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Emergency Cardiac Surgery in Patients with Acute Coronary Syndromes: A Review of the Evidence and Perioperative Implications of Medical and Mechanical Therapeutics

Charles Brown, MD, Brijen Joshi, MD, and Nauder Faraday, MD

Anesthesiology and Critical Care Medicine, The Johns Hopkins University School of Medicine

Ashish Shah, MD and David Yuh, MD

Division of Cardiac Surgery, Department of Surgery, The Johns Hopkins University School of Medicine

Jeffrey J. Rade, MD

Division of Cardiology, Department of Medicine, The Johns Hopkins University School of Medicine

Charles W. Hogue, MD

Anesthesiology and Critical Care Medicine, The Johns Hopkins University School of Medicine

Abstract

Patients with acute coronary syndromes who require emergency cardiac surgery present complex management challenges. The early administration of antiplatelet and antithrombotic drugs has improved overall survival for patients with acute myocardial infarction, but to achieve maximal benefit, these drugs are given before coronary anatomy is known and before the decision to perform percutaneous coronary interventions or surgical revascularization has been made. A major

Corresponding Author: Charles W. Hogue, MD, The Johns Hopkins University School of Medicine, Anesthesiology and Critical Care Medicine, The Johns Hopkins Hospital, 600 N. Wolfe St, Tower 711, Baltimore, MD 21287, Phone: 410-614-1516, FAX: 410-955-0994, chogue2@jhmi.edu.

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bleeding event secondary to these drugs is associated with a high rate of death in medically treated patients with acute coronary syndrome possibly due to subsequent withholding of antiplatelet and antithrombotic therapies that otherwise reduce the rate of death, stroke, or recurrent myocardial infarction. Whether the added risk of bleeding and blood transfusion in cardiac surgical patients receiving such potent antiplatelet or antithrombotic therapy before surgery specifically for acute coronary syndromes affects long-term mortality has not been clearly established. For patients who do proceed to surgery, strategies to minimize bleeding include stopping the anticoagulation therapy and considering platelet and/or coagulation factor transfusion and possibly rFVIIa administration for refractory bleeding. Mechanical hemodynamic support has emerged as an important option for patients with acute coronary syndromes in cardiogenic shock. For these patients, perioperative considerations include maintaining appropriate anticoagulation, ensuring suitable device flow, and periodically verifying correct device placement. Data supporting the use of these devices are derived from small trials that did not address long-term postoperative outcomes. Future directions of research will seek to optimize the balance between reducing myocardial ischemic risk with antiplatelet and antithrombotics versus the higher rate perioperative bleeding by better risk-stratifying surgical candidates and by assessing the effectiveness of newer reversible drugs. The effects of mechanical hemodynamic support on long-term patient outcomes needs more stringent analysis.

An early invasive strategy that includes coronary angiography and often percutaneous coronary interventions (PCI) leads to improved survival compared with conservative medical management (e.g., IV thrombolytics) for patients with an acute coronary syndrome (ACS) such as unstable angina, non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI).¹ In the United States (U.S.) an estimated 1.3 million PCIs are performed annually (70% with drug-eluting stent placement) underscoring the large public health implications of aggressive coronary artery disease management.² Patients may require emergent coronary artery bypass graft (CABG) surgery when the coronary artery disease is not amenable to PCI or when complications develop. Fortunately, the rates of complications from PCI (e.g., coronary artery dissection or abrupt vessel closure) have markedly declined since the introduction of intracoronary stents. In a case series from the Mayo Clinic, the incidence of emergency CABG after PCI decreased significantly from 2.9% in the “pre-stent era” to 0.7% in the “initial stent era” to 0.3% currently ($P < 0.001$).³ Nonetheless, the in-hospital mortality rate for emergency CABG was high and unchanged from 1979 to 2003 (10% to 14%). Caring for patients who require emergency cardiac surgery after PCI is increasingly complex and challenging owing to the aggressive use of new antiplatelet and antithrombotic drugs for patients with ACS and the increasing emergency use of mechanical support for hemodynamic stabilization. The purpose of this review is to provide a summary of data from recent large, randomized, controlled trials that have examined the benefit of antiplatelet and antithrombotic drugs on major outcomes for patients with ACS. We will focus on therapies recommended for evidence-based treatments of ACS and provide strategies of perioperative management for patients receiving this therapy. We will further review data supporting the use of new percutaneous mechanical circulatory support devices and their implications for managing patients undergoing emergency cardiac surgery.

PERIOPERATIVE IMPLICATIONS OF ANTIPLATELET AND ANTITHROMBOTIC AGENTS IN ACS

The pathophysiologic basis of ACS is coronary artery plaque disruption that results in platelet adhesion, thrombus formation, and artery obstruction. Reestablishing coronary flow with thrombolytic therapy or early PCI is the primary treatment for acute myocardial infarction (MI).^{4,5} Therapy with aspirin and unfractionated heparin (UFH) to interfere with

ongoing platelet-fibrin formation has been clearly established to reduce death and reinfarction in patients with ACS.^{6,7} Nonetheless, patients with ACS are at persistent short- and long-term risk for recurrent MI and death. This heightened risk may be related in part to the weak antiplatelet effects of aspirin and the limitations of UFH, including its ineffectiveness at inhibiting the enzymatic action of thrombin that is already bound to fibrin clot.⁸ Continued thrombin activity not only promotes further fibrin clot formation but may also activate platelets since thrombin is a potent platelet agonist capable of stimulating aggregation even in the presence of aspirin inhibition of thromboxane A₂ production.^{8,9} As a result, there has been considerable research to develop more robust antiplatelet drugs and thrombin inhibitors that inactivate both soluble and “clot-bound” fibrin. Extensive data now support the benefits of antiplatelet and antithrombotic agents in the setting of ACS and PCI as reviewed by others.^{7,10–12} Current recommendations for antiplatelet and antithrombotic therapy in ACS and for PCI are summarized in Table 1.

For patients who require emergency CABG surgery, one must weigh the net benefits of the antiplatelet and antithrombotic drugs against the added risks for perioperative bleeding and blood transfusion that are independently associated with morbidity and mortality.^{13–15} There is no standard definition of major bleeding episodes in clinical trials of antiplatelet and antithrombotic drugs, although definitions evolving from two seminal trials of thrombolysis after MI are often quoted.^{16,17} Criteria for major bleeding in nonsurgical patients include intracranial bleeding, cardiac tamponade, or bleeding from any site associated with >50 g/dL decrease in hemoglobin. Examples of minor nonsurgical bleeding include bleeding from any site associated with >30 g/dL but <50 g/dL decrease in hemoglobin, hematuria, hemoptysis, hematemesis, or transfusion. Nonetheless, definitions among studies are highly variable and often a composite of all bleeding events or major bleeding unrelated to CABG surgery. Thus, a gastrointestinal bleeding event that is self-limiting after blood transfusion may be counted in the outcome with the same weight as a catastrophic intracerebral bleeding event. Regardless, a major bleeding event is associated with a 5-fold higher risk of death within 30 days in patients with ACS.¹⁸ The reason for the higher risk is not clear but it may be related to associated hypotension and blood transfusion resulting from bleeding. Alternatively, the link between a major bleeding event and mortality may be due to discontinuation of antiplatelet and antithrombotic drugs as a result of bleeding that in turn leads to recurrent myocardial ischemia from withholding of these effective treatments.

Unfortunately, risk factors for bleeding overlap with those for adverse outcome from myocardial reinfarction and, thus, are of little value for individually balancing the risk versus benefit of aggressive antithrombotic therapies.¹⁹ Pocock et al.²⁰ recently reported analysis of the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, which involved 13,819 patients with NSTEMI randomized to UFH with a glycoprotein (GP) IIb/IIIa inhibitor, bivalirudin plus a GP IIb/IIIa inhibitor, or bivalirudin alone. These authors reported that two risk factors were common for major nonCABG-related bleeding and reinfarction: age and ST-segment changes on the admission electrocardiogram (ECG). The impact of the latter ECG changes on mortality was particularly significant early after admission but not 30 days after the event, whereas bleeding complications were associated with mortality throughout the observation and for up to 1 year. Admission ST-segment ECG changes might identify patients at high risk for reinfarction who might benefit the most from aggressive antithrombotic therapy.¹⁹ Discontinuing antiplatelet and antithrombotic drugs during the seminal event would predispose this group of patients to risks of recurrent ischemic events. The effect of a bleeding event on long-term outcome was speculated to result from restrictive use of antithrombotic therapy after hospital discharge. Of importance, 37% of the 1647 patients undergoing CABG surgery in the ACUITY trial had a major bleeding episode.²⁰ The incidence of death within one year of treatment was not different

for patients with a major bleeding episode after CABG surgery than in those without major bleeding (HR, 1.01; 95% confidence interval, 0.70 to 1.46, $P = 0.96$). These data might imply that appropriate antiplatelet or antithrombotic therapy should be restarted after CABG surgery once the bleeding episode has been controlled.

ADP-P2Y₁₂ Receptor Antagonist

Platelet ADP-P2Y₁₂ receptor activation is an important mechanism of thrombus formation in ACS. Several pivotal trials have established that including a P2Y₁₂ receptor antagonist in combination with aspirin can help reduce the frequency of death, reinfarction, or stroke in patients with ACS (Table 2).^{21–26} The thienopyridine clopidogrel has become the primary P2Y₁₂ receptor antagonist for patients with ACS. A limitation of this agent is that it is a prodrug that requires a two-step CYP isoenzyme-dependent activation process in the liver. Polymorphisms in CYP enzymes necessary for converting clopidogrel to its active metabolite are associated with reduced platelet inhibition and worse clinical outcome.^{7,27–29} Clopidogrel metabolism may also be influenced by other CYP-dependent drugs, such as proton pump inhibitors.^{7,30}

The newer thienopyridine, prasugrel, has been suggested to provide more consistent and greater platelet inhibition than clopidogrel.^{7,31,32} Although also a prodrug, there is no measurable variability in the activating enzymes of prasugrel. A clinical limitation with both clopidogrel and prasugrel is irreversible P2Y₁₂ receptor blocking effects that are particularly a concern for patients who need CABG surgery. Ticagrelor is a new antiplatelet drug that reversibly binds the P2Y₁₂ receptor.

