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Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

Left Atrial Appendage Occlusion vs Warfarin for Nonvalvular AF

By Andrew J. Boyle, MBBS, PhD
Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco

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

SOURCES: Reddy VY, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation 2.3-year follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trial. *Circulation* 2013;127:720-729. Alli O, et al. Quality of life assessment in the randomized PROTECT AF trial of patients at risk for stroke with non-valvular atrial fibrillation. *J Am Coll Cardiol* 2013; Feb. 28. [Epub ahead of print.]

Atrial fibrillation (AF) is a major source of morbidity in patients and cost to the health care community. In the presence of risk factors for thromboembolism, AF is associated with an increased risk of stroke, and this risk is reduced with warfarin. However, warfarin has limitations, including the risk of bleeding and the need for regular blood tests. The left atrial appendage (LAA) is thought to be a nidus for thrombus that can result in stroke or systemic embolism. The Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation (PROTECT AF) trial was a randomized controlled trial of percutaneous device closure of the LAA with the Watchman device vs continued warfarin therapy. In these studies, Reddy and colleagues present the final long-term outcomes of this trial, and Alli et al present the quality-of-life (QOL) outcomes.

The main inclusion criteria for the PROTECT AF study were age > 18 years; a history of paroxysmal, persistent, or permanent nonvalvular AF plus at least one additional stroke risk factor (age ≥ 75

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years, hypertension, diabetes mellitus, heart failure, prior stroke, transient cerebral ischemic attack, or systemic thromboembolism); and eligibility for warfarin therapy, i.e., a CHADS2 score ≥ 1. Exclusion criteria were the presence of atrial septal defect, mechanical prosthetic heart valve, patent foramen ovale accompanied by atrial septal aneurysm (because of the potential for paradoxical embolization), left ventricular ejection fraction < 30%, intracardiac thrombus, morphologically complex (mobile or ulcerated) aortic atheroma, or symptomatic carotid artery disease. Patients (n = 707) were randomized in a 2:1 fashion to receive the device or continue warfarin. The initial results have been presented, but in these studies we are given the longer-term efficacy and safety outcomes, and the QOL outcomes.

For patients randomized to Watchman device implantation (n = 463), warfarin was continued for ≈ 45 days, followed by clopidogrel for 4.5 months and then lifelong aspirin. In the warfarin group (n = 244), the time in therapeutic range was 66%. In the study by Reddy et al, after 2.3 ± 1.1 years of follow-up (1588 patient years), the event rates of the composite primary efficacy endpoint of stroke, systemic embolism, and cardiovascular death were 3.0% and 4.3% (percent per 100 patient years) in the Watchman and warfarin groups, respectively (relative risk [RR], 0.71; 95% confidence interval [CI], 0.44-1.30% per year), which met the criteria for non-inferiority. There were more primary safety events in the Watchman group (5.5% per year; 95% CI, 4.2-7.1% per year) than in the control group (3.6% per year, 95% CI, 2.2-5.3% per year; RR, 1.53; 95% CI, 0.95-2.70% per year). When the effect of LAA closure was isolated from complications of implantation and concomitant transient anticoagulation in a secondary analysis, the Watchman device was superior to warfarin (probability of superiority = 0.953). Among patients with stroke before they entered the study, the two strategies were equally effective, with rates of 5.3% per year and 8.2% per year, respectively, (RR, 0.64; 95% CI, 0.24-1.74% per year). Similar trends were seen in patients with CHADS2 scores ≥ 2. The authors conclude that the "local" strategy of LAA closure is noninferior to "systemic" anticoagulation with warfarin, and that PROTECT AF has, for the first time, implicated the LAA in the pathogenesis of stroke in AF.

In the study by Alli et al, QOL using the SF-12-V2 measurement tool was obtained at baseline and 12 months in a subset of 547 patients (361 device and 186 warfarin patients). The analysis cohort consisted of those for whom either paired QOL data were available after 12 months of follow-up or in patients who died. In the device and warfarin arms respectively, the total physical score improved in 34.9% and 24.7%, and was unchanged in 29.9% and 31.7% ($P = 0.01$). There was a significant improvement in QOL in patients randomized to device for total physical score, physical function, and in physical role limitation compared to controls. Interestingly, there were significant differences in the change in total physical score among warfarin-naïve and not-warfarin-naïve subgroups in the device group compared to controls, but larger gains were seen with the warfarin-naïve subgroup with a 12-month change of 1.3 ± 8.8 vs -3.6 ± 6.7 ($P = 0.0004$) device compared to warfarin. The authors conclude that patients with nonvalvular AF at risk for stroke treated with LAA closure have favorable QOL changes at 12 months vs patients treated with warfarin.

■ COMMENTARY

The results of these studies are very provocative, suggesting that for patients with any type of nonvalvular AF (paroxysmal, persistent, or permanent), closure of the LAA can result in similar outcomes to warfarin with improved QOL. Based on these results, the device has been approved in Europe and now carries a class IIB recommendation in the European guidelines. However, it should be emphasized that this device is not FDA approved for use in the United States.

