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CLINICAL CARDIOLOGY ALERT

A monthly update of developments in cardiovascular disease

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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, Rakesh Mishra, MD, reports no consultant, stockholder, speaker's bureau, or other financial relationship with any company related to this field of study.

A Better Antiplatelet Drug?

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque

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

Sources: Wiviott SD, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357;2001-2015; Bhatt DL. Intensifying platelet inhibition — navigating between Scylla and Charybdis. *N Engl J Med*. 2007;357:2078-2081.

TREATMENT OF CARDIOVASCULAR DISEASE CONTINUES TO EMPHASIZE pharmacologic anti-platelet therapy. The platelet is the target of many medications, as thrombosis is an extremely common problem, resulting in acute coronary syndromes, cerebral vascular events, and conditions such as atrial fibrillation. Many efforts are underway to develop reliable and effective antiplatelet agents that have a minimal risk for bleeding. Prasugrel (Pras), not yet approved by the FDA, is a potent thienopyridine that acts as a prodrug similar to clopidogrel; both require conversion to an active metabolite before binding to the platelet receptor P2Y12. The TRITON-TIMI 38 trial is a phase III study in ACS patients undergoing scheduled percutaneous coronary intervention (PCI); almost all had an angioplasty; a small percentage had bypass surgery. Pras was compared to clopidogrel in this large randomized study, testing the hypothesis whether inhibition of adenosine diphosphate induced platelet aggregation with Pras would be more beneficial and/or safer than clopidogrel. The study also was designed to establish dose response relationships between the two drugs, particularly in terms of variability of effectiveness.

Wiviott and colleagues enrolled 13,608 patients with ACS who were scheduled to receive PCI or had undergone cardiac catheterization. Of the enrolled patients, three-quarters had non-ST segment elevation MI or moderate-to-high risk unstable angina; 25% had an ST elevation MI (3500 patients). Study drug therapy included a loading dose of Pras 60 mg, or 300 mg of clopidogrel in those who had a PCI. Decisions about cardiac catheterization and angioplasty were left to the discretion of the physician. Patients who had PCI received main-

VOLUME 27 • NUMBER 1 • JANUARY 2008 • PAGES 1-8

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tenance dosing with Pras or clopidogrel, 10 and 75 mg/day, respectively. All patients were on aspirin. Mean study interval was 6-15 months. The primary efficacy end point was a composite of death from CV causes, nonfatal MI, or nonfatal stroke during follow-up. Secondary end points at one month and 90 days included the primary composite, as well as death from CV causes, nonfatal MI, urgent target vessel revascularization, stent thrombosis, and a composite of multiple cardiovascular events. TIMI bleeding rates were assessed in all patients; major bleeding had to be unrelated to coronary bypass surgery. Study centers included 707 sites in 30 countries, with treatment between November 2004 and January 2006; the mean duration of therapy was 14.5 months. Half the patients received at least one drug- eluting stent, and virtually all patients had a PCI at the time of randomization.

Results: There was a major reduction in risk of the primary end point in the unstable angina/NSTEMI group in the Pras cohort of 18% ($P = 0.002$). In the ST elevation cohort, there was a 21% reduction in risk in Pras patients. Overall, 12% of the clopidogrel patients had a primary end point compared to 9.9% in the Pras group, resulting in a 19% reduction, $P < 0.001$. Similar findings were noted at 3 days and persisted throughout follow-up. From day three to the completion of the study, the primary end point had occurred in 6.9% of clopidogrel patients vs 5.6% of Pras subjects, hazard ratio 0.80, $P = 0.003$. The major component of benefit was acute myocardial infarction, reduced by 2.3% in Pras Subjects (7.4%) vs clopidogrel (9.7%). There was no difference in the rate of stroke or cardiovascular death. Also, Pras showed superior efficacy in major prespecified subgroups, without significant interactions. Benefit with Pras, with regard to the primary end point, was found both with and without glycoprotein IIB-3A receptor antagonist therapy (21% reduction in risk). Diabetics tended to have a greater benefit with Pras, 12.2% patients vs 17% in clopidogrel patients. In 10,500 patients without diabetes, the primary end point was greater in the clopidogrel group by 14%, $P = 0.02$. Significant reductions with Pras were seen for all the prespecified secondary end points, including early target vessel revascularization. Pras was beneficial for cardiovascular death, non-fatal MI, non-fatal stroke, rehospitalization for ischemia, and stent thrombosis. Bare metal stent subjects had a 52% reduction in hazard ratio $P < 0.001$ compared to patients who had at least one DES, hazard ratio of 0.43, $P < 0.001$.

