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INSIDE

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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.

Contraindicated Medications Increase Risk of PCI in Dialysis Patients

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: Tsai TT, et al. Contraindicated medication use in dialysis patients undergoing percutaneous coronary intervention. *JAMA*. 2009;302(22):2458-2464

Anticoagulation during percutaneous coronary intervention (PCI), although necessary to prevent thrombus formation on the interventional equipment, can lead to significant morbidity from bleeding complications, particularly if the dosage is excessive. Several antithrombins are approved for use, including unfractionated heparin, enoxaparin, bivalirudin, and fondaparinux. In addition to antithrombins, glycoprotein IIb/IIIa inhibitors, such as eptifibatide, abciximab, or tirofiban, are often used during PCI. Due to their renal clearance, enoxaparin and eptifibatide are contraindicated in patients with end-stage renal failure on hemodialysis. Tsai et al utilized the National Cardiovascular Data Registry (NCDR) to examine the use of these agents in dialysis patients undergoing PCI. Between January 2004 and August 2008, data from over 1.3 million PCI procedures in 829 hospitals were entered into the NCDR database; among these, 24,656 (1.8%) were performed on patients receiving hemodialysis. After excluding patients who were taking warfarin or had received fibrinolytics, as well as those who received infrequently used antithrombotics such as tirofiban, argatroban, lepirudin, dalteparin, or nadroparin, 22,778 patients were included in the analysis.

Results: Of these 22,778 dialysis patients undergoing PCI, 5,084 (22.3%) received a contraindicated antithrombotic medication. Enoxaparin was used in 2,375 (47%), eptifibatide was used in 3,261 (64%) and both were used in 552 cases (11%); their use was associated with higher in-hospital bleeding and mortality. Tsai et al performed multivariable analysis to account for factors associated with

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increased risk of in-hospital mortality (including cardiogenic shock, age, salvage, urgent, or emergent PCI, pre-procedure intra-aortic balloon pump insertion, decreased left ventricular ejection fraction, presentation with acute MI, diabetes, chronic lung disease; treatment approaches including non-stent devices; and lesion characteristics including left main and proximal left anterior descending disease) and in-hospital bleeding (age, gender, previous heart failure, peripheral vascular disease, no previous PCI, New York Heart Association/Canadian Cardiovascular Society Functional Classification class IV heart failure, myocardial infarction, and cardiogenic shock). After multivariable analysis, patients receiving contraindicated antithrombotic mediations had a 66% increased risk of major bleeding and a 24% higher in-hospital mortality. To further analyze the relationship between the use of contraindicated anti-thrombotic medication, Tsai et al performed a propensity matching, and identified 5,079 pairs. Using this model, there was a 63% increase in major bleeding, but the increase in mortality was no longer statistically significant.

Secondary endpoints were the rates of major bleeding and death with each individual agent. Major bleeding rates were higher with enoxaparin than unfractionated heparin or bivalirudin (5.0% vs. 3.9% vs. 3.0%, respectively; $p < 0.001$) in dialysis patients undergoing PCI. Similarly, rates of in-hospital death were also higher (6.0% vs. 5.4% vs. 3.0%, respectively; $p < 0.001$). The use of eptifibatide was not significantly associated with bleeding or mortality. The association between the use of contraindicated antithrombotics and bleeding and mortality appeared to be strongest in patients presenting with acute coronary syndromes. Tsai et al conclude that in a sample of dialysis patients undergoing PCI, 22.3% received a contraindicated antithrombotic medication, which was associated with a significantly increased risk of in-hospital major bleeding.

■ COMMENTARY

This study is disturbing for the fact that many physicians are inappropriately prescribing contraindicated medications and may, thereby, be harming their patients. Whether this staggeringly high rate of inappropriate prescribing is through lack of knowledge of the contraindications to the use of these agents or due to disregard of the medication labeling is unknown. Patients with renal failure are already at higher risk of complications from PCI. Tsai et al show us that administering inappropriate antithrombotics can further increase their peri-procedural risk of bleeding and death. Fortunately, this is an area of medicine that can be improved by education of physicians and by putting systems in place to prevent medication errors, such as electronic medication alerts.

Although this is a retrospective registry study, not a prospective study, the findings are strengthened by the large number of patients included in the analysis. This study underscores the importance of real-world registries in the medical literature. Although randomized, controlled trials are necessary in assessing new therapies, only registries like this can monitor day-to-day clinical practice for areas where improvement is needed. This study is a wake-up call for interventional cardiologists — it behooves us all to know, and follow, the labeling for antithrombotic agents when treating patients on dialysis. ■

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Questions & Comments

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Intensive Lipid Lowering in ACS Patients Undergoing PCI

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

Source: Gibson CM, et al. Effect of Intensive Statin Therapy on Clinical Outcomes Among Patients Undergoing Percutaneous Coronary Intervention for Acute Coronary Syndrome PCI-PROVE IT: A PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) Substudy. *J Am Coll Cardiol*. 2009;54:2290-2295.

Intensive lipid lowering with statin therapy (atorvastatin 80 mg) in patients presenting with acute coronary syndromes (ACS) resulted in improved outcomes compared to treatment with moderate lipid lowering (pravastatin 40 mg) in the PROVE-IT TIMI-22 study (Cannon et al. *N Engl J Med*. 2004;350:1495-1504), which included patients treated conservatively, as well as those treated with percutaneous coronary intervention (PCI). Whether this effect holds true in patients treated with PCI is unknown. Therefore, Gibson et al performed a post-hoc analysis of the PROVE-IT TIMI 22 study and analyzed the outcomes of those patients who had PCI during the index hospitalization for ACS.

