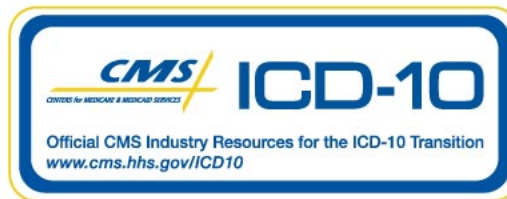


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J. Am. Coll. Cardiol. 1999;34;1-8

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JACC

JOURNAL of the AMERICAN COLLEGE of CARDIOLOGY



LATE-BREAKING CLINICAL TRIALS

Results From Late-Breaking Clinical Trials Sessions at ACCIS '99 and ACC '99

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LATE-BREAKING TRIALS IN INTERVENTIONAL CARDIOLOGY

Optimal Angioplasty Versus Primary Stenting (OPUS)

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Despite the enormous popularity of stents, their superiority over balloon angioplasty has never been demonstrated. Four hundred seventy-nine patients scheduled for percutaneous revascularization were randomized to either primary stenting or a strategy of initial balloon angioplasty followed by provisional stenting only when necessary. Seventy percent of the patients had single-vessel disease; 99% of patients in the primary stenting arm received a stent, compared with 37% in the provisional stenting arm. After six months, the combined incidence of death, myocardial infarction (MI) and target vessel revascularization was significantly reduced from 14.9% in the provisional stenting arm to 6.1% in the primary stenting arm ($p = 0.003$). Nearly all the difference was due to a reduction in the rate of target vessel revascularization (10% vs. 4%). Differences between the two groups became evident at two months. For the initial procedure, primary stenting was about \$1,000 more expensive. By six months, however, the total costs for primary stenting were slightly less expensive than the costs for provisional stenting.

Commentary. This trial adds to the body of evidence that argues in favor of routine stent use in appropriate vessels. The study also emphasizes an extremely low rate of target vessel revascularization, particularly in the primary stenting group. The low rate of clinical events over the first six-month follow-up rendered primary stenting a less expensive approach than potential stenting. Application of the results of this study to clinical practice must be made with recognition that the arteries studied were 3 mm or more in diameter, 20 mm or less in length and with either mild or no calcification.

Fast Revascularization During Instability in Coronary Artery Disease (FRISC II): An Early Invasive Versus Early Noninvasive Strategy in Unstable Coronary Artery Disease

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The value of an early invasive treatment of patients with acute coronary syndromes has been controversial. In this first presentation from the FRISC II group, 2,433 patients with unstable coronary disease were randomized after 48 h to an invasive strategy consisting of catheterization followed by revascularization within seven days, or a noninvasive strategy in which patients underwent angiography only if they had a positive exercise test, refractory or severe ischemia or MI. All patients were treated with aspirin, beta-adrenergic blocking agents and the low molecular weight heparin (dalteparin) until revascularization in the invasive group and for at least five days in the noninvasive group.

At six months, the rate of death or MI was reduced by 21% from 12% in the noninvasive group and 9.5% in the invasive group ($p = 0.045$). Among men, the invasive strategy resulted in a highly significant 34% reduction in the combined end point ($p = 0.002$) and a significant 52% reduction in mortality from 3.2% to 1.5% ($p = 0.03$). Among women, there was no evidence of a beneficial effect with an invasive strategy. In men as well as in women, there was an approximately 50% reduction in symptoms of angina and need for readmissions during the six-month follow-up.

Only 14% of patients in the noninvasive group underwent angiography during the first six days of hospitalization. By six months, however, 48% had undergone angiography. At six months, the revascularization rate was 38% in the noninvasive group versus 78% in the invasive group.

Commentary. This study fuels the debate over conservative versus invasive treatment of acute coronary syndromes. Unlike the Veterans Affairs Non-Q-Wave Infarction Strategies In-Hospital (VANQWISH) and Thrombolysis in Myocardial Infarction (TIMI) trials, the results of this trial argue in favor of an invasive approach. Like the VANQWISH trial, the FRISC II trial had a large number of crossovers in the conservative group (revascularization rate of 38%), but in this case, the crossovers do not detract from the results.

