEMENT OF DIABETES MELLITUS IN PATIENTS WITH HEART FAILURE

The cardiovascular safety of antidiabetic drugs raised concern following a controversy with rosiglitazone, a thiazolidinedione that was developed in the early 2000s. A meta-analysis suggested an increased risk of myocardial infarction in patients treated with rosiglitazone, a concern that was not confirmed by subsequent analyses. Nevertheless, this prompted the Food and Drug Administration, followed by the European Medicines Agency, to establish rules regarding development programs of new antidiabetic drugs in order to detect potential harm in terms of cardiovascular events.

OLDER ANTIDIABETIC DRUGS

There is a lack of robust data on the cardiovascular safety of sulfonylureas, metformin, and insulin because these drugs were widely used for patients with diabetes mellitus before the onset of evidenced-based medicine. Therefore, most of the available data are derived from observational studies.

Although heart failure is a classic contraindication for the use of metformin due to the risk of lactic acidosis, there is no signal for potential harm when using this

drug in patients with diabetes and heart failure. On the contrary, observational data suggest that metformin is associated with improved outcomes, such as mortality, compared with the control therapy of sulfonylurea. Data regarding sulfonylureas are somewhat difficult to interpret, but some large observational studies suggest that the risk of heart failure is significantly increased compared with metformin, particularly with first generation sulfonylureas.⁴

Although insulin is associated with water and sodium retention and sympathetic nervous system activation during hypoglycemia, there are no data suggesting harm in terms of cardiovascular outcomes in patients with diabetes. One randomized controlled trial, ORIGIN, was conducted with insulin glargine, and it showed no increase in heart failure hospitalizations in the insulin arm compared with the control arm.⁵

NEWER ANTIDIABETIC DRUGS

Thiazolidinediones

Pioglitazone and rosiglitazone, two thiazolidinediones, were developed in large outcome trials in combination with traditional antidiabetic drugs. Both drugs are associated with a substantial increase in the risk of heart failure since these PPAR- γ agonists upregulate a channel in the kidneys, that leads to sodium retention. As a result, these drugs should not be used in patients with diabetes who have overt heart failure or significantly impaired cardiac function.

DPP4 inhibitors

DPP4 inhibitors are a widely used new class of glucose-lowering agents. They were tested in large outcome trials and were shown to be neutral toward myocardial ischemic events. However, saxagliptin, which was tested in the SAVOR-TIMI 53 trial, was surprisingly associated with a 27% increased risk of heart failure hospitalizations compared with the control arm.⁶ Older patients and patients with a history of heart failure or high baseline plasma BNP levels were more likely to develop heart failure. Another DPP4 inhibitor, sitagliptin, was tested in a large outcome trial, TECOS⁷; however, there was no negative signal on heart failure events with this compound. There is no plausible biological explanation for why saxagliptin was associated with an increased risk of heart failure; although, DPP4 has multiple substrates, including vasoactive peptides, it also degrades BNP so that inhibition of DPP4 results in elevated levels of this peptide, which has beneficial effects on the cardiovascular system. The play of chance cannot be excluded to explain why saxagliptin was associated with an increased risk of heart failure events in SAVOR-TIMI 53.

Nevertheless, when considering the introduction of a DPP4 inhibitor in a patient with diabetes and heart failure, preference should be given to sitagliptin due to its neutral effect on heart failure hospitalizations.

GLP-1 analogs

This new drug class has been extensively studied in patients with diabetes mellitus. The long-acting GLP-1 analog liraglutide was tested in LEADER, whereas the very long-acting semaglutide was evaluated in SUSTAIN.^{8,9} Both drugs significantly reduced the primary outcome in patients with diabetes and a high cardiovascular risk; however, there was a nonsignificant risk reduction in heart failure hospitalizations. These results were also observed in the recently presented EXSCEL trial that used the long-acting exenatide, where there was no increase (but also no improvement) in the risk of cardiovascular events, specifically in heart failure hospitalizations. However, two small studies conducted in HFREF patients with or without diabetes mellitus provided a negative signal on outcomes. One potential explanation is that GLP-1 analogs increase heart rate; this effect might be harmful in patients with reduced cardiac function as demonstrated in heart failure. In addition, only a minority of patients enrolled in the large outcome trials had a history of heart failure. Therefore, uncertainty remains on the cardiovascular safety of GLP-1 analogs in patients with a reduced ejection fraction.

