Choosing Pharmacotherapy for Primary PCI in Acute Myocardial Infarction

A review of the agents and strategies commonly used during percutaneous intervention for ST-segment elevated myocardial infarction.

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Mortality from ST-segment elevated acute myocardial infarction (STEMI) has steadily improved during the past 2 decades. Much of this improvement is attributed to the advent of therapies that promote rapid restoration of infarct vessel patency, initially via pharmacologic means using fibrinolytic agents and subsequently using the mechanical approach of percutaneous coronary intervention (PCI). The success of mechanical reperfusion in acute myocardial infarction (AMI) has caused rapid PCI, with a door-to-balloon time <90 minutes, to become the benchmark of modern treatment in STEMI. The remarkable success of PCI, however, is due in part to improvements in the array of pharmacologic agents available to assist and support the reperfusion process. For the purposes of this review, these agents will be discussed in two groups: those affecting the hematological aspects of the procedure, which are summarized in Table 1, and those primarily affecting hemodynamics. In addition, other adjunctive pharmacologic agents that strongly benefit secondary prevention and mortality after recovery from STEMI and PCI are addressed in this article.

**HEMATOLOGICAL AGENTS**

**Anticoagulants**

*Unfractionated heparin.* The traditional anticoagulant of choice during PCI, unfractionated heparin (UFH) continues to enjoy an advantage of familiarity and relatively convenient monitoring with activated clotting times (ACT) in the catheterization laboratory. Most operators are comfortable using the ACT to achieve a specific level of anticoagulation, checking periodically throughout the case to ensure that this level is maintained. Further advantages of UFH include the ability to reverse its effects with protamine and the relative safety in patients with renal impairment. UFH is a relatively nonselective anticoagulant that primarily inhibits thrombin by enhancing the activity of antithrombin III and, as seen in Figure 1, inhibits factor Xa as well. Heparin has several drawbacks, including its inability to act upon clot-bound thrombin, variable dose response, potential to activate platelets, and the risk of heparin-induced thrombocytopenia (HIT). These limitations have led to investigation of heparin alternatives, including low-molecular-weight heparins (LMWHs) and direct thrombin inhibitors. At present, however, UFH remains the standard anticoagulation...
strategy for primary PCI in STEMI, usually in combination with glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors (Figure 2).

Low-molecular-weight heparin. LMWH consists of varying lengths of saccharide chains, the shorter of which are more potent inhibitors of factor Xa, the upstream promoter of thrombin production. The net effect provides enhanced inhibition predominantly of factor Xa and, to a lesser degree, thrombin (Figure 1), without the platelet activation seen with UFH. This translates to more predictable anticoagulation compared to UFH, with a lower risk of HIT. Although other LMWHs, such as dalteparin and reviparin, have been studied, enoxaparin is the most widely used and available agent.

A large number of clinical trials have compared enoxaparin versus UFH in conjunction with fibrinolytic therapy in the treatment of STEMI and have consistently shown improved efficacy in ischemic endpoint reduction at the cost of a slight increase in bleeding complications. Unfortunately, there are no prospective, randomized trials comparing enoxaparin to UFH in the context of a primary PCI management strategy of STEMI. The PCI Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (ExTRACT TIMI 25) study reported outcomes of a subgroup of 4,676 patients who underwent PCI after initial treatment with fibrinolytics and either enoxaparin (N=2,272) or UFH (N=2,404) and showed a 23% reduction in the relative risk of 30-day death or MI in the enoxaparin group (P<.001), without an increase in bleeding events. Extrapolation of these results to a primary PCI (PPCI) setting is difficult because PCI therapy was not randomized and was performed in a relatively small percentage of the total study participants within 30 days of the index MI. Furthermore, fewer PCIs were performed with enoxaparin, and an average delay to PCI of >12 hours was observed with enoxaparin compared to UFH.

