Therapeutic Adjuncts for Immediate Transfer to the Catheterization Laboratory in Patients with Acute Coronary Syndromes

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Early coronary intervention in patients with non–ST-segment elevation myocardial infarction (MI) and unstable angina may be made safer and more efficacious with concomitant therapies, including glycoprotein IIb/IIIa inhibitors and low-molecular-weight heparins. Stent placement has been shown to improve procedural success and reduce major in-hospital complications when compared with balloon angioplasty alone in patients with unstable angina. However, unstable angina remains a major hazard for adverse coronary events in long-term follow-up after elective stent placement. The currently available glycoprotein IIb/IIIa inhibitors—eptifibatide, tirofiban, and abciximab—have each been shown to reduce ischemic events before percutaneous coronary intervention when administered to patients presenting with non–ST-segment elevation acute coronary syndromes in large clinical trials. The adjunctive role of low-molecular-weight heparins in this scenario has been largely unexplored. Enoxaparin, when given before angiography or percutaneous coronary intervention, has been shown to be superior to unfractionated heparin in preventing major coronary events. In this review, an algorithm for treatment of non–ST-segment elevation acute coronary syndromes is presented and the current role of these newer adjunctive pharmacotherapies is explored. In the future, combinations of these agents may prove to be most beneficial in patients undergoing early percutaneous coronary intervention.
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For the past decade, controversy has surrounded the establishment of an optimal treatment approach for patients with acute coronary syndromes. Contrasting differences have evolved in the management of patients with ST-segment elevation myocardial infarction (MI) versus non–ST-segment elevation MI. Primary percutaneous coronary intervention and antiplatelet therapy with aspirin and clopidogrel are currently recommended for patients with an evolving anterior MI and heart failure. In centers with no catheterization facilities, administration of standard thrombolytic therapy is appropriate for achieving early coronary perfusion.

The initial approach to treatment for patients with unstable angina or non–ST-segment elevation MI, who represent a heterogeneous group having a wide-ranging level of risk, is less clear. Determining the optimal treatment strategy for these patients has centered on whether "invasive" or "conservative" management is appropriate. In patients with non–ST-segment elevation MI, a strategy of recommending routine angiography for patients considered to be at "low risk" might not result in optimal clinical benefits. Historically, most physicians have prescribed a period of rest and stabilization for these patients because of the potential hazard for adverse clinical events (death, MI, or the requirement for urgent coronary revascularization) previously associated with early percutaneous coronary intervention in this patient population.

Concomitant therapies, including coronary stent placement, glycoprotein IIb/IIIa inhibition, low-molecular-weight heparins, and combinations of these treatments have shown promise for making earlier coronary intervention safer and more efficacious. Current trends in the use of these adjunctive therapies, as well as the potential for routinely incorporating them in the early treatment course of patients with unstable angina and non–ST-segment elevation MI, are the focus of this review.

EARLY INTERVENTION IN PATIENTS WITH UNSTABLE ANGINA

Prior studies have shown an increased incidence of major hospital complications associated with percutaneous transluminal coronary angioplasty (PTCA) performed at the time of diagnostic angiography (ad hoc) in patients with unstable angina.[1,2] A similar hazard has been shown in patients with unstable angina who undergo PTCA early in their treatment course. As described by Myler et al,[3] patients having PTCA within 1 week after the onset of unstable angina had a lower procedural success rate (79% vs 88%, $p < 0.05$) and a higher major cardiac event rate (11.5% vs 4.7%, $p < 0.05$) than did patients with stable angina (Figure 1). This study was a retrospective analysis of 2,122 consecutive patients (62% stable, 38% unstable angina) who underwent elective (or semielective) PTCA between 1982 and 1985. Serious complications oc-

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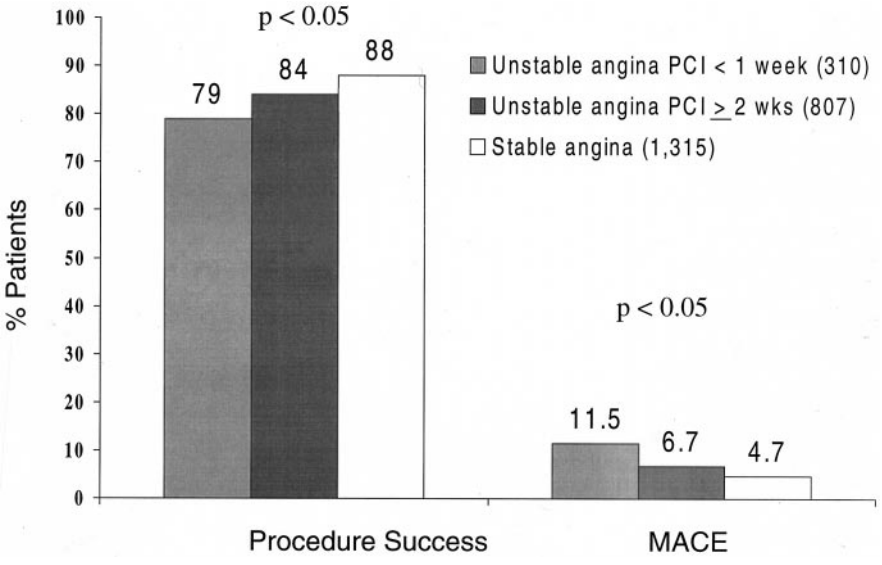

