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ABSTRACT & COMMENTARY

Another Affirmation for Rhythm Control in Atrial Fibrillation

By Joshua Moss, MD

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Dr. Moss reports he is a consultant for Abbott, Biosense Webster, and Boston Scientific.

SYNOPSIS: A rhythm control strategy implemented less than one year after atrial fibrillation diagnosis was associated with significant reduction in adverse cardiovascular outcomes when compared to usual care.

SOURCE: Kirchhof P, Camm AJ, Goette A, et al. Early rhythm control therapy in patients with atrial fibrillation. *N Engl J Med* 2020;383:1305-1316.

The landmark AFFIRM randomized trial[1] has long been cited as evidence that rhythm control therapy is not superior to rate control for atrial fibrillation (AF), but treatment for AF has evolved since its publication. The potential adverse effects of antiarrhythmic drugs (particularly amiodarone) and the importance of therapeutic anticoagulation regardless of treatment strategy are better appreciated, and a mortality benefit has been associated with catheter ablation in patients with cardiomyopathy.

Kirchhof et al sought to assess whether modern rhythm control therapy for AF would reduce the risk for cardiovascular complications. The authors randomized 2,789 adults (nearly half women) at 135 centers in 11 countries with AF diagnosed less than one year before to early rhythm control vs. "usual care," in which rhythm control therapies were added only to mitigate symptoms after adequate rate control was achieved. Patients had to be older than age 75 years or have other risk factors for stroke similar to those in the widely used CHA_2DS_2-VASc score. The first primary outcome was a composite of death from stroke, hospitalization, or cardiovascular causes with exacerbated heart failure or acute coronary syndrome. The second primary outcome was nights spent in the hospital annually. The authors also assessed several secondary outcomes, including quality of life and cognitive function.

Patients were enrolled a median of 36 days after the first diagnosis of AF. In the rhythm control arm, about 87% of patients received an antiarrhythmic drug

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initially (19.6% amiodarone) and 8% underwent ablation. By two years, about 46% of patients were on an antiarrhythmic drug (11.8% on amiodarone) and 19% had undergone ablation; sinus rhythm was found in 82%. The mean CHA_2DS_2-VASc score was 3.4, and 88% of patients remained on oral anticoagulants at two years.

In the usual care arm, 96% of patients were managed initially without any rhythm control therapy. By two years, about 8% were on an antiarrhythmic drug (2.8% on amiodarone) and 7% had undergone ablation; sinus rhythm was found significantly less often (in 61%). The mean CHA_2DS_2-VASc score was 3.3, and 91% of patients remained on oral anticoagulants at two years.

The trial ended early for efficacy after a median of 5.1 years of follow-up. There were 3.9 first primary outcome events for every 100 person-years in the rhythm control arm, significantly less than the 5.0 events for every 100 person-years in the usual care arm (hazard ratio, 0.79; 95% confidence interval, 0.66-0.94; $P = 0.005$). Significant differences were not found in nights spent in the hospital nor in secondary outcomes. Both left ventricular function and cognitive function remained stable at two years. More than 70% of patients in both groups were asymptomatic at years one and two.

Overall safety outcomes did not differ significantly between groups. However, stroke and death rates were lower in the rhythm control group (stroke significantly so at 2.9% vs. 4.4%). Meanwhile, serious adverse events were more common: more toxic effects of drug therapy (0.7% vs. 0.2%), drug-induced bradycardia (1% vs. 0.4%), bleeding and tamponade related to ablation (0.7% vs. 0.1%), and hospitalization for AF (0.8% vs. 0.2%). The authors concluded that a rhythm control strategy implemented less than one year after an AF diagnosis vs. usual care was associated with significant reduction in adverse cardiovascular outcomes.

■ COMMENTARY

A critically important study in 2002, AFFIRM simply is no longer representative of modern approaches to AF management. As in the Kirchhof et al study, rhythm control was achieved primarily with antiarrhythmic drugs. However, amiodarone was used at some point in > 60% of patients, compared with 12% of patients at two years in the Kirchhof et al study. That is a dramatic difference, especially considering that more than 25% of rhythm control patients in AFFIRM experienced an adverse event or clinical finding prompting discontinuation of a drug. Only 63% of patients were in sinus rhythm at five years in the AFFIRM rhythm control arm, and only about 70% of patients in that arm continued anticoagulation (with warfarin, the only choice of oral agent at the time). Stroke rate was ~1% per year, and most strokes occurred in patients in whom warfarin had been stopped or in whom the INR was subtherapeutic.

The Kirchhof et al study is more representative of current rhythm control techniques, with less amiodarone use, more consistent thromboembolic prophylaxis with more reliable oral anticoagulants, and addition of catheter ablation as a treatment option. By two years, substantially more patients in the rhythm control arm had undergone catheter ablation than were on amiodarone (19% vs. 12%), and even 7% of patients in the usual care arm had an ablation. The outcomes in the Kirchhof et al study reflect the changes in care that have evolved over the past 18 years: sinus rates were higher, serious adverse events related to antiarrhythmic drug therapy occurred in only 37 out of 2,789 patients (2% in the rhythm control arm and 0.6% in the usual care arm), and overall stroke rates were lower (3.7% vs. 8.2% in AFFIRM). With these overall improvements in mind, early rhythm control also was associated with a significant reduction in the primary outcome of death from stroke, cardiovascular causes, and hospitalization with acute coronary syndrome or exacerbated heart failure. Considering the individual components of the composite outcome, the hazard ratio for death from cardiovascular causes was 0.72 (0.52-0.98) and 0.65 for stroke (0.44-0.97). Death from cardiovascular causes was rare in this population, but using an early rhythm control strategy in 100 patients over about three years could prevent such a death compared to usual care.

As always, limitations must be considered. Overall, about 7% of patients withdrew, and researchers lost about 7% of subjects

to follow-up. Catheter ablation, although used more than amiodarone, still accounted for a relatively small proportion of patients treated (even though this has been shown in other trials to be superior to drug therapy for maintenance of sinus rhythm). Nevertheless, no longer should rate and rhythm control be considered equivalent in a typical patient with recent-onset AF, even when asymptomatic. With shared decision-making about the potential risks of antiarrhythmic drugs and/or catheter ablation, early restoration and maintenance of sinus rhythm should be strongly considered. ■

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ABSTRACT & COMMENTARY

The Effect of Age on Cholesterol-Lowering Therapy

By Michael H. Crawford, MD, Editor

SYNOPSIS: Investigators analyzed data on the effect of age on cardiovascular (CV) outcomes and LDL cholesterol-lowering by alirocumab vs. placebo in recent acute coronary syndrome patients. They found alirocumab can lower the rate of CV events regardless of age — and produce increasing absolute benefit with age.

SOURCE: Sinnaeve PR, Schwartz GG, Wojdyla DM, et al. Effect of alirocumab on cardiovascular outcomes after acute coronary syndromes according to age: An ODYSSEY OUTCOMES trial analysis. *Eur Hear J* 2020;41:2248-2258.

The dearth of older patients in studies of LDL cholesterol-lowering has left uncertainty about the advisability of statin therapy in patients older than age 75 years. Recently, Sinnaeve et al conducted a prespecified analysis of the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With alirocumab (ODYSSEY OUTCOMES) trial. They assessed the effect of age on cardiovascular outcomes and LDL cholesterol-lowering effects of alirocumab vs. placebo in patients with a recent (< 12 months) acute coronary syndrome (ACS) and LDL levels above target (> 70 mg/dL) on maximally tolerated, high-intensity statin therapy.

The investigators were blinded to the treatment assignment and LDL levels. The primary endpoint was major adverse cardiovascular events (MACE), which was a composite of cardiac death, myocardial infarction, stroke, or unstable angina requiring hospitalization. The mean age of the 18,924 patients was 59 years (27% were > age 65 years and 5% > age 75 years). Because of the paucity of patients in the latter group, the data analysis was dichotomized at age 65 years. Older patients were more likely to be women and to be living with other cardiovascular disease. Adherence to the study drug and the degree of LDL lowering were similar in both age groups.

Mean LDL levels at three years were 63 mg/dL in those < age 65 years and 57 mg/dL in those > age 65 years vs. 102 mg/dL and 97 mg/dL, respectively, in the placebo groups. Relative risk reductions were similar for both groups: age > 65 years HR, 0.78; 95% CI, 0.68-0.81 and age < 65 years HR, 0.89; 95% CI, 0.80-1.0; *P* for the interaction = 0.19. The HR for all-cause death was 0.77 (95% CI, 0.62-0.95 in the age > 65 years group) and 0.94 (95% CI, 0.77-1.15; *P* interaction = 0.46).