Although extrapolated from non-STEMI (NSTEMI) patients, the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa inhibitors (SYNERGY) PCI substudy, comparing enoxaparin to UFH using an early invasive strategy, provides important additional insight regarding enoxaparin use in the PCI management of MI. Patients crossing over from one treatment

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**Figure 2.** Suggested decision-making algorithm for selection of antiplatelet and anticoagulation therapy during primary PCI for STEMI. Institutional policies and individual operators’ interpretation of current evidence determine selection of one strategy over another.
(UFH or enoxaparin) to the other during the course of therapy had a greater risk of serious bleeding problems, suggesting that the operator should generally continue with the original anticoagulant, whether LMWH or UFH. Additional concerns with enoxaparin during PCI for STEMI include reports of guiding catheter and guidewire thrombosis and inability to readily measure anticoagulant thrombosis and inability to readily measure anticoagulant effect during the PCI procedure.\textsuperscript{11,12} LMWH appears to be compatible in conjunction with GP IIb/IIIa inhibitors in routine PCI but has not been evaluated in a PPCI strategy for STEMI.\textsuperscript{13} Thus,

| TABLE 1. ANTIPLATELET AND ANTICOAGULANT AGENT USE DURING PPCI FOR STEMI |
|-----------------------------------------------|-------------------------------|-----------------------------|
| Advantages | Disadvantages | Strength/Availability of Evidence for STEMI Primary PCI |
| Aspirin | Strong mortality benefit, inexpensive | GI mucosal irritation | ++++ |
| Clopidogrel | Strong mortality benefit | Increased bleeding risk if emergency CABG | ++++ |
| Ticlopidine | Can be used if clopidogrel allergy | Neutropenia TTP | + |
| Prasugrel | More rapid onset, more potent platelet inhibition | Increased bleeding risk versus clopidogrel | ++ |
| Unfractionated heparin | Effect easily titrated/monitored, reversible with protamine, inexpensive, readily available | Less potent versus other anticoagulants, variable dose-response, cannot act on clot-bound thrombin, may activate platelets, risk of HIT | +++ (UFH has been the accepted standard anticoagulant, though few data show superiority) |
| LMWH-enoxaparin | Inhibition of Xa > thrombin (upstream blockade of thrombin generation), ease of use, less risk of HIT | Not easily reversible, not easily monitored, less safe in renal failure | ++ |
| Fondaparinux | Selective Xa inhibition benefit (upstream blocking of thrombin generation), lower bleeding risk | Guiding catheter thrombosis, no ischemic benefit in PCI | + |
| Bivalirudin | Works against clot-bound thrombin, no platelet activation, can be used with HIT, lower bleeding risk | No rapid reversal, clopidogrel preload required for maximal ischemic efficacy, expense | +++ |
| Hirudin | Similar to bivalirudin | Longer half-life, higher bleeding risk | – |
| Argatroban | Similar to bivalirudin, can be used in renal failure | Limited data in PCI, no data in PPCI for STEMI | – |
| Abciximab | Decreased thrombotic complications, reinfarction | Increased bleeding, thrombocytopenia, long duration of effect | +++ |
| Eptifibatide | Likely similar efficacy as abciximab, short duration of effect | Increased bleeding, thrombocytopenia, renal adjustment | + |
| Tirofiban | Likely similar efficacy as abciximab, short duration of effect | Bleeding, thrombocytopenia, renal adjustment | + |
unless further evidence becomes available, the primary role of LMWH in STEMI is as an adjunctive anticoagulant therapy in patients receiving primary fibrinolytic therapy.

