AHC Media

Vol. 33, Issue 1, January 2014
www.ahcmedia.com

Clinical Cardiology [ALERT]

Critical analysis of the latest clinical research in cardiovascular medicine

ABSTRACT & COMMENTARY

Is Atrial Fibrillation Associated with Silent Cerebral Emboli?

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Dr. Gerstenfeld does research for Biosense Webster, Medtronic, and Rhythmia Medical.

SOURCE: Gaita F, et al. Prevalence of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function. *J Am Coll Cardiol* 2013;62:1990-1997.

It is well known that patients with paroxysmal or persistent atrial fibrillation (AF) and appropriate risk factors are at increased risk of embolic stroke. However, the question of whether patients with AF on anticoagulant therapy are at higher risk of asymptomatic thomboemboli and cognitive dysfunction is unknown. In this study, patients with paroxysmal and persistent atrial fibrillation were recruited, along with matched control patients in sinus rhythm, from a cardiology clinic. All patients underwent diffusion weighted magnetic resonance imaging (MRI) of the brain, which is the best method for detecting asymptomatic or silent cerebral ischemia (SCI). The presence and number of SCIs were compared among patients with paroxysmal AF, persistent AF, and control. There were 90 patients with paroxysmal AF, 90 with persistent AF, and 90 control patients recruited. The baseline characteristics showed that 70% of paroxysmal AF patients and 73% of persistent AF patients had a CHA_2DS_2-VASc score ≥ 1. In addition, 43% of paroxysmal AF patients and 88% of persistent AF patients were taking oral anticoagulants. On MRI, at least one region of SCI on MRI was found in 80 (89%) patients with paroxysmal AF, 88 (92%) with persistent AF, and 41 (46%) controls. MRI lesions were bilateral in 90% of patients, suggesting an embolic etiology. The number of areas of SCI per patient was significantly higher in persistent than in paroxysmal

Financial Disclosure: *Clinical Cardiology Alert's* Editor, Michael H. Crawford, MD, reports no financial relationships relevant to this field of study, and peer reviewer, Ethan Weiss, MD, is a scientific advisory board member for Bionovo. Managing Editor, Neill Kimball, and Executive Editor, Leslie Coplin, report no financial relationships relevant to this field of study.

Clinical Cardiology [ALERT]

Clinical Cardiology Alert, ISSN 0741-4218, is published monthly by AHC Media LLC, One Atlanta Plaza 950 East Paces Ferry Road NE Suite 2850 Atlanta, GA 30326.

POSTMASTER: Send address changes to *Clinical Cardiology Alert*, P.O. Box 550669, Atlanta, GA 30355.

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GST Registration Number: R128870672. Periodicals Postage Paid at Atlanta, GA, 30304 and at additional mailing offices.

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AF, and both were greater than controls (persistent = 41.1 ± 28.0; paroxysmal = 33.2 ± 22.8; control = 12.0 ± 26.7; $P < 0.01$). On multivariate analysis, including use of oral anticoagulants and the CHA_2DS_2-VASc score, the presence of AF was independently associated with SCI (odds ratio, 7.2; 95% confidence interval, 2.3-22.3; P -0.001). The authors concluded that patients with AF had more SCI and worse cognitive function than matched controls in sinus rhythm.

■ COMMENTARY

AF remains the most common supraventricular arrhythmia, responsible for more hospitalizations and outpatient visits than any other arrhythmia. Several large randomized studies, including AFFIRM,[1] have not demonstrated any mortality benefit to maintenance of sinus rhythm. The incidence of asymptomatic thromboemboli has come to attention after several studies found asymptomatic thromboemboli after catheter ablation of AF, and in one study associated with cognitive decline.[2] However, another large, retrospective study found that patients who underwent catheter ablation and remained in sinus rhythm had a lower incidence of dementia than those remaining in AF.[3] The current study raises further suspicion that AF may lead to silent embolic events in many patients, and that these events may lead to subtle cognitive decline. This study also finds that embolic rates are higher for persistent compared to paroxysmal AF patients, a finding that makes sense, but has not been shown in prior studies. Of course there are no prospective data to suggest that maintenance of sinus rhythm, through pharmacologic or interventional means, will reduce that risk. However, the implications are provocative.

