

Primary Angioplasty Compared with Thrombolysis: New Issues in the Era of Glycoprotein IIb/IIIa Inhibition and Intracoronary Stenting

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The past decade has witnessed a dramatic expansion in the scope of both mechanical and pharmacologic methods for opening occluded arteries in patients with acute myocardial infarction. Although the relative merits of conventional balloon angioplasty and thrombolysis have been evaluated, this old debate is being eclipsed by new comparisons. New device technologies, such as intracoronary stenting; more potent and more fibrin-specific thrombolytic agents; and new antithrombotic and antiplatelet agents all offer the potential for improved outcomes. But despite these recent developments, the time-dependent open artery hypothesis—which states that the achievement of early, full, and sustained reperfusion is associated with better outcomes—remains essentially unchanged. This article reviews data on the ability of six revascularization strategies—stand-alone thrombolysis, conventional percutaneous transluminal coronary angioplasty, stenting, glycoprotein IIb/IIIa inhibitors plus thrombolytic agents, glycoprotein IIb/IIIa inhibitors plus interventions, and the combination of pharmacologic and mechanical interventions—to produce early, full, and sustained reperfusion.

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Although strategies for opening occluded arteries in patients with acute myocardial infarction have evolved rapidly over the past two decades, the time-dependent open artery hypothesis itself—that the reestablishment of early, full, and sustained reperfusion results in improved clinical outcomes—remains unchanged. Pharmacologic strategies may be better at providing early reperfusion, but mechanical interventions may come closer to inducing full and sustained reperfusion. Clinical outcomes are related to the attainment of not just one but all three goals.

Substantial debate has surrounded discussion of the relative merits of thrombolysis and conventional primary percutaneous transluminal coronary angioplasty (PTCA). Recent improvements in both mechanical and pharmacologic strategies, however, beg for new comparisons. Many early randomized trials tested the efficacy of primary PTCA against that of streptokinase or the older, 3-hour dosing regimens

of tissue plasminogen activator (tPA), but newer, more potent, and more fibrin-specific agents, alone or combined with glycoprotein IIb/IIIa antagonists, may prove superior. Reduced dosing of adjunct heparin or safer antithrombotic agents may reduce risk for hemorrhagic stroke. Similarly, intracoronary stenting now challenges the primacy of conventional PTCA. Finally, despite initial concerns about the safety of combining pharmacologic and interventional strategies, new data suggest that such combinations may be both safe and efficacious now that adjunct therapy with stenting, ticlid/clopidogrel, and glycoprotein IIb/IIIa inhibitors is available. This paper reviews the strengths and limitations of six old and new strategies: stand-alone thrombolysis, conventional PTCA, stenting, glycoprotein IIb/IIIa inhibitors plus thrombolytic agents, glycoprotein IIb/IIIa inhibitors plus interventions, and the combination of pharmacologic and mechanical interventions.

Conventional Percutaneous Transluminal Coronary Angioplasty Compared with Thrombolysis

Although the benefits of thrombolysis compared with placebo have been well established in randomized trials enrolling approximately 100 000 patients (International Study of Infarct Survival [ISIS], Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio [GISSI], and Global Use of Strategies To Open Occluded Arteries [GUSTO]), trials comparing thrombolysis with primary PTCA have been relatively small, with only 2606 patients enrolled to date in 10 randomized trials (1-7). The largest single trial, GUSTO IIb (7), enrolled more than 1000 patients and showed that primary PTCA was beneficial in reducing the composite end point of death, recurrent myocardial infarction, or stroke at 30 days (9.6% compared with 13.7%; $P = 0.033$) but that this benefit was attenuated at 6 months (14.1% compared with 16.1%; $P > 0.2$). The CIs are wide in these small trials and, as a result, a mortality benefit at 30 days for primary PTCA compared with early-generation thrombolytic agents is evident

only when the data from all randomized trials (1–7) are combined in a meta-analysis (4.4% compared with 6.5%; $P = 0.02$). Although no learning curve is associated with the administration of thrombolytic agents, many of the primary PTCA trials were conducted at centers that have considerable operator and institutional expertise in the delivery of primary PTCA. It is unclear whether these results can be generalized to the community setting. Indeed, registry data from the community hospital setting (8) have shown no difference in mortality rates between the two strategies (in-hospital mortality rates, 5.6% for PTCA and 5.5% for thrombolysis).

