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Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

Intensive Lipid Lowering and Coronary Plaque Regression

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.

SOURCE: Nicholls SJ, et al. Effect of two intensive statin regimens on progression of coronary disease. *N Engl J Med* 2011;365:2078-2087.

Recent clinical trials utilizing intravascular ultrasound (IVUS) to quantify coronary artery plaque burden have demonstrated that statin therapy has the potential to arrest the progression of coronary artery disease, and even to effect a small amount of plaque regression. Rosuvastatin is more effective than atorvastatin in reducing low-density lipoprotein (LDL) and increasing high-density lipoprotein (HDL) levels. Whether this translates into more effective plaque regression is not known. Accordingly, Nicholls and colleagues performed a large, multicenter clinical trial to compare the effects of high-dose atorvastatin vs high-dose rosuvastatin on coronary artery plaque burden.

Patients undergoing clinically indicated coronary angiography who had evidence of non-obstructive coronary plaque (< 50% stenosis) were recruited. The patients underwent IVUS analysis and were then randomized to one of two treatment arms: atorvastatin 80 mg daily or rosuvastatin 40 mg daily. Patients were excluded if they had intensive lipid lowering therapy for more than 3 months in the prior year, if they had low LDL levels (< 100 mg/dL in statin-naïve patients and < 80 mg/dL in statin-treated patients), uncontrolled hypertension, heart failure, renal dysfunction, or liver disease. The study aimed to treat for 104 weeks and then repeat the IVUS evaluation. The primary endpoint was percent atheroma volume (PAV), the percentage of the vessel wall that is occupied by atherosclerotic plaque.

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Clinical Cardiology [ALERT]

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A total of 1385 patients were randomized to high-dose atorvastatin (n = 691) or high-dose rosuvastatin (n = 694). After 104 weeks of treatment, 75% of patients remained in the study and underwent follow-up IVUS (n = 519 atorvastatin; n = 520 rosuvastatin). There were no differences in baseline demographic or clinical variables.

Rosuvastatin treatment resulted in lower LDL levels (62.6 ± 1.0 vs 70.2 ± 1.0 mg/dL; $P < 0.001$) and higher HDL levels (50.4 ± 0.5 vs 48.6 ± 0.5; $P = 0.01$) than atorvastatin. Both atorvastatin and rosuvastatin resulted in modest plaque regression. The primary endpoint, PAV, decreased in both the atorvastatin group (-0.99%) and the rosuvastatin group (-1.22%), but the difference between groups was not significant ($P = 0.17$). Both agents induced plaque regression in the majority of patients (63.2% with atorvastatin and 68.5% with rosuvastatin; $P = 0.07$). The side-effect profiles were similar with both medications. The authors conclude that maximal doses of rosuvastatin and atorvastatin resulted in significant regression of coronary atherosclerosis. Despite the lower levels of LDL and the higher level of HDL cholesterol achieved with rosuvastatin, a similar degree of regression was seen in the two treatment groups.

■ COMMENTARY

Coronary atherosclerosis is a progressive disease. Statins have the capacity to reduce the rate of progression of disease. This study demonstrates the ability of two intensive statin regimens to actually reverse the disease process, albeit to a modest extent. The use of IVUS at two time-points is probably the most accurate way to demonstrate small changes in plaque volume. Although there is a small risk with performing invasive IVUS, this study was important to demonstrate this effect. Clearly, serial IVUS evaluation of the coronary arteries is not warranted on an individual patient basis, but the study demonstrates an important principle of lipid-lowering therapy: intensive statin use not only prevents plaque progression over 2 years, it actually induces a small degree of plaque regression.

This study had a relatively short follow-up period, as most patients will be on statin therapy for much longer than 2 years. It remains unknown whether the longer-term effects of such intensive statin therapy on coronary plaque and cardiac event rates will differ between the two treatments. There was a trend toward greater reduction in atheroma volume with rosuvastatin that did not reach statistical significance. Perhaps over a 5- or 10-year period there may well be a difference between agents, but more studies are needed to determine this. The short follow-up, though, shows that a relatively rapid plaque regression can be achieved with current medical therapy. What are the effects of moderate lipid lowering on plaque regression (atorvastatin 40 mg or rosuvastatin 20 mg)? Are the highest statin doses actually necessary, or can lower doses of statins also lead to plaque regression? This question also remains unanswered. Concerns have been raised about the safety of statins in the long term. These concerns should be allayed by the recently published 11-year follow-up of the Anglo-Scandinavian Cardiac Outcomes Trial study,[1] which showed continued benefit of atorvastatin over placebo. However, the long-term safety of rosuvastatin has not yet been demonstrated.

Although a formal cost-effectiveness analysis was not performed in this study, one could imagine that with atorvastatin going generic, there is a potential for real cost savings to the health care system with this aggressive approach to secondary prevention. This study confirms that intensive lipid lowering is beneficial in patients with established coronary artery disease, and that following the clinical guidelines, which recommend this approach, will result in better outcomes for our patients. There appears to be little difference between these two statin regimens at 2 years of follow-up. ■

Reference

1. Sever PS, et al. The Anglo-Scandinavian Cardiac Outcomes Trial: 11-year mortality follow-up of the lipid-lowering arm in the U.K. *Eur Heart J* 2011;32: 2525-2532.