The combination of aspirin with clopidogrel reduces the risk of recurrent ischemic events after PCI with stenting by 3.9% compared with aspirin alone.³³ Recently it has been highlighted that patients may need the dual antiplatelet therapy for at least 1 year, if not indefinitely, after intracoronary artery insertion of a drug-eluting stent.³⁴ Analysis of the Duke Cardiovascular Database revealed that for patients with a drug-eluting stent, use of aspirin with clopidogrel was associated with a lower rate ($P < 0.001$) of death (0% vs 3.5%) or death and MI (0% vs 4.5%) than aspirin therapy alone.³⁵

Use of dual antiplatelet therapy results in conflicting goals for patients who need cardiac surgery. That is, the benefits of these drugs in preserving myocardium and improving survival are balanced against the added risk of perioperative bleeding and transfusion. Preoperative aspirin alone decreases the risk for MI, improves saphenous vein graft patency, and improves survival after CABG surgery, with minimal increased risk for perioperative bleeding and transfusion.¹¹ Dual therapy with aspirin and clopidogrel, however, has been documented to lead to higher rates of bleeding, blood transfusion, mediastinal re-exploration, longer tracheal intubation, and hospitalization for patients who continue therapy within 5 days of CABG surgery.^{36–39} Dual antiplatelet therapy is also associated with a higher risk of infection after CABG surgery; an increase in risk that is independent of baseline comorbidities and perioperative transfusion status.⁴⁰ Some reports suggest higher mortality for patients who receive clopidogrel up to the time of CABG surgery, but this is not a consistent finding.^{36,37,39} The latter data are limited by the fact that they are derived from observational studies. Undergoing CABG surgery within 5 days of receiving clopidogrel may identify a high-risk category of patients who require urgent revascularization.

Current recommendations are to stop clopidogrel for 5 or more days and prasugrel for 7 days before cardiac surgery (Table 1 and Appendix). The needed duration of withdrawal of ticagrelor before cardiac surgery to reduce bleeding risk is not yet known. In vitro studies suggest that platelet function after 3 days of cessation of ticagrelor is similar to that observed

after 5 days of withholding clopidogrel.⁴¹ Nonetheless, available data are insufficient to answer the question of whether the reduced risk of bleeding associated with discontinuing clopidogrel before surgery is worth the added risk of myocardial ischemic events.¹¹ In the Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28), 3491 patients were randomized to receive clopidogrel (300 mg load then 75 mg/day) or placebo in the setting of fibrinolytic therapy and UFH or low-molecular-weight heparin (LMWH) for STEMI.⁴² Of this cohort, 136 patients underwent CABG surgery during the initial hospitalization. For patients who stopped the study medication <5 days before surgery, the rates of major bleeding were 11.4% in the clopidogrel group and 10.5% in the placebo group (absolute risk reduction, 0.9%; CI 13.5 to 15.3%, $P = 1.0$). The 30-day composite end point of cardiovascular death, MI, or repeat revascularization for those undergoing CABG surgery <5 days after discontinuing medication was 20% in the clopidogrel group and 26.3% in the placebo group (OR 0.73, 95% CI, 0.23 to 2.33). In both the CURE and CLARITY-TIMI 28 trials, the majority of improvements in outcomes with clopidogrel were from a reduction in events before cardiac catheterization.^{23,42}

For patients undergoing acute cardiac catheterization laboratory intervention, another approach for reducing exposure to antiplatelet therapy might be to withhold therapy until the coronary anatomy is defined and the choice of myocardial revascularization strategy (i.e., PCI versus CABG surgery), if any, is determined. However, this approach (“downstream” administration) might deny patients with ACS the benefit of platelet inhibition during the period of greatest risk. Nonetheless, as many as one-third of intermediate- to high-risk patients with NSTEMI are found to have minimal coronary artery disease at the time of coronary angiography.⁴³ Administering potent antiplatelet drugs on presentation (“upstream” or before coronary angiography) exposes such patients to unnecessary risk of such therapy. Withholding antiplatelet therapy until after “angiographic triage” does not appear to increase the risk of ischemic complications for patients who eventually undergo PCI after NSTEMI.⁴³ The reversible binding of ticagrelor to the P2Y₁₂ receptor may make it clinically useful for patients in whom the coronary anatomy is not known and, thus, for whom the choice of PCI or CABG surgery cannot be immediately determined. In the PLATO study, though, there was no difference in the rates of bleeding or transfusion between patients who received ticagrelor and those who received clopidogrel before undergoing CABG surgery, but the rates of noncardiac surgery bleeding and intracranial hemorrhage were higher in the ticagrelor group (Table 2).²⁵

Glycoprotein IIb/IIIa Receptor Inhibitors

GP IIb/IIIa receptors are constitutively expressed on the platelet surface and undergo conformational changes after platelet activation to become competent to bind fibrinogen. Interplatelet cross-bridging via fibrinogen leads to platelet aggregation and plug formation. Inhibitors of the GP IIb/IIIa receptor have been shown to benefit subgroups of patients with ACS (Table 3).^{7,44–51} GP IIb/IIIa inhibitors can be divided into competitive and noncompetitive receptor blocking drugs. Tirofiban and eptifibatide are competitive receptor inhibitors. In contrast, abciximab is a human/murine monoclonal antibody to the GP IIb/IIIa receptor that nearly irreversibly blocks the receptor. Return to 50% GP IIb/IIIa receptor inhibition after abciximab treatment requires nearly 12 h after stopping the drug.⁵² Boersma et al.⁵³ performed a meta-analysis of six randomized trials of GP IIb/IIIa inhibitor treatment in 31,402 patients with ACS who received conservative management. After 30 days, there was a 9% reduction in the odds of death or MI with GP IIb/IIIa inhibitors compared with placebo or control therapy (10.8% vs 11.8%; odds ratio 0.91; 95% CI, 0.84 to 0.98; $P = 0.015$). GP IIb/IIIa inhibitor therapy can result in major bleeding and thrombocytopenia. Improper dosing of GP IIb/IIIa inhibitors was implicated as a contributing factor in bleeding in retrospective analysis.¹¹ In that study, older age, female sex, renal insufficiency, low

body weight, diabetes, and congestive heart failure were associated with GP IIb/IIIa dosing outside of guidelines. Recent analysis of data from the National Cardiovascular Data Registry involving 829 U.S. hospitals and 22,778 patients found that contraindicated medications were used in 22.3% of patients on dialysis who were undergoing PCI.⁵⁴ The risk of major bleeding was linked to improper medication administration. Analysis of data from the other multicenter data showed no difference in transfusion rates and major bleeding in patients undergoing surgery after receiving abciximab compared with placebo.⁵⁵ These data do not apply to emergency CABG surgeries, because many patients stopped abciximab >12 h before surgery. Others report high rates of bleeding and transfusion when abciximab is given <12 h after CABG surgery.⁵⁶ Tirofiban and eptifibatide each have a shorter half-life than abciximab (~2 h), a feature that allows for more rapid dissipation of their antiplatelet effects and decreases the risk of bleeding in patients who require urgent or emergent CABG surgery.^{57,58} These drugs should be discontinued 4 hrs before surgery to reduce the risk of bleeding (Appendix).

Low-molecular-weight Heparin

LMWHs are 5000-Dalton or less fragments of UFH that have better bioavailability than UFH and produce less platelet activation and sensitization.⁷ Similar to UFH, LMWH acts via antithrombin to inhibit thrombin, but it also inhibits activated factor X. The latter effect is greater with shorter fragment length. Monitoring the effectiveness of anticoagulation with LMWH is problematic because the partial thromboplastin time is insensitive to therapeutic doses of LMWH. Measuring antifactor Xa activity is one approach that is increasingly considered. Importantly, LMWHs are excreted by the kidneys, necessitating dose adjustment in the presence of renal impairment.^{7,59} Only 60% of the anticoagulant effect of LMWH can be reversed with protamine.⁷ In the presence of bleeding, it has been suggested that 1 mg of protamine be given for each 100 antifactor Xa units if LMWH was given within 8 h.⁶⁰

One commonly used LMWH is enoxaparin. Compared with UFH, enoxaparin treatment, when added to aspirin with or without a GP IIb/IIIa receptor inhibitor, has been shown to be beneficial for low-risk patients with unstable angina or NSTEMI managed medically.^{61–63} However, in some trials, higher rates of bleeding were observed with enoxaparin than with UFH.⁶⁴ The use of LMWH as a procedural anticoagulant for PCI was found not to lead to higher rates of bleeding complications compared with UFH.^{65,66} In the one analysis,⁶⁷ the primary outcome of non-CABG-related major bleeding at 48 h was lower in patients receiving 0.5 mg/kg of enoxaparin than in those receiving UFH (5.9% vs 8.5%, $P = 0.01$) but not in those receiving 0.75 mg/kg of enoxaparin (6.5%, $P = 0.051$).

A meta-analysis of six randomized trials that compared enoxaparin and UFH in 21,946 patients with NSTEMI found no difference in the incidence of death at 30 days after treatment (3.0% vs 3.0%; odds ratio, 1.00; 95% confidence interval, 0.85 to 1.17).⁶⁸ A reduction in the occurrence of the combined end point of death or nonfatal MI at 30 days was noted for patients receiving enoxaparin compared with UFH (10.1% vs 11.0%; OR, 0.91; 95% CI, 0.83 to 0.99). Overall, there was no difference in the rate of blood transfusion (OR, 1.01; 95% CI, 0.89 to 1.14) or major bleeding (OR, 1.04; 95% CI, 0.83 to 1.30). Enoxaparin has been evaluated in *high-risk* patients with ACS managed with an early invasive strategy (Table 4).^{7,10,64,69–71}

The relationship between enoxaparin and CABG-related bleeding events depends on the timing of surgery after cessation of antithrombotic therapy.¹⁵ In the SYNERGY trial, 18.1% of 9053 patients eventually underwent CABG surgery.⁷² Of those undergoing CABG surgery, nearly 50% underwent CABG within 72 h of angiography. Patients who received early CABG surgery had more bleeding events (39.2% vs 29.4%, $P < 0.001$) but not death or MI compared with patients who did not undergo the surgery. The risk of bleeding was

reduced when surgery was delayed >18 h after stopping enoxaparin and GP IIb/IIIa receptor inhibitors. It is recommended that enoxaparin be discontinued 12 to 24 hrs before cardiac surgery to decrease the risk of bleeding (Appendix).

Direct Thrombin Inhibitors

Direct thrombin inhibitors (DTIs) block thrombin's ability to convert fibrinogen to fibrin, activate coagulation factors XI, X, and XII, as well as platelets.⁷ Of the available DTIs, bivalirudin is the only drug recommended for patients with ACS (Table 1). Bivalirudin is a 20-amino acid synthetic peptide that has a biphasic effect on thrombin. Initially, bivalirudin is a noncompetitive inhibitor of thrombin, but it is slowly cleaved by thrombin, allowing for some eventual functional recovery.⁷ The half-life of bivalirudin is 25 min and determined by proteolysis and renal clearance.