Dichotomizing the data at age 75 years produced similar results: HR for MACE in both groups was 0.85. Analyzing age as a continuous variable showed advancing age raised the risk of MACE and the absolute reduction in MACE with alirocumab. The number needed to treat to prevent one MACE at three years was 43 at age 45 years, 26 at age 75 years, and 12 at age 85 years. More patients experienced severe adverse events in the age > 65 years group, but there was no difference between alirocumab and placebo. The authors concluded that in patients with recent ACS, alirocumab reduces MACE, regardless of age — but with increasing absolute benefit (not harm) with advancing age. Thus, aggressive LDL lowering should not be withheld from older patients.

■ COMMENTARY

Elderly patients with cardiovascular disease often are undertreated, presumably over fear of adverse effects, polypharmacy, potential drug-drug interactions, or the concept that they have fewer years left to gain. In this prespecified analysis of the ODYSSEY OUTCOMES study, the authors noted those older than age 65 years were on less intense statin regimens at baseline and rarely were taking ezetimibe, despite their recent ACS event. Since the safety profile of alirocumab is similar to placebo, investigators believed this might be a good way to lower LDL cholesterol to target (< 70 mg/dL) in elderly patients. Hence, this analysis of the ODYSSEY OUTCOMES trial is of interest. Sinnaeve et al showed that not only did intensive lowering of LDL reduce MACE and all-cause death in post-ACS patients age

older than 65 years, but it did so with increased absolute benefit compared to younger patients. Also, these results were obtained without any increase in adverse events over placebo. This resulted in a progressively smaller number needed to treat to prevent one MACE to an impressive 12 in those age 85 years.

These data are similar to two other randomized, controlled trials published while ODYSSEY OUTCOMES was conducted. In the PROVE-IT TIMI 22 study of atorvastatin vs. pravastatin in post-ACS patients, at age > 70 years the number needed to treat was 13 vs. 44 for those < age 70 years.[1] In the similar IMPROVE-IT study of adding ezetimibe to simvastatin therapy, those > age 75 years had a number needed to treat of 11.[2] Other researchers confirmed these results further in the Cholesterol Treatment Trialists meta-analysis 8.[3]

In addition, reducing MACE in older patients should improve quality of life and lower medical care costs. Thus, a strong picture is emerging that older patients with coronary artery disease should be treated with LDL-lowering therapy as aggressively as younger patients.

There were a few limitations to the Sinnaeve et al analysis. The low end age cutoff for enrollment of 40 years and the dichotomization at age 65 years was by trial design. The number of very elderly patients was small, so estimates of effectiveness and safety in those > age 80 years is less precise. All the patients were on maximally tolerated, high-intensity statins at baseline, and few were on ezetimibe. Considering the entry criteria for the study, it is unlikely many were frail, so the results are less likely to apply to sicker elderly patients. Although the follow-up duration for this study was long (four years, median 2.8 years), it is difficult to estimate years gained beyond the trial duration. However, the consistency of the data with other studies supports the conclusion that aggressive lipid-lowering for secondary prevention in elderly patients is important. ■

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ABSTRACT & COMMENTARY

Using Sacubitril/Valsartan to Treat Heart Failure with Preserved Ejection Fraction

By Jamie L. W. Kennedy, MD, FACC

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Dr. Kennedy reports no financial relationships relevant to this field of study.

SYNOPSIS: An analysis of renal outcomes in the PARAGON-HF trial revealed sacubitril/valsartan slows progression of kidney disease in patients with heart failure with preserved ejection fraction compared to valsartan alone.

SOURCE: McCausland FR, Lefkowitz MP, Claggett B, et al. Angiotensin-neprilysin inhibition and renal outcomes in heart failure with preserved ejection fraction. *Circulation* 2020;142:1236-1245.

Heart failure with preserved ejection fraction (HFpEF) is common, accounting for half of heart failure diagnoses. However, evidence-based treatment options remain elusive — and not for lack of effort. Historically, HFpEF was understood as the result of left ventricular hypertrophy and fibrosis caused by long-standing hypertension, diabetes, and often coronary disease. But increasingly, the contribution of endovascular dysfunction has been recognized. Furthermore, diseases such as cardiac amyloidosis and variant forms of hypertrophic cardiomyopathy are diagnosed more often. It is likely unintentional inclusion of these patients in early HFpEF trials blunted the effect of potentially efficacious therapies.

