Review

Contemporary Treatment of Unstable Angina and Non-ST-Segment-Elevation Myocardial Infarction (Part 2)

Shehzad Sami, MD
James T. Willerson, MD

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From: *Department of Cardiology, Texas Heart Institute at St. Luke's Episcopal Hospital and The University of Texas Medical School at Houston, Houston, Texas 77030*

Address for reprints: *Shehzad Sami, MD, 6770 Bertner Ave., Suite C550A, Houston, TX 77030*

E-mail: *shehzadsami76@yahoo.com*

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In Part 1 of this review, we discussed how plaque rupture is the most common underlying cause of most cases of unstable angina/non-ST-segment-elevation myocardial infarction (UA/NSTEMI) and how early risk stratification is vital for the timely diagnosis and treatment of acute coronary syndromes (ACS). Now, in Part 2, we focus on the medical therapies and treatment strategies (early conservative vs early invasive) used for UA/NSTEMI. We also discuss results from various large randomized controlled trials that have led to the contemporary standards of practice for, and reduced morbidity and death from, UA/NSTEMI.

In summary, ACS involving UA/NSTEMI is associated with high rates of adverse cardiovascular events, despite recent therapeutic advances. Plaque composition and inflammation are more important in the pathogenesis of ACS than is the actual degree of arterial stenosis. As results from new trials challenge our current practices and help us develop the optimal treatment strategy for UA/NSTEMI patients, the cornerstones of contemporary treatment remain early risk stratification and aggressive medical therapy, supplemented by coronary angiography in appropriately selected patients.

An early-invasive-treatment strategy is of most benefit to high-risk patients, whereas an early-conservative strategy is recommended for low-risk patients. Adjunctive medical therapy with acetylsalicylic acid, clopidogrel or another adenosine diphosphate antagonist, glycoprotein IIb/IIIa inhibitors, and either low-molecular-weight heparin or unfractionated heparin, in the appropriate setting, further reduces the risk of ischemic events secondary to thrombosis. Short- and long-term inhibition of platelet aggregation should be achieved by appropriately evaluating the risk of bleeding complications in these patients. ***(Tex Heart Inst J 2010;37(3):262-75)***

Acute coronary syndrome (ACS) refers to the array of clinical signs and symptoms produced by acute myocardial ischemia, including unstable angina (UA), non-ST-segment-elevation myocardial infarction (NSTEMI), and ST-segment-elevation myocardial infarction (STEMI).[1] Each condition shares common pathophysiologic origins related to the instability and rupture of atherosclerotic vulnerable plaques.[2] Unstable angina and NSTEMI are differentiated one from the other primarily by their severity—whether the ischemia is prolonged enough to lead to structural myocardial damage and to the release of detectable markers of myocardial injury, most commonly troponin I, troponin T, or creatine kinase MB.[3]

For the past 20 years, the optimal treatment strategy for UA/NSTEMI patients has been an area of great debate: should initial treatment be invasive or conservative? Despite the debate, it is now widely accepted that the initial medical therapy for patients with suspected ACS should include relieving the ischemia and preventing further myocardial damage. How clinicians go about this is largely dictated by the initial risk assessment and continued patient monitoring in a controlled environment. Hemodynamically unstable patients with refractory ischemic pain are monitored in a critical care environment and are taken to the cardiac catheterization laboratory as soon as possible. Most patients' conditions stabilize after a brief period of medical therapy, at which time they can be further triaged according to ACS guidelines.[4]

In Part 1 of this review, we discussed how plaque rupture/fissuring is the most common underlying pathophysiologic cause of most UA/NSTEMI cases and how early risk stratification is vital for the timely diagnosis and treatment of ACS. Now,

in Part 2, we focus on the medical therapies and treatment strategies (early conservative vs early invasive) used for UA/NSTEMI. We also discuss results from various large randomized controlled trials that we believe have led to the contemporary standards of practice for, and reduced morbidity and death from, UA/NSTEMI.

Specific Pharmacologic Treatments

Nitrates. Nitroglycerin has an endothelium-independent vasodilatory effect on the coronary and peripheral vascular beds. Nitrates dilate venous capacitance vessels and peripheral arterioles. Their predominant effect is a decrease in preload, with a lesser effect on afterload. Consequently, nitrates lead to a decrease in both myocardial wall stress and oxygen demand. The vasodilatory effect of nitrates on the coronary arteries is associated with an increase in endothelial guanylate activity and a consequent increase in cyclic guanosine monophosphate. They also relieve coronary spasm in atherosclerotic vessels and increase oxygen delivery to the subendocardial region that is supplied by the severely narrowed coronary artery.

Results from the Fourth International Study of Infarct Survival (ISIS-4)[5] and Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico (GISSI-3)[6] suggest that there is no survival benefit or decrease in recurrent myocardial infarction (MI) when nitrates are used routinely or selectively. Intravenous nitroglycerin should be used in patients who have refractory ischemic discomfort, and the dosage should be titrated to reduce systolic blood pressure to between 100 and 130 mmHg and to maintain a heart rate <100 beats/min. However, in patients who have refractory hypertension, nitrates alone are relatively ineffective antihypertensive agents and should be used to achieve a goal of a 10% reduction in the mean arterial pressure. In such instances, intravenous nitroglycerin should be used in conjunction with β-blockers, angiotensin-converting enzyme inhibitors, or both if possible.

Nitroglycerin is contraindicated in patients who have taken sildenafil, tadalafil, or vardenafil in the previous 24 hours, because it may lead to a sudden drop in blood pressure, an MI, or death.[7] It is also contraindicated in patients who have systemic hypotension, marked tachycardia, or severe aortic valve stenosis. Nitrates have also been associated with hypotension in patients with relatively low right-sided heart filling pressures and in patients with inferior infarcts for whom increased right ventricular filling pressures are required to maintain their systolic blood pressures within an acceptable range.

β-Adrenergic Blockers. β-Blockers decrease sinus node rate and atrioventricular node conduction velocity, systolic blood pressure, and contractile responses at rest and during exercise. By reducing contractility and slowing the heart rate, they decrease myocardial oxygen demand and increase the length of diastole—a major determinant of coronary blood flow. All of these properties make them good anti-ischemic agents, especially when used in the presence of hypertension and tachycardia.

However, the clinical trial data that form the basis for recommendations of β-blocker use are relatively few. In 1988, results from an overview of the contemporary medical literature showed that β-blockers led to a 13% relative reduction in the risk of progression from UA to an MI.[8] More recently, Ellis and colleagues[9] performed a pooled analysis of 5 randomized, placebo-controlled clinical trials of patients receiving glycoprotein (GP) IIb/IIIa receptor blockade with abciximab during percutaneous coronary intervention (PCI), in order to determine the efficacy of β-blocker therapy among patients who present with ACS. Their results showed that the mortality rate was reduced by approximately 50% both at 30 days and at 6 months in patients who received β-blockers. Therefore, it is generally recommended that ACS patients without contraindications should receive their initial dose of an oral β-blocker within the first 24 hours of medical therapy. β-Blockers are contraindicated in patients with hypotension, active reactive airway disease, a PR interval >0.24 seconds, or 2nd-degree atrioventricular block.

Calcium Channel Blockers. Calcium channel blockers (CCBs) decrease slow calcium channel transport into cells, leading to reduced myocardial contraction and relaxation of vascular smooth muscle, which increases coronary blood flow. They also decrease afterload and heart rate, while relaxing the left ventricle and increasing arterial compliance to varying degrees. Calcium channel blockers can be divided into 2 major classes: dihydropyridines (for example, nifedipine and amlodipine) and nondihydropyridines (for example, diltiazem and verapamil). They are not routinely given to UA/NSTEMI patients because of a lack of convincing evidence that they actually reduce death in this patient population. Results from most of the trials involving CCBs that were conducted in the 1980s show that these agents improve patient symptoms only modestly. We do know, however, that, in the absence of β-blockers, short-acting nifedipine should be avoided in patients with suspected ACS, because of its potential for increasing adverse events.[10] In general, CCBs can be used as a 3rd-line anti-ischemic agent—after nitrates and β-blockers—in patients who have elevated blood pressure or angina at rest or in patients for whom the use of β-blockers is contraindicated.

