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INSIDE

More Late-Breaking Clinical Trials Presented at the American College of Cardiology Meeting

CONFERENCE COVERAGE

DINAMIT

DRS. STUART CONNOLLY AND STEFAN HOHNLOSER PRESENTED results from the Defibrillator In Acute Myocardial Infarction Trial (DINAMIT). Prior studies had shown that patients with recent myocardial infarction and left ventricular dysfunction are at high risk for death in the period after myocardial infarction. It has also been shown that impaired cardiac autonomic modulation is associated with both arrhythmic events and sudden death. Therefore, the DINAMIT investigators began a study on primary prevention of death with implantable cardioverter defibrillators including patients with recent (within 6-40 days) myocardial infarction, a left ventricular ejection fraction of ≤ 35%, and depressed heart rate variability. Patients with New York Heart Association class IV heart failure were excluded. Importantly, patients who underwent either coronary artery bypass grafting or 3-vessel percutaneous angioplasty after the myocardial infarction were also excluded.

Patients were enrolled at 73 centers in 10 countries. Most of the centers were either in Canada or Europe. There were only 2 US centers. Enrollment began in April 1998 and was concluded in September 2002. The mean follow-up was 2.5 years, and 674 patients were randomized. The primary outcome was mortality from all causes. Baseline demographics were as follows: male gender, 76%; mean age, 61.5 years; histories of prior infarct, 35%; diabetes, 30%; hypertension, 46%; and anterior myocardial infarction location, 72%. Slightly more than half of the patients had overt congestive heart failure during the index myocardial infarction. Mechanical ventilation was required for stabilization in 10% of the patients and intra-aortic balloon counterpulsation in 6%. During the index myocardial infarction, 65% of the patients received acute reperfusion therapy. Among those who did receive reperfusion therapy, 52% of those in the ICD group and 35% of those in the control group received only intravenous thrombolytics. Data about coronary anato-

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my either at the time of the initial infarct or at a follow-up catheterization were not reported, but the left ventricular ejection fraction was 28% in both groups. At enrollment, 87% of the patients were receiving a beta adrenergic blocker, 95% were on an ACE inhibitor, 79% were on lipid-lowering drugs, and 92% were on antiplatelet agents.

Multivariate analysis of survival showed no improvement in mortality with ICD therapy. The annual mortality rate was 7.5% in the ICD group vs 6.9% in the control group. The hazard ratio for ICD therapy was 1.08 (95% confidence interval, 0.76-1.55; $P = .66$). There was a marked decrease in the number of deaths classified as arrhythmic in the ICD group, but it did not result in improvement of overall mortality. In conclusion, the authors felt that ICD therapy did not reduce mortality in high-risk patients early after myocardial infarction.

COMMENT BY JOHN DiMARCO, MD, PhD

DINAMIT is another important study that deals with the use of ICD therapy for primary prevention of death. Most studies of either secondary or primary prevention of death in patients with established heart disease have shown a mortality reduction of between 20% and 30%. In DINAMIT, reduction in arrhythmic mortality was seen, but no decrease in overall mortality was observed. The reason for this is uncertain based on the data released so far. However, one might speculate that recurrent ischemic events were very important in this group. From the data presented so far, it appears that many patients were incompletely revascularized at the time of the index myocardial infarction. Patients with incomplete revascularization would have formed a high-risk subgroup unlikely to derive optimal benefit from an ICD. It is possible that ischemic events or changes in ventricular remodeling leading to end-stage heart failure were more important than arrhythmias arising from scar in determining mortality in these patients. A recent paper from the MADIT II Trial by Wilbur et al[1] showed that there was no benefit in a subgroup of patients who received their defibrillator within the first 18 months after myocardial infarction. Again, this probably represents our poor ability to risk-stratify patients for deaths due to primary arrhythmia as opposed to progressive myocardial disease in patients with recent major events.