Neprilysin inhibitors increase the concentration of natriuretic peptides, which results in coronary vasodilation and inhibition of cardiomyocyte hypertrophy. Renal effects include higher glomerular filtration rate (eGFR), inhibition of sodium reabsorption, and suppression of renin and aldosterone. Preliminary studies revealed the combination of sacubitril/valsartan lowered NT-proBNP, shrank left atrial size, and improved New York Heart Association (NYHA) functional class compared to valsartan alone, prompting the PARAGON-HF study.

The PARAGON-HF study authors enrolled 4,822 patients with left ventricular ejection fraction (LVEF) 45%

or higher. Patients presented with stable NYHA class II-IV symptoms requiring treatment with diuretics, age ≥ 50 years, left atrial enlargement or left ventricular hypertrophy, and elevated NT-proBNP on a sliding scale based on sinus rhythm vs. atrial fibrillation and recent heart failure hospitalization. Patients with hypotension (systolic blood pressure < 110 mmHg), severe chronic kidney disease (eGFR < 30 mL/min/1.73 m^2), or hyperkalemia (> 5.2) at baseline were excluded.

Patients with potential alternative explanations for functional limitations, such as severe pulmonary disease, anemia (hemoglobin < 10 g/dL), or morbid obesity, were excluded. Patients with a history of reduced ejection fraction (< 40%), congenital heart disease, constrictive pericarditis, or significant valvular heart disease were excluded, as were patients with known infiltrative, genetic, hypertrophic, peripartum, viral, or chemotherapy-induced cardiomyopathies. Patients were randomized to either valsartan (target dose = 160 mg twice daily) or sacubitril/valsartan (target dose = 97/103 mg twice daily) after a run-in period to ensure tolerance of both agents.

Patients were, on average, age 72.8 years, and 51.7% were women. Most were NYHA class II (77%) or III (19%). Race was predominantly white (81.5%), followed by Asian (12.7%) and Black (2.2%). Most enrolled patients lived in Central or Western Europe, followed by Asia-Pacific, North America, and Latin America. Baseline BMI was 30 kg/m^2, eGFR was 63 mL/min/1.73m^2, systolic blood pressure was 130 mmHg, LVEF was 58%, and NT-proBNP was 910 pg/mL. Most patients were hypertensive (95%), half had been hospitalized for heart failure, 43% were diabetic, 37% were living with coronary disease, and one-third exhibited atrial fibrillation or flutter.

The median duration of follow-up was 35 months. The primary outcome was a composite of heart failure hospitalizations and cardiovascular death. Overall, the rate of the primary outcome was 12.8 per 100 patient-years in the sacubitril/valsartan group and 14.6 per 100 patient-years in the valsartan group (rate ratio, 0.87; 95% CI, 0.75-1.01).

Interestingly, a subgroup analysis suggested women benefited from sacubitril/valsartan (rate ratio, 0.73; 95% CI, 0.59-0.90) while men did not (rate ratio, 1.03; 95% CI, 0.85-1.25). Other secondary analyses revealed more patients in the sacubitril/valsartan arm demonstrated improved quality of life and NYHA class.

McCausland et al more completely analyzed the effect on renal function. There was a prespecified composite secondary renal endpoint: 50% or greater decline in eGFR from baseline, the development of end-stage renal disease, or death from kidney disease.

Additional analyses concerned the rate of decline in renal function over time. At baseline, the average eGFR was 63 ± 19 mL/min/1.73m^2. The composite renal outcome occurred in 1.4% of the sacubitril/valsartan group vs. 2.7% of the valsartan group (HR, 0.50; P = 0.001). This outcome was driven primarily by the reduction in eGFR component: 1.1% of sacubitril/valsartan patients vs. 2.5% of valsartan patients (HR, 0.44; 95% CI, 0.28-0.69). There was no statistical difference in the rate of progression to end-stage renal disease or death from renal causes.

In a time-based analysis, eGFR declined 2 mL/min/1.73m^2 annually in the sacubitril/valsartan group compared to 2.7 mL/min/1.73m^2 in the valsartan group (P < 0.001). When the outcomes were analyzed by baseline renal function, there was no significant difference. The authors concluded sacubitril/valsartan slows progression of kidney disease in patients with HFpEF.

