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Critical analysis of the latest clinical research in cardiovascular medicine

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ABSTRACT & COMMENTARY

PCSK9 Inhibitors in Acute Coronary Syndrome Patients

By Michael H. Crawford, MD, Editor

SYNOPSIS: Compared to adding placebo, using the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab in post-acute coronary syndrome patients on maximally tolerated, high-intensity statins with low-density lipoprotein (LDL) cholesterol levels higher than 70 mg/dL lowered LDL and reduced the number of major adverse cardiac events.

SOURCES: Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;379:2097-2107.

Burnett JR, Hooper AJ. PCSK9 – A journey to cardiovascular outcomes. *N Engl J Med* 2018;379:2161-2162.

The authors of a study in which statins were administered with or without ezetimibe observed improved outcomes in post-acute coronary syndrome (ACS) patients compared to those receiving placebo. Proprotein convertase subtilisin/kexin type 9 (PCSK9) promotes degradation of low-density lipoprotein (LDL) receptors on the liver, resulting in high serum levels of LDL cholesterol. Monoclonal human antibodies to PCSK9 have been shown to reduce the risk of cardiovascular events in stable coronary artery disease or high cardiovascular risk patients in whom LDL-C remained > 100 mg/dL despite maximum tolerated, high-intensity statin therapy.

PCSK9 inhibitors have not been tested in ACS patients. Thus, a group of researchers conceived the ODYSSEY OUTCOMES trial. It was a multicenter, randomized, double-blind, placebo-controlled trial of adults with ACS in the one to 12 months before trial entry who scored an LDL-C of > 70 mg/dL on at least two weeks of high-intensity statin therapy at the maximum tolerated doses. The PCSK9 inhibitor alirocumab (75 mg or placebo) was injected subcutaneously every two weeks. Alirocumab doses were adjusted to achieve an LDL-C of 25-50 mg/dL but not < 15 mg/dL. The primary endpoint was a combination of coronary death, myocardial infarction (MI), stroke, or unstable angina requiring hospitalization. Investigators randomized 18,924 patients from 1,315 sites in 57 countries. MI was the qualifying ACS event in 83%. Ninety-two percent of patients had an LDL-C > 70 mg/dL, and most underwent revascularization during the qualifying event. Patients

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were followed for a median of 2.8 years. About 15% of patients in both groups dropped out of the study for a variety of reasons other than death.

LDL-C decreased from an average of 92 mg/dL to 40 mg/dL at four months, to 48 mg/dL at 12 months, and to 66 mg/dL at 48 months. For those patients on placebo, average LDL-C levels were 93 mg/dL at four months, 96 mg/dL at 12 months, and 103 mg/dL at 48 months. The primary endpoint occurred in 9.5% of the treatment group and 11.1% of the placebo group (hazard ratio [HR], 0.85; 95% confidence interval [CI], 0.78-0.93; $P < 0.001$). Death occurred in 3.5% of the treatment group and 4.1% of the placebo group (HR, 0.85; 95% CI, 0.73-0.98). The benefits of treatment were greater in patients with LDL-C levels of > 100 mg/dL. The adverse event rates were similar in the two groups, except for injection site reactions, which happened in 3.8% of patients in the treatment group and in 2.1% of patients in the placebo group. The authors concluded that among recent ACS patients on high-intensity statins with or without ezetimibe therapy and LDL-C levels > 70 mg/dL, therapy with alirocumab was associated with lower LDL-C levels and fewer adverse cardiovascular events compared to patients on placebo.

■ COMMENTARY

In high-risk patients, such as the ACS patients in this study, we are abandoning the pooled risk equation and looking at LDL-C targets again. This makes sense given the old axiom was that in post-ACS patients, their LDL-C levels were too high, regardless of the measurement. However, clinicians did not really know how low those levels should go. As more studies were conducted over the last decade, the post-ACS LDL-C target decreased from < 130 mg/dL to < 100 mg/dL to < 70 mg/dL to < 50 mg/dL. These extremely low levels of LDL-C became possible for many patients after the PCSK9 inhibitors were synthesized.