The PROTECT AF trial is a well-designed study with large numbers of patients for a device trial (although small numbers for a drug trial). The consistency of the results across subgroups and across

intention-to-treat and per-protocol analyses, as well as in the landmark analysis (after the brief period of warfarin in the device group), strengthen the conclusions drawn by the authors. However, several issues should be noted. First, patients with significant aortic and carotid atheroma were excluded, as were patients who cannot tolerate warfarin. The role of LAA occlusion in these patient groups remains to be studied. Second, the follow-up period was really only medium-term (2.3 years) and long-term data will be necessary to definitely make conclusions between groups. Third, the cost effectiveness of this strategy has yet to be presented in the U.S. system. Some patients may prefer a single procedure to avoid long-term warfarin, and the QOL data suggest this is a reasonable strategy. But what costs this will impose and who will pay remain to be determined. Overall, however, these data are encouraging that we may one day be able to offer our patients a "local" strategy to reduce the risk of stroke as an alternative to systemic anti-coagulation, and they may feel better for it. ■

ABSTRACT & COMMENTARY

Tight vs Loose Rate Control in Permanent Atrial Fibrillation

By John P. DiMarco, MD, PhD

Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

Dr. DiMarco does research for Medtronic, is a consultant for Medtronic, Novartis, and St. Jude, and is a speaker for Boston Scientific.

SOURCE: Groenveld HF, et al. Rate control efficacy in permanent atrial fibrillation: Successful and failed strict rate control against a background of lenient rate control. Data from RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation). *J Am Coll Cardiol* 2013;61:741-778.

The Rate Control Efficacy in Permanent Atrial Fibrillation (RACE II) trial compared strict rate control vs lenient rate control in patients with permanent atrial fibrillation. In this substudy, the RACE II investigators report results based on three groups of patients: those with successful strict rate control, those with unsuccessful rate control, and those with lenient rate control. In RACE II, lenient rate control was defined as a resting heart rate < 110 beats per minute (bpm). Strict rate control required a resting heart rate < 80 bpm and a heart rate < than 110 bpm during moderate exercise. The primary outcome was a composite of cardiovascular morbidity and mortality. Patients in the strict rate control group were classified as failures if one of the heart rate criteria was not met. Heart rate control was assessed at the end of a dose-adjustment phase. Quality of life was assessed with a several instruments, including the Medical Outcome Study SF-36, the University of Toronto AF Severity Scale, and the Multidimensional Fatigue Inventory 20.

There were 608 patients included in this analysis. In the strict rate control group, 203 patients achieved strict rate control and 98 patients did not meet target heart rate. The reasons for failure of strict rate control included manifest drug-related adverse affects, no or acceptable symptoms despite faster heart rates, and an inability to achieve rate control with drug therapy. Among the patients in the lenient rate control group, 69% were controlled with a single AV nodal blocking agent or did not require any drug therapy for rate control. Only 31% required two or more AV nodal blocking agents. In contrast, in the strict rate control group, 72% of patients required two or more agents. There was no difference in the primary outcome after the dose-adjustment phase with 27 of 203 (13.3%) in the successful strict control group, 14 of 98 (14.3%) in the failed strict control group, and 35 of 307 (11.4%) in the lenient group reaching a primary endpoint. There also were no differences between the three groups in all-cause mortality or when patients with an ejection below 40% were analyzed separately. During follow-up, additional visits were more frequently required in the strict rate control group. There were no significant changes in mean ejection fractions in any of the three groups over time. There was also no change in any of the reported symptom scales or in quality of life between the three groups. The authors conclude that lenient rate control is as effective as strict rate control even if patients who fail to achieve strict rate control are excluded.

■ COMMENTARY

RACE II data have now shown that very intense heart rate control in patients with atrial fibrillation is not required for reasonable short-term outcomes. However, physicians should still be cautious in accepting heart rates in the upper portion of the acceptable range. Most of the patients in the

RACE II lenient control group had resting rates below 100 bpm, so we would expect them to do reasonably well. We must also remember that tachycardia-associated cardiomyopathies at slower heart rates (110-130 bpm) may take years to develop and RACE II was a relatively short-term study. I continue to try to keep the resting heart rate in a range I know to be safe (70-90 bpm) and will reevaluate patients outside this range or with symptoms at more frequent intervals. ■

ABSTRACT & COMMENTARY

Does Therapeutic Hypothermia Cause Stent Thrombosis?

By Andrew J. Boyle, MBBS, PhD
Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco

SOURCE: Penela D, et al. Hypothermia in acute coronary syndrome: Brain salvage versus stent thrombosis? *J Am Coll Cardiol* 2013;61:686-687.

Therapeutic hypothermia (THT) in survivors of cardiac arrest due to shockable rhythm is associated with improved neurological outcomes. Acute coronary syndromes (ACS) are frequently the cause of cardiac arrest, and these patients often undergo percutaneous coronary intervention (PCI) during the index hospitalization. THT may be associated with alterations in the coagulation system, which poses a risk to patients following PCI. In this study, Penela and colleagues present retrospective data on patients surviving cardiac arrest treated with THT at their hospital.