■ COMMENTARY

PARAGON-HF was a negative trial, although several intriguing findings may lead to positive trials in the future. Chronic kidney disease complicates half of heart failure; thus, preventing progressive renal dysfunction is an important goal.

The series of disappointing HFpEF trials continues with the recent publication of VITALITY-HFpEF (vericiguat) and CAPACITY HFpEF (praliciguat).[1,2] PARAGON-HF suggests treatment with sacubitril/valsartan slows progression of renal disease in patients with HFpEF as compared to valsartan, in addition to the suggestion of benefit in women, improvement in NYHA class, and quality of life.

A wise friend asked me if SGLT2 inhibitors are efficacious in systolic heart failure because we all are prediabetic. He might be on to something. I am disappointed McCausland et al did not break down outcomes by presence or absence of diabetes. I also am disappointed the authors did not assess proteinuria. Trials of SGLT2 inhibitors dapagliflozin and empagliflozin in patients with HFpEF are in progress. I suspect they will demonstrate clear benefit. For now, cardiologists should consider substituting sacubitril/valsartan for ACE or ARB in HFpEF patients in whom borderline renal function is present. ■

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ABSTRACT & COMMENTARY

Are Anti-Inflammatory Drugs Useful in Malignant Pericardial Effusion?

By Michael H. Crawford, MD, Editor

SYNOPSIS: Researchers studied patients with malignant pericardial effusion treated with pericardiocentesis and then anti-inflammatory agents if signs of adhesions or constriction were observed in post-drainage echocardiograms. Compared to NSAIDs and steroids, the authors found colchicine administration for 60 days reduced the rate of subsequent all-cause mortality and recurrent pericardial effusion.

SOURCE: Kim SR, Kim EK, Cho J, et al. Effect of anti-inflammatory drugs on clinical outcomes in patients with malignant pericardial effusion. *J Am Coll Cardiol* 2020;76:1551-1561.

Pericardial effusion (PE) is a common complication of malignancies and may be caused by metastases to the pericardium, an immune reaction to chemotherapy or pericardial damage resulting from radiotherapy. Despite the poor prognosis of many of these patients, therapy to preserve cardiac hemodynamics so that therapy of the malignancy can proceed is important. Pericardiocentesis (PCC) with placement of a drain performed under echocardiographic guidance is a safe and effective treatment for avoiding or treating pericardial tamponade. However, over time, adhesions and pericardial constriction (PC) can develop, which complicates cancer therapy. Since anti-inflammatory agents may reduce the reaction that leads to constriction, Kim et al investigated the incidence of PC and the effect of colchicine on long-term outcomes after PCC for malignancy-associated PE. After eliminating patients with no follow-up echoes, the authors identified 376 cancer patients who underwent PCC from 2007 to 2018 and followed them for a minimum of 24 months. After drainage fell below 30 mL/day, the catheter was removed, and a follow-up echo was performed within three days. Patients with adhesions or evidence of constriction after catheter removal were treated with an anti-inflammatory agent per their physician's choice (colchicine, NSAIDs, or steroids). Researchers gave colchicine for one to three months, ibuprofen was tapered over two weeks, and steroids were administered depending on the patient's response to therapy.

The primary outcome was a composite of all-cause mortality and re-PCC or pericardial window for recurrent PE. Men made up 56% of the patients, and the mean age of all patients was 57 years. Advanced lung cancer invading the pericardium was the most common diagnosis. About two-thirds underwent chemotherapy, and 27% radiotherapy. Pericardial tamponade was evident in 87%. The initial PCC was successful 97% of the time. Over the two-year follow-up, 26% of patients developed recurrent PE, and 46% developed CP. Colchicine was used in 24% of patients for a mean of 63 days. Initial clinical characteristics were not different in the colchicine group vs. the rest of the patients, but colchicine-treated patients exhibited more post-PCC adhesion and constriction and post-PCC NSAID use. The colchicine group was much less likely to reach the primary endpoint (adjusted HR, 0.60; 95% CI, 0.45-0.81; $P = 0.001$) compared to the non-colchicine group. This result persisted after propensity score matching (HR, 0.55; 95% CI, 0.37-0.82; $P = 0.003$). Also, the results were consistent across multiple subgroups. The authors concluded that in patients with malignant PEs undergoing PCC, colchicine administration for one to three months improves clinical outcomes.