A meta-analysis of 11 randomized trials involving 35,970 patients with ACS found that patients who had received at least 7 days of DTI therapy had a lower risk of death or MI after 30 days than patients who had received UFH (7.4% vs 8.2%; OR 0.91; 95% CI, 0.84 to 0.99, $P = 0.02$).⁷³ This result stemmed mostly from a reduction in the rate of MI that occurred in 2.8% of DTI-treated patients and 3.5% of UFH-treated patients ($P < 0.001$). Studies in which bivalirudin was evaluated in patients with ACS undergoing PCI have reported lower rates of death with DTIs than with UFH (Table 5).^{74–79} Interpretation of the results of many of the trials has been debated with respect to the adequacy of anticoagulation in the control patients, endpoint definitions, and study patient populations.⁷

The lack of a specific antidote for DTIs may complicate perioperative management of patients requiring emergency cardiac surgery. Nonetheless, the short half-life of bivalirudin may allow for clearance of the drug in all patients except for those with renal dysfunction. Interestingly, a pooled analysis of three randomized trials in which 35 of 12,921 patients had coronary artery perforation during PCI revealed that patients treated with bivalirudin had outcomes similar to those treated with UFH and a GP IIb/IIIa receptor inhibitor.⁸⁰ The feasibility of anticoagulation with bivalirudin during cardiac surgery with or without cardiopulmonary bypass (CPB) has been demonstrated including in patients with heparin-induced thrombocytopenia.^{81–84} Although not significant, there was trend for higher rates of bleeding end points including chest re-exploration for patients receiving bivalirudin compared with UFH. These studies, though, were not powered to adequately assess the safety of bivalirudin for anticoagulation during cardiac surgery. It is recommended that bivalirudin be discontinued 3 or more hours before cardiac surgery to reduce the risk for bleeding (Appendix).

Factor Xa Inhibitors

Fondaparinux is a synthetic pentasaccharide that activates antithrombin III by inducing a conformational change in the enzyme. The activated antithrombin III then irreversibly inhibits factor Xa.⁸⁵ It is administered subcutaneously with once-a-day dosing. Prospectively randomized, double-blind trials have shown that, compared with enoxaparin, fondaparinux reduces the incidence of venous thromboembolism after major orthopedic surgery, without a difference in bleeding events.⁸⁵

The OASIS-5⁸⁶ and OASIS-6⁸⁷ trials evaluated the use of fondaparinux in patients with NSTEMI and STEMI, respectively (Table 6). Major bleeding was lower with fondaparinux than with enoxaparin in OASIS-5 but not versus usual care in the OASIS-6 trial. Notably, patients with major bleeding in the former study had higher mortality (13.2% vs 2.8%), reinfarction (11.9% vs 3.6%), or stroke (3.5% vs 0.7%) 30 days after randomization ($P < 0.001$) compared to those without major bleeding regardless of treatment group. The

observed decrease in mortality with fondaparinux compared to enoxaparin resulted from its ability to reduce major bleeding. Rates of mortality, MI, and recurrent ischemia were similar for patients receiving fondaparinux and enoxaparin who underwent PCI. Higher rates of thrombus formation were observed on the PCI catheters in the fondaparinux group, an effect that could be avoided by coadministration of UFH. Fondaparinux should be stopped 24 hrs before cardiac surgery to decrease the risk of bleeding (see Appendix).

MANAGEMENT OF PERIOPERATIVE BLEEDING

There are no specific evidence-based guidelines for managing bleeding due to coagulopathy in the cardiac surgical patient who has received antiplatelet or antithrombotic drugs for ACS.⁸⁸ Suggested management for such patients is listed in Table 7. As a general principle, patients who require emergent cardiac surgery and are receiving antiplatelet or antithrombotic drugs should first stop the drug. Performing CABG surgery without CPB is one consideration if the patient is a suitable candidate. If CPB is planned, the dose of heparin should not be reduced in the presence of such drugs, because incomplete inhibition of thrombin may lead to secondary platelet activation and consumption.⁸⁸ Platelet transfusion is typically the first line of therapy for bleeding in patients receiving antiplatelet therapy before surgery. In fact, some evidence suggests that clopidogrel's antiplatelet effects can be reversed with platelet transfusions.^{89,90} Nonetheless, platelets should not be transfused prophylactically.

Several pharmacologic strategies have been proposed for managing patients who are receiving antiplatelet drugs before cardiac surgery, including antifibrinolytic therapy and desmopressin.⁸⁸ Plasma-derived and synthetic coagulation factor concentrates such as fibrinogen, factor XIII, and recombinant-activated FVIIa (rFVIIa) have been used in patients with excessive perioperative bleeding.⁸⁸⁻⁹¹ Because these components are either pasteurized or synthesized by recombinant DNA technology, there is a reduced risk of infectious agent transmission compared with allogeneic blood transfusion. rFVIIa is specifically indicated for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to factor VIII or factor IX or for the treatment of bleeding episodes and the prevention of bleeding in surgical interventions or invasive procedures in patients with acquired hemophilia.⁹² Although not entirely elucidated, the mechanism of the hemostatic effects of rFVIIa appear to be local generation of thrombin at the site of vessel injury.⁹³ The U.S. Food and Drug Administration has recently added a "black box" warning to prescribing information for the coagulation factor VIIa drug NovoSeven® (Novo Nordisk, Inc., Princeton, NJ) to warn about serious thrombotic adverse events when the product is used outside of labeled indications.⁹⁴

Procoagulant proteins are normally localized to the site of vascular injury by endothelial-based and systemic antithrombotic and fibrinolytic processes as previously reviewed.^{88,91} As a result, few activated coagulation proteins escape the site of endothelial disruption, and those that do are rapidly inactivated by antithrombotic factors such as antithrombin III and tissue factor pathway inhibitor. The fine balance between prothrombotic and antithrombotic processes can be disrupted perioperatively. For example, patients may have a deficiency of antithrombotic proteins or have prothrombotic conditions induced by surgical trauma/inflammation and blood coagulation factor administration. Of particular concern is that administration of rFVIIa in excess of that needed to stop microvascular bleeding may overwhelm antithrombotic processes and lead to systemic thrombus formation and organ injury.

Mortality and complication rates of patients who receive rFVIIa for uncontrolled bleeding after cardiac surgery have been reported to range from 19% to 40%, but these studies lacked

a control group for comparison.^{95–99} The rates of serious adverse events in 51 patients receiving rFVIIa for life-threatening bleeding after cardiac surgery were not higher than those of propensity-matched controls.¹⁰⁰ In a multicenter study, Gill et al.⁹⁵ randomized patients with life-threatening bleeding after cardiac surgery to receive in a double-blind design either placebo ($n = 68$), 40 mcg/kg rFVIIa ($n = 35$), or 80 mcg/kg rFVIIa ($n = 69$). Compared with the placebo group, fewer patients receiving rFVIIa underwent reoperation for bleeding ($P = 0.03$) or required allogeneic transfusions ($P = 0.01$). There were more serious adverse events in patients receiving rFVIIa than in those receiving placebo (placebo, 7%; 40 mcg/kg rFVIIa, 14%, $P = 0.25$; 80 mcg/kg rFVIIa, 12%, $P = 0.43$). The odds ratio (95% CI) for a serious adverse event in patients receiving 40 mcg/kg rFVIIa, 80 mcg/kg rFVIIa, and both rFVIIa combined was 2.16 (0.58 to 8.12), 1.61 (0.50 to 5.25), and 1.67 (0.50 to 5.47), respectively. Nonetheless, this study was underpowered to accurately assess the risk for serious adverse events from rFVIIa administration. Furthermore, patients receiving rFVIIa were older, had longer duration of CPB, and received more transfusions before randomization. Thus, before using rFVIIa in patients with life-threatening bleeding after cardiac surgery, one must balance the potential benefits of avoiding events associated with poor outcome (e.g., massive blood transfusion, mediastinal re-exploration for bleeding) against the unknown safety of the compound.

ACUTE MECHANICAL CIRCULATORY SUPPORT

Several mechanical options are available to support the circulation of patients with cardiogenic shock, including an intraaortic balloon pump (IABP), percutaneous extracorporeal membrane oxygenation (ECMO), and left ventricular assist devices (LVAD). Insertion of an IABP in patients with acute MI and cardiogenic shock may decrease mortality, particularly when early myocardial revascularization is performed.^{101–103} Although it decreases left ventricular preload and after-load, an IABP may not preserve left ventricular myocardial mass.^{104,105}

Circulatory Support with Extracorporeal Membrane Oxygenation

The clinical use of ECMO was first described for treating patients with acute respiratory distress syndrome.^{106,107} Initially, use of this application with the then commonly used CPB film or bubble oxygenators was limited by problems such as hemolysis and platelet consumption.¹⁰⁸ These limitations were somewhat overcome with the introduction of the silicone membrane oxygenator.¹⁰⁹ Gas transfer with the latter is across a solid, flat woven membrane that is sealed at the edges to allow blood to flow over an envelope containing gases. These membranes are suitable for long-term use because they have high biocompatibility. However, silicone membranes have rather inefficient gas exchange and so require a large surface area, large priming volume, long duration for priming, a high pressure gradient, and high resistance to flow.¹⁰⁹ These limitations led to the development of hollow-fiber polypropylene microporous oxygenators that have more efficient gas exchange, smaller surface area, require less priming volume, and require a lower pressure gradient. Leakage of plasma proteins across the microporous membrane diminishes oxygen transport, limiting the duration of use of these oxygenators to <6 to 8 h.¹¹⁰

More recently, polymethylpentene oxygenators have been introduced for ECMO that overcome plasma leakage associated with polypropylene oxygenators.¹¹¹ These oxygenators are microporous sheets rather than hollow fibers, are easy to prime, have high gas exchange efficiency, and high biocompatibility similar to that seen with silicone oxygenators. Early experience with polymethylpentene oxygenators supports their suitability for long-term ECMO support.^{112,113}

The exact device used for ECMO depends on short-notice availability. Simplified cardiopulmonary support system (CPS) ECMO devices are often kept assembled but not primed for rapid deployment. These devices include a centrifugal pump and are composed of a microporous hollow polypropylene fiber oxygenator similar to those used during CPB.

The clinical use of bedside ECMO has been most thoroughly evaluated for patients with pulmonary failure.¹⁰⁸ There are no data from randomized trials that have evaluated the use of ECMO for management of patients with cardiogenic shock. A meta-analysis of 11 clinical series and nine case reports involving 135 adult patients receiving ECMO after cardiac arrest, though, reported survival to hospital discharge in 56% of patients 17 to 40 years old compared with 9% survival in patients >67 years.¹¹⁴ In another series of 975 patients, survival to discharge, 30-day survival, and 1-year survival were higher for patients who received ECMO ($n = 59$) after 10 min of cardiopulmonary resuscitation (CPR) than for propensity-matched controls who received only CPR ($n = 113$).¹¹⁵ Using data gathered from 116 member centers of the Extracorporeal Life Support Organization registry, Thiagarajan et al.¹¹⁶ reported that of 295 adult patients who underwent ECMO after cardiac arrest, 27% survived to hospital discharge. In contrast, a survey of outcomes from 14,720 cardiac arrests showed survival after in-hospital CPR to be 17%.¹¹⁷ Factors associated with survival after ECMO-supported CPR based on multivariate logistic regression analysis were acute myocarditis (OR, 0.18; 95% CI, 0.05 to 0.69) and use of percutaneous cannulation techniques (OR, 0.42; 95% CI, 0.21 to 0.87).

