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Clinical Cardiology [ALERT]

Critical analysis of the latest clinical research in cardiovascular medicine

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ABSTRACT & COMMENTARY

What Causes MINOCA?

By Michael H. Crawford, MD, Editor

SYNOPSIS: A systematic imaging protocol of coronary angiography, optical coherence tomography, and cardiac MRI in women clinically diagnosed with myocardial infarction with non-obstructive coronary artery disease revealed a cause in 84%, with three-quarters exhibiting an ischemic etiology.

SOURCE: Reynolds HR, Maehara A, Kwong RY, et al. Coronary optical coherence tomography and cardiac magnetic resonance imaging to determine underlying causes of MINOCA in women. *Circulation* 2020; Nov 14. doi: 10.1161/CIRCULATIONAHA.120.052008. [Online ahead of print].

Myocardial infarction with non-obstructive coronary artery disease (MINOCA) is an infrequent event largely confined to women, which can produce considerable subsequent adverse events and long-term mortality. Clinical and autopsy studies have revealed various vascular and non-vascular mechanisms for this syndrome, but early diagnosis of the underlying cause would greatly facilitate management.

Investigators from the Women's Heart Attack Research Program (HARP) designed a comprehensive imaging protocol to identify the causes of MINOCA in patients referred for coronary angiography after the clinical diagnosis of acute MI. Those with < 50% stenosis of all coronary arteries were studied by optical coherence tomography (OCT) at the time of angiography. Later, they underwent cardiac magnetic resonance imaging (CMR) within one week of presentation. Exclusion criteria included alternative explanations for troponin elevation, prior history of obstructive CAD, recent use of vasoactive agents, impaired renal function, pregnancy, and treatment with thrombolytic therapy. Also, patients with MI caused by supply demand mismatch were excluded.

OCT and CMR findings were integrated to identify the most likely cause of MINOCA in each patient. Of 301 women enrolled at 16 sites, there was interpretable OCT imaging in at least one coronary artery for 145, and they were included in this analysis. Their median age was 60 years, and 50% were non-Hispanic white. Non-ST elevation MI was the working diagnosis at the time of admission in 97% of patients.

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The ECG was abnormal in 65% of patients. In the 111 who underwent an acute echocardiogram, 44% exhibited a segmental wall motion abnormality. At angiography, the sites categorized 54% of the coronary arteries as normal. The core lab found no patient with zero stenosis (3% had 1-10%, 62% had 11-30%, and 35% had 31-50% stenosis).

By OCT, a definite or probable lesion was found in 46% of patients. The most frequent abnormality was plaque disruption (in 39%). In 3.4% of patients, thrombus without disruption of plaque was found, and 2.1% exhibited intimal bumping suggestive of spasm. One patient experienced a coronary dissection, and there was more than one finding for five patients. In a multivariate analysis, an OCT culprit lesion was independently associated with older age (OR, 1.05) and diabetes (OR, 5.41).

CMR, performed a median six days after MI onset, was interpretable in 116 of 145 patients with an interpretable OCT image. A late gadolinium enhancement distribution consistent with infarction was found in 33% of patients, almost all of whom showed evidence of myocardial edema. A regional injury pattern with more extracellular volume was found in 21% of subjects. Myocarditis was found in 15%. In 3%, Takotsubo cardiomyopathy was found, and 2% exhibited non-ischemic cardiomyopathy. The remaining 26% were normal on CMR.

Of the 116 women who underwent both OCT and CMR, 98 exhibited abnormalities on one or both studies, resulting in a final diagnosis of MI in 64%, myocarditis in 15%, Takotsubo in 3%, and non-ischemic cardiomyopathy in 2%. No cause could be identified for the remaining 16%. The authors concluded that among women with the clinical diagnosis of MINOCA, OCT plus CMR identified a cause in 84%, with 75% ischemic and 25% non-ischemic or alternative diagnoses to MI.