The safety profile of Pras was not as good as clopidogrel, with greater bleeding risk. Major bleeding was .8% with clopidogrel vs 2.4% Pras. Life-threatening bleeds in Pras patients were also higher, 1.4% vs 0.9%, and fatal bleeding was greater in Pras patients, 0.4% vs 0.1%. Instrumentation-related bleeding and non-fatal, life-threatening bleeding were greater with Pras, as were all major and minor hemorrhages. Nevertheless, Wiviott et al concluded that there was a net clinical benefit favoring Pras (13.9% vs 12.2%), with a hazard ratio of 0.87, $P = 0.004$. Intracranial hemorrhage, or procedural bleeds, was greater in clopidogrel patients, 2.4 oz vs 2.2%. Wiviott et al state "as a result of the discordance between the efficacy result and the safety results, extensive subgroup analyses were carried out." Three groups of patients were noted to have a different risk profile than the main cohort; these include previous stroke or TIA; patients greater than 75years; and patients weighing less than 60 Kg. None of these groups had benefit from Pras, and clopidogrel patients had lower rates of complications. There was ". . . significant harm from Pras among patients with a history of cardiovascular events." However, in individuals who had none of these three risk factors, the risk gradient favored Pras by 26%, $P < 0.001$. Thus, Wiviott et al found a "substantially favorable net clinical benefit from the use of Pras."

Wiviott et al conclude that a 60 mg loading dose reduced multiple cardiovascular outcomes in patients with ACS, with a "significant 2.2% absolute reduction in the rate of the primary efficacy end point of fatal and nonfatal cardiovascular causes and nonfatal MI

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

SENIOR VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
ASSOCIATE PUBLISHER Lee Landenberger.
MANAGING EDITOR: Leslie Hamlin.
MARKETING PRODUCT MANAGER: Shawn DeMario.

GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

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

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

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1 year with Free AMA Category 1 credits: $319
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Managing Editor, at (404) 262-5416 or e-mail at leslie.hamlin@ahcmedia.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

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and stroke. Rates of ischemic events were reduced by 24%, with an absolute reduction of 2.3%.

COMMENTARY

The Triton-Timi 38 data are comparable to a number of studies indicating a significant reduction in ischemic events with aspirin, thienopyridines, and glycoprotein 2B-3A receptor antagonists, all of which have also demonstrated increased bleeding rates. In the CURE trial, the odds of major bleeding was increased by 38%, and in the Antithrombotic Trials Collaboration, aspirin increased major bleeding risk by 60%. In the present study, major hemorrhage was increased by 32% with Pras and there was "an increase in the rate of life threatening bleeding with Pras, including an increase in fatal major hemorrhage." Subgroup analyses of stroke patients, the elderly, and individuals weighing less than 60 Kg are of interest and require further exploration. It is noteworthy that patients with a prior stroke clearly did worse and had more frequent intracranial bleeding. Nevertheless, the "large majority of patients without any of these risk factors had a significant net clinical benefit with the Pras regiment study," with a hazard ratio of 0.80, $P < 0.001$.

Wiviott et al underscore prior data that with Pras, comparable dosage has been shown to "generate higher and more consistent levels of active metabolite than treatment with approved doses of clopidogrel," resulting in higher levels of mean inhibition of platelet aggregation, lower inter-patient variability, and fewer patients considered to have hyporesponsiveness." Wiviott et al note a "more rapid onset of an intra-antiplatelet effect with Pras" and a continued benefit of platelet inhibition with a higher than standard loading dose of clopidogrel. Pras 60 mg "has been shown to result in greater inhibition of platelet aggregation than use of clopidogrel (600/75 mg) in patients with chronic CAD." The data confirm a significantly greater inhibition of platelet aggregation with Pras.

The final conclusion is that the hypothesis of enhanced oral P2Y12 inhibition has been supported by doses used in this study, however, with an increase in major bleeding. Wiviott et al do not provide an algorithm for safe use of Pras or Clopidogrel and suggest that "clinicians need to weigh the benefits and risk of intensive inhibition of platelet aggregation."

