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INSIDE

Financial Disclosure:

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

Clopidogrel for Two Years after Drug-eluting Stents?

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD
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Dr. Boyle reports no financial relationships relevant to this field of study.

Source: Tanzilli G et al. Effectiveness of two-year clopidogrel + aspirin in abolishing the risk of very late thrombosis after drug-eluting stent implantation (from the TYCOON [Two-Year ClOpidOgrel Need study). *Am J Cardiol*. 2009;104:1357-1361.

THE OPTIMAL DURATION FOR DUAL ANTI-PLATELET THERAPY (DAT) after drug-eluting stent (DES) implantation remains unknown. Based on autopsy data, DES do not endothelialize as completely or quickly as bare metal stents (BMS). Guidelines advocate prolonged DAT for DES, which is currently 12 months. However, some studies suggest there is a clinical risk of very late stent thrombosis in patients with DES, occurring > 12 months after implantation. This may be particularly true in real-world settings, where DES use in off-label settings, such as multiple stents and bifurcation lesions, may carry a higher risk of late or very late stent thrombosis than in the low-risk populations studied in the pivotal clinical trials. Whether more prolonged DAT would reduce this risk has not been systematically studied. Accordingly, Tanzili et al performed a prospective registry study of patients undergoing percutaneous coronary intervention (PCI).

Over a two-year period from 2003 to 2004, all patients undergoing uncomplicated PCI who were administered DAT were enrolled. Exclusion criteria were cardiogenic shock, use of brachytherapy, use of investigational stents, and inability to take DAT. All patients had pre-loading with aspirin 325 mg and clopidogrel 300 mg, all received intra-procedural heparin, and the use of glycoprotein IIb/IIIa inhibitors was at the operator's discretion (used in approximately 31% of cases). Post-procedure, patients receiving BMS (n = 450) received clopidogrel for one month, patients receiving DES in 2003 (173) received clopidogrel for 12 months, and patients receiving DES in 2004 received clopidogrel for 24 months; all patients

VOLUME 29 • NUMBER 1 • JANUARY 2010 • PAGES 1-8

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received ongoing aspirin 100 mg daily. Patients were followed for four years and the primary endpoint of the study was definite or probable stent thrombosis. Secondary endpoints included cardiac death, myocardial infarction (MI), target lesion revascularization (TLR), and target vessel revascularization (TVR). Early-stent thrombosis was defined as < 30 days, late-stent thrombosis (LST) was 30 days-1 year, and very late stent thrombosis (VLST) was > 1 year from the index procedure.

Baseline demographics were well matched between all groups (BMS, DES with 12-month DAT, DES with 24-month DAT). More bifurcation lesions were treated in the 24-month group, but otherwise angiographic and procedural variables were similar.

Stent thrombosis occurred most frequently in patients treated with DES and 12 months DAT. Total stent thrombosis occurred in 0.7%, 3% and 0.4% in the BMS, DES with 12-month DAT and DES with 24-month DAT respectively (p = 0.02). This was primarily due to increased VLST in the 12-month DAT group (0%, 2% and 0% in the BMS, DES with 12-month DAT and DES with 24-month DAT respectively, p = 0.03). No cases of stent thrombosis were seen after two years in any group. However, between 1-2 years after the index procedure, patients who stopped clopidogrel after 12 months had a 2% rate of stent thrombosis. Notably, self-reported compliance with DAT was 96%-98% at the end of the DAT period. There was no difference between the groups in cardiac mortality. Patients receiving BMS had higher TLR and TVR as expected, but there was no difference between the DES patients receiving 12-month DAT and those receiving 24-month DAT. The authors conclude that a two-year dual anti-platelet regimen with aspirin and clopidogrel can prevent the occurrence of very late stent thrombosis after PCI with DES.

■ COMMENTARY

As more long-term data emerge regarding DES and the risk of stent thrombosis, registry data are important in generating new hypotheses that can then be formally tested in prospective, randomized, controlled trials. This interesting dataset from Tanzilli and colleagues suggests that VLST occurs in approximately 2% of patients in the second year following DES implantation if clopidogrel is ceased at one year, as is the current recommendation. Several important factors require comment. Firstly, the rate of VLST is higher than reported in other series. It is not clear in what clinical context these VLST events occurred, such as the perioperative setting, which may confound the data. Secondly, we are not told which DES were used, and the stent thrombosis rates differ between stent types. Finally, the small numbers and non-randomized nature of the study makes this hypothesis-generating, and we should not change clinical practice on the results of a single registry alone. However, the suggestion that extending the DAT duration to 24 months reduces hard clinical end-points is intriguing and worthy of further study. Their demonstration of no stent thrombosis events from two years to four years of follow-up after ceasing clopidogrel underscores the long-term safety of DES in current real-world clinical practice. ■

Clinical Cardiology Alert, ISSN 0741-4218, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305. The statement of ownership will be printed in the November issue.

MANAGING EDITOR: Leslie Hamlin.
ASSOCIATE PUBLISHER Russ Underwood.
DIRECTOR of MARKETING : 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.

AHC Media LLC

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Questions & Comments

Leslie Hamlin,
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Left Main Stenting

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

Source: Buszman P et al. Early and long-term results of unprotected left main coronary artery stenting. The LE MANS (Left Main Coronary Artery Stenting) registry. *J Am Col Cardiol*. 2009;54:1500-1511.

STENOSIS OF THE LEFT MAIN CORONARY ARTERY HAS traditionally been an indication for coronary artery bypass graft (CABG) surgery. However, recent studies have shown that percutaneous coronary intervention (PCI) of unprotected left main (ULM) lesions can achieve similar short- and medium-term results to CABG. Accordingly, the ACC/AHA guidelines for PCI

were revised last month to include PCI of left main coronary stenoses as a class IIb indication, instead of class III. The revised guidelines state that "PCI of the left main coronary artery with stents as an alternative to CABG may be considered in patients with anatomic conditions that are associated with a low risk of PCI procedural complications and clinical conditions that predict an increased risk of adverse surgical outcomes" [Kushner et al. *J Am Coll Cardiol*. 2009;54:2205-2241]. With little long-term outcome data to support the revised guidelines, this report from the LE MANS registry was published at around the same time the guidelines were changed, and gives us some insight into the long-term outcomes of ULM stenting. The LE MANS study randomized 105 patients to PCI with stenting or CABG for ULM stenosis (> 50%), and these results have been previously published. Patients who were not deemed suitable for randomization were enrolled in either PCI or CABG registries; herein, Buszman et al present the results of their PCI registry.