Patients presenting with ACS (myocardial infarction [MI] or high-risk unstable angina) were screened for total cholesterol 240mg/dL if statin-naïve or 200 mg/dL if they were already taking statins. Within 10 days of presentation, they were randomized 1:1 in a double-blind fashion to receive atorvastatin 80 mg daily or pravastatin 40 mg daily. If low-density lipoprotein (LDL) remained 125mg/dL, the pravastatin could be increased to 80 mg daily. The main outcome measure of this analysis was time to the occurrence of one of the components of the primary endpoint of PROVE-IT TIMI 22: death, MI, unstable angina requiring hospitalization and revascularization at least 30 days after randomization, and stroke. Additional outcome measures included target vessel revascularization (TVR) and non-target vessel revascularization (non-TVR). Patients were followed for two years.

Results: Of the 4,162 patients enrolled in the trial, 2,868 underwent PCI during the initial hospitalization and were eligible for this analysis. Among this PCI cohort, the baseline characteristics between those randomized to atorvastatin 80 mg and those randomized to pravastatin 40 mg were similar, with the exception of peripheral arterial disease being more prevalent in the pravastatin group. Baseline LDL was 106 mg/dL in both groups. This dropped to 89 mg/dL in the pravastatin group and 57 mg/dL in the atorvastatin group at 30 days ($p < 0.001$). Baseline C-reactive protein (CRP) was 13.2 mg/dL, and dropped to 2.14 mg/dL in the pravastatin group and 1.55 in the atorvastatin group ($p < 0.001$). Patients treated with intensive lipid-lowering therapy exhibited significant reductions in the primary composite endpoint (death, MI, stroke or unstable angina requiring hospitalization, and revascularization) compared to patients treated with moderate lipid-lowering therapy (21.5% vs. 26.5% in the atorvastatin 80 mg and the pravastatin 40 mg groups, respectively; $p = 0.001$). Several secondary endpoints were also significantly reduced in the intensive lipid-lowering group: recurrent ischemia (13.0% vs. 17.1%; $p < 0.001$), rehospitalization for unstable angina (3.3% vs. 4.7%; $p < 0.001$), and revascularization 30 days after randomization (16.6% vs. 21.0%; $p = 0.002$) in the atorvastatin 80 mg and pravastatin 40 mg groups, respectively. In addition, there were non-significant trends favoring the intensive lipid-lowering group in all-cause mortality (1.5% vs. 2.5%, $p = 0.057$) and MI (5.8% vs. 7.7%, $p = 0.052$). Intensive lipid-lowering therapy resulted in lower rates of TVR (11.4% vs. 15.4%, $p < 0.001$) and non-TVR (8.0% vs. 10.5%, $p < 0.001$) than moderate lipid-lowering therapy. However, after adjustment for on-treatment LDL and CRP levels, only the reduction in TVR remained significant. Interestingly, the cohort from the original study that was treated medically instead of with PCI, and did not appear to benefit from intensive over moderate lipid-lowering therapy. Gibson et al conclude that among patients with ACS who undergo PCI, intensive statin therapy reduces major adverse cardiac events compared with moderate-dose statin therapy.

■ COMMENTARY

Intensive statin therapy improves outcomes following hospitalization for ACS. Gibson et al asked whether this held true in patients who had PCI during their ACS hospitalization and found, somewhat unexpectedly, that this only held true in the PCI patients. Patients treated medically had no statistically significant improvement in the primary outcome in this post-hoc analysis of PROVE-IT TIMI 22 (24.5% vs. 25.2%, $p = 0.779$) when treated with intensive lipid-lowering therapy. Their data are consistent with several recent studies demonstrating the benefits of high-dose statin therapy immediately prior to PCI. In this study, statin therapy was commenced after the PCI procedure, suggesting there may be incremental benefit in high-dose statins before PCI and then continued for two years thereafter. Importantly, their data were collected during the time of bare-metal stents and may, therefore, not apply to patients receiving drug-eluting stents and prolonged dual anti-platelet therapy. It is not clear if the achieved LDL level or the change in LDL correlated with the occurrence of the primary outcome in this substudy. Thus, we do not know if the observed effects are due to more effective lipid lowering or to the pleiotropic effects of statins. Regardless, this study reinforces the need for aggressive lipid-lowering therapy in patients undergoing PCI for ACS. ■

Niacin and Vascular Diseases

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Sources: Lee JMS, et al. Effects of high-dose modified-release nicotinic acid on atherosclerosis and vascular function. *J Am Coll Cardiol*. 2009; 54: 1787-1794. Taylor AJ, et al. Extended-release niacin or ezetimibe and carotid intima-media thickness. *.N Engl J Med*. 2009;361:2113-2122.

TWO RECENT STUDIES HAVE DEMONSTRATED THE BENEficial effects of nicotinic acid (niacin) on carotid artery atherosclerosis. Lee et al, from the United Kingdom, performed a double-blind, randomized, controlled study of 2 gm daily of sustained release niacin added to statin therapy in 71 patients with a low HDL-cholesterol (< 40 mg/dL) and either: 1) diabetes and coronary artery disease; or 2) peripheral arterial disease. The primary endpoint was carotid wall area by MRI after one year of therapy. Statin therapy was determined by the primary physician, and no LDL-cholesterol (C) level was required for study inclusion.

Results: The average baseline LDL-C was 85 mg/dL, and the HDL-C was about 38 mg/dL. Niacin increased HDL-C by 23% to 48 mg/dL and lowered LDL-C by 19% to 69 mg/dL at one year. MRI carotid wall area was reduced by 1.1 mm^2 on niacin, compared to an increase of 1.2 mm^2 on placebo ($p = 0.03$). Lee et al concluded that in patients with vascular disease on statins with LDL-C < 100 mg/dL, niacin reduces atherosclerosis within one year.

