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Myocardial Ischemia and Infarction

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ANTITHROMBOTIC STRATEGIES

The international Reduction of Atherothrombosis for Continued Health (REACH) registry was an enormous undertaking, involving more than 68,000 stable patients with coronary artery disease (CAD), cerebral vascular disease, peripheral arterial disease, and/or multiple atherothrombotic risk factors (1). At baseline, most of the patients in this contemporary registry were on optimal therapy: 75% on lipid-lowering therapy, 73% on angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, 79% on antiplatelet therapy, and nearly one-half were taking beta-blockers.

This large global registry gives us an idea of the natural history of these patients, whether they have disease or just numerous risk factors. The results were a little discouraging. One-year follow-up data, available in 92% of patients, indicated that cardiovascular (CV) death, myocardial infarction (MI), stroke, or hospitalization occurred in 12.9% of the REACH registry subjects. In patients with established disease, the overall incidence of these major events was 14.5%, whereas in those with risk factors only, the event rate was 5.4%. Hard events—death, MI, or stroke—occurred in 3.5% of the registry patients at one year, although the incidence of these hard events increased in patients with multiple sites of established disease. Bleeding rates were low and intervention rates were modestly elevated, although most of the interventions were performed in peripheral vessels. The investigators concluded that atherothrombosis should be addressed as a global disease and events need to be decreased; the high event rate was disconcerting given the good therapy most patients received, and this requires attention.

In various randomized trials, investigators have focused on antithrombotic approaches in both stable and unstable patients with CAD. In the Clopidogrel for High Atherothrombotic Risk, Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, patients with established CV disease at baseline or at high risk for an adverse event because of multiple risk factors were randomized to low-dose aspirin alone versus aspirin plus clopidogrel 75 mg/day. There was no significant difference between these two groups on follow-up, but the addition of clopidogrel when there was evidence of established CV disease at baseline produced a 12% reduction in the primary efficacy end point (6.9% vs. 7.9%; $p = 0.046$) (2). Given the small amount of benefit seen, we clearly need to know the cost efficacy of this approach before we routinely prescribe clopidogrel to all patients with CV disease.

In the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, researchers evaluated heparin plus glycoprotein (GP) IIb/IIIa inhibition versus bivalirudin with GP IIb/IIIa inhibition or bivalirudin alone in moderate- to high-risk acute coronary syndrome (ACS) patients undergoing an early invasive strategy. The trial involved 13,800 patients; 99% of the patients underwent angiography at a median of 20 h after hospital admission, 56% underwent percutaneous coronary intervention (PCI), and 11% underwent subsequent coronary artery bypass graft surgery (3). The primary end points included an ischemic composite end point (death, MI, or unplanned revascularization); a composite of net clinical benefit, which included the ischemic composite end point plus major bleeding; or major bleeding by itself; all were calculated at 30 days.

Statistical analysis was performed for noninferiority as well as for superiority, and these were both predefined. The results showed that the ischemic composite was similar between groups, but major bleeding was seen less in the bivalirudin alone group, including retroperitoneal bleeds, access site bleeds, a decrease in hemoglobin, and the need for transfusion. Bivalirudin plus a GP IIb/IIIa inhibitor was noninferior to the heparin arm. The net clinical benefit was superior in the bivalirudin alone group versus heparin plus GP IIb/IIIa inhibition, based solely on the lower bleeding rates with bivalirudin (Fig. 1). In conclusion, the investigators suggested that bivalirudin can be substituted for either heparin or enoxaparin in these moderate- to high-risk ACS patients undergoing an early invasive strategy with the use of GP IIb/IIIa inhibitors. However, compared with either heparin or enoxaparin with GP IIb/IIIa inhibition, bivalirudin alone has a greater net clinical benefit because of less bleeding.

Another study dealing with high-risk ACS patients was presented by Dr. Adnan Kastrati, for the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT 2) trial (4). In this trial, patients with rest pain and either ST-segment changes or an elevated baseline troponin set to undergo PCI were all pretreated with clopidogrel 600 mg at least 2 h before intervention. They were then randomized to standard-dose abciximab versus placebo at the time of intervention. The primary efficacy end point was a composite of death, MI, or urgent revascularization within 30 days, and safety was assessed as Thrombolysis In Myocardial Infarction (TIMI) bleeding. In the 2,022 patients randomized, abciximab significantly reduced the end point from 11.9% to 8.9%. Clinical benefit was seen only in the group with a baseline

