Best of the ACC Scientific Sessions 2006

Highlights from the American College of Cardiology Scientific Sessions, March 11-14, 2006, Atlanta, GA

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Key words: Abciximab • Atherosclerosis • Atorvastatin • Bivalirudin • Circumferential pulmonary vein ablation • Drug-eluting stents • Folic acid • Glycoprotein IIb/IIIa • Heparin • Myocardial infarction • Patent foramen ovale closure • Peripheral ultrafiltration therapy • Prehypertension • Rosuvastatin • ST-segment elevation • Vitamin B_6

The 2006 American College of Cardiology (ACC) Scientific Sessions provided a forum for the presentation and discussion of important research advances in every area of cardiovascular medicine. Our board members report on some of the most important findings announced in Atlanta.

Bivalirudin During Percutaneous Coronary Intervention

Direct thrombin inhibitors bind with thrombin and can block both thrombin and fibrin-bound thrombin. Unlike heparin, they do not rely on binding with antithrombin 3 for their anti-thrombotic effect.[1] They are much more predictable than heparin and are unaffected by platelet factor 4. A meta-analysis of 11 randomized trials by the Direct Thrombin Inhibitor Trialist Collaborative Group involving over 35,000 patients with acute coronary syndromes showed these agents to be superior to heparin, with a reduced death and myocardial infarction (MI) rate and reduced bleeding.[2] A limitation of these earlier trials was that they did not evaluate the use of low molecular weight heparins or the combined use of heparin and glycoprotein (GP) IIb/IIIa agents. The Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events II (REPLACE 2) trial evaluated bivalirudin plus bailout GP IIb/IIIa compared to heparin plus GP IIb/IIIa agents.[3] The patients enrolled in this study were largely at low risk. Bivalirudin was not inferior to heparin plus GP IIb/IIIa agents in the occurrence of death, MI, and urgent revascularization. It was, however, associated with a reduced risk of bleeding complications. The use of bivalirudin compared to that of heparin plus GP IIb/IIIa agents in patients with acute coronary syndromes undergoing an invasive strategy has not been previously studied.

The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial was presented by Dr. Gregg W. Stone of Columbia University in the late-breaking clinical trials session at the ACC meeting.[4] The study was a multi-center randomized trial involving more than 600 centers

worldwide.[5] The study included 13,819 patients with moderate- or high-risk acute coronary syndromes who underwent cardiac catheterization within 72 hours. Patients were randomized into 3 treatment groups: heparin (either unfractionated heparin or enoxaparin) plus a GP IIb/IIIa inhibitor (n = 4603), bivalirudin plus a GP IIb/IIIa inhibitor (n = 4604), or bivalirudin alone (n = 4612). In the first 2 groups, a second randomization took place in which the GP IIb/IIIa inhibitor was given either upstream prior to the percutaneous coronary intervention (PCI) (usually on admission) or at the time of PCI. All patients were urged to receive clopidogrel before the procedure, but only 60% did. The primary endpoint was net clinical benefit defined as the composite of death, MI, unplanned revascularization for ischemia, and major bleeding at 30 days. Bleeding was assessed using a more liberal definition than in previous trials. This index included intracranial bleeding, intraocular bleeding, a reduction in hemoglobin of > 4 gm/dL without overt bleeding or of > 3 gm/dL with overt bleeding, and any transfusion. The patients were primarily treated with PCI (56%), and only 11% underwent bypass surgery.

The results demonstrated a significantly lower incidence in the primary endpoint in the bivalirudin group as compared to the heparin plus a GP IIb/IIIa group (10.1% vs 11.7%, $P = .015$) (Figure 1). This effect was driven by a lower major bleeding rate in the bivalirudin group. Other bleeding measures, such as thrombolysis in myocardial infarction (TIMI) major bleeding, were also lower with bivalirudin, although the major bleeding rate was lower (0.9% vs 1.8%). Bivalirudin plus GP IIb/IIIa was not different from heparin + GP IIb/IIIa in any endpoint.

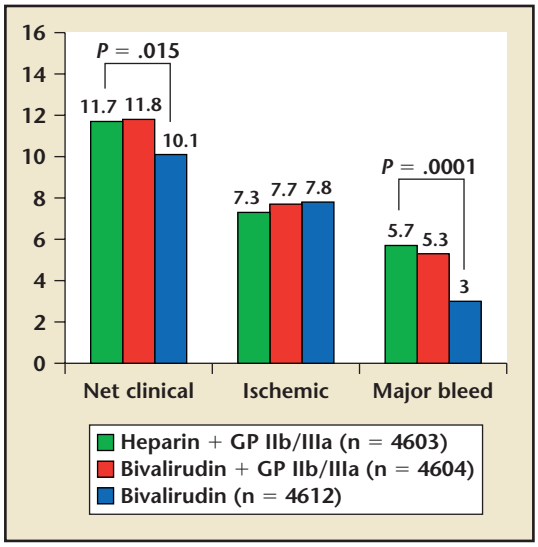


Figure 1. *The 30-day results of the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, showing a superior outcome with bivalirudin over heparin plus glycoprotein (GP) IIb/IIIa agents in both net clinical benefit and major bleeding endpoints. Net clinical benefit is defined as the combined endpoint of death, myocardial infarction, unplanned revascularization, and major bleeding. The ischemic endpoint is the above definition without bleeding. Adapted with permission from Stone GW.*[4]

The trial also had an interesting sub-study evaluating the benefit of administering GP IIb/IIIa antagonists upstream as compared to administering them at the time of catheterization. Among patients in whom use of the GP IIb/IIIa inhibitor was deferred until the PCI, approximately 62% were treated with eptifibatide, 33% with abciximab, and 4% with tirofiban. In patients receiving upstream use of a GP IIb/IIIa agent, 65.4% received eptifibatide, 34% received tirofiban, and 1% received abciximab (Figure 2). The primary endpoint was again net clinical benefit. The study was designed as a noninferiority trial. As with the main trial, 56% of patients had PCI an average of 19 hours after admission. In the deferred group, 55.7% received a GP IIb/IIIa agent. The primary endpoint was met in 11.7% of the upstream group and 11.7% of the deferred group. Death, MI, and unplanned revascularization were slightly lower in the routine group (7.1% vs 7.9%, $P = .044$ for noninferiority). Bleeding was significantly lower in the deferred group (6.1% vs 4.9%, $P = .0009$). When viewed in light of the overall trial, the bivalirudin alone group did better than the groups receiving heparin with upstream or deferred GP IIb/IIIa, with similar rates of death, MI, and unplanned revascularization, but with a lower bleeding rate. In a further subset analysis, the duration between randomization and catheterization related to outcome as well. The net clinical benefit was 9.8% for catheterization performed within 2 to 3 hours of presentation, 9.7% for it performed < 18 hours, and 14.8% for it performed > 18 hours. This nonrandomized component of the study supports early treatment within 18 hours of presentation.

The treatment of moderate- to high-risk patients with acute coronary syndrome is complicated and involves a growing list of agents and strategies, including aspirin, clopidogrel, heparin (with either unfractionated heparin or enoxaparin), or bivalirudin, as well as anti-ischemic medication, including β-blockers and revascularization. The proper agents, the proper dose, and the optimal selection of agents before and during PCI have remained uncertain, with all interventions showing benefit when compared to no therapy.

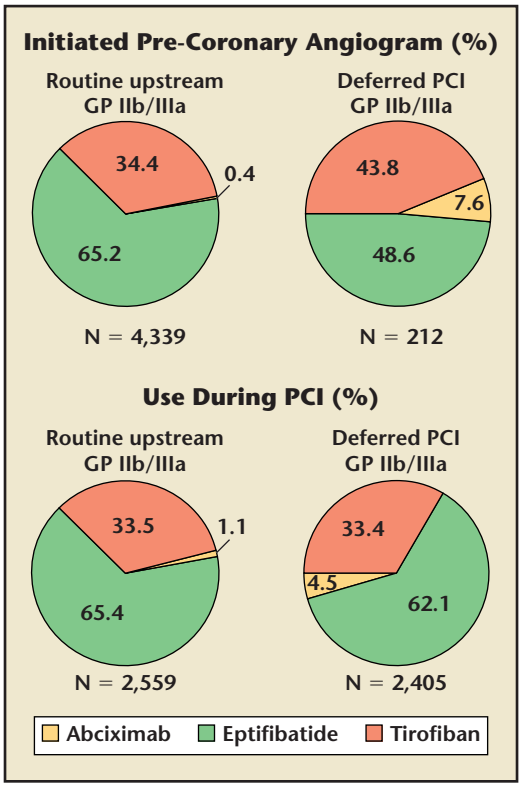


Figure 2. *Glycoprotein (GP) IIb/IIIa selection. Adapted with permission from Stone GW.[4] PCI, percutaneous coronary intervention.*

We are now in the phase of investigation where different treatment regimens are being compared to each other, and the ACUITY trial has helped bring clarity to some of the controversy. The study confirms the findings of the Direct Thrombin Inhibitor Trialist Collaborative Group and the REPLACE 2 trial by showing that bivalirudin is better than any combination of heparins with or without GP IIb/IIIa agents. Although the benefit is confined to reduced bleeding, this effect is not insignificant because a growing number of trials have shown that bleeding or the need for transfusions is related to a much poorer outcome. The results of the study simplify the management to a single agent and will likely be embraced by the interventional community. The major limitation of the study is that the dose of enoxaparin might have been too high and that intravenous (IV) administration might have maximized early benefit. Recent studies suggest that lower IV doses maintain efficacy with lower bleeding. To complicate the picture further, results from the Organization to Assess Strategies for Ischaemic Syndromes (OASIS) 5 trial that were presented at the European Society of Cardiology and recently published in the *New England Journal of Medicine* showed not only a reduction in bleeding with fondaparinux, a long-acting factor Xa inhibitor, when compared to enoxaparin but also a significant reduction in mortality at 30 days and 6 months in more than 20,000 patients.[6] Why the ACUITY trial failed to also show a reduction in mortality despite a significantly lower bleeding rate is unclear.