An editorial by Bhatt supports the belief that TRITON-TIMI38 confirms the concept that increased platelet inhibition is associated with greater suppression of clinical events in ischemic heart disease patients. He points out that this study had more fatal events from anti-platelet therapy, more than has been seen in the other large trials. He asks, "how then, is the clinician to decide which agent to use? There is not one easy answer to this question."

This very large trial appears to be a role model of outstanding clinical research, with careful description of patients, close patient follow-up, and consistent results between the two antiplatelet drugs. At the time of this writing, it is not known whether Pras will be approved for marketing; but if so, it clearly provides the cardiologist with another arrow in the quiver for treatment of acute coronary syndrome. It is clear that patients with known or suspected cerebral vascular disease should not be given Pras, and individuals with a small body mass also should be guarded against receiving standard doses of either clopidogrel or Pras. Diabetics did well in this study, but elderly patients did not. Wiviott et al's suggestion that patients should be carefully selected before choosing a thienopyridine seems a bit unrealistic, as Pras is not available, and that sufficient discussion needs to take place regarding guidelines for use of more potent antiplatelet therapy. Certainly one consideration should be the dose of Pras. If one looks at the Kaplan-Meier curve, it is immediately clear that the major events occurred extremely early in the trial, with a very rapid upslope for both Clopidogrel and Pras. It does seem appropriate, then, that studies with Pras at a lower loading dose than 60 mg and a lower daily dose should be tested. While it is clear that Pras is more potent than clopidogrel, these are rather arbitrary doses, including the 60 mg Pras loading dose which has not been tested adequately for safety and efficacy, other than in this study. The issue is whether lowering the dose of Pras will maintain its outstanding vascular protective actions, with less bleeding and no loss of efficacy. The loading dose of clopidogrel of 300 mg is also a potential culprit in that many events were very early and presumably occurred in and around the time of peak concentrations of the drug. The same can be said about Pras, although we have no prior clinical data to help us analyze this phenomenon.

Finally, it should be recognized that the results of this trial are very robust, with respect to reduction of hard cardiovascular end points when the more potent thienopyridine is used. This is not an academic matter; the benefits from Pras are consistent, but bleeding is a big problem. It, therefore, behooves clinicians and investigators to untangle the dosing knot as rapidly as possible. ■

Warfarin vs Clopidogrel Plus Aspirin for Atrial Fibrillation

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: Hohnloser SH, et al. Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy: An ACTIVE W substudy. *J Am Coll Cardiol*. 2007;50:2156-2161.

THE ATRIAL FIBRILLATION CLOPIDOGREL TRIAL WITH Irbesartan for Prevention of Vascular Events (ACTIVE W) is a noninferiority trial comparing anticoagulation with warfarin to therapy with aspirin plus clopidogrel for stroke prevention in patients with atrial fibrillation. ACTIVE W enrolled 6706 patients and is the largest atrial fibrillation anticoagulation trial completed to date. Patients in ACTIVE W could have either paroxysmal atrial fibrillation or sustained (ie, persistent or permanent) atrial fibrillation. ACTIVE W was halted when warfarin anticoagulation was observed to be superior to aspirin and clopidogrel. In this paper, Hohnloser and colleagues look at the stroke rates in paroxysmal vs other types of atrial fibrillation and examine the effects of anticoagulation in these subsets.

In ACTIVE W, 1202 patients had paroxysmal atrial fibrillation, 891 patients had persistent atrial fibrillation, and 4604 had permanent atrial fibrillation. In this paper, the patients with persistent or permanent atrial fibrillation were analyzed together as a sustained atrial fibrillation group. Patients with paroxysmal atrial fibrillation were slightly younger, had a shorter history of atrial fibrillation, more commonly had hypertension as their primary cardiac diagnosis, and had less valvular disease, heart failure, and diabetes compared to ACTIVE W patients with sustained atrial fibrillation. Their mean CHADS 2 risk score was also lower (1.79 ± 1.03 vs 2.04 ± 1.12).