Antiplatelet Therapy

Acetylsalicylic Acid (Aspirin). Platelet activation and aggregation after vulnerable plaque rupture—with resultant thromboses of varying degrees—are key com-

ponents in the pathophysiology of ACS. Acetylsalicylic acid (ASA), or aspirin, causes irreversible acetylation of serine 529 of cyclooxygenase (COX-1) in platelets and the endothelium,[11,12] thereby preventing thromboxane A_2 (TXA_2) production and resultant platelet aggregation.

Studies have shown that ASA reduces the risk of angina, death, or MI by approximately 30% in patients with coronary artery disease (CAD).[13,14] In 1994, the Antiplatelet Trialists' Collaboration[13] performed a collaborative meta-analysis of 174 randomized trials of antiplatelet therapy. The analysis included 70,000 high-risk patients whose conditions were divided into 4 categories: 1) acute myocardial infarction (AMI), 2) a history of MI, 3) a history of stroke or transient ischemic attack (TIA), and 4) any other relevant medical history (UA, stable angina, vascular surgery, angioplasty, atrial fibrillation, valvular disease, peripheral vascular disease, etc.). In these high-risk patients, the incidence of nonfatal MI and nonfatal stroke was reduced by approximately one third and vascular death by approximately one sixth.[13]

The same type of meta-analysis was repeated in 2002, this time including 287 studies that involved 135,000 patients for comparing antiplatelet therapy with its absence in a control group and 77,000 patients for comparing different antiplatelet regimens. Results from this study showed that the indications for antiplatelet therapy could be broadened and that there was a lower death rate among patients with all types of vascular disease. Antiplatelet therapy reduced the risk of serious vascular events (nonfatal MI, nonfatal stroke, or vascular death) by about one quarter, not only among patients with UA, AMI, or stroke or TIA, but also among patients with CAD, peripheral arterial disease, and those at high risk for emboli.[14]

Both meta-analyses also established that ASA has proven efficacy across a broad range of dosages, with no evidence that therapeutic efficacy differs within the 75 to 150 mg per day dosing range. Currently, it is recommended that a full dose (325 mg) of ASA be given in the acute setting and until 1 month after patients undergo PCI, with or without stent placement. Thereafter, the dose may be reduced to between 81 mg and 150 mg, taken indefinitely.

Although the above data show that ASA is beneficial for preventing and treating vascular disease, ASA does not prevent all thrombotic events from recurring. In fact, patients who have an ischemic event and are taking aspirin actually may have worse outcomes than do patients who are not taking aspirin.[15] It was this observation that led to the concept of "aspirin resistance"[16,17]—a term that has been used when ASA is ineffective for protecting patients from thrombotic complications, for prolonging bleeding times, or for decreasing TXA_2 production.[17] Potential causes of aspirin resistance include inadequate dosing, drug interactions, genetic polymorphisms of COX-1 and other genes involved in TXA_2 production, and upregulation of non-platelet sources of TXA_2 production.[18] Unfortunately, the optimal treatment for aspirin resistance, if any, is unknown. The medical literature has yet to conclusively study the clinical effectiveness of altering aspirin therapy on the basis of a laboratory finding of aspirin resistance, but available evidence shows that altering aspirin therapy after a laboratory finding of aspirin resistance could be both safe and helpful.[19]

Thienopyridines. Thienopyridines, such as ticlopidine, clopidogrel, and the newer agent prasugrel, block $P2Y_{12}$ receptor signaling to prevent production of adenyl cyclase, thereby inhibiting platelet activation through adenosine diphosphate (ADP). They also limit ADP-mediated conversion of GPIIb/IIIa to its active form. Their mechanism of action is independent of and complementary to that of aspirin, and the combination of agents is superior to aspirin alone.[20,21] Because thienopyridines take longer than aspirin to cause irreversible antiplatelet effects, a loading dose usually is administered.

Ticlopidine, a 1st-generation thienopyridine, in combination with ASA, is associated with reducing rates of vascular death and MI by 46% in NSTEMI patients.[22] It has also been shown to be superior to oral anticoagulants in preventing thrombotic complications after coronary stent placement.[23] However, it is used less frequently than the newer thienopyridines in current clinical practice because of its potential for side effects: primarily rash, nausea, neutropenia, and thrombocytopenia.[24]

Clopidogrel, a 2nd-generation thienopyridine, is the most widely studied and used ADP-receptor-blocking agent. Initial data regarding clopidogrel are derived from the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study,[25] which included 19,185 patients with known atherosclerotic vascular disease. When compared with aspirin, clopidogrel resulted in a 9% relative risk reduction in adverse cardiovascular events (vascular death, MI, or ischemic stroke), without a significant increase in bleeding. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial[20] enrolled 12,562 patients. Risk of the primary composite endpoint (cardiovascular death, MI, or stroke) was reduced 20% with the use of clopidogrel, with consistent reductions observed in the individual components during 3 to 12 months (mean, 9 mo) of follow-up. Clopidogrel therapy was associated with an increase of 1% in the absolute risk of major bleeding.

Results from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial[21] confirmed those of the CAPRIE and CURE trials. The CHARISMA trial, which had a longer follow-up period (median duration, 28 mo), showed that clopidogrel plus aspirin was not

significantly more effective than aspirin alone in reducing the rate of MI, stroke, or death from cardiovascular causes among patients with stable cardiovascular disease or multiple cardiovascular risk factors. However, in a subgroup of patients with clinically evident atherothrombosis, the rate of the primary composite endpoint was 6.9% in patients given clopidogrel and 7.9% in those given a placebo.

The PCI-CURE trial[26] studied a subset of patients from the CURE trial who were undergoing PCI, and results showed that pretreatment with clopidogrel for a median of 6 days before PCI was associated with a 31% reduction in cardiovascular death or MI (including events before and after PCI).[26] However, the increasingly routine early-invasive treatment of UA/NSTEMI patients makes a wait of 6 days before cardiac catheterization unlikely. A loading dose of clopidogrel (600 mg) achieves maximal inhibition of platelet aggregation at a faster rate and has the obvious benefit of lasting for up to 30 days in low- to intermediate-risk patients undergoing elective PCI, even without GPIIb/IIIa inhibition.[27] This approach, however, does not apply to high-risk patients for whom GPIIb/IIIa inhibitors have an additive beneficial effect.

In UA/NSTEMI patients with a history of gastrointestinal (GI) bleeding, ASA and clopidogrel should be given with other agents, such as proton pump inhibitors (PPIs), that minimize the risk of recurrent GI bleeding. (Study results have shown that morbidity and death increase in UA/NSTEMI patients who experience GI bleeding due to anticoagulant or antithrombotic therapy.[4]) Clopidogrel therapy must also be stopped 4 to 7 days before elective coronary artery bypass grafting (CABG), to prevent excessive intraoperative and postoperative bleeding.[20,28,29] As a result, clinicians might have to delay giving clopidogrel to patients who are undergoing early coronary angiography (within 48 hr of hospital admission), until it is clear that these patients will not undergo a CABG procedure within the next several days.

Despite the clinical benefit achieved with the combination of clopidogrel and ASA in UA/NSTEMI patients undergoing PCI, a considerable number of patients continue to experience cardiovascular events. Inhibition of platelet aggregation alone cannot be expected to abolish all recurrent ischemic events.[30] However, there is growing evidence to support broad variability among individual patient responses to clopidogrel. This "clopidogrel resistance" is associated with a higher risk of recurrent ischemic complications.[31] Because clopidogrel is a prodrug administered orally, approximately 85% of it is hydrolyzed by esterases in the blood into an inactive carboxylic acid derivative, while only 15% of it is metabolized by the liver's cytochrome P450 (CYP) system to generate an active metabolite.[32] The mechanisms underlying the variability of response to clopidogrel remain unclear, but some hypotheses include poor patient compliance, differences in clopidogrel dosing, gastric absorption problems, and varying availability and clearance of the active metabolite.[33] However, genetic factors—including polymorphisms of hepatic CYP, especially of CYP3A—have received special attention recently and increasingly are being used in mainstream medical diagnosis and therapy.[34]

Proton pump inhibitors (for example, omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole) inhibit the function of the proton pump that is responsible for the final step in gastric acid secretion. They are metabolized to varying degrees by CYP isoenzymes, and, in some cases, also inhibit them.[35] Recently, there have been reports of concerns[36,37] that PPIs may interfere with clopidogrel's ability to inhibit platelet aggregation, thereby increasing the risk of rehospitalization or death in association with ACS. Juurlink and associates[36] conducted a population-based, nested, case-control study that included 13,636 patients who started clopidogrel therapy between 1 April 2002 and 31 December 2007, after being dischared from the hospital for treatment of MI. Of those patients, 734 were readmitted with an AMI within 90 days of hospital discharge and identified as study patients, while 2,057 patients were identified as event-free control patients. After extensive multivariable adjustment, the use of PPIs was associated with an increased risk of reinfarction (adjusted odds ratio [OR], 1.27; 95% confidence interval [CI], 1.03–1.57). In a stratified analysis, pantoprazole, which does not inhibit CYP, was not associated with hospital readmission for MI (adjusted OR, 1.02; 95% CI, 0.70–1.47).[36] Ho and colleagues[37] reported similar findings in a retrospective cohort study of 8,205 ACS patients who were discharged from 127 Veterans Affairs hospitals between 1 October 2003 and 31 January 2006. Combined use of clopidogrel and a PPI was associated with an increased risk of death from or rehospitalization for ACS when compared with use of clopidogrel alone (adjusted OR, 1.25; 95% CI, 1.11–1.41).[37]

Prasugrel is an orally administered $P2Y_{12}$ receptor antagonist that is more potent, more rapid in onset, and more consistent in its inhibition of platelet aggregation than are currently approved doses of clopidogrel. In the Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) trial,[38] 13,608 moderate- to high-risk patients with ACS (with or without ST-segment elevation) were randomly assigned to receive prasugrel or clopidogrel during PCI. Median follow-up was 15 months. Results showed that prasugrel significantly reduced the composite endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke by 19%, when compared with clopidogrel.[38] In a subgroup analysis, prasugrel also reduced MI by 24%, the need for urgent revascularization by

34%, and stent thrombosis by 52%.[39] However, the beneficial effect also was associated with a 0.5% absolute increase in non-CABG-related TIMI major bleeding and life-threatening bleeding and a 0.3% absolute increase in fatal bleeding.[38] A landmark analysis of the TRITON-TIMI 38 trial (the only endpoint–outcome study of prasugrel to date) showed that patients with a history of TIA or stroke, those who were 75 years or older, and those who weighed less than 60 kg were especially at risk of bleeding—mainly during the maintenance phase.[39,40] These data prompted the U.S. Food and Drug Administration to issue an advisory in February 2009 regarding the use of prasugrel in the abovementioned patient populations.[41]

Three novel nonthienopyridine antiplatelet agents are in advanced stages of clinical testing in patients who have CAD. Cangrelor and AZD6140 are direct and reversible inhibitors of the platelet $P2Y_{12}$ receptor, whereas SCH 530348 is an oral protease-activated receptor-1 antagonist.

Glycoprotein IIb/IIIa Inhibitors. Platelets are activated through multiple pathways; however, the "final common pathway" of platelet activation and aggregation involves a conformational change of the GPIIb/IIIa receptors from a resting state to an active state. The activated GPIIb/IIIa receptors undergo bivalent binding with soluble ligands, with fibrinogen, and, under high shear conditions, with von Willebrand factor, which leads to fibrinogen-mediated cross-linking of platelets—a key event in thrombus formation and thrombosis.[42] Because they block the final common pathway of platelet aggregation, GPIIb/IIIa inhibitors are potent inhibitors of platelet aggregation by all types of stimuli (for example, ADP, serotonin, collagen, and thrombin).

At the present time, 3 types of GPIIb/IIIa inhibitors are used clinically: abciximab, tirofiban, and eptifibatide. All 3 are pharmacodynamically and pharmacokinetically different, and the outcomes of their clinical trials and subsequent recommendations for clinical application are also different. Abciximab is a recombinant human-murine chimeric Fab fragment with a half-life of 10 minutes. Tirofiban hydrochloride is a low-molecular-weight nonpeptide derivative of tyrosine with a half-life of 1.3 hours. Eptifibatide is a cyclic heptapeptide that selectively inhibits the RGD sequence of the GPIIb/IIIa receptors and has a half-life of 150 minutes.

Abciximab was initially studied in percutaneous transluminal coronary angioplasty (PTCA) trials, in the present era of the early 1990s. Immediate and short-term ischemic complications, such as thrombus formation in the epicardial artery, periprocedural MI, a 30% restenosis rate at 1 year, and thromboembolism of the coronary microvasculature—all of which are related to the exposure of the subendothelial matrix after balloon angioplasty—were the main factors that limited PTCA's early use and prevented its expansion into other catheter-based therapies for treating CAD. However, the advent of GPIIb/IIIa inhibitors revolutionized the use of catheter-based therapies in the treatment of peripheral artery disease, cerebrovascular atherosclerotic disease, and various forms of CAD, as well as stable angina, UA, NSTEMI, and STEMI. Results from the Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial showed that in relatively high-risk patients (those with UA, evolving MI, or complex angiographic lesion morphology) who were given abciximab, there was a 35% reduction in the primary composite endpoint (death, MI, or recurrent ischemia) compared with patients who received a placebo.[43]

The c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial[44] enrolled 1,265 patients with UA who were scheduled to undergo PTCA. Results showed a 30% relative reduction, within 30 days after PTCA, in the primary endpoint of death (any cause), MI, or recurrent ischemia requiring urgent revascularization. Furthermore, abciximab reduced the rate of MI before, during, and after PTCA, even in patients given nitrates and heparin.[44] Subanalyses of the CAPTURE trial also revealed that abciximab facilitated thrombus resolution and prevented recurrent ischemia, as measured by continuous electrocardiographic monitoring.

These trials clearly establish the role of abciximab in the setting of PCI and in the management of UA/NSTEMI patients when an invasive strategy is chosen. However, the Global Use of Strategies to Open Occluded Coronary Arteries IV–Acute Coronary Syndrome (GUSTO IV-ACS) trial[45] studied 7,800 UA/NSTEMI patients who were not scheduled to undergo early revascularization. Patients were randomly assigned to receive a placebo, an abciximab bolus plus a 24-hour infusion, or an abciximab bolus plus a 48-hour infusion. All patients received aspirin and either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). The primary endpoint was death or MI at 30 days after randomization. Results showed that abciximab administration provided no benefit, even in a subgroup of patients who had elevated troponin levels.[45] On the basis of these results, the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines[4] do not recommend the use of abciximab in UA/NSTEMI patients whose initial treatment strategy is conservative.

In the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) study,[46] 3,232 patients with UA were randomly assigned to receive either heparin or tirofiban for 48 hours. Results showed a 32% reduction in the rate of death, MI, or refractory ischemia at 48 hours (3.8% with tirofiban vs 5.6% with heparin), but there was no significant difference in the composite endpoint at 30 days (15.9% in the tirofiban group vs 17% in the heparin group; $P=0.34$).[46]

TABLE I. Glycoprotein IIb/IIIa Trials

Trial	Patients' Drug	Population	Endpoint	Results
EPIC[43]	Abciximab	UA patients; evolving MI patients; those with complex angiographic lesions	Composite of death, MI, or recurrent ischemia	35% reduction in the occurrence of the primary endpoint (8.3% vs 12.8%; *P*=0.008)
CAPTURE[44]	Abciximab	Refractory UA patients undergoing PTCA	MI or recurrent ischemia requiring urgent revascularization within 30 days	30% relative reduction in the occurrence of the endpoint (11.3% vs 15.9%; *P*=0.012)
GUSTO IV-ACS[45]	Abciximab	UA/NSTEMI patients not undergoing early revascularization (within 24 hours)	Death or MI at 30 days	No benefit to giving abciximab to patients being treated conservatively
PRISM[46]	Tirofiban	UA patients	Death, MI, or refractory ischemia at 48 hours	32% reduction in the occurrence of the endpoint (3.8% vs 5.6%; RR=0.67; 95% CI, 0.48–0.92; *P*=0.01)
PRISM-PLUS[47]	Tirofiban only vs heparin only vs tirofiban plus heparin	UA/NSTEMI patients	Death, MI, or refractory ischemia at 7 days	Excessive death at 7 days in patients receiving tirofiban only
PURSUIT[48]	Integrilin	NSTEMI patients	Death and MI at 30 days	1.5% absolute reduction in the occurrence of the primary endpoint (14.2% vs 15.7%; *P*=0.04)
Boersma E, et al., meta-analysis[49]	Drugs used in 6 GPIIa/IIIb trials until 2002	Moderate- to high-risk UA/NSTEMI patients	Death or MI	9% reduction in the odds of death or MI (10.8% vs 11.8%; OR, 0.91; 95% CI, 0.84–0.98; *P*=0.015); 15% reduction in patients with NSTEMI