There are several limitations to this study, including the relatively small sample size and retrospective nature of the study. The high incidence of asymptomatic embolic events in the control population (46%) is difficult to explain, and may suggest that the MRI is a bit too sensitive. However, the authors convincingly argue that the pattern seen on the majority of MRIs is highly suggestive of chronic thromboembolic disease. Finally, during the study period, most patients were anticoagulated with warfarin, where time in therapeutic range (TTR) is often only ~50% and lower TTR has been associated with dementia.[4] Whether the results would be similar with patients on newer oral anticoagulants is unknown. Will there be a prospective study of the effect of rate vs rhythm control on asymptomatic thomboemboli? The ongoing CABANA study,[5] which randomizes patients to catheter ablation vs medical therapy, will examine this in a substudy. However, we are currently limited by the absence of an effective means to maintain sinus rhythm 100% of the time in AF patients, particularly those with persistent AF. So stay tuned — the relationship of asymptomatic cerebral emboli and dementia may reopen the issue of whether maintenance of sinus rhythm should be the goal in patients with AF. ■

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ABSTRACT & COMMENTARY

Safety of Eplerenone in Heart Failure Patients

By Michael H. Crawford, MD, Editor

SOURCES: Eschalier R, et al. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: Analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure). *J Am Coll Cardiol* 2013;62:1585-1593. Bart BA, Nelson S. Eplerenone: Another drug to add to the mix? *J Am Coll Cardiol* 2013;62:1594-1595.

Mineralocorticoid receptor antagonists (MRA) reduce hospitalizations and mortality in symptomatic heart failure patients due to systolic dysfunction treated with ACEI/ARB and beta-blockers. However, their use is suboptimal in practice surveys because of concerns about safety and the belief that randomized trials excluded high-risk patients. Also, observational studies have shown no benefit of spironolactone. Thus, the investigators in the Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF) evaluated the safety and efficacy of eplerenone (25-50 mg/day) in the prespecified subgroup of high-risk patients characterized by age ≥ 75 years, diabetes, chronic kidney disease, and systolic blood pressure < 123 mmHg. Patients in EMPHASIS-HF were > age 55 years, New York Heart Association Functional class II, EF < 30%, on ACEI/ARB plus beta-blockers, a cardiac hospitalization < 6 months, and a BNP > 250 pg/mL. Patients with glomerular fibrillation rate (GFR) < 30 mL/min/1.73m^2 or need for a potassium-sparing diuretic were excluded. The endpoints for this analysis were abnormal potassium levels, hyperkalemia leading to study discontinuation, hospitalization for hyperkalemia or worsening renal function, a change in GFR, and the primary endpoint of hospitalization for heart failure or cardiovascular death. In the 2737 patients randomized to eplerenone or placebo, eplerenone reduced the risk of cardiac death and heart failure hospitalization (hazard ratio 0.63; 95% confidence interval, 0.54-0.74; $P < 0.001$) and was 0.54-0.66 in the high-risk subgroups. Overall and in the high-risk subgroups, eplerenone increased the incidence of potassium > 5.5 mmol/L, but not > 6.0. Also, eplerenone increased the risk of hospitalization for hyperkalemia as well as study drug discontinuation for adverse events overall and in the high-risk groups. The authors concluded that eplerenone, when carefully up titrated and monitored in symptomatic, systolic heart failure patients, results in a favorable risk-benefit ratio even in patients at high risk for renal dysfunction, hyperkalemia, or hypotension.

■ COMMENTARY

MRAs for heart failure have been a tough sell to clinicians in the trenches for several reasons. Physicians see the major hassle of the close monitoring of potassium, renal function, and blood pressure required, which is poorly reimbursed. Also, they fear the liability of a drug that could theoretically raise potassium to levels where sudden death is a reality. Patients see this as one more drug added to the many others they are taking. Heart-failure polypharmacy increases costs, and the likelihood of drug interactions and adverse effects. In addition, observational studies have shown hyperkalemia rates in the 25-40% range, not the 12% overall seen in this study. The highest rate observed in this study was 17% in those in the GFR between 30-60 group. Since the primary endpoint was reduced by 37%, the authors conclude that the benefits of MRAs outweigh the risks.

It should be pointed out that their patients were highly selected. They excluded those with uncontrolled hypertension, potassium values > 5.0, GRF < 30, mental illness, alcohol or drug dependence, liver disease, and cytochrome P450 CYP 3A4 inducer or inhibitor use. Also, dosing was titrated carefully starting with 25 mg every other day for those with a GFR between 30-49, and the maximum dose was 50. Mean dose was 40 mg/day. If the potassium was between 5.5-5.9, the dose was readjusted and if > 6.0 eplerenone was stopped. Potassium was monitored carefully at 1 week post any initiation or dose change, then at 1 month and every 4-6 months thereafter. Finally, they emphasize that their conclusions are limited to the type of patients they selected and that they have to be carefully monitored. Whether this tight patient selection and monitoring is feasible in real-world practice is questionable.

With regard to risk, they point out that although mild increases in potassium were observed in the whole trial population and the high-risk subgroups, potassium values > 6.0 were not more frequent compared to placebo. However, they had few patients with very high values, so the study was not powered to assess potassium > 6.0. Also, they did not observe worsening renal function or hypotension as compared to placebo therapy in any high-risk subgroup. Thus, they believe that with careful patient selection and monitoring, the benefits of MRA therapy in symptomatic systolic heart failure patients outweigh the risks. With regard to the observational studies that showed higher adverse event rates, they point out that some of those studies included heart failure patients with preserved EF, those with GRF < 30, and some on potassium-sparing diuretics. Such patients were excluded from this study and are not candidates for MRA therapy. In addition, some had a preponderance of older patients compared to this study. Finally, most of the observational studies used spironolactone, which may not have the same risk-benefit ratio as eplerenone. ■

ABSTRACT & COMMENTARY

Spironolactone for Heart Failure

By Michael H. Crawford, MD, Editor

SOURCE: Lee KK, et al. Effectiveness and safety of spironolactone for systolic heart failure. *Am J Cardiol* 2013;112:1427-1432.

In order to assess the safety and efficacy of spironolactone combined with other recommended drugs for systolic heart failure, these investigators from Kaiser Permanente Northern California studied 2358 patients with newly diagnosed heart failure, a left ventricular ejection fraction (LVEF) < 40%, and no previous mineralocorticoid receptor antagonist (MRA) use. Patients were excluded if their serum creatinine was > 2.5 mg/dL or their potassium was > 5.0 mEq/L. Spironolactone was initiated in 521 patients (22%) and they were followed for a median of 2.5 years. The spironolactone cohort was younger, had fewer comorbidities, and was more likely to be on other heart failure therapies, including digoxin and potassium supplementation. Also, they had higher GFR, but lower LVEFs. After adjustments for different patient characteristics and concurrent use of other heart failure therapies, spironolactone was not associated with death (hazard ratio [HR], 0.93; 95% confidence interval [CI], 0.60-1.44) or all-cause hospitalization (HR, 0.91; 95% CI, 0.77-1.08). Lower death rates were associated with the use of an angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), and beta-blockers (HR, 0.47; 95% CI, 0.44, 0.38, respectively), as was reduced hospitalization (HR, 0.60; 95% CI, 0.73, 0.52). Spironolactone use adjusted for potential confounders was associated with a higher rate of severe hyperkalemia (HR, 3.46; 95% CI, 1.97-6.06), but not kidney injury (HR, 0.66; 95% CI, 0.42-1.05). Also, lower GFR correlated with acute kidney injury and severe hyperkalemia on spironolactone. The authors concluded that in a diverse, community-based population with new systolic heart failure, spironolactone did not reduce death or hospitalization, but did increase the incidence of hyperkalemia.

■ COMMENTARY

This study adds to the current observational literature on the lack of effectiveness of spironolactone for systolic heart failure in real-world settings. As compared to prior studies, it has several strengths. First, it only included patients with a new diagnosis of heart failure, which eliminates the survivor bias. Second, they eliminated patients with prior spironolactone use, which reduces the responder bias. Third, they knew all the drugs each patient was taking and for how long. Finally, they had serial laboratory results on all the patients. Limitations of this study, besides being observational, include a lack of exact knowledge of the dose of spironolactone the patients were on and that the spironolactone patients were sicker than the rest the patients, since guidelines at the time recommended MRAs for class III-IV heart failure patients.

The adverse effects of spironolactone were similar to those in randomized trials, which suggests that they were not the cause of the difference in response. Of the three randomized, placebo-controlled trials, only one (RALES) used spironolactone, the other two used eplerenone. One major difference between this study and RALES is that beta-blocker use was only 11% in RALES vs 82% in this study. Thus, perhaps MRA therapy is more beneficial if patients are not on beta-blockers. The two trials using eplerenone were on guideline-driven therapy, so the beneficial effects of eplerenone cannot be ascribed to deficiencies in other recommended therapies. Also, it is possible that eplerenone is more effective than spironolactone, but to date there have been no head-to-head comparisons of these two MRAs.

What should clinicians do at this point? In patients who meet the entry criteria of the three randomized trials (RALES, EMPHASIS, EPHESUS) and in whom close monitoring of blood pressure, potassium, and creatinine can be accomplished, it would be reasonable to start a MRA. In patients not meeting trial entry criteria, but who have no contraindications to MRAs, it would be reasonable to start a MRA if they are not optimally managed on class I guidelines care. However, all patients started on MRA need careful follow-up. Patients on potassium-sparing diuretics or potassium replacement are at high risk, as are patients with renal impairment or hypotension. MRAs are problematic in such patients and preference should be given to ACEIs/ARBs and beta-blockers, which clearly improve survival. ■

New Clinical Practice Guidelines — Q&A with Dr. Crawford

The American College of Cardiology and the American Heart Association released new guidelines for preventing heart disease and stroke. Michael H. Crawford, MD, Editor of *Clinical Cardiology Alert,* provides expert opinion and commentary on why these new guidelines are so important.

1. What is the significance of these new guidelines?

The new guidelines change the focus of cholesterol lowering treatment from cholesterol levels to the patient's risk of developing atherosclerotic cardiovascular disease (ASCVD). The committee recognized that despite decades of study, there are not strong data to support the use of LDL-cholesterol targets in individual patients. This is no surprise to clinicians who see myocardial infarction patients with cholesterol values in the normal range. We were taught that they still needed cholesterol-lowering therapy because their levels are too high for them. By focusing on an individual patient's risk, this problem is circumvented.

2. What are the biggest changes from the previous guidelines?

The new guidelines describe four groups of high-risk patients that need cholesterol-lowering therapy. The first three are not different from the old guidelines: patients with known atherosclerotic disease, diabetics, and those with an LDL > 190 mg/dL. The fourth is new — non-diabetic patients aged 40-75 years with LDL cholesterol between 70-189 mg/dL and a 10-year risk of ASCVD of ≥ 7.5%. The second big change is that cholesterol lowering is defined as LDL cholesterol lowering, since there is insufficient data to support other targets. The third change is that LDL lowering therapy should be statins only, since there are insufficient data to support the use of other agents alone or in combination with statins.

3. Why are these changes important?

These changes are important because they represent a shift in our assessment of how best to manage ASCVD and the risk of ASCVD. The most difficult part will be deciding who is at high risk for developing ASCVD. Once that decision is made, treatment actually becomes much simpler and straightforward.

4. What does this mean for physicians in their daily practice?

Physicians now have to assess who has a ≥ 7.5% risk of developing ASCVD in 10 years, and this is the main area of controversy with the new guidelines. The committee developed a new risk calculator that included data on African Americans, which is a defect of the commonly used Framingham risk calculator that was developed from data in largely European Americans. However, critics have commented that the new calculator overestimates risk to the extent that one-third of Americans between 40-75 years of age and every man older than 65 years would need statin therapy. Whether this is appropriate or not is debatable, but clearly more work needs to be done on risk calculation methods. In borderline risk cases, the physician should consider other factors that are not in the risk calculator, such as family history of premature ASCVD, LDL > 160 mg/dL, hs CRP ≥ 2.0, a coronary CT calcium score > 300 or the 75th percentile, and an ABI < 0.9. Second, LDL cholesterol will still need to be measured to guide therapy. The goal now is to lower LDL at least 30-50% depending on how high it is at baseline, rather than aiming for a specific numerical target. Third, the non-statin, cholesterol-lowering therapies are not necessary, but can be considered if the patient cannot take statins or can only tolerate low doses. Fourth, the new guidelines exclude patients < 40 years or > 75 years old, with symptomatic heart failure or end-stage renal disease. Physicians must use their own judgment with these patients.

