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Angioplasty and stenting in acute coronary syndromes: Who, when, how, and why

ABSTRACT

PTCA and stenting now form an integral part of therapy for acute coronary syndromes and are important in achieving the optimal clinical outcome.

KEY POINTS

In ST-elevation MI, outcomes with angioplasty and stenting appear superior to those with thrombolysis, but only if the technology is available and skilled staff can be mobilized quickly.

At smaller hospitals, many physicians start thrombolytic agents in high-risk patients with acute ST-elevation MI and then transport them to referral centers for possible angioplasty.

The best approach to mechanical reperfusion in acute MI appears to be coronary stenting with adjunctive intravenous unfractionated heparin, aspirin, a glycoprotein IIb/IIIa inhibitor, and either ticlopidine or clopidogrel.

If possible, patients with unstable angina or non-ST-elevation MI should be referred for angiography and possible revascularization if they have a high-risk profile or if medical therapy fails.

Whether all patients with unstable angina or non-ST-elevation MI require an aggressive interventional approach is not known with certainty, but newer techniques and adjunctive therapies may more clearly tip the balance in favor of aggressive therapy.

P HYSICIANS ARE STILL WRESTLING with questions about when and how to use mechanical interventions (ie, percutaneous transluminal coronary angioplasty [PTCA] with or without stenting) instead of or in addition to medical therapy. This article examines the evidence on the following questions about percutaneous mechanical intervention in acute coronary syndromes:

- Who should be referred to the catheterization laboratory for angiography and, if necessary, PTCA or stenting?
- What is the optional strategy and timing for intervention?
- What is the optimal adjuvant medical therapy?

IN ST-ELEVATION MI, PTCA IS SUPERIOR TO THROMBOLYSIS

Trials of thrombolytic agents in ST-elevation MI brought home two important points:

Survival is linked to coronary reperfusion. The more patients who achieve full antegrade perfusion (TIMI grade 3 flow), the greater the survival rate.^{1,2}

Thrombolysis often fails. Thrombolytic agents established TIMI grade 3 flow in the infarct-related artery in only 30% to 50% of cases and had a reocclusion rate of 5% to 10%.^{3,4}

Could PTCA do better? To date, 10 randomized studies (each with ≥ 100 patients) compared the outcomes with primary PTCA vs various thrombolytic agents. (The number of patients, however, was much less than the 60,000 in randomized placebo-controlled trials of thrombolytic agents.⁵)

Primary angioplasty is superior to tPA in acute MI

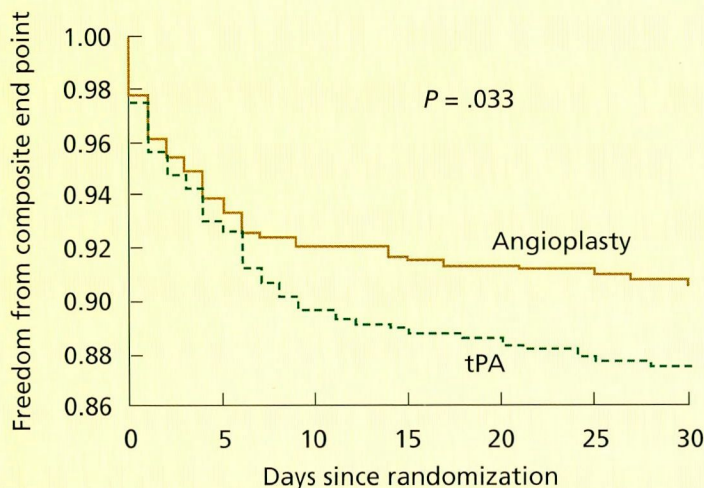


FIGURE 1. Kaplan-Meier curves for freedom from death, reinfarction, and disabling stroke in patients randomized to primary angioplasty or thrombolytic therapy in the GUSTO IIb trial.