Although the benefits of primary PTCA have been ascribed to the achievement of superior flow, the mechanism of benefit may in fact be more complex. Primary PTCA may ultimately achieve a higher patency rate, but thrombolytic therapy may actually open more arteries very early (before 60 minutes), depending on the “door-to-balloon” time (9, 10) (Figure). Sustained patency rather than early

patency may be the beneficial mechanism of primary PTCA. Indeed, the pooled risk for reocclusion is nearly twofold higher for patients receiving thrombolysis than for patients receiving primary PTCA (3.7% compared with 7.2%; $P < 0.001$) (11). Because angiographically documented reocclusion is associated with a threefold increase in mortality rate (11.0% compared with 4.5%; $P = 0.01$) (12), this higher risk for reocclusion may partly account for the higher mortality rate seen among patients receiving thrombolysis in randomized trials (11). Although half of the mortality benefit of tPA compared with streptokinase had occurred by 24 hours and although this benefit was hypothesized to be mediated by higher rates of normal blood flow (Thrombolytic in Acute Myocardial Infarction [TIMI] grade 3 flow) at 90 minutes in the GUSTO I (Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries) trial (13), it is notable that no difference was seen in adverse outcomes between patients receiving primary PTCA and pa-

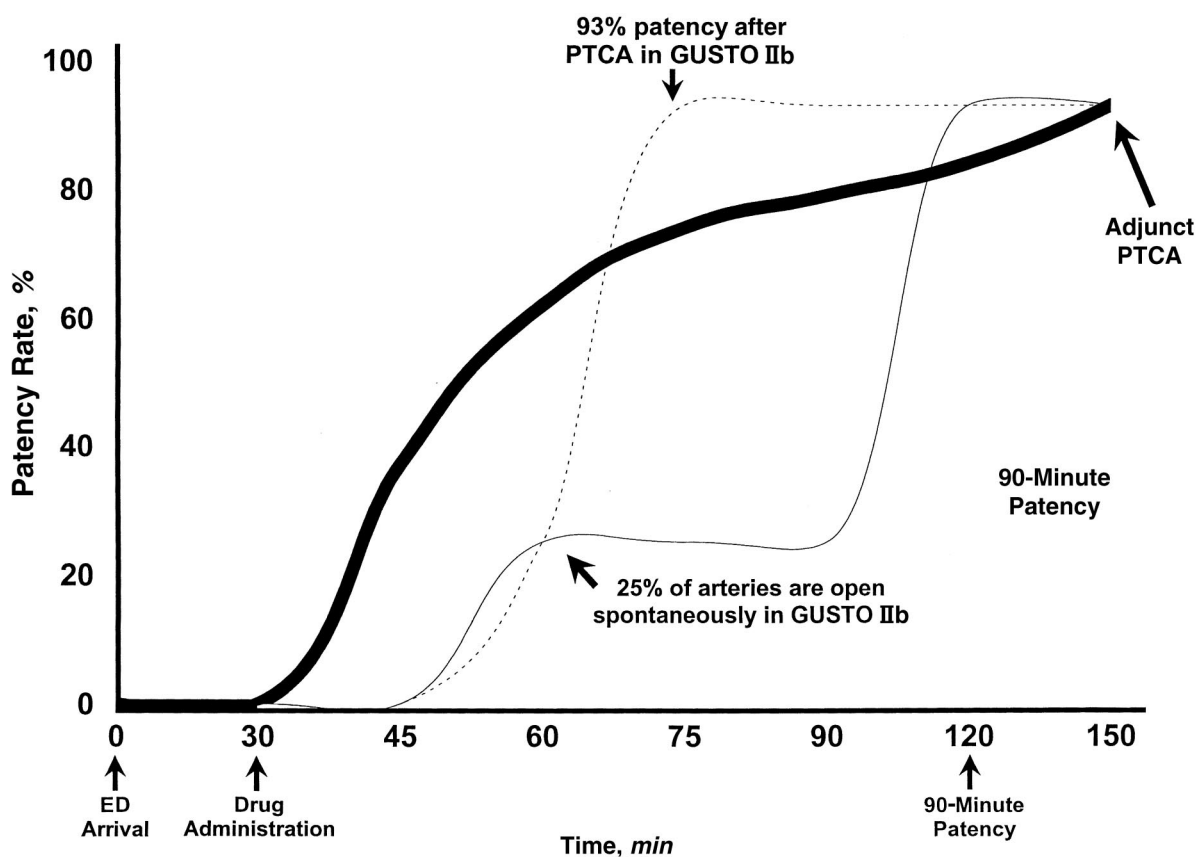


Figure. Speed and patency associated with several strategies for opening arteries in patients with myocardial infarction. For a patient who arrives at the emergency department (ED) at time 0, most hospitals administer a thrombolytic agent 30 minutes later. According to Kawai and colleagues (10) (thick line), patency rates are 37% at 15 minutes after administration (45 minutes after presentation), 62% at 30 minutes after administration, 74% at 45 minutes after administration, and 84% at 90 minutes after administration. For a patient who has primary percutaneous transluminal coronary angioplasty (PTCA) with a “door-to-balloon” time of 120 minutes (thin solid line), the Global Use of Strategies To Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO) IIb trial (7) shows that the rate of spontaneous vessel opening is 25%. There is a period during which the patency rate achieved with a thrombolytic agent exceeds that reached with primary PTCA. At 120 minutes, however, the patency rate achieved with PTCA (93%) exceeds that reached with thrombolysis (84%). If primary PTCA is done more quickly, with a door-to-balloon time of 75 minutes (dotted line), then at 75 minutes, the patency rate seen with the interventional strategy (93%) exceeds that seen with thrombolysis (74%). Thus, the interventional strategy achieves superior patency at 75 or 120 minutes, but thrombolysis may open a substantial number of vessels more quickly before performance of the intervention.

tients receiving thrombolysis early in GUSTO IIb (7). Indeed, the adverse event curves did not begin to diverge until 1 to 2 weeks, at a time when reocclusion may have started (7). In the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trials (12), half of the reocclusions that occurred after administration of thrombolytic agents occurred between the first and second week. Reinfarction may account for some of the difference in mortality rates between the two strategies, but one third of the incremental risk for death seen with early-generation thrombolytic agents has also been ascribed to the higher risk for hemorrhagic stroke associated with these agents (0.1% compared with 1.1%; $P < 0.001$). This higher risk carries with it a 66% risk for death (1). Thus, any mortality benefit of primary PTCA compared with early-generation thrombolytic agents may not derive exclusively from improved early flow. Although full flow may eventually be achieved more often with PTCA, thrombolysis may achieve flow earlier, and any benefits in clinical outcomes seen with primary PTCA may be due in part to sustained flow (that is, to reduced reocclusion) and reduced risk for hemorrhagic stroke.

Intracoronary Stenting

For 1357 patients who had stents placed within the first 24 hours after acute myocardial infarction (excluding patients with stents placed for PTCA failure), a pooled analysis showed that the 30-day mortality rate was low at 2.4% (11, 14). This rate is lower than both the 4.5% pooled mortality rate in primary PTCA trials ($P = 0.007$) and the 6.4% pooled mortality rate for thrombolytic therapy ($P < 0.001$) (11, 14). The pooled incidence of complications was also low: Stent thrombosis occurred in 1.5% of patients (17 of 1163), despite implantation of a metallic endoprosthesis in a thrombotic lesion, and coronary artery bypass graft surgery was required in 1.3% of patients (11 of 816). This rate is lower than the 6.4% rate (70 of 1129 patients; $P < 0.001$) reported with PTCA (11, 14).