**Fondaparinux.** Fondaparinux is a pentasaccharide synthetic compound that selectively inhibits activated factor X (Figure 1). It was evaluated as an alternative to UFH in patients with STEMI undergoing PCI in the Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS-6) trial. Although fondaparinux was associated with reduction in death/MI overall, this benefit was only seen in patients for whom a noninvasive strategy (ie, fibrinolytic or other medical therapy) was chosen. In patients undergoing PCI, fondaparinux compared to UFH was associated with increased thrombotic complications and a slightly higher risk of death/MI, although not statistically significant. Guiding catheter thrombosis with fondaparinux had also been reported in previous studies. Accordingly, additional anticoagulation using UFH or bivalirudin is necessary if fondaparinux is used in a PCI setting. Given the lack of data supporting fondaparinux in PCI and concerns of increased thrombotic complications, there is currently no defined role for this agent in PCI management of STEMI.

**Direct Thrombin Inhibitor Anticoagulants.** Agents in this class of medications have a theoretical advantage over UFH in their ability to bind both clot-bound and unbound thrombin, with improved efficacy and specificity. Several clinical trials have shown similar efficacy outcomes and reduced bleeding complications with the use of direct thrombin inhibitors compared to UFH+GP IIb/IIIa inhibitors during PCI for stable coronary artery disease and acute coronary syndromes. Bivalirudin. Bivalirudin is a bivalent hirudin analog direct thrombin inhibitor with a short half-life permitting high-level thrombin inhibition during infusion with fairly prompt reversibility upon discontinuation of therapy. Although safety and efficacy of bivalirudin are well established in elective PCI and NSTEMI, until recently, only limited evidence supported the use of bivalirudin with PCI in STEMI.

Thirty-day results of the Harmonizing Outcomes with Revascularization and Stents in AMI (HORIZONS AMI) study, however, provide new evidence of a possible benefit for bivalirudin in STEMI. The results of HORIZONS AMI are robust and may justify selection of bivalirudin as an alternative to UFH in PCI management of STEMI. However, a bivalirudin monotherapy strategy is widely believed to require early loading with high-dose clopidogrel to prevent early adverse ischemic events compared to UFH+GP IIb/IIIa inhibition. The HORIZONS AMI protocol mandated clopidogrel loading before angiography, which has been shown to be an important predictor of favorable outcomes in NSTEMI patients receiving bivalirudin. A typical scenario in which bivalirudin monotherapy could be considered optimal in STEMI would be a patient who presents having already been on chronic clopidogrel or who received a loading dose of 600 mg of clopidogrel in the emergency department before arrival in the catheterization laboratory (Figure 2). Institutional policies regarding the use of bivalirudin in primary PCI for the treatment of STEMI should consider the safety, efficacy, and cost, as well as the willingness of surgeons to perform emergent cardiac surgery when clopidogrel has been used before angiography.

**Other direct thrombin inhibitors.** A number of studies have evaluated the use of hirudin in the setting of fibrinolysis for STEMI. The use of hirudin during PCI for STEMI, however, is not as well established as bivalirudin and has not been evaluated in clinical trials. As with hirudin, limited experience is available with argatroban, either alone or with GP IIb/IIIa inhibitors for PCI in STEMI. However, there are some data to support the use of argatroban as an alternative to heparin with fibrinolytic therapy of STEMI and as adjunctive treatment in routine PCI. Currently, the role
of argatroban in PCI for STEMI is limited to patients with significant impairment of renal function with a history of HIT.

Platelet Inhibitors

**Aspirin.** Aspirin effectively inhibits platelet activation by reducing thromboxane A2 production and has long been a therapeutic cornerstone for treatment of AMI and for secondary prevention. The 2004 ACC/AHA Guidelines for STEMI give a class I recommendation for immediate aspirin therapy. Although aspirin is typically administered before the patient’s arrival to the catheterization laboratory, the importance of this agent in restoring and maintaining vessel patency mandates that the interventionist confirm that it is received before PCI.