FIGURE 1. Coronary angioplasty for angina pectoris. Procedural success (*left*) and major coronary event rates ([MACE]; *right*) are shown for patients with both stable or unstable angina and early (vs deferred) percutaneous coronary intervention (PCI). (Data are from *Circulation*.[3])

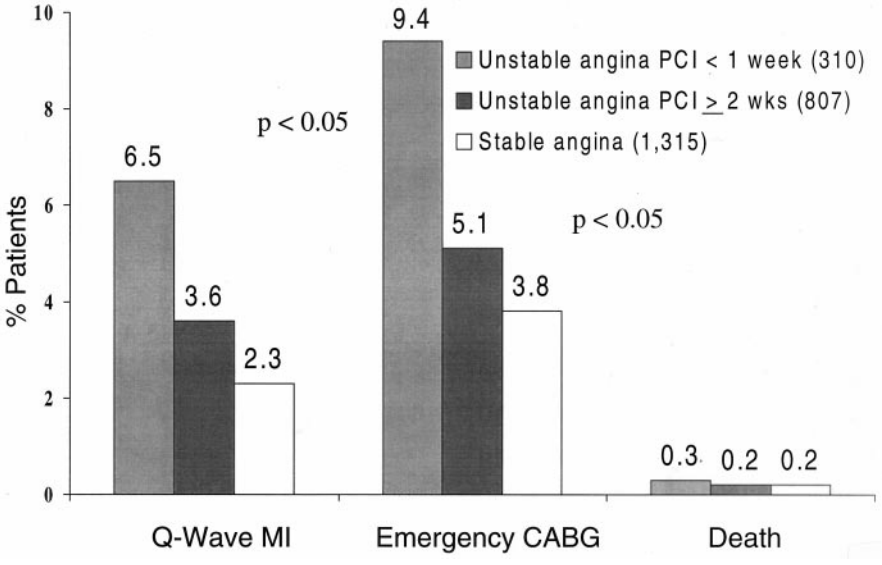

FIGURE 2. Major complications after percutaneous coronary intervention (PCI) for angina pectoris. The incidence of major complications, including Q-wave myocardial infarction (MI), emergency coronary artery bypass grafting (CABG), and death are shown for patients by angina status (stable vs unstable) and timing of PCI (early vs deferred). (Data are from *Circulation*.[3])

curred in 4.7% of stable versus 6.7% of deferred unstable angina patients (Figure 1). Patients who underwent early PTCA (<1 week) after onset of angina had significantly higher complication rates (major cardiac events), including a higher incidence of both Q-wave MI and emergency coronary artery bypass grafting (CABG) than did those patients who had PTCA ≥2 weeks after symptom onset ($p < 0.05$; Figure 2). Indeed, no differences in clinical outcomes were observed between patient groups (unstable vs stable angina) when angioplasty was undertaken ≥2 weeks after angina symptom onset.

ADJUNCTIVE THERAPIES TO PERCUTANEOUS CORONARY INTERVENTION IN UNSTABLE ANGINA

Coronary stents: Coronary stent placement may improve procedural success and reduce major hospital complications when compared with standard balloon angioplasty in patients with unstable angina. In a large retrospective nonrandomized analysis of patients treated at the Mayo Clinic, those patients with unstable angina who underwent coronary stent implantation (vs balloon angioplasty) had a reduction in mortality

TABLE 1 In-hospital and 1-year Follow-up in Patients with Unstable Angina Undergoing Stent Placement Versus Stent and/or Percutaneous Transluminal Coronary Angioplasty (PTCA) Procedures

Variable	PTCA (%) (n = 5,656)	Stent ± PTCA (%) (n = 1,976)	p Value
Clinical success	83.8	95.9	<0.00001
In-hospital deaths	2.6	1.5	0.003
CABG <24 hr	3.6	0.9	<0.00001
Q-wave MI	1.1	1.0	0.62
Follow-up (1 year)			
Death	3.4	3.0	0.25
CABG	19.6	6.5	<0.00001
Angina	47.4	23.5	<0.00001
Q-wave MI	1.9	0.4	<0.00001
Repeat procedure	30.6	13.8	<0.00001

CABG = coronary artery bypass grafting; MI = myocardial infarction.
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and in the need for CABG (Table 1).[4] In this study, the hospital and late (1 year) outcome results for 5,656 patients who had PTCA only were compared with those for 1,976 patients who received coronary stents.[4] Stents alone do not eliminate the risk of adverse ischemic events associated with unstable angina. Multivariate analyses have defined unstable angina as a major hazard for adverse coronary events during long-term follow-up after elective coronary stent deployment.[5,6]

This potential "hazard" for coronary events in patients with unstable angina was present in the early randomized comparative trials of invasive versus conservative treatment strategies, such as the Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH) trial.[7] VANQWISH was conducted before the era of glycoprotein IIb/IIIa blockade and stent implantation. In this trial, 920 patients with non–Q-wave MI were randomly assigned to either an invasive strategy (n = 462) (routine coronary angiography followed by myocardial revascularization) or a conservative strategy (n = 458) (medical therapy with noninvasive testing and subsequent invasive management if indicated). The composite occurrence of death or nonfatal infarction appeared to be higher in the invasively managed group. On closer analysis by hospital discharge status, the "hazard" for death or nonfatal MI in the invasive-strategy group occurred while patients were in the hospital (36 vs 15 events, p = 0.004) and was less at 1 year (111 vs 85 events, p = 0.05). Those patients who survived to hospital discharge in the VANQWISH trial had an advantage after the invasive strategy treatment.