Taylor et al, from the United States, performed a prospective, randomized, parallel group, open-label study of the addition of either extended-release niacin (2 gm/day) or ezetimibe (10 mg/day) to baseline statin therapy in 363 patients with coronary artery disease, or its equivalent, and reported the results in the 208 patients who had completed 14 months of follow-up when the study was stopped due to a lack of efficacy in one group. The primary endpoint was change in carotid intima-media thickness (CIMT) at 14 months. Entry criteria included an LDL cholesterol < 100 mg/dL and HDL-C < 50 mg/dL for men and < 55 for women.

Results: In the niacin treated group, HDL-C increased by 18% from 43 to 50 mg/dL and decreased 5% in the ezetimibe group ($p < .001$). LDL-C decreased 18% in the ezetimibe group and 10% in the niacin group ($p < .01$). CIMT decreased significantly in the niacin group, but was unchanged in the ezetimibe group ($p = .003$). The incidence of major cardiovascular events was also lower in the niacin group vs. ezetimibe (1 vs. 5%, $p = .04$). Taylor et al concluded that niacin is superior to ezetimibe in combination with a statin for reducing CIMT in patients with CAD or its equivalent.

■ COMMENTARY

In these two studies, known vascular disease patients on statins with reasonable LDL-C levels (< 100 mg/dL) but relatively low HDL-C (< 40 or < 50-55) were treated by the addition of high-dose niacin (2 gm/day). Both showed reductions in atherosclerosis, as measured by CIMT or carotid MRI. In both studies, measures of atherosclerosis increased in the control groups. The increase observed with placebo is not surprising, but an increase with ezetimibe was, and caused the Taylor et al study to be terminated early. In the placebo-controlled study, the mechanism is unclear since niacin reduced LDL-C and triglycerides and increased HDL-C. In the ezetimibe control study, both lowered LDL-C, although the effect was greater with ezetimibe; only niacin reduced triglycerides and increased HDL-C. It would appear that raising HDL-C and lowering triglycerides trumps further lowering of LDL-C when it is already < 100 mg/dL. However, a study of torcetrapib, which raised HDL-C 72%, showed an increase in mortality; thus, it may not be as simple as raising HDL-C. Some drugs may have other effects which mitigate the effects of otherwise favorable changes in lipid levels.

The major limitation to the more widespread use of niacin is adverse events, even with the slow release preparations used in these studies. In the placebo-controlled study, flushing occurred in 36% of the subjects; 15% withdrew from the study, largely for adverse effects. In the ezetimibe-controlled study, 37% withdrew from the niacin arm mainly because of adverse events such as flushing, pruritus, and GI upset. No one was withdrawn because of liver or muscle function test abnormalities. Thus, the statin-niacin combination seems safe. Newer agents that combine a flushing blocking drug with niacin may prove to be better tolerated.

Although these studies use a surrogate endpoint rather than clinical events, the results are encouraging that relatively low HDL-C levels, even when LDL-C is < 100 mg/dL, identify individuals in whom the addition of high-dose niacin may improve outcome. ■

Off-pump Coronary Bypass Surgery vs. Traditional CABG — Is There a Winner?

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: Shrover AL, et al. On-pump versus off-pump coronary-artery bypass surgery. *N Engl J Med*. 2009;361: 1827-1837

Coronary revascularization without cardiopulmonary bypass has become quite successful, in part because of the belief that off-pump coronary bypass procedures are safer than on-pump surgery. However, the literature is conflicting. Some studies support better outcomes with off-pump coronary revascularization; others do not. This study (the ROOBY Trial) was designed to answer the question whether off-pump or on-pump CABG was safer.

ROOBY was a controlled study performed in 18 VA medical centers, carried out from February 2002 through May 2008. The major outcomes were morbidity and mortality at both 30 days and one year. The secondary outcomes included status of grafting and/or revascularization. Results reported on the primary short-term and one-year events were a composite of death or complications (reoperation, cardiac arrest, coma, stroke, or renal failure) within one year after surgery. The primary long-term endpoint was death or non-fatal MI within one year after surgery. Secondary endpoints included completeness of revascularization, graft patency at one year after surgery, as well as neuropsychological outcomes at one year. A total of 2,203 patients undergoing urgent or elective CABG were assigned to an off-pump or on-pump procedure.

Results: There were no significant differences between off-pump and on-pump CABG in the 30-day composite outcome (7% and 5.6%, respectively, p = NS). At the end of one year, the composite outcome was higher for off-pump than on-pump CABG patients (9.9% vs. 7.4%, p = 0.04). The proportion of subjects with fewer grafts than planned was higher in off-pump patients than in on-pump CABG patients, (17.8% vs. 11.1%, p = 0.001). The rate of graft patency was lower in the off-pump cohort as compared to the on-pump group (82.6% vs. 87.8%, p = 01). Importantly, there was no difference in neuropsychological outcomes. Shrover et al concluded that the patients in the off-pump group had worse outcomes and less graft patency at one year as compared to the on-pump group, and neuropsychological outcomes were not better in the off-pump group.

■ COMMENTARY

Concerns about the adequacy of coronary on-pump revascularization helped drive interest in off-pump CABG. Use of the pump itself has been suggested to have complications, including a systemic inflammatory response, cerebral dysfunction, myocardial dysfunction, and abnormal hemodynamics. These factors contributed to the concept that off-pump procedures were safer. However, subsequent studies have not all concluded that off-pump procedures are safer than on-pump CABG. The ROOBY outcomes are reassuring, particularly for on-pump CABG.