5. What does this mean for patients?

Patients are going to have to lose their fixation on their cholesterol numbers and start thinking about lowering their risk in many ways. Hopefully, this new focus will encourage patients to modify risk factors beyond cholesterol. Also, patients should stop relying on unproven remedies for lowering their risk and seriously consider major lifestyle modifications and statin therapy if necessary.

6. What are the next steps physicians and patients should take?

Physicians need to develop a brief talk on the new guidelines to educate their patients. It could be given to each patient as a paper handout, posted on a website, or played on a video in the waiting room. Patients need to consider that medicine is not a static field and changes to how we manage ASCVD and the risk of ASCVD will change over time, but that these changes are for the better. ■

ABSTRACT & COMMENTARY

TAVR in the Real World: The Initial 18 months' Experience in the United States

Jeffrey Zimmet, MD, PhD

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

SOURCE: Mack MJ, et al. Outcomes following transcatheter aortic valve replacement in the United States. *JAMA* 2013;310:2069-2077.

Transcatheter aortic valve replacement (TAVR) was introduced commercially in the United States following the November 2011 FDA approval of the Edwards SAPIEN device. This approval was based on the PARTNER trial, a single, multicenter, randomized, controlled trial that compared TAVR with standard therapy in patients with inoperable and high-risk aortic stenosis. It is well-recognized that results obtained in such trials by selected high-volume centers with expert teams under controlled circumstances may not be matched once the device is approved and moved to a more "real-world" setting. The American College of Cardiology and the Society of Thoracic Surgeons have collaborated to create a process for rollout of this device, including not only training and credentialing of operators and centers, but also a national registry for postmarketing surveillance. Mack and colleagues report the results from this Transcatheter Valve Therapy (TVT) registry in this article.

Between November 2011 and May 2013, results were obtained from 7710 U.S. TAVR cases performed at 224 centers. Of the procedures reported, 20% were in patients who were considered "inoperable" in terms of open surgical AVR, and 80% were considered high-risk but operable. The median age of patients was 84 years, and 49% were female. The mean STS predicted risk of operative mortality (STS PROM) was 7% in both high-risk and inoperable groups. A large proportion of patients pre-procedure had advanced heart failure, with 81% reporting NYHA class III or IV heart failure symptoms.

In terms of the procedure itself, the transfemoral approach was the most common route of access (64%), followed by the transapical approach (29%). The procedure resulted in successful device implantation in 92% of cases. More than one transcatheter valve was used in 2.9% of procedures. Death during the procedure was uncommon (0.8%), as was conversion to open aortic valve surgery (1%). Despite the low intraprocedural death rate, in-hospital mortality was significantly higher at 5.5%. Major complications tracked in the registry included stroke (2.0%), major vascular injury (6.4%), acute renal insufficiency (5.5%), major bleeding (3.5%), and need for new pacemaker or ICD (6.6%). Median hospital stay was 6 days. At 30 days, the incidence of death rose to 7.6%, stroke occurred in 2.8%, and aortic valve reintervention was necessary in 0.5%. The authors concluded that in a U.S. postmarket registry, TAVR results are comparable to prior published, controlled trial data.

■ COMMENTARY

Surgical aortic valve replacement (AVR) is the second most common cardiac surgical procedure performed in the United States. Multiple studies have demonstrated that well over 30% of patients with severe aortic stenosis are denied AVR due to a high risk of surgical complications. These numbers do not necessarily include patients who are never referred for surgery, either because their physicians believe they are too high-risk or because the patients themselves will not consider open heart surgery. In this vein, TAVR is a transformative procedure, opening the door to many patients who would not otherwise be treated.