Now, the issue is how low is too low. Most ACS patients on a PCSK9 inhibitor in the Schwartz et al study showed LDL-C levels < 50 mg/dL but > 25 mg/dL. Eight percent had levels < 15 mg/dL; for these patients, investigators ended PCSK9 drug administration. On the other hand, for 28% of patients assigned to alirocumab, researchers had to double the dose to 150 mg to reduce their LDL-C levels to < 50 mg/dL. It is comforting that in this trial, the incidence of adverse events was similar between the two groups (except for injection site reactions). These reactions were itching, redness, and swelling, which caused 26 patients to drop out of the trial.

The strengths of this trial included a sufficiently large group of patients in each group and an appropriate follow-up period to assess outcomes robustly. The primary composite endpoint was statistically significant, but none of the secondary endpoints, including the individual components of the primary endpoints, were. The number needed to treat was 49 for four years to prevent one primary event; the number was 16 for patients with LDL-C levels > 100 mg/dL.

Despite these underwhelming results, this study will change clinical practice for ACS patients. However, due to the current relatively high cost of PCSK9 inhibitors and the need to inject them, only the highest-risk patients will be targeted, such as those with LDL-C levels > 100 mg/dL, after maximum tolerated, high-intensity statins and ezetimibe have been prescribed. The big question going forward: How low does one lower LDL-C for primary prevention? Yes, we are going back to LDL-C levels. ■

ABSTRACT & COMMENTARY

Testing Safety, Efficacy of Pharmacotherapy in Hospitalized Heart Failure Patients

By Van Selby, MD

Assistant Professor of Medicine, University of California, San Francisco Cardiology Division, Advanced Heart Failure Section

Dr. Selby reports he is a consultant for Alnylam Pharmaceuticals and Akcea Therapeutics.

SYNOPSIS: In patients hospitalized for acute decompensated heart failure with reduced ejection fraction, administering sacubitril-valsartan led to more improvement in levels of cardiac biomarkers compared to enalapril, with no adverse safety signals.

SOURCE: Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med* 2018; Nov 11. doi: 10.1056/NEJMoa1812851. [Epub ahead of print].

In patients with heart failure with reduced ejection fraction (HFrEF), hospitalization for acute decompensated heart failure (ADHF) is common and associated with high morbidity and mortality. In a large clinical trial of ambulatory patients with HFrEF, initiation of sacubitril-valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), was associated with significant improvements in mortality and rehospitalization. However, investigators have not evaluated the safety or efficacy of initiating sacubitril-valsartan among patients hospitalized for ADHF.

The authors of the PIONEER-HF trial enrolled patients with HFrEF during a hospitalization for ADHF. After hemodynamic stabilization, patients were randomized to sacubitril-valsartan (titrated to a target dose of 97/103 mg twice daily) or enalapril (target dose 10 mg twice daily). The primary endpoint was the change in N-terminal pro B-type natriuretic peptide (NT-proBNP) from baseline through eight weeks.

Investigators randomized 881 patients, 34% of whom presented with no prior history of heart failure and 52% of whom were naïve to angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB). Compared to patients randomized to enalapril, the reduction in NT-proBNP concentration was significantly greater in the sacubitril-valsartan group (46.7% reduction in the sacubitril-valsartan group vs. 25.3% reduction in the enalapril group; $P < 0.0001$). Sacubitril-valsartan also was associated with a significant reduction in the exploratory outcome of rehospitalization for heart failure. There were no significant differences in rates of worsening angioedema, symptomatic hypotension, hyperkalemia, renal function, or study drug discontinuation between the two groups. The authors concluded that among patients with HFrEF who are hospitalized for ADHF, administering sacubitril-valsartan was associated with a greater reduction in NT-proBNP concentration compared to enalapril, with no significant differences in key safety endpoints.

■ COMMENTARY

In the landmark PARADIGM-HF trial, sacubitril-valsartan was associated with a significantly lower risk of death from cardiovascular causes or hospitalization for heart failure compared to enalapril among ambulatory patients with chronic HFrEF who already were treated with ACE inhibitors or ARBs. The PIONEER-HF study adds to the evidence base supporting sacubitril-valsartan for treatment of HFrEF. Velazquez et al demonstrated that sacubitril-valsartan can be initiated safely in patients still hospitalized for ADHF, resulting in greater reductions in key cardiac biomarkers compared to enalapril.