This is an important and useful report, which is consistent with somewhat better cardiovascular outcomes in typical CABG subjects (i.e., men in their 60's with relatively normal LV systolic function who undergo on-pump multivessel CABG revascularization). Overall survival was comparable at one year, but cardiac deaths were lower in the on-pump group, possibly indicating better and more complete revascularization.

It is likely that both sides of the controversy will continue the dialog of which approach is superior. What is clear is that the ROOBY data and outcomes have resulted in an increased likelihood for outstanding performance. The possible shift to use of the on-pump approach more often and decreased off-pump surgery could change the picture of off-pump CABG — I suspect not. The ROOBY study is supportive of both approaches. Experience, good skills, and a careful selection of the patient are likely to result from this publication, but off-pump procedures will continue to be performed by highly experienced surgeons who can replicate or improve on the ROOBY physicians. Also, patient preference for less invasive surgery will continue to drive off-pump surgery.

The statistical difference between the two groups is valid but modest. The issue of residents performing the surgery more commonly in on-pump subjects is interesting and would be expected to tip the results toward the more experienced physicians performing off-pump surgery, but this didn't happen. However, it is unclear how many of the surgeons were closely involved in the procedures. These data may indicate that there was some patient selection during the study that influenced operating room surgeon selection in unstable or difficult subjects. Other studies of this important surgical issue have come to different conclusions. In spite of all the data provided, it is likely that surgical experience, senior surgeon selection, graft selection, and minor differences could have influenced the group data. Thus, it does appear that either approach is reasonable, as long as greater surgical experience and increased skills favor better outcomes. Not all patients are alike, and one approach does not fit all. Surgeon skill, patient anatomy, and pump preference trump a standardized approach in the operating room. That is good news for all. ■

Value of VT Ablation Prior to ICD Placement

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: Kuck K-H, et al, for the VTACH study group. Catheter ablation of stable ventricular tachycardia before defibrillator implantation in patients with coronary heart disease (VTACH): A multicentre randomized controlled trial. *Lancet*. 2010;375:31-40

THE VENTRICULAR TACHYCARDIA ABLATION IN CORONARY Heart Disease (VTACH) study tested the hypothesis that mapping and prophylactic catheter ablation of ventricular tachycardia prior to implantable cardioverter defibrillator (ICD) insertion in patients with hemodynamically stable ventricular tachycardia (VT) would improve clinical outcomes. VTACH was a multicenter, randomized trial conducted in 16 European centers. Patients were eligible for inclusion if they had at least one clinical episode of documented, stable VT, coronary artery disease with prior myocardial infarction, and an ejection fraction ≤ 50%. The clinical VT could not have caused cardiac arrest or syncope, and the measured blood pressure during VT had to be > 90 mmHg. Unstable patients, or those with other contraindications to catheter ablation, were excluded. Patients were randomized in a 1:1 ratio to either VT ablation followed by ICD implantation or ICD implantation alone. VT ablation was guided 3D electroanatomical or non-contact mapping, entrainment mapping, and responses to stimulation. Scar mapping and exclusion was also permitted. Patients in both groups received an ICD provided by a single manufacturer to allow uniform data collection. The ICD programming consisted of a VF zone with a cutoff rate of 200 bpm to 220 bpm and a VT zone with a cutoff cycle length that was 60 m/sec longer than the cycle length of the slowest documented VT. Antiarrhythmic drug use was discouraged in general but permitted at the investigator's discretion.

The primary endpoint for the study was the time from ICD implant to recurrence of any sustained VT or VF. Secondary endpoints were survival free of serious clinical events, the number of appropriate ICD interventions, and quality of life as measured by the SF-36 general health survey.

The 16 participating centers enrolled 110 patients in VTACH. Three enrolled patients were excluded, leaving 107 patients in the final study population. At initial electrophysiologic study, monomorphic VT was induced in 94 of these 107 (88%) of patients. Fifty-two patients were randomized to receive catheter ablation. However, seven of these patients did not complete the ablation procedure. Two had intra-procedural events (transient ST segment elevation or a transient cerebral ischemic event), two had no inducible VT and no scar suitable for modification was identified, one had access failure, one had a technical problem, and one refused ablation. Among the 45 patients who received VT ablation, 3D contact or non-contact mapping was used in 43 patients and conventional entrainment mapping in two patients. Three patients received repeat ablation procedures approximately two months after the initial procedure. Among the 55 patients in the ICD group, 12 patients eventually crossed over to VT ablation. The mean time to cross-over was 219 days after the ICD implant. Antiarrhythmic drugs were used sporadically in both groups. At one year, 12 of 46 patients in the ablation group (26%) and 13 of 48 patients in the control group (27%) were on amiodarone. The first recurrence of any ECG or electrogram documented sustained ventricular arrhythmia, VT, or ventricular fibrillation (VF) occurred after a median of 18.6 months in the ablation group and 5.9 months in the control group. By life-table analysis, 59% of the ablation patients and 40% of the ICD-only patients were free from any VT or VF at the 12-month time point. After 24 months, 47% of the ablation patients, compared to 29% of the ICD patients, were free from VT or VF. When subgroups patients with ejection fractions > 30% and/or < 30% were analyzed separately; the former group, with less ventricular dysfunction, showed a significant improvement in survival free from VT or VF, whereas the latter group did not. Secondary endpoints were also analyzed at the 24-month time point. The cardiac hospitalization rate was 33.6% in the ablation group vs. 54.6% in the ICD-only group. The incidence of VT storm was 25% in the ablation group and 30.3% in the ICD only group. There was no difference between groups in mortality, with five deaths in the ablation group and four deaths in the control group. Quality-of-life data were available from slightly over half the patients at both 12 and 24 months. There were no significant differences between the two groups in any of the measures.