■ COMMENTARY

The usual treatment for significant PEs in cancer patients is pericardial drainage, with the catheter left in place until fluid drainage is at or near zero. This occurs mainly to relieve symptoms or prevent impending cardiac tamponade. This aspect of the Kim et al study is not novel, but little formal study data on its effectiveness exist. It is encouraging that pericardial drainage was successful and complication-free 97% of the time. There was only one death despite four cases of cardiac perforation and two cases of pneumothorax. Median duration of indwelling catheter was four days, but most of the fluid was drained in the first day. The post-catheter removal echocardiogram showed adhesions in 71% and constriction in 37%. Thus, the unique aspect of this study was the treatment with anti-inflammatory agents in the patients who showed evidence of adhesions and constriction after drainage.

The principle weakness of the study was that the choice of specific anti-inflammatory was at the treating physician's discretion. Colchicine and NSAIDs were the most common agents administered, but NSAIDs were only given for a short time, presumably to treat symptoms. About 20% of the patients received steroids. This analysis focused on comparing the colchicine-treated patients to those who did not receive colchicine. It showed the use of colchicine was associated with significantly less all-cause mortality and repeat pericardial drainage over the two-year follow-up. Steroid use was associated with an increase in mortality and subsequent PCC, but this could be because sicker patients were treated with steroids. In fact, in a multivariate analysis, steroid use was no longer significant ($P = 0.07$). NSAID

use did not affect short- or long-term outcomes. Inspection of the Kaplan-Meier curves showed the benefits of colchicine therapy waned after one year, which perhaps is not surprising in these patients. Why is this study important? The one-year survival of advanced cancer patients with PE in the Kim et al study was 30%, which is higher than that observed in older studies. Such patients are living longer today thanks to better cancer treatments, so abrogating the problem of recurrent PE or PC is of value to the patient. Also, because such patients are living longer, advanced complications like PE are becoming more frequent. Thus, using a relatively well-tolerated drug like low-dose colchicine for up to three months seems justified. Some physicians prefer a surgical or percutaneous pericardial window for malignant PE, but these procedures carry higher complication rates than PCC. In terminal cases with recurrent PE, pericariodesis can be considered, but this often is a painful procedure. Of course, this is a one-center, observational experience, so it can only be hypothesis-generating. Considering the alternatives, it seems reasonable to use now in appropriate patients. ■

ABSTRACT & COMMENTARY

Prophylactic PCI for Vulnerable Plaques

By Jeffrey Zimmet, MD, PhD

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Dr. Zimmet reports no financial relationships relevant to this field of study.

SYNOPSIS: In this proof-of-concept trial, treatment of non-flow limiting vulnerable plaque by PCI with bioabsorbable stents resulted in no significant difference in lesion-related events compared with optimal medical therapy, but there was a trend toward less angina driven revascularization in the stented group.

SOURCE: Stone GW, Maehara A, Ali ZA, et al. Percutaneous coronary intervention for vulnerable coronary atherosclerotic plaque. *J Am Coll Cardiol* 2020; Sep 22;S0735-1097(20)37240-5. doi: 10.1016/j.jacc.2020.09.547. [Online ahead of print].

Plaque rupture events leading to myocardial infarction (MI) do not necessarily occur in areas with significant stenosis and flow limitation. Instead, the theory goes, areas of significant plaque burden containing a necrotic lipid core and covered with a thin cap of tissue represent "vulnerable" plaques that lead to acute coronary syndromes. The study of vulnerable plaque has been hampered by the dual problems of how to identify them and what to do about them once identified. First, intravascular imaging with a combination of intravascular ultrasound (IVUS) and near infrared spectroscopy (NIRS) has demonstrated a track record of recognizing and categorizing such plaque, with the obvious caveat that it requires an invasive procedure to do so. Indeed, the 2019 Lipid Rich Plaque study showed this technology can help identify both patients and plaques that are at significantly elevated risk for subsequent events.[1]

The PROSPECT ABSORB trial was designed to examine the results of treating such vulnerable plaques by stenting, specifically with the Absorb bioresorbable vascular scaffold (BVS). To this end, patients who presented with MI and had undergone successful percutaneous coronary intervention (PCI) of all ischemic lesions underwent imaging with a combined NIRS-IVUS catheter (Infraredx, Bedford, MA). Those who met a prespecified threshold for vulnerable plaque in angiographically non-obstructive lesions were eligible for participation. The authors examined 902 patients with MI, leading to the identification of 182 patients at 15 sites who were randomized to treatment with Absorb BVS or to medical therapy alone. Of 93 patients randomized to treatment with the Absorb, 92 underwent successful BVS implantation. One patient was found to have a vessel larger than the Absorb allows and was treated with a metallic drug-eluting stent. All patients were treated with guideline-directed medical therapy, including dual antiplatelet therapy, for six to 12 months and high-intensity statins. Overall adherence rates were high.