From 1997-2008, 252 patients were enrolled after undergoing ULM stenting with either bare-metal stents (BMS, n=158) or drug-eluting stents (DES, n=94). Exclusion criteria were ST elevation myocardial infarction (STEMI) presentation, occluded left main, and the presence of any patent bypass grafts to the left coronary artery. The mean age of subjects was 69 years, 24% were diabetic, and 69% were male. Mean EuroSCORE was 62.8, and distal left main involvement was present in 59%. Reasons not to perform CABG were high surgical risk in 52%, patient preference in 12%, and anatomical suitability (ostial or mid-shaft) of ULM lesion for PCI in 35%. In the PCI procedure, direct stenting was the preferred technique, with lesion predilatation reserved for critical and calcified lesions. Distal ULM disease was preferentially treated with stenting across the ostium of the circumflex into the left anterior descending artery, with provisional angioplasty, T-stenting or culotte of the circumflex ostium, according to the operator's discretion. DES were recommended for vessels with reference diameter < 3.8 mm and BMS if > 3.8 mm. Within the DES group, paclitaxel-eluting stents were used in 64% and limus derivatives in the remainder. Intra-aortic balloon counterpulsation was used in 6.3%, heparin was the anti-thrombin for all cases, and glycoprotein IIb/IIIa inhibitors were used in 24%. All patients received aspirin therapy (300 mg loading followed by 150 mg daily for life) and thienopyridine loading followed by maintenance dose, early in the study ticlopidine and later clopidogrel. Dual anti-platelet therapy was continued in 55%, 21%, and 17% at one year, two years, and beyond two years from the index procedure, respectively. Patients were followed from 1-11 years (mean 3.8 years). The primary endpoint was death; major adverse cardiovascular and cerebral events (MACCE — a composite of death, myocardial infarction [MI], stroke, target lesion revascularization [TLR], and stent thrombosis) and comparisons between DES and BMS were secondary endpoints.

Within 30 days from the index procedure, mortality was 1.6%; MACCE occurred in 4.8%. Acute stent thrombosis occurred in two patients, and sub-acute stent thrombosis occurred in one patient. At one year after the index procedure, survival was 93% and MACCE-free survival was 82%. Fifty-six percent of patients had surveillance angiography at 6-12 months, and 12% were found to have restenosis. At long-term follow-up, after a mean of four years, mortality was 14%, of which 11% were considered cardiac in origin. According to Kaplan-Meier analysis, the five-year survival was 78%, and the 10-year survival was 69%. There was one definite, very late stent thrombosis, probable stent thrombosis occurred in 1.2% late (30-days to 1-year), and 2% was very late (> 1 year). Survival was significantly better in patients with isolated left main disease or left main + single or double vessel disease, compared to patients with left main + triple vessel disease ($p = 0.02$). Multivariate analysis showed the only independent predictor of death was depressed ejection fraction < 50%.

Patients receiving DES were more often diabetic (31% vs. 20%, $p = 0.06$), more likely to present with acute coronary syndromes (ACS; 69% vs. 54%, $p = 0.04$), had higher surgical risk (EuroSCORE 6.8 3.9 vs. 5.6 3.8, $p = 0.01$), had smaller caliber left main (3.4 0.5 vs. 3.7 1.0mm, $p = 0.01$), and more involvement of the distal bifurcation (72% vs. 51%, $p = 0.001$). Despite the higher-risk profile of patients receiving DES, DES use was associated with lower incidence of MACCE (15% vs. 26%, $p = 0.04$) and TLR (3% vs. 10%, $p = 0.04$) at four-year follow-up. There was no difference in mortality or risk of MI between DES and BMS. Sub-group analysis of patients with distal left main disease also revealed higher survival and MACCE-free survival with DES use. The authors conclude that stenting of ULM lesions is feasible and offers good long-term outcome. Implantation of DES decreased the risk of long-term MACCE and, particularly, improved survival in patients with distal ULM lesions.

■ COMMENTARY

Buszman et al present data from their registry that strengthens the argument in favor of PCI for ULM stenosis. Their early, 30-day mortality rate of 1.6% compares favorably against historical surgical controls, based upon

the EuroSCORE risk profile. However, the absence of a randomized control group of patients undergoing CABG surgery reduces our ability to draw firm conclusions from their data, as in any registry series. Several factors are important to highlight from their data. Firstly, as in the SYNTAX study, the patients who had left main + triple vessel disease did worse than those with isolated left main or left main + single- or double-vessel disease. These patients should still have CABG surgery considered as the first option for revascularization. Secondly, the rates of definite or probable stent thrombosis were low but not insignificant (nine patients out of 252) over a mean of four years. They were seen late in three and very late (i.e., more than 1 year from the index procedure) in six patients. This underscores the need for long-term dual anti-platelet therapy. The ability to comply with extended dual anti-platelet therapy should be a critical part of decision-making in deciding on the most appropriate revascularization strategy in all patients. Finally, it is important to note that sub-group analyses should be interpreted with caution in this study, because the study was not specifically designed to compare DES and BMS for patient outcomes. However, with a subtle shift in the treatment paradigm for ULM disease, this longer-term safety data is reassuring. ■

Statins and Bypass Surgery — Is There a Benefit?

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: M. A. Koening, MD et al. Statin use and neurologic morbidity after coronary artery bypass grafting. *Neurology*. 2009;73:1.