During a median follow-up of 1.3 years, there were 25 strokes and 4 non-CNS systemic embolic events among the 1202 patients with paroxysmal atrial fibrillation, compared with 136 strokes and 20 non-CNS systemic embolic events in the 5495 patients with sustained atrial fibrillation. This yields an embolic event rate of 2.0 per 100 patient years in patients with paroxysmal atrial fibrillation compared with 2.2 in patients with sustained atrial fibrillation (relative risk 0.87, 95% confidence interval 0.59 to 1.30, $P = 0.50$). After adjusting for baseline variables, the relative risk was 0.94. There was no difference in the incidence of stroke and non-CNS systemic embolism according to treatment allocation, based on the type of atrial fibrillation. Oral anticoagulation was superior to clopidogrel plus aspirin for the prevention of stroke and non-CNS embolism in both types of atrial fibrillation. The relative risk for stroke or non-CNS systemic embolism was 2.09 in the aspirin plus clopidogrel group among those with sustained atrial fibrillation and 1.61 among those with paroxysmal atrial fibrillation. Bleeding rates were higher on clopidogrel and aspirin, but there was no difference in bleeding rates based on the pattern of atrial fibrillation.

Hohnloser et al concluded that patients with paroxysmal and sustained atrial fibrillation have similar risks for stroke and non-CNS embolism, and that oral anticoagulation is more effective than antiplatelet therapy in both types of atrial fibrillation.

COMMENTARY

The prior evidence for recommendations of anticoagulation in patients with paroxysmal, as opposed to sustained, atrial fibrillation are based on only a small number of patients in randomized clinical trials. These trials used an older definition of paroxysmal atrial fibrillation and were conducted almost 20 years ago. Since then, stroke rates in all patients with atrial fibrillation has declined, with the decline possibly due to better therapy of hypertension and associated conditions. In this paper, however, Hohnloser et al show that paroxysmal atrial fibrillation, using a current definition, carries the same risk for stroke as does sustained atrial fibrillation, at least in patients with enough atrial fibrillation to warrant entry into the trial.

The major questions in dealing with patients with paroxysmal atrial fibrillation is the lower limit of frequency or duration of atrial fibrillation that is required to increase the risk of stroke. This paper shows that paroxysmal or self-terminating episodes have approximately the same prognostic significance as sustained episodes, but the paper does not provide a true estimate of atrial fibrillation burden in these patients. It is still unknown whether patients with only rare or very short episodes are also at increased risk. In clinical practice, an estimate of total atrial fibrillation burden is impossible in most patients since it is well recognized that silent episodes of atrial fibrillation are frequent. There is, however, a study ongoing that is using pacemaker memory to document the prevalence of symptomatic and asymptomatic runs of atrial fibrillation and correlate this with the risk for stroke. ■

Carotid Disease and CABG

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Van der Heyden J, et al. Staged carotid angioplasty and stenting followed by cardiac surgery in patients with severe asymptomatic carotid artery stenosis: Early and long-term results. *Circulation*. 2007;116:2036-2042.

THE MANAGEMENT OF PATIENTS WITH SIGNIFICANT carotid artery disease, who need coronary artery bypass surgery (CABG), especially if the carotid disease is asymptomatic, is controversial. In the absence of randomized trials, this report of carotid artery stenting followed by CABG in 356 patients with severe asymptomatic carotid disease is of interest. Asymptomatic was defined as no ipsilateral cerebral event in 4 months, and significant carotid disease was defined as > 80% luminal diameter reduction. Exclusion criteria included severe diffuse carotid atherosclerosis, chronic total occlusions, and long preocclusive lesions (sting sign). The primary end point was death and stroke for 30 days post CABG; secondary end points included myocardial infarction (MI). CABG was scheduled 14 to 30 days post carotid stenting, and aspirin and clopidogrel were discontinued 5 days before surgery, if possible.

Carotid stenting was successful in 98% of the patients. Death or stroke occurred in 5%; MI in 2%. Distal protection devices were used in 40% of patients. Periprocedure events were less within distal protection (2.2 vs 3.8%), but the difference was not statistically significant (P = .50). Between carotid stenting and CABG (mean 22 days), there was one death due to arrhythmias, 2 MIs, 5 episodes of unstable angina, 5 ipsilateral strokes (one severe), and 8 transient ischemic attacks. In the 3% of patients who had non-fatal cerebral events following CABG, carotid duplex ultrasound showed good stent apposition without in-stent restenosis or thrombosis. One patient died of cerebral hemorrhage. Van der Heyden et al concluded that the favorable periprocedural and 30-day results of carotid stenting in asymptomatic carotid stenosis patients before CABG suggest that this may be an attractive alternative treatment for patients with combined carotid and coronary artery disease.

COMMENTARY

Management of the patients with concomitant carotid and coronary artery disease is challenging, and there is no clearly preferable approach. Much debate in the past has revolved around when to do carotid endarterectomy (CEA): before, with, or after CABG. After CABG never gained much traction in the past because of the risk of going into cardiopulmonary bypass with significant carotid disease. Older data suggest about a 15% stroke rate with CABG when carotid lesions are > 80%. However, with off-pump surgery, this tactic could be more acceptable. Most of the debate has centered around CEA before or with CABG. Non-randomized experience shows an average MI rate of 3.6% for synchronous surgery and 6.5% for staged procedures, but this difference could be explained by selection biases; sicker patients were selected for a staged approach. The carotid stenting followed by CABG approach would seem competitive based on this study, where the MI rate was 2% and the death or stroke rate was 5%. Only a randomized trial could effectively answer this question, but may never be done.

The long-term survival for up to 5 years in this study was 76%, and freedom from death or stroke was 71%. These data are pretty good for patients with significant carotid and coronary disease. Interestingly, survival was better in women (84%). Also, age > 80 years was associated with a higher risk of a cerebral event. Repeat stenting or CEA was infrequent, and in those with cerebral events, no restenosis or thrombosis was observed in the stented site. These data are certainly encouraging.

The major issue with applying this management approach is timing. Carotid stenting should be followed with aspirin and clopidogrel indefinitely, but this increases the risk of bleeding with CABG. In lieu of these data, Van der Heyden et al devised their approach as follows: if delaying CABG was not feasible (one third of patients), they operated on antiplatelet drugs; in the other two-thirds, CABG was delayed; 14-30 days in half and > 30 days in the rest. Using this approach, no stent thrombosis or increase in bleeding was observed. They believed that a delay of 2-3 weeks was best, if possible. Although not a randomized trial, this formable experience suggests that carotid stenting followed by CABG in < 30 days is a viable option to CEA either before or with CABG. ■

Driving and ICD Shocks for Ventricular Arrhythmias

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: Albert CM, et al. Driving and implantable cardioverter-defibrillator shocks for ventricular arrhythmias: Results from the TOVA study. *J Am Coll Cardiol*. 2007;50: 2233-2240.

THE TRIGGERS OF VENTRICULAR ARRHYTHMIA (TOVA Study) was a multicenter, prospective, cohort study that examined lifestyle and psychological triggers that might result in implantable cardioverter-defibrillator (ICD) shocks for ventricular tachycardia (VT) or ventricular fibrillation (VF). The study enrolled 1188 patients who had ICDs for either primary or secondary prevention indications. At entry, and during follow-up exams, patients were asked about their driving experience. They were asked whether or not they drove a car, and to estimate how long a period they drove each week. Data on ICD discharges were collected at each study visit, and each patient was asked to report ICD shocks within 72 hours of the event. A standard post shock set of questions included data about time from last exposure to driving. Stored electrograms from shock episodes were retrieved, analyzed, and the shocks classified as either appropriate or inappropriate shocks. Using a case cross-over analysis, Albert and colleagues computed an incidence rate ratio for the association between driving and episodes of VT or VF. In this study, the period of interest included the driving time and the two subsequent 30-minute periods.

The majority of patients (80%) in TOVA reported that they drove a car at least once per week. Driving was more common among younger and better educated patients. Patients who drove were more likely to be men or Caucasian and were less likely to have diabetes, hypertension, congestive heart failure, or a left ventricular ejection fraction less than 30%. Patients with recent ICD implants drove less frequently, but even among those with recent implants, 75% reported driving at least once per week and 39% were driving more than twice per day.

During a median follow-up of 562 days, there were 324 ICD shocks for VT or VF among the 1188 patients in the study, for a shock frequency rate of 1 per 56,260 patient hours. A post-shock interview was completed for 66% of these episodes. Since some patients had multiple shocks in a single episode, there were 193 ICD shock episodes included in the final analysis. Of these, 44 shock episodes among 23 patients occurred either during, or within one hour of, driving a car. The relative risk of an ICD shock for VT or VF associated with driving was 2.24 compared to all other times during the study. Despite this increase in relative risk, the absolute risk was still low (1 episode per 25,116 person hours). The increased risk associated with driving was, however, not evident during driving itself. The highest risk time period was the 30 minutes immediately after driving. Of the 44 ICD shocks that occurred within one hour of driving, only 7 occurred while driving, 30 occurred in the 30 minutes immediately after driving, and 7 occurred in the following 30 minutes. Further examination of activities in the 30 minutes after driving revealed a possible relationship with physical exertion and anger. Examination of potential modifiers of the risk for ICD shock associated with driving was not revealing. Importantly, there was no evidence that beta blocker use significantly modified risk.