CAPTURE = c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina; CI = confidence interval; EPIC = Evaluation of c7E3 for the Prevention of Ischemic Complications; GP= glycoprotein; GUSTO IV-ACS = Global Use of Strategies to Open Occluded Coronary Arteries IV–Acute Coronary Syndrome; MI = myocardial infarction; NSTEMI = non-ST-segment-elevation myocardial infarction; OR = odds ratio; PRISM = Platelet Receptor Inhibition in Ischemic Syndrome Management; PRISM-PLUS = Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms; PTCA = percutaneous transluminal coronary angioplasty; PURSUIT = Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; RR = risk ratio; UA = unstable angina

In the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial,[47] 1,915 patients with UA and non-Q-wave MI were randomly assigned to receive heparin, tirofiban, or both. Patients also received ASA in the absence of any contraindications. The tirofiban-only arm was stopped prematurely because of excess death at 7 days (4.6% vs 1.1% in the heparin-only arm). The greatest benefit was seen in the group receiving both heparin and tirofiban, for whom the frequency of the composite endpoint (7-day death, MI, or refractory ischemia) was reduced (17.9% vs 12.9% in the heparin-only arm). The observed benefit was sustained at 30 days (18.5% vs 22%) and at 6 months (27.7% vs 32%).[47] The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial[48] enrolled 9,461 patients who had NSTEMI. Results showed that the administration of eptifibatide resulted in a 10% reduction in the relative risk of death and MI at 30 days.[48]

These early trials, along with a comprehensive meta-analysis by Boersma and colleagues[49] in 2002, further clarified and unequivocally established the importance of GPIIb/IIIa inhibitors in the management of moderate- to high-risk UA/NSTEMI patients (Table I). Boersma's meta-analysis pooled 31,402 patients from 6 GPIIb/IIIa trials for ACS. Results showed a 10.8% event rate in the GPIIb/IIIa inhibitor group (n=18,297), versus an 11.8% event rate in the placebo group (n=13,105), and a 9% reduction in the odds ratio of death or MI (*P*=0.015) (Fig. 1). The benefit was largest (15% reduction in the odds ratio of death or MI) in a subset of patients who had evidence of myocardial necrosis, as suggested by elevated troponin levels. No reduction in the odds ratio was seen in patients whose troponin levels were within normal range. The magnitude of the treat-

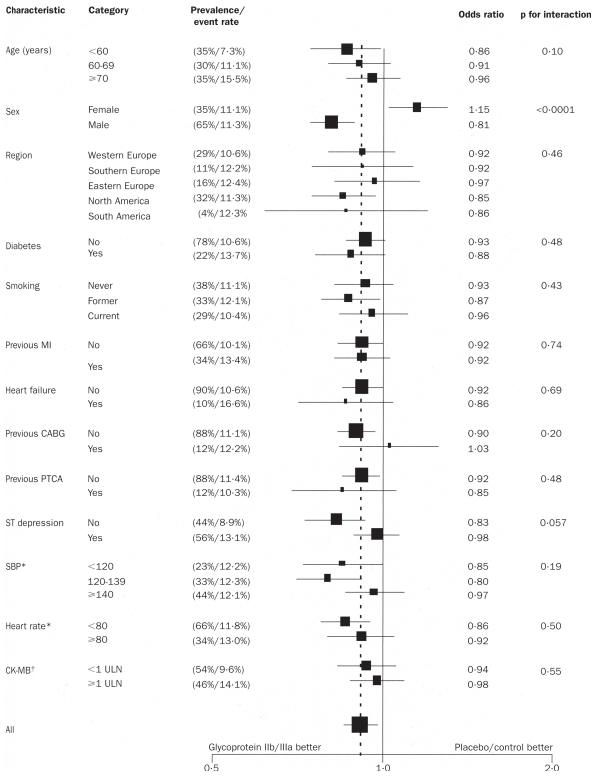

Fig. 1 *Odds ratio of 30-day death or myocardial infarction in subgroups of patients according to important clinical baseline characteristics.*

CABG = coronary artery bypass grafting; CK = creatine kinase; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; SBP = systolic blood pressure

Odds ratio represents pooled trial-specific odds ratios by the method of Cochrane-Mantel-Haenszel. Data are presented on a logarithmic scale. P *value corresponds with subgroup x treatment interaction term in a logistic regression model, with adjustments for between-trial outcome differences.*

**Blood pressure and heart rate not recorded in GUSTO-IV.*
†Data on creatine kinase MB missing in 7,469 patients.

Reprinted with permission from: Boersma E, Harrington RA, Moliterno DJ, White H, Theroux P, Van de Werf F, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials [published erratum appears in Lancet 2002;359(9323):2120]. Lancet 2002; 359(9302):189-98.[49]

ment effect also was found to be greater in patients who underwent a PCI procedure within 5 days.[49]

Although it is clear that GPIIb/IIIa inhibitors are useful in UA/NSTEMI patients undergoing invasive procedures, the optimal timing for the initiation of these agents has not been clearly established. Various trials are ongoing not only to clarify this matter of timing, but also to avoid heterogeneity of practice across the country. The Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment-Elevation Acute Coronary Syndrome (EARLY ACS) trial[50] was a collaboration involving the Virtual Coordinating Center for Global Collaborative Cardiovascular Research (VIGOUR) and the Thrombolysis in Myocardial Infarction (TIMI) Study Group. Between May 2004 and August 2008, a total of 9,494 high-risk NSTEMI patients undergoing an invasive procedure at study centers in 29 countries were randomly assigned to receive either eptifibatide ≥12 hours before angiography (the early-eptifibatide group) or a matching placebo infusion with provisional use of eptifibatide after angiography (the delayed-eptifibatide group). Results showed no statistical difference in the primary efficacy endpoint of a composite of death, MI, or recurrent ischemia requiring urgent revascularization, or in the occurrence of a thrombotic complication during PCI (9.3% in the early-eptifibatide group vs 10% in the delayed-eptifibatide group; $P=0.23$). However, early use of eptifibatide was associated with an increased risk of nonfatal bleeding and the need for transfusion.[50]

Anticoagulants

Unfractionated Heparin. Unfractionated heparin is a glycosaminoglycan comprising multiple different polysaccharide chain lengths of varying molecular weights. It exerts its anticoagulative effect by activating and accelerating the proteolytic activity of plasma cofactor antithrombin (AT). Heparin binds to the lysine site on AT, producing a conformational change at the arginine-reactive site that converts AT from a slow, progressive thrombin (factor IIa) inhibitor to a rapid inhibitor of thrombin and factor Xa, thereby preventing thrombus propagation.[51] Only one third of any given dose of heparin actually binds to AT and exerts its anticoagulative effect. Heparin also binds to a number of different circulating plasma proteins (acute phase reactants), blood cells, and endothelial cells, which contributes to its differing anticoagulative effects in different patients. Therefore, close and frequent monitoring of the activated partial thromboplastin time is necessary to ensure that a safe therapeutic range is maintained.

Théroux and colleagues[52] performed a double-blind, randomized, placebo-controlled trial involving 479 UA/NSTEMI patients who were randomly assigned to receive a placebo, ASA, heparin, or heparin plus ASA. The incidence of MI was reduced from 11.9% in the placebo group to 3.3% in the ASA group ($P=0.012$), 0.8% in the heparin group ($P<0.0001$), and 1.6% in the heparin plus ASA group ($P=0.001$). Similarly, the incidence of refractory angina was reduced from 22.9% in the placebo group to 16.5% in the ASA group ($P<0.01$), 8.5% in the heparin group ($P=0.002$), and 10.7% in the heparin plus ASA group ($P=0.11$). Interestingly, the combination of heparin plus ASA was found to be no more beneficial than heparin alone.[52] However, Oler and colleagues[53] performed a meta-analysis using data from 6 randomized trials that included 1,353 patients and found that patients who received a combination of

UFH and ASA had a 33% risk reduction in cardiovascular death and MI (95% CI, 2%–56%) than did patients who received a placebo.[53]

The ACC/AHA Guidelines[4] state that patients with NSTEMI should receive heparin, unless contraindicated. Although the optimal duration of heparin therapy is not well established, most trials of UFH involving UA/NSTEMI patients recommend continuing heparin therapy for 2 to 5 days.