Two other intriguing results of this trial were an ex-

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tremely low mortality rate in both groups and the lack of benefit of the invasive strategy in women. Could the low mortality rate speak to a benefit of five to seven days of antithrombotic therapy before invasion as applied in this study, or were the FRISC II patients relatively more stable than in other studies? The lack of benefit to women poses the same questions that are usually raised—specifically, were women seen later in the course of disease, were they older, did they have more comorbid factors such as diabetes, or was the size of the coronary arteries a deciding factor?

The ADMIRAL Study: Abciximab With Percutaneous Transluminal Coronary Angioplasty (PTCA) and Stent in Acute Myocardial Infarction (AMI)

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The role of abciximab in the setting of AMI has not yet been fully tested. Three hundred patients with AMI were randomized to either abciximab or placebo before undergoing PTCA or stent implantation. More patients in the abciximab group had a history of MI (14.8% vs. 8%). At 24 h, the TIMI-3 flow rates were 86% in the abciximab group and 78% in the placebo group ($p < 0.05$). Left ventricular function was higher in the abciximab group than in the placebo group at 24 h (55% vs. 51%; $p < 0.05$).

The primary end point of the trial, the combined incidence of death, recurrent MI and urgent target vessel revascularization at 30 days, was reduced by 46.5% from 20% in the placebo group to 10.7% in the abciximab group ($p < 0.03$). The individual components of the end point all favored abciximab: death was reduced from 4.7% to 3.3%, recurrent MI from 4.7% to 2% and urgent target vessel revascularization from 14% to 6% ($p = 0.03$).

The rate of major bleeding at 30 days was not significantly higher in the abciximab group (4% vs. 2.6%), but a significant increase in minor bleeding was observed (6.7% vs. 1.3%; $p = 0.02$).

Commentary. The accumulated data supporting the benefit of coupling abciximab with thrombolytics or angioplasty in the treatment of AMI is rather convincing. This study adds to those data. The improved TIMI-3 flow at 24 h with abciximab should convert to improved myocardial preservation, and indeed, left ventricular function at 24 h was better in the abciximab group. In addition, the use of abciximab ensured better short-term stability (30-day incidence of death, recurrent MI and urgent target vessel revascularization was reduced). The major reluctance to using abciximab has been concern about hemorrhagic complications. The ADMIRAL study results should help allay these concerns.

The Evaluation of Xemilofiban in Controlling Thrombotic Events (EXCITE) Trial: 30-Day and Six-Month Results

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Following the success of the intravenous glycoprotein IIb/IIIa inhibitors, great hope has been held for oral formulations of these drugs. In the largest prospective, randomized trial ever performed in interventional cardiology, 7,262 patients undergoing percutaneous coronary revascularization were randomized to placebo, low-dose or high-dose xemilofiban, an oral IIb/IIIa inhibitor. Twelve percent of patients presented with MI; the rest were evenly divided between stable and unstable angina. More than two-thirds of the patients received a stent.

At six months, the rate of death, nonfatal MI or urgent revascularization, the primary end point of the trial, was 13.6% for placebo, 14.1% for low-dose and 12.6% for high-dose xemilofiban-treated patients, a difference that did not achieve statistical significance. There was a trend toward a reduction in the rate of MI in the high-dose xemilofiban group and a slight but troublesome trend toward an excess of deaths and MI in the low-dose xemilofiban group.

In the first two days there was a significant reduction in events in the active treatment groups, but this finding was offset by an increase in events between day 2 and day 14. In a subgroup analysis, diabetic patients appeared to benefit from xemilofiban.

Commentary. Although the EXCITE trial will be dismissed as a negative study and will persuade the pharmaceuticals industry not to release this agent, the benefit of treatment seen during the first two days should not be dismissed. What does this fact tell us about the glycoprotein IIb/IIIa inhibitors (dosage, delivery or tolerance) or the pathophysiology of angioplasty? The unique benefit of this class of platelet inhibitors in diabetics seen in this study echoes previous studies of these drugs.

