

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.

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**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.

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**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.

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**Farag M, Spinhakis 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 thrombolysis, 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, non-fatal 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.

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**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.

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**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.

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**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.

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**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.

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**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.

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**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.

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**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.

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**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.

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**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.

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**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-García 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.

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**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 ( $\geq 140/90$  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.

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**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 is 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.

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**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- $\gamma$  signaling, which results in an accumulation of myocardial triglycerides, lipotoxic damage, and left ventricular dysfunction.

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**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.

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**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.

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**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.

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**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 anti-coagulant-naïve 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.

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**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  $\beta$ -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.

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**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.

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**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 cardiomegaly; 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.

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**Rodríguez 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  $\beta$  (TGF- $\beta$ ) signaling via a TGF- $\beta$ /Smad3 pathway, leading to an increased expression of  $\alpha$ -smooth muscle actin, lysyl oxidase, connective tissue growth factor, and tissue inhibitor of metalloproteinase-1. The increased TGF- $\beta$  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 TGF $\beta$ /Smad-3 signaling in the myocardium.

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**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.

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**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.

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**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.

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**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.

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**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.

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**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 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.

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**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<sup>-/-</sup>/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 P2Y<sub>1</sub>-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.

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**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.

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**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 diabetes was 35 for those with heart failure, 50 years for those with hypertension or diabetes, and 55 years for those with vascular diseases.

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**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.

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**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 bi-plane 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.

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**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 association 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.

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**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.

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**Reeh J, Thering 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.

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**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.

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

While  $\beta$ -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  $\beta$ -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.  $\beta$ -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.

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**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.

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**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 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  $\leq 6$  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  $\leq 6$  hours.

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**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.

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**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.

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**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.

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**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.

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**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 non-inferior 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.

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**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.

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**Kojima S, Matsui K, Hiramitsu S, et al. Febuxostat for Cerebral and Cardiovascular 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 cardio-renal 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.

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**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 pre-specified 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.

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**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.

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**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, Liebrechts 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.

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**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. ■

# July 2019

**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  $\geq 160$  or  $\geq 90$  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.

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**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.

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**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.

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**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 is 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.

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**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.

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**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.

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**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.

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**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 ( $\geq 60$  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.

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**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.

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**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—Melody™ 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.

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**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 functional 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. ■

## August 2019

**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.

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**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.

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**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 value 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.

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**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.

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**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.

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**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 adverse 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.

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**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.

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**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 P2Y<sub>12</sub> 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,  $\geq 3$  stents implanted,  $\geq 3$  lesions treated, bifurcation percutaneous coronary intervention with  $\geq 2$  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-1 $\beta$  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-1 $\alpha$ , IL-1 $\beta$ , or both on the development and evolution of atheromata. Outward remodeling was impaired when neutralizing IL-1 $\alpha$  or both IL-1 $\alpha$  and IL-1 $\beta$ , but not when neutralizing IL-1 $\beta$  during early atherogenesis. Neutralizing IL-1 $\beta$  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-1 $\alpha$  is involved in artery remodeling, but IL-1 $\beta$  is involved in driving inflammation.

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**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.

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**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. ■

# September 2019

**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 phase 1/2a 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  $\geq 90$  or  $\geq 200$  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 levels, 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, Gudbjörnsdóttir 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/m<sup>2</sup>). 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.

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**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.

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**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, programmed 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.

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**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.

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**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 lipoprotein(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.

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**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.

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**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 105949 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.

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**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.

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**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. ■

# October 2019

**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-naïve (n=6800; mean age, 63.45 years; women, 22.35%). In patients who were pretreated with digoxin, mortality and heart failure hospitalizations were significantly higher, showing that prescribing digoxin is an indicator of disease severity and worse prognosis.

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**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.

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**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<sup>+</sup> current and inducing a persistent Na<sup>+</sup> current.

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**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 m<sup>2</sup>, 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.

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**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.

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**Friebel J, Weithauer 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  $\beta$  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.

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**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 aureus* 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.

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**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.

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**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.

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**Weeke PE, Kelleman 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. ■

# November 2019

**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.

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**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.

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**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.

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**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%.

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**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.

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**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 patients with and without cardiovascular disease.

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**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.

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**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.

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**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.

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**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.

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**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  $\geq 50\%$  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. ■

## December 2019

**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.

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**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.

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**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 ( $\geq 2$  months) in late adulthood ( $\geq 60$  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.

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**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 VO<sub>2</sub>.

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**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.

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**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, prostate, 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.

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**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 myocardial-

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  $\gamma$ , granzyme B, and perforin.

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**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.

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**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  $\text{Ca}^{2+}$  was significantly elevated, leading to increased diastolic tension and impaired relaxation. There are two possible mechanisms contributing to this increased diastolic intracellular  $\text{Ca}^{2+}$ : (i)  $\text{Ca}^{2+}$  removal through the  $\text{Na}^{+}/\text{Ca}^{2+}$  exchanger is reduced, possibly due to higher intracellular  $\text{Na}^{+}$  concentrations; and (ii) increased myofilament  $\text{Ca}^{2+}$  sensitivity. ■