Low-Molecular-Weight Heparin. Low-molecular-weight heparin is derived from heparin by chemical or enzymatic depolymerization, which yields fragments approximately one third the size of heparin. Most of the fragments contain fewer than 18 saccharide units and catalyze the inactivation of factor Xa more than of factor IIa (UFH inhibits factors Xa and IIa equally).[54] Compared with UFH, LMWH has lower plasma-protein binding and therefore a more predictable anticoagulative effect, has a greater bioavailability, is conveniently administered in subcutaneous doses (once/day or twice/day), and requires less frequent laboratory monitoring. Because LMWH is cleared by the kidneys, dosing should be decreased to half in patients with creatinine clearances of <30 mL/min and avoided altogether in patients with severe renal insufficiency.

In the Fast Revascularization during Instability in Coronary Artery Disease (FRISC) trial,[55] 1,506 patients at 23 Swedish hospitals were randomly assigned to receive 1) dalteparin (120 IU/kg with a maximal dose of 10,000 IU, twice daily), 2) UFH during the first 5 to 7 days of hospitalization and then dalteparin (7,500 IU subcutaneously, daily), or 3) a placebo for 35 to 45 days on an outpatient basis. The primary endpoint was the incidence of a new MI or death within the first 6 days of starting treatment. All patients without contraindications received ASA, β-blockers, and nitrates, as needed. During the first 6 days, dalteparin was associated with a 63% relative risk reduction in death or MI (1.8% in the treatment group vs 4.8% in the placebo group). At 40 days, differences in the incidence of MI and death in patients receiving dalteparin persisted, although a subgroup analysis revealed that dalteparin's effect was mostly confined to patients who were nonsmokers.[55]

In the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) trial,[56] 3,171 UA/NSTEMI patients were randomly assigned to receive enoxaparin (1 mg/kg twice daily) or continuous intravenous UFH (for a minimum of 48 hr to a maximum of 8 d). At 14 days, the risk of death, MI, or recurrent angina was significantly lower in the enoxaparin patients than in the UFH patients (16.6% vs 19.8%; $P=0.019$). Even at 30 days, the benefit remained (19.8% vs 23%; $P=0.016$), but at the cost of increased minor bleeding. There was no significant change in the incidence of major bleeding (6.5% vs 7%).[56]

In the Thrombolysis In Myocardial Infarction 11B (TIMI 11B) trial,[57] 3,910 UA/NSTEMI patients were randomly assigned to receive either enoxaparin or UFH for 3 to 8 days while in the hospital and then either a placebo or enoxaparin through day 43 on an outpatient basis. The primary endpoint was death, MI, or the need for urgent revascularization. At 8 days, there was a 14.6% risk reduction (12.4% in the enoxaparin group vs 14.5% in the UFH group), and at 43 days, there was a 12.3% risk reduction (17% in the enoxaparin group vs 19.7% in the UFH group). During hospitalization, there was no difference in major bleeding rates between the 2 groups; however, during the 5-week outpatient phase, the risk of major bleeding doubled in the enoxaparin group (vs placebo). These data suggest that enoxaparin may be more effective than UFH for reducing death and serious cardiac ischemic events during the acute management of UA/NSTEMI patients, without causing a significant increase in the rate of major bleeding.[57]

A meta-analysis[58] of the approximately 22,000 UA/NSTEMI patients enrolled in 6 randomized trials comparing enoxaparin and UFH showed a relative risk reduction of 9% in the combined endpoint of death or MI at 30 days for patients receiving enoxaparin (10.1% vs 11% with UFH). There were no significant differences in major bleeding at 7 days.[58] Results of this study show that the use of enoxaparin was consistently beneficial when an early-conservative strategy was implemented.

Recent trials have also compared enoxaparin and UFH for use in early-invasive strategies. The Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial was a randomized, open-label study of 10,027 high-risk UA/NSTEMI patients who were treated with an early-invasive strategy.[59] The primary endpoint was all-cause death or nonfatal MI at 30-day follow-up. The primary endpoint occurred in 14.5% of patients receiving UFH and in 14% of patients receiving enoxaparin (a nonsignificant 3% risk reduction). However, use of enoxaparin was associated with a 20% increase in TIMI major bleeding in UA/NSTEMI patients undergoing invasive procedures, especially CABG procedures.[59] Similarly, in a study by Blazing and colleagues (the A to Z trial),[60] results showed that the event rates in 3,987 patients receiving the GPIIb/IIIa inhibitor tirofiban were similar to those in patients receiving enoxaparin and those receiving UFH. The primary endpoint was a composite of death, new MI, or refractory ischemia within 7 days. However, the incidence of TIMI major bleeding not related to CABG revealed an event rate of 15% in the enoxaparin group compared with 4% in the UFH group.[60]

Compared with UFH, enoxaparin appears to be superior in reducing ischemic events in UA/NSTEMI

patients who are treated with early-conservative strategies. However, we must carefully interpret the apparent lack of benefit demonstrated in trials of early-invasive strategies (for example, the SYNERGY and A to Z trials) and the increased bleeding complications associated with the use of enoxaparin. It is important to remember that many of the UA/NSTEMI patients in those studies had already received one or more other antithrombin agents before being randomly assigned to a treatment arm, there was a high rate of patient crossover, and neither study was blinded.[61]

Factor X Inhibitors. Fondaparinux is a synthetic sulfated pentasaccharide that binds to AT early in the coagulation cascade, thereby indirectly inhibiting factor Xa. Its specificity and selectivity, combined with its long half-life and 100% bioavailability, enables once-daily anticoagulation without the need to monitor the activated clotting time. Fondaparinux inhibits factor Xa within the clot itself without inhibiting platelet function, which prevents thrombus progression and enhances AT's effectiveness in a safe manner.

In the Organization to Assess Strategies for Ischemic Syndromes (OASIS)-5 trial,[62] 20,078 patients were randomly assigned to receive either fondaparinux (2.5 mg/d) or enoxaparin (1 mg/kg, twice daily; once daily in patients with renal dysfunction) for a mean of 6 days to evaluate the primary efficacy outcome of death, MI, or refractory ischemia at 9 days. The primary safety objective was to determine whether fondaparinux was superior to enoxaparin in preventing major bleeding. Approximately 40% of patients in both groups underwent PCI, and approximately 15% of patients in both groups underwent CABG. Results of the OASIS-5 trial successfully showed that fondaparinux was statistically equivalent to enoxaparin with respect to the primary efficacy endpoint at 9 days (5.8% vs 5.7%, respectively). The composite of death, MI, refractory ischemia, or major bleeding at 9 days occurred in 7.3% of fondaparinux patients versus 9% of enoxaparin patients (hazard ratio, 0.81; 95% CI, 0.73–0.89; $P<0.001$). The efficacy was maintained for up to 6 months. Major bleeding at 9 days was significantly lower with fondaparinux than with enoxaparin (2.2% vs 4.1%; $P<0.001$).[62]

However, results from a study by the MICHELANGELO OASIS-5 Steering Committee[63] showed that fondaparinux increased the rate of guiding-catheter thrombus formation (29 episodes [0.9%] with fondaparinux vs 8 episodes with enoxaparin [0.3%]; OR=3.59; 95% CI, 1.64–7.84).[63] As a result, the steering committee amended the protocol to require an extra bolus of UFH during PCI in patients receiving fondaparinux, after the intravenous dose of fondaparinux was properly flushed from the catheter.[4] On the basis of data from the OASIS-5 trial, the 2007 ACC/AHA Guidelines give fondaparinux a class 1B recommendation for use in patients under treatment with either an early-invasive or an early-conservative approach.