Circulatory Support with Percutaneous Left Ventricular Assist Devices

Insertion of a LVAD in patients with cardiogenic shock restores systemic perfusion and reduces systemic inflammation that accompanies and aggravates poor left ventricular function.^{102,118} Several case series have shown improved in-hospital survival with an aggressive strategy that includes LVAD insertion with early revascularization.^{102,118} LVADs can be inserted either surgically or percutaneously. Experience with the former is widespread in most busy cardiac surgical centers, but percutaneous LVAD (pLVAD) is being used increasingly and offers the advantage of prompt insertion and early restoration of hemodynamics and organ perfusion.

Three pLVADs are approved for use in the U.S.: the TandemHeart (Cardiac Assist, Inc., Pittsburgh, PA; Fig. 1) and the Impella LP 2.5 and Impella LP 5.0 (Abiomed, Danvers, MA; Fig. 2). The TandemHeart device provides circulatory support through a 21F venous cannula inserted trans-septally into the left atrium. It returns oxygenated blood via the femoral artery by using a centrifugal pump^{102,119} and provides a flow of 4.0 L/min. The Impella Recover LP 2.5 system is an axial rotary pump mounted on a catheter with 4.0 mm external diameter that is placed across the aortic valve via a retrograde arterial approach.¹⁰² The pump outlet and motor are positioned in the aorta. The Impella LP 5.0 pump has a diameter of 7.3 mm at its outflow and diameter of 6.3 mm for the portion positioned in the heart. The Impella pump is controlled by a microelectric motor at a maximal flow of 2.5 L/min for the LP 2.5 and 5.0 L/min for the LP 5.0 device.

Preliminary use of the TandemHeart has been reported in a small, single-center case series.^{119–122} In a retrospective analysis of data from 18 patients who developed cardiogenic shock after MI, the TandemHeart was used for an average of 4 ± 3 days and achieved a mean flow of 3.2 ± 0.6 L/min. Cardiac index improved from 1.7 ± 0.3 L/min/m² before insertion to 2.4 ± 0.6 L/min/m² after pLVAD insertion ($P < 0.001$). The 30-day mortality rate was 44%.¹¹⁹ Limb ischemia was reported in 15% of patients.¹⁰² In a multicenter study, patients with cardiogenic shock from MI or cardiac heart failure were randomized to treatment with an IABP ($n = 14$) or the TandemHeart ($n = 19$).¹²³ The mean duration of support was 2.5 days.

Compared with patients with an IABP, those receiving the TandemHeart had higher cardiac index and mean arterial blood pressure and lower pulmonary capillary wedge pressure.

Thiele et al.¹²⁴ randomized patients who were undergoing PCI because of post-MI cardiogenic shock to either IABP ($n = 20$) or pLVAD support with the TandemHeart ($n = 21$). The primary outcome measure, cardiac power index, was improved by pLVAD support from 0.22 (IQ range, 0.19 to 0.30) to 0.37 W/m² (IQ range, 0.30 to 0.47, $P < 0.001$). In the IABP group, cardiac power index increased from 0.22 (IQ range 0.18 to 0.30) to 0.28 W/m² (IQ range, 0.24 to 0.36, $P = 0.02$ but $P = 0.004$ compared with pLVAD). Severe bleeding ($n = 19$ vs $n = 8$, $P = 0.002$) and limb ischemia ($n = 7$ vs $n = 0$, $P = 0.009$) were more common in the pLVAD group, but 30-day mortality was similar (IABP 45% vs pLVAD 43%, log-rank, $P = 0.86$). The mean duration of support was 2.5 days.

The feasibility of the Impella Recover LP 2.5 system was examined in a series of 19 high-risk patients undergoing PCI.¹²⁵ Maximal support was for 120 min, and the device was removed after the procedure. The Impella LP 5.0 has been used in patients with ventricular failure after cardiac surgery, after MI, and in patients with cardiomyopathy or myocarditis.^{126–128} Seyfarth et al.¹¹⁵ prospectively randomized 26 patients with cardiogenic shock to receive either an IABP ($n = 13$) or Impella Recover LP 2.5 pLVAD ($n = 12$). Cardiac index after 30 min of support was increased in patients with the Impella LP2.5 compared with patients who received the IABP (increase 0.49 ± 0.46 L/min/m² vs 0.11 ± 0.31 L/min/m², $P = 0.02$). Overall 30-day mortality was 46% in both groups. While these studies show the feasibility of using both pLVAD systems, the small sample size precludes an assessment of safety and efficacy.

The general indications for pLVAD placement include 1) providing temporary support of severe, reversible left ventricular failure until revascularization or recovery, 2) providing temporary support for high-risk PCI when there is a large area of at-risk myocardium, and 3) bridging support to permanent LVAD or heart transplantation.¹²⁹ Relative contraindications are severe right ventricular failure, severe peripheral vascular disease, and coagulopathy.

Perioperative Considerations

Arterial and venous cannulation for ECMO can be percutaneous or via a cut-down such as of the femoral vessels. Anticoagulation for ECMO by a silicone oxygenator is usually targeted to an activated clotting time (ACT) in the range of 200 s. Complications of ECMO include air embolism, coagulation and platelet consumption leading to bleeding and blood transfusion, stroke, infection, and multiorgan failure leading to death.¹⁰⁸

In contrast, ECMO that is performed via a CPS system that uses a CPB-type oxygenator requires full anticoagulation. For pLVADs, the goal of anticoagulation is an ACT >250 s during device insertion and >200 s during support. Physical examination and checking the pulse by palpation or with Doppler methods is required at least hourly.

Clinical management of patients receiving ECMO has been previously reviewed.¹⁰⁸ Bloodflow with ECMO and CPS is set to achieve normotension, normal pH, and satisfactory oxygen saturation. This is typically achieved with a pump flow of 50 to 80 mL/kg/min and a sweep gas flow of 50 to 80 mL/kg/min at an $F_{I}O_2$ of 1.0. When venous-arterial ECMO is used, lung ventilation can be minimized to limit peak inspiratory pressure to <25 cmH₂O.

Special perioperative considerations with the TandemHeart include monitoring of the left atrial cannula with transesophageal echocardiography (Fig. 3). Displacement of the cannula into the right atrium results in a right-to-left shunt and systemic perfusion with deoxygenated blood. An assessment of the abdominal aorta and iliac and femoral arteries

should be considered to exclude arterial atherosclerosis or stenosis before placement of the Impella device. Echocardiography should be used to exclude left ventricular thrombus and to examine the aortic valve for abnormalities and aortic valve regurgitation. Monitoring the position of the Impella device with transesophageal echocardiography is necessary to ensure correct positioning and to monitor for aortic regurgitation (Fig. 4). Because of the high-speed rotary pump, hemolysis can occur with the Impella Recover LP 2.5 or 5.0, usually within the first 24 h. Weaning can be considered when the cardiac index is >2.0 L/min/m², the mean arterial blood pressure is >70 mmHg, there is minimal inotropic support, and there is no evidence of end-organ hypoperfusion.

CONCLUSIONS

The aggressive use of antiplatelet and antithrombotic drugs has improved outcomes in patients presenting with NSTEMI or STEMI. However, for those patients who proceed to emergency cardiac surgery, mortality has remained high, and perioperative management is complex. To achieve maximal benefit, antiplatelet and antithrombotic drugs are given before coronary anatomy is known and before the risk of proceeding to surgery has been defined. For patients who do proceed to surgery, strategies to minimize bleeding include stopping the anticoagulation therapy and considering platelet/coagulation factor transfusion or rFVIIa administration for refractory bleeding. Mechanical hemodynamic support has emerged as an important option for patients in cardiogenic shock who proceed to surgery. For these patients, perioperative considerations include maintaining appropriate anticoagulation, ensuring appropriate device flow, and periodically verifying correct device placement. Future directions of research will seek to optimize the balance between reducing myocardial ischemic risk with antiplatelet and antithrombotics versus the higher rate perioperative bleeding by better risk-stratifying surgical candidates and by assessing the effectiveness of newer reversible drugs. The effect of mechanical hemodynamic support on long-term patient outcomes needs more stringent analysis.

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Appendix Summary of Clinical Implications of Recommended Antiplatelet and Antithrombotic Drugs for Acute Coronary Artery Syndromes

Antiplatelet Drugs

Drug

Aspirin

Mechanism of Action

- Irreversibly inhibits cyclooxygenase-1 interrupting platelet activation via prostaglandin pathway.

Perioperative Considerations

- Preoperative aspirin lowers the risk for MI, improves saphenous vein graft patency, and improves survival after CABG surgery

Recommendations for Drug Withdrawal before Cardiac Surgery

- There is minimal increased risk for perioperative bleeding and transfusion when aspirin is continued until the time of surgery

Drugs

Clopidogrel, Prasugrel, and Ticagrelor

Mechanism of Action

- Inhibition of platelet ADP-P2Y₁₂ receptor activation.
- Clopidogrel is a pro-drug that requires a 2-step liver CYP isoenzyme-dependent activation.
- Polymorphisms involving CYP enzymes and CYP inhibitors such as proton pump inhibitors may reduce platelet inhibition.
- Clopidogrel characterized by slow onset and variable effect with inadequate clinical response in 15% to 30% of patients.
- Clopidogrel 75 mg and 600 mg requires 5 days and 8 hrs, respectively, for 50% platelet inhibition.
- Prasugrel provides more consistent and greater platelet inhibition than clopidogrel. 1–3 Prasugrel is a pro-drug but there is no measurable variability in the activating enzymes.
- Clopidogrel and prasugrel are irreversible P2Y₁₂ receptor blockers.
- Ticagrelor is a reversible P2Y₁₂ receptor blocker.

Perioperative Considerations

- Dual therapy with aspirin and clopidogrel is associated with higher rates of bleeding, blood transfusion, mediastinal re-exploration, longer tracheal intubation, and hospitalization for patients who continue therapy within 5 days of CABG surgery.
- Clopidogrel may also be associated with a higher risk of infection after CABG surgery.
- Bleeding risk higher with prasugrel than clopidogrel
- Whether ticagrelor lowers the risk of perioperative bleeding compared with clopidogrel or prasugrel for patients undergoing CABG surgery is not yet established.

Recommendations for Drug Withdrawal before Cardiac Surgery

- Clopidogrel should be stopped 5 to 7 days before surgery.
- Prasugrel should be stopped at least 7 days before surgery.
- Duration for withdrawal of ticagrelor is not yet established. In vitro studies suggest that ticagrelor should be stopped 72 hrs before surgery.

Drugs

Abciximab, Tirofiban and Eptifibatide

Mechanism of Action

- GP IIb/IIIa receptor inhibition blocking fibrinogen binding and platelet aggregation.
- Tirofiban and eptifibatide are competitive receptor inhibitors.
- Abciximab is a human/murine monoclonal antibody to the GP IIb/IIIa receptor that nearly irreversibly blocks the receptor.

