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Financial Disclosure:

Clinical Cardiology Alert's physician editor, Michael H. Crawford, MD, is on the speaker's bureau for Pfizer. The peer reviewer, Rakesh Mishra, MD, reports no consultant, stockholder, speaker's bureau, or other financial relationship with any company related to this field of study.

Diabetes and Revascularization Techniques: Some Good News!

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

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Dr. Abrams serves on the speaker's bureau for Merck, Pfizer, and Parke-Davis.

Source: Daemen J, et al. Multivessel coronary revascularization in patients with and without diabetes mellitus: 3-year follow-up of the ARTS-II (Arterial Revascularization Therapies Study-II) trial. *J Am Coll Cardiol*. 2008;52:1957-1967.

DIABETICS ARE KNOWN TO HAVE HIGHER RATES OF RESTENOSIS after revascularization than non-diabetic subjects. Controversy about whether bare-metal stents (BMS) or coated stents (drug eluting with sirolimus) are better in diabetics, and the superior outcomes of coronary artery bypass graft surgery (CABG) in diabetics when compared to BMS remains to be seen. The older ARTS-I trial and other trials have demonstrated that CABG is superior to BMS in multivessel disease, particularly in diabetics. ARTS-II represents a more recent trial to assess percutaneous revascularization (PCI) with sirolimus-eluting stents (SES), comparing outcomes with CABG and PCI with BMS in ARTS-I; safety and efficacy were the primary endpoints. Non-diabetics and diabetics in ARTS-II were followed for three years, using the results of CABG and BMS in ARTS-I as a historical comparison.

ARTS-I was a multi-center European study that enrolled 1,200 patients from April 1997 to June 1998 in two groups: BMS and PCI, and CABG. In ARTS-II, 607 patients were enrolled between February 2003 and November 2003. The primary endpoints in ARTS-II were safety and efficacy of SES in comparison to CABG and BMS in ARTS-I subjects over three years. The primary efficacy endpoint was a composite of death, MI, CVA, and repeat revascularization. Enrolled patients had to have at least two severe lesions in different epicardial vessels. CK-MB measurements were used, but troponin data was not available. The ARTS-II cohort had more three-vessel disease patients, type C lesions, and more stents per patient than ARTS-I patients.

VOLUME 28 • NUMBER 2 • FEBRUARY 2009 • PAGES 9-16

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Results: The primary endpoint was significantly lower in the ARTS-II cohort (OR 0.41, CI 0.26 to 6.4) compared to ARTS-I PCI, and was similar to ARTS-I CABG. Also, death, MI, and stroke were significantly lower in ARTS-II vs ARTS-I PCI (OR 0.55, CI 0.34-0.91) and ARTS-I CABG (0.56, CI 0.35-0.92).

ARTS-II diabetics had higher rates of hypertension and elevated cholesterol compared to ARTS-I subjects. ARTS-II patients had more high-risk individuals, with more three-vessel disease, type C lesions, and more stents utilized. The primary endpoint in ARTS-II was similar to ARTS-I PCI and CABG. However, death, MI, and stroke rates were lower in ARTS-II patients as compared to ARTS-I PCI (OR 0.72), and similar to, ARTS-I CABG. Insulin-using diabetics had worse outcomes (but low numbers of patients after adjustment). Diabetes was the strongest predictor of major events in ARTS-II. The incidence of major events in diabetics was significantly higher than in non-diabetic patients, driven mostly by repeat revascularization. Surprisingly, stent thrombosis at three years was similar in ARTS-II diabetic and non-diabetic patients (6.9% vs 6.3%), but 23% of ARTS-II diabetics with a major event had stent thrombosis. In ARTS-II, at three years, diabetics had an 81% increased risk for repeat revascularization compared to non-diabetics, but lower than that observed in the ARTS-I CABG group. There was a 44% lower need for repeat revascularization in ARTS-II diabetics. Overall, there was a 70% higher risk for major events in diabetics compared to non-diabetics in ARTS-II. Stent thrombosis was 3.8%, equal in both groups of patients. Daemen et al concluded that PCI with SES or CABG is safer and more efficacious than PCI with BMS in diabetics, as well as non-diabetics.

■ COMMENTARY

The finding that coated stents in diabetic patients with multivessel disease may level the playing field vs CABG, reflects an important improvement in the revascularization approach to diabetics with severe CAD. Considerable older data have demonstrated poorer clinical outcomes in CABG-treated, multivessel-disease diabetic patients. However, not all reports have found differences in mortality with PCI or CABG in diabetics. ARTS-II, a comparative report on PCI in CAD patients with and without diabetes, does appear to support improved clinical outcome in diabetics with drug-eluting stents.

The data in ARTS-I and in ARTS-II reflect older studies (ie. 10 years ago in ARTS-I (no coated stents) and 5-6 years ago in ARTS-II) using PCI patients receiving SES. Troponin levels were not obtained and/or reported, making the identification of non-ST-elevation MI in subjects difficult. Multiple factors in diabetes (small vessel size, increased platelet activity, aggressive atherosclerosis, higher restenosis rates, and decreased survival) vs non-diabetics are all well documented. This report is not surprising, confirming a true advantage for SES in diabetics. This seems reasonable, although controversy over surgical revascularization and contemporary PCI remains in diabetes.

Daemen et al emphasize that many current trials are underway to further delineate the relationships of PCI and CABG. Studies to be watched for as to whether or not PCI with SES or paclitaxil stents is truly equivalent to CABG include: FREEDOM, CARDIA, SYNTAX. At present, PCI using SES, or perhaps paclitaxil, could be a genuine alternative to CABG. The results of large-scale, randomized trials are eagerly awaited to validate these findings. ■

Cilostazol Reduces Restenosis and Repeat Procedures after Peripheral Arterial Interventions

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

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

Clinical Cardiology Alert, ISSN 0741-4218, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

ASSOCIATE PUBLISHER Russ Underwood.
MANAGING EDITOR: Leslie Hamlin.
MARKETING PRODUCT MANAGER: Schandale Kornegay.

GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Clinical Cardiology Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $42. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Source: Soga Y, et al. Efficacy of cilostazol after endovascular therapy for femoropopliteal artery disease in patients with intermittent claudication. *J Am Coll Cardiol*. 2009;53: 48-53.

Percutaneous intervention for peripheral arterial disease (PAD) results in improvement in claudication symptoms but is complicated by a high rate of restenosis. Cilostazol is an anti-platelet agent that also has anti-restenosis effects, and has been shown to reduce restenosis from bare-metal stents in coronary arteries. Whether cilostazol can reduce restenosis following endovascular therapy (EVT) in peripheral arterial disease is not known.

Accordingly, Soga et al performed a randomized, multi-center, open-label clinical trial of cilostazol 200 mg/day vs placebo for two years following EVT of symptomatic de novo femoral artery lesions. The study was performed in Japan, and 78 patients, ages 18-80 years, with claudication due to a > 50% femoropopliteal lesion, without any inflow lesion, and with a patent outflow artery, were included. Ankle-brachial pressure indices were < 0.9. Exclusion criteria included prior lower extremity bypass surgery, prior EVT in the femoropopliteal region, acute limb ischemia, or severe symptoms. All patients were taking low-dose aspirin and ticlopidine prior to the procedure, with aspirin continued long-term and ticlopidine continued for four weeks post-EVT. Balloon angioplasty was performed for 60 seconds, followed by implantation of self-expanding stents for residual stenoses of > 30%, or flow-limiting dissections. Patients were followed clinically, as well as with Duplex ultrasonography. The primary endpoint was freedom from target vessel revascularization (TVR) after two years, with secondary endpoints of binary restenosis rate, freedom from target lesion revascularization (TLR), and major adverse cardiac events (MACE — death, nonfatal MI, stroke, percutaneous or surgical repeat revascularization, and leg amputation).

Patients receiving cilostazol (n = 39) or placebo (n = 39) were well-matched in terms of baseline clinical and procedural characteristics. Approximately 80% were male, 35% diabetic, 40% current smokers, and the average age was 70 years. The average lesion lengths were approximately 125 mm, and the pre-procedure stenosis severity was 78%; post stenosis 26%. The percentage of patients receiving stents was 41% in the cilostazol group and 51% in the control group. There was no difference in the incidence of occluded vessels or stent fracture. Cilostazol therapy resulted in a significant reduction in the primary outcome of repeat revascularization. After 24 months, the freedom from TLR and TVR was significantly higher in the cilostazol group than in the control group (87.2% vs 67.6%, $p < 0.05$; 84.6% vs 62.2%, $p = 0.04$, respectively). Binary restenosis was found in 43 (55.1%) patients (cilostazol 43.6% vs control 70.3%; $p = 0.02$), and eight had complete occlusion (cilostazol, 5.1% vs control, 16.2%; $p = 0.12$). Freedom from MACE was also significantly higher in the cilostazol group compared with the control group (79.5% vs 48.7%, $p = 0.006$). The resting ankle-brachial pressure index was significantly better at 24 months in the cilostazol group compared with the control group (0.81 vs 0.72, $p < 0.05$). Importantly, 89.7% of the cilostazol group took the drug as directed. Cilostazol was stopped in two patients for palpitations, and two other patients stopped or reduced the dose of the drug themselves. Soga et al concluded that cilostazol, in combination with aspirin, reduces restenosis and repeat revascularization after EVT for femoropopliteal disease in claudicant patients.

■ COMMENTARY

Cilostazol is approved by the FDA at a dose of 100 mg twice daily for use in PAD. It has been shown to improve claudication symptoms in medically managed PAD and to reduce restenosis in bare-metal coronary artery stents. This study adds to the current literature by showing that cilostazol reduces restenosis in PAD managed by percutaneous intervention. Patients with PAD are at high risk of acute coronary syndromes, and stroke and anti-platelet therapy can reduce these risks. In this study, the benefits of cilostazol on restenosis and MACE were in addition to aspirin therapy. Stented patients received ticlopidine for four weeks after the procedure only. It is not known whether the benefits of cilostazol would persist in addition to longer-term ticlopidine, or in combination with clopidogrel, which is the more commonly used thienopyridine in the United States. Many PAD patients will be taking dual anti-platelet therapy for co-existent coronary or cerebrovascular disease, and it is not clear if the current results can be extrapolated to these patients.

It bears mentioning that cilostazol can precipitate or worsen heart failure, and is, therefore, contraindicated in patients with any degree of heart failure. Soga et al do not mention whether they screened patients for heart failure prior to enrollment, nor whether any heart failure developed during follow-up, but there was no excess of mortality in the cilostazol group. In addition, although this was a prospective, randomized study, it was open-label, which can introduce some reporting bias. Furthermore, the use of stents, and the type of stents used, was at the operators' discretion, which may also introduce some bias. Despite these limitations, this study adds to our knowledge base for PAD, and may help avoid restenosis and costly repeat procedures in patients undergoing peripheral interventions. ■

Posterior ECG Leads Improve the Detection of Left Circumflex Coronary Artery Occlusion

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

Source: Aqel RA, et al. Usefulness of three posterior chest leads for the detection of posterior wall acute myocardial infarction. *Am J Cardiol*. 2009;103:159-164.

Optimal management of transmural myocardial infarction (MI) depends on rapid reperfusion of the occluded infarct artery. Therefore, accurate early diagnosis is the cornerstone of initial patient assessment in the emergency department. It is recommended that a standard 12-lead electrocardiogram (ECG) be performed within 10 minutes of presentation to diagnose ST-elevation MI, but diagnosis of infarction in the left circumflex coronary artery (LCCA) territory remains difficult. In a significant number of patients with LCCA occlusion, the standard 12-lead ECG may show no ST-elevation at all, and these patients may, therefore, not be referred for urgent reperfusion. Accordingly, Aqel et al performed a study to determine the utility of using three posterior chest leads to detect ischemia in the LCCA territory.