The DINAMIT data will leave clinicians with a continuing clinical problem. The data would suggest that ICD implant is not beneficial in patients with recent myocardial infarction. However, clinicians must still deal with patients with recent myocardial infarctions who by all clinical criteria are at high risk. At present, data from randomized trials indicate that an aggressive revascularization strategy and optimal medical therapy are the only interventions of proven clinical benefit. It is likely that Medicare and other insurers will restrict the use of ICDs in these subgroups unless some more effective risk stratification for arrhythmias as the primary mechanism for death can be identified. ■

Reference

1. Wilbur DJ, et al. *Circulation*. 2004;109:1082-1084.

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EDITORIAL GROUP HEAD: Lee Landenberger.
MANAGING EDITOR: Robert Kimball.
ASSOCIATE MANAGING EDITOR: Christie Messina Petrone.
MARKETING PRODUCT MANAGER: Schandale Kornegay.

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SCD-HeFT

DR. GUST BARDY PRESENTED THE RESULTS FROM THE Sudden Cardiac Death and Heart Failure Trial (SCD-HeFT). The primary hypothesis for SCD-HeFT was to determine if either amiodarone or a shock-only implantable cardioverter defibrillator (ICD) reduced all-cause mortality compared to placebo in patients with either ischemic or nonischemic New York Heart Association class II or III congestive heart failure with systolic dysfunction. Patients were enrolled in 148 sites in the United States, Canada, and New Zealand. The total enrollment was 2521 patients. Enrollment began in September 1997 and ended in July 2001 when the target enrollment number had been reached. Follow-up was continued until the end of October 2003. Patients were randomized to either drug therapy or ICD therapy. The

drug therapy group then was again randomized to either amiodarone or placebo, and drugs were prescribed in a double-blind fashion. Patients who received amiodarone received a 4-week period of intermediate dose loading and then were treated with between 200 mg and 400 mg per day depending upon their body weight. Patients who received an ICD received a single-chamber ICD that was programmed to deliver VF therapy only with a fibrillation detection interval of 320 msec. Back-up ventricular pacing was provided, if required, at a rate of 50 bpm with hysteresis from 34 bpm.

The mean age of the patients enrolled was 60 years. Females compromised 23% of the group; 23% were non-Caucasian. Heart failure had been present for a mean duration of 24.5 months. The mean left ventricular ejection fraction was 25%. Seventy percent of the group had New York Heart Association class II congestive heart failure, with the remainder having class III. Ischemic heart disease was the primary diagnosis in 52%, and the remaining 48% had a nonischemic cardiomyopathy. Coronary artery bypass grafting or revascularization had been performed before trial entry in 37% of the patients. The mean QRS duration was 112 msec, with 41% of the patients having a QRS duration of ≥ 120 msec. Medications for heart failure were carefully followed in the study. At baseline, 96% of the patients were receiving either an ACE inhibitor or an angiotensin receptor blocker, 69% were receiving a beta-blocker, 19% were receiving spironolactone, and 82% were receiving loop diuretics. Appropriate pharmacologic therapy was well maintained throughout the study.

Mortality was analyzed by intention to treat. In the placebo group, the mortality rate was close to linear throughout the study, with an actuarial rate of 7.2% per year. Amiodarone therapy produced no improvement in mortality. The hazard ratio for amiodarone vs placebo was 1.06 (P = .529). A subgroup analysis suggested a slightly higher mortality in patients with class III congestive heart failure who received amiodarone, but all other subgroups had no significant differences in mortality. In contrast, ICD therapy showed significant benefit. Over the 5 years of the study, there was a 23% reduction in mortality with ICD therapy vs placebo. The hazard ratio was 0.73 (97.5% confidence interval, 0.62-0.96; P = .007). Subgroup analysis suggested significantly increased benefit in patients with class II congestive heart failure and in patients who were enrolled outside the United States. Importantly, there was no difference between patients who had ischemic heart disease or nonischemic heart disease as the etiology for their heart failure.

COMMENT BY JOHN DiMARCO, MD, PhD

SCD-HeFT is a very important trial. It clarifies some of the major issues confronting physicians who are attempting to use either drug therapy or ICD therapy for the primary prevention of sudden cardiac death. Numerous prior studies have looked at the use of amiodarone for primary prevention of death after myocardial infarction and in patients with congestive heart failure. Among patients with recent myocardial infarction, a slight benefit had been suggested but was not present in all trials. In patients with congestive heart failure, one study (GESICA) suggested decreased mortality, whereas another study (CHF-STAT) showed no benefit. The current data confirm that amiodarone produces no benefit in patients with congestive heart failure in overall mortality. Therefore, the use of amiodarone should be only for control of symptoms.