STATINS HAVE BEEN USED IN AN INCREASING NUMBER and variety of conditions. This large, 10-year cohort study from John Hopkins Neurology Department and Cardiac Surgery Group uses a post-hoc analysis to examine the issue of whether statin use prior to Coronary Bypass Graft Surgery (CABG) would decrease post-op morbidity, specifically stroke and encephalopathy, as well as cognitive decline. Encephalopathy included delirium, mental status changes, and poor arousal occurring for more than 24 hours after CABG surgery. The basis of this study is the known statin modulated decrease in adverse outcomes in some studies after vascular procedures, such as carotid endarterectomy and arterial bypass. The post hoc analysis of consecutive patients undergoing CABG was undertaken in the decade 1997 to 2007. Patients were carefully followed for development of post-op neurologic deficits and CVA, including overt stroke. Careful post-op analyses were performed, usually by a neurologist. All new focal neurologic deficits were recorded; MRI and CT scans were often available (data not provided). Adverse outcomes were collated beginning 24 or more hours after surgery. Among a total of 5,121 CABG patients, 54% were taking pre-op statins. Use of statins prior to CABG rose from 35% in 1997, increasing to 60%-65% in 2007.

Results: Encephalopathy was noted in 8.6% of the cohort, and stroke was observed in 3.2%: overall, 11.8% or 604 patients met at least one primary endpoint. Statin users were also examined by propensity score, with no deviation from the main cohorts. Their adjusted propensity score was 0.958. MRI studies demonstrated multiple lesions in watershed territories; risk factors for watershed infarcts included intra-operative hypotension and arteriosclerosis, suggesting that strokes result from a combination of hypo-perfusion and emboli. There was no significant difference in CV mortality, MI, or length of stay between statin users and non-users. The authors conclude that preoperative statin use was not associated with a decreased incidence of stroke and encephalopathy post CABG.

■ COMMENTARY

This study is of clinical interest with the unexpected observation that pre-op statin use did not appear to be of benefit. Other reports are not consistent with this study, but none are as sophisticated, detailed, and well-designed as this trial. The patient base is quite large, with more than 5,000 subjects, half of whom were taking pre-operative statins. Given the still-increasing utilization of statins for a multitude of clinical conditions, it seems somewhat surprising that the results of statin usage are negative. It would seem that the endpoints of encephalopathy, overt stroke, and MI are clinically relevant and, somewhat surprisingly, statin use seemed ineffective in decreasing morbidity or mortality in post-CABG patients. The authors emphasize the role of watershed infarcts with multiple lesions in watershed territories. They suggest adverse outcomes occur due to a combination of hypo-perfusion and atheroemboli.

This is not a prospective, controlled trial. Prior use of statins is unknown, and the doses used prior to CABG

were likely to have been inadequate in many patients. Also, statin potency has increased over the 10 years of this study. The authors do refer to a number of published reports with positive outcomes in other vascular beds, but they are much smaller and shorter studies, and not in CABG patients. However, a randomized, placebo-controlled trial would be unlikely to occur. Consequently, I recommend that patients who survive should be on a potent statin, especially in those with hypertension, diabetes, and all of the traditional risk factors. In most subjects, hopefully, high-dose statins will be used before a clinical event occurs. This report is somewhat unexpected, but it does not address the problem of relating the results to contemporary high-dose statin therapy and appropriate patient selection. ■

ACE Inhibitors and CABG Outcomes

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Sources: Miceli A, et al. Effects of angiotensin-converting enzyme inhibitor therapy on clinical outcomes in patients undergoing coronary artery bypass grafting. *J Am Coll Cardiol*. 2009;54:1778-1784. Bach DS. Angiotensin-converting enzyme inhibitor therapy at the time of coronary artery bypass surgery. *J Am Coll Cardiol*. 2009;54:1785-1786.

The preoperative use of angiotensin-converting enzyme inhibitors (ACEI) with coronary artery bypass graft (CABG) surgery is controversial. Thus, these investigators from the United Kingdom performed a retrospective, observational study of patients undergoing isolated CABG who did not have cardiogenic shock. The final population included over 9,000 patients, 51% of whom received preoperative ACEI. To avoid bias, a propensity score matched analysis was done on 3,052 patients on ACEI and a control group of equal number. The primary endpoint was in-hospital mortality. In the original group, there were many significantly different clinical variables between the ACEI and the non-ACEI groups, as you would expect, but the smaller matched groups were similar on all these measures.

Results: Overall mortality was 1%, and preoperative ACEI doubled this risk (1.3% vs. 0.7%, OR 2.0, CI 1.17 3.42, $p = 0.013$). Also, renal dysfunction, atrial fibrillation, and use of inotropic support were more common in the ACEI group. There was no difference in myocardial infarction and stroke. The authors concluded that preoperative ACEI use was associated with increased mortality, renal dysfunction, atrial fibrillation, and use of inotropic support in CABG patients.

■ COMMENTARY

The controversy over ACEI use preoperatively with CABG surgery concerns two viewpoints: *pro*, ACEI lower blood pressure and are vasculoprotective, anti-inflammatory, and anti atherosclerotic; *con*, ACEI cause vasodilation and an increased need for fluids, inotropic agents, and vasoconstrictors. The data from the study support the latter. It is well known that hypotension causes renal dysfunction, yet ACEI are recommended for diabetics to prevent deterioration in renal function. Clearly, there is a difference between preoperative use and chronic use in ambulatory patients with coronary artery disease (CAD). The lack of effect on atrial fibrillation is disappointing since this is a common complication of CABG that increases adverse events and prolongs hospital stay. Theoretically, an ACEI should reduce atrial pressure and volume and the stimulus for atrial fibrillation, but this was not observed. Should we hold ACEI for patients undergoing CABG?