A number of differences exist between the studies. In the OASIS 5 trial, fondaparinux was administered for 5 days, whereas in the ACUITY trial, bivalirudin was administered only through the catheterization. A longer duration of anti-thrombotic therapy may be important in ACS. In addition, the outcome of the subgroup of 7000 patients in the OASIS Trial who underwent PCI was similar to the PCI group in the ACUITY trial, with equal mortality but a lower bleeding rate when compared to groups receiving heparin. Thus, PCI may have a more powerful positive influence on reducing mortality than bleeding has on increasing it. There is little question that we will need more information from the ACUITY trial to fully understand the role of bivalirudin in clinical practice, but the trial has shown that bivalirudin had improved safety and equal efficacy to current therapy, and its use will undoubtedly increase as a result.

[David P. Faxon, MD, FACC, FAHA]

Rosuvastatin and Coronary Plaque Size

At the ACC meeting, Dr. Steven Nissen of the Cleveland Clinic in Ohio presented data from A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Atheroma Burden (ASTEROID).[7] The 24-month ASTEROID trial examined the effects of 40 mg/d of rosuvastatin on coronary plaque size. Intravascular ultrasound (IVUS)-derived measures of coronary disease were used to test the hypothesis that marked low-density lipoprotein cholesterol (LDL-C) reduction, along with a significant high-density lipoprotein cholesterol (HDL-C) increase, would favor regression of atherosclerosis. Patients enrolled in the study required coronary angiography for a clinical indication, typically stable or unstable chest pain, or an abnormal functional test. Inclusion criteria included presence of 1 obstruction, with more than 20% luminal

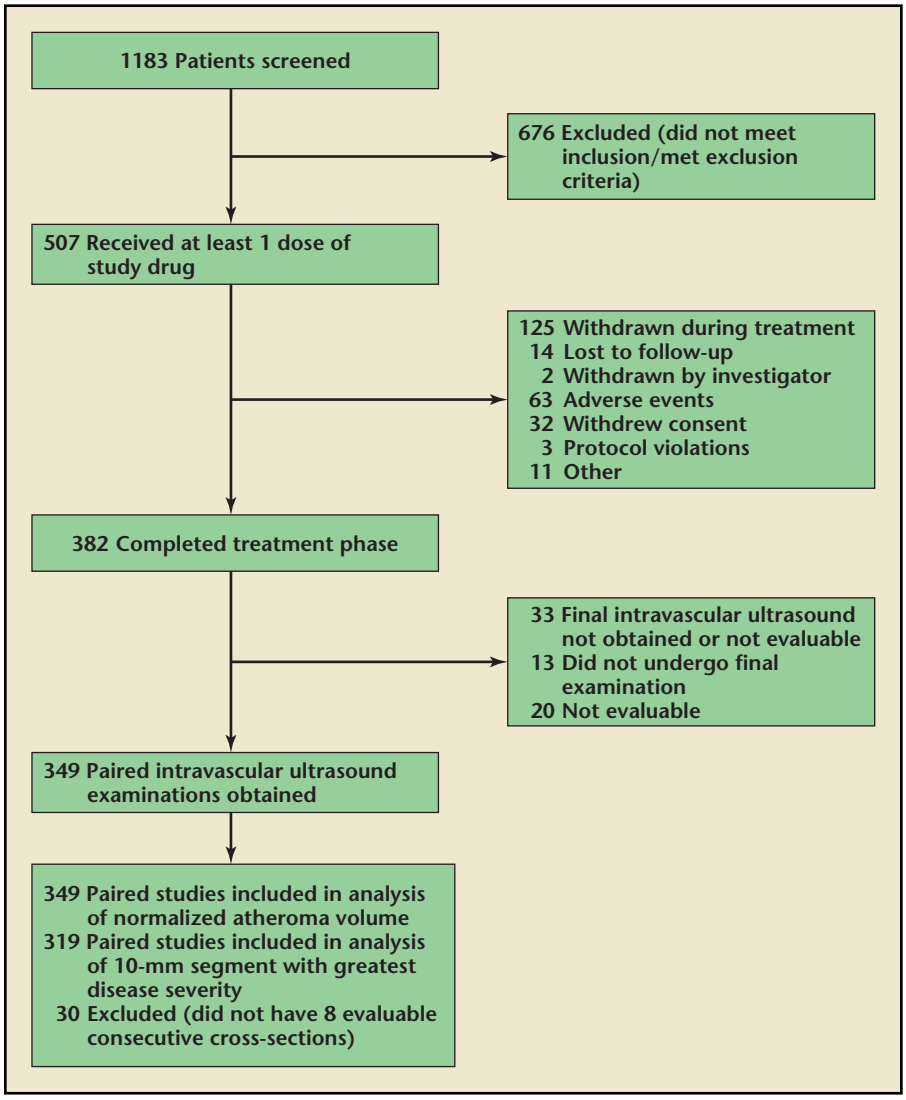


Figure 3. *Subjects in A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Atheroma Burden (ASTEROID). Reprinted with permission from Nissen SE, et al.*[7]

diameter narrowing in any coronary vessel, as long as the IVUS-targeted vessel had not undergone angioplasty. Patients were excluded if they were already on statins or had lesions with > 50% luminal narrowing throughout the segment. A total of 507 patients met the inclusion criteria, including a baseline IVUS result, and were treated with rosuvastatin 40 mg/d (Figure 3). Of these, 349 patients underwent a follow-up IVUS study at 24 months. Reasons for not being included in the follow-up IVUS analysis included withdrawal of consent or withdrawal for other reasons. Overall, 63 patients were withdrawn for an adverse event. The primary endpoint of the study was a change in percent atheroma volume and change in atheroma volume in the 10-mm subsegment with the greatest disease. The prespecified secondary endpoint was change in total atheroma volume.

Rosuvastatin treatment resulted in significant reductions in mean LDL-C (from 130 mg/dL to 60 mg/dL, $P < .001$) and increases in mean HDL-C (from 43 mg/dL to 49 mg/dL, $P < .001$). The drug was well tolerated, without any cases of rhabdomyolysis and with rates of elevated hepatic enzymes comparable to those in other trials that used maximum doses. Two years of treatment with rosuvastatin significantly reduced mean percent atheroma volume and mean atheroma volume in the most diseased 10-mm vessel subsegment, and decreased the secondary endpoint of total atheroma volume (Table 1, Figure 4). These findings demonstrate regression of atherosclerosis with 2-year rosuvastatin therapy. The regression of coronary atherosclerosis was noted in nearly all subgroups, including men and women as well as older and younger patients, and in most subgroups defined by lipid levels.

This landmark study has created significant excitement by providing the first evidence for coronary plaque regression in a large IVUS-based statin trial in which 2 years of treatment with a high-dose statin was the active therapy. This trial achieved greater reductions in LDL-C and increases in HDL-C compared to previous statin trials. The results suggest that large decreases in LDL-C and simultaneous increases in HDL-C can promote coronary plaque regression in a significant proportion of patients.

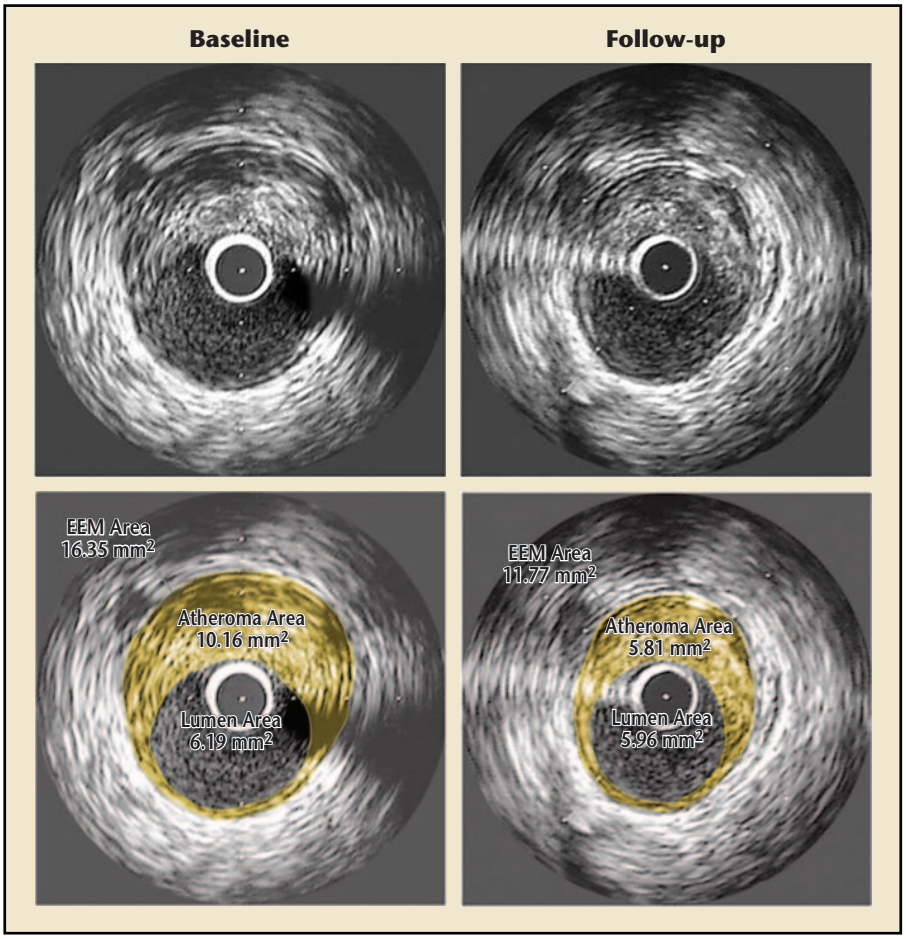
Several questions remain unanswered because the trial lacked a placebo control and a comparator statin. Is the regression-promoting effect unique to rosuvastatin, or is it simply a function of marked LDL-C reduction and HDL-C increase? Furthermore, data linking favorable changes in IVUS-related atherosclerosis parameters to clinical event