Early-Conservative and Early-Invasive Strategies

Coronary angiography aids in defining the extent and location of CAD and in directing the definitive care strategy (for example, PCI with stent placement, CABG, or medical management). However, because angiography is an invasive procedure, there is a small risk of serious complications—occurring in anywhere from 1 in 1,000 cases to 1 in 500 cases—including hematoma at the access site, arrhythmia, cardiac tamponade, hypotension, an allergic reaction to the contrast medium, a cerebrovascular accident, MI, or death. Therefore, coronary angiography should be used only in patients for whom the procedure's benefits outweigh its risks.

With this principle in mind, 2 pathways of treatment for UA/NSTEMI patients have emerged: the early-invasive strategy (also called the initial invasive strategy) and the early-conservative strategy (also called the initial conservative strategy or ischemia-guided strategy). In the early-invasive strategy, all patients without contraindications undergo coronary angiography with the intent to perform revascularization within 4 to 24 hours of hospital admission. On the other hand, the early-conservative strategy consists of aggressive medical therapy for all patients and coronary angiography only for those with certain risk factors, such as advanced age, a history of MI, a previous revascularization, ST-segment deviation, a depressed left ventricular ejection fraction of ≤0.40, heart failure, and any high-risk features on noninvasive stress testing.[4]

As our understanding of the underlying pathophysiology of ACS has evolved during the past 20 years, new potential therapeutic targets have emerged, leading to the successful development and clinical application of novel drugs. These advances, along with newer and safer catheters and stents, continue to change the balance between risks and benefits associated with invasive procedures in patients with UA/NSTEMI. Many of the large clinical trials and registries reported each year continue to help us refine our decision-making process regarding early-invasive versus early-conservative strategies. Results from trials performed in the 1990s showed no benefit to an early-invasive strategy; however, results from trials performed in the post-stent era that incorporated newer antiplatelet and anticoagulative therapies have consistently shown the benefit of an early-invasive strategy in medium- to high-risk UA/NSTEMI patients.

The Thrombolysis In Myocardial Infarction-IIIB (TIMI-IIIB) trial,[64] which was the 1st large randomized trial to compare an early-invasive strategy to an early-conservative strategy in UA/NSTEMI patients,

included 1,473 patients who were randomly assigned in a 2 × 2 design to receive either tissue-plasminogen activator or a placebo and either an early-invasive strategy (early coronary angiography followed by revascularization when the anatomy was suitable) or an early-conservative strategy (early coronary angiography followed by revascularization if initial medical therapy was unsuccessful). The endpoint for the comparison between strategies was a composite of death, MI, or abnormalities on an exercise stress test at 6 weeks. There was no significant difference in the occurrence of the composite endpoint between the groups (18.1% in the early-conservative group vs 16.2% in the early-invasive group; $P=0.33$). However, the average length of initial hospitalization (10.2 d vs 10.9 d; $P=0.01$), the incidence of rehospitalization within 6 weeks (7.8% vs 14.1%; $P<0.001$), and the number of days of rehospitalization (365 d vs 963 d; $P<0.001$) all were significantly lower in the early-invasive group.[64]

In the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial,[65] 920 patients at 17 Veterans Affairs hospitals across the United States were randomly assigned to either an early-conservative strategy (medical therapy and noninvasive testing, with subsequent coronary angiography in patients with spontaneous or inducible ischemia) or an early-invasive strategy (routine coronary angiography within 1 to 3 days of hospital admission, followed by myocardial revascularization). The combined endpoint of death and nonfatal MI occurred in 3.3% of patients in the early-conservative-strategy group and 7.7% in the early-invasive-strategy group at the time of hospital discharge ($P=0.004$), in 5.6% and 10.3% at 1 month ($P=0.012$), and in 18.5% and 24% at 1 year ($P=0.05$). The difference disappeared at 23 months' follow-up.[65]

The Fragmin and Fast Revascularisation during Instability in Coronary Artery Disease-II (FRISC-II) trial[66] was a prospective, randomized, multicenter study in which 2,457 patients from 58 Scandinavian hospitals were randomly assigned to either an early-invasive treatment strategy or an early-conservative treatment strategy with placebo-controlled long-term LMWH (dalteparin) for 3 months. Coronary angiography was performed within the first 7 days in 96% of patients in the early-invasive group and in 10% of patients in the early-conservative group. After 6 months (the intended follow-up period for the study), the incidence of the composite endpoint of death or MI was 9.4% in the early-invasive group and 12.1% in the early-conservative group ($P=0.031$). In addition, there was a significant decrease in the incidence of MI in the early-invasive group compared with the early-conservative group (7.8% vs 10.1%; $P=0.045$). Furthermore, angina symptoms and hospital readmissions were reduced by 50% with the use of the early-invasive strategy. The greatest advantages of the early-invasive strategy were seen in high-risk patients whose electrocardiograms showed ST-segment depression (indicative of ischemia) or whose troponin T levels were at least 0.03 μg/L (indicative of myocardial damage).[66]

In the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction 18 (TACTICS–TIMI 18) trial,[67] 2,220 UA/NSTEMI patients were randomly assigned to either an early-invasive treatment strategy (routine coronary angiography within 4 to 48 hours of hospital admission and revascularization, as appropriate) or to a more conservative strategy (medical management in all patients and coronary angiography only in patients with spontaneous or inducible ischemia). All patients received aspirin, heparin, and tirofiban. The incidence of the primary endpoint of a composite of death, nonfatal MI, and rehospitalization for ACS at 6 months was 15.9% with use of the early-invasive strategy and 19.4% with use of the early-conservative strategy ($P=0.025$). The rate of death or nonfatal MI at 6 months was similarly reduced in both groups ($P<0.05$). The benefits of the early-invasive strategy were greatest only in medium- and high-risk patients, who were defined as having elevated cardiac troponin T levels (>0.01 ng/mL) or cardiac troponin I levels (>0.1 ng/mL); an electrocardiogram demonstrating ST-segment deviation; or a TIMI risk score of at least 3. In the absence of these features, both strategies had similar outcomes.[67]

The Randomized Intervention Treatment of Angina (RITA-3)[68] was a large, randomized, multicenter trial of 1,810 UA/NSTEMI patients who were randomly assigned to either an early-invasive-strategy group or an early-conservative-strategy group. The coprimary endpoints were a combined rate of death, nonfatal MI, or refractory angina at 4 months and a combined rate of death or nonfatal MI at 1 year. The incidence of coprimary endpoints was 9.6% in the early-invasive-strategy group and 14.5% in the early-conservative-strategy group (risk ratio [RR]=0.66, 95% CI, 0.51–0.85; $P=0.001$), and this difference was attributed mainly to a decrease in the incidence of refractory angina in the early-invasive-strategy group. Rates of death and MI were similar in both treatment groups at 1 year (7.6% vs 8.3%; RR=0.91; 95% CI, 0.67–1.25; $P=0.58$).[68]

Using data from RITA-3, Henriksson and colleagues[69] evaluated the cost-effectiveness of an early-invasive strategy by calculating costs in pounds sterling (2003–2004 £ values) and quality-adjusted life years (QALYs) and combining them into an incremental cost-effectiveness ratio. Results showed that, at a threshold of £20,000/QALY, an early-invasive strategy would likely be cost-effective in 1% of low-risk patients, 35% of intermediate-risk patients, and 95% of high-risk patients. Therefore, an early-invasive strategy appears most cost-effective in medium- to high-risk UA/NSTEMI patients.[69]

In 2005 and 2006, 3 large meta-analyses[70-72] compared an early-invasive strategy with an early-conservative strategy in combination with newer medical therapies (thiopyridines, LMWH, and GPIIb/IIIa inhibitors) and interventional devices (coronary stents). In their meta-analyses of 7 trials that included 9,212 patients, Mehta and colleagues[70] found that the endpoint of death or MI was reduced from 14.4% in the selective-invasive group to 12.2% in the routine-invasive group (OR=0.82; 95% CI, 0.72–0.93; *P*=0.001). Higher-risk patients with elevated cardiac biomarker levels at baseline benefited more from routine intervention, with no significant benefit observed in lower-risk patients with negative baseline marker levels.[70] Similarly, Hoenig and associates[71] showed that an invasive strategy yielded a 33% risk reduction in the incidence of early and intermediate refractory angina and rehospitalization. They also found that the routine use of GPIIb/IIIa inhibitors combined with an early-invasive strategy was associated with a reduction in MI and in the combined endpoint of MI and death—but only in patients with high-risk features, including those with elevated troponin levels. An invasive approach caused excess bleeding at the access site, but not an increased risk of stroke.[71] Finally,