Randomized Comparison of Percutaneous Myocardial Revascularization (PMR) Versus Medical Therapy: Six-Month Outcome (Potential Angina Class Improvement From Myocardial Channels/PACIFIC Trial)

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Transmyocardial laser revascularization has emerged in recent years as an important palliative therapy for severe angina patients who are ineligible for revascularization. A percutaneous version of this procedure, using a yttrium aluminum garnet laser system developed by Cardiogenesis, was studied in the PACIFIC study. Two hundred twenty-one patients with class III or class IV angina on maximal medical therapy and with evidence of reversible ischemia were randomized to PMR or medical therapy.

The PACIFIC trial was a one-year study. An interim six-month analysis showed that 70% of the patients treated with PMR had class 0 to 2 angina at six months, compared with less than 15% in the control group. Half of the PMR patients had an improvement of at least two classes in their angina classification, compared with only 6% of patients in the control arm. At six months, PMR patients had a 30% increase in their exercise time, compared with a 5% improvement in the control group.

In the PMR group, there was one death at 29 days and one case of tamponade requiring pericardiocentesis. There were no periprocedural MIs or strokes.

Commentary. The results of the PACIFIC study should be viewed as encouraging, but not convincing, in terms of PMR's benefits. First, the number of patients studied is relatively small. Second, the presentation was an interim analysis at six months. Furthermore, the patients were not blinded to treatment modality, so the placebo effect on the improvement of angina classification in the PMR group must be considered. Finally, the 30% improvement in exercise time converts to only an additional 120 s in walking. Although this improvement is impressive, an unblinded observer can easily lengthen exercise time.

LATE-BREAKING CLINICAL TRIALS I: CARDIAC THERAPEUTICS

Should We Emergently Revascularize Occluded Coronary Arteries for Cardiogenic Shock (SHOCK) Trial—An International Randomized Trial of Emergency PTCA/Coronary Artery Bypass Graft (CABG): Results of the SHOCK Trial

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Core Laboratory Angiographic Findings, Angioplasty Results and Relation to Treatment Effect: Results From the Randomized SHOCK Trial

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Although cardiogenic shock is the single largest cause of death among patients hospitalized for AMI, the best treatment strategy for this extremely vulnerable population has never been determined. Three-hundred-two patients with cardiogenic shock within 36 h of AMI were randomized to a strategy of emergency revascularization (ERV) or a strategy of initial medical stabilization (IMS). Balloon pump support was encouraged in both arms, and thrombolysis was strongly encouraged in the IMS patients.

Ninety-seven percent of patients assigned to ERV had coronary angiography, and 87% were revascularized. Forty-nine percent of the 152 ERV patients had PTCA 0.9 h after randomization, and 38% had CABG 2.7 h after randomization.

The 30-day mortality rate, the primary end point of the trial, was 46.7% in the ERV group versus 56% in the IMS group. This 17% reduction in relative risk was not statistically significant. Preliminary analysis of an important secondary end point, six-month mortality, found a significant benefit of ERV compared with IMS (54% vs. 65%, $p = 0.04$).

Subgroup analysis found that those patients under 75 years of age experienced the most benefit of ERV. The six-month mortality rate for patients under 75 was 48% in the ERV group versus 69% in the IMS group.

Commentary. The SHOCK trial confirms that cardiogenic shock after an AMI carries a very high mortality. Unfortunately, the study did not find that ERV significantly reduced the 30-day mortality. Preliminary analysis of six-month mortality coupled with a favorable trend at 30 days, however, suggests that the strategy of ERV should not yet be forsaken, particularly in patients younger than 75 years.

The hope is that physicians would continue to approach this condition in an investigative manner without conviction that one or the other approach is best and that the issue will be resolved only by continued investigation.

Fragmin and Early Revascularization During Instability in Coronary Artery Disease (FRISC II)

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The role of low molecular weight heparins used to treat unstable coronary disease is unclear. In this second presentation from the FRISC II group, patients with unstable coronary disease received open-label dalteparin, a low molecular weight heparin, for at least five days or until scheduled early revascularization. Patients were then randomized to either continued dalteparin or placebo for three months.