Kuck et al conclude that prophylactic catheter ablation in patients with hemodynamically stable VT should be considered along with defibrillator implantation in patients, particularly if the left ventricular ejection fraction is > 30%.

■ **COMMENTARY**

The results of the VTACH study illustrate both the benefits and problems of catheter ablation for ventricular tachycardia. It should be noted that the patients in VTACH were good candidates for catheter ablation. They had hemodynamically stable clinical episodes of ventricular tachycardia so induction and mapping of the tachycardia was highly probable. The results show that catheter ablation, performed by experienced operators, did decrease the frequency of VT or VF recurrence. However, more than half of the ablation patients still had at least one VT or VF episode by two years of follow-up even though some of them were also treated with antiarrhythmic drugs. Other studies using amiodarone or sotalol, as well as some investigational antiarrhythmics have shown that ICD therapy frequency can be decreased by prophylactic drug therapy. This study would have been more clinically relevant if it had compared catheter ablation to antiarrhythmic therapy in patients receiving ICDs for secondary prevention. Unfortunately, neither catheter ablation nor drug therapy is reliable enough to eliminate the placement of an ICD in patients with hemodynamically significant, sustained arrhythmias, and both approaches should be looked at as beneficial adjuncts to, rather than replacements for, ICD therapy.

Techniques for catheter ablation of VT continue to evolve. As of yet, the benefits of an early ablation strategy are not great enough to justify a recommendation that prophylactic VT ablation be considered for all patients as proposed by VTACH investigators. Decisions about either ablation or drug therapy should be individualized based on arrhythmia frequency, the ability of antitachycardia pacing to terminate arrhythmias without symptoms, and patient preferences. ■

FDA and Medical Devices

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: Dhruva SS, et al. Strength of study evidence examined by the FDA in premarket approval of cardiovascular devices. *JAMA*. 2009;302:2679-2685

In this paper, Dhruva et al examine the types of studies that were involved in premarket approval (PMA) of cardiovascular devices by the FDA over a seven-year period. PMA applications are required for novel or high-risk medical devices, a relatively small fraction of the new medical devices marketed each year. In the PMA application, the sponsor submits data to the FDA to document the safety and effectiveness of the proposed device. After a PMA is granted, the FDA makes available a summary of the safety and effectiveness data, the SSED report, which it evaluated before granting the PMA. In this study, Dhruva et al reviewed the SSED reports from cardiovascular PMAs issued between 2000 and 2007. The types and numbers of devices covered were coronary stents (12), vascular stents (21), ablation catheters or systems (8), pacemaker or defibrillator systems or components (14), ventricular assist devices (2), cardiac valves (4), and occlusion devices or sealants (17). Supporting these 78 PMAs were 123 studies. Sixty-five percent of the PMAs were supported by a single study; only eight PMAs were supported by more than two studies.

Of the 123 studies included, only 33 (27%) of the SSEDs that were reviewed were randomized and just 17 were blinded. Except for studies on cardiac stents, most device studies were neither randomized nor blinded. Follow-up time varied by type of device, ranging from 365 days for intracardiac devices and endovascular grafts to one day for femoral artery hemostasis devices. Definition of a primary study endpoint was inconsistent. In fact, 17 of 123 studies (14%) did not state a specific primary endpoint. Many other studies reported multiple endpoints but did not explicitly specify one as the primary endpoint. Frequently, endpoint data were not compared with data from concurrent controls. Even when a control group was reported, in 34 instances, the controls were retrospective. Most primary endpoints were surrogate endpoints; for example, target lesion revascularization for a coronary stent, primary patency for an endoprosthesis, or lead implant success for a pacemaker or defibrillator lead and longer-term clinical outcomes were not reported.

Other findings of interest were also described in the review. Many studies did not include data from training, lead-in, or roll-in patients, and some studies had only a post-hoc analysis of a primary endpoint. Twenty-seven percent of the studies were performed completely outside the United States.

Dhruva et al conclude that their data suggest that there are significant limitations in publicly available data for the evidence leading to PMA of cardiovascular devices. They encourage the FDA to require higher quality studies, as well as make the data from these studies available for public analysis and comment.

■ COMMENTARY

The FDA has well-established protocols for approval of new drug applications. In most instances, the new drug, or new indication for an approved drug, must be supported by two randomized, controlled studies, each of which must achieve statistical significance. Rarely, a single large study may be powerful enough to justify approval. The compound must prove itself to be either superior to placebo for the proposed indication or non-inferior to an accepted therapy for the condition being treated. The primary endpoint must be stated clearly. Applications based only on superiority of secondary endpoints are often not approved.

Such a rigorous approach has not been taken with PMA applications for medical devices, even class III devices that have significant risk potential. The approval of medical devices has some features notably different from that for drugs. Devices change rapidly as technology advances, and the life span of an individual model may only be quite short. Device failures may not appear for several years after implantation and often occur with a frequency that would be undetectable in the usual PMA application trial sample. These and other dissimilarities have led to a very individualized approach to the approval process for many devices. This paper by Dhruva et al emphasizes our need to improve the requirements for device approval. More robust initial trials and better post-market approval follow-up studies should be routinely required, and the FDA should be provided with adequate resources for analyzing all the data. As devices become more commonly used, we must continue to improve their safety and efficacy. Although it is unlikely that the same criteria now used for new drug applications will always be applicable to device trials, it is clear that more rigorous criteria need to be established for these high-cost, high-risk, but potentially life-saving technologies. ■

CME Questions

7. The FDA approval process for medical devices:
a. closely follows that for drugs.
b. requires dummy device-controlled studies.
c. is highly individualized.
d. requires U.S.-based supporting studies.

