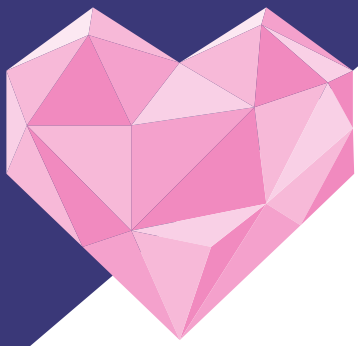
Snapshots of the Year:

The Lancet



January 2019

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

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

February 2019

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

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

March 2019

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

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

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

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

April 2019

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

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

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

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

June 2019

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

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

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

July 2019

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

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

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

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

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

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

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

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

August 2019

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

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

September 2019

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

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

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

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

October 2019

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

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

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

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

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

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

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

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

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

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

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

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

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

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

November 2019

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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