The primary objective concerned the efficacy of continued dalteparin versus placebo in the 2,105 patients handled with a noninvasive treatment strategy. In this comparison there were no significant differences between the dalteparin and placebo groups in the rate of death or MI at three months, the prespecified end point (6.7% in the dalteparin group vs. 8% in the placebo group; $p = 0.2$). In a post-hoc analysis, however, the investigators found a significant reduction in events at 45 days in the dalteparin group (3.7% vs. 6.7%; $p = 0.003$). Serious bleeds occurred more often in the dalteparin group than in the placebo group (4.1% vs. 1.7%). There were five intracranial hemorrhages in the dalteparin group and none in the placebo group.

Drug assignment did not significantly alter the outcome in the portion of the trial in which patients were randomized to an invasive or a noninvasive treatment strategy. In the invasive arm, the rate of death or MI at six months was 9.8% in the placebo group and 9.2% in the dalteparin group. In

the noninvasive arm, the rate was 12.7% in the placebo group and 11.5% in the dalteparin group.

Commentary. This second portion of the FRISC II study should be interpreted to show no benefit of long-term (three months) use of low molecular weight heparin in patients with unstable angina. Furthermore, the long-term use carries an increased risk of bleeding. The benefit of administering low molecular weight heparin for a short duration and the lack of an added benefit by its more prolonged use seems to be in accord with the pathophysiology of unstable angina. Perhaps the only unresolved issue is the correct interval for “short-duration” heparin therapy.

Multicenter Unsustained Tachycardia Trial (MUSTT)

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This trial was conducted to assess the role of electrophysiologic (EP) studies in guiding antiarrhythmic therapy. Seven-hundred-four patients with coronary artery disease, nonsustained ventricular tachycardia, left ventricular ejection fractions less than 40% and inducible sustained ventricular tachycardia were randomized to standard treatment or EP-guided antiarrhythmic therapy. In the EP-guided group, patients first received type IA drugs, propafenone or sotalol. After failing at least one antiarrhythmic drug, patients were eligible to receive another antiarrhythmic drug or an implantable cardioverter defibrillator (ICD). Patients in the EP-guided arm were evenly divided between drug therapy and the ICD. Patients in both groups received beta-blockers and angiotensin-converting enzyme (ACE) inhibitors when there were no contraindications.

The rate of arrhythmic death or cardiac arrest was significantly reduced in the EP arm at 24 months (12% vs. 18%) and at 60 months (25% vs. 32%). A trend toward a reduction in overall mortality was also observed.

In a post-hoc analysis, the entire beneficial effect in the EP-guided group was found to occur in the group of patients who received the ICD. No beneficial effects were found in the patients who received antiarrhythmic drugs. Reductions in total mortality were also found only in the EP-guided patients who received the ICD.

Commentary. The results of the MUSTT should be very troubling to physicians. The study rather conclusively demonstrates that there is therapy available (ICD implantation) that significantly reduces mortality in a given subset of patients (coronary artery disease, nonsustained ventricular tachycardia, left ventricular ejection fraction less than 40% and inducible ventricular tachycardia).

The troubling issue is how we in the cardiology community will apply this expensive therapy on a national scale in a subset of patients with reduced long-term survival despite

this therapy. The study again demonstrates the inefficacy of antiarrhythmic drugs in these patients.

Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF)

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Beta-blockers are rapidly becoming standard therapy for the treatment of heart failure. In the MERIT-HF trial, 3,991 heart failure patients in Europe and the U.S. were randomized to placebo or metoprolol. Most of the patients were in New York Heart Association class II (41%) or class III (55%); two-thirds of patients had ischemic heart disease.

Metoprolol was started at either 12.5 mg or 25 mg/day and titrated upward on a weekly basis to between 100 mg and 200 mg/day for an average daily dose of 159 mg. Background usage of ACE inhibitors, diuretics and digitalis was very high. In the metoprolol group, 14% of patients discontinued their medication, compared with 15.5% in the placebo group.