Following FDA approval, the number of U.S. medical centers performing the TAVR procedure rapidly expanded from the 35 PARTNER hospitals to 224 clinical sites. How do the results reported in the TVT "real-world" registry compare with the results of the tightly controlled PARTNER trial? In terms of the patients themselves, the risk profile of patients reported in the registry appears lower than that in the trial. The STS-PROM in the registry was only 7% for both high-risk and inoperable patients, while PARTNER reported scores of more than 11%. While it is well recognized that the STS calculator fails to capture many elements of operative risk, this likely represents some element of so-called "risk creep," whereby the procedure is offered to somewhat lower-risk patients over time. Despite this, mortality rates were similar to those reported in PARTNER. Among those receiving the procedure via the transfemoral

route, 30-day mortality rates in the inoperable and high-risk patients were 6.7% and 5.0%, which are comparable to the rates of 5% and 3.7% reported in similar groups in PARTNER. The 30-day mortality rate among nontransfemoral patients in the high-risk subgroup was 10.8%, which is slightly higher than the 8.7% rate reported in the as-treated analysis of PARTNER. In-hospital and 30-day stroke rates from the registry, reported at 2.3% and 2.5%, compared favorably with the 4.7%, 30-day stroke rate from the PARTNER inoperable group.

Notably, major vascular complications and major bleeding were significantly lower in the registry compared with the trial (6.4% and 3.5%, compared with 11% and 9.3%), despite use of the same first-generation TAVR devices with large sheath sizes. This most likely represents a combination of better patient screening and a shortening of the learning curve from both worldwide experience and the use of a mandated educational program run by the device manufacturer.

Overall, this report demonstrates the success of the U.S. strategy of controlled dissemination of TAVR technology. As experience grows and devices improve, continued reporting of data at this level of detail will assist in further refinement of the process and will influence future recommendations for TAVR use. ■

ABSTRACT & COMMENTARY

The CORAL Trial: Is This the End for Renal Artery Stenting?

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SOURCE: Cooper CJ, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med* 2013; Nov. 18. [Epub ahead of print.]

Renal artery stenosis (RAS) caused by atherosclerosis is a common finding among patients with vascular disease. Indeed, the prevalence of renal artery stenosis has been estimated to be as high as 7% in community studies of patients older than 65 years. Early uncontrolled studies of renal angioplasty and stenting suggested potential benefits, both in terms of blood pressure control and renal function. To date, however, randomized trials have failed to replicate these findings. Prior randomized trials have been criticized on multiple counts, including enrolling patients with relatively mild, nonsignificant disease.

In the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial, the authors sought to compare clinical outcomes in patients with RAS and either systemic hypertension or renal dysfunction who were randomized to medical therapy alone or with renal artery stenting. During the study period between May 2005 and January 2010, 947 patients were randomly assigned to stenting plus medical therapy or to medical therapy alone. The primary endpoint was a composite of hard clinical events: death from cardiac or renal causes, stroke, myocardial infarction, hospitalization for congestive heart failure, progressive renal dysfunction, or the need for permanent hemodialysis. Patients with angiographic renal artery stenosis of at least 80% could be enrolled directly. Those with stenosis between 60% and 80% could be included if a systolic pressure gradient of at least 20 mmHg was documented. Notably, in contrast to prior studies, all angiograms were evaluated by a central core laboratory. Initially, patients were required to have systemic hypertension with a systolic blood pressure (SBP) of at least 155 mmHg while on at least two medications. Subsequently, however, the minimum BP requirement was removed, and patients could be enrolled if they had chronic kidney disease, defined by a glomerular filtration rate (GFR) of < 60. All patients were treated with an aggressive medical regimen with protocol-specified medications. This included the ARB candesartan with or without the addition of hydrochlorothiazide, and the combination of amlodipine and atorvastatin. Patients were treated to a target blood pressure of 140/90, or to the lower target of 130/80 in the presence of diabetes or chronic kidney disease.