Table 1
Regression of Atherosclerosis With 2-Year Rosuvastatin Therapy

Variables	Change from Baseline	*P* value
LDL-cholesterol (mg/L) HDL-cholesterol (mg/L)	−53.2% +14.7%	
Percent atheroma volume	Mean −0.98 ± 3.15 Median −0.79 95% CI, −1.21 to −0.53	$P < .001$ vs baseline (% of patients with regression = 63)
Percent atheroma volume in the most diseased 10-mm segment	Mean −6.1 ± 10.1 mm^3 Median −5.6 mm^3 97.5% CI, −6.8 to −4.0 mm^3	$P < .001$ vs baseline (% of patients with regression = 78)
Total atheroma volume	Mean −14.7 ± 25.7 mm^3 Median −12.5 mm^3 95% CI, −15.1 to −10.5 mm^3	$P < .001$ vs baseline (% of patients with regression = 78)

LDL, low-density lipoprotein; HDL, high-density lipoprotein. Data from Nissen SE, et al.[7]

Figure 4. *Two years of treatment with rosuvastatin resulted in significant reductions in mean percent atheroma volume and mean atheroma volume in the most diseased 10-mm vessel subsegment, in addition to decreases in the secondary endpoint of total atheroma volume. Reprinted with permission from Nissen SE, et al.[7] EEM, external elastic membrane.*



reduction are lacking, and therefore the clinical relevance of these findings remains to be defined. It is likely and plausible that regression of lesions would result in clinical benefit; however, it is also plausible that favorable changes in plaque composition, without a reduction in plaque size, reduce the propensity for plaque rupture and thrombosis (the so-called plaque stabilization). Finally, regression has also been previously demonstrated in other trials that used combination lipid-modifying drugs and coronary angiography, such as the Familial Atherosclerosis Treatment Study (FATS),[8] the Atherosclerosis Treatment Study (HATS),[9] and The St. Thomas' Atherosclerosis Regression Study (STARS).[10]

[Prediman K. Shah, MD, FACC, FACP, FCCP]

Abciximab Beneficial for Acute Coronary Syndrome Patients With Elevated Troponin T Undergoing PCI

To assess whether abciximab improves outcomes in high-risk patients with non–ST-segment elevation acute coronary syndromes who are undergoing PCI after pretreatment with clopidogrel, Kastrati and colleagues[11] conducted the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 2 trial, an international, randomized, double-blind, placebo-controlled study that enrolled 2022 patients (Figure 5). Inclusion criteria were:

- Angina (an episode with an accelerating pattern or prolonged over 29 minutes, or recurrent episodes at rest or with minimal effort in the preceding 48 hours) accompanied by an elevated troponin T level or finding of new ST-segment depression or transient ST elevation.

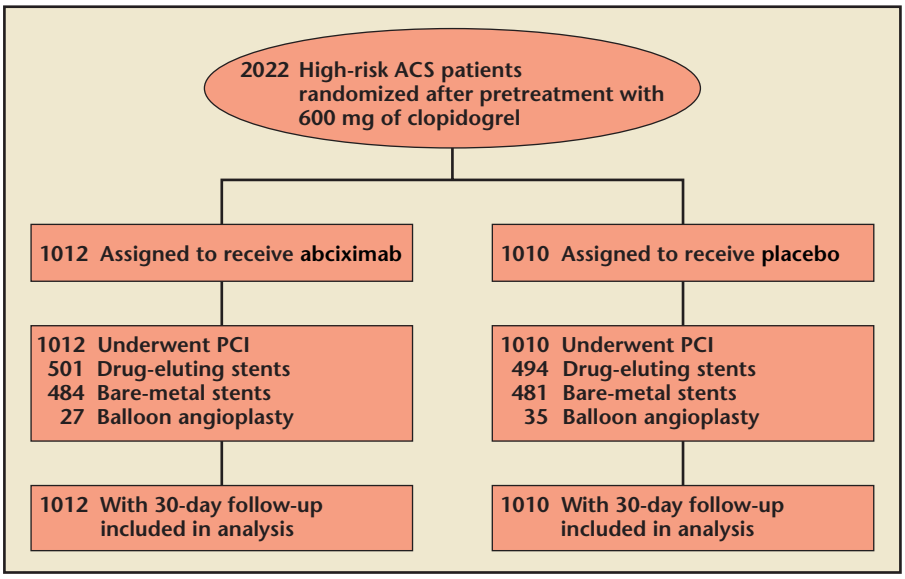


Figure 5. *Subjects in the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 2 trial. Adapted with permission from Kastrati A, et al.[11] ACS, acute coronary syndrome, PCI, percutaneous coronary intervention.*

- New or presumed new left bundle branch block.
- A lesion in a native vessel or bypass graft requiring PCI.

Patients were excluded if they had persistent ST elevation, hemodynamic instability, increased risk of bleeding, refractory hypertension, anemia, thrombocytosis, or thrombocytopenia.

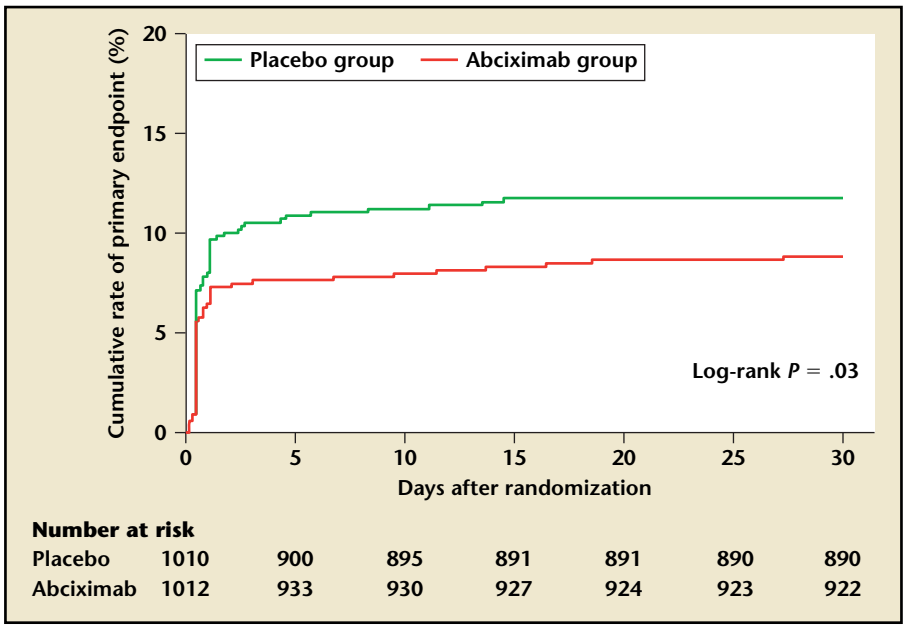
All patients received a 600-mg oral dose of clopidogrel, at least 2 hours prior to PCI, and 500 mg of oral or intravenous aspirin. The protocol recommended PCI within 6 hours of the acute coronary syndrome diagnosis. Patients were randomized after the decision was made at the time of angiography to proceed with PCI, but before the guide wire crossed the lesion. Patients in the abciximab group received 0.25 mg/kg bolus followed by 0.125 μg/kg/min for 12 hours plus heparin at 70 units/kg. Post-PCI therapy included 150 mg/d of clopidogrel until discharge for a maximum of 3 days, then 75 mg/d along with 200 mg/d of aspirin.

Patients in the abciximab group experienced a relative 25% reduction in the composite primary endpoint of death, MI, or urgent target vessel revascularization occurring within 30 days after randomization (Figure 6).

The benefit of abciximab was observed in patients who had elevations of troponin T but not in those patients with normal troponin T (Figure 7). Abciximab appeared to benefit patients regardless of whether they were diabetic and regardless of when the clopidogrel loading dose was administered (Figure 8).

The results of ISAR-REACT 2 complement the results of ISAR-REACT,[12] in which a group of lower-risk patients undergoing elective PCI did not benefit from the addition of abciximab to clopidogrel. What is clear from the ISAR-REACT 2 trial is that patients presenting with an acute coronary syndrome with *any* elevation of troponin T undergoing PCI benefited from the use of abciximab in addition to the 600-mg loading dose of clopidogrel. The benefit occurred early and in a variety of subgroups, including those who received clopidogrel at least 3 hours prior to the PCI. There was no increased incidence of hemorrhagic complications in this group.

