Snapshots of the Year:

JAMA

January 2019

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

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

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

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

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

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

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

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

February 2019

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

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

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

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

March 2019

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

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

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

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

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

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

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

April 2019

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

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

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

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

May 2019

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

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

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

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

June 2019

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

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

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

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

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

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

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

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

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

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

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

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

July 2019

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

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

August 2019

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

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

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

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

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

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

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

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

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

September 2019

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

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

October 2019

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

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

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

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

November 2019

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

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

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

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

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

December 2019

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

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

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

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

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

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

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