The FDA approved sacubitril-valsartan in 2015. Current practice guidelines give a strong class Ia recommendation for its use in chronic HFrEF. However, use of sacubitril-valsartan remains somewhat limited, with the authors of large registry studies finding that as few as 15% of eligible patients actually receive the drug. Given the magnitude of benefit observed in PARADIGM-HF, this slow uptake is disappointing. There are many potential reasons why providers may choose not to prescribe sacubitril-valsartan, with uncertainty regarding possible side effects likely a significant concern. In this regard, the results of PIONEER-HF should be reassuring and make it difficult to argue that sacubitril-valsartan is riskier than tried-and-true ACE inhibitors.

Another important aspect of PIONEER-HF is the inclusion of patients who were naïve to ACE inhibitors or ARBs; this was the first large trial to evaluate the efficacy of sacubitril-valsartan in such patients. Subgroup analyses showed that patients benefited from sacubitril-valsartan regardless of prior ACE/ARB use. Therefore, the findings support de novo treatment

with sacubitril-valsartan in HFrEF. Furthermore, providers can feel empowered to start sacubitril-valsartan in patients while they still are hospitalized. Hospitalization often provides an opportunity to reassess and improve a patient's medication regimen.

A primary limitation of this study is the use of a surrogate endpoint (change in NT-proBNP) rather than a "hard" outcome such as death or rehospitalization. However, several clinical trials, including PARADIGM-HF, have demonstrated that changes in NT-proBNP levels are a powerful predictor of outcomes among this population. It also is important to remember that sacubitril-valsartan was initiated only when specific criteria were met. During the six hours preceding the initial dose, patients were required to register a systolic blood pressure of at least 100 mmHg, with no escalation of intravenous diuretics or use of intravenous vasodilators. Patients could not receive intravenous inotropes during the 24 hours before starting the study drug.

PIONEER-HF is an important clinical trial for everyone who treats HFrEF and could increase the use of sacubitril-valsartan in HFrEF. The findings should increase comfort with the safety profile of sacubitril-valsartan and encourage clinicians to at least consider initiating it in patients hospitalized for ADHF. ■

ABSTRACT & COMMENTARY

Cardiac MRI for Prognosis in Aortic Stenosis

By Michael H. Crawford, MD, Editor

SYNOPSIS: The authors of a consortium observational study of patients with severe aortic stenosis undergoing valve replacement found that a pre-procedure cardiac MRI that detects myocardial fibrosis is predictive of post-procedure mortality and may be useful for making decisions about valve replacement in asymptomatic patients.

SOURCES: Musa TA, Treibel TA, Vassiliou VS, et al. Myocardial scar and mortality severe aortic stenosis. *Circulation* 2018;138:1935-1947.

Cavalcante JL, Sorajja P. Not too little and not too late. *Circulation* 2018;138:1948-1950.

Myocardial scar tissue has been identified as a critical factor in the transition between compensated and decompensated aortic stenosis (AS). Scar tissue can be detected by cardiac MRI (CMR) using late gadolinium enhancement (LGE). A United Kingdom consortium evaluated the utility of LGE-CMR for identifying long-term mortality in patients undergoing aortic valve replacement. The secondary endpoint was cardiovascular (CV) death. All 674 patients at six U.K. centers with severe AS who underwent a CMR and aortic valve replacement were included. Surgical aortic valve replacement (SAVR) was performed on 399 patients, and transcatheter AVR (TAVR) was performed on 275 patients. Patients with any LGE detected were more likely to be male, to have experienced a myocardial infarction (MI), and to exhibit more left ventricular (LV) dysfunction. After a median 3.6 years of follow-up, 22% of patients had died; almost half of these deaths were CV-related.