Over a 2-year period, 28 patients surviving out-of-hospital cardiac arrest with initial ventricular fibrillation were treated with THT. They administered saline at 4° Celsius, 30 mL/kg over 30 minutes starting in the emergency room. Once in the intensive care unit, they used the Arctic Sun device to maintain body temperature at 33° for 24 hours, followed by slow rewarming. Coronary angiography was performed in 18 patients (65%), of whom 15 had a final diagnosis of ACS. Ten of these patients had ST elevation myocardial infarction (STEMI) and PCI was performed in 11 patients, with a mean door-to-balloon time of 78 ± 39 minutes. All patients undergoing PCI received intravenous heparin and guideline-based antiplatelet therapy: clopidogrel 600 mg loading dose and aspirin 300-500 mg loading dose followed by standard maintenance regimens. Definite stent thrombosis occurred in five patients (31.2%); acute in one patient and subacute in four patients. Four of these occurred in bare-metal stents, and all occurred in patients who had originally presented with ST elevation. Four were diagnosed angiographically and one at autopsy. The mean time from primary PCI to thrombotic event was 174 ± 146 hours (range, 8-376 hours). In addition, two patients had a thrombotic complication that was not related to PCI: one patient had a pulmonary embolism and another patient had a deep vein thrombosis, both occurring before discharge. There were no bleeding complications. During the same period, the authors' institution performed 2737 PCI procedures, of which 42% were primary PCI. The rate of definite stent thrombosis during that period was 0.44% in patients without THT and 0.7% in patients undergoing primary PCI. The authors conclude that THT is associated with a disturbingly high number of cases of stent thrombosis, despite guideline-based antithrombotic therapy, and that new research is needed to determine the cause of these episodes, as well as the optimal antithrombotic therapy in these patients.

■ COMMENTARY

Patients suffering out-of-hospital cardiac arrest have a poor prognosis. THT has been shown to improve their neurologic prognosis, but a definite effect on the heart has not been shown. In this study, Penela and colleagues present a single-center, retrospective experience of patients who present after surviving out-of-hospital cardiac arrest and an initial shockable rhythm. Despite being a high-volume PCI center, the numbers are small. The actual number of patients having definite stent thrombosis was only five. We are not told how many patients fulfilled criteria for probable or possible stent thrombosis. However, despite the small absolute numbers, the proportion of patients after THT suffering stent thrombosis compared to primary PCI patients not treated with THT is alarming (31% vs 0.7%). The stent thrombosis cases occurred from 8 hours to 16 days post PCI. The cause is not likely to be a

mechanical or technical problem in such a high-volume center whose stent thrombosis rates in other cases are consistent with prior published data. The authors suggest that this could be due to an effect of hypothermia on platelet aggregation, which may explain the early stent thrombosis. Why, then, would stent thrombosis occur up to 16 days later when all the platelets exposed to THT are likely to have been replaced by normal turnover (circulating life of platelets is around 1 week)? That is not so easily explained. Perhaps there is an effect on the fibrinolytic or thrombosis pathways independent of the platelet. This may also explain the occurrence of deep venous thrombosis and pulmonary embolism in two patients. Regardless of the cause, the signal from this study suggests that these patients are at very high risk of stent thrombosis. These data should be validated in larger cohorts. Until that time, we should be vigilant for stent thrombosis and make every attempt to use meticulous procedural technique and optimal anticoagulant and anti-platelet therapy in these patients. ■

ABSTRACT & COMMENTARY

Hemorrhagic Stoke with Dual Antiplatelet Therapy

By Michael H. Crawford, MD, Editor

SOURCE: Ducrocq G, et al. A history of stoke/transient ischemic attack indicates high risks of cardiovascular event and hemorrhagic stroke in patients with coronary artery disease. *Circulation* 2013;127:730-738.

The REduction of Atherothrombosis for Continued Health (REACH) study is an international registry of patients on antithrombic therapy that provides an opportunity to evaluate the risk of ischemic and bleeding outcomes in patients with coronary artery disease (CAD). Among 26,380 REACH patients with CAD, there were 4460 (17%) with a history of prior stroke/transient ischemic attack (TIA). The prior cerebrovascular event (CVE) patients were older, more frequently female, and more likely to have diabetes, hypertension, or atrial fibrillation as compared to the rest of the CAD patients. Also, they were more likely to be taking dual antiplatelet therapy and oral anticoagulants. Over a 4-year follow-up, the CAD plus CVE patients had a higher death rate (18% vs 11%) and more cardiovascular events (25% vs 13% death, myocardial infarction, or stroke). Stroke was especially common (13% vs 4%) with twice as many hemorrhagic strokes. The increased risk for hemorrhagic stroke was greatest the first year and was particularly high in those on dual antiplatelet therapy (hazard ratio [HR], 5.21; 95% confidence interval [CI], 1.24-21.90). Oral anticoagulants plus dual antiplatelet therapy augmented the risk, but not anticoagulant therapy alone. Bleeding rates were higher in the CAD plus CVE vs the rest of the CAD patients (3.5% vs 2.5%). The authors concluded that in CAD patients, a history of CVE increased the risk of subsequent cardiovascular events, including hemorrhagic stroke, which was especially augmented in those on dual antiplatelet therapy in the first year after a prior CVE.