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Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
ACS	= acute coronary syndrome
ACUITY	= Acute Catheterization and Urgent Intervention Triage Strategy
CAD	= coronary artery disease
CHARISMA	= Clopidogrel for High Atherothrombotic Risk, Ischemic Stabilization, Management, and Avoidance
CV	= cardiovascular
ECG	= electrocardiogram
GFR	= glomerular filtration rate
GP	= glycoprotein
ExTRACT	= Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment
ISAR-REACT	= Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment
LDL	= low-density lipoprotein
MI	= myocardial infarction
NCEP	= National Cholesterol Education Program
OASIS	= Organization to Assess Strategies for Ischemic Syndromes
PEACE	= Prevention of Events with Angiotensin-Converting Enzyme Inhibition
PCI	= percutaneous coronary intervention
PTCA	= percutaneous transluminal coronary angioplasty
REACH	= Reduction of Atherothrombosis for Continued Health
STEMI	= ST-segment elevation myocardial infarction
TIMI	= Thrombolysis In Myocardial Infarction

elevated troponin level, and in this group, there was an absolute 5.5% reduction with the use of abciximab. Of some surprise was the fact that there was no increase in bleeding with abciximab.

Dr. Salim Yusuf presented the Organization to Assess Strategies for Ischemic Syndromes-6 (OASIS-6) trial, which involved 12,092 ST-segment elevation myocardial infarction (STEMI) patients treated with either thrombolytic therapy or PCI within 12 h of symptom onset (5). It was a randomized double-blind comparison of fondaparinux 2.5 mg daily versus standard-dose unfractionated heparin in patients for whom heparin was indicated; or, for those patients with a contraindication to unfractionated heparin, the comparison was between fondaparinux 2.5 mg daily versus placebo. The heparin was given for two days, the fondaparinux for nine days.

The primary efficacy end point was death or re-infarction at 30 days, and the safety end point was severe bleeding. Primary PCI was performed in 31% of patients, with lytic therapy used in 45%, and no reperfusion therapy at all in 23% of patients. At 30-day follow-up, fondaparinux reduced the incidence of death or re-infarction (9.7% vs. 11.2%; $p = 0.008$). Throughout the trial, there was a statistically significant decrease in mortality with fondaparinux. The benefit was only seen among patients undergoing thrombolytic therapy or no reperfusion; PCI patients showed no benefit. The OASIS-6 investigators reported a tendency for fewer severe bleeding events ($p = 0.13$) with fondaparinux and a significant reduction in cardiac tamponade ($p = 0.02$) in the fondaparinux group. They concluded that for STEMI patients not undergoing primary PCI, fondaparinux as used in this trial reduced mortality and re-infarction without increasing severe bleeding.

The STEMI patients also were the focus of the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis In Myocardial Infarction 25 (ExTRACT-TIMI 25) study, which involved 20,479 patients randomized <6 h after onset and treated with any fibrinolytic agent (6). Patients received either enoxaparin for 7 days, which was age-adjusted with a lower dose for patients >75 years old, or unfractionated heparin for at least 48 h. The primary efficacy end point was all-cause death or nonfatal re-infarction at 30 days; the safety end point was major bleeding as in the OASIS-6 trial.

At 30 days, death or MI was significantly reduced with enoxaparin treatment, as was death, MI, or urgent revascularization; nonfatal MIs also were reduced 33% with the study drug (Table 1). Major bleeds, however, increased from 1.4% to 2.1% with enoxaparin, although there was no increase in intracranial hemorrhages, which were found in about 0.7% of the patient population. Antman et al. (6) concluded that for STEMI patients, enoxaparin for 7 days was superior to unfractionated heparin for 48 h.

I agree very much with the conclusions; both STEMI studies suggest that long-term antithrombins may be needed with fibrinolytic therapy and not just for the usual one or two days of heparin therapy. However, there will likely be less impact from these trials in the U.S. and in

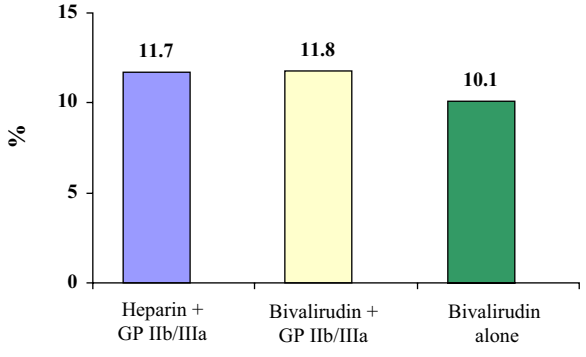

Figure 1. Acute Catheterization and Urgent Intervention Triage Strategy Trial (ACUITY): 30-day composite net clinical benefit (death, myocardial infarction, revascularization for ischemia, or major bleeding), showing superiority of bivalirudin alone versus heparin plus glycoprotein (GP) IIb/IIIa inhibitors ($p = 0.015$). Combination of bivalirudin and GP IIb/IIIa inhibitors was noninferior to heparin plus GP IIb/IIIa inhibitors.