They studied 53 consecutive patients undergoing clinically indicated percutaneous coronary intervention (PCI) of the LCCA. Standard 12-lead ECGs were performed, and they also recorded tracings from three posterior leads, V7, V8 and V9, in the left posterior axillary line at the 5th interspace, at the left midscapular line at the 5th interspace, and at the left paraspinal border at the 5th interspace, respectively. They excluded patients with ST-elevation MI, previous coronary artery bypass surgery, and uninterpretable baseline ECGs. After the baseline 15-lead ECG was recorded, the angioplasty balloon was inflated in the LCCA for 120 seconds. The 15-lead ECG was performed after balloon inflation and then every 30 seconds. ECGs were analyzed by two cardiologists. Because there is controversy regarding the cut-off for ST-elevation in the posterior leads, with some advocating 1 mm and others suggesting 0.5 mm; Aqel et al analyzed their data using both cutoffs.

Their patients were recruited at a Veterans Affairs Medical Center, were all male, 63 ± 9 years of age, 47% were diabetic, 34% had prior MI, and 47% had prior PCI. The procedural indication was stable angina in 43%, unstable angina in 43%, and non-ST-elevation MI in 13%. Importantly, there were no collaterals to the distal LCCA territory observed in any patient. The site of balloon occlusion was ostial or proximal in all patients. The posterior leads showed more ST elevation than any of the standard 12 leads ($p < 0.0001$). Using a cutoff of 1 mm S elevation in two contiguous leads, the use of posterior leads increased the detection of LCCA occlusion from 34% to 62%. Using a cutoff of 0.5 mm ST elevation in two contiguous leads, the use of posterior leads increased the detection of LCCA occlusion from 38% to 74%. If 0.5 mm is detected in any lead, the rate of detection of LCCA occlusion is increased from 47% to 77%. Aqel et al conclude that the 15-lead ECG identified more patients with posterior myocardial wall ischemia because of temporary balloon occlusion of the LCCA than the 12-lead ECG. This information may enhance the detection of posterior MI in the emergency department, and potentially facilitate early institution of reperfusion therapy.

■ COMMENTARY

This study is consistent with previous studies that have shown very poor sensitivity of standard 12-lead ECGs in detecting posterior MI due to LCCA occlusion. The data suggest that addition of the posterior leads to the standard 12 leads results in an approximate doubling of the diagnosis of LCCA occlusion. This is a rapid and inexpensive test that can be easily performed in the emergency room, and may enhance diagnosis of posterior ischemia in patients with an otherwise normal ECG. This may, in turn, facilitate earlier reperfusion in this patient cohort. Thus, the presence of a normal 12-lead ECG in patients whose symptoms are very suggestive of MI should prompt further investigation with extra ECG leads, or even an echocardiogram.

Several limitations of this study should be noted. First, the patients were all male, VA patients, and were predominantly Caucasian. Therefore, the results may not be applicable to all patient subgroups. Second, the balloon inflations were all ostial or proximal and, therefore, the sensitivity for ischemia caused by more distal LCCA occlusion may be lower than seen in this study. Third, the duration of ischemia was short, only two minutes. Although ECG changes usually occur early within this time frame, differences from clinical thrombotic occlusion of the LCCA with thrombus propagation over time may not be appreciated in this type of study. Despite these limitations, this study serves as a reminder that the standard 12-lead ECG has poor sensitivity for detecting LCCA occlusion, and that posterior leads may approximately double this sensitivity. ■

Perioperative Beta Blockers

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Bangalore S, et al. Perioperative beta blockers in patients having non-cardiac surgery: a meta-analysis. *Lancet*. 2008;372:1962-1976.

THE ACC/AHA GUIDELINES RECOMMEND PERIOPERATIVE beta blockers for those already on them, patients undergoing vascular surgery, or those having intermediate- to high-risk surgery with established coronary heart disease, or at high risk of having it. However, recent studies have shown no beneficial effect of perioperative beta blockers and potential for harm. Thus, Bangalore et al conducted a meta-analysis of randomized, controlled trials of safety and efficacy outcomes of perioperative beta blockers assessed for 30 days post-non-cardiac surgery. The efficacy outcomes of interest were total mortality, cardiovascular mortality, myocardial infarction, stroke, and heart failure. The safety outcomes of interest were bronchospasm, bradycardia, and hypotension. The selection criteria were met by 33 trials out of 112 surveyed, and included over 12,000 patients. Beta-blocker therapy did not result in any significant reduction in total mortality, cardiovascular mortality, or heart failure, but did reduce myocardial infarction (OR = 0.65, 95% CI 0.54-0.79, NNT 63). However, stroke was increased (OR = 2.0, 1.27-3.68, NNH = 293), as was bradycardia (NNH = 22) and hypotension, requiring therapy (NNH = 17); bronchospasm was not affected. An assessment of the trial methodology showed that only 13 had a low risk of bias. The beneficial results for myocardial infarction were driven by the 20 trials with a high risk of bias. Bangalore et al concluded that randomized trial data do not support the use of beta blockers preoperatively to prevent cardiovascular events in non-cardiac surgery patients.