All but one patient had clinical follow-up available at 24 months, and 167 underwent follow-up angiography and IVUS at a median of 25 months. Unsurprisingly, minimum lumen area measured by IVUS was significantly wider in patients treated with the scaffold compared with those treated with medical therapy alone (6.9 ± 2.6 mm^2 in BVS-treated lesions compared to 3.0 ± 1.0 mm^2 in medical therapy alone-treated lesions). Binary restenosis, defined as diameter stenosis > 50% within the scaffolded segment, was present at follow-up in four of 86 BVS-treated lesions. Stenoses > 50% were seen in 12 of 80 lesions in the medical therapy arm ($P = 0.02$). Regarding clinical outcomes, the primary safety outcome of target lesion failure was not different between the two groups (4.3% vs. 4.5%). A nonsignificant trend was seen toward fewer "lesion-related MACE" events in the BVS-treated arm (4.3% vs. 10.7%; OR, 0.38; 95% CI,

0.11-1.28; $P = 0.12$). The absolute difference here was caused primarily by fewer episodes of angina-driven revascularization, not by MI. The authors concluded interventional treatment of non-flow-limiting lesions with high plaque burden was safe and resulted in larger lumen size at follow-up. They argued this justifies a larger randomized trial powered to detect clinical outcomes.

■ COMMENTARY

Can stenting of non-obstructive coronary lesions, identified by intravascular imaging as vulnerable plaques, prevent downstream events such as MI? Or, alternatively, does the risk of the stenting procedure itself, or that of restenosis, outweigh the potential benefits of mechanical stabilization? How reliable is the combination of IVUS and NIRS at identifying troublesome lesions? From a scientific standpoint, these are interesting questions. For the most part, answers remain elusive.

To these points, this trial provided some valuable insight. Among patients who had recently suffered an MI, identification of nonobstructive vulnerable plaque by the study definition was made in only one in five patients. The primary safety endpoint, target-lesion failure at two years, occurred in fewer than 5% of patients, regardless of treatment assignment. Although the more inclusive endpoint of lesion-related MACE appeared to show a trend favoring the scaffold group, even this trend was driven primarily by angina requiring revascularization, not by MI or cardiac death. Even if this trend were borne out to be statistically significant in a larger trial, the benefit would be of treating the lesion now rather than treating it later, at a cost of unnecessarily scaffolding many more vessels. A larger trial is, by all accounts, in the works. For now, identification and interventional treatment of vulnerable plaque remains a goal. ■

REFERENCE

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

CME/CE QUESTIONS

1. **A small trial of prophylactic stenting of vulnerable but non-stenotic coronary plaques vs. medical therapy at 25 months showed:**
   a. larger minimum lumen area.
   b. lower target lesion failure.
   c. fewer cardiovascular events.
   d. improved survival rates.

2. **A recent study of aggressive LDL cholesterol-lowering in age > 65 years post-acute coronary syndrome patients with alirocumab therapy vs. those age < 65 years showed:**
   a. higher LDL levels.
   b. higher relative risk reductions.
   c. lower all-cause death rates.
   d. smaller number needed to treat.

3. **A recent study of rhythm control vs. rate control of newly diagnosed atrial fibrillation showed the rhythm control strategy was associated with fewer:**
   a. adverse effects of therapy.
   b. major adverse cardiovascular events.
   c. declines in cognitive function.
   d. declines in left ventricular function.

4. **An observational study of patients with malignant pericardial effusions with evidence of adhesions or constriction post-pericardiocentesis who were treated with colchicine vs. those who were not showed:**
   a. the initial pericardiocentesis was successful in 80%.
   b. recurrent pericardial effusion was more common than constriction.
   c. lower mortality rates and fewer recurrent effusions.
   d. fewer surgical pericardiectomies.

5. **Sacubitril/valsartan compared to valsartan alone in patients with heart failure and preserved ejection fraction showed significant beneficial effects in:**
   a. heart failure hospitalization.
   b. cardiac death.
   c. progression of renal disease.
   d. men.