ABSTRACT & COMMENTARY

Underuse of Statins in Patients with Coronary Artery Disease

By Andrew J. Boyle, MBBS, PhD

Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco

SOURCE: Arnold SV, et al. Statin use in outpatients with obstructive coronary artery disease. *Circulation* 2011;124:2405-2410.

The benefits of statin use in patients with proven coronary artery disease (CAD) are well established. Current guidelines recommend that this patient group, which is at high risk for recurrent events, be treated to LDL cholesterol levels < 100 mg/dL. Clinical trials have shown that similar reduction in risk for future cardiac events is achieved with statin therapy, despite the LDL level at initiation. Even patients whose LDL is < 100 mg/dL at initiation of statin therapy derive clinical benefits from statins. Whether there is general adherence to the secondary prevention guidelines in ambulatory clinical practice is not known. Accordingly, Arnold and colleagues used the American College of Cardiology's Practice INNovation And CLinical Excellence (PINNACLE) registry. This registry study includes data on ambulatory cardiac outpatients collected from 24 practices in 111 practice locations in 18 states.

Patients with obstructive CAD were defined as those with diagnoses of prior myocardial infarction (MI), prior percutaneous coronary intervention (PCI), or prior coronary artery bypass graft surgery (CABG). After excluding those with contraindications to statin therapy, 38,775 patients with obstructive CAD were identified. Statin therapy was prescribed for 77.8%, 17% were untreated, 16.6% received both a statin and a non-statin lipid-lowering medication, and 5.3% received only a non-statin lipid-lowering medication.

Patients without medical insurance were less likely to receive a statin (risk ratio [RR] 0.94; $P = 0.039$). Patients were more likely to receive a statin if they were male (RR 1.10; $P < 0.001$), hypertensive (RR 1.07; $P = 0.003$), had prior CABG (RR 1.09; $P < 0.001$), or had prior PCI (RR 1.11; $P < 0.001$). A history of diabetes and prior MI were weakly associated with a greater likelihood of receiving statin therapy. Among the patients who did not receive any lipid-lowering therapy, 46.7% had LDL levels > 100 mg/dL. The authors conclude that despite robust clinical trial evidence, a substantial number of patients with obstructive CAD remain untreated with statins. A small proportion were treated with non-statin therapy and one in six patients was simply untreated; only half of the untreated patients had LDL < 100 mg/dL. These findings illustrate important opportunities to improve lipid management in outpatients with obstructive CAD.

■ COMMENTARY

The benefits of stain therapy in those with obstructive CAD are clear. This study is an important wake-up call to clinicians to be vigilant about aggressive secondary prevention measures in this high-risk patient group. Unfortunately, this study is unable to provide the reasons for nonprescription of statins. We are left to ponder if this represents intolerance of statins that was not documented, physician oversight, patient unwillingness to adhere to a statin regimen, or other reasons. Prior small studies have also suggested low adherence rates to statin therapy, which is congruent with the data presented here. However, this study provides a more contemporary look at statin usage in secondary prevention with a larger sample size. Furthermore, we are not told how the data are logged for the PINNACLE registry. Prior MI may have represented a demand ischemia event, rather than a ruptured plaque with atherothrombotic occlusion of a coronary artery.

Lipid levels were available in approximately half of the patients who were not receiving lipid-lowering therapy. Nearly 50% had elevated LDL levels > 100 mg/dL. The authors postulate that the group with LDL < 100 mg/dL were not treated because physicians thought their LDL was at goal and they would not benefit from statin therapy. In fact, the opposite is true. Even those who begin with a low LDL derive clinical benefit from statins. Thus, both those with a high LDL and those with a low LDL should have been treated with lipid lowering, preferably a statin, and this represents a significant treatment gap. This study reminds us that we should all be vigilant that our patients are receiving guideline-based secondary prevention measures. ■

Blood Pressure Target to Prevent Cardiovascular Events

By Michael H. Crawford, MD, Editor

SOURCES: Mancia G, et al. Blood pressure targets recommended by guidelines and incidence of cardiovascular and renal events in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET). *Circulation* 2011;124:1727-1736. Chalmers J. Is a blood pressure target of 130/80 mm Hg still appropriate for high risk patients? *Circulation* 2011;124:1700-1702.

Guidelines recommend aggressive systolic blood pressure (BP) goals (< 130/80 mmHg) in patients at high risk for cardiovascular (CV) events. However, there are few data to support this recommendation. Thus, investigators from the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) used this database to determine the outcomes of achieving a BP < 140/90 vs < 130/80. This trial compared telmisartan to ramipril to both. Since the outcomes were not different, this analysis combined all three groups and adjusted for baseline differences. The primary endpoint was CV mortality, myocardial infarction (MI), stroke, or heart failure hospitalization. Secondary endpoints included renal function parameters. They identified four groups based on the percentage of visit blood pressures (BPs) at the two targets (< 25%, 25-49%, 50-74%, and ≥ 75%). All patients had a minimum of seven visits. As the percent of visits with BP control to either target increased, there was a progressive decrease in stroke and albuminuria. However, no difference in MI or heart failure hospitalization was demonstrated. Also, the primary endpoint of total CV events was reduced by increasing the frequency of BP control to the < 140/90 target, but not the 130/80 target. The authors concluded that achieving the guideline target of < 130/80 reduced stroke and improved renal protection, but did not prevent cardiac events. Achieving the < 140/90 target did protect the patients from cardiac events.