Glycoprotein IIb/IIIa blockade: In recent years, several large clinical trials have shown that treatment with glycoprotein IIb/IIIa inhibitors, when used prophylactically for percutaneous coronary intervention or as adjunctive treatment for acute coronary syndromes, reduces the incidence of subsequent death or MI. Glycoprotein IIb/IIIa is a platelet surface membrane receptor that mediates binding of activated platelets to fibrinogen and subsequent thrombus formation. Glycoprotein IIb/IIIa inhibition can be accomplished by administration of a monoclonal antibody Fab fragment (abciximab) or by small molecules (eptifibatide, tirofiban) that mimic the protein segment recognized by the glycoprotein IIb/IIIa receptor to prevent fibrinogen binding.[8]

There are 3 currently available glycoprotein IIb/IIIa receptor inhibitors: a peptide inhibitor, eptifibatide; a nonpeptide inhibitor, tirofiban; and a chimeric antibody fragment, abciximab, each of which can bind the receptor and inhibit platelet aggregation. All 3 of these glycoprotein IIb/IIIa inhibitors have been shown to reduce ischemic events before percutaneous coronary intervention when administered early to patients with non–ST-segment elevation in 3 respective trials: Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT)[9]; Platelet Receptor inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and symptoms (PRISM-PLUS)[10]; and c7E3 Fab Anti Platelet Therapy in Unstable REfractory angina (CAPTURE).[11]

The hazard for adverse clinical events after coronary intervention is not eliminated by pretreatment with the low-molecular-weight heparin dalteparin. Glycoprotein IIb/IIIa blockade was not used in the Fragmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) trial.[12] In this multicenter trial, 2,457 patients with non–ST-segment elevation acute coronary syndrome were randomly assigned to either an early invasive or noninvasive treatment strategy after 5–7 days of open-label treatment with dalteparin. After randomization to revascularization strategy, a second randomization to either prolonged subcutaneous dalteparin (90 IU twice daily for 3 months) or placebo was performed. At 6 months, the composite endpoint of death or MI occurred in 9.4% of the invasive strategy group (113 of 1,207 patients) compared with 12.1% in the noninvasively managed group (148 of 1,226 patients). In examining the effects of dalteparin, during 3 months of double-blind treatment, there was a significant decrease in the composite endpoint of death or MI in favor of dalteparin over placebo (6.7% vs 8.0%). The Kaplan-Meier curves representing the occurrence of the composite endpoint of death or MI over time illustrate the persistent relative hazard associated with an early invasive treatment strategy at 30 days (Figure 3). However, by 6-month follow-up, the composite endpoint was observed less frequently in invasively treated patients. Thus, an early invasive treatment strategy may be advantageous over a noninvasive strategy in reducing the rate of death, MI, or both, to 6 months. The "early hazard" of early revascularization remains evident in the absence of glycoprotein IIb/IIIa blockade.

In the PURSUIT trial, the glycoprotein IIb/IIIa inhibitor eptifibatide proved beneficial beyond heparin and aspirin therapy alone by reducing the incidence of adverse ischemic outcomes in patients with non–ST-segment elevation acute coronary syndrome.[9] Interestingly, most of the benefit attributable to eptifibatide in PURSUIT was observed in those patients who under-

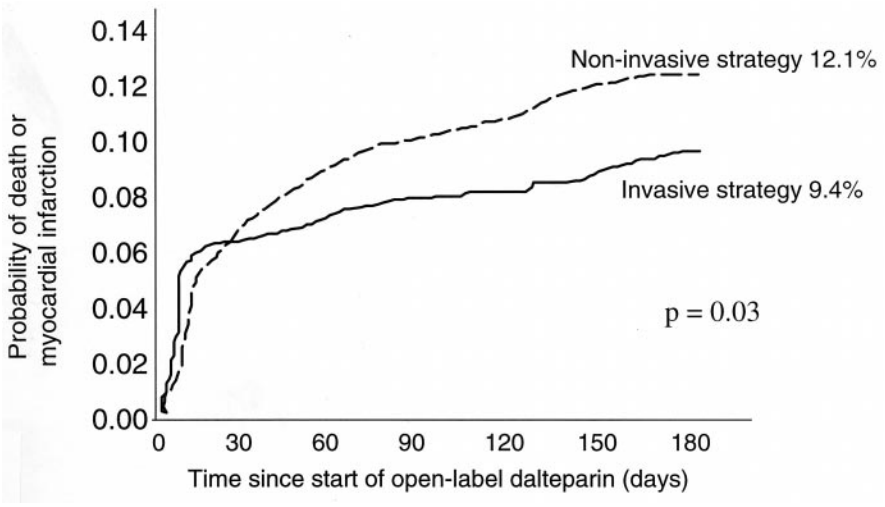

FIGURE 3. Composite occurrence of death or myocardial infarction by treatment allocation (noninvasive vs invasive) in the FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) trial (Kaplan-Meier curves). The "hazard" of an early invasive strategy is replaced by net benefit at 6-month follow-up. (Adapted with permission from *Lancet.*[12])