In SCD-HeFT, the investigators observed a 23% reduction in overall mortality with the use of ICD therapy. This is consistent with the mortality reduction seen in other primary prevention trials. It clearly establishes that there is benefit in patients with nonischemic heart disease as well as in patients with ischemic heart disease. It also confirms that benefit is seen in patients with both normal QRS durations and wide QRS durations.

The final important observation from SCD-HeFT is the marked improvement in total mortality produced with recent innovations in pharmacologic therapy. The overall mortality seen in SCD-HeFT was only 7.2% per year. This is a 28% reduction from what was initially estimated when the study was planned. It is important to note, however, that ICD therapy is an additive to the improvement produced by pharmacologic therapy. However, as mortality in patients with heart failure declines, the absolute benefit seen with a 23% mortality reduction drops to under 2% per year. This relatively low absolute benefit may make Medicare and other insurers reluctant to approve ICD implants in all patients who have heart failure and left ventricular dysfunction.

Although SCD-HeFT did not show benefit in a subgroup of patients with class III congestive heart failure, it should be remembered that another trial in patients with nonischemic cardiomyopathy (DEFINITE) showed increased benefit in patients with class III congestive heart failure. Congestive heart failure class may be difficult to estimate since it depends on the patient's current status and where he is in terms of his pharmacologic management. Therefore, I don't think too much weight should be placed on the observation at this time.

In conclusion, SCD-HeFT is a critical trial, which confirms the benefits of ICD therapy in patients with heart failure. It also clarifies the role of amiodarone in these

patients. We can now expect major discussions with the Centers for Medicare & Medicaid Services and other insurers about the cost-effectiveness of the mortality reduction in these patients. It will be important for payers to accept the importance of these data before ICD therapy can be widely used in patients with heart failure. ■

PROVE IT

Source: Cannon CP, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495-1504.

PROVE IT IS A LONG-AWAITED LATE-BREAKING CLINICAL trial presented at the American College of Cardiology Annual Meeting in March. This was a comparison of 2 different statins and doses in patients with an acute coronary syndrome (ACS). The complete study was published in the April 8, 2004, *New England Journal of Medicine* and was released on its web site before publication.

PROVE IT was funded by Bristol-Myers Squibb and Sanyko and was designed as a noninferiority trial to assess whether there would be a difference in clinical outcomes in ACS patients given either pravastatin (P) or atorvastatin (A) in different doses. This study was carried out in 8 countries and 250 hospitals; the final cohort was 4152 patients, average age of 58, 78% male, who were hospitalized with either unstable angina or myocardial infarction (MI). The majority of subjects underwent revascularization (70% percutaneous coronary intervention [PCI]). After stabilization, and within 10 days of presentation, patients were randomized to 40 mg of P or 80 mg of A. Of note, this study used a 2-by-2 factorial design, with a separate investigation of a 10-day course of the antibiotic gatifloxacin or placebo; the results of this component are not yet available. There were a number of exclusions, most significantly including acute MI within 6 months, bypass surgery within 2 months, or use of inhibitors of the cytochrome P-450 3A4 system. Patients could be randomized if they had been on lipid-modifying therapy prior to admission if total cholesterol was < 200 mg/dL at the time of initial screening. The cholesterol entry cutpoint for statin non-users was < 240 mg/dL measured within 24 hours of admission. Of note, prior statin therapy was reported in 25% of the entire cohort, which included 37% smokers, 50% hypertensives, 18% diabetics, 18% prior MI, and 15% prior PCI. Baseline lipids were cholesterol 180 mg/dL; LDL 106; HDL 39; and triglycerides 155. Patients all had dietary counseling and frequent visits/blood work. The trial ended in late 2003, with an average follow-up of 24 months (range, 18-36), at which time 925 prespecified 925 events were reported. Primary end points were all-cause death, MI, revascularization for unstable angina, any revascularization 30 days after enrollment, and stroke. There were a variety of secondary end points, most consisting of individual primary end points. A definition on noninferiority was established after consideration of 2-year event rates. This was not demonstrated; atorvastatin was superior to pravastatin.