The authors evaluated 52 clinical parameters potentially predictive of mortality. LGE-CMR revealed that scar tissue was present in 51% of all study patients. In about one-third of these patients, the scar tissue was in an MI pattern. The factors independently associated with mortality were age (hazard ratio [HR], 1.5; 95% confidence interval [CI], 1.11-2.04; $P < 0.01$), Society of Thoracic Surgeons risk score (HR, 1.12; 95% CI, 1.03-1.22; $P < 0.01$), and scar presence (HR, 2.39; 95% CI, 1.4-4.1; $P = 0.001$). Also, the presence of scar tissue compared to no scar tissue independently predicted mortality (26% vs. 13%; $P = 0.001$) and CV mortality (15% vs. 5%; $P = 0.002$) regardless of the valve replacement procedure. Every 1% increase in scar burden was associated with an 11% higher mortality and an 8% higher CV mortality. The authors concluded that myocardial scar detected by LGE-CMR was independently associated with two-fold higher mortality in patients with severe AS after valve replacement regardless of the replacement technique.

■ COMMENTARY

Current intervention decision-making in AS patients is mainly concerned with symptoms, the severity of AS, and left ventricular (LV) systolic function. Since AS is largely a disease of older individuals, symptoms often are hard to define. Cardiologists assess AS severity mainly using echocardiography, which is complex and subject to potential errors. Reduced LV function probably is a late manifestation of AS, which increases the risk of replacement procedures.

Aortic valve replacement mortality is in the range of 1-2% by SAVR or TAVR. Thus, newer, more sensitive markers of when to replace the valve are needed. The results of previous observational studies have suggested that LV hypertrophy, abnormal exercise

tests, nonsustained ventricular tachycardia on ECG monitoring, degree of valve calcification on imaging, or biomarkers such as BNP or troponin may identify higher-risk patients before classic indicators appear. However, none of these have reached wide-spread use or a class I recommendation in guidelines. Part of the reason for this slow uptake of new indicators for valve replacement is the lack of prospective randomized, controlled trials. The studies that have been conducted so far involved measuring a marker preoperatively and then seeing whether it predicts mortality after valve replacement. This study of LGE-CMR is of the same design, but it is compelling because the presence of myocardial fibrosis cannot be good.

Should clinicians start using LGE-CMR in decision-making for intervention in AS? Several considerations temper enthusiasm for adopting LGE-CMR for this purpose. First, high-quality CMR is not readily available outside specialized centers and is costly. Second, scarring is common; it was detected in half the patients. Also, in two-thirds of the patients with fibrosis detected, it was noninfarct-related. Many cardiac conditions can lead to patchy myocardial fibrosis, which makes relating it to AS potentially problematic. In fact, some have advocated using LGE positivity as a futility marker in AS. Perhaps its presence means a cardiologist waited too long to start treatment. Such advocates may have a point as almost one-quarter of the patients in this study were dead after 3.6 years of median follow-up. There are other limitations to this study. Selection biases existed; patients with pacemakers or implantable cardioverter-defibrillators and advanced renal disease were excluded due to the requirements for CMR. The authors did not analyze invasive hemodynamics or biomarkers, and there was no follow-up CMR. Also, myocardial fibrosis can occur due to aging alone. Some studies have shown that valve replacement is associated with new scar formation. In addition, investigators lumped SAVR and TAVR together; during the study period, TAVR techniques likely improved. Interestingly, mortality was higher among TAVR patients at all time points, but these data were not adjusted for age.

Currently, the use of any parameters outside of what is recommended in the guidelines is experimental. Fortunately, there are two randomized trials underway that may help inform the use of other markers for decision-making in AS in the future. One is a prospective evaluation of using newer indicators vs. the guideline recommendations (EVOLVED-AS). The other concerns the use of TAVR in asymptomatic patients with severe AS (EARLY-TAVR). Although the creators of EARLY-TAVR are not using CMR for decision-making, the trial will be important for establishing the validity of replacing the aortic valve in asymptomatic patients with severe AS vs. watchful waiting for guideline indications. ■

ABSTRACT & COMMENTARY

Chronic Kidney Disease Discourages Appropriate Use of Angiography and PCI in NSTEMI

By Jeffrey Zimmet, MD, PhD

Associate Professor of Medicine, University of California, San Francisco; Director, Cardiac Catheterization Laboratory, San Francisco VA Medical Center

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

SYNOPSIS: This retrospective study of patients presenting with non-ST-segment elevation myocardial infarction showed higher mortality among patients with chronic kidney disease and lower use of coronary angiography and percutaneous coronary intervention.