At one year, total mortality was reduced by 34%, from 11% in the placebo group to 7.2% in the metoprolol group ($p = 0.0062$). The two groups began to diverge after three months of treatment. Cardiovascular deaths were reduced by 38%, sudden death by 41% and death due to progressive heart failure by 49%.

The beneficial effects of metoprolol were consistent across all subgroups, regardless of age, gender, etiology of heart failure or presence or absence of diabetes, hypertension or previous MI.

Commentary. The MERIT-HF is an important study that conclusively establishes the benefit of selective beta-blockers in reducing mortality in patients with heart failure. It is important to note the consistency of benefit across all subgroups. The results of this study should place beta-blockers in the class of standard therapy for class II or III heart failure. The lack of class IV patients in the study leaves the use of beta-blockers in this functional class unanswered. Furthermore, notation should be made that these beneficial effects were obtained with relatively high doses of the drug. The exact mechanism of mortality remains undefined, because the drug lowered both sudden death and death by heart failure.

**LATE-BREAKING CLINICAL TRIALS II:
CORONARY ARTERY DISEASE**

Assessment of the Safety and Efficacy of a New Thrombolytic: TNK-tPA Trial (ASSENT-2)

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Two new thrombolytic agents—variants of the well-established tPA molecule—have now completed large clinical trials. In the first thrombolytic mega-trial presented at the American College of Cardiology 48th Annual Scientific

Session, 16,950 patients with AMI were randomized to either tPA or TNK-tPA, a mutant form of tPA with increased fibrin specificity that can be administered as a single-bolus injection.

The 30-day mortality rate was nearly identical in the two groups: 6.16% in the TNK-tPA group and 6.18% in the tPA group. The overall stroke rates were 1.78% and 1.66%, respectively. The rates of intracerebral hemorrhage also were very close: 0.93% and 0.94%, respectively. TNK-tPA treatment resulted in a significant reduction in mild to moderate bleeding complications (26% vs. 28.1%, $p = 0.002$).

With one exception, there were no significant differences among subgroups. In patients treated more than 4 h after the onset of symptoms, mortality was 7.04% in the TNK-tPA group versus 9.19% in the tPA group.

Designed as an equivalence trial, ASSENT-2 successfully demonstrated that TNK-tPA did not cause a clinically significant excess in events.

Commentary. The large number of patients required to establish that a new thrombolytic agent is superior to tPA has led to the equivalency trials, such as ASSENT-2 and Intravenous n or tPA for Treatment of Infarcting Myocardium Early (InTime-II). If the two agents can be established as essentially equal, then the physician's choice of agent may depend on ease of delivery, cost or possible benefit in a subgroup of patients. A comparison of the results of the two studies does suggest that the presence of increased fibrin specificity of a thrombolytic agent may confer a measure of protection from the hemorrhagic complications of thrombolysis.

A Phase III Trial of Novel Bolus Thrombolytic Lanoteplase (nPA): InTime-II

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In this second thrombolytic mega-trial presented at the American College of Cardiology 48th Annual Scientific Session, 15,078 patients were randomized on a 1:2 basis to either tPA or lanoteplase, a tPA mutant that is somewhat less fibrin specific than tPA and that can be administered as a single-bolus injection.

At 30 days, the rate of death was very similar in the two groups: 6.6% in the tPA group versus 6.77% in the lanoteplase group. Although the overall stroke rate was not significantly elevated in the lanoteplase group (1.52% in the tPA group vs. 1.89% in the lanoteplase group), the rate of intracerebral hemorrhage was increased in the lanoteplase group (0.62% vs. 1.13%, $p = 0.003$).

Major and moderate bleeding complications occurred equally in both groups; however, there were more mild bleeding complications in the lanoteplase group than in the tPA group (19.6% vs. 14.7%, $p < 0.001$).

Like the ASSENT-2 study, InTime-II was designed as an equivalence trial and succeeded in demonstrating that lanoteplase was equivalent to tPA with respect to mortality.