■ COMMENTARY

This study has important clinical implications. Among CAD patients, a history of CVE is common (17% in this study) and these patients have a higher risk of subsequent cardiovascular events such as cardiac death, myocardial infarction, and stroke. Thus, they are candidates for aggressive antithrombic therapy, including dual antiplatelet therapy and, in some cases, oral anticoagulants. However, they also have higher rates of bleeding, including hemorrhagic stroke, especially if they are on dual antiplatelet therapy. Hence, we have a therapeutic dilemma. Although the absolute risk of hemorrhagic stroke was small (0.6%) vs ischemic stroke (12%), it is most often fatal. In fact, the authors speculated that the incidence of hemorrhagic stroke may have been underestimated because some were classified as sudden deaths only.

These observations have been seen in other trials. For example, the use of prasugrel in acute coronary syndromes in patients with prior CVEs showed an increase in hemorrhagic stroke (HR, 1.54; 95% CI, 1.02-2.32; $P = 0.04$). Also, in the MATCH study, among patients with a recent CVE, those on dual antiplatelet therapy vs clopidogrel alone showed a higher rate of major bleeding and little effect on ischemic events.

Given these findings, how do we manage CAD

patients with a history of CVE? This study provides some guidance. Those with a prior TIA have far less risk than those with a prior stroke. So, only stoke patients should create caution with regard to dual antiplatelet therapy. Also, the first year after a CVE was the highest risk period, so perhaps those in this time frame should be treated with single antiplatelet therapy or have coronary stenting delayed if possible. What to do with oral anticoagulation therapy is not clear from this study due to small numbers, but triple therapy in post CVE patients would probably be especially risky. ■

ABSTRACT & COMMENTARY

Prosthetic Valve Thrombosis

By Michael H. Crawford, MD, Editor

SOURCE: Ozkan M, et al. Comparison of different TEE-guided thrombolytic regimens for prosthetic valve thrombosis. *JACC Cardiovasc Imaging* 2013; 6:206-216.

The use of thrombolysis for prosthetic valve thrombosis (PVT) is controversial and various guidelines rate it differently. However, since PVT carries a significant mortality risk, more information on proposed therapies would be valuable. Thus, this single-center experience with thrombolysis for PVT is of value. Over a 16-year period at an academic hospital in Istanbul, Turkey, five different thrombolytic regimens were used sequentially. This experience was analyzed to determine the most effective regimen. Because of mortalities approaching 20% with surgery for PVT, thrombolysis was first-line treatment for almost all patients, with surgery reserved for those with major contraindications for thrombolytics or those in whom it failed. Their experience started in 1993 (3-hour infusion of streptokinase) and this protocol was changed in 1997 to a 24-hour infusion when the complication rate was noted to be the same as surgery. In 2001, tissue plasminogen activator (tPA) was used in three sequential protocols based on the results of the prior protocol. Because of concern for bleeding, heparin was not administered with thrombolysis, only afterward. In 182 consecutive patients, 220 episodes of PVT were treated. The overall success rate was 83% and was highest for the last protocol (85.5%), but was not significantly different across all five. The complication rate was significantly lower for the final protocol (10.5% vs 37.5%) as compared to the first protocol ($P < 0.05$), and there were no deaths during use of the final protocol vs six deaths (17%) using the four prior regimens. Intracranial hemorrhage occurred in seven patients (two died) and seven had ischemic strokes (four died). Thus, all six deaths (2.17%) were related to cerebral complications. By multivariate analysis, prior stroke/TIA was predictive of death (odds ratio, 3.47; 95% CI, 1.32-9.11; $P = 0.01$). The final protocol was a 6-hour infusion of 25 mg of tPA without a bolus repeated once 24 hours later (up to 6 times if necessary). The authors concluded that a low-dose, slow infusion of tPA without a bolus — and repeated if necessary — was an effective and safe thrombolytic regimen in patients with PVT.

■ COMMENTARY

PVT is an infrequent but urgent problem that doesn't lend itself well to a randomized trial. Also, the guidelines of various organizations are not consistent. Although most agree that if surgery is very high risk or if the PVT is right sided where emboli can do less harm, thrombolysis is worth trying. Some believe you can treat small left-sided thrombi with thrombolysis and some believe that only obstructive thrombi should be considered for thrombolysis. In addition, there is no agreement on what thrombolytic regimen should be used. Thus, this large, systematic experience at one center is of interest.

In this study, about half the patients had nonobstructive thrombi by transesophageal echocardiography, which was done in all on entry and after therapy was given. Their contraindications for thrombolysis included asymptomatic nonobstructive PVT without evidence of systemic emboli and diameter < 10 mm. Also, they excluded anyone < 3 weeks from an ischemic stroke. Their criteria for successful thrombolysis were: Doppler echo resolution of the increased gradient, symptomatic improvement, and a decrease in thrombus diameter of > 75%. If all three were met, it was considered complete resolution and < 3 but > 0 was considered partial resolution; both were included in their 85% final

success rate. Why 15% were resistant to therapy is unknown, but they point out that pannus is difficult to distinguish from thrombus by echo.

