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CLINICAL CARDIOLOGY ALERT

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INSIDE

Late-Breaking Trials from the European Society of Cardiology Congress in Vienna, Austria

CONFERENCE COVERAGE

CHARM

THE 3 CHARM STUDIES (CANDESARTAN IN HEART FAILURE ASSESSment of Reduction in Mortality and Morbidity) and their combined results were presented at the ESC meeting and published in *Lancet* in September.[1-4] Since angiotensin II type 1 receptor blockers (ARB) have pharmacologic effects beyond that of angiotensin converting enzyme inhibitors (ACEI), there is the potential to further improve outcomes in patients with heart failure beyond that observed with ACEI, beta blockers, and spironolactone. Also, ARBs may be the ideal agent for those intolerant to ACEI. Thus, the CHARM investigators compared candesartan administration to placebo in 3 groups of patients with symptomatic heart failure (NYHA class II-IV): those with left ventricular ejection fraction (LVEF) > 40% (CHARM-preserved); < 40% and on ACEI (CHARM-added); and < 40% but ACEI-intolerant (CHARM-alternative). Overall, 7601 patients were randomized to candesartan titrated to a target dose of 32 mg/d or placebo and followed for at least 2 years (mean, 38 months). The primary end point for all 3 trials was cardiovascular death or hospital admission for heart failure management. Patients were excluded for abnormal renal function, elevated serum potassium, and symptomatic hypotension, as well as other standard exclusions. Total mortality and other secondary end points were also assessed.

Overall, the candesartan-treated patients showed an absolute reduction in total mortality of 1.6%, which was statistically significant after adjustment for covariates (hazard ratio, .90, 95% CI .82-.94; $P = .032$). The combined end point of cardiovascular death and hospitalization for heart failure was highly significantly reduced by candesartan (unadjusted HR .84, CI l77-.91; $P < .0001$). There was also a reduction in the number of patients developing diabetes (6% vs 7.4%; $P = .02$). Subgroup analysis showed similar benefits regardless of age, sex, NYHA class, and other drug therapy. Adverse effects surveillance showed more renal insufficiency and hyperkalemia in the

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candesartan group: Creatinine doubled in 6% vs 4%; P = .002; and potassium > 6 mmol/L 2% vs 1%; P = .017. Candesartan also lowered blood pressure an average of 5/3 mm Hg (P < .001). In CHARM-added, the primary end point was also reduced by candesartan (HR .85, CI .75-.96; P = .01) as it was in CHARM-alternative (HR .77, CI .67-.89; P = .0004). However, in CHARM-preserved it was not. Only heart failure admissions were reduced in CHARM-preserved (230 vs 279; P = .017). The investigators concluded that candesartan is generally well tolerated and reduces cardiovascular deaths and hospitalizations for heart failure in patients with symptomatic heart failure and LVEF < 40% regardless of other therapy including ACEI and beta blockers. It has a moderate effect on preventing hospital admissions in those with heart failure and LVEF > 40%.

COMMENT BY MICHAEL H. CRAWFORD, MD

This is the largest heart failure trial undertaken to date, and it used the novel approach of prospectively combining 3 complementary trials to determine the effect on total mortality. It is also another example of the danger in relying on subgroup analyses in other trials to make recommendations. In Val-Heft patients on ACEI, beta blockers and valsartan had increased mortality, suggesting that polypharmacy in heart failure therapy may have its limits. CHARM used the same entry criteria as Val-Heft and prospectively tested this hypothesis in a larger group of patients only to find that there was no difference in the effect of candesartan in those on ACEI and beta blockers. In addition, this is the first trial to show a mortality benefit with an ARB. This was not the case for studies involving losartan or valsartan, although these trials were smaller. This raises the issue of whether all ARBs are the same or whether some are superior. Finally, this is the first trial to show that ARBs have any benefit in patients with heart failure and LVEF > 40%. The reason for this benefit is not clear from the study since no measures of diastolic function were performed.

