Snapshots of the Year:

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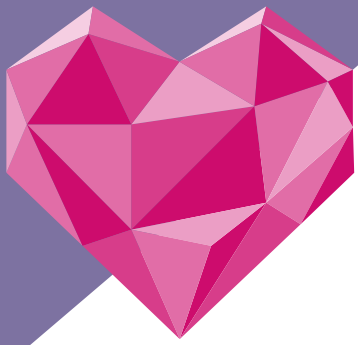

January 2019

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

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

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

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

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

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

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

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

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

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

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

February 2019

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

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

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

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

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

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

March 2019

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

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

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

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

April 2019

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

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

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

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

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

May 2019

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

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

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

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

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

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

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

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

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

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

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

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

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

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

June 2019

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

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

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

July 2019

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

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

August 2019

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

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

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

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

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

September 2019

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

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

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

October 2019

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

December 2019

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

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

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