Perioperative Considerations

- Return to 50% GP IIb/IIIa receptor inhibition after abciximab treatment requires nearly 12 h after stopping the drug.
- Therapy with any agent can result in major bleeding and thrombocytopenia
- Tirofiban and eptifibatide have a half-life of ~ 2 hrs

Recommendations for Drug Withdrawal before Cardiac Surgery

- Discontinue tirofiban or eptifibatide 4 hrs before surgery.

Anti-Thrombotic Drugs

Drug

Unfractionated Heparin

Mechanism of Action

- Bovine and porcine sources
- Indirectly inhibits thrombin by first binding to anti-thrombin.

Perioperative Considerations

- Clinical use easily monitored with PTT and ACT
- Reversal with protamine
- Prolonged infusion can result in reduction in anti-thrombin activity
- Heparin induced thrombocytopenia with/without thrombosis
- Does not effectively blocks thrombin that is bound to thrombus (“clot bound thrombin”)

Recommendations for Drug Withdrawal before Cardiac Surgery

- Varies between institutions but infusions commonly continued until the time of surgery.

Drug

Enoxaparin

Mechanism of Action

- Low molecular weight heparin (LMWH) are $\leq 5,000$ -Dalton fragments of unfractionated heparin)
- Require antithrombin to inhibit thrombin

- Inhibits activated Factor X and thrombin (anti-factor Xa/IIa ratio ranges from 1.9 to 3.8).
- Better bioavailability than unfractionated heparin; subcutaneous administration.
- Less platelet activation and sensitization than unfractionated heparin.
- Excreted by the kidneys necessitating dose adjustment in the presence of renal impairment

Perioperative Considerations

- Partial thromboplastin time is insensitive to therapeutic doses.
- Measuring anti-factor Xa activity should be considered.
- Protamine may reverse 60% of the effect of LMWH.
- In presence of bleeding, 1 mg protamine can be given for each 100 anti-factor Xa units if LMWH was given within 8 hrs

Recommendations for Drug Withdrawal before Cardiac Surgery

- Discontinue enoxparin 12 to 24 hrs before surgery.

Drugs

Bivalirudin, Lepirudin, Argatroban, Dabigatran

Mechanism of Action

- Direct thrombin inhibitors blocking thrombin's ability to convert fibrinogen to fibrin, activate coagulation factors XI, X, and XII, and platelets.
- Bivalirudin is a 20-amino acid synthetic peptide with a half-life of 25 min (determined by proteolysis and renal clearance).

Perioperative Considerations

- No direct antagonist, thus, the continued use increases the risk for perioperative bleeding
- Bivalirudin most commonly used direct thrombin inhibitor
- The short half-life of bivalirudin may allow for clearance of the drug in all patients except for those with renal dysfunction.
- Bivalirudin is cleared by proteolysis and kidneys; half-life approximately 25 min.
- Dabigatran is orally active direct thrombin inhibitor.

Recommendations for Drug Withdrawal before Cardiac Surgery

- Bivalirudin should be stopped > 3 hrs before surgery
- Argatroban should be stopped 4 hrs before surgery
- Lepirudin should be stopped 10 hrs before surgery

Drug

Fondaparinux

Mechanism of Action

- Synthetic pentasaccharide inhibits activated factor X (factor Xa inhibitor)
- Dose independent clearance and long half-life more predictable than direct thrombin inhibitors.
- Fixed dose and subcutaneous administration.
- No effect on thrombin that is already formed that may contribute catheter thrombus during PCI.
- Not reversed with protamine.

Perioperative Considerations

- Major perioperative bleeding can occur but the risk is lower than with enoxaparin.

Recommendations for Drug Withdrawal before Cardiac Surgery

- Discontinue fondaparinux 24 hrs before CABG surgery.

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Figure 1.

Figure 1.

Diagram of Tandem Heart device (Cardiac Assist, Inc., Pittsburgh, PA). Pulmonary venous drainage is from the left atrium via a cannula inserted through the right atrium and then advanced across the atrial septum. Arterial outflow is from an external centrifugal pump via the femoral artery. Reprinted with permission from Thiele et al. *Circulation* 2001;104:2917 to 2922¹¹⁹

Figure 2.

Picture of Impella LP 2.5 (Abiomed, Danvers, MA) device. The distal end of the catheter is advanced in a retrograde approach from the femoral artery through the aortic valve into the left ventricle. The inflow inlet of the rotary pump is positioned in the left ventricle while the outflow orifice is positioned in the ascending aorta. Bloodflow of 2.5 L/min and 5.0 L/min can be achieved with the LP2.5 and LP 5.0 devices, respectively. Reprinted with permission from Valgimigli et al. *Catheter Cardiovasc Interv* 2005;65:263 to 267.¹³⁰

Figure 3.

Figure 3. Intraoperative transesophageal echocardiographic image of inflow cannula of the TandemHeart positioned across the atrial septum into the left atrium. Reprinted with permission from Pretorius et al. *Anesth Analg* 2006;103:1412 to 1413.¹³¹

Figure 4. Transesophageal echocardiography image of Impella percutaneous left ventricular assist device (labeled 1) placed across the aortic valve (arrow) into the left ventricle (LV). LA = left atrium; RV = right ventricle. Reprinted with permission Intensive Care Med 2006;32:329 to 33.¹³²

Table 1

Summary of recommendations for the use of antiplatelet and antithrombotic agents for patients with acute coronary syndromes.^{10,12}

Condition	Recommendation Level	
	Class I	Class IIa
Unstable Angina/Non-ST Segment Elevation MI	<p>Aspirin with either clopidogrel or an IV GP IIb/IIIa inhibitor before angiography</p> <p>Abciximab is the choice for GP IIb/IIIa therapy only if there is no delay to angiography and PCI is likely; otherwise, IV eptifibatide or tirofiban is the preferred choice of GP IIb/IIIa inhibitor</p>	<p>Both clopidogrel and an intravenous GP IIb/IIIa inhibitor.</p> <p>Upstream GP IIb/IIIa antagonist can be omitted before angiography if bivalirudin is selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 h earlier</p> <p>Anticoagulant therapy should be added to antiplatelet therapy as soon as possible after presentation. Regimens with established efficacy include enoxaparin and UFH (<i>Level of evidence: A</i>) and bivalirudin and fondaparinux (<i>Level of Evidence B</i>).</p>
Initial <i>conservative</i> strategy	Clopidogrel should be added to ASA and anticoagulant therapy as soon as possible after admission	<p>In setting of recurrent ischemia with clopidogrel, aspirin, and anticoagulant therapy, it is reasonable to add a GP IIb/IIIa antagonist before diagnostic angiography.</p> <p>Regimens that use either enoxaparin or UFH (<i>Level of Evidence: A</i>) or fondaparinux (<i>Level of Evidence: B</i>) have established efficacy. For patients at increased risk of bleeding, fondaparinux is preferable.</p> <p>Enoxaparin or fondaparinux are preferable to UFH unless CABG is planned within 24 h.</p>
ST Segment Elevation MI	<p>If PCI is planned, 300 to 600 mg of clopidogrel or prasugrel 60 mg should be given as soon as possible before primary PCI.</p> <p>For non-primary PCI,</p> <ol style="list-style-type: none"> If the patient has received fibrinolytic therapy and has been given clopidogrel, clopidogrel should be continued (<i>Level of Evidence: C</i>); If the patient has received fibrinolytic therapy without a thienopyridine, a loading dose of 300 to 600 mg of clopidogrel should be given (<i>Level of Evidence: C</i>); If the patient did not receive fibrinolytic therapy, either a loading dose of 300 to 600 mg of clopidogrel should be given or, once the coronary anatomy is known and PCI is planned, a loading dose of 60 mg of prasugrel should be 	<p>Treatment with GP IIb/IIIa receptor antagonists abciximab (<i>Level of Evidence B</i>), tirofiban (<i>Level of Evidence B</i>), or eptifibatide (<i>Level of Evidence: B</i>) at the time of PCI (with or without stenting) in selected patients with STEMI</p>

Condition	Recommendation Level	
	Class I	Class IIa
PCI	given promptly and no later than 1 h after the PCI (<i>Level of Evidence: B</i>).	
	For primary PCI in patients receiving ASA and a thienopyridine, supportive anticoagulant regimens include continued UFH; adjust dose to maintain therapeutic activated clotting time levels, taking into account whether GP IIb/IIIa receptor antagonists have been administered.	
	Bivalirudin is useful for primary PCI with or without prior treatment with UFH.	
	Bivalirudin anticoagulation is reasonable for patients at high risk for bleeding (<i>Level of Evidence: B</i>).	
	Patients receiving a drug eluting stent: clopidogrel 75 mg daily should be given for at least 12 months	
	Patients receiving a bare metal stent clopidogrel should be given for a minimum of 1 month and ideally up to 12 months	
	In patients taking a thienopyridine in whom CABG is planned and can be delayed, it is recommended that the drug be discontinued to allow for dissipation of the antiplatelet effect. (<i>Level of Evidence: C</i>) The period of withdrawal should be at least 5 days in patients receiving clopidogrel (<i>Level of Evidence: B</i>) and at least 7 days in patients receiving prasugrel (<i>Level of Evidence: C</i>), unless the need for revascularization and/or the net benefit of the thienopyridine outweighs the potential risks of excess bleeding (<i>Level of Evidence: C</i>).	
	In STEMI patients with a prior history of stroke and transient ischemic attack for whom primary PCI is planned, prasugrel is not recommended as part of a dual-antiplatelet therapy regimen. (<i>Level of Evidence: C</i>)	

PCI: percutaneous coronary artery intervention; CABG=coronary artery bypass graft; GP=glycoprotein; NSTEMI=non-ST segment elevation myocardial infarction; PCI= percutaneous coronary intervention; MI = myocardial infarction; STEMI=ST elevation myocardial infarction; UFH=unfractionated heparin; GP=glycoprotein; NSTEMI=non-ST segment elevation myocardial infarction; UFH=unfractionated heparin. Recommendation Classification: Class I: benefits >>> risk; Class II: benefits >> risk; Class III: benefits > risk. Level of Evidence A: data derived from multiple prospectively randomized, double-blind, placebo controlled trials; Level of Evidence B: Data from single randomized trial or non-randomized trials; Level C: expert opinion, case series; standard of care.^a

^ahttp://www.americanheart.org/downloadable/heart/1279224109481Methodology_Manual%206.2010.pdf

Prospectively randomized, controlled, blinded trials evaluating major outcomes for patients receiving P2Y₁₂ receptor antagonist for acute coronary artery syndromes. Main outcomes of the study are summarized and those that were positive for the intervention versus control arms are shaded in blue. Studies in which bleeding events were higher in the intervention arm than control arm are shaded in red. Note that specific definitions of bleeding for each analysis are summarized in the relevant column while definitions arising from the Thrombolysis in Myocardial Infarction (TIMI) trial¹⁶ and the Global Utilization of Streptokinase and t-PA for Occluded coronary arteries (GUSTO) trial¹⁷ are summarized at the bottom of the Table.

Table 2

Trial	Condition	Agent	n	Main Outcome	Bleeding Events
CURE ²¹ 2001	ACS/NSTEMI Approximately 20% of patients underwent revascularization. Less than 2% received thrombolytic therapy.	Clopidogrel vs. placebo Clopidogrel for 3–12 months. All patients received aspirin.	1256	Clopidogrel treatment led to a decreased primary outcome compared to placebo (9.3% vs 11.4%; RR, 0.72, 95% CI, 0.57–0.90, P<0.001). <i>Primary outcome: composite of cardiovascular deaths, MI, or stroke.</i>	Significantly more CURE major bleeding in clopidogrel arm, but equivalent life-threatening bleeding compared with placebo. <i>CURE major bleeding: substantially disabling bleeding, intraocular bleeding leading to loss of vision, or bleeding requiring at least 2 units of blood.</i> <i>CURE life threatening bleeding: fatal bleeding episode, decrease in hemoglobin of >5g/dl, hypotension requiring inotropes, surgical exploration, symptomatic intracranial hemorrhage, or transfusion of >4 units of blood.</i>
CURE CABG ²³ 2004	ACS/NSTEMI Patients are the subset of the CURE trial, who underwent CABG during initial hospitalization. The median duration before surgery after randomization was 12 days (IQ range, 8–19 days).	Clopidogrel vs. placebo All patients received aspirin.	1013	Clopidogrel treatment led to a non-significant decrease in the primary outcome compared to placebo (14.5% vs 16.2%; RR, 0.89; 95% CI, 0.71 to 1.11). Benefits of clopidogrel were due mainly to decrease in primary outcome in the pre-surgery period . <i>Primary outcome: composite of cardiovascular deaths, MI, or stroke.</i>	There was a non-significant trend towards more bleeding in the clopidogrel group vs. placebo. (9.6% vs. 7.5% RR 1.27, 95% CI, 0.96–1.69, P=0.095) For patients who stopped the drug <5 days before CABG surgery, 9.6% of clopidogrel patients and 6.3% of placebo patients experienced major bleeding (P=0.06). The need for re-exploration also trended higher when clopidogrel was continued <5 days before surgery (RR 1.79, 95% CI, 0.85–3.74). For patients who stopped the drug ≥5 days before surgery, there was no difference in the rates of major bleeding (clopidogrel, 4.4% vs placebo, 5.3%) There was 1 additional life-threatening bleeding event in patients undergoing CABG surgery per 1000 treated patients.
Clarity TIMI 28 2005 ²⁴	STEMI All patients were scheduled for angiography 2–8 days after randomization and study drug administration.	Clopidogrel vs. placebo All patients received a fibrinolytic, aspirin, and when appropriate, heparin. Unless clinically indicated, GIIIBIIA was permitted only after angiography.	3491	Clopidogrel treatment led to decreased primary endpoint compared to the placebo group. (15% vs 21.7%; P<0.001). At 30 days, clopidogrel treatment decreased secondary endpoint by 20% (14.1% vs 11.6%, P=0.02) <i>Primary endpoint: Composite of occluded infarct-related artery at angiography or death or recurrent MI before angiography</i> <i>Secondary endpoint: At 30 days, composite of death from cardiovascular causes, recurrent MI, or recurrent ischemia requiring revascularization</i>	No difference in rates of TIMI major or minor bleeding through the day after angiography. At 30 days, no difference between rates of TIMI major or minor bleeding. Among patients who underwent CABG (n=136), no difference in rates of TIMI major or minor bleeding at 30 days.
COMMIT Collaborative Group ²² 2005	STEMI Patients scheduled for primary PCI were	Clopidogrel vs. placebo All patients received aspirin. Fibrinolytics	45,852	Clopidogrel treatment led to a decreased primary endpoint compared with placebo (9.2% vs 10.1%; P=0.002) or 9 fewer	No difference in the rate of COMMIT life-threatening bleeding for patients receiving clopidogrel versus aspirin (0.58% vs 0.55%, respectively; P=0.59).

Trial	Condition	Agent	n	Main Outcome	Bleeding Events
	excluded. Overall ~ 3% underwent elective PCI.	could be used pre- randomization. Other anti-platelet medication was avoided, unless clinically indicated.		events per 1000 patients treated for 2 weeks. Clopidogrel treatment also led to a decreased co-primary endpoint of all-cause mortality during treatment period. (7.5% vs. 8.1%, $P=0.03$) <i>Primary endpoint: composite of death, reinfarction, or stroke</i>	Rates of bleeding between treatments no different in patients > 70 years or in those receiving fibrinolytic. <i>COMMIT life-threatening bleeding: Composite of bleeding that required transfusion, fatal bleeding, and cerebral bleeding.</i>
Triton TIMI ²⁶ 2007	<u>NSTEMI</u> or <u>STEMI</u> Moderate or high risk patients who were scheduled for PCI	Prasugrel vs. Clopidogrel Study medication for 6– 15 months All patients received aspirin. ~66% of patients received heparin. ~55% of patients received GIIb/IIIa inhibitors	13,608	After an average of 14.5 months, prasugrel treatment led to a decreased primary outcome compared to clopidogrel (9.9% vs. 12.1%; HR, 0.81, 95% CI, 0.73 to 0.90; $P<0.001$). The superiority of prasugrel compared with clopidogrel was seen within 3 days of therapy. <i>Primary endpoint: composite of cardiovascular death, nonfatal MI, or stroke</i>	TIMI major bleeding was more common in patients receiving prasugrel compared with clopidogrel (2.4% vs 1.8%; HR, 1.32; 95% CI, 1.03 to 1.68; $P=0.03$). Fatal TIMI major bleeding was more common with prasugrel Higher rates of bleeding in patients who underwent CABG and were initially treated with prasugrel vs clopidogrel (13.4% vs 3.2%; HR, 4.73, 95% CI, 1.90– 11.82, $P<0.001$).
PLATO ²⁵ 2009	<u>NSTEMI</u> or <u>STEMI</u> ~64% of patients underwent PCI during study	Ticagrelor vs. Clopidogrel Study medication for 12 months All patients received aspirin and heparin. 26% of patients received GIIb/IIIa inhibitors Patients undergoing PCI after randomization received an additional dose of their study drug	18,624	After 12 months, ticagrelor treatment led to a decreased primary endpoint compared to clopidogrel (9.8% vs 11.7%; HR, 0.84, 95% CI, 0.77–0.92, $P<0.001$). Side effects with ticagrelor included ventricular pauses, ↑ uric acid levels, and ↑ creatinine. <i>Primary endpoint: composite of cardiovascular death, MI, or stroke</i>	No difference in the frequency of PLATO major bleeding between the ticagrelor and clopidogrel groups (11.6% vs 11.2%; $P=0.43$) or in frequency of TIMI major bleeding or PLATO major life-threatening bleeding. Ticagrelor was associated with more major bleeding not related to CABG surgery than clopidogrel (4.5% vs 3.8%, $P=0.03$) including more fatal intracranial bleeding, but there were fewer non-cranial fatal bleeds in the ticagrelor group. <i>PLATO major life-threatening bleeding: fatal bleeding, intracranial bleeding, cardiac tamponade, hypovolemic shock requiring inotropes, hemoglobin decrease >5g/dl, transfusion of >4 units PRBC PLATO major bleeding: bleeding that caused permanent significant disability, decrease in hemoglobin >3g/dl, or transfusion of 2–3 units blood.</i>

CABG=coronary artery bypass graft; CI=confidence interval; HR=hazard ratio; NSTEMI=non-ST segment elevation myocardial infarction; PCI=percutaneous coronary intervention; RR=relative risk;
STEMI=ST elevation myocardial infarction; IQ = interquartile; ACS = acute coronary syndrome; MI = myocardial infarction

TIMI Major Bleeding: Intracranial bleeding; overt bleeding with a decrease in hemoglobin > 5g/dl or a decrease in hematocrit >15%

TIMI Minor Bleeding: Spontaneous gross hematuria; spontaneous hematemesis; observed bleeding with decrease in hemoglobin > 3g/dl but < 15%.

Gusto Major Bleeding: Deadly bleeding; intracerebral bleeding; substantial hemodynamic compromise requiring treatment

Gusto Moderate Bleeding: Bleeding requiring transfusion

Gusto Minor Bleeding: Other bleeding not requiring transfusion or causing hemodynamic compromise.

Table 3

Prospectively randomized, controlled, blinded trials evaluating major outcomes for patients receiving glycoprotein IIb/IIIa receptor inhibitors for acute coronary artery syndromes. Main outcomes of the study are summarized and those that were positive for the intervention versus control arms are shaded in blue. Studies in which bleeding events were higher in the intervention arm than control arm are shaded in red. Note that specific definitions of bleeding for each analysis are summarized in the relevant column while definitions arising from the Thrombolysis in Myocardial Infarction (TIMI) trial¹⁶ and the Global Utilization of Streptokinase and t-PA for Occluded coronary arteries (GUSTO) trial¹⁷ are summarized at the bottom of the Table.

Trial	Condition	Agent	n	Main Outcome	Bleeding Events
impact II ⁴⁹ 1997	Patients undergoing PCI-elective or emergent.	High dose epifibatide vs. Low dose epifibatide vs. Placebo All patients received aspirin and heparin	4010	Low dose, but not high dose, epifibatide reduced the primary endpoint vs placebo. (9.1% vs 11.6%; P=0.035) <i>Primary endpoint: composite of death, MI, unplanned revascularization, or coronary stenting for abrupt closure</i>	Epifibatide did not increase TIMI major bleeding or rates of transfusion
CAPTURE ⁴⁷ 1997	UNSTABLE ANGINA Patients with refractory unstable angina, who had undergone angiograms, and were scheduled for angioplasty	Abciximab vs. Placebo Medication administered after angiography, before angioplasty. All patients received heparin and aspirin.	1265	At 30 days, abciximab significantly reduced the primary endpoint vs. placebo (11.3% vs 15.9%; P= 0.012) <i>Primary endpoint: composite of death, MI, or urgent intervention for recurrent ischemia</i>	The rate of TIMI major bleeding was higher in patients receiving abciximab versus placebo (3.8% vs 1.9%; P=0.043) Thrombocytopenia was more frequent in the abciximab group vs. placebo (5.6% vs. 1.3%)
PRISM PLUS ⁵⁰ 1998	UNSTABLE ANGINA/ NSTEMI 90% underwent angiograms with 30% receiving a percutaneous intervention and 23% undergoing CABG.	Tirofiban vs. UFH vs. Tirofiban + UFH All patients received aspirin.	1915	At 7 days, Tirofiban + UFH led to decreased primary outcome compared to UFH alone (12.9% vs 17.9%; RR 0.68; 95% CI 0.53-0.88; P= 0.004). This endpoint was also reduced at 30 days and 6 months. The study was stopped prematurely for the tirofiban group because of an excess of mortality compared to UFH <i>Primary outcome: composite of death, MI, or recurrent ischemia</i>	TIMI major bleeding trended to occur more frequently in patients receiving tirofiban + UFH vs. UFH alone (1.4% vs 0.8%; P= 0.23) Thrombocytopenia was infrequent and rapidly reversible upon cessation of study drug.
PURSUIT ⁵¹ 1998	ACUTE CORONARY SYNDROME Study designed to administer therapy as early as possible, i.e. within 24h of admission. <25% received PCI. <15% underwent CABG.	Epifibatide vs. Placebo Aspirin at discretion of treating physician. Heparin was recommended.	10948	Epifibatide reduced the primary outcome compared to placebo (14.2% vs 15.7%; P= 0.04) <i>Primary outcome: composite of death or MI by 30 days</i>	For patients receiving epifibatide versus placebo, there were increased rates of TIMI major bleeding (10.6% vs 9.1%; P=0.02) and GUSTO severe bleeding (1.5% vs 0.9%; P<0.001) There were more transfusions among patients receiving epifibatide versus placebo (11.6% vs 9.2%; RR 1.3; 95% CI 1.1-1.4) Patients undergoing CABG had increased bleeding, and accounted for 80% of the patients with major bleeding.
ESPRIT ⁴⁸ 2000	Patients scheduled for stent implantation, who would not routinely be treated with at GIIb/IIIa inhibitor.	Epifibatide vs. Placebo Study medication administered immediately before PTCA.	2064	Epifibatide treatment reduced the primary endpoint compared to placebo. (6.6% vs 10.5%; P= 0.0015) The secondary endpoint (primary endpoint at 30 days) was reduced in patients receiving epifibatide versus placebo (6.8% vs 10.5%; P=0.0034)	The rate of TIMI major bleeding was minimal overall, but was higher in patients receiving epifibatide (1.3% vs 0.4%; P=0.027) 2 cases of profound thrombocytopenia in the treatment group. They resolved spontaneously.

Trial	Condition	Agent	n	Main Outcome	Bleeding Events
ISAR-REACT 2 ⁴⁶ 2006	ACS/NSTEMI Patients undergoing PCI who had already received clopidogrel. 50% received a stent.	Abciximab plus UFH vs. Placebo with UFH. All patients received clopidogrel and aspirin.	2022	Abciximab treatment led to a decreased primary endpoint compared to placebo. (8.9% vs 11.9%; RR, 0.75; 95% CI, 0.58-0.97; P=0.03). <i>Primary endpoint: composite of death, MI, or urgent target vessel revascularization within 30 days</i>	No difference in the rate of TIMI major or minor bleeding or need for transfusion between treatment groups. Profound thrombocytopenia (platelet count < 20 × 10 ⁹ cells/L) more common in abciximab group compared with placebo group.
FINESSE ⁴⁴ 2008	STEMI Patients undergoing PCI <6h after onset of symptoms	Early abciximab + reteplase then PCI vs. Early abciximab then PCI vs. Abciximab at PCI vs. Abciximab received aspirin and either UFH or enoxaparin	2425	The primary outcome was not different for patients in the early abciximab + reteplase then PCI group, the early abciximab then PCI group, or abciximab at PCI groups (9.8%, 10.5%, and 10.7%, respectively, (P=0.55)). <i>Primary outcome: Composite of all cause mortality, ventricular fibrillation occurring more than 48 h after randomization, cardiogenic shock, and congestive heart failure at 90 days after randomization</i>	The rates of non-cranial TIMI major or minor bleeding were more common in the abciximab/reteplase then PCI compared with the abciximab at PCI group (14.5% vs 6.9%, P<0.001) and the early abciximab then PCI group compared with the abciximab at PCI group (10.1% vs 6.9%, P<0.05). This included higher rate of red blood transfusion in the abciximab/reteplase +PCI vs. abciximab at PCI group. There was no differences in the rate of thrombocytopenia.
EARLY-ACS ⁴⁵ 2009	ACS/NSTEMI Patients undergoing early invasive management strategy. ~60% underwent PCI. ~13% underwent CABG.	Early eptifibatide vs. Delayed provisional eptifibatide after angiography All patients received aspirin and heparin. Most patients received clopidogrel.	9492	The primary outcome was not different in the early versus delayed eptifibatide group (9.3% vs 10.0%; OR, 0.92; 95% CI, 0.80 to 1.06; P=0.23). <i>Primary outcome: composite of death, MI, recurrent ischemia requiring urgent revascularization, or thrombotic complication during PCI</i>	Early-eptifibatide group had higher rates of TIMI major bleeding (2.6% vs 1.8%; OR 1.42; 95% CI 1.07-1.89, P=0.02) No difference in GUSTO severe bleeding between groups. However, the early-eptifibatide group had more GUSTO moderate bleeding and more red-cell transfusions. No difference between groups in the rate of thrombocytopenia.

CI=confidence interval; MI=myocardial infarction; NSTEMI=non-ST segment elevation myocardial infarction; OR=odds ratio; PCI=percutaneous coronary intervention; RR=relative risk; STEMI=ST elevation myocardial infarction; UFH=unfractionated heparin; CABG = coronary artery bypass graft

TIMI Major Bleeding: Intracranial bleeding; overt bleeding with a decrease in hemoglobin > 5g/dl or a decrease in hematocrit >15%

TIMI Minor Bleeding: Spontaneous gross hematuria; spontaneous hematemesis; observed bleeding with decrease in hemoglobin > 3g/dl but < 15%.

Gusto Major Bleeding: Deadly bleeding; intracerebral bleeding; Substantial hemodynamic compromise requiring treatment

Gusto Moderate Bleeding: Bleeding requiring transfusion.

Gusto Minor Bleeding: Other bleeding not requiring transfusion or causing hemodynamic compromise.

Prospectively randomized, controlled, blinded trials evaluating major outcomes for patients receiving enoxaparin for acute coronary artery syndromes. Main outcomes of the study are summarized and those that were positive for the intervention versus control arms are shaded in blue. Studies in which bleeding events were higher in the intervention arm than control arm are shaded in red. Note that specific definitions of bleeding for each analysis are summarized in the relevant column while definitions arising from the Thrombolysis in Myocardial Infarction (TIMI) trial¹⁶ and the Global Utilization of Streptokinase and t-PA for Occluded coronary arteries (GUSTO) trial¹⁷ are summarized at the bottom of the Table.

Table 4

Trial	Condition	Agent	n	Main Outcome	Bleeding Events
"A to Z" Investigation ⁶⁹ 2004	ACS/NSTEMI ~60% of patients underwent PCI within 8 days	Enoxaparin + tirofiban vs. UFH + tirofiban All patients received aspirin.	3987	Enoxaparin was not inferior to UFH in terms of primary endpoint (8.4% vs 9.4%; HR, 0.88; 95% CI, 0.71–1.08). <i>Primary outcome: composite of death, MI, or refractory ischemia at 7 days.</i>	There was no difference in combined rates of TIMI major and minor bleeding. Increased rate of TIMI major bleeding in enoxaparin group from independent assessment (0.8% vs 0.2%; $P=0.01$). However this difference was not seen using investigator reported data. Use of enoxaparin was associated with 1 additional major bleeding episode for each 200 patients treated
SYNERGY trial ⁷⁰ 2004	ACS/NSTEMI High risk patients treated with early invasive strategy. ~47% underwent PCI.	Enoxaparin vs. UFH. All patients received aspirin. GIIb3A inhibitor use encouraged.	10,027	No difference in primary outcome between enoxaparin and UFH treated patients (14% vs 14.5%; OR, 0.96; 95% CI, 0.86–1.06). <i>Primary outcome: composite of all-cause mortality or nonfatal MI by 30 days</i>	Increased frequency of TIMI major bleeding with enoxaparin compared to UFH (9.1% vs 7.6%, $P=0.008$). Most of the increase in major bleeding was CABG-related ($P=0.08$).
EXTRACT-TIMI ²⁵ ⁶⁴ 2006	STEMI Patients who were scheduled for fibrinolysis. 23% underwent PCI.	Enoxaparin during hospitalization vs. UFH for at least 48 h. All patients received aspirin. Clopidogrel at physician's discretion	20,506	Enoxaparin treatment reduced the primary outcome compared to UFH (9.9% vs 12.0%; 17% reduction in relative risk, $P<0.001$. <i>Primary outcome: composite of death or nonfatal recurrent MI through 30 days.</i>	Increased TIMI major bleeding in the enoxaparin group compared to UFH (2.2% vs 1.4 %, $P<0.001$) The composite of death, nonfatal reinfarction, or nonfatal intracranial hemorrhage more common in patients treated with UFH compared with enoxaparin (12.2 % vs 10.1%, $P<0.001$).
PCI ExTRACT-TIMI ²⁵ ⁷¹ 2007	STEMI Patients in the ExTRACT-TIMI 25 trial who received fibrinolytic therapy and subsequently underwent PCI	Enoxaparin during hospitalization vs. UFH for at least 48 h. All patients received fibrinolytic therapy and aspirin. Clopidogrel at physician's discretion	4,676	Fewer patients receiving enoxaparin underwent PCI through 30 days than those receiving UFH (22.8% vs 24.2%; $P=0.027$). Among patients who underwent PCI by 30 days, enoxaparin treatment led to a decreased primary outcome compared to UFH (10.7% vs. 13.8%; 0.77 RR; $P<0.001$).	There were no differences in TIMI major bleeding in patients receiving enoxaparin versus UFH (1.4% vs 1.6%).

CI=confidence interval; HR=hazard ratio; MI=myocardial infarction; NSTEMI=non-ST segment elevation myocardial infarction; OR=odds ratio; PCI=percutaneous coronary intervention; RR=relative risk; STEMI=ST elevation myocardial infarction; UFH=unfractionated heparin; ACS = acute coronary syndrome

TIMI Major Bleeding: Intracranial bleeding; overt bleeding with a decrease in hemoglobin > 5g/dl or a decrease in hematocrit >15%

TIMI Minor Bleeding: Spontaneous gross hematuria; spontaneous hematemesis; observed bleeding with decrease in hemoglobin > 3g/dl but < 15%.

Gusto Major Bleeding: Deadly bleeding; intracerebral bleeding; Substantial hemodynamic compromise requiring treatment

Gusto Moderate Bleeding: Bleeding requiring transfusion.

Gusto Minor Bleeding: Other bleeding not requiring transfusion or causing hemodynamic compromise.

Table 5

Prospectively randomized, controlled, blinded trials evaluating major outcomes for patients receiving bivalirudin for acute coronary artery syndromes. Main outcomes of the study are summarized and those that were positive for the intervention versus control arms are shaded in blue. Studies in which bleeding events were higher in the intervention arm than control arm are shaded in red. Note that specific definitions of bleeding for each analysis are summarized in the relevant column while definitions arising from the Thrombolysis in Myocardial Infarction (TIMI) trial¹⁶ and the Global Utilization of Streptokinase and t-PA for Occluded coronary arteries (GUSTO) trial¹⁷ are summarized at the bottom of the Table.