Figure 6. *Kaplan-Meier analysis of the cumulative incidence of the composite endpoint of death, myocardial infarction, or urgent target vessel revascularization. Adapted with permission from Kastrati A, et al.[11]*



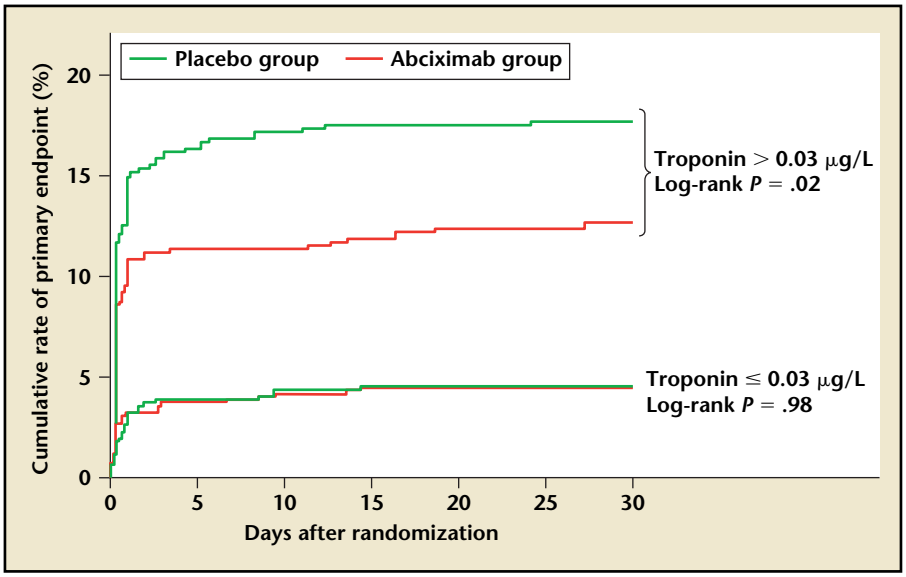
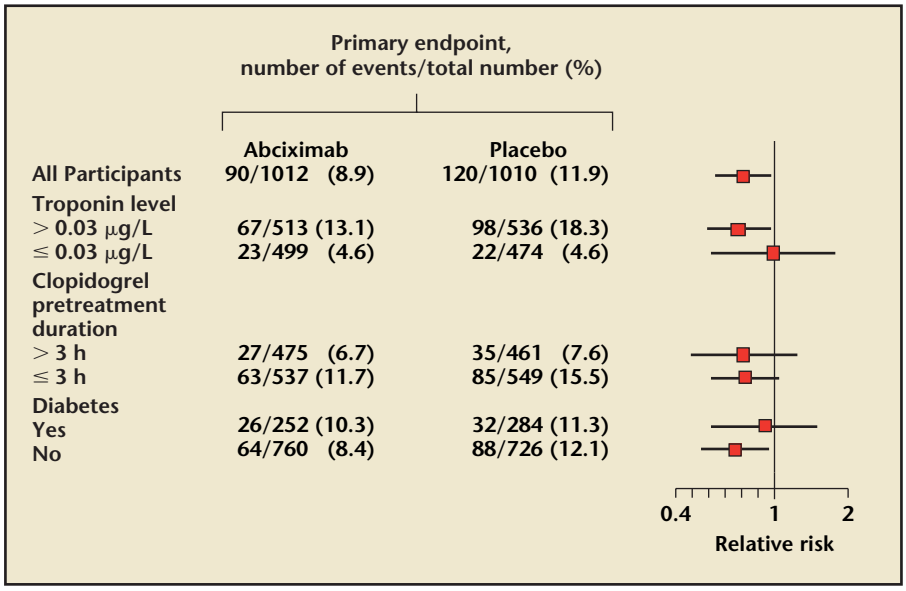


Figure 7. *Kaplan-Meier analysis of the cumulative incidence of the composite endpoint of death, myocardial infarction, or urgent target vessel revascularization comparing groups with elevated and normal troponin T. Adapted with permission from Kastrati A, et al.*[11]

A variety of reasons may possibly explain the benefit observed with abciximab in this population. Aspirin and clopidogrel do not overcome the platelet-activating effect of unfractionated heparin in this higher-risk PCI group that is more prone to thrombotic complications. Resistance to clopidogrel or aspirin therapy may have had greater impact in this higher-risk population. Will third-generation thienopyridines, such as prasugrel, which have a more rapid and complete effect on platelet activation, provide additional effects in this population?

Figure 8. *Subgroup analysis showing relative benefit of patients receiving abciximab. Adapted with permission from Kastrati A, et al.*[11]



Based on the results of this study, patients who present with an acute coronary syndrome with any elevation of troponin and who undergo PCI with the use of unfractionated heparin and clopidogrel should be treated with abciximab.

Rosuvastatin and Atorvastatin in Hispanic Populations

The Study Assessing Rosuvastatin in the Hispanic Population (STARSHIP) trial[13] was designed to assess the efficacy of rosuvastatin and atorvastatin in lowering LDL-C levels in Hispanic populations. The results were presented by Dr. Ramon Lloret of the Cardiovascular Center of South Florida.

The study included 696 Hispanic American patients with hypercholesterolemia and moderate to high risk of coronary heart disease events. They were randomized to 1 of 4 open-label treatments: rosuvastatin 10 mg, rosuvastatin 20 mg, atorvastatin 10 mg, or atorvastatin 20 mg.

After 6 weeks of therapy, rosuvastatin 10 mg and 20 mg had significantly greater efficacy than milligram-equivalent doses of atorvastatin in reducing LDL-C, non–HDL-C, and total cholesterol. National Cholesterol Education Program Adult Treatment Panel III LDL-C targets were reached by 78% of patients on rosuvastatin 10 mg compared with 60% of patients on atorvastatin 10 mg, and by 90% of high-risk patients on rosuvastatin 20 mg compared to 60% on atorvastatin 20 mg. All 4 treatments were well tolerated; 1 patient in the atorvastatin 20 mg group had liver function tests > 3 times the upper limit of normal on 2 consecutive measurements. Proteinuria was observed in 5 patients on rosuvastatin and in 1 patient on atorvastatin. There were no cases of myopathy or creatine kinase > 10 times the upper limit of normal.

Drug-Eluting Stent Versus Bare Metal Stent After Clopidogrel Discontinuation

The Basel Stent Cost-effectiveness Trial—Late Thrombotic Events (BASKET LATE)[14] evaluated the thrombotic complication rate following clopidogrel discontinuation in patients randomized to receive a drug-eluting stent (DES) (499 patients received either sirolimus or paclitaxel) or a bare metal stent (244 patients). The primary endpoint was cardiac death or MI in the first year following discontinuation of clopidogrel.

The incidence of cardiac death or MI was 4.9% in the DES group versus 1.3% in the group receiving bare metal stents ($P = .01$). The incidence of MI was increased in the DES group (4.1% vs 1.3%, $P = .04$) (Figure 9).

The results of this study seem to indicate the need for longer-term antiplatelet therapy with a thienopyridine in patients undergoing DES placement. In addition, the data would support the selection of a bare metal stent in patients who will be undergoing any type of surgery or procedure that would preclude the use of aspirin or a thienopyridine within the first 18 months following stent placement, or who may be at a high risk of bleeding complications that would cause an interruption of antiplatelet therapy.

Circumferential Pulmonary Vein Ablation for Paroxysmal Atrial Fibrillation

The Ablation for Paroxysmal Atrial Fibrillation (APAF)[15] trial evaluated treatment with circumferential pulmonary vein ablation (CPVA) compared with conventional antiarrhythmic medical therapy among patients with paroxysmal atrial fibrillation (AF).

Patients were randomized to CPVA (n = 99) or to antiarrhythmic medical therapy (n = 99) with flecainide (n = 33), sotalol (n = 33) or amiodarone (n = 33). After a 1-month run-in phase during which antiarrhythmic medication was uptitrated in both arms, ablation was performed in patients randomized to CPVA. The protocol was to encircle all 4 pulmonary veins with 3 additional lines to prevent atrial tachycardias when medical therapy was discontinued in the CPVA group. Patients were allowed to cross over after 3 months. The primary endpoint was freedom from recurrent atrial arrhythmias at 1 year.

Only preliminary data are available for 150 patients. At 9 months of follow-up, 87% of patients in the CPVA group and 29% in the medical therapy group were free from recurrent AF and atrial tachycardia ($P < .001$). Of the 8 patients in the CPVA group who had recurrent AF, a repeat ablation procedure was performed in 3 patients, of whom 1 still had additional recurrent AF. Of the 52 patients in the medical therapy group who had recurrent AF, 38 underwent CPVA, of whom 4 still had additional recurrent AF. There was a significant decrease in left atrial diameter at 12 months in patients randomized to CPVA ($P < .05$), but no difference in the medical therapy group.

The investigators concluded that in patients with paroxysmal AF, treatment with CPVA was associated with reduction in recurrent AF and atrial tachycardia compared to conventional medical therapy with antiarrhythmic drugs.