Specific Results

The Kaplan-Meier event rates of the primary end point demonstrated a 16% reduction in favor of A (26.3% P and 22.4% A; $P = .005$). Secondary end points of coronary death, MI, or revascularization were reduced by 14% with A ($P = .03$). MI or urgent revascularization were reduced by 25% with A ($P < .001$). Individual end points included a 14% reduction in need for revascularization and 29% decrease in recurrent unstable angina but no significant decrease in death, MI, or stroke. Of note, the benefit of A was greater among patients with a baseline LDL of > 125 mg/dL (RR, 34%), compared to a 7% event differential for those with a baseline LDL of < 125 mg/dL (P for interaction = .02). Discontinuation rates were approximately 22% at 1 year and 30% at 2 years, with no differences between the drugs. There were slightly more liver enzyme abnormalities with high-dose A, whereas myalgias were comparable between the 2 statins. The authors conclude that "more intensive lipid lowering significantly decreased" major clinical events. They believe that the specific benefit with A was predicted by the degree of lipid lowering. LDL levels achieved at the end of the study were 95 mg/dL for P and 62 mg/dL for A ($P < .001$). In the approximately 1000 patients who had previously been on statin therapy, LDL levels were unchanged by P but fell by an additional 32% with A ($P = .001$). CRP declined from 12 mg/L to 2.1 with P and 1.3 with A ($P < .001$). While the P values for mortality were not significant, there was a 28% reduction of this end point; the investigators suggest that high-dose A may "decrease the risk of fatal events." Event benefits were noted as early as 30 days after trial entry and became significant at 6 months. Contrary to the MIRACL trial, there was no reduction in stroke rates. Patients who had been on statin therapy at the onset of hospitalization showed no benefit, nor did those with a baseline LDL cholesterol of < 125 mg/dL. The authors conclude that the continued benefit throughout the study period of 2 and a half years probably results from a "slower rate of progression of atherosclerosis," but they recognize that the positive early outcomes suggest a benefit from rapid stabilization of plaque as well as decreased atheroscle-

rotic progression. They conclude that the LDL cholesterol goal for patients with established CAD may be lower than the < 100 mg/dL recommended in current guidelines for patients with acute coronary syndromes.

COMMENT BY JONATHAN ABRAMS, MD

This is an important study that adds considerable fuel to the argument that "lower is better" with regard to total, and particularly LDL, cholesterol in the management of patients with overt coronary artery disease. Some are bewildered why Bristol-Myers Squibb would have funded a study with this outcome. In fact, at the time of the study design, there was considerable debate as to how low LDL cholesterol needs to be. The CARE (post-MI) investigators, many involved in the PROVE IT study, had stressed that an LDL goal of 125 mg/dL might be sufficient based on the analysis of the CARE data. Thus, CARE subjects who started at < 125 mg/dL did not appear to benefit from P, and lowering LDL beyond 125 mg/dL did not produce a greater efficacy. This controversial viewpoint was greatly debated, but the argument has disappeared with the advent of more statin data. The 125 mg/dL debate may have been a major factor in the design of PROVE IT, which was initiated to document that P was noninferior to high-dose A. There is no placebo arm in PROVE IT; therefore, one cannot conclude that P produced no benefit. Whether high-dose A had effects beyond aggressive LDL cholesterol lowering (ie, pleiotropic actions of statins) cannot be determined. In the recently published REVERSAL Trial,[1] Nissen has suggested that the benefits of high-dose A in stabilizing coronary artery atheroma burden, as well as decreasing progression of disease as assessed by intravascular ultrasound, was derived from vascular effects beyond cholesterol lowering (ie, pleotropism). However, until there are more convincing data, it is reasonable to conclude that the benefits of lipid modification with statins is related solely to the degree of LDL cholesterol lowering; there has not been a single outlier in all the statin trials. If other agents were available that had the efficacy and potency of the statins, there is no reason to believe that they would not achieve comparable reductions in major CV end points. I agree with the authors that in regard to current guidelines, we must consider a further reduction in the target LDL, based on PROVE IT and REVERSAL. Nevertheless, the major problem in lipid therapy in CAD or in patients at high risk for vascular disease is the inadequate proportion of individuals on any lipid-modifying therapy, as well as the failure to reach the LDL target of < 100 mg/dL. The latter goal is widely accepted; PROVE IT and REVERSAL strongly support that lower indeed is better in patients with established disease (and perhaps high-risk healthy individuals). However, individuals who were on a statin at trial entry received no benefit, in spite of the fact that those randomized to A had an additional 32 mg/dL lowering of baseline LDL cholesterol. This suggests that the benefits from statins are considerably reduced as ambient LDL approaches 100 mg/dL, an argument also suggested by the CARE trial results, but not concordant with the HOPE trial. Another explanation is that pre-study use of statins had already induced considerable vascular stabilization (although not enough to eliminate all events). On the other hand, in the three-quarters of the PROVE IT cohort who were not previously on a statin, there is no question that the differential between the median LDL in the A and P cohorts was responsible for decreasing hard events. Atorvastatin lowered LDL to a median of 62 mg/dL, the lowest of any lipid trial to date, and a new benchmark for lipid studies. ■