■ COMMENTARY

These results are consistent with prior studies. INVEST showed that achieving the lower target BP in diabetics was not associated with fewer CV events. Also, in ACCORD-BP, which studied hypertensive diabetics, achieving a lower target (mean systolic of 119) reduced stroke but not CV mortality or MI. Although the mechanisms for these observations are not revealed in these studies, it is reasoned that the coronary circulation requires a higher BP as compared to the brain and kidney. Thus, lowering diastolic pressure excessively in those with coronary disease would be expected to result in myocardial ischemia.

With regard to lowering BP, there is clearly a J-shaped mortality curve because organ function requires a certain level of perfusion. As the editorial with this article points out, it is unclear whether the point of increased risk is within the usual BPs achieved in clinical practice and whether it is different in patients with various disease. This study, like previous ones, does not show a definite J curve, but rather that there is no further benefit after lowering BP to < 140/90 in cardiac endpoints. However, those at risk for stroke or renal disease may benefit from a target of < 130/80. The authors suggest that in Asians, who have a higher risk of stroke than Caucasians, the lower target may be more appropriate. However, their study does not directly address this issue.

The major weakness of this study is that it is a non-randomized post hoc observational assessment. Any conclusions are hypothesis generating and a randomized outcome study will need to be done to definitively answer the question of BP targets in hypertensive patients. However, at this time, there are few data to support the more aggressive targets. On the other hand, there seems to be little harm in achieving BPs lower than 130/80. Most studies rarely achieve BPs lower than 110/70, so this seems like a safe lower limit for most patients. The real problem in hypertension is getting patients to the accepted level of < 140/90. Most surveys show that only about 50-60% of treated patients achieve this conservative target. At this time, we should be focusing on getting most of our patients to < 140/90 and not worry about lowering their BP too much as long as it is > 110/70. Of course there are going to be exceptions to this. Older patients with diffuse atherosclerosis will tolerate a wider pulse pressure; so a target of < 150/90 may be appropriate with diastolics to 60 acceptable. ■

ABSTRACT & COMMENTARY

Ideal Blood Pressure to Prevent Recurrent Stroke

By Michael H. Crawford, MD, Editor

SOURCE: Ovbiagele B, et al. Level of systolic blood pressure within the normal range and risk of recurrent stroke. *JAMA* 2011;306:2137-2144.

The AHA/ASA 2011 guidelines on stroke prevention in those with a prior stroke or transient ischemic attack (TIA) recommend a blood pressure (BP) target of < 120/80 mmHg. However, the data to support this recommendation are sparse. Thus, these investigators performed a post hoc analysis of the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) to assess the risk of recurrent stroke with maintaining low normal BP as compared to higher BPs. This study included 20,330 patients who had had a nonembolic ischemic stroke within 120 days before randomization to four regimens: aspirin plus dipyridamole vs clopidogrel, or telmisartan vs placebo. The primary endpoint was recurrent stroke. The secondary endpoint was stroke, myocardial infarction (MI), or vascular mortality. Other treatment was at the primary physician's discretion and the mean follow-up was 2.5 years. There was no difference between the therapies in the two comparisons; so all the patients were included in this post hoc analysis of BP levels. The patients were divided into five systolic BP (SBP) groups: very low (< 120), low (120-129), high-normal (130-139), high (140-149), and very high (≥ 150). The primary endpoint was observed in 8% of the very low SBP patients; 7% of the low SBP groups; 7% of the high-normal group; 9% of the high group; and 14% of the very high patients. Compared to the high-normal group, the risk was higher in the very low group (adjusted hazard ratios [HRs] 1.29; 95% confidence interval, 1.07-1.56). Similar results were seen when the high and very high SBP groups were compared to the high normal group. The combined secondary endpoint followed a similar pattern. The authors concluded that in patients with a recent non-embolic ischemic stroke, the SBP associated with the lowest risk of recurrent stroke was 130-139 mmHg. SBPs higher or lower than this range were associated with a higher risk.

■ COMMENTARY

This study defines a SBP sweet spot of 130-139 for preventing recurrent strokes based on adjusted HRs, but there is little penalty for pressures < 130 mmHg. Prior studies have suggested that there is no J curve for stroke prevention in hypertension treatment, but it is unclear how many patients in these studies had prior stroke. This study tends to confirm this perception, but does show a small increase in strokes at very low SBP levels. Thus, the patient with a prior stroke may not benefit from very low SBPs. This may be because they have cerebrovascular disease and need a somewhat higher perfusion pressure, but not usually above a SBP 140 mmHg.

There are several limitations to this study. It is not a randomized trial specifically targeted at the issue of SBP levels and recurrent stroke. The BP data were office based and performed by the primary doctor's staff. Recent studies have shown that research staff-generated BPs are more accurate than usual office BPs, as would be expected. Despite these limitations, aggressive BP lowering has not been proven to prevent recurrent stroke and the authors believe we should roll back our guidelines to < 140/90. ■

ABSTRACT & COMMENTARY

Dronedarone Disappoints

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: Connolly SJ, et al, for the PALLAS Investigators. Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med* 2011;15;365: 2268-2276.