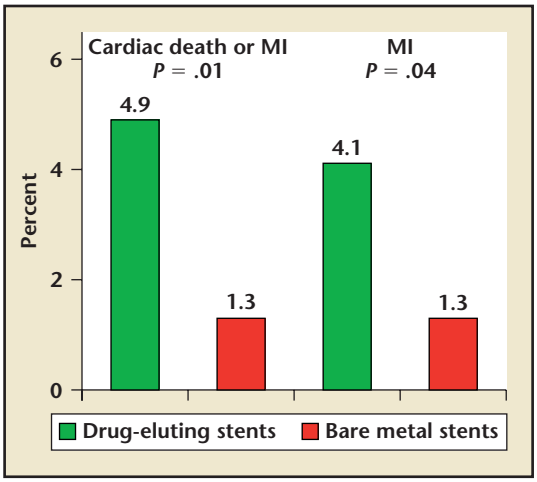


Figure 9. *The incidence of cardiac death or myocardial infarction (MI) and MI. Adapted with permission from Pfisterer ME, et al.*[14]

Use of a Zotarolimus-Eluting Stent

The ZOMAXX-IVUS Study (Percutaneous Coronary Revascularization Using A Trilayer Phosphorylcholine-Coated Zotarolimus-Eluting Stent: The ZoMaxx IVUS Trial) results were presented by Dr. A. Abazid.[16] The ZoMaxx Drug-Eluting Coronary Stent System features proprietary application of a biologically inert coating called Pharmacoat™, intended to enable steady drug elution over time, and proprietary application of Abbott's patent-protected immunosuppressant drug, zotarolimus, which has been studied for the reduction of vessel re-narrowing. The system's TriMaxx™ stent platform is made of stainless steel and tantalum to enable enhanced visibility under x-ray, with thin struts and low crossing profile to facilitate stent placement. ZOMAXX IVUS was a clinical, angiographic, and IVUS trial conducted in

40 patients with a mean age of 59 years. Eighty percent of patients had hyperlipidemia, 40% had diabetes, and 40% had a prior MI. The mean lesion length stented was 14.4 mm.

Before treatment with a ZoMaxx stent, percent diameter stenosis—the percent of vessel blocked with disease—was 70%. Following stent placement, the in-stent segment percent diameter stenosis improved to 5.1% and in-segment stenosis improved to 19%.

Late lumen loss, a measure of the change in vessel diameter between the time immediately following stent placement and (in the case of ZOMAXX IVUS) at 4 months, was 0.20 mm in-stent and 0.17 mm in-segment. In-stent net volume obstruction, the amount of blockage that re-formed inside the stent in the 4 months following the initial procedure, was 6.5%. Follow-up studies incorporating angiographic follow-up beyond 4 months as well as the results of the randomized ZoMaxx-1 study will provide additional data to expand upon these registry findings. [Norman E. Lepor, MD, FACC, FAHA]

The HOPE 2 Trial

This trial, which was presented at the ACC session and published simultaneously in the *New England Journal of Medicine,*[17] randomly assigned 5522 patients aged 55 years or older who had vascular disease or diabetes to daily treatment with a combination of 2.5 mg of folic acid or vitamin B_6 and 1 mg of vitamin B_{12} or to placebo for an average follow-up of 5 years. The objective was to demonstrate that decreasing homocysteine levels would be associated with a lower rate of death due to cardiovascular causes, MI, and stroke (composite primary endpoint).

Approximately 83% of patients had coronary artery disease (MI in 54%), 40% had diabetes, and 12.4% had experienced a prior stroke or a transient ischemic attack. Active treatment resulted in a significant decrease in plasma homocysteine levels, but absolutely no difference in the incidence of the composite primary endpoint (relative risk 0.95, 95% CI, 0.84-1.03, $P = .41$). There was no reduction in cardiovascular death or MI, but, somewhat unexpectedly, a reduction in stroke but not in transient ischemic attack. More patients in the active treatment group were hospitalized with unstable angina.

An epidemiologic association, even if biologically plausible, does not necessarily imply a cause-and-effect relationship.

This is a convincingly neutral trial, and outcomes were not different among patients living in areas with and without folate fortification in food, although at first glance it would appear that a trend was present. I agree with the trial authors that the differences between unstable angina and stroke outcomes were probably due to chance, but in regard to the latter, ongoing trials might provide further clarification.

The findings from this trial are consistent with those from another trial published in the same issue of the *New England Journal of Medicine*.[18] This trial evaluated 3749 patients with a recent MI in Norway, a country without folate fortification of food. In regard to the composite endpoint of recurrent MI, stroke, and sudden cardiac death, there was a trend toward an increased risk in the active treatment arm (relative risk, 1.22; 95% CI, 1-1.50; $P = .05$). Similarly, in 2 other smaller trials, lowering homocysteine levels was of no benefit in regard to stroke prevention or reduction of cardiovascular events.[19,20] Multiple prior epidemiologic studies have identified homocysteine as a potential risk factor for coronary artery disease. Experimentally, homocysteine causes oxidative stress, damages endothelium, and may be prothrombotic.[21] Homocysteine is, in many ways, an attractive therapeutic target because it can be lowered easily, safely, and inexpensively.

This series of trials, therefore, comes somewhat as a disappointment and reminds us yet again that an epidemiologic association, even if biologically plausible, does not necessarily imply a cause-and-effect relationship. In this respect, the trials of homocysteine join others such as the trials of hormone replacement therapy in women, beta-keratin, and vitamin E: another example of what Thomas Henry Huxley (1825-1895) referred to as "the slaying of a beautiful hypothesis by an ugly fact." Moreover, these trials emphasize the value of subjecting potentially attractive therapies to the rigorous scrutiny of randomized, controlled trials.

An accompanying editorial by Loscalzo[22] points out that the failure of these trials does not necessarily imply that the homocysteine hypothesis is incorrect. An alternative explanation is that vitamin therapy aimed at reducing homocysteine levels may have potentially adverse effects that offset its homocysteine-lowering benefit. The metabolic pathways involve a complex, and simply lowering homocysteine levels by folic acid may result in the generation of other potentially toxic metabolic byproducts. Needed are alternative approaches to lowering homocysteine concentrations, such as increasing conversion of homocysteine to cysteine in the

liver or enhancing the urinary secretion of the amino acid.
[Bernard J. Gersh, MB, ChB, DPhil, FRCP]

Treating Prehypertension With an Angiotensin Receptor Blocker

There has been strong interest in prehypertension, recently defined as the range of blood pressures between normal (120/80 mm Hg) and hypertensive (140/90 mm Hg). In particular, should we encourage people with this condition to undertake lifestyle modifications to try and delay the onset of clinical hypertension, or could there be a basis for prescribing antihypertensive medications? Data from rat models of hypertension have indicated that blockers of the renin-angiotensin system, administered for short time periods early in the lives of these animals, can substantially modify the later history of their hypertension.

The Trial of Preventing Hypertension (TROPHY)[23] was undertaken to learn whether a 2-year treatment period with an angiotensin receptor blocker in prehypertensive patients might delay or modify the development of clinical hypertension. Patients were generally healthy individuals between the ages of 30 and 65 years with blood pressures in the prehypertension range. A total of 809 satisfied the study entry criteria after 3 consecutive weeks of confirming that their blood pressures fell within the appropriate range. Patients were then randomized in this double-blind trial into 2 groups: 1 group received the angiotensin receptor blocker candesartan 16 mg/d for 2 years; the other group received placebo. After this initial 2-year period, the study reverted to a single-blind 2-year period during which all patients received placebo. The primary endpoint of the trial was the development of clinical hypertension, which was defined as follows: the presence of systolic blood pressure of 140 mm Hg or more, or of diastolic blood pressure of 90 mm Hg or more, at any 3 visits throughout the total 4-year study; a single reading in excess of 160/100 mm Hg; a reading in excess of 140/90 mm Hg at the final study visit; or a decision by investigators that it was clinically necessary to interrupt study treatments and initiate conventional antihypertensive therapy. All blood pressure readings were made with automated equipment that eliminated observer bias or error.

The average age of the patients was 49 years, 59% were men, mean body mass index was 30, and the mean baseline blood pressure was 134/85 mm Hg (by automated device). By the end of the initial 2-year period, significantly more patients in the placebo group had developed hypertension than in the actively treated group (40.4% vs 13.6%, $P < .001$). By the end of the full 4-year study period, 63% of placebo-treated patients and 53.2% of actively treated patients were hypertensive ($P = .007$). The relative risk (for developing hypertension) after 2 years was 0.34 (95% CI, 0.25-0.44) and after 4 years was 0.84 (95% CI, 0.75-0.95). In essence, this result represented a significant 16% reduction in new-onset hypertension in the actively treated group by the end of the study. Blood pressure values were significantly lower in the actively treated group than in the placebo group during the initial 2 years of the trial, but by the end of the study—2 years after active treatment had been discontinued—the systolic blood pressure in the former candesartan group was lower by 2.0 mm Hg ($P = .037$) and diastolic blood pressure was lower by 1.1 mm Hg ($P = .073$). Subgroup analysis of the main result showed that the reduction in new-onset hypertension in the candesartan group was significant for patients aged both ≥ 50 or < 50, and likewise was significant for both men and women, for those with body mass index ≥ 30 or < 30, and for white patients (a similar trend was seen for black patients, but there was insufficient power to adequately test the effect in this subgroup). Adverse events were similar for both the placebo and candesartan-treated groups. Overall, both treatment regimens were well tolerated. There were only 7 major cardiovascular events during the course of this trial; 1 occurred in the candesartan group, and 6 in the placebo group.

This trial demonstrated the feasibility of a pharmacologic intervention in prehypertensive people at risk of becoming hypertensive. During the period of active therapy, there was a sharp reduction in incident hypertension in patients receiving the angiotensin receptor blocker. However, by 2 years after the cessation of treatment, much of this benefit had been lost, although the relative difference in hypertension rates of 16% still significantly favored the actively treated group. The investigators estimated that this intervention, on average, delayed new-onset hypertension by about 12 months.