Reference

1. Nissen SE, et al. *JAMA*. 2004;291:1071-1080.

Exercise Training for Angina

ABSTRACT & COMMENTARY

Synopsis: *A 12-month program of regular exercise in selected patients with chronic stable angina and significant CAD resulted in a higher event-free survival and exercise capacity at lower costs than PCI.*

Source: Hambrecht R, et al. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: A randomized trial. *Circulation*. 2004;109:1371-1378.

Although percutaneous coronary interventions (PCI) are highly efficacious in acute coronary syndromes, their benefit in chronic stable exercise-induced angina is less clear. Thus, Hambrecht and associates from Leipzig, Germany, randomized 101 men with class I-III angina younger than 70 years of age to 20 minutes of exercise per day or PCI after routine coronary angiography showed significant coronary artery disease (CAD). Exclusion criteria included negative stress tests for ischemia, recent myocardial infarction, left main or proximal left anterior descending disease, ejection fraction < 40%, and insulin-dependent diabetes. Over 12 months, exercise training exhibited a higher event-free survival as compared to PCI (88 vs 70%; *P* =

.023). The difference in events was mainly due to rehospitalizations for ischemic events and revascularization. There were no deaths. Repeat angiography showed that 32% of exercise patients had CAD progression vs 45% of the PCI patients ($P = .035$). Significant improvements in stress myocardial perfusion were observed in both groups, but the increase in exercise oxygen consumption was greater in the exercise group (16% vs 2%; $P < .001$). The cost needed to gain one angina class was $3,429 in the exercise group vs $6,956 in the PCI group ($P < .001$). Hambrecht et al concluded that a 12-month program of regular exercise in selected patients with chronic stable angina and significant CAD resulted in a higher event-free survival and exercise capacity at lower costs than PCI.

COMMENT BY MICHAEL H. CRAWFORD, MD

Previous single-center experience has shown increased survival and exercise tolerance in CAD patients treated with exercise training, but no randomized trials have been done. For that reason, this trial is of interest. It generally agrees with other medical vs revascularization trials, and it is not surprising that exercise training increased exercise tolerance more than PCI, since most CAD patients are sedentary despite our advice to exercise. Interestingly, both groups experienced a reduction in angina, which is consistent with other studies of revascularization, but less well established for exercise training. Since coronary lesion regression was not seen with exercise training, the mechanism of this benefit is unclear but may be due to improved vasomotor tone. That the reduced total direct costs were less in the exercise-training group is not surprising because of the cost of the initial PCI. However, the decrease in subsequent hospitalizations and procedures in the exercise group is less expected. This suggests that in such low-risk patients, the complications of PCI end up negating its benefits as compared to conservative therapy. Of course, drug-eluting stents were not used. Perhaps they would have significantly reduced the 15% restenosis rate observed in the PCI group and altered the conclusions of this study. Also, this is a small trial, so the conclusions must be tempered. In addition, these were very low-risk patients as evidenced by the zero death rate. Thus, the major implication of this small, randomized trial is that medical therapy with exercise training is a viable alternative to PCI in low-risk patients with chronic stable angina due to CAD. Of course, only selected patients will be able to adhere to this consistent exercise program, but for those who are motivated, exercise training plus maximal medical therapy may be highly effective. The COURAGE trial is testing the hypothesis that maximal medical therapy plus PCI will be better for patients with CAD than maximal medical therapy alone, but this trial does not include formal exercise training. I believe American physicians have given up on getting Americans, especially women, to exercise regularly. Perhaps this approach will only work in Europe and other places where regular exercise is more accepted. It is interesting to speculate on what PCI, maximal medical therapy, and exercise could do. ■