Of the 459 patients in the stent group, 434 underwent successful stenting. Of the 472 patients in the medical therapy group, 19 crossed over to stenting. In an intention-to-treat analysis, the study showed no difference in occurrence of the primary endpoint between the medical therapy and stenting groups over a mean follow-up of 43 months (35.1% and 35.8%, respectively; hazard ratio, 0.94; 95%

confidence interval, 0.76-1.17; $P = 0.58$). There was a small but significant difference in BP between the two groups, with the stenting group showing a mean decrease of 2.3 mmHg compared with the medical therapy group. The authors concluded that in patients with atherosclerotic RAS, renal artery stenting did not reduce subsequent clinical events as compared to intensive medical therapy.

■ COMMENTARY

CORAL is a well-done study that contributes significantly to an important question in cardiovascular medicine. For patients with moderately severe RAS and either hypertension or chronic renal disease, stenting did not have additive value in preventing clinical events on top of good medical therapy.

A few points are worth mentioning here. First, enrolling patients in studies such as this is challenging. Indeed, it took nearly 5 years to complete enrollment in this trial, and in the end only 947 of the originally intended 1080 patients were enrolled. Modifications resulting in inclusion of less-sick patients were made after initiation of the trial, primarily to address slow enrollment issues. Notably, the initial requirement of hypertension with a SBP of at least 155 mmHg while on two or more drugs was removed, allowing patients with chronic kidney disease without hypertension to be enrolled. This reflects the real-world balance struck between defining the population with possible benefit from renal artery stenting and attaining adequate patient enrollment to complete the study. The observed event rate of 20% at 2 years in the medical therapy group was half of the expected rate. While this beneficial effect of aggressive medical therapy is encouraging, the low event rate also reduces the power of the trial to detect a difference between groups.

Were the right patients examined here? In terms of severity of RAS, CORAL did a better job than prior studies, enrolling patients with mean angiographic stenosis of 73%. In a subgroup analysis looking only at patients with stenosis > 80%, the results were unchanged, with no significant difference in outcomes between medical and stent groups. CORAL shows us that with appropriate medical therapy, the majority of patients with RAS will do well clinically. However, it does not erase the need to look at our patients individually and to recognize that not all patients fit within the study constraints. Patients in this study were on a mean of only two antihypertensive medications at the time of enrollment, and three by study end. These are clearly not the patients who are failing medical management on four or more medications. Patients with truly critical stenosis, bilateral RAS, or RAS affecting a single functioning kidney were not significantly represented. Likewise, patients presenting with critical RAS and recurrent pulmonary edema despite optimal medical therapy were not part of the study group. Whether future trials will be able to address these less-common and difficult-to-enroll populations is doubtful. ■

CME Questions

1. Silent cerebral infarctions by MRI are most common with:
   a. persistent atrial fibrillation.
   b. intermittent atrial fibrillation.
   c. atrial flutter.
   d. AV nodal re-entrant tachycardia.

2. Renal artery stenting of significant atherosclerotic renal artery stenosis in patients with hypertension or renal dysfunction resulted in:
   a. reduction of a combined endpoint.
   b. reduced blood pressure.
   c. improved renal function.
   d. All of the above

3. A TAVR registry has shown:
   a. a 2% procedural death rate.
   b. an in-hospital mortality of 10%.
   c. a stroke rate of 5%.
   d. a pacemaker in 7%.

4. Eplerenone therapy in systolic heart failure patients resulted in:
   a. reduced death plus heart failure hospitalization
   b. an increase in serum potassium > 5.5 mmol/L
   c. no worsening of renal function
   d. All of the above

5. An observational study of spironolactone therapy in systolic heart failure showed:
   a. reduced death and hospitalizations.
   b. increased serum potassium.
   c. worsening renal function.
   d. hypotension.

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3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

If you have any questions about the process, please call us at (800) 688-2421, or outside the U.S. at (404) 262-5476. You can also fax us at (800) 284-3291, or outside the U.S. at (404) 262-5560. You can also email us at: customerservice@ahcmedia.com.

On behalf of AHC Media, we thank you for your trust and look forward to a continuing education partnership.

Sincerely,

Lee Landenberger
Continuing Education Director
AHC Media