Although this study did not provide dramatic results, it has emphasized some key points. First, an active intervention early in the history of hypertension can slow the progression of this condition; second, this intervention is well tolerated and does not appear to be associated with any adverse outcomes; and third, the transition from prehypertension to clinical hypertension—as witnessed in the placebo group—is remarkably high. Over 60% of prehypertensive patients became frankly hypertensive by the end of the 4-year trial.

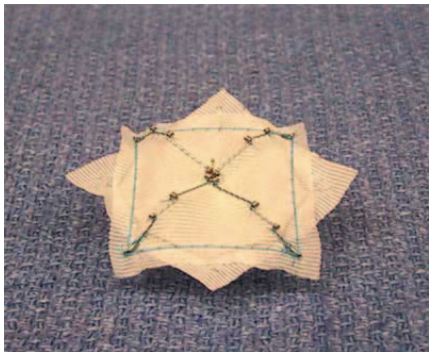
One of the most important conclusions from this study is that there is a legitimate need to develop effective strategies for dealing with prehypertension. It could be argued that the intervention tested in TROPHY came too late in the lives of the study patients. Their average age was 49, and it is entirely possible that meaningful attempts to alter the natural history of hypertension should be targeted at far younger ages, perhaps in the 20s or early 30s. It is also possible that a longer duration of active therapy may be necessary to make a strong impact in preventing the development of hypertension. TROPHY was a good start to understanding this process, and should be expected to lead to further trials that can test differing strategies for delaying or preventing the onset of clinical hypertension.
[Michael A. Weber, MD]

Patent Foramen Ovale Closure and Migraine

The estimated prevalence of migraine headache in the general population is approximately 10% to 12%.[24,25] Those patients who have migraine with aura have a 47% incidence of a patent foramen ovale (PFO) compared to controls, and those with the greatest degree of left-to-right shunting have a 7-fold increase in migraine with aura.[26] Observational data have suggested that closure of the PFO may dramatically improve migraine symptoms.[27-29] The Migraine Intervention with STARFlex® Technology (MIST) I trial,[30] reported by Dr. Andrew Dowson from Kings College Hospital, London, United Kingdom, is the first double-blind, prospectively randomized trial conducted to investigate whether percutaneous closure of a PFO could have a clinical impact on migraine sufferers. Migraine sufferers are often frustrated with current therapies to reduce the number and severity of headaches, and the trial had no problem finding patients, completing the enrollment process 6 months ahead of time.

A total of 432 patients were screened at 13 centers in the United Kingdom from January 2005 to July 2005. The patients had to be refractory to at least 2 classes of migraine medication and must have had migraines for at least 1 year. All had to have at least 5 migraine headache days per month, and those with prior stroke were excluded. All had echocardiography that included saline microcavitation documentation of a right-to-left shunt. Screening showed a shunt in 260 patients (an enormous 60.2%), a large PFO in 163 (37.7%), and a frank atrial septal defect in 3 (0.7%). Of the 163 PFO patients recruited, the study enrolled 147 patients (ages 18 to 60 years), and 135 completed the trial at the 6-month follow-up. Patients were randomized to either percutaneous PFO closure (n = 74) with the STARflex® septal occluder device (NMT Medical, Boston, MA) or to a sham procedure (n = 73) consisting of general anesthesia and a groin incision. Figure 10 is an example of the double umbrella device used. All patients were treated with aspirin and clopidogrel for 3 months after the procedure and followed for an additional 3 months. Those enrolled in the procedure group had a baseline mean of 136.1 hours of migraine per month compared to 116.8 hours in the sham procedure group.

Figure 10. *The STARflex® device is shown here. Printed with permission from NMT Medical, Inc.*



The primary endpoint of the study was the complete cessation of migraines. Secondary endpoints included at least a 50% drop in the frequency of headaches or a 50% drop in the duration of headaches. A "headache burden" factor was determined that simply amounted to the product of the number of headaches multiplied by their duration each month. Table 2 outlines the major reported findings.

Although the reductions in migraine frequency and burden seen in

Table 2
Major Findings of the Migraine Intervention With STARFlex® Technology (MIST) I Trial

Endpoint	Patent Foramen Ovale Closure	Sham Procedure	*P* value
Headache cessation (n)	3 patients	3 patients	NS
50% reduction in headache frequency	42%	23%	0.038
Reduction in headache burden	37%	17%	0.033

Adapted with permission from Dowson A.[30]

the PFO group were significant, the hope that the migraine headaches would be eliminated was not borne out by the study, despite its excellent design. In fact, about two thirds of the patients had no reduction in their headache burden following PFO closure. Currently, a second trial (MIST II) is being conducted in the United States using a similar study design. MIST II will enroll 600 patients (300 to each arm) with a longer (1-year) follow-up. MIST II began patient entry in January 2006, and results should help clarify the role of PFO closure in this setting by providing a larger sample size for analysis. In addition, MIST III is being planned as an extension of the first MIST trial. It will give sham patients the option of device closure and will then evaluate whether the migraine headaches are reduced in the period after PFO closure compared to after sham closure.

Why PFO closure might work to reduce migraine episodes remains a mystery, although presumably some protein or other factor normally metabolized or trapped by the lungs might bypass the pulmonary bed and trigger the migraine event as a result of right-to-left shunting. To further confuse the picture, one report on the incidence of migraines after atrial septal defect closure found a reduced number of events in those with prior migraines, but a new onset of migraines in some patients who had never had them before![31]

Based on the results of the MIST I trial, it seems fair to conclude that percutaneous closure might help with migraine symptoms in patients with a PFO and demonstrable right-to-left shunting . . . but then again, it might not. The larger MIST II trial should shed considerably more light on the issue.

[Thomas Bashore, MD, FACC, FAHA]

Enoxaparin Versus Unfractionated Heparin With Fibrinolysis for ST-Segment Elevation MI

Pharmacologic reperfusion therapy for patients with ST-segment elevation myocardial infarction (STEMI) continues to evolve in an attempt to provide rapid and sustained infarct artery patency without significantly increasing the incidence of major bleeding. The use of antithrombin agents as part of the reperfusion regimen is associated with a higher rate of infarct artery patency following fibrinolytic therapy and a lower rate of re-infarction. Enthusiasm for the use of low molecular weight heparins in comparison to unfractionated heparin in this setting is due to their ease of subcutaneous administration, more predictable anticoagulant effect, lack of need for laboratory monitoring, and lower rate of resultant thrombocytopenia.

The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (EXTRACT)-Thrombolysis in Myocardial Infarction (TIMI) 25 study[32] was designed to compare enoxaparin and unfractionated heparin as adjunctive therapy for fibrinolysis. Accordingly, 20,506 patients with STEMI were randomly assigned to receive enoxaparin or matching placebo (adjusted to age and renal function) until hospital discharge, or unfractionated heparin or matching placebo with an intravenous bolus of 60 U/kg for 48 hours. The study medications were administered in a double-blind fashion with the use of a double-dummy design between 15 minutes before and 30 minutes after the initiation of fibrinolysis. The primary efficacy endpoint was the composite of death from any cause or nonfatal recurrent MI at 30 days. The main secondary endpoint was the composite of death, nonfatal MI, or recurrent ischemia requiring revascularization. Net clinical benefit served as an additional secondary endpoint and consisted of the composite of death, nonfatal MI, or nonfatal disabling stroke. Two other prespecified net clinical benefit endpoints were defined as death, nonfatal recurrent MI, or nonfatal major bleeding; and death, nonfatal MI, or nonfatal intra-cranial hemorrhage.

The findings of this study were presented by Dr. Elliott Antman of Boston, MA, on behalf of the TIMI investigators. As expected, baseline clinical and risk factors, in addition to fibrinolytic regimen and additional guideline-based medical therapy, were similar between groups and similar to those seen in contemporary studies of STEMI patients. By design, enoxaparin was continued for a median of 7 days, and unfractionated heparin was continued for a median of 2 days. At 30 days, the primary efficacy endpoint occurred in 9.9% of enoxaparin patients and in 12.0% of unfractionated heparin patients, a 17% reduction in relative risk ($P < .001$) (Figure 11). The decrease in death or nonfatal recurrent MI in the enoxaparin group was consistent across the prespecified subgroups, including gender, infarct location, patients with diabetes, and those with prior MI, as well as in patients who underwent PCI within 30 days or who were treated medically. Of note, the benefit of enoxaparin in comparison to unfractionated heparin was apparent at 48 hours, at which time there was a 33% reduction in the relative risk of nonfatal MI ($P < .002$).