Trial	Condition	Agent	n	Main Outcome	Bleeding Events
Bittle et al ⁷⁸ 1995	ACS Patients who were scheduled for urgent angioplasty	Bivalirudin vs. UFH All patients received aspirin. No clopidogrel administered	4098	Equivalent primary outcome in patients receiving bivalirudin versus UFH (11.4% vs 12.2%; OR 0.9; 95% CI 0.8–1.1; P=0.44) In the high-risk subgroup with postinfarction angina, the primary outcome was reduced in patients receiving bivalirudin versus UFH (9.1% vs 14.2%; OR 0.6; 95% CI 0.4–0.9; P=.04) <i>Primary endpoint: composite of death, MI, abrupt vessel closure, or rapid deterioration of cardiac origin</i>	Lower rates of major bleeding in patients receiving bivalirudin versus UFH (3.8% vs. 9.8%; OR 0.4; CI 0.3–0.5; P< .001 Lower rates of transfusion in patients receiving bivalirudin versus UFH (3.7% vs 8.6%; OR 0.4; 95% CI 0.3–0.6; P<0.001) In the high risk subgroup of patients with postinfarction angina, lower rates of major bleeding in patients receiving bivalirudin versus UFH (3% vs. 11.1%; OR 0.3; 95% CI 0.1–0.5; P< .001 .) <i>Major bleeding: decrease in hemoglobin >3g/dl, transfusion, intracranial bleeding, or retroperitoneal bleeding.</i>
REPLACE-2 trial ⁷⁴ 2003	Stable or unstable angina undergoing urgent or elective PCI	Bivalirudin +/- provisional GP IIb/IIIa inhibitor vs UFH heparin + GP IIb/IIIa inhibitor All patients received aspirin. 85% received clopidogrel.	6010	There was no difference in primary outcome between Bivalirudin +/- provisional GP IIb/IIIa inhibitor and UFH heparin + GP IIb/IIIa inhibitor (9.2% vs 10.0%; OR 0.92; 95% CI 0.77–1.09; P=0.32) <i>Primary outcome: composite of death, MI, or urgent repeat revascularization, or in-hospital major bleeding at 1 month</i>	Lower rates of major bleeding in the bivalirudin group versus the UFH group. (2.4% vs 4.1%; P < 0.001) <i>Major bleeding: intracranial, intraocular, or retroperitoneal hemorrhage, overt blood loss with decrease in hemoglobin < 3g/dl, decrease in hemoglobin >4g/dl, transfusion of 2 units PRBC.</i>
ACUTY trial ⁷⁶ 2006	ACS Moderate to high risk patients managed with early invasive strategy. 56% underwent PCI. ~10–12% underwent CABG	UFH/enoxaparin + GP IIb/IIIa inhibitor vs. Bivalirudin + GP IIb/IIIa inhibitor vs. Bivalirudin. All patients received aspirin. Clopidogrel was strongly encouraged.	13,819	At 30 days, bivalirudin + GP IIb/IIIa inhibitor was noninferior in terms of primary outcome to UFH + GP IIb/IIIa inhibitor, (7.7% and 7.3%, respectively). Bivalirudin alone was non-inferior to UFH + GP IIb/IIIa inhibitor for primary outcome (7.8% and 7.3%; RR, 1.08; 95% CI, 0.93–1.24; P=0.32). <i>Primary outcome: composite of death, MI, or unplanned revascularization for ischemia</i>	No difference in rates of major bleeding for patients receiving bivalirudin + GP IIb/IIIa inhibitor vs. UFH + GP IIb/IIIa inhibitor (5.3% and 5.7%). Bivalirudin alone was associated with less major bleeding than use of UFH + GP IIb/IIIa inhibitor (3.0% vs 5.7%; P<0.001; RR, 0.53; 95% CI, 0.43–0.65) <i>Major bleeding: within 25–35 days, occurrence of intracranial or intraocular bleeding, hemorrhage requiring intervention, hematoma >5cm, hemoglobin decrease >3–4g/dl, reoperation for bleeding, transfusion.</i>
HORIZONS-AMI ⁷⁷ 2008	STEMI High-risk patients scheduled to undergo primary PCI. 95% of patients who did undergo PCI received stents	Bivalirudin vs. UFH + GP IIb/IIIa inhibitor All patients received aspirin and clopidogrel/ticlopidine	3602	Bivalirudin treatment led to decreased primary outcome compared to UFH + GP IIb/IIIa inhibitor (9.2% vs 12.1%; RR, 0.76; 95% CI 0.63–0.92; P=0.005). Increased risk of acute stent thrombosis in patients receiving bivalirudin vs UFH + GP IIb/IIIa inhibitor.	Primary outcome difference between groups mainly due to lower rate of major bleeding in patients receiving bivalirudin vs UFH with GP IIb/IIIa inhibitor (4.9% vs 8.3%; RR, 0.60; 95% CI, 0.46–0.77; P<0.001) Decreased TIMI major bleeding for bivalirudin group (3.1% vs 5%; P=0.002), but no difference in severe bleeding using criteria from GUSTO trial.

Trial	Condition	Agent	n	Main Outcome	Bleeding Events
ISAR REACT 3 ⁷⁹ 2008	Stable or unstable angina undergoing PCI All patients were undergoing PCI (bare metal or DES)	Bivalirudin vs. UFH Patients received study medication immediately before the lesion was crossed by the guidewire during PCI All patients were pre-treated with aspirin and clopidogrel	4570	No difference in primary outcome between patients receiving bivalirudin versus UFH (8.3% vs 8.7%; RR 0.94; 95% CI 0.77–1.15; P = 0.57) <i>Primary outcome: composite of death, MI, urgent target vessel revascularization, major bleeding</i>	Decreased moderate, severe, and profound thrombocytopenia in bivalirudin group <i>Major bleeding: occurrence of intracranial or intraocular bleeding, hematoma >5cm, hemoglobin decrease >3–4g/dl, reoperation for bleeding, transfusion.</i> Decreased incidence of TIMI major bleeding in patients receiving bivalirudin versus UFH (3.1% versus 4.6%; RR 0.66; 95% CI 0.49–0.90; P=0.008)

CI=confidence interval; GP=glycoprotein; HR=hazard ratio; MI=myocardial infarction; PCI=percutaneous coronary intervention; RR=relative risk; STEMI=ST elevation myocardial infarction; UFH=unfractionated heparin; DES = drug eluting stent; ACS = acute coronary syndrome; CABG = coronary artery bypass graft

TIMI Major Bleeding: Intracranial bleeding: overt bleeding with a decrease in hemoglobin > 5g/dl or a decrease in hematocrit >15%

TIMI Minor Bleeding: Spontaneous gross hematuria; spontaneous hematemesis; observed bleeding with decrease in hemoglobin > 3g/dl but < 15%.

Gusto Major Bleeding: Deadly bleeding; intracerebral bleeding; Substantial hemodynamic compromise requiring treatment

Gusto Moderate Bleeding: Bleeding requiring transfusion.

Gusto Minor Bleeding: Other bleeding not requiring transfusion or causing hemodynamic compromise

Table 6

Prospectively randomized, controlled, blinded trials evaluating major outcomes for patients receiving fondaparinux for acute coronary artery syndromes. Main outcomes of the study are summarized and those that were positive for the intervention versus control arms are shaded in blue. Studies in which bleeding events were higher in the intervention arm than control arm are shaded in red. Note that specific definitions of bleeding for each analysis are summarized in the relevant column while definitions arising from the Thrombolysis in Myocardial Infarction (TIMI) trial¹⁶ and the Global Utilization of Streptokinase and t-PA for Occluded coronary arteries (GUSTO) trial¹⁷ are summarized at the bottom of the Table.

Trial	Condition	Agent	n	Main Outcome	Bleeding Events
OASIS-5 ⁸⁶ 2006	ACS In the hospital, 34 % of patients underwent PCI.	Fondaparinux vs. Enoxaparin All patients received aspirin. Patients undergoing catheterization received other standard treatments that included P2Y12 receptor blockers, GP IIb/IIIa inhibitors, or UFH (all not randomized).	20,078	Fondaparinux was noninferior to enoxaparin for reducing the primary outcome (5.8% vs 5.7%; HR 1.01; 95% CI, 0.90– 1.13). There were fewer deaths at 30 days (295 vs 352, P=0.02) and 180 days (574 vs 638, P=0.05) in fondaparinux-treated versus enoxaparin-treated patients. <i>Primary outcome: composite of death, MI or refractory ischemia at nine days</i>	Major bleeding at 9 days was lower with fondaparinux than with enoxaparin (2.2% vs 4.1%; HR, 0.52; P<0.001). This difference persisted in long-term follow-up. TIMI major bleeding and fatal bleeding were also significantly reduced in the fondaparinux group. <i>Major bleeding: >2 units of blood transfused, decrease in hemoglobin > 3g/dl, intracranial/ intraocular/retroperitoneal/fatal bleeding, or bleeding requiring surgical intervention</i>
OASIS-6 ⁸⁷ 2006	STEMI In the hospital, 37% of patients underwent PCI.	Fondaparinux vs. Usual care (placebo or heparin as clinically indicated) All patients received aspirin	12,092	Fondaparinux treatment led to decreased primary outcome compared to usual care (9.7% vs 11.2%; HR, 0.86; 95% CI, 0.77–0.96; P=0.008). Mortality was lower with fondaparinux therapy for patients receiving thrombolytic therapy (HR, 0.79; P=0.003) and those not receiving any reperfusion therapy (HR, 0.80; P=0.03). No benefit of fondaparinux was observed for patients undergoing PCI. <i>Primary outcome: composite of death or reinfarction at 30 days</i>	There was no difference in the incidence of TIMI major bleeding episodes in patients receiving fondaparinux versus usual care (P=0.13).

CI=confidence interval; GP=glycoprotein; HR=hazard ratio; MI=myocardial infarction; NSTEMI=non-ST segment elevation myocardial infarction; PCI=percutaneous coronary intervention; STEMI=ST elevation myocardial infarction; UFH=unfractionated heparin; ACS = acute coronary syndrome

TIMI Major Bleeding: Intracranial bleeding; overt bleeding with a decrease in hemoglobin > 5g/dl or a decrease in hematocrit >15%

TIMI Minor Bleeding: Spontaneous gross hematuria; spontaneous hematemesis; observed bleeding with decrease in hemoglobin > 3g/dl but < 15%.

Gusto Major Bleeding: Deadly bleeding; intracerebral bleeding; Substantial hemodynamic compromise requiring treatment

Gusto Moderate Bleeding: Bleeding requiring transfusion.

Gusto Minor Bleeding: Other bleeding not requiring transfusion or causing hemodynamic compromise.

Table 7

Summary of management strategies for coagulopathic bleeding after cardiac surgery.

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- Stop antiplatelet and antithrombotic agents
 - Consider off-pump coronary artery bypass graft surgery
 - Administer full-dose of heparin if cardiopulmonary bypass planned
 - Platelet transfusion
 - Fresh frozen plasma or factor concentrates when available
 - Consider off-label use of recombinant factor VIIa after full consideration of risk versus benefits.
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