■ COMMENTARY

Although I am not a big fan of meta-analyses, this one was very carefully done, and raises some interesting points. First, it exhibits how few excellent trials on this topic exist. Out of 112 reports of randomized, controlled trials of perioperative beta-blocker use with 30-day outcome data, only 33 met their quality inclusion criteria. Of those, only 13 were considered low risk for bias. The large, positive trial of Poldermans et al,[1] published in the *New England Journal of Medicine*, drove the positive data about outcomes with beta blockers, but was considered highly biased by Bangalore et al because many of the high-risk patients they studied should have been on beta blockers for other indications (eg, heart failure, post myocardial infarction); in the Poldermans study, myocardial infarction decreased 44%. Second, much of the negative data on beta blockers were driven by the POISE study,[2] which was considered low risk for bias. If POISE is eliminated, the reduction in myocardial infarction increases from 35% to 53% with beta blockers. Bangalore et al correctly point out that the doses of beta blockers used in POISE was eight times the equivalent dose of the agent used in the Poldermans study. Thus, some of the negative effects in POISE may have been due to giving such a large dose of beta blockers to beta-blocker naive patients. Third, sensitivity analyses showed that outcomes were better if beta blockers were titrated to a heart rate of < 75 beats/min and if they were administered for 24 hours or less. The latter is interesting since the largest percentage of perioperative events are thought to occur 48-120 hours after surgery.

So what do we do with this new data? It seems clear that if your patient is already on beta blockers for clear indication, he/she should stay on them. Those who should be on beta blockers for other reasons should be started on them early enough to titrate the dose to appropriate levels prior to surgery. All others should be considered on a case-by-case basis. For example, someone with known coronary artery disease, or who is highly likely to have it, and is undergoing high-risk surgery, may be an acceptable candidate, if he/she seems able to tolerate beta blockers. It is always ideal to have a few weeks to start therapy. The higher risk of beta-blocker complications in POISE was associated with the administration of high doses without titration just before surgery. This is probably not a good idea. Also, I agree with Bangalore et al that perioperative beta blockers should not be a practitioner performance measure until the issue is clarified further. ■

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Cardiac Resynchronization in Mild Heart Failure Patients

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

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Dr. DiMarco is a consultant for Novartis, and does research for Medtronic and Guidant

Source: Linde C, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol*. 2008;52:1834-1843.

The resynchronization reverses remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial tested the hypothesis that cardiac resynchronization therapy (CRT) would benefits patients with New York Heart Association (NYHA) functional class I and II heart failure and a prolonged QRS duration. Patients were eligible for inclusion if they were currently in NYHA class I or II with prior heart failure symptoms, on optimal medical therapy for at least three months. All patients were in sinus rhythm, had a QRS duration > 120 m/sec, a left ventricular ejection fraction (LVEF) < 40%, and a left ventricular end-diastolic dimension > 55 mm. Patients with recent (within three months) class III or IV symptoms were excluded.

Baseline evaluations included a quality-of-life assessment, a six-minute walk test, and 2-D Doppler flow echocardiography. All patients received a CRT device, either a defibrillator (CRT-D) or pacemaker (CRT-P). After successful implantation, patients were randomly assigned in a 2:1 ratio to CRT-ON or CRT-OFF for 12 months. Patients were seen at 1, 3, 6, and 12 months. Study examinations for endpoints were performed by heart failure staff blinded to treatment assignment. Device follow-up was carried out by unblinded electrophysiology staff. Clinical events were adjudicated by an endpoint committee blinded to treatment assignment.

The primary endpoint of the study was a composite heart failure evaluation that classified patients as worsened, improved, or unchanged. Since class I patients (asymptomatic at baseline) could not improve, the percentage of patients worsened was the primary efficacy comparison. Secondary endpoints included changes in left ventricular end-systolic volume index (LVESVI), six-minute walk distance, heart failure hospitalizations, and mortality.

A total of 642 patients were enrolled, and underwent, attempted implant of a CRT device. Successful implants were achieved in 621 patients (97%). Eleven patients were excluded, leaving a final group of 610 subjects, 419 programmed CRT-ON and 191 programmed CRT-OFF. Mean values for important clinical parameters were similar between the two groups: age 62 years; 79% male; 82% class II; 53% ischemic heart disease; QRS duration 154 m/sec; six-minute walk distance of 388 m; LVEF 26%. CRT-D devices were used in 84% of the patients. At one year, 16% of the patients in the CRT-ON group manifested worsened heart failure compared to 16% in the CRT-OFF group ($p = 0.10$). Subgroup analysis suggested benefits among those with lower LVEFs, wider QRS durations, and non-ischemic cardiomyopathy. Only 12 deaths occurred during the study; three in the CRT-OFF group and nine in the CRT-ON group. Paired LVESVI data, available in 80% of the participants, showed a change of -18.4 ± 29.5 mL/m^2 with CRT-ON vs -1.3 ± 23.4 mL/m^2 with CRT-OFF. The reduction in LVESVI was noted to be greater among the patients with a non-ischemic cardiomyopathy. LVEF also improved with CRT. There were no significant improvements in six-minute walk distances or quality-of-life scores. Among patients with a CRT-D device, there was a favorable trend toward fewer episodes of ventricular arrhythmias. Although there were 222 total hospitalizations in the study group, only 32 hospitalizations were judged to be heart failurerelated; 17 in the CRT-ON group and 15 in the CRT-OFF group. Time-to-first heart failure hospitalization was significantly prolonged by active CRT.

Since all patients in both study groups received a left ventricular lead, complications were reported for the entire group. Implant complications were noted in 4% of the patients, but some of these may have been unrelated to the LV lead implant. However, after the initial procedure, there were 41 LV lead dislodgements and 14 cases of diaphragmatic stimulation that required intervention.

Linde et al concluded that CRT improved measures of left ventricular function in patients with asymptomatic or mildly symptomatic heart failure and a prolonged QRS duration. They note that although heart failure-related hospitalizations were reduced, quality-of-life scores, exercise capacity, and the percentage with worsened heart failure did not change significantly during the course of the study.

■ COMMENTARY

Although there are some positive aspects in the results of the REVERSE trial, the overall conclusion should be that preemptive intervention with CRT in patients with no or mild symptoms of heart failure must await further data.

In REVERSE, all patients received a left ventricular

lead. Thus, all were subject to the 16% lead- or system-related complication rate observed in the study. If reoperations and additional hospital days were included only for the CRT-ON group, then any clinical benefit associated with CRT would presumably be negated or reversed. Eliminating complications likely to be solely due to the LV lead from group comparisons, certainly biases results in favor of CRT. It is understandable that Linde et al anticipated that they might show benefit with CRT and could, therefore, offer CRT later to the control group without the need for a second procedure. However, if this approach is taken, complications related solely to CRT should count only against the active therapy group.