SGLT inhibitors

A cotransporter of sodium and glucose exists in the proximal tubule (type 1 and principally type 2) of the kidneys (type 2) and in the gut (type 1). In normal conditions, this cotransporter reabsorbs the totality of the glucose that is filtered in the glomeruli together with sodium. Blocking this cotransporter with inhibitors causes an osmotic glycosuria that leads to better glycemic control in diabetes mellitus and better sodium excretion. Empagliflozin and canagliflozin have been tested in large outcome trials, EMPA-REG OUTCOME and CANVAS, respectively, in large populations of diabetic patients with a high cardiovascular risk.^{10,11} Both trials showed a significant reduction in the primary end point, which is mainly driven by a reduction in mortality and a spectacular reduction in heart failure hospitalizations. The beneficial effect on heart failure events remains unclear; however, possible hypotheses for SGLT inhibitors include a diuretic effect without neurohormonal stimulation, a reduction in blood pressure, an improvement in kidney function, and a direct myocardial metabolic effect. The benefit observed on heart failure events prompted companies developing SGLT inhibitors to consider conducting new clinical trials on heart failure patients with or without diabetes mellitus and with or without a reduced ejection fraction. While these trials are conducted, SGLT inhibitors appear to be a treatment of choice for patients with diabetes mellitus and heart failure. The safety issues are mainly urine infections and an increase in the risk of amputations that is possibly related to the hemoconcentration.

CONCLUSION

The combination of diabetes mellitus and heart failure is common and it is associated with poor outcomes. The management of HFREF is similar in patients with

or without diabetes mellitus, although there is an increased risk of hyperkalemia when using renin-angiotensin-aldosterone system inhibitors. Thiazolidinediones should not be used in patients with heart failure. There is uncertainty regarding the safety of saxagliptin in patients with heart failure, whereas another DPP4 inhibitor, sitagliptin, is neutral. GLP-1 analogs have a beneficial effect on cardiovascular events, but there is some concern on their use in patients with diabetes and a reduced ejection fraction. Finally, SGLT inhibitors have a strong beneficial effect on heart failure events, although the mechanism of this effect remains unclear. ■

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PERCUTANEOUS CORONARY ANGIOPLASTY: 40-YEAR ANNIVERSARY

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The year 2017 was remarkable as it was the 40th anniversary of the first percutaneous transluminal coronary angioplasty, which was performed on September 16, 1977 by Andreas Grüntzig in Zurich, Switzerland. This revolutionary achievement changed the scope of angiographic procedures from purely diagnostic to therapeutic. The procedure offered an alternative to surgical revascularization because it was not only a symptom-resolving, but also a life-saving procedure. It is hard to imagine modern cardiology without interventions. The number of coronary angiographies performed in the US exceeds 1 million per year, with a percutaneous intervention comprising almost half of the procedures, which results in a direct cost of over \$30 billion; similar trends are observed in Europe.¹ There is no doubt that the fast-progressing advances in the management of coronary artery and valvular heart diseases dramatically increased patient survival and quality of life.

HISTORICAL PERSPECTIVE: HEART CATHETERIZATION

From an historical perspective, it should be noted that percutaneous procedures would not have been possible to pursue without the tremendous efforts of Grüntzig's predecessors. After the French physiologist Claude Bernard recorded intracardiac pressures in animals and introduced the term cardiac catheterization in 1844, it took many years before human cardiac catheterization was documented for the first time. In 1929, the German physician Werner Forssmann, who was searching for the most efficacious routes of drug delivery and who did not quite adhere to the institutional rules, succeeded to puncture the antecubital vein and advance a urethral catheter to the right atrium of his own heart. Admiration of his courageous endeavors was renowned in 1956 when Nobel Prize candidates Andre F. Cournand and Dickinson W. Richards proposed that the committee include Forssmann, who actually inspired their work, as the third nominee. Ironically, after Forssmann's death, the clinic, which had fired the intern Forssmann for this experiment and invalidated his medical license, was named after him in 1979.

CORONARY ANGIOGRAPHY

Despite the lack of recognition, further evolution of the Nobel Prize-winning idea of heart catheterization translated into widespread use of this procedure for diagnostic assessments. However, the increase in the precision of catheterization using selective coronary imaging has helped elaborate surgical and interventional treatment strategies. Since 1958, the American cardiologist Frank Mason Sones, Chief of Pediatric Cardiology at the Cleveland Clinic, started performing selective imaging of the coronary arteries. During diagnostic ventriculo- and aortography in a 29-year-old patient with rheumatic disease, Sones inadvertently visualized the right coronary artery by injecting 30 mL of contrast medium into the aorta. As it appeared to be safe in terms of life-threatening arrhythmias, this play of chance inspired further clinical investigations. In 1966, Sones et al published data summarizing the correlates of angiography with the clinical data from 1000 patients.² The tedious work of Sones paved the way for his colleague, surgeon Rene Favaloro, to invent coronary artery bypass grafting, which was successfully performed at the Cleveland Clinic in 1967. Since then, Sones has performed more than 10 000 catheterizations, mainly using a brachial approach, which, due to local bleeding complications, may not have been the optimal approach in all cases.

The introduction of the safe artery catheterization technique by the Swedish radiologist Sven Ivar Seldinger in 1953 and the fashioning of preshaped catheters by Melvin Paul Judkins in 1967 led to further widespread use and ease of the manipulations. These remarkable techniques have been used in millions of procedures and they continue to be used today.

PERCUTANEOUS ANGIOPLASTY

Searching for less invasive alternatives for the management of atherosclerotic disease and following the concept of remodeling, which was introduced in 1964 by the radiologist Charles Dotter, Andreas Grüntzig worked on better options for lesion dilatation. Experimental procedures utilized a home-assembled, single-lumen, preshaped dilatation catheter with a “sausage-shaped distensible segment (balloon) at the tip.”³ Thus, the first-in-man percutaneous transluminal coronary angioplasty was preceded by performing a relatively large series of peripheral arterial lesion dilatations to gain experience. In February 1974, Grüntzig started with the treatment of superficial femoral artery stenosis, and, in 1977, he reported promising follow-up results from 250 patients with periphery artery disease, showing >70% patency of the iliac and femoropopliteal arteries 2 years after the procedure.

Extensive animal studies on intraoperative coronary artery balloon dilatations translated into uneventful percutaneous transluminal coronary angioplasties, which offered an alternative to coronary artery bypass grafting to 5 male patients with refractory angina and severe stenotic coronary lesions.³ These endeavors were supported by the surgeon Ake Senning, who was Head of the Heart Surgery Clinic at the Zurich University Hospital and who coauthored the publication that came out a year later. The results of a somewhat larger clinical study (n=50) claimed a procedural success rate of 64% and reduced the need for emergency bypass surgery by 10%.⁴ Therefore, based on the analysis of their experiences, as the only available data at the time, Grüntzig considered “patients with the single-vessel disease... to be the most suitable for the procedure” and hypothesized that “only 10 - 15 percent of candidates for bypass surgery have lesions suitable for this procedure.”

CORONARY ARTERY STENTING: BARE-METAL STENTS

The limitations and nonencouraging long-term results of percutaneous transluminal coronary angioplasty appeared to be constraints to the rapid recognition of the clinical value of this technique. Further investigations focused on protecting the vessel from restenosis and thrombosis. Cesare Gianturco, an Italian radiologist, presented Andreas Grüntzig’s z-shaped circular wire, and he was the first to use the term “stent.” There were several physicians working on the concept of providing support to the arterial wall, and so a new era began on March 28, 1986, which was marked by Jacques Puel performing a “double-helix” “Wallstent” metal device implantation. Shortly after, in June 1986, Ulrich Sigwart expanded the indications for coronary interventions by performing rescue stenting of an occlusive left anterior descending coronary artery proximal dissection. Then, the Institutional Review Board approved coronary stenting for abrupt closure after percutaneous transluminal coronary angioplasty, restenosis, saphenous vein graft stenosis, and periphery artery stenosis.⁵

The initial enthusiasm with bare-metal stent implantations was tempered by the increasing number of stent thrombosis, which resulted in an extensive search for newer antithrombotic agents and efficacious medical treatment regimens. Dual antiplatelet therapy appeared to be a successful measure to prevent in-stent thrombosis; it was validated in 1996 by the French cardiologist Marie-Claude Morice. As the management of acute thrombotic events advanced, questions were raised concerning the proper management of potentially fatal acute coronary syndromes. The usefulness of PCI for treating patients with acute coronary syndromes was highly debated; however, it received recognition after the PAMI trial, which demonstrated the efficacy of primary PCI vs on-site thrombolysis in selected patient populations. Currently, there is no doubt that PCI is an urgent lifesaving procedure in patients with acute coronary syndromes.

DRUG-ELUTING STENTS

However, despite a better management of thrombotic issues via prescription of dual antiplatelet therapy and optimal stent apposition and deployment, stent restenosis remained the main issue until the discovery of a way to manage the proliferative phase of neointimal hyperplasia and constrictive remodeling. In 1996, Robert Falotico identified sirolimus, or rapamycin, a failed antibiotic, but potent inhibitor of smooth cell proliferation and migration, as an appropriate agent for stent coating. Going from bench to bedside, the randomized RAVEL trial elucidated the superiority of sirolimus-coated stents over bare-metal stents for reducing restenosis, thus opening a new era for a wider use of coronary stenting.⁶

BIODEGRADABLE STENTS

Although early in-stent restenosis was sufficiently managed by first- and second-generation drug-eluting stents, later in-stent stenosis development became a concern. Very late stent restenosis may result from impaired artery physiology, chronic endothelial degeneration, and a local inflammatory response to the coating polymer. Therefore, the idea of successfully placing self-degrading, bioresorbable stents was developed. This paradigm shift in interventional cardiology, along with proper medical therapies, offers a potential opportunity to restore vascular physiology.

GOING BEYOND

Numerous pivotal changes in the use of interventional procedures have occurred during the last decades. Due to accumulated evidence, eg, SYNTAX trial data, broader alternatives to surgical revascularization have been offered, such as left main coronary artery stenting in patients with an acceptable anatomy.⁷ PCIs have dramatically changed the scope of surgical operations. In patients with structural heart disease, such as valvular disease, and congenital heart defects, the number of interventions and the variety of commercially available devices is steadily rising. Today, thousands of transcatheter aortic valve replacements have been performed worldwide, affecting the survival in elderly patients; the annual number of these procedures exceeded the number of conventional surgical aortic valve replacements in some European countries.⁸

Although the role of PCI could not be overestimated, another “back to the future” event has occurred recently. After the ORBITA trial outcome results, we are returning to the discussion of whether stable patients with coronary heart disease should undergo PCI or merely continue to take optimized medical therapy.⁹ In many ways, the results of this first placebo-controlled study in PCI patients receiving optimal medical therapy may not substantially affect the number of PCIs performed in patients with stable angina, but it brings into focus the importance and efficacy of medical therapy in patients with stable coronary artery disease.

Summarizing experiences gained in the evolving area of cardiology and looking back at the tremendous efforts of outstanding professionals, such as Andeas Grüntzig, Charles Dotter, Frank Mason Sones, Sven Ival Seldinger, Melvin Paul Judkins, and many others, it is now evident how powerful thought and endeavor could be to protect human life. ■

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NEWS FROM THE 2017 AMERICAN HEART ASSOCIATION CONGRESS

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The 2017 American Heart Association (AHA) Scientific Sessions took place in Anaheim, CA, USA from November 11 to 15, 2017. A special highlight was the presentation of the new guidelines for the prevention, detection, evaluation, and management of high blood pressure in adults as a collaborative guideline of the AHA together with the American College of Cardiology (ACC) and several other organizations.¹ Furthermore, in the aftermath of the presentations and publications of the CANTOS trial results^{2,3} during the Annual Congress of the European Society of Cardiology (ESC) in Barcelona in September, some relevant additional analyses from this innovative anti-inflammatory treatment were presented.⁴ In addition, a large trial examining the effect of bicarbonate and acetylcysteine on renal outcomes after angiography (PRESERVE trial) was presented.⁵ Finally, additional highlights from the field of heart failure and post-myocardial infarction will be summarized here.

NEW GUIDELINES FOR HYPERTENSION

For the treatment of high blood pressure, the 2013 ESC guidelines⁶ define grade 1 hypertension as a blood pressure of 140-159/90-99 mm Hg (systolic/diastolic), grade 2 as 160-179/100-109 mm Hg, and grade 3 as any blood pressure \geq 180/110 mm Hg. A blood pressure of 130-139 mm Hg is categorized as “high normal.” In the meantime, the SPRINT trial⁷ showed that intensive blood pressure treatment, targeting a systolic blood pressure $<$ 120 mm Hg, reduced the primary composite end point of myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes, but also all-cause mortality compared with standard treatment with a usual blood pressure target of 140 mm Hg. However, a post hoc analysis of the ONTARGET and TRANSCEND trials⁸ revealed that a J-shaped relation between blood pressure lowering and outcome existed, with an optimal risk reduction at an achieved blood pressure of \approx 130 mm Hg, but a re-increase in risk at values $<$ 120 mm Hg.

In the newest guidelines, the four major points include: (i) a strong emphasis on the accuracy of blood pressure measurements using out-of-office blood pressure

measurements to confirm the diagnosis and for drug titration; (ii) a new approach to the decision-making process for a treatment that incorporates the underlying cardiovascular risk; (iii) lower targets for blood pressure during the management of hypertension; and (iv) strategies to improve blood pressure control with an emphasis on lifestyle approaches (treatment cornerstone). Accordingly, the new AHA/ACC guidelines on hypertension redefined the thresholds for high blood pressure as follows:

Normal blood pressure: <120 mm Hg systolic and <80 mm Hg diastolic

Elevated blood pressure: 120-129 mm Hg systolic and <80 mm Hg diastolic

Stage 1 hypertension: 130-139 mm Hg systolic or 80-89 mm Hg diastolic

Stage 2 hypertension: ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic

With this new definition, the prevalence of hypertension in the US population increased from $\approx 32\%$ to $\approx 46\%$ overnight, according to the presenter and lead author of the new AHA/ACC guidelines, Professor Whelton. However, the treatment consequences were also adapted. By lowering the definition of hypertension, the guidelines recommend an earlier intervention to prevent further blood pressure increases and the complications of hypertension. For patients who have stage 1 hypertension, but otherwise have a low cardiovascular risk (ie, no clinical cardiovascular disease and a 10-year atherosclerotic cardiovascular disease risk $< 10\%$), the guidelines recommend nonpharmacological approaches, mostly lifestyle changes, and a repeat blood pressure evaluation within 3 to 6 months. For patients who have stage 1 hypertension and an estimated 10-year atherosclerotic cardiovascular disease risk $\geq 10\%$, they recommend that the patients be managed initially with a combination of nonpharmacological and antihypertensive drug therapy, and have a repeat blood pressure evaluation in 1 month (in addition to lifestyle changes). The cardiovascular risk can be assessed with the atherosclerotic cardiovascular disease risk calculator, which is available online (<http://tools.acc.org/ASCVD-Risk-Estimator-Plus/>) or as a smartphone application. The risk is considered "elevated" when the value is $\geq 10\%$ (for heart disease or stroke) and/or if the patient has manifest clinical cardiovascular disease, chronic kidney disease, or diabetes mellitus. When a patient has an elevated risk and stage 1 hypertension, the guidelines recommend a treatment with at least one antihypertensive drug. If a patient has stage 2 hypertension, treatment with two or more antihypertensive drugs plus lifestyle changes are recommended.

Salt sensitivity may be a marker for increased cardiovascular disease and all-cause mortality risk independently of blood pressure. The new guidelines specified that certain groups with various demographic, physiological, and genetic characteristics tend to be particularly sensitive to the effects of dietary sodium on blood pressure. Salt sensitivity is especially common in blacks, older adults, and those

with a higher level of blood pressure or comorbidities, such as chronic kidney disease, diabetes mellitus, or the metabolic syndrome. Therefore, the new guidelines highlight that the current techniques for recognizing salt sensitivity are impractical in routine clinical practice, so salt sensitivity is best considered as a group characteristic.

Reinforcing the importance of lifestyle changes for the prevention and treatment of hypertension, a trial that investigated effects of nutritional sodium reduction and the application of the so-called DASH diet (Dietary Approaches to Stop Hypertension) was presented.⁹ The DASH diet is rich in fruits, vegetables, and low-fat dairy products, and it was shown to reduce saturated fat and cholesterol. Both the DASH diet and lowering sodium led to meaningful reductions in blood pressure in 412 patients who are naive of medical treatment, with the largest effects observed in patients with a baseline blood pressure between 150 and 160 mm Hg. In these patients, the combination of DASH and a low sodium diet reduced systolic blood pressure by up to 20 mm Hg.⁹ These results highlight the importance of lifestyle changes, particularly choosing the right diet for the prevention and treatment of hypertension.

ANTI-INFLAMMATORY TREATMENT WITH CANAKINUMAB: WHICH PATIENTS BENEFIT THE MOST?

It is well established that inflammation plays an important pathophysiological role in atherosclerosis in general, in coronary artery disease, in particular. At the 2017 ESC congress, the results of the CANTOS trial were presented and published.^{2,3} In CANTOS, anti-inflammatory treatment of patients with a previous myocardial infarction with canakinumab, an antibody targeting interleukin 1 β , reduced the levels of the inflammatory marker CRP, the incidence of the primary end point (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death),² and interestingly, also the incidence of lung cancer and lung cancer mortality.³ Two major downsides of this innovative treatment regimen are that it is very expensive and that the overall risk reduction achieved (15%) was moderate. At the AHA congress, Ridker presented a further analysis of CANTOS, which revealed that, in those patients who responded to the first single dose of canakinumab with a reduction in CRP to <2 mg/L, the drug reduced cardiovascular mortality and all-cause mortality by 31%.⁴ Furthermore, the risk to develop or die from lung cancer was reduced by 71% in those patients with a CRP <2 mg/L. In contrast, in those patients in whom the CRP values remained at 2 mg/L or above, no significant risk reduction in all-cause, cardiovascular, or lung cancer mortality was achieved.⁴ These results may help to stratify treatment to those with the highest benefit by a simple clinical read-out (ie, reduction in CRP after an initial dose).

PREVENTION OF ANGIOGRAPHY-INDUCED ACUTE KIDNEY INJURY

The application of contrast media in the context of cardiac catheterization or other forms of angiography imposes a risk of acute kidney injury. It has been assumed that urinary alkalization and/or scavenging reactive oxygen species may mitigate renal tubular epithelial cell injury induced by contrast media. However, several smaller clinical trials that tested the use of acetylcysteine or sodium bicarbonate had inconsistent results. Therefore, the PRESERVE trial assessed the impact of sodium bicarbonate and acetylcysteine vs standard treatment (including sodium chloride infusion) on renal function (ie, need for dialysis, persistent increase in serum creatinine level of more than 50% at 90 days) and death after angiography in a much larger population.⁵ However, in 4993 patients randomized to acetylcysteine vs placebo or sodium bicarbonate vs sodium chloride in a 2 x 2 fashion, none of these treatments improved the occurrence of this composite end point vs standard treatment.⁵ Therefore, it is recommended to treat patients with sodium chloride only and avoid the application of acetylcysteine or sodium bicarbonate as a prophylaxis for acute kidney injury before angiography.

LEFT VENTRICULAR SYSTOLIC DYSFUNCTION AS AN IMPORTANT PREDICTOR OF OUTCOME IN CARIOGENIC SHOCK

A common cause for acute heart failure, particularly cardiogenic shock, is myocardial infarction. At the AHA congress, the data from the FAST-MI program were presented. Here, the outcomes of 4156 patients with myocardial infarction were assessed and related to LVEF at baseline.¹⁰ Three percent of patients with myocardial infarction had cardiogenic shock. An early percutaneous coronary intervention was performed more often in patients with systolic dysfunction (ie, LVEF \leq 40%) than without. Cardiogenic shock was associated with an impaired 3-year outcome in patients with an LVEF \leq 40% or $>$ 40%. However, an LVEF \leq 40% carried a more than 2-fold elevated risk of 3-year outcomes in patients with cardiogenic shock and acute myocardial infarction.¹⁰

OTHER HEART FAILURE TRIALS

One major focus of clinical heart failure trial results presented at the AHA congress was on the cardiovascular effects of SGLT2 inhibitors. The treatment of patients with diabetes has been a therapeutic dilemma for many years, since several glucose-lowering treatments increased or did not lower cardiovascular end points, particularly heart failure end points. A change in paradigm was achieved with the EMPA-REG OUTCOME trial, in which the treatment of patients with diabetes who were at a high cardiovascular risk with the SGLT2 inhibitor empagliflozin was associated with a substantial reduction in cardiovascular, heart failure, and total mortality.¹¹ Since EMPA-REG, many more studies have tried to elucidate the

mechanism of action that accounts for this result, and whether this has been a class effect or a result specific for empagliflozin.

Meanwhile, data from the CANVAS program were published, revealing that the SGLT2 inhibitor canagliflozin also reduced the combined primary end point of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke.¹² However, an unexpected increase in the rate of amputations occurred, especially the toes and metatarsals.¹² To assess whether empagliflozin could also pose a risk to those patients at a particularly high risk for amputations, ie, those with peripheral artery disease, a post hoc analysis of the EMPA-REG OUTCOME trial was conducted.¹³ However, in the 623 (of a total of 7022) patients with peripheral artery disease in EMPA REG OUTCOME, empagliflozin reduced the risk of total mortality by 38%, with no increase in amputations (HR, 0.84). Therefore, it is still unclear why canagliflozin, but not empagliflozin, increased the rate of amputations.

In the CVD-REAL Nordic Registry, real life data of the SGLT2 inhibitor dapagliflozin vs dipeptidyl peptidase-4 inhibitors were assessed in a population of 40 908 patients with a 1:3 propensity score matching between 2012 and 2015. In this analysis, dapagliflozin was associated with a 21% lower rate of MACE (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular mortality), a 38% lower rate of heart failure hospitalizations, and a 41% lower rate of all-cause mortality.¹⁴ These data reinforce the idea that SGLT2 inhibitors may have benefits on heart failure outcomes as a class effect. Further prospective trials will have to confirm these observations.

According to the current ESC guidelines for the treatment of heart failure, treatment with ivabradine should be initiated in addition to β -blockers in patients with sinus rhythm and a heart rate ≥ 70 /min. At the AHA congress, Yuri Lopatin presented the results from the Optimize Heart Failure program¹⁵ from 414 patients hospitalized for heart failure. The main results from this nonrandomized trial were that patients who were discharged on ivabradine and a β -blocker had a more efficient lowering of their heart rate, a further improvement in LVEF, and a reduction in death and rehospitalization. Therefore, these observational data suggest that adding ivabradine to the treatment in patients who are in the hospital due to decompensation is safe and presumably helpful to improve cardiac function and avoid rehospitalization. ■

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Abbreviations & Acronyms



ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACE 1950	Akershus Cardiac Examination 1950
ACTION-HF	impACT of companION therapy in patients with Heart Failure
AEGIS	Apo-I Event reducinG in Ischemic Syndromes
AHA	American Heart Association
ANGPTL3	angiotensin-like 3
APPEAR	Angina Prevalence and Provider Evaluation of Angina Relief
ARB	angiotensin receptor blocker
ARNi	angiotensin receptor-neprilysin inhibitor
ASCOT-LLA	Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm
ATHOS-3	Angiotensin II for the Treatment of High-Output Shock
ATLAS	Assessment of Treatment with Lisinopril And Survival
ATLAS ACS 2–TIMI-51	Anti-Xa Therapy to Lower cardiovascular events in Addition to Standard therapy in subjects with Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction 51
ATTRACT	Acute venous Thrombosis: Thrombus Removal with Adjunctive Catheter-directed Thrombolysis
AUGUSTUS	evAlUation of the safety of apixaban vs vitamin K antaGonist and aspirin vs aspirin placebo in patients with atrial fibrillation and acUte coronary Syndrome or percuTaneoUS coronary intervention
BEAUTIFUL	morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction
BEST	Beta-blocker Evaluation of Survival Trial
BETonMACE	effect of the Bromodomain Extraterminal Domain inhibitor RVX000222 on time to Major Adverse Cardiovascular Events in high-risk type 2 diabetes subjects with coronary artery disease

BIOFLOW V	BIOTRONIK - a prospective randomized multicenter study to assess the safety and effectiveness of the orsiro siroLimus eluting coronary stent system in the treatment Of subjects With up to three de novo or restenotic coronary artery lesions - V
BLAST-AHF	Biased Ligand of the Angiotensin receptor STudy in Acute Heart Failure
BNP	brain natriuretic peptide
CABG	coronary artery bypass graft
CADENCE	Coronary Artery Disease in gENERal practiCE
CALM-FIM_EUR	Controlling And Lowering blood pressure with the MobiusHD, First In Man, in EUROpe study
CANTOS	Canakinumab Antiinflammatory Thrombosis Outcome Study
CANVAS	CANagliflozin cardioVascular Assessment Study
CHA₂DS₂-VASc	Congestive heart failure, Hypertension, Age, Diabetes, previous Stroke/transient ischemic attack-VAScular disease (peripheral arterial disease, previous myocardial infarction, aortic atheroma) and Sex category
CHARM	Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity
CIBIS-ELD	Cardiac Insufficiency Blsoprolol Study in ELDerly
CLOSE	patent foramen ovale CLOSurE or anticoagulants vs antiplatelet therapy to prevent stroke recurrence
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation StrategieS
CROS	Cardiac Rehabilitation Outcome Study
CULPRIT-SHOCK	CULPRIT lesion only PCI versus multivessel PCI in cardiogenic shock
DAPT	dual antiplatelet therapy
DETO2X-SWEDEHEART	Determination of the Role of OXYgen in suspected acute myocardial infarction SWEDish web system for Enhancement and development of evidence-based care in HEART disease evaluated according to recommended therapies

DEVOTE	cardiovascular safety of insulin DEgludec Vs insulin glargine in patients with type 2 diabetes at high risk Of cardiovascular events Evaluation
DIG	Digitalis Investigation Group
DPP4	dipeptidyl peptidase-4
EDIFY	prEserveD left ventricular ejection fraction chronic heart Failure with ivabradine study
EFFORTLESS	Evaluation of FactORs impacTing cLinical outcome and cost EffectiveneSS of the subcutaneous implantable cardioverter-defibrillator
eGFR	estimated glomerular filtration rate
EMPA-REG OUTCOME	Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes
EPHESUS	Eplerenone Post-AMI Heart failure Efficacy and SURvival Study
EuroCaReD	European Cardiac Rehabilitation registry and Database
EURO-FILLING	EUROpean validation study of the accuracy of E/e' in estimating left ventricular FILLING pressure
EuroSCORE	European System for Cardiac Operative Risk Evaluation I
EXSCEL	EXenatide Study of Cardiovascular Event Lowering
FOURIER	Further cardiovascular OUtcomes Research with PCSK-9 Inhibition in subjects with Elevated Risk
GLP-1	glucagon-like peptide 1
Gore REDUCE	GORE® HELEX® septal occluder / GORE® CARDIOFORM septal occluder and antiplatelet medical management for REDUction of recurrent stroke or imaging-confirmed transient ischemic attack in patients with patent foramen ovale
GUIDE-IT	GUIDing Evidence-based therapy using biomarker Intensified Treatment in heart failure
GUSTO IIb	Global Use of Strategies To Open occluded coronary arteries in acute coronary syndromes IIb
GWTG-CAD	Get With The Guidelines-Coronary Artery Disease
HASBLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/ alcohol concomitantly

HEAAL	Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan
HF-ACTION	Heart Failure and A Controlled Trial Investigating Outcomes of exercise trainiNg
HFPEF	heart failure with preserved ejection fraction
HFREF	heart failure with reduced ejection fraction
HR	heart rate
hsCRP	high sensitivity C-reactive protein
ICCAD	International Congress on Innovations in Coronary Artery Disease
ICD	implantable cardioverter-defibrillator
IMPACT-AF	IMProve treatment with AntiCoagulanTs in patients with Atrial Fibrillation
INFORM	INduction with Foley OR Misoprostol study
iPS	induced pluripotent stem cells
LDL-C	low-density lipoprotein cholesterol
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results
LV	left ventricular
LVEDP	left ventricular end-diastolic pressure
LVEF	left ventricular ejection fraction
MI	myocardial infarction
MOCHA	Multicenter Oral Carvedilol Heart failure Assessment
MRA	mineralocorticoid receptor antagonist
MR CLEAN	Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands
NOAC	non-vitamin K oral anticoagulants
NSTEMI	non-ST-segment elevation myocardial infarction
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
ORBITA	Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina
ORIGIN	Outcome Reduction with an Initial Glargine Intervention

ORION-1	evaluation of the effect Of inclisiran (ALN-PCSSc) tTreatment on low density llpOprotein cholesterol
PAMI	Primary Angioplasty in Myocardial Infarction
PARADIGM-HF	Prospective comparison of Angiotensin Receptor-neprilysin inhibitor with an Angiotensin-converting enzyme inhibitor to Determine Impact on Global mortality and Morbidity in Heart Failure
PCI	percutaneous coronary intervention
PCSK-9	proprotein convertase subtilisin/kexin type 9
PCWP	pulmonary capillary wedge pressure
PPAR-γ	peroxisome proliferator-activated receptor-γ
PRECISE-DAPT	PRedicting bleeding Complications In patients unDERgoing stent implantation and subsequent Dual AntiPlatelet Therapy score
PROMINENT	Pemafibrate to Reduce cardiovascular OutCOmes by reducing triglycerides IN diabetic patiENTS
PURE	Prospective Urban Rural Epidemiology
QUALs	quality-adjusted life years
RALES	Randomized ALdactone Evaluation Study
RAVEL	RANdomized study with the sirolimus-coated Bx VELOCITY balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions
RCT	randomized controlled trial
REACH	REduction of Atherothrombosis for Continued Health
RED-HF	Reduction of Events by Darbepoetin alpha in Heart Failure
RE-DUAL PCI	Randomized Evaluation of DUAL therapy with dabigatran vs triple therapy with warfarin in patients with AF that undergo a PCI with stenting
RELAX-AHF	RELAXin in Acute Heart Failure
RESPECT	Randomized Evaluation of recurrent Stroke comparing Patent foramen ovale closure to Established Current standard of care Treatment
REVEAL	Randomized EVALuation of the Effects of Anacetrapib through Lipid modification

SAVOR-TIMI 53	Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus–Thrombolysis In Myocardial Infarction 53
SERVE-HF	treatment of sleep-disordered breathing with predominant central sleep apnea by adaptive SERvo-VEntilationin patients with Heart Failure
SGLT2	sodium glucose cotransporter 2
SIMPLE	Shockless IMPLant Evaluation
SOCRATES-PRESERVED	SOluble guanylate Cyclase stimulatO in heArT failurE patientS with PRESERVED ejection fraction
SPPARM-α	selective peroxisome proliferator-activated receptor α modulator
SPRINT	Systolic Blood Pressure Intervention Trial
SPYRAL HTN-OFF MED	renal denervation with the symplicity SPYRAL™ multi-electrode renal denervation system in patients with uncontrolled HyperTensioN in the absence Of antihypertensive MEDication
STEMI	ST-segment elevation myocardial infarction
SURTAVI	SURgical Replacement and Transcatheter Aortic Valve Implantation
SUSTAIN	SemagLUtide and cardiovaScular ouTcomes in pATleNts with type 2 diabetes
SYNTAX	SYnergy between percutaneous coronary interventioN with TAXus and cardiac surgery
TECOS	Trial Evaluating Cardiovascular Outcomes with Sitagliptin
Telereab-HBP	Telerehabilitation Home-Based Programme
TOPCAT	Treatment Of Preserved Cardiac function heart failure with an Aldosterone anTagonist
TRICS III	Transfusion Requirements In Cardiac Surgery
TROPICAL-ACS	Testing RespOnsiveness to Platelet Inhibition on Chronic AntiplateLet treatment for Acute Coronary Syndromes
TRUE-AHF	Trial of Ularitide Efficacy and Safety in Acute Heart Failure
VIVA	Vlborg Vascular trial

Instructions for Authors



INSTRUCTIONS FOR AUTHORS

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Examples 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.

● Chapter in a book

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

● Web-based material

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

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