■ COMMENTARY

MINOCA is thought to represent 5-15% of MI patients; many of these are women. Post-MI adverse events occur in about 25% and mortality in about 11% over five years. The authors of clinical and autopsy studies have identified various potential mechanisms of MINOCA. Vascular causes include plaque rupture, erosion, and cavitation; coronary spasm, embolism, and dissection; and combinations of these. Non-vascular causes include myocarditis, Takotsubo syndrome, and cardiomyopathy. MINOCA is not thought to include microvascular disease despite its predominance in women.

In any given case, a precise mechanistic diagnosis likely would aid in acute and long-term treatment. For example, the treatment and secondary prevention of myocarditis differs greatly from those of myocardial ischemia/infarction. Thus, this analysis from the HARP study is of interest.

OCT is superior to angiography and intravascular ultrasound for identifying subtle coronary lesions and plaque characteristics, whereas CMR is superior for identifying myocardial injury caused by ischemia, inflammation, or other causes. Combining these two techniques makes sense for evaluating MINOCA patients. Unfortunately, even in this research study, there were significant challenges in successfully accomplishing both imaging modalities. Of 301 patients, there were interpretable OCT studies for only 145. Of those, only 59% studied all three main coronary arteries. Of the 145 with successful OCT, there were interpretable CMRs for 116.

Perhaps the most surprising finding is that of 145 patients who underwent OCT, the site investigators thought 53% of these patients had normal coronary arteries, whereas none of the 145 patients did according to OCT. Of course, the definition of normal coronary arteries may have been different between the two studies. OCT revealed about two-thirds of the patients had at least one stenosed artery at 11-30%. For a little more than another one-third of patients, there were 31-50% stenoses. Clearly, there was a disconnect between angiography and OCT.

On the other hand, not all showed evidence of MI or myocardial injury on CMR. Many of these coronary plaques were not the MINOCA culprits. Plaque disruption by OCT did correlate with CMR findings, which strengthens the conclusion that these were culprit lesions. These disruptions could have caused small thrombi that briefly occluded the artery (or embolized distally or provoked transient coronary spasm). The low incidence of spasm detection may have been caused by nitroglycerin administered during angiography or arterial vasodilators given in radial cases. No provocative tests for spasm were conducted. Also, 40% of patients with normal CMR studies exhibited culprit lesions on OCT, yet another disconnect. These sophisticated imaging techniques could aid cardiologists with their diagnosis and treatment of MINOCA. However, these techniques are challenging to accomplish in this clinical setting and may not always give the most helpful information. ■

ABSTRACT & COMMENTARY

Left Ventricular Size, Function Predictors of Outcomes in Chronic Aortic Regurgitation

By Michael H. Crawford, MD, Editor

SYNOPSIS: In a large cohort of asymptomatic patients with hemodynamically significant chronic aortic regurgitation, volumetric left ventricular size and function measurements were equally discriminant in identifying patients at higher risk for mortality vs. traditional linear measurements.

SOURCE: Yang LT, Anand V, Zambito EI, et al. Association of echocardiographic left ventricular end-systolic volume and volume-derived ejection fraction with outcome in asymptomatic chronic aortic regurgitation. *JAMA Cardiol* 2020; Nov 4;e205268. doi: 10.1001/jamacardio.2020.5268. [Online ahead of print].

Current guidelines recommend using linear echocardiographic measurements of the left ventricle (LV) to identify which asymptomatic patients with chronic aortic regurgitation (AR) may benefit from valve replacement. Most echo labs measure LV volumes, too, yet little information exists about the prognostic value of volumetric measures in patients with chronic AR. Yang et al sought to assess whether LV volumes and volume derived ejection fraction (EF) were associated with mortality in asymptomatic patients with chronic moderately severe to severe AR vs. traditional linear measurements of LV size and function. The authors retrospectively identified adult patients with moderately severe to severe chronic AR between 2004 and early 2019. They excluded patients with typical symptoms of AR, other more-than-mild valve lesions, prior valve surgery, cyanotic congenital heart disease, carcinoid heart disease, and those who underwent surgery for AR within two months of the index echo. The final population included 492 patients (mean age, 60 years; 86% men) in whom linear and volumetric LV measurements and measurements of AR severity were made. The primary outcome was all-cause death.