FROM THE GLOBAL USE OF STRATEGIES TO OPEN OCCLUDED CORONARY ARTERIES IN ACUTE CORONARY SYNDROMES (GUSTO IIb) ANGIOPLASTY SUBSTUDY INVESTIGATORS. A CLINICAL TRIAL COMPARING PRIMARY CORONARY ANGIOPLASTY WITH TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE MYOCARDIAL INFARCTION. *N ENGL J MED* 1997; 336:1621-1628.

Of these 10 studies, GUSTO IIb⁶ was the largest (with 1,138 patients at 57 centers in 9 countries) and used the best thrombolytic strategy (tissue plasminogen activator—tPA—given on an accelerated or “front-loaded” schedule over 1.5 hours). In the PTCA group, 73% of patients achieved restoration of normal (TIMI grade 3) flow. In addition, by 30 days, the combined primary end point of death, reinfarction, or disabling stroke had occurred in 9.6% of the PTCA group vs 13.6% of the tPA group ($P = .033$, **FIGURE 1**). Individually, all components of the primary end point were reduced, though not significantly.

Contrary to expectations, the decrease in mortality with PTCA occurred not in the first 24 hours but between days 5 and 10. This suggests that the benefit of PTCA lay not in increasing the chances of restoring TIMI 3 flow, but in sustaining flow after reperfusion. In addition, the relative benefit declined over time. At 6 months, the incidence of the composite end point was 13.3% in the PTCA

group and 15.7% in the tPA group (P not significant), perhaps because there was a high rate of restenosis at the site of angioplasty.

Weaver et al⁷ and Cucherat and Tremeau,⁸ in separate analyses of the major trials comparing PTCA with thrombolysis, agreed that primary PTCA leads to a significantly lower rate of mortality and nonfatal reinfarction at 30 days or discharge.

However, in registry studies, the results are less impressive.⁹⁻¹² Tiefenbrunn et al⁹ reported that although the incidence of stroke and recurrent ischemia was higher with tPA, there was no significant difference between the two treatments in the in-hospital mortality rate or the incidence of congestive heart failure or recurrent MI. The reason for this apparent lack of benefit from PTCA may be that in the “real world” (ie, community hospitals) patients face a longer delay between presentation and PTCA than at academic medical centers, and the operators have less PTCA experience.¹³

■ IN ST-ELEVATION MI, WHO SHOULD GO TO THE CATH LAB?

TABLE 1 outlines the most widely accepted indications in acute ST-elevation MI for referral to the catheterization laboratory for angiography and, if appropriate, PTCA with or without stenting.

Patients at hospitals that use PTCA as primary therapy

Before you can send a patient to the catheterization laboratory, your hospital has to *have* a catheterization laboratory, with a skilled team available 24 hours a day and protocols whereby patients can rapidly undergo a diagnostic angiogram and, if necessary, emergency PTCA. Only about 20% of hospitals in the United States and 10% in Europe are equipped to do this,¹⁴ but at these hospitals, data from randomized studies support using mechanical interventions as primary therapy for acute ST-elevation MI.

Patients with contraindications to thrombolysis

Contraindications to thrombolysis are common reasons for referral to the catheterization laboratory. The GISSI 2 investigators¹⁵



reported that 15% of their study population could not be randomized for this reason. Cragg et al¹⁶ reported a similar prevalence in a large retrospective analysis.

Patients with a contraindication to thrombolysis have a significantly higher in-hospital mortality rate than do thrombolysis-eligible patients. Where possible therefore, this subset of patients should be referred for angioplasty or stenting.

High on the list of contraindications to thrombolysis are factors that increase the risk of intracerebral hemorrhage: advanced age, hypertension, female gender, low body weight, and history of stroke. And with good reason: In the GUSTO-1 study,³ 0.72% of patients treated with tPA and standard intravenous heparin had an intracranial bleed, and of these, 60% died and 25% suffered significant disability. In contrast, only 0.1% of patients undergoing mechanical reperfusion had intracranial bleeding in the EPILOG study¹⁷ and 0% in the EPISTENT study,¹⁸ which are representative of contemporary interventional trials.