went percutaneous coronary intervention within 72 hours of enrollment. A total of 10,948 patients were enrolled in this study and were randomly assigned to receive either a bolus and infusion of eptifibatide or placebo, in addition to standard therapy, for a treatment phase of 72 hours. Randomized treatment allocation was continued for up to 96 hours if percutaneous coronary intervention was performed near the end of the initial 72-hour period. The primary endpoint of the PURSUIT trial was the composite occurrence of death or nonfatal MI at 30 days after enrollment. For patients undergoing percutaneous coronary intervention within 72 hours of randomization, there was a 31% reduction in the composite endpoint to 30 days in those who received treatment with eptifibatide versus placebo (11.6% vs 16.7%, $p = 0.01$). In those patients who did not undergo early (<72 hrs) percutaneous coronary intervention, a 7% reduction in the composite endpoint was observed in favor of eptifibatide versus placebo (14.5% vs 15.6%, $p = 0.23$). Thus, a 5-fold greater reduction in the composite occurrence of death or MI to 30 days was observed in patients having percutaneous coronary intervention within 72 hours who were randomly allocated to receive eptifibatide compared with patients who did not undergo early percutaneous coronary intervention.

In the Platelet Receptor Inhibition for Ischemic Syndrome Management (PRISM)[13] and PRISM-PLUS[10] studies, the glycoprotein IIb/IIIa receptor inhibitor tirofiban in combination with heparin and aspirin was associated with a lower incidence of ischemic events in patients presenting with non–ST-segment acute coronary syndromes. In PRISM-PLUS, patients ($n = 1,915$) were initially randomly assigned to receive either tirofiban, heparin, or the combination of tirofiban plus heparin in conjunction with aspirin. Study drugs were infused for a mean ($\pm$SD) of 71.3 $\pm$ 20 hours. After the initial 48 hours of therapy, angiography and angioplasty could be performed, if indicated. The study was stopped early for the group receiving treatment with tirofiban alone (no heparin) because of excess mortality at 7 days (4.6% tirofiban alone vs 1.1% for heparin). Furthermore, at 7 days, the composite primary endpoint of the trial (death, MI, or refractory ischemia) was lower in patients who received tirofiban plus heparin compared with those receiving heparin alone (12.9% vs 17.9%; relative risk [RR], 0.68; 95% confidence interval [CI], 0.53–0.88; $p = 0.004$). Similar results were seen at 30 days.

The CAPTURE trial was designed to determine whether abciximab therapy could improve clinical outcomes in patients with refractory angina pectoris who were candidates for percutaneous coronary intervention.[11] In CAPTURE, 1,266 patients were enrolled and randomly assigned to treatment with either abciximab or placebo after baseline coronary angiography. Abciximab (or placebo) was infused for 18–24 hours before the performance of PTCA. Study medication infusion was terminated 1 hour after percutaneous coronary intervention in this trial. By 30-day follow-up, the primary endpoint (death, MI, or urgent intervention for recurrent ischemia) was observed in 71 (11.3%) of 630 patients who received treatment with abciximab compared with 101 (15.9%) of 635 patients receiving placebo ($p = 0.012$). At 6-month follow-up, 193 patients in each group had experienced death, MI, or repeat intervention. Interestingly, the benefit attributable to abciximab therapy in the CAPTURE trial after a 1-hour postpercutaneous coronary intervention infusion was considerably less than the magnitude of benefit observed in prior studies that employed a 12-hour postprocedural abciximab infusion.[14,15]

At the Ohio Heart Health Center, abciximab was incorporated into practice guidelines for percutaneous coronary intervention in patients with unstable angina starting in 1996. The impact of using abciximab ad-

TABLE 2 Unstable Angina 1995–1998: Ohio Heart Health Center at The Christ Hospital

	1995	1997	1998
Patients (n)	94	321	352
Age (yr) mean (±SD)	62 (11.1)	61 (11.8)	63 (12.1)
Male (%)	70	63	63
Diabetic (%)	32	27	27
LVEF, mean (±SD)	0.51 (11)	0.54 (11)	0.55 (9)
No. vessels stenosed >50% (%)			
1	38	49	52
2	34	30	30
3	28	21	16
4	0	0	2
No. lesions PCI (%)			
≥2	43	38	37
≥3	7	7	5
≥4	1	2	1

LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

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junctive pharmacotherapy is illustrated in a study conducted at The Christ Hospital in Cincinnati, Ohio, which examined 3 separate cohorts of patients with unstable angina undergoing percutaneous coronary intervention by Ohio Heart Health Center operators (Table 2).[16] The first cohort represents the second quarter of 1995, which was the first quarter that abciximab was commercially available for use in the United States. The second 2 cohorts represent the first half of years 1997 and 1998, respectively, after the implementation of guideline-driven administration of abciximab.[17,18] There were no demographic or procedural differences between these populations. During this time frame, the use of abciximab during percutaneous coronary intervention increased from 16% to 75%, and stent use increased from 19% to 81% (Figure 4). The average preprocedural length of hospitalization was concurrently reduced from 0.96 (±1.31) to 0.26 days (±0.61), and total hospital stay from 2.82 (±2.01) to 1.59 (±1.95) days, in 352 consecutive patients.[17,18] The same operators were able to achieve a 57% reduction in major hospital complications (death, Q-wave MI, or requirement for urgent revascularization), and 98% event-free survival was observed to hospital discharge, which occurred within 48 hours in 85% of these patients. Furthermore, an 81% reduction in requirement for urgent revascularization (percutaneous or surgical) to 30 days was achieved (Figure 5).