Another limitation of REVERSE is its relatively short follow-up duration. In asymptomatic or mildly symptomatic patients with heart failure, it is likely that clinical benefits associated with LV remodeling will begin to accrue only with prolonged therapy. Linde et al have clearly shown CRT results in favorable LV remodeling, and a longer study may have shown benefit. Fortunately, the European investigators in REVERSE are continuing the trial and plan at least a two year follow-up report. We should get a better estimate of the value of preemptive CRT when those data become available. Another study currently underway, MADIT-CRT, is a larger trial enrolling similar patients using single chamber ICDs vs CRT-D devices. In MADIT-CRT, the primary endpoint is a composite of mortality and heart failure hospitalization, and all patients will be followed for at least two years. Since complications of CRT will only be seen in the active therapy group, MADIT-CRT should provide more definitive data about the value of early intervention in these patients. ■

Catheter Ablation vs Antiarrhythmic Drugs for Atrial Fibrillation

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: Jais P, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation*. 2008;118:2498-2505.

The catheter ablation versus antiarrhythmic Drugs for Atrial Fibrillation (A4) study compared radio-frequency catheter ablation to antiarrhythmic therapy in selected patients with paroxysmal atrial fibrillation (PAF). Patients were eligible for the study if they had frequent episodes of symptomatic PAF that had been present for at least six months. All patients had experienced recurrence during at least one prior antiarrhythmic drug trial prior to enrollment. Patients were randomized to either a treatment strategy based on catheter ablation or on serial antiarrhythmic drug trials for a 90-day period. During this stabilization period, patients could undergo up to three catheter ablation procedures (pulmonary vein isolation ± additional left or right atrial linear of focal ablations) or enroll in up to three antiarrhythmic drug trials using single- or combination-drug therapy. Follow-up started at 91 days and continued through day 365. Data routinely collected during the evaluation period included 12-lead ECGs, quality-of-life questionnaires, AF symptom frequency and severity check lists, and 24-hour Holter recordings at baseline and at 3, 6, and 12-month follow-ups. Treadmill exercise testing and 2-D echocardiograms were performed at baseline and one year. The primary endpoint was the proportion of patients free of recurrent AF between days 91 and 365. Any episode of AF of > 3 minutes duration, either reported by the patient or documented by an ECG, was considered a valid endpoint. Cross-over was permitted after a single episode of recurrent AF during the days 91-365.

The study group included 112 patients with the following characteristics: 84% male; mean age of 51.1 years; AF episode median frequency of 12/month; hypertension 26%; structural heart disease 24%; mean left ventricular ejection fraction 64%; 2.1 prior antiarrhythmic drug trials. Four randomized patients were excluded due to either withdrawal of consent or poor compliance with drug therapy.

Fifty-three patients underwent catheter ablation, with a median of two procedures per patient. Repeat procedures were required due to either pulmonary vein reconnection, gaps in prior ablation lines, or emergence of non-pulmonary vein foci. Forty-six catheter ablation patients (89%) remained free of recurrent AF without antiarrhythmic drugs from days 91 to 365; five patients randomized to catheter ablation required antiarrhythmic drugs for AF suppression.

Fifty-five patients were initially treated with an antiarrhythmic drug therapy strategy. Of these, 13 (27%; $p < 0.0001$ vs ablation strategy) remained free of recurrent AF during the nine-month study evaluation period. Thirty-seven patients (63%) crossed over to an ablation approach after 192 ± 80 days.

There were no differences between the ablation and the drug therapy groups in left atrial or left ventricular size, or left ventricular ejection fraction. Catheter ablation patients experienced a significant decrease in AF burden, calculated

as the mean numbers of hours of AF per 24-hour Holter recording. Quality-of-life, symptom frequency, and symptom severity scores improved in both groups, but the improvement was significantly better in the ablation-strategy patients. Exercise duration and the maximum work load achieved were higher in the ablation-strategy group.

Procedural complications were noted in five patients. There were two pericardial tamponades requiring paracentesis, two groin hematomas, and one pulmonary vein stenosis that was treated with a stent. Antiarrhythmic therapy resulted in one case of hyperthyroidism. There were two deaths in the drug-strategy group that were considered to be due to causes unrelated to the trial.

Jais et al concluded that a catheter ablation strategy is superior to repeat drug trials in patients with PAF who have had recurrent episodes during one or more previous trials.

■ COMMENTARY

The A4 trial confirms the clinical observation that pulmonary vein isolation is an effective treatment for selected patients with highly symptomatic PAF. The study results, however, should definitely not be interpreted as proof that catheter ablation should be preferred over drug therapy in all, or even most, patients with PAF.

The patients in this trial were nearly ideal candidates for a catheter ablation approach. They were relatively young, and most had normal ventricular function and left atrial dimensions. They were highly symptomatic, with very frequent episodes of PAF, and had already had recurrent symptoms despite a mean of two prior antiarrhythmic drug trials. Most electrophysiologists would currently refer such a patient for catheter ablation if there were no contraindications. However, these patients are not really representative of most patients with PAF who may be considerably older and have fewer or better tolerated episodes in association with some form of structural heart disease.

Time-to-first event is an endpoint that has frequently been used in trials of drugs for atrial fibrillation. For the purpose of a clinical trial, a time-to-first event analysis has the advantage that it is easy to measure and has been shown to correlate, in general, with other measures of antiarrhythmic effect. However, the real goal of drug therapy in atrial fibrillation is not total suppression of recurrent AF, but a decrease in overall frequency and severity. A single recurrence during drug therapy is rarely a "clinical failure." Since catheter ablation is designed to eliminate AF completely, a comparison of the two strategies, using a single recurrence as the primary endpoint, may not be the most clinically relevant approach. Even in this trial, if events such as repeat procedures or hospital admissions during the first 90 days were counted as endpoints, the results may not have seemed so much in favor of an ablation strategy.