Albert et al go on to discuss potential causes for the increased risk of ICD shocks in the period immediately after driving. They cite other studies showing that exposure to particulate matter alters autonomic tone, and they postulate that this may contribute to the risks seen.

Albert et al conclude that although the risk for ICD shocks during driving is low, the period immediately after driving is associated with increased frequency of ICD shock delivery, and that the mechanism for this increased in arrhythmia risk is unknown.

COMMENTARY

The American Heart Association and the Heart Rhythm Society have recently revised their recommendations for driving done by patients with implantable defibrillators (*Circulation*. 2007;115:1170-1176). For patients with a history of sustained VT or VF, in whom the ICD is used for secondary prevention, the guidelines recommend that driving be restricted for 6 months after each episode. For patients who receive their ICD for primary prevention indications, the recommendation is to not restrict driving unless they develop a spontaneous arrhythmia that requires ICD therapy. At that point, the restrictions would be the same as in the secondary prevention group. Despite these guidelines, many patients regard driving as a necessity, and other studies have reported that 70%-80% of patients resume driving, with medical approval. A similar pattern was noted in the TOVA trial, which is the first study that has

systematically evaluated associations between driving and ICD shock episodes. Fortunately, although there is a relationship between ICD shocks and driving, the increase in risk was low and did not occur during the act of driving itself. Why shocks should occur with an increased frequency in the period immediately after driving remains uncertain. Although the TOVA investigators describe possible relationships to anger, exertion, and changes in autonomic tone, the lack of influence of beta blocking therapy suggests that other, as yet unknown, factors may be involved. ■

Biomarker in Peripheral Arterial Disease

ABSTRACT & COMMENTARY

By Andrew Boyle, MBBS, PhD

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

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

Source: Wilson AM, et al. Beta2-microglobulin as a biomarker in peripheral arterial disease: Proteomic profiling and clinical studies. *Circulation*. 2007;116:1396-1403.

Peripheral arterial disease (PAD) is an exceedingly common manifestation of atherosclerosis. Its presence heralds an increased risk for death from coronary artery disease (CAD) and stroke, yet it continues to go unrecognized in a large proportion of patients. To improve our ability to non-invasively detect PAD, Wilson and colleagues developed a simple screening test. In an elegant series of three studies, they have discovered the presence of elevated levels of beta-2 microglobulin in the serum of patients with PAD, and then validated this as a predictive marker of the disease.

In their "discovery study," subjects with (n = 45) and without PAD (n = 43) were recruited, and peripheral serum was analyzed with proteomic profiling. This technique allows quantification of large numbers of serum proteins at one time (1619 proteins in this case). They found several proteins that were statistically significantly elevated in PAD patients, and went on to identify one of them as beta-2 microglobulin. Beta-2 microglobulin levels correlated with claudication time and correlated inversely with ankle-brachial index (ABI). Next, they performed a "confirmation" study, comparing serum levels of beta-2 microglobulin in a different group of subjects known to have PAD (n = 20) vs those without PAD (n = 20). Importantly, these patients were age- and gender-matched. Serum microglobulin levels were higher in those with PAD and independently predicted low ABI.

Having screened a large number of serum proteins as potential biomarkers in their discovery study and identified and confirmed beta-2 microglobulin as an independent marker of PAD in patients with known disease, Wilson et al went on to validate this as a predictor of PAD in their "validation" study. They recruited patients referred for coronary angiography (n = 237) and correlated beta-2 microglobulin levels with ABI. These patients represent a high-risk cohort for atherosclerosis. They found that beta-2 microglobulin levels were higher in patients with PAD, regardless of the presence or absence or CAD. The odds ration for CAD in patients with elevated beta-2 microglobulin was 7.2. In addition, the combination of high sensitivity C-reactive protein (hsCRP) and beta-2 microglobulin correlated with PAD diagnosis independent of other risk factors.

Wilson et al conclude that beta-2 microglobulin is elevated in PAD, that its level correlates with disease severity, and that further studies should be performed to confirm its clinical utility.