Candesartan therapy in this setting did result in adverse effects: 2.4% developed serum potassiums > 6 mmol/L, and 6.5% doubled their creatinine levels. Interestingly, 39 of the patients randomized to candesartan had a history of angioedema on ACEI, yet only 3 experienced mild angioedema on candesartan. Thus, angioedema on ACEI does not appear to be a contraindication to candesartan. Other issues with this study include the potential beneficial effects of blood pressure lowering, especially in the LVEF > 40% group. Further lowering blood pressure could also be of value in the low EF groups. On the other hand, trying to get a heart failure patient on ACEI, beta blockers, spironolactone, and ARB at doses used in trials without excessive blood pressure lowering will be a challenge. Of interest, in CHARM-added, 100% were on ACEI, but only 55% were on beta blockers and 17% were on spironolactone. Also, the combination of 3 drugs that block the rennin-angiotensin system if applied in an unselected population could result in even more dangerous hyperkalemia than was observed in this study. Finally, the addition of candesartan to patients with heart failure and low LVEF on treatment with other agents will result in 1 death prevented per 63 cases treated, which is within the range we usually consider cost effective. It appears that heart failure treatment is getting more difficult and complicated with each new trial. ■

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EUROPA

Source: Fox KM and EUROPA Investigators. *Lancet*. 2003;362:782-788.

THE EUROPEAN TRIAL OF REDUCTION OF CARDIAC events with perindopril in patients with stable coro-

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nary artery disease (EUROPA) study tested the hypothesis that perindopril in patients with stable coronary artery disease (CAD), but without heart failure or substantial hypertension, will reduce cardiovascular deaths, myocardial infarction (MI), and cardiac arrest. In this randomized, double-blind, placebo-controlled multicenter study, 13,655 patients were entered with previous MI (64%), coronary revascularization (55%), or a positive stress test only (5%). Exclusion criteria included clinical evidence of heart failure, blood pressure < 110 mm Hg systolic or > 180/100 mm Hg, or renal insufficiency. The primary end point was a combination of CV death, MI, and resuscitated cardiac arrest. All patients underwent a run in a period of 4 weeks on perindopril before randomization and 1437 (11%) were not randomized due to hypotension (2%), elevated potassium, or creatinine (1%) and other intolerances. The remaining 12,218 patients were treated with perindopril 8 mg/d or placebo. The mean follow-up was 4.2 years. The largely male population was also taking platelet inhibitors (92%), beta blockers (62%), and lipid-lowering therapy (58%). The primary end point was reached in 8% of the perindopril patients and 10% of the placebo patients, which is a 20% relative risk reduction (95% CI 9-29%; $P = .0003$). The results were consistent across all predefined subgroups including age, sex, hypertension, diabetes, and other drug therapy. When the primary end point was broken down, cardiovascular mortality alone was not significantly reduced, nor were total mortality or cardiac arrest, but MI was. The average blood pressure reduction on perindopril was 5/2 mm Hg. During the randomized portion of the trial, 23% of patients on perindopril withdrew from treatment vs 21% of placebo patients. More perindopril patients experienced cough and hypotension, but other adverse effects were similar between the 2 groups. Fox and colleagues concluded that treatment with perindopril plus other preventive medications should be considered in all patients with CAD even without apparent heart failure or substantial hypertension.

COMMENT BY MICHAEL H. CRAWFORD, MD

Previous studies have shown that angiotensin converting enzyme inhibitors (ACEI) reduce morbidity and mortality in heart failure, left ventricular dysfunction, post-MI, hypertension, and high risk for vascular disease patients. These results extend the secondary prevention role of ACEI to stable CAD patients. Fox et al chose perindopril because it is a long-acting ACEI with high tissue penetration that has been shown to have anti-ischemic, anti-atherosclerosis, and positive left ventricular remodeling effects. Perindopril has similar properties to ramapril, which was used in the HOPE study. Whether other ACEIs would perform similarly is not known. One unknown in the EUROPA study is the patients' left ventricular function. Although most probably had normal or near normal left ventricular function, some may have had reduced function since 64% had a previous MI. Thus, some of the observed benefit may have been due to patients with reduced left ventricular function. Also, it is hard to know how much of the benefit observed was due to blood pressure lowering since only patients with substantial hypertension were excluded (> 180/100 mm Hg). Finally, although the drug appeared well tolerated, 11% were excluded in the run-in phase on perindopril and another 23% withdrew during the study. So despite the intentions of Fox et al, only two-thirds of the enrolled patients could take perindopril long term. In a less selected general population of CAD patients, this figure is likely to be lower. However, given the growing mass of positive data for secondary prevention with ACEI, it appears that ACEI and perhaps the long-acting, tissue-penetrating ACEIs should be part of the regimen of aspirin, statins, beta blockers, and other risk factor-lowering strategies in all CAD patients. ■

TAXUS IV

Source: Stone GW, Ellis S. Presented September 15, 2003, at the annual Transcatheter Cardiovascular Therapeutics Symposium in Washington, DC.

DRS. GREGG STONE AND STEPHEN ELLIS PRESENTED the 9-month clinical and angiographic results from TAXUS IV, which was designed to assess the safety and efficacy of the TAXUS™ slow-release polymer-based paclitaxel-eluting Express2 stent (Boston Scientific) in a broad cross-section of patients. This study randomized 1326 patients to receive the TAXUS™ stent or the bare metal Express2 stent. Lesions were single, de novo, between 10-28 mm in length, in vessels > 2.5 mm, and less than 3.75 mm in diameter. All patients received pre-randomization ASA 325 mg, and clopidogrel 300 mg was recommended. Patients were stratified by presence of diabetes and vessel diameter prior to randomization. All patients received clopidogrel 75 mg daily for 6 months after procedure. Clinical follow-up was obtained at 1, 4, and 9 months and is planned yearly for 5 years. The primary end point was ischemia-driven target vessel revascularization (TVR) at 9 months.

A total of 662 patients underwent TAXUS™ stent implantation, and 652 received control stents. There were no significant differences between the groups with regard to baseline clinical features. A total of 23.4% of TAXUS™ patients and 25% of control patients were diabetic ($P = .52$). There were no differences between the groups with

regard to baseline angiographic or procedural characteristics. GP IIb-IIIa inhibitors were used in 57.7% of TAXUS™ patients and 56.7% of controls (P = NS). Acute angiographic results were equivalent between the 2 groups. At 30 days, there were no differences between the groups with regard to MACE or any of its individual components (cardiac death, MI, target lesion revascularization (TLR), or TVR. At 9 months, TVR was reduced by 61% in the TAXUS™ group (4.7% vs 12.0%; $P < .0001$) and TLR was reduced by 73% (3.0% vs 11.3%; $P < .0001$). Nine-month MACE was significantly lower in the TAXUS™ group (8.5% vs 15.0%; $P = .0002$), driven by the need for repeat revascularization, as there were no differences in the rates of cardiac death or MI. Subgroup analysis demonstrated significant reductions in restenosis among LAD vs non-LAD location, diabetics (particularly those receiving insulin), in small vessels (< 3.0 mm), and in long lesion subsets. Stent thrombosis rates were low, with 4 (0.6%) in the TAXUS™ group and 5 (0.8%) in the control group. Angiographic follow-up obtained in 559 patients demonstrated lower rates of binary angiographic restenosis (> 50% diameter stenosis) and lower rate loss in the patients receiving the TAXUS™ stent. In conclusion, TAXUS IV demonstrates that the paclitaxel-eluting TAXUS™ stent is safe and highly effective in reducing clinical and angiographic restenosis in a clinically relevant population of patients undergoing coronary stent implantation.

COMMENT BY SARAH M. VERNON, MD

To say that the results of TAXUS IV have been highly anticipated would be an understatement. Interventional cardiologists in the United States have been quick to embrace the Cypher sirolimus-eluting Bx-VELOCITY stent (Johnson & Johnson) based primarily on the results of the SIRIUS study. However, enthusiasm has been tempered somewhat by inconsistent availability, some limitations in stent flexibility and deliverability, and by early reports suggesting that stent thrombosis rates have been higher in clinical practice than were reported in clinical trials. An embargo leak prior to the presentation of TAXUS IV resulted in a drop in stock price of Johnson & Johnson, the makers of the only drug-eluting coronary stent currently FDA approved. Boston Scientific initially filed data with the FDA in June 2003, and the results of TAXUS IV are scheduled to be reviewed by the FDA on November 20, 2003, which the company hopes would put the TAXUS™ stent on track for approval late in 2003.

What TAXUS IV does not tell us is how this stent will perform in comparison to the Cypher sirolimus-eluting stent currently in clinical use. Data addressing this question may, or may not, become available in the future. The start of the 1200-patient REALITY trial comparing the Cypher and TAXUS™ stents head-to-head has been delayed and may not go forward as planned. ■

ISAR-COOL

Source: Neumann F, Kastrati AP-MG. *JAMA*. 2003; 290:1593-1599.