At a median follow-up of 5.4 years, 25% of the patients underwent aortic valve surgery (AVS) a median 14 months after their index echo. Of the patients undergoing AVS, 46% developed typical symptoms, 12% developed LVEF < 50%, 5% had LV end-systolic dimension (ESD) > 50 mm or LV end-systolic volume index (ESVi) > 25 mm/m^2, and 22% developed LV end-diastolic dimension (EDD) > 65 mm (all class I or II indications). Overall mortality was 17% during follow-up. Of these 83 patients, 66 died under medical follow-up, and 17 died after AVS.

A multivariate analysis showed linear LVEF, LVESDi, LVESVi, and volumetric LVEF all were independently associated with mortality with similar C statistics (0.83-0.84). The curves for continuous risk of death started to rise at linear and volumetric LVEFs < 60%, LVESVi more than 40-45 mL/m^2, and LVESDi more than 21-22 mm/m^2. However, as dichotomized variables, LVESVi > 45 mL/m^2 exhibited a higher risk of death (HR, 1.93; 95% CI, 1.1-3.4; P = 0.02), whereas LVESDi > 20 mm/m^2 did not (P = 0.32). The authors concluded that in asymptomatic patients with chronic moderately severe to severe AR, LVESVi and volumetric LVEF were equally valuable for identifying those at higher risk of death as LVESDi and linear LVEF. Also, an LVESVi > 45 mL/m^2 was significantly associated with more death.

■ COMMENTARY

One of the main reasons many echocardiographic labs still measure M-mode LV dimensions and their fractional change is that the 2017 AHA/ACC guidelines still recommend their use for decision-making in chronic AR patients.[1] Volumetric measurements,

especially of EF, could be better, but this has not been established. Thus, this study by Yang et al is of interest. Surprisingly, volumetric measurements were equal, but not better than linear measurements for predicting mortality in chronic asymptomatic AR patients. However, when cutpoints suggested by other studies were used, LVESVi > 45 mL/m^2 was statistically significant at predicting mortality, whereas LVESDi > 20 mm/m^2 was not. Also, LVESVi was superior to LVEDVi at predicting mortality. This suggests LVESVi is the volume measure to follow if one does not want to rely on M-mode echoes.

The results with EF were surprising in a couple of ways. First, EF by either linear estimations or volumetric calculations were equally discriminatory for mortality. The formula used for estimating EF from linear measurements was not specified in the methods. The references the authors quoted were not supportive of any of the methods that have been proposed (e.g., the Teichholz formula, Quinones equation) in comparison to volumetric measurements. Second, mortality rates started to increase at < 60%. The guidelines cutpoint for considering surgery in an asymptomatic patient is < 50%, and the lower limit of normal for two-dimensional volumetric LVEF is 55%. It seems LVEF by any means lacks precision for establishing a decision cutpoint in chronic AR. This aligns with my general suspicion of using ratios for any clinical decisions. Cardiologists often do not know whether the numerator or the denominator is driving the value.

There were limitations to this study. It was retrospective, observational, and occurred at one center. The presence or absence of symptoms was not verified by exercise testing. The authors did not exclude patients with atypical symptoms, which were present in 7% of the study population. About 10% of patients underwent only single-plane volumetric measurements because of technical difficulties. (Although < 10% were rejected for inadequate images). The study population was relatively young (mean age, 60 years), with 37% presenting with a bicuspid aortic valve. There were few deaths (17% mortality rate), which hinders the precision of the mortality risk estimates. Also, only deaths under medical surveillance were considered in the mortality risk calculations, which were 80% of the total deaths. Twenty percent of total deaths occurred within 30 days of surgery, which was performed on 121 patients (25%) during follow-up, resulting in a 14% surgical mortality. In addition, no other outcomes were considered, such as hospitalizations for heart failure or cardiac death in particular. Finally, these data may not be applicable to patients with chronic AR who are suitable candidates for transcutaneous valve replacement. ■

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ABSTRACT & COMMENTARY

Time is of the Essence with Colchicine Treatment of Myocardial Infarction

By Michael H. Crawford, MD, Editor

SYNOPSIS: An analysis of the COLCOT study of colchicine administration after myocardial infarction (MI) showed the benefit of this therapy for preventing subsequent cardiovascular events was greatest when therapy was initiated within three days after MI onset.