Their final protocol complication rate of 5% with no deaths is similar to the results of using thrombolytics in acute myocardial infarction. There was no surgical group reported but these morbidity/mortality rates are lower than those reported by others. However, surgical patients are probably a higher risk group in general. In comparing the various protocols, it becomes clear that the secret to their success is no bolus, low doses infused slowly, and no heparin until the thrombolytic is in. This approach probably enhances safety because it produces less emboli. The downside is having to repeat the infusion in a significant number of patients. Their final protocol required more than three infusions for success in 21 of the 124 patients treated (17%). Whether the same results or better ones could be obtained with some of the newer thrombolytics is unknown, but since tPA is still available, I would tend to go with their regimen until more data are forthcoming. ■

ABSTRACT & COMMENTARY

Can Cardiac Resynchronization Therapy Use be Expanded?

By John P. DiMarco, MD, PhD
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Dr. DiMarco does research for Medtronic, is a consultant for Medtronic, Novartis, and St. Jude, and is a speaker for Boston Scientific.

SOURCE: Thibault B, et al. Cardiac resynchronization therapy in patients with heart failure and a QRS complex < 120 milliseconds: The Evaluation of Resynchronization Therapy for Heart Failure (LESSER-EARTH) Trial. *Circulation* 2013;127:873-881.

The Evaluation of Resynchronization Therapy for Heart Failure (LESSER-EARTH) trial tested the hypothesis that cardiac resynchronization therapy in addition to optimal medical therapy would benefit patients with severe congestive heart failure but no pacing indication and a QRS duration < 120 milliseconds (msec). Patients were recruited from 12 Canadian sites. Patients were eligible for inclusion if they had a clinical indication for an implantable cardioverter defibrillator (ICD), a left ventricular ejection fraction ≤ 35%, a QRS duration < 120 msec, and symptoms of heart failure with a 6-minute walk test distance ≤ 400 meters. Evidence for left ventricular dyssynchrony was not required. Patients with permanent atrial fibrillation, with factors other than heart failure that would limit exercise testing, and those with recent myocardial infarction or cardiac surgery were excluded. Patients with prior pacemakers or ICDs were eligible if their percentage of ventricular pacing was < 5%.

All patients underwent an attempted placement of or upgrade to a CRT-D system. They then entered a 2- to 8-week run-in period during which CRT was programmed (off) with an AV delay set ≥ 325 msec. During this run-in period, the function of the CRT system was assessed and an optimal pharmacologic regimen established. Baseline submaximal exercise and 6-minute walk tests were performed and quality-of-life questionnaires administered. Left ventricular function, geometry, and synchrony were assessed by echocardiography. These evaluations were repeated 6 and 12 months after randomization to either CRT-On or CRT-Off. The primary outcome was submaximal exercise duration. This was assessed using progressive exercise treadmill exercise with an individualized ramp protocol. The slope and speed were individually programmed. The test was terminated due to exhaustion, after 25 minutes of exercise at baseline, or after 45 minutes during follow-up testing.

The study was terminated prematurely for futility after only 159 patients were enrolled. Only 85 patients were randomized; 74 patients did not undergo randomization due to either problems with the CRT system (34), inability to perform exercise testing (5), an exercise duration > 25 minutes (11), or for miscellaneous other reasons (21). There was no difference in improvement in the duration of submaximal exercise in patients with (32.3%) and those without (37.1%) active CRT. Quality of measurements showed an improvement during the run-in phase and then showed no difference between patients with and without active CRT therapy. Assessment of left

ventricular size and function showed intraventricular dyssynchrony induced by CRT that had not been present at baseline. There was no difference between the proportion of patients who had improvement in left ventricular and diastolic dimensions in the two groups. Adverse events were more common in the active CRT group. There were only two deaths during the study, both in the active CRT group, with one due to heart failure and one due to cancer. Five patients with active CRT were hospitalized 15 times for heart failure compared to four patients with inactive CRT who were hospitalized once each.

■ COMMENTARY

When CRT was first introduced, there was widespread hope that electrical resynchronization would benefit a broad spectrum of patients with heart failure and left ventricular dysfunction. It was even postulated that patients with a normal baseline QRS might benefit. Over the years, we have learned that although CRT remains a very effective intervention, its benefits are seen only in selected patient groups. The greatest potential benefits are seen in those with left bundle branch block or in those who require right ventricular pacing and QRS durations > 150 msec. The benefits are less predictable in patients with a shorter QRS duration or a non-left bundle QRS pattern and, as shown here, in patients with a normal QRS, CRT is more likely to harm than to help. ■

CME Questions

1. Stent thrombosis can be caused by:
   a. not taking antiplatelet therapy.
   b. resistance to antiplatelet therapy.
   c. therapeutic hypothermia.
   d. All of the above

2. A percutaneously delivered left atrial occlusion device for preventing systemic thromboemboli has been shown to be:
   a. superior to warfarin.
   b. non-inferior to warfarin.
   c. inferior to warfarin.
   d. equivalent to warfarin.

3. A history of a cerebrovascular event increases the risk of:
   a. cardiac death.
   b. myocardial infarction.
   c. stroke.
   d. All of the above

4. The safest and most effective approach to thrombolytic therapy for prosthetic valve thrombosis is:
   a. bolus tPA, repeated once if necessary.
   b. bolus tPA followed by a high dose over 2 hours.
   c. a high-dose infusion over 3 hours.
   d. a low-dose infusion over 6 hours.

