Dialogues in Cardiovascular Medicine

Aims & Scope

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

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The compilation of article summaries presented in this issue of *Dialogues in Cardiovascular Medicine* was prepared by Dr Sherri Smith. Summaries are provided for all research articles on cardiology published between January 1, 2019 and December 31, 2019 in the *European Heart Journal, JAMA, the Lancet*, and *the New England Journal of Medicine*; reviews and guidelines were excluded.

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Year in Cardiology

2019

EDITORIAL

The pace of research in cardiology appears to be growing exponentially with new and important findings that may influence clinical practice, happening on a regular basis. Most of this research is published in the major general medical journals, namely the *New England Journal of Medicine, Lancet,* and *JAMA*. Increasingly, the *European Heart Journal* is becoming a leading specialist journal in cardiovascular disease where such research may be found.

As it is becoming increasingly challenging for doctors to keep up with the latest publications, we have decided to devote the Year in Cardiology to all the original cardiovascular publications from the previous year found in the *New England Journal of Medicine, Lancet, JAMA,* and the *European Heart Journal*. Each paper has been reported in an objective manner with no selection bias so that the readers may draw their own conclusions as to the merit of the published work and how it may influence clinical thinking as well as their clinical practice.

In many ways, 2019 may be considered the year of "chronic stable angina" with the culmination of several papers being published over the recent couple of years aimed at a better understanding of the medical treatment and outcomes of this condition, notably four papers—two by Ferrari et al[1,2] and two by Sorbets et al.[3,4] In the face of antianginal drugs having similar efficacy and evidence levels, choosing among the drugs and proffering sufficient guidelines is tricky at best; therefore, to address this, Ferrari and colleagues set about generating a different and individualized approach to treatment and developed the diamond approach.[1] The new diamond approach received more support following a systematic review on double-blind, parallel-group, randomized studies on angina treatment in patients with stable coronary artery disease, which showed no superiority of one angina drug over another in either the treatment of angina or in the prolongation of total exercise duration; in addition, only 3 of the 13 studies included showed equivalence between three drug classes, ie, β-blockers, calcium antagonists, and I_f channel inhibitors.[2]

Furthermore, a post-hoc analysis of the prospective, observational, longitudinal CLARIFY registry[3] showed that β-blockers did not reduce the 5-year outcome except within the first year following myocardial infarction; however, calcium antagonists did not have any effect on mortality rates. The recently published 5-year outcomes analysis of CLARIFY[4] showed that the enrolled patients had a higher rate of exposure to secondary prevention measures and a lower rate of major cardiovascular events than was shown in previous registries. The analysis revealed that differences in patient profiles led to different prognoses; for example, angina

was associated with a poor prognosis, but only in those patients who had experienced a previous myocardial infarction, further lending weight to the idea and implementation of a patient-tailored approach to treatment.

In addition to these 4 papers on "chronic stable angina," the European Society of Cardiology published, in the *European Heart Journal,* a new set of guidelines in 2019.[5] The guidelines were revised from the previous version to focus on chronic coronary syndrome instead of stable coronary artery disease, as it was stated that the patient population was not homogenous and that there were several distinct categories of "stable coronary artery disease" each requiring different treatment strategies.

We hope that you enjoy this summary of the outstanding cardiovascular research published in 2019 and look forward to another exciting year to come in cardiovascular science.

ROBERTO FERRARI, MD, PhD; **KIM FOX**, MD, FRCP

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3. Sorbets E, Steg PG, Young R, et al. β-blockers, calcium antagonists, and mortality in stable coronary artery disease: an international cohort study. *Eur Heart J.* 2019;40(18):1399-1407.
4. Sorbets E, Fox KM, Elbez Y, et al. Long-term outcomes of chronic coronary syndrome worldwide: insights from the international CLARIFY registry. *Eur Heart J.* 2020;41(3):347-356.
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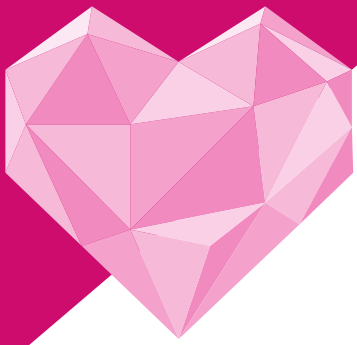
Snapshots of the Year:

European Heart Journal



January 2019

Byrne RA, Alfonso F, Schneider S, et al. Prospective, randomized trial of bioresorbable scaffolds vs. everolimus-eluting stents in patients undergoing coronary stenting for myocardial infarction: the Intracoronary Scaffold Assessment a Randomized evaluation of Absorb in Myocardial Infarction (ISAR-Absorb MI) trial. *Eur Heart J.* 2019;40(2):167-176.

Previous trials have shown a higher rate of device failure of bioresorbable scaffolds compared with conventional drug-eluting stents; however, only one trial made the comparison in patients undergoing percutaneous coronary intervention for acute myocardial infarction. The ISAR-Absorb MI trial, a prospective, randomized, multicenter, noninferiority, clinical trial, compared everolimus-eluting bioresorbable scaffolds with durable polymer everolimus-eluting stents in patients with an acute myocardial infarction (n=262; mean age, 62.5 years; women, 22.5%). The primary end point was the percentage diameter of stenosis in-segment at coronary angiography 6 to 8 months after the intervention. Everolimus-eluting bioresorbable scaffolds were noninferior to everolimus-eluting stents for the primary end point.

Caselli S, Serdoz A, Mango F, et al. High blood pressure response to exercise predicts future development of hypertension in young athletes. *Eur Heart J.* 2019;40(1):62-68.

Certain athletes have higher blood pressure levels at peak exercise compared with untrained individuals; however, the prognostic significance of this response is not clear. This study compared athletes with a high blood pressure response to exercise with athletes with a normal blood pressure response to exercise to determine if a high blood pressure response increases the risk of hypertension (n=1876; mean age, 26 years; women, 34%). Over a mid-term period, the high blood pressure response to exercise resulted in an increased risk for incident hypertension.

Da Dalt L, Ruscica M, Bonacina F, et al. PCSK9 deficiency reduces insulin secretion and promotes glucose intolerance: the role of the low-density lipoprotein receptor. *Eur Heart J.* 2019;40(4):357-368.

While proprotein convertase subtilisin/kexin type 9 (PCSK9) loss of function genetic variants result in lower low-density lipoprotein cholesterol levels, there is higher plasma glucose levels, as well as an increased risk of type 2 diabetes mellitus. This study investigated the molecular mechanisms involved in this association using mouse models by performing glucose tolerance tests and insulin tolerance tests, as well as assessing insulin and C-peptide plasma levels, pancreas morphology, and cholesterol accumulation in pancreatic islets. PCSK9

critically controls the expression of low-density lipoprotein receptors in the pancreas, which is independent of circulating PCSK9.

Farag M, Spinthakis N, Gue YX, et al. Impaired endogenous fibrinolysis in ST-segment elevation myocardial infarction patients undergoing primary percutaneous coronary intervention is a predictor of recurrent cardiovascular events: the RISK PPCI study. *Eur Heart J.* 2019;40(3):295-305.

Endogenous fibrinolysis is a process to prevent thrombotic occlusions and infarction following initiation of coronary thrombosis, meaning that impaired endogenous fibrinolysis could be marker for patients with ST-segment elevation myocardial infarction who remain at high cardiovascular risk. The RISK PPCI study, a prospective, observational study, investigated whether assessing for impaired endogenous fibrinolysis could help identify patients with ST-segment elevation myocardial infarction who remain at high cardiovascular risk despite dual antiplatelet therapy and primary percutaneous coronary intervention (n=496; mean age, 63 years; women, 22.2%). The primary end point was the occurrence of major adverse cardiovascular events (ie, the composite of cardiovascular death, nonfatal myocardial infarction, including stent thrombosis, or stroke. In the patient population assessed, endogenous fibrinolysis assessment can identify those patients who remain at very high cardiovascular risk.

Lemkes JS, Janssens GN, van der Hoeven NW, et al. Timing of revascularization in patients with transient ST-segment elevation myocardial infarction: a randomized clinical trial. *Eur Heart J.* 2019;40(3):283-291.

It is challenging to determine whether patients with acute coronary syndrome who initially have an ST-segment elevation myocardial infarction (STEMI) on the electrocardiogram, which then normalizes before reperfusion therapy (transient STEMI) should receive an immediate invasive strategy and percutaneous coronary intervention (STEMI-like) or a delayed invasive approach (NSTEMI-like). The TRANSIENT trial, a prospective, investigator-initiated, randomized controlled clinical study, evaluated the two treatment options—STEMI-like and NSTEMI-like—in patients with transient STEMI with symptoms of any duration (n=142; mean age, 62.3 years; women, 30.5%). The primary end point was myocardial infarct size measured by cardiac magnetic resonance imaging at day 4. In patients with transient STEMI, the use of either a STEMI-like or NSTEMI-like approach did not influence the infarct size.

Seijkens TTP, Poels K, Meiler S, et al. Deficiency of the T cell regulator Casitas B-cell lymphoma-B aggravates atherosclerosis by inducing CD8+ T cell-mediated macrophage death. *Eur Heart J.* 2019;40(4):372-382.

The mechanism by which macrophages and T cells mediate atherosclerosis is unknown. As the E3-ligase Casitas B-cell lymphoma-B (CBL-B) is a negative regulator of T cell activation and is expressed in macrophages, this study analyzed the expression of CBL-B in human atherosclerotic plaques during atherosclerosis using a mouse model. CBL-B stops CD8+ T cell activation during atherogenesis, which inhibits plaque inflammation and progression of atherosclerosis toward an unfavorable high-risk plaque phenotype.

Sondergaard KB, Wissenberg M, Gerds TA,et al. Bystander cardiopulmonary resuscitation and long-term outcomes in out-of-hospital cardiac arrest according to location of arrest. *Eur Heart J.* 2019;40(3):309-318.

In several countries, nationwide initiatives have been implemented to facilitate cardiopulmonary resuscitation in out-of-hospital cardiac arrest by bystanders. This analysis of the nationwide Danish Cardiac Arrest Registry was carried out to examine the importance of public or residential location of arrest on temporal changes in bystander cardiopulmonary resuscitation and outcomes (n=25 505; mean age, 70 years; women, 69.9%). The primary study outcome was bystander cardiopulmonary resuscitation according to location of arrest. Bystander cardiopulmonary resuscitation and 30-day survival more than doubled in both public and residential out-of-hospital cardiac arrest locations.

Zimmermann FM, Omerovic E, Fournier S, et al. Fractional flow reserve-guided percutaneous coronary intervention vs. medical therapy for patients with stable coronary lesions: meta-analysis of individual patient data. *Eur Heart J.* 2019;40(2):180-186.

As there is uncertainty about the role of percutaneous coronary interventions for stable epicardial coronary lesions in reducing death and myocardial infarction This systematic review and meta-analysis of individual patient data compared fractional flow reserve–guided percutaneous coronary intervention with medical therapy for patients with stable coronary lesions from the FAME 2, DANAMI-3-PRIMULTI, and Compare-Acute trials (n=2400; mean age, 62.9 years; women, 21.5%). The prespecified primary outcome was a composite of cardiac death or myocardial infarction. The analysis showed that, compared with medical therapy, fractional flow reserve–guided percutaneous coronary intervention reduced the composite of cardiac death or myocardial infarction, which was driven by a decreased risk of myocardial infarction. ■

February 2019

Doimo S, Fabris E, Piepoli M, et al. Impact of ambulatory cardiac rehabilitation on cardiovascular outcomes: a long-term follow-up study. *Eur Heart J.* 2019;40(8):678-685.
While cardiac rehabilitation is recommended for patients after ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, coronary artery bypass graft, and planned percutaneous coronary intervention, it is significantly underutilized. This long-term follow-up study compared the 5-year incidence of cardiovascular mortality and hospitalization for cardiovascular causes between patients who attended an ambulatory cardiac rehabilitation program with those patients who did not (n=1280; mean age, 67 years; women, 28.5%). This real-world study showed that the incidence of the composite end point was lower in the group receiving cardiac rehabilitation, but this result was driven by a lower incidence of hospitalizations for cardiovascular causes.

Gutman SJ, Costello BT, Papapostolou S, et al. Reduction in mortality from implantable cardioverter-defibrillators in non-ischaemic cardiomyopathy patients is dependent on the presence of left ventricular scar. *Eur Heart J.* 2019;40(6):542-550.
The benefits of a primary prevention implantable cardioverter-defibrillator implantation are well established for patients with ischemic cardiomyopathy and reduced left ventricular ejection fraction; however, data concerning benefits in patients with nonischemic cardiomyopathy are less robust. This observational cohort study investigated the mortality benefits of primary prevention implantable cardioverter-defibrillator implantation in patients with nonischemic cardiomyopathy with or without a left ventricular scar (n=452; mean age, 53.4 years; women, 24.3%). The primary outcome was all-cause mortality. A mortality reduction was only observed in patients with nonischemic cardiomyopathy and the presence of a left ventricular scar.

Lassen MCH, Biering-Sørensen SR, Olsen FJ, et al. Ratio of transmitral early filling velocity to early diastolic strain rate predicts long-term risk of cardiovascular morbidity and mortality in the general population. *Eur Heart J.* 2019;40(6):518-525.
The ratio of early mitral inflow velocity to global diastolic strain rate (E/e'sr) has been shown to be a significant predictor of cardiac events in specific patient populations; however, its utility for predicting cardiovascular events in a general population has not yet been analyzed. This longitudinal cohort study assessed the prognostic significance of E/e'sr in the general population (n=1238; mean age, 56.9 years; women, 57.8%). The primary end points were cardiovascular disease due to either incident heart failure or acute myocardial infarction. E/e'sr not only

provides independent and incremental prognostic information regarding cardiovascular morbidity and mortality, but it is also a stronger predictor of cardiac events than E/e' alone.

Mahmoud AN, Gad MM, Elgendy AY, Elgendy IY, Bavry AA. Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of randomized controlled trials. *Eur Heart J.* 2019;40(7):607-617.

The evidence for using aspirin for the primary prevention of cardiovascular events is controversial. One meta-analysis concluded that aspirin reduces all-cause mortality, myocardial infarction, and ischemic stroke and increases the risk of major bleeding, and another meta-analysis concluded that aspirin reduces nonfatal myocardial infarctions, with little or no effect on all-cause or cardiovascular mortality. With new data from recent, large-scale, randomized trials being reported, the goal of this meta-analysis was to provide updated information on the efficacy and safety of aspirin in patients with no prior history of atherosclerotic cardiovascular disease (n=157 248; mean age, 61.3 years; women, 52%). The primary efficacy outcome was all-cause mortality, and the primary safety outcome was major bleeding. This meta-analysis concluded that aspirin did not reduce the incidence of all-cause mortality, but it did increase the incidence of major bleeding.

Messika-Zeitoun D, Nickenig G, Latib A, et al. Transcatheter mitral valve repair for functional mitral regurgitation using the Cardioband system: 1 year outcomes. *Eur Heart J.* 2019;40(5):466-472.

There is high operative morbidity and mortality associated with surgical correction of mitral regurgitation. The Cardioband™ Mitral Valve Reconstruction System, a transcatheter implant designed to reduce mitral annulus size and mitral regurgitation severity, was developed in the hopes of reducing the morbidity and mortality rates. This study, a single-arm, prospective multicenter trial, assessed the safety, performance, and efficacy of the Cardioband system in patients with moderate or severe secondary mitral regurgitation on guideline-recommended medical therapy (n=62; mean age, 72 years; women, 28%). In the 1-year outcome analysis, the Cardioband mitral system demonstrated acceptable performance and safety, with a significant reduction in mitral regurgitation and significant functional improvements.

Obokata M, Reddy YNV, Melenovsky V, Pislaru S, Borlaug BA. Deterioration in right ventricular structure and function over time in patients with heart failure and preserved ejection fraction. *Eur Heart J.* 2019;40(8):689-697.

In patients with heart failure with preserved ejection fraction, there is a higher rate of morbidity and mortality in the presence of right ventricular dysfunction.

As the natural history, predictors, and the prognostic impact of right ventricular dysfunction in patients with heart failure with preserved ejection fraction, this study investigated the chronic changes, ie, clinical, structural, functional, and hemodynamic characteristics, in the structure and function of the right ventricle in these patients (n=271; mean age, 71 years; women, 56%). Compared with the left ventricle, there is a greater deterioration in the structure and function of the right ventricle, showing a 20% increase in the diastolic area and a 10% decrease in the fractional area change.

Pennells L, Kaptoge S, Wood A, et al; Emerging Risk Factors Collaboration. Equalization of four cardiovascular risk algorithms after systematic recalibration: individual-participant meta-analysis of 86 prospective studies. *Eur Heart J.* 2019;40(7):621-631.

Risk prediction algorithms are used as a strategy for the primary prevention of cardiovascular disease; however, as there are several algorithms, the selection of an optimal one is not easy. This individual-participant meta-analysis used data from 86 prospective studies to perform head-to-head comparisons of four algorithms–Framingham risk score, Systematic COronary Risk Evaluation, pooled cohort equations, and Reynolds risk score–in participants without cardiovascular disease at baseline (n=360 737; mean age, 59 years; women, 47.5%). The comparison was carried out both before and after recalibration. The principal outcome was the composite of cardiovascular disease events during the initial 10-year period of follow-up as defined by each algorithm. Before recalibration, the performance of the risk algorithms varied greatly; however, after recalibration, the performance was almost equal between the algorithms.

Shanbhag SM, Greve AM, Aspelund T, et al. Prevalence and prognosis of ischaemic and non-ischaemic myocardial fibrosis in older adults. *Eur Heart J.* 2019;40(6):529-538.

The ICELAND-MI cohort, a substudy of the AGES-Reykjavik study, previously showed that mortality rates were similar between patients with clinically recognized myocardial infarction and patients with evidence of unrecognized myocardial infarction from cardiac magnetic resonance imaging. This study used the ICELAND-MI cohort to test whether major patterns of myocardial scar and fibrosis associated with nonischemic cardiomyopathies would indicate a higher risk of heart failure and death (n=900; mean age, 76 years; women, 49.3%). The primary study outcome was a composite of time to hospitalization for heart failure or death. Major nonischemic patterns of myocardial fibrosis predicted a worse prognosis vs no myocardial fibrosis/scar.

Vlastra W, Chandrasekhar J, Muñoz-Garcia AJ, et al. Comparison of balloon-expandable vs. self-expandable valves in patients undergoing transfemoral transcatheter aortic valve implantation: from the CENTER-collaboration. *Eur Heart J.* 2019;40(5):456-465.

In patients with aortic valve stenosis, treatment with transcatheter aortic valve implantation is a life-saving, minimally-invasive option; however, adequately sized trials comparing balloon-expandable valves with self-expandable valves are lacking. The CENTER-collaboration, an international collaboration that collected data from 10 registries or clinical trials, analyzed clinical outcomes between balloon-expandable valves and self-expandable valves in patients with severe aortic valve stenosis undergoing transfemoral transcatheter aortic valve implantation (n=12 381; mean age, 82 years; women, 58%). The primary end points were mortality from any cause and stroke within the first 30 days following the implantation procedure. Compared with patients receiving self-expandable valves, patients receiving balloon-expandable valves had a lower incidence stroke and pacemaker implantation; however, there was no statistically significant difference in the rate of mortality between the two valve types.

Yoon SH, Whisenant BK, Bleiziffer S, et al. Outcomes of transcatheter mitral valve replacement for degenerated bioprostheses, failed annuloplasty rings, and mitral annular calcification. *Eur Heart J.* 2019;40(5):441-451.

Identifying predictors for adverse outcomes from surgical or transcatheter mitral valve replacement is essential in order to properly select the right approach to treat mitral valve disease. The TMVR registry, an international, multicenter, observational study, evaluated the outcomes of transcatheter mitral valve replacement in patients with degenerated bioprostheses (valve-in-valve), failed annuloplasty rings (valve-in-ring), and severe mitral annular calcification (valve-in-mitral annular calcification) (n=521; mean age, 72.6 years; women, 54.1%). The primary end points were all-cause mortality at 30 days and 1 year. Despite having a higher surgical risk, transcatheter mitral valve replacement provided excellent outcomes for patients with degenerated bioprostheses. In addition, the risk of mortality after transcatheter mitral valve replacement was higher both in patients with failed annuloplasty rings and in patients with severe mitral annular calcification. ■

March 2019

Atasoy S, Johar H, Peters A, Ladwig KH. Association of hypertension cut-off values with 10-year cardiovascular mortality and clinical consequences: a real-world perspective from the prospective MONICA/KORA study. *Eur Heart J.* 2019;40(9):732-738.

The SPRINT trial showed that reducing systolic blood pressure to 120 mm Hg (vs 130 mm Hg) led to an impressive relative risk reduction in cardiovascular disease events and mortality, whereas an extended meta-analysis did not show a favorable effect of lowering blood pressure in patients with a baseline systolic blood pressure <140 mm Hg. This study used data from the MONICA/KORA study, a prospective population-based study, to evaluate the clinical value of a lower blood pressure cut-off for stage 1 hypertension (130-139 mm Hg systolic or 80-89 mm Hg diastolic) vs the currently established stage 2 cut-off (≥140/90 mm Hg) (n=11 603; mean age, 47.26 years; women, 48.4%). This analysis showed that the lower blood pressure cut-off increased the prevalence of hypertension.

Barco S, Mahmoudpour SH, Planquette B, Sanchez O, Konstantinides SV, Meyer G. Prognostic value of right ventricular dysfunction or elevated cardiac biomarkers in patients with low-risk pulmonary embolism: a systematic review and meta-analysis. *Eur Heart J.* 2019;40(11):902-910.

The 2014 ESC guidelines on the management of acute pulmonary embolism proposed that, in patients with a pulmonary embolism with a low clinical risk based on the Pulmonary Embolism Severity Index alone could justify early discharge without the need for further testing. This systematic review and meta-analysis evaluated the prognostic function of right ventricular dysfunction and elevated troponin or natriuretic peptide levels in low-risk patients with acute pulmonary embolism (n=7536). The primary outcome was all-cause mortality at 30 days or during hospitalization. In low-risk patients with an acute pulmonary embolism, the presence of right ventricular dysfunction on admission was associated with early mortality.

Böhm M, Mahfoud F, Townsend RR, et al. Ambulatory heart rate reduction after catheter-based renal denervation in hypertensive patients not receiving anti-hypertensive medications: data from SPYRAL HTN-OFF MED, a randomized, sham-controlled, proof-of-concept trial. *Eur Heart J.* 2019;40(9):743-751.

The SPYRAL HTN-OFF MED trial, a randomized sham-controlled trial, showed that renal denervation using a multielectrode catheter lowers ambulatory blood pressure in nonmedicated hypertensive patients. This post-hoc analysis of the trial describes the effects of renal denervation on heart rate (n=80; mean age, 54.3

years; women, 28.9%). Heart rate was analyzed for various daytime and nighttime periods. Compared with sham-treated patients, the average and minimum morning heart rates were significantly lower at 3 months.

Choi YJ, Kim SH, Kang SH, et al. Reconsidering the cut-off diastolic blood pressure for predicting cardiovascular events: a nationwide population-based study from Korea. *Eur Heart J.* 2019;40(9):724-731.

Literature in continually providing information about the association between high blood pressure and cardiovascular risk; however, it remains uncertain whether there is a J-curve association for predicting cardiovascular risk and if systolic and diastolic blood pressure independently predict cardiovascular outcomes. Therefore, to address these issues, this study analyzed the association of systolic and diastolic blood pressure with cardiovascular events in patients who had never received antihypertensive medical treatment and had no history of cardiovascular disease by evaluating data from the National Health Insurance Services-Health Screening Cohort in Korea (n=290 600; mean age, 53.6 years; women, 41.9%). The primary end point was major cardiovascular events, ie, a composite of cardiac death, myocardial infarction, stroke, and heart failure. Elevated blood pressure was shown to be a strong predictor of future cardiovascular events, with both systolic and diastolic blood pressure being associated with an increased risk of cardiovascular events.

Costantino S, Akhmedov A, Melina G, et al. Obesity-induced activation of JunD promotes myocardial lipid accumulation and metabolic cardiomyopathy. *Eur Heart J.* 2019;40(12):997-1008.

In patients with heart failure, metabolic cardiomyopathy is an emerging cause of left ventricular dysfunction; however, the mechanisms behind this are not well understood. This study tested the hypothesis that Jun D, a member of the activator protein 1 complex, is a factor involved in obesity-induced metabolic cardiomyopathy using neonatal rat ventricular myocytes, gain- and loss-of-function mutant mice, and myocardial biopsies from obese and nonobese patients. JunD is a target of the microRNA miR-494-3p, and JunD was shown to regulate peroxisome proliferator-activated receptor-γ signaling, which results in an accumulation of myocardial triglycerides, lipotoxic damage, and left ventricular dysfunction.

Czopek A, Moorhouse R, Guyonnet L, et al. A novel role for myeloid endothelin-B receptors in hypertension. *Eur Heart J.* 2019;40(9):768-784.

Endothelin-1 is the most potent endogenous vasoconstrictor that binds two receptors—endothelin A and endothelin B. There is a correlation between the distribution of subendothelial macrophages and endothelial function; in addi-

tion, angiotensin-converting enzyme inhibition improves endothelial function and reduces the number of vascular macrophages. Selective endothelin A receptor antagonism reduced macrophage infiltration. Using an in vitro mouse model, macrophage numbers and phenotypes were modified to analyze the hypertensive effects of endothelin 1, angiotensin II, and salt. In addition, the effects of macrophage depleting or nondepleting therapies on blood pressure and endothelial function were analyzed in patients with small vessel vasculitis. Macrophage depletion increased the chronic hypertensive response to both endothelin 1 and salt, and, compared with nondepleting therapies, patients who received macrophage-depleting immunotherapy, had higher blood pressure and worse endothelial function.

Franck G, Even G, Gautier A, et al. Haemodynamic stress-induced breaches of the arterial intima trigger inflammation and drive atherogenesis. *Eur Heart J.* 2019;40(11):928-937.

Inflammation contributes to the generation of atherogenesis; however, it is unclear how mechanical wounding, such as erythrocyte infiltration into the subintimal space, contributes to inflammation and subsequent atherogenesis. This study used histology, immunofluorescence, high-resolution episcopic microscopy, and scanning electron microscopy on human coronary samples from explanted hearts to investigate the role of hemodynamic stress-induced endothelial breaches in triggering inflammation-driven atherogenesis. Human coronary samples showed signs of blood entry (detected by the presence of iron, ferritin, and glycophorin A) in the subintimal space. This study shows that hemodynamic forces trigger endothelial breaches, which allows for erythrocyte infiltration, leading to accumulation of iron and formation of lipid droplets and cholesterol crystals, followed by an increase in cell adhesion molecules on the endothelial cells, thus triggering the inflammation with granulocyte recruitment and the formation of fatty streaks at the site of intimal wounding.

Holmqvist F, Kesek M, Englund A, et al. A decade of catheter ablation of cardiac arrhythmias in Sweden: ablation practices and outcomes. *Eur Heart J.* 2019;40(10):820-830.

Based on data from controlled trials and single-center experiences, catheter ablation has become the treatment of choice for tachyarrhythmias; however, there is a paucity of convincing real-world efficacy and safety data. This study used data from a national population-based registry in Sweden to study the type of arrhythmias treated, the procedural characteristics, and the efficacy and safety of treatment (n=26 642; mean age, 57 years; women, 38%). The types of ablations performed changed during the study period with a substantial increase in the procedure being performed for atrial fibrillation (+430%), ventricular tachycardia (+240%), and

premature ventricular contraction (+350%). Procedure and fluoroscopy time and radiation doses were reduced for all ablation types, especially for atrial fibrillation, ventricular tachycardia, and premature ventricular contraction. The overall event rate was low, with the highest rates being observed for atrial fibrillation (2.8%), ventricular tachycardia (4.5%), and premature ventricular contraction (3.4%); the most common adverse event was pericardial effusion and/or tamponade.

Kim TH, Yang PS, Yu HT, et al. Effect of hypertension duration and blood pressure level on ischaemic stroke risk in atrial fibrillation: nationwide data covering the entire Korean population. *Eur Heart J.* 2019;40(10):809-819.

While hypertension is an important risk factor for stroke in general, there is little information about the association between hypertension and the risk of ischemic stroke in patients with atrial fibrillation. This study used data from a national health claims database in Korea to assess this association in oral anticoagulant-naive nonvalvular atrial fibrillation patients (n=246 459; mean age, 61 years; women, 41.7%). The study end point was ischemic stroke, which was defined with any admission diagnosis of ischemic stroke with concomitant brain-imaging studies. A longer duration of hypertension was shown to be associated with an increased risk of ischemic stroke; however, strictly controlling systolic blood pressure can attenuate the risk of stroke.

Norrish G, Field E, Mcleod K, et al. Clinical presentation and survival of childhood hypertrophic cardiomyopathy: a retrospective study in United Kingdom. *Eur Heart J.* 2019;40(12):986-993.

While information on the epidemiology, etiology, and survival, along with morphological descriptions of the clinical phenotype at presentation for childhood hypertrophic cardiomyopathy is available, the effect of changing screening practices on the age of presentation, etiology, and survival from childhood hypertrophic cardiomyopathy has not been assessed. This retrospective, longitudinal multicenter cohort analyzed the clinical characteristics and outcomes of children diagnosed with hypertrophic cardiomyopathy (n=687; median age, 5.2 years; women, 36.8%). In infants, the common etiology was RASopathy or inborn errors of metabolism. The overall rates of mortality and sudden cardiac death have not changed, but they are higher in adults with hypertrophic cardiomyopathy.

Odening KE, Bodi I, Franke G, et al. Transgenic short-QT syndrome 1 rabbits mimic the human disease phenotype with QT/action potential duration shortening in the atria and ventricles and increased ventricular tachycardia/ventricular fibrillation inducibility. *Eur Heart J.* 2019;40(10):842-853.

Patients with the lethal genetic channelopathy short-QT syndrome 1 often develop early-onset atrial fibrillation, ventricular tachycardia, and sudden cardiac death; however, the information available about the mechanisms, triggers, and consequences for risk stratification is scarce. In addition, there is no available animal model to aide in the research efforts. Therefore, this project was designed to generate a rabbit model using oocyte-microinjection of β-myosin-heavy-chain-promoter-KCNH2/HERG-N588K constructs, to characterize the transgenic rabbits using in vivo ECG, electrophysiological studies, magnetic resonance imaging, and ex vivo action potential measurement, and to investigate electrical remodeling using patch clamp, real-time PCR, and western blots. The transgenic short-QT syndrome 1 rabbits were shown to mimic the human disease phenotype on all levels with shortened QT/action potential measurements and increased inducibility of ventricular tachycardia and ventricular fibrillation.

O'Shaughnessy MM, Liu S, Montez-Rath ME, Lafayette RA, Winkelmayer WC. Cause of kidney disease and cardiovascular events in a national cohort of US patients with end-stage renal disease on dialysis: a retrospective analysis. *Eur Heart J.* 2019;40(11):887-898.

The risk for cardiovascular events is increased in patients with end-stage renal disease; however, it is unknown whether this risk changes with different underlying causes of kidney failure. This retrospective population-based study used data from the United States Renal Data System registry to evaluate the extent that the cause of kidney disease is an independent contributor to the increased cardiovascular event risk (n=658 168; mean age, 54.3 years; women, 45.6%). The main cardiovascular outcome was a composite of first myocardial infarction, first ischemic stroke, or cardiovascular death, with the follow-up time starting on day 91 after dialysis initiation. High cardiovascular event rates were associated with patients with end-stage renal disease on dialysis; these rates vary significantly depending on the underlying cause of end-stage renal disease.

Raju H, Parsons S, Thompson TN, et al. Insights into sudden cardiac death: exploring the potential relevance of non-diagnostic autopsy findings. *Eur Heart J.* 2019;40(10):831-838.

Histological or structural abnormalities have been observed in patients with unexplained sudden cardiac death, including left ventricular hypertrophy, myocardial inflammatory infiltrates, noncritical coronary artery disease, idiopathic ventricular myocardial fibrosis, and cardiomegalyl; however, no evidence exists to explain the

autopsy findings. This cohort study compared demographic and histopathological characteristics of uncertain cardiac autopsy findings among unexplained sudden cardiac death cases (n=98; mean age, 27.5 years; women, 40%) and matched noncardiac premature deaths. Primary arrhythmia syndromes are the dominant familial cardiogenetic diagnoses among both uncertain sudden unexplained death and true sudden arrhythmic death syndrome cases. While nondiagnostic or uncertain histological findings are associated with sudden unexplained death, they cannot be considered causative.

Rodriguez P, Sassi Y, Troncone L, et al. Deletion of delta-like 1 homologue accelerates fibroblast-myofibroblast differentiation and induces myocardial fibrosis. *Eur Heart J.* 2019;40(12):967-978.

In patients with heart failure, myocardial fibrosis is a major determinant of clinical outcomes. Fibrosis is characterized by the accumulation of myofibroblasts. Delta-like homologue-1 (Dlk1), a gene that encodes a transmembrane protein in the epidermal growth factor–like family, is critical in the cell differentiation process; however, there is no information of about the role of this gene in the heart. This study used Dlk1-knockout mice to determine if Dlk1 is involved in the differentiation of cardiac fibroblasts into myofibroblasts and in the regulation of myocardial fibrosis. In the absence of Dlk1, the differentiation of fibroblasts into myofibroblasts occurred along with an increase in transforming growth factor β (TGF-β) signaling via a TGF-β/Smad3 pathway, leading to an increased expression of α-smooth muscle actin, lysyl oxidase, connective tissue growth factor, and tissue inhibitor of metalloproteinase-1. The increased TGF-β signaling leads to accumulation of myofibroblasts, deposition of collagen, activation of profibrotic markers, myocyte hypertrophy, and cardiac dysfunction. This study shows, for the first time, that Dlk1 negatively regulates the differentiation of cardiac fibroblasts into myofibroblasts by interfering with TGFβ/Smad-3 signaling in the myocardium.

Shah R, Wilkins E, Nichols M, et al. Epidemiology report: trends in sex-specific cerebrovascular disease mortality in Europe based on WHO mortality data. *Eur Heart J.* 2019;40(9):755-764.

Mortality due to cerebrovascular disease has declined across Europe; however, no study has analyzed the trends in cerebrovascular disease and its subtypes within all European countries. This study used sex-specific mortality data to analyze sex-specific trends in cerebrovascular disease, as well as the subtypes of ischemic stroke, hemorrhagic stroke, and subarachnoid hemorrhage in Europe. The incidence of hemorrhagic stroke has been plateauing, whereas ischemic stroke mortality has been increasing. More research is needed on the inequalities in current stroke mortality outcomes and trends; in addition, the causes behind any recent plateauing of total cerebrovascular disease or its subtypes needs to be studied further. ■

April 2019

Chua W, Purmah Y, Cardoso VR, et al. Data-driven discovery and validation of circulating blood-based biomarkers associated with prevalent atrial fibrillation. *Eur Heart J.* 2019;40(16):1268-1276.