Dronedarone was approved by the FDA in the United States for the treatment of patients with atrial fibrillation (AF) several years ago. FDA approval was largely based on the results of the ATHENA trial, which reported that dronedarone reduced the primary outcome of unplanned hospitalization for cardiovascular causes or death with significant reductions in cardiovascular deaths, stroke, and hospitalization for acute coronary syndromes. In ATHENA, post-study subgroup analysis indicated that even patients who were in AF at all visits showed benefit. This observation led to the design and conduct of the current study. Permanent Atrial Fibrillation Outcome Study Using Dronedarone On Top of Standard Therapy (PALLAS) was designed to test whether dronedarone would reduce major cardiovascular events in patients with permanent AF. Patients were eligible for enrollment if they had permanent AF that had been present for at least 6 months. Eligible patients also had to be at least 65 years of age with one or more of the following risk factors: coronary artery disease, prior stroke of TIA, congestive heart failure (class II or class III or recent admission), a depressed left ventricular ejection fraction, and peripheral arterial disease. Patients older than 75 years of age with hypertension and diabetes were also eligible. Patients were randomly assigned to receive either dronedarone (400 mg twice daily) or matching placebo. Patients were then followed clinically. The first co-primary outcome was a composite of stroke, myocardial infarction, systemic embolism, and death from cardiovascular causes. The second co-primary outcome was unplanned cardiovascular hospitalization or death.

Study enrollment began on July 19, 2010. On July 5, 2011, the study was terminated for safety reasons by the Data Monitoring Committee. At that time, a total of 3236 patients had undergone randomization with a median follow-up of 3.5 months. The patients had a mean age of 75 years and almost 70% had been in permanent AF for more than 2 years. Resting ventricular rates at baseline were well controlled in both groups. The mean $CHADS_2$ score was elevated at 2.9. A slightly higher proportion of patients converted to sinus rhythm during dronedarone therapy, 23 of 621 patients (3.7%), compared to 9 of 638 patients (1.4%) in the placebo group. Mean heart rate was reduced by 7.6 ± 14.5 bpm in the dronedarone group and remained stable in the placebo group. The systolic blood pressure was slightly decreased and the mean corrected QT interval was slightly increased by dronedarone. Serum digoxin concentrations also increased on dronedarone. Before termination of the study, study medication had been permanently discontinued in 21% of 348 dronedarone patients compared to 11% of 178 patients in the placebo group. The first co-primary outcome occurred in 43 patients receiving dronedarone and in 19 patients receiving placebo for a hazard ratio (HR) of 2.29, $P = 0.002$. The second co-primary outcome occurred in 127 patients receiving dronedarone compared to 67% receiving placebo (HR 1.95, $P < 0.001$). Overall, there were 25 deaths in the dronedarone group and 13 in the placebo group. Cardiovascular deaths were noted in 21 dronedarone patients compared to only 10 placebo patients. Stroke occurred in 23 patients in the dronedarone group compared to 10 in the placebo group (HR 2.32, $P = 0.02$). Unplanned cardiovascular hospitalizations were also more common in patients receiving dronedarone (HR 1.97, $P < 0.001$). Other drug-related adverse events included diarrhea, nausea and vomiting, dyspnea, and bradycardia. An elevation of alanine aminotransferase occurred in 21 patients receiving dronedarone (1.5%) compared to 7 (0.5%) receiving placebo. The increased risk for dronedarone on the two co-primary composite outcomes was consistent across all subgroups analyzed.

The authors conclude that among high-risk patients with permanent AF, direct and indirect toxic effects of dronedarone lead to adverse clinical events. There is no apparent benefit of dronedarone in patients who remain in permanent AF.

■ COMMENTARY

The market release of dronedarone in 2009 was welcomed by most physicians who treat patients with AF. Although data suggested that dronedarone might not be as potent as amiodarone in suppressing recurrent AF, the drug appeared to be very well tolerated. The ATHENA trial, the largest antiarrhythmic drug trial ever performed, was also the first trial in which an antiarrhythmic drug was associated with decreased hospitalizations and mortality. Over the last 2 years, however, most of the new data about dronedarone has been negative. There have been at least two cases of fulminant hepatic failure in patients on dronedarone, and liver function test monitoring is now recommended. Interactions with other compounds, including dabigatran, via P-glycoprotein inhibition, were reported. Now the PALLAS study raises questions about cardiac and vascular safety and seems to contradict the favorable results seen in ATHENA. The mechanisms responsible for the adverse events seen in PALLAS are not known. The authors speculate about the role of increased digoxin levels but only about one-third of the patients in PALLAS were taking digoxin. Dronedarone does lower heart

rate during AF and it's possible that lower heart rates may not always be beneficial. Dronedarone might also convert some patients from continuous to intermittent AF and the resulting instability may have adverse consequences.

For now, both the European and U.S. regulators have left dronedarone on the market. However, in my personal practice, I will now restrict it to patients with either no structural heart disease or only uncomplicated, mild hypertension. ■

ABSTRACT & COMMENTARY

New Replacement for Amiodarone?

By John P. DiMarco, MD, PhD

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

SOURCE: Kowey PR, et al, on behalf of the ALPHEE Study Investigators. Efficacy and safety of celivarone, with amiodarone as calibrator, in patients with an implantable cardioverter-defibrillator for prevention of implantable cardioverter-cefibrillator interventions or death: The ALPHEE Study. *Circulation* 2011;124:2649-2660.

Celivarone is a noniodinated analog of amiodarone that is currently in clinical trials. This report gives us data about the effect of celivarone on ventricular arrhythmias in patients with implantable cardioverter-defibrillators (ICDs).

The study was designed to enroll only very high-risk patients. Patients were eligible for inclusion if they had an ICD for primary prevention and had received at least one ICD intervention for ventricular tachycardia (VT) or ventricular fibrillation (VF) in the previous month; if they had an ICD placed for secondary prevention with either a clinical episode VT or VF; or if they had an ICD intervention in the previous month. Patients were also required to have a left ventricular ejection fraction of ≤ 40%. Patients who met entry criteria were randomized to receive, in double-blind fashion, once daily oral celivarone at a dose of 50 mg, 100 mg, or 300 mg daily, amiodarone (600 mg for 10 days followed by 200 mg thereafter), or placebo. Patients were then followed at monthly intervals for 6 months and then every 3 months until completion of the study. Stored electrograms were analyzed by a trained electrophysiologist to classify any ICD interventions as either appropriate or inappropriate. The primary efficacy endpoint for the trial was the occurrence of an appropriate ICD intervention (shock or antitachycardia pacing) or sudden death analyzed using a time to first event approach. A secondary efficacy endpoint was occurrence of all ICD shock, including both appropriate and inappropriate shocks, or death from any cause.

The study enrolled 486 patients and the median duration of treatment was 9 months. The clinical characteristics at baseline were similar in all groups. The mean age was 64 years and 89% were male. The mean left ventricular ejection fraction was 29%, and 86% of the patients had a history of congestive heart failure.

An appropriate ICD intervention or sudden death was experienced by 62% of the patients in the placebo group, by 67%, 59%, and 55% of the patients in the celivarone 50-mg, 100-mg, and 300-mg daily groups, respectively, and by 45% of the patients in the amiodarone group. There were six sudden deaths in the trial with one in the placebo group, one in the celivarone 300 mg group, and four in the amiodarone group. None of the hazard ratios (HRs) for the primary endpoint were significantly different for any of the celivarone group vs the placebo group. There was a trend toward a decrease in the primary endpoint in the amiodarone group (HR = 0.7, P = 0.13). Life table analysis of the time to the primary endpoint showed no statistically significant differences between the curves for any of celivarone groups and the placebo group. For the secondary endpoint, the proportion of patients experiencing any ICD shock or death was 44% in the placebo group, 45%, 37%, and 42% in the celivarone, 50-mg, 100-mg, and 300-mg groups, respectively, and 26% in the amiodarone group. Although shocks were less frequent in the amiodarone group, all-cause mortality was increased in this group. There were 14 deaths in the amiodarone group with a HR vs placebo of 3.327. In general, celivarone was reasonably well tolerated. The most common treatment emergent adverse events were recurrent ventricular arrhythmias and neurological events. Adverse events related to the gastrointestinal, pulmonary, endocrine, and musculoskeletal systems were not increased in the celivarone groups vs placebo.

The authors conclude that in this study celivarone at any of the three doses was not effective in

preventing ventricular arrhythmia-triggered ICD interventions. Although amiodarone was effective in preventing ICD interventions, an increase in mortality rate greater than placebo was noted in the amiodarone group.

■ COMMENTARY

The results in this study will probably end the celivarone development program as an antiarrhythmic drug. Two earlier Phase II trials using celivarone in patients with atrial fibrillation had also shown no significant benefit. This large and extremely well-done trial using ICD interventions in a very high-risk population as the most important endpoint also clearly shows no benefit. This is an extremely disappointing result since there is an important unmet clinical need for well-tolerated agents that can decrease ICD shock frequency and thereby improve the tolerability of ICD therapy. Celivarone, which was designed to avoid the risks of thyroid dysfunction and organ toxicity associated with tissue accumulation seen with amiodarone, had been regarded as a potentially useful new agent.

The other important observation in this trial is that there were trends for increase in both sudden death and total mortality seen in the amiodarone group. This was seen despite the observation that amiodarone decreased the frequency of both appropriate and inappropriate shocks. A similar signal was also seen in patients with Class III heart failure in the Sudden Cardiac Death — Heart Failure Trial but has not been seen in other studies using amiodarone. However, the observation here should make clinicians think twice before they start amiodarone in patients with advanced heart failure. It also raises questions about the use of a reduction in ICD therapies as an endpoint in a study of an antiarrhythmic drug. To my knowledge, this is the first time that a decrease in ICD shocks has been associated with an increase in mortality. ■

CME Questions

1. Celivarone as compared to amiodarone in heart failure patients with an ICD resulted in:
a. lower total mortality.
b. fewer ICD shocks.
c. less ventricular tachyarrhymias.
d. None of the above

2. Maximum doses of rosuvastatin vs atorvastatin resulted in:
a. higher LDL levels.
b. higher HDL levels.
c. lower triglyceride levels.
d. improved plaque regression.