8. Prophylactic VT ablation prior to ICD placement:
a. decreases the complication rate of ICD placement.
b. decreases subsequent VT/VF.
c. reduces mortality.
d. All of the above

9. Which of the following drugs is contraindicated in dialysis patients?
a. Enoxaparin
b. Eptifibatide
c. Bivalirudin
d. A and B

10. Which of the following agents has been shown to reduce atherosclerosis?
a. Welchol
b. Niacin
c. Ezetimibe
d. Cheerios

11. A randomized comparison of on-pump vs. off-pump CABG showed:
a. no difference in death or MI at one year.
b. less incomplete revascularizations.
c. higher graft patency.
d. All of the above

12. High doses of a potent statin in ACS patients improves outcomes:
a. in all ACS patients.
b. in medically treated patients.
c. in those undergoing PCI.
d. A and C

Answers: 7. (c); 8. (b); 9. (d); 10. (b); 11. (d); 12. (d)

CME Objectives

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

• discuss the most current information related to cardiac illness and the treatment of cardiac disease;

• explain the advantages and disadvantages, as well as possible complications, of interventions to treat cardiac illness;

• discuss the advantages, disadvantages and cost-effectiveness of new and traditional diagnostic tests in the treatment of cardiac illness; and

• discuss current data regarding outpatient care of cardiac patients. ■

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The essential monthly primary care update

By Louis Kuritzky, MD

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Prevention of diabetes: The long-term outlook

Source: Diabetes Prevention Program Research Group; et al. *Lancet* 2009;374:1677-1686.

NUMEROUS RANDOMIZED CLINICAL trials show that a variety of interventions can prevent the development of type 2 diabetes (DM2) in subjects with prediabetes (i.e., impaired glucose tolerance, defined as a 2-hour post-load glucose of 140-199 mg/dL). Lifestyle interventions (i.e., intensive diet and exercise programs) are generally at least as effective as pharmacotherapy (e.g., metformin, rosiglitazone, orlistat). Some experts quibble with the term "prevent," preferring instead to indicate that our prediabetes interventions simply "delay" diabetes. Since persons at high risk for DM2 are likely to remain in a high-risk group indefinitely, the long-term picture of interventions to prevent DM2 is important.

The Diabetes Prevention Program (DPP) was one of the largest diabetes prevention trials ever performed. At 2.8 years, incidence of DM2 was reduced 58% with lifestyle, and 31% with metformin (compared to placebo). A recent report by the Diabetes Prevention Program Research Group provides a window of insight into data 10 years from the date of randomization.

Compared to placebo, subjects in the lifestyle intervention group had a 34% reduction in new onset DM2; the metformin group had an 18% risk reduction.

Follow-up of subjects enrolled in the DPP indicates a long-term risk reduction in development of DM2 attained with lifestyle or metformin intervention. Whether you call it prevention or delay, less DM2 at 10 years is a good thing. ■

Does it matter how we lower LDL?

Source: Taylor AJ, et al. *N Engl J Med* 2009;361:2113-2122.

BASED UPON A PRESUMED DIRECT relationship between LDL lowering and reduction in CV events for persons with vasculopathy, many clinicians enthusiastically embraced the combination of ezetimibe (EZT) and statins, especially when therapeutic LDL goals were difficult to attain with a statin alone. After the ENHANCE trial, which questioned the ability of EZT to effectively regress carotid atherosclerosis, clinicians began to rethink the issue, fueled additionally by disappointing data from trials of torceptrapib, an HDL-raising drug, which not only did not reduce CV events, but actually worsened CV risk, and was subsequently withdrawn from consideration for FDA approval.

A single clinical trial, the Coronary Drug Project, showed CV risk reduction with niacin in long-term follow-up. Because of adverse effects that limit more universal use of niacin, agents that were much better tolerated (like EZT) appeared to be a more suitable choice.

A clinical trial was performed to evaluate the comparative efficacy of extended-release niacin with EZT in persons with known coronary disease or with a CHD risk equivalent (e.g., DM). All subjects were already on a statin and had achieved an LDL < 100 mg/dL. Over 14 months, the performance of niacin to regress carotid intima-media thickness was significantly greater than EZT. Indeed, the incidence of CV events was significantly lower in the niacin group also (1% vs 5%).

Although EZT is effective in reducing LDL, it has not been shown to have a favorable effect upon CV or vascular surrogate endpoints; hence, its use must be reconsidered. ■

Identifying risk factors for falls in seniors

Source: Leveille SG, et al. *JAMA* 2009;302:2214-2221.

AMONG OLDER ADULTS, FALLS REMAIN in the top 10 causes of death. Risk factors for falls include vitamin D status, cognitive status, physical decline, and mobility impairment. The epidemiologic magnitude of fall risk has motivated the search for other risk factors.

Leveille et al studied a population of community-dwelling senior citizens (age > 70 years) in the greater Boston area. Each participant (n = 749) was assessed for chronic pain, and reassessed on a monthly basis for 18 months. During this interval, subjects reported 1029 falls.

Subjects were stratified into pain scores by tertile. Most pain syndromes were associated with disorders like osteoarthritis, and included individuals with a single painful area as well as multiple symptomatic sites.

There was a linear relationship between pain scores and risk for falls. Subjects with two or more painful sites had approximately 20% greater risk of falls when compared to persons without pain. Although one might think that analgesic use prompted by joint pain might explain a greater incidence of

falls, such a relationship was not demonstrable in this population.