In addition, as compared with unfractionated heparin, enoxaparin also significantly decreased the secondary endpoint of death, nonfatal MI, and urgent revascularization (11.7% vs 14.5%, $P < .001$) (Table 3). However, the rates of TIMI major bleeding were significantly increased in the enoxaparin group (2.1%) versus

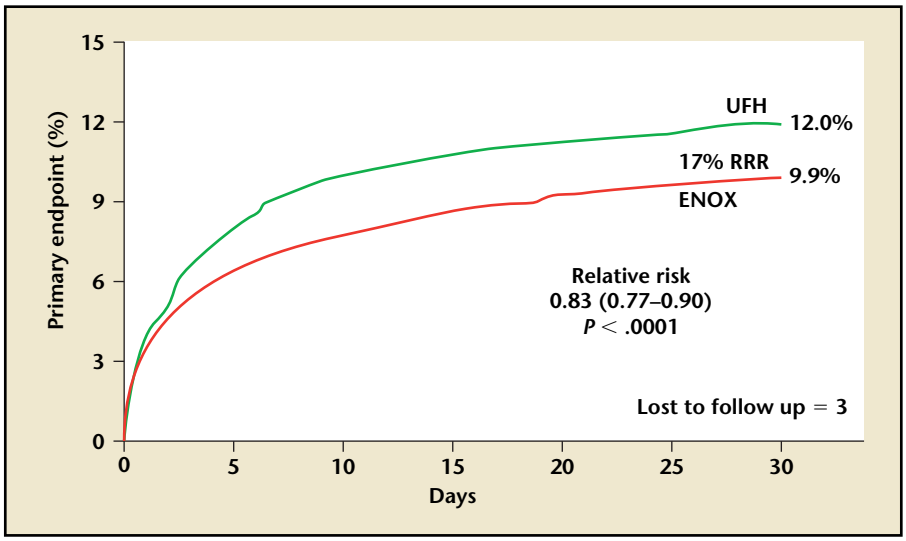


Figure 11. *Primary endpoint of death or nonfatal myocardial infarction. ITT, intention to treat; UFH, unfractionated heparin; RRR, relative risk reduction; ENOX, enoxaparin. Adapted with permission from Antman E.*[32]

the unfractionated heparin group (1.4%), with a 55% increase in relative risk ($P < .001$), although the rates of intra-cranial hemorrhage were similar. The net clinical benefit endpoints (composite of efficacy and safety) revealed a reduction in absolute event rates of between 1.8% and 2.2% or a reduction in relative risk of 14% to 18% in the enoxaparin group.

Table 3
Outcomes at 30 Days in the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (EXTRACT)–Thrombolysis in Myocardial Infarction (TIMI) 25 Study

Outcome	Enoxaparin (n = 10,256) (%)	Unfractionated Heparin (n = 10,223) (%)	Relative Risk	*P* value
Primary endpoint (death or MI)	1017 (9.9)	1223 (12.0)	0.83	< .001
Death	708 (6.9)	765 (7.5)	0.92	= .11
Nonfatal MI	309 (3.0)	458 (4.5)	0.67	< .001
Urgent revascularization	213 (2.1)	286 (2.8)	0.74	< .001
Death, nonfatal MI, or urgent revascularization	1199 (11.7)	1479 (14.5)	0.81	< .001
Major bleeding (including ICH)	211 (2.1)	138 (1.4)	1.53	< .001
Net clinical benefit: death, nonfatal MI, or nonfatal ICH	1040 (10.1)	1250 (12.2)	0.83	< .001
Net clinical benefit: death, nonfatal MI, or nonfatal major bleeding	1128 (11.0)	1305 (12.8)	0.86	< .001

MI, myocardial infarction; ICH, intracranial bleeding. Adapted with permission from Antman E.[32]

The authors concluded that in patients with STEMI who are treated with fibrinolytic therapy, a strategy of administering enoxaparin throughout the index hospitalization is superior to the current strategy of administering unfractionated heparin for 48 hours, but is associated with an increase in major bleeding. They recommended that the findings be interpreted in the context of net clinical benefit.

The results of this trial demonstrate that for every 1000 STEMI patients treated with fibrinolytic therapy, enoxaparin results in 15 fewer nonfatal reinfarctions, 7 fewer urgent revascularization procedures, and 6 fewer deaths, in addition to 4 additional episodes of nonfatal major bleeding. As discussed by Dr. Antman, 3 factors may have contributed to the differences observed: superiority of enoxaparin as an antithrombin agent, longer duration of treatment with enoxaparin, and perhaps a rebound increase in thrombotic events after discontinuation of unfractionated heparin. The superiority of enoxaparin may be based upon a relatively greater proximal inhibition of the coagulation cascade events, owing to a greater ratio of antifactor Xa to antifactor IIa activity and is supported by the observation of a significant decrease in the relative risk of nonfatal MI at 30 days. The longer duration of enoxaparin treatment likely contributed to a more sustained antithrombin effect (and increase in bleeding complications), although it is noteworthy that the secondary endpoint of death, nonfatal MI, and urgent revascularization was significantly lower at 48 hours in the enoxaparin group (and continuation of unfractionated heparin for more than 48 hours has not been shown to prevent infarct artery reocclusion following successful reperfusion).

Whether the benefit of enoxaparin will be extended to patients treated with clopidogrel or to patients with renal insufficiency will require further study and careful consideration of the increase in bleeding risk.
[Alice K. Jacobs, MD, FACC, FAHA]

Atorvastatin for Reduction of Myocardial Dysrhythmia After Cardiac Surgery

For several years, investigators have entertained the possibility that postcardiac surgery AF has an underlying inflammatory etiology. This notion has led to the hypothesis that agents that reduce inflammation might reduce the incidence of postoperative AF. The Atorvastatin for Reduction of Myocardial Dysrhythmia After Cardiac Surgery (ARMYDA-3)[33] trial tested the hypothesis that statins, because of their anti-inflammatory effects, might reduce the incidence of this postoperative complication.

In the ARMYDA-3 trial, 200 patients (statin-naïve and with no prior history of AF) scheduled for elective coronary artery bypass graft surgery or heart valve replacement/repair were randomized to treatment with atorvastatin 40 mg/d or placebo beginning 1 week before surgery. The primary endpoint was in-hospital postoperative AF lasting more than 5 minutes. Secondary endpoints included the 30-day incidence of major adverse cardiovascular and cerebral events. This study was also designed to evaluate the correlation between C-reactive protein (CRP) levels and the occurrence of AF.

Compared with the placebo recipients, the atorvastatin patients developed postoperative AF significantly less often (35% vs 57%, $P < .003$). The incidence of death, MI, and revascularization were the same in the atorvastatin and placebo groups, but the average length of hospital stay was significantly shorter in the atorvastatin group than in the placebo group, at 6.3 days versus 6.9 days ($P < .001$). This study also found that serum levels of CRP were significantly higher in the patients who experienced AF than in those who did not.

These intriguing results validate the hypothesis that AF might have an inflammatory basis, and imply that agents that reduce inflammation may decrease the incidence of this complication. The limitations of this study include its small size and the fact that it was performed at only one center. Larger, multicenter studies are required to confirm the encouraging data.
[Karol E. Watson, MD, PhD]

Peripheral Ultrafiltration Therapy for Patients Hospitalized With Heart Failure and Congestion

Volume overload (congestion) leads to the majority of hospitalizations for heart failure. Use of intravenous loop diuretics has been the standard of care to remove excess volume during hospitalization for acute decompensated heart failure. Although loop diuretics induce diuresis/natriuresis and help relieve symptoms of congestion, there are also physiologic effects that may be deleterious, including further activation of neurohormones, increase in systemic vascular resistance, reduction in stroke volume, and decrease in glomerular filtration rate.[34] Prior small clinical studies have suggested that ultrafiltration may allow for fluid removal in patients with congestive heart failure without many of the adverse physiologic effects of loop diuretics.[35,36] Earlier ultrafiltration systems required central venous access and the removal of significant blood volume for extracorporeal treatment, limiting use. A newer peripheral ultrafiltration device (Aquadex™ FlexFlow™, CHF Solutions, Brooklyn Park, MN) differs from older ultrafiltration devices by receiving blood from one of the patient's peripheral veins and holding only about 33 mL outside the body at a given time.[35] Up to 500 cc per hour of fluid can be removed, and this isotonic fluid contains approximately 3 times the amount of sodium (~3 gm/fluid L) than hypotonic urine.[36]

The randomized Ultrafiltration vs IV Diuretics for Patients Hospitalized for Acute Decompensated CHF (UNLOAD)[37] trial compared peripheral ultrafiltration versus IV loop diuretics in addition to other standard of care medications. In the trial, 200 patients with acute decompensated heart failure were equally randomized at 28 institutions to peripheral ultrafiltration or standard IV diuretic therapy (loop diuretic IV bolus or continuous infusion). Patients were assessed at 48 hours and as long as 90 days. The coprimary endpoints were weight loss at 48 hours after randomization and dyspnea score at 48 hours. There were a variety of secondary endpoints.

The UNLOAD trial results were presented by Dr. Maria Rosa Costanzo (Edward Hospital Center, Naperville, IL) (Table 4). The mean age of the patients was 62 years, 69% were male, the mean New York Heart Association Class was 3.4, left ventricular ejection fraction was < 0.40 in 70%, mean systolic blood pressure was 127 mm Hg, heart rate was 82 beats/min, sodium was 139 mEq/L, blood urea nitrogen was 32 mg/dL, creatinine was 1.5 mg/dL, and natriuretic peptide was 1280 ng/mL. Background medical therapy included angiotensin-converting enzyme inhibitors in 49%, angiotensin receptor antagonists in 17%, β-blockers in 65%, aldosterone

Table 4
Results From the Randomized Ultrafiltration vs IV Diuretics for Patients Hospitalized for Acute Decompensated CHF (UNLOAD) trial

Endpoints	Ultrafiltration (n = 83)	IV Loop Diuretics (n = 84)	*P* value
48 hours			
Weight loss, primary endpoint (mean kg)	5.0	3.1	.001
Dyspnea score, primary endpoint	6.4	6.1	.35
Net fluid loss (mean L)	4.6	3.3	.001
K < 3.5 mEq/L (%)	1	12	.018
Need for vasoactive drugs (%)	3	13	.015
90 days			
Rehospitalization (%)	18	32	.022
Rehospitalization days (mean)	1.4	3.8	.022
Unscheduled office/ emergency department visits (%)	21	44	.009

Adapted with permission from Costanzo MR.[37]

antagonists in 21%, and diuretics in 80% (mean furosemide dose equivalents of 125 mg/d).