Aspirin Dosage in ACS

ABSTRACT & COMMENTARY

Synopsis: *The dose of aspirin after discharge for acute coronary syndromes may affect the 6-month clinical course.*

Source: Quinn MJ, et al. Aspirin dose and six-month outcome after an acute coronary syndrome. *J Am Coll Cardiol*. 2004;43:972-978.

The well-documented benefits of aspirin in a diverse spectrum of patients with atherosclerosis have been observed with a wide dose range (75-1500 mg). Although 75-325 mg is most frequent in the United States, little is known about the comparative efficacy in this dose range. Thus, Quinn and colleagues analyzed the GUSTO IIb and PURSUIT databases, which were large acute coronary syndrome (ACS) studies. GUSTO IIb included ST elevation ACS; PURSUIT did not. GUSTO IIb studied heparin vs hirudin and streptokinase vs tissue plasminogen activator in the ST elevation patients; aspirin therapy was at the discretion of the treating physician. PURSUIT studied eptifibatide vs placebo, and aspirin doses of 80-325 mg were recommended. In both studies, the initial aspirin dose was known, and in PURSUIT the discharge dose was also recorded. For this study, initial or discharge doses < 150 mg were compared to > 150 mg in 20,521 patients enrolled in these 2 studies (96% of the total study populations). The primary end points were death, myocardial infarction (MI), or stroke between hospital discharge and 6 months of follow-up. Low-dose aspirin (< 150 mg) was prescribed in 30%. Those receiving intermediate dose (> 150 mg) were younger, were often ST elevation MI, and generally sicker than the low-dose group. At 6 weeks, 1310 patients had a primary event, and there was no effect of aspirin dose on the frequency of the composite end point

even after adjustment for the considerable imbalances between the 2 groups. However, intermediate-dose aspirin was associated with a reduction in 6-month MI rates (HR, .79; 95% CI, .64-.98; *P* = .03) but had a trend toward increased stroke rates (HR, 1.59; CI, .95-2.65; *P* = .08). In a highly matched subgroup of 8531 patients, the reduction in MI was no longer significant (HR, .83; CI, .66-1.05; *P* = .12) with intermediate-dose aspirin, but the increase in stroke was (HR, 1.74; CI, 1.01-3.02; *P* = .05). Quinn et al concluded that the dose of aspirin after discharge for acute coronary syndromes may affect the 6-month clinical course.

COMMENT BY MICHAEL H. CRAWFORD, MD

This retrospective, observational analysis is the largest study to address the issue of aspirin dosage in ACS, and the results are counterintuitive and provocative. In the larger, unmatched, adjusted database, the intermediate dose reduced subsequent MI, but there was a trend toward increased stroke. In the smaller, but highly matched subgroup, there was no effect on subsequent MI, but stroke risk was almost doubled. Such results fly in the face of data showing that in up to 20% of ACS patients there is resistance to the effect of aspirin, which can be overcome with larger doses. These data suggest that any benefit from increased aspirin dosage is difficult to demonstrate and may be offset by increased stroke. No analysis of these data showed mortality benefits for higher aspirin dose. The results are consistent with 2 older, randomized, controlled studies of aspirin for primary prevention. The US Physician study showed reduced MI in physicians randomized to aspirin 325 mg/d but no gain in mortality due to increases in stroke rates. The British Physicians study of 500 or more mg aspirin a day showed no benefit on MI or mortality and a significantly higher stroke rate. In the late ’80s when those studies were released, there was much criticism of the studies (eg, British physicians smoked), etc. However, there has been a trend toward lower aspirin doses, and all 3 Western cardiology associations (EHA, AHA, ACC) recommend 75-325 mg/d for coronary artery disease patients. This analysis suggests that doses > 150 mg may be harmful. Clearly, the incidence of bleeding and GI toxicity is less with lower doses of aspirin in other studies. This study did not have such data. Also, whether the patients received aspirin and at what dose during follow-up is unknown. So any conclusions from this study must be tempered. In addition, the effect of aspirin may be different in different vascular beds. It is generally thought that ACS stimulates platelet activity and may require higher aspirin doses than peripheral vascular disease. Accordingly, what would be appropriate aspirin doses at this stage of our knowledge? I would recommend 150 mg/d for ACS in the hospital and 75 mg/d at discharge for the first 6 months. The appropriate dose beyond 6 months is unclear. ■