Before we decide, it is worth noting that this study has several limitations. Although theoretically attractive, propensity score matching may not eliminate all bias from non-randomized studies, and there were considerable differences between those on and not on ACEI before matching, as you can imagine. Also, ACEI may not be the culprit, but rather a marker for some adverse patient characteristic that was not measurable. If you want to apply the results of the study, there are important details missing from this report. What was the duration of ACEI therapy; the dose; the agent? What about angiotensin receptor blockers and aldosterone antagonists? If you hold ACEI preoperatively, when can you restart?

In the accompanying editorial, Dr. Bach describes ACEI as one of the four pharmacologic pillars of secondary prevention in CAD, along with aspirin, beta blockers, and statins. However, all four drugs may not be appropriate for all patients. One should consider the risk vs. benefit of each. Today, hospitals and practitioners are rated on how many of their patients are on these drugs at admission and at discharge. This tends to drive formulaic, algorithm-driven medicine, which may not always be appropriate. Recently, our percentage of patients with left ventricular dysfunction discharged on ACEI dropped from 100% to below targets. Hospital administrators wondered what happened. It turned out that the drop was due to patients post-CABG. Clearly, our surgeons had

gotten wind of this controversy and voted with their pens. We are trying to get them to re-institute ACEI therapy before the patient leaves the hospital, but it is an uphill battle. More data, especially randomized, prospective data, would be welcome on this controversial topic. ■

Bi-ventricular vs. RV Apical Pacing

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

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

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

Source: Yu C-M, et al. Biventricular pacing in patients with bradycardia and normal ejection fraction. *N Engl J Med*. 2009;361:2123-2134.

YU ET AL REPORT A MULTI-CENTER TRIAL EVALUATING the relative benefits of right ventricular apical pacing compared to biventricular pacing in patients with a standard indication for pacing and a baseline preserved left ventricular ejection fraction. The Pacing to Avoid Cardiac Enlargement (PACE) study was a multi-center trial testing this hypothesis. Patients with a standard pacing indication of either AV conduction disease or sinus node dysfunction received atrial synchronized biventricular pacemakers at the time of their initial implant. Two days after successful implantation of the device, the patients were randomly assigned to either right ventricular apical pacing or biventricular pacing and their pacemakers reprogrammed appropriately. All devices were programmed to the DDDR mode with a lower rate limit of 60 bpm and an upper tracking rate of 140 bpm. Baseline assessments included echocardiography with core lab readings, a six-minute walk test, and a quality-of-life assessment using the SF-36. Patients were then followed at routine intervals for one year. The two primary endpoints of the study were changes in left ventricular ejection fraction and changes in left ventricular end-systolic volume at 12 months. Secondary endpoints included distance coverage during the six-minute walk test, quality-of-life measures on the SF-36, and heart failure hospitalizations. Echocardiographic assessment of left ventricular ejection fraction was done using either real time 3-D echocardiography or, if this was not available, 2-D echocardiography.

Over a three-year period, a total of 251 patients were screened for participation. One hundred and ninety-three patients were eligible for the trial, but 16 had unsuccessful implantation of a left ventricular pacing lead. The remaining 177 patients were randomly assigned to either biventricular pacing (89) or right ventricular apical pacing (88). The mean age for the group was 68 years, and 54% were male. The groups were similar with regard to heart rate, QRS duration, and cardiac diagnoses at baseline. The mean left ventricular ejection fraction for the entire group was 61.7%. Fifty-seven percent of the patients received their pacemaker because of advanced atrioventricular block and 43% because of sinus node dysfunction.

Long-term data from four patients were not included in the analysis. Two patients were lost to follow-up; one patient died, and one patient had echo images that were inadequate for analysis. Two patients had diaphragmatic stimulation during left ventricular pacing that could not be corrected with reprogramming but were analyzed with the biventricular pacing group according to the intention-to-treat principle.

Biventricular pacing resulted in a significantly better left ventricular ejection fraction than did right ventricular apical pacing at 12 months (58.9 + 9.1% vs. 62.2 + 7.0%; $p < 0.01$). This translated to a decreased ejection fraction over a 12-month period of 6.7% in the right ventricular pacing group vs. no significant change in the biventricular pacing group. Left ventricular end systolic volume also was better with biventricular pacing. The absolute difference between the groups was 8.1 mL at 12 months; clinical variables showed little difference. There was no difference in the distance covered during the six-minute walk, with both pacing groups having an increase over baseline of more than 30 meters at 12 months. Similarly, there was no difference in quality-of-life measures, as assessed by the SF-36. There were 11 hospitalizations for heart failure; six in the right ventricular pacing group and five in the biventricular pacing group. Only two of these patients had a left ventricular ejection fraction of less than 45% at 12 months. Seven patients in the biventricular pacing group had diaphragmatic pacing, but this could be managed with reprogramming with continuing biventricular pacing in five.

The authors conclude that right ventricular apical pacing results in better ejection fractions and left ventricular systolic volumes compared to standard right ventricular conventional pacing. However, at 12-month follow-up, these changes do not correlate with a decrease in clinical events or in quality of life changes.

■ **COMMENTARY**

Numerous studies have shown that right ventricular apical pacing induces ventricular dyssynchrony, and some studies have suggested that excessive or unnecessary right ventricular apical pacing results in clinical events. This paper is in agreement with these observations but still leaves open the question of whether the added cost and risk for procedural complications associated with current techniques for biventricular pacing would be justified in patient without systolic heart failure at baseline. In this study, there was a 7% deterioration in left ventricular ejection fraction and an 8 mL change in left ventricular end systolic volume associated with right ventricular apical pacing. However, at least over a 12-month time period, these changes did not result in an increased frequency in heart failure hospitalizations and no changes in functional capacity or quality of life measures. These hemodynamic improvements were achieved at the cost of 16 unsuccessful initial implants and seven patients who had left ventricular lead-related problems during the one year follow-up. At this time, therefore, it seems that standard biventricular pacing cannot be justified without evidence that clinical outcomes can be favorably affected. In patients with sinus node dysfunction, alternate strategies to avoid unnecessary right ventricular pacing are available and seem a better first option. ■

Appropriate Utilization of ICDs

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: Packer, DL, Impact of implantable cardioverter-defibrillator, amiodarone, and placebo on the mode of death in stable patients with heart failure. *Circulation*. 2009; 120:2170-2176

In this paper, packer et al report on the modes of death in patients in the Sudden Cardiac Death-Heart Failure Trial (SCD-HeFT). That trial compared the effects of single-chamber implantable cardioverter--defibrillators (ICDs), amiodarone, and placebo in patients with ischemic or nonischemic cardiomyopathy, a left ventricular ejection fraction < 35%, and NYHA Class II or III heart failure. Overall, SCD-HeFT demonstrated superiority of ICD therapy over both placebo and amiodarone in this population.