SOURCE: Bouabdallaoui N, Tardif J-C, Waters DD, et al. Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT). *Eur Hear J* 2020;41:4092-4099.

Myocardial infarction (MI) is associated with acute inflammation of the myocardium, which is involved in the detrimental remodeling process. Recent attempts to modulate inflammation in MI patients have produced modest success, including the use of colchicine, which is a potent but inexpensive anti-inflammatory agent.

In the original report on the Colchicine Cardiovascular Outcomes Trial (COLCOT), low-dose colchicine administered within 30 days after MI was shown to reduce subsequent ischemic cardiovascular (CV) events by 23% vs. placebo.[1] However, many individual events were not affected, and absolute differences in events were small. Bouabdallaoui et al examined whether the timing of colchicine initiation played any role in the outcomes. COLCOT was an international, multicenter, randomized, double-blinded trial of colchicine 0.5 mg daily vs. placebo administered within 30 days of an MI and continued for three months. Exclusion criteria were severe heart failure, reduced left ventricular ejection fraction (< 35%), recent stroke, or other inflammatory diseases. All patients underwent guideline-directed management of their MI, including

percutaneous coronary intervention (PCI) when indicated. The primary efficacy endpoint was a composite of CV death, cardiac arrest, MI, stroke, or urgent revascularization. The authors studied three periods for colchicine initiation: days 0-3 (in-hospital), days 4-7 (early post-discharge), and day 8-30 (late post-discharge). Of 4,745 patients enrolled, 4,661 patients were available for this analysis. The mean day of colchicine initiation was 14 days, with 26% at days 0-3, 15% at days 4-7, and 59% at days 8-30. Patients mostly were men (81%; mean age, 61 years), and 93% underwent PCI. Patients with therapy initiation at days 0-3 were younger, more often smokers, had less hypertension and diabetes, and more often were treated with PCI.

The primary endpoint occurred in 4.3% of the colchicine group initiated in the earliest period vs. 8.3% of the placebo group (HR, 0.52; 95% CI, 0.32-0.84; $P = 0.007$). The colchicine and placebo rates were 6% for both groups in the days 4-7 group and 5.7% and 7.1% after day 8 (P = NS). Also, many components of the primary endpoint were significantly lower in the colchicine patients treated early, including CV death (HR, 1.04), cardiac arrest (HR, 0.33), MI (HR, 0.58), stroke (HR, 0.21), and urgent revascularization (HR, 0.35). The authors concluded the early in-hospital initiation of low-dose colchicine after MI and continuing for 30 days results in fewer CV events over two years vs. placebo.

■ COMMENTARY

Myocardial necrosis activates complement, which mobilizes white blood cells. In turn, this amplifies the damage to the myocardium and extends detrimental remodeling after MI. Colchicine interferes with microtubule polymerization in white cells, which hinders their effectiveness. This results in less myocardial damage in experimental models of MI. Inflammation also plays an important role in the progression of atherosclerosis. If persistent, this would increase the risk of future vascular events. A recent study of the anti-inflammatory agent canakinumab showed a 15% reduction in CV events in patients with stable ischemic heart disease. The original analysis of the COLCOT study revealed a 23% reduction in composite CV events after MI, but little effect on individual events. This reanalysis of the COLCAT study by time of administration of colchicine exhibits a 48% reduction in CV events after MI when colchicine is administered within three days of MI onset. This makes sense if one considers the inflammatory response after MI begins almost immediately and is largely over in a week, to be replaced by fibroblast proliferation. Also of interest is the observation that stroke is much less likely, suggesting colchicine produces anti-inflammatory effects on the vasculature, too.

This could be the most provocative post-MI treatment study in quite a while. Colchicine is inexpensive; produces few side effects at this low, once-a-day dose; and only has to be given for 30 days to reap the benefits. Of course, this was a relatively small trial; the authors explored only three time frames. It would take a larger trial to parse the timing of administration more precisely. The real question is whether cardiologists should start administering colchicine to all early post-MI patients who are not contraindicated to it. Administering the drug may lower the incidence rate of post-MI pericarditis. For early adopters, this work may be enough, but I would like to see a confirmatory study. ■

REFERENCE

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ABSTRACT & COMMENTARY

Expanding Uses for Direct Oral Anticoagulants: Bioprosthetic Heart Valves?

By Michael H. Crawford, MD, Editor

SYNOPSIS: A randomized, controlled trial of rivaroxaban vs. warfarin in patients with atrial fibrillation and a bioprosthetic valve revealed rivaroxaban is noninferior to warfarin for the prevention of major cardiovascular events and the avoidance of major bleeding events over 12 months.

SOURCE: Guimarães HP, Lopes RD, de Barros E Silva PGM, et al. Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve. *N Engl J Med* 2020;383:2117-2126.

Rivaroxaban (RO) has been shown to be noninferior to warfarin for preventing stroke in patients with atrial fibrillation (AF). However, patients with prosthetic heart valves were excluded from these trials. Based on favorable outcomes in small pilot studies and subgroup analyses of larger observational studies, Guimarães et al conducted a multicenter, randomized, controlled trial of RO vs.

warfarin in patients with AF or flutter and a bioprosthetic mitral valve in 49 sites in Brazil.

Inclusion criteria were adults with paroxysmal, persistent, or permanent AF and a bioprosthetic mitral valve who were either receiving or about to receive an oral anticoagulant. Exclusion criteria included extremely high risk of bleeding, transient AF after surgery, and contraindications to the study drugs. The RO dose was 20 mg daily (or 15 mg daily if estimated creatinine clearance was 30-49 mL/min/1.73m^2). Warfarin was dose-adjusted to maintain an INR of 2-3, measured at least monthly. Follow-up visits were conducted at one, three, six, nine, and 12 months. Stroke and bleeding risk were assessed by the CHA_2DS_2-VASc and HAS-BLED scores. The primary outcome was a composite of death, major cardiovascular events, or major bleeding at 12 months. The primary safety outcomes were bleeding events classified by the ROCKET AF trial criteria and the BARC criteria.

Between 2016 and 2019, the authors randomized 1,005 patients, and only six were lost to follow-up. The mean age was 59 years, 62% were Black or multiracial, and 96% had AF. The mean CHA_2DS_2-VASc score was 2.6, the mean HAS-BLED score was 1.6, and 62% of patients underwent mitral valve replacement one to 10 years before study inclusion.

Study drug discontinuation was observed in 10% of the RO group and 7% of the warfarin group. In the intention to treat analysis, the time to the primary outcome was 348 days in the RO group and 340 days in the warfarin group ($P < 0.001$ for noninferiority). In the as-treated analysis, it was 350 days with RO and 340 days with warfarin. In the subgroup with valve replacement less than three months before enrollment, the results favored RO, with a time to the primary endpoint of 349 days vs. 314 days in the warfarin group.

The primary outcome event occurred in 6.4% of the RO group and 19% of the warfarin group (HR, 0.31; 95% CI, 0.12-0.79). The secondary outcome of death from cardiovascular causes or thromboembolic events was 3.4% with RO and 5.1% with warfarin (HR, 0.65; 95% CI, 0.35-1.2). Total stroke was 0.6% with RO and 2.4% with warfarin (HR, 0.25; 95% CI, 0.07-0.88). Valve thrombosis was 1% with RO and 0.6% with warfarin. Major bleeding occurred in 1.4% of the RO group and 2.6% of the warfarin group (HR, 0.54; 95% CI, 0.21-1.35). There were no intracranial bleeds with RO and five in the warfarin group. The authors concluded that in patients with AF and a bioprosthetic mitral valve, RO was noninferior to warfarin for preventing death, major cardiovascular outcomes, or major bleeding at one year.

■ COMMENTARY

The failure of the direct oral anticoagulants (DOAC) to prevent thromboembolic events in patients with mechanical prosthetic heart valves vs. warfarin was a great disappointment. The theory as to why is mechanical valves activate components of the clotting cascade that are not activated by stagnant blood in atria or other perturbations of natural tissue. However, with transcatheter valves increasingly used instead of surgery for failed bioprostheses, the longitudinal durability of mechanical valves is becoming less important. Many patients who would have received a mechanical valve because of their young age or other reasons now are receiving bioprostheses.