Commentary. The large number of patients required to establish that a new thrombolytic agent is superior to tPA has led to the equivalency trials, such as ASSENT-2 and InTime-II. If the two agents can be established as essentially equal, then the physician's choice of agent may depend on ease of delivery, cost or possible benefit in a subgroup of patients. A comparison of the results of the two studies does suggest that the presence of increased fibrin specificity of a thrombolytic agent may confer a measure of protection from the hemorrhagic complications of thrombolysis.

Gruppo Italiano Per Lo Studio Della Sopravvivenza Nell'Infarto (GISSI) Prevention Study

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The protective effects of fish oil supplements and vitamin E have been long debated. Within three months of an MI, 11,324 patients were randomized to an n-3 polyunsaturated fatty acid (PUFA) supplement (1 g daily), a vitamin E supplement (300 mg daily), both or neither. Baseline therapy included antiplatelet therapy in 90% of patients, beta-blockers in 40%, and ACE inhibitors in 50%.

At 42 months' follow-up, patients who received n-3 PUFA had a significant 10% relative risk reduction in the combined rate of death plus nonfatal MI and nonfatal stroke compared with those who did not receive n-3 PUFA (12.4% vs. 13.7%, $p = 0.045$). In contrast, treatment with vitamin E caused a nonsignificant 4.7% relative risk reduction in the combined end point. All of the beneficial effects of n-3 PUFA were due to a 20% reduction in the risk of death.

There were no significant interactions between the two treatments. Both treatments were well tolerated. Gastrointestinal intolerance was the most commonly reported side effect.

Commentary. The GISSI Prevention Study demonstrates a vascular protective effect of fish oil supplements in patients with coronary atherosclerosis. Previous studies have demonstrated discordant results on atherosclerosis in terms of fish and fish oil consumption on coronary artery disease. Perhaps the difference in results relates to appropriate dosage or to the end points measured. For example, whether the beneficial effect is on plaque progression or thrombus prevention would be a strong determinant of the appropriate end points to be measured.

The study did not confirm the reduction in the risk of cardiovascular death and nonfatal MI noted in the Cambridge Heart Antioxidant Study (CHAOS). The difference in GISSI and CHAOS is a lower dose of vitamin E in GISSI (300 mg vs. 400 to 800 mg). Furthermore, CHAOS, unlike GISSI, did include strokes as an end point. The questions posed by these results revolve around whether

there is a critical dose (greater than 300 mgm) of vitamin E necessary for the beneficial effect, whether the addition of strokes changes the results or whether the larger study exposes fallacy in the smaller study.

Effects of ACE Inhibition and/or Lipid Lowering on Coronary Atherosclerosis: The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT)

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This angiographic trial sought to determine the effects of a cholesterol-lowering “statin” and an ACE inhibitor, separately and in combination, on the progression of coronary artery disease in patients with normal cholesterol levels. In a 2 × 2 factorial design, 460 coronary artery disease patients were randomized to enalapril, simvastatin, both or neither. Coronary angiography was performed at baseline and at 48 months.

Simvastatin, but not placebo, caused a significant reduction in total cholesterol and low-density lipoprotein cholesterol levels. In addition, simvastatin, but not placebo, slowed the rate of progression of atherosclerosis by nearly 50%, as measured by quantitative coronary angiography. Enalapril had a neutral effect on lipids and on the progression of atherosclerosis. There were no significant interactions between enalapril and simvastatin.

For clinical events, enalapril therapy was associated with a significant reduction in the combined rate of death, MI or stroke, whereas simvastatin caused a significant reduction in the rate of angioplasty procedures.

Commentary. This trial was primarily a confirmation of previous studies. The effects of simvastatin on total cholesterol and low-density lipoprotein cholesterol were predicted by the results of the 4-S study. The effect of lipid lowering on the progression of atherosclerosis was noted previously in the Familial Atherosclerosis Treatment Study (FATS).

In terms of clinical events, the Survival and Ventricular Enlargement (SAVE) trial demonstrated the reduction in fatal and nonfatal cardiovascular events by ACE inhibition and, again, 4-S demonstrated a reduction in coronary intervention by use of simvastatin. This study did not show a significant interaction between the two drugs, which is not particularly surprising.

