



EDUCATIONAL OBJECTIVE: Readers will prescribe antiplatelet and anticoagulant therapy after acute coronary syndromes according to evidence-based guidelines

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Anticoagulation and antiplatelet therapy in acute coronary syndromes

ABSTRACT

Antiplatelet and anticoagulant drugs are the mainstay of treatment of acute coronary syndrome (ACS). The last 30 years have seen the development of various agents, a deeper understanding of the pathobiology of this disease, and an evolution in its treatment. We review the role of contemporary agents in ACS and highlight key clinical trials of these agents.

KEY POINTS

Although antiplatelet and anticoagulant drugs reduce the risk of ischemic events, including coronary death, they also increase the risk of bleeding, reducing their net benefit. But the risk of bleeding can be managed.

All patients experiencing an ACS should receive a single dose of aspirin 325 mg and should be instructed to chew it; this should be followed by 81 mg daily.

Patients who are not expected to undergo coronary artery bypass grafting on an urgent basis should also receive clopidogrel, prasugrel, or ticagrelor.

Glycoprotein IIb/IIIa inhibitors are being used less now than in the past.

The use of unfractionated heparin is being challenged by newer parenteral anticoagulants, ie, bivalirudin, enoxaparin, and fondaparinux.

The role of oral anticoagulants (warfarin, rivaroxaban, apixaban, and dabigatran) in ACS is uncertain.

ANTIPLATELET AND ANTICOAGULANT drugs are a cornerstone of the medical treatment of acute coronary syndrome (ACS), reducing the rates of both morbidity and death.¹⁻⁴ However, reductions in ischemic events with these drugs have uniformly been accompanied by increases in bleeding complications, which reduce the net benefit.⁵ Thus, clinical research has been exploring ways to maximize the benefit while minimizing the risk.

Here, we review the guidelines and evidence supporting the use of antiplatelet and anticoagulant drugs in ACS.

ACUTE CORONARY SYNDROMES WITH OR WITHOUT ST ELEVATION

A key distinction when treating ACS is whether the electrocardiogram shows ST-segment elevation. In cases of non-ST-elevation ACS (ie, unstable angina or non-ST-elevation myocardial infarction), a second key question is whether the initial strategy will be invasive (with angiography performed urgently) or conservative (with angiography performed later). In ST-elevation myocardial infarction, another distinction is how perfusion is to be restored, ie, with primary percutaneous coronary intervention or with thrombolysis. All these questions affect the choice of antiplatelet and anticoagulant therapy.

FIGURE 1 and FIGURE 2 summarize the guidelines of the American College of Cardiology Foundation and American Heart Association.^{1,2,6,7}

Drugs discussed in this article

abciximab (ReoPro)	enoxaparin (Lovenox)	protamine sulfate
apixaban (Eliquis)	eptifibatide (Integrelin)	rivaroxaban (Xarelto)
aspirin	fondaparinux (Arixtra)	ticagrelor (Brilinta)
bivalirudin (Angiomax)	heparin	tirofiban (Aggrastat)
clopidogrel (Plavix)	omeprazole (Prilosec)	warfarin (Coumadin)
dabigatran (Pradaxa)	prasugrel (Effient)	

Acronyms of trials discussed in this paper

- ACUITY**—The Acute Catheterization and Urgent Intervention Triage Strategy trial³²
- APPRAISE-2**—The second Apixaban for Prevention of Acute Ischemic Events trial⁵⁰
- ATLAS ACS 2-TIMI 51**—The Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome—Thrombolysis In Myocardial Infarction 51 trial⁴⁹
- ATOLL**—The Acute STEMI Treated With Primary PCI and Intravenous Enoxaparin or UFH to Lower Ischemic and Bleeding Events at Short- and Long-Term Follow-up trial⁴³
- CARS**—Coumadin Aspirin Reinfarction Study⁴⁷
- CHAMP**—The Combination Hemotherapy and Mortality Prevention study⁴⁸
- CLOVIS-2**—The second Clopidogrel and Response Variability Investigation Study¹⁸
- CURE**—The Clopidogrel in Unstable Angina to Prevent Recurrent Events trial¹⁶
- ESSENCE**—The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events trial⁴⁰
- EXTRACT-TIMI 25**—Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment—Thrombolysis in Myocardial Infarction 25 trial⁴²
- HORIZONS-AMI**—The Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction trial³⁵
- ISAR-REACT**—The Intracoronary Stenting and Antithrombotic Regimen—Rapid Early Action for Coronary Treatment trial³⁴
- ISIS-2**—The second International Study of Infarct Survival⁹
- OASIS-5**—The fifth Organization to Assess Strategies in Acute Ischemic Syndromes trial⁴⁴
- OASIS-6**—The sixth Organization to Assess Strategies in Acute Ischemic Syndromes trial⁴⁵
- PLATO**—The Platelet Inhibition and Patient Outcomes trial^{22,26}
- PURSUIT**—The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy trial³¹
- RE-DEEM**—The Randomized Dabigatran Etxilate Dose Finding Study in Patients With Acute Coronary Syndromes trial⁵¹
- SYNERGY**—The Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors trial⁴¹
- TRIOLOGY-ACS**—The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes trial²⁵
- TRITON-TIMI 38**—Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel—Thrombolysis in Myocardial Infarction 38²⁴
- WARIS II**—The second Warfarin, Aspirin, Reinfarction Study⁴⁶

ANTIPLATELET THERAPY

Aspirin for all

Aspirin irreversibly acetylates the enzyme cyclooxygenase-1, blocking intraplatelet formation of thromboxane A2 (FIGURE 3), a potent platelet aggregator and endothelial vasoconstrictor. Large clinical trials have confirmed that aspirin reduces morbidity and mortality rates by as much as 50% in patients with ACS.⁸

The **ISIS-2 trial**⁹ found that giving aspirin early in the emergency department significantly reduced the mortality rate.

The **Antithrombotic Trialists’ Collaboration**,¹⁰ in a meta-analysis of randomized controlled trials comparing different doses of aspirin in high-risk ACS patients, found no greater benefit for doses of aspirin higher than 162 mg per day when used long-term.

How to use. During an ACS, the patient should receive one dose of aspirin 325 mg (the standard high-dose pill in the United States). This dose should be chewed, as buccal absorption results in more rapid systemic effects.¹¹

Thereafter, the patient should take 81 mg per day, continued indefinitely. The 81-mg dose also applies to patients who undergo a percutaneous coronary intervention with a drug-eluting stent.⁷ Previous recommendations called for higher doses, but studies have shown that higher doses pose a higher risk of bleeding without additional clinical benefit. The use of enteric-coated aspirin does not reduce this risk,¹² and its delayed release may in fact cause aspirin “pseudoresistance.”¹³

The concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided, as NSAIDs reversibly bind to platelets, thus preventing aspirin from binding.¹⁴ As aspirin washes out of the body, NSAIDs may then become unbound from platelets, leaving platelets activated.

P2Y12 receptor inhibitors: Clopidogrel, prasugrel, ticagrelor

These agents bind to P2Y12 receptors on platelets to inhibit adenosine diphosphate-mediated platelet activation (FIGURE 3). Clopidogrel and prasugrel are irreversible prodrugs, whereas ticagrelor binds reversibly.

Non-ST-elevation acute coronary syndrome

→ With initial invasive strategy

Dual antiplatelet therapy with aspirin plus clopidogrel, ticagrelor, or eptifibatide

Anticoagulation with unfractionated heparin, enoxaparin, bivalirudin, or fondaparinux

→ Percutaneous coronary intervention planned

Dual antiplatelet therapy, including aspirin. If not given before intervention, start clopidogrel, ticagrelor, prasugrel, eptifibatide, or tirofiban and continue oral dual antiplatelet therapy for 12 months, but consider stopping early if risks outweigh benefits; hold these agents if angiography is to be done immediately; if angiography is planned within 24 hours, clopidogrel or ticagrelor is reasonable

Discontinue anticoagulation after percutaneous coronary intervention in uncomplicated cases

→ Coronary artery bypass grafting planned

Discontinue clopidogrel 5 days before, prasugrel 7 days before, and ticagrelor 5 days before surgery

Continue unfractionated heparin; discontinue enoxaparin 12–24 hours before surgery and start unfractionated heparin; discontinue fondaparinux 24 hours before and start unfractionated heparin; discontinue bivalirudin 3 hours before and start unfractionated heparin

→ Medical therapy planned

If no significant coronary artery disease is present, give antiplatelet and anticoagulation at physician's discretion

If coronary artery disease is present, discontinue glycoprotein IIb/IIIa inhibitor if started previously; give clopidogrel or ticagrelor for 1 year

Anticoagulation. If started before angiography, continue unfractionated heparin for 48 hours; enoxaparin or fondaparinux for duration of hospitalization or up to 8 days

→ With initial conservative strategy

Dual antiplatelet therapy with aspirin plus clopidogrel or ticagrelor for up to 12 months (reasonable to add eptifibatide or tirofiban if high-risk features are present and patient is not at high bleeding risk, particularly if troponin-positive)

Anticoagulation with enoxaparin, fondaparinux, or (less preferred) unfractionated heparin

→ **If the patient has high-risk features**, clinical instability, or heart failure and angiography is planned, see options under initial invasive strategy, above

→ **If the patient has low-risk features** or no angiography is planned

Dual antiplatelet therapy is recommended for 12 months with aspirin and either clopidogrel or ticagrelor

Unfractionated heparin for 48 hours; or enoxaparin or fondaparinux for duration of hospitalization or up to 8 days

Medication doses: **aspirin** 162–325 mg at initial contact, then 81 mg daily; **bivalirudin** 0.1 mg/kg intravenous (IV) bolus, then 0.25 mg/kg/h infusion; **clopidogrel** 600 mg, then 75 mg once daily; **enoxaparin** (with initial invasive strategy); if age < 75, 30 mg IV bolus, then 1 mg/kg twice a day subcutaneously 15 minutes after bolus; if age ≥ 75, no bolus, 0.75 mg/kg twice a day subcutaneously (maximum 75 mg for first 2 doses), for creatinine clearance less than 30 mL/min, 1 mg/kg every 24 hours subcutaneously; **enoxaparin** (with initial conservative or medical therapy) 1 mg/kg subcutaneously twice a day; **eptifibatide** 180 µg/kg IV bolus, then 2.0 µg/kg/min, reduce by 50% in patients with estimated creatinine clearance less than 50 mL/min; **fondaparinux** (with initial invasive strategy) 2.5 mg intravenous bolus, then 2.5 mg subcutaneously every 24 hours, contraindicated if creatinine clearance is less than 30 mL/min; **fondaparinux** (with initial conservative strategy) 2.5 mg subcutaneously every 24 hours, contraindicated if creatinine clearance is less than 30 mL/min; **prasugrel** 60 mg, then 10 mg once daily; **ticagrelor** 180 mg, then 90 mg twice daily; **unfractionated heparin** 60 IU/kg IV bolus, then 12 IU/kg infusion to achieve 1.5–2 times control

FIGURE 1. Suggested algorithm for antiplatelet and anticoagulant therapy in the management of non-ST-elevation acute coronary syndrome

BASED ON THE 2012 FOCUSED UPDATE OF THE 2007 AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION/AMERICAN HEART ASSOCIATION GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH UNSTABLE ANGