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EDITORIAL

I graduated in 1981. Thus, it is difficult not to feel a little bit sad when thinking about the extraordinary steps forward that cardiology witnessed in the previous decades. Current treatments of all major cardiovascular diseases still seem to be founded on those great achievements. However, cardiology is still moving forward and major changes have occurred, including in this last year, which may, in fact, be more than in the years before. Without any pretense of being comprehensive, I will just take this occasion to briefly present some of these impressive advances.

Prevention

Dyslipidemia. Major advances occurred in the treatment of dyslipidemia and diabetes. The REDUCE-IT trial showed that administration of a high-dose highly purified eicosapentaenoic acid ethyl ester to patients with established cardiovascular disease or diabetes, high triglycerides, and low LDL cholesterol levels reduced plasma triglycerides and, more importantly, major adverse cardiovascular events (MACE), cardiovascular death, stroke, or myocardial infarction (MI) by 25%. These results are in marked contrast with the neutral results of trials with n-3 fatty acids that had no effect on MACE in the ASCEND and VITAL trials in 2018, and they might be explained by the drug's anti-inflammatory and antiplatelet actions and by lowering triglyceride levels.

Hypercholesterolemia. In 2018, the second major trial of PCSK-9 inhibition with a human monoclonal antibody, the ODISSEY trial, was concluded. The administration of alirocumab led to a 1.6% reduction in the rate of MACE in patients with a previous acute coronary syndrome and with LDL cholesterol levels ≥70 mg/dL, non–HDL cholesterol levels ≥100 mg/dL, or apolipoprotein B levels ≥80 mg/dL despite high-dose statin therapy. Practical recommendations for the use of PCSK-9 inhibitors were also published.

Diabetes. In 2018, confirmation of the favorable effects of SGLT2 inhibitors on cardiovascular outcomes was obtained. In previous trials in diabetic patients at high cardiovascular risk, both empagliflozin and canagliflozin reduced cardiovascular death and heart failure (HF) hospitalizations. These beneficial effects were confirmed this year with dapagliflozin in the DECLARE-TIMI 58 trial. SGLT2 inhibitors have neutral effects on nonfatal stroke or MI and their favorable effects are specific for cardiovascular death and, namely, HF events. There is the potential for favorable effects in patients with HF, independently of concomitant diabetes; this hypothesis is being tested in ongoing trials.

Antithrombotic strategies. When used in primary prevention, aspirin did not reduce cardiovascular events and increased the hemorrhagic risk, even in subjects at high risk, such as those with diabetes (ASCEND trial) or the elderly (ASPREE

trial). New avenues for antithrombotic treatment in secondary prevention were opened by the COMPASS trial, where the combination of low-dose rivaroxaban and aspirin led to a reduction in MACE (primary end point) and deaths, compared with aspirin alone, in patients with chronic atherosclerotic vascular disease.

Imaging

Major progress occurred with all imaging modalities, including (i) echocardiography, where global longitudinal strain established its role as an early measurement of left ventricular (LV) systolic dysfunction; (ii) cardiac magnetic resonance (CMR), with major studies about tissue characterization, T1 mapping, and extracellular volume assessment; (iii) coronary computed tomography (CT); (iv) nuclear imaging with quantitative coronary flow measurement and perfusion imaging with positron emission tomography (PET); and (v) fusion imaging with CMR/PET and CT/PET showing the relation between anatomical and functional abnormalities. In 2018, the results of the SCOT-HEART trial were presented and published, showing that patients who were referred to outpatient clinics for stable angina and received standard treatment, mainly based on exercise electrocardiography, plus coronary CT had a reduction in the primary end point of death or MI, mainly driven by a reduction in nonfatal MI, during a 5-year follow-up vs patients who received standard therapy alone. Interestingly, no difference in the revascularization procedures between treatment arms was observed at 5 years, suggesting that the beneficial effects of coronary CT were mainly caused by better secondary prevention.

Arrhythmias, valve disease, and heart failure

These three topics were tightly related in 2018 and, more than ever, results of major trials were extremely stimulating, although, to some extent, not conclusive. Atrial fibrillation (AF) and HF often coexist, but it is unproven whether AF treatment affects HF outcomes. This hypothesis was tested in CASTLE-AF where patients with paroxysmal or persistent AF, HF, and a LV ejection fraction (EF) ≤35% who underwent AF ablation were almost 3-fold more likely to be in sinus rhythm during follow-up. AF ablation was associated with a reduction in the primary composite end point of all-cause death or worsening HF compared with conventional treatment during a median follow-up of 37.8 months; in addition, death and HF events alone were reduced in the AF ablation group. In addition to CASTLE-AF, the larger CABANA trial compared AF ablation with conventional treatment in patients with AF >65 years old or, if <65 years old, with ≥1 risk factor for stroke. There were no between-group differences in the primary end point, a composite of death, disabling stroke, serious bleeding, or cardiac arrest, and there was no difference in cardiovascular mortality. Limitations have been discussed for both of these trials and the effects of AF ablation on cardiovascular outcomes need to be shown in further trials, with quality of life as the main indication for AF ablation.

There is an even greater controversy regarding the results of two major outcome trials on the percutaneous treatment of secondary mitral regurgitation (MR) in HF patients with the MitraClip device. Secondary MR is associated with poorer outcomes in HF patients. Percutaneous treatment with the MitraClip device was effective in reducing MR, well tolerated, and associated with an improvement in quality of life measurements in observational studies. However, outcome data can only come from prospective, controlled, trials. Unfortunately, the results of two studies, concluded in 2018, could not be more different. In MITRA-FR, MR was reduced to ≤2 in 90% of the patients with HF, secondary MR, and reduced LVEF (15% to 40%) who were randomized to optimal treatment and MitraClip vs those randomized to ongoing optimal treatment with drugs and cardiac resynchronization therapy, if indicated. However, there was no difference in the primary end point of death or HF hospitalization at 12 months, death alone, and hospitalization alone. In addition, symptoms improved to a similar extent in both groups. In contrast, the COAPT trial showed that conventional treatment plus MitraClip reduced HF hospitalizations and all-cause mortality (primary end point), improved quality of life, functional capacity, and MR, and reduced LV volumes (prespecified secondary end points) in patients with HF and secondary MR at 2 years vs optimal conventional treatment with drugs. While it seems unlikely that the differences between the two trials regarding sample size, follow-up duration, and primary end points can explain the differences observed in the results, perhaps the differences in the inclusion criteria (ie, smaller effective regurgitant orifice area and larger LV volumes) and patient selection may explain the differences. Another randomized outcome trial, Reshape-HF-2, with a composite of cardiovascular death or HF rehospitalizations as the primary end point, is ongoing.

Heart failure

HF remains a major cause of morbidity and mortality; its impact was further shown by the 2018 publication of the National Audit of HF in England and Wales, a large epidemiological study with >500 000 patients. This study confirmed the increase in HF hospitalizations in the last decade with a persistently poor prognosis. The inpatient mortality and the 3-year mortality were about 5% and 30%, respectively, for patients <75 years old and they increased to 12% and 60%, respectively, for those >75 years old. The benefits of medical treatment with the association of ACE inhibitors/ARBs or ARNI and β-blockers and mineralocorticoid antagonists and ivabradine, when indicated, was confirmed in 2018 by meta-analyses and observational studies. Further indirect confirmation of the role of medical treatment came from the TRED-HF trial. In this study, 51 patients with recovered dilated cardiomyopathy and no symptoms, LVEF >50%, normal LV end-diastolic volume, and low BNP values were randomized to continuation of ongoing treatment or its withdrawal. Treatment withdrawal was associated with worsening LV function and an increase in heart rate and NT-proBNP values in 40% of the patients, showing that the disease is never fully "cured" and is ongoing in a significant proportion of our patients.

After the PIONEER trial, which studied sacubitril/valsartan vs enalapril initiated in patients hospitalized for HF, and other studies showing the importance of drug compliance and adherence to evidence-based treatment, neurohormonal antagonist treatment may undergo a potential widening of the indications of ARNI to hospitalized patients. Major advances in HF treatment may come from (i) the treatment of comorbidities, such as AF and MR (see above); (ii) the administration of SGLT2 inhibitors; or (iii) the treatment of iron deficiency (ongoing trials). The most positive results have come from treating transthyretin amyloidosis with tafamidis in the ATTR-ACT trial, which showed that patients with transthyretin amyloid cardiomyopathy who were treated with tafamidis (80 mg or 20 mg) had a lower rate of all-cause mortality and cardiovascular hospitalizations vs placebo. These favorable effects on outcomes were also accompanied by a lower rate of decline in the 6-minute walk test distance and quality of life.

Further results regarding devices, from simpler devices (eg, cardiac contractility modulation or an interatrial septal device to reduce left atrial pressure) to new LV assist devices, were presented in 2018. The 2-year outcomes of the MOMENTUM-3 trial showed that the new magnetically levitated centrifugal continuous-flow circulatory pump increase the survival free of disabling stroke and reduced the overall rate of stroke, and it also led to fewer reoperations for pump malfunctioning compared with the mechanical-bearing axial continuous-flow pump.

Conclusions

Major advances occurred in the diagnosis and treatment of cardiovascular disease in 2018 and this short editorial is not meant to summarize or even rank them at all. As a general consideration, we may note a gradual shift toward a more focused treatment, targeting the specific abnormalities in each single patient. At a simpler level, this concerns specific mechanisms of cardiovascular risk as well as of disease severity and progression, as is the case of cardiac and noncardiac comorbidities in HF patients. However, greater granularity may be foreseen in the future with the advances in imaging modalities and biomarkers, allowing greater accuracy and, hence, efficacy.

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Snapshot in Cardiology

SNAPSHOT IN CARDIOLOGY

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These articles were taken from the New England Journal of Medicine, The Lancet, *and* JAMA *between January 1, 2018 and December 31, 2018. All research articles on cardiology were included; reviews and guidelines were excluded.*

JANUARY

Al-Lamee R, Thompson D, Dehbi HM, et al; ORBITA investigators. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet*. 2018;391(10115):31-40.
The multicenter, randomized ORBITA trial, which analyzed PCI vs placebo for angina relief, showed that, in patients with angina and severe coronary stenosis, percutaneous coronary intervention did not increase exercise time compared with placebo.

Anand SS, Bosch J, Eikelboom JW, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet*. 2018;391(10117):219-229.
The COMPASS trial showed that, in patients with peripheral artery disease, low-dose rivaroxaban taken twice a day plus aspirin once a day reduced major adverse cardiovascular and limb events vs aspirin alone. Although major bleeding was increased, fatal or critical organ bleeding was not.

Connolly SJ, Eikelboom JW, Bosch J, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet*. 2018;391(10117):205-218.
The COMPASS trial showed that, in patients with stable coronary artery disease, the addition of rivaroxaban to aspirin lowered major vascular events, but increased major bleeding. Overall, there was also a significant net benefit in favor of rivaroxaban plus aspirin, including a 23% reduction in death.

Feldman TE, Reardon MJ, Rajagopal V, et al. Effect of mechanically expanded vs self-expanding transcatheter aortic valve replacement on mortality and major adverse clinical events in high-risk patients with aortic stenosis: the REPRISE III randomized clinical trial. *JAMA*. 2018;319(1):27-37.
The REPRISE III trial showed that, in high-risk patients with severe, symptomatic aortic stenosis, the use of a mechanically expanded valve was not inferior to a self-expanding valve for the primary safety end point or the primary effectiveness end point.

Friedman DJ, Piccini JP, Wang T, et al. Association between left atrial appendage occlusion and readmission for thromboembolism among patients with atrial fibrillation undergoing concomitant cardiac surgery. *JAMA*. 2018;319(4):365-374.
In older patients (≥65 years old) with atrial fibrillation undergoing cardiac surgery (ie, coronary artery bypass grafting, mitral valve surgery with or without coronary artery bypass grafting, or aortic valve surgery with or without coronary artery bypass grafting), surgical left atrial appendage occlusion was

associated with a lower risk of readmission for thromboembolism over 3 years compared with no surgical left atrial appendage occlusion.

Kwong JC, Schwartz KL, Campitelli MA, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. *N Engl J Med*. 2018;378(4):345-353.

This self-controlled case-series study showed that, in patients hospitalized for acute myocardial infarction that occurred within 1 year before and 1 year after a positive test for influenza, there was a significant association between respiratory infections, especially influenza, and acute myocardial infarction.

Montaigne D, Marechal X, Modine T, et al. Daytime variation of perioperative myocardial injury in cardiac surgery and its prevention by Rev-Erbα antagonism: a single-centre propensity-matched cohort study and a randomised study. *Lancet*. 2018;391(10115):59-69.

In patients with severe aortic stenosis and preserved left ventricular ejection fraction, perioperative myocardial injury was significantly lower in those who underwent isolated aortic valve replacement surgery in the afternoon. An ex-vivo analysis of human myocardium showed transcriptional alterations in circadian gene expression with the nuclear receptor Rev-Erbα being highest in the morning, suggesting that Rev-Erbα antagonism may be a pharmacological strategy for cardioprotection.

Nogueira RG, Jadhav AP, Haussen DC, et al; DAWN Trial Investigators. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378(1):11-21.

Thrombectomy plus standard care resulted in better 90-day disability outcomes post-treatment in patients with acute stroke who had been well 6 to 24 hours prior to the stroke and who had a mismatch between clinical deficit and infarct vs standard care alone.

Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ; CANTOS Trial Group. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. *Lancet*. 2018;391(10118):319-328.

The CANTOS showed that, in patients with a history of myocardial infarction, reaching a high-sensitivity C-reactive protein concentration <2 mg/L with canakinumab resulted in a 25% reduction in major adverse cardiovascular events and a 31% reduction in both cardiovascular mortality and all-cause mortality, whereas no significant benefit was observed with high-sensitivity C-reactive protein concentrations ≥2 mg/L.

Varenne O, Cook S, Sideris G, et al; SENIOR Investigators. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. *Lancet*. 2018;391(10115):41-50.

The SENIOR trial showed that, among elderly patients (≥75 years old) who underwent primary coronary intervention, the combination of a drug-eluting stent and a short duration of dual antiplatelet therapy is better than the combination of a bare-metal stent and a similar duration of dual antiplatelet therapy regarding the occurrence of all-cause mortality, myocardial infarction, stroke, and ischemia-driven target lesion revascularization.

FEBRUARY

Conrad N, Judge A, Tran J, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet*. 2018;391(10120): 572-580.

This population-based study showed that, from 2002 to 2014, despite seeing a decrease in the incidence of heart failure, the estimated absolute number of individuals with newly diagnosed heart failure in the UK increased, as did the estimated absolute number of prevalent heart failure cases. In addition, socioeconomic disparities were observed for heart failure incidence and age at onset.

de Winter RJ, Katagiri Y, Asano T, et al. A sirolimus-eluting bioabsorbable polymer-coated stent (MiStent) versus an everolimus-eluting durable polymer stent (Xience) after percutaneous coronary intervention (DESSOLVE III): a randomised, single-blind, multicentre, non-inferiority, phase 3 trial. *Lancet*. 2018;391(10119):431-440.

The DESSOLVE III trial showed that MiStent, a sirolimus-eluting bioabsorbable polymer stent, was noninferior to the everolimus-eluting durable polymer stent for a device-oriented composite clinical end point at 12 months in an all-comer population.

Huffman MD, Mohanan PP, Devarajan R, et al; ACS QUIK Investigators. Effect of a quality improvement intervention on clinical outcomes in patients in India with acute myocardial infarction: the ACS QUIK randomized clinical trial. *JAMA*. 2018;319(6):567-578.

The ACS QUIK trial showed that, in patients with acute myocardial infarction in Kerala, India, the use of a quality improvement intervention, which included audit and feedback, checklists, patient education materials, and links to emergency cardiovascular care and quality improvement training, did not decrease the major adverse cardiovascular events at 30 days compared with usual care.

Marrouche NF, Brachmann J, Andresen D, et al; CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med*. 2018;378(5):417-427.

The CASTLE-AF trial showed that treating atrial fibrillation in patients with heart failure using catheter ablation resulted in a significantly lower rate of the composite end point of death from any cause or hospitalization for worsening heart failure than in those receiving medical therapy.

Weisbord SD, Gallagher M, Jneid H, et al; PRESERVE Trial Group. Outcomes after angiography with sodium bicarbonate and acetylcysteine. *N Engl J Med*. 2018;378(7):603-614.

The PRESERVE trial showed that, among patients at high risk for renal complications who were undergoing angiography, there was no benefit of intravenous sodium bicarbonate over intravenous sodium chloride or of oral acetylcysteine over placebo for the prevention of death, the need for dialysis, or persistent decline in kidney function at 90 days or for the prevention of contrast-associated acute kidney injury.

MARCH

Bath PM, Woodhouse LJ, Appleton JP, et al; TARDIS Investigators. Antiplatelet therapy with aspirin, clopidogrel, and dipyridamole versus clopidogrel alone or aspirin and dipyridamole in patients with acute cerebral ischaemia (TARDIS): a randomised, open-label, phase 3 superiority trial. *Lancet*. 2018;391(10123):850-859.

The TARDIS trial showed that, among patients with recent cerebral ischemia, the incidence and severity of recurrent stroke or transient ischemic attack did not differ between intensive antiplatelet therapy with three agents and guideline-recommended therapy (ie, aspirin plus dipyridamole or clopidogrel alone). In addition, the intensive therapy resulted in a significantly higher risk of major bleeding.

Dziadzko V, Clavel MA, Dziadzko M, et al. Outcome and undertreatment of mitral regurgitation: a community cohort study. *Lancet*. 2018;391(10124):960-969.

This community cohort study showed that, despite the poor outcomes associated with isolated mitral regurgitation, only a minority of affected patients undergo mitral (or any type of cardiac) surgery, even when all means to diagnose and treat the disease are available and accessible.

Hahn JY, Song YB, Oh JH, et al; SMART-DATE investigators. 6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. *Lancet*. 2018;391(10127):1274-1284.

The SMART-DATE trial showed that a 6-month duration of dual antiplatelet therapy, compared with 12 months, in patients with acute coronary syndrome who underwent percutaneous coronary intervention with current-generation drug-eluting stents resulted in an increased risk of myocardial infarction.

Head SJ, Milojevic M, Daemen J, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. *Lancet*. 2018;391(10124):939-948.

This systematic review showed that coronary artery bypass grafting resulted in a mortality benefit compared with percutaneous coronary intervention in patients with multivessel disease, particularly those with diabetes and higher coronary complexity, but not in patients with left main disease.

McManus RJ, Mant J, Franssen M, et al; TASMINH4 Investigators. Efficacy of self-monitored blood pressure, with or without telemonitoring, for titration of antihypertensive medication (TASMINH4): an unmasked randomised controlled trial. *Lancet*. 2018;391(10124):949-959.

The TASMINH4 trial showed that, in patients with poorly controlled hypertension, the use of self-monitoring, with or without telemonitoring, to titrate antihypertensive medication results in significantly lower blood pressure than titration guided by clinic readings.

APRIL

Banegas JR, Ruilope LM, de la Sierra A, et al. Relationship between clinic and ambulatory blood-pressure measurements and mortality. *N Engl J Med*. 2018;378(16):1509-1520.
An analysis of a registry-based, multicenter, national cohort that included 63 910 adults recruited from 2004 through 2014 in Spain showed that ambulatory blood pressure measurements were a stronger predictor of all-cause and cardiovascular mortality than clinic blood pressure measurements.

Berwanger O, Santucci EV, de Barros E Silva PGM, et al; SECURE-PCI Investigators. Effect of loading dose of atorvastatin prior to planned percutaneous coronary intervention on major adverse cardiovascular events in acute coronary syndrome: the SECURE-PCI randomized clinical trial. *JAMA*. 2018;319(13):1331-1340.
The SECURE-PCI trial showed that periprocedural loading doses of atorvastatin did not reduce the rate of 30-day major adverse cardiovascular events in patients with acute coronary syndrome and a planned invasive management with percutaneous coronary intervention.

McDermott MM, Spring B, Berger JS, et al. Effect of a home-based exercise intervention of wearable technology and telephone coaching on walking performance in peripheral artery disease: the HONOR randomized clinical trial. *JAMA*. 2018;319(16):1665-1676.
The HONOR trial showed that a home-based exercise program, which involved using wearable activity monitoring and telephone coaching for patients with peripheral artery disease, did not improve walking performance at the 9-month follow-up appointment vs usual care.

Mehra MR, Goldstein DJ, Uriel N, et al; MOMENTUM 3 Investigators. Two-year outcomes with a magnetically levitated cardiac pump in heart failure. *N Engl J Med*. 2018;378(15):1386-1395.
The MOMENTUM 3 trial showed that, in patients with advanced heart failure, a fully magnetically levitated centrifugal-flow pump was superior to a mechanical-bearing axial-flow pump with regard to survival free of disabling stroke or reoperation to replace or remove a malfunctioning device.

Navarese EP, Robinson JG, Kowalewski M, et al. Association between baseline LDL-C level and total and cardiovascular mortality after LDL-C lowering: a systematic review and meta-analysis. *JAMA*. 2018;319(15):1566-1579.
This meta-analysis showed that patients with a high baseline level of low-density lipoprotein cholesterol (>100 mg/dL) had a greater reduction in the risk of total and cardiovascular mortality when receiving a more intensive therapy to lower low-density lipoprotein cholesterol vs those who received a less intensive therapy.

Victor RG, Lynch K, Li N, et al. A cluster-randomized trial of blood-pressure reduction in black barbershops. *N Engl J Med*. 2018;378(14):1291-1301.
Among non–Hispanic black male barbershop patrons with uncontrolled hypertension, health promotion by barbers resulted in larger reductions in blood pressure when coupled with medication management in barbershops by specialty-trained pharmacists.

MAY

Yu K, Qiu G, Chan KH, et al. Association of solid fuel use with risk of cardiovascular and all-cause mortality in rural China. *JAMA*. 2018;319(13):1351-1361.
In rural areas of China, higher risks of cardiovascular and all-cause mortality was associated with the use of solid fuels for cooking and heating; however, this risk may be reduced by switching to clean fuels and using ventilation.

Zhao Q, Zhu Y, Xu Z, et al. Effect of ticagrelor plus aspirin, ticagrelor alone, or aspirin alone on saphenous vein graft patency 1 year after coronary artery bypass grafting: a randomized clinical trial. *JAMA*. 2018;319(16):1677-1686.
In patients undergoing elective coronary artery bypass grafting, graft patency after 1 year significantly increased in those receiving ticagrelor plus aspirin vs those receiving aspirin alone.

Zheng SL, Roddick AJ, Aghar-Jaffar R, et al. Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2018;319(15):1580-1591.
This meta-analysis showed that, in patients with type 2 diabetes, the use of sodium-glucose cotransporter 2 inhibitors or glucagon-like peptide 1 agonists was associated with lower mortality than the use of dipeptidyl peptidase 4 inhibitors.

Brilakis ES, Edson R, Bhatt DL, et al; DIVA Trial Investigators. Drug-eluting stents versus bare-metal stents in saphenous vein grafts: a double-blind, randomised trial. *Lancet*. 2018;391(10134):1997-2007.
During a 12-month follow-up of patients undergoing stenting of de-novo saphenous vein bypass graft lesions, no significant differences in outcomes were found between patients receiving drug-eluting stents and those receiving bare-metal stents.

Gaudino M, Benedetto U, Fremes S, et al; RADIAL Investigators. Radial-artery or saphenous-vein grafts in coronary-artery bypass surgery. *N Engl J Med*. 2018;378(22):2069-2077.
The RADIAL investigators showed that radial-artery grafts for coronary artery bypass grafting procedures resulted in lower rates of adverse cardiac events and a higher rate of patency after a 5-year follow-up period than did saphenous vein grafts.

McIntyre WF, Um KJ, Alhazzani W, et al. Association of vasopressin plus catecholamine vasopressors vs catecholamines alone with atrial fibrillation in patients with distributive shock: a systematic review and meta-analysis. *JAMA*. 2018;319(18):1889-1900.
This meta-analysis showed that, in patients with distributive shock, the combination of vasopressin and catecholamine vasopressors was associated with a lower risk of atrial fibrillation compared with catecholamines alone.

Pylypchuk R, Wells S, Kerr A, et al. Cardiovascular disease risk prediction equations in 400 000 primary care patients in New Zealand: a derivation and validation study. *Lancet*. 2018;391(10133):1897-1907.
Pooled cohort equations, which are based mainly on old patient cohorts, overestimate the risk of cardiovascular disease in New Zealand, as evidenced by a large prospective cohort study. This study was representative of typical patients in primary care in New Zealand who were recommended for cardiovascular disease risk assessment, showing that most patients are now at a low risk of cardiovascular disease.

Yao X, Gersh BJ, Holmes DR et al. Association of surgical left atrial appendage occlusion with subsequent stroke and mortality among patients undergoing cardiac surgery. *JAMA*. 2018;319(20):2116-2126.
Performing surgical occlusion of the left atrial appendage in patients during cardiac surgery (eg, coronary artery bypass graft or valve surgery) reduced the risk of subsequent stroke and all-cause mortality vs patients not undergoing surgical left atrial appendage occlusion during surgery.

JUNE

Azizi M, Schmieder RE, Mahfoud F, et al; RADIANCE-HTN Investigators. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. *Lancet*. 2018;391(10137):2335-2345.
The RADIANCE-HTN SOLO trial showed that, compared with a sham procedure, endovascular ultrasound renal denervation reduced ambulatory blood pressure at 2 months in patients with combined systolic-diastolic hypertension in the absence of medications.

Devereaux PJ, Duceppe E, Guyatt G, et al; MANAGE Investigators. Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): an international, randomised, placebo-controlled trial. *Lancet*. 2018;391(10137):2325-2334.
The MANAGE trial showed that, in patients who had myocardial injury after noncardiac surgery (MINS), dabigatran 110 mg twice daily lowered the risk of major vascular complications, with no significant increase in major bleeding.

Estruch R, Ros E, Salas-Salvadó J, et al; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med*. 2018;378(25):e34.
The multicenter trial PREDIMED showed that, in people at high cardiovascular risk in Spain, the incidence of major cardiovascular events was lower among those assigned to a Mediterranean diet supplemented with extra-virgin olive oil or nuts than among those assigned to a reduced-fat diet.

JULY

Kandzari DE, Böhm M, Mahfoud F, et al; SPYRAL HTN-ON MED Trial Investigators. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet*. 2018;391(10137):2346-2355.
The SPYRAL HTN-ON MED trial showed that, compared with a sham control, renal denervation in the main renal arteries and branches significantly reduced blood pressure, with no major safety events.

Selak V, Kerr A, Poppe K, et al. Annual risk of major bleeding among persons without cardiovascular disease not receiving antiplatelet therapy. *JAMA*. 2018;319(24):2507-2520.
This prospective cohort study determined a baseline bleeding risk estimate in people without cardiovascular disease who were not taking antiplatelet therapy, which could be useful in the decision-making process for the primary prevention of cardiovascular disease.

Kim JM, Stewart R, Lee YS, et al. Effect of escitalopram vs placebo treatment for depression on long-term cardiac outcomes in patients with acute coronary syndrome: a randomized clinical trial. *JAMA*. 2018;320(4):350-358.
In patients with recent acute coronary syndrome and depression, a 24-week treatment with escitalopram vs placebo lowered the risk of major adverse cardiac events, ie, a composite of all-cause mortality, myocardial infarction, and percutaneous coronary intervention, after a median of 8.1 years.

Steinhubl SR, Waalen J, Edwards AM, et al. Effect of a home-based wearable continuous ECG monitoring patch on detection of undiagnosed atrial fibrillation: the mSToPS randomized clinical trial. *JAMA*. 2018;320(2):146-155.
The mSToPS trial, a direct-to-participant randomized clinical trial showed that, among individuals at high risk for atrial fibrillation, immediate monitoring with a self-applied wearable electrocardiogram patch led to a higher diagnosis rate of atrial fibrillation after 4 months than did delayed monitoring.

Xaplanteris P, Fournier S, Pijls NHJ, et al; FAME 2 Investigators. Five-year outcomes with PCI guided by fractional flow reserve. *N Engl J Med*. 2018;379(3):250-259.
In patients with angiographically significant stenoses, ie, patients with at least one hemodynamically significant stenosis (fractional flow reserve [FFR], ≤0.80), FFR-guided percutaneous coronary intervention plus medical therapy significantly lowered the rate of the primary composite end point of death, myocardial infarction, or urgent revascularization at 5 years vs medical therapy alone.

AUGUST

Benger JR, Kirby K, Black S, et al. Effect of a strategy of a supraglottic airway device vs tracheal intubation during out-of-hospital cardiac arrest on functional outcome: the AIRWAYS-2 randomized clinical trial. *JAMA*. 2018;320(8):779-791.
The AIRWAYS-2 trial showed that, among patients with nontraumatic out-of-hospital cardiac arrest, an advanced airway management strategy that used a supraglottic airway device did not result in a favorable functional outcome at 30 days when compared with a tracheal intubation.

Malhotra A, Dhutia H, Finocchiaro G, et al. Outcomes of cardiac screening in adolescent soccer players. *N Engl J Med*. 2018;379(6):524-534.
The English Football Association cardiac screening program, which consisted of a health questionnaire, physical examination, electrocardiography, and echocardiography, showed that 0.38% of adolescent soccer players had diseases associated with sudden cardiac death.

Mente A, O'Donnell M, Rangarajan S, et al. Urinary sodium excretion, blood pressure, cardiovascular disease, and mortality: a community-level prospective epidemiological cohort study. *Lancet*. 2018;392(10146):496-506.
Data from the PURE study showed that sodium intake was associated with an increase in cardiovascular disease and stroke, but only in communities with an average sodium intake >5 g/day.

Perkins GD, Ji C, Deakin CD, et al; PARAMEDIC2 Collaborators. A randomized trial of epinephrine in out-of-hospital cardiac arrest. *N Engl J Med*. 2018;379(8):711-721.
While the use of epinephrine in adults with an out-of-hospital cardiac arrest significantly improved the rate of 30-day survival vs placebo, its use resulted in more survivors having severe neurologic impairment.

Rawshani A, Rawshani A, Franzén S, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2018;379(7):633-644.
Patients with diabetes have a higher risk of death and cardiovascular outcomes than the general population; however, patients with type 2 diabetes in whom the five risk-factor variables (glycated hemoglobin levels, low-density lipoprotein cholesterol levels, albuminuria, smoking, and blood pressure) were within the target ranges, appeared to have little or no excess risk of death, myocardial infarction, or stroke when compared with the general population.

Rawshani A, Sattar N, Franzén S, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *Lancet*. 2018;392(10146):477-486.
This register-based cohort study of individuals with type 1 diabetes in Sweden showed that an important determinant of survival and cardiovascular outcomes was the age at the onset of type 1 diabetes, with the highest excess risk occurring in women.

Rothwell PM, Cook NR, Gaziano JM, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. *Lancet*. 2018;392(10145):387-399.
Low doses of aspirin (75-100 mg) effectively prevented vascular events in patients who

weighed <70 kg, but not in 80% of men and 50% of women weighing >70 kg. However, high doses of aspirin effectively prevented vascular events in patients weighing ≥70 kg.

Samieri C, Perier MC, Gaye B, et al. Association of cardiovascular health level in older age with cognitive decline and incident dementia. *JAMA*. 2018;320(7):657-664.

In older adults, the risk of dementia and the rate of cognitive decline were lower for those with an optimal cardiovascular health level (defined by the American Heart Association as nonsmoking, body mass index <25, regular physical activity, eating fish ≥2 times per week and fruits and vegetables at least 3 times a day, cholesterol <200 mg/dL [untreated], fasting glucose <100 mg/dL [untreated], and blood pressure <120/80 mm Hg [untreated]).

Sweeting MJ, Masconi KL, Jones E, et al. Analysis of clinical benefit, harms, and cost-effectiveness of screening women for abdominal aortic aneurysm. *Lancet*. 2018;392(10146):487-495.

While national screening programs reduced deaths from abdominal aortic aneurysm in men and are cost-effective, this analysis shows that an abdominal aortic aneurysm screening program for women, designed to be similar to that used to screen men, is unlikely to be cost-effective.

Wang HE, Schmicker RH, Daya MR, et al. Effect of a strategy of initial laryngeal tube insertion vs endotracheal intubation on 72-hour survival in adults with out-of-hospital cardiac arrest: a randomized clinical trial. *JAMA*. 2018;320(8):769-778.

This multicenter, pragmatic, cluster-crossover clinical trial showed that, among adults with an out-of hospital cardiac arrest, an initial airway management with a laryngeal tube insertion significantly improved the 72-hour survival rate vs an endotracheal intubation.

Webster R, Salam A, de Silva HA, et al; TRIUMPH Study Group. Fixed low-dose triple combination antihypertensive medication vs usual care for blood pressure control in patients with mild to moderate hypertension in Sri Lanka: a randomized clinical trial. *JAMA*. 2018;320(6):566-579.

The TRIUMPH study showed that, among patients with mild-to-moderate hypertension, low-dose triple blood pressure–lowering therapy increased the proportion of patients who achieved their target blood pressure goal vs usual care.

SEPTEMBER

Bohula EA, Wiviott SD, McGuire DK, et al; CAMELLIA–TIMI 61 Steering Committee and Investigators. Cardiovascular safety of lorcaserin in overweight or obese patients. *N Engl J Med*. 2018;379(12):1107-1117.
The CAMELLIA–TIMI 61 trial showed that, in a high-risk population of overweight or obese patients, lorcaserin, a selective serotonin 2C receptor agonist that modulates appetite, facilitated sustained weight loss without causing a higher rate of major cardiovascular events compared with placebo.

Gaziano JM, Brotons C, Coppolecchia R, et al; ARRIVE Executive Committee. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2018;392(10152):1036-1046.
The ARRIVE trial analyzed the effects of aspirin vs placebo on the time to the first occurrence of cardiovascular death, myocardial infarction, unstable angina, stroke, or transient ischemic attack; however, the event rate was much lower than expected, meaning that the role of aspirin in primary prevention among patients at moderate cardiovascular risk could not be addressed.

Gupta A, Mackay J, Whitehouse A, et al. Long-term mortality after blood pressure-lowering and lipid-lowering treatment in patients with hypertension in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Legacy study: 16-year follow-up results of a randomized factorial trial. *Lancet*. 2018;392(10153):1127-1137.
The ASCOT Legacy Study, a 16-year follow-up study of the ASCOT trial, demonstrated long-term beneficial effects on mortality of antihypertensive treatment with a calcium channel blocker–based treatment regimen and lipid lowering with a statin; patients who received an amlodipine-based treatment had fewer stroke deaths and patients on atorvastatin had fewer cardiovascular deaths more than 10 years later.

Jeger RV, Farah A, Ohlow MA, et al; BASKET-SMALL 2 Investigators. Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial. *Lancet*. 2018;392(10150):849-856.
The BASKET-SMALL 2 trial showed that, in patients with de-novo lesions (<3 mm in diameter) in coronary vessels and an indication for percutaneous coronary intervention, drug-coated balloons are noninferior to drug-eluting stents regarding major adverse cardiovascular events.

Koehler F, Koehler K, Deckwart O, et al. Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): a randomised, controlled, parallel-group, unmasked trial. *Lancet*. 2018;392(10152):1047-1057.
The TIM-HF2 trial showed that a structured remote patient management intervention, when used in a well-defined population of patients with heart failure, could reduce the percentage of days lost due to unplanned cardiovascular hospital admissions and all-cause mortality.

Lansky A, Wijns W, Xu B, et al; TARGET All Comers Investigators. Targeted therapy with a localised abluminal groove, low-dose sirolimus-eluting, biodegradable polymer coronary stent (TARGET All Comers): a multicentre, open-label, randomised non-inferiority trial. *Lancet*. 2018;392(10153):1117-1126.

The TARGET All Comers study showed that, in patients with symptomatic or asymptomatic coronary artery disease and objective evidence of myocardial ischemia who qualified for a percutaneous coronary intervention, the FIREHAWK drug-eluting stent was noninferior to the XIENCE everolimus-eluting stent.

Maurer MS, Schwartz JH, Gundapaneni B, et al; ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379(11):1007-1016.
The multicenter, international, double-blind, placebo-controlled, phase 3 ATTR-ACT trial showed that, in patients with transthyretin amyloid cardiomyopathy, tafamidis not only reduced all-cause mortality and cardiovascular-related hospitalizations, but also reduced the decline in functional capacity and quality of life vs placebo.

Mazer CD, Whitlock RP, Fergusson DA, et al; TRICS Investigators and Perioperative Anesthesia Clinical Trials Group. Six-month outcomes after restrictive or liberal transfusion for cardiac surgery. *N Engl J Med*. 2018;379(13):1224-1233.
The TRICS trial showed that, in patients undergoing cardiac surgery who were at a moderate-to-high risk of death, a restrictive strategy of red-cell transfusion was noninferior to a liberal strategy concerning the composite outcome of death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis 6 months after surgery.

Newby DE, Adamson PD, Berry C, et al; SCOT-HEART Investigators. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med*. 2018;379(10):924-933.
In patients with stable chest pain who had been referred to a cardiology clinic for evaluation, a significantly lower rate of death from coronary heart disease or nonfatal myocardial infarction at 5 years was obtained when coronary computed tomographic angiography was added to standard care, without significantly increasing the rate of coronary angiography or coronary revascularization.

Oikonomou EK, Marwan M, Desai MY, et al. Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data. *Lancet*. 2018;392(10151):929-939.
The CRISP-CT study, a post-hoc analysis of outcome data on consecutive patients undergoing coronary computed tomography angiography, showed that the perivascular fat attenuation index enhances cardiac risk prediction and restratification vs the current coronary computed tomography angiography by providing a quantitative measure of coronary inflammation.

Olgin JE, Pletcher MJ, Vittinghoff E, et al; VEST Investigators. Wearable cardioverter-defibrillator after myocardial infarction. *N Engl J Med*. 2018;379(13):1205-1215.
Patients with an acute myocardial infarction and an ejection fraction of 35% or less who received a wearable cardioverter-defibrillator plus guideline-directed therapy did not have a significantly lower rate of the primary end point of arrhythmic death compared with those who received only guideline-directed therapy.

Pilgrim T, Piccolo R, Heg D, et al. Ultrathin-strut, biodegradable-polymer, sirolimus-eluting stents versus thin-strut, durable-polymer, everolimus-eluting stents for percutaneous coronary revascularisation: 5-year outcomes of the BIOSCIENCE randomised trial. *Lancet*. 2018;392(10149):737-746.

The BIOSCIENCE trial, a randomized, single-blind, multicenter, noninferiority trial, showed that the 5-year risk of target lesion failure in all-comer patients undergoing a percutaneous coronary intervention was similar between biodegradable-polymer sirolimus-eluting stents and durable-polymer everolimus-eluting stents.

Shah ASV, Anand A, Strachan FE, et al; High-STEACS Investigators. High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. *Lancet*. 2018;392(10151):919-928.

Despite showing that the use of a high-sensitivity cardiac troponin assay in patients admitted to emergency departments with suspected acute coronary syndrome resulted in 17% being reclassified as patients with myocardial injury or infarction, use of the assay did not alter the subsequent incidence of myocardial infarction or cardiovascular death at 1 year.

Spyropoulos AC, Ageno W, Albers GW, et al; MARINER Investigators. Rivaroxaban for thromboprophylaxis after hospitalization for medical illness. *N Engl J Med*. 2018;379(12):1118-1127.

The MARINER trial showed that medically ill patients who were at an increased risk for venous thromboembolism who received rivaroxaban for 45 days after hospital discharge did not have a significantly lower risk of symptomatic venous thromboembolism and death due to venous thromboembolism compared with placebo.

Valgimigli M, Frigoli E, Leonardi S, et al; MATRIX Investigators. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. *Lancet*. 2018;392(10150):835-848.

The MATRIX program, a program of three nested, randomized, multicenter, open-label, superiority trials in patients with acute coronary syndrome in Italy, the Netherlands, Spain, and Sweden, showed that, in patients with acute coronary syndrome, radial access was associated with lower rates of net adverse clinical events vs femoral access, but not major adverse cardiovascular events at 1 year; however, bivalirudin was not associated with lower rates of major adverse cardiovascular events or net adverse clinical events vs unfractionated heparin.

Vranckx P, Valgimigli M, Jüni P, et al; GLOBAL LEADERS Investigators. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet*. 2018;392(10151):940-949.

The GLOBAL LEADERS trial showed that ticagrelor plus aspirin for 1 month followed by ticagrelor alone for 23 months was not superior to 12 months of standard dual antiplatelet therapy followed by 12 months of aspirin alone in the prevention of all-cause mortality or new Q-wave myocardial infarction 2 years after a percutaneous coronary intervention.

OCTOBER

Gray WA, Keirse K, Soga Y, et al; IMPERIAL investigators. A polymer-coated, paclitaxel-eluting stent (Eluvia) versus a polymer-free, paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised, non-inferiority trial. *Lancet*. 2018;392(10157):1541-1551.

The IMPERIAL study, in a comparison of the safety and efficacy of the polymer-coated, paclitaxel-eluting Eluvia stent with the polymer-free, paclitaxel-coated Zilver PTX stent for treatment of femoropopliteal artery segment lesions, showed that the Eluvia stent was noninferior to the Zilver PTX stent in terms of primary patency and major adverse events at 12 months.

Hernandez AF, Green JB, Janmohamed S, et al; Harmony Outcomes Committees and Investigators. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet*. 2018;392(10157):1519-1529.

In patients ≥40 years old who have type 2 diabetes and cardiovascular disease, a subcutaneous injection of the glucagon-like peptide 1 receptor agonist albiglutide (30 to 50 mg) once a week in addition to their standard care was superior to a matched volume of placebo with respect to major adverse cardiovascular events.

Howard G, Cushman M, Moy CS, et al. Association of clinical and social factors with excess hypertension risk in black compared with white US adults. *JAMA*. 2018;320(13):1338-1348.

This prospective cohort study in patients with incident hypertension showed that key factors mediating the racial difference between black and white adults in the US include a Southern diet score, the dietary ratio of sodium to potassium, and education level. In addition, waist circumference and body mass index also were key factors among women.

McNeil JJ, Wolfe R, Woods RL, et al; ASPREE Investigator Group. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med*. 2018;379(16):1509-1518.

In adults ≥70 years of age or older (or ≥65 years of age among blacks and Hispanics in the United States) and no cardiovascular disease, dementia, or disability, the use of low-dose aspirin as a primary prevention strategy resulted in a significantly higher risk of major hemorrhage, but it did not significantly lower the risk of cardiovascular disease vs placebo.

Stone GW, Ellis SG, Gori T, et al; ABSORB IV Investigators. Blinded outcomes and angina assessment of coronary bioresorbable scaffolds: 30-day and 1-year results from the ABSORB IV randomised trial. *Lancet*. 2018;392(10157):1530-1540.

The ABSORB IV study showed that, in patients with stable coronary artery disease or acute coronary syndromes who were ≥18 years old, polymeric bioresorbable vascular scaffolds had noninferior 30-day and 1-year rates of target lesion failure and angina vs metallic drug-eluting stents.

von Birgelen C, Zocca P, Buiten RA, et al. Thin composite wire strut, durable polymer-coated (Resolute Onyx) versus ultrathin cobalt-chromium strut, bioresorbable polymer-coated (Orsiro) drug-eluting stents in

allcomers with coronary artery disease (BIONYX): an international, single-blind, randomized non-inferiority trial. *Lancet*. 2018;392(10154):1235-1245.
In this noninferiority trial in an all-comer population in Belgium, Israel, and the Netherlands, the Resolute Onyx stent was shown to be noninferior to the Orsiro stent concerning the combined safety and efficacy end point at the 1-year follow-up assessment.

Willeit P, Ridker PM, Nestel PJ, et al. Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events: individual patient-data meta-analysis of statin outcome trials. *Lancet*. 2018;392(10155):1311-1320.
This individual patient-data meta-analysis of seven randomized, placebo-controlled, statin outcome trials showed that elevated levels of lipoprotein(a) both at baseline and while taking statins had an independent and approximately linear relation with the risk of cardiovascular disease.

Zannad F, Anker SD, Byra WM, et al; COMMANDER HF Investigators. Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. *N Engl J Med*. 2018;379(14):1332-1342.
The double-blind, randomized COMMANDER HF trial showed that, in patients with chronic heart failure, a left ventricular ejection fraction ≤40%, coronary artery disease, and elevated plasma concentrations of natriuretic peptides, but not atrial fibrillation, rivaroxaban 2.5 mg twice daily in addition to standard care after treatment for an episode of worsening heart failure did not significantly lower the rate of death, myocardial infarction, or stroke vs placebo.

NOVEMBER

Borlaug BA, Anstrom KJ, Lewis GD, et al; NHLBI Heart Failure Clinical Research Network. Effect of inorganic nitrite vs placebo on exercise capacity among patients with heart failure with preserved ejection fraction: the INDIE-HFpEF randomized clinical trial. *JAMA*. 2018;320(17): 1764-1773.
The INDIE-HFpEF trial showed that, in patients with heart failure with preserved ejection fraction, a 4-week treatment of inhaled inorganic nitrite did not significantly improve exercise capacity vs placebo.

Dehghan M, Mente A, Rangarajan S, et al; PURE Study Investigators. Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study. *Lancet*. 2018;392(10161):2288-2297.
Contrary to the current dietary guidelines that recommend minimizing the consumption of whole-fat dairy products, the PURE study showed that there was an association between the consumption of dairy productions and a lower risk of mortality and major cardiovascular disease events.

Schwartz GG, Steg PG, Szarek M, et al; ODYSSEY OUTCOMES Committees and investigators. alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379(22):2097-2107.
In patients who have had an acute coronary syndrome and are receiving high-intensity statin therapy, alirocumab, a human monoclonal antibody to proprotein convertase subtilisin-kexin type 9, lowered the risk of recurrent ischemic cardiovascular events vs placebo.

Son JS, Choi S, Kim K, et al. Association of blood pressure classification in Korean young adults according to the 2017 American College of Cardiology/ American Heart Association guidelines with subsequent cardiovascular disease events. *JAMA*. 2018;320(17):1783-1792.

In young Korean adults, the presence of stage 1 and stage 2 hypertension, compared with normal blood pressure, was associated with an increased risk of subsequent cardiovascular disease events.

Thiele H, Akin I, Sandri M, et al; CULPRIT-SHOCK Investigators. One-year outcomes after PCI strategies in cardiogenic shock. *N Engl J Med*. 2018;379(18):1699-1710.

While the risk of 30-day death or renal replacement therapy was lower in patients with acute myocardial infarction and cardiogenic shock who were assigned culprit-lesion-only percutaneous coronary intervention vs immediate multivessel percutaneous coronary intervention, there were no between-group differences in mortality at the 1-year follow-up.

van Sloten TT, Tafflet M, Périer MC, et al. Association of change in cardiovascular risk factors with incident cardiovascular events. *JAMA*. 2018;320(17):1793-1804.

Among a group of participants without cardiovascular disease who received follow-up care over a median of 18.9 years, no consistent relationship was identified between the risk of cardiovascular disease and the direction of change in the composite metric of cardiovascular health as measured using the 7 metrics of the American Heart Association.

Yano Y, Reis JP, Colangelo LA, Set al. Association of blood pressure classification in young adults using the 2017 American College of Cardiology/American Heart Association Blood pressure guideline with cardiovascular events later in life. *JAMA*. 2018;320(17):1774-1782.

An analysis of the CARDIA study showed that young adults (<40 years old) with elevated blood pressure, stage 1 hypertension, and stage 2 hypertension had a significantly higher risk of subsequent cardiovascular disease events than did the young adults (<40 years old) with normal blood pressure.

DECEMBER

Choi SH, Weng LC, Roselli C, et al; DiscovEHR study and the NHLBI TOPMed Consortium. Association between titin loss-of-function variants and early-onset atrial fibrillation. *JAMA*. 2018;320(22):2354-2364.
Among patients with early-onset atrial fibrillation (ie, onset of atrial fibrillation in patients <66 years old), there was a statistically significant association between loss-of-function variants of the titin gene and early-onset atrial fibrillation.

Inohara T, Manandhar P, Kosinski AS, et al. Association of renin-angiotensin inhibitor treatment with mortality and heart failure readmission in patients with transcatheter aortic valve replacement. *JAMA*. 2018;320(21):2231-2241.
Patients who were prescribed a renin-angiotensin system inhibitor at hospital discharge after a transcatheter aortic valve replacement had a significantly lower risk of mortality and heart failure readmission.

Obadia JF, Messika-Zeitoun D, Leurent G, et al; MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med*. 2018;379(24):2297-2306.
In patients who have chronic heart failure with reduced left ventricular ejection fraction and severe secondary mitral valve regurgitation, there was no difference between percutaneous mitral valve repair and medical therapy alone concerning the rate of death or unplanned hospitalization for heart failure at 1 year.

Stone GW, Lindenfeld J, Abraham WT, et al; COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379(24):2307-2318.
Among patients with heart failure who have moderate-to-severe or severe secondary mitral regurgitation due to left ventricular dysfunction, transcatheter mitral valve repair lowered the rate of hospitalization for heart failure and lowered all-cause mortality within 24 months of follow-up vs medical therapy alone.

Wadhera RK, Joynt Maddox KE, Wasfy JH, Haneuse S, Shen C, Yeh RW. Association of the hospital readmissions reduction program with mortality among Medicare beneficiaries hospitalized for heart failure, acute myocardial infarction, and pneumonia. *JAMA*. 2018;320(24):2542-2552.
Among Medicare beneficiaries, the Hospital Readmissions Reduction Program was significantly associated with an increase in 30-day postdischarge mortality after hospitalization for heart failure and pneumonia, but not for acute myocardial infarction. ■

Prevention, Diagnosis, & Treatment

MANAGING ATRIAL FIBRILLATION: FROM SCREENING TO TREATMENT SELECTION

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The year 2018 was a year where many events related to atrial fibrillation occurred. Results from major trials in the field of atrial fibrillation were published this year in different areas of research: screening for atrial fibrillation (DIGITAL-AF), rhythm control therapy (RACE 3), and pulmonary vein isolation for atrial fibrillation (CASTLE-AF and CABANA). The results of these trials were presented at this year's ESC congress, Heart Rhythm Society Scientific Sessions, or published after being presented last year at a major congress.

SCREENING FOR ATRIAL FIBRILLATION

An important aspect of atrial fibrillation is screening. In the guidelines, opportunistic screening has a class I recommendation, but what is the best screening method? This year, the results of DIGITAL-AF were presented at the ESC congress in Munich.[1] DIGITAL-AF examined the feasibility and effectiveness of screening with a smartphone-based app. In a local newspaper, the app was advertised with a free token for downloading. In total, 12 328 individuals had already downloaded the app in the first 48 hours. By means of photoplethysmography (putting the left index finger in front of the smartphone camera), an analysis of the cardiac arrhythmia was made. In total, 9889 (80%) participants had a regular rhythm, 136 (1.1%) had atrial fibrillation, 2111 (17%) had other irregular rhythms, and 191 (2%) had measurements of insufficient quality to be analyzed. Not all patients were known to have atrial fibrillation; in total, around 40 patients were newly diagnosed. Since smartphone use is widespread today (also among the elderly) and smartphone watches are becoming more advanced with ECG monitoring capacities, health care providers will likely see more digital referrals in the near future.

NEWS ON ANTICOAGULATION

Also at this year's ESC congress, data from the GARFIELD-AF registry was presented. GARFIELD-AF is a registry used to prospectively track daily anticoagulation practice globally and to study the uptake of non–vitamin K antagonist therapy in atrial fibrillation. It was shown than non–vitamin K antagonists are superior

to vitamin K antagonists in reducing 2-year mortality in higher risk patients (CHA_2DS_2-VASc score ≥2)[2,3]; there was a 19% relative risk reduction. However, the most interesting fact was that patients who concomitantly started anticoagulation and antiplatelet therapy (as compared with anticoagulation alone) at the time of diagnosis had a nonsignificantly higher risk of bleeding (HR, 1.45; 95% CI, 0.94-2.23; *P*=ns), but importantly, an increase in mortality (HR, 1.31; 95% CI, 1.05-1.62) with an increased risk for stroke (HR, 1.60; 95% CI, 1.08-2.35). Moreover, there appeared to be an ever-worse prognosis for those not having an indication for the use of antiplatelets (no peripheral artery disease); in these patients, the HR was 1.48 vs 1.31 (for having an indication) for mortality, stroke, and major bleeding.[2,3] So, it is very important to evaluate anticoagulation and antiplatelet therapy at the time of atrial fibrillation diagnosis and to make the right choices in terms of therapy.

Other news on anticoagulation is that, in 2018, andexanet alfa (a recombinant modified FXa protein with no enzymatic activity), which was designed to bind and sequester factor Xa and thus reverse anticoagulation for apixaban and rivaroxaban, was approved by the U.S. Food and Drug administration in patients who need it in case of life-threatening or uncontrolled bleeding.[4]

NEWS ON RHYTHM CONTROL STRATEGIES

Presented last year at the annual meeting of the ESC and published this year in the *European Heart Journal* was the RACE 3 trial.[5] RACE 3, tested whether the addition of upstream or targeted therapy (mineralocorticoid receptor antagonist, statins, and ACE inhibitors or ARBs, cardiac rehabilitation with focus on exercising, dietary restrictions, and counseling) could improve sinus rhythm maintenance in 240 patients treated with rhythm control for persistent atrial fibrillation. At follow-up, the patients who were randomized to the upstream therapy group had lower blood lipid levels, lower brain natriuretic peptide levels, and lower blood pressure than did the control group. After 1-year of follow-up, more patients were in sinus rhythm (during a 7-day Holter follow-up) in the upstream or targeted therapy group compared with only guideline-recommended rhythm control. In addition, quality of life was improved in the upstream therapy arm, even in patients who were in atrial fibrillation at 1 year. RACE 3 taught us that a careful consideration of associated cardiovascular conditions and lifestyle modifications improves sinus rhythm maintenance. Where RACE 3 patients were predominantly treated with medical rhythm control (7 patients underwent pulmonary vein isolation), CASTLE-AF and CABANA were completely focused on ablation.

PULMONARY VEIN ISOLATION: THE IDEAL RHYTHM CONTROL STRATEGY?

Two major trials have seen daylight in 2018: CASTLE-AF and CABANA.[6,7] CASTLE-AF randomized patients with symptomatic paroxysmal or persistent atrial fibrilla-

tion who had failed antiarrhythmic drug therapy (or had side effects) and were in New York Heart Association class II-IV with a left ventricular ejection fraction equal or below 35% (and importantly had an implanted cardioverter defibrillator) to either undergo catheter ablation (n=179) or pharmacological therapy (which could be either rate or rhythm control, n=184).[6] The primary end point was a composite of death from any cause or heart failure hospital admission. The catheter ablation group had a relative risk reduction in the primary outcome of 38%; mortality rates were 28.5% vs 44.6% after a median 38-month follow-up. Furthermore, catheter ablation also reduced cardiovascular death by 51% and the cardiovascular mortality rate by 11.2% vs 22.3%. Furthermore, the burden of atrial fibrillation (as measured by the device) at all follow-up visits was significantly lower in the catheter ablation group than in the medical group. Overall, the conclusion of this (nonblinded) trial was that atrial fibrillation in the presence of heart failure confers a worse prognosis and the reduction in atrial fibrillation by catheter ablation improves overall survival. There are some important concerns about the generalizability of the findings of this trial: only patients with heart failure who could tolerate all heart failure medications were included, the number of patients with ischemic etiology was low compared with other heart failure trials, and the total inclusion period was over 8 years with only 363 patients included.

Another ablation trial, CABANA, was presented at this year's Heart Rhythm Society Scientific Sessions.[7] In CABANA, 2204 patients were included at 126 sites worldwide (during a 7-year period); all patients were considered candidates for catheter ablation. Patients were randomized to either drug therapy, which could be rate or rhythm control (with use of antiarrhythmic drugs), or to catheter ablation and then at least all pulmonary veins were isolated (some got additional lines ablated). The primary outcome was a composite of clinical events, including death, stroke, serious bleeding, or cardiac arrest. There were also some secondary end points: including quality of life. The primary outcome was seen in 89 patients (8%) randomized to the ablation arm and 101 patients (9.2%) randomized to drug therapy. Catheter ablation did not produce a significant reduction in the primary end point and in all-cause mortality (HR, 0.86; 95% CI, 0.65-1.15; *P*=0.3). None of the components of the primary end point differed significantly. In addition, this trial has some major limitations: 102 patients (9.2%) did not undergo catheter ablation. In the drug therapy group, 301 patients (27.5%) crossed over and did undergo an ablation. Interestingly (and controversially), in a per-protocol analysis, ablation did reduce the rate of the primary end point by 27% (HR, 0.73; 95% CI, 0.54-0.99; *P*=0.046), but this remains very speculative as the trial was not powered to do this analysis. Therefore, we should wait for more data; for example, the results of the EAST trial are expected in the upcoming years. In the meantime, a major change in our current atrial fibrillation ablation practice is not expected.

CONCLUSIONS

In different areas of atrial fibrillation management, important results were published in 2018. Screening for atrial fibrillation is becoming more advanced with smartphone-based apps and watches. Starting anticoagulation is essential in atrial fibrillation and should be carefully performed. Targeted therapies of underlying conditions and lifestyle modifications are important for maintaining long-term rhythm control. Catheter ablation can be safely performed in selected patients with heart failure and atrial fibrillation. Whereas the superiority of catheter ablation was difficult to assess due to high crossover rates and as a reduction in mortality (by rhythm control) has not been proven, atrial fibrillation treatment should remain focused on symptoms and patient preferences. ■

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NEWS ON CARDIAC REHABILITATION IN 2018

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EUROASPIRE V: CARDIAC REHABILITATION AND SECONDARY PREVENTION PERFORMANCE INDICATORS ARE STILL LESS THAN OPTIMAL IN EUROPE

EUROASPIRE is a survey of secondary preventive care in patients 1 year after hospitalization for an acute coronary event or hospitalization for revascularization. The latest results of this survey, EUROASPIRE V, represent an audit of the implementation of the 2016 Joint European Society of Cardiology/European Atherosclerosis Society lipid guidelines.[1] Briefly, EUROASPIRE included findings from 8261 secondary prevention patients (mean age, 64 years; 26% female) who were enrolled by 131 centers across 27 countries.[2] The first findings were also compared with the previous studies. Results showed that performance indicators of secondary prevention are still less than optimal, similarly to previous EUROASPIRE surveys, and that the ESC guidelines regarding lifestyle changes could be implemented more effectively, particularly when it comes to promoting smoking cessation, physical activity participation, nutrition management, hypertension control, and lipid control.

In particular, only 46% of the European population are advised to follow a cardiac prevention or rehabilitation program, and the cardiac rehabilitation attendance (at least half of the session), if advised, is only 68%. Finally, attendance in cardiac rehabilitation programs among all patients is only 31%. In addition, other secondary prevention measures are poorly implemented (eg, lipid management across Europe). While the majority of patients (84%) were receiving lipid-lowering therapy (the majority statins), only about one-third of these patients (32%) attained the recommended LDL cholesterol goal of <1.8 mmol/L (<70 mg/dL); similarly, poor lipid goal attainment was reported for non–HDL cholesterol (32%). This poor goal attainment is likely to be due to poor uptake of high-intensity statin therapy; less than half (43%) of the patients were maintained on high-intensity statin therapy after discharge from the hospital.

The findings from EUROASPIRE V highlight the need for renewed efforts for implementing the guidelines to improve management in very high-risk patients in the secondary prevention setting in Europe.

NEW AMERICAN PERFORMANCE AND QUALITY MEASURES FOR CARDIAC REHABILITATION

The American College of Cardiology (ACC) and American Heart Association (AHA) have released a new set of performance and quality measures for cardiac rehabilitation published online on March 29th in the *Journal of the American College of Cardiology*.[3] Similarly to our continent, also in the other part of the Atlantic, the 2017 AHA Heart Disease and Stroke Statistics report highlights the large number of patients who require cardiac rehabilitation each year, and are missing this valuable opportunity, including 625 000 patients discharged from US hospitals after acute coronary syndrome, 954 000 patients who underwent percutaneous coronary interventions, 500 000 patients discharged with a new diagnosis of heart failure, and 397 000 who underwent coronary artery bypass graft surgery. Yet, despite strong evidence demonstrating the benefits of cardiac rehabilitation, it remains "underutilized." However, good data concerning cardiac rehabilitation participation rates and completion rates are still lacking.

The ACC/AHA Task Force on Performance Measures first issued cardiac rehabilitation performance measures in 2007 and published a focused update in 2010. The latest version includes six performance measures (two revised, four new) and adds three quality measures. The revised cardiac rehabilitation performance measures address referral from the inpatient (performance measure 1) and outpatient (performance measure 3) settings. Performance measure 1 on cardiac rehabilitation referral from an inpatient setting states that all patients hospitalized with a cardiac rehabilitation–eligible diagnosis or procedure should be referred to an outpatient cardiac rehabilitation program prior to discharge. Performance measure 3 on cardiac rehabilitation referral from an outpatient setting states that all outpatients who are eligible for cardiac rehabilitation and have not yet participated in cardiac rehabilitation should be referred to an outpatient cardiac rehabilitation program. For both, the task force notes that, if the patient declines cardiac rehabilitation referral, referral order and patient materials should not be sent to the receiving cardiac rehabilitation program against the patient's wishes. Cardiac rehabilitation referral would still be met as long as other aspects of cardiac rehabilitation referral have been met (cardiac rehabilitation referral recommended and documented).

Noteworthy specific new recommendations have been developed to implement cardiac rehabilitation for patients with heart failure. In fact, new performance measures advise that patients with heart failure with reduced ejection fraction should be referred for cardiac rehabilitation and include measures to assess enrollment in cardiac rehabilitation. Referral to exercise training is advised for patients with heart failure from the inpatient setting (performance measure 2) and the outpatient setting (performance measure 4).

The first step in cardiac rehabilitation participation is cardiac rehabilitation enrollment; therefore, the performance measures address claims-based enrollment (performance measure 5a) and registry/electronic health record–based enrollment (performance measure 5b). The option to use claims-based data is included to allow flexibility in the assessment for health care organizations that may wish to use claims-based data, with or without the use of registry/electronic health record data. The same goes for organizations that may wish to use registry/electronic health record data as opposed to claims-based data.

The three cardiac rehabilitation quality measures deal with enrollment, adherence, and communication. The rational is based on the evidence that patient outcomes and adherence are better the sooner the patients enter cardiac rehabilitation. Furthermore, the number of sessions patients attend correlate with better outcomes: a graded dose response in which attending 36 or more cardiac rehabilitation sessions is associated with lower risks for death and myocardial infarction at 4 years compared with attending fewer sessions. Quality measure 3 deals with cardiac rehabilitation communication between the cardiac rehabilitation program and the health care provider to ensure good coordination of care.

EUROPREVENT 2018: CARDIOVASCULAR REHABILITATION AT ITS HIGHEST LEVELS

The 2018 EuroPrevent congress, the official scientific meeting of the European Association of Preventive Cardiology, took place in Ljubljana (April 19-21, 2018) where several very interesting aspects of preventive cardiology and cardiac rehabilitation were highlighted, all supported by an evidence-based approach.

In cardiac rehabilitation, in particular, a regular sauna was shown to have positive effects on vascular physiology, morbidity, and mortality in patients with cardiac disease.[4] However, alternating between heat exposure and cold water immersion should be avoided because it may trigger acute coronary syndromes and arrhythmias. Yoga was shown to improve left ventricular ejection fraction and inflammatory markers in cardiovascular diseases and heart failure, which, in addition to pharmacological therapy, has also shown beneficial effects in cardiac arrhythmia treatment.[5]

The latest information regarding the most important trials on e-Health in cardiac rehabilitation was presented, including the EU-Care Project, implemented with EU Horizon 2020 funds. The project, dedicated to elderly cardiac patients undergoing rehabilitation, aims to compare conventional cardiac rehabilitation programs to innovative mobile telemonitoring protocols.[6] The SmartCare-CAD trial, has the objective of investigating the efficacy of cardiac telerehabilitation vs center-based cardiac rehabilitation.[7] The EduHeart I trial aims to study the efficacy of combined conventional cardiac care with e-learning in cardiac rehabilitation.[8] The REMOTE

cardiac rehabilitation trial, aimed at assessing the effects and noninferiority of mobile health technologies for the remote delivery of rehabilitation exercise programs, was also discussed.[9]

CARDIAC REHABILITATION AND OUTCOMES

Controversial data are available on the effect of outpatient cardiac rehabilitation on prognosis. The impact of ambulatory cardiac rehabilitation on cardiovascular outcomes was analyzed in a 5-year, follow-up study in the center-north of Italy involving 839 patients who attended the cardiac rehabilitation program planned at discharged vs 441 patients who were discharged without any program of cardiac rehabilitation. While no difference in mortality was observed, the composite outcome of hospitalizations for cardiovascular causes and cardiovascular mortality were lower in the cardiac rehabilitation group compared with the no cardiac rehabilitation group (18% vs 30%, $P<0.001$), which was driven by lower hospitalizations for cardiovascular causes (15 vs 27%, $P<0.001$). In a multivariable Cox proportional hazard analysis, a cardiac rehabilitation program was an independent predictor of a lower occurrence of the composite outcome (hazard ratio, 0.55; $P<0.001$), while, in the propensity-matched analysis, the cardiac rehabilitation group experienced lower total mortality (10% vs 19%; $P=0.002$) and cardiovascular mortality rates (9% vs 35%; $P=0.008$) compared with the no cardiac rehabilitation group.[10]

The PATIENT CARE registry in Germany demonstrated an improvement in LDL-C target achievement rates through cardiac rehabilitation for patients after ST-segment elevation or non–ST-segment elevation myocardial infarction.[11] A total of 1408 patients were analyzed who started cardiac rehabilitation on average 19±10 days after the index event and lasted for 22±4 days. At discharge, 96.7% of patients received statins and 13.0% received another lipid-lowering medication in addition to a statin. The rate of patients with LDL-C on target according to the European Society of Cardiology/European Atherosclerosis Society dyslipidemia guidelines (<70 mg/dL [1.8 mmol/L] or at least a 50% reduction in the baseline value) was increased from 21.4% at cardiac rehabilitation admission to 41.9% at discharge after cardiac rehabilitation. Most patients (95.2%) completed the cardiac rehabilitation and 88% returned to their former work full time.

A previous meta-analysis noted that, among the different components of cardiac rehabilitation, a key role was played by exercise training. This dogma has been challenged by the Toronto Health Economics and Technology Assessment (THETA) Collaborative research team, who undertook a systematic review and network meta-analysis of randomized controlled trials evaluating the role of the different core components of cardiac rehabilitation on clinical outcomes: nutritional counseling, risk factor modification, psychosocial management, patient education, and exercise training. Ultimately, 148 randomized controlled trials (50 965

participants) were included. The authors found that each component, individual or in combination, was associated with mortality and/or morbidity, and concluded that recommendations for comprehensive cardiac rehabilitation are warranted.[12]

VENTRICULAR ASSIST DEVICE

Exercise-based cardiac rehabilitation has also been proposed for heart failure patients with a ventricular assist device to help in the recovery of the patient's functional capacity. However, the existing evidence in support of exercise therapy in these patients remains limited. After a review of the current knowledge on the causes of the persistence in the limitation in exercise capacity in ventricular assist device recipients and concerning the benefit of exercise therapy in patients with a ventricular assist device, the Heart Failure Association of the European Society of Cardiology has developed a document to provide practical advice on implementing exercise training. This approach includes appropriate screening to avoid complications and then starting with early mobilization, then the prescription is individualized to meet the needs of each patient. Finally, gaps in the knowledge are discussed.[13]

NEW ITALIAN POSITION PAPER ON "MINIMAL CARE" INTERVENTIONS OF THE NURSE, PHYSIOTHERAPIST, DIETICIAN, AND PSYCHOLOGIST IN CARDIOVASCULAR REHABILITATION

In cardiac rehabilitation, different professionals in coordination, each with their own specific competence, carry out care activities. A new Italian position paper analyzed the role and the specific interventions performed by the nurse, physiotherapist, dietician, and psychologist in order to identify what constitutes minimal care, ie, the main activities of each team member in the cardiac rehabilitation implementation, in clinical factors. The following factors were considered: the level of clinical care complexity (determined both by the disease and by comorbidity factors), the "area" complexity (ie, the specific level of competence required by each professional), the setting (ie, whether the care is performed in an inpatient or outpatient setting), and the duration of the rehabilitation intervention.[14] ■

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GROUNDBREAKING ADVANCES IN CARDIOVASCULAR RESEARCH

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Highlighting the numerous scientific breakthroughs we witnessed last year in the cardiovascular field is a daunting task. Between several important discoveries, we selected groundbreaking advancements in three areas of cardiovascular research that hold great promise for the years to come: (i) therapeutic approaches targeting metabolic remodeling in heart failure; (ii) a novel methodology to interrogate gene expression patterns of single cell types; and (iii) the emerging connection between heart failure and cancer.

NEW THERAPEUTIC TARGETS: METABOLIC REMODELING IN CARDIOVASCULAR DISEASE

One of the most arduous challenges of basic research in cardiology is the quest for novel therapeutic approaches to treat heart failure. In fact, in spite of our quite sophisticated understanding of the molecular mechanisms underlying cardiac dysfunction, heart failure therapy has been based for a long time on blockade of neurohormonal activation, ventricular unloading, and heart rate control, the introduction of neprilysin inhibitors was the only innovation in the last 25 years. In contrast, agents directly targeting cardiac myocyte function are not currently available for the treatment of chronic heart failure in the clinical arena.

Targeting deranged cardiac metabolism is emerging as one of the most promising approaches in preclinical models of heart failure, and studies published last year have provided new exciting insights into this field. In particular, numerous cutting-edge studies have further elucidated the relationship between intermediary metabolism and cellular regulatory pathways in the heart and vasculature. An outstanding example is the study by Lehmann et al published in *Nature Medicine*,[1] which demonstrated that the hexosamine biosynthetic pathway has downstream effects on excitation-contraction coupling in cardiac myocytes by inducing posttranslational modifications of proteins involved in calcium handling. As hexosamine biosynthetic pathway activation is observed in response to numerous cardiac stressors, this maladaptive pathway is a potential target for novel therapeutic approaches aimed at ameliorating contractility in the failing heart.

Another example of the detrimental impact of metabolic remodeling on cardiac function was provided by the elegant mechanistic study by Tsushima et al[2] based on a mouse model of lipotoxicity, ie, the accumulation of toxic lipid intermediates in cardiac myocytes. In this setting, an increase in myocardial fatty acid uptake enhanced mitochondrial fission by inducing posttranslational modifications of proteins involved in mitochondrial dynamics. Mitochondrial fission is the process of organelle division that leads to removal of damaged mitochondria and enables metabolic adaptations in response to an elevation in energy demand, as elucidated by another landmark study published last year in *Circulation Research*.[3] However, pathological mitochondrial fission results in fragmentation of the mitochondrial network, thereby leading to cardiomyopathy. The study by Tsushima et al[2] revealed that a key mediator in this maladaptive process is oxidative stress, suggesting that lipotoxicity-induced cardiac dysfunction might be rescued by mitochondria-targeted antioxidant agents. Since lipotoxicity is a hallmark of diabetic cardiomyopathy,[4] and intramyocardial accumulation of toxic lipid intermediates was reported in heart failure patients with and without diabetes,[5] these studies hold great translational value.

Although promising, these mechanistic insights are still far from being tested in clinical trials. In contrast, experimental evidence demonstrating the benefit associated with supplementation with nicotinamide adenine dinucleotide (NAD) precursors might already be sufficient to warrant testing this approach in heart failure patients.[6] A study published in *Circulation*[7] strongly corroborated this model by proving the benefit of NAD augmentation on contractile function in two mouse models of heart failure, namely a genetic mouse model of dilative cardiomyopathy and the widely used model of acute pressure overload by transverse aortic constriction. Intriguingly, supplementation with NAD precursors was also shown to decrease susceptibility to acute kidney injury in mice and humans.[8] However, the mechanisms underlying the beneficial effects of NAD supplementation are far from being fully elucidated. NAD plays a key role in energy metabolism by donating the electrons harvested by Krebs cycle dehydrogenases to the electron transport chain complexes. In addition, NAD is an essential cosubstrate of sirtuins, a family of enzymes catalyzing posttranslational modifications of proteins involved in a variety of cellular functions. Future studies should be aimed at resolving which NAD function(s) is the dominant driver of its cardioprotective activity, a pursuit which will be facilitated by the recent identification of the protein mediating import of NAD precursors inside the cell.[9] In the meantime, this therapeutic approach appears ripe for translation to the clinical arena.

NEW TECHNOLOGIES: SINGLE-CELL RNA SEQUENCING

The development of genome-wide transcriptome profiling has led to great advancements in our knowledge of gene expression landscapes. However, until

recent years, this approach was limited to the analysis of extracts from whole tissue lysates, consequently losing any information regarding individual cellular populations. This limitation was recently overcome due to the development of new methodologies enabling the amplification of small amounts of RNA. The novel technique, coined single-cell RNA sequencing, has enabled researchers to generate unbiased maps of cellular heterogeneity, and represents a potent tool for the identification of molecular mechanisms of disease.

The study by Gladka et al published last year was the first to experiment with this new approach in the adult heart.[10] In this study, single-cell sequencing led to the identification of a new mediator involved in the activation of cardiac fibroblasts in response to injury. By applying the single-cell RNA sequencing approach to the vasculature, Cochain et al investigated the leukocyte infiltrate in murine atherosclerotic aortas.[11] This study identified three distinct macrophage populations, two of which are specifically associated with atherosclerotic plaques, and recognized the existence of a previously unappreciated macrophage subtype. In a back-to-back study, Winkels et al combined single-cell RNA sequencing with mass cytometry, outlining an atlas of the immune cell repertoire in atherosclerotic plaques.[12]

Overall, these studies support the concept that the use of a single marker to discriminate cellular subtypes is a reductive approach, whereas assessing gene expression patterns provides a more accurate picture of cellular heterogeneity and has the potential to unravel new cell-specific pathways associated with cardiovascular disease.

NEW MECHANISTIC INSIGHTS: THE DANGEROUS LIAISON BETWEEN HEART FAILURE AND CANCER

For the last decades, the focus of cardio-oncology has been the prevention of cardiovascular disease in oncology patients and cancer survivors who carry a higher risk of cardiovascular events compared with the general population.[13] In the last years, a previously overlooked connection between heart failure and cancer was unraveled by epidemiological studies reporting a higher risk of incident cancer in heart failure patients compared with individuals without heart failure.[14-16] While many confounding factors can underlie this association, such as the increased medical attention received by patients newly diagnosed with heart failure, a preclinical study by Meijers et al[17] shed light on a novel and intriguing scenario, ie, that heart failure might represent a pro-oncogenic condition. In this study, sham-operated or infarcted mouse hearts were transplanted into the necks of mice carrying a mutated adenomatous polyposis coli gene, making these mice prone to developing intestinal tumors. Compared with mice being transplanted with sham-operated hearts, animals receiving infarcted failing hearts developed

a substantially higher tumor burden due to the release of mitogenic factors from the failing myocardium. As mice receiving heart transplantations in the cervical region retained their own healthy heart, the investigators could demonstrate that the pro-oncogenic activity of the failing myocardium is independent of hemodynamic factors. This study opens up an entirely novel field of research where the challenge will be to elucidate this and possibly additional mechanisms linking heart failure to cancer. For instance, it has been proposed that neurohormonal activation, which is a hallmark of heart failure with reduced ejection fraction, might influence tumor biology via β-adrenergic receptors expressed by cancer cells and the tumor microenvironment, consequently promoting progression and dissemination of neoplasms.[18]

CONCLUSIONS

The field of cardiovascular basic science is evolving at a steady pace, and those discussed here are only three of the exciting advancements made in 2018. We look forward to the upcoming years, which will hopefully witness the translation of these groundbreaking preclinical studies to the clinical arena. ■

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CHANGING THE FACE OF HEART FAILURE TREATMENT: RESULTS FROM THREE PIVOTAL STUDIES

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Several studies importantly affecting the treatment of patients with heart failure were reported at the 2018 American Heart Association Scientific Sessions. In this article, we will review three of them.

TRED-HF

Among the most important and unique studies was TRED-HF (Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy). This small (51 patients) pilot study featured an open-label, randomized, phased withdrawal (ie, standard drug therapy was withdrawn according to a prespecified drug-by-drug schedule, not all at once) of guideline-directed medical therapy in patients who were devoid of heart failure symptoms, were receiving standard multidrug, guideline-based therapy (including loop diuretic, β-blocker, ACE inhibitor, ARB, or MRA, or a combination of these drugs), and who had manifested LVEF ≤40%, abnormal left ventricular end diastolic volume, and an NT-proBNP concentration ≥250 ng/L (ie, who had had HFREF) an average of 4.9 years from the time that the diagnosis was made and therapy begun and who then improved on therapy to a non–heart failure, noncardiomyopathic state with LVEF that had increased at least 10% to >50%, with normal left ventricular end diastolic volume and NT-proBNP concentration <250 ng/L (average=72 ng/L). At the end of 6 months after randomized withdrawal, a comparison was made of the number of patients in each group that remained "recovered." At that point, therapy was reestablished among those from whom it had been withdrawn and was withdrawn among 25 of the 26 in whom it had been continued and follow-up continued in this cohort.

The results were relatively dramatic. During the initial 6-month follow-up interval, 11 of the 25 patients who were randomized to drug withdrawal (44%) relapsed to their pretherapy state. Medication withdrawal resulted in a mean 9.5% decrease in LVEF versus baseline, a 15 bpm increase in heart rate, a 7 mm Hg rise in diastolic

blood pressure, and a 5.1 point decrease in the Kansas City Cardiomyopathy Questionnaire score, the latter a substantial and clinically meaningful deterioration. Of the 26 patients who continued their prerandomization therapy, none relapsed (between-group difference $P<0.0001$). No patient in either group died, but 3 serious adverse events, none cardiovascular, occurred in the withdrawal group. However, among the 25 patients who underwent withdrawal after completing therapy during the initial 6-month on therapy follow-up, 9 relapsed (a Kaplan-Meier event rate of 36%).

None of the data enabled prediction of those patients who would relapse. Although the study was small, the results were so very consistent that reasonably firm conclusions can be drawn. Specifically, among patients with HFREF, withdrawal of therapy should not usually be attempted, at least until we can predict who will relapse. As the study's presenter, John Halliday, PhD, of Imperial College, London, stated, "Improvement in function represents remission rather than permanent recovery for many patients."

For clinicians, patients, and drug regulatory professionals, the study is highly illuminating. For several distinct cardiovascular indications, multiple drugs now are FDA- and EMA-approved. Once one or several drugs are thus approved, a new drug of another group (so-called "class") for the same indication usually must be tested on a background that includes the already approved drug(s). This is true primarily for ethical reasons, so that all study subjects can be expected to realize the benefits for which the earlier drugs were approved and administered. Therefore, application of the new drug after approval requires simultaneous treatment with the drugs that were used as background drugs during the pivotal clinical trials. To justify stopping one or several of the background drugs, new appropriately designed clinical trials would be needed. Such trials are complex and expensive and generally have not been performed for most indications. Therefore, as new therapies are introduced, the "cocktail" administered for some common conditions, like HFREF, becomes progressively larger, more expensive, and potentially associated with increasing adverse events, implications for pregnancy, or deleterious interactions with drugs given for other indications. TRED-HF is the first trial to assess the risk of discontinuing background drugs for HFREF once clinical and objective indications of reversal of the underlying pathophysiology have been identified.

The results of this pilot study strongly suggest that, at least for HFREF, the current multidrug standard therapy should continue indefinitely. This study can be expected to serve as a template for the study of background removal for other conditions.

PIONEER-HF

Another important and potentially practice-changing study was PIONEER-HF (Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode). This study compared the effects of the sacubitril-valsartan combination versus enalapril on NT-proBNP change and adverse events among 881 patients with HFREF and acute decompensated heart failure randomized between the two treatments. The data were presented by Eric J. Velazquez, MD of Yale University, US (Yale was one of the institutions participating in this TIMI-organized study).

Study patients were ≥18 years of age with an LVEF ≤40% and a NT-proBNP concentration ≥1600 pg/mL or a BNP concentration ≥400 pg/mL and who had received a primary clinical diagnosis of acute decompensated heart failure, including signs and symptoms of fluid overload. Patients were enrolled ≥24 hours and ≤10 days after the initial presentation to the hospital and were still hospitalized when initiated into the study. Prior to randomization, patients needed to be hemodynamically stable (as indicated by systolic blood pressure ≥100 mm Hg for the preceding 6 hours, no increase in intravenous diuretic dose and no intravenous vasodilators during the preceding 6 hours and no intravenous inotropic drugs for the preceding 24 hours).

Compared with baseline values, NT-proBNP concentration decreased significantly (P<0.001) more (46.7%) at 4 and 8 weeks of randomized therapy in the sacubitril–valsartan group than in the enalapril group (which manifested a 25.3% decrease). Although NT-proBNP is a nonvalidated surrogate for clinical alterations, it does suggest that reduction in fluid overloading was highly unlikely to be less effective on the combination drug than on enalapril. Importantly, the rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema did not differ significantly between the two treatments.

The importance of the results of PIONEER-HF is that the use of the sacubitril-valsartan combination, found to be superior to enalapril in patients with chronic stable HFREF and not to have unacceptable safety problems in that setting in the PARADIGM-HF trial, can also be administered in the setting of acute decompensated heart failure without loss of efficacy and without incurring an adversity penalty. Without these data, therapy-naive patients with acute decompensated heart failure would need to begin with enalapril or some other ACE inhibitor or ARB and, when stabilized, transition to the combination drug. Thus, PIONEER-HF allows more efficient management of patients with acute decompensated heart failure than had been possible previously, with the likelihood that the mortality benefits of sacubitril-valsartan can be realized earlier than they might be with the current staged-therapy protocol.

OPTIMIZE HEART FAILURE CARE: EFFECT OF ADHERENCE TO GUIDELINES VS REHOSPITALIZATION

Several drugs have been tested for their effects on hospitalization for HFREF. The SHIFT study also assessed the effect of therapy on rehospitalization rates, demonstrating a significant drug-mediated reduction in rehospitalization when that drug was employed on a background of the remainder of guideline-based HFREF therapy. However, the effect of adherence to guideline-recommended therapy has not been systematically assessed from prospectively collected data. In a study mounted by collaborating investigators from institutions within the Russian Federation, data from an international prospective multicenter Optimize Heart Failure Care program that were collected over 12 months from 635 patients hospitalized with worsening heart failure were analyzed to assess the effects of physicians' and patients' adherence to guideline-based therapy on rehospitalization. Physicians' prescribing adherence was classified as good (use of drugs from all guideline-recommended heart failure medication groups), moderate (use of more than half the recommended medication groups), or poor (use of less than or equal to half the guideline-recommended medication groups). Patients' adherence was assessed by patient-reported compliance via a purpose-designed questionnaire. Again, three groups were defined: good (always took all prescribed medications at target doses), moderate (sometimes failed to take all prescribed drugs), or poor (patients failed to take all prescribed medications). As explained by Yuri Lopatin, MD of the Volgograd State Medical University, Volgograd, Russian Federation, who presented the study, after 12 months of follow-up, physicians' adherence did not reveal a clear pattern of hospitalization reduction compared with baseline, but rehospitalization was significantly higher than baseline ($P<0.0001$) when patients' adherence was poor in any physicians' adherence group. The authors concluded that educational initiatives are necessary for both physicians and patients if optimal impact of current drug therapy is to be achieved.

Many other important studies relating to heart failure were presented, but these three have particularly important implications for current care. ■

OPTIMIZE HEART FAILURE CARE AROUND THE WORLD

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Keywords: *ivabradine; heart failure management; Optimize Heart Failure Care program*

One of the most important conditions for the successful management of patients with heart failure is building an effective or, as described in the current ESC/HFA guidelines on heart failure, a "seamless" system of care, which covers both the community and the hospital throughout the health care journey.[1] In line with this, team-based or multidisciplinary care is proclaimed a cornerstone approach to reducing the burden of care and ensuring positive outcomes in patients with heart failure.[2-5] Another crucial aspect of the successful management of heart failure is effective coordination of efforts by the patient, health care providers, and the health care system itself. Each of these stakeholders plays a particular role in heart failure management, which cannot be fulfilled by other participants in the process.

REDUCING MORTALITY IN PATIENTS WITH HEART FAILURE

Over the past three decades, significant progress has been made in cutting mortality in patients with heart failure with reduced ejection fraction. However, the high rehospitalization rate remains a great challenge for patients with heart failure, health care providers, and communities in most countries of the world. Solving this problem requires an integrated approach with the involvement of all stakeholders in heart failure care. For example, it is possible to reduce the rate of readmissions only by penalizing hospitals with higher readmission rates; however, such an approach would be associated with an increase in mortality.[6] Similarly, it is impossible to expect a positive reduction in a high rehospitalization rate without the adherence of physicians and patients to the modern management of heart failure.[7,8] This global challenge is further complicated by the fact that the organization and quality of care for patients with heart failure can significantly differ from country to country.[9,10] All of the above factors determine the need to develop universal programs that would optimize heart failure care, regardless of the country or region where they are being implemented.

OPTIMIZE HEART FAILURE CARE PROGRAM: GLOBAL INITIATIVE FOR PATIENTS WITH HEART FAILURE

The Optimize Heart Failure Care program (www.optimize-hf.com) is a good example of a global initiative to improve the prescription of guideline-recommended drug therapies, patient education and engagement, and postdischarge planning for patients hospitalized with heart failure.[11] This program was initiated in 2013 and, as of the beginning of 2019, has already been implemented in 45 countries. The program includes instruments, such as best practice clinical protocols for local adaptation, pre- and postdischarge checklists, and "My HF Passport," a printed and smart phone application to enhance patients' understanding of heart failure, encourage their involvement in care, and improve treatment adherence. The cornerstone of the successful implementation of the Optimize Heart Failure Care program has been its flexibility to be adapted to local needs and languages, as well as the use of inexpensive clinician- and patient-focused tools. As a result, some of the participating hospitals began to use the entire program or supplemented it with new components, while others focused only on clinician- or patient-focused tools. Furthermore, the need for a close collaboration between health care professionals, on which the program is based, determined the success of the implementation of the developed tools across heart failure care services. Regular educational meetings with health care professionals who were involved in the Optimize Heart Failure Care program facilitated the sharing of personal experiences and results of heart failure interventions, as well as raising the awareness about the effects of guideline-recommended heart failure management on the mortality and the rate of rehospitalizations.

WORLDWIDE IMPLEMENTATION OF THE OPTIMIZE HEART FAILURE CARE PROGRAM

The implementation of the Optimize Heart Failure Care program in different parts of the world has shown clinically important results. According to data from the Philippines and Vietnam,[12,13] the program was easy to implement and resulted in an improvement in both the prescription of the guideline-recommended heart failure medications and the clinical status of patients with heart failure, as well as reducing the rate of adverse outcomes. It was recommended to continuously monitor the performance measures on a yearly basis and run the program continuously and repeatedly, since new physicians and new patients with heart failure were regularly included into the program. The introduction of the Optimize Heart Failure Care program in Brazil, Colombia, and Costa Rica also led to an improvement in heart failure care and, as a result, to a better prognosis for patients with heart failure.[14-16]

EARLY INITIATION OF IVABRADINE IN THE VULNERABLE PHASE OF HEART FAILURE

Several groups participating in the Optimize Heart Failure Care program investigated the effect of an early initiation of ivabradine therapy during the vulnerable phase of heart failure. The data, which were obtained from nine Colombian specialized heart failure hospitals, showed that optimized control of clinical parameters and the use of the guideline-recommended therapy at discharge from the hospital improved the clinical status and outcomes during a 30-day follow-up.[17,18] The early initiation of ivabradine therapy in stabilized patients in sinus rhythm and a heart rate ≥70 bpm who were hospitalized for worsening heart failure was well tolerated and it was associated with a clinical improvement and reduced rates of decompensation and readmissions during the vulnerable phase of heart failure. Moreover, the optimization of the heart rate–lowering therapy led to a reduction in the cost of treatment for the health care system.[19]

The study, which was performed in eight post–Soviet countries (Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Russia, Ukraine, and Uzbekistan) demonstrated the beneficial effect of in-hospital optimization of the heart rate–lowering therapy on overall mortality and rehospitalization in patients with a heart rate ≥70 bpm hospitalized for worsening heart failure.[20] Physicians participating in the program were free to choose their own strategy of in-hospital administration of a β-blocker alone or together with ivabradine. At 12 months of follow-up, all-cause mortality or heart failure hospitalization was significantly lower with β-blocker plus ivabradine than with β-blockers alone. In addition, a significantly greater improvement in quality of life from admission to 12 months was seen with β-blocker plus ivabradine versus β-blockers alone. Interestingly, with β-blocker plus ivabradine, significantly more patients achieved ≥50% of the target doses for β-blockers at 12 months vs at admission, while the effect was nonsignificant with β-blockers alone.

CONCLUSIONS

In general, the optimization of heart failure care can be realized at any stage of heart failure treatment, although currently hospitalized patients after stabilization of their clinical status are considered the most promising group. Last year, investigators from the University Hospital of Heidelberg, Germany presented the novel concept of an advanced heart failure unit embedded in an academic hospital infrastructure to optimize heart failure care in patients with acute heart failure, decompensated chronic heart failure, and, in particular, in advanced and terminal forms of acute and chronic heart failure.[21] This dedicated unit, with a multidisciplinary team, became a new model for the integration of modern pharmacological, interventional, surgical, and supportive heart failure therapy in high-risk patients including high-urgency heart transplant candidates with advanced heart failure.

The range of available treatment options for patients with heart failure, particularly for patients with a reduced ejection fraction, includes medications, cardiac devices, surgery, and lifestyle modifications. Therefore, the decision to optimize heart failure care will always be complex, based on a large number of factors, including the patient's clinical status, comorbidities, medication nonadherence, potential therapeutic inertia, and many others. It appears quite evident that a personalized approach to the optimization of heart failure treatment is mandatory.

Currently, the prescription rate of the guideline-recommended classes of heart failure medications is relatively satisfactory; however, the dosage of these therapies remains suboptimal.[7,22] This means that, in the absence of contraindications and intolerance, the optimization of heart failure treatment should be focused on achieving target doses or at least the highest tolerated doses of heart failure medications. At the same time, the reasons for nonprescription, nontitration, or withdrawal of guideline-recommended heart failure medications, for instance, symptomatic hypotension, worsening renal function, hyperkalemia, and bradycardia, should be the subject of special attention by all heart failure care providers.

Measuring natriuretic peptides and imaging studies may provide additional information for decision-making on optimizing heart failure treatment. However, it is important to emphasize that clinicians should interpret changes in the concentration of natriuretic peptides or deterioration of the left ventricular systolic function and remodeling primarily in the context of worsening heart failure symptoms and prognosis. Persistent or worsening heart failure symptoms, adverse clinical events, laboratory, and imaging data can be helpful for the detection of heart failure patients at high risk of disease progression or death. All this information is essential for the reevaluation of heart failure care and the referral of patients to dedicated heart failure specialists. At this stage of optimizing heart failure care, the appropriateness of advanced therapies, including heart transplantation or mechanical circulatory would be considered.

Any efforts associated with the optimization of heart failure care should be harmonized with the current guidelines for heart failure management. This is especially important when novel agents are included in the algorithm of heart failure treatment. The most recent guidelines[1,22] recommend a transition from ACE inhibitors or angiotensin receptor blockers to a angiotensin receptor-neprilysin inhibitor to further reduce morbidity and mortality in patients with symptomatic chronic heart failure with reduced ejection fraction. In this regard, a process of switching to a novel agent implies the implementation of the current heart failure guidelines, rather than the optimization of heart failure treatment. A discussion on how to optimize angiotensin receptor-neprilysin inhibitor therapy in patients with heart failure has already started. The primary results of the

TRANSITION study have demonstrated the safety and tolerability of an early initiation of sacubitril–valsartan in patients admitted for acute decompensated heart failure after hemodynamic stabilization.[24] In addition, data from the recently published trial PIONEER-HF showed that the initiation of sacubitril–valsartan in patients with heart failure with reduced ejection fraction, who were hospitalized for acute decompensated heart failure, led to a greater reduction in the concentration of N-terminal pro–B type natriuretic peptide compared with enalapril therapy.[25] Nevertheless, a larger trial on this issue powered for clinical end points is still required.

The optimization of heart failure care is one of the most important tasks for real-world clinical practice. Based on available data, it can be argued that the optimization of heart failure management, especially during the vulnerable phase of the clinical course of the disease, reduces the rate of death and rehospitalizations. Further studies, which may provide new ideas and new tools to optimize heart failure care, are extremely needed. ■

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PERCUTANEOUS CORONARY INTERVENTION AND OPTIMAL MEDICAL THERAPY AT THE CROSSROADS IN STABLE CAD MANAGEMENT

Will the ISCHEMIA trial define a clear path forward?

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Keywords: *ISCHEMIA; percutaneous coronary intervention; stable CAD*

Patients with obstructive CAD represent a clinical continuum that ranges from subjects who may be asymptomatic (including those with or without ischemia) to those with well-recognized chronic exertional angina, to those who exhibit profound angina symptoms at rest (consistent with acute coronary syndromes), including those with STEMI or NSTEMI. It is now widely accepted that all patients with established CAD should be prescribed multifaceted, pharmacologic secondary prevention therapies, including intensive lifestyle intervention. In the aggregate, this is often referred to as "optimal medical therapy," a term that came into widespread usage as a result of the COURAGE trial.[1] Such robust therapy has been shown to mitigate progression of atherosclerosis and to prevent MI and cardiovascular death in both nondiabetic and diabetic patients.[1,2]

While there is little controversy regarding the clinical benefit and utility of revascularization in patients with acute coronary syndromes (particularly primary PCI in patients with STEMI and expedited PCI in patients with NSTEMI or unstable angina),[3-5] there is a paucity of scientific evidence to support the clinical benefit of PCI in patients with stable CAD. Over the past decade, landmark randomized clinical trials and meta-analyses comparing initial management strategies in patients with stable CAD have demonstrated no significant reduction in "hard" clinical end points (all-cause mortality, cardiac death, or MI) among patients treated with PCI vs optimal medical therapy.[1,2,6-9] One possibility for this discrepancy of PCI benefit in patients with acute coronary syndromes, as compared with patients who have stable CAD, is that the former group may have more ischemic myocardium at risk of necrosis, whereas patients with stable CAD may have less ischemic myocardium and hence may be at a lower risk—thus making it difficult to discern an advantage of PCI on clinical event reduction. Moreover, the main advantage derived from early revascularization is improved short-term angina relief and improved quality of

life, and often a reduction in myocardial ischemia, though these putative benefits have been challenged recently.[10]

Thus, important questions remain regarding how best to approach the initial management of patients with stable CAD, such as whether one or more high-risk subgroups (defined by either coronary anatomy or functional ischemic burden) could be identified who would benefit from early revascularization and whether PCI for symptom relief alone in patients with stable CAD is justified. The focus of this paper will be to address the role of PCI and optimal medical therapy, particularly in the management of patients with stable CAD with a moderate-to-high risk, and to marshal available scientific evidence from clinical trials to clarify whether greater usage of optimal medical therapy in the setting of PCI may have additive benefits to improve clinical outcomes.

REVIEW OF CLINICAL TRIALS OF OPTIMAL MEDICAL THERAPY WITH OR WITHOUT PCI IN PATIENTS WITH STABLE CAD

Two major randomized clinical trials during the past 15 years (COURAGE and BARI 2D)[1,2] showed no reduction in death or the composite end points of death/MI or death/MI/stroke with PCI during periods of follow-up ranging from 5 to 7 years. Both studies provided a compelling rationale for deferred revascularization and an upfront trial of optimal medical therapy, including intensive pharmacotherapy and lifestyle intervention as secondary prevention. Moreover, these findings of strategic equivalence between PCI and optimal medical therapy have now been observed to persist for up to 15 years.[11] In addition, the more recent FAME 2 trial[6] showed that, among patients with stable CAD randomized to fractional flow reserve (FFR)-guided PCI plus medical therapy or to medical therapy alone, there was no overall difference in the end points of cardiac mortality, the composite of cardiac mortality or nonfatal MI, or in all-cause mortality; although, for the primary composite end point of death, MI, or urgent revascularization, there was a significantly lower rate in the PCI group (4.3%) vs the medical therapy alone group (12.7%; $P<0.001$). This difference, however, was driven solely by a lower rate of urgent revascularizations in patients assigned to PCI vs medical therapy (1.6% vs 11.1%; $P<0.001$) during a relatively limited (mean 7-month) follow-up.[11] Moreover, an extended follow-up of the FAME-2 trial to both 2 and 5 years failed to show a durable benefit of FFR-guided PCI on the clinical outcomes of death and/or MI.[12,13]

UNRESOLVED ISSUES IN THE CONTROVERSY OF PCI VS OPTIMAL MEDICAL THERAPY IN STABLE CAD MANAGEMENT

However, it remains unclear whether the extent and magnitude of myocardial ischemia in the setting of obstructive CAD is the principal driver of subsequent cardiac events—notably spontaneous (type 1) MI and the composite of MI and car-

diovascular death. Both the COURAGE[1] and BARI-2D trials[2] did not explicitly require that all enrolled patients demonstrate moderate-to-severe ischemia on noninvasive testing and, while all patients in COURAGE did have objective evidence of baseline myocardial ischemia, most of these randomized patients appeared to have mild-to-moderate ischemia. In addition, all prior contemporary "strategy trials"[1,2,6,12,13] comparing optimal medical therapy with or without PCI were uniformly undertaken after the results of coronary angiography were known to the study investigators, which introduced the possibility that bias may have led to the investigators' decision not to randomize patients to optimal medical therapy or PCI once the coronary anatomic results were apparent. Thus, we have not yet addressed (nor answered) the pivotal question of whether timely revascularization may improve clinical outcomes in patients with stable CAD with flow-limiting CAD and moderate-to-severe baseline ischemia.

It seems both logical and intuitive that targeting revascularization to lesions causing substantial ischemia may further improve outcomes. Many myocardial perfusion imaging studies have demonstrated a strong relationship between the extent of underlying baseline myocardial ischemia and prognosis. In one study of 1137 patients with chest pain and suspected CAD in whom thallium imaging was performed, a strong graded association was present between the number of abnormal ischemic segments and the 6-year rate of cardiac death and MI.[14] In another study of 205 patients with angiographic CAD, there was a greater reduction in cardiac death or MI at 10 years in patients with a normal vs abnormal thallium scan (83% vs 58%; P=0.005).[15] In addition, in a large study of 10 627 patients in whom stress myocardial perfusion imaging was performed (671 of whom were treated with early revascularization), the mean 1.9-year rate of cardiac mortality in nonrevascularized patients increased from 0.7% in those with no ischemia to 6.7% in those with >20% ischemia.[16] Finally, in a substudy of 314 COURAGE trial patients who underwent serial rest/stress myocardial perfusion imaging before and after randomization to PCI plus optimal medical therapy vs optimal medical therapy alone at 6 to 18 months (mean 374±50 days),[17] there was a graded relationship between the amount of residual ischemia on the repeat myocardial perfusion imaging scan and subsequent death or MI; although, after adjustment for baseline variables and treatment, this was not significant (P=0.09). However, only ≈33% of these patients had at least moderate (≥10%) ischemia at baseline.[17] Thus, it remains unclear whether the extent and magnitude of myocardial ischemia in the setting of obstructive CAD in patients with stable CAD is the principal driver of subsequent cardiac events—notably spontaneous (type 1) MI and the composite of MI and cardiovascular death.

WILL THE RESULTS OF THE ISCHEMIA TRIAL SETTLE THIS UNCERTAINTY OF POTENTIAL PCI BENEFIT?

The primary objective of the ISCHEMIA trial (ClinicalTrials.gov Identifier: NCT01471522) is to determine whether an initial invasive strategy of cardiac catheterization and optimal revascularization (with PCI or coronary artery bypass surgery as determined by the local heart team) plus optimal medical therapy will reduce the primary composite end point of cardiovascular death, nonfatal MI, resuscitated sudden cardiac death, or hospitalization for unstable angina or heart failure, in a time-to-first event analysis, during an average 3.5-year follow-up in patients with stable CAD with moderate or severe ischemia and medically controllable or absent symptoms vs an initial conservative strategy of optimal medical therapy alone (with catheterization reserved for failure of optimal medical therapy).[18] The major secondary end points are the composite end point of cardiovascular death or MI and angina-related quality of life. The trial is sponsored by the U.S. National Heart, Lung, and Blood Institute. Blinded coronary computed tomographic angiography is performed prior to randomization to exclude those with significant left main CAD and no obstructive CAD. Enrollment began in late 2012 and 5179 patients have been successfully randomized as of January 2018[19]; the trial is projected to conclude on June 30, 2019. ISCHEMIA thus aims to address limitations of previous strategy trials by: (i) enrolling patients before catheterization, so that anatomically high-risk patients are not excluded; (ii) enrolling a higher risk group with at least moderate ischemia; (iii) minimizing crossovers; (iv) using contemporary drug-eluting stents and physiologic-guided decision-making (FFR) to achieve complete ischemic (rather than anatomic) revascularization; and (v) being adequately powered to demonstrate whether routine revascularization improves a prognostically important composite clinical outcome in patients with stable CAD with at least moderate ischemia.

CONCLUSION

In summary, while PCI has been shown to reduce death or MI in patients with STEMI and in many high-risk patients with NSTEMI, definitive data are lacking at present to validate whether clinical event reduction with PCI can be achieved in higher risk patients with stable CAD who have significant ischemia at baseline. It is anticipated that the results of the ISCHEMIA trial can define a clear path forward in terms of providing more enlightened decision-making in an important population of patients whose optimal management remains uncertain for clinicians. For these reasons, the ISCHEMIA trial findings will very likely have important implications regarding global clinical practice guidelines for years to come. ■

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Guidelines, Registries, & Trials

FIRST-LINE ANTI-ISCHEMIC AGENTS FOR STABLE CORONARY ARTERY DISEASE: INSIGHTS FROM CLARIFY

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Keywords: *β-blockers; calcium antagonists; coronary artery disease; prognosis*

Over the last decades, with the advent of primary reperfusion therapy, evidence-based secondary prevention medication, and new diagnostic tools, the profile of patients with coronary artery disease and their prognosis have changed considerably. However, little is known about the demographics, characteristics, and prognosis of contemporary patients with stable coronary artery disease.

The CLARIFY registry (ISRCTN43070564) was built to be a useful resource for understanding the current epidemiology of stable coronary artery disease. Some results were presented at the 2018 ESC congress in Munich, especially an analysis on "First-line anti-ischemic agents use and long-term clinical outcomes in stable coronary artery disease. Insights from the CLARIFY study," which was presented by Sorbets E for Steg PG, Young R, et al.

THE CLARIFY REGISTRY

The rationale and methods were described previously.[1] Briefly, between November 2009 and June 2010, 32703 patients with stable coronary artery disease were enrolled in 45 countries by 2898 practitioners (general practitioners and specialists) from rural, suburban, and urban areas. Each physician screened consecutive outpatients in order to enroll 10 to 15 participants.

In order to enroll patients representative of several aspects of contemporary stable coronary artery disease, participants had to meet at least one of the following inclusion criteria: prior MI >3 months, prior revascularization by percutaneous coronary angioplasty or coronary artery bypass graft >3 months, chest pain with proven myocardial ischemia, or coronary angiography showing at least one coronary stenosis >50%. Exclusion criteria were conditions that could interfere with follow-up or life expectancy, including cancer or severe heart failure. Follow-up was done by clinicians yearly up to 5 years. Medical care was at the discretion of each physician. To ensure data quality, every year, 1% of the sites were randomly

selected for onsite audits. At these sites, 100% of the data for all patients were audited for source documentation and accuracy. All patients gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki and local ethical approval was obtained in each country.

The CLARIFY registry was supported by Servier. The sponsor had no role in the study design, data analysis, and interpretation, or in the decision to submit the manuscript for publication, but assisted with the set-up, data collection, and management of the study in each country. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

ASSESSMENT OF THE USE OF FIRST-LINE, ANTI-ISCHEMIC AGENTS

This study was a post-hoc analysis of CLARIFY that was designed to assess the association between β-blockers or calcium antagonists and outcomes in patients with contemporary stable coronary artery disease. Indeed, there is still uncertainty about the benefit of β-blockers in such patients without an impaired left ventricular ejection fraction: the use of β-blockers in patients with stable coronary artery disease is only derived from old randomized clinical trials performed in the acute MI or postacute MI phase, mainly before the start of primary reperfusion therapy. Recently, some registries raised the question of their benefit is patients with stable coronary artery disease. Regarding calcium antagonists, randomized clinical trials that did not enroll contemporary patients failed to demonstrate a beneficial effect on mortality and there is no large registry investigating this drug class in patients with stable coronary artery disease.

Considering this need for contemporary data, two nonmutually exclusive analyses were performed over the CLARIFY registry: one according to β-blocker use at baseline and one according to calcium antagonist use at baseline. Analyses were restricted to patients where all available data were entered in a large, multivariable, adjustment model accounting for cardiovascular risk factors, burden of the cardiovascular disease (including left ventricular ejection fraction, history of heart failure, atrial fibrillation or coronary revascularization, number of involved vascular beds, etc), treatments (aspirin and statins), geographical zones, and pulmonary comorbidities. Some of these potential confounders were summarized by the REACH cardiovascular event risk score entered in the model.[2]

The primary outcome was all-cause death and the secondary outcomes were cardiovascular death and the composite of cardiovascular death or MI. Some sensitivity analyses assessed the use of anti-ischemic agents over time, considering the last available data from the yearly follow-up. Other sensitivity analyses assessed the daily doses of β-blockers.

BASELINE CHARACTERISTICS

β-Blocker users

The analysis of β-blocker use could be performed after multivariable adjustment with no missing data in 22 004 patients from the 32 703 enrolled in CLARIFY. At baseline, more than three-quarters received a β-blocker, mainly bisoprolol (35.6%), metoprolol (27.2%), carvedilol (12.6%), atenolol (12.3%), and nebivolol (6.5%), but only 13.3% received the full β-blocker dose. Among patients not receiving a β-blocker, 39.6% did not receive them due to symptoms of intolerance or contraindication, mainly asthma/chronic obstructive pulmonary disease or bradycardia. Compared with those not receiving a β-blocker, those receiving a β-blocker were younger, with more cardiovascular risk factors, a larger history of prior MI, less peripheral artery disease, less asthma, and more angina symptoms. They had a lower left ventricular ejection fraction and received more secondary prevention therapies. Despite these differences in baseline characteristics, these groups had a similar theoretical cardiovascular risk as assessed by the REACH cardiovascular risk score.

Calcium antagonist users

The analysis of calcium antagonist use could be performed in 22 006 patients from the 32 703 enrolled in CLARIFY. At baseline, nearly one-quarter received calcium antagonists, mainly dihydropyridines (79.8%). Compared with those not receiving a calcium antagonist, those receiving calcium antagonists were older, with more cardiovascular risk factors, a lower history of prior MI, more peripheral artery disease, and more angina symptoms. They had a higher left ventricular ejection fraction and did not receive more secondary prevention therapies. Despite these differences in baseline characteristics, these two groups had a similar REACH cardiovascular risk score, which was comparable with the β-blocker study cohorts.

CLINICAL OUTCOMES

β-Blocker use

According to β-blocker use at baseline and after multivariable adjustment, there was no difference in the risk of all-cause death (HR for use, 0.94; 95% CI, 0.84-1.06), cardiovascular death (HR, 0.91; 95% CI, 0.79-1.05), or cardiovascular death and MI (HR, 1.03; 95% CI, 0.91-1.16). In the subset of patients with a history of MI ≤1 year prior to enrollment, β-blocker use at baseline was associated with a risk reduction in all-cause death (205 events [7.0%] for users vs 59 [10.3%] for nonusers; HR, 0.68; 95% CI, 0.50-0.91; *P*=0.01), driven by a risk reduction in cardiovascular death (132 events [4.5%] for users vs 49 [8.5%] for nonusers; HR, 0.52; 95% CI, 0.37-0.73; *P*=0.0001) and a risk reduction in cardiovascular death and MI (212 events [7.2%] for users vs 59 [10.3%] for nonusers; HR, 0.69; 95% CI, 0.52-0.93; *P*=0.01). In patients

enrolled beyond 1 year after a MI, between 1 and 3 years as well as over 3 years, there was no difference in the risk of all outcomes.

For the sensitivity analyses, regarding treatment use over time, the results were consistent with no difference in the risk of outcomes. Regarding doses at baseline and after categorization by less than a half dose, half to less than a full dose, and a full dose, the event risks were not modified by dose levels, regardless of the outcomes.

Calcium antagonist use

According to calcium antagonist use at baseline and after multivariable adjustment, there was no difference in the risk of all-cause death (HR for use, 1.02; 95% CI, 0.91-1.13), cardiovascular death (HR, 1.01; 95% CI, 0.88-1.16), or cardiovascular death and MI (HR, 1.05; 95% CI, 0.94-1.17). There was no difference in the risk of all outcomes, regardless of the time elapsed since the MI prior to enrollment, by 1 year, between 1 and 3 years, and over 3 years.

DISCUSSION

In this large, international, contemporary registry of patients with stable coronary artery disease, with a high level of evidence-based secondary prevention therapies, and after a large multivariable adjustment, including left ventricular ejection fraction, β-blocker use was associated with a reduction in 5-year mortality, which was driven by a reduction in cardiovascular mortality, but only in patients with a prior MI ≤1 year. In stable patients without a history of MI or with a prior MI >1 year, β-blocker use was not associated with a reduction in mortality. Calcium antagonist use was not associated with a better prognosis regardless of the clinical profile and the history of MI.

These results are consistent with prior registries (REACH,[3] FAST MI,[4] Kaiser Permanente database,[5] and the French health care database[6]) that had some limitations addressed in the present study. CLARIFY was not restricted to a single area, collected left ventricular ejection fraction value, and, for β-blockers, the daily doses and the reasons for not using them. Of course, there were some limitations to this study. Outcomes were not adjudicated. However, it is interesting to highlight that the results were consistent for nonadjudicated outcomes and for all-cause mortality. Even after a large multivariable adjustment, residual confounding data from measured or unmeasured variables cannot be excluded (in particular as relates to indication bias). Thus, randomized controlled trials are needed to confirm these results. A large, powered randomized trial would be required to settle the issue of whether first-line anti-ischemic agents affect prognosis and outcomes in patients with stable coronary artery disease. However, it is uncertain whether it would be feasible to mobilize the resources and obtain the patient numbers that are to address this question adequately.

CONCLUSION

Combined with the previous literature, the present analysis suggests that, in contemporary coronary artery disease, β-blockers should be preferentially used in the year following the MI. Beyond 1 year after the MI or in patients with stable coronary artery disease without a previous MI, both β-blockers and calcium antagonists may be used for symptom relief, but do not appear to be associated with a survival benefit. ■

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A LOWER BLOOD PRESSURE TARGET IN HYPERTENSIVE PATIENTS: UPDATE ON THE RECENT HYPERTENSION GUIDELINES

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Using a threshold of 140/90 mm Hg, the global prevalence of hypertension is estimated to be over 1 billion.[1] Elevated BP is the leading cause of death and disability-adjusted life years worldwide.[2] While it has long been demonstrated that a reduction in elevated BP decreases the risk of death and cardiovascular events,[3] the optimal BP target remains a matter of debate.

Most hypertension guidelines issued from 2011 to 2015 agreed on a threshold of 140/90 mm Hg both to define hypertension and as a treatment target. The ACC/AHA guidelines on high BP,[4] issued in 2017, generated a worldwide debate by lowering the threshold defining hypertension and the treatment target, from 140/90 to 130/80 mm Hg. The 2018 ESC/ESH guidelines for the management of arterial hypertension[5] kept the definition of hypertension above 140/90 mm Hg, but recommended a target of 130/80 mm Hg, in line with the American guidelines.

We will give a brief overview on these recent guidelines, with a focus on the thresholds for hypertension definition, treatment initiation, and treatment target. We will discuss the underlying evidence for these new guidelines, and the reasons why clinicians are not unanimously convinced they should apply a lowered threshold in daily practice.

DEFINITION OF HYPERTENSION

A major change in the 2017 American guidelines was the replacement of the decades-old 140/90 mm Hg threshold defining hypertension with a new lower threshold: 130/80 mm Hg. A systolic BP of 130–139 or a diastolic BP of 80–89 now defines stage 1 hypertension, while any values above 140/90 mm Hg define stage 2 hypertension. This new definition increased the estimated prevalence of hypertension in the US from 32% to 46%,[6] and generated heated controversies.

In this context of strong intellectual stances by hypertension experts, the much-awaited European guidelines, issued in the summer of 2018, maintained

the hypertension definition unchanged from the previous 2013 guidelines: a systolic BP of 130–139 and/or a diastolic BP of 85–89 define a "high-normal" BP, while grade 1, 2, and 3 hypertension are defined by a systolic BP/diastolic BP of 140–159/90–99, 160–179/100–109, and ≥180/≥110 mm Hg, respectively.

TREATMENT TARGET AND TREATMENT THRESHOLD

The American guidelines lowered the BP target to below 130/80 mm Hg for all patients, with important considerations on how to reach this lower target. In all treated patients, treatment should be intensified to reach 130/80 mm Hg. In previously untreated patients with systolic BP between 130 and 139 mm Hg or diastolic BP between 80 and 89 mm Hg, only those with or at high risk for cardiovascular disease (including those ≥65 years old) should be treated pharmacologically. In the large majority of the patients newly diagnosed with hypertension, nonpharmacological therapy alone is recommended.

The European guidelines, in line with the American guidelines, also lowered BP targets for most patients: the treatment goal for systolic BP should be 130 mm Hg "or lower, if tolerated" in most patients (with the exception of patients with chronic kidney disease and patients ≥65 years, for whom the target is 130–139 mm Hg). The diastolic BP target was lowered to below 80 mm Hg for all patients. Importantly, treatment initiation remained at 140/90 mm Hg for most patients, but it was extended to patients with "high-normal" BP (as defined above) who are at very high risk, "especially those with coronary artery disease."

Noteworthy, because of the differences in the thresholds defining hypertension, the initiation of pharmacological treatment, and the treatment target, the major difference in the definition of hypertension between the American and European guidelines does not actually translate into a major difference in the clinical management of patients. Indeed, on the one hand, the US guidelines recommend pharmacological treatment for patients with BP 130–139/80–89 mm Hg (grade 1 hypertension) only when they are at high cardiovascular risk, and, on the other hand, the European guidelines recommended to "consider drug treatment" in very high-risk patients with a BP of 130–139/85–89 mm Hg ("high-normal BP"). For all treated patients (except patients ≥65 years old or with chronic kidney disease), the common new target is 130/80 mm Hg. A remaining subtle difference is the threshold of diastolic BP for drug initiation in high-risk patients (80 vs 85 mm Hg).

UNDERLYING EVIDENCE FOR LOWER BP TARGETS

The rationale for more-intensive treatment in high-risk patients is the greater absolute risk reduction as baseline cardiovascular risk increases.[7] The lowered threshold of 130/80 mm Hg largely results from the reduced rate of cardiovascular events observed in the intensive treatment arm of the SPRINT trial and from

several recent large meta-analyses showing that intensive BP lowering was associated with decreased cardiovascular events.[8,9] In SPRINT, 9361 patients with baseline systolic BP higher than 130 mm Hg who were at high cardiovascular risk, but without diabetes or previous stroke, were randomly assigned to standard (<120 mm Hg) or intensive (<140 mm Hg) BP–lowering treatment. The trial was stopped early after a median follow-up of 3.3 years because of a significant 25% reduction in the primary composite outcome and a 27% reduction in mortality.

However, patients in SPRINT were carefully followed-up in the setting of a randomized trial and BP values were measured under unattended conditions to minimize any white-coat effect, but may underestimate casual BP values by 10 to 15 mm Hg. Therefore, the guideline committees advocated for a target BP of 130 mm Hg and not 120 mm Hg as in the SPRINT trial. In addition, these considerations led hypertension experts to warn that the SPRINT target, if translated into community practice, may have deleterious effects because the same targets obtained in routine clinical practice would potentially lie within the left part of the so-called "J-curve," where excessive BP lowering may be harmful.

TREATMENT INITIATION FOR PATIENTS WITH CORONARY ARTERY DISEASE

Patients with established coronary artery disease are clearly a high-risk group in which earlier treatment initiation is recommended by both guidelines. As a result of the new guidelines, patients with coronary artery disease so far considered as normotensive, should now be treated to reach a BP below 130/80 mm Hg. However, the benefits of a more-intensive BP control have not been consistently observed for patients with coronary artery disease.

In this context, we analyzed data from nearly 6000 patients with coronary artery disease and no history of hypertension (BP <140/90 mm Hg) from the CLARIFY registry.[10] CLARIFY is a large, international, prospective cohort that included 32 703 patients with stable coronary artery disease in 45 countries, with a 5-year follow up. The results showed that a systolic BP above 130 mm Hg was not associated with an increased risk of mortality or cardiovascular events (myocardial infarction or stroke) compared with patients whose blood pressure was optimal according to the recent guidelines, ie, 120–129 mm Hg. In contrast, a diastolic BP above 80 mm Hg was associated with an increased risk compared with 70–79 mm Hg. These results do not support the new systolic threshold of 130 mm Hg for patients with coronary artery disease, but are in favor of a lower diastolic BP target, below 80 mm Hg.

Overall, in the absence of dedicated studies for patients with coronary artery disease, this new 130/80 mm Hg target and treatment threshold is not evidence-based in this population, and clinicians are not unanimously convinced they should apply this lowered threshold in daily practice.

LOWER SAFETY BOUNDARIES

Aside from the similarities in both guidelines highlighted above, the European guidelines introduced a major novelty compared with both previous European and US guidelines, namely lower safety boundaries, at 120/70 mm Hg. The European guidelines defined target ranges rather than just upper limits of BP targets. The target range for systolic BP is 120–130 mm Hg for patients younger than 65 and 130–139 mm Hg for patients older than 65, while the diastolic BP target range is 70–79 mm Hg for all patients.

This word of caution against excessive lowering of BP relies on several observational studies, including a study from our team conducted on the CLARIFY registry in 2016.[11] In 22 672 patients treated for hypertension, we showed that achieved systolic BP <120 mm Hg and achieved diastolic blood pressure <70 mm Hg were both associated with a marked increased risk of mortality, myocardial infarction, and hospitalization for heart failure, independently of potential confounding factors. The concern of a "J-curve" is particularly relevant for patients with coronary artery disease because a low diastolic BP may compromise myocardial perfusion, but an increased risk at low BP values was observed in many other populations, and the lower safety boundaries of the European guidelines apply to all treated patients.

Of note, targeting optimal BP ranges for both components of BP will yield situations when clinicians will have to prioritize whether they should aim for an optimal systolic BP or an optimal diastolic BP. In the CLARIFY registry, of the 27 310 patients requiring antihypertensive drug treatment according to recent guidelines, such discordance between systolic and diastolic BP values with regards to their respective targets is observed in half of the patients.[12] As data to guide the optimal strategy when BP components are dissociated are lacking, the recent European guidelines highlight another remaining gap in evidence and that the saga of the BP targets is not over.

CONCLUSION

In conclusion, largely influenced by the results of the SPRINT trial, recent hypertension recommendations advocated for a more intensive treatment in hypertensive patients and for an earlier initiation of pharmacological treatment in high-risk patients. Improving global BP control with a target below 140/90 mm Hg is an indisputable public health priority, but the expected risk/benefit ratio of a reinforced treatment to reach less than 130/80 mm Hg for all patients remains uncertain. ■

Conflicts of interest

The author declares support for congress registration from Servier.

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BIG DATA: BRIDGING THE GAP BETWEEN REAL-WORLD AND TRIAL EVIDENCE

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The potential of the analysis of big data to improve health care and the understanding of diseases is impressive. How to use real-world evidence to support the approval of new indications for old drugs or for postapproval matters is currently a hot topic of discussion. At the 15th Global Cardiovascular Clinical Trialists Forum held on November 29–December 1, 2018 in Washington, DC, US, trialists, regulators, payers, industries, practitioners, and patients provided different perspectives about the use of big data to support drug development.

REAL-WORLD DATA

Real-world data consist of electronic health records, product and disease registries, patient-generated data, and, overall, all the data on patient health status and health care utilization collected by different sources. Analysis of real-world data leads to real-world evidence. Real-world data analyses and trials are not opposites, but provide complementary evidence. Indeed, randomized clinical trials (RCTs) allow the efficacy of treatments to be tested, but enroll selected populations, and are useless without effective implementation strategies to maximize the utilization of the new treatments. On the other hand, analyses of real-world data cannot be used to test treatment efficacy because of confounding factors and bias, but allow for the assessment of the association between drug use and the risk of outcomes. Compared with trials, real-world data analyses are cheaper and more generalizable (ie, less inclusion/exclusion criteria, meaning that they reflect real-world practice). Due to the large sample size, they foster the identification of the occurrence of rare clinical events, which may be underestimated in a trial population. Thus, real-world data may be key for the investigation of safety, tolerability, ease of use, cost, effectiveness, and implementation of treatments in daily clinical practice, aspects that are as important as efficacy in the development journey of a new drug. The importance of real-world evidence has been well recognized by regulators. In the 21st Century Cures Act, the FDA announced a new drug-development modernization plan. Although RCTs are considered gold standards to support medical product approval decisions, their limitations are acknowledged. Regulators aim that real-world evidence may be the key to answer

most of the critical questions unanswered by RCTs, particularly those about the effects of a drug in broader populations and over a more extended period of time than in the RCTs.[1] The FDA is actively working to integrate real-world evidence into the process of medical product development.[1]

Registry-based randomized clinical trials

Real-world evidence and randomization can be integrated to provide a novel study design, namely prospective, registry-based RCTs (RRCTs), which allows the advantage of conducting an RCT, ie, randomization, with all the pros of using real-world data, such as large clinical registries (ie, less selected populations, real-world practice settings, larger number of events and potential for identifying rare events, lower costs) to be combined.[2] In an RRCT, a registry is used to identify eligible patients who are randomized to receive the treatment or the control after attaining consent to participate, and to collect patients' baseline characteristics. A registry can also be used to collect key outcomes, making it possible to follow-up patients longer, but at a lower cost than in RCTs. When appropriate, open-label randomization, limited monitoring procedures, and no centralized event adjudication may be adopted, which further contributes to simplifying the study design and reduce costs, but have well-known limitations.[2]

Observational studies based on real-world data cannot assess efficacy of a treatment due to the limitation of a lack of randomization, but can provide important hypotheses to test in subsequent interventional RCTs. An analysis of the SCAAR registry, which is part of the SWEDEHEART registry, showed that the use of thrombectomy as an adjunct to percutaneous coronary intervention in patients with STEMI was associated with an increased risk of death after adjustment for several potential confounders.[3] This real-world evidence inspired the investigators to test the same hypothesis in a randomized setting.

Thus, the RRCT TASTE[4] was designed to test manual thrombus aspiration on top of primary percutaneous coronary intervention vs percutaneous coronary intervention alone in patients with STEMI. An open-label design was adopted and the primary end point was mortality at 30 days. The SCAAR registry enrolls all consecutive patients undergoing coronary intervention in Sweden and Iceland and allowed for the identification of eligible patients for the TASTE trial. Inclusion criteria were very few, such as diagnosis of STEMI with percutaneous coronary intervention planned after coronary angiography. All baseline and procedural data were entered directly into the registry. Randomization was performed by an online randomization module within the SCAAR registry. An initial oral consent was requested before randomization and the agreement to participate had to be confirmed by written informed consent within 24 hours. Data for the primary end point (mortality at 30 days) were obtained by linking SCAAR with the national

population registry, whereas those for the secondary end points (30-day hospitalization for MI, stent thrombosis, target-vessel revascularization, target-lesion revascularization, composite of death or MI) were extracted from SWEDEHEART and the Swedish national patient registry. Linkage between Swedish disease health registries and governmental health and statistical registries was done using the 10-digit personal identity number assigned at birth (or immigration) to every Swedish resident. The TASTE trial randomized 7244 patients, 3621 were assigned to thrombus aspiration and 3623 to conventional percutaneous coronary intervention. The cost of this RRCT was around 400 000 USD (beyond the ordinary costs of the registry), which is extremely low when compared with the expenditures required for running an industry-funded RCT (around 10 million USD for an RCT of equivalent size). The TASTE trial did not show any benefit in terms of a reduction in 30-day mortality in patients randomized to thrombus aspiration before percutaneous coronary intervention vs percutaneous coronary intervention alone in patients with STEMI. Real-world data also allow the implementation of trial evidence in clinical practice to be verified. Indeed, after the publication of the TASTE RRCT, an analysis of SCAAR/SWEDEHEART reported a sudden decrease in the use of thrombus aspiration in the setting explored in the trial, highlighting a successful implementation of the TASTE findings in clinical practice.

Several RRCTs have followed the TASTE trial, with most of them testing invasive procedures or short-term pharmacological treatments. The SPIRRIT-HFPEF trial is the first RRCT testing a chronic treatment in heart failure and is currently enrolling patients (end of enrollment planned for 2020, end of the follow-up planned for 2022).[5] Briefly, it is a phase 4, randomized, multicenter, safety/efficacy, parallel assignment, intention-to-treat, open-label treatment, event-driven interventional trial testing spironolactone (or eplerenone) on top of usual care vs usual care alone in patients with heart failure with an ejection fraction >40%. SPIRRIT-HFPEF is sponsored and managed by the nonprofit academic research organization Uppsala Clinical Research center. The Swedish Heart Failure Registry, which is linked to other national health registries, such as the Patient Registry, the Dispensed Drug Registry, and the LISA registry, by the Swedish personal identity number, provide baseline and outcome data. The primary outcome is cardiovascular death. Cause of death is adjudicated by an independent clinical end point committee. A short and simple written consent form has to be signed at the time of randomization. During the course of the study, patients are followed up according to the routine care and provide serum/plasma creatinine and potassium assessments on 5 occasions.

CONCLUSIONS

The "big data" session at the 2018 Cardiovascular Clinical Trialists Forum has clearly highlighted the potential of using real-world data to improve health care. Real-world data may actively contribute to improve the process of developing new treatments and the implementation of their use in medical practice. Real-world data is a friend, rather than an enemy, of RCTs, and they complement one another. A coordinated effort by all stakeholders is needed to implement the use of real-world data in the evidence-generation process. ■

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WHERE ARE WE WITH THE EUROBSERVATIONAL RESEARCH PROGRAMME IN 2018?

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Overall, 14 papers have been published in 2018 reporting information derived from ESC-EORP registries. A selection of the scientific production is reported below in different areas of cardiovascular diseases.

HEART FAILURE

Heart failure and atrial fibrillation frequently coexist, atrial fibrillation being the most common arrhythmia in heart failure. Atrial fibrillation increases the risk of thromboembolic complications (particularly ischemic stroke) and may impair cardiac function, leading to worsening symptoms of heart failure. It is well known that an episode of heart failure precipitated by atrial fibrillation is generally associated with a more benign prognosis once atrial fibrillation is converted to sinus rhythm or heart rate is well under control. On the contrary, new-onset atrial fibrillation in a patient with established heart failure is associated with a worse outcome, probably because it is both a marker of a sicker patient and because it impairs cardiac function. Patients with chronic heart failure and permanent atrial fibrillation have a worse outcome than those in sinus rhythm, although this is largely explained by more advanced age and heart failure severity.

These concepts are valid for heart failure in general, but it is not clearly understood what the role of atrial fibrillation is in patients with heart failure and different levels of ejection fraction. An ad-hoc analysis of the EORP Heart Failure Long-Term registry was conducted on 14 964 patients to compare the characteristics and the 1-year prognostic role of atrial fibrillation among patients with HFREF (ejection fraction <40%), those with HFMEF (ejection fraction between 40% and 49%), and those with HFPEF (ejection fraction ≥50%).[1] The prevalence of atrial fibrillation was 26% in patients with HFREF, 29% in patients with HFMEF, and 39% in patients with HFPEF. Atrial fibrillation was associated with older age, reduced functional capacity and more severe physical signs of heart failure. Crude rates of mortality and heart failure hospitalization were higher in patients with atrial fibrillation compared with those in sinus rhythm, in each ejection fraction group. The multivariable analysis, adjusted for the most important confounding factors,

showed that atrial fibrillation was independently associated with a higher mortality in patients with HFPEF, while it was not in patients with HFREF and HFMEF. These findings were similar in both acute and chronic heart failure patients.

This analysis of the Heart Failure Long-Term registry showed that the prevalence of atrial fibrillation increases with increasing ejection fraction and that atrial fibrillation was associated with increased all-cause mortality only in patients with HFPEF and associated with heart failure hospitalizations only in patients with HFPEF and HFMEF. With a higher ejection fraction, atrial fibrillation may contribute to the progression of heart failure and worsen outcomes; whereas, with a lower ejection fraction, atrial fibrillation may be more of a bystander, where heart failure itself and its severity determine the outcomes.

ATRIAL FIBRILLATION

The role of sex and body weight on the outcomes of patients with atrial fibrillation is not completely understood. An analysis of the EORP AF Long-Term registry tried to clarify these open issues in a large population of "real-world" patients with atrial fibrillation.[2] Among 2540 atrial fibrillation patients (38.9% female; median age, 69) with 1-year follow-up data available, 28.3% had a normal BMI, 42.7% were overweight, and 29.0% were obese. Obese patients were younger and with a more prevalent history of diabetes mellitus and hypertension (P<0.001). The study showed that all-cause mortality was significantly different according to BMI among female patients (normal BMI, 9.3%; overweight, 5.3%; obese, 4.3%; P=0.023), but not among male patients (P=0.748). The composite outcome of thromboembolic events and death was also significantly different, as it was lower in obese females (P=0.035). Among males, bleeding events were significantly more frequent in obese patients (P=0.035). The multivariable Cox analysis, adjusted for the most relevant confounding factors, showed that BMI was not independently associated with all-cause mortality.

Another registry, the Atrial Fibrillation Ablation Long-Term registry (AFA-LT), was analyzed in an attempt to answer a relevant question[3]: how are patients managed during the 1-year follow-up period after atrial fibrillation ablation? A follow-up visit was not performed systematically in all patients: of the 3593 who underwent an ablation procedure, 1-year follow-up was performed in 3180 (88.6%), with 52.8% being conducted by clinical visit, 44.2% by telephone contact, and 3.0% by contact with the general practitioner. The absence of an appropriate assessment following the procedure is surely a gap in clinical practice. The number of clinical visits and, even more importantly, of cardiac rhythm monitoring was shown to be at least suboptimal. In this context, with respect to the arrhythmia, 34.2% had a documented recurrence of atrial arrhythmia during the 12-month follow-up period. Recurrences were more frequent in persistent (39.8%) and long-

standing persistent (43.7%) than in paroxysmal atrial fibrillation (31.4%) (P<0.0001). Recurrences were mainly due to atrial fibrillation (29.0%), while only a minority of cases suffered an atypical atrial flutter or tachycardia (5.5%). At the follow-up visit, 45.5% of patients were still treated with an anti-arrhythmic drug and two-thirds were on oral anticoagulation. Insufficient guideline adherence to anticoagulation management was observed, since 26.5% of patients with CHA_2DS_2-VASc ≥2 were not receiving anticoagulation. The AFA-LT registry showed that a more structured and systematic rhythm monitoring and a more appropriate prevention of thromboembolic events with oral anticoagulants are needed to improve the outcome of these patients undergoing atrial fibrillation ablation.

CHRONIC ISCHEMIC CARDIOVASCULAR DISEASE

The 6-month follow-up of the Chronic Ischemic Cardiovascular Disease ESC Pilot registry was also published in 2018.[4] The results suggest that more effort should be directed into improving the best practices in agreement with the current guidelines. The rate of relevant clinical events during this medium-term follow-up was surprisingly high: of the 2203 patients considered for the analysis, 2.6% died (the majority of fatal events were cardiovascular) and 22.5% were hospitalized for any cause, mostly for cardiovascular causes (18.4%). The composite of all-cause death or all-cause rehospitalization occurred in 23.7% of the patients and the composite of cardiovascular death or cardiovascular hospitalization occurred in 19.5%.

Independent predictors of all-cause mortality/hospitalization were age, a history of previous peripheral revascularization, chronic kidney disease, or chronic obstructive pulmonary disease. During the follow-up period, while a reduction in the rate of prescriptions for statins was not observed, a decrease in the rate of prescriptions for ACE inhibitors, angiotensin receptor blockers, β-blockers, and aspirin was reported. This observation can explain, at least in part, the high rate of clinical events observed in the medium-term period of the follow-up. The conclusion is that, in this contemporary European registry of patients with chronic ischemic cardiovascular disease, the rate of severe clinical outcomes at 6 months was high and was mainly influenced by age and comorbidities. The medical management of chronic ischemic cardiovascular disease was suboptimal, emphasizing the need for ad-hoc programs aimed at implementing guideline adherence and follow-up procedures in order to improve quality of care and, as a consequence, patient outcomes.

CARDIOMYOPATHIES

The Cardiomyopathy Registry of the EURObservational Research Programme is a prospective, observational, and multinational registry of consecutive patients with four cardiomyopathy subtypes: hypertrophic cardiomyopathy, dilated

cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and restrictive cardiomyopathy. In 2018, the baseline characteristics and the management of the 3208 patients enrolled in the registry were published.[5] The most common diagnosis was hypertrophic cardiomyopathy (54.2%), then dilated cardiomyopathy (39.3%), arrhythmogenic right ventricular cardiomyopathy (4.4%), and restrictive cardiomyopathy (2.1%). In addition, left ventricular noncompaction was reported in 4.1% of all patients.

β-Blockers were the most frequently prescribed drugs (80.6% of all patients). Implantable cardioverter defibrillators were reported in a high rate of cases (25.9% of the whole population; 81.4% for primary prophylaxis), most frequently, as expected, in patients with arrhythmogenic right ventricular cardiomyopathy (56.6% of patients) followed by dilated cardiomyopathy (31.7%), hypertrophic cardiomyopathy (19.9%), and restrictive cardiomyopathy (9.1%). These findings document the burden of life-threatening arrhythmias in these clinical conditions. A pacemaker was implanted in 10.2% of the whole cohort, most frequently in patients with dilated cardiomyopathy (14.3%) and least frequently in arrhythmogenic right ventricular cardiomyopathy (2.8%).

The study clearly shows the diversity and the different frequency of diagnostic tests that were performed in the various areas of Europe for assessment of the cardiomyopathy, management of symptoms, or stratification of risk. This is also clearly documented by the rate of use of MRI, performed in nearly one-third of all patients, or by genetic testing, performed in about one-third of patients. The large differences observed among the various geographic areas suggest that comparing the organization of health care systems for cardiomyopathies in the various countries may provide valuable insights that can be used to improve health care services in Europe. Since recommendations or expert consensus for the management of the patients and their families are now available, it can be hypothesized that variations in service provision are mostly related to economical or structural reasons than to the clinical knowledge of health care professionals dealing with these clinical conditions.

PREGNANCY IN CARDIAC DISEASE

The ROPAC registry is one of the most productive registries of EORP. In 2018, a paper describing the story of pregnant women with rheumatic mitral valve disease was published.[6] Rheumatic heart disease is a major problem in emerging countries, while, in more developed economies, this clinical condition is quite rare and typically found in recent immigrants. In emerging countries, rheumatic valve disease is the most common cardiac disease in pregnant women and the most important cause of maternal death. The situation has improved in the last decades and the ROPAC registry can provide an updated figure of maternal and fetal morbidity and mortality.

Of the 2966 pregnant women included in the ROPAC registry, 390 (13%) women had rheumatic mitral valve disease. Mean age was 29 years, and 26.4% of women were primigravida. The majority lived in countries with an emerging economy (75.4%) and they were known to have a mitral valve disease before pregnancy (75.1%). Caesarean section was performed in the majority of these women (52%). In a large proportion of them, Caesarean section was planned for an obstetric reason; in 20% of cases, a Caesarean section was planned for cardiac reason. Although mortality was only 1.9% during pregnancy, approximately 50% of the women with severe rheumatic mitral stenosis and 23% of those with moderate mitral stenosis developed heart failure during pregnancy. Miscarriage before the 24th week occurred in 3.6% of the cases, fetal mortality after the 24th week of gestation occurred in just 1% of the cases. Low birth weight was observed in more than 16% of cases.

The authors concluded that a close follow-up during pregnancy could allow for an early recognition of symptoms and a timely intervention to avoid an unfavorable maternal or fetal outcome. ■

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Abbreviations & Acronyms

ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
ACS QUIK	Acute Coronary Syndrome QUality Improvement in Kerala
AFA-LT	Atrial Fibrillation Ablation Long-Term registry
AHA	American Heart Association
ARB	angiotensin receptor blocker
ARRIVE	Aspirin to Reduce Risk of Initial Vascular Events
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
ATTR-ACT	Transthyretin Amyloidosis Cardiomyopathy Clinical Trial
BASKET-SMALL 2	BASel Kosten Effektivitäts Trial–drug-coated balloons versus drug-eluting stents in SMALL vessel interventions
BARI 2D	Bypass Angioplasty Revascularization Investigation 2–Diabetes
BMI	body mass index
BNP	brain natriuretic peptide
BP	blood pressure
CABANA	Catheter ABlation vs ANti-arrhythmic drug therapy for Atrial fibrillation
CAD	coronary artery disease
CAMELLIA-TIMI 61	Cardiovascular And MEtaboLic effects of Lorcaserin In overweight And obese patients–Thrombolysis In Myocardial Infarction 61
CANTOS	Canakinumab Antiinflammatory Thrombosis Outcome Study
CARDIA	Coronary Artery Risk Development In young Adults
CASTLE-AF	Catheter Ablation versus Standard conventional Treatment in patients with LEft ventricular dysfunction and Atrial Fibrillation
CHA_2DS_2-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
CLARIFY	prospeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease

COMMANDER HF	COMparison of the efficacy and safety of rivaroxaban with placebo for reducing the risk of death, Myocardial infArctioN or stroke in subjects with heart failure and significant coronary artery Disease following an episode of decompensated Heart Failure
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation StrategieS
CRISP-CT	Cardiovascular RISk Prediction using Computed Tomography
DESSOLVE III	DES with Sirolimus and a bioabsorbable pOLymer for the treatment of patients with de noVo lEsion in the native coronary arteries
DIGITAL-AF	DIGITAL non-interventional Atrial Fibrillation screening
EAST	Early therapy of Atrial fibrillation for StrokE prevention
EORP	EURobservational research Programme
ESC	European Society of Cardiology
ESH	European Society of Hypertension
EUROASPIRE	EUROpean Action on Secondary and Primary prevention by Intervention to Reduce Events
FAST-MI	French registry of acute ST-elevation or non–ST-elevation myocardial infarction
FFR	fractional flow reserve
GARFIELD-AF	Global Anticoagulant Registry in the FIELD-Atrial Fibrillation
HDL	high-density lipoprotein
HFA	Heart Failure Association
HFMEF	heart failure with midrange ejection fraction
HFPEF	heart failure with preserved ejection fraction
HFREF	heart failure with reduced ejection fraction
HONOR	HOme-based moNitORed exercise for PAD
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LVEF	left ventricular ejection fraction
MANAGE	MANAGEment of myocardial injury after noncardiac surgery

MARINER	Medically ill patient Assessment of Rivaroxaban versus placebo IN reducing post-discharge venous thromboEmbolism Risk
MI	myocardial infarction
MOMENTUM	Multicenter study Of MagLev tEchNology in paTients Undergoing Mechanical circulatory support therapy with HeartMate 3
MRA	mineralocorticoid receptor antagonist
MRI	magnetic resonance imaging
(mSToPS)	mHealth Screening to Prevent Strokes
NAD	nicotinamide adenine dinucleotide
NSTEMI	non–ST-segment elevation myocardial infarction
NT-proBNP	N-terminal pro-brain natriuretic peptide
ORBITA	Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina
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
PIONEER-HF	Sacubitril–Valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode
PREDIMED	PREvención con DIeta MEDiterránea
PRESERVE	PREvention of SERious adVerse Events following angiograph
PURE	Prospective Urban Rural Epidemiology
RACE 3	Routine versus Aggressive upstream rhythm Control for prevention of Early atrial fibrillation in heart failure
RADIAL	Radial Artery Database International Alliance
RCT	randomized controlled trial
REACH	REduction of Atherothrombosis for Continued Health
REMOTE	Remote exercise monitoring trial for exercise-based cardiac rehabilitation
REPRISE III	REpositionable Percutaneous Replacement of stenotic aortic valve through Implantation of lotus valve SystEm
ROPAC	Registry Of Pregnancy And Cardiac disease

RRCT	registry-based RCTs
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
SECURE-PCI	Statins Evaluation in Coronary Procedures and Revascularization
SENIOR	SYNERGY II Everolimus elutiNg stent In patients Older than 75 years undergoing coronary Revascularisation associated with a short dual antiplatelet therapy
SHIFT	Systolic Heart failure treatment with the If inhibitor ivabradine Trial
SMART-DATE	SMart Angioplasty Research Team-safety of 6-month duration of Dual Antiplatelet ThErapy after percutaneous coronary intervention in patients with acute coronary syndromes
SPIRRIT-HFPEF	Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction
SPRINT	Systolic Blood Pressure Intervention Trial
STEMI	ST-segment elevation myocardial infarction
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based bare in Heart disease Evaluated According to Recommended Therapies
TARDIS	Triple Antiplatelets for Reducing Dependency after Ischaemic StrokeA
TARGET All Comers	TARGETed therapy with a localised abluminal groove, low-dose sirolimus-eluting, biodegradable polymer coronary stent
TASMINH4	Telemonitoring And/or Self-Monitoring of blood pressure IN Hypertension 4
TASTE	Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia
TIM-HF2	Telemedical Interventional Management in Heart Failure II
TIMI	Thrombolysis in Myocardial Infarction
TRANSITION	posT-discharge tReatment initiation with sacubitril/valsartan in heArt failure patieNtS with reduced ejectIon-fracTion hospItalised for an acute decOmpensation eveNt
TRICS III	Transfusion Requirements In Cardiac Surgery
TRIUMPH	Translational Initiative on Unique and novel strategies for Management of Patients with Heart failure

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