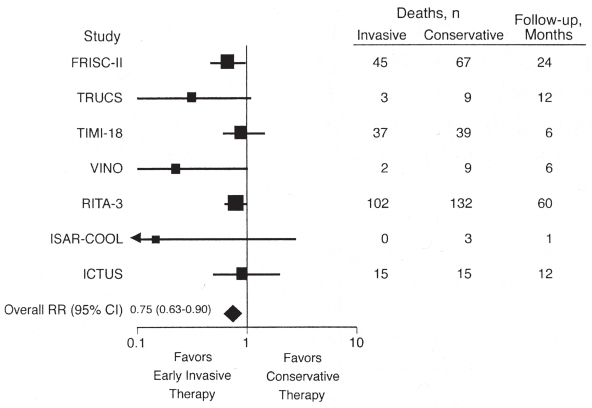

Fig. 2 *Relative risk of all-cause mortality for early invasive therapy compared with conservative therapy at a mean follow-up of 2 years. The results show a long-term survival benefit from early invasive therapy.*

CI = confidence interval; FRISC-II = Fragmin and Fast Revascularization during Instability in Coronary Disease-II; ICTUS = Invasive versus Conservative Treatment in Unstable Coronary Syndromes; ISAR-COOL = Intracoronary Stenting with Antithrombotic Regimen Cooling Off; RITA-3 = Randomized Intervention Trial of Unstable Angina-3; RR = relative risk; TIMI-18 = Thrombolysis In Myocardial Infarction-18; TRUCS = Treatment of Refractory Unstable Angina in Geographically Isolated Areas without Cardiac Surgery; VINO = Value of First Day Coronary Angiography/Angioplasty in Evolving Non–ST-Segment Elevation Myocardial Infarction

Reprinted with permission from: Bavry AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. J Am Coll Cardiol 2006;48(7):1319-25.[72]

Bavry and colleagues' meta-analysis[72] of 7 trials, which included 8,375 patients, found that, after 2 years' follow-up, the rate of all-cause mortality was 4.9% in the early-invasive group versus 6.5% in the early-conservative group (RR=0.75; 95% CI, 0.63–0.90; *P*=0.001) (Fig. 2).[72]

The optimal timing of intervention in UA/NSTEMI patients treated with an initially invasive strategy has not been clearly established, and most trials performed to date show wide variations in the timing of angiography. Recently, however, the Timing of Intervention in Acute Coronary Syndromes (TIMACS) trial,[73] a large, multicenter, randomized trial, attempted to answer this important clinical question. The TIMACS trial began as a substudy of the larger OASIS-5 trial[63] and continued recruiting another 3,031 patients who were randomly assigned to either a routine early-intervention group (n=1,593; coronary angiography within 24 hr of randomization) or a delayed-intervention group (n=1,438; coronary angiography performed 36 hr after randomization). The primary outcome (1st occurrence of a composite of death, new MI, or stroke at 6 mo) occurred in 9.6% of patients in the early-intervention group and in 11.3% of patients in the delayed-intervention group (*P*=0.15). Further analysis of the data revealed a 35% reduction in the primary outcome in high-risk patients (GRACE risk score, >140) (13.9% in the early-intervention group vs 21% in the delayed-intervention group; *P*=0.006).[73]

Conclusions

In summary, ACS involving UA/NSTEMI is associated with high rates of adverse cardiovascular events, despite recent therapeutic advances. We do know, however, that plaque composition and inflammation are more important in the pathogenesis of ACS than is the actual degree of arterial stenosis. As results from new trials challenge our current practices and help us develop the optimal treatment strategy for UA/NSTEMI patients, the cornerstone of contemporary treatment remains early risk stratification and aggressive medical therapy, supplemented by coronary angiography in appropriately selected patients. A thorough patient history, serial electrocardiographic monitoring, and cardiac biomarker measurement all aid in assessing the risk of death and recurrent events, from the time UA/NSTEMI patients arrive at the emergency department, throughout their hospitalization, and beyond. An early-invasive-treatment strategy is of most benefit to high-risk patients, whereas an early-conservative strategy is recommended for low-risk patients. Adjunctive medical therapy with ASA, clopidogrel, GPIIb/IIIa inhibitors, and either LMWH or UFH, in the appropriate setting, further reduces the risk of ischemic events secondary to thrombosis. Anticoagulation and short- and long-term inhibition of platelet aggregation should be

achieved by appropriately evaluating the risk of bleeding complications in each patient; this is important in enhancing both short- and long-term event-free survival.

References

1. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction [published erratum appears in J Am Coll Cardiol 2001;37(3): 973]. J Am Coll Cardiol 2000;36(3):959-69.
2. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation 2003;108(14):1664-72.
3. Apple FS, Jesse RL, Newby LK, Wu AH, Christenson RH; National Academy of Clinical Biochemistry; IFCC Committee for Standardization of Markers of Cardiac Damage. National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: Analytical issues for biochemical markers of acute coronary syndromes. Circulation 2007;115(13):e352-5.
4. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine [published erratum appears in Circulation 2008; 117(9):e180]. Circulation 2007;116(7):e148-304.
5. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. Lancet 1995;345(8951):669-85.
6. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. Lancet 1994;343(8906):1115-22.
7. Cheitlin MD, Hutter AM Jr, Brindis RG, Ganz P, Kaul S, Russell RO Jr, Zusman RM. ACC/AHA expert consensus document. Use of sildenafil (Viagra) in patients with cardiovascular disease. American College of Cardiology/American Heart Association [published erratum appears in J Am Coll Cardiol 1999;34(6):1850]. J Am Coll Cardiol 1999;33(1): 273-82.
8. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. II. Unstable angina, heart failure, primary prevention with aspirin, and risk factor modification. JAMA 1988;260(15):2259-63.
9. Ellis K, Tcheng JE, Sapp S, Topol EJ, Lincoff AM. Mortality benefit of beta blockade in patients with acute coronary syndromes undergoing coronary intervention: pooled results from the Epic, Epilog, Epistent, Capture and Rapport Trials. J Interv Cardiol 2003;16(4):299-305.
10. Furberg CD, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. Circulation 1995;92(5):1326-31.
11. Patrono C, Coller B, FitzGerald GA, Hirsh J, Roth G. Platelet-active drugs: the relationships among dose, effectiveness, and side effects: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126(3 Suppl):234S-264S.
12. Loll PJ, Picot D, Garavito RM. The structural basis of aspirin activity inferred from the crystal structure of inactivated prostaglandin H2 synthase. Nat Struct Biol 1995;2(8):637-43.
13. Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration [published erratum appears in BMJ 1994;308(6943):1540]. BMJ 1994; 308(6921):81-106.
14. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324(7329):71-86.
15. Alexander JH, Harrington RA, Tuttle RH, Berdan LG, Lincoff AM, Deckers JW, et al. Prior aspirin use predicts worse outcomes in patients with non-ST-elevation acute coronary syndromes. PURSUIT Investigators. Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy. Am J Cardiol 1999;83(8):1147-51.
16. Bhatt DL, Topol EJ. Scientific and therapeutic advances in antiplatelet therapy. Nat Rev Drug Discov 2003;2(1):15-28.
17. Patrono C. Aspirin resistance: definition, mechanisms and clinical read-outs. J Thromb Haemost 2003;1(8):1710-3.
18. Hankey GJ, Eikelboom JW. Aspirin resistance. Lancet 2006; 367(9510):606-17.
19. Michelson AD, Cattaneo M, Eikelboom JW, Gurbel P, Kottke-Marchant K, Kunicki TJ, et al. Aspirin resistance: position paper of the Working Group on Aspirin Resistance. J Thromb Haemost 2005;3(6):1309-11.
20. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation [published errata appear in N Engl J Med 2001;345(20):1506 and N Engl J Med 2001;345(23):1716]. N Engl J Med 2001;345(7):494-502.
21. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006; 354(16):1706-17.
22. Balsano F, Rizzon P, Violi F, Scrutinio D, Cimminiello C, Aguglia F, et al. Antiplatelet treatment with ticlopidine in unstable angina. A controlled multicenter clinical trial. The Studio della Ticlopidina nell'Angina Instabile Group. Circulation 1990;82(1):17-26.
23. Urban P, Macaya C, Rupprecht HJ, Kiemeneij F, Emanuelsson H, Fontanelli A, et al. Randomized evaluation of anticoagulation versus antiplatelet therapy after coronary stent implantation in high-risk patients: the multicenter aspirin and ticlopidine trial after intracoronary stenting (MATTIS). Circulation 1998;98(20):2126-32.
24. Love BB, Biller J, Gent M. Adverse haematological effects of ticlopidine. Prevention, recognition and management. Drug Saf 1998;19(2):89-98.
25. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996;348(9038):1329-39.
26. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and

aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358(9281):527-33.
27. Kandzari DE, Berger PB, Kastrati A, Steinhubl SR, Mehilli J, Dotzer F, et al. Influence of treatment duration with a 600-mg dose of clopidogrel before percutaneous coronary revascularization. J Am Coll Cardiol 2004;44(11):2133-6.
28. Mehta RH, Roe MT, Mulgund J, Ohman EM, Cannon CP, Gibler WB, et al. Acute clopidogrel use and outcomes in patients with non-ST-segment elevation acute coronary syndromes undergoing coronary artery bypass surgery. J Am Coll Cardiol 2006;48(2):281-6.
29. Chu MW, Wilson SR, Novick RJ, Stitt LW, Quantz MA. Does clopidogrel increase blood loss following coronary artery bypass surgery? Ann Thorac Surg 2004;78(5):1536-41.
30. Wiviott SD, Antman EM. Clopidogrel resistance: a new chapter in a fast-moving story. Circulation 2004;109(25):3064-7.
31. Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Bhatt DL, Topol EJ. Variability in platelet responsiveness to clopidogrel among 544 individuals. J Am Coll Cardiol 2005;45(2):246-51.
32. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Alfonso F, Macaya C, Bass TA, Costa MA. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. J Am Coll Cardiol 2007;49(14):1505-16.
33. Oqueli E, Hiscock M, Dick R. Clopidogrel resistance. Heart Lung Circ 2007;16 Suppl 3:S17-28.
34. Frere C, Cuisset T, Morange PE, Quilici J, Camoin-Jau L, Saut N, et al. Effect of cytochrome p450 polymorphisms on platelet reactivity after treatment with clopidogrel in acute coronary syndrome. Am J Cardiol 2008;101(8):1088-93.
35. Li XQ, Andersson TB, Ahlstrom M, Weidolf L. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. Drug Metab Dispos 2004;32(8):821-7.
36. Juurlink DN, Gomes T, Ko DT, Szmitko PE, Austin PC, Tu JV, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ 2009;180(7):713-8.
37. Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, Rumsfeld JS. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA 2009;301(9):937-44.
38. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357(20):2001-15.
39. Wiviott SD, Braunwald E, McCabe CH, Horvath I, Keltai M, Herrman JP, et al. Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. Lancet 2008;371(9621):1353-63.
40. Murphy SA, Antman EM, Wiviott SD, Weerakkody G, Morocutti G, Huber K, et al. Reduction in recurrent cardiovascular events with prasugrel compared with clopidogrel in patients with acute coronary syndromes from the TRITON-TIMI 38 trial. Eur Heart J 2008;29(20):2473-9.
41. Alexander W. FDA advisory committee meeting on prasugrel for acute coronary syndromes. P T 2009;34(3):155-6.
42. Topol EJ, Byzova TV, Plow EF. Platelet GPIIb-IIIa blockers. Lancet 1999;353(9148):227-31.
43. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC Investigation. N Engl J Med 1994;330(14):956-61.
44. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study [published erratum appears in Lancet 1997;350(9079):744]. Lancet 1997;349(9063):1429-35.
45. Simoons ML; GUSTO IV-ACS Investigators. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomised trial. Lancet 2001;357(9272):1915-24.
46. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. N Engl J Med 1998;338(21):1498-505.
47. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators [published erratum appears in N Engl J Med 1998;339(6):415]. N Engl J Med 1998;338(21):1488-97.
48. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. N Engl J Med 1998;339(7):436-43.
49. Boersma E, Harrington RA, Moliterno DJ, White H, Theroux P, Van de Werf F, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials [published erratum appears in Lancet 2002;359(9323):2120]. Lancet 2002;359(9302):189-98.
50. Giugliano RP, White JA, Bode C, Armstrong PW, Montalescot G, Lewis BS, et al. Early versus delayed, provisional eptifibatide in acute coronary syndromes. N Engl J Med 2009;360(21):2176-90.
51. Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest 2001;119(1 Suppl):64S-94S.
52. Theroux P, Ouimet H, McCans J, Latour JG, Joly P, Levy G, et al. Aspirin, heparin, or both to treat acute unstable angina. N Engl J Med 1988;319(17):1105-11.
53. Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. JAMA 1996;276(10):811-5.
54. Weitz JI. Low-molecular-weight heparins. N Engl J Med 1997;337(10):688-98.
55. Swahn E, Wallentin L. Low-molecular-weight heparin (Fragmin) during instability in coronary artery disease (FRISC). FRISC Study Group. Am J Cardiol 1997;80(5A):25E-29E.
56. Cohen M, Demers C, Gurfinkel EP, Turpie AG, Fromell GJ, Goodman S, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. N Engl J Med 1997;337(7):447-52.
57. Antman EM, McCabe CH, Gurfinkel EP, Turpie AG, Bernink PJ, Salein D, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. Circulation 1999;100(15):1593-601.

58. Petersen JL, Mahaffey KW, Hasselblad V, Antman EM, Cohen M, Goodman SG, et al. Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non-ST-segment elevation acute coronary syndromes: a systematic overview. JAMA 2004;292(1):89-96.
59. Ferguson JJ, Califf RM, Antman EM, Cohen M, Grines CL, Goodman S, et al. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. JAMA 2004;292(1):45-54.
60. Blazing MA, de Lemos JA, White HD, Fox KA, Verheugt FW, Ardissino D, et al. Safety and efficacy of enoxaparin vs unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes who receive tirofiban and aspirin: a randomized controlled trial [published erratum appears in JAMA 2004;292(10):1178]. JAMA 2004;292(1):55-64.
61. Califf RM, Petersen JL, Hasselblad V, Mahaffey KW, Ferguson JJ. A perspective on trials comparing enoxaparin and unfractionated heparin in the treatment of non-ST-elevation acute coronary syndromes. Am Heart J 2005;149(4 Suppl): S91-9.
62. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators, Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med 2006; 354(14):1464-76.
63. MICHELANGELO OASIS-5 Steering Committee, Mehta SR, Yusuf S, Granger CB, Wallentin L, Peters RJ, et al. Design and rationale of the MICHELANGELO Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS)-5 trial program evaluating fondaparinux, a synthetic factor Xa inhibitor, in patients with non-ST-segment elevation acute coronary syndromes. Am Heart J 2005;150(6):1107.
64. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. Circulation 1994;89(4):1545-56.
65. Boden WE, O'Rourke RA, Crawford MH, Blaustein AS, Deedwania PC, Zoble RG, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators [published erratum appears in N Engl J Med 1998;339(15):1091]. N Engl J Med 1998;338(25):1785-92.
66. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Lancet 1999;354(9180):708-15.
67. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001;344(25):1879-87.
68. Fox KA, Poole-Wilson PA, Henderson RA, Clayton TC, Chamberlain DA, Shaw TR, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. Lancet 2002;360(9335):743-51.
69. Henriksson M, Epstein DM, Palmer SJ, Sculpher MJ, Clayton TC, Pocock SJ, et al. The cost-effectiveness of an early interventional strategy in non-ST-elevation acute coronary syndrome based on the RITA 3 trial. Heart 2008;94(6):717-23.
70. Mehta SR, Cannon CP, Fox KA, Wallentin L, Boden WE, Spacek R, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. JAMA 2005;293(23):2908-17.
71. Hoenig MR, Doust JA, Aroney CN, Scott IA. Early invasive versus conservative strategies for unstable angina & non-ST-elevation myocardial infarction in the stent era. Cochrane Database Syst Rev 2006;3:CD004815.
72. Bavry AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. J Am Coll Cardiol 2006;48(7):1319-25.
73. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand JP, Faxon DP, et al. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med 2009;360(21):2165-75.