SCD-HeFT enrolled a total of 2,521 subjects who were randomized in equal proportions to a single-lead ICD programmed to a shock-only mode, amiodarone, or placebo. An independent events committee blinded to treatment reviewed available documentation after treatment-identifying data had been removed. Deaths during the study were classified as witnessed or unwitnessed, sudden or nonsudden, cardiac or noncardiac. Cardiac deaths were also evaluated to see if they were associated with ventricular tachyarrhythmias, bradyarrhythmias, worsened heart failure, or other cardiac causes. Death during sleep was considered to be due to a ventricular tachyarrhythmia if the event was unexpected and occurred in the absence of acceleration of heart failure symptoms. In the case of an event due to a bradyarrhythmia, ECG documentation at the onset of the event was required. Death occurring in a subject with progressively worsening heart failure over the preceding three to four months in whom long-term survival was not expected was classified as a heart-failure death, even if the final event was an arrhythmia.

During follow-up, there were 666 deaths. These included 182, 240, and 244 patients randomized to ICD, amiodarone, or placebo, respectively. Compared to placebo, ICD therapy resulted in a 23% reduction in all-cause mortality and a 24% reduction in cardiac mortality. There was no significant difference in total or cardiac mortality between the amiodarone and placebo groups. The mode of cardiac death differed between groups. In the ICD group, there were 122 cardiac deaths. Of these, 37 (30%) were due to tachyarrhythmia, one due to bradyarrhythmia (0.8%), 72 (59%) due to heart failure, and 12 (10%) due to other causes. In the amiodarone group, there were 162 cardiac deaths. Of these, 75 (46%) were due to tachyarrhythmia, five (3%) due to a bradyarrhythmia, 67 (41%) due to heart failure, and 15 (9%) due to other causes. There were 167 cardiac deaths in the placebo group. This included 95 (57%) due to tachyarrhythmia, three (2%) due to bradyarrhythmia, 66 (40%) due to heart failure, and three (2%) due to other causes. The adjusted hazard ratio for tachyarrhythmic death in subjects randomized to amiodarone compared to those randomized to placebo was not statistically significant (adjusted HR 0.84; $p = 0.25$), indicating that amiodarone did not decrease arrhythmia mortality in SCD-HeFT. By contrast, the adjusted hazard ratio for tachyarrhythmic death for ICD therapy vs. placebo was highly significant, with a hazard ratio of 0.40, $p < 0.001$. There were no statistically significant differences between the rates for heart failure death between the three groups. Noncardiac and unclassifiable deaths accounted for 23% of the deaths in the study. There was a slight increase in the number of unclassified deaths in the amiodarone and placebo groups (24 and 24) vs. the ICD therapy group (12),

but the total of other than cardiac deaths was not statistically significant between the three groups.

The authors also examined the influence of baseline New York Heart Association (NYHA) heart failure class on mortality. In patients with NYHA class II heart failure, ICD therapy reduced cardiac mortality and sudden tachyarrhythmic deaths (adjusted HR 0.026) compared with placebo. However, there was no difference between treatment groups in heart-failure mortality among the class II patients. By contrast, ICD therapy had no effect on any mode of death in those with New York Heart Association class III heart failure. Amiodarone was associated with an increase in noncardiac mortality in the group with New York Heart Association class III heart failure (adjusted HR 1.68). The effects of ICD therapy were independent of the etiology for heart failure, with similar improvements in cardiac and sudden cardiac mortality seen in patients with both ischemic and nonischemic causes for heart failure.

The authors conclude that amiodarone decreased sudden death, which was presumed to be caused ventricular tachyarrhythmia in patients with New York Heart Association class II heart failure. Patients with class III heart failure have higher relative rates of nonsudden death and receive little benefit from ICD therapy.

■ COMMENTARY

This paper helps us further understand the potential and the limitations of ICD therapy. As has also been reported by the MADIT II investigators (see Goldenberg et al. *J Am Coll Cardiol*. 2008;51:288-296), there seems to be a "sweet spot" for ICD therapy. Among patients at low risk for sudden death, the costs and possible complications of ICD therapy outweigh the relatively small, potential, absolute benefits. Among sicker patients, there are more sudden deaths, but heart-failure deaths begin to predominate, and ICD therapy, although technically effective, offers little long-term benefit. The key is to identify patients in that "sweet spot." In SCD-HeFT, patients with Class II CHF symptoms benefitted from ICD therapy, but patient with Class III symptoms did not. In MADIT II, several risk factors were identified. Patient with either none or more than three risk factors failed to benefit. These observations are sobering in view of the fact that the national ICD registry shows that almost half of the ICDs implanted for primary sudden death today in the United States are given to patients classified as having Class III symptoms. Admittedly, some of these patients also receive resynchronization therapy devices, and that added feature should substantially improve the overall risk-to-benefit ratio in appropriate patients. Despite a wealth of trial-based evidence, we still have much to learn about how to best use ICD therapy. ■

CME Questions

1. **Biventricular vs. right ventricular apical pacing results in:**
   a. improved ejection fraction.
   b. reduced heart failure rates.
   c. better six-minute walk test.
   d. improved quality of life.

2. **The best candidates for ICD therapy in heart-failure patients with EF < 35% are NYHA class:**
   a. I.
   b. II.
   c. III.
   d. IV.