Sodium-Proton Exchange Inhibition With Cariporide in Patients at Risk of Necrosis: Main Results of the Guard During Ischemia Against Necrosis (GUARDIAN) Trial

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Cariporide is a novel agent that inhibits the sodium-hydrogen exchange system, which plays a central role in cell necrosis following ischemia. This study randomized 11,590 patients at high risk for ischemia to one of three doses of cariporide or placebo. Patients were included if they had

unstable angina or non-Q-wave MI or were undergoing high-risk angioplasty or high-risk bypass surgery.

The rate of death or MI at 36 days—the primary end point of the trial—was 13.4% in the placebo group, 13.5% in the low-dose group, 14.1% in the mid-dose group and 12.2% in the high-dose group. The 10% reduction in the high-dose group did not achieve statistical significance, and a clear dose-response relationship was not observed.

There were no significant differences between the 45% of patients in the trial who were enrolled because they had an acute coronary syndrome and the 30% of patients who underwent angioplasty. However, among the 25% of patients who had bypass surgery, there was a significant reduction in events in the high-dose cariporide group (16.7% for placebo vs. 12.8% for high-dose cariporide). Furthermore, the incidence of Q-wave MI was reduced in all entry diagnostic groups. The drug was well tolerated and was not associated with an increase in serious side effects.

Commentary. The GUARDIAN trial addresses a new component of the ischemic process. The study fails to establish the efficacy of cariporide, an inhibitor of the sodium-hydrogen exchange system. Although there was a significant reduction in ischemic events in patients undergoing high-risk bypass surgery after receiving cariporide, such results of subgroup analysis should receive further scrutiny and study before being accepted.

Double-Blind, Placebo-Controlled Trial of Recombinant Human Vascular Endothelial Growth Factor (VEGF): VEGF in Ischemia for Vascular Angiogenesis (VIVA) Trial

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Administering VEGF is one of many approaches now being explored to induce angiogenesis in patients with peripheral and coronary disease. In this trial, 178 patients with severe angina who were considered ineligible for mechanical revascularization were randomized to placebo or one of two doses of VEGF, administered as a 20-min intracoronary infusion followed by 4-h intravenous infusions on days 3, 6, and 9.

There were no significant differences among the groups in the treadmill exercise time at 60 days—the primary end point of the trial. Exercise time increased in all three groups: by 43 s in the placebo group, 26 s in the low-dose VEGF group and 32 s in the high-dose VEGF group. Similarly, there were no significant differences among the groups in the change in angina classification. Results at 120 days are not yet available.

Treatment with VEGF appeared to be safe and well tolerated. Two deaths, both in the placebo group, occurred in the trial. Similarly, three placebo patients, but no VEGF patients, developed cancer.

Commentary. It is difficult and probably inappropriate to place much emphasis on this study showing no benefit of

VEGF. The number of patients was small, the primary end point of the study is relatively imprecise and the follow-up was short. Angiogenesis is an exciting approach to ischemic disease, whose most effective method of induction is yet to be defined.

LATE-BREAKING CLINICAL TRIALS III

Fibrinogen Receptor Occupancy Study (FROST) Trial: Safety and Preliminary Efficacy of a One-Month Treatment With Lefradafiban in Patients With Unstable Angina

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This trial was designed to study the safety and preliminary efficacy of one-month treatment with lefradafiban, an oral IIb/IIIa inhibitor. Lefradafiban is a pro-drug that is converted in the body to fradafiban, which can be administered intravenously.

More than 500 patients with unstable angina were randomized to receive placebo or one of three doses of lefradafiban for up to one month. The high-dose group was discontinued by the data and safety monitoring committee due to excessive bleeding complications. At one month, more than 50% of patients in both the active treatment and placebo groups had withdrawn from treatment. The largest number of withdrawals were a result of patients proceeding to a revascularization procedure, but adverse events increased as the dose of lefradafiban was increased. Few bleeding events were major, but lefradafiban caused a significant, dose-related escalation in bleeding events.