5. Which of the following is *not* an indication for cardiac resynchronization in symptomatic heart failure patients?
   a. QRS < 120 msec
   b. QRS > 150 msec
   c. Left bundle branch block
   d. Right ventricular pacing required

6. Strict rate control of permanent atrial fibrillation results in:
   a. less mortality.
   b. less morbidity.
   c. fewer symptoms.
   d. None of the above

CME Objectives

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

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

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A Relationship Between Nocturia and Hypertension

Source: Feldstein CA. *J Am Soc Hypertens* 2013;7:75-84.

Nocturia could easily be misconstrued as a "nuisance" symptom since, after all, nobody dies from nocturia … or do they? Indeed, urinary frequency and nocturia have been associated with greater risk for nocturnal falls and hip fracture; hence, nocturia can be much more than just a nuisance.

Clinicians are used to identifying nocturia as a symptom associated with benign prostatic hyperplasia, overactive bladder, uncontrolled diabetes, uncontrolled congestive heart failure, use of diuretics, and (less commonly) interstitial cystitis. What is only minimally recognized, however, is the emerging observation that hypertension is associated with nocturia.

Several plausible mechanisms can explain the nocturia/hypertension relationship: hypertension-induced alterations in glomerular filtration or tubular transport, activation of atrial natriuretic peptide from ventricular wall stress induced by hypertension, and resetting of the pressure-natriuresis relationship in the kidney, to name a few.

Feldstein indicates that the prevalence of nocturia in untreated hypertension patients may be as high as 33%. Since nocturia can be both a burdensome symptom and lead to significant morbidity (and mortality), clinicians may wish to specifically inquire about nocturia when encountering hypertension patients. ■

Peripheral Artery Disease: Helping Patients to Walk the Walk

Source: Ahimastos AA, et al. *JAMA* 2013; 309:453-460.

Currently available treatments for peripheral artery disease (PAD) are only modestly effective. PAD portends increased risk of cardiovascular disease; hence, most PAD patients should be receiving pharmacotherapy with a statin and an antiplatelet agent (usually clopidogrel).

Because one of the quality-of-life limiting factors in advanced PAD is disease-mediated diminution in walking distance and walking time, incorporation of pharmacotherapy to improve these limitations is also considered important. Unfortunately, the two FDA-approved treatments (pentoxifylline and cilostazol) for symptoms of PAD provide only a modest increase in walking distance (25% or less). Smoking cessation and exercise advice remain critically important, but are too often not heeded.

Ramipril is an angiotensin-converting enzyme (ACE) inhibitor that has been used in numerous major clinical trials, including the HOPE trial, ONTARGET trial, REIN trial, and others. Use of ramipril is usually predicated on 1) its ability to lower blood pressure, 2) its ability to improve outcomes in congestive heart failure, or 3) its ability to improve albuminuria.

Based on results seen in a small pilot trial that suggested favorable results of ramipril on treadmill time in subjects with PAD, Ahimastos et al performed a larger randomized clinical trial (n = 212).

At the conclusion of the 6-month trial of ramipril 10 mg/day vs placebo, pain-free walking time had increased by more than 50% in the ramipril group, but only 10% in the placebo group.

Although the mechanism for improved function is speculative, it has been noted that ACE inhibitors increase skeletal muscle blood flow; indeed, this has been the mechanism to which improved insulin sensitivity in diabetics has been attributed. Ramipril may offer a new avenue to improve functionality in patients with PAD. ■

Long-Term Functional Outcomes After Localized Prostate Cancer Treatment

Source: Resnick MJ, et al. *N Engl J Med* 2013;368:436-445.

When prostate cancer is localized, either radical prostatectomy (RPT) or external beam radiation (EBR) can often be curative. The adverse effect profile of these two interventions, however, may be meaningfully different and such differences might also be time-dependent.

Resnick et al studied men (n = 1164) from the Prostate Cancer Outcomes Study who had been enrolled between the ages of 55-74 and had localized prostate cancer. More than 80% of the men had a Gleason score of 7 or less. The prevalence of urinary incontinence (UI) and erectile dysfunction (ED) were compared among these men at years 2, 5, and 15.

Prostatectomy subjects were five to six times more likely to have incontinence at

2 years and 5 years than EBR subjects. Similar disadvantage was seen in the prevalence of ED (two- to four-fold increased incidence in the RPT group). At the 15-year conclusion of their observations, no differences between groups remained. However, one would anticipate, for instance, a substantial incremental increase in ED as men age *with or without intervention*; hence, the fact that between-group differences are eliminated by 15 years provides little solace for the men who suffer the adverse effects in the interim! ■

The Word 'GPR40 Modulator' May Soon be Entering Our Vocabulary

Source: Basu A, et al. *Diabetes Care* 2013;36:185-187.

The search for safe and effective agents to treat type 2 diabetes (DM2) continues, with hypoglycemia often being a limiting adverse effect of otherwise highly efficacious agents.

It has been observed that free fatty acids (FFA) play a role in glucose homeostasis, although the story line is complex. Acutely, elevations of FFA *stimulate* beta cell secretion of insulin. *Chronic* FFA elevations result in an impaired insulin response to high glucose levels, a phenomenon known as lipotoxicity.

The mechanism by which FFA impacts insulin secretion has been elegantly worked out and includes the G-protein-coupled receptor (GPR40). Because GPR is involved not only in insulin secretion, but also plays a role in obesity and dyslipidemia, its potential as a multimodal intervention has looked promising.