**Thienopyridines.** By inhibiting the platelet P2Y12 receptor, the thienopyridine class of medications (ticlopidine, clopidogrel) prevents adenosine-diphosphate–dependent platelet activation. Although ticlopidine was the first drug approved in this family, serious side effects such as neutropenia and thrombotic-thrombocytopenia purpura prevent its routine use in treating MI. In the setting of modern PCI with stenting for acute coronary syndromes, the addition of clopidogrel to aspirin is well established in reducing adverse clinical endpoints, including death, MI, and stroke. The overwhelming evidence has resulted in a class I recommendation for clopidogrel in the recent ACC/AHA 2007 Focused Update on STEMI guidelines. A loading dose of 300 to 600 mg orally should be given as soon as possible before PCI, with 600 mg preferred due to more rapid achievement of therapeutic levels.

For patients undergoing primary PCI, there is lack of consensus about whether to load clopidogrel in the emergency room, or to wait until the time of catheterization and PCI. There is a slight but significant increased risk of bleeding with clopidogrel administered before treatment if the patient requires cardiac surgery. However, the use of direct CABG as a primary reperfusion therapy in STEMI and the likelihood of emergency cardiac surgery in the setting of PPCI of STEMI are both rare (<5%), and as such, these considerations should not have a significant impact on treatment strategies.

Furthermore, many surgeons are willing to operate on patients who have received a clopidogrel loading dose before angiography because the bleeding risk in such individuals appears to be less than that for patients on chronic clopidogrel therapy. Decisions regarding early thienopyridine use in patients with STEMI are best made at the institutional level with multidisciplinary input from cardiology, cardiac surgery, and emergency medicine. Early loading with clopidogrel appears to have the most significant impact when a bivalirudin strategy is selected with primary PCI or when GP IIb/IIIa inhibitors are not utilized (Figure 2).

The latest drug in the thienopyridine class, prasugrel, has a faster onset and is more potent than either of its predecessors, making it a potentially attractive agent for use in PPCI treatment of STEMI. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON) TIMI-38 study evaluated prasugrel in >13,000 patients with acute coronary syndromes (26% with STEMI) and showed a 22% reduction in the incidence of cardiac death, MI, or stroke compared to clopidogrel (HR, 0.78; 95% CI, 0.65–0.97; P = .02). Unfortunately, the efficacy benefits of prasugrel were offset somewhat by a 32% increase in all types of bleeding (minor, major, and fatal). Nevertheless, the net clinical benefit still showed a slight advantage of prasugrel over clopidogrel with the inclusion of major bleeding and all-cause mortality in the composite endpoint (HR, 0.87; 95% CI, 0.79–0.95; P = .004). The bleeding risk with prasugrel appears to be greater than that for patients with a history of stroke and those who undergo CABG. Thus, use of prasugrel in patients with STEMI may be limited to patients with a low risk of bleeding who have already undergone angiography and are selected to undergo PCI, rather than upstream initiation of therapy in the emergency department.

Cangrelor, an intravenous P2Y12 receptor antagonist (nonthienopyridine) currently under investigation, has shown promise as a rapid-onset, short-acting platelet inhibitor in AMI.

**GP IIb/IIIa inhibitors.** The benefits of GP IIb/IIIa inhibition in PPCI treatment of STEMI are well established for abciximab. Consistent reductions in nonfatal reinfarction have been seen in trials of abciximab, both with fibrinolysis and PCI. A significant reduction in early and late mortality has also been demonstrated in patients receiving abciximab during PPCI. These trials have shown that major bleeding is not significantly increased in patients treated with abciximab, although vascular access site bleeding is more common. Furthermore, upstream abciximab use is associated with higher infrarct artery patency at the time of angiography, and this is a strong predictor of improved outcomes. Our institution’s STEMI protocol calls for early initiation of GP IIb/IIIa in the emergency department (especially for outside hospital transfers for PPCI), a class IIa recommendation in the 2004 STEMI guidelines.

To date, there have been no published randomized, controlled trials comparing abciximab to the small-molecule GP IIb/IIIa agents (eptifibatide and tirofiban) in PPCI treatment of STEMI. However, several small trials have shown a
possible benefit of these agents, and a randomized trial comparing eptifibatide to abciximab in PPCI for STEMI is underway. Using cautionary application of the “class effect” argument, we and others (eptifibatide comprised nearly 50% of Gp IIb/IIia in HORIZONS AMI) primarily use eptifibatide for PPCI due to its shorter duration of action compared to abciximab. Concerns about bleeding complications with abciximab in the event of emergency cardiac surgery, however, may be exaggerated, and platelet transfusion is effective in reversing the effects of abciximab.

HEMODYNAMICALLY ACTIVE AGENTS

Beta-Blockade

As in the case of fibrinolysis or noninvasive management of STEMI, a PPCI treatment strategy of STEMI should utilize guidelines-based therapies, as appropriate, after assessment of individual patient factors. Beta-adrenergic receptor blockers have long been known to reduce mortality, reinfarction, and arrhythmic events in the post-MI period. Current guidelines recommend the use of beta-blockers for all STEMI patients (in the absence of contraindications), preferably by oral route (class I recommendation) to reduce infarct extension. Recent controversy has arisen regarding intravenous beta-blockers, currently a class IIa recommendation, after a large Chinese trial found no difference in overall survival but a significant increase in death from cardiogenic shock after giving intravenous metoprolol. Based on these results, beta-blockers should be withheld in the setting of cardiogenic shock and should be used cautiously in patients with borderline hypotension, pulmonary edema, or other evidence of significant left ventricular dysfunction.

ACE Inhibition/Angiotensin Receptor Blockade

Substantial mortality benefits and possibly improved ventricular remodeling are seen with early administration of angiotensin-converting enzyme (ACE) inhibitors, particularly in patients with an anterior wall MI, pulmonary edema, or reduced ejection fraction <40%. A smaller, but significant benefit may be seen for ACE inhibitors in all patients with MI in the absence of hypotension (class IIa recommendation). An angiotensin receptor blocker is a suitable alternative, with the same indications and contraindications as an ACE inhibitor.

Inotrope and Vasopressor Agents

Although the treatment of cardiogenic shock is beyond the scope of this article, a thorough understanding of inotrope and vasopressor pharmacology, as well as the ability to use mechanical supportive devices, is essential in the management of STEMI. A modern coronary care unit with well-trained nurses, technicians, and critical care specialists is imperative to achieve low mortality rates and optimal clinical outcomes in STEMI patients.

OTHER ADJUNCT PHARMACOLOGY FOR PCI IN AMI

Pain management protocols using nitrates and opiate analgesics, although not directly involved with infarct artery patency and clinical outcomes, are nevertheless an essential component of STEMI care. Insulin infusion or other intensive blood glucose control protocols are also strongly recommended in STEMI, particularly for high-risk patients. Early initiation of statin therapy is important both for lipid-lowering and pleiotropic benefits. Nephroprotection is also a concern during STEMI, although pretreatment strategies are not generally available due to the requirement for immediate angiography and revascularization of STEMI patients. The use of N-acetylcysteine for prevention of contrast-induced nephropathy is controversial; however, one study has shown significant reductions not only in the occurrence of contrast-induced nephropathy, but also in short-term mortality when STEMI patients received n-acetylcysteine 1,200 mg intravenously before angiography and PPCI.

SUMMARY

Modern reperfusion therapy with rapid primary PCI has emerged as the preferred treatment of STEMI. Important differences in anticoagulation and antiplatelet strategies necessitate a complete understanding of the advantages and drawbacks to using a particular strategy, as well as familiarity with the clinical evidence supporting each regimen. Appropriate medical therapy in the peri- and post-MI period is essential to optimize clinical outcomes and achieve secondary prevention with reductions in long-term adverse events. Although the technical and mechanical aspects of primary PCI will improve and change, adjunctive pharmacologic therapy will continue to play an important role in STEMI management.

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