■ COMMENTARY

Wilson et al have used the novel technique of proteomic profiling of PAD patients' blood to identify a possible biomarker of PAD. This marker, beta-2 microglobulin, is clearly elevated in association with the presence of PAD, and the levels correlate positively with claudication time and negatively with ABI. Importantly, this correlation exists even in the presence of atherosclerosis in another vascular bed, the coronary arteries. However, their data does not necessarily translate into a clinically relevant biomarker yet. Although they have taken an important first step in identifying a possible biomarker for PAD, significant concerns still exist about its applicability before we can advocate widespread clinical uptake.

Firstly, what happens in other disease states with elevated beta-2 microglobulin, such as lymphoma or multiple myeloma? Does this correlation still hold true, or should these patients be excluded. Secondly, some patients with significant PAD have normal ABI, and these would have been included in the normal group in these studies, thereby confounding the results. Thirdly, they have demonstrated that high beta-2 microglobulin is associated with PAD, but how accurate will a single reading be in determining the presence or absence of PAD in a single patient? Finally, would more aggressive treatment of these individuals, above that required

by their existing risk factor profile, affect their long-term prognosis? These questions remain unanswered at this time, and are the subject of future studies. Accordingly, at this time, measurement of beta-2 microglobulin cannot be recommended for screening for PAD. Hopefully, a non-invasive screening test for PAD will one day identify patients who will benefit from more aggressive risk factor modification to prevent cardiovascular events. ■

CME Questions

1. **Prasugrel vs clopidogrel in acute coronary patients showed:**
   a. reduced composite of death, stroke and MI.
   b. reduced MI alone.
   c. increased major bleeding.
   d. All of the above

2. **Warfarin vs aspirin plus clopidogrel for atrial fibrillation showed:**
   a. reduced strokes.
   b. reduced systemic emboli.
   c. increased bleeding complications.
   d. All of the above

3. **Carotid artery stenting prior to CABG is a viable alternative to:**
   a. staged carotid endarterectomy (CEA) followed by CABG.
   b. synchronous CEA and CABG.
   c. intensive statin therapy.
   d. A and B

4. **The highest frequency of ICD shocks for VT/VF occurs:**
   a. 30 minutes before automobile driving.
   b. during automobile driving.
   c. within 30 minutes after driving
   d. 30-60 minutes after driving.

Answers: 1. (d); 2. (d); 3. (d); 4. (c)

CME Objectives

The objectives of Clinical Cardiology Alert are to:

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

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

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

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

PHARMACOLOGY WATCH

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

FDA Warnings Dominate Pharmaceutical News

In this issue: *FDA warnings for existing drugs dominate pharmaceutical news this month. The FDA and its advisory committees have issued warnings on erythropoiesis-stimulating agents, oseltamivir (Tamiflu) and zanamivir (Relenza) for the treatment of influenza, rosiglitazone (Avandia) for the treatment of type 2 diabetes, varenicline (Chantix) to help stop smoking, the beta agonist salmeterol (Serevent), and modafinil (Provigil) for use in children. The FDA has also asked for marketing suspension of Bayer's aprotinin (Trasylol). These warnings represent a new push by the FDA to regulate existing drugs for safety after they have been approved for marketing. It also comes at a time when the FDA is cleaning up its advisory committee processes, especially with regard to limiting potential conflict of interest by advisory committee members. A summary of the new committee processes can be found at www.FDA.gov.*

Erythropoiesis-stimulating agents (ESAs) are the subject of new warnings from the FDA. The drugs, Aranesp, Epogen, and Procrit are used to treat anemia associated with cancer chemotherapy and chronic kidney failure. For cancer patients, several studies have shown that the drugs promote tumor growth and decrease survival rates in patients with advanced breast, head neck, lymphoid, and non-small cell lung cancer when given in doses that achieve a hemoglobin level of 12 g/dl or greater—the target in clinical practice. There is currently no evidence to know whether the ESA's promote tumor growth or shorten survival in patients who achieve hemoglobin levels less than 12 g/dl. The warning also specifically states that ESA's should only be used in cancer patients to treat chemotherapy-related anemia, not other causes of anemia associated with cancer and stress, and that the drug should be discontinued once chemotherapy is discontinued. For patients with chronic kidney failure, the new warnings states that ESA's should be used to maintain hemoglobin levels between 10 to 12g/dl. Higher hemoglobin levels increase risk for death and serious cardiovascular events such as stroke, heart attack, or heart failure. Finally, the new labeling emphasizes that there is no data that demonstrates that ESA's improve symptoms associated with anemia such as quality of life, fatigue, or patient well-being for patients with cancer or for patients with HIV undergoing AZT therapy.