Since bioprostheses are more similar to native valves, it makes sense to test whether DOACs would provide equivalent protection from thrombotic events as warfarin. Small subgroups of the ARISTOTLE trial (apixaban) and the ENGAGE AF trial (edoxaban) of AF patients had bioprosthetic valves placed more than three months before enrollment and showed favorable results. The same was true for a small pilot study of dabigatran in patients with bioprosthetic valves.[1-3] Also, a larger trial of edoxaban in patients with bioprosthetic valves with or without AF showed zero deaths, thromboembolic events, or intracranial hemorrhages on edoxaban vs. 3.7% in warfarin patients, with no difference in major bleeds over three months.[4]

Encouraged by these preliminary findings, Guimarães et al found patients with AF and a bioprosthetic mitral valve were free of major cardiovascular or bleeding events for 7.4 days longer than those on warfarin at one year. This result was statistically noninferior for RO, but not superior to warfarin. Also, secondary outcomes such as stroke (0.6% RO vs. 2.4% warfarin), bleeding, and valve thrombosis were similar. However, the incidence of these events were low, so interpret them with caution. In addition, Guimarães et al included patients who underwent mitral valve replacement within three months and found superior results for RO. Again, this was a smaller subgroup.

There were limitations to this study. It was open label, so the reporting of events could have been biased. However, a blinded, independent panel adjudicated outcomes. Also, it is challenging to blind a study with warfarin since the INR monitoring is hard to keep secret. Still, a trial with less frequent endpoints and smaller subgroup analyses are of limited validity. Finally, the authors correctly noted their results do not apply to those with bioprosthetic aortic valves, mechanical valves, or native valve mitral stenosis. Currently, in these groups, warfarin remains the recommendation. ■

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ABSTRACT & COMMENTARY

A New Treatment for Refractory Hyperlipidemia

By Michael H. Crawford, MD, Editor

SYNOPSIS: In patients with familial hypercholesterolemia who are not at target LDL cholesterol levels on maximum-tolerated doses of statins and PCSK9 inhibitors, evinacumab, which inhibits angiopoietin-like 3, reduces LDL by more than 50% at the highest doses with few side effects requiring drug discontinuation vs. placebo.

SOURCE: Rosenson RS, Burgess LJ, Ebenbichler CF, et al. Evinacumab in patients with refractory hypercholesterolemia. *N Engl J Med* 2020; Nov 15. doi: 10.1056/NEJMoa2031049. [Online ahead of print].

Angiopoietin-like 3 (ANGPTL3) regulates lipid metabolism by inhibiting lipoprotein lipase and endothelial lipase. Patients without functioning ANGPTL3 record low levels of LDL cholesterol, triglycerides, and HDL cholesterol. Also, they are at a reduced risk of coronary artery disease. Evinacumab is a human monoclonal antibody against ANGPTL3 and lowers LDL cholesterol by means not involving the LDL receptor.

Rosenson et al assessed the efficacy and safety of subcutaneous and intravenous evinacumab vs. placebo in patients with refractory hypercholesterolemia despite therapy with maximum-tolerated doses of statins and a PCSK9 inhibitors, with or without ezetimibe. The authors conducted the study in 85 sites across 20 countries. They enrolled 272 patients with either heterozygous familial hypercholesterolemia or non-heterozygous hypercholesterolemia and clinically diagnosed cardiovascular disease. Refractory hyperlipidemia was defined as an LDL cholesterol level > 70 mg/dL with atherosclerotic disease or greater than 100 mg/dL without atherosclerotic disease.

Patients were randomized to receive subcutaneous treatment or intravenous treatment at various doses. Intravenous evinacumab was administered every four weeks and subcutaneous every one or two weeks. The primary endpoint was percent change from baseline in the LDL cholesterol level at 16 weeks. The various drug dose and route of administration groups included 30 to 40 patients each. Six patients did not receive treatment, so the final intention to treat population was 266. The heterozygous variant was present in 72% of patients. The differences in LDL cholesterol between baseline and week 16 in the subcutaneous evinacumab at 450 mg weekly, 300 mg weekly, and 300 mg every two weeks groups were -56%, -53%, and -39%, respectively ($P = 0.001$ for all). The differences in the intravenous groups at 15 mg/kg and 5 mg/kg were -51% ($P = 0.001$) and -24%. All atherogenic lipoprotein levels decreased with evinacumab, except lipoprotein (a).