An algorithm for treatment of non–ST-segment elevation acute coronary syndrome has evolved from the Ohio Heart Health Center experience and is shown in Figure 6.[16] This algorithm defines risk first before triage to treatment strategy. Risk can be discerned at the bedside by angina symptom complex, ST depression, an elevated troponin level, or obvious hemodynamic compromise. Patients at high risk are eligible for administration of glycoprotein IIb/IIIa inhibitors early "upstream" or after admission to the catheterization laboratory. High-risk patients undergo early coronary angiography for definition of the anatomy, and percutaneous coronary intervention as indicated and feasible, because platelet glycoprotein IIb/IIIa blockade eliminates the risk associated with early percutaneous coronary intervention. Patients who are not at high risk undergo observation and provocative stress testing and can be triaged to the catheterization laboratory based on objective evidence for myocardial ischemia.

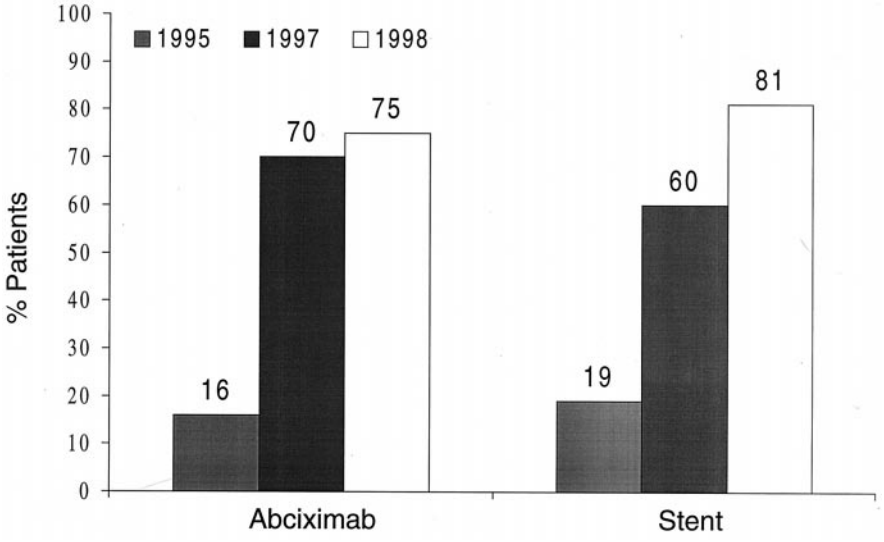

FIGURE 4. From the Ohio Heart Health Center interventionists at The Christ Hospital, Cincinnati, Ohio. Use of abciximab and intracoronary stent deployment during percutaneous intervention in patients with unstable pectoris by patient cohort (1995 vs 1997 vs 1998). Abciximab use increased from 16% to 75% and stent use increased from 19% to 81% during this time frame. During the last 2 time periods, abciximab had been incorporated into the practice guidelines. (Reprinted with permission from Mosby, Inc. *Am Heart J.*[16])

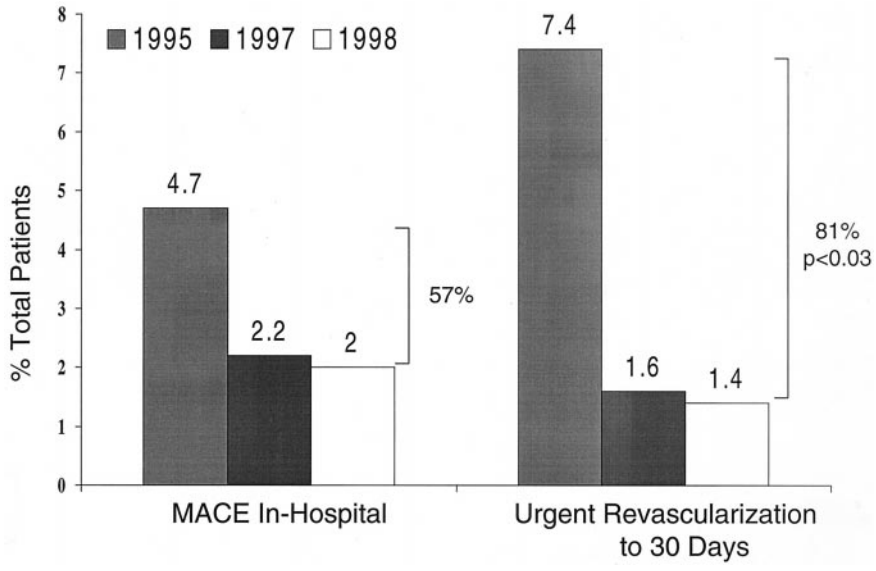

FIGURE 5. From the Ohio Heart Health Center interventionists at The Christ Hospital, Cincinnati, Ohio. Adverse clinical outcomes after percutaneous coronary intervention in patients with unstable angina for sequential cohorts of patients (1995 vs 1997 vs 1998). Major in-hospital cardiac events ([MACE] death, Q-wave MI, and urgent coronary revascularization) were reduced by 57% comparing 1995 and 1998 cohorts. Additionally, the requirement for urgent revascularization to 30 days after percutaneous intervention was reduced by 81%. (Reprinted with permission from Mosby, Inc. *Am Heart J.*[16])