The intracoronary stenting with antithrombotic Regimen Cooling Off (ISAR-COOL) study results were initially presented at the 2002 American Heart Association Scientific Session. This study randomized high-risk acute coronary syndrome (ACS) patients (those with elevated troponin or ST-segment depression) to receive antithrombotic pretreatment for 3-5 days or for less than 6 hours prior to catheterization and intervention. The antithrombotic regimen studied consisted of intravenous heparin and tirofiban, ASA (500 mg IV bolus, followed by 100 mg PO twice daily), and clopidogrel (600 mg loading dose followed by 75 mg twice daily). The primary end point was the composite of large nonfatal MI (Q-waves, new LBBB or CKMB 5 × normal) or death at 30 days. Bleeding complications were also assessed and defined using standard TIMI trial definitions.

A total of 410 patients were randomized between February 2000 and April 2002. The antithrombotic pretreatment and early intervention groups were well matched in terms of baseline clinical characteristics, entry criteria, and CAD burden. Definitive treatment (method of revascularization) was comparable between the 2 groups. Of the antithrombotic pretreated patients, 64.3% underwent PCI (91.7% received stents), and 7.7% underwent CABG; of the early intervention patients, 70.4% underwent PCI (86.7% received stents), and 7.9% underwent CABG. The primary end point was reached in 11.6% (21 MIs, 3 deaths) of the antithrombotic pretreatment group and in 5.9% (12 MIs, no deaths) of the early intervention group (P = .04). The difference on outcome between the groups was attributable to events occurring prior to intervention, with equal event rates occurring after intervention was completed. There was no difference in bleeding complication rates between the groups. Neumann and Kastrati concluded that deferral of coronary intervention for prolonged antithrombotic treatment did not improve outcome in ACS patients undergoing revascularization when compared with "immediate" intervention using an early and intense antiplatelet regimen.

COMMENT BY SARAH M. VERNON, MD

The "early invasive" approach to the management of

patients with acute coronary syndromes (ACS), particularly in those patients with high-risk features such as positive biomarkers or ST segment depression, has emerged as the superior strategy for reducing adverse cardiac events in this patient population. "Early" catheterization and revascularization, by percutaneous coronary intervention in most cases, has become the standard of care in the management of ACS. At the same time, early administration of increasingly potent antiplatelet and antithrombotic therapies have also been shown to improve outcomes in patients with ACS and in many patients undergoing PCI. The concept of "cooling off" the patient with ACS has considerable appeal, in part because of what we know about the pathobiology of passivation of the unstable coronary plaque, and in part because we know that complication rates of PCI are higher in patients with unstable syndromes. The CREDO1 trial (reviewed in the December 2002 issue of *Clinical Cardiology Alert*) demonstrated the benefit of clopidogrel administered as a 300-mg loading dose before PCI and continued long term for 1 year, well beyond the standard port-procedural duration of 1 month. Subgroup analysis from CREDO showed that periprocedural outcomes were better when patients were pretreated with clopidogrel more than 6 hours prior to PCI. This has led many of us to initiate clopidogrel loading as early as possible in the management of the ACS patient destined for early invasive management. However, given the CREDO data, should we delay catheterization to give clopidogrel time to work?

ISAR-COOL only partly addresses this issue. The delay to catheterization of 3-5 days was quite long—longer, in fact, than most hospitalizations for ACS in this country (with the exception of the late Friday admission deferred for the weekend for scheduled catheterization on Monday morning). This study doesn't tell us whether waiting 1 hour or 6 hours or 12 after initiation of antithrombotic therapy yields the best outcomes with PCI. However, the end point of this study is quite "hard" and despite the extremely potent antithrombotic regimen used in this study, 6.3% of patients treated more conservatively experienced a large MI or death while waiting to undergo catheterization and revascularization. This study suggests that high-risk patients should be treated as early as possible with the full complement of antithrombotic and antiplatelet drugs available and should be sent to the cardiac cath lab promptly (and probably not waiting until the following Monday). ■

Reference

1. Steinhubl SR, et al. *JAMA*. 2002;288:2411-2420.

Intensity of Anticoagulation in Atrial Fibrillation

ABSTRACT & COMMENTARY

Synopsis: *Anticoagulation that results in an INR of 2.0 or more reduces both the frequency and severity of stroke among patients with nonvalvular atrial fibrillation. Lower intensity anticoagulation was significantly less effective.*

Source: Hylek EM, et al. *N Engl J Med*. 2003;349:1019-1026.