Studies in humans have shown that GPR40 agonists live up to the expectation that they lower glucose, with a very low risk of hypoglycemia. For instance, a head-to-head comparison with the sulfonylurea glimepiride found hypoglycemic episodes to be six-fold lower with the GRP40 agonist.

In an era of a burgeoning population of DM2 patients, we look forward to the addition of pharmacotherapies that safely complement our current options. ■

A More Effective Regimen for *H. pylori* Eradication

Source: Liou JM, et al. *Lancet* 2013;381: 205-213.

In the United States, peptic ulcer disease is caused primarily by two culprits: nonsteroidal anti-inflammatory drugs and *Helicobacter pylori* (and their combination). Evolution of pharmacotherapy for *H. pylori* currently employs combinations of amoxicillin (AMOX), metronidazole (METR), clarithromycin (CLAR), and a proton pump inhibitor (PPI). Unfortunately, over time *H. pylori* eradication rates with such regimens have fallen to as low as 80% or less. Is there a better way?

Liou at al randomized *H. pylori*-positive Taiwanese adults (n = 900) to one of three regimens — 1) Sequential 10 days: PPI + AMOX for 5 days followed by PPI + CLAR + METR for 5 days; 2) Sequential 14 days: PPI + AMOX for 7 days followed by PPI + CLAR + METR for 7 days; or 3) Standard 14 days: PPI + AMOX + CLAR for 14 days. The PPI used in this clinical trial was lansoprazole.

Adverse effect profiles of the three regimens were similar. Eradication rates were statistically significantly higher using sequential regimens (10 days = 87%, 14 days = 91%) than in standard regimens (82%).

Reflecting an increased recognition of problematic CLAR resistance at the end of the initial comparison trial, treatment failures from each regimen were assigned to receive an additional 14-day sequential course of treatment in which levofloxacin was substituted for CLAR. Eradication rates from this "rescue" population (regardless of which initial regimen they had received) were 80%.

Based on this large dataset, the authors suggest that sequential treatment regimens should become first line. ■

Uric Acid: How Much of a Bad Guy?

Source: Rosendorff C, et al. *J Clin Hypertens* 2013;15:5-6.

Uric acid (URA) has become the object of intense scrutiny of late, with more than its share of accusations linking it to hypertension and heart disease. The relationship between URA and gout is incontrovertible, though not necessarily universal. That is, in persons who develop gout, risk of future attacks is definitely related to absolute URA plasma levels. However, among persons without gout, elevations of URA appear to be well tolerated without evident toxicity in most: In asymptomatic adults with URA levels > 9.0 mg/dL, only about 5% per year go on to manifest acute gout.

The association of URA with hypertension, myocardial infarction, and even congestive heart failure is acknowledged. Whether this relationship is *causal*, and if a causal relationship is determined, whether lowering of URA will be beneficial remains to be determined. Remember the enthusiasm attendant to the recognition that homocysteine was associated with cardiovascular disease, heightened by the assurance that lowering homocysteine was simple and safe (B vitamins and folate), soon thereafter torpedoed by the interventional trials that failed to show improved outcomes in subjects whose homocysteine levels were reduced?

Despite the growing enthusiasm for criminalizing URA, we still do not have a large randomized, controlled trial indicating that modulation of URA improves hard endpoints. Until then, since all medications that reduce URA have their own bundle of potential misadventure to consider, we should watch and wait. ■

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PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

Is This the End of the Road for Calcium Supplementation?

In this issue: Calcium supplementation in women; type 2 diabetes treatments and pancreatitis risk; treating chronic idiopathic urticaria; rivaroxaban and VTE; and FDA actions.

High calcium intakes in women

Another study suggests that calcium supplementation may lead to excess all-cause mortality and cardiovascular disease in otherwise healthy women. Researchers studied more than 61,000 Swedish women for 19 years. Diet and calcium intake, including calcium supplementation, were assessed with the primary outcome being death from all causes and cause-specific cardiovascular disease, ischemic heart disease, and stroke. Higher *dietary* intake of calcium (> 1400 mg/day) was associated with a higher death rate from all causes compared to intake between 600-1000 mg/day (hazard ratio [HR], 1.40; 95% confidence interval [CI], 1.17-1.67). Higher calcium intake was also linked to increased risk of cardiovascular disease (HR, 1.49; CI, 1.09-2.02) and ischemic heart disease (HR, 2.14; CI, 1.48-3.09). There was no higher risk of stroke. Intake of calcium in tablet form > 1400 mg/day was associated with 2.5 times greater risk of death from all causes (HR, 2.57; CI, 1.19-5.55). The authors conclude that higher intakes of calcium in women are associated with higher death rates from all causes as well as increased rates of cardiovascular disease but not stroke (*BMJ* published online Feb. 13, 2013. DOI: org/10.1136/bmj.f228). Previous studies have focused more on stroke risk associated with calcium showing mixed results. This well-done study, along with previously published data from the Women's Health Initiative, provides ample evidence to rethink calcium supplementation for the 60% of middle-aged and older American women who are regular users of calcium supplements. The U.S. Preventive Services Task Force came to the same conclusion (even before this study was published) with publication of updated guidelines in February stating that "current evidence is insufficient to assess the balance of the benefits and harms of combined vitamin D and calcium supplements for the primary prevention of fractures in postmenopausal women or men." They further state there is no evidence to support use of more than 1000 mg of calcium and 400 mcg of vitamin D per day and recommends against using doses lower than 1000 mg of calcium and 400 mcg of vitamin D. Their rationale is that supplementation does not reduce fracture risk but does increase the risk of renal stones in otherwise healthy women. This does not apply to women with osteoporosis or vitamin D deficiency (*Ann Intern Med*, published online Feb. 26, 2013). ■