Catheter ablation is now a well-established procedure for patients with PAF, but it remains a first choice option only for highly selected patients. Even in these patients, future efforts to reduce the need for repeat procedures are needed for the full promise of catheter ablation to be realized. ■

CME Questions

6. Cilostazol after peripheral arterial stenting:
a. reduces restenosis.
b. reduces MACE.
c. reduces target vessel revascularization.
d. All of the above

7. Detection of circumflex coronary artery occlusion by ECG can be enhanced by:
a. right-sided precordial leads.
b. left posterior precordial leads.
c. moving the precordial leads up one interspace.
d. moving the precordial leads down one interspace.

8. Perioperative beta blockade is indicated:
a. if the patient is already on it.
b. for all high-risk surgery patients.
c. for all vascular surgery patients.
d. All of the above

9. Catheter ablation for atrial fibrillation:
a. is now the treatment of choice.
b. is superior for chronic atrial fibrillation.
c. is useful in paroxysmal atrial fibrillation.
d. has been shown to be ineffective.

10. Cardiac resynchronization therapy in patients with low EF and QRS >120 ms is most useful:
a. in NYHA class I and II.
b. in NYHA class III and IV.
c. in ischemic cardiomyopathy.
d. in diabetics.

11. Symptomatic diabetics with multivessel CAD are best treated with:
a. bare-metal stents.
b. drug-eluting stents (DES).
c. CABG.
d. DES or CABG.

Answers: 6. (d); 7. (b); 8. (a); 9. (c); 10. (b); 11. (d)

CME Objectives

The objectives of *Clinical Cardiology Alert* are to:

• present the latest information regarding illness and treatment of cardiac disease;

• discuss the pros and cons of these interventions, as well as possible complications;

• discuss the pros, cons, and cost-effectiveness of new and traditional diagnostic tests; and

• present the current data regarding outpatient care of cardiac patients. ■

Clinical Briefs in
Primary Care
The essential monthly primary care update
By Louis Kuritzky, MD
Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*
VOLUME 14, NUMBER 2 PAGES 3-4 FEBRUARY 2009

White coat hypertension and Type 2 diabetes

Source: Kramer CK, et al. Impact of white coat hypertension on microvascular complications in Type 2 diabetes. *Diabetes Care* 2008;31:2233-2237.

THE PREPONDERANCE OF EVIDENCE about the impact of hypertension (HTN) on CV and renal (CV&R) endpoints is based upon measurement of BP in the office. For more than 3 decades, HTN specialists have recognized that office BP is only one way to view the burden of HTN. Indeed, either 24-hr ambulatory BP monitoring or even home BP self-monitoring correlates better with CV&R endpoints than office BP. One explanation for the inaccuracy of office BP is that some patients' BP rises when in the medical setting, yet remains essentially normal at other times: white coat hypertension (WCH). Although some examiners have pointed out that WCH portends enhanced proclivity to develop frank hypertension, and ought to be considered of greater importance when target organ damage is present, others have opined that WCH exists, but if BP is otherwise normal, no intervention (save enhanced vigilance for the development of frank HTN) is necessary.

Kramer et al studied a population of Type 2 diabetics (DM2) comparing the prevalence of nephropathy and retinopathy in persons with WCH (n = 46) as compared to normotensives (n = 117).

DM2 subjects with WCH had a 2 times greater prevalence of nephropathy and 2.7 times greater prevalence of retinopathy (adjusted for confounders). Although the pathogenetic role played by WCH remains controversial, the associations discerned in this observational study merit concern. ■

Vitamin K and insulin resistance

Source: Yoshida M, et al. Effect of vitamin K supplementation on insulin resistance in older men and women. *Diabetes Care* 2008;31:2092-2096.

CLINICIANS TRADITIONALLY ASSOCIATE vitamin K (VitK) with the coagulation system, especially as it relates to antithrombotic therapy with agents like coumadin. Although a biologically plausible mechanism remains to be identified, a recent observational study reported a positive linear relationship: Higher amounts of dietary or supplemental VitK were associated with higher insulin sensitivity. Another small study indicated better glucose disposal (through better insulin sensitivity) after VitK supplementation in healthy men.

To investigate this phenomenon further, Yoshida et al studied healthy, non-diabetic adults (age 60-70; n = 355) by comparing levels of insulin resistance before and 36 months after VitK supplementation or placebo.

At the trial end, no changes were seen in levels of insulin resistance among female subjects. On the other hand, male subjects evidenced a statistically significant improvement in insulin resistance. Whether VitK supplementation might have a salutary effect in diabetics or others with overt insulin resistance syndromes (e.g., impaired glucose tolerance, obesity, polycystic ovary syndrome) remains to be clarified. ■

Aspirin for all? Not so fast...

Source: Ogawa H, et al. Low dose aspirin for primary prevention of atherosclerotic events in patients with Type 2 diabetes. *JAMA* 2008;300: 2134-2141.

THE SYLLOGISTIC PROCESS THAT LED US all to accept the utility of ASA in prevention of CVD in diabetics seemed innocent enough: a) ASA reduces CV events in persons with CVD, and b) Diabetes is considered a CV risk equivalent; therefore, c) ASA must reduce CV events in persons with diabetes.

Despite the quite consistent advocacy for ASA to reduce CV events in persons without known CVD (i.e., primary prevention), such primary prevention has never been shown to reduce mortality. And while adult diabetics older than age 40 have similar or even greater risk of sustaining a myocardial infarction than a non-diabetic who has already had an MI, the mechanisms inducing MI might be different in diabetics than non-diabetics; we cannot assume that just because aspirin benefits one population, it will indeed benefit another population whose background risk factors differ (for instance, diabetics typically have smaller, more dense, more atherogenic LDL than non-diabetics).