HYLEK AND COLLEAGUES REPORT ON THE EFFECTS OF varying intensities of oral anticoagulation on the frequency and severity of strokes among patients with atrial fibrillation. The data were obtained from a longitudinal database of adult patients with nonvalvular atrial fibrillation enrolled in the Kaiser Permanente of Northern California health care system. The cohort included 13,559 patients. Patients who suffered an ischemic stroke were identified by review of hospitalization and billing claims data. The use of warfarin and aspirin at the time of stroke was determined by a review of emergency room data or hospital admission notes. The INR value was recorded at presentation or, if admission data were not available, from a recent clinic visit. Prior anticoagulation data were obtained from pharmacy and laboratory records. Stroke was classified using a modified Rankin scale. Mortality data (30 day) were obtained from health plan records. The independent effect of antithrombotic therapy on 30-day mortality was assessed using a Cox proportional hazard model.

During an 18-month period, 618 patients with atrial fibrillation and ischemic stroke were identified, but 22 were excluded from analysis because of incomplete data or because they had an intracerebral hemorrhage due to thrombolytic or heparin therapy after their initial presentation.

Of the remaining 596 patients, 188 (32%) were taking warfarin, 160 (27%) were taking aspirin, and 248 (42%) were taking neither drug. Among those on warfarin, the median INR was 1.7, and 62% of the values were less than 2.0. Historical data from these patients obtained prior to their presentation showed a median INR value of 2.2.

Stroke severity was strongly correlated with 30-day mortality. In turn, anticoagulation intensity had a significant influence on the severity of stroke. Among patients taking warfarin, 15% of those with an INR below 2.0 either died or were discharged with a severe stroke as compared with 5% of those with an INR of 2.0 or

greater. Patients with an INR of less than 1.5 had an outcome similar to those with an INR of 1.5-1.9. Patients who were not taking anticoagulants had worse outcomes, with 22% either dead or discharged with a severe stroke. Among patients taking aspirin, 13% either died or were discharged with a severe stroke. After adjustment for baseline variables, the medication group remained a significant predictor of outcome. Compared to patients with an INR of 2.0 or greater, patients not taking any anticoagulant had a relative hazard for death of 4.9. Patients taking aspirin had a hazard ratio of 2.5. Patients with an INR below 2.0 had a hazard ratio of 3.4.

Incidence rates of ischemic stroke in the entire cohort were also calculated for patients taking warfarin. If the INR was < 1.5, the rate was 7.7 per 100 person-years. For INR values between 1.5 and 1.9, the stroke rate was 1.9 per 100 person-years. For values from 2.0 to 3.9, stroke rates were below 0.9 per 100 person-years. Higher stroke and intracerebral hemorrhage rates were noted when INR values were 4.0 or greater.

Hylek et al conclude that anticoagulation that results in an INR of 2.0 or more reduces both the frequency and severity of stroke among patients with nonvalvular atrial fibrillation. Lower intensity anticoagulation was significantly less effective.

COMMENT BY JOHN P. DiMARCO, MD, PhD

This paper provides important observational data concerning anticoagulation in patients with atrial fibrillation. Current guidelines recommend maintaining an INR between 2.0 and 3.0 in patients with atrial fibrillation and one or more risk factors for stroke, but it suggests use of a lower INR target (1.5-1.9) in patients older than 75 years of age because of an increased risk for bleeding.[1] The data in this paper do not support this suggestion. This lower-target INR will provide some protection against stroke but does not mitigate the severity of stroke should one occur.

Management of warfarin anticoagulation is challenging. Up to one-third of patients screened may have strong contraindications to anticoagulation at presentation. Bleeding, both major and minor, is frequent during long-term anticoagulation. Even in clinical trials, only 60-65% of INR values are within the therapeutic range. Although the concept of using a lower target INR to reduce bleeding risk might seem attractive, this paper points out significant limitations to this approach. The safety margin for patients with a lowered target is too small for this approach to be used unless bleeding during therapy necessitates it.

Unfortunately, this paper does not include information on why each anticoagulation approach was chosen for individual patients. Many of those taking either no anticoagulant or aspirin might have had firm contraindications to warfarin therapy. This paper highlights the difficult risk:benefit analysis required of clinicians managing patients with atrial fibrillation. Clearly, if anticoagulation is prescribed, efforts to ensure adequate INR values must be taken. ■

Reference

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Depressed Platelets

ABSTRACT & COMMENTARY

Synopsis: *Sertraline contributed to a decrease in platelet activation over and above either aspirin or thienopyridines, and the SSRI "might represent an attractive additional advantage for patients with depression and comorbid coronary artery disease and stroke."*

Source: Serebruany VL, et al. *Circulation*. 2003;108: 939-944.

It is well known that clinical depression is common after acute myocardial infarction and unstable angina and is associated with considerably higher mortality. Up to 2- to 5-fold increases in mortality risk have been reported; multiple reports have linked depression in acute coronary syndrome (ACS) patients with decreased survival. A number of observations suggest that depression may be related to enhanced platelet activation as well as endothelial dysfunction. In 2002, the results of SADHART were published.[1] This multicenter trial was carried out in the United States and Canada; 356 clinically depressed patients following ACS were randomized to placebo or sertraline for a period of 6 months. The sertraline (selective serotonin reuptake inhibitor or SSRI) cohort demonstrated a trend toward a reduction in morbidity and mortality without an increase in risk; there was no statistically significant reduction in major end points. Other studies have been reported suggesting that SSRI treatment in post-MI and stroke patients may be beneficial, but as yet, there is no hard evidence that pharmacologic treatment of depression improves survival in these patients. The present report is a substudy assessing platelet and endothelial biomarkers from 5 SADHART outpatient sites. All measurements were made at baseline, 6, and 16 weeks. This subset of 64 patients from SADHART represents 17.5% of the entire study. Assessment of depression was made clinically as well as using validated tools; all patients met DSM-IV criteria for major

depression. Platelet biomarkers included platelet factor 4, ß-thromboglobulin, and platelet/endothelial cell adhesion molecule-1 (PECAM-1). P-selectin, vascular cell adhesion molecule-1 (VCAM-1), E-selectin, thromboxane B_2, and prostacyclin were also measured using meticulous techniques in highly standardized and experienced laboratories. The primary end point of the substudy was a change in components of platelet function at week 6 compared to baseline, as well as week 16.

Results

The 64 post-ACS patients in the platelet substudy were generally similar to the other 305 SADHART patients, although there were some minor inequities in a variety of clinical end points. The biomarker data support a role for sertraline in modulating several measurements of platelet function. Placebo and sertraline patients experienced a decrease in platelet markers over the 4-month period, but the reductions were for the most part greater in the SSRI cohort. For instance, decreases from baseline were statistically significant in 12 of 16 measurements in the sertraline group compared to only 8 of 16 in the placebo group. Using a repeated-measures ANOVA, sertraline was superior to placebo regarding measurements of platelet activation (eg, ßTG at 6 and 16 weeks and at 16 weeks for P-selectin). "Biomarker changes were numerically greater on drug than placebo in 14 of the 16 observations." Serebruany et al conclude that sertraline was associated with reductions in platelets/endothelial activation, which may reflect a beneficial component resulting in increased survival in depressed patients, as suggested but not proven by the main SADHART study and other trials. Serebruany et al suggest that the platelet effects of SSRIs may represent an independent therapeutic modality other than treatment of depression and that these effects might be applicable to nondepressed patients with coronary artery disease. They suggest, "SSRIs might represent an attractive class of dual agents for treating depression, as well as protecting patients from secondary vascular events by simultaneously inhibiting platelet activation." They emphasize the considerable increase in mortality in depressed patients with ACS, which may be present in as many as 40% of individuals, a minority of which develop major depression. In the Cardiac Arrhythmia Pilot Study in post-AMI patients with ventricular arrhythmias, the depressed patients had up to a 20-fold increased mortality from cardiac arrest at 1 year. Other studies in depressed patients have shown alterations in platelet function, as well as increases in serotonin 5HT receptor binding sites on the platelet surface. Several abnormalities in depressed subjects have been reported relating to platelet serotonin receptors; elevated ß-TG and PF4 have been documented as well as a variety of other serotonin abnormalities. Serebruany et al conclude that the sertraline-related platelet alterations in this small cohort, particularly decreases in BTG and E-selectin, may represent significant evidence of improved platelet function. PECAM-1 and VCAM-1 did not change significantly. Serebruany et al suggest that the results may indicate that some SSRI effects are directed at the platelet level rather than the brain. No single biomarker appears to be indicative of SSRI action. Multiple markers of platelet activation increase immediately after an ACS and decrease over time. Most of the patients in this study were on aspirin or a thienopyridine; thus, if sertraline did induce a significant effect on platelet activation, it would be in addition to the platelet anti-aggregatory affects of aspirin and clopidogrel and presumably with a different mechanism. Serebruany et al are convinced that "excessive transcardiac accumulation of serotonin" is an adverse phenomenon and that activated platelets resulting in local release of serotonin may be associated with vasoconstriction and recurrent cycles of platelet aggregation. Animal models would appear to support a protective effect of serotonin receptor antagonists. Serebruany et al conclude that sertraline contributed to a decrease in platelet activation over and above either aspirin or thienopyridines and that the SSRI "might represent an attractive additional advantage for patients with depression and comorbid coronary artery disease and stroke."