3. Lowering blood pressure to < 130/80 vs 140/90 resulted in:
a. fewer myocardial infarctions.
b. fewer strokes.
c. less albuminuria.
d. B and C

4. A lower risk of recurrent stroke was observed in a study at which systolic blood pressure levels?
a. < 120
b. 120-129
c. 130-139
d. 140-149

5. What percent of patients with known CAD were not treated with statins in a recent survey?
a. 1 in 3
b. 1 in 4
c. 1 in 5
d. 1 in 6

6. Dronedarone vs placebo in patients with permanent atrial fibrillation resulted in:
a. less atrial fibrillation.
b. lower mortality.
c. fewer strokes.
d. A and C

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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Barrett's Esophagus: What's the Risk?

Source: Hvid-Jensen F, et al. Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med* 2011;365:1375-1383.

FOR UNKNOWN REASONS, ADENOCARcinoma of the esophagus (E-ca) is experiencing the most rapid increase of any known cancer in the United States. Although the absolute incidence of E-ca pales next to lung, prostate, or breast cancer, the inexplicable proliferation of this cancer has spurred increased scrutiny of at-risk individuals. Barrett's esophagus, which is felt to represent an attempt at protective epithelial remodeling in response to the trauma of acid exposure, occurs in as many as 10% of individuals undergoing endoscopy for symptoms of GERD. Once Barrett's is identified, consensus group guidelines suggest ongoing surveillance, despite the absence of outcomes trials indicating that such surveillance improves survival.

The Danish Pathology Registry and Cancer Registry provide an opportunity to review data accrued for the entire population of Denmark. Follow-up of persons with Barrett's esophagus (n = 11,029) over a median of 5.2 years of observation identified 197 cases of E-ca, for an annual incidence of 0.12%. Likelihood of developing E-ca was increased in persons with higher degrees of dysplasia. Based on these data, the authors suggest that ongoing surveillance of Barrett's esophagus might wisely be limited to those with demonstrated dysplasia, since the incidence of E-ca in persons without dysplasia was so very low. ■

Life Expectancy: The Japanese Are #1

Source: Murray CJ. Why is Japanese life expectancy so high? *Lancet* 2011; 378:1124-1125.

EVEN THOUGH JAPAN SPENDS ESSENTIALLY half of what the United States spends on health care (8.5% of their gross domestic product vs 16.4% of ours), they have ranked No. 1 in life expectancy for 30 years. To what might we attribute their success?

That Japan provides universal health coverage can certainly be responsible for a portion of their favorable outcomes, but other factors are also at play. For instance, Japanese public health programs to reduce salt intake and become more aggressive about blood pressure control are credited with substantial reductions in stroke. Indeed, such Japanese hypertension programs have evoked a substantial decline in blood pressure among the population as a whole, especially in women (the gender in which successful blood pressure control is conspicuously less prominent in the United States).

Although it is difficult to measure the direct impact of one additional factor — educational attainment — on health, epidemiologic surveys do consistently indicate a linear relationship between education and positive health outcomes. The generally high educational attainment among Japanese may be a critically important factor.

Current health trends suggest that Japan may not stay in the No. 1 slot: Inadequate tobacco control and a rising BMI among the population, unless counteracted, may incur similar health decrements as have been seen in other nations. ■

The Calcium/Cardiovascular Disease Link

Source: Sabanayagam C, Shankar A. Serum calcium levels and hypertension among U.S. adults. *J Clin Hypertens* 2011;13:716-721.

THE RELATIONSHIP BETWEEN CALCIUM INtake — through diet and/or supplements — and vascular health is complex. Some recent epidemiologic surveys have found a positive association between calcium supplements and adverse cardiovascular (CV) outcomes, as well as vascular calcification (i.e., more CV disease and calcification with calcium supplementation than without). Because hypertension (HTN) is the most common vascular antecedent to adverse CV events, investigation of the relationship of calcium to blood pressure (BP) is pertinent.

The National Health and Nutrition Examination Survey (NHANES) has published cross-sectional data from diverse populations throughout the United States for more than 30 years. The authors obtained data from the NHANES population (n = 12,403) of adults over age 20 seeking to examine the relationship between serum calcium levels and BP.

Persons in the highest quartile of serum calcium were 1½ times more likely to have HTN than those in the lowest quartile. Even when adjusted for age, race, alcohol, body mass index, cholesterol, C-reactive protein, glomerular filtration rate, serum albumin, vitamin D,

and phosphorus, the relationship between calcium and BP remained.

Several mechanisms through which calcium might incur increased risk of HTN have been offered, including a direct vascular effect, parathyroid activity, and renal vasoconstriction. Before concluding that calcium is simply a "bad guy," it is important to recognize that several reports have shown that *dietary* calcium is *inversely* related to HTN. ■

What Factors Lead to Acquisition of *Clostridium difficile*?

Source: Loo VG, et al. Host and pathogen factors for *Clostridium difficile* infection and colonization. *N Engl J Med* 2011;365:1693-1703.

The toxicity associated with intestinal habitation by *Clostridium difficile* ranges from asymptomatic colonization to life-threatening infection. In the United States, *C. difficile* is the most common cause of health care-associated diarrhea. Although the association of *C. difficile* with use of antibiotics and/or hospitalization is clear and well established, why certain individuals fall prey to infection/colonization — whereas most do not — remains ill-defined.

Loo et al performed a prospective study of patients admitted to Canadian hospitals over 15 months (n = 4143). Subsequent to hospital admission, *C. difficile* infection was identified in 2.8% (n = 117) and colonization in 3% (n = 123); excluded from these numbers were the 4.4% of individuals who were already *C. difficile* colonized upon admission.