Long-Term Aspirin Therapy

ABSTRACT & COMMENTARY

Synopsis: *Long-term treatment with aspirin is associated with a progressive diminution in platelet sensitivity to the drug.*

Source: Pulcinelli FM, et al. Inhibition of platelet aggregation by aspirin progressively decreases in long-term treated patients. *J Am Coll Cardiol*. 2004;43:979-984.

THE LONG-TERM BENEFITS OF ASPIRIN THERAPY IN patients after acute coronary syndromes (ACS) are poorly understood, especially in light of newer oral antiplatelet agents. Thus, Pulcinelli and associates from Rome studied 150 ACS patients taking aspirin (100 or 330 mg/d) and compared these to 80 matched patients taking ticlopidine. In vitro platelet aggregation tests were done serially before and during antiplatelet therapy for 24 months. In vitro tests of platelet aggregation were significantly prolonged at 2 months compared to baseline after aspirin but progressively declined at 6, 12, and 24 months. At 24 months, about 40% of patients had returned to their baseline values. The effect of aspirin was not related to whether they were on 100 or 330 mg/d. The effect of ticlopidine was constant over the 24 months. Pulcinelli et al concluded that long-term treatment with aspirin is associated with a progressive diminution in platelet sensitivity to the drug.

COMMENT BY MICHAEL H. CRAWFORD, MD

Although this is an in vitro study with no clinical outcome data, the results are interesting and support newer practices in treating ACS patients. The progressive decline in aspirin’s effect on platelets to a point where almost half are unresponsive at 24 months may partly explain the recurrence of major adverse cardiac events in patients on aspirin long term. Also, these observations support the results of CREDO, which suggested that clopidrogrel should be added for long-term platelet inhibition in post-ACS patients since there was no decrease in the effect of ticlopidine in this study. Should aspirin be stopped after 6 months or a year to

reduce the risk of bleeding, other GI toxicity, and possibly stroke? Probably not, as not all patients respond to adenosine diphosphate inhibitors. In this study, 9% showed no effect of ticlopidine, and other studies have shown up to 15% resistance to clopidrogrel. Thus, at this point, long-term antiplatelet therapy after ACS should include aspirin at 75 mg/d and clopirdrogrel 75 mg/d. The duration of such treatment is unclear but may be indefinite. ■

CME Questions

28. AICD placement in patients with EF < 35% and recent MI showed:
a. reduced arrhythmic deaths.
b. reduced total deaths.
c. improved EF.
d. a and b

29. In patients with heart failure due to systolic dysfunction randomized to AICD or drug therapy:
a. AICD reduced mortality.
b. amiodarone reduced mortality.
c. AICD's benefit was confined to ischemic cardiomyopathy.
d. a and c

30. Statin therapy after acute coronary syndromes:
a. should be started before discharge.
b. should decrease LDL < 100 mg/dL.
c. should decrease LDL < 80 mg/dL.
d. a and c

31. Exercise training vs PCI for chronic stable angina showed:
a. a higher event-free survival for exercise.
b. improved exercise performance.
c. lower costs.
d. All of the above

32. The optimal dose of aspirin in post-ACS patients is:
a. 75 mg.
b. < 150 mg.
c. > 150 mg.
d. > 325 mg.

33. The effectiveness of aspirin on platelet aggregation in vitro:
a. persists indefinitely.
b. progressively decreases over 24 months.
c. is superior with brand names than generics.
d. is stable for 18 months, then declines.

Answers: 28(a); 29(a); 30(d); 31(d); 32(b); 33(b)