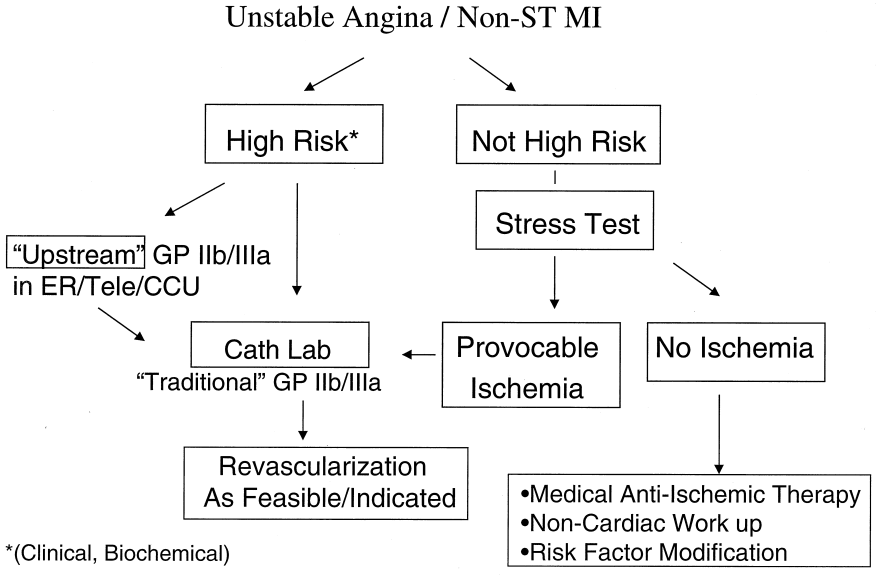

FIGURE 6. Schematic algorithm for care of patients with unstable angina or non–ST-segment elevation myocardial infarction (MI). High risk is determined by clinical and biochemical markers. Patients determined to be at high risk may be offered platelet glycoprotein (GP) IIb/IIIa blockade before coronary angiography for medical stabilization or at time of coronary angiography if percutaneous coronary intervention is planned. Patients who are not high risk undergo continued observation and stress testing. Cath Lab = catheterization laboratory; CCU = coronary care unit; ER = emergency department; tele = telemetry unit. (Reprinted with permission from Mosby, Inc. *Am Heart J.*[16])

Low-molecular-weight heparins: In recent years, randomized controlled trials of unfractionated heparin administered after successful coronary angioplasty have demonstrated no benefit for reduction of ischemic complications and an increase in cost and bleeding complications after percutaneous coronary intervention. Because of excess cost and bleeding risk, the practice of routine heparin administration after successful coronary intervention has been abandoned.

Although the adjunctive role of low-molecular-weight heparins is largely unexplored, they may offer the following advantages: (1) a stable and predictable

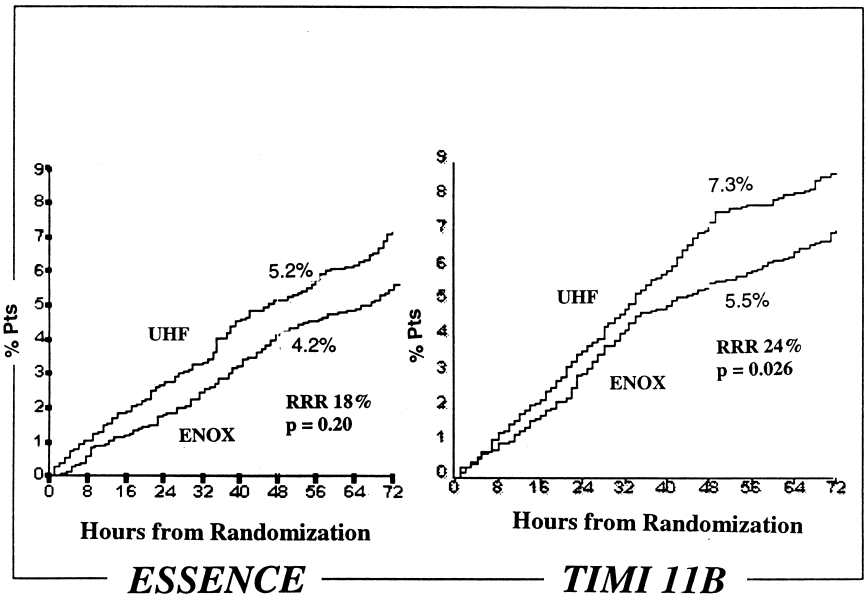

FIGURE 7. Kaplan-Meier plots of the time to first event of the primary endpoint of death, MI, or urgent revascularization over the first 2 days of treatment for the Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-wave Coronary Events (ESSENCE) (*left*) and Thrombolysis in Myocardial Infarction (TIMI) 11B (*right*) trials. A direct comparison of intravenous unfractionated heparin (UFH) and subcutaneous enoxaparin (ENOX) is shown. Pts = patients; RRR = relative risk reduction. (Data are from *N Engl J Med*[21] and *Circulation*.[20])

anticoagulant dose response, which may eliminate the need for monitoring; (2) simpler administration by the subcutaneous route[19]; (3) resistance to neutralization by platelet factor 4; (4) greater antifactor Xa activity; (5) lesser antifactor IIa activity; and (6) relative absence of clinical "rebound." Thus, low-molecular-weight heparins may be an attractive treatment option for acute coronary syndromes.

Two landmark trials compared the efficacy and safety of subcutaneous enoxaparin with unfractionated heparin for patients with unstable angina or non–Q-wave myocardial infarction: the Thrombolysis in Myocardial Infarction (TIMI) 11B trial[20] and the Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-wave Coronary Events (ESSENCE) trial.[21] Both trials showed enoxaparin to be superior to unfractionated heparin for preventing death and cardiac ischemic events. Patients in these trials were randomly assigned to either enoxaparin subcutaneously (1 mg/kg twice daily) or unfractionated heparin intravenously with activated partial thromboplastin time (aPTT) monitoring. The median duration of therapy in both trials was similar (3.0 days in TIMI 11B and 2.6 days in ESSENCE). Thus, low-molecular-weight heparin appears to be a valuable adjunctive treatment to give upstream, before the performance of coronary angiography or percutaneous coronary intervention. Enoxaparin therapy was associated with an 18–24% reduction in death, MI, or requirement for urgent revascularization during the initial 48 hours of therapy (Figure 7). In a meta-analysis of these trials, enoxaparin (vs unfractionated heparin) was associated with a 20% reduction in the occurrence of death or serious cardiac ischemic events that was evident within the first few days of treatment and persisted for 43 days after enrollment.[22] These data establish "level of evidence A" in support of this therapy.

Combination enoxaparin–abciximab therapy: Two multicenter open-label trials have been undertaken to evaluate the safety of either enoxaparin (0.75 mg/kg) administered concomitantly with abciximab (NICE-4) or enoxaparin (1.0 mg/kg) administered alone (NICE-1) to patients undergoing percutaneous coronary intervention.[23] The NICE-4 study enrolled 818 patients undergoing percutaneous coronary intervention with a US Food and Drug Administration (FDA)–approved device, excluding planned rotational atherectomy. In this study, a bolus dose of enoxaparin (0.75 mg/kg) was followed by the standard bolus and 12-hour infusion of abciximab. No heparin was administered after the procedure, and vascular access sheaths were removed 4 hours after the bolus dose of enoxaparin. Vascular closure devices were not allowed by protocol. The primary criterion for evaluation was the incidence of major hemorrhage or transfusion according to Thrombolysis in Myocardial Infarction (TIMI) criteria. There were no major non-CABG bleeding episodes in the first 557 patients enrolled, and the final analysis revealed a 0.2% incidence in 818 patients. Minor bleeding and the need for transfusion were uncommon. With respect to clinical outcomes, the composite occurrence of death, MI, or urgent revascularization to 30 days after enrollment was 2.8%.

The relative benefit of combined enoxaparin and abciximab versus the experience with enoxaparin alone (NICE-1) can be shown by comparing the 2 studies, NICE-4 versus NICE-1.[23,24] There were more

than 800 patients in each treatment group with similar demographics. The addition of abciximab to reduced dose (0.75 mg/kg) enoxaparin did not increase bleeding complications and, in fact, was associated with 38% less major non-CABG bleeding than was observed after the administration of full dose (1.0 mg/kg) enoxaparin alone. No interaction between abciximab and enoxaparin based on measured levels (mean ± SD) of anti-Xa activity was observed, although enhanced inhibition of free thrombin generation as reflected by prothrombin fragment 1.2 levels was observed after combination enoxaparin and abciximab.[24]

Comparing NICE 4 to NICE 1, the addition of abciximab to reduced-dose enoxaparin was associated with 65% fewer composite clinical endpoint (death, MI, or urgent revascularization) events. This apparent synergism between enoxaparin and abciximab for inhibition of thrombin generation and reduction in clinical ischemic events is supported by in vitro data from recent investigations[25,26] that suggest optimum inhibition of free thrombin generation requires the combination of enoxaparin and abciximab (vs either agent alone).

CONCLUSION

Both platelet glycoprotein IIb/IIIa blockade and low-molecular-weight heparin provide benefit to patients with non–ST elevation acute coronary syndrome. Optimal long-term clinical outcomes are achieved by combining glycoprotein IIb/IIIa inhibitors and revascularization. High-risk patients should have early coronary angiography and glycoprotein IIb/IIIa inhibitor therapy. The combination of abciximab and enoxaparin for percutaneous coronary intervention appears safe and effective. Hospital length of stay should not be prolonged to accommodate platelet glycoprotein IIb/IIIa drug infusion. From our experience, "fast-track" percutaneous coronary intervention, which incorporates abciximab glycoprotein IIb/IIIa blockade and low-molecular-weight heparin, will provide optimal procedural efficiency and clinical outcomes.

1. Hartzler GO, Rutherford BD, McConahay DR, Johnson WL, Giorgi LV. "High risk" percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1988; 61(suppl):33G–37G.

2. Adele C, Vaitkus PT, Wells SW, Zehnacker JB. Cost advantages of an ad hoc angioplasty strategy. *J Am Coll Cardiol* 1998;31:321–325.