For patients at risk of noncerebral bleeding, it is best to evaluate each case individually. This group is diverse and includes postoperative patients and patients with a history of gastrointestinal bleeding. Many factors enter into the choice of therapy, such as the type of surgery, the duration of time since surgery, and the findings on endoscopy.

On the other hand, PTCA and stenting also carry a risk of hemorrhage because of the need for adjunctive drug therapy, discussed later in this article.

Patients for whom thrombolysis fails

Failed reperfusion often results in referral to the catheterization laboratory. Nevertheless, this approach has not been demonstrated conclusively to be superior to conservative medical therapy, which usually consists of continued antiplatelet therapy, angiotensin-converting enzyme (ACE) inhibitors and beta-blockers when tolerated, and hemodynamic support.

One problem is that studies comparing “rescue” angioplasty vs conservative therapy are hard to perform, because few operators are willing to randomize patients to conservative

TABLE 1

Indications for angiography and possible angioplasty in patients with ST-elevation MI

Hospital uses PTCA and stenting as primary reperfusion therapy

Contraindications to thrombolysis

- Stroke in previous 6 months
- Recent trauma or major surgery
- Noncompressible vascular punctures
- Severe uncontrolled hypertension (SBP > 180, unresponsive to therapy)
- High risk of intracranial bleeding

Failed thrombolysis

Cardiogenic shock

Occlusion of a saphenous vein graft

therapy who are clinically ill and have an occluded infarct-related artery. Moreover, in one study that did manage to recruit enough patients (the RESCUE study¹⁹), patients with a first anterior MI for whom thrombolysis failed who were randomized to rescue angioplasty did have a lower incidence of the combined end point of death or severe heart failure than did patients managed conservatively, but at 30 days there was no difference between the groups in their resting ejection fractions, the primary end point of the study.

Another problem: How can we quickly and accurately tell that thrombolysis has failed? The usual clinical markers of reperfusion—relief of chest pain, resolution of ST elevation, and “reperfusion” arrhythmias—do not adequately discriminate between those who did or did not achieve coronary patency.^{20,21} For example, Califf et al²⁰ found that more than half of patients with clinical evidence of failed reperfusion after thrombolysis actually had a patent infarct-related artery. In addition, so-called reperfusion arrhythmias (accelerated idioventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, and second-degree and third-degree AV block) had no value in detecting early reperfusion.^{20,21} (The RESCUE study¹⁹ avoided this problem by requiring angiographic docu-

Consider PTCA in those at risk for intracerebral hemorrhage

mentation of failed reperfusion for enrollment.)

Nuclear scintigraphy is noninvasive and can detect reperfusion accurately, but many hospitals do not have it available. In addition, it may delay patients with failed reperfusion from getting to the catheterization laboratory and thus prove detrimental to their outcomes.

For these reasons, many physicians at hospitals without a catheterization laboratory transfer their patients, especially those at high risk, to referral centers immediately after starting thrombolytics. This approach seems prudent for patients with any evidence of hemodynamic compromise or large or anterior MIs, and could reduce the time needed to start aggressive intervention should thrombolysis fail.

Patients in cardiogenic shock

When cardiogenic shock complicates acute MI, 65% to 85% of patients die. Several retrospective studies demonstrated better outcomes if such patients were referred for angiography followed by either percutaneous or surgical revascularization.²²⁻²⁵

Randomized studies in this situation are hard to perform, owing to difficulty in recruiting patients. For example, the SMASH study²⁶ was terminated prematurely after randomizing only 55 patients, owing to difficulty in recruitment.

More recently the SHOCK trial²⁷ randomized 302 patients to undergo either emergency revascularization or a strategy of medical therapy that encouraged use of intraaortic balloon counterpulsation, thrombolytic therapy if possible, and delayed revascularization if indicated. Emergency revascularization did not affect the primary end point: the mortality rate at 30 days was 46.7% in the emergency revascularization group vs 56% in the medical therapy group ($P = .11$). However, the mortality rate was significantly lower in the emergency revascularization group than in the conservative therapy group at 60 days (50.3% vs 63.1%, $P = .027$) and at 1 year (59% vs 75%, $P = .009$).²⁸ This divergence in mortality with time remains unexplained. The benefit of early revascularization was independent of the method of revascularization.²⁹

Younger patients fared better with revascularization than older patients did. Patients

younger than 75 years (a prespecified subgroup) had a lower mortality rate with revascularization than those managed conservatively at 30 days (41.4% vs 56.8%, $P = .021$), at 6 months (44.9% vs 65%, $P = .003$), and at 1 year (55% vs 76%, $P = .002$). In patients older than 75 years, however, revascularization was associated with a trend toward increased mortality at 30 days (75% vs 53.1%, $P = .162$), 6 months (79.2% vs 56.3%, $P = .087$), and 1 year (79% vs 71%, $P = .794$).

The investigators advise caution in interpreting these data, given the multiple testing in subgroup analyses. Overall, however, the SHOCK data do support an aggressive approach, including revascularization, in patients with shock complicating acute MI, especially those younger than 75 years.

Patients with occluded vein grafts

Patients with suspected occlusion of saphenous vein grafts respond poorly to thrombolytic therapy,³⁰ perhaps because they often have a large clot burden in the occluded graft. If you suspect that a vein graft is occluded, it is usually prudent to refer the patient for interventional therapy.

■ IN ST-ELEVATION MI, INTERVENTION SHOULD BE DONE QUICKLY

In treating acute ST-elevation MI, minutes count. In the GUSTO IIb study,³¹ the longer the interval between when the patient first entered the emergency department and when the angioplasty balloon was first inflated (the "door-to-balloon" time), the higher the mortality rate (FIGURE 2).

Accordingly, hospitals are striving to reduce their door-to-balloon times. Ideally, it should be less than 60 minutes and certainly less than 2 hours.

The clock does not start at the door, however: it starts when the artery first becomes occluded. Randomized studies generally enrolled patients who presented within 6 to 12 hours of symptom onset, or between 6 and 24 hours of symptom onset if there was evidence of ongoing ischemia. But using the onset of symptoms as a marker of onset of occlusion is sometimes flawed, because occlusion of the culprit vessel is often a very dynamic process.

It is difficult to tell that thrombolysis has failed

The longer the 'door-to-balloon' time, the higher the mortality rate

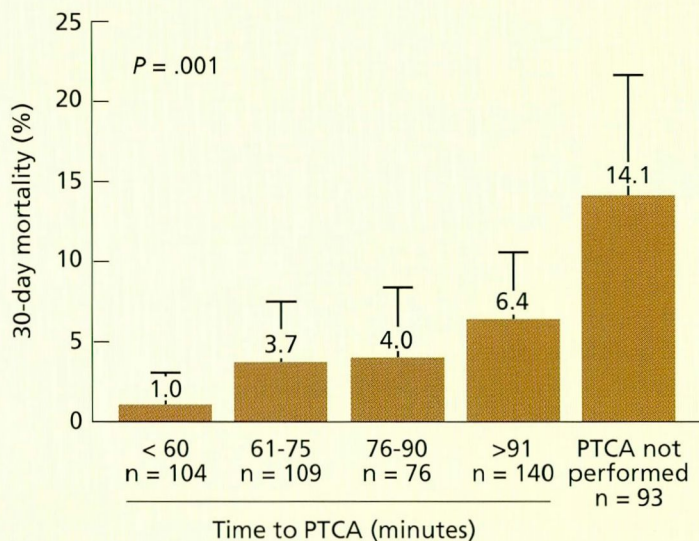


FIGURE 2. Relationship between the time from study enrollment to first balloon inflation (the "door-to-balloon" time) and the mortality rate at 30 days in the GUSTO IIb study.

FROM BERGER PB, ELLIS SG, HOLMES DR, JR, ET AL. RELATIONSHIP BETWEEN DELAY IN PERFORMING DIRECT CORONARY ANGIOPLASTY AND EARLY CLINICAL OUTCOME IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION: RESULTS FROM THE GLOBAL USE OF STRATEGIES TO OPEN OCCLUDED ARTERIES IN ACUTE CORONARY SYNDROMES (GUSTO-IB) TRIAL. *CIRCULATION* 1999; 100:14-20.

IN ST-ELEVATION MI, WHICH LESIONS SHOULD BE TREATED?

Intervention is usually performed only in the lesion in the infarct-related artery. The primary goal is to restore normal antegrade flow (TIMI grade 3), as thrombolytic trials demonstrated TIMI 3 flow to be the strongest predictor of survival.^{1,2} In addition, patients with patent vessels but reduced flow (ie, TIMI grade 2) at angiography following an MI have a worse outcome compared with those with TIMI 3 flow. Intervention would therefore seem reasonable for all lesions producing TIMI 2 flow or less, although no trials specifically addressed this issue.

What about vessels with TIMI 3 flow but significant residual stenosis on angiography, which occurs in 5% to 10% of patients?⁶ The need for intervention in this situation is controversial. If the residual stenosis exceeds

70%, most interventionalists would probably proceed with mechanical therapy, assuming that such a stenosis would limit flow and likely cause future ischemia. The benefits of this approach have also not been proven.

Other factors also need to be considered. Is the proximal vessel tortuous? Is the lesion located at a bifurcation with large side branches? Is the reference vessel more than 3 mm in diameter? Is the lesion calcified? All these increase the risk of an adverse event during mechanical intervention.

WHO SHOULD GET A STENT?

In early reports, stents were troubled by a high rate of thrombosis, especially in acute MI patients, leading some to conclude that stents should be contraindicated in acute MI.³² Since then, improvements in stent deployment and antiplatelet therapy gave interventionalists the confidence to insert stents in the thrombotic environment of acute MI lesions.

The major advantage of stenting is that stents reduce the potential for abrupt vessel closure due to residual intimal dissections, a common problem after balloon dilatation. It was also hoped that stents would improve outcomes in the longer term by reducing the rate of restenosis, as had been demonstrated in patients with stable and unstable angina.^{33,34} Without stents, up to 50% of MI patients who undergo angioplasty have restenosis within 6 months.³⁵

The initial experience with stents in acute ST-elevation MI was in patients who underwent PTCA and had intracoronary stents placed because of dissection or a suboptimal result (15% to 25% of patients). This led to nine randomized trials involving approximately 2,600 patients, comparing stenting with PTCA alone.

In the largest of these studies (STENT-PAMI, 900 patients),³⁶ stents resulted in an initially better angiographic result compared with PTCA alone, although with slightly reduced TIMI grade 3 flow rates (89% vs 92%). At 6 months, patients who received a stent had a significantly lower incidence of restenosis, which presumably accounted for the significant reduction in total and ischemia-driven target-vessel revascularization.



In other studies,³⁷ stents reduced the incidence of reinfarction and repeat revascularization. However, no stent-in-acute-MI trial has demonstrated a benefit in in-hospital or 30-day mortality, and the results for mortality at 6 to 12 months are somewhat inconsistent.

Nevertheless, PTCA with stenting is currently the preferred method of catheter-based reperfusion in acute ST-elevation MI, when feasible.

■ PATIENTS WITH UNSTABLE ANGINA OR NON-ST-ELEVATION MI

Unstable angina and non-ST-elevation MI are very heterogeneous in their clinical presentation,³⁸ even though both arise from erosion or rupture of an atherosclerotic plaque.³⁹

Angiography reveals occlusion of the culprit vessel in more than 90% of patients with ST-elevation MI, but in only 20% to 40% of patients with non-ST-elevation MI and in 10% to 20% of patients with unstable angina.³⁹

Thrombolytic agents have no benefit in patients with non-ST-elevation acute coronary syndromes.⁵ This observation has led to a less aggressive approach to the immediate management of these patients, with an emphasis on controlling ischemia rather than restoring normal antegrade flow in the coronary artery. Even so, approximately 60% of patients who present with an unstable coronary syndrome undergo angiography at some point during the hospital stay.⁴⁰

Which patients with unstable angina or non-ST-elevation MI should undergo angiography?

Patients whose symptoms cannot be controlled by drugs are candidates for early angiography and revascularization. In addition, a number of clinical and diagnostic indicators predict a high risk for adverse cardiac events (TABLE 2),³⁸ and if present, these findings argue in favor of early aggressive management.

Why not send *all* patients with unstable angina or non-ST-elevation MI for angiography and possible revascularization? Unfortunately only a few randomized studies examined this issue, and they differed in their findings. TABLE 3 summarizes the three largest studies to date.

Of these, the results of the TIMI IIIb⁴¹

TABLE 2

Clinical and diagnostic variables associated with increased risk of adverse cardiac events in patients with unstable angina

ECG findings

Persistent ST-segment depression

Clinical presentation

Angina at rest within the last 48 hours

Angina within 2 weeks of acute MI

Need for intravenous nitrates to control ischemia

Advanced age

Diabetes

Biochemical markers

Elevated troponin I or T

Echocardiographic findings

Reduced left ventricular function

Anterior wall involvement

Noninvasive testing

Reversible perfusion defects on nuclear imaging

Increased lung uptake on nuclear imaging

Wall motion abnormalities on stress echocardiogram

and VANQWISH⁴² studies support taking a conservative approach and restricting angiography to patients with spontaneous angina or exercise-induced angina or ischemia. Of note, however: neither study used glycoprotein IIb/IIIa inhibition or stents during percutaneous revascularization. (If they had, aggressive management might have given better results.) In addition, many of the patients in the TIMI IIIb study received thrombolytics before undergoing PTCA, which limits the applicability of the study. A further criticism of the VANQWISH study is that the mortality rate for coronary artery bypass grafting (CABG) in the group that underwent invasive treatment was 11.6%, which is three to four times the acceptable mortality rate for this operation, markedly attenuating the possible benefits of early revascularization.

In contrast, in the FRISC II study,⁴³ an early invasive strategy of routine angiography and revascularization resulted in a significant reduction in the 3-month incidence of death or MI compared with conservative management (ie, angiography driven by refractory

TABLE 3

Summary of major studies comparing conservative vs early invasive management for patients with unstable angina and non-ST-elevation MI

	TIMI IIIB ⁴¹	VANQWISH ⁴²	FRISC II ⁴³			
No. of patients	1,473	920	2,457			
Entry criteria	Non-Q-wave MI Unstable angina	Non-Q-wave MI	Unstable angina			
Percent of patients undergoing angiography						
Conservative treatment group	64%	48%	47%			
Invasive treatment group	98%	98%	98%			
Mean time to catheterization	1.5 days	2 days	4 days			
Revascularization rates						
Conservative treatment group	49%	33%	37%			
Invasive treatment group	61%	44%	77%			
Timing of outcomes	42 days	1 year	6 months			
	OUTCOMES					
	DEATH	NONFATAL MI	DEATH	DEATH OR MI	DEATH	MI
Conservative treatment group	2.5%	5.7%	5.4%	23%	2.9%	7.8%
Invasive treatment group	2.4%	5.1%	3.9%	14%	1.9%	10.1%

clinical symptoms or provokable ischemia). The glycoprotein IIb/IIIa inhibitor abciximab was used in only 10% of cases, although stenting was used in 64% of all percutaneous revascularization procedures.

The applicability of this study, which was performed in Sweden, to clinical practice in the United States may be confounded by the time-to-treatment: a mean of 4 days for percutaneous intervention and 7 days for CABG. During this time, all patients received dalteparin, a low-molecular-weight heparin (LMWH), subcutaneously. In the United States, economic pressures to shorten hospital length of stays make delaying definitive therapy for 4 to 7 days virtually impossible.

Why the difference in outcomes between the FRISC II study and the other two? A possible explanation is that in the FRISC II study, 77% of the patients in the invasive therapy group underwent revascularization by 6 months, compared with only 37% in the conservative therapy group. In contrast, the rates were much more similar between groups in the other two studies (TABLE 3).

The OASIS registry reported that although patients with unstable angina in the United States undergo invasive therapy and revascularization more often than do similar patients in other countries, they do not have a lower rate of cardiovascular death or MI.⁴⁰ However, they do have a lower rate of refractory angina and readmission for unstable angina, which suggests that revascularization may improve quality of life but not survival.

Which lesions warrant intervention?

The comments above relating to patients with ST-elevation MI largely apply also to patients with non-ST-elevation MI and unstable angina. With the increased use of stents and glycoprotein IIb/IIIa inhibitors, multivessel percutaneous intervention in acute coronary syndromes is becoming more common, with the aim of complete revascularization. Because of the lower incidence of occlusion in this setting, the culprit vessel is not as easy to identify but can usually be located by a combination of ECG findings, functional testing, and angiographic appearance.



What is the optimal percutaneous intervention?

No randomized trials were designed specifically to compare interventional strategies in patients with unstable angina and non-ST-elevation MI, but a large body of data from retrospective and randomized studies has demonstrated the safety and efficacy of PTCA in these patients.

An analysis of all patients who underwent PTCA in the TIMI IIIb trial demonstrated an angiographic success rate of approximately 95% and a low incidence of acute adverse events (MI 2.7%, CABG 1.4%, death 0.5%).⁴¹ At 1 year, the combined rate of death, MI, or stroke was 9.3%; 28% of patients required an additional revascularization procedure. In retrospective studies, the initial success rates were somewhat lower (85%–89%), with a higher incidence of procedure-related mortality (1.3%), MI (6.3%), and need for emergency CABG (6.8%).⁴⁴ These acute complication rates are higher than for patients with stable angina. Following initial successful angioplasty, the short-term and long-term prognosis is good and roughly equivalent to that in patients with stable angina, despite the increased rate of restenosis.

Stenting in the setting of unstable angina and non-ST-elevation MI has been examined in many retrospective studies. These studies suggest that stenting is safe and effective when used as primary therapy, or when used following a suboptimal result or threatened closure with PTCA.^{45–47} A subanalysis of the EPIS-TENT study¹⁸ allowed a comparison of stenting vs PTCA in patients with unstable angina. Stenting with adjunctive abciximab proved superior to PTCA with adjunctive abciximab. Interestingly, patients treated with PTCA and abciximab had a lower incidence of primary events rate compared with the stent-alone group, indicating the importance of adjunctive therapy.

■ ADJUVANT THERAPY FOR CORONARY INTERVENTIONS

A number of drugs improve both the short-term and long-term outcomes following intervention in acute coronary syndromes.

TABLE 4

Antiplatelet agents used to prevent stent thrombosis

Before the procedure

Aspirin 325 mg (immediately on presentation and daily thereafter)

Ticlopidine 500 mg or clopidogrel 300 mg (ideally given 24 hours before the procedure but certainly once coronary anatomy is known and percutaneous intervention is planned)

After the procedure

Aspirin 325 mg once daily (lifelong)

Ticlopidine 250 mg twice daily or clopidogrel 75 mg twice daily (2–4 weeks)

Antiplatelet therapy

Aspirin (usually 325 mg) should be given to all patients before undergoing a coronary intervention and daily indefinitely thereafter. In fact, all patients with a possible acute coronary syndrome should receive an aspirin tablet immediately upon presentation.

Ticlopidine or clopidogrel should also be given to patients who require stents (TABLE 4). These agents should be started as soon as a percutaneous intervention is anticipated, ideally 24 hours before the procedure. This may not be possible in an acute ST-elevation MI, but should be possible in most cases before planned interventions.

Starting these medications empirically without a knowledge of the patient's coronary anatomy may pose a risk, however. If the patient requires surgery these medications increase the risk of bleeding during CABG and may delay the surgery or increase its risk.

Leon et al⁴⁸ reported that the incidence of stent thrombosis with a combination of aspirin and ticlopidine was 0.5%, which was significantly less than with either aspirin alone or a combination of aspirin and warfarin.

However, ticlopidine is associated with significant blood dyscrasias and hemorrhagic complications. Severe neutropenia (absolute white cell count $< 1,200 \times 10^9/L$) and thrombocytopenia (platelet count $< 80,000 \times 10^9/L$) occur in approximately 0.5% of cases. In addition, there have been reports of thrombotic thrombocytopenia purpura and

Start ticlopidine or clopidogrel as soon as PTCA is planned

aplastic anemia⁴⁹ in association with ticlopidine therapy. These blood dyscrasias tend to occur after 2 weeks of therapy. Since subacute stent thrombosis is rarely seen after the first 2 weeks in patients receiving the combination of aspirin and ticlopidine,^{48,50} continuing ticlopidine beyond 14 days is difficult to justify. Berger et al⁵¹ demonstrated the safety of using ticlopidine for only 2 weeks following intervention.

Because of the risk of blood dyscrasias with ticlopidine, many interventionalists now prefer clopidogrel. Moussa et al⁵² retrospectively analyzed the effectiveness of clopidogrel and aspirin vs ticlopidine and aspirin. At 1 month there was no difference in the incidence of stent thrombosis (1.5% vs 1.4%) or major adverse cardiac events (3.1% vs 2.4%) between the two groups. The probability of any side effect (neutropenia, diarrhea, rash) was significantly higher in the ticlopidine-aspirin group (10.6% vs 5.3%). The results of the CLASSICS study⁵³ support the conclusion that clopidogrel is as effective and better tolerated than ticlopidine. Clopidogrel has replaced ticlopidine as the antiplatelet agent of choice for coronary interventions at our institution and is usually continued for 2 to 4 weeks.

Glycoprotein IIb/IIIa inhibitors

All three of the currently licensed glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatid, and tirofiban) have been found useful as adjuncts to angioplasty and stenting, both in acute ST-elevation MI⁵³⁻⁵⁸ and in non-ST-elevation MI and unstable angina.⁵⁹ If possible, starting these agents 24 to 72 hours before the procedure may contribute to improved outcomes.

Heparin

If a glycoprotein IIb/IIIa inhibitor is not used, heparin is usually given as a bolus of 100 U/kg to achieve an activated clotting time (ACT) of > 300 seconds. Patients usually receive fur-

ther boluses during the procedure to maintain an ACT of at least 300 seconds.

If a glycoprotein IIb/IIIa inhibitor is used, the optimal heparin dosage may be lower. The EPILOG study used low-dose heparin (a 70 U/kg bolus before the procedure and additional boluses during the procedure) to achieve and maintain an ACT of at least 200 seconds during the procedure.

Following PTCA, the continued use of heparin may lead to increased bleeding complications without any therapeutic benefit.^{17,56,60} The efficacy of postprocedural heparin in patients who receive stents remains debatable.

Low-molecular-weight heparins. LMWHs have been used in the treatment of patients with acute coronary syndromes,^{61,62} but their use during coronary interventions has not been fully investigated. Because we cannot monitor anti-factor Xa activity (the major therapeutic target for LMWHs) in the catheterization laboratory, most operators prefer unfractionated heparin. If an intervention is anticipated, we recommend switching to unfractionated heparin if possible and allowing approximately 8 to 12 hours after the last dose of LMWH before proceeding with an intervention, or longer for patients with renal impairment. This precaution is particularly advised in patients in whom glycoprotein IIb/IIIa inhibitor use is anticipated.

Thrombin inhibitors

Although direct thrombin inhibitors have many theoretical advantages over heparin, at present they have a limited application in interventions in patients with acute coronary syndromes. The only direct thrombin inhibitor currently approved is lepirudin (a recombinant hirudin). Data on the use of this agent in coronary interventions are lacking, although it has been used for parenteral anticoagulation in patients with heparin-induced thrombocytopenia (the major indication for thrombin inhibitors).⁶³

We switch to unfractionated heparin before procedures

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