The incidence of side effects with subcutaneous evinacumab that occurred in at least 5% of the subjects included injection site erythema in 6% vs. 3% on placebo and myalgia in 5% vs. zero on placebo. Adverse events with intravenous evinacumab that occurred in more than 5% of the subjects included abdominal pain in 6% vs. zero with placebo, dizziness in 7% vs. zero with placebo, and nausea 7% vs. zero with placebo. The authors concluded using evinacumab significantly reduced LDL cholesterol levels by more than 50% at maximal doses in patients with refractory hypercholesterolemia with few side effects requiring drug discontinuation vs. placebo.

■ COMMENTARY

In many patients with familial hypercholesterolemia, LDL levels remain above guideline targets despite statins and PCSK9 inhibitors. Some produce adverse effects, especially to statins, that also limit the dose tolerated. Thus, there is residual need for other agents to reduce LDL cholesterol. This is the case especially in those with atherosclerotic disease or at high risk for it when one considers the 2016 ESC and ACC/AHA guidelines recommend an LDL < 70 mg/dL for such patients and the 2019 ESC guidelines recommend < 55 mg/dL.

Evinacumab in the Rosenson et al study is impressive at reducing LDL in these high-risk patients with familial hypercholesterolemia and others at high risk of atherosclerotic vascular disease. With either subcutaneous or intravenous administration, the LDL levels had decreased significantly by two weeks and continued for 16 weeks. Side effects were common in the treatment groups and the placebo groups, but serious adverse effects requiring drug discontinuation above that seen with placebo were few and only observed at the highest doses. Evinacumab reduces triglycerides, which are atherogenic, whereas PCSK9 inhibitors do not. Evinacumab also decreases apolipoprotein B, which is associated with reduced cardiovascular disease risk. In addition, evinacumab reduces HDL cholesterol. However, in those with naturally occurring low ANGPTL3 function, there is no increase in cardiovascular disease risk.

There were limitations to the Rosenson et al study. The size of each dose and administration group were small, and the study was not ethnically diverse. Also, only one-third of patients were on ezetimibe. In addition, it was a short-term study, and the authors did not provide outcome data. Still, evinacumab looks promising, and cardiologists need an additional class of drugs to treat patients with very high LDL cholesterol levels. I look forward to longer-term studies with outcome data. ■

CME/CE QUESTIONS

1. **A large, longitudinal, observational study of patients with hemodynamically significant aortic regurgitation suggests the cutoff for left ventricular ejection fraction for considering surgery should be:**
   a. < 50%.
   b. < 55%.
   c. < 60%.
   d. < 70%.

2. **Evinacumab lowers LDL cholesterol in patients on statins and PCSK9 inhibitors by:**
   a. 25%.
   b. 50%.
   c. 75%.
   d. 85%.

3. **Most patients with MI and non-obstructive coronary artery disease have:**
   a. atherosclerosis.
   b. coronary dissection.
   c. coronary spasm.
   d. myocarditis.

4. **For optimal benefit, colchicine should be started within how many days of MI onset?**
   a. Three days
   b. 4-7 days
   c. 8-14 days
   d. 14-30 days

5. **A study of rivaroxaban vs. warfarin for patients with atrial fibrillation and a bioprosthetic mitral valve showed what regarding cardiovascular outcomes?**
   a. Superiority
   b. Non-inferiority
   c. More intracranial bleeds
   d. Fewer fatalities

CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the most current information related to cardiac illness and the treatment of cardiac disease;
- explain the advantages and disadvantages, as well as possible complications, of interventions to treat cardiac illness;
- discuss the advantages, disadvantages, and cost-effectiveness of new and traditional diagnostic tests in the treatment of cardiac illness; and
- discuss current data regarding outpatient care of cardiac patients.