Diabetes therapies and pancreatitis risk

Glucagonlike peptide 1 (GLP-1) mimetics (e.g., analogs of GLP-1 and dipeptidyl peptidase IV inhibitors) used for the treatment of type 2 diabetes might increase the risk of pancreatitis, according to a recent population-based, case-control study. Using a large population database of

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type 2 diabetics, 1269 cases of acute pancreatitis were identified and those patients were matched with 1269 controls with similar risk factors (age, sex, diabetes mellitus complications, etc). After adjusting for available confounders, current use of GLP-1 based therapies (exenatide [Byetta] and sitagliptin [Januvia]) more than doubled the risk for acute pancreatitis (adjusted odds ratio 2.24, 95% CI, 1.36-3.68). The authors state that "Our findings suggest a significantly increased risk of hospitalization for acute pancreatitis associated with the use of sitagliptin or exenatide among adult patients with type 2 diabetes mellitus" (*JAMA Intern Med* published online Feb. 25, 2013. DOI: 10.1001/jamainternmed.2013.2720). Both drugs already carry a boxed warning regarding pancreatitis. ■

Omalizumab for idiopathic urticaria

Chronic idiopathic urticaria is one of the most frustrating entities to treat as many patients do not respond to antihistamines, even in high doses. Now, a new study suggests that omalizumab (Xolair), an IgE monoclonal antibody used to treat asthma, may be effective in these patients. Patients with moderate-to-severe chronic idiopathic urticaria (n = 323) were randomized to SQ injections of omalizumab every 4 weeks for three total injections at doses of 75 mg, 150 mg, 300 mg, or placebo. The primary outcome was itch-severity score. The 75 mg dose was no better than placebo, but the two higher doses showed significant reductions in itching, with the 300 mg dose being the most effective. The higher dose was also associated with the highest risk of side effects, however, at about 6%. The authors conclude that omalizumab was effective in these patients who were previously symptomatic despite antihistamines. The study was sponsored by the drug manufacturers Genentech and Novartis Pharma (*N Engl J Med* published online Feb. 24, 2013. DOI: 10.1056/NEJMoa1215372). ■

Rivaroxaban for VTE prevention

Rivaroxaban, the oral Xa inhibitor, is as effective as enoxaparin in preventing venous thromboembolism (VTE) in patients with acute medical illnesses, but with a higher risk of bleeding, according to a new study. More than 8100 acutely ill hospitalized patients were randomized to 10 days of enoxaparin 40 mg SQ daily or 35 days of rivaroxaban 40 mg orally with matching placebos. The primary outcome of asymptomatic or symptomatic VTE occurred in 2.7% of patients in both groups by day 10. By day 35, the rates were 4.4% for rivaroxaban and 5.7% for enoxaparin ($P = 0.02$). However, the bleeding rate was more than double in the rivaroxaban group at day 10 (2.8% vs 1.2%, $P < 0.001$) and even higher at day 35 (4.1% vs 1.7%, $P < 0.001$). The authors conclude that rivaroxaban was noninferior to enoxaparin for standard duration thromboprophylaxis (10 days) and reduced the risk of VTE at 35 days with an increased risk of bleeding (*N Engl J Med* 2013;368:513-523). ■

FDA actions

A new selective estrogen receptor modulator (SERM) has been approved for the treatment of dyspareunia due to vulvar and vaginal atrophy in postmenopausal women. Ospemifene appears to benefit vaginal epithelium without significant effect on the endometrium. The drug's safety and efficacy was established in three clinical trials of nearly 1900 postmenopausal women with vulvar and vaginal atrophy who were randomly assigned to ospemifene or placebo. After 12 weeks, the first two trials showed statistically significant improvement in dyspareunia while the third trial supported the long-term safety of the drug. The drug is contraindicated in women with genital bleeding, estrogen-dependent cancer, or thromboembolic disease. The risk of stroke and VTE was higher than baseline but lower than the rates seen with estrogen replacement therapy. Ospemifene comes with a boxed warning regarding endometrial hyperplasia and abnormal vaginal bleeding. Common side effects include hot flashes, vaginal discharge, muscle spasms, and sweating. It will be marketed by Shionogi Inc. as Osphena.

The FDA has approved ado-trastuzumab emtansine for use as a single agent in patients with late-stage, HER2-positive breast cancer. The drug is approved for patients who have already been treated with trastuzumab and taxane separately or in combination. Approval was based on a study of nearly 1000 women with metastatic breast cancer in which progression-free survival was about 3 months longer with the drug compared to lapatinib plus capecitabine, and overall survival was about 6 months longer. Ado-trastuzumab emtansine is marketed by Genentech as Kadcyla. ■