Although clinical outcomes in these nonrandomized studies were favorable, limitations are evident. One is the possibility of the "harvest effect," whereby many stents may have been placed late in persons who survived the first few critical hours after acute myocardial infarction; mortality rates are highest in these persons. Second, given concerns about reocclusion due to outflow obstruction, many stents may have been placed in arteries with TIMI grade 3 flow and therefore may have simply been "window dressing" in patients who were destined to have excellent outcomes by virtue of good flow before stenting. Finally, many of these early series

were reported from centers that are highly experienced in the techniques of intracoronary stenting; the generalizability of the results remains to be determined.

These preliminary data were from nonrandomized studies, but primary stenting was recently compared with conventional primary PTCA in several randomized trials. Suryapranata and colleagues (15) showed superior rates of 6-month cardiac event-free survival (that is, absence of death, reinfarction, or target vessel revascularization) for primary stenting compared with primary PTCA (95% compared with 80%; $P < 0.002$). In this relatively small trial of 227 hemodynamically stable patients from a single high-volume center, improvement in the composite primary end point was driven primarily by reduced rates of reinfarction (1% compared with 7%; $P < 0.04$) and target vessel revascularization (4% compared with 17%; $P < 0.002$). Mortality rates did not differ (2% compared with 3%; $P > 0.2$). Angiographic follow-up was not available in Suryapranata and colleagues' trial (15). However, the preliminary 6-month results of the Primary Angioplasty in Myocardial Infarction (PAMI) Heparin-Coated Stent trial (Grines C. George Washington University Symposium, American Heart Association meeting, Dallas, Texas, 1998) show that although 30-day and 6-month mortality rates did not differ between the two strategies, stenting reduced rates of angiographically proven restenosis at 6 months (23.4% compared with 37.4%; $P = 0.007$); ischemia-driven target vessel revascularization (7.5% compared with 17.0%; $P < 0.001$); and the composite end point of death, recurrent myocardial infarction, stroke, or ischemic target vessel revascularization (12.4% compared with 20.1%; $P = 0.01$).

If randomized trials comparing stenting with pharmacologic strategies are considered, quantitative angiographic data from 2006 patients in the TIMI studies show that many patients may require stents in small vessels—27% smaller than 2.5 mm, 37% smaller than 2.75 mm, and 50% smaller than 3.0 mm (14). These sizes may be less than optimal for a stent. This is particularly relevant to left anterior descending arteries, which tend to be smaller than the other coronary arteries (2.96 ± 0.87 mm [$n = 739$] compared with 3.20 ± 0.89 mm [$n = 1267$]; $P < 0.001$) (14). Of left anterior descending arteries, one third are smaller than 2.5 mm, a diameter less than the smallest stent currently available (14). Smaller vessels also carry a higher risk for adverse outcomes: In Suryapranata and colleagues' trial (15), the relative risk for adverse outcomes was 2.3 times higher in patients with a reference vessel smaller than 3.0 mm. Although 1457 patients consented to participate in the PAMI stent trial, only 900 were deemed suitable for random assignment to

possible stent placement. In Suryapranata and colleagues' trial, only 50% of patients were considered suitable for the study; 34% were rejected because they had vessels smaller than 3.0 mm.

Registry data from randomized trials are critical in defining the baseline characteristics and outcomes of excluded patients. Patients excluded from Suryapranata and colleagues' trial (15) had a greater incidence of multivessel disease ($P < 0.001$), were more likely to have Killip class 4 heart failure ($P < 0.05$), were less likely to have a lesion in a left anterior descending artery, had smaller vessels ($P < 0.001$), and had a higher mortality rate (7% for excluded patients compared with 3% for PTCA recipients and 2% for stent recipients; $P < 0.05$). The numbers and outcomes of patients with smaller vessels must be more fully defined. If randomized trials comparing stenting with pharmacologic strategies are undertaken, determining the generalizability of the techniques will require defining the proportion, baseline characteristics, and outcomes of patients who are ineligible for stenting.

The PAMI No SOS (No Surgery on Site) study is now addressing the need for access to immediate emergency bypass surgery, given the low rates of emergency bypass surgery with intracoronary stenting. Further large-scale studies are needed to determine the relative importance of operator experience in determining outcome. Newer stents are smaller, more compliant, less thrombogenic, and more easily placed in patients with complex anatomy, and they need ongoing evaluation.

Combination Therapy with Glycoprotein IIB/IIIa Inhibitors

Stand-alone thrombolytic agents, including such newer agents as recombinant plasminogen activator (rPA), TNK, and novel plasminogen activator, all restore TIMI grade 3 flow in approximately 60% of patients (16–18). Combining fibrinolytic agents (which act on the fibrinous component of a clot) with glycoprotein IIB/IIIa inhibitors (which act on the platelet component of a clot) may further improve angiographic efficacy. Combination therapy also allows the use of lower doses of thrombolytic agents, and this may reduce the risk for intracranial hemorrhage. Platelet inhibition may also reduce the risk for early reocclusion after thrombolytic therapy. Thrombolytic agents may induce a prothrombotic state and, in the process of thrombus resolution, may expose the underlying ruptured plaque and the activated platelets within it. In the setting of acute coronary syndromes or percutaneous intervention, a meta-analysis of 32 135 patients showed that glycoprotein IIB/IIIa inhibitors reduced mortality rates,

rates of recurrent myocardial infarction, and rates of repeated revascularization (19). Thus, glycoprotein IIB/IIIa inhibitors may be a suitable adjunct to both pharmacologic and mechanical interventions in acute myocardial infarction.

Results from trials of adjunct glycoprotein IIB/IIIa inhibitors with full-dose thrombolytic therapy (TAMI-8 [20] and IMPACT-AMI [Integrilin to Manage Platelet Aggregation and Combat Thrombosis in Acute MI; 22]) or reduced-dose thrombolytic therapy (TIMI-14 [23–25], SPEED [Strategies for Patency Enhancement in Emergency Department; 26], the pilot studies of GUSTO IV, and INTRO-AMI [Integrilin and Reduced Dose Thrombolytic in Acute MI]) have shown improvements in the rate of TIMI grade 3 flow (range, 57% to 79%) (20–24; Topol E. Results of the SPEED trial. Presented at the American Heart Association meeting, Dallas, Texas, 1998). Patency rates as high as 94% have been reported, and these rates approach those reported with primary PTCA (1–7). In addition, the higher rates of TIMI grade 3 flow were achieved very early, by 60 minutes, and this flow was seen in 73% of patients who received combination therapy compared with 43% of patients treated with front-loaded tPA ($P = 0.002$) (22–24). In trials of reduced-dose thrombolytic therapy with full-dose abciximab, no increase in bleeding complications has been seen (23–25; Topol E. Results of the SPEED trial. Presented at the American Heart Association meeting, Dallas, Texas, 1998).

The potential mortality benefits attributable to these improvements in flow in thrombolytic trials can be modeled as follows. A pooled analysis of 1492 patients in angiographic trials showed that front-loaded tPA yields TIMI grade 3 flow in 60% of patients and produces 82% patency rates. Among 5498 patients with angiographic data, mortality rates were 3.7% for those with TIMI grade 3 flow, 6.1% for those with TIMI grade 2 flow, and 9.3% for those with TIMI grade 0 or 1 flow (11). Given the distribution of the TIMI flow grades and their associated event rates, mortality rates of 5.2% for tPA recipients and 4.4% for combination therapy recipients might be expected ($P = 0.025$ with 7500 patients per study group). Large-scale mortality trials may have higher event rates than angiographic trials and, if the predicted mortality rate for front-loaded tPA is adjusted upward by a factor of 1.37 to match that seen in recent large-scale mortality trials (such as GUSTO III), mortality rates of 7.2% and 6.1% might be found ($P = 0.03$ with 5000 patients per study group) (25). Thus, the combination of low-dose thrombolytic agents and glycoprotein IIB/IIIa inhibitors may yield another 1–percentage point improvement in mortality rates. These optimistic projections must be tempered, however, by the obser-

vation that the advantage in rates of TIMI grade 3 flow for rPA compared with tPA in the RAPID (Retaplastase versus Alteplase Patency International Dose Ranging Trial) II trial (16) did not translate into a mortality benefit in the GUSTO III trial (25). The upcoming GUSTO IV trial of acute myocardial infarction will evaluate risk for death and intracranial hemorrhage in a very large cohort treated with abciximab plus rPA.

The efficacy of glycoprotein inhibition in the setting of primary PTCA was also assessed in the ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) (26). Abciximab significantly reduced the incidence of death, reinfarction, or urgent revascularization at all time points (at 7 days, this incidence was 9.9% in the placebo group compared with 3.3% in the abciximab group [$P = 0.003$]; at 30 days, it was 11.2% compared with 5.8% [$P = 0.03$]; and at 6 months, it was 17.8% compared with 11.6% [$P = 0.05$]). If elective revascularization is included in the end point (the primary end point of the trial), the differences are no longer significant. Although no intracranial hemorrhage was seen among the 483 patients, the risk for arterial site bleeding was higher in abciximab recipients (16.6% compared with 9.5% in the placebo group; $P = 0.02$).

Revascularization strategies in acute myocardial infarction have focused largely on epicardial stenosis, but the microvasculature may also play a role in flow delays. In acute myocardial infarction, flow is slowed not only in the culprit artery but also in the uninvolved arteries, indicating that acute myocardial infarction results in global flow delays (27). Recently, Neumann and coworkers (28) showed that glycoprotein IIb/IIIa inhibition enhanced improvement in peak coronary flow velocity from baseline to 14 days, despite a lack of difference in percentage diameter stenosis in controls and treated patients. This improvement in microvascular perfusion was associated with a concomitant improvement in regional wall motion (28). Ongoing and future trials will evaluate the efficacy of other drugs targeted at the microvasculature, such as leukocyte inhibitors to prevent downstream plugging and calcium-channel blockers or adenosine to improve microvascular flow.

Combining Pharmacologic and Interventional Approaches

As an adjunct to thrombolysis, angioplasty might intuitively be expected to improve flow, relieve residual stenoses, and reduce reocclusion. However, early randomized trials did not show a clinical benefit for angioplasty routinely performed immediately after thrombolysis compared with thrombolysis

alone, probably because of higher risks for intramural hemorrhage in the arterial wall and for abrupt closure (29–31). These trials are now outdated because they preceded the widespread use of stents, aspirin, ticlid/clopidogrel, and glycoprotein IIb/IIIa inhibitors and the monitoring of activated clotting times. The recent Primary Angioplasty Combined with Thrombolysis (PACT) trial (Ross AM. Results of the PACT trial. Presented at the American College of Cardiology Meeting, Atlanta, Georgia, 1998) incorporated these current practice patterns and showed that two strategies (half-dose tPA plus intervention) could be combined without increasing the risk for adverse outcomes (major bleeding, hemorrhagic stroke, subsequent emergency revascularization, or recurrent myocardial infarction) over the risk seen with intervention alone. Patients receiving half-dose tPA (a 50-mg bolus) had a 60.5% patency rate before PTCA; this was significantly higher than the 33.8% rate seen in patients who were not pretreated with tPA. Success rates for PTCA were similar in the tPA and placebo groups (93.0% and 95.1%). The PACT trial reaffirmed the time-dependent nature of the open artery hypothesis: Patients who had successful thrombolysis and TIMI grade 3 flow before PTCA had improved ejection fractions (ejection fraction, 62%) compared with patients who had delayed restoration of TIMI grade 3 flow after PTCA (58%) and those who never had restoration of TIMI grade 3 flow (55%) ($P = 0.001$).

The time-dependent nature of the open artery hypothesis is further supported by registry data from more than 3500 patients in the National Registry of Myocardial Infarction (32). Interventional strategies alone achieve high rates of normal TIMI grade 3 flow; however, if this flow is achieved late (if the door-to-balloon time exceeds 2 hours), the mortality rate is 50% higher than if the flow is achieved in less than 2 hours (>9% compared with 6.9% in patients with door-to-balloon times <1 hour and 5.7% in patients with door-to-balloon times of 1 to 2 hours) (32). Thus, restoration of TIMI grade 3 flow is necessary but not sufficient: To optimize outcomes, this flow must also be restored quickly.

The use of glycoprotein IIb/IIIa inhibitors in conjunction with both thrombolytic agents and percutaneous intervention was recently reported from a nonrandomized substudy of the GUSTO III acute myocardial infarction trial (33). Among the patients treated with adjunct or rescue intervention after thrombolysis, those who received abciximab ($n = 81$) had a mortality rate of 3.7% and those who did not receive abciximab ($n = 306$) had a mortality rate of 9.8% ($P = 0.04$). There was also a tendency for the incidence of death, recurrent myocardial infarction, or stroke to be reduced in abciximab recipients (8% compared with 21%; $P = 0.07$). The ongoing

Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial should shed light on the question of whether the combination of glycoprotein IIb/IIIa antagonists and stenting offers superior outcomes compared with stenting alone in the setting of acute myocardial infarction. TNK, a new thrombolytic agent that is more fibrin-specific than tPA, tended to reduce intracranial hemorrhage in patients older than 75 years of age (1.72% compared with 2.62%; $P = 0.18$) and to reduce mild to moderate bleeding ($P = 0.002$) in the ASSENT (Assessment of the Safety and Efficacy of a New Thrombolytic Agent) II trial (Van de Werf F. Results of the ASSENT II trial. Presented at the American College of Cardiology Meeting, New Orleans, Louisiana, 9 February 1999). The safety profile of this single-bolus agent may allow it to be very efficacious in combination with glycoprotein IIb/IIIa antagonists and interventional strategies. Thus, combinations of pharmacologic and interventional approaches may offer dual benefits with respect to the open artery hypothesis by safely coupling early opening achieved by using a pharmacologic strategy with full and sustained reperfusion created by using a mechanical approach.

Making the Choice

Deciding whether to administer a thrombolytic agent or to perform primary PTCA or stenting is a complex and multifactorial choice. Administration of thrombolytic agents has only a modest learning curve, and many physicians and centers should be able to obtain consistent results. Thrombolytic agents may be effective in some situations in which complex anatomy may render a lesion unapproachable by percutaneous methods. On the other hand, an interventional approach allows patients with left main or extensive disease to be triaged early to immediate coronary artery bypass graft surgery. Thrombolytic agents, if stored and administered in the emergency department, may be given rapidly 24 hours per day in most hospitals; in contrast, an in-hospital, on-call team prepared to quickly perform primary PTCA at all times may create enormous institutional costs. Indeed, much of the challenge associated with the use of interventional strategies lies in their timely implementation. Given the low event rates in patients younger than 55 years of age and patients with uncomplicated, inferior myocardial infarctions (mortality rate, 3% to 4%), it will be difficult for either strategy to show superiority in these subgroups. Much of the potential for improvement lies in high-risk patients: patients with anterior infarctions, elderly patients,

women, and patients who are hemodynamically compromised.

In deciding between thrombolytic therapy and primary PTCA or stenting, one must ask the complicated question, At this time of day at this hospital, how can I most safely and quickly (in less than 2 hours) open this patient's artery with the best flow and keep the artery open?

Future Directions

The numerous permutations of interventional and pharmacologic strategies require ongoing re-evaluation. Careful attention must be paid to the generalizability of the results obtained. We must identify the subgroups of patients that will receive the greatest benefit from each strategy so that we can afford the technologies that have been developed and deliver cost-effective care. The challenge associated with pharmacologic reperfusion strategies lies not only in safely improving 90-minute flow but also in sustaining that flow and limiting reocclusion. The challenge associated with mechanical strategies lies in decreasing door-to-balloon times and optimizing treatment of smaller vessels. If "time is myocardium," now may be the time to combine the speed of a pharmacologic strategy in restoring patency with the speed of flow after more definitive (albeit later) mechanical intervention. Whereas the past decade has given us TIMI and PAMI, perhaps now a "JIMI" (Joint Intervention in Myocardial Infarction) approach will safely offer the best of two potentially complementary strategies.

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