Ogawa et al published a multicenter prospective randomized trial of ASA (81-100 mg/d) vs placebo in adult, Japanese Type 2 diabetics (n = 2539). None of the subjects had sustained a known CV event, and all were free of clinically manifest PAD at baseline. The primary endpoint of the trial was a

composite of fatal and nonfatal CVD events, ACS, new angina, and TIA.

After a follow-up of 4.37 years (median), although there was a trend towards reduced atherosclerotic events in the ASA group, the results were not statistically significant. The conclusion of the authors: "…low-dose ASA as primary prevention did not reduce the risk of CV events." ■

Non-fasting triglycerides and risk of stroke

Source: Freiberg JJ, et al. Nonfasting triglycerides and risk of ischemic stroke in the general population. *JAMA* 2008;300:2142-2152.

THE CONSISTENT AND STRONG RELATIONship between LDL and adverse CV events, coupled with widely replicated risk reduction achieved with statins, leaves little doubt about the risk-benefit ratio of such intervention. On the other hand, both the relationship between triglycerides (TRGs) and CV events, and the benefits of lowering elevated TRGs are much less well established.

The Copenhagen City Heart Study has been following approximately 14,000 men and women since 1976. Although TRGs are typically measured fasting, the authors of this paper measured non-fasting TRG (nf-TRG) to gain insight into CV risk associated.

An analysis was performed comparing 6 incremental levels of nf-TRG. The reference level was nf-TRG < 89 mg/dL. Risk for stroke was assessed for men and women, at increments of 89 mg/dL, from an nf-TRG level of 89 mg/dL to > 443 mg/dL. For both men and women, ischemic stroke increased with increasing levels of nf-TRG. For instance, individuals with nf-TRG > 443 mg/dL had a hazard ratio 2.5-3.8 times greater than persons with nf-TRG < 89 mg/dL.

These intriguing findings suggest that nf-TRG might be useful, in concert with LDL, as a target for CV risk reduction. Of course, whether intervention to modulate nf-TRG is appropriate will depend on future interventional trials documenting that reduction of nf-TRG is beneficial. ■

ACE/CCB or ACE/HCTZ for HTN: Which is better?

Source: Jamerson K, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high risk patients. *N Engl J Med* 2008;359:2417-2428.

JNC 7 IS PROBABLY THE CONSENSUS DOCument most utilized by U.S. clinicians to make decisions about HTN. The ALLHAT trial was instrumental in establishing the equal efficacy of chlorthalidone, amlodipine, and lisinopril in reference to mortality, with some subgroups (CHF, stroke) showing superiority of chlorthalidone. These results led to the suggestion that diuretic therapy be a foundation of HTN treatment.

Clinical trials have consistently demonstrated that only a minority of patients are able to have their HTN controlled on monotherapy, and little direction has been available to guide therapy about which combination of agents provides best outcomes. The ACCOMPLISH trial was designed to compare outcomes in HTN patients (n = 11,506) considered to be high-risk because of substantial comorbidity (e.g., PAD, LVH, MI, stroke, CKD). The two regimens compared were ACE/CCB (benazepril/amlodipine) and ACE/HCTZ (benazepril/hydrochlorothiazide). The primary endpoint was a composite of CV death, nonfatal MI/stroke, hospitalization for angina, sudden death resuscitation, and revascularization.

The trial was stopped early at 36 months when the clear advantage of ACE/CCB was seen: a 20% relative risk reduction for the primary endpoint. In situations where clinicians are choosing combination therapy, ACE/CCB has been superior to ACE/HCTZ. Because HCTZ and chlorthalidone are not identical, there is some controversy over whether results would have been the same had chlorthalidone (the agent used in ALLHAT) been used instead. At the current time, since the vast majority of prescriptions for an antihypertensive diuretic in the United States employ HCTZ, these results should be generalizable to most practice situations. ■

Putting sunscreen to the test

Source: Sang SQ, et al. In vitro assessments of UVA protection by popular sunscreens available in the United States. *J Am Acad Dermatol* 2008;59:934-942.

SPF STANDS FOR "SUN PROTECTION FACtor," but if FDA recommendations change, the name will soon stand for "Sunburn Protection Factor" because of the recognition that current SPF testing reflects erythema effects of UVA light in the 320-340 nm and UVB light in the 290-320 nm wavelengths, but does not necessarily reflect efficacy for other photodamaging wavelengths. UVA light in the 340-400 nm range is also dermotoxic, but impact of sunscreen on this light component has not previously been included in labeling. In August 2007, the FDA suggested a new rating scale which includes a ratio of UVA 340-400 nm (termed UVA1) to total UV light absorption. Agents that have low efficacy for absorbing UVA1, even though they have good efficacy for other wavelengths, would be rated lower in overall efficacy.

An analysis of 13 OTC sunscreen products using the new FDA criteria found 8 to provide medium protection and 5 to provide high protection. All but one of the selected products had an SPF of at least 30. If the proposed FDA metric becomes widely accepted, consumers will have an opportunity to better appraise the overall efficacy of sunscreen products. ■

Clinical Briefs in Primary Care is published monthly by AHC Media LLC.

Associate Publisher: Coles McKagen. **Editor:** Stephen Brunton, MD. **Senior Managing Editor:** Paula Cousins. This is an educational publication designed to present scientific information and opinion to health professionals, stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for the layman.

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PHARMACOLOGY WATCH

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

How Best to Control Hypertension?

In this issue: Drug combinations for hypertension; tenecteplase for out-of-hospital cardiac arrest; CAM most commonly used for back, neck, and arthritis pain; FDA Actions.