As has been noted in previous observational studies, older age, antibiotic use, and use of proton pump inhibitors (PPI) or histamine-type 2-receptor antagonists (H2RA) were each associated with *C. difficile* colonization and infection. The mechanism by which PPI/H2RA use is associated with *C. difficile* remains speculative, but is attributed to disturbance of bacterial flora. Whether more restraint in use of antibiotics, PPI, or H2RA medications will reduce the incidence of serious *C. difficile* infections remains to be determined. ■

The Relationship Between Sleep and Hypertension

Source: Bansil P, et al. Associations between sleep disorders, sleep duration, quality of sleep, and hypertension: Results from the National Health and Nutrition Examination Survey, 2005 to 2008. *J Clin Hypertens* 2011;13:739-743.

It is probably obstructive sleep apnea (OSA) with which clinicians most familiarly associate hypertension (HTN). Indeed, some recent trials have found a remarkably high prevalence of previously unsuspected OSA in persons with resistant HTN. What about other sleep variances, such as persons with sleep movement disorders (e.g., restless legs, sleep apnea), short sleep (< 7 hrs/night), or poor sleep? The authors report on data obtained through the most recent National Health and Nutrition Examination Survey obtained through direct interview with 10,308 adults.

Overall, persons with HTN were statistically significantly more likely to have a sleep disorder than normotensive individuals (11% vs 6%). "Poor sleep" did not appear to be a relevant factor, but less than 7 hours of sleep nightly was. No gender or ethnicity differences were detected.

In contrast to prior data sets, this study did not find a consistent relationship specifically with sleep disorders and HTN. Rather, it was in persons who reported both a sleep disorder *and* short sleep that risk of HTN rose steeply: this combination was associated with more than a doubling of risk. Finally, the authors also note that more than two-thirds of persons with sleep problems had not discussed their issues with a health professional. ■

DPP4 Inhibitors are Associated with Reduced Risk of Hip Fracture

Source: Monami M, et al. Dipeptidyl peptidase-4 inhibitors and bone fractures: A meta-analysis of randomized clinical trials. *Diabetes Care* 2011;34:2474-2476.

In an era where concern about adverse consequences of pharmacotherapy on bone health are prominent — proton pump inhibitors associated with increased risk of hip fracture, bisphosphonates associated with an increased risk of spiral femoral fractures, and even thiazolidinediones noted to increase fracture risk — a more sanguine headline is certainly welcome.

The dipeptidyl peptidase-4 inhibitors (DPP-4) currently include three agents: sitagliptin, saxagliptin, and linagliptin, each of which provides a fairly similar degree of glucose reduction. The physiologic activity of GLP-1 (the primary pathway through which DPP-4 treatment enhances glucose control) includes activation of osteoblasts and inhibition of osteoclasts. Animal studies have shown that DPP-4 agents actually increase bone density, but no large, long-term clinical trial has confirmed a relationship between DPP-4 and fractures in humans.

Monami et al performed a meta-analysis on trials of DPP-4 inhibitors lasting 6 months or longer from which data on fractures was able to be extracted. Based on 28 trials of DPP-4 treatment (n = 11,880) vs comparator (n = 9175), the odds ratio for fracture was 40% less in persons receiving DPP-4 than in comparator. DPP-4 appear to have a protective effect on bone. ■

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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, Travel Medicine Advisor.*

Rivaroxaban Now Approved for Stroke Prevention

In this issue: New indication for rivaroxaban; new study on warfarin testing; medications causing adverse drug events; niacin as an add-on therapy; and FDA actions.

Rivaroxaban for atrial fibrillation patients

Rivaroxaban (Xarelto), Janssen Pharmaceutical's once-a-day oral Xa inhibitor, has been approved for reducing the risk of stroke in patients with atrial fibrillation. The drug was previously approved for prophylaxis of deep vein thrombosis in patients undergoing hip or knee replacement. Rivaroxaban is the second "non-warfarin" oral anticoagulant to be approved for this indication after the direct thrombin inhibitor dabigatran (Pradaxa). The approval was based on the ROCKET AF trial, a double-blind, randomized, noninferiority comparative trial with warfarin, which showed a rate of stroke or systemic embolism of 2.1% per year for rivaroxaban and 2.4% per year for warfarin. The study looked at 14,000 patients over 700 days of follow-up. Rates of major and non-major bleeding were the same with the two drugs, although the rate of intracranial hemorrhage was lower for rivaroxaban while the rate of GI bleeding was lower with warfarin. ROCKET AF showed noninferiority of rivaroxaban vs warfarin but not superiority (*N Engl J Med* 2011;365:883-891). The approval sets up a major marketing showdown between Janssen and Boehringer Ingelheim, the manufacturer of dabigatran, for this multibillion dollar market. Meanwhile, Pfizer and Bristol-Myers Squibb are jointly developing a third drug — apixaban, also a factor Xa inhibitor — which is undergoing an "accelerated review" by the FDA with approval likely in March 2012. All three drugs have the potential disadvantage of the lack of an antidote, a problem that seems to be plaguing dabigatran with more than 250 fatal bleeding episodes reported worldwide since the drug was approved in 2010. A recent report suggests that prothrombin complex concentrate may be an effective reversal agent for rivaroxaban but not dabigatran (*Circulation* 2011;124:1573-1579). ■

Warfarin testing every 12 weeks?