3. **Preoperative CABG ACEI use resulted in:**
   a. increased mortality.
   b. more renal dysfunction.
   c. more use of inotropic support.
   d. All of the above

4. **Stenting for unprotected left main coronary artery disease is competitive with surgery for:**
   a. isolated left main lesions.
   b. left main plus 1-2 vessel disease.
   c. left main plus 3 vessel disease.
   d. A and B

5. **Preoperative statins with CABG results in:**
   a. reduced mortality.
   b. fewer strokes.
   c. less encephalopathy.
   d. None of the above

6. **Prevention of late-stent thrombosis is best accomplished by extending dual antiplatelet therapy for:**
   a. six months.
   b. one year.
   c. two years.
   d. four years.

Answers: 1. (a); 2. (b); 3. (d); 4. (d); 5. (d); 6. (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. ■

CLINICAL CARDIOLOGY ALERT®
A monthly update of developments in cardiovascular disease

CUMULATIVE INDEX

Volume 28, Numbers 1-12, Pages 1-96

January 2009—December 2009

Dear *Clinical Cardiology Alert* Subscriber:

This issue of your newsletter marks the start of a new continuing medical education (CME) semester and provides us with an opportunity to review the procedures.

Clinical Cardiology Alert, sponsored by AHC Media LLC, provides you with evidence-based information and best practices that help you make informed decisions concerning treatment options and physician office practices. Our intent is the same as yours — the best possible patient care.

Upon completing this program, the participants will be able to:

1. discuss the most current information related to cardiac illness and the treatment of cardiac disease;
2. explain the advantages and disadvantages, as well as possible complications, of inter ventions to treat cardiac illness;
3. discuss the advantages, disadvantages and cost-effectiveness of new and traditional diag nostic tests in the treatment of cardiac illness; and
4. discuss current data regarding outpatient care of cardiac patients.

Each issue of your newsletter contains questions relating to the information provided in that issue. After reading the issue, answer the questions at the end of the issue to the best of your ability. You can then compare your answers with the correct answers provided in an answer key in the newsletter. If any of your answers were incorrect, please refer back to the source material to clarify any misunderstanding.

At the end of the semester, you will receive an evaluation form to complete and return in an envelope we will provide. Please make sure you sign the attestation verifying that you have completed the activity as designed. Once we have received your completed evaluation form, we will mail you a letter of credit. This activity is valid 36 months from the date of publication. This CME activity is intended for the cardiologist.

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Cynthia Molnar
Director of Continuing Education
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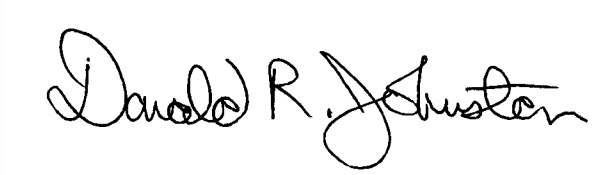

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Clinical Briefs in
Primary Care™
The essential monthly primary care update
By Louis Kuritzky, MD
Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

VOLUME 15, NUMBER 1 PAGES 1-2 JANUARY 2010

The relationship of FPG and A1c to diabetic retinopathy

Source: Cheng YJ, et al. Association of A1C and fasting plasma glucose levels with diabetic retinopathy prevalence in the U.S. population. *Diabetes Care* 2009;32:2027-2032.

THE IDEA THAT A1c MIGHT BE A REASONABLE metric to make the diagnosis of diabetes has been kicking around for more than a decade. Only very recently has there been advocacy from the ADA that A1c may be an acceptable method for diagnosis of diabetes (A1c ≥ 6.2%); a primary reason for this shift in perception is the widespread adoption of a nationally standardized A1c testing method. Ultimately, diagnosis is intended to go beyond simply categorizing an individual as diabetic or non-diabetic; rather, it is intended to predict risk for important complications of diabetes like retinopathy.

The NHANES (National Health and Nutrition Examination Survey) is a cross-sectional sampling of non-institutionalized civilian adults. From the NHANES 2005-2006 study population, a group of adults age ≥ 40 years had assessment of retinopathy, A1c, and fasting plasma glucose (FPG).

There was a steep increase in frequency of retinopathy at an A1c ≥ 5.5%. Although a similar increased risk was seen at a FPG of 126 mg/dL, overall, the A1c was a better predictor than FPG. Since A1c may be obtained whether or not the subject has fasted, it may become a more convenient (as well as more sensitive) method than FPG for identifying risk of retinopathy. ■

Getting the most bang for your buck with lipid measurement

Source: The Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;302:1993-2000.

THE EMERGING RISK FACTORS COLLABORATION collected data from prospective observational studies of persons without CV disease at baseline (n = 69 studies, with 302,430 participants). Lipid fractions measured in these studies included LDL, HDL, apo B, and apo A1. Risk for incurring CV endpoints was stratified for each lipid fraction.

Triglycerides have always been the lipid fraction demonstrating the weakest association to CVD endpoints. In this data set, although the unadjusted hazard ratio for triglycerides demonstrated increased hazard, adjusted hazard ratios were not convincing. In contrast, subjects with the lowest HDL levels showed an almost 3-fold greater hazard ratio for CV events than those in the highest third. The ratio of apo B:apo A1 was also an important CV risk predictor.

Interestingly, measurement of total cholesterol, HDL, apo B, and apo A1 in the non-fasting state did not appear to appreciably alter their predictive value. Sufficient information for risk prediction, according to these data, is obtained by simply measuring cholesterol levels (total and HDL). Additionally, the authors were not able to identify any significant additional CV risk prediction by adding triglyceride levels to their calculations.

The simplicity of focusing upon total and HDL cholesterol, and being able to use non-fasting results, may enable clinicians to more readily gather predictive information on a wider population of patients. ■

Nortriptyline, gabapentin, or both for neuropathic pain

Source: Gilron I, et al. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: A double-blind, randomised controlled crossover trial. *Lancet* 2009;374:1252-1261.