3. Myler RK, Shaw RE, Stertzer SH, Bashour TT, Ryan C, Hecht HS, Cumberland DC. Unstable angina and coronary angioplasty. *Circulation* 1990;82(suppl II):II-88–II-95.

4. Singh M, Holmes DR, Garratt KN, Bell MR, Berger PB, Rihal CS, Schwartz RS, Hammes L. Stents versus conventional PTCA in unstable angina. (Abstr.) *J Am Coll Cardiol* 1999;33:29A.

5. Fernández-Avilés F, Alonso JJ, Durán JM, Gimeno F, Ramos B, de la Fuente L, Munoz JC, Serrador A, Bermejo J, de la Torre M. Long-term prognosis of patients with unstable angina undergoing coronary stenting. (Abstr.) *J Am Coll Cardiol* 1999;33:391A.

6. Angioi M, Danchin N, Alla F, Gangloff C, Sunthorn H, Rodriguez RM, Preiss JP, Grentzinger A, Houplon P, Juilliere Y, Cherrier F. Long-term outcome in patients treated by intracoronary stenting with ticlopidine and aspirin, and deleterious prognostic role of unstable angina pectoris. *Am J Cardiol* 2000;85:1065–1070.

7. Boden WE, O'Rourke RA, Crawford MH, Blaustein AS, Deedwania PC, Zoble RG, Wexler LF, Kleiger RE, Pepine CJ, Ferry DR, Chow BK, Lavori PW, for the Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. Outcomes in patients with acute non–Q-wave MI randomly assigned to an invasive as compared with a conservative management strategy. *N Engl J Med* 1998;338:1785–1792.

8. Califf RM, Holmes DR Jr. Should the emergence of new agents change the management of patients with acute coronary syndromes without ST-segment elevation? *Am Heart J* 1999;138:S586–S594.

9. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med* 1998;339:436–443.

10. The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non–Q-wave myocardial infarction. *N Engl J Med* 1998;338: 1488–1497.

11. The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet* 1997;349:1429–1435.

12. Fragmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999;354:701–707.

13. The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998;338:1498–1505.

14. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994;330:956–961.

15. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 1997;336:1689–1696.

16. Kereiakes DJ, McDonald M, Broderick T, Roth EM, Whang DD, Martin LH, Howard WL, Schneider J, Shimshak T, Abbottsmith CW. Platelet glycoprotein IIb/IIIa receptor blockers: an appropriate-use model for expediting care in acute coronary syndromes. *Am Heart J* 2000;139:S53–S60.

17. Kereiakes DJ, McDonald M, Broderick T, Roth EM, Whang DD, Martin LH, Howard W, Schneider J, Shimshak T, Abbottsmith C. Abciximab provides cost efficient, safely expedited care for unstable angina. (Abstr.) *Eur Heart J* 1999; 20:1542.

18. Kereiakes DJ. Preferential benefit of platelet glycoprotein IIb/IIIa receptor blockade: specific considerations by device and disease state. *Am J Cardiol* 1998;81(suppl):49E–54E.

19. Weitz JI. Low-molecular-weight heparins. *N Engl J Med* 1997;337:688–698.

20. Antman EM, McCabe CH, Gurfinkel EP, Turpie AGG, Bernink PJLM, Salein D, de Luna AB, Fox K, Lablanche J-M, Radley D, Premmereur J, Braunwald E, for the TIMI 11B Investigators. 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: 1593–1601.

21. Cohen M, Demers C, Gurfinkel EP, Turpie AGG, Fromell GJ, Goodman S, Langer A, Califf RM, Fox KAA, Premmereur J, Bigonzi F, for the Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-wave Coronary Events Study Group. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. *N Engl J Med* 1997;337:447–452.

22. Antman EM, Cohen M, Radley D, McCabe C, Rush J, Premmereur J, Braunwald E, for the TIMI 11B (Thrombolysis in Myocardial Infarction) and ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-wave Coronary Events) Investigators. Assessment of the treatment effect of enoxaparin for unstable angina/non–Q-wave myocardial infarction: TIMI 11B–ESSENCE meta-analysis. *Circulation* 1999;100:1602–1608.

23. Kereiakes DJ, Fry E, Matthai W, Niederman A, Barr L, Brodie B, Zidar J, Casale P, Christy G, Moliterno D, et al. Combination enoxaparin and abciximab therapy during percutaneous coronary intervention: "NICE guys finish first." *J Invasive Cardiol* 2000;(12 suppl A):1A–5A.

24. Kereiakes DJ, Grines C, Fry E, Barr L, Matthai W, Broderick TM, Lengerich R, Cohen M, Esent P. Abciximab-enoxaparin interaction during percutaneous coronary intervention: results of the NICE 1 and 4 trials. (Abstr.) *J Am Coll Cardiol* 2000;92A.

25. Holmes MB, Schneider DJ, Sobel BE, Mann KG. An integrated assay for assessment of combined antiplatelet and antithrombotic therapy. (Abstr.) *Circulation* 1999;(suppl I):100:I-328.

26. Li Y, Spencer FA, Becker RC. Synergistic effects of GP IIb/IIIa antagonists and heparin on platelet-dependent procoagulant activity and thrombin generation. (Abstr.) *Circulation* 1999;(suppl I):100:I-303.