Ultrafiltration of peripheral venous blood removed more fluid than conventional diuretic therapy. The weight loss at 48 hours was 5.0 kg with peripheral filtration versus 3.1 kg with IV diuretic ($P = .001$). However, there was no difference in dyspnea score, with both groups of patients improving to a similar degree. Peripheral ultrafiltration was well tolerated. Fewer patients in the ultrafiltration group than those treated with diuretics required rescue therapy with vasoactive drugs (48 hours: 3% vs 12%, $P = .015$).

Ultrafiltration was not associated with hypokalemia, and there were significantly more patients with hypokalemia (K < 3.5 mEq/L) in the IV loop diuretics group (12% vs 1%, $P = .018$). There were no adverse changes in serum creatinine; however, renal function was similar at 48 hours with either treatment. Ultrafiltration treatment allowed patients to take lower dosages of oral diuretics after discharge compared with diuretic treatment. Deaths up to 90 days were 9 (9.6%) with ultrafiltration and 11 (11.6%) with loop diuretics (not significant).

Ultrafiltration of peripheral venous blood led to significantly reduced rehospitalization rates compared with standard diuresis: At 90 days, the loop diuretics rehospitalization rate was 32% versus the ultrafiltration rate of 18% ($P = .022$). Total days in the hospital were reduced from 330 days with IV diuretics to 123 days with ultrafiltration.

There was little or no relationship between changing symptom status and the volume of fluid removed from patients with either therapy. Yet with similar improvement in measured symptoms between ultrafiltration and loop diuretics, the clinical outcomes were very different. This result challenges the current practice of using symptomatic responses alone to guide treatment of acute decompensated heart failure. Fluid removal did correlate significantly with readmission rates in this trial.

In summary, the UNLOAD trial demonstrated among patients hospitalized with acute decompensated heart failure that ultrafiltration of peripheral venous blood removed more fluid and led to significantly reduced rehospitalization rates compared with standard diuresis, without causing hypokalemia or untoward renal effects. These findings suggest that ultrafiltration is more effective than conventional therapy with loop diuretics for removal of excess salt and water in hospitalized heart failure patients, and that this strategy is associated with sustained clinical benefits. [Gregg C. Fonarow, MD, FACC]

Dr. Fonarow discloses that he has received a research grant from CHF Solutions.

DES in Patients Undergoing Primary PCI for Acute MI

Despite the widespread use of DES in clinical settings beyond the approved indications, relatively limited data exist to support its use in patients undergoing primary PCI for acute MI. The Paclitaxel-Eluting Stent versus Conventional Stent for STEMI (PASSION)[38] trial is 1 of the 2 initial randomized trials evaluating clinical outcomes with drug-eluting and bare metal stents among patients with acute STEMI.

At 2 centers in the Netherlands, 619 patients presenting within 6 hours of onset of acute MI symptoms were randomized to treatment

with either the paclitaxel-eluting stent (TAXUS®, Boston Scientific, Natick, MA) or a conventional, bare metal stent (Express Stent™, Boston Scientific). The primary endpoint was the 1-year occurrence of major adverse events, defined as the composite of cardiovascular death, recurrent MI, and/or target lesion revascularization. Antithrombotic therapies (including the use of GP IIb/IIIa inhibitors) were prescribed according to the treating physician's discretion.

Baseline clinical characteristics did not statistically vary between the 2 treatment groups, but were remarkable for a low prevalence of diabetes (~11%). Overall, angiographic characteristics were also similar between the 2 groups, except that a higher proportion of patients in the paclitaxel group had the right coronary artery as the infarct-related vessel. There were no differences in stent diameter, stent length, or procedural success between groups.

At 1 year, despite a trend toward fewer events in the paclitaxel group, the primary endpoint of major adverse events did not statistically differ compared with the bare metal stent cohort (12.6% vs 8.7%, $P = .12$). In particular, there were no significant differences regarding outcomes of death (6.5% vs 4.8%, $P = .39$) and ischemia-driven target lesion revascularization (7.4% vs 6.2%, $P = .23$). Stent thrombosis occurred in 3 patients in each group.

In summary, among patients undergoing primary percutaneous revascularization for STEMI, treatment with paclitaxel-eluting stents was not associated with a difference in the primary composite endpoint of the 1-year occurrence of death, repeat MI, or target lesion revascularization when compared to bare metal stents. Although outcomes of death and repeat MI have not routinely differed between DES and bare metal stents, the absence of a significant reduction in target lesion revascularization is likely in part related to the lack of protocol-specified follow-up angiography, in which clinical restenosis—rather than angiographic restenosis—drives the need for repeat revascularization.

The Cypher® Stent in Acute MI Treated With Balloon Angioplasty

The Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty (TYPHOON)[39] trial was a multi-center, prospective trial of 712 patients presenting within 12 hours of symptom onset of acute ST-elevation MI who were randomized to open-label treatment with either the sirolimus-eluting CYPHER® stent (Cordis Corporation, Miami Lakes, FL) or a bare metal stent. The primary endpoint of the study was the 1-year occurrence of target vessel failure, defined as target vessel revascularization, cardiac death, and/or recurrent MI. In addition, a prespecified subgroup of 200 patients underwent angiographic follow-up at 8 months. Principal exclusion criteria were treatment with fibrinolytic therapy, Killip classification > 2, left ventricular ejection fraction $< 30\%$, history of previous MI, or unprotected left main or bifurcation lesions. Patients were treated with aspirin and clopidogrel for a minimum of 6 months following the index procedure.

Overall baseline clinical characteristics did not significantly differ between treatment groups, except that patients in the bare metal stent group were older and more likely to have a history of prior percutaneous revascularization. Time to treatment and procedural characteristics were also similar, except for a significantly smaller stent diameter and longer stent length in the sirolimus group. In addition, an infarct-related artery involving the left anterior descending artery was significantly more common in the sirolimus group. GP IIb/IIIa inhibitors were administered in approximately 70% of patients.

At 1 year, the primary endpoint of target vessel failure occurred in 14.3% of patients in the bare metal group and in 7.3% in the sirolimus group ($P = .0036$), a difference principally driven by the lower incidence of target vessel revascularization in the sirolimus cohort (13.4% vs 5.6%, $P < .001$). Target lesion revascularization was also significantly lower with sirolimus-eluting stents (12.6% vs 3.7%, $P < .0001$). Further, among patients undergoing angiographic follow-up, measures of in-stent late loss and binary restenosis were significantly lower in the sirolimus-eluting stent group. Notably, stent thrombosis occurred in 3.6% and 3.4% of patients in the bare metal and sirolimus-eluting stent groups, respectively (not significant), with all but 1 event in the sirolimus group occurring < 30 days following revascularization.

In this randomized trial comparing sirolimus-eluting and bare metal stents in primary percutaneous revascularization for ST-elevation MI, treatment with the sirolimus-eluting stent was associated with significant reductions in 1-year target vessel failure, target vessel and lesion revascularization, and the 8-month occurrence of angiographic restenosis. There were no significant differences in death, recurrent MI, or stent thrombosis, despite an unexpectedly high incidence of stent thrombosis in both groups. Compared with the PASSION trial, however, the TYPHOON study included angiographic follow-up in a subgroup of patients, allowed randomization to any bare metal stent, and excluded patients with complex lesion morphologies and Killip class > 2 MI.

The inability to compare outcomes between these 2 trials therefore merits further comparative trials of DES in acute MI. ■

[David E. Kandzari, MD]

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Main Points

- In patients with moderate- or high-risk acute coronary syndromes undergoing cardiac catheterization, bivalirudin reduced bleeding better than heparins with or without glycoprotein IIb/IIIa agents. Bleeding or the need for transfusions is related to a much poorer outcome.
- Two years of rosuvastatin therapy was associated with regression of atherosclerosis.
- Patients who present with an acute coronary syndrome with any elevation of troponin and who undergo percutaneous coronary intervention with the use of unfractionated heparin and clopidogrel should be treated with abciximab.
- Bare metal stents might be preferable in patients who will be undergoing any type of surgery or procedure that would preclude the use of aspirin or a thienopyridine within the first 18 months following stent placement or who may be at a high risk of bleeding complications that would cause an interruption of antiplatelet therapy.
- In patients with paroxysmal atrial fibrillation, circumferential pulmonary vein ablation was associated with reduction in recurrent atrial fibrillation and atrial tachycardia compared to conventional therapy with antiarrhythmic drugs.
- A combination of 2.5 mg of folic acid or vitamin B_6 significantly decreased plasma homocysteine levels, but was not associated with a lower rate of death due to cardiovascular causes, myocardial infarction, and stroke.
- An active intervention early in the history of hypertension can slow its progression. The transition from prehypertension to clinical hypertension is remarkably high.
- In patients with ST-segment elevation myocardial infarction who are treated with fibrinolytic therapy, a strategy of administering enoxaparin throughout the index hospitalization is superior to the current strategy of administering unfractionated heparin for 48 hours, but is associated with an increase in major bleeding.
- Atrial fibrillation might have an inflammatory basis, and agents that reduce inflammation may decrease the incidence of this complication.
- Ultrafiltration of peripheral venous blood led to significantly reduced rehospitalization rates compared with standard diuresis.
- In patients undergoing primary percutaneous revascularization for ST-elevation myocardial infarction, a sirolimus-eluting stent significantly reduced 1-year target vessel failure, target vessel and lesion revascularization, and the 8-month occurrence of angiographic restenosis.

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