NEUROPATHIC PAIN (NPN), SUCH AS post-herpetic neuralgia or diabetic peripheral neuropathic pain, often requires what has been described as rational polypharmacy: the combination of multiple agents in an attempt to gain maximum therapeutic advantage while minimizing adverse effects. Both nortriptyline and gabapentin have achieved some success in modulation of NPN as monotherapy. Since the mechanism of action of these agents is complementary, a trial of their combination has intellectual appeal. When choosing among antidepressants for analgesic effects, norepinephrine re-uptake inhibition appears to be a critical component. Hence, SSRIs have minimal effect, but tricyclics (e.g, amitriptyline, nortriptyline), SNRIs (e.g., duloxetine, venlafaxine), and highly selective norepinephrine re-uptake inhibitors (e.g., milnacipran) effectively reduce pain.

Combination nortriptyline and gabapentin provided significantly greater pain reduction than either agent alone. No serious adverse effects were seen in either mono- or combination therapy. Clinicians are already commonly applying combination therapies to neuropathic pain syndromes; it is gratifying to encounter sound evidence supporting this practice. ■

Which insulin regimen for type 2 diabetes

Source: Holman RR, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009; 361:1736-1747.

THE MOST RECENTLY PUBLISHED ADA/EASD consensus algorithm for management of type 2 diabetes (DM2) suggests that when the combination of metformin and lifestyle is insufficient to control diabetes, either sulfonylurea (if close to goal) or insulin is the most well-validated next step. Because there are many different insulins to choose from, the clinician may be uncertain whether basal insulin (i.e., detemir, glargine, NPH), prandial insulin (i.e., regular insulin or rapid-acting insulin analog), or biphasic insulin (a combination containing a basal as well as prandial insulin) should be preferred.

Holman et al performed a 3-year trial in DM2 subjects (n = 708) not at A1c goal with the combination of metformin and a sulfonylurea. Subjects were randomized to biphasic insulin aspart (BIA) bid, prandial insulin aspart (PIA) tid, or insulin detemir (DET) qd (some received detemir bid).

At 3 years, there was no statistically significant between-group difference in A1c attained. Hypoglycemia was least frequent in the DET group, and most common in the PIA cohort. Weight gain was least in the DET group, and greatest in the PIA group.

All regimens were successful in attaining goal A1c. Because hypoglycemia and/or weight gain are often deal breakers for our patients, basal insulin regimens may be preferred. ■

Cardioprotective effects of ACE inhibitors in African American men

Source: Papademetriou V, et al. Protective effects of angiotensin-converting enzyme inhibitors in high-risk African American men with coronary heart disease. *J Clin Hypertens* 2009;11: 621-626.

THE HOPE TRIAL CONVINCED MANY experts that midlife adults (age ≥ 55 years) with existing vasculopathy (history of CAD, CVD, diabetes and CV risk factors) will have improved outcomes on an ACE inhibitor (ramipril, to be specific). There is controversy about whether African Americans achieve similar risk reduction as other ethnicities; for instance, in the SOLVD CHF trial, retrospective analysis suggested less benefit for some endpoints in African Americans.

Papademetriou reviewed electronic records from the Washington, DC, VA Medical Center to study African American study subjects who had CAD documented by catheterization (n = 810). Subjects were parsed into those who had vs had not been treated with an ACE inhibitor.

Over a study period of 3-10 years (mean, 6.8 years), the relative risk reduction for CAD mortality was more than 30% in those treated with ACE inhibitors. All-cause mortality was 80% higher in African American patients who had *not* been treated with ACE inhibitors. Because many African American patients have relatively low renin levels, some clinicians have doubted whether CV benefits would be readily achieved with ACE inhibitors. This data analysis suggests substantial benefit from ACE inhibitor treatment in African Americans with CAD. ■

Missed opportunity: Aldosterone antagonists in heart failure

Source: Albert NM, et al. Use of aldosterone antagonists in heart failure. *JAMA* 2009;302:1658-1665.

THE SEMINAL RALES TRIAL (RANDOMized Aldactone Evaluation Study), in which patients with NYHA Class III-IV systolic heart failure received either aldactone or placebo in addition to standard-of-care treatment (e.g., ACE inhibitors, beta blockers, digoxin) indicated that the utilization of this well tolerated, inexpensive treatment could reduce mortality by as much as 30%.

One might anticipate that such benefits would result in widespread utilization of aldosterone antagonists in heart failure.

Albert et al reviewed data from more than 200 U.S. hospitals, encompassing 43,625 patient admissions for heart failure over the 2005-2007 time period. By this time, the RALES data were more than 5 years old. Contraindications to this life-saving treatment are few, with hyperkalemia being the most common.

According to their analysis, less than 33% of patients with heart failure who were eligible for treatment with an aldosterone antagonist (i.e., without contraindications) received one. With proper monitoring, aldosterone antagonist therapy reduces risk, is safe, and is well tolerated. Although aldosterone antagonist use improved over time (from a baseline rate of 28% to an end-of-study rate of 34%), much opportunity of reduction of mortality was missed. ■

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

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Niacin Beats Ezetimibe Head to Head

In this issue: *Statin and niacin increase HDL-C, omeprazole reduces effectiveness of clopidogrel, darbepoetin increases risk of stroke, statins decrease risk of gallstone disease, FDA Actions.*

Statin plus niacin or ezetimibe?