Combination therapy for hypertension

What's the best drug combination with an ACE inhibitor for treatment of hypertension in patients at risk for cardiovascular disease? Current guidelines recommend a diuretic, as witnessed by the number of ACE inhibitor/diuretic combination products that are currently marketed. However, a new study suggests that the calcium channel antagonist may be a better selection than a diuretic. Researchers from several medical schools in the United States and Sweden randomized 11,506 patients with hypertension who were at high risk for cardiovascular events to receive treatment with either benazepril plus amlodipine or benazepril plus hydrochlorothiazide. The primary endpoint was a composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. The average patient was 68 years old at entry and the group included patients with a history of ischemic heart disease, peripheral vascular disease, stroke, LVH, and diabetes. The study was terminated early after 3 years when it was found that the benazepril/amlodipine group had a significantly lower risk of the primary endpoint: 9.6% vs 11.8% (hazard ratio 0.80; 95% confidence interval, 0.72-0.92; $P = 0.002$). This represents a 2.2% absolute risk reduction and a 19.6% relative risk reduction in the benazepril/amlodipine group vs benazepril/hydrochlorothiazide. The authors conclude that the combination of benazepril/amlodipine is superior to benazepril/hydrochlorothiazide in reducing cardiovascular events in patients with hypertension who are at risk (Jamerson K, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high risk patients. *N Engl J Med* 2008;359:2417-2428). An accompanying editorial from the chair of the seventh report of the Joint National Committee on hypertension suggests it is time to re-examine the recommendation of initial therapy with a thiazide-type diuretic. He also states, however, that regardless of the drugs chosen for treatment of hypertension, the most important factor is reducing blood pressure to goal levels (Chobanian AV. Does it matter how hypertension is controlled? *N Engl J Med* 2008;359:2485-2488).

A survival benefit with tenecteplase?

Thrombolytic therapy during out-of-hospital cardiac arrest does not improve outcomes according to a new study. There has been considerable interest in thrombolytic therapy during cardiopulmonary resuscitation since it has been shown that 70% of these arrests are due to acute myocardial infarction or pulmonary embolism. European researchers randomized 1050 patients with witnessed out-of-hospital cardiac arrest to tenecteplase or placebo during cardiopulmonary

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resuscitation. The primary endpoint was 30-day survival and the secondary endpoints were hospital admission, return of spontaneous circulation, 24-hour survival, survival to hospital discharge, and neurologic outcomes. The trial was discontinued early when it was found that there was no survival benefit with tenecteplase. Thirty-day survival was 14.7% with tenecteplase and 17% with placebo. Secondary outcomes similarly showed no benefit from tenecteplase. The authors conclude that when tenecteplase was used during advanced life support for out-of-hospital cardiac arrest there was no improvement in outcomes in comparison to placebo (Bottiger BW, et al. Thrombolysis during resuscitation for out-of-hospital cardiac arrest. *N Engl J Med* 2008;359:2651-2662).

CDC report on CAM use

There is a 40% chance that your patients are using complementary and alternative remedies according to new report from the Centers for Disease Control & Prevention. Not including vitamins and minerals, the use of a complementary and alternatives medicine (CAM) in adults and children has increased in the last 5 years. Treatments include non-vitamin, non-mineral natural products (fish oil, flaxseed oil, echinacea), chiropractic or osteopathic manipulation, deep breathing exercises, massage, and meditation. Children are also using alternative treatments, especially if their parents use them. Despite lack of evidence of efficacy, echinacea is the most common remedy used by children. In adults, use of CAM treatments for URIs is actually down, perhaps indicating better patient education. Back pain, neck pain, and arthritis pain are the most common reasons why people turn to CAM, according to this recent survey. These results point out the need to query patients about the use of complementary and alternative medicines.

FDA Actions

The FDA is requiring a boxed warning on sodium phosphate bowel-cleansing products because of the risk of acute phosphate nephropathy associated with use of these products. Sodium phosphate cleansing products are most commonly used as bowel preparation for procedures such as colonoscopy. According to the warning, the products Visicol® and OsmoPrep® should be used with caution in people older than age 55; those suffering from dehydration, kidney disease, colitis, or delayed bowel emptying; and people taking other medications that may affect kidney function. These products should also not be used in conjunction with other oral laxatives containing sodium phosphate, and over-the-counter products, such as Fleet® Phospho-Soda®, should also be used with caution if given in a high dose to the patient population at risk.

The FDA is requiring a warning on all anti-epileptic drugs regarding the risk of suicidal thoughts and behavior. The warning is based on review of nearly 200 studies that showed that patients on anti-epileptic drugs were at almost twice the risk of suicidal behavior or thoughts compared to patients on placebo. Along with the warning, the agency is also requiring a Medication Guide for patients as part of its Risk Evaluation and Mitigation Strategy. Over 20 drugs will be required to change their labeling including the commonly used agents phenytoin, carbamazepine, divalproex, gabapentin, lamotrigine, primidone, and topiramate.

The FDA is considering a ban on the long-acting beta agonists salmeterol (Serevent®) and formoterol (Foradil®) for the treatment of asthma. An expert committee comprised of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee voted unanimously to withdraw the indication for the treatment of asthma for the two drugs based on evidence from meta-analyses showing increased risk of death associated with use of long-acting beta agonist when not paired with a steroid inhaler. The committee did not vote to ban Advair® or Symbicort®, inhalers that combine a long-acting beta agonist with a steroid. If the FDA follows the subcommittee's recommendations, the drugs would no longer be indicated for treatment of asthma but would remain on the market to treat chronic obstructive pulmonary disorders. The FDA has not indicated when it will act on the subcommittee's recommendations.

The FDA has approved fenofibric acid (Trilipix™) for use with a statin for the treatment of dyslipidemia. This is the first fibrate approved for use with statins. The approval is based on a large trial in which the drug was used in combination with rosuvastatin (Crestor®), atorvastatin (Lipitor®), and simvastatin (Zocor®). There have been safety concerns about using fibrates and statins together, particularly gemfibrozil, but the newer generation fibrates appear safer. Abbott, the manufacturer of Trilipix, is collaborating with AstraZeneca to develop a fenofibric acid/rosuvastatin fixed combination product within the next year. ■