SOURCE: Murray J, Balmuri A, Saurav A, et al. Impact of chronic kidney disease on utilization of coronary angiography and percutaneous coronary intervention, and their outcomes in patients with non-ST elevation myocardial infarction. *Am J Cardiol* 2018;122:1830-1836.

Chronic kidney disease (CKD) is a strong independent predictor of cardiac disease, profoundly affecting cardiovascular health and outcomes. CKD also clearly affects provider behavior, especially regarding the use of iodinated contrast agents and the fear of contrast-induced nephropathy. Given that a substantial proportion of patients presenting with acute coronary syndromes also carry a diagnosis of renal dysfunction, this is a highly pertinent issue that has been studied at length. Murray et al took a broad view of this problem, using the National Inpatient Sample to study trends

in coronary angiography use and both percutaneous and surgical revascularization in patients with CKD presenting with non-ST-segment elevation myocardial infarction (NSTEMI). Patients were classified based on renal function into three groups: those without a CKD diagnosis, those with CKD who did not require dialysis, and those with CKD who required renal replacement therapy (RRT). For each group, the authors assessed outcomes that included mortality, length of stay, and hospitalization costs.

Among 3,654,586 hospital admissions for NSTEMI between 2001 and 2012, most were without significant CKD (group 1). A total of 533,387 patients had CKD without need for RRT (group 2), and 107,696 patients had CKD and required RRT (group 3). Reported in-hospital mortality rates were significantly higher in patients with CKD (8.6% in group 3, 6.9% in group 2) compared with those without CKD (3.9%) even after adjusting for other predictors. Mortality rates improved modestly over the study period (from 5.8% in 2001 to 3.9% in 2011), with a more marked improvement among patients in group 2 (from 13.3% in 2001 to 5.9% in 2012).

While just over half of the entire cohort underwent invasive coronary angiography, the rates differed significantly among groups, with the highest rate among those without CKD and the lowest among those with CKD who did not require RRT (54%, 36.1%, and 45.9% undergoing cardiac cath in groups 1, 2, and 3, respectively). Although the use of cardiac cath increased over the study period (from 42% in 2001 to 60% in 2012), coronary angiography rates remained significantly lower in groups 2 and 3. On the other hand, PCI rates increased significantly over the course of the study, especially among CKD patients. The use of PCI in patients in group 1 doubled over the study period, while it nearly quadrupled in group 2. Between 2001 and 2012, the overall rate of CABG use in NSTEMI patients did not change significantly, except in group 3, which saw a steady rise in CABG rates (from about 5% to about 7%). In a multivariate logistic regression analysis, PCI was associated with a lower risk of mortality (odds ratio, 0.31; $P < 0.001$) across all three groups, regardless of CKD. The authors drew several conclusions. CKD is associated with a higher risk of short-term mortality in patients hospitalized for NSTEMI. Patients with NSTEMI are less likely to undergo invasive cardiac cath and PCI if they have concurrent CKD. Use of coronary angiography and PCI have increased in all patients over time (more so among patients with CKD). Finally, cath and PCI were associated with better short-term survival rates, even after adjusting for baseline risk.