At 30 days, the rate of death, MI and any event requiring intervention was 33% in the placebo group, 31% in the low-dose lefradafiban group, 22% in the mid-dose lefradafiban group and 25% in the high-dose lefradafiban group.

Commentary. Like the EXCITE trial, the FROST trial does not establish a benefit for the long-term (30-day) administration of oral IIb/IIIa inhibitors. Furthermore, this study demonstrates an increase in bleeding events associated with the use of the drug.

Orbofiban in Patients With Unstable Coronary Syndromes (OPUS)-TIMI 16 Trial

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This was the first large, phase III trial of an oral IIb/IIIa inhibitor in patients with acute coronary syndromes. The study randomized 10,302 patients to placebo, 50 mg b.i.d. orbofiban throughout the trial, or 50 mg b.i.d. orbofiban for 30 days followed by 30 mg b.i.d. orbofiban.

The trial was originally intended to enroll 12,000 patients but was stopped prematurely due to increased mortality at 30 days in one of the two treatment arms. The mortality rate at 30 days was 1.4% in the placebo group, 2.3% in the

orbofiban 50/30 group and 1.6% in the orbofiban 50/50 group.

The primary end point of the trial, the 30-day combined rate of death, MI, ischemic events requiring revascularization or hospitalization or stroke, was 10.7% in the placebo group, 9.7% in the orbofiban 50/30 group and 9.3% in the orbofiban 50/50 group, representing an 11% reduction in the combined orbofiban groups. This difference failed to achieve statistical significance. Most of the benefits in the orbofiban groups were due to reductions in urgent revascularizations.

The same pattern was evident at 300 days follow-up, with an excess of deaths in the orbofiban-treated groups partly offset by a reduction in urgent revascularizations. Orbofiban therapy was associated with a significant increase in the risk of bleeding, including major or severe bleeding. Analysis of the cause of deaths in the trial suggested that the excess deaths seen with orbofiban may have been due to new thrombotic events. Certain subgroups (patients without heart failure or those with normal renal function) showed no excess mortality and greater benefit, suggesting that these groups deserve further study in future trials of this class of drugs.

Commentary. The accumulated data of the OPUS-TIMI 16, EXCITE and FROST trials speak rather convincingly against the long-term (30-day) use of any oral IIb/IIIa inhibitor. The 30-day administration of these agents seems to offer no benefit in terms of reduction of ischemic events and poses a risk for bleeding complications. The suggestion that the excess deaths seen with orbofiban is due to new thrombotic events is puzzling.

Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS) Trial

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Ticlopidine and aspirin are standard anticoagulant therapy for stent implantation. Clopidogrel has been proposed as an agent that may be as effective as ticlopidine but without causing some of the adverse events associated with ticlopidine.

In addition to receiving aspirin for 28 days, 1,020 patients undergoing stent implantation were randomized for 28 days to daily ticlopidine, 75 mg clopidogrel daily or a 300-mg loading dose of clopidogrel on day 1 followed by a daily 75 mg dose. The primary end point of the trial was the combined incidence at 28 days of major bleeding, neutropenia, thrombocytopenia or early discontinuation of the study drug. The composite end point was reduced from 9.1% in the ticlopidine group to 6.3% in the clopidogrel 75 group and to 2.9% in the clopidogrel 300/75 group.

Nearly all of the difference in the combined end point was due to a lower rate of early discontinuation of therapy in the

clopidogrel groups. The chief causes of discontinuation in the ticlopidine group were allergic reactions and gastrointestinal or skin disorders.

Commentary. This study confirms the experience of many U.S. cardiologists. The surprising finding is that patients receiving the loading dose of clopidogrel had significantly fewer side effects than those receiving only the maintenance dose. It is hoped that the published study will

comment on the comparative effectiveness of the agents in terms of preventing stent thrombosis and will offer an explanation for the paradox of a larger dose of a drug causing fewer side effects.

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Discussion

J. Am. Coll. Cardiol. 1999;34;1-8

This information is current as of February 12, 2012

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