Raising HDL-cholesterol (HDL-C) with niacin plus a statin is superior to lowering LDL-cholesterol (LDL-C) with ezetimibe plus statin in reversing atherosclerosis according to the widely reported ARBITER trial published on-line in the *New England Journal of Medicine* in November and simultaneously reported at the American Heart Association meeting in Orlando, FL. The trial enrolled more than 200 patients with coronary heart disease or a coronary heart disease equivalent who were receiving long-term statin therapy with an LDL-C < 100 mg/dL along with an HDL-C < 50 mg/dL for men or 55 mg/dL for women. The patients were randomly assigned to receive extended-release niacin (target is 2000 mg/day) or ezetimibe (10 mg/day). The primary endpoint was the difference in change from baseline in mean and maximal carotid intima-media thickness after 14 months. The trial was terminated early in July of 2009. Both drugs were effective in their roles — the mean HDL-C in the niacin group increased by 18.4% over the 14-month study period ($P < 0.001$) and the mean LDL-C level in the ezetimibe group decreased by 19.2% ($P < 0.001$). Niacin significantly reduced LDL-C and triglycerides as well, while ezetimibe lead to a reduction in HDL-C and triglycerides. Niacin was superior to ezetimibe in reducing the primary endpoint, leading to a reduction of both mean ($P = 0.001$) and maximal carotid intima-media thickness ($P \leq 0.001$ for all comparisons). Paradoxically, greater reductions in LDL-C seen with ezetimibe were significantly associated with increases in the carotid intima-media thickness. The incidence of major cardiovascular events was also lower in the niacin group than in the ezetimibe group (1% vs 5%; $P = 0.04$ by the chi square test) (published on-line at: www.nejm.org; Nov. 15, 2009).

The study has received enormous attention not only because of the primary endpoint, but also because of the significant reduction in major adverse cardiac events in the niacin group, even though the numbers were quite small. At least one editorialist laments the early termination of the study and feels that it is impossible to make recommendations regarding the "adjuvant agent of choice" based on the small numbers (The HALTS Trial — Halting Atherosclerosis or Halted Too Early; published on-line at: www.nejm.org; Nov. 15, 2009). Still, this study provides enough evidence to consider adding niacin to a statin in patients who are at risk of or have low HDL-C. It also deals another blow to ezetimibe (Zetia®) and its partner drug ezetimibe/simvastatin (Vytorin®).

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

Omeprazole's effect on clopidogrel

The FDA has issued a warning regarding the combination of clopidogrel (Plavix®) with omeprazole (Prilosec®) citing new data that suggest that the combination reduces clopidogrel's effectiveness by about half. Studies reported in 2009 suggested that omeprazole may block clopidogrel's conversion to its active metabolite via CYP2C19, an enzyme that is inhibited by omeprazole. New studies requested by the FDA from the manufacturers confirm a significant interaction between the two drugs, which can significantly hinder clopidogrel's ability to prevent platelet aggregation in patients at risk for heart disease. Omeprazole and clopidogrel are commonly prescribed together to prevent GI bleeding. At this time it is unclear whether this interaction extends to other proton pump inhibitors, although physicians are encouraged to avoid a combination of clopidogrel with esomeprazole (Nexium®, cimetidine (Tagamet®), and other drugs known to inhibit CYP2C19. The FDA is recommending that patients who need GI protection in conjunction with clopidogrel may safely use ranitidine (Zantac®), famotidine (Pepcid®), nizatidine (Axid®), or oral antacids.

Darbepoetin and risk of stroke

Darbepoetin alfa (Aranesp®) is commonly used in patients with chronic kidney disease and diabetes for the treatment of anemia. A new study suggests that the drug may be associated with increased risk of stroke in this patient population. More than 4000 patients with diabetes, chronic kidney disease, and anemia were randomly assigned to darbepoetin alfa to achieve a hemoglobin level of 13 g/dL or placebo with rescue darbepoetin alfa if hemoglobin levels dropped < 9 g/dL. The primary endpoints were the composite outcomes of death or cardiovascular event, and death or end-stage renal disease. After a follow up of 2.5 years, darbepoetin alfa was ineffective at preventing either primary outcome, and, more importantly, the rate of fatal or nonfatal stroke occurred almost twice as often in the treatment group (101 patients assigned to darbepoetin alfa vs 53 patients assigned to placebo; HR, 1.92; 95% confidence interval, 1.38-2.68; $P < 0.001$). The authors conclude that the use of darbepoetin alfa in patients with diabetes, chronic kidney disease, and moderate anemia who are not undergoing dialysis did not reduce the outcome of death, cardiovascular events, or renal events, but was associated with increased risk of stroke. For many "this risk will outweigh the potential benefits" of the drug (*N Engl J Med* 2009;361:2019-2032). Erythropoiesis-stimulating agents have come under fire in the treatment of cancer-associated anemia, and now in renal patients as well. As pointed out in an accompanying editorial, the risks and benefits of these agents must be weighed, namely an increased risk of stroke vs a perceived improvement in quality of life (*N Engl J Med* 2009; 361:2089-2090).

Statins and gallstone disease

Statins have been shown to reduce the risk of cardiovascular disease and death from all causes. Now another potential benefit is being reported: Statins may reduce gallstone disease. Utilizing a large patient database from the United Kingdom, researchers looked at the risk of developing gallstones followed by cholecystectomy in relation to exposure to lipid-lowering agents. The longer patients took statins, the lower the risk for gallstone disease, with patients who had filled 20 or more prescriptions noticing 36% reduction in risk (AOR, 0.64; 95% confidence interval, 0.59-0.70). The authors conclude that long-term use of statins is associated with a decrease risk of gallstones followed by cholecystectomy (*JAMA* 2009;302:2001-2007).

FDA Actions

The FDA has approved a new topical treatment for the treatment of post-herpetic neuralgia (PHN). The capsaicin 8% patch must be applied to the skin by a health care professional since placement may be quite painful, requiring the use of a local topical anesthetic. The patch is applied for one hour during which patients must be monitored, including observation for increases in blood pressure. The patches may be cut to conform to the area of pain and up to 4 patches may be used. The one-hour application is reported to provide up to 12 weeks of reduced pain from PHN. The capsaicin 8% patch will be manufactured by Lohmann Therapie-Systems and distributed by NeurogesX as Qutenza™.

The FDA has approved romidepsin for the treatment of cutaneous T-cell lymphoma in patients who received at least one prior systemic therapy. The drug is a histone deacetylase inhibitor, the first of a new class of antineoplastics. Romidepsin will be marketed as Istodax® by Gloucester Pharmaceuticals. ■