■ COMMENTARY

It should come as no surprise that CKD is associated with a higher risk of mortality as well as longer length of stay and higher hospital costs among patients presenting with NSTEMI. It also is not surprising that patients with CKD are offered invasive diagnostic and therapeutic options at lower rates compared with those with normal renal function. The fact that patients with CKD on RRT were offered these procedures at higher rates compared with those not on RRT strongly suggests that concern for causing acute kidney injury by contrast-induced nephropathy is a major deciding factor when it comes to using invasive approaches in this subset of patients. The Murray et al study supports a mortality benefit of an invasive approach in patients with NSTEMI and CKD, a population for whom there is little direct evidence and about whom guidelines are noncommittal. Overall, the results of this study are encouraging. Although the authors rightly noted the systematic underuse of invasive therapies in the CKD population, their data clearly show an increase in coronary revascularization use over the study period, with a marked concomitant improvement in mortality specific to the nondialysis CKD group. Of course, treatment decisions should be individualized; however, cardiac cath and PCI should not be withheld from these patients who stand to benefit. ■

ABSTRACT & COMMENTARY

Noninvasive Mapping and Ablation of Ventricular Tachycardia: Evidence Builds for Novel Approach

By Joshua Moss, MD

Associate Professor of Clinical Medicine, Cardiac Electrophysiology, Division of Cardiology, University of California, San Francisco

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

SYNOPSIS: In 19 patients with treatment-refractory episodes of ventricular tachycardia or frequent premature ventricular contractions, stereotactic body radiation therapy was highly effective at reducing arrhythmia burden without acute toxicity.

SOURCE: Robinson CG, Samson PP, Moore KMS, et al. Phase I/II trial of electrophysiology-guided noninvasive cardiac radioablation for ventricular tachycardia. *Circulation* 2018. Published online Nov. 10, 2018. Available at: https://bit.ly/2TKlq4d. Accessed Dec. 5, 2018.

The field of cardiac electrophysiology has advanced rapidly regarding ablation of cardiac arrhythmias, albeit with little change to the types of ablation energy delivered. Management of patients with ventricular tachycardia (VT) in the setting of myocardial scarring remains a challenge. Treatment failures are common when scarring is extensive or critical areas are inaccessible with available technology. Ablation procedures for VT also may take many hours to complete. Complications, while infrequent, can be serious.

Robinson et al sought to further assess the safety and efficacy of entirely noninvasive techniques for both identifying arrhythmia substrate and delivering ablation energy, expanding upon their previously published case series.[1] In a prospective, single-arm, Phase I/II trial conducted at a single center, the authors used a synthesis of imaging studies and body surface-based electrophysiological mapping to guide treatment with stereotactic body radiotherapy (SBRT). Patients received a single dose of 25 Gy via SBRT to target areas of ventricular scarring determined to harbor the re-entrant VT circuit. Follow-up, including serial chest CTs, was performed at predetermined intervals until 12 months. The primary safety endpoint was defined as the rate of serious adverse events within 90 days (grade 3 toxicity requiring hospitalization or any grade 4 or 5 toxicity). The primary efficacy endpoint, following a six-week blanking period, was defined as reduction in the number of implantable cardioverter defibrillator (ICD) treatments or 24-hour premature ventricular contraction (PVC) burden between the six-month periods before and after SBRT.

Nineteen patients (17 male) with a median age of 66 years were enrolled. To be eligible, subjects had to have experienced at least three episodes of sustained VT (17 of 19 patients) or cardiomyopathy related to PVCs (2 of 19) and to have failed at least one antiarrhythmic medication and one catheter ablation procedure. Eleven patients had an ischemic cardiomyopathy. Median baseline ejection fraction (EF) was 25%. Patients were excluded if they had received prior radiotherapy, had New York Heart Association class IV heart failure, or were deemed unlikely to live 12 months even in the absence of VT. Median treatment time for delivery of SBRT was 15.3 minutes (range, 5.4-32.3).

All but one patient experienced a significant reduction in ventricular tachyarrhythmia or PVC burden, with a reduction of at least 75% in 17 of 19 patients. Excluding the six-week post-SBRT blanking period, the median number of VT episodes decreased from 119 in the six-month period pretreatment to three in the six-month period post-treatment. ICD therapies also declined significantly, from a median of four ICD shocks to zero and 81 antitachycardia pacing therapies to 3.5.

There was no acute toxicity attributed to the SBRT. Serious adverse events up to 90 days included one instance each of pericarditis requiring corticosteroids, heart failure requiring hospitalization, nausea/vomiting, and transaminitis. Transient fatigue and hypotension requiring adjustment of antihypertensive medications were common. There was one patient death at 17 days after treatment that was attributed to a nursing home accident unrelated to the study. The authors concluded that in patients with treatment-refractory episodes of VT or frequent PVCs, stereotactic body radiation therapy reduced arrhythmia burden significantly and without acute toxicity.