An FDA panel is recommending new warnings on the flu drugs oseltamivir (Tamiflu-Roche) and zanamivir (Relenza-Glaxo) regarding abnormal psychiatric behavior associated with the drugs. This issue came up last year with a number of reports from Japan of erratic behavior including jumping from buildings resulting in deaths in patients taking the

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) 262-5413. E-mail: iris.young@ahcmedia.com.

drugs. Many of the cases involved children. Japan has already taken the step of warning prescribers not to use the drugs in those aged 10 to 19. The panel reports 700 cases of psychiatric adverse events associated with both drugs, and 25 potential deaths in patients taking Tamiflu. No fatalities have been reported with Relenza. Both companies insist their drugs are safe and suggest that it is difficult to know if symptoms are caused by influenza or by medications. In the meantime Roche has agreed to stronger warnings for Tamiflu. Both medications reduce the symptoms of influenza and reduce the duration by approximately one-and-a-half days.

The manufacturers of rosiglitazone (Avandia-GlaxoSmithKline) have agreed to add new information to the existing black box warning regarding the potential increased risk of heart attacks associated with drug. The FDA's press release states that "People with type 2 diabetes who have underlying heart disease or who are at high risk of heart attack should talk with their health-care provider about the revised warning as they evaluate treatment options. FDA advises health-care providers to closely monitor patients who take Avandia for cardiovascular risks." Rosiglitazone is approved for treatment of type 2 diabetes as single therapy or in combination therapy with metformin, sulfonylureas or other oral anti-diabetes treatments. GSK has been asked by the FDA to conduct a long-term study to evaluate the potential cardiovascular risks of rosiglitazone.

The FDA has issued an "Early Communication" regarding varenicline (Chantix), Pfizer's prescription medication to help adults stop smoking. Pfizer has received reports describing suicidal ideation and erratic behavior in some patients taking the drug which have been submitted to the FDA. The Agency is soliciting any additional similar cases from Pfizer and will complete analysis when more data is available and then communicate conclusions and recommendations. In the meantime the FDA recommends health-care providers monitor patients taking Chantix for behavior and mood changes.

An expert panel of the FDA is also recommending a new warning for the long acting beta agonist salmeterol (Serevent-GlaxoSmithKline) regarding use in children. Nine new adverse event reports including five deaths in children using the drug had been reported in the last year as well as reports of increased hospitalizations and asthma-related deaths in children. Before a final recommendation is made by the FDA, review of other long-acting beta agonists will also be included, including formoterol (Foradil), Novartis' long-acting beta agonist and GlaxoSmithKline's Advair which is a combination inhaler of salmeterol and fluticasone. There is some evidence that steroid inhalers mitigate the risk of asthma-related deaths in patients taking long-acting beta agonists.

An FDA panel is recommending stronger warnings for use of modafinil (Provigil) in children. The drug is approved to treat certain sleep disorders in adults, and is not approved for use in children, but is occasionally used off label for the treatment of attention deficit hyperactivity disorder. The drug's labeling was recently updated to warn of serious skin reactions and psychological problems such as hallucinations and suicidal ideation.

Bayer Pharmaceuticals is complying with the FDA's request for a marketing suspension of aprotinin (Trasylol). The drug, which is used to control bleeding during heart surgery, is the subject of a large Canadian study, the preliminary results of which have shown an increased risk of death associate with the drug.

FDA Actions

The FDA has approved over-the-counter sales of cetirizine 5 mg plus pseudoephedrine HCL 120 mg (Zyrtec-D) for adults and children aged 12 years and older. The product has been available as a prescription drug since 2001 for the treatment of upper respiratory allergies.

The FDA has approved several new generics for marketing. Oxcarbazepine (Trileptal) will soon be available as a generic in 150, 300, and 600 mg strengths the treatment of partial seizures in adults and children. Hydrocodone/ibuprofen (Vicoprofen) is also approved as a new generic. The drug is approved for short-term treatment of acute pain. Rivastigmine (Exelon) will be available in generic 1.5, 3, 4 .5, and 6 mg strengths for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia assisted with Parkinson's disease. ■