Why pain is associated with falls is uncertain. Perhaps pain leads to deconditioning, leading to falls. There is also some support for cognitive effects of chronic pain that might lead to lesser executive alacrity, impairing the ability to respond to precipitants of a fall. It remains to be shown whether superior pain control will reduce fall risk. ■

Resistance vs aerobic exercise and COPD

Source: O'Shea S, et al. *Chest* 2009; 136:1269-1283.

COPD IS CURRENTLY THE 4TH MOST common cause of death in the United States. Other than smoking cessation, only oxygen therapy in late-stage disease has been shown to modify disease. Pharmacotherapy provides improvements in symptoms and pulmonary function tests, but has not been shown to alter disease progression.

Physical deconditioning is commonplace in COPD. Indeed, the pathologic phenomenon seen in COPD of dynamic hyperinflation — an even greater diminution in ability to utilize expiratory reserve during exercise than at rest — helps explain why COPD patients may lack enthusiasm for aerobic exercise. Resistance exercise trials indicate that COPD patients can improve muscle strength, but whether such improvements translate into incremental symptomatic benefit or ability to participate in activities of daily living is uncertain.

O'Shea et al performed a meta-analysis of 18 controlled trials employing progressive resistance exercises for COPD patients. The data show some benefits of resistance exercise in ability to rise from a sitting position and climb stairs; however, trials comparing aerobic training vs resistance training indicated more favorable outcomes for activities like cycling, and that resistance training added to aerobic training provides little if any additional benefit. Finally, studies that indicated resistance training benefits for activities of daily living were ranked as having higher risk of bias. More studies specifically addressing the effects of resistance training upon functionality in COPD are needed. ■

Breast cancer outcomes and soy intake

Source: Shu XO, et al. *JAMA* 2009;302: 2437-2443.

ESTROGEN (EST) IS FELT TO PLAY A role in the development of breast cancer (BCA), and modulation of estrogen is utilized as a treatment for BCA. Soy foods contain a large amount of phytoestrogens, which impact natural estrogen receptors. Soy components have also been shown to possess anticancer effects. Ultimately, whether dietary soy affects important outcomes like survival or progression of disease among subjects with cancers that may be estrogen-sensitive — like BCA — is critical to ascertain.

Shu et al studied data from the Shanghai Breast Cancer Survival Study, which provides a population of Chinese breast cancer survivors (n = 5042). After approximately 4 years of follow-up, the relationship between soy intake and BCA recurrence, overall mortality, and BCA-related deaths was evaluated. There was a consistent, linear, and inverse relationship between soy intake and mortality and BCA recurrence. When compared with persons in the lowest quartile of soy intake, those in the highest quartile enjoyed a 29% lower relative risk of mortality, and a 32% lower risk of BCA recurrence.

The relationship between soy intake and favorable outcomes was not altered by estrogen receptor-positive or -negative status or tamoxifen use.

Average soy intake in U.S. women (1-6 mg/day) is markedly less than Chinese women (47 mg/d). Whether incremental dietary soy increases in the U.S. population will translate into risk reduction has not been determined. ■

Oxygen therapy for cluster headache

Source: Cohen A, et al. *JAMA* 2009; 302:2451-2457.

THE PAIN OF CLUSTER HEADACHE (CLUS) is among the most severe of any clinical syndrome. The advent of triptans, especially sumatriptan injection, has restructured the landscape of CLUS management, since SQ sumatriptan has been shown to provide effective CLUS pain relief within 15 minutes. Unfortunately, since some patients with CLUS have multiple attacks per day, for multiple days, triptan dosing limitations preclude use in these high-frequency sufferers. Additionally, CLUS patients with CAD are unable to use triptans.

Another first-line CLUS treatment is high-flow oxygen (OXY). Advantageous aspects of oxygen treatment include its low adverse-effect profile, ability to be combined with other treatments, and applicability for multiple attacks within a short time frame. Despite commonplace clinical use, trial data on OXY are quite limited.

Cohen et al performed a randomized placebo-controlled study to compare 100% oxygen vs room air (both delivered at 12 L/min for 15 minutes). Study participants (n = 109) were followed for 5 years, with instructions to treat at least 4 attacks of CLUS with either OXY or placebo (room air). All subjects received indistinguishable separate tanks of 100% oxygen and room air, and were instructed to alternate tanks for sequential CLUS episodes in their home.

The primary endpoint of the study was percent of individuals pain-free at 15 minutes. OXY was much superior to air (78% vs 20% pain free). Randomized, placebo-controlled confirmation of our clinical practice supports continued appropriateness of OXY for CLUS. ■

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Dabigatran: An Oral Direct Thrombin Inhibitor

In this issue: Results from a Phase 3 study of dabigatran, intensive lipid-lowering in CVD, H1N1 vaccine dosing and efficacy, and FDA Actions.

Anticoagulation without monitoring?

Dabigatran is an oral direct thrombin inhibitor, currently being used in many countries as an alternative to warfarin. It is anxiously awaited in this country primarily because, unlike warfarin, it does not require monitoring with blood tests. The drug has been shown to be as effective as warfarin in preventing stroke in patients with atrial fibrillation (*N Engl J Med* 2009;361:1139-1151).