COMMENT BY JONATHAN ABRAMS, MD

Careful scrutiny of the biomarker data in this platelet substudy of SADHART does confirm that sertraline diminishes platelet biomarkers more than placebo at 16 weeks, although some of the differences are not statistically significant. Many comparisons are not significant at a single time point, although sertraline vs placebo across all weeks was found to be effective in reducing ß-TG (P = .005) and E-selectin (P = .013). All other markers were not different from placebo when compared across the entire 16 weeks of the study. It is difficult to know whether these data reflect random noise, differences in platelet activation, or a clinically relevant finding that sertraline does contribute to a decreased risk of coronary and cerebral vascular disease. The results of SADHART as well as other antidepressant trials have been disappointing, and at the present time a uniform approach cannot be advocated in post-MI individuals who are depressed. The EnrichD trial of counseling failed to decrease mortality in depressed patients. Nevertheless, counseling or psychotherapy, as well as careful selection of an antidepressant agent, particularly an SSRI, clearly are indicated in the substantial number of patients who develop clinical depression. However, one problem is the rapid turnover of ACS subjects in the hospital environment, often with an

invasive cardiologist caring for the patients during the short-term hospitalization. This may decrease the likelihood of detection of depression unless carefully sought by trained personnel, particularly during the hospital setting. Depressed patients often have psychomotor slowing and may be more likely to be noncompliant with medications, exercise, and diet; it is not surprising that mortality rates are higher, although it is unlikely that major depression in the present era carries the enormous risk when compared to many years ago before the advent of IIb/IIIa receptor blockers, clopidogrel, and routine treatment with statins, ACE inhibitors, and beta blockers. In addition, there is evidence that depression may be related to immune abnormalities as well as endothelial dysfunction.

The SADHART investigators are to be congratulated on the meticulous approach they took to the issue of platelet function. However, the actual number of individuals studied is quiet small, reflecting less than 20% of the entire SADHART population. One cannot make definitive conclusions about the SSRI-platelet hypothesis until large trial results are available. ■

Reference

1. Sertraline AntiDepressant Heart Attack Randomized Trial. *JAMA*. 2002;288:701-709.

CME Questions

21. ACE inhibitors are indicated for secondary prevention in patients:

a. post-MI.
b. with LV dysfunction.
c. with stable CAD.
d. All of the above

22. In patients with nonvalvular atrial fibrillation, the recommended INR is:

a. 1.5-1.9.
b. 2.0-3.0.
c. 2.5-3.5.
d. None of the above

23. Sertraline therapy in acute myocardial infarction patients:

a. reduced mortality.
b. reduced subsequent nonfatal events.
c. reduced platelet activation.
d. All of the above

24. The new paclitaxel eluting stent:

a. reduced cardiac death.
b. reduced MI.
c. reduced instent restenosis.
d. All of the above

Answers: 21(d); 22(b); 23(c); 24(c)

Annual Statement of Ownership, Management, and Circulation

United States Postal Service
Statement of Ownership, Management, and Circulation

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