■ COMMENTARY

This study is an extension of the smaller case series of five patients published by the same group last year, a series that generated considerable excitement as well as many questions. As a prospective Phase I/II trial, the goal was to evaluate both efficacy and safety endpoints in preparation for a multicenter trial scheduled to start in 2019. As with the initial case series, SBRT was effective in achieving dramatic reductions in VT burden. The authors also demonstrated reduction in antiarrhythmic drug use, most notably amiodarone. Importantly, there was only one serious adverse event in the first 90 days after therapy that was believed to probably be related to therapy — an episode of pericarditis at day 80 that improved with steroid therapy. Lower-grade adverse events included pericardial effusions and radiation pneumonitis.

It is interesting that two patients were included with high PVC burden and cardiomyopathy (rather than sustained VT), an indication for SBRT not pursued in the original case series. In those patients, 24-hour PVC burden declined from 24% to 2% and from 26% to 9%, respectively. There was an attendant improvement in EF (13% and 8%, respectively). Catheter ablation for PVCs often can be performed with a high rate of success and low risk of complications, but there are some common areas of PVC origin that are relatively inaccessible to catheters; novel techniques such as SBRT are

needed. Finally, both the patient experience and improvements in quality of life are noteworthy. SBRT therapy lasted a median of 15 minutes, after which patients could simply go home. In contrast, complex VT ablation procedures can involve a day-long experience on a procedure table, particularly when addressing arrhythmias refractory to other therapies, and one or more nights in the hospital. After the SBRT procedure, patients reported significant improvement in perceived health change and social functioning categories on quality of life surveys, with no significant decline in any domain.

It is important to remember that this therapy remains investigational, and results have not yet been reproduced outside the original center. Longer-term adverse effects of SBRT for this indication also remain unknown. However, the reproducibility and sustainability of the results in this larger population are reassuring and should increase interest in this technology as part of research protocols in high-volume tertiary care medical centers.

Overall, the use of SBRT for refractory VT and PVCs shows great promise and may prove to be an exciting, safe, and effective treatment modality in the management of this challenging patient population. ■

REFERENCE

1. Cuculich PS, Schill MR1, Kashani R, et al. Noninvasive cardiac radiation for ablation of ventricular tachycardia. *N Engl J Med* 2017;377:2325-2336.

CME/CE QUESTIONS

1. Which measure in patients with asymptomatic severe aortic stenosis is *not* independently predictive of mortality after valve replacement?

a. Cardiac MRI myocardial fibrosis

b. Age

c. Society of Thoracic Surgeons operative risk score

d. Surgical valve replacement vs. transcatheter aortic valve replacement

2. For post-acute coronary syndromes, PCSK9 inhibitors plus a statin vs. statin plus placebo results in:

a. lower low-density lipoprotein cholesterol levels.

b. fewer major adverse cardiovascular events.

c. fewer strokes.

d. Both a and b

3. Entry criteria for a study involving focused body radiation therapy for refractory scar-based ventricular arrhythmias included:

a. at least one episode of sustained ventricular tachycardia (VT).

b. recurrent VT despite amiodarone therapy.

c. at least one failed ablation attempt.

d. left ventricular ejection fraction < 35%.

4. The initiation of sacubitril-valsartan vs. enalapril therapy in patients hospitalized and stabilized with acute decompensated heart failure due to reduced left ventricular ejection fraction resulted in:

a. lower N-terminal pro b-type natriuretic peptide levels.

b. shorter hospital stays.

c. reduced 30-day mortality.

d. fewer episodes of hyperkalemia.

5. Which of the following is most correct concerning non-ST-segment elevated myocardial infarction patients with chronic kidney disease vs. those without chronic kidney disease?

a. Higher in-hospital mortality

b. Less frequent percutaneous coronary intervention (PCI) use

c. Lower hospital mortality if PCI used

d. All of the above