One of the major disadvantages of warfarin over the newer anticoagulants is the need for frequent prothrombin time monitoring and dose adjustment. Most guidelines recommend a maximum interval of 4 weeks between testing. A new study suggests that stable patients may be safely tested at 12-week intervals. A total of 226 patients who were on a stable dose of warfarin for at least 6 months were assigned to testing every 4 weeks, while the other half had blood tests done every 4 weeks, but sham INRs within the target range were reported for two of the three 4-week periods. The percentage of time in the therapeutic range was 74.1% in the 4-week group compared with 71.6% in the 12-week group (noninferiority $P = 0.020$ for a 7.5% point margin). Patients in the 12-week group had fewer dose changes and secondary outcomes, including major bleeding, thromboembolism, and death that were no different between the two groups. The authors conclude that assessment of warfarin dosing every

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12 weeks seems to be safe and noninferior to assessment every 4 weeks, although they recommend further study (*Ann Intern Med* 2011;155:653-659). This study is important given the marked cost differential between warfarin and dabigatran or rivaroxaban. Some patients, especially if they pay for their own medications, may opt to remain on warfarin if they are on a stable dose, especially if they only require testing four times a year. ■

Adverse drug events in the elderly

Although low cost, warfarin remains one of the most dangerous medications in common usage. In fact, hospitalizations for adverse events in the elderly are much more likely to be caused by commonly used medications, such as warfarin, rather than medications classified as high risk in the elderly, according to a new study from the CDC. Researchers used a national database of adverse drug events from 2007-2009 to estimate the frequency and rates of hospitalization after emergency department visits for adverse events in older adults to assess the risk of specific medications causing this hospitalization. It is estimated that adverse drug events led to nearly 100,000 hospitalizations during the 2-year period with nearly half among adults 80 years of age or older. Nearly two-thirds of the hospitalizations were due to unintentional overdoses. Four medications or medication classes were implicated alone or in combination in 67% of hospitalizations including warfarin (33.3%), insulins (13.9%), oral antiplatelet agents (13.3%), and oral hypoglycemic agents (10.7%). High-risk medications were implicated in only 1.2% of hospitalizations. The authors suggest that efforts to promote the safe management of antithrombotic and antidiabetic agents have the potential to substantially reduce harm to our older patients (*N Engl J Med* 2011;365:2002-2012). This study points out that we may be spending too much effort in managing "high-risk" medications in the elderly, while warfarin alone is responsible for a third of medication-related hospitalizations. ■

Is it time to retire niacin?

An editorial published online in the *New England Journal of Medicine* asks, "Niacin at 56 Years of Age — Time for an Early Retirement?" Retirement may be the logical next step after publication of the AIM-HIGH trial (see *Pharmacology Watch* July 2011), the National Heart Lung and Blood Institute's trial comparing niacin plus intensive statin therapy with intensive statin therapy alone in patients with established cardiovascular disease. The study was halted early when it was found that the addition of 1500-2000 mg of niacin per day to simvastatin, despite significantly raising HDL levels an average of 7 points, had no effect on the primary endpoint, which was a composite of the rate of death from coronary artery disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven coronary or cerebral revascularization (primary endpoint 16.4% niacin group, 16.2% placebo group; $P = 0.79$) (*N Engl J Med* published online November 15, 2011). The accompanying editorial suggests there is lack of evidence to support niacin as an add-on therapy in patients with cardiovascular disease who have well-controlled LDL cholesterol levels. Additionally, long-acting niacin is relatively expensive and frequently causes flushing — two additional factors that argue against continued use of the drug except, perhaps, in patients who are intolerant of statins (*N Engl J Med* published online November 15, 2011). ■

FDA actions

The news isn't much better for fenofibrate. The FDA has issued a safety communication for the cholesterol lowering medication stating that the drug may not lower the risk of major cardiovascular events based on data from the ACCORD Lipid trial. ACCORD (similar in design to AIM-HIGH) evaluated the efficacy and safety of fenofibrate plus simvastatin vs simvastatin alone in patients with type 2 diabetes. There was no significant difference in the risk of experiencing a major adverse cardiac event between the two groups, and women may have even experienced an increase in the risk for major adverse cardiac events with combination therapy vs simvastatin alone. The FDA is requiring the manufacturer of Trilipix brand fenofibric acid to conduct a clinical trial to evaluate the cardiovascular effects of the drug in patients at high risk for cardiovascular disease who are already taking statins (www.fda.gov/Drugs/DrugSafety/ucm278837.htm).

The FDA has approved a new formulation of zolpidem for treatment of insomnia in patients who wake up in the middle of the night and have difficulty returning to sleep. Zolpidem, originally marketed as Ambien and now available as a generic, is a short-acting hypnotic. The new product is a lower dose sublingual formulation that comes in a 1.75 mg dosage recommended for women and 3.5 mg for men. The lower dose for women is recommended because women clear the drug more slowly than men. It can be used if the patient has at least 4 hours of bedtime remaining. Zolpidem sublingual is marketed by Transcept Pharmaceuticals as Intermezzo. ■

Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

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2011 Subject Index: Volume 30, Numbers 1-12

AHC Media

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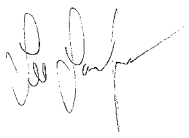

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