A new study published in December 2009 compares the two drugs in the treatment of acute venous thromboembolism. In a randomized, double-blind, non-inferiority trial, patients with acute venous thrombus embolism were given a median of 9 days of parenteral anticoagulation therapy, then were randomized to oral dabigatran (150 mg twice a day) or warfarin that was dose-adjusted to achieve an INR of 2.0-3.0. The primary outcome was 6-month incidence of recurrent symptomatic, objectively confirmed venous thromboembolism and related deaths. Of the patients randomized to receive dabigatran, 2.4% had recurrent venous thromboembolism compared to 2.1% of patients on warfarin (difference in risk of 0.4%; 95% confidence interval [CI], -0.8 to 1.5; $P < 0.001$ for the prespecified non-inferiority margin). Major bleeding episodes occurred in 1.6% of patients on dabigatran vs 1.9% of patients on warfarin. Episodes of any bleeding were 16.1% with dabigatran and 21.9% with warfarin. There was no difference in the number of deaths, acute coronary syndromes, or abnormal liver function tests between the two groups. Treatment was discontinued due to adverse events in 9% of patients on dabigatran and 6.8% of patients on warfarin. The authors concluded that for treatment of acute venous thromboembolism, a fixed dose of dabigatran is as effective as warfarin, has similar safety, but does not require laboratory monitoring (*N Engl J Med* 2009;361:2342-2352).

Physicians and patients alike in the United States have been awaiting an orally effective anticoagulant that doesn't require monitoring. Dabigatran, a direct thrombin inhibitor, may soon fill that role. The drug, which has the additional advantage of having minimal drug and food interactions, has been available in Canada and Europe for almost 2 years, and with the completion of Phase 3 trials such as this one, there is speculation the FDA may take action this year. ■

Intensive lipid-lowering and CVD

Follow-up analysis of two of the most famous lipid-lowering trials confirms that intensive lipid-lowering therapy continues to be beneficial in the longer term. The PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) trial, first published in 2004,

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compared moderate lipid-lowering using standard-dose pravastatin to intensive lipid-lowering with high-dose atorvastatin after acute coronary syndrome. The study showed high-dose therapy significantly reduced the occurrence of death, myocardial infarction, stroke, and unstable angina requiring hospitalization or revascularization occurring more than 30 days after the event. The new post-hoc analysis (*J Am Coll Cardiol* 2009; 54:2358-2362) followed patients for up to 2 years and showed continued benefit in reduction of the primary endpoint (16%; P = 0 .005) with high-dose therapy, as well as reduction of additional events (19%; P = 0.009).

The IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) study compared high-dose atorvastatin with usual dose simvastatin for the prevention of events subsequent to a first event. The study was published in 2005, and while not showing reduction in mortality in the 4.8 years of study, it did show a reduction in secondary cardiovascular outcomes with high-dose therapy. The new analysis looked at not only time to first event, but also second, third, fourth, and fifth events. High-dose therapy significantly reduced subsequent events by 17%-28%. The authors concluded that continued intensive statin therapy continues to be more effective than standard statin therapy, even beyond the first vascular event (*J Am Coll Cardiol* 2009;54:2353-2357).

Both these studies suggest that staying the course with intensive lipid-lowering in patients with cardiovascular disease is an effective long-term strategy. ■

H1N1 dosing and efficacy

Three recent studies in the Dec. 17, 2009, *New England Journal of Medicine* confirm that a single dose of the H1N1 vaccine is effective for most healthy adults and children age 3 and older. In the first study, 240 patients were equally divided to receive 15 µg or 30 µg of hemagglutinin antigen by IM injection. By day 21, antibody titers of 1:40 were observed in 95.0% of patients who received the 15 µg dose and 89.1% of patients who received the 30 µg dose (*N Engl J Med* 2009;361:2405-2413).

In the second study from China, antibody titers were done at 21 days after a first injection of 15 µg with or without adjuvant. A titer of 1:40 was achieved in 75% of subjects between age 3 and 11, 97.1% of subjects between age 12 and 17, 97.1% of subjects between age 18 and 60, and 79.1% of subjects age 61 and older. Alum adjuvant did not significantly raise antibody titers. Although a second injection at 21 days raised antibody titers, the authors conclude that a single dose of 15 µg induced a typically protective antibody response in the majority of subjects between age 12 and 60 (*N Engl J Med* 2009;361:2414-2423).

In the third study, standard H1N1 vaccine was compared to a MF59-adjuvanted vaccine (derived from cell culture rather than egg-based). A number of injection schedules were tested. Local reactions and muscle aches were more frequent in the MF59-adjuvanted vaccine. Although higher antibody titers were seen with the adjuvanted vaccine, significant titers were also seen within non-adjuvanted vaccine within 2-3 weeks (*N Engl J Med* 2009;361:2424-2435).

These findings confirm data previously published in the *Lancet* in the fall of 2009 confirming that one dose of the H1N1 vaccine seems adequate, although two doses may be required for younger children. Currently, the Centers for Disease Control and Prevention (CDC) recommends two doses for children younger than age 10, but the recommendations may change based on these findings.

In related news, the CDC is reporting that safety data regarding the H1N1 vaccine is "reassuring," with a rate of serious complications such as Guillain-Barré syndrome no higher than "background rates." The rate of adverse event reporting has been higher with the H1N1 vaccine compared to seasonal flu; however, most of these reports have been for mild reactions and may be attributed to the higher rate of awareness associated with the new vaccine. ■

FDA Actions

The FDA has approved the first generic version of donepezil (Aricept®) for the treatment of Alzheimer's disease. The new generic will be marketed as 5 mg and 10 mg orally disintegrating tablets, which dissolve on the tongue and do not need to be swallowed. Generic donepezil is expected to be available later this year. ■

An FDA advisory panel is recommending expansion of the indication for rosuvastatin (Crestor®) to include patients with normal cholesterol levels and no history of cardiovascular disease. The recommendation is based on the JUPITER trial, which showed a reduction in cardiovascular risk in patients with normal LDL cholesterol but high C-reactive protein who were treated with rosuvastatin. ■