Systematic screening for atrial fibrillation is warranted, especially in at-risk populations; however, clinical risk factors associated with atrial fibrillation are only modest in their ability to predict atrial fibrillation. Blood biomarkers could be useful in screening for atrial fibrillation, but studies to date have only analyzed one or a few at a time. This study quantified 40 cardiovascular biomarkers in patients with atrial fibrillation or two or more CHA2DS2-VASc risk factors (n=720). In addition, the study used logistic regression with forward selection and machine-learning algorithms to determine clinical risk factors, imaging parameters, and biomarkers associated with atrial fibrillation. Atrial fibrillation was associated with three clinical risk factors (ie, age, male sex, and body mass index) and three biomarkers (ie, increased brain natriuretic peptide, increased fibroblast growth factor-23, and reduced tumor necrosis factor–related apoptosis-induced ligand-receptor 2).

Diller GP, Kempny A, Babu-Narayan SV, et al. Machine learning algorithms estimating prognosis and guiding therapy in adult congenital heart disease: data from a single tertiary centre including 10 019 patients. *Eur Heart J.* 2019;40(13):1069-1077.

Considering that it is very complicated and time consuming to create a risk-stratification model for adult patients with congenital heart disease, machine-learning options may be the best option available. This retrospective study tested whether machine-learning algorithms would have comparable accuracy with manual data mining in terms of categorizing patients into diagnostic subgroups, disease complexity subsets, and functional classes (n=10 019; mean age, 36.3 years; women, 49%). The study showed that the machine-learning algorithms were useful for estimating prognosis and as a potential aid to guide therapy in this group of patients.

Markovitz AR, Stuart JJ, Horn J, et al. Does pregnancy complication history improve cardiovascular disease risk prediction? Findings from the HUNT study in Norway. *Eur Heart J.* 2019;40(14):1113-1120.

Some data is available suggesting that pregnancy complications, such as pre-eclampsia, gestational hypertension, preterm delivery, or small for gestational age, are risk factors for cardiovascular disease in women. Therefore, this population-based, prospective cohort study linked data from the HUNT1 and HUNT2

studies with the Medical Birth Registry of Norway, validated hospital records, and the Norwegian Cause of Death Registry to determine whether adding pregnancy complications to the NORRISK 2 risk prediction model would improve the fit, calibration, discrimination, and reclassification of the model for parous women (n=26 544; mean age, 52 years). The cardiovascular end points were nonfatal myocardial infarction, fatal coronary heart disease, and nonfatal or fatal stroke. Adding pregnancy complications to the NORRISK 2 risk prediction model did not improve the 10-year cardiovascular disease risk prediction.

Redfors B, Dworeck C, Haraldsson I, et al. Pretreatment with P2Y12 receptor antagonists in ST-elevation myocardial infarction: a report from the Swedish Coronary Angiography and Angioplasty Registry. *Eur Heart J.* 2019;40(15):1202-1210.
Despite a lack of evidence, the guidelines support pretreating patients with ST-segment elevation myocardial infarction with P2Y12 receptor antagonists. The Swedish Coronary Angiography and Angioplasty Registry investigated associations between pretreatment with P2Y12 receptor antagonists and the risk of adverse outcomes (n=44 804; mean age, 67.5 years; women, 29%). The primary end point was all-cause death within 30 days. The registry showed that pretreating patients with ST-segment elevation myocardial infarction with P2Y12 receptor antagonists did not improve clinical outcomes.

Saw J, Starovoytov A, Humphries K, et al. Canadian spontaneous coronary artery dissection cohort study: in-hospital and 30-day outcomes. *Eur Heart J.* 2019;40(15):1188-1197.
While spontaneous coronary artery dissection (SCAD) is an important cause of myocardial infarction, it has been underdiagnosed and poorly understood. This multicenter, prospective, observational study investigated the natural history of nonatherosclerotic spontaneous coronary artery dissection. The study collected data on baseline demographics, in-hospital characteristics, precipitating/predisposing conditions, angiographic features, in-hospital major adverse events, and 30-day major adverse cardiovascular events (n=750; mean age, 51.8 years; women, 88.5%). Spontaneous coronary artery dissection predominantly affects women and presents with myocardial infarction. Survival is good with conservative treatment, but significant cardiovascular complications occurred within 30 days.

Shehata N, Mistry N, da Costa BR, et al. Restrictive compared with liberal red cell transfusion strategies in cardiac surgery: a meta-analysis. *Eur Heart J.* 2019;40(13):1081-1088.
Anemia is common in patients undergoing cardiac surgery, but it is not clear whether a restrictive strategy of red blood cell transfusion at lower hemoglobin concentrations is inferior to a liberal strategy at higher hemoglobin concentrations.

Therefore, this systematic review, meta-analysis, and trial performed a sequential analysis of randomized controlled trials comparing restrictive and liberal red blood cell transfusion strategies (n=9092). The primary outcome was mortality within 30 days of surgery. Restrictive transfusion strategies did not result in a statistically significant increase in the risk of mortality within 30 days of surgery, myocardial infarction, renal failure, stroke, infections, or arrhythmias; however, these strategies reduced the patients' exposure to red blood cells.

Tikkanen E, Gustafsson S, Knowles JW, Perez M, Burgess S, Ingelsson E. Body composition and atrial fibrillation: a Mendelian randomization study. *Eur Heart J.* 2019;40(16):1277-1282.

Some studies have indicated that obesity, as well as a higher fat-free mass, ie, having mostly muscle mass, is associated with an increased risk of atrial fibrillation. However, there is no information on whether these associations are independent causal processes. This observational and Mendelian randomization analysis was conducted to understand the independent causal roles of fat-free mass and fat mass on atrial fibrillation (n=502 619; mean age, 56.5 years; women, 54%). Increases in fat-free mass and fat mass independently cause an increased risk of atrial fibrillation, with the association with atrial fibrillation being stronger with fat-free mass. The association between fat-free mass and atrial fibrillation was similar in both sexes; however, the association between fat mass and atrial fibrillation was stronger in women than in men.

Wu J, Hall M, Dondo TB, et al. Association between time of hospitalization with acute myocardial infarction and in-hospital mortality. *Eur Heart J.* 2019;40(15):1214-1221.

The time of day that patients present to the hospital have been shown to affect mortality rates; however, no studies have assessed whether there is an association between time of hospitalization and in-hospital mortality for patients with an acute myocardial infarction. This study used data from MINAP, a countrywide acute coronary syndrome registry in England and Wales, to determine if there is a correlation between time of hospitalization and in-hospital mortality (n=615 035; mean age, 70 years; women, 34%). The outcome measure was in-hospital mortality in patients with an acute myocardial infarction. The analysis showed that there was no significant difference between time of hospitalization and in-hospital mortality.

Xu T, Magnusson Hanson LL, Lange T, et al. Workplace bullying and workplace violence as risk factors for cardiovascular disease: a multi-cohort study. *Eur Heart J.* 2019;40(14):1124-1134.

This multicohort study assessed the association between bullying and violence at work and cardiovascular disease in working men and women aged 18-65 years who were free of cardiovascular disease from three cohort studies from Sweden and Denmark. Exposure to workplace bullying and violence was measured at baseline using self-reports. The study assessed incident cardiovascular disease, including coronary heart disease and cerebrovascular disease (n=79 201; mean age, 43.3 years; women, 53%). Bullying and violence are stressors that put people are at higher risk of cardiovascular disease. ■

May 2019

Asami M, Windecker S, Praz F, et al. Transcatheter aortic valve replacement in patients with concomitant mitral stenosis. *Eur Heart J.* 2019;40(17):1342-1351.

While a recent analysis of the STS/ACC/TVT registry showed that mitral stenosis occurred in 11.6% of patients undergoing transcatheter aortic valve replacement and that there was an association between severe mitral stenosis and increased mortality, the analysis did not investigate the impact of disease etiology on clinical outcomes. This study performed a retrospective analysis of prospectively acquired echocardiographic data to analyze the impact of mitral stenosis on clinical outcomes in patients undergoing transcatheter aortic valve replacement for aortic stenosis and determine if the etiology of mitral stenosis leads to different effects on clinical outcomes (n=971; mean age, 82.2 years; women, 49.3%). The primary end point was cardiovascular death within 1 year after transcatheter aortic valve replacement. At 30 days postprocedure, patients with mitral stenosis had a higher risk of cardiovascular death, disabling stroke, and the Valve Academic Research Consortium 2 early composite safety end point (ie, composite of all-cause mortality, all stroke, life-threatening bleeding, acute kidney injury, coronary artery obstruction requiring intervention, major vascular complication, valve-related dysfunction requiring repeat procedure). One year after the procedure, patients with mitral stenosis had a higher risk of cardiovascular death and disabling stroke.

Bekeredjian R, Szabo G, Balaban Ü, et al. Patients at low surgical risk as defined by the Society of Thoracic Surgeons Score undergoing isolated interventional or surgical aortic valve implantation: in-hospital data and 1-year results from the German Aortic Valve Registry (GARY). *Eur Heart J.* 2019;40(17):1323-1330.

Transcatheter aortic valve implantation has been established for the treatment of patients with severe aortic valve stenosis who are inoperable or at a high surgical risk. In 2017, its use was expanded to patients with intermediate risk; however, patients as low surgical risk are still recommended to undergo surgical aortic valve replacement. This study analyzed data from the GARY registry, the largest, prospective, multicenter registry to monitor the safety and efficacy of interventional and surgical aortic valve procedures in Germany, to compare transcatheter aortic valve implantation with surgical aortic valve replacement in low-risk patients (patients with a Society of Thoracic Surgeons score <4%) (n=20 549; mean age, 70.84 years; women, 37.1%). The major end point was survival (in-hospital, 30-day, and 1-year survival). In a weighted comparison, the 1-year survival rates were similar between the two procedures, with a higher in-hospital survival for patients undergoing transcatheter aortic valve implantation. The 30-day survival data were similar to the in-hospital survival data.

Boriani G, Ruff CT, Kuder JF, et al. Relationship between body mass index and outcomes in patients with atrial fibrillation treated with edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial. *Eur Heart J.* 2019;40(19):1541-1550.

The prevalence of obesity in patients with atrial fibrillation is very high; however, according to a retrospective analysis of the AFFIRM trial, obese patients with atrial fibrillation had a better survival rate, even though the risk of mortality increases with increasing body mass index in the general population. In addition, body mass index is not a major risk factor for bleeding or stroke in patients with atrial fibrillation; therefore, this study set out to analyze the relationship between body mass index and pharmacokinetic, pharmacodynamic, and clinical outcomes in patients with atrial fibrillation who were enrolled in the ENGAGE AF-TIMI 48 trial, a three-group, randomized, double-blind, double-dummy study that compared two dose regimens of edoxaban with warfarin (n=21 028; median age, 71; women, 43.6%). While higher body mass index was significantly and independently associated with lower risks of stroke/systemic embolic events, ischemic stroke/systemic embolic events, and death, it was associated with an increased risk of major and major or clinically relevant non-major bleeding.

Bouchareb R, Boulanger MC, Tastet L, et al. Activated platelets promote an osteogenic programme and the progression of calcific aortic valve stenosis. *Eur Heart J.* 2019;40(17):1362-1373.

During calcific aortic valve stenosis, there is an increase in circulating platelet-derived microparticles; however, it is uncertain what role platelets have in calcific aortic valve stenosis. This study used scanning electron microscopy and functional assays in isolated human valve interstitial cells and platelets and in LDLR−/−/ApoB100/100/IGFII (on a C57Bl/6J mouse background) mice to investigate the role of platelets in the pathobiology of calcific aortic valve stenosis. Platelet aggregates with fibrin were present in endothelium-denuded areas of calcific aortic valve stenosis, and, in isolated valve interstitial cells, collagen-activated platelets induced an osteogenic program and progression of calcific aortic valve stenosis by activating the purinergic receptor P2Y1-glycoprotein IIb/IIIa-LysoPA pathway. In IGFII mice with calcific aortic valve stenosis, treatment with activated platelets accelerated the development of calcific aortic valve stenosis, whereas treatment with Ki16425, a LysoPA receptor antagonist, prevented the progression of calcific aortic valve stenosis. These results demonstrate that platelet activation promotes progression of calcific aortic valve stenosis.

Chao TF, Chen SA, Ruff CT, et al. Clinical outcomes, edoxaban concentration, and anti-factor Xa activity of Asian patients with atrial fibrillation compared with non-Asians in the ENGAGE AF-TIMI 48 trial. *Eur Heart J.* 2019;40(19):1518-1527.

The risks of ischemic stroke and bleeding in Asian patients with atrial fibrillation may be higher than that of non-Asians patients with atrial fibrillation. The ENGAGE AF-TIMI 48 trial analyzed the clinical outcomes, edoxaban concentrations, and anti-factor Xa activity between Asian and non-Asian patients (n=21 104; mean age, 69.8 years; women, 35.8%). The trough levels of edoxaban concentration and anti-FXa activity were also compared and correlated with the efficacy and safety of edoxaban vs warfarin. Asian patients treated with warfarin had a higher-adjusted risk of intracranial hemorrhage than non-Asian patient, but the rate of ischemic stroke was similar between the groups. The trough edoxaban concentration and anti-factor Xa activity were lower for Asian patients than for non-Asian patients. Compared with warfarin, higher doses of edoxaban were associated with preserved efficacy for stroke prevention and a favorable safety profile for Asian patients.

Chao TF, Lip GYH, Lin YJ, et al. Age threshold for the use of non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with atrial fibrillation: insights into the optimal assessment of age and incident comorbidities. *Eur Heart J.* 2019;40(19):1504-1514.

The risk of stroke is high in patients with atrial fibrillation; however, when the risk of stroke is assessed, age and comorbidities are determined at baseline and

outcomes later. This method of assessing risk does not account for the accumulation of comorbidities as the patient ages. This study analyzed three methods of assessing stroke–dynamic, ideal, and conventional–and attempted to report the age-treatment thresholds for the use of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation without or with only one comorbidity from the CHA2DS2-VASc score, based on an "ideal method" of stroke risk assessments (n=70 059; mean age, 67.7 years; women, 42.2%). Despite having the same CHA2DS2-VASc score, the age thresholds for using NOACs differed depending on the comorbidities among patients with atrial fibrillation, ie, the age threshold in patients with atrial fibrillation was 35 for those with heart failure, 50 years for those with hypertension or diabetes, and 55 years for those with vascular diseases.

Chen K, Breitner S, Wolf K, et al; KORA Study Group. Temporal variations in the triggering of myocardial infarction by air temperature in Augsburg, Germany, 1987-2014. *Eur Heart J.* 2019;40(20):1600-1608.

Epidemiological studies have shown that exposure to high and low temperatures increased morbidity and mortality in patients with cardiovascular disease; however, there has been no information available about the effect of temperature in patients with myocardial infarction. Therefore, this time-stratified, case-crossover study used data from the MONICA/KOR MI registry, a population-based myocardial infarction registry in Germany, to determine if short-term temperature exposure was associated with the occurrence of myocardial infarction (n=27 310; mean age, 62.5 years; women, 27%). Over the 28-year period, there was a nonsignificant decrease in cold-related myocardial infarction risks and a significant increase in heat-related myocardial infarction relative risks. The increase in heat-related myocardial infarction relative risks was even more pronounced in patients with diabetes mellitus and hyperlipidemia.

Costopoulos C, Timmins LH, Huang Y, et al. Impact of combined plaque structural stress and wall shear stress on coronary plaque progression, regression, and changes in composition. *Eur Heart J.* 2019;40(18):1411-1422.

Atherosclerotic plaques are subject to both plaque structural stress and wall shear stress. However, studies have not assessed whether there is an association between plaque structural stress and plaque development or assessed how wall shear stress affects plaque composition or how different wall shear stress and plaque structural stress are associated with changes within the plaque or in their development. This study used virtual-histology intravascular ultrasound and biplane coronary angiography in patients with typical angina with nonstenotic, but significant coronary lesions in the left anterior descending artery to assess the association between plaque structural stress and wall shear stress and both plaque

development and plaque composition (n=40; mean age, 53.4 years; women, 47%). High plaque structural stress was associated with an increase in the necrotic core and a larger decrease in fibrous tissue and fibrofatty tissue in the entire cohort, and there was no change in plaque burden or plaque area in areas with either progression or regression. High wall shear stress was associated with a decrease in plaque burden and plaque area and a decrease in fibrous tissue and fibrofatty tissue, with a larger decrease in fibrous tissue, in the entire cohort.

Letnes JM, Dalen H, Vesterbekkmo EK, Wisløff U, Nes BM. Peak oxygen uptake and incident coronary heart disease in a healthy population: the HUNT Fitness Study. *Eur Heart J.* 2019;40(20):1633-1639.

Cardiorespiratory fitness is associated with all-cause and cardiovascular mortality, but it is typically predicted from submaximal or peak workload on a treadmill or cycle ergometer and not by using cardiopulmonary exercise testing with a direct gas-analysis of peak oxygen uptake. The HUNT3 Fitness study, a substudy of the HUNT3 study, assessed the associateion of peak oxygen uptake and fatal or nonfatal coronary heart disease events or coronary revascularization in a low-risk cohort (n=4527; mean age, 48.2 years; women, 51%). The primary end point was diagnosis of or death from coronary heart disease or coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), whichever came first. Peak oxygen uptake was associated with coronary heart disease across the fitness continuum.

Oldgren J, Steg PG, Hohnloser SH, et al. Dabigatran dual therapy with ticagrelor or clopidogrel after percutaneous coronary intervention in atrial fibrillation patients with or without acute coronary syndrome: a subgroup analysis from the RE-DUAL PCI trial. *Eur Heart J.* 2019;40(19):1553-1562.

The RE-DUAL PCI trial showed that the risk of major or clinically relevant nonmajor bleeding events was reduced with dabigatran (both 110 mg and 150 mg) dual therapy without aspirin, with noninferiority for overall thromboembolic events with dabigatran dual therapy compared with warfarin triple therapy with both aspirin and a P2Y12 inhibitor. In this subgroup analysis of the RE-DUAL PCI trial, a prospective, randomized, open-label study, the safety and efficacy of dabigatran dual antithrombotic therapy (dabigatran [110 mg and 150 mg] plus a P2Y12 inhibitor) was compared with warfarin triple therapy (warfarin plus a P2Y12 inhibitor plus aspirin) (n=2725; mean age, 70.75 years; women, 24%). The primary end point was major or clinically relevant non-major bleeding events. Compared with warfarin triple therapy, the benefits of both dabigatran 110 mg and 150 mg dual therapy in reducing bleeding risks were consistent across subgroups of patients with or without acute coronary syndromes, as well as patients treated with ticagrelor or clopidogrel.

Østergaard L, Valeur N, Wang A, et al. Incidence of infective endocarditis in patients considered at moderate risk. *Eur Heart J.* 2019;40(17):1355-1361.
Risk stratification is important for patients who are at risk for infective endocarditis; however, not much work has been done to characterize the moderate risk group. To address this unmet need, this study used nationwide registries from Denmark to determine the incidence of infective endocarditis in patients thought to be at a moderate risk for infective endocarditis (ie, patients with acquired valvular dysfunction [aortic stenosis or aortic regurgitation, mitral stenosis, regurgitation, or prolapse, and rheumatic heart disease], patients with hypertrophic cardiomyopathy, and patients with a cardiac implantable electronic device (n=137 901; median age, 71.1; women, 37.7%). When compared with a control population, moderate-risk individuals with valve disorder, a cardiac implantable electronic device, and hypertrophic cardiomyopathy have a higher risk of infective endocarditis, but this risk was lower for all three categories when compared with high-risk patients.

Reeh J, Therming CB, Heitmann M, et al. Prediction of obstructive coronary artery disease and prognosis in patients with suspected stable angina. *Eur Heart J.* 2019;40(18):1426-1435.
The ESC guidelines recommend using the updated Diamond–Forrester prediction model; however, this study tested the hypothesis that this model overestimates the probability of coronary artery disease. This retrospective, observational study of patients undergoing noninvasive testing or invasive coronary angiography for stable coronary artery disease to determine the prevalence of obstructive coronary artery disease in the Diamond–Forrester risk categories and to develop and test a new model (n=3903; mean age, 57.9 years; 55.5%). The prognostic end point was a composite of all-cause mortality, myocardial infarction, unstable angina, heart failure, and ischemic stroke. The Diamond–Forrester prediction model was shown to overestimate the likelihood of coronary artery disease. The new prediction model was able to identify patient subgroups with a low likelihood of obstructive coronary artery disease and good prognosis.

Seeger J, Kapadia SR, Kodali S, et al. Rate of peri-procedural stroke observed with cerebral embolic protection during transcatheter aortic valve replacement: a patient-level propensity-matched analysis. *Eur Heart J.* 2019;40(17):1334-1340.
As a result of randomized trials not being sufficiently powered to analyze stroke reduction, the role of cerebral embolic protection in transcatheter aortic valve replacement is controversial. This patient-level pooled analysis of data from the SENTINEL US IDE trial, CLEAN TAVI study, and SENTINEL-Ulm study was designed to validate the impact of the dual-filter cerebral embolic protection device on periprocedural stroke in transcatheter aortic valve replacement patients (n=1066; mean age, 81.1 years; women, 52.9%). The primary end point was procedural stroke within

72 hours after a transcatheter aortic valve replacement. Compared with unprotected procedures, transcatheter aortic valve replacement with the dual-filter cerebral embolic protection device significantly lowered the rate of periprocedural stroke.

Sorbets E, Steg PG, Young R, et al; CLARIFY Investigators. β-blockers, calcium antagonists, and mortality in stable coronary artery disease: an international cohort study. *Eur Heart J.* 2019;40(18):1399-1407.

While β-blockers and calcium antagonists are recommended for the treatment of angina in patients with stable coronary disease, there is no data for calcium antagonists concerning a benefit on mortality and only a few trials showing that calcium antagonists have a benefit on cardiovascular morbidity in patients with stable coronary artery disease. The CLARIFY registry, a prospective observational longitudinal registry of patients with stable coronary artery disease, was designed to assess the association between the use of β-blockers or calcium antagonists and clinical outcomes (n=44 010; mean age, 64.4 years; women, 77.5%). The primary outcome was all-cause mortality. β-Blockers were associated with a lower 5-year mortality rate, but only in patients who were enrolled in the year following a myocardial infarction; however, calcium antagonists were not associated with superior mortality reductions, with or without a history of myocardial infarction.

Tesarz J, Eich W, Baumeister D, Kohlmann T, D'Agostino R, Schuster AK. Widespread pain is a risk factor for cardiovascular mortality: results from the Framingham Heart Study. *Eur Heart J.* 2019;40(20):1609-1617.

Etiological associations of widespread pain, a new separate diagnostic code in the ICD-11, and cardiovascular diseases have been shown in studies; however, studies on mortality risk in individuals with widespread pain have reported inconsistent results. The Framingham Heart Study, a longitudinal multigenerational study, evaluated whether there was an increase in mortality in a large population-based cohort with widespread pain (n=4689; mean age, 60.3 years; women, 55.1%). Hazard ratios for widespread pain were calculated for all-cause mortality, controlling for sex and age, cardiovascular risk factors, cancer history, lifestyle factors, and current medication. Widespread pain was associated with higher hazard ratios for cardiovascular causes of death.

Wang C, Bangdiwala SI, Rangarajan S, et al. Association of estimated sleep duration and naps with mortality and cardiovascular events: a study of 116 632 people from 21 countries. *Eur Heart J.* 2019;40(20):1620-1629.

Sleep is regarded as an important lifestyle behavior that can affect the risk of cardiovascular disease and death; however, studies provide conflicting results due the difficulty in objectively measuring sleep. Therefore, this large-scale, in-

ternational prospective cohort study estimated total sleep duration based on the amount of time spent in bed and daytime nap duration based on self-reported time to assess whether there was an association between total daily total daily sleep duration and daytime nap duration with death and major cardiovascular events (n=116 632; mean age, 50.7 years; women, 41.5%). The primary outcome was time to all-cause mortality plus major cardiovascular events, ie, fatal cardiovascular events and nonfatal myocardial infarction, stroke, and heart failure. Sleeping ≤6 hours per day and >8 hours per day were associated with an increased risk of the composite outcome and daytime nap duration was associated with an increased risk of the composite outcome when nighttime sleep duration was >6 hours, but not when the nighttime sleep duration was ≤6 hours.

Wang KL, Lopes RD, Patel MR, et al. Efficacy and safety of reduced-dose non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: a meta-analysis of randomized controlled trials. *Eur Heart J.* 2019;40(19):1492-1500.

Non-vitamin K antagonist oral anticoagulants (NOACs) have a favorable benefit-harm profile in patients with atrial fibrillation; however, depending on patient or clinical factors, dose reductions are required. This meta-analysis was conducted to evaluate the efficacy and safety of reduced-dose NOACs vs warfarin and to understand if the effects of low-dose NOACs were different from the effects of full-dose NOACs in patients with atrial fibrillation (n=46 426; mean age, 75 years; women, 44%). The primary outcomes of interest were stroke or systemic embolism and major bleeding. Compared with patients eligible for full-dose NOACs, the risk of thromboembolic and hemorrhagic complications was greater for patients eligible for reduced-dose NOACs. After proper dose adjustments, the benefit-harm profile, when compared with warfarin, was improved for NOACs.

Yu HT, Shim J, Park J, et al. When is it appropriate to stop non-vitamin K antagonist oral anticoagulants before catheter ablation of atrial fibrillation? A multicentre prospective randomized study. *Eur Heart J.* 2019;40(19):1531-1537.

A recent expert consensus statement recommends periprocedural uninterrupted non-vitamin K antagonist oral anticoagulants during catheter ablation for atrial fibrillation, although there have been no clear randomized trials. This prospective, open-label, randomized, multicenter trial evaluated the safety and efficacy of uninterrupted, single-dose skipped, and 24-hour skipped non-vitamin K antagonist oral anticoagulants in patients scheduled for atrial fibrillation catheter ablation (n=326; mean age, 58.3 years; women, 25.5%). The primary end point was the incidence of bleeding events within 1 month after ablation. The efficacy and safety between the three types of non-vitamin K antagonist oral anticoagulants in this study were comparable. ■

June 2019

Ameloot K, De Deyne C, Eertmans W, et al. Early goal-directed haemodynamic optimization of cerebral oxygenation in comatose survivors after cardiac arrest: the Neuroprotect post-cardiac arrest trial. *Eur Heart J.* 2019;40(22):1804-1814.
Observational studies have shown that there is an association between higher mean arterial pressure or the absence of hypotension and better functional outcomes in patients after a cardiac arrest. To confirm these observational results, the Neuroprotect post–cardiac arrest trial, a multicenter, randomized, parallel-group, open-label, assessor-blinded, monitored, and investigator-driven clinical trial, tested whether an early goal directed hemodynamic optimization strategy targeting a higher mean arterial pressure within 36 hours of cardiac arrest would reduce anoxic brain damage (n=107; mean age, 64 years; women, 25%). The primary outcome was the extent of anoxic brain damage. While targeting a higher mean arterial pressure is safe and improves cerebral oxygenation, it does not improve anoxic brain damage.

Aradi D, Gross L, Trenk D, et al. Platelet reactivity and clinical outcomes in acute coronary syndrome patients treated with prasugrel and clopidogrel: a pre-specified exploratory analysis from the TROPICAL-ACS trial. *Eur Heart J.* 2019;40(24):1942-1951.
Several nonrandomized and observational studies have shown that patients with high platelet reactivity on clopidogrel have a higher risk of ischemic complications and patients with low platelet reactivity have a higher risk of bleeding; however, there is uncertainty around using platelet function testing to predict clinical outcomes. This prespecified substudy of TROPICAL-ACS, an investigator-initiated, randomized, parallel-group, open-label, assessor-blinded, multicenter trial in patients with biomarker positive acute coronary syndrome undergoing percutaneous coronary intervention, assessed the association between high platelet reactivity, low platelet reactivity, and clinical outcomes between patients receiving prasugrel and platelet function testing–guided clopidogrel or prasugrel (n=1261; mean age, 58.41 years; women, 21.7%). The composite ischemic end point was cardiovascular death, myocardial infarction, or stroke. The outcomes were similar between the two groups; in addition, low platelet reactivity was shown to be a strong and independent predictor of bleeding.

Ben-Yehuda O, Chen S, Redfors B, et al. Impact of large periprocedural myocardial infarction on mortality after percutaneous coronary intervention and coronary artery bypass grafting for left main disease: an analysis from the EXCEL trial. *Eur Heart J.* 2019;40(24):1930-1941.

Despite many studies, the prognostic implications of periprocedural myocardial infarction after percutaneous coronary intervention and coronary artery bypass grafting are uncertain. This prespecified analysis of the EXCEL trial, a large-scale, contemporary, multicenter, prospective, randomized trial on patients with and without periprocedural myocardial infarction undergoing left main coronary artery intervention randomized to percutaneous coronary intervention with everolimus-eluting stents vs coronary artery bypass grafting, assessed: (i) the 3-year prognosis; (ii) whether the prognosis varied with the treatment modality; and (iii) the relationship between creatinine kinase-MB thresholds and mortality (n=1858; mean age, 65.5 years; women, 75.3%). Periprocedural myocardial infarction was associated with cardiovascular and all-cause death at 3 years and it was more common after coronary artery bypass grafting than after percutaneous coronary intervention.

Cadrin-Tourigny J, Bosman LP, Nozza A, et al. A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J.* 2019;40(23):1850-1858.

As patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC) have a predisposition to ventricular arrhythmias and sudden cardiac death and as studies have been limited by small patient populations, this observational, retrospective, longitudinal cohort study was designed to help develop a model to predict incident ventricular arrhythmias and sudden cardiac death in patients with ARVC (n=528; mean age, 38.16 years; women, 55.3%). The primary study outcome was the first sustained ventricular arrhythmia, ie, a composite of the occurrence of sudden cardiac death, sudden cardiac arrest, spontaneous sustained ventricular tachycardia, ventricular fibrillation/flutter, or appropriate implantable cardioverter-defibrillator intervention. The model developed was shown to accurately distinguish patients who had incident sustained ventricular arrhythmia from those who did not.

Chen L, Song J, Chen X, et al. A novel genotype-based clinicopathology classification of arrhythmogenic cardiomyopathy provides novel insights into disease progression. *Eur Heart J.* 2019;40(21):1690-1703.

As patients with arrhythmogenic cardiomyopathy display a large heterogeneity in the clinical, genetic, and pathological presentations, this study used explanted hearts (n=60) from patients with arrhythmogenic cardiomyopathy to assess their clinical characteristics, genotype, cardiac magnetic resonance imaging, and pathology to provide comprehensive information on end-stage arrhythmogenic cardiomyopathy. Using unsupervised clustering, this study was able to generate a new pathological classification with distinct genotypes that indicated different potential mechanisms.

García-Fernández FJ, Osca Asensi J, Romero R, et al; RM-ALONE Trial Investigators. Safety and efficiency of a common and simplified protocol for pacemaker and defibrillator surveillance based on remote monitoring only: a long-term randomized trial (RM-ALONE). *Eur Heart J.* 2019;40(23):1837-1846.

Remote monitoring in patients with cardiac implantable electronic devices is noninferior to conventional follow-up, reduces the time for a clinical decision, can prevent worsening conditions in using only remote interrogation, and reduces inappropriate shocks. The RM-ALONE trial, a prospective, randomized, multicenter clinical trial, assessed the safety and efficiency of remote monitoring for the surveillance of cardiac implantable electronic devices in patients with pacemakers and implantable cardiac defibrillators (n=294; mean age, 72.7 years; women, 35.7%). The primary safety objective was noninferiority of following up cardiac implantable electronic devices with a single remote protocol of remote interrogation every 6 months in addition to remote monitoring compared with face-to-face visits every 6 months plus remote monitoring follow-up. The RM-ALONE protocol of remote monitoring plus remote interrogation demonstrated noninferiority to face-to-face visits plus remote monitoring.

Herring N, Tapoulal N, Kalla M, et al; OxAMI Study. Neuropeptide-Y causes coronary microvascular constriction and is associated with reduced ejection fraction following ST-elevation myocardial infarction. *Eur Heart J.* 2019;40(24):1920-1929.

During prolonged sympathetic activation, the cotransmitter neuropeptide-Y (NPY) is released, leading to vasoconstriction in many vascular beds. NPY is elevated in patients undergoing a primary percutaneous coronary intervention after an ST-segment elevation myocardial infarction. This study tested the hypothesis that myocardial NPY levels are correlated with reperfusion and subsequent recovery following primary percutaneous coronary intervention by trying to determine if and how NPY constricts the coronary microvasculature (n=109; mean age, 65 years; women, 28%). Patients with the highest coronary sinus levels of NPY had a signifi-

cantly lower coronary flow reserve and a higher microvascular resistance index; in addition, they had significantly higher myocardial edema and microvascular obstruction and significantly lower ejection fractions and ventricular dilatation.

Kojima S, Matsui K, Hiramitsu S, et al. Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy. *Eur Heart J.* 2019;40(22):1778-1786.

The recent FEATHER cohort study on patients with hyperuricemia showed no differences in the risk of all-cause death and cardiovascular events between febuxostat and allopurinol; however, the CARES randomized trial showed that febuxostat increased all-cause mortality and cardiovascular mortality compared with allopurinol. The FREED study, an investigator-initiated, multicenter, prospective, randomized open-label, blinded end point, two-arm parallel treatment groups study, aimed to determine the occurrence of cerebral, cardiovascular, and renal events in elderly patients with hyperuricemia who were at risk for cerebral, cardiovascular, or renal disease with febuxostat vs conventional therapy with lifestyle modifications (n=1070; mean age, 75.7 years; women, 30.9%). The primary composite end point was fatal and nonfatal cerebral, cardiovascular, and renal events, and death other than cerebral or cardiorenal vascular disease during the study period. Febuxostat significantly lowered the levels of serum uric acid, which in turn was associated with a clear reduction in renal events.

Nazerian P, Mueller C, Vanni S, et al. Integration of transthoracic focused cardiac ultrasound in the diagnostic algorithm for suspected acute aortic syndromes. *Eur Heart J.* 2019;40(24):1952-1960.

Diagnosing acute aortic syndromes is difficult especially considering that the imaging tests required for a conclusive diagnosis cannot be performed in all patients for several reasons. The ESC has suggested that transthoracic echocardiography, particularly focused cardiac ultrasound (FoCUS), is an appropriate first-line imaging technique; however, FoCUS needs proper validation. This prespecified subanalysis of the ADvISED study, a multicenter, prospective, diagnostic accuracy study, of patients with suspected acute aortic syndromes who underwent FoCUS for detection of direct/indirect signs of acute aortic syndromes was designed to provide field validation of FoCUS (n=839; mean age, 62 years; women, 35.6%). The analysis showed that FoCUS had an additive value when assessing for acute aortic syndromes and the direct FoCUS signs can identify patients requiring advanced imaging tests.

Olsen T, Jørgensen OD, Nielsen JC, Thøgersen AM, Philbert BT, Johansen JB. Incidence of device-related infection in 97 750 patients: clinical data from the complete Danish device-cohort (1982-2018). *Eur Heart J.* 2019;40(23):1862-1869.

Cardiac implantable electronic devices are used to treat cardiac arrhythmias safely and effectively; however, device-related infection is a severe complication that leads to high levels of morbidity and mortality, but the long-term incidence of device-related infections is unknown. This device cohort study investigated the long-term incidence rates of device-related infections for different types of cardiac implantable electronic devices (eg, pacemakers and implantable cardioverter-defibrillators) (n=97 732; median age, 70 years; women, 28.7%). The lowest incidence of device-related infections occurred with pacemakers, but the incidence was considerably higher for other types of devices. Several factors, such as implantation of complex devices (implantable cardioverter-defibrillators and cardiac resynchronization therapy), reoperations, prior device-related infections, male sex, and younger age, were associated with a higher risk of device-related infections.

Potts JE, Iliescu CA, Lopez Mattei JC, et al. Percutaneous coronary intervention in cancer patients: a report of the prevalence and outcomes in the United States. *Eur Heart J.* 2019;40(22):1790-1800.

While percutaneous coronary interventions are increasingly being used for coronary revascularization in multimorbid patients, ie, patients who are older, with more comorbidities and more extensive coronary artery disease, limited information is available concerning outcomes in patients with a coexistent diagnosis of cancer. This study analyzed data from the National Inpatient Sample for hospital discharges in the US to investigate the outcomes in patients who undergo percutaneous coronary intervention with a previous (n=224 128; median age, 73.8 years; women, 43.5%) or current (n=51 381; median age, 71.3 years; women, 42.6%) diagnosis of cancer or no cancer (n=6 086 339; median age, 64 years; women, 33.6%). The in-hospital clinical outcomes included in-hospital mortality, cardiac complications, postoperative stroke, bleeding, and vascular complications. In patients undergoing percutaneous coronary interventions, a current diagnosis of lung cancer was associated with greater in-hospital mortality and any in-hospital complication, a current diagnosis of colon cancer was associated with a higher rate of any complication and bleeding, but not mortality, a current diagnosis of breast cancer was not associated with in-hospital mortality or any of the complications studied, a current diagnosis of prostate cancer was associated with only an increased risk of bleeding, and a previous diagnosis of lung cancer was independently associated with increased in-hospital mortality.

Räber L, Yamaji K, Kelbæk H, et al. Five-year clinical outcomes and intracoronary imaging findings of the COMFORTABLE AMI trial: randomized comparison of biodegradable polymer-based biolimus-eluting stents with bare-metal stents in patients with acute ST-segment elevation myocardial infarction. *Eur Heart J.* 2019;40(24):1909-1919.

As the long-term outcomes of biolimus-eluting stents with a biodegradable polymer vs bare-metal stents in patients with ST-segment elevation myocardial infarction are unavailable, this study provides the 5-year clinical outcomes after stent implantation. This study performed a follow-up of patients included in the COMFORTABLE AMI trial, a multicenter, randomized, assessor-blinded, superiority trial of biolimus-eluting stents vs bare-metal stents in patients with ST-segment myocardial infarction undergoing a primary percutaneous coronary intervention (n=1157; mean age, 60.6 years; women, 20.7%). The prespecified primary end point was the composite of major adverse cardiovascular events including cardiac death, target vessel-related reinfarction, and ischemia-driven target lesion revascularization within 12 months. At 5 years, compared with bare-metal stents, biolimus-eluting stents reduced the risk of major adverse cardiac events, which was driven by a lower risk of target vessel-related reinfarction and ischemia-driven target lesion revascularization.

Sehested TSG, Carlson N, Hansen PW, et al. Reduced risk of gastrointestinal bleeding associated with proton pump inhibitor therapy in patients treated with dual antiplatelet therapy after myocardial infarction. *Eur Heart J.* 2019;40(24):1963-1970.

While the combination of dual antiplatelet therapy lowers the risk of recurrent cardiovascular events after a myocardial infarction, it increases the risk of bleeding. The COGET trial showed that proton pump inhibitor treatment reduced bleeding in patients taking clopidogrel and aspirin. Due to a lack of real-world data on effectiveness of proton pump inhibitor treatment, this study used data from Danish nationwide registries to assess the effectiveness of proton pump inhibitors in the prevention of upper gastrointestinal bleeding in patients using dual antiplatelet therapy following myocardial infarction (n=46 301; median age, 69 years; women, 36.8%). The primary outcome was major upper gastrointestinal bleeding (ie, hospital admission or death from primary diagnoses denoting bleeding [bleeding ulcer, hematemesis, hemorrhagic gastritis and duodenitis, esophageal varices with bleeding, and Mallory Weiss bleeding]). Proton pump inhibitor therapy was associated with a reduced risk of upper gastrointestinal bleeding.

Veselka J, Faber L, Liebregts M, et al. Short- and long-term outcomes of alcohol septal ablation for hypertrophic obstructive cardiomyopathy in patients with mild left ventricular hypertrophy: a propensity score matching analysis. *Eur Heart J.* 2019;40(21):1681-1687.

Considering that alcohol septal ablation in patients with hypertrophic obstructive cardiomyopathy leads to a thinning of the basal interventricular septum, the European guidelines only recommend using this procedure in patients with an interventricular septum thickness >16 mm. Currently, no studies have evaluated the short- and long-term outcomes of alcohol septal ablation in patients with an interventricular septum thickness <16 mm (mild hypertrophy); therefore, this retrospective, propensity score matched study set out to investigate the outcomes in this patient group (n=1505; mean age, 58.4 years; women, 50%). The outcomes assessed were the occurrence of post-alcohol septal ablation ventriculoseptal defects, 30-day major cardiovascular adverse events (ie cardiovascular death, electrical defibrillation for ventricular tachycardia/fibrillation, cardiac tamponade, and pacemaker implantation), 30-day all-cause mortality, long-term all-cause death, left ventricular gradient reduction, and improvement in functional status, and the rate of reintervention. Patients with an interventricular septum thickness <16 mm had more early complications attributable to the procedure, especially due to a higher need for pacemaker implantations; however, their long-term survival was better than patients with an interventricular septum thickness ≤16 mm.

Wasserstrum Y, Barriales-Villa R, Fernández-Fernández X, et al. The impact of diabetes mellitus on the clinical phenotype of hypertrophic cardiomyopathy. *Eur Heart J.* 2019;40(21):1671-1677.

Hypertrophic cardiomyopathy in elderly patients is often associated with two major comorbidities, ie, diabetes mellitus and hypertension. While it is known that diabetes mellitus increases the burden of morbidity and hospitalizations and increases left ventricular mass, left ventricular hypertrophy, and atrial size in patients with heart failure, it is uncertain what effects diabetes mellitus has in patients with hypertrophic cardiomyopathy. This study was designed to assess the clinical phenotype of diabetes mellitus in patients with hypertrophic cardiomyopathy by analyzing the clinical characteristics of patients who were aged ≥40 years and who were diagnosed with hypertrophic cardiomyopathy (n=937; mean age, 61.5 years; women, 38%). Patients with hypertrophic cardiomyopathy and diabetes mellitus were older, with a higher rate of comorbidities, such as obesity, hypertension, coronary disease, and renal failure; in addition, these patients also had a higher rate of diastolic dysfunction, pulmonary hypertension, atrial fibrillation, and conduction disease. Lastly, these patients had a significantly higher 15-year mortality rate; however, there were no differences in sudden cardiac death, appropriate implanted cardioverter-defibrillator therapy, or heart transplantation. ■

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Barra S, Duehmke R, Providência R, et al. Very long-term survival and late sudden cardiac death in cardiac resynchronization therapy patients. *Eur Heart J.* 2019;40(26):2121-2127.

The CeRtiTuDe cohort study showed that the excess mortality in patients with cardiac resynchronization therapy with a pacemaker (CRT-P) at the 2-year follow-up is mostly related to an increase in non-sudden cardiac disease. This multicenter study investigated the very long-term outcomes and late causes of death in patients after cardiac resynchronization therapy with a defibrillator and not a pacemaker (n=1775; mean age, 66.8 years; women, 25%). The primary end points were all-cause mortality and late sudden cardiac death. While progressive heart failure death was the most common cause of death, sudden cardiac death was only a cause of mortality in a small proportion of cases.

Böhm M, Schumacher H, Teo KK, et al. Cardiovascular outcomes and achieved blood pressure in patients with and without diabetes at high cardiovascular risk. *Eur Heart J.* 2019;40(25):2032-2043.

The ONTARGET and TRANSCEND studies showed no differences in outcomes in patients with or without diabetes following treatment with ramipril, telmisartan, or both in patients after myocardial infarction, stroke, peripheral artery disease, or at high cardiovascular risk. This secondary analysis investigated the association between achieved blood pressure values and cardiovascular risk in patients with or without diabetes (n=30 937; mean age, 66.5 years; women, 29.7%). The primary outcome was the composite of cardiovascular death, myocardial infarction, stroke, and hospital admission for heart failure, where the composite outcome, the individual components of the composite outcome, and all-cause death were assessed in this secondary analysis. The risk of cardiovascular outcomes and death were higher both in patients with on-treatment blood pressure values ≥160 or ≥90 mm Hg and in patients with on-treatment blood pressure values <120 or <70 mm Hg (except stroke in the second case). In addition, the risks are higher in all blood pressure ranges in patients with diabetes.

Chiesa ST, Masi S, Shipley MJ, et al. Carotid artery wave intensity in mid- to late-life predicts cognitive decline: the Whitehall II study. *Eur Heart J.* 2019;40(28):2300-2309.

While an association has been made between arterial phenotypes in mid-life and the development of adverse structural brain changes, accelerated cognitive decline, and increase risk of dementia using surrogate markers, a direct relationship between the mechanism and future cognitive decline has not been demonstrat-

ed. This study used data from the Whitehall II study, an ongoing cohort study of people with novel carotid wave intensity measures in mid- to late-life with serial measures of cognitive function, to assess whether peak intensity of carotid artery forward-travelling compression wave intensity is associated with cognitive decline (n=3191; mean age, 60.75 years; women, 25%). The study showed that higher forward-travelling compression wave intensity at baseline was associated with accelerated cognitive decline.

Cox SR, Lyall DM, Ritchie SJ, et al. Associations between vascular risk factors and brain MRI indices in UK Biobank. *Eur Heart J.* 2019;40(28):2290-2300.
While it is known that several vascular risk factors increase the risk of cerebrovascular disease and dementia, limited information is available concerning the associations between multiple vascular risk factors and detailed aspects of macro- and microstructure of the brain in a large group of middle and older aged adults. This study used data from the UK Biobank to examine the burden of vascular risk on global and regional measures of gray and white brain matter (n=9722; mean age, 61.97 years; women, 52.51%). A larger number of vascular risk factors were found to be associated with greater brain atrophy, lower grey matter volume, and poorer white matter health, with smoking, diabetes, and hypertension being the most consistent across brain measures.

Douros A, Tölle M, Ebert N, et al. Control of blood pressure and risk of mortality in a cohort of older adults: the Berlin Initiative Study. *Eur Heart J.* 2019;40(25):2021-2028.
Controversy exists regarding the optimal blood pressure targets for elderly patients, with the 2018 ESC/ESH guidelines recommending a target systolic blood pressure <140 mm Hg for elderly patients aged up to 80 years, while recommending individualized treatment strategies for elderly patients aged >80 years. Therefore, this population-based observational study used data from the Berlin Initiative Study to determine whether lowering blood pressure below 140/90 mm Hg lowered the risk of all-cause mortality in a cohort of patients aged ≥70 years (n=1628; mean age, 80.85 years; women, 52.1%). Lowering blood pressure to <140/90 mm Hg increased the risk of mortality in elderly patients with previous cardiovascular events.

Fosbøl EL, Park LP, Chu VH, et al; ICE-PLUS Investigators. The association between vegetation size and surgical treatment on 6-month mortality in left-sided infective endocarditis. *Eur Heart J.* 2019;40(27):2243-2251.
Patients with left-sided infective endocarditis with large vegetations (ie, nidus of endocardial infection) have a higher risk of embolization and early death. Some studies show that surgery for left-sided vegetation in infective endocarditis

reduces the incidence of embolization, but not 6-month mortality; however, information in lacking for patients with vegetation >10 mm. The ICE-PLUS registry, a prospective, multinational registry, analyzed the association between surgery and 6-month mortality according to vegetation size (n=1006; median age, 62.2 years; women, 33.5%). Compared with small vegetation size, vegetation size >10 mm was associated with a higher rate of embolic events and mortality and that early surgery was associated with a lower 6-month mortality.

Friberg L, Andersson T, Rosenqvist M. Less dementia and stroke in low-risk patients with atrial fibrillation taking oral anticoagulation. *Eur Heart J.* 2019;40(28):2327-2335.
Recent data have shown that the risk of developing dementia in patients with atrial fibrillation was almost reduced by 50% in those receiving oral anticoagulants. However, the recommendations suggest that only atrial fibrillation patients who are at a high risk of stroke receive oral anticoagulant, but not in patients with a low stroke risk. This retrospective study assessed whether patients with atrial fibrillation and a low risk of stroke would benefit from oral anticoagulation considering the risks of dementia and intracerebral bleeding (n=44 127; mean age, 59.25 years; women, 32.1%). The study end points were a new diagnosis of dementia, ischemic stroke, intracerebral bleeding, and a composite of the three. Oral anticoagulants reduced the risk of dementia, and there was an overall lower risk for the composite end point. However, the benefit was limited to patients >65 years old.

Ghimire A, Fine N, Ezekowitz JA, Howlett J, Youngson E, McAlister FA. Frequency, predictors, and prognosis of ejection fraction improvement in heart failure: an echocardiogram-based registry study. *Eur Heart J.* 2019;40(26):2110-2117.
Certain patients with heart failure show improvements in left ventricular ejection fraction with treatment; they are classified as patients with heart failure with ejection fraction recovery (HFrecEF). This retrospective echocardiogram-based study analyzed the prevalence, predictors, and prognosis of patients with HFrecEF (n=10 641; mean age, 68.8 years; women, 43.3%). The outcomes analyzed were all-cause mortality, all-cause hospitalizations, all-cause emergency room visits, heart failure–specific hospitalizations or emergency room visits, left ventricular assist device implantation, or cardiac transplant after their second echocardiogram. Patients with HFrecEF were more likely to be younger, female, and were more likely to have hypertension, atrial fibrillation, or cancer; in addition, they had a substantially better prognosis than did those with persistent heart failure with reduced ejection fraction.

Gili S, Cammann VL, Schlossbauer SA, et al. Cardiac arrest in takotsubo syndrome: results from the InterTAK Registry. *Eur Heart J.* 2019;40(26):2142-2151.

Takotsubo syndrome can be associated with different complications, such as cardiogenic shock and life-threatening arrhythmias. Cardiac arrest is a major threat in patients with takotsubo syndrome; however, the long-term implications are unknown. The International Takotsubo Registry, a multicenter prospective and retrospective registry, assessed the incidence and impact of cardiac arrest in patients with takotsubo syndrome (n=2098; mean age, 64.6 years; women, 43.4%). The main outcomes were 60-day and 5-year mortality. Mortality–both at 60 days and at 5 years–was higher in patients with cardiac arrest than in those without. Two factors–T-wave inversion and intracranial hemorrhage–were associated with higher mortality at 60 days following cardiac arrest, but female sex lowered this risk.

Guala A, Teixidó-Tura G, Rodríguez-Palomares J, et al. Proximal aorta longitudinal strain predicts aortic root dilation rate and aortic events in Marfan syndrome. *Eur Heart J.* 2019;40(25):2047-2055.

While detecting aortic dilation and performing prophylactic aortic root surgery has improved life expectancy in patients with Marfan syndrome, additional imaging markers are needed to improve risk stratification because measuring aortic root diameter has some limitations. This study used cardiac magnetic resonance to analyze proximal aorta longitudinal and circumferential strain and distensibility for the ability to predict the rate of aortic root dilation and occurrence of aortic events in patients with Marfan syndrome (n=117; mean age, 25.3 years; women, 58%). In addition to aortic root diameter, proximal aorta longitudinal strain, but not circumferential strain and distensibility, was an independent predictor of aortic root diameter growth rate and aortic events.

Jamaly S, Carlsson L, Peltonen M, Jacobson P, Karason K. Surgical obesity treatment and the risk of heart failure. *Eur Heart J.* 2019;40(26):2131-2138.

Obese people have a 2-fold higher risk of developing heart failure than normal-weight people, with a 5% to 7% increase in risk for each increment of body mass index. The SOS study found that performing bariatric surgery as a primary prevention measure reduced mortality and cardiovascular morbidity. This prospective matched cohort study assessed whether bariatric surgery in obese people would lower the risk of new-onset heart failure (n=4033; mean age, 47.95 years; women, 71%). The main outcome was the first-time detection of heart failure. During a median follow-up of 22 years, bariatric surgery, compared with the control, reduced the risk of developing heart failure.

Kim D, Yang PS, Yu HT, et al. Risk of dementia in stroke-free patients diagnosed with atrial fibrillation: data from a population-based cohort. *Eur Heart J.* 2019;40(28):2313-2323.

Even though atrial fibrillation is thought to be a risk factor for dementia, data from longitudinal studies have been inconsistent. Therefore, this study used data from a longitudinal, community-based, and smoke-free elderly (≥60 years old) cohort of patients to determine the effect of atrial fibrillation on developing dementia (n=262 611; mean age, 71.2 years; women, 51.7%). The risk of dementia—both Alzheimer and vascular dementia—increased significantly in patients with incident atrial fibrillation. The risk of dementia increased in all subgroups, with the exception of patients with chronic kidney disease, malignancy, heavy alcohol consumption, and a previous myocardial infarction. Oral anticoagulation had a preventive effect on the development of dementia.

Kundi H, Popma JJ, Reynolds MR, et al. Frailty and related outcomes in patients undergoing transcatheter valve therapies in a nationwide cohort. *Eur Heart J.* 2019;40(27):2231-2239.

Frailty is a major factor contributing to mortality after transcatheter mitral valve repair and transcatheter aortic valve replacement; therefore, to optimize patient screening for the procedures, it is recommended to screen for frailty. However, there is a lack of consensus concerning the frailty assessment tools. This nationwide cohort study assessed the prevalence of frailty based on the recently validated ICD-10-based Hospital Frailty Risk Score and the impact of frailty on outcomes in patients undergoing transcatheter aortic valve replacement or transcatheter mitral valve repair (n=32 277; mean age, 80.8 years; women, 47.3%). The primary outcome was all-cause 1-year mortality. The results show that the Hospital Frailty Risk Score was beneficial for identifying people who had a greater risk of mortality after undergoing transcatheter valve procedures.

Nazif TM, Chen S, George I, et al. New-onset left bundle branch block after transcatheter aortic valve replacement is associated with adverse long-term clinical outcomes in intermediate-risk patients: an analysis from the PARTNER II trial. *Eur Heart J.* 2019;40(27):2218-2227.

New-onset left bundle branch block (LBBB) is associated with a modest increase in cardiovascular mortality, but not all-cause mortality, but the clinical impact after transcatheter aortic valve replacement is unclear. This cohort analysis of intermediate-risk patients treated with transcatheter aortic valve replacement assessed clinical outcomes associated with new-onset LBBB (n=1179; mean age, 81 years; women, 46.8%). At 2 years, new-onset LBBB was associated with increased rates of all-cause mortality, cardiovascular mortality, rehospitalization, and new pacemaker implantations.

Nordmeyer J, Ewert P, Gewillig M, et al. Acute and midterm outcomes of the post-approval MELODY Registry: a multicentre registry of transcatheter pulmonary valve implantation. *Eur Heart J.* 2019;40(27):2255-2264.
Transcatheter pulmonary valve implantation (TPVI) is important in the treatment of patients with congenital heart disease and right ventricular outflow tract dysfunction. Two balloon-expandable devices are available—MelodyTM and SAPIEN XT. The MELODY registry, an investigator-initiated, multicenter registry, was designed to develop a multicenter registry on the Melody valve in a large cohort of patients with congenital heart disease (n=845; mean age, 21 years; women, 33%). The primary end points were a composite of TPVI-related follow-up events, ie, death, reoperation, or reintervention >48 hours after TPVI, as well as TPVI infective endocarditis. The incidence of TPVI-related events was around 4.2% per person per year and the incidence of TPVI infective endocarditis was 2.3% per person per year. Invasively measured residual right ventricle to pulmonary artery pressure gradient at the time of the TPVI procedure was associated with a risk of TPVI-related events and the risk of TPVI infective endocarditis.

Petrus AHJ, Dekkers OM, Tops LF, Timmer E, Klautz RJM, Braun J. Impact of recurrent mitral regurgitation after mitral valve repair for functional mitral regurgitation: long-term analysis of competing outcomes. *Eur Heart J.* 2019;40(27):2206-2214.
While recurrent mitral regurgitation sometimes occurs after mitral valve repair for functional mitral regurgitation, its impact on long-term survival is unknown. This study analyzed the long-term clinical and echocardiographic outcomes in patients with ischemic heart disease after mitral valve repair with revascularization for function mitral regurgitation (n=261; mean age, 69 years; women, 33%). The primary end point was the recurrence of mitral regurgitation. The incidence of recurrent mitral regurgitation was low with favorable clinical outcomes; however, recurrent mitral regurgitation after surgery was associated with an increased risk of mortality. ■

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Ahn JM, Kim H, Kwon O, et al. Differential clinical features and long-term prognosis of acute aortic syndrome according to disease entity. *Eur Heart J.* 2019;40(32):2727-2736.
The ASAN AAS registry, an observational cohort registry, was designed to show that a study with a large population of patients with intramural hematoma is needed to truly understand the impact on prognosis in patients with acute aortic syndrome (n=1012; mean age, 59.2 years; women, 45%). The primary outcome was

defined as death from aortic events, such as death due to acute aortic syndrome or associated surgical procedures and sudden death not explained by causes other than aortic diseases. In patients with acute aortic syndrome, intramural hematoma was an independent factor associated with in-hospital mortality and both acute and long-term mortality.

Buccheri S, James S, Lindholm D, et al. Clinical and angiographic outcomes of bioabsorbable vs. permanent polymer drug-eluting stents in Sweden: a report from the Swedish Coronary and Angioplasty Registry (SCAAR). *Eur Heart J.* 2019;40(31):2607-2615.

Despite the fact that bioabsorbable polymer drug-eluting stents have consistently been shown to be noninferior to drug-eluting stents with permanent polymers, there has been little real-world data on the comparative performance. This study used data from the SCAAR registry, a Swedish nationwide, web-based registry with data from patients undergoing coronary angiography or percutaneous coronary intervention, to explore the comparative outcomes (n=57 487; mean age, 67.8 years; women, 26.6%). The primary outcomes were the incidence of clinically relevant restenosis and definite stent thrombosis (ie, the presence of symptoms suggestive of an acute coronary syndrome and angiographic evidence of thrombus) up to 2 years. There were no between-group differences for restenosis or definite stent thrombosis.

Christersdottir T, Pirault J, Gisterå A, et al. Prevention of radiotherapy-induced arterial inflammation by interleukin-1 blockade. *Eur Heart J.* 2019;40(30):2495-2503.

Due to a lack of adequate samples, the mechanisms behind radiotherapy-induced cardiovascular disease, an emerging problem in cancer survivors, are poorly understood. This study used irradiated human arterial biopsies that were collected during microvascular autologous free tissue transfer for cancer reconstruction to assess the vascular inflammatory patterns in cancer survivors, to replicate the results in an animal model, and determine whether IL-1 receptor antagonism could be a potential treatment. Genes associated with the inflammasome were significantly induced, which was also associated with elevated levels of procaspase and caspase-1 proteins. In human irradiated arteries, mRNA levels were increased for inflammasome-associated chemokines (CCL2 and CCL5) and the adhesion molecule VCMA1; in addition, the number of infiltrating macrophages increased. In a mouse model, the results were similar and treatment with the IL-1 receptor antagonist anakinra reduced mRNA levels of Ccl2 and Ccl5 and reduced the expression of I-Ab major histocompatibility class II antigen.

Glineur D, Grau JB, Etienne PY, et al. Impact of preoperative fractional flow reserve on arterial bypass graft anastomotic function: the IMPAG trial. *Eur Heart J.* 2019;40(29):2421-2428.

Even though the use of fractional flow reserve to guide revascularization decisions is routine practice in interventional cardiology, there is limited information on the role of preoperative fractional flow reserve in patients undergoing coronary artery bypass grafting. The IMPAG study, a prospective, double-blind observational study, investigated whether there is a correlation between target vessel preoperative fractional flow reserve valve and anastomotic function after surgical revascularization using a multi-arterial grafting strategy (n=64 patients; mean age, 66.2 years). The primary outcome was the association between target vessel pre-operative fractional flow reserve value and anastomotic function 6 months after surgery. This study showed that there is a significant association between the components of the primary outcome.

Jones DA, Rathod KS, Koganti S, et al. The association between the public reporting of individual operator outcomes with patient profiles, procedural management, and mortality after percutaneous coronary intervention: an observational study from the Pan-London PCI (BCIS) Registry using an interrupted time series analysis. *Eur Heart J.* 2019;40(31):2620-2629.

While public reporting of health care is becoming more common, there is controversy surrounding the benefit and risk profile of public reporting. This observational cohort study analyzed data from the Pan-London PCI registry to assess whether the introduction of individual operator–specific outcome reporting after percutaneous coronary intervention was associated with a change in patient risk factor profiles, procedural management, or 30-day mortality outcomes in a large cohort of consecutive patients (before public reporting: n=83 894; mean age, 64.16 years; women, 25.7%; after public reporting: n=39886; mean age, 65.36 years; women, 24.4%). The primary clinical outcome was all-cause mortality. After the introduction of public reporting, the 30-day mortality rates were reduced, with no increase in risk-averse behavior.

Johnson NP, Li W, Chen X, et al. Diastolic pressure ratio: new approach and validation vs. the instantaneous wave-free ratio. *Eur Heart J.* 2019;40(31):2585-2594.

The instantaneous wave-free ratio is used to determine whether a stenosis is the cause of a blood-flow limitation in coronary arteries with subsequent ischemia. This study performed a post-hoc analysis of the diastolic pressure ratio metric against the instantaneous wave-free ratio to test for unique physiologic properties of the wave-free period when making resting coronary pressure measurements (n=833; mean age, not available; women, 24%). Despite having a different technical approach, the diastolic pressure ratio was shown to be numerical equivalent to the instantaneous wave-free ratio.

Leisegang MS, Bibli SI, Günther S, et al. Pleiotropic effects of laminar flow and statins depend on the Krüppel-like factor-induced lncRNA MANTIS. *Eur Heart J.* 2019;40(30):2523-2533.

Studies have shown that the long noncoding RNA MANTIS is involved in vascular regeneration, pulmonary arterial hypertension, and tumor endothelium; however, the transcriptional regulation of MANTIS is unknown. This study used RNA sequencing, CRISPR activation, overexpression, and RNA interference to identify the transcriptional regulation for MANTIS to assess the functional relevance and therapeutic potential of the pro-angiogenic long non-coding RNA MANTIS in vascular disease development. Endothelial monocyte adhesion via an ICAM-1-dependent manner is increased in the absence of MANTIS. Laminar flow and HMG-CoA reductase inhibitors induce the expression of MANTIS via epigenetic rearrangements and the transcription factors KLF2 and KLF4, which, when there are mutations in KLF binding motifs, blocked flow-induced MANTIS expression. These results show that MANTIS is regulated KLF2 and KLF4.

Li XS, Obeid S, Wang Z, et al. Trimethyllysine, a trimethylamine N-oxide precursor, provides near- and long-term prognostic value in patients presenting with acute coronary syndromes. *Eur Heart J.* 2019;40(32):2700-2709.

Trimethyllysine (TML) serves as a nutrient precursor of the gut microbiota-derived metabolite. Trimethylamine N-oxide (TMAO) was identified using untargeted metabolomics and circulating TMAO was subsequently shown to be associated with the risk for major adverse cardiovascular events, thrombotic events, as well as near- and long-term edverse events. In recent untargeted metabolomics studies, the amino acid N6, N6, N6-trimethyl-L-lysine (TML) was associated with cardiovascular disease risk. This study was designed to determine the relationship between systemic levels of TML and both near- and long-term cardiovascular disease and mortality risk in patients presenting to the emergency department with chest pain and in patients presenting with adjudicated acute coronary syndrome (n=530; mean age, 62.4 years; women, 42.5%). The outcomes were all-cause mortality (cardiac, vascular, and noncardiovascular causes of death) and major adverse cardiovascular events (composite of myocardial infarction, stroke, revascularization, or all-cause mortality). TML levels were associated with major adverse cardiac events over both 30 days and 6 months and were independent of traditional cardiovascular risk factors and indices of renal function. In addition, elevated TML levels were associated with incident long-term all-cause mortality and major adverse cardiovascular events.

Li Z, Solomonidis EG, Meloni M, et al. Single-cell transcriptome analyses reveal novel targets modulating cardiac neovascularization by resident endothelial cells following myocardial infarction. *Eur Heart J.* 2019;40(30):2507-2520.
Considering that chronic heart failure after an acute myocardial infarction is increasing, it is necessary to have a better understanding of the pathways that regulate coronary vasculature regeneration. This study performed a single-cell transcriptome analysis in an endothelial cell–specific multispectral lineage-tracing mouse model to understand the origin and clonal dynamics of endothelial cells associated with neovascularization in the adult mouse heart following myocardial infarction. The study shows that cardiac endothelial cells mediate therapeutic angiogenesis post-myocardial infarction.

Marinković G, Grauen Larsen H, et al. Inhibition of pro-inflammatory myeloid cell responses by short-term S100A9 blockade improves cardiac function after myocardial infarction. *Eur Heart J.* 2019;40(32):2713-2723.
The underlying pathophysiology of the role of neutrophils in patients with a myocardial infarction is unclear. The pro-inflammatory alarmin S100A8/A9 is highly expressed in neutrophils and it is released in the myocardium and circulation after myocardial ischemia. S100A9 stimulates hematopoietic stem cell proliferation in the bone marrow, increases neutrophil and monocyte egression in the blood stream and recruitment into the ischemic myocardium. This study assessed whether the release of S100A8/A9 is associated with heart failure development in patients with acute coronary syndrome (n=524) and in mouse models of myocardial infarction. In mouse models of myocardial infarction, short-term blockage of S100A9 with the inhibitor ABR-238901 inhibits inflammation and improves cardiac function. In humans, high levels of plasma S100A8/A9 during the acute event were associated with an increased rate of hospitalization for heart failure during follow-up as well as with a lower left ventricular ejection fraction at 1 year.

Rueda F, Borràs E, García-García C, et al. Protein-based cardiogenic shock patient classifier. *Eur Heart J.* 2019;40(32):2684-2694.
Evidence is showing that cardiogenic shock is both a result of pump failure and a systemic inflammatory status in the context of multiorgan failure. This study used quantitative proteomics on the Barcelona discovery cohort, a prospective, single-center, all-comers study on patients with ST-segment elevation myocardial infarction complicated by cardiogenic shock, to develop a protein-based biomarker set that could be used as a new cardiogenic shock risk assessment stratification score in terms of short-term mortality (n=145; mean age, 69 years; women, 35%). Mass spectrometry produced 2654 quantified proteins not previously associated with cardiogenic shock, then, after relative protein quantification between survivors and nonsurvivors, 51 proteins were identified and evaluated

in an independent cohort using targeted proteomics and cross-validation that identified 4 proteins. The 4 proteins identified—L-FABP, B2MG, ALDOB, IC1—substantially improved risk prediction when measured within 24 hours of admission for cardiogenic shock.

Schunkert H, Boening A, von Scheidt M, et al. Randomized trial of ticagrelor vs. aspirin in patients after coronary artery bypass grafting: the TiCAB trial. *Eur Heart J.* 2019;40(29):2432-2440.

Early graft failure is a common occurrence following coronary artery bypass grafting, which is driven by platelet aggregation, which, when compared with patients without early graft failure, is more resistant to aspirin. Ticagrelor, an oral, reversibly binding, and direct-acting P2Y12 receptor antagonist, could be an aspirin alternative. The TiCAB trial, an investigator-initiated, randomized, double-blind, parallel-grouped, placebo-controlled, phase 3 trial, tested whether ticagrelor monotherapy would lower the incidence of cardiovascular events in patients undergoing coronary artery bypass grafting when compared with placebo (n=1859; mean age, 66.7 years; women, 15%). The primary efficacy end point was a composite of cardiovascular death, myocardial infarction, stroke, and repeat revascularization 12 months after coronary artery bypass grafting. No significant between-group differences were observed for the primary efficacy end point.

Serruys PW, Takahashi K, Chichareon P, et al. Impact of long-term ticagrelor monotherapy following 1-month dual antiplatelet therapy in patients who underwent complex percutaneous coronary intervention: insights from the Global Leaders trial. *Eur Heart J.* 2019;40(31):2595-2604.

Newer antiplatelet agents, which are faster, more potent, and more consistent, may be an alternative to standard dual antiplatelet therapies. This post-hoc analysis of the Global Leaders trial, a multicenter, prospective, open-label randomized clinical trial, compared the effect of 1-month dual antiplatelet therapy followed by a 23-month ticagrelor monotherapy in patients with complex percutaneous coronary intervention (ie, having at least one of the following: multivessel percutaneous coronary intervention, ≥3 stents implanted, ≥3 lesions treated, bifurcation percutaneous coronary intervention with ≥2 stents, or total stent length >60 mm) with the reference therapy, ie, 12-month aspirin monotherapy following 12-month dual antiplatelet therapy (n=15 450; mean age, 64.75 years; women, 22.8%). The primary end point was the composite of all-cause death or new Q-wave myocardial infarction at 2 years. Compared with the reference therapy, the experimental therapy significantly reduced the risk of the primary end point with complicated percutaneous coronary intervention, but not uncomplicated percutaneous coronary intervention.

Vromman A, Ruvkun V, Shvartz E, et al. Stage-dependent differential effects of interleukin-1 isoforms on experimental atherosclerosis. *Eur Heart J.* 2019;40(30):2482-2491.
Recently, the CANTOS trial showed that selective neutralization of IL-1β reduces the risk of recurrent cardiovascular events in patients with residual inflammatory risk despite taking guideline-directed therapy. This study used a mouse atherosclerosis model to examine the effect of selective neutralization of IL-1α, IL-1β, or both on the development and evolution of atheromata. Outward remodeling was impaired when neutralizing IL-1α or both IL-1α and IL-1β, but not when neutralizing IL-1β during early atherogenesis. Neutralizing IL-1β led to a lower inflammatory state during atherogenesis, reduced the size of an established atheromata, and increased the plasma levels of IL-10. The results show that IL-1α is involved in artery remodeling, but IL-β is involved in driving inflammation.

Xu S, Xu Y, Liu P, et al. The novel coronary artery disease risk gene JCAD/KIAA1462 promotes endothelial dysfunction and atherosclerosis. *Eur Heart J.* 2019;40(29):2398-2408.
While genome-wide association studies have shown that a genetic variant of the JCAD gene is a risk allele for coronary artery disease, its role in the pathophysiology of coronary artery disease is unknown. The study used an athero-susceptible apolipoprotein E deficient mouse model to test whether JCAD deficiency would reduce the atherosclerotic burden. JCAD deficiency suppresses vascular inflammation, improves vascular activity, and inhibits atherogenesis. The study showed that JCAD activates YAP/TAZ/TEAD through an interaction with TRIOBP, which stabilizes F-actin stress fiber, resulting in expression of inflammatory genes in endothelial cells that ultimately leads to the formation of atherosclerotic plaques.

Zeng L, Ntalla I, Kessler T, et al; UK Biobank CardioMetabolic Consortium CHD Working Group. Genetically modulated educational attainment and coronary disease risk. *Eur Heart J.* 2019;40(29):2413-2420.
Epidemiological studies have shown an inverse correlation between the number of years spent in school and the risk of coronary artery disease; however, it is uncertain whether there is a genetic component in this relationship. Therefore, this study investigated the role of genetics in the relationship between educational attainment and the risk of coronary artery disease. A strong link was found between the genetic education score and modifiable risk factors, including smoking, body mass index, and hypertension. ■

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Alexander VJ, Xia S, Hurh E, et al. N-acetyl galactosamine-conjugated antisense drug to APOC3 mRNA, triglycerides and atherogenic lipoprotein levels. *Eur Heart J.* 2019;40(33):2785-2796.

Apolipoprotein C-III (apoC-III) is key in determining the levels of serum triglycerides by inhibiting lipoprotein(a) activity and by inhibiting hepatic uptake of plasma triglyceride-rich lipoprotein; elevated apoC-III levels are associated with hypertriglyceridemia and coronary heart disease. RNA-targeted therapies are a new therapeutic approach that involves using triantennary N-acetyl galactosamine (GalNAc3)–modified antisense oligonucleotides. This phase1/2a study, double-blind, randomized, placebo-controlled, dose-escalation study, tested the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple doses of AKCEA-APOCIII-LRx, a GalNAc3-modified antisense oligonucleotide that selectively inhibits apoC-III protein synthesis, in healthy volunteers with triglyceride levels ≥90 or ≥200 mg/dL (n=40; mean age, 52.9 years; women, 28%). Treatment with AKCEA-APOCIII-LRx was well tolerated with no significant adverse events and it led to a significant decrease in plasma apoC-III and triglycerides leveles, as well as a reduction in total cholesterol, apolipoprotein B, very-low-density lipoprotein cholesterol, and non-high-density lipoprotein cholesterol and an increase in high-density lipoprotein cholesterol.

Berkelmans GFN, Gudbjörnsdottir S, Visseren FLJ, et al. Prediction of individual life-years gained without cardiovascular events from lipid, blood pressure, glucose, and aspirin treatment based on data of more than 500 000 patients with type 2 diabetes mellitus. *Eur Heart J.* 2019;40(34):2899-2906.

While lipid, blood pressure, glucose, and aspirin treatment are effective for the prevention of cardiovascular disease at a group level, there are important differences among individuals that changes the effectiveness of treatment, especially for patients with type 2 diabetes. This study set about validating the DIAL model, a prediction tool for individualizing lifelong cardiovascular disease prevention in people with type 2 diabetes by predicting the life-years gained without myocardial infarction or stroke (nderivation=292 042 and nvalidation=97 342; mean age, 65 years; women, 44%). After validation, this model was shown to reliably predict cardiovascular disease–free life expectancy, as well as the effects of lifelong prevention in terms of cardiovascular disease–free life-years gained.

Chen GC, Arthur R, Iyengar NM, et al. Association between regional body fat and cardiovascular disease risk among postmenopausal women with normal body mass index. *Eur Heart J.* 2019;40(34):2849-2855.

Postmenopausal women often experience metabolic alterations that may put them at an increased risk for cardiovascular disease. This study assessed whether regional body fat deposits (trunk or leg fat) are associated with an altered risk of cardiovascular disease in 161 808 postmenopausal women aged 50 to 79 years with normal body mass index (18.5 to <25 kg/m2). The primary outcome was the first occurrence of major cardiovascular disease (ie, coronary heart disease, stroke, or both). Women with a higher percentage of trunk fat had an increased risk of cardiovascular disease, while women with a higher percentage of leg fat had a decreased risk of cardiovascular disease.

Cheung JW, Cheng EP, Wu X, et al. Sex-based differences in outcomes, 30-day readmissions, and costs following catheter ablation of atrial fibrillation: the United States Nationwide Readmissions Database 2010-14. *Eur Heart J.* 2019;40(36):3035-3043.

While women are less likely than men to be referred for catheter ablation, there is little data available on sex-based differences in outcomes. This study used data from the United States Nationwide Readmissions Database to analyze the sex-based outcomes, 30-day readmission rates, and cost for following catheter ablation in patients with atrial fibrillation (n=54 597 admissions for catheter ablation for atrial fibrillation; mean age, 64.3 years; women, 37.7%). The primary end point of this study was 30-day all-cause readmission. Compared with men, women had a higher rate of 30-day all-cause readmission rates; in addition, female sex was independently associated with readmission for atrial fibrillation and atrial tachycardia, cardiac causes, and all causes.

Feng T, Vegard M, Strand LB, et al. Weight and weight change and risk of atrial fibrillation: the HUNT study. *Eur Heart J.* 2019;40(34):2859-2866.

While it is known that obesity is associated with a risk of atrial fibrillation, little information is available about the effects of long-term obesity, recent obesity, and weight change on the development of atrial fibrillation. The HUNT study, a large, population-based study, analyzed the cumulative effects of obesity and weight change on the risk of atrial fibrillation in individuals aged ≥20 years who had no history of atrial fibrillation (n=15 214; mean age, 66.6 years; women, 57.5%). The study shows that long-term obesity and body mass index change are associated with an increased risk of atrial fibrillation; obesity occurring earlier in life and body mass index change were associated with cumulative effects on the development of atrial fibrillation. The increased risk of atrial fibrillation was not restricted to obese people as the risk was also higher in people who were overweight.

Gatzoulis KA, Tsiachris D, Arsenos P, et al. Arrhythmic risk stratification in post-myocardial infarction patients with preserved ejection fraction: the PRESERVE EF study. *Eur Heart J.* 2019;40(35):2940-2949.

Among patients with preserved left ventricular systolic function after a myocardial infarction, it is a difficult task to identify potential future arrhythmic sudden death. The PRESERVE EF study, a multicenter, prospective, observational cohort study, tested the hypothesis that, in the presence of noninvasive risk factors, programed ventricular stimulation would increase the diagnostic accuracy and value of this risk stratification strategy in this population (n=575; mean age, 57; women, 13.8%). The primary end point was the occurrence of major adverse events. This approach was able to identify a subpopulation of patients after a myocardial infarction with a preserved left ventricular ejection fraction who would benefit from a timely prevention with an implantable cardioverter-defibrillator.

Hohnloser SH, Camm J, Cappato R, et al. Uninterrupted edoxaban vs. vitamin K antagonists for ablation of atrial fibrillation: the ELIMINATE-AF trial. *Eur Heart J.* 2019;40(36):3013-3021.

While the use of edoxaban, compared with a vitamin K antagonist, has been shown to have superior efficacy and a lower risk of bleeding in the long-term treatment of patients with atrial fibrillation, no data is available supporting the uninterrupted periprocedural use of edoxaban during atrial fibrillation ablation. The ELIMINATE-AF trial, a multinational, multicenter, randomized, open-label, parallel-group study, compared the safety and efficacy of once-daily edoxaban 60 mg with vitamin K antagonists in patients with atrial fibrillation undergoing catheter ablation (n=614; mean age, 60.5 years; women, 28.5%). The primary end point was time to the first occurrence of all-cause death, stroke (ischemic, hemorrhagic, or undetermined), or International Society of Thrombosis and Haemostasis–defined major bleeding between the end of the ablation procedure and the end of treatment (90 days). Compared with vitamin K antagonists, the incidence of the primary end point was low with edoxaban.

Langsted A, Kamstrup PR, Nordestgaard BG. High lipoprotein(a) and high risk of mortality. *Eur Heart J.* 2019;40(33):2760-2770.

Despite knowing that lipoprotein(a) is associated with a high risk of cardiovascular disease, such as myocardial infarction and aortic valve stenosis, no randomized, double-blind evidence is available to show that lowering lipoprotein(a) reduces the risk of cardiovascular disease. This study used data from two prospective studies to assess the association between lipoprotein(a) levels and the risk of mortality, specifically if the associations are due to a low number of lipoprotein kringle-IV type 2 (LPA KIV-2) repeats (n=67 761; mean age; 59.2 years; women, 56.4%). Patients had a higher risk of mortality when they had high levels of lipprotein(a) with a low number of LPA KIV-2 repeats.

Leclercq C, Burri H, Curnis A, et al. Cardiac resynchronization therapy non-responder to responder conversion rate in the more response to cardiac resynchronization therapy with MultiPoint Pacing (MORE-CRT MPP) study: results from phase I. *Eur Heart J.* 2019;40(35):2979-2987.

While 60% to 65% of patients receive benefits from cardiac resynchronization therapy, the rest of the patients are nonresponders. The MORE-CRT MPP phase 1 study, a prospective, randomized, multicenter study, was conducted to analyze the effect of MultiPoint™ Pacing in patients who were nonresponders to standard biventricular pacing after 6 months (n=467; mean age, 68 years; women, 20.3%). The primary end point was the percentage of nonresponders who converted to responders at 12 months compared with baseline. At the end of follow-up, compared with biventricular pacing, MultiPoint™ Pacing did not significantly increase the echocardiographic response.

Mazidi M, Katsiki N, Mikhailidis DP, Sattar N, Banach M. Lower carbohydrate diets and all-cause and cause-specific mortality: a population-based cohort study and pooling of prospective studies. *Eur Heart J.* 2019;40(34):2870-2879.

While it has been established that eating a balanced diet and staying active have positive benefits on cardiovascular health, the type of diet is less established, especially low-carbohydrate diets. This population-based cohort study assessed the relationship between a low-carbohydrate diet and all-cause and case-specific (ie, cardiovascular disease, stroke, and cancer) mortality (n=24 825; mean age, 47.6 years; women, 51.4%). People with the lowest carbohydrate intake had the highest risk of mortality for overall, cardiovascular, cerebrovascular, and cancer mortality. Additionally, compared with obese people, nonobese people showed a higher association between a low-carbohydrate diet and overall.

McIntyre WF, Connolly SJ, Wang J, et al. Thromboembolic events around the time of cardioversion for atrial fibrillation in patients receiving antiplatelet treatment in the ACTIVE trials. *Eur Heart J.* 2019;40(36):3026-3032.

In order to restore sinus rhythm in patients with atrial fibrillation, cardioversion is often performed; however, it is unknown whether cardioversion causes thromboembolic events. Therefore, to evaluate causality, this study used prospectively collected data on patients who had received cardioversion in the antiplatelet arms of the ACTIVE trials (n=962; mean age, 65.5 years; women, 42.1%). The primary outcome was the monthly risk of a thromboembolic event (ischemic stroke, systemic embolism, or transient ischemic attack). The thromboembolic risk increased 30 days before and 30 days after cardioversion, with the risk being highest in hospitalized patients.

Rasmussen KL, Tybjærg-Hansen A, Nordestgaard BG, Frikke-Schmidt R. Plasma levels of apolipoprotein E, APOE genotype, and all-cause and cause-specific mortality in 105 949 individuals from a white general population cohort. *Eur Heart J.* 2019;40(33):2813-2824.

Low levels of apolipoprotein E have been associated with an increased risk of dementia, while high levels have been associated with an increased risk of ischemic heart disease. This prospective cohort study assessed whether plasma apolipoprotein E levels are associated with all-cause and cause-specific mortality and whether this association is independent of isoform differences due to the APOE genotype (n=104 153; mean age, 58.2%). High plasma levels of apolipoprotein E were associated with increased all-cause, cardiovascular, and cancer mortality, but from a noncausal nature.

Stiekema LCA, Stroes ESG, Verweij SL, et al. Persistent arterial wall inflammation in patients with elevated lipoprotein(a) despite strong low-density lipoprotein cholesterol reduction by proprotein convertase subtilisin/kexin type 9 antibody treatment. *Eur Heart J.* 2019;40(33):2775-2781.

While it is known that lipid-lowering therapy with a statin or lipoprotein apheresis reduces arterial wall inflammation in patients with an increased cardiovascular risk, the effect of lipid-lowering therapy on arterial wall inflammation in patients with elevated lipoprotein(a) levels is unknown. The ANITSCHKOW study, a phase 3b, multicenter, randomized, double-blind, placebo-controlled trial, investigated the effects of evolocumab, a drug that lowers low-density lipoprotein cholesterol and lipoprotein(a), on arterial inflammation (n=129; median age, 59.75 years; women, 53.45%). The primary end point was percentage change from baseline in most diseased segment target-to-background ratio of the index vessel (left carotid, right carotid, or thoracic aorta). Compared with placebo, evolocumab reduced low-density lipoprotein cholesterol by 60.7% and lipoprotein(a) by 13.9%; however, this did not translate into a reduction in arterial wall inflammation.

Tzoulaki I, Castagné R, Boulangé CL, et al. Serum metabolic signatures of coronary and carotid atherosclerosis and subsequent cardiovascular disease. *Eur Heart J.* 2019;40(34):2883-2896.

As the molecular pathways underlying atherosclerotic disease are not well characterized, this study used untargeted metabolic profiling with high-resolution proton nuclear magnetic resonance spectroscopy to analyze the serum metabolic signature of subclinical atherosclerosis in the coronary or carotid arteries (n=7436; mean age, 62.6 years; women, 47.1%). The identified metabolites associated with atherosclerosis showed disturbances in interconnected pathways related to lipid, fatty acid, and carbohydrate metabolism, branched chain amino acid and aromatic acid metabolism, the tricarboxylic acid and urea cycles, and muscle me-

tabolism. In addition to being associated with atherosclerosis, these metabolites were also associated with incident cardiovascular disease events.

van der Werf C, Lieve KV, Bos JM, et al. Implantable cardioverter-defibrillators in previously undiagnosed patients with catecholaminergic polymorphic ventricular tachycardia resuscitated from sudden cardiac arrest. *Eur Heart J.* 2019;40(35):2953-2961.

In patients at risk for sudden cardiac death, implantable cardioverter-defibrillators are a class I indication; however, in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT), implantable cardioverter-defibrillator shocks are often ineffective, and they may even trigger fatal electrical storms. This study analyzed data from the International CPVT Registry, a multicenter, retrospective, observational registry, to assess the efficacy and complications of implantable cardioverter-defibrillators in patients with CPVT who presented with a sentinel event of sudden cardiac arrest while undiagnosed and therefore untreated (n=136; mean age, 14 years; women, 75%). The primary outcome was sudden cardiac arrest. In this patient population, survival was not increased in those receiving an implantable cardioverter-defibrillator.

White HD, Steg PG, Szarek M, et al; ODYSSEY OUTCOMES Investigators. Effects of alirocumab on types of myocardial infarction: insights from the ODYSSEY OUTCOMES trial. *Eur Heart J.* 2019;40(33):2801-2809.

Reducing low-density lipoprotein cholesterol by using statins and PCSK9 inhibitors reduces the risk of myocardial infarction; however, little information is available concerning the effects on different types of myocardial infarction. This prespecified analysis of the ODYSSEY OUTCOMES trial, a multicenter, randomized, double-blind, placebo-controlled trial, analyzed the effects of alirocumab on different types of myocardial infarction in patients with a recent acute coronary syndrome and elevated low-density lipoprotein cholesterol despite statin therapy (n=18 924; mean age, 60.67 years; women, 28.4%). The primary composite end point was death due to coronary heart disease, nonfatal myocardial infarction, fatal and nonfatal ischemic stroke, or unstable angina requiring hospitalization. Adding alirocumab to intensive statin therapy reduced the incidence of type 1 and type 2 myocardial infarction. ■

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Aguirre Dávila L, Weber K, Bavendiek U, et al. Digoxin-mortality: randomized vs. observational comparison in the DIG trial. *Eur Heart J.* 2019;40(40):3336-3341.
The DIG trial, a large randomized trial of digoxin in patients with heart failure, previously showed that digoxin significantly reduced heart failure hospitalizations, but that it had a neutral effect on mortality. This additional analysis of the DIG trial was designed how to assess whether adjustment in an observational analysis would have the same treatment effect estimate as the randomization-based analysis of the DIG trial by comparing the main results of the DIG trial with an observational, nonrandomized comparison in patients who were pretreated with digoxin or digoxin-naive (n=6800; mean age, 63.45 years; women, 22.35%). In patients who were pretreated with dioxin, mortality and heart failure hospitalizations were significantly higher, showing that prescribing digoxin is an indicator of disease severity and worse prognosis.

Arbel Y, Ben-Assa E, Puzhevsky D, et al. Forced diuresis with matched hydration during transcatheter aortic valve implantation for Reducing Acute Kidney Injury: a randomized, sham-controlled study (REDUCE-AKI). *Eur Heart J.* 2019;40(38):3169-3178.
In patients undergoing a percutaneous coronary intervention, forced diuresis with matched hydration reduces the incidence of acute kidney injury; however, the role of this procedure on acute kidney disease in patients after a transcatheter aortic valve implantation is unknown. The REDUCE-AKI study, a single-center, prospective, randomized, double-blind, sham-controlled clinical trial, investigated the effects of forced diuresis with matched intravenous hydration vs sham treatment in patients undergoing transcatheter aortic valve implantation on acute kidney disease (n=136; mean age, 84.35 years; women, 41%). The primary end point was the reduction in the rate of acute kidney injury according to the Valve Academic Research Consortium-2 acute kidney classification. In contrast to the results in patients undergoing a percutaneous coronary intervention, forced diuresis did not reduce the incidence of acute kidney injury.

Belbachir N, Portero V, Al Sayed ZR, et al. RRAD mutation causes electrical and cytoskeletal defects in cardiomyocytes derived from a familial case of Brugada syndrome. *Eur Heart J.* 2019;40(37):3081-3094.
While it is known that Brugada syndrome predisposes patients to ventricular arrhythmias and sudden cardiac death, the genetic basis and cellular mechanisms are still mostly unknown. This study performed a whole-exome genetic sequencing analysis on a large family who were affected by Brugada syndrome to try to iden-

tify specific genes or gene mutations involved in disease susceptibility and the pathogenesis of Brugada syndrome. The study identified one rare nonsynonymous substitution (p.R211H) in RRAD, the gene encoding the Ras Associated with Diabetes (RAD) GTPase. The p.R211H variant induces a gain of function of RAD, thereby reducing the amplitude of the Na+ current and inducing a persistent Na+ current.

Bjursten H, Rasmussen M, Nozohoor S, et al. Infective endocarditis after transcatheter aortic valve implantation: a nationwide study. *Eur Heart J.* 2019;40(39):3263-3269.
While transcatheter aortic valve implantation is used to treat high-risk patients with severe aortic stenosis, little information is available about its use in younger and lower-risk patients. This retrospective, nationwide, all-comers, follow-up study of patients treated with transcatheter aortic valve implantation used data from three registries to analyze the incidence, risk factors, clinical presentation, and outcomes after prosthetic valve endocarditis (n=103; mean age, 40 years; women, 38.8%). Risk factors for prosthetic valve endocarditis were body surface area, estimated glomerular filtration rate <30 mL/min/1.73 m2, critical preoperative state, mean preprocedural valve gradient, amount of contrast dye used, transapical access, and atrial fibrillation. The incidence of prosthetic valve endocarditis was similar to surgical bioprostheses.

Ekström K, Lehtonen J, Nordenswan HK, et al. Sudden death in cardiac sarcoidosis: an analysis of nationwide clinical and cause-of-death registries. *Eur Heart J.* 2019;40(37):3121-3128.
Cardiac sarcoidosis is still not well known; therefore, this study analyzed the role of unexpected sudden cardiac death as a manifestation of cardiac sarcoidosis. The MIDFIN study group keeps a registry of adult patients with cardiac sarcoidosis and this study evaluated 351 cases of cardiac sarcoidosis from the MIDFIN registry (mean age, 52 years; women, 72%) showing that high-grade atrioventricular block was the most common first sign of cardiac sarcoidosis followed by heart failure, unexpected fatal or aborted sudden cardiac death, and sustained ventricular tachycardia.

Friebel J, Weithauser A, Witkowski M, et al. Protease-activated receptor 2 deficiency mediates cardiac fibrosis and diastolic dysfunction. *Eur Heart J.* 2019;40(40):3318-3332.
Extracellular matrix remodeling is a common factor between patients with heart failure with preserved ejection fraction and patients with pathological cardiac aging. Protease-activated receptor 1 and 2 (PAR1 and PAR2) activation is associated with cardiac fibrosis, and PAR1 expression is associated with heart failure severity, diastolic dysfunction, and prognosis in patients with heart failure with preserved ejection fraction; however, the role of PAR2 in patients with heart failure

with preserved ejection fraction, age-dependent cardiac fibrosis, or diastolic dysfunction is unknown. This study analyzed whether PAR2 deficiency is associated with age-dependent cardiac fibrosis and diastolic dysfunction in both mice and humans (n=14; mean age, 62.3 years; women, 35.7%). Chronic PAR2 deficiency was associated with cardiac fibrosis and diastolic dysfunction. The hypothesis generated from the study is that PAR2 negatively regulates caveolin-1 expression, which upregulates both transforming growth factor β and PAR1 signalling, thus affecting myocardial collagen deposition.

Habib G, Erba PA, Iung B, et al; EURO-ENDO Investigators. Clinical presentation, aetiology and outcome of infective endocarditis. Results of the ESC-EORP EURO-ENDO (European infective endocarditis) registry: a prospective cohort study. *Eur Heart J.* 2019;40(39):3222-3232.

Considering that, for infective endocarditis, the epidemiology has changed, new strategies have been developed to improve diagnosis and prognosis, new imaging techniques are being tested, and early surgery is recommended, but with no confirmed benefits on prognosis. The EURO-ENDO registry, a prospective, multicenter, observational study, was designed to analyze the management and outcomes of patients with infective endocarditis (n=3116; mean age, 59.25 years; women, 31.1%). The primary objective was to evaluate the outcome of patients diagnosed with infective endocarditis. The analysis shows that infective endocarditis occurs more frequently in men around 60 years of age, with the most frequent types being prosthetic infective endocarditis, intracardiac device-related infective endocarditis, nosocomial, staphylococcal, and enterococcal endocarditis are more frequent. Mitral valve repair is underutilized in the treatment of infective endocarditis, but the use of mechanical valve replacement is declining. Most importantly, the prognosis of infective endocarditis is still very poor.

Liesenborghs L, Meyers S, Lox M, et al. Staphylococcus aureus endocarditis: distinct mechanisms of bacterial adhesion to damaged and inflamed heart valves. *Eur Heart J.* 2019;40(39):3248-3259.

The incidence and mortality of Staphylococcus aureus endocarditis has increased over recent years in part because the pathogenesis is still unknown. This study used a newly developed 3D confocal microscopy endocarditis mouse model to analyze the initial step on S aureus endocarditis, ie, adhesion to the cardiac valve, in different risk states, such as endothelial damage, endothelial activation, and valve inflammation. Valve damage predisposed the mice to endocarditis by allowing S aureus to adhere to the von Willebrand factor and fibrin using Sortase A-dependent adhesins. Cardiac valve damage also predisposed mice to endocarditis by releasing cell-bound von Willebrand factor due to activation of the endothelium.

Morrow DA, Velazquez EJ, DeVore AD, et al. Cardiovascular biomarkers in patients with acute decompensated heart failure randomized to sacubitril-valsartan or enalapril in the PIONEER-HF trial. *Eur Heart J.* 2019;40(40):3345-3352.

The PIONEER-HF trial, a multicenter, randomized, double-blind, double-dummy, active-controlled trial, showed that the sacubitril-valsartan combination was well tolerated, with a greater reduction in N-terminal pro-brain natriuretic peptide concentration, and reduced the exploratory composite of cardiovascular death or rehospitalization for heart failure. In this substudy of the PIONEER-HF trial, a prospectively nested biomarker substudy, the early- and near-term effects of initiating the sacubitril-valsartan combination were compared with enalapril in hospitalized patients with acute decompensated heart failure following hemodynamic stabilization (n=694; median age, 62 years; 27%). The primary objective was to measure the change in concentration of three biomarkers (ie, circulating high-sensitivity troponin T (hsTnT), soluble suppression of tumorigenicity 2 (sST2), and urinary cGMP) at baseline, 1, 2, 4, and 8 weeks. Compared with enalapril, the sacubitril-valsartan combination led to a significantly greater decline in hsTnT and sST2 and an increase in serial urinary cGMP, which were sustained at 8 weeks.

Østergaard L, Bruun NE, Voldstedlund M, et al. Prevalence of infective endocarditis in patients with positive blood cultures: a Danish nationwide study. *Eur Heart J.* 2019;40(39):3237-3244.

While many studies have studied the association between a blood stream infection with Staphylococcus aureaus and the prevalence of infective endocarditis, few studies have looked at other blood stream infections. This study used data from a Danish nationwide study to evaluate the prevalence of infective endocarditis in patients with blood stream infections with bacteria typically associated with infective endocarditis (ie, Enterococcus faecalis, S aureus, Streptococcus spp, and coagulase negative staphylococci) (n=69 021; median age, 68.68 years; women, 43.5%). The highest prevalence of infective endocarditis was observed in patients with E faecalis, followed by S aureus, Streptococcus spp, and coagulase negative staphylococci. Compared with female patients, male patients had a higher prevalence of infective endocarditis for E faecalis, Streptococcus spp, and coagulase negative staphylococci.

Siontis GCM, Overtchouk P, Cahill TJ, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. *Eur Heart J.* 2019;40(38):3143-3153.

As more evidence from randomized controlled trials become available on the safety and efficacy of transcatheter aortic valve implantation in low-risk patients with severe aortic stenosis. This meta-analysis evaluated randomized controlled trials that compared transcatheter aortic valve implantation with surgical aortic

valve implantation in patients with severe aortic stenosis (n=8020; mean age, 85.4 years; women, 41%). The primary outcome was all-cause mortality up to 2 years. Transcatheter aortic valve implantation reduced all-cause mortality and stroke regardless of the baseline surgical risk and type of transcatheter heart valve system.

Tadros R, Tan HL, El Mathari S, et al; ESCAPE-NET Investigators. Predicting cardiac electrical response to sodium-channel blockade and Brugada syndrome using polygenic risk scores. *Eur Heart J.* 2019;40(37):3097-3107.

The use of sodium-channel blockers has been associated with arrhythmias, but there is variability in the cardiac electrical response, which is still a mystery. This study was designed to find predictors of ajmaline-induced PR and QRS changes and type I Brugada syndrome electrocardiogram by using data from published genome-wide association studies and performing a regression analysis to calculate polygenic risk scores for PR interval (PRSPR), QRS duration (PRSQRS), and Brugada syndrome (PRSBrS) (n=1368; mean age, 43.2 years; women, 49.5%). This study shows that genetic factors underlie the variability of cardiac electrical response to sodium-channel blockers; predictors of this variability include PRSBrS, family history, and a baseline ECG.

Weeke PE, Kellemann JS, Jespersen CB, et al. Long-term proarrhythmic pharmacotherapy among patients with congenital long QT syndrome and risk of arrhythmia and mortality. *Eur Heart J.* 2019;40(37):3110-3117.

While it is recommended that patients with congenital long QT syndrome avoid drugs that can cause torsades de pointes, it is unknown what the relationship is between the importance of treating conditions, such as hypertension or infection, and the use of QT-prolonging drugs. This study combined a Danish congenital long QT syndrome population with nationwide registries to determine whether treatment with torsades de pointes risk drugs before and after diagnosis of congenital long QT syndrome was associated with a risk of hospitalization for ventricular arrhythmias or all-cause mortality (n=279; mean age, 31.8 years; women, 63.8%). The primary outcome was the time to the first claimed torsades de pointes risk drug. The study identified that the use of torsades de pointes risk drugs were commonly used after diagnosis, there was a steady overall increase in their use after diagnosis, and the risk factors for treatment with torsades de pointes risk drugs include older age at diagnosis and previous treatment with torsades de pointes risk drugs. ■

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Chiesa ST, Charakida M, McLoughlin E, et al. Elevated high-density lipoprotein in adolescents with type 1 diabetes is associated with endothelial dysfunction in the presence of systemic inflammation. *Eur Heart J.* 2019;40(43):3559-3566.

The AdDIT trial showed that patients with type diabetes as early as 20 years of age had endothelial dysfunction, as well as an increase in high-density lipoprotein (HDL) cholesterol. HDL cholesterol can transform from a protective anti-inflammatory molecule to a dysfunctional pro-inflammatory equivalent. This study used a subset of patients included in the AdDIT trial to assess the vasoprotective properties of HDL cholesterol and its relationship with endothelial function (n=100; mean age, 14.25 years; women, 54%). In conditions of high inflammation, HDL-mediated nitric oxide bioavailability is decreased, HDL-mediated superoxide production is increased, and then endothelial function is compromised.

Czesnikiewicz-Guzik M, Osmenda G, Siedlinski M, et al. Causal association between periodontitis and hypertension: evidence from Mendelian randomization and a randomized controlled trial of non-surgical periodontal therapy. *Eur Heart J.* 2019;40(42):3459-3470.

Inflammation is an important contributor to hypertension; however, it is unknown how or if periodontitis, one of the most common inflammatory conditions worldwide, causes hypertension. This study used both Mendelian randomization to assess whether there was a causal relationship between periodontitis and hypertension and a single-center, parallel-group, randomized controlled trial to assess the effects of nonsurgical periodontal therapy on blood pressure in patients with hypertension (n=101; mean age, 54.5 years; women, 44%). The primary outcome for the trial was the average systolic 24-hour ambulatory blood pressure at 2 months. The Mendelian analysis showed that there was a significant relationship between single nucleotide polymorphisms linked with periodontitis and blood pressure phenotypes. Compared with control periodontal treatment (ie, supragingival scaling), intensive periodontal treatment (ie, sub- and supragingival scaling/chlorhexidine) improved periodontal status at 2 months, which was accompanied by a substantial reduction in mean systolic blood pressure.

Garimella PS, Lee AK, Ambrosius WT, et al. Markers of kidney tubule function and risk of cardiovascular disease events and mortality in the SPRINT trial. *Eur Heart J.* 2019;40(42):3486-3493.

While biomarkers for kidney tubule injury, inflammation, and fibrosis are established risk markers for adverse kidney and cardiovascular disease outcomes, data is lacking on the associations between biomarkers for kidney tubular function and

adverse clinical outcomes in patients with chronic kidney disease. This analysis of the SPRINT trial, an open-label clinical trial on patients with systolic blood pressure >130 mm Hg and a high risk of cardiovascular disease events, analyzed three biomarkers (ie, alpha-1 microglobulin, beta-2 microglobulin, and uromodulin) to assess whether better tubular function would lower the risk of cardiovascular events and mortality in participants with prevalent chronic kidney disease (n=2377; mean age, 73 years; women, 40%). The primary outcome was a composite cardiovascular end point that included myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or death from cardiovascular causes. After adjustment for confounding factors, such as estimated glomerular filtration rate, albuminuria, beta-2 microglobulin, and uromodulin, a two-fold higher alpha-1 microglobulin concentration was associated with a 26% greater risk for the composite cardiovascular event end point, whereas higher beta-2 microglobulin, after adjusting for confounding factors, was not associated with a greater risk of the composite cardiovascular end point. After adjusting for confounding factors, a two-fold higher uromodulin concentration was associated with a lower risk of cardiovascular events, but not mortality.

Giral P, Neumann A, Weill A, Coste J. Cardiovascular effect of discontinuing statins for primary prevention at the age of 75 years: a nationwide population-based cohort study in France. *Eur Heart J.* 2019;40(43):3516-3525.

Due to a lack of consistent data on the role of statin therapy for the primary prevention of cardiovascular disease in people aged >75 years, the guidelines do not have recommendations for or against statin use; therefore, it is unclear what effects stopping statin therapy will have in this group of people. This retrospective cohort study used data from the French national health insurance claims database to assess how statin discontinuation affects cardiovascular outcomes in previously adherent 75-year-old patients treated for primary prevention (n=120 173; women, 59.2%). The outcome was hospital admission for a cardiovascular event. Discontinuing statin therapy increased risk of being admitted for a cardiovascular event by 33%.

Hall KT, Kessler T, Buring JE, et al. Genetic variation at the coronary artery disease risk locus GUCY1A3 modifies cardiovascular disease prevention effects of aspirin. *Eur Heart J.* 2019;40(41):3385-3392.

Genome-wide association studies have identified common variants of GUCY1A3 that increase the risk for coronary artery disease and myocardial infarction and impaired platelet inhibition upon nitric oxide stimulation; however, it is unknown

whether the GUCY1A3 risk allele influences the outcomes following aspirin therapy. This study analyzed whether the GUCY1A3 genotype rs7692387, which, when homozygous, reduces the sensitivity to platelet inhibition, interacts with aspirin treatment (n=23 294; mean age, 54.7 years). The effects on rates of major cardiovascular disease, stroke, and myocardial infarction were assessed. In individuals homozygous for the GUCY1A3 risk allele, aspirin, in primary prevention, reduced the incidence of cardiovascular disease events compared with heterozygous individuals.

Jeong SW, Kim SH, Kang SH, et al. Mortality reduction with physical activity in patients with and without cardiovascular disease. *Eur Heart J.* 2019;40(43):3547-3555.

While physical activity is often recommended by the guidelines for secondary cardiovascular disease prevention, little data is available about the relationship between physical activity and mortality in patients with pre-existing cardiovascular disease. This population-based cohort study investigated the relationship between the benefits of physical activity and cardiovascular disease (n=441 798; mean age, 59.5 years; women, 46.5%). The primary study outcome measure was all-cause mortality. As the level of physical activity increases per week, the relative risk of mortality decreases in both patents with and without cardiovascular disease.

Mahfoud F, Böhm M, Schmieder R, et al. Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPLICITY Registry. *Eur Heart J.* 2019;40(42):3474-3482.

Even though studies and registries have shown that renal denervation can lead to sustained reduction in blood pressure, long-term data are not available. This trial used data from the Global SYMPLICITY registry, a prospective, open-label, single-arm, observational registry, to assess the long-term effectiveness, safety, and effects of renal denervation on renal function 3 years after the renal denervation procedure (n=2237; mean age, 61 years; women, 42%). The primary objective was the assessment of the procedural and long-term safety of renal denervation in a real-world setting, with recommended follow-up for 3 years. The reduction in systolic blood pressure observed after renal denervation was sustained at the 3-year follow-up for both office and 24-hour ambulatory systolic blood pressure. In addition, there were no long-term safety concerns reported following the procedure.

Mehra MR, Vaduganathan M, Fu M, et al. A comprehensive analysis of the effects of rivaroxaban on stroke or transient ischaemic attack in patients with heart failure, coronary artery disease, and sinus rhythm: the COMMANDER HF trial. *Eur Heart J.* 2019;40(44):3593-3602.

While the COMMANDER HF trial showed that there was no significant reduction in the primary composite end point of death, myocardial infarction, or stroke with rivaroxaban 2.5 mg twice daily plus aspirin compared with aspirin alone in patients with heart failure with reduced ejection (HFREF), the risk of stroke seemed lower with the addition of rivaroxaban. This post-hoc analysis of COMMANDER HF in patients with a recent episode of worsening chronic HFREF, sinus rhythm, coronary artery disease was conducted to assess the effect of low-dose rivaroxaban on the incidence, timing, type, and severity of stroke or transient ischemic attack, the clinical predictors of the stroke or transient ischemic attack occurrence, and the net clinical benefit of rivaroxaban treatment (n=5022; mean age, 66.4 years; women, 22.9%). The main neurological outcome was the time to the first all-cause stroke or transient ischemic attack. The main safety outcome was fatal bleeding or bleeding into a critical space with a potential to cause permanent disability. Compared with placebo, treatment with rivaroxaban significantly reduced the main neurological end point by 32% with a similar rate for the main safety end point.

Mohan M, Al-Talabany S, McKinnie A, et al. A randomized controlled trial of metformin on left ventricular hypertrophy in patients with coronary artery disease without diabetes: the MET-REMODEL trial. *Eur Heart J.* 2019;40(41):3409-3417.

Left ventricular hypertrophy is the most powerful prognostic factor in patients with coronary artery disease, where regression of this hypertrophy can reduce the incidence of major cardiovascular events. Several factors, such as blood pressure, insulin resistance, and central obesity, are implicated in the development of left ventricular hypertrophy. As metformin has been shown to improve insulin sensitivity and reduce insulin resistance, the MET-REMODEL study, a single-center, double-blind, placebo-controlled trial, tested the hypothesis that metformin may lead to a regression in left ventricular hypertrophy in patients who have coronary artery disease, with insulin resistance and/or prediabetes (n=63; mean age, 64.6 years; women, 25%). The primary end point was to determine whether metformin induces regression of left ventricular mass index using cardiac magnetic resonance imaging. Compared with the placebo group, the metformin group had a significantly reduced left ventricular mass index, as well as left ventricular mass, body weight, office systolic blood pressure, and oxidative stress.

Oikonomou EK, Williams MC, Kotanidis CP, et al. A novel machine learning-derived radiotranscriptomic signature of perivascular fat improves cardiac risk prediction using coronary CT angiography. *Eur Heart J.* 2019;40(43):3529-3543.

Considering that inflammation is not the only process involved in atherogenesis, this study set about assessing whether additional biomarkers of adverse fibrotic and microvascular perivascular adipose tissue, in addition to the biomarker Fat Attenuation Index, could help improve cardiac risk prediction. The goal of the study was to analyze the radiomic profile of coronary perivascular adipose tissue to help predict cardiac risk (n=167; mean age, 67 years; women, 16.2%). Using a machine learning-based analysis of traditional CCTA scans, a high-risk radiomic signature (fat radiomic profile [FRP]) was identified, which, by capturing more permanent structural changes in perivascular adipose tissue, significantly improves the risk prediction for adverse clinical events.

Rohde LE, Rover MM, Figueiredo Neto JA, et al. Short-term diuretic withdrawal in stable outpatients with mild heart failure and no fluid retention receiving optimal therapy: a double-blind, multicentre, randomized trial. *Eur Heart J.* 2019;40(44):3605-3612.

Patients with heart failure often receive a loop diuretic during an episode of acute decompensation; however, few studies have analyzed the risks and benefits associated with chronic diuretic use. The ReBIC trial, a randomized double-blind, placebo-controlled trial, tested the safety and tolerability of withdrawing low-dose furosemide in stable outpatients with heart failure (n=188; mean age, 60.95 years; women, 25.5%). The two coprimary end points were the area under the curve of serial assessments of the dyspnea using a visual analog scale from baseline to the end of follow-up and the proportion of patients maintained without loop diuretics during the follow-up period. Compared with continuous administration, withdrawal of furosemide did not lead to a significant difference in dyspnea and withdrawal was not associated with an increased reuse of additional diuretics.

van der Wal HH, Grote Beverborg N, Dickstein K, et al. Iron deficiency in worsening heart failure is associated with reduced estimated protein intake, fluid retention, inflammation, and antiplatelet use. *Eur Heart J.* 2019;40(44):3616-3625.

Despite the plethora of information available showing that iron deficiency has adverse clinical and prognostic consequences in patients with chronic heart failure, the pathophysiology and etiology are not clearly understood. This study analyzed patients with heart failure from the BIOSTAT-CHF study to identify the determinants of iron deficiency and sex-specific clinical and biochemical predictors of iron deficiency (n=2357; mean age, 68.9 years; women, 26.1%). The study shows that the independent determinants of iron deficiency in patients with heart failure were female sex, lower estimated protein intake, higher heart rate, presence of peripheral edema and orthopnea, chronic kidney disease, lower hemoglobin lev-

els, higher C-reactive protein levels, lower serum albumin levels, and the use of P2Y12 inhibitors; however, none of these determinants were sex-specific. The independent biomarkers for iron deficiency in patients with heart failure were mainly pro-inflammatory markers; paraoxonase 3 and tartrate-resistant acid phosphatase type 5 are downregulated in patients with heart failure and iron deficiency.

Zhang C, Jiang L, Xu L, et al. Implications of N-terminal pro-B-type natriuretic peptide in patients with three-vessel disease. *Eur Heart J.* 2019;40(41):3397-3405.
Both B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are established biomarkers for the diagnosis and prognosis of heart failure; however, it is unknown how useful these biomarkers will be for three-vessel coronary artery disease. This post-hoc analysis of data from a large prospective cohort of patients with three-vessel disease (ie, patients with angiographically confirmed stenosis of ≥50% in all three main epicardial coronary arteries with or without involvement of the left main artery) undergoing medical therapy alone, percutaneous coronary intervention, and coronary artery bypass grafting assessed whether baseline NT-proBNP levels can improve risk stratification and support for therapeutic decision-making (n=6597; mean age, 60.97 years; women, 19.85%). The primary end point was all-cause death. Higher NT-proBNP levels was associated with an increased risk of all-cause death, cardiac death, and major adverse cardiac and cerebrovascular events. In addition, NT-proBNP was shown to be useful in risk stratification, where NT-proBNP levels was significantly related to the association between treatment strategy and long-term outcomes. ■

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Abdel-Qadir H, Thavendiranathan P, Austin PC, et al. Development and validation of a multivariable prediction model for major adverse cardiovascular events after early stage breast cancer: a population-based cohort study. *Eur Heart J.* 2019;40(48):3913-3920.
Despite the higher risk of heart failure, cerebrovascular disease, and other cardiovascular disorders in women with early-stage breast cancer, there are no validated methods to estimate cardiovascular prognosis. Therefore, this study was designed to develop a model that could estimate the risk of major adverse cardiovascular events in women with early-stage breast cancer (n=90 104; mean age, 61 years). The primary outcome was major adverse cardiovascular events, ie, a composite of hospitalizations for acute myocardial infarction, unstable angina, transient ischemic attack, stroke, peripheral vascular disease, and heart failure, as well as death

from circulatory disease. The model incorporated the following risk factors shown to be associated with the incidence of major adverse cardiovascular events: age, hypertension, diabetes, ischemic heart disease, atrial fibrillation, heart failure, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, and chronic kidney disease. The evaluation of the developed model shows that it is able to predict major adverse cardiovascular events with good discrimination and calibration.

Blom MT, Oving I, Berdowski J, van Valkengoed IGM, Bardai A, Tan HL. Women have lower chances than men to be resuscitated and survive out-of-hospital cardiac arrest. *Eur Heart J.* 2019;40(47):3824-3834.

As previous studies on sex differences in patients with out-of-hospital cardiac arrest have yielded unclear results, this population-based cohort study used data from the ongoing, prospective community-based registry ARREST to analyze the sex differences related to care provision and outcomes after out-of-hospital cardiac arrest (n=5717; mean age, 67.1 years; women, 28%). Odds ratios were calculated for an association with sex and the chance of a resuscitation attempt by Emergency Medical Services, shockable initial rhythm, and in-hospital treatment. In addition, the study assessed the sex differences as regards overall survival and survival at successive stages of care. Compared with men, women were less like to receive out-of-hospital resuscitation by a bystander, and, in those who received resuscitation, the odds of overall survival to hospital discharge were lower.

Bonde AN, Blanche P, Staerk L, et al. Oral anticoagulation among atrial fibrillation patients with anaemia: an observational cohort study. *Eur Heart J.* 2019;40(46):3782-3790.

The standard treatment for patients with atrial fibrillation is oral anticoagulant, which increases the risk of major bleeding; however, in patients with atrial fibrillation and anemia, which increases the risk of bleeding, it is uncertain what the benefits and risks of oral anticoagulation will be in this group of patients. This study used data from Danish nationwide registries to assess the risk of stroke/thromboembolism and major bleeding associated with anemia in patients with atrial fibrillation (n=18 734; mean age, 79.4 years; women, 50.17%). Compared with patients without anemia, the risk of major bleeding increased in patients with moderate and severe anemia. Compared with patients with moderate and severe anemia, oral anticoagulants reduced the risk of stroke/thromboembolism in patients with no or mild anemia.

de Vries TI, Eikelboom JW, Bosch J, et al. Estimating individual lifetime benefit and bleeding risk of adding rivaroxaban to aspirin for patients with stable cardiovascular disease: results from the COMPASS trial. *Eur Heart J.* 2019;40(46):3771-3778a.

The COMPASS trial, a double-blind, randomized, placebo-controlled clinical trial, showed that rivaroxaban 2.5 mg twice daily plus aspirin was superior to aspirin alone in preventing major cardiovascular events and all-cause mortality in secondary prevention. This study was designed to develop a model to estimate the absolute individual lifetime treatment benefit or harm of rivaroxaban plus aspirin in patients with stable cardiovascular disease in terms of cardiovascular disease and major bleeding risk (n=35 529; mean age, 64 years; women, 24%). The lifetime models for benefit and risk of major bleeding developed were able to predict patients with stable cardiovascular disease, which will help identify those patients who will have a long-term net benefit from taking rivaroxaban plus aspirin by having additional cardiovascular disease–free life expectancy and a low risk of major bleeding.

Gargiulo G, Goette A, Tijssen J, et al. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. *Eur Heart J.* 2019;40(46):3757-3767.

Many trials (ie, PIONEER-AF PCI, RE-DUAL PCI, AUGUSTUS, and ENTRUST-AF PCI) have compared the safety and efficacy of dual antithrombotic therapy with triple antithrombotic therapy in patients with atrial fibrillation and acute coronary syndrome or who underwent a percutaneous coronary intervention; however, these trials were not sufficiently powered to assess the effect of treatment on cerebrovascular or cardiac ischemic events. This meta-analysis was conducted on non-vitamin K antagonist oral anticoagulant–based randomized trials comparing dual and triple antithrombotic therapy in patients with atrial fibrillation and percutaneous coronary intervention or acute coronary syndrome (n=10 260; mean age, 70.28 years; women, 25.89%). The primary safety bleeding end point was International Society on Thrombosis and Haemostasis major bleeding or clinically relevant non-major bleeding at the longest available follow-up (between 6 and 14 months). Compared with triple antithrombotic therapy, dual antithrombotic therapy significantly lowered the primary safety end point, but it significantly increased the incidence of stent thrombosis. No significant differences were observed between dual and triple antithrombotic therapy regarding all-cause and cardiovascular death, stroke, and major adverse cardiovascular events.

Heianza Y, Zheng Y, Ma W, et al. Duration and life-stage of antibiotic use and risk of cardiovascular events in women. *Eur Heart J.* 2019;40(47):3838-3845.

While many studies are showing an association between antibiotic use and cardiovascular and sudden cardiac death in the short term, data concerning the association with long-term cardiovascular events are lacking. Using data from the Nurses' Health Study on cumulative antibiotic use during adulthood, this study assessed the association between the duration of antibiotic use and cardiovascular risk and the association between the life-stage of antibiotic use with cardiovascular risk (n=36 429; mean age, 69.4 years). The composite end point was coronary heart disease (nonfatal myocardial infarction or fatal coronary heart disease) and total stroke (nonfatal or fatal). Women who had long-term antibiotic treatment (≥2 months) in late adulthood (≥60 years) had a significantly increased risk of cardiovascular disease and there was a trend for an increase in the risk of cardiovascular disease in women taking antibiotics in middle adulthood (40 to 59 years), but there was no significant relationship between the use of antibiotics in young adulthood (20 to 39 years) and the risk of cardiovascular disease.

Lafreniere-Roula M, Bolkier Y, Zahavich L, et al. Family screening for hypertrophic cardiomyopathy: is it time to change practice guidelines? *Eur Heart J.* 2019;40(45):3672-3681.

Family screening for hypertrophic cardiomyopathy is currently done at 10 to 12 years of age, with early screening reserved for individuals with an early growth spurt, family history of sudden cardiac death, and before participating in competitive sports; however, this guideline-recommended practice could miss detecting individuals with earlier-onset disease. This single-center, retrospective cohort study assessed whether the current age cut off was too high, thereby missing early-onset disease, which could have a strong impact on outcomes (n=524; mean age, 7.7 years; women, 44.8%). Current guidelines recommend initiating family screening for hypertrophic cardiomyopathy (HCM) after the ages of 10 or 12 unless early screening criteria are met. The primary outcome was the earliest major cardiac event, ie, death, sudden cardiac death, or need for major cardiac interventions (myectomy, implantable cardioverter-defibrillator insertion, transplantation). Of the children tested, 52.5% with phenotype-positive hypertrophic cardiomyopathy were <10 years of age, with 41% of major cardiovascular events occurring in children before the age of 10. Of the children with phenotype-positive hypertrophic cardiomyopathy, 31% did not meet the criteria for early screening.

Obokata M, Kane GC, Reddy YNV, et al. The neurohormonal basis of pulmonary hypertension in heart failure with preserved ejection fraction. *Eur Heart J.* 2019;40(45):3707-3717.

In patients with heart failure with preserved ejection fraction, pulmonary hypertension is common, and it is typically caused by passive elevation in left heart filling pressure; however, recent studies have shown that these patients have worse pulmonary vascular load with impaired right ventricular reserve; however, the underlying neurohormonal mechanism responsible for the abnormal right-ventricular-pulmonary artery coupling is unknown. This study tested the hypothesis that patients with heart failure with preserved ejection fraction would have higher plasma levels of C-terminal pro-endothelin-1 (CT-proET-1) and mid-regional pro-adrenomedullin (MR-proADM) (n=58; mean age, 65.5 years; women, 50%). In patients with heart failure with preserved ejection fraction, the levels of CT-proET-1 and MR-proADM were increased at rest and during exercise, whereby the levels were strongly correlated with mean pulmonary artery pressure and pulmonary capillary wedge pressure and inversely correlated with pulmonary artery compliance. Baseline CT-proET-1 and MR-proADM levels were associated with worse right ventricular diastolic reserve, reduced cardiac output responses to exercise, and more severely impaired peak VO2.

Reddy YNV, Obokata M, Wiley B, et al. The haemodynamic basis of lung congestion during exercise in heart failure with preserved ejection fraction. *Eur Heart J.* 2019;40(45):3721-3730.

It is known that, in patients with heart failure, extravascular lung water increases due to fluid filtration caused by pulmonary capillary hypertension due to left heart failure; however, the role for right heart failure has not been determined. This study investigated the mechanisms involved in extravascular lung water development in patients with heart failure with preserved ejection fraction during exercise by assessing the invasive hemodynamics, performing a lung ultrasound and echocardiography, sampling blood gas, and analyzing expired gas (n=61; mean age, 66 years; women, 51.5%). Compared with the group of patients without extravascular lung water, patients with extravascular lung water had higher pulmonary capillary wedge pressure, pulmonary artery pressure, and right atrial pressure, as well as worse right ventricular-pulmonary artery coupling.

Roos-Hesselink J, Baris L, Johnson M, et al. Pregnancy outcomes in women with cardiovascular disease: evolving trends over 10 years in the ESC Registry Of Pregnancy And Cardiac disease (ROPAC). *Eur Heart J.* 2019;40(47):3848-3855.

Maternal mortality rates related to heart disease are increasing worldwide, especially in western countries. The ROPAC registry, an international, prospective, observational registry of pregnant women with congenital heart disease, valvular heart disease, cardiomyopathy, or ischemic heart disease, was designed to provide detailed information on the impact that various cardiovascular diseases have on maternal and fetal mortality and morbidity (n=5739; mean age, 29.5 years). The primary end point was maternal mortality and/or heart failure. The incidence of mortality and/or heart failure was highest in patients with pulmonary arterial hypertension, followed by patients with cardiomyopathy.

Sturgeon KM, Deng L, Bluethmann SM, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. *Eur Heart J.* 2019;40(48):3889-3897.

While it is known that cancer survivors have an increased risk of cardiovascular diseases, it is unclear what the best primary prevention method is to use. The goal of this population-based observational study was to characterize the mortality risk of cardiovascular disease for multiple cancer sites according to the continuous calendar year, age at diagnosis, and follow-up time after diagnosis (n=3 234 256). Cancer survivors who had cancer of the urinary bladder, larynx, prostrate, corpus uteri, rectum, breast, and kidney and renal pelvis had the highest rate of death due to cardiovascular diseases (>10%), whereas cancer survivors who had cancer of the lung, liver, brain, stomach, gallbladder, multiple myeloma, pancreas, esophagus, and ovary cancer had the lowest rate of death due to cardiovascular disease (<10%). Cancer survivors (all sites) diagnosed before the age of 55 had a 10-fold greater risk of cardiovascular mortality compared with the general population. The highest risk of cardiovascular mortality occurs within the first year after a cancer diagnosis (all sites), which remains high throughout the follow-up period.

Tang TT, Zhu YC, Dong NG, et al. Pathologic T-cell response in ischaemic failing hearts elucidated by T-cell receptor sequencing and phenotypic characterization. *Eur Heart J.* 2019;40(48):3924-3933.

While preclinical studies have shown that inflammatory responses, with a well-characterized T-cell response, are involved in adverse ventricular remodeling after a myocardial infarction, the T-cell response in failing hearts in patients with a previous myocardial infarction are unknown. This study used next-generation sequencing, flow cytometry, and TR-PCR to analyze histopathological abnormalities, T-cell receptor repertoires, human leucocyte antigen alleles, phenotypes, and functional profiles of T cells in samples from patients with a previous myocardi-

al infarction. T cells from patients with ischemic failing hearts have a restricted and clonally expanded T-cell receptor repertoire, have tissue specificity, show increased proliferation, have memory- and effector-like characteristics, and produce large amounts of interferon γ, granzyme B, and perforin.

Van't Klooster CC, Ridker PM, Hjortnaes J, et al. The relation between systemic inflammation and incident cancer in patients with stable cardiovascular disease: a cohort study. *Eur Heart J.* 2019;40(48):3901-3909.

Low-grade inflammation not only has an important role in atherosclerotic disease, but it is also related to a higher risk of incident cancer. This prospective cohort study evaluated the relationship between systemic low-grade inflammation and the risk of recurrent cardiovascular disease (ie, myocardial infarction, stroke, or vascular death) and incident cancer in patients with stable cardiovascular disease using C-reactive protein levels (n=7178; mean age, 69.44 years; women, 25.4%). The concentration of C-reactive protein concentration was related to total cancer, especially lung cancer.

Wu H, Yang H, Rhee JW, et al. Modelling diastolic dysfunction in induced pluripotent stem cell-derived cardiomyocytes from hypertrophic cardiomyopathy patients. *Eur Heart J.* 2019;40(45):3685-3695.

Patients with hypertrophic cardiomyopathy have diastolic dysfunction, which can progress to diastolic heart failure; however, the cellular pathogenic mechanism of diastolic dysfunction is unclear. This study used an induced pluripotent stem cell–derived cardiomyocyte (iPSC-CMs) model to determine the cellular pathophysiology of diastolic dysfunction. In hypertrophic cardiomyopathy iPSC-CMs, diastolic intracellular Ca2+ was significantly elevated, leading to increased diastolic tension and impaired relaxation. There are two possible mechanisms contributing to this increased diastolic intracellular Ca2+: (i) Ca2+ removal through the Na+/Ca2+ exchanger is reduced, possibly due to higher intracellular Na+ concentrations; and (ii) increased myofilament Ca2+ sensitivity. ■

Snapshots of the Year:

JAMA

January 2019

Ference BA, Kastelein JJP, Ray KK, et al. Association of triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease. *JAMA.* 2019;321(4):364-373.

It is currently unknown whether reducing plasma triglyceride levels, which, like low-density lipoprotein (LDL) cholesterol, are also transported in the plasma by apolipoprotein B–containing lipoprotein particles, also lowers the risk of cardiovascular events to the same extent as lowering (LDL) cholesterol. Mendelian randomization analyses were used to assess the association between genetic scores composed of either a triglyceride-lowering variant in the lipoprotein lipase gene or LDL cholesterol–lowering variants in the LDL receptor gene and the risk of cardiovascular events (n=654 783 participants; mean age, 62.7 years; women, 51.4%). The primary outcome was the odds ratio for coronary heart disease, ie, the composite of coronary death, myocardial infarction, or coronary revascularization. The results showed that, for each unit difference in apolipoprotein B, the lower risk of coronary heart disease was similar between lowering LDL levels and lowering triglyceride levels.

McCartney PJ, Eteiba H, Maznyczka AM, et al; T-TIME Group. Effect of low-dose intracoronary alteplase during primary percutaneous coronary intervention on microvascular obstruction in patients with acute myocardial infarction: a randomized clinical trial. *JAMA.* 2019;321(1):56-68.

Microvascular obstruction is a complication resulting from failed microvascular reperfusion after a primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction. The T-TIME trial, a randomized, double-blind, parallel-group, phase 2 clinical trial, assessed the effect of alteplase, a low-dose intracoronary fibrin-specific fibrinolytic drug, on microvascular obstruction in patients with an ST-segment elevation myocardial infarction (n=440; mean age, 60.5 years; women, 15%). The primary end point was microvascular obstruction (percent of left ventricular mass determined using late gadolinium-enhanced magnetic resonance image) measured 2 to 7 days after reperfusion. The trial showed that, compared with placebo, alteplase did not reduce the level of microvascular obstruction when given during primary percutaneous interventions.

Rosenstock J, Perkovic V, Johansen OE, et al; CARMELINA Investigators. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. *JAMA.* 2019;321(1):69-79.

Patients with type 2 diabetes have an increased cardiovascular risk. Treatment with dipeptidyl peptidase 4 inhibitors have demonstrated cardiovascular safety; however, little information is available in these patients who also have a high risk of cardiorenal events. The CARMELINA trial, a randomized, placebo-controlled, multicenter, noninferiority trial, evaluated how linagliptin, a selective dipeptidyl peptidase 4 inhibitor, affected both cardiovascular and kidney outcomes in patients with type 2 diabetes over a median of 2.2 years (n=6991; mean age, 65.9 years; women, 37%). The primary outcome measure was the time to the first occurrence of the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The trial results showed that linagliptin plus usual care was noninferior to usual care alone on the risk of the composite end point; however, linagliptin did not show any benefit on the secondary kidney composite outcome.

Zheng SL, Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: a systematic review and meta-analysis. *JAMA.* 2019;321(3):277-287.

Despite the well-established evidence on the beneficial effects of aspirin for the secondary prevention of stroke and myocardial infarction, the evidence for primary prevention is not clear. Therefore, this systematic review and meta-analysis analyzed 13 randomized clinical trials that enrolled >1000 patients without cardiovascular disease to assess the role of aspirin in the primary prevention of cardiovascular and bleeding events (n=164 225 participants; median age, 62 years; women, 53%). For cardiovascular events, the primary outcome was a composite of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke, and, for bleeding events, the primary outcome was any major bleeding. Compared with no aspirin, aspirin significantly reduced the composite cardiovascular outcome, but it increased the risk of major bleeding events. ■

February 2019

Lerman BJ, Popat RA, Assimes TL, Heidenreich PA, Wren SM. Association of left ventricular ejection fraction and symptoms with mortality after elective noncardiac surgery among patients with heart failure. *JAMA.* 2019;321(6):572-579.

Globally, heart failure is a risk factor for postoperative mortality; however, little information is available about how the different subtypes of heart failure, eg, left ventricular ejection fraction and presence or absence of heart failure symptoms, affect surgical outcomes. This retrospective cohort study analyzed 609 735 patients undergoing elective noncardiac surgery (7.9% with heart failure [mean age, 68.6 years; women, 2.9%] and 92.1% without heart failure [mean age, 59.4 years; women, 9.1%]) to assess the association between heart failure severity and the risk of and postoperative mortality. The primary outcome measure was all-cause, 90-day, postoperative mortality. Compared with patients without heart failure, patients with heart failure, both asymptomatic and symptomatic, had a higher risk of 90-day postoperative mortality.

Van Spall HGC, Lee SF, Xie F, et al. Effect of patient-centered transitional care services on clinical outcomes in patients hospitalized for heart failure: the PACT-HF randomized clinical trial. *JAMA.* 2019;321(8):753-761.

Heart failure hospitalizations and rehospitalizations reduce patient quality of life and are associated with mortality. Approximately 40% of all early heart failure rehospitalizations occur due to poor transitional care. The PACT-HF trial, a stepped-wedge cluster randomized trial, assessed the effectiveness of patient-centered care transitions in a heart failure model of transitional care in patients hospitalized for heart failure on outcomes after hospital discharge (n=2494; mean age, 77.7 years; women, 50.4%). The primary outcomes were hierarchically ordered as composite all-cause readmission, emergency department visit, or death at 3 months and all-cause readmission or emergency department visit at 30 days. The trial showed no significant differences in the primary outcome between those receiving transition care and those receiving usual care. ■

March 2019

Blomström-Lundqvist C, Gizurarson S, Schwieler J, et al. Effect of catheter ablation vs antiarrhythmic medication on quality of life in patients with atrial fibrillation: the CAPTAF randomized clinical trial. *JAMA.* 2019;321(11):1059-1068.

In randomized trials on catheter ablation for atrial fibrillation, neither quality of life nor symptom measures have been used as a primary end point. The CAPTAF trial, a randomized clinical trial, assessed the effect of catheter ablation on quality of life at the 12-month follow-up visit in patients with atrial fibrillation despite taking antiarrhythmic medications (n=155; mean age, 56.1 years; women, 22.6%). The primary outcome was the General Health subscale score from the Medical Outcomes Study 36-Item Short-Form Health Survey at baseline and 12 months. The General Health score increase significantly in patients receiving ablation procedures vs those receiving antiarrhythmic medications alone.

Yau TM, Pagani FD, Mancini DM, et al; Cardiothoracic Surgical Trials Network. Intramyocardial injection of mesenchymal precursor cells and successful temporary weaning from left ventricular assist device support in patients with advanced heart failure: a randomized clinical trial. *JAMA.* 2019;321(12):1176-1186.

In patients with advanced heart failure that is refractory to medical therapy, left ventricular assist device therapy is the main surgical option to help improve myocardial function and survival; however, few patients recover sufficiently for explant. This randomized, phase 2, clinical trial assessed the efficacy and safety of intramyocardial injections of mesenchymal precursor cells during left ventricular assist device implantation (n=159; mean age, 56 years; women, 11.3%). The primary efficacy end point was the proportion (out of 3 assessments) of successful temporary weans from full to minimal support from the left ventricular assist device. Compared with the sham treatment (injection of a cryoprotective medium), injection of mesenchymal precursor cells did not result in a statistically significant difference in successful weaning from the left ventricular assist device support at 6 months.

Zhong VW, Van Horn L, Cornelis MC, et al. Associations of dietary cholesterol or egg consumption with incident cardiovascular disease and mortality. *JAMA.* 2019;321(11):1081-1095.

Despite having research data from several decades, controversy still exists concerning the relationship between consumption of dietary cholesterol and cardiovascular disease and mortality. Therefore, this study analyzed pooled data from 6 prospective US cohorts to determine if there was an association between dietary cholesterol consumption the primary outcome, ie, incident cardiovas-

cular disease (defined as a composite end point of fatal and nonfatal coronary heart disease, stroke, heart failure, and cardiovascular disease death from other causes) and all-cause mortality (n=29 615; mean age, 51.6 years; women, 55.1%). This studied concluded that, among US adults, a higher consumption of dietary cholesterol or eggs was significantly associated with higher risk of the primary outcome in a dose-response manner. ■

April 2019

Mark DB, Anstrom KJ, Sheng S, et al; CABANA Investigators. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA.* 2019;321(13):1275-1285.

Compared with conventional medical therapy, catheter ablation more effectively restores sinus rhythm in patients with symptomatic atrial fibrillation; however, its effect on long-term quality of life is uncertain. The CABANA trial used two quality of life measures to determine the effect of catheter ablation on quality of life (n=2204; median age, 68 years; women, 37%). The coprimary quality of life end points were the summary score of the Atrial Fibrillation Effect on Quality of Life questionnaire and the frequency score and severity score of the Mayo AF-Specific Symptom Inventory questionnaire at 12 months. Among patients with symptomatic atrial fibrillation, catheter ablation led to clinically important and significant incremental benefits on symptoms and quality of life.

Packer DL, Mark DB, Robb RA, et al; CABANA Investigators. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA.* 2019;321(13):1261-1274.

While atrial fibrillation is the most common cardiac tachyarrhythmia, it is a challenge to treat, as some patients remain asymptomatic, while others are symptomatic. Evidence is lacking from large randomized trials comparing catheter ablation with medical therapy. Therefore, the CABANA trial, an investigator-initiated, multicenter, prospective, randomized, open-label, clinical trial, assessed catheter ablation with conventional medical therapy in symptomatic patients with atrial fibrillation (n=2204; median age, 68 years; women, 37%). The primary end point was a composite of death, disabling stroke, serious bleeding, or cardiac arrest. Compared with medical therapy, catheter ablation did not lead to a significant reduction in patients with atrial fibrillation; however, events rates and treatment crossovers were lower than expected. ■

May 2019

Chan MTV, Wang CY, Seet E, et al; POSA Study Investigators. Association of unrecognized obstructive sleep apnea with postoperative cardiovascular events in patients undergoing major noncardiac surgery. *JAMA.* 2019;321(18):1788-1798.

While unrecognized obstructive sleep apnea is known to increase cardiovascular risks, it is unknown how sleep apnea affects cardiovascular risk in the perioperative period. The POSA study, a prospective cohort study, assessed the association between obstructive sleep apnea and the 30-day risk of cardiovascular complications after major noncardiac surgery in patients with no prior diagnosis of sleep apnea (n=1218; mean age, 67 years; women, 40.2%). The primary outcome was a composite of myocardial injury, cardiac death, heart failure, thromboembolism, atrial fibrillation, and stroke within 30 days of surgery. Obstructive sleep apnea was associated with a higher rate of the primary outcome, but it was only significant in patients with severe obstructive sleep apnea.

Wise RA, Chapman KR, Scirica BM, et al. Effect of aclidinium bromide on major cardiovascular events and exacerbations in high-risk patients with chronic obstructive pulmonary disease: the ASCENT-COPD randomized clinical trial. *JAMA.* 2019;321(17):1693-1701.

As there is some concern that long-acting muscarinic antagonists increase cardiovascular morbidity or mortality in patients with chronic obstructive pulmonary disease, this study was designed to assess the cardiovascular safety and efficacy of aclidinium bromide in patients with chronic obstructive pulmonary disease and cardiovascular disease or risk factors. The ASCENT-COPD trial, a multicenter randomized, placebo-controlled, double-blind, parallel-design study, randomized patients with moderate to very severe chronic obstructive pulmonary disease and either a history of cardiovascular disease or at least 2 atherothrombotic risk factors to aclidinium bromide or placebo (n=3589; mean age, 67.2 years; women, 41.3%). The primary safety end point was the time to the first major adverse cardiovascular event over 3 years and the primary efficacy end point was the annual chronic obstructive pulmonary disease exacerbation rate during the first year of treatment. The results showed that aclidinium bromide 400 µg twice daily was noninferior to placebo for the risk of major adverse cardiovascular events. ■

June 2019

Ekker MS, Verhoeven JI, Vaartjes I, Jolink WMT, Klijn CJM, de Leeuw FE. Association of stroke among adults aged 18 to 49 years with long-term mortality. *JAMA.* 2019;321(21):2113-2123.

Of all the stroke cases worldwide, 10% to 15% occur in adults between the ages of 18 and 49; however, due to these low numbers, it is difficult to estimate the mortality rates by age, sex, and stroke subtypes. This registry- and population-based study was initiated to analyze mortality rates in young adults following a stroke (n=15 527; median age, 44 years; women, 53.3%). The primary outcome was all-cause cumulative mortality at the end of follow-up, stratified for age, sex, and stroke subtype in 30-day survivors. Compared with the general population, 30-day survivor patients after the first stroke had an increased risk of mortality 15 years later.

Hahn JY, Song YB, Oh JH, et al; SMART-CHOICE Investigators. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. *JAMA.* 2019;321(24):2428-2437.

As neither short-term nor long-term dual antiplatelet therapy provides the best results following a percutaneous coronary intervention, P2Y12 inhibitor monotherapy after short-duration dual antiplatelet therapy is being tested as a new alternative treatment option. The SMART-CHOICE trial, an investigator-initiated, multicenter, open-label, noninferiority, randomized study, compared P2Y12 inhibitor monotherapy after short-term (3 months) dual antiplatelet therapy with 12-month dual antiplatelet therapy in patients undergoing percutaneous coronary intervention with drug-eluting stents (n=2993; mean age, 64 years; women, 26.6%). The primary end point was major adverse cardiac and cerebrovascular events, ie, a composite of all-cause death, myocardial infarction, or stroke at 12 months after the index procedure. There were no between-group differences in all-cause death, myocardial infarction, or stroke, but the rate of bleeding was significantly lower in the P2Y12 inhibitor group than in the dual antiplatelet therapy group.

Huded CP, Tuzcu EM, Krishnaswamy A, et al. Association between transcatheter aortic valve replacement and early postprocedural stroke. *JAMA.* 2019;321(23):2306-2315.

While transcatheter aortic valve replacement has become an established method to treat aortic stenosis, it has a similar risk of postprocedural stroke as surgical aortic valve replacement. This retrospective cohort study used data from the STS/ACC/TVT registry to analyze the trends in strokes after transcatheter aortic valve replacement and to assess whether there was an association between 30-

day mortality and stroke or medical therapy (n=101 430; median age, 83 years; women, 47.1%). The study outcomes were the rates of 30-day stroke, transient ischemic attack, and any neurologic event (stroke or transient ischemic attack). The rates for 30-day stroke remained stable in all patients. The occurrence of a stroke was associated with a significant increase in 30-day mortality; however, it was not associated with whether the patients were treated (or not) with either dual antiplatelet therapy at hospital discharge or with oral anticoagulant therapy at hospital discharge.

Shah SJ, Voors AA, McMurray JJV, et al. Effect of neladenoson bialanate on exercise capacity among patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA.* 2019;321(21):2101-2112.

The available treatments for patients with heart failure with preserved ejection fraction are ineffective. In preclinical trials, neladenoson bialanate, a first-in-class partial adenosine A1 receptor agonist, when compared with full adenosine A1 receptor agonists, improves mitochondrial function, enhances sarco/endoplasmic reticulum 2a activity, optimizes energy substrate utilization, reverses ventricular remodeling, and provides anti-ischemic cardioprotective effects without the adverse effects seen with full agonists. The PANACHE trial, a phase 2b, randomized, parallel-group, dose-finding, double-blind, multicenter clinical trial, assessed whether neladenoson bialanate could improve exercise capacity, physical activity, cardiac biomarkers, and quality of life in patients with heart failure with preserved ejection fraction with elevated natriuretic peptide levels (n=305; mean age, 74 years; women, 53%). The primary efficacy end point was the absolute change from baseline in the 6-minute walk test distance after 20 weeks of treatment; the minimal clinically important difference was an increase of 40 meters. Compared with placebo, there was no clinically relevant improvement in the primary end point for all doses of neladenoson bialanate (5 mg, 10 mg, 20 mg, 30 mg, and 40 mg).

Watanabe H, Domei T, Morimoto T, et al; STOPDAPT-2 Investigators. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. *JAMA.* 2019;321(24):2414-2427.

The optimal duration of dual antiplatelet therapy after percutaneous coronary interventions with drug-eluting stents in not clear. The STOPDAPT trial showed that treating patients for 3 months with dual antiplatelet therapy followed by aspirin monotherapy after implantation of a drug-eluting stent resulted in acceptable ad-

verse events. The STOPDAPT-2 trial, a multicenter, open-label, adjudicator-blinded, randomized clinical trial, tested the hypothesis that reducing the duration of dual antiplatelet therapy could be possible with newer-generation drug-eluting stents without causing an increase in cardiovascular events. The trial compared treatment with dual antiplatelet therapy for 1 month vs 12 months in patients following implantation of a cobalt-chromium everolimus-eluting stent (n=2974; mean age, 68.6 years; women, 22%). The primary end point was a composite of cardiovascular and bleeding events (cardiovascular death, myocardial infarction, definite stent thrombosis, ischemic or hemorrhagic stroke, or Thrombolysis in Myocardial Infarction major or minor bleeding). Not only was 1-month dual antiplatelet therapy noninferior to 12-month dual antiplatelet therapy, it was also superior to the 12-month therapy. ■

July 2019

Johnston KC, Bruno A, Pauls Q, et al; Neurological Emergencies Treatment Trials Network and the SHINE Trial Investigators. Intensive vs standard treatment of hyperglycemia and functional outcome in patients with acute ischemic stroke: the SHINE randomized clinical trial. *JAMA.* 2019;322(4):326-335.

As hyperglycemia during acute ischemic stroke is frequent and associated with worse outcomes, it is important to find an optimal treatment of hyperglycemia in patients with acute ischemic stroke. The SHINE trial, a randomized clinical trial with blinded outcome assessment, investigated the efficacy of intensive vs standard blood glucose control in adult patients with hyperglycemia and acute ischemic stroke (n=1151; mean age, 66 years; women 46%). The primary efficacy outcome was the proportion of patients with a favorable outcome at 90 days after randomization. There were no significant between-group differences in the functional outcome at 90 days. ■

August 2019

Duncan MS, Freiberg MS, Greevy RA Jr, Kundu S, Vasan RS, Tindle HA. Association of smoking cessation with subsequent risk of cardiovascular disease. *JAMA.* 2019;322(7):642-650.

While smoking is a known risk factor for cardiovascular disease and that quitting smoking reduces this risk, the pattern of cardiovascular risk reduction after quitting smoking is unknown. This retrospective analysis used the prospectively collected data from the Framingham Heart Study to determine the association between incident cardiovascular disease and years from the time of quitting smoking in patients with no baseline cardiovascular disease (n=8770; mean age, 42.2 years; women, 55%). The main outcome measure was incident cardiovascular disease (myocardial infarction, stroke, heart failure, or cardiovascular death). Compared with patients who are currently smoking, patients who quit smoking within 5 years had a significantly lower rate of incident cardiovascular disease. Compared with patients who have never smoked, patients who quit smoking no longer had a significant association with the risk of incident cardiovascular disease between 10 and 15 years after quitting.

Nasrallah IM, Pajewski NM, Auchus AP, et al; SPRINT MIND Investigators. Association of intensive vs standard blood pressure control with cerebral white matter lesions. *JAMA.* 2019;322(6):524-534.

While intensive systolic blood pressure control is effective in reducing cardiovascular disease morbidity and mortality, it is unknown how intensive control affects brain health in older adults with a risk of vascular disease. The SPRINT trial showed that intensive systolic blood pressure control reduced the rate of mild cognitive impairment. This substudy of SPRINT assessed the effect of intensive blood pressure treatment on cerebral white matter lesion and brain volumes in patients aged 50 years or older who had a systolic blood pressure between 130 and 180 mm Hg and an increased cardiovascular risk (n=670; mean age, 67.3 years; women, 40.4%). The primary MRI outcome was the change in total white matter lesion volume from baseline. Compared with standard systolic blood pressure control (<140 mm Hg), intensive blood pressure control (120 mm Hg) led to a significantly smaller increase in mean white matter lesion volume.

Walker KA, Sharrett AR, Wu A, et al. Association of midlife to late-life blood pressure patterns with incident dementia. *JAMA.* 2019;322(6):535-545.

An association has been made between high (and sometimes low) blood pressure and cognitive decline and dementia, but it is unknown how the chronicity

of blood pressure changes throughout life affects cognitive outcomes. Data from the ongoing ARIC study, a prospective population-based cohort study, tested the hypothesis that longer midlife hypertension durations with subsequent low blood pressure put patients at a higher risk of dementia. The study specifically investigated the association between midlife to late-life blood pressure patterns and incident dementia, mild cognitive impairment, and late-life cognitive change (n=4761; mean age, 75; women, 59%). The primary outcome was dementia onset after visit 5. Compared with patients who remained normotensive, the risk of dementia was higher in patients with both midlife and late-life hypertension as well as in patients with midlife hypertension and late-life hypotension. The risk of mild cognitive impairment was only observed in patients with midlife hypertension and late-life hypotension.

Yang WY, Melgarejo JD, Thijs L, et al; IDACO Investigators. Association of office and ambulatory blood pressure with mortality and cardiovascular outcomes. *JAMA.* 2019;322(5):409-420.

While the guidelines all recommend assessing blood pressure via ambulatory blood pressure monitoring, it is unclear which index has the highest association with adverse health outcomes, eg, overall mortality and cardiovascular-specific fatal and nonfatal outcomes. This longitudinal population-based cohort study was set up to investigate the strength of the association between blood pressure indexes and a composite cardiovascular event (n=11 135; median age, 54.7 years; women, 49.3%). The coprimary end points were total mortality and a composite cardiovascular event (cardiovascular mortality combined with nonfatal coronary events, heart failure, and stroke). Two blood pressure indexes–24-hour and nighttime–were associated with a higher risk of all-cause mortality and a composite cardiovascular outcome. ■

September 2019

Desai AS, Solomon SD, Shah AM, et al; EVALUATE-HF Investigators. Effect of sacubitril-valsartan vs enalapril on aortic stiffness in patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA.* 2019;322(11):1077-1084.
The PARADIGM-HF trial showed that, compared with enalapril, the sacubitril-valsartan combination reduced the primary composite outcome of cardiovascular death or heart failure hospitalizations in patients with heart failure and reduced ejection fraction. It has been hypothesized that these benefits are related to hemodynamic effects and cardiac remodeling. The EVALUATE-HF trial, a multicenter, randomized, double-blind, double-dummy trial, compared the effects of the sacubitril-valsartan combination with enalapril on central aortic stiffness and cardiac remodeling in patients with heart failure with reduced ejection fraction (n=464; mean age, 67.3 years; women, 23.5%). The primary end point was the between-group difference for the change in aortic characteristic impedance from baseline to week 12. Compared with enalapril, treatment with the sacubitril-valsartan combination did not significantly reduce central aortic stiffness.

Januzzi JL Jr, Prescott MF, Butler J, et al; PROVE-HF Investigators. Association of change in N-terminal pro-B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. *JAMA.* 2019;322(11):1085-1095.
Long-term therapy with the sacubitril-valsartan combination has been shown to lower the rates of cardiovascular disease, heart failure hospitalizations, and mortality and improve the quality of life in patients with heart failure and reduced ejection fraction (HFREF) vs enalapril, but the mechanism behind the benefits is unclear. The PARADIGM-HF trial showed that the combination reduced the concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP); however, it is not known yet whether this reduction is associated with reverse left ventricular remodeling, as is seen with guideline-directed medical therapies. The PROVE-HF study, a phase 4, 52-week, prospective, open-label, single-group study of patients initiated with sacubitril-valsartan treatment, investigated whether NT-proBNP changes in patients with HFREF after treatment with the sacubitril-valsartan combination are associated with changes in cardiac volume and function (n=794; mean age, 65.1 years; women, 28%). The primary end point of this study was the correlation between the changes in NT-proBNP concentrations and cardiac remodeling from baseline to 12 months. At 12 months, there was a significant increase in LVEF and significant decreases in left ventricular end-diastolic volume index, left ventricular end-systolic volume index, left atrial volume index, and early diastolic filling velocity and early diastolic mitral annular velocity. ■

October 2019

Aminian A, Zajichek A, Arterburn DE, et al. Association of metabolic surgery with major adverse cardiovascular outcomes in patients with type 2 diabetes and obesity. *JAMA.* 2019;322(13):1271-1282.

While a few, small, randomized controlled trials have shown that metabolic surgery significantly improves cardiometabolic risk factors in obese patients with type 2 diabetes, there is little information available about the effect of metabolic surgery on cardiovascular outcomes. This retrospective, observational, matched-cohort study assessed how metabolic surgery compared with usual care on incident major adverse cardiovascular events in obese patients with type 2 diabetes (n=13 722; median age, 53.6 years; women, 64.85%). The primary outcome was the incidence of extended major adverse cardiovascular events (composite of the first occurrence of all-cause mortality, coronary artery events, cerebrovascular events, heart failure, nephropathy, and atrial fibrillation). Compared with usual care, metabolic surgery significantly lowered the risk of incident major adverse cardiovascular events.

Ference BA, Bhatt DL, Catapano AL, et al. Association of genetic variants related to combined exposure to lower low-density lipoproteins and lower systolic blood pressure with lifetime risk of cardiovascular disease. *JAMA.* 2019;322(14):1381-1391.

As conducting a long-term randomized trial to assess the relationship between exposure to lower low-density lipoprotein cholesterol and lower systolic blood pressure and the lifetime risk of cardiovascular disease is unlikely, this study was set up to use genetic variants associated with lower low-density lipoprotein cholesterol levels and systolic blood pressure to be able to estimate the association between lifetime exposure and the lifetime risk of cardiovascular disease (n=438 952; mean age, 65.2 years; women, 54.1%). The primary outcome was major coronary events defined as a composite of coronary death, nonfatal myocardial infarction, or coronary revascularization. Exposure to increasing genetic risk scores and lower low-density lipoprotein cholesterol levels and systolic blood pressure was associated, in a dose-dependent manner, with a lower risk of major coronary events. ■

November 2019

Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease: the CLEAR Wisdom randomized clinical trial. *JAMA.* 2019;322(18):1780-1788.

For patients with very high cardiovascular risk or those with heterozygous familial hypercholesterolemia, statin therapy to lower cholesterol is not sufficient, meaning other treatment options are needed. Bempedoic acid alone or in combination with statins or ezetimibe significantly lowers low-density lipoprotein cholesterol, suggesting that it could be a possible future treatment option. The CLEAR Wisdom trial, a phase 3, randomized, double-blind, placebo-controlled clinical trial, assessed the efficacy of bempedoic acid vs placebo in lowering low-density lipoprotein cholesterol in patients with atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolemia, or both and persistent hypercholesterolemia (n=779; mean age, 64.3 years; women, 36.3%). The primary end point was percent change from baseline in LDL-C level at week 12. Compared with placebo, bempedoic acid lowered low-density lipoprotein cholesterol significantly more at week 12. In addition, bempedoic acid significantly reduced non-high-density lipoprotein cholesterol, total cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein.

Parker WF, Anderson AS, Gibbons RD, et al. Association of transplant center with survival benefit among adults undergoing heart transplant in the United States. *JAMA.* 2019;322(18):1789-1798.

As the number of people with heart failure with a priority status for a heart transplant has increased, the Organ Procurement and Transplant Network updated the heart allocation system; however, the benefits of the new system have not been assessed. This observational registry-based study investigated whether there was an association between different transplant centers and survival benefits in the US heart allocation system (n=29 199; mean age, 52 years; women, 26%). The primary outcome was the survival benefit associated with heart transplant as quantified by the estimated improvement in absolute 5-year survival gained by undergoing heart transplant. There was an association between transplant center and survival benefits, but the 5-year survival was not significantly different between centers with high and low survival benefits.

Callum J, Farkouh ME, Scales DC, et al. Effect of fibrinogen concentrate vs cryoprecipitate on blood component transfusion after cardiac surgery: the FIBRES randomized clinical trial. *JAMA.* 2019;322(20):1966-1976.
For patients with excessive bleeding and acquired hypofibrinogenemia after cardiac surgery, the guidelines recommend treatment with either cryoprecipitate or fibrinogen concentrate. The FIBRES study, an investigator-initiated, multicenter, randomized clinical trial, investigated whether fibrinogen concentrate is noninferior to cryoprecipitate for patients undergoing cardiac surgery with cardiopulmonary bypass who have bleeding-related hypofibrinogenemia (n=735; median age, 64 years; women, 30%). The primary efficacy outcome was cumulative allogeneic blood component units administered for 24 hours after termination of cardiopulmonary bypass. The study showed that fibrinogen concentrate was noninferior to cryoprecipitate regarding the primary outcome. ■

December 2019

Damrauer SM, Chaudhary K, Cho JH, et al. Association of the V122I hereditary transthyretin amyloidosis genetic variant with heart failure among individuals of African or Hispanic/Latino ancestry. *JAMA.* 2019;322(22):2191-2202.
While it is known that hereditary transthyretin amyloid cardiomyopathy due to a transthyretin V122I variant causes heart failure in elderly people of African ancestry, it is unknown how this variant affects other African populations, such as Hispanic/Latino populations. This cross-sectional cohort analysis was designed to evaluate the association between the V122I variant and heart failure (n=3724; median age, 64 years; women, 53%). The primary outcome was prevalent heart failure at the time of data extraction. The study showed that there was a significant association between the V122I genetic variant and heart failure in other African populations.

Kozhuharov N, Goudev A, Flores D, et al; GALACTIC Investigators. Effect of a strategy of comprehensive vasodilation vs usual care on mortality and heart failure rehospitalization among patients with acute heart failure: the GALACTIC randomized clinical trial. *JAMA.* 2019;322(23):2292-2302.
In patients with chronic heart failure with reduced ejection fraction, patients with acute heart failure still have very high rates of morbidity and mortality. High doses of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers were more beneficial in patients with chronic heart failure than were low doses. The GALACTIC trial, an investigator-initiated, open-label, blinded end point, mul-

tinational, multicenter randomized trial, investigated how an early intensive and sustained treatment with vasodilators affected outcomes in patients with acute heart failure (n=781; median age, 78 years; women, 36.9%). The primary end point was a composite of all-cause mortality or rehospitalization for acute heart failure at 180 days. Compared with usual care, there was no significant difference in the primary end point with the early intensive and sustained vasodilation strategy.

Schermerhorn ML, Liang P, Eldrup-Jorgensen J, et al. Association of transcarotid artery revascularization vs transfemoral carotid artery stenting with stroke or death among patients with carotid artery stenosis. *JAMA.* 2019;322(23):2313-2322.

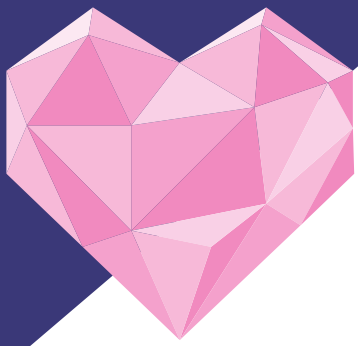
While it has been shown that transfemoral carotid artery stenting leads to higher rates of perioperative stroke than does carotid endarterectomy; however, it is unclear what effect the recently introduced technique of transcarotid artery revascularization with flow reversal would have on outcomes. This exploratory propensity score-matched analysis of prospectively collected data on asymptomatic and symptomatic patients undergoing transcarotid artery revascularization and transfemoral carotid artery stenting for carotid artery stenosis was conducted to provide an updated analysis and information on the benefits of transcarotid artery revascularization concerning the risk of stroke or death (n=5251; mean age, 71.65 years; women, 35.4%). The exploratory outcomes included in-hospital stroke or death (a composite end point), stroke, death, myocardial infarction, and transient ischemic attack, as well as ipsilateral stroke or death at 30 days and at 1 year. The analysis showed that the risk of in-hospital stroke or death was significantly lower with transcarotid artery revascularization compared with transfemoral carotid artery stenting.

Honigberg MC, Zekavat SM, Aragam K, et al. Association of premature natural and surgical menopause with incident cardiovascular disease. *JAMA.* 2019;322(24):2411-2421.

In an earlier analysis, a modest association was observed between premature menopause (<40 years of age) and an increased risk of heart failure; however, robust data are lacking concerning the risk of developing cardiovascular diseases and the specific cardiovascular risk factors in these women. This population-based cohort study used data from the large-scale, observational UK Biobank to investigate whether premature menopause was associated with developing cardiovascular disease in the future (n=144 260; mean age, 59.9 years). The primary outcome was a composite of incident coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation or flutter, ischemic stroke, peripheral artery disease, and venous thromboembolism. When compared with postmenopausal women, the risk of the composite outcomes was slightly, but significantly, higher. ■

Snapshots of the Year:

The Lancet



January 2019

Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet.* 2019;393(10166):61-73.
In patients with dilated cardiomyopathy who, after treatment, become asymptomatic with recovered cardiac function and symptom resolution, there is little evidence showing whether these patients need to continue treatment indefinitely. The TRED-HF trial, an open-label, pilot, randomized trial, studied phased withdrawal of treatment for heart failure (n=51; median age, 55 years; women, 33.5%). The primary end point was a relapse of dilated cardiomyopathy within 6 months, defined by at least one of the following four parameters: (i) a reduction in left ventricular ejection fraction by >10%, but <50%; (ii) an increase in left ventricular end-diastolic volume by >10% and to higher than the normal range; (iii) a 2-fold increase in baseline N-terminal pro-B-type natriuretic peptide concentration and to >400 ng/L; or (iv) clinical evidence of heart failure, based on signs and symptoms as adjudicated by the research team. The trial showed that, in patients with previous dilated cardiomyopathy who were now asymptomatic, phased withdrawal of heart failure medications will lead to a relapse following treatment withdrawal.

Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet.* 2019;393(10166):31-39.
The effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular outcomes have been studied in large cardiovascular outcome trials in patients with type 2 diabetes, showing that they had greater effects on major adverse cardiovascular events in certain subgroups. This systematic review and meta-analysis was conducted on randomized, placebo-controlled, cardiovascular outcome trials on sodium-glucose cotransporter-2 inhibitors in patients with type 2 diabetes (n=34 322; mean age, 63.43; women, 33.9%). The efficacy outcomes were major adverse cardiovascular events (myocardial infarction, stroke, or cardiovascular death), the composite of cardiovascular death or hospitalization for heart failure, and progression of renal disease. Sodium-glucose cotransporter-2 inhibitors moderately reduced major adverse cardiovascular events in patients with type 2 diabetes, but only in the subgroup with atherosclerotic cardiovascular disease. In addition, sodium-glucose cotransporter-2 inhibitors robustly reduced hospitalizations for heart failure and progression of renal disease regardless of whether the patients had existing atherosclerotic cardiovascular disease or a history of heart failure. ■

February 2019

Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet.* 2019;393(10170):407-415.

Evidence is available showing that for every 1.0 mmol/L reduction in low-density lipoprotein cholesterol with a statin, the risk of major vascular events is reduced. However, the rates for statin use have been declining with increasing age. This meta-analysis analyzed 28 randomized trials on statin therapy among 6 different age groups, ie, ≤55 years, 56-60 years, 61-65 years, 66-70 years, 71-75 years, and >75 years (n=186 801; mean age, 70.2 years; women, 34%). The main outcomes were major coronary events (ie, nonfatal myocardial infarction or coronary death), coronary revascularization, stroke, site-specific cancers, and cause-specific mortality. The analysis showed that statin therapy significantly reduces major vascular events (ie, the composite of major coronary events, coronary revascularization, and stroke) over all ages, with the exception of patients aged 75 years or older where there is less direct evidence. ■

March 2019

Anderson CS, Huang Y, Lindley RI, et al; ENCHANTED Investigators and Coordinators. Intensive blood pressure reduction with intravenous thrombolysis therapy for acute ischaemic stroke (ENCHANTED): an international, randomised, open-label, blinded-endpoint, phase 3 trial. *Lancet.* 2019;393(10174):877-888.

While a contraindication for using intravenous alteplase in patients with ischemic stroke is having a systolic blood pressure >185 mm Hg, the optimal blood pressure target for optimal results is unknown. The ENCHANTED trial, an international, multicenter, prospective, randomized, open-label, blinded end point trial with a 2×2 partial-factorial design, assessed the effectiveness of low-dose vs standard-dose alteplase and intensive versus guideline-recommended blood pressure control in patients ≥18 years old with acute ischemic stroke and a systolic blood pressure ≥150 mm Hg (n=2196; mean age, 66.9 years; women, 38%). The primary outcome measure was a shift in measures of functioning according to the full range of scores on the mRS, a global, seven-level assessment of disability, which was assessed at 90 days in the intention-to-treat population. An intensive blood pressure lowering (target systolic blood pressure 130 to 140 mm Hg within 1 hour) was shown to be safe; however, the observed reduction in intracranial hemorrhage did not improve clinical outcomes compared with guideline-recommended treatment.

Zaman A, de Winter RJ, Kogame N, et al; TALENT trial investigators. Safety and efficacy of a sirolimus-eluting coronary stent with ultra-thin strut for treatment of atherosclerotic lesions (TALENT): a prospective multicentre randomised controlled trial. *Lancet.* 2019;393(10175):987-997.

Supraflex is a sirolimus-eluting coronary stent with an ultrathin stent thickness of 60 µm that demonstrated a low incidence of major adverse cardiac events in the FLEX-Registry; however, it has not been analyzed in a randomized clinical trial. The TALENT trial, a prospective, randomized, controlled, single-blind, multicenter study, compared the Supraflex stent with the standard of care for atherosclerotic lesions (n=1435; median age, 65.5 years; women, 23.85%). This trial was a noninferiority comparison concerning the device-oriented composite primary end point of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularization. The trial showed that, in an all-comer population, a sirolimus-eluting stent with a biodegradable polymer coating and ultra-thin struts (Supraflex) was noninferior to an everolimus-eluting stent with a durable polymer coating (Xience) at 12 months. ■

April 2019

Hamada H, Suzuki H, Onouchi Y, et al; KAICA Trial Investigators. Efficacy of primary treatment with immunoglobulin plus ciclosporin for prevention of coronary artery abnormalities in patients with Kawasaki disease predicted to be at increased risk of non-response to intravenous immunoglobulin (KAICA): a randomised controlled, open-label, blinded-endpoints, phase 3 trial. *Lancet.* 2019;393(10176):1128-1137.

Recent genome-wide studies have identified genetic variants of the ITPKC and CASP2 genes that confer susceptibility to Kawaskai disease, a disease that primarily affects infants and young children. The gene variants are thought to increase cell signaling via the calcium-nuclear factor of activated T-cell pathway, resulting in increased inflammation. The KAICA trial, a randomized, open-label, blinded end point trial, investigated the efficacy and safety of intravenous immunoglobulin and cyclosporin combination therapy vs conventional intravenous immunoglobulin therapy in children with Kawasaki disease who were predicted to be unresponsive to intravenous immunoglobulin therapy (n=173; mean age, 37.75 months; women, 43%). The primary end point was the incidence of coronary artery abnormalities from treatment day 3 to week 12. The trial showed that intravenous immunoglobulin plus cyclosporin was safe and effective as the primary treatment to prevent coronary artery abnormalities in Japanese patients with refractory Kawasaki disease.

Villanueva C, Albillos A, Genescà J, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet.* 2019;393(10181):1597-1608.

For patients with cirrhosis, portal hypertension is a main determinant for the development of decompensation, which is characterized by variceal hemorrhage, ascites occurrence, or hepatic encephalopathy. The PREDESCI trial, an investigator-initiated, randomized, double-blind, placebo-controlled, multicenter clinical trial, analyzed whether long-term treatment of patients with compensated cirrhosis and clinically significant portal hypertension (hepatic venous pressure gradient ≥10 mm Hg) using β-blockers would prevent disease progression to clinical decompensation or death (n=201; mean age, 59.5 years; women, 30.25%). The primary outcome was decompensation of cirrhosis (ie, appearance of ascites, gastrointestinal bleeding related to portal hypertension, or overt hepatic encephalopathy) or death. In patients with compensated cirrhosis and clinically significant portal hypertension without high-risk varices, treatment with β-blockers reduced the incidence of ascites.■

June 2019

Piccolo R, Bonaa KH, Efthimiou O, et al; Coronary Stent Trialists' Collaboration. Drug-eluting or bare-metal stents for percutaneous coronary intervention: a systematic review and individual patient data meta-analysis of randomised clinical trials. *Lancet.* 2019;393(10190):2503-2510.

When comparing drug-eluting stents, the comparison is often made between the new-generation and the early-generation stents; however, few comparisons have focused on new-generation drug-eluting stents vs bare-metal stents. Therefore, this meta-analysis was carried out on randomized clinical trials on new-generation drug-eluting stents or bare-metal stents among patients undergoing percutaneous coronary interventions (n=26 616; mean age, 66 years; women, 24.6%). The primary outcome was a composite of cardiac death or myocardial infarction. The analysis showed that drug-eluting stents reduced the risk of the primary outcomes by reducing the risk of myocardial infarction, definite stent thrombosis, and target vessel revascularizations, which was better than that obtained with bare-metal stents.

Spahn DR, Schoenrath F, Spahn GH, et al. Effect of ultra-short-term treatment of patients with iron deficiency or anaemia undergoing cardiac surgery: a prospective randomised trial. *Lancet.* 2019;393(10187):2201-2212.
Treating iron deficiency in patients with congestive heart failure improves functional status and reduces hospital admissions and mortality. Therefore, there are recommendations to treat iron deficiency preoperatively especially in patients with impaired left ventricular function undergoing cardiac surgery. This single-center, randomized, double-blind, parallel-group controlled study assessed whether treating anemia or iron deficiency in patients scheduled for elective isolated coronary artery bypass grafting, valve surgery, or the combination of the two could reduce perioperative red blood cell transfusions and improve perioperative outcomes (n=484; mean age, 68 years; women, 34.5%). The primary end point was the number of red blood cell transfusions administered during the first 7 days, until death or hospital discharge, whichever came first. In patients with anemia or isolated iron deficiency, those who received a combination treatment of intravenous iron, subcutaneous erythropoietin alpha, vitamin B12, and oral folic acid the day before surgery had a lower rate of red blood cell and total allogeneic blood product transfusions than did patients receiving placebo. ■

July 2019

Bornstein NM, Saver JL, Diener HC, et al; ImpACT-24B investigators. An injectable implant to stimulate the sphenopalatine ganglion for treatment of acute ischaemic stroke up to 24 h from onset (ImpACT-24B): an international, randomised, double-blind, sham-controlled, pivotal trial. *Lancet.* 2019;394(10194):219-229.
In preclinical studies on stroke models, sphenopalatine ganglion stimulation increases cerebral blood flow in the collateral circulation, stabilizes the blood-brain barrier, and reduces infarct volume. In a pilot randomized trial, stimulation of the sphenopalatine ganglion indicated that there is a potential benefit on functional outcome improvements. The ImpACT-24B trial, a multinational, randomized, sham-controlled, double-blind, adjunct to standard of care, parallel-group trial, investigated whether starting sphenopalatine ganglion stimulation within 24 hours after an acute ischemic stroke improved functional outcomes (n=1520; mean age, 70.5 years; women, 50%). The primary efficacy end point was an improvement beyond expectation on the 3-month mRS of global disability. In patients with anterior-circulation acute ischemic stroke not undergoing reperfusion therapy, active sphenopalatine ganglion stimulation is safe for patients who are ineligible for thrombolytic therapy.

Campbell BCV, Ma H, Ringleb PA, et al; EXTEND, ECASS-4, and EPITHET Investigators. Extending thrombolysis to 4.5-9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. *Lancet.* 2019;394(10193):139-147.

While the guidelines suggest giving alteplase between 0 and 4.5 hours after presenting with an acute ischemic stroke, there is little information available on its use in patients beyond this 4.5-hour window. This systematic review and meta-analysis on individual patient data assessed functional outcomes from using alteplase (vs placebo) after the 4.5-hour window from stroke onset (n=414; mean age, 72.6 years; women, 43%). The primary outcome was the proportion of patients with excellent functional outcome (ie, an mRS score of 0 to 1 at 3 months; this score was adjusted for pretreatment clinical severity and age. Compared with placebo, alteplase helped patients with ischemic stroke who were beyond 4.5 hours from stroke onset achieve better functional outcomes. While the rate of symptomatic intracerebral hemorrhage was higher with alteplase, there was no difference observed for the rate of mortality.

Gerstein HC, Colhoun HM, Dagenais GR, et al; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet.* 2019;394(10193):121-130.

Glucagon-like peptide-1 (GLP-1) receptor agonists reduce cardiovascular events in patients with type 2 diabetes and mean glycated hemoglobin A1c (HbA1c) concentration ≥80% who are ≥50 years old. The GLP-1 receptor agonist dulaglutide has been approved for the management of hyperglycemia in patients with type 2 diabetes due to evidence showing that it safely reduces glucose concentrations, blood pressure, weight, and albuminuria. The REWIND trial, a multicenter, randomized, double-blind, placebo-controlled trial, investigated whether dulaglutide, added to the diabetes medications given to patients ≥50 years old with type 2 diabetes, would reduce the incidence of cardiovascular outcomes (n=9901; mean age, 66.2 years; women, 46.35%). The primary end point was the first occurrence of any component of the composite outcome of nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes or unknown causes. The study showed that weekly subcutaneous injections of dulaglutide 1.5 mg reduced cardiovascular outcomes in both men and women with or without previous cardiovascular disease.

Rissanen TT, Uskela S, Eränen J, et al; DEBUT Trial Investigators. Drug-coated balloon for treatment of de-novo coronary artery lesions in patients with high bleeding risk (DEBUT): a single-blind, randomised, non-inferiority trial. *Lancet.* 2019;394(10194):230-239.

In patients with a high bleeding risk, the optimal procedure for percutaneous coronary intervention is unknown. Therefore, the DEBUT trial, an investigator-initiated,

randomized, single-blind, multicenter, noninferiority trial, assessed whether a percutaneous coronary intervention using a drug-coated balloon-only strategy was noninferior to using a bare-metal stent in patients with ≥1 risk factor for bleeding and a de-novo coronary artery lesion (n=208; mean age, 76.9 years; women, 37%). The primary end point was major adverse cardiovascular events (ie, a composite of cardiovascular mortality, nonfatal myocardial infarction, or ischemia-driven target-lesion revascularization) at 9 months. The study showed that, in the patient group analyzed, percutaneous coronary intervention with a drug-coated balloon (paclitaxel and iopromide) was superior to bare-metal stents. ■

August 2019

NCD Risk Factor Collaboration (NCD-RisC). Long-term and recent trends in hypertension awareness, treatment, and control in 12 high-income countries: an analysis of 123 nationally representative surveys. *Lancet.* 2019394(10199):639-651.
Data concerning how high-income countries compare as regards hypertension awareness, treatment, and control or how they compare in terms of performance over time. This study used data on hypertension trends from national health examination surveys that measured blood pressure in the general population in 12 high-income countries. The analysis showed that, despite the improvements in hypertension awareness, treatment, and control, the blood pressure–control rates have reached a plateau; however, these rates varied between the countries analyzed.

Schunk SJ, Zarbock A, Meersch M, et al. Association between urinary dickkopf-3, acute kidney injury, and subsequent loss of kidney function in patients undergoing cardiac surgery: an observational cohort study. *Lancet.* 2019;394(10197):488-496.
In patients undergoing cardiac surgery, the most frequent complication is acute kidney injury, with an incidence of 26.0% to 28.5%. In a murine model of chronic kidney disease, genetic nullification of dickkopf-3, a glycoprotein that modulates the Wnt/β-catenin signaling pathway, a pathway, which, when activated, promotes chronic kidney disease after acute kidney injury, prevents kidney disease progression. This observational cohort study investigated the association between the ratio of preoperative urinary concentrations of dickkopf-3 to creatinine and postoperative acute kidney injury (n=733; mean age, 63.6 years; women, 31%). In patients undergoing elective cardiac surgery, preoperative urinary concentrations of the renal tubular stress marker dickkopf-3 was shown to be an independent predictor for both postoperative acute kidney injury and a subsequent loss of kidney function. ■

September 2019

Attia ZI, Noseworthy PA, Lopez-Jimenez F, et al. An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction. *Lancet.* 2019;394(10201):861-867.
Current screening methods for atrial fibrillation require prolonged monitoring and are cost prohibitive, meaning that a low-cost, widely available, and noninvasive test would be very beneficial to help predict those patients who will have atrial fibrillation (n=180 922; mean age, 60.3 years; women, 50.4%). The primary outcome of this study was the ability of the artificial intelligence–enhanced ECG to identify patients with atrial fibrillation using a standard 10-second, 12-lead ECG recorded during sinus rhythm. The results from 180 922 patients showed that an artificial intelligence–enabled ECG acquired during normal sinus rhythm helps identify individuals with atrial fibrillation.

Bhatt DL, Steg PG, Mehta SR, et al; THEMIS Steering Committee and Investigators. Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial. *Lancet.* 2019;394(10204):1169-1180.
Patients with stable coronary artery disease and diabetes with a previous percutaneous coronary intervention have a high risk of ischemic events. The standard treatment is aspirin; however, it is unknown whether aspirin plus the $P2Y_{12}$ receptor agonist ticagrelor would be beneficial. The THEMIS trial, a phase 3, randomized, double-blind, placebo-controlled trial, investigated the use of ticagrelor plus aspirin (vs aspirin alone) in patients ≥50 years old with both type 2 diabetes receiving antihyperglycemic drugs for at least 6 months and stable coronary artery disease, as well as one of three other mutually nonexclusive criteria, ie, a history of previous percutaneous coronary intervention or coronary artery bypass grafting, or documentation of angiographic stenosis ≥50% in at least one coronary artery (n=19220; median age, 66 years; women, 31.5%). The primary efficacy outcome was measured in the intention-to-treat population and was a composite of cardiovascular death, myocardial infarction, or stroke. In patients with diabetes, stable coronary artery disease, and a previous percutaneous coronary intervention, ticagrelor plus aspirin reduced cardiovascular death, myocardial infarction, and stroke, but it increased major bleeding events.

Easterling T, Mundle S, Bracken H, et al. Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial. *Lancet.* 2019;394(10203):1011-1021.
During pregnancy, hypertension is the most common medical disorder, which also means that pregnant women have a greater risk of developing cardiovascular risk factors (hypertension, type 2 diabetes, and obesity), chronic kidney disease, premature cardiovascular disease, and cardiovascular mortality. Treating hypertension disorders during pregnancy is typically done using intravenous drug administration; however, evaluations of oral medications are scarce. This multicenter, parallel-group, open-label, randomized controlled trial compared the efficacy and safety of three oral drugs (ie, labetalol, nifedipine retard, and methyldopa) for the management of severe hypertension during pregnancy (n=894; maternal age, 25.53 years). The primary outcome was blood pressure control (ie, systolic blood pressure between 120 and 150 mm Hg and diastolic blood pressure between 70 and 100 mm Hg) within 6 hours of drug intake with no adverse outcomes. All three oral antihypertensive agents reduced blood pressure to the reference range in most women. Patients receiving nifedipine retard had a higher frequency of achieving the primary outcome vs those receiving either labetalol or methyldopa.

Strongman H, Gadd S, Matthews A, et al. Medium and long-term risks of specific cardiovascular diseases in survivors of 20 adult cancers: a population-based cohort study using multiple linked UK electronic health records databases. *Lancet.* 2019;394(10203):1041-1054.
Vast improvements have been made in survival rates for cancer patients; however, the effects of cancer treatments on the long-term cardiovascular disease risk in cancer survivors is unknown. This population-based cohort study used data from large-scale electronic health records from UK databases to identify cohorts of survivors of the 20 most common site-specific cancers who were 18 years or older and alive 12 months after diagnosis and age-, sex-, and general-matched controls with no history of cancer (n=9371; mean age, 63.5 years; women, 41.85%). The outcomes of the study were fatal or nonfatal coronary artery disease (angina, myocardial infarction, revascularization procedures, and sudden cardiac arrest), stroke (hemorrhagic and ischemic stroke), arrhythmia, venous thromboembolism (deep vein thrombosis and pulmonary embolism), heart failure and cardiomyopathy combined, pericarditis, valvular heart disease, and peripheral vascular disease. Compared with the controls, survivors of most site-specific cancers had an increased mid- to long-term risk for one or more cardiovascular diseases, with substantial variations between cancer sites. ■

October 2019

Agarwal R, Rossignol P, Romero A, et al. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet.* 2019;394(10208):1540-1550.

In patients with uncontrolled resistant hypertension, spironolactone is effective at reducing blood pressure, but, in patients with chronic kidney disease, its use is restricted by hyperkalemia. The AMBER trial, a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, assessed the safety and efficacy of patiromer, a sodium-free, nonabsorbed, K+-binding polymer that is used to lower serum K+ in patients with hyperkalemia, to enable spironolactone use for blood pressure control in patients with chronic kidney disease and resistant hypertension (n=295; mean age, 68.15 years; women, 48%). The primary end point was the difference between treatment groups in the proportion of patients remaining on spironolactone at week 12. Patiromer use result in more patients being able to continue spironolactone treatment with less hyperkalemia.

Bauer A, Klemm M, Rizas KD, et al; EU-CERT-ICD Investigators. Prediction of mortality benefit based on periodic repolarisation dynamics in patients undergoing prophylactic implantation of a defibrillator: a prospective, controlled, multicentre cohort study. *Lancet.* 2019;394(10206):1344-1351.

For patients with ischemic or nonischemic cardiomyopathy and a reduced left ventricular ejection fraction, the guidelines recommend prophylactic implantation of implantable cardioverter defibrillators; however, a small percentage of patients experience malignant arrhythmias. The EU-CERT-ICD trial, a prospective investigator-initiated, nonrandomized, controlled, cohort study, evaluated the hypothesis that periodic repolarization dynamics could be used to predict the treatment effect of prophylactic implantable cardioverter-defibrillator implantation on mortality (n=1371; mean age, 62.1 years; women, 18.5%). The primary end point was all-cause mortality and, in the implantable cardioverter-defibrillator group, the coprimary end point was the occurrence of a first appropriate implantable cardioverter-defibrillator shock. Periodic repolarization dynamics were able to predict mortality reductions associated with prophylactic implantable cardioverter-defibrillator implantation.

Hausenloy DJ, Kharbanda RK, Møller UK, et al; CONDI-2/ERIC-PPCI Investigators. Effect of remote ischaemic conditioning on clinical outcomes in patients with acute myocardial infarction (CONDI-2/ERIC-PPCI): a single-blind randomised controlled trial. *Lancet.* 2019;394(10207):1415-1424.

Remote ischemic conditioning applied to the arm of patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention reduces myocardial infarct size; however, whether this procedure is effective in reducing the incidence of cardiac death and hospitalization for heart failure is unknown. The CONDI-2/ERIC-PPCI, an international, investigator-initiated, prospective, single-blind, randomized controlled trial, compared sham-simulated remote ischemic conditioning with remote ischemic condition in patients with a suspected ST-segment elevation myocardial infarction who were eligible for primary percutaneous coronary intervention (n=5115; mean age, 63.5 years; women, 23.2%). The primary end point was cardiac death or hospitalization for heart failure at 12 months in the intention-to-treat population. Remote ischemic conditioning does not improve cardiac death or hospitalization for heart failure.

Iglesias JF, Muller O, Heg D, et al. Biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents in patients with ST-segment elevation myocardial infarction (BIOSTEMI): a single-blind, prospective, randomised superiority trial. *Lancet.* 2019;394(10205):1243-1253.

Newer-generation drug-eluting stents have improved clinical outcomes among patients with acute ST-segment elevation myocardial infarction compared with bare-metal stents and early-generation durable polymer drug-eluting stents. However, no randomized controlled trials have compared newer-generation drug-eluting stents. The BIOSTEMI study, an investigator-initiated, multicenter, prospective, single-blind, randomized superiority trial, compared an ultrathin strut biodegradable polymer sirolimus-eluting stent with a thin strut durable polymer everolimus-eluting stent in patients with an acute ST-segment elevation myocardial infarction undergoing a primary percutaneous coronary intervention (n=1300; mean age, 62.7 years; women, 24%). The primary end point was target lesion failure, a composite of cardiac death, target vessel myocardial reinfarction, and clinically-indicated target lesion revascularization within 1 year of the index procedure. The study showed that biodegradable polymer sirolimus-eluting stents were superior to durable polymer everolimus-eluting stents as concerns target lesion failure at 1 year.

Santema BT, Ouwerkerk W, Tromp J, et al. Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study. *Lancet.* 2019;394(10205):1254-1263.
Even though there are no known sex differences in the pharmacokinetics of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers in patients with heart failure with reduced ejection fraction, the guidelines recommend the same doses for both men and women. This post-hoc analysis of the BIOSTAT-CHF trial, a multinational, prospective, observational study, evaluated which patients will have a poor clinical outcome despite receiving evidence-based heart failure treatment (n=1710; mean age, 72 years; women, 23.5%). The primary outcome was a composite of time to all-cause mortality or hospitalization for heart failure. The study showed that, compared with men, women with heart failure with reduced ejection fraction might need lower doses of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers.

Schwalm JD, McCready T, Lopez-Jaramillo P, et al. A community-based comprehensive intervention to reduce cardiovascular risk in hypertension (HOPE 4): a cluster-randomised controlled trial. *Lancet.* 2019;394(10205):1231-1242.
Hypertension is the leading cause of cardiovascular disease globally, but the acquisition of hypertension control is poor. The HOPE 4 trial was an open, community-based, cluster-randomized controlled trial involving individuals with new or poorly controlled hypertension from 30 communities in Colombia and Malaysia (n=1371; mean age, 65.45 years; women, 56%) . The purpose of the study was to test whether a health care model involving nonphysician health care workers, primary care physicians, and family, as well as the provision of effective medications would be effective in reducing the risk of cardiovascular disease. Patients receiving care via the comprehensive model of care had a substantial improvement in blood pressure control and cardiovascular disease risk.

Thuijs DJFM, Kappetein AP, Serruys PW, et al; SYNTAX Extended Survival Investigators. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. *Lancet.* 2019;394(10206):1325-1334.
The SYNTAX trial, a noninferiority trial that compared percutaneous coronary intervention using first-generation, paclitaxel-eluting stents with coronary artery bypass grafting in patients with de-novo 3-vessel and left main coronary artery disease, reported similar survival rates among patients receiving percutaneous coronary intervention or coronary artery bypass grafting after 5 years of follow-up. The SYNTAX Extended Survival (SYNTAXES) study, an investigator-driven extension study, examined all-cause death after 10 years of follow-up in patients randomly assigned to percutaneous coronary intervention or coronary artery bypass grafting

in the SYNTAX trial (n=1800; mean age, 65.1 years; women, 22.5%). The primary end point was all-cause death at 10 years. After the 10-year follow-up, no significant differences were observed in all-cause death between percutaneous coronary intervention using first-generation paclitaxel-eluting stents and coronary artery bypass grafting. Coronary artery bypass grafting resulted in a significant survival benefit in patients with 3-vessel disease, but not in patients with left main coronary artery disease.

Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet.* 2019;394(10206):1335-1343.

Edoxaban is a non-vitamin K antagonist oral anticoagulant that is as effective as a vitamin K antagonist in preventing stroke or systemic embolism and a lower incidence of bleeding and death from cardiovascular causes. However, there is no information on the effects of edoxaban plus a P2Y12 inhibitor. The ENTRUST-AF PCI trial, a randomized, multicenter, open-label, noninferiority phase 3b trial, analyzed the safety and efficacy of an edoxaban regimen (vs a vitamin K antagonist) in patients with atrial fibrillation requiring oral anticoagulation and who had a successful percutaneous coronary intervention for stable coronary artery disease or acute coronary syndrome (n=1506; mean age, 69.5 years; women, 25.5%). The primary end point was a composite of major or clinically relevant nonmajor bleeding within 12 months. Compared with the vitamin K antagonist–based regimen, the edoxaban-based regimen was noninferior for bleeding without significant differences in ischemic events. ■

November 2019

Lanz J, Kim WK, Walther T, et al; SCOPE I Investigators. Safety and efficacy of a self-expanding versus a balloon-expandable bioprosthesis for transcatheter aortic valve replacement in patients with symptomatic severe aortic stenosis: a randomised non-inferiority trial. *Lancet.* 2019;394(10209):1619-1628.

Due to the variability in transcatheter aortic valve replacement systems (eg, mechanism of deployment, size, potential for repositionability, and hemodynamics performance, and risk of atrioventricular conductance disturbances), it is difficult to predict clinical outcomes. The SCOPE I trial, an investigator-initiated, multicenter, assessor-masked, randomized controlled trial, assessed the safety and efficacy of the self-expanding ACURATE neo with the balloon-expandable SAPIEN 3 transcatheter aortic valve replacement prosthesis in patients with severe, symptomatic aortic stenosis undergoing transfemoral transcatheter aortic valve replacement (n=739; mean age, 82.8 years; women, 57%). The primary end point was a combination of two VARC-2–derived end points at 30 days (ie, all-cause death, any stroke, life-threatening or disabling bleeding, major vascular complications, coronary artery obstruction requiring intervention, acute kidney injury, rehospitalization for valve-related symptoms or congestive heart failure, valve-related dysfunction requiring a repeat procedure, and valve-related dysfunction determined by echocardiography. The self-expanding ACURATE neo device was noninferior to the balloon-expandable SAPIEN 3 device.

Nickenig G, Weber M, Lurz P, et al. Transcatheter edge-to-edge repair for reduction of tricuspid regurgitation: 6-month outcomes of the TRILUMINATE single-arm study. *Lancet.* 2019;394(10213):2002-2011.

Even though tricuspid regurgitation is associated with high morbidity and mortality, there are very few treatment options. The TRILUMINATE trial, a prospective, multicenter, single-arm study, investigated the safety and effectiveness of TriClip, a minimally invasive transcatheter tricuspid valve repair system, to reduce tricuspid regurgitation. The primary efficacy end point was a reduction in tricuspid regurgitation severity by at least one grade at 30 days postprocedure, with a performance goal of 35%, analyzed in all patients who had an attempted tricuspid valve repair procedure upon femoral vein puncture (n=85; mean age, 77.8 years; women, 66%). The primary safety end point was a composite of major adverse events at 6 months, with a performance goal of 39%. The TriClip system was shown to be safe and effective for reducing tricuspid regurgitation by at least one grade.

Suchard MA, Schuemie MJ, Krumholz HM, et al. Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis. *Lancet.* 2019;394(10211):1816-1826.

As there are no new real-world comparative effectiveness studies on common antihypertensive drugs with respect to outcomes, there is uncertainty concerning the optimal monotherapy option for treating patients with hypertension. The LEGEND-HTN study, a large-scale, comparative effectiveness and safety study, investigated common antihypertensive drug treatments using a new-user cohort design (n=4 893 591) The three primary effectiveness end points were acute myocardial infarction, hospitalization for heart failure, and stroke. The study supports equivalence among drug classes for initiating monotherapy for hypertension, except for thiazide or thiazide-like diuretics, which show superiority to angiotensin-converting enzyme inhibitors and inferiority to non-dihydropyridine calcium channel blockers.

Waksman R, Di Mario C, Torguson R, et al; LRP Investigators. Identification of patients and plaques vulnerable to future coronary events with near-infrared spectroscopy intravascular ultrasound imaging: a prospective, cohort study. *Lancet.* 2019;394(10209):1629-1637.

The ability to predict cardiovascular events in patients with coronary artery disease is low; therefore, near-infrared spectroscopy intravascular ultrasound imaging was developed to detect lipid-rich plaques. The LRP study, a prospective cohort study, sought to establish a relationship between lipid-rich plaques detected by near-infrared spectroscopy intravascular ultrasound imaging at unstented sites and subsequent coronary events from new culprit lesions in patients with suspected coronary artery disease who underwent cardiac catheterization with possible ad hoc percutaneous coronary intervention (n=1271; median age, 64 years; women, 31%). The hierarchal primary end point was all major adverse cardiovascular events reported up until 24 months and included the following events: cardiac death, cardiac arrest, nonfatal myocardial infarction, acute coronary syndrome, revascularization by coronary artery bypass grafting or percutaneous coronary intervention, and readmission to hospital for angina with stenosis >20% in diameter with progression related and unrelated to the treatment at index procedure. The study showed that the use of near-infrared spectroscopy imaging of nonobstructive territories was safe. ■

December 2019

Brunner FJ, Waldeyer C, Ojeda F, et al. Application of non-HDL cholesterol for population-based cardiovascular risk stratification: results from the Multinational Cardiovascular Risk Consortium. *Lancet.* 2019;394(10215):2173-2183.

The relationship between blood lipid concentrations and the long-term incidence of cardiovascular disease is unclear, as was the relationship between lipid-lowering therapy and cardiovascular disease outcomes. This risk-evaluation and risk-modeling study used data from the Multinational Cardiovascular Risk Consortium to estimate the long-term probabilities for a cardiovascular disease events based on non-high-density lipoprotein cholesterol and to model the risk reduction in cardiovascular disease upon receiving lipid-lowering treatment (n=398 846; median age, 51 years; women, 48.7%). The primary composite end point was the first occurrence of the coronary heart disease event or ischemic stroke. This study showed that the concentration of non-high-density lipoprotein cholesterol in the blood is strongly associated with a long-term risk of atherosclerotic cardiovascular disease.

Nakashima T, Noguchi T, Tahara Y, et al. Public-access defibrillation and neurological outcomes in patients with out-of-hospital cardiac arrest in Japan: a population-based cohort study. *Lancet.* 2019;394(10216):2255-2262.

Of the patients who have an out-of-hospital cardiac arrest, approximately 80% do not have a sustained return of spontaneous circulation after receiving public-access defibrillation; however, the neurological outcomes and survival outcomes have not been evaluated; therefore, this population-based cohort study was designed to assess these outcomes (n=27 329; mean age, 64 years; women, 20%). The primary outcome was a favorable neurological outcome at 30 days after the an out-of-hospital cardiac arrest. Compared with patients who did not receive public-access defibrillation, those who received public-access defibrillation had a significantly higher rate of favorable neurological outcomes.

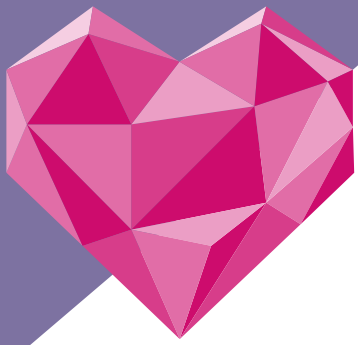
Mullen M, Jin XY, Child A, et al; AIMS Investigators. Irbesartan in Marfan syndrome (AIMS): a double-blind, placebo-controlled randomised trial. *Lancet.* 2020;394(10216):2263-2270.

Marfan syndrome is associated with cardiovascular complications, including aortic root dilatation, dissection, and rupture; these complications are the leading cause of morbidity and mortality in patients with Marfan syndrome. The AIMS trial, a placebo-controlled, double-blind randomized trial, evaluated the effects of irbesartan, a long-acting selective angiotensin-1 receptor inhibitor, on the aortic

dilatation rate in patients with Marfan syndrome (n=192; median age, 18 years; women, 52%). The primary outcome measure was the absolute change in aortic root diameter per year as measured by transthoracic echocardiography. Compared with placebo, irbesartan led to a reduction in the rate of aortic root dilatation over a 5-year observation period. ■

Snapshots of the Year:

The New England Journal of Medicine



January 2019

Bhatt DL, Steg PG, Miller M, et al; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med.* 2019;380(1):11-22.
Patents with high levels of triglycerides have a higher risk of ischemic events. While treatment with icosapent ethyl, a purified eicosapentaenoic acid ethyl ester, lowers triglyceride levels, there is no data showing that if, by lowering the triglyceride levels, the risk of ischemic events is also lower. REDUCE-IT, a phase 3b randomized, double-blind, placebo-controlled trial, compared icosapent ethyl (2 g twice daily with food) with a placebo in patients with cardiovascular disease or diabetes and other risk factors who have elevated triglyceride levels despite the use of statins. The primary efficacy end point was a composite of cardiovascular death, nonfatal myocardial infarction (including silent myocardial infarction), nonfatal stroke, coronary revascularization, or unstable angina in a time-to-event analysis. The study showed that icosapent ethyl given at 2 g twice daily significantly lowered the risk of ischemic events vs placebo.

Manson JE, Cook NR, Lee IM, et al; VITAL Research Group. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med.* 2019;380(1):23-32.
While omega-3 fatty acids have shown good results in small to medium sized trials for the primary prevention of cardiovascular disease, the results are less clear in large trials. The VITAL trial, a randomized, double-blind, placebo-controlled trial, with a two-by-two factorial design, investigated the role of omega-3 in the primary prevention of cardiovascular disease and cancer in men aged ≥50 years and women aged ≥55 years in the United States. The primary end points were major cardiovascular events (composite of myocardial infarction, stroke, and death from cardiovascular causes) and invasive cancer of any type. In the patient group analyzed, omega-3 fatty acid supplementation did not lower the incidence of major cardiovascular events or cancer vs placebo.

Manson JE, Cook NR, Lee IM, et al; VITAL Research Group. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med.* 2019;380(1):33-44.
Measuring the efficacy of vitamin D supplementation is confounded by factors, such as by outdoor physical activity, adiposity, and general nutritional status. Data from large randomized trials on vitamin D supplementation are lacking and trials attempting to analyze the effects of vitamin D supplementation are often limited by use of low doses of vitamin D, insufficient statistical power, short duration, lack of rigorous end-point adjudication, or a combination of these factors. The VITAL trial, a randomized, double-blind, placebo-controlled trial, with a two-by-

two factorial design, investigated the role of high-dose vitamin D (2000 IU) in the primary prevention of cardiovascular disease and cancer in men aged ≥50 years and women aged ≥55 years in the United States. The primary end points were invasive cancer of any type and major cardiovascular events (composite of myocardial infarction, stroke, and death from cardiovascular causes).Vitamin D supplementation did not lower the incidence of invasive cancer or cardiovascular events among men aged 50 years or older and women aged 55 years or older in the US vs placebo.

Taggart DP, Benedetto U, Gerry S, et al; Arterial Revascularization Trial Investigators. Bilateral versus single internal-thoracic-artery grafts at 10 years. *N Engl J Med.* 2019;380(5):437-446.

Using left internal-thoracic-artery grafts has been well established for the treatment of patients with symptomatic advanced coronary artery disease; however, it hypothesized that using bilateral arterial grafts would improve survival even more than a single arterial graft. The ART trial, a two-group, multicenter, randomized, unblinded trial, randomized patients to bilateral internal-thoracic-artery grafts or a standard single left internal-thoracic-artery graft during coronary artery bypass grafting. The primary outcome was death from any cause at 10 years of follow-up. No significant between-group differences were observed in the rate of all-cause death at 10 years among patients undergoing bilateral internal thoracic artery grafting or those undergoing single internal thoracic artery grafting.

Wiviott SD, Raz I, Bonaca MP, et al; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2019;380(4):347-357.

Sodium–glucose cotransporter 2 inhibitors have been shown to reduce the risk of hospitalization for heart failure, predominantly in patients with type 2 diabetes and established cardiovascular disease, as well as delaying the progression of kidney disease. The cardiovascular safety dapagliflozin, a selective sodium–glucose cotransporter 2 inhibitor, has not yet been defined. The DECLARE-TIMI 58 trial, a randomized, double-blind, multinational, placebo-controlled, phase 3 trial, investigated the role of dapagliflozin vs placebo in patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease. The primary safety outcome was major adverse cardiovascular events (cardiovascular death, myocardial infarction, or ischemic stroke), and the two primary efficacy outcomes were major adverse cardiovascular events and a composite of cardiovascular death or hospitalization for heart failure. Treatment with dapagliflozin

did not affect the rate of major adverse cardiovascular events when compared with placebo; however, dapagliflozin lowered the rate of cardiovascular death or hospitalization for heart failure.

Zenati MA, Bhatt DL, Bakaeen FG, et al; REGROUP Trial Investigators. Randomized trial of endoscopic or open vein-graft harvesting for coronary-artery bypass. *N Engl J Med.* 2019;380(2):132-141.

While endoscopic vein-graft harvesting, a minimally invasive technique designed to reduce the rate of harvest-site complications is effective in reducing the incidence of leg-wound healing complications, its safety has not been evaluated in large trials with a long-term follow-up. The REGROUP trial, a randomized, intention-to-treat, multicenter trial, investigated the clinical outcomes of open or endoscopic vein-graft harvesting among patients undergoing coronary artery bypass grafting. The primary outcome was the first occurrence of a major adverse cardiac event (composite of death from any cause, nonfatal myocardial infarction, or repeat revascularization) in a time-to-event analysis. No significant differences were observed in the risk of major adverse cardiac events between those randomized to open vein-graft harvesting and those randomized to endoscopic vein-graft harvesting. ■

February 2019

Carrier M, Abou-Nassar K, Mallick R, et al; AVERT Investigators. Apixaban to prevent venous thromboembolism in patients with cancer. *N Engl J Med.* 2019;380(8):711-719.

Although using parenteral thromboprophylaxis reduces the risk of venous thromboembolism among ambulatory patients undergoing chemotherapy, it is associated with an increased risk of major bleeding, a high cost, and the inconvenience of daily injections. The use of direct oral antithrombotic agents may be beneficial in this patient group due to its convenience, low cost, and route of administration. The AVERT trial, a randomized, placebo-controlled, double-blind clinical trial, compared the oral factor Xa inhibitor apixaban (2.5 mg twice daily) with placebo in in ambulatory patients with cancer at an intermediate-to-high risk for venous thromboembolism. The primary efficacy outcome was the first episode of objectively documented major venous thromboembolism (proximal deep-vein thrombosis or pulmonary embolism) within the first 180 days after randomization. Compared with placebo, using apixaban 2.5 mg twice daily for thromboprophylaxis significantly lowered the rate of venous thromboembolism; however, apixaban increased the rate of major bleeding episodes.

Khorana AA, Soff GA, Kakkar AK, et al; CASSINI Investigators. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. *N Engl J Med.* 2019;380(8):720-728.

In patients with cancer, the risk of thromboembolism is very high; however, the guidelines do not recommend using thromboprophylaxis routinely due to the low absolute benefit. The CASSINI, a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3b trial, assessed the safety and efficacy of rivaroxaban, a potent, oral, highly selective direct factor Xa inhibitor, thromboprophylaxis in patients with a solid tumor or lymphoma. The primary efficacy end point was a composite of objectively confirmed symptomatic or asymptomatic proximal deep-vein thrombosis in a lower limb, symptomatic deep-vein thrombosis in an upper limb, or distal deep-vein thrombosis in a lower limb, symptomatic or incidental pulmonary embolism, and death from venous thromboembolism. The primary safety end point was the occurrence of major bleeding as defined by the International Society on Thrombosis and Hemostasis during the intervention period. In high-risk ambulatory patients with cancer, rivaroxaban 10 mg daily did not significantly lower the incidence of venous thromboembolism or venous thromboembolism–related deaths in the 180-day trial period; however, during the intervention period, rivaroxaban substantially lowered the incidence of such events, with a low incidence of major bleeding.

Velazquez EJ, Morrow DA, DeVore AD, et al; PIONEER-HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med.* 2019;380(6):539-548.

The sacubitril-valsartan combination, an angiotensin receptor and neprilysin inhibitor, is indicated for the treatment of patients with symptomatic heart failure with reduced ejection fraction; however, it is unknown whether this combination is effective and safe among patients hospitalized for acute decompensated heart failure. The PIONEER-HF trial, a multicenter, randomized, double-blind, active-controlled trial, investigated the in-hospital initiation of sacubitril-valsartan therapy vs enalapril therapy in patients admitted for acute decompensated heart failure with reduced ejection fraction. The primary efficacy outcome was the time-averaged proportional change in the concentration of N-terminal pro–B-type natriuretic peptide from baseline through weeks 4 and 8. In patients with heart failure with reduced ejection fraction, sacubitril-valsartan therapy led to a greater reduction in the concentration of NT-proBNP than did enalapril therapy; however, there were no significant between-group differences concerning the rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema. ■

March 2019

Ference BA, Ray KK, Catapano AL, et al. Mendelian randomization study of ACLY and cardiovascular disease. *N Engl J Med.* 2019;380(11):1033-1042.
ATP citrate lyase, an enzyme in the cholesterol biosynthesis pathway upstream of the statin target hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), has become a new target for lipid-lowering therapy. This study compared variants in ATP citrate lyase that mimic the effect of an ATP citrate lyase inhibitor with variants in HMGCR that mimic the effect of a statin in order to estimate the clinical effect of lowering plasma low-density lipoprotein cholesterol via ATP citrate lyase inhibition. The primary efficacy outcome for the study was major cardiovascular events (defined as a composite of the first occurrence of myocardial infarction, coronary revascularization, ischemic stroke, or coronary death). Both inherited variants in the genes encoding ATP citrate lyase and HMGCR appeared to lower plasma low-density lipoprotein cholesterol using the same mechanism of action and they had similar effects on the risk of cardiovascular disease per unit decrease in low-density lipoprotein cholesterol.

Landoni G, Lomivorotov VV, Nigro Neto C, et al; MYRIAD Study Group. Volatile anesthetics versus total intravenous anesthesia for cardiac surgery. *N Engl J Med.* 2019;380(13):1214-1225.
Volatile (inhaled) anesthetic agents have been identified as a key nonsurgical intervention to improve survival among patients undergoing major surgery, with studies showing that volatile anesthetic agents have cell-protective effects by modulating of G-protein–coupled receptors, intracellular signaling pathways, gene expression, potassium channels, and mitochondrial function; in addition, they have been shown to reduce biomarkers of myocardial injury. The MYRIAD trial, a pragmatic, randomized, single-blind trial, analyzed whether volatile anesthetics, compared with total intravenous anesthesia, during coronary artery bypass grafting would lower the number of deaths. The primary outcome was death from any cause at 1 year. There was no difference in death from any cause between volatile or total intravenous anesthesia.

Ray KK, Bays HE, Catapano AL, et al; CLEAR Harmony Trial. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. *N Engl J Med.* 2019;380(11):1022-1032.
While the use of bempedoic acid, an inhibitor of ATP citrate lyase, reduces low-density lipoprotein cholesterol in short-term studies, limited data are available on the safety and efficacy of bempedoic acid in long-term studies. The CLEAR trial, a 52-week, randomized, double-blind, placebo-controlled, parallel-group,

phase 3 trial, evaluated the safety, side-effect profile, and efficacy of bempedoic acid therapy in addition to the maximally tolerated dose of statins in patients with atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolemia, or both. The primary end point of the trial was overall safety. Compared with placebo, treatment with bempedoic acid added to maximally tolerated statin therapy significantly lowered low-density lipoprotein cholesterol levels without increasing the incidence of overall adverse events.■

April 2019

Lemkes JS, Janssens GN, van der Hoeven NW, et al. Coronary angiography after cardiac arrest without ST-segment elevation. *N Engl J Med.* 2019;380(15):1397-1407.
The guidelines on cardiopulmonary resuscitation recommend performing emergency coronary angiography in selected patients after out-of-hospital cardiac arrest, even in patient without ST-segment elevation; however, no data from randomized controlled trials is available to support this recommendation. The COACT trial, an investigator-initiated, randomized, open-label, multicenter trial, investigated immediate coronary angiography vs delayed angiography in patients who had been successfully resuscitated after cardiac arrest and who did not have ST-segment elevation on ECG. The primary end point of the trial was survival at 90 days. There was no difference between performing an immediate coronary angiography and a percutaneous coronary intervention (if needed) and performing a coronary angiography after neurologic recovery.

Lopes RD, Heizer G, Aronson R, et al; AUGUSTUS Investigators. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med.* 2019;380(16):1509-1524.
It is complicated to select the best anticoagulation therapy in patients with atrial fibrillation who have an acute coronary syndrome or have undergone percutaneous coronary intervention due to adverse events. The AUGUSTUS trial, a prospective, multicenter, two-by-two factorial, randomized clinical trial, assessed the safety and efficacy of treatment with apixaban vs a vitamin K antagonist and of treatment with aspirin vs placebo in patients with atrial fibrillation who had a recent acute coronary syndrome or underwent percutaneous coronary intervention (or both) and the planned use of a P2Y12 inhibitor for at least 6 months. The primary outcome

was major or clinically relevant nonmajor bleeding. Compared with the use of a vitamin K antagonist, aspirin, or both, the use of the combination of a P2Y12 inhibitor and apixaban (without aspirin) reduced the bleeding events and hospitalizations, but there were no significant differences in the incidence of ischemic events.

Mehra MR, Uriel N, Naka Y, et al; MOMENTUM 3 Investigators. A fully magnetically levitated left ventricular assist device -final report. *N Engl J Med.* 2019;380(17):1618-1627.
In the prespecified 6-month and 2-year interim outcome analyses of smaller trial cohorts from the randomized MOMENTUM 3 trial, the incidence of pump thrombosis in patients with advanced-stage heart failure was lower with a left ventricular assist devices with a centrifugal-flow pump vs those devices with an axial-flow pump, with a lower incidence of nondisabling stroke with the centrifugal-flow pump. The final analysis of the MOMENTUM trial on the entire trial population showed that a left ventricular assist device with a centrifugal-flow pump was superior to a device with an axial-flow pump in terms of survival free of disabling stroke or reoperation to replace or remove a malfunctioning device.

Pluymaekers NAHA, Dudink EAMP, Luermans JGLM, et al; RACE 7 ACWAS Investigators. Early or delayed cardioversion in recent-onset atrial fibrillation. *N Engl J Med.* 2019;380(16):1499-1508.
In current practice, it is common for patients with recent-onset atrial fibrillation to receive pharmacologic or electrical cardioversion immediately to restore sinus rhythm; however, data are lacking on the necessity of immediate restoration of sinus rhythm. The RACE 7 ACWAS trial, a multicenter, randomized noninferiority trial, assessed whether a "wait-and-see" approach was noninferior to early cardioversion for obtaining sinus rhythm in patients with hemodynamically stable, recent-onset (<36 hours), symptomatic atrial fibrillation. The primary end point was the presence of sinus rhythm on ECG recorded at the 4-week trial visit. Delayed cardioversion was shown to be noninferior to early cardioversion at 4 weeks regarding the restoration of sinus rhythm. ■

May 2019

Bhatt DL, Pollack CV, Weitz JI, et al. Antibody-based ticagrelor reversal agent in healthy volunteers. *N Engl J Med.* 2019;380(19):1825-1833.
The combination of an oral P2Y12 receptor antagonist with aspirin is a leading antiplatelet therapy; however, this combination leads to a higher bleeding risk and the P2Y12 inhibitor effects cannot be reversed with a plasma transfusion.

This single-center, randomized, double-blind, placebo-controlled, single-ascending-dose, phase 1 trial evaluated the safety, efficacy, and pharmacokinetic profiles of PB2452, a monoclonal antibody fragment that binds ticagrelor with high affinity, in healthy volunteers aged 18 to 50 years who were pretreated with ticagrelor. The primary efficacy outcome was reversal of the antiplatelet effects of ticagrelor. Intravenous PB2452 led to an immediate and sustained reversal of the antiplatelet effects of ticagrelor.

Diener HC, Sacco RL, Easton JD, et al; RE-SPECT ESUS Steering Committee and Investigators. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med.* 2019;380(20):1906-1917.

While rivaroxaban treatment is as effective as aspirin in preventing recurrent stroke after a presumed embolic stroke from an undetermined source, it is unclear whether dabigatran would be effective in preventing recurrent strokes after this type of stroke. The RE-SPECT ESUS trial, an international, double-blind, parallel-group, randomized trial, assessed the compare the efficacy and safety of dabigatran with aspirin for the prevention of recurrent stroke in patients with a recent embolic stroke of an undetermined source. The primary efficacy outcome was recurrent stroke of ischemic, hemorrhagic, or unspecified type, assessed in a time-to-event analysis. Dabigatran was not superior to aspirin for the prevention of a recurrent stroke, and, while dabigatran did not increase the incidence of major bleeding, it increased the incidence of clinically relevant nonmajor bleeding events.

Lederle FA, Kyriakides TC, Stroupe KT, et al; OVER Veterans Affairs Cooperative Study Group. Open versus endovascular repair of abdominal aortic aneurysm. *N Engl J Med.* 2019;380(22):2126-2135.

The short-term results using endovascular repair vs open repair of asymptomatic abdominal aortic aneurysms showed decreased mortality, while the long-term results show that this decrease in mortality is no longer seen. The extended follow-up analysis from the OVER Veterans Affairs Cooperative study, a randomized, controlled, multicenter trial of abdominal aortic aneurysm repair strategies with a primary outcome of all-cause mortality, showed that the overall survival rates were similar between endovascular repair and open repair; however, more patients with endovascular repair underwent more secondary therapeutic procedures.

Ma H, Campbell BCV, Parsons MW, et al; EXTEND Investigators. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. *N Engl J Med.* 2019;380(19):1795-1803.

The current guidelines restrict the initiation of intravenous thrombolytic therapy to within 4.5 hours of stroke onset; however, some patients with salvageable brain tissue may also benefit from thrombolysis beyond this 4.5-hour window.

The EXTEND trial, a phase 3, investigator-initiated, multicenter, randomized, placebo-controlled trial, investigated the initiation of intravenous alteplase between 4.5 hours and 9 hours after stroke onset or on awakening with stroke symptoms in patients who had an ischemic stroke, but with salvageable brain tissue detected on automated perfusion imaging. The primary outcome was a score of 0 or 1 on the modified Rankin scale at 90 days. Compared with placebo, alteplase treatment, given within 9 hours after the onset of a stroke, increased the percentage of patients with no or minor neurologic deficit.

Mack MJ, Leon MB, Thourani VH, et al; PARTNER 3 Investigators. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med.* 2019;380(18):1695-1705.

It is clear that the major outcomes between transcatheter aortic valve replacement and surgical aortic valve replacement are similar in patients with aortic stenosis at a high risk of death; however, little is known about the outcomes in patients at low risk. The PARTNER trial, a multicenter, randomized trial, compared transcatheter aortic valve replacement using a transfemoral placement of a third-generation balloon-expandable valve with standard surgical aortic valve replacement in patients with severe aortic stenosis and a low risk of death with surgery. The primary end point was a composite of death from any cause, stroke, or rehospitalization 1 year after the procedure. Compared with standard surgical aortic valve replacement, transcatheter aortic valve replacement significantly lowered the rate of the composite of death, stroke, or rehospitalization at 1 year.

Popma JJ, Deeb GM, Yakubov SJ, et al; Evolut Low Risk Trial Investigators. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med.* 2019;380(18):1706-1715.

Transcatheter aortic-valve replacement is a good alternative to surgery in patients with severe aortic stenosis who are at increased risk for death from surgery; however data is lacking on the results of transcatheter aortic valve replacement in patient who have a low risk of death from surgery. The Evolut Low Risk Trial, a multinational, randomized, noninferiority clinical trial, assessed the safety and effectiveness of transcatheter aortic valve replacement with a self-expanding bioprosthesis, compared with surgical aortic valve replacement, in patients at a low risk of death from surgery. The primary safety and effectiveness end point was a composite of death from any cause or disabling stroke at 24 months. Transcatheter aortic-valve replacement with a self-expanding bioprosthesis was noninferior to surgical aortic valve replacement.

Tarakji KG, Mittal S, Kennergren C, et al; WRAP-IT Investigators. Antibacterial envelope to prevent cardiac implantable device infection. *N Engl J Med.* 2019;380(20):1895-1905.
Even though infections remain a major source of complications with significant morbidity and mortality after placement of cardiac implantable electronic devices, data is limited concerning newer prophylactic strategies. The WRAP-IT trial, a multicenter, randomized, controlled, prospective, single-blind, postmarketing, interventional clinical trial, assessed the safety and effectiveness of using the absorbable, multifilament mesh envelope, which improves cardiac implantable electronic device stabilization in the subcutaneous pocket and elutes the antibiotics minocycline and rifampin, as adjunctive therapy to standard infection-prevention strategies. The primary end point was major cardiac implantable electronic device infections within 12 months (365 days) after the procedure. Compared with the standard-of-care infection prevention strategies alone, the use of an absorbable, antibiotic-eluting envelope with cardiac implantable electronic devices significantly lowered the incidence of major infections. ■

June 2019

Nagel E, Greenwood JP, McCann GP, et al; MR-INFORM Investigators. Magnetic resonance perfusion or fractional flow reserve in coronary disease. *N Engl J Med.* 2019;380(25):2418-2428.
To guide revascularization in patients with stable angina, two strategies are often employed–myocardial-perfusion cardiovascular magnetic resonance imaging and invasive angiography with measurement of fractional flow reserve; however, whether one is noninferior to the other has not yet been determined. The MR-INFORM trial, an unblinded, investigator-led, international, multicenter, comparative-effectiveness, noninferiority trial, tested the hypothesis that an initial management strategy based on myocardial-perfusion cardiovascular MRI would be noninferior to a strategy guided by invasive angiography and fractional flow reserve measurement in patients with symptoms of stable angina and risk factors for coronary artery disease. The primary outcome was a composite of major adverse cardiac events (death from any cause, nonfatal myocardial infarction, or target-vessel revascularization) at 12 months. Patients who were randomized to myocardial-perfusion cardiovascular magnetic resonance imaging had a lower incidence of coronary revascularization vs the patients who were randomized to invasive angiography and fractional flow reserve measurement.

Neumann JT, Twerenbold R, Ojeda F, et al. Application of high-sensitivity troponin in suspected myocardial infarction. *N Engl J Med.* 2019;380(26):2529-2540.
The COMPASS-MI study assessed a risk-assessment tool that integrated the concentrations of high-sensitivity troponin I or T at presentation to the emergency department with a suspected myocardial infarction, the dynamic changes occurring during serial sampling, and the time between sample acquisitions. The short-term prognostic end point was the composite of subsequent myocardial infarction or death from any cause at 30 days. The long-term prognostic end point was the composite of subsequent myocardial infarction or death from any cause assessed at 1 year and 2 years. Patients with lower concentrations of high-sensitivity troponin when presenting to the emergency department with symptoms suggestive of a myocardial infarction had a lower likelihood of myocardial infarction and short-term risk of cardiovascular events.

Ojji DB, Mayosi B, Francis V, et al; CREOLE Study Investigators. Comparison of dual therapies for lowering blood pressure in black Africans. *N Engl J Med.* 2019;380(25):2429-2439.
While it is known that black patients in sub-Saharan Africa often require 2 or more drugs to control their hypertension, the information on the best combination therapy is lacking. The CREOLE study, a randomized, 3-group clinical trial in sub-Saharan Africa, assessed the blood pressure–lowering efficacy of three drug combinations: (i) a calcium channel blocker plus a thiazide diuretic (hydrochlorothiazide); (ii) a calcium channel blocker (amlodipine) plus an angiotensin-converting enzyme inhibitor (perindopril); and (iii) an angiotensin-converting enzyme inhibitor (perindopril) plus a thiazide diuretic (hydrochlorothiazide). The primary end point was the mean change in the 24-hour ambulatory systolic blood pressure between baseline and 6 months. Black patients in sub-Saharan Africa with uncontrolled hypertension achieved better blood pressure–lowering results with amlodipine plus either hydrochlorothiazide or perindopril than they did with perindopril plus hydrochlorothiazide at 6 months. ■

July 2019

Flint AC, Conell C, Ren X, et al. Effect of systolic and diastolic blood pressure on cardiovascular outcomes. *N Engl J Med.* 2019;381(3):243-251.
Considering that the relationship between systolic and diastolic blood pressure is unclear, this retrospective cohort study assessed whether the burdens of systolic and diastolic hypertension each independently predict the risk of adverse cardio-

vascular outcomes. The primary outcome in our study was a composite of the first episode of myocardial infarction, ischemic stroke, or hemorrhagic stroke during the observation period, with an event defined as hospitalization with a discharge diagnosis matching one of the components of the composite primary outcome. While both the burden of systolic hypertension and the burden of diastolic hypertension independently predicted adverse outcomes for the composite outcome of myocardial infarction, ischemic stroke, or hemorrhagic stroke, elevated systolic blood pressure had a stronger effect on the composite outcome. ■

August 2019

Husain M, Birkenfeld AL, Donsmark M, et al; PIONEER 6 Investigators. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2019;381(9):841-851.

While the cardiovascular safety for the subcutaneous form of the glucagon-like peptide-1 receptor agonist semaglutide has been demonstrated, data are needed for oral form. PIONEER 6, an event-driven, randomized, double-blind, placebo-controlled, assessed cardiovascular risk of oral semaglutide among patients with type 2 diabetes to rule out any excess cardiovascular risk. The primary outcome was the time from randomization to the first occurrence of a major adverse cardiovascular event, a composite of death from cardiovascular causes (including undetermined causes of death), nonfatal myocardial infarction, or nonfatal stroke. In patients with type 2 diabetes at high cardiovascular risk, oral semaglutide was not inferior to placebo.

Metra M, Teerlink JR, Cotter G, et al; RELAX-AHF-2 Committees Investigators. Effects of serelaxin in patients with acute heart failure. *N Engl J Med.* 2019;381(8):716-726.

The RELAX-AHF trial showed that serelaxin, a recombinant form of human relaxin-2, lowered the incidence of worsening heart failure during hospitalization, and, in an exploratory analysis, serelaxin lowered cardiovascular mortality at 180 days vs placebo. The RELAX-AHF-2 trial, a multicenter, randomized, double-blind, placebo-controlled, event-driven trial, assessed whether serelaxin in addition to standard care in patients with acute heart failure could lower cardiovascular mortality at 180 days, as well as the incidence of worsening heart failure in the first 5 days than placebo. The two primary efficacy end points were death from cardiovascular causes at 180 days and worsening heart failure at 5 days. Compared with placebo, serelaxin neither reduced the incidence of cardiovascular death nor did it reduce the incidence of worsening heart failure.

Panza JA, Ellis AM, Al-Khalidi HR, et al. Myocardial viability and long-term outcomes in ischemic cardiomyopathy. *N Engl J Med.* 2019;381(8):739-748.
The relationship between the assessment of myocardial viability and the long-term treatment effect of coronary artery bypass grafting in patients with ischemic cardiomyopathy is unclear. The goals of the STICH trial, a prospective, multicenter, randomized, nonblinded trial, evaluated the hypothesis that coronary artery bypass grafting in combination with appropriate medical therapy would improve survival outcomes better than appropriate medical therapy alone in patients with coronary artery disease and a left ventricular ejection fraction ≤35%. The primary outcome was death from any cause. The assessment of myocardial viability was not associated with a long-term benefit of coronary artery bypass grafting in patients with an ischemic cardiomyopathy. ■

September 2019

Muñoz D, Uzoije P, Reynolds C, et al. Polypill for cardiovascular disease prevention in an underserved population. *N Engl J Med.* 2019;381(12):1114-1123.
For people with a low socioeconomic status who have high rates of cardiovascular disease, a polypill strategy containing low doses of medications with proven benefits for the prevention of cardiovascular disease may be beneficial. This two-group, open-label, randomized, controlled, clinical trial compared polypill therapy with usual care. The two primary outcomes were changes in systolic blood pressure and low-density cholesterol levels from baseline to 12 months. Compared with standard care, the polypill-based strategy resulted in greater reductions in systolic blood pressure and low-density lipoprotein cholesterol levels.

Yasuda S, Kaikita K, Akao M, et al; AFIRE Investigators. Antithrombotic therapy for atrial fibrillation with stable coronary disease. *N Engl J Med.* 2019;381(12):1103-1113.
Combining antiplatelet therapy with anticoagulation therapy results in a higher risk of bleeding, making it difficult to choose the most effective antithrombotic therapy for patients with atrial fibrillation and stable coronary artery disease. The AFIRE trial, a multicenter, randomized, open-label, parallel-group trial, investigated treatment with the non–vitamin K antagonist oral anticoagulated rivaroxaban to determine if it was noninferior to combination therapy with rivaroxaban plus an antiplatelet agent in patients with atrial fibrillation and stable coronary artery disease and one of the following condition, ie, a history of percutaneous coronary intervention, including angioplasty with or without stenting, at least 1 year before enrollment; a history of angiographically confirmed coronary artery disease (with stenosis ≥50%)

not requiring revascularization; or a history of coronary artery bypass grafting at least 1 year before enrollment. The primary efficacy end point was the composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause, and the primary safety end point was major bleeding. Rivaroxaban monotherapy was noninferior to combination therapy for efficacy; however rivaroxaban monotherapy was superior for safety. ■

October 2019

Claassens DMF, Vos GJA, Bergmeijer TO, et al. A genotype-guided strategy for oral P2Y12 inhibitors in primary PCI. *N Engl J Med.* 2019;381(17):1621-1631.

Clopidogrel is a prodrug that is transformed into its active metabolite via hepatic cytochrome P450 enzymes, where the active metabolite irreversibly inhibits the P2Y12 receptor. Clopidogrel has a similar efficacy to ticagrelor and prasugrel; however, in certain patients clopidogrel has a lower response due to genetic variants, eg, CYP2C19*2 and CYP2C19*3 loss-of-function alleles. The POPular Genetics trial, an investigator-initiated, randomized, open-label, assessor-blinded trial, evaluated whether a whether a CYP2C19 genotype–guided strategy for selecting oral P2Y12 inhibitors can reduce the risk of bleeding without increasing the thrombotic risk in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention with stent implantation. The two primary outcomes were (i) the combined outcome of net adverse clinical events, which included death from any cause, myocardial infarction, definite stent thrombosis, stroke, or major bleeding at 12 months and (ii) PLATO major bleeding or minor bleeding at 12 months. The CYP2C19 genotype–guided strategy was noninferior to standard treatment with ticagrelor or prasugrel at 12 months with respect to thrombotic events and it resulted in a lower incidence of bleeding.

Luirink IK, Wiegman A, Kusters DM, et al. 20-Year follow-up of statins in children with familial hypercholesterolemia. *N Engl J Med.* 2019;381(16):1547-1556.

While the short-term efficacy of statin therapy in children is well established, longer follow-up studies evaluating changes in the risk of cardiovascular disease are scarce. This single center cross-sectional study provides data from a 20-year follow-up study of statin therapy in children with familial hypercholesterolemia who were previously participants in a placebo-controlled trial evaluating the 2-year efficacy and safety of pravastatin. Initiation of statin therapy during childhood in patients with familial hypercholesterolemia slowed the progression of carotid intima-media thickness and reduced the risk of cardiovascular disease in adulthood.

Mehta SR, Wood DA, Storey RF, et al; COMPLETE Trial Steering Committee and Investigators. Complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med.* 2019;381(15):1411-1421.

While treating culprit lesions in patients with ST-segment elevation myocardial infarction with percutaneous coronary intervention reduces the risk of cardiovascular death or myocardial infarction, it is unclear whether treating nonculprit lesions with percutaneous coronary intervention will reduce the risk of cardiovascular death or myocardial infraction even more. The COMPLETE trial, a multinational, randomized trial, investigated complete revascularization (consisting of percutaneous coronary intervention of all suitable nonculprit lesions) vs no further revascularization in patients with ST-segment elevation myocardial infarction and multivessel coronary artery disease who had undergone a successful culprit-lesion percutaneous coronary intervention. The coprimary end points were (i) the composite of death from cardiovascular causes or new myocardial infarction and (ii) the composite of death from cardiovascular causes, new myocardial infarction, or ischemia-driven revascularization. Compared with percutaneous coronary intervention of the culprit lesion only, complete revascularization was superior in reducing both of the coprimary end points.

Schüpke S, Neumann FJ, Menichelli M, et al; ISAR-REACT 5 Trial Investigators. Ticagrelor or prasugrel in patients with acute coronary syndromes. *N Engl J Med.* 2019;381(16):1524-1534.

In patients with acute coronary syndromes, prasugrel and ticagrelor are superior to clopidogrel; however, data comparing prasugrel with ticagrelor are lacking. The ISAR-REACT 5 trial, multicenter, randomized, open-label trial, evaluated treatment with either ticagrelor or prasugrel in patients who presented with acute coronary syndromes. The primary end point was the composite of death, myocardial infarction, or stroke at 1 year. Compared with ticagrelor, prasugrel significantly lowered the incidence of death, myocardial infarction, or stroke; however there were no between-group differences in the incidence of major bleeding was not significantly different between the two groups.

Solomon SD, McMurray JJV, Anand IS, et al; PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med.* 2019;381(17):1609-1620.

Among patients with heart failure with reduced ejection fraction, the sacubitril-valsartan combination reduced the risk of hospitalization for heart failure or death from cardiovascular causes; however, data are lacking from patients with heart failure with preserved ejection fraction. The PARAGON-HF trial, a randomized, double-blind, active-comparator trial, evaluated, evaluated the sacubitril-valsartan combination in patients with heart failure with preserved ejection fraction.

The primary outcome was a composite of total (first and recurrent) hospitalizations for heart failure and death from cardiovascular causes. For this patient group, the sacubitril-valsartan combination did not significantly lower the rate of the primary outcome.

Steg PG, Bhatt DL, Simon T, et al; THEMIS Steering Committee and Investigators. Ticagrelor in patients with stable coronary disease and diabetes. *N Engl J Med.* 2019;381(14):1309-1320.

While ticagrelor helps protect against cardiovascular events when added to aspirin in patients with acute coronary syndromes and in high-risk patients with previous myocardial infarction, there are limited data available for patients with stable coronary artery disease and diabetes mellitus who have not had a myocardial infarction or stroke but who are at a high risk for cardiovascular events. The THEMIS trial, randomized, double-blind trial, investigated the efficacy and safety of ticagrelor plus aspirin vs aspirin plus placebo in this population. The primary efficacy outcome was a composite of cardiovascular death, myocardial infarction, or stroke, and the primary safety outcome was major bleeding. Compared with patients receiving aspirin plus placebo, patients receiving ticagrelor plus aspirin had a lower incidence of ischemic cardiovascular events; however, the incidence of major bleeding was higher. ■

November 2019

François B, Cariou A, Clere-Jehl R, et al; CRICS-TRIGGERSEP Network and the ANTHARTIC Study Group. Prevention of early ventilator-associated pneumonia after cardiac arrest. *N Engl J Med.* 2019;381(19):1831-1842.

Survival rates and neurological outcomes in patients after an out-of-hospital cardiac arrest with shockable rhythm are poor. The use of targeted temperature management at 32°C to 36°C is recommended to help improve the morbidity and mortality rates; however, this method is associated with a higher risk of secondary infections. The ANTHARTIC trial, a randomized, double-blind, placebo-controlled trial, tested the hypothesis that hypothesized that systematic administration of empirical 2-day antibiotic therapy with amoxicillin and clavulanate could prevent early ventilator-associated pneumonia and related complications in patients with out-of-hospital cardiac arrest treated with targeted temperature management. The primary outcome was the onset of early ventilator-associated pneumonia during the first 7 days of hospitalization. Compared with placebo, the 2-day course of antibiotic therapy lowered the incidence of early ventilator-associated pneumonia.

McMurray JJV, Solomon SD, Inzucchi SE, et al; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2019;381(21):1995-2008.

It is known that sodium-glucose cotransporter 2 inhibitors reduce the risk of a first hospitalization for heart failure in patients with type 2 diabetes; however, information is lacking on the use of these inhibitors in patients with heart failure with reduced ejection fraction with or without type 2 diabetes. The DAPA-HF trial, a phase 3, placebo-controlled trial, prospectively evaluated the efficacy and safety of the sodium-glucose cotransporter 2 inhibitor dapagliflozin in patients with heart failure and a reduced ejection fraction. The primary outcome was a composite of worsening heart failure or death from cardiovascular causes. Irrespective of the presence of diabetes, dapagliflozin reduced the risk of worsening heart failure or death from cardiovascular causes vs placebo.

Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med.* 2019;381(21):2032-2042.

Patients with an acute coronary syndrome or who have undergone a percutaneous coronary intervention, the risk of thrombotic events can be lowered by using dual antiplatelet therapy with aspirin and a P2Y12 receptor inhibitor vs by using aspirin alone; however, the risk of adverse events remains high. Options include using a more potent P2Y12 inhibitor or extending the duration of dual antiplatelet therapy to lower the residual ischemic risk, but at a price of increased bleeding. The TWILIGHT trial, a randomized, placebo-controlled trial, evaluated whether ticagrelor monotherapy after a patient undergoing a percutaneous coronary intervention who is at high risk for ischemic or hemorrhagic complications has completed a 3-month course of dual antiplatelet therapy with ticagrelor plus aspirin would be superior to ticagrelor plus aspirin. The primary end point was the first occurrence of BARC type 2, 3, or 5 bleeding between randomization and 1 year in a time-to-event analysis. Compared with the combination therapy, ticagrelor monotherapy after 3 months of dual antiplatelet therapy lowered the incidence of clinically relevant bleeding, with no higher risk of death, myocardial infarction, or stroke.

Perez MV, Mahaffey KW, Hedlin H, et al; Apple Heart Study Investigators. Large-scale assessment of a smartwatch to identify atrial fibrillation. *N Engl J Med.* 2019;381(20):1909-1917.

An Apple Watch application can use intermittent, passively detected pulse rate data in an algorithm that identifies episodes suggestive of atrial fibrillation. The Apple Heart Study, a prospective, single-group, open-label, siteless, pragmatic study, analyzed the ability of an application that uses an irregular pulse notification algorithm to identify atrial fibrillation. The two coprimary outcomes were

atrial fibrillation with a duration ≥30 seconds on ECG patch monitoring in a participant who received an irregular pulse notification and simultaneous atrial fibrillation on ECG patch monitoring during intervals when the participant had an irregular tachogram. The analysis showed that the probability of receiving an irregular pulse notification was low, and of the participants who received notification of an irregular pulse, 34% had atrial fibrillation on subsequent ECG patch readings; 84% of the notifications were in agreement with atrial fibrillation.

Stone GW, Kappetein AP, Sabik JF, et al; EXCEL Trial Investigators. Five-year outcomes after PCI or CABG for left main coronary disease. *N Engl J Med.* 2019;381(19):1820-1830.
While the use of percutaneous coronary interventions with new drug-eluting stents in patients with left main coronary artery disease has become an accepted treatment, long-term outcomes from randomized trials comparing percutaneous coronary interventions with new drug-eluting stents with coronary artery bypass grafting. This international, open-label, multicenter, randomized trial compared percutaneous coronary intervention using thin-strut cobalt–chromium fluoropolymer-based everolimus-eluting stents with coronary artery bypass grafting in patients with left main coronary artery disease. The primary outcome was the composite of death from any cause, stroke, or myocardial infarction at 3 years. There were no significant differences observed between the two procedures. ■

December 2019

Lascarrou JB, Merdji H, Le Gouge A, et al; CRICS-TRIGGERSEP Group. Targeted temperature management for cardiac arrest with nonshockable rhythm. *N Engl J Med.* 2019;381(24):2327-2337.
Considering that cardiac arrest with nonshockable rhythms are predominant and the fact that the effects of the guideline-recommended treatment of moderate therapeutic hypothermia are unclear, new data is required to identify the ideal therapy. The HYPERION trial, an investigator-initiated, open-label, blinded-outcome-assessor, pragmatic, multicenter, randomized controlled trial, was designed to assess whether moderate therapeutic hypothermia vs targeted normothermia would improve neurologic outcomes in patients in a coma who had been successfully resuscitated after cardiac arrest with nonshockable rhythm (n=581; median age, 67.15 years; women, 34.8%). The primary outcome was survival with a favorable day-90 neurologic outcome (ie, a Cerebral Performance Category scale score of 1 or 2). Compared with targeted normothermia, patients who received moderate therapeutic hypothermia for 24 hours had a higher percentage of favorable neurologic outcomes.

Tardif JC, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med*. 2019;381(26):2497-2505.

Colchicine, an orally-administered potent anti-inflammatory medication, inhibits tubulin polymerization and microtubule generation, thereby possibly affecting cellular adhesion molecules, inflammatory chemokines, and the inflammasome. The LoDoCo trial, a prospective, randomized, observer-blinded end point design (not placebo controlled), showed that the use of colchicine in patients with stable coronary disease resulted in a lower rate of cardiovascular events. The COLCOT trial, a randomized, double-blind, placebo-controlled, investigator-initiated trial, investigated the effects of colchicine on cardiovascular outcomes in patients who had a myocardial infarction within 30 days before trial enrollment, who had completed planned percutaneous revascularization procedures, and who were treated according to the national guidelines (n=4745; mean age, 60.55 years; women, 19.15%). The primary efficacy end point was a composite of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization in a time-to-event analysis. Compared with placebo, colchicine significantly lowered the risk of ischemic cardiovascular events. ■

Abbreviations & Acronyms

ACTIVE	Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events
AdDIT	Adolescent Type 1 Diabetes cardio-renal Intervention Trial
ADvISED	Aortic Dissection Detection Risk Score Plus D-dimer in Suspected Acute Aortic Dissection
AFIRE	Atrial Fibrillation and Ischemic events with Rivaroxaban in patients with stable coronary artery diseasE
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
AGES- Reykjavík	Age, Gene/Environment Susceptibility–Reykjavík
AIMS	Aortic Irbesartan Marfan Study
ANTHARTIC	Antibiotherapy During Therapeutic Hypothermia to Prevent Infectious Complications
ARREST	AmsteRdam REscustation STudies
ARIC	Atherosclerosis Risk In Communities study
ART	Arterial Revascularization Trial
ARVC	arrhythmogenic right ventricular cardiomyopathy
ASCENT-COPD	effect of Aclidinium bromide on major cardiovaSCular events and ExacerbatioNs in high-risk patienTs with Chronic Obstructive Pulmonary Disease
AUGUSTUS	evAlUation of the safety of apixaban vs vitamin K antaGonist and aspirin vs aspirin placebo in patients with atrial fibrillation and acUte coronary Syndrome or percuTaneoUS coronary intervention
AVERT	Apixaban for the Prevention of Venous Thromboembolism in High-Risk Ambulatory Cancer Patients
BIOSTAT-CHF	a systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure
BIOSTEMI	BIOdegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents in patients with ST-segment Elevation Myocardial Infarction

BNP	brain natriuretic peptide
CABANA	Catheter ABlation vs ANti-arrhythmic drug therapy for Atrial fibrillation
CANTOS	Canakinumab Antiinflammatory Thrombosis Outcome Study
CAPTAF	Catheter Ablation compared with optimized Pharmacological Therapy for Atrial Fibrillation
CARES	Cardiovascular safety of febuxostat and Allopurinol in patients with gout and caRdiovascular morbiditiES
CARMELINA	Cardiovascular and Renal Microvascular Outcome Study With Linagliptin
CBL-B	Casitas B-cell lymphoma-B
CHA2DS2-VASc	Congestive heart failure, Hypertension, Age, Diabetes, previous Stroke/transient ischemic attack–VAscular disease (peripheral arterial disease, previous myocardial infarction, aortic atheroma) and Sex category
CLARIFY	prospeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease
CLEAR	Cholesterol Lowering via bEmpedoic Acid, an ATP citrate lyase-inhibiting Regimen
COACT	Coronary Angiography after Cardiac ArresT
COLCOT	Colchicine Cardiovascular Outcomes Trial
COMMANDER AMI	Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation StrategieS
COMPLETE	COMPLETE vs culprit-only revascularization to treat multi-vessel disease after early PCI for STEMI
CONDI2/ERIC-PPCI	effect of remote ischaemic CONDItioning on Clinical Outcomes in ST-segment Elevation myocaRdial InfarCtion patients undergoing PPCI

CPVT	catecholaminergic polymorphic ventricular tachycardia
CREOLE	Comparison of thREe cOmbination therapies in Lowering blood pressurE in black Africans
CRT	cardiac resynchronization therapy
DANAMI-3-PRIMULTI	third DANish study of optimal Acute treatment of patients with ST-segment elevation Myocardial Infarction: PRIMary PCI in patients with ST-elevation myocardial infarction and multivessel disease: treatment of cUlprit Lesion only or complete revascularizaTIon
DAPA-HF	DAPAgliflozin on the incidence of worsening heart failure or cardiovascular death in patients with chronic Heart Failure
DEBUT	Drug-Eluting Balloon in stable and Unstable angina: a randomized controlled non-inferiority Trial
DECLARE-TIMI 58	Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58
DIG	Digitalis Investigation Group
E/e'sr	ratio of early mitral inflow velocity to global diastolic strain rate
ELIMINATE-AF	a Prospective, Randomized, Open-Label, Blinded Endpoint Evaluation (PROBE) Parallel Group Study Comparing Edoxaban vs. VKA in Subjects Undergoing Catheter Ablation of Non-valvular Atrial Fibrillation
ENCHANTED	Enhanced Control of Hypertension and Thrombolysis Stroke Study
ENGAGE AF-TIMI 48	Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48
ENTRUST-AF-PCI	Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen following successful coronary stenting in atrial fibrillation patients
ESC	European Society of Cardiology
ESH	European Society of Hypertension

EU-CERT-ICD	EUropean Comparative Effectiveness Research to Assess the Use of Primary ProphylacTic Implantable Cardioverter Defibrillators
EVALUATE-HF	Effects of Sacubitril/Valsartan vs Enalapril on Aortic Stiffness in Patients With Mild to Moderate HF With Reduced Ejection Fraction
EXCEL	Evaluation of XIENCE vs Coronary artery bypass surgery for Effectiveness of Left main revascularization
FAME	Fractional flow reserve versus Angiography for Multivessel Evaluation
FEATHER	Febuxostat vs Placebo Randomized Controlled Trial Regarding Reduced Renal Function in Patients With Hyperuricaemia Complicated by Chronic Kidney Disease Stage 3
FIBRES	FIBrinogen REplenishment in Surgery
FREED	Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy
GALACTIC-HF	Goal directed AfterLoad reduction in Acute CongesTIve Cardiac decompensation
GARY	German Aortic Valve Registry
GLP-1	glucagon-like peptide 1
HCM	hypertrophic cardiomyopathy
HDL	high-density lipoprotein
HFREF	heart failure with reduced ejection fraction
HFrecEF	heart failure with ejection fraction recovery
HOPE-3	Heart Outcomes Prevention Evaluation
hs-TnI	high-sensitivity troponin I
hs-TnT	high-sensitivity troponin T
HUNT	Nord-Trøndelag Health Study
HYPERION	Therapeutic Hypothermia After Cardiac Arrest in Non Shockable Rhythm

ImpACT-24B	IMPlant Augmenting Cerebral blood flow Trial-24B
ISAR-Absorb MI	Intracoronary Scaffold Assessment a Randomized evaluation of Absorb in Myocardial Infarction
ISAR-REACT	Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment
LBBB	left bundle branch block
LDL	low-density lipoprotein
LoDoCo	Low-Dose Colchicine trial
MOMENTUM	Multicenter study Of MagLev tEchNology in paTients Undergoing Mechanical circulatory support therapy with HeartMate 3
MYRIAD	Volatile Anesthetics to Reduce Mortality in Cardiac Surgery
NOAC	non-vitamin K oral anticoagulants
NSTEMI	non–ST-segment elevation myocardial infarction
NT-proBNP	N-terminal pro-brain natriuretic peptide
ODYSSEY	evaluation Of carDiovascular outcomes after an acute coronarY Syndrome during treatment with alirocumab
ONTARGET	ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
PACT-HF	Patient-Centered Care Transitions in HF
PANACHE	trial on the oral Partial Adenosine A1 receptor agonist Neladenoson bialanate over 20 weeks in pAtients with Chronic Heart failure with preserved Ejection fraction
PARADIGM-HF	Prospective comparison of Angiotensin Receptor–neprilysin inhibitor with an Angiotensin-converting enzyme inhibitor to Determine Impact on Global mortality and Morbidity in Heart Failure
PARAGON-HF	Prospective comparison of ARNi with ARB Global Outcomes in heart failure with preserved ejectioN fraction
PARTNER 3	Placement of aoRtic TraNscathetER valves

PCI	percutaneous coronary intervention
PCSK-9	proprotein convertase subtilisin/kexin type 9
PIONEER-HF	Sacubitril–Valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode
POSA	Postoperative vascular complications in unrecognized Obstructive Sleep Apnea
PREDESCI	β-blockers to PREvent DEcompenSation of CIrrhosis with portal hypertension
PRESERVE	PREvention of SERious adVerse Events following angiograph
PROVE-HF	Effects of Sacubitril/Valsartan Therapy on Biomarkers, Myocardial Remodeling and Patient-reported Outcomes in Heart Failure With Reduced Left Ventricular Ejection Fraction
RACE 7 ACWAC	Acute Cardioversion Versus Wait and See-approach for Symptomatic Atrial Fibrillation in the Emergency Department
ReBIC	Rede Brasileira de Estudos em Insuficiência Cardíaca
REDUCE-AKI	Reducing Acute Kidney Injury
REDUCE-IT	Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial
REGROUP	Randomized Endovein Graft Prospective
RELAX-AHF	RELAXin in Acute Heart Failure
RE-SPECT ESUS	Randomized, double-blind, Evaluation in Secondary stroke Prevention comparing the Efficacy and safety of the oral thrombin inhibitor dabigatran etexilate versus aCeTylsalicylic acid in patients with Embolic Stroke of Undetermined Source
REWIND	Researching cardiovascular Events with a Weekly INcretin in Diabetes
ROPAC	Registry Of Pregnancy And Cardiac disease
SCAAR	Swedish Coronary Angiography and Angioplasty Registry

SCAD	spontaneous coronary artery dissection
SCOPE I	Safety and efficacy of the Symetis ACURATE Neo/TF COmParEd to the Edwards SAPIEN 3 bioprosthesis
SHINE	Stroke Hyperglycemia Insulin Network Effort
SMART-CHOICE	SMART angioplasty research team: Comparison between P2Y12 antagonist monotherapy vs dual antiplatelet tHerapy in patients undergOing Implantation of Coronary drug-Eluting stents
SPRINT	Systolic Blood Pressure Intervention Trial
SPYRAL HTN-OFF MED	renal denervation with the symplicity SPYRAL™ multi-electrode renal denervation system in patients with uncontrolled HyperTensioN in the absence Of antihypertensive MEDication
ST2	suppresion of tumorigenicity 2
STEMI	ST-segment elevation myocardial infarction
STICH	Surgical Treatment for IschemiC Heart failure
STOPDAPT-2	ShorT and OPtimal duration of Dual AntiPlatelet Therapy after everolimus-eluting cobalt-chromium stent
STS	Society of Thoracic Surgeons
SYNTAX	SYnergy between percutaneous coronary interventioN with TAXus and cardiac surgery
TALENT	Thin Strut Sirolimus-eluting Stent in All Comers Population vs Everolimus-eluting Stent
TGF-β	Transforming growth factor β
THEMIS	A Study Comparing Cardiovascular Effects of Ticagrelor Versus Placebo in Patients With Type 2 Diabetes Mellitus
TiCAB	Ticagrelor in Coronary Artery Bypass grafting
TMVR	Transcatheter Mitral Valve Replacement registry
TPVI	transcatheter pulmonary valve implantation
TRANSCEND	Telmisartan Randomised AssessmeNt Study in ACE intolerant subjects with cardiovascular Disease

TRANSIENT	timing of revascularisation in patients with TRANSIENT ST-segment elevation myocardial infarction
TRED-HF	Therapy withdrawal in REcovered Dilated cardiomyopathy – Heart Failure
TRILUMINATE	Evaluation of Treatment With Abbott Transcatheter Clip Repair System in Patients With Moderate or Greater Tricuspid Regurgitation
TROPICAL-ACS	Testing RespOnsiveness to Platelet Inhibition on Chronic AntiplateLet treatment for Acute Coronary Syndromes
T-TIME	Trial of Low-dose Adjunctive alTeplase During prIMary PCI
TWILIGHT	Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention
VITAL	VITAmin D and omega-3 triaL
WRAP-IT	Worldwide Randomized Antibiotic envelope infection PreventIon Trial

Instructions for Authors

INSTRUCTIONS FOR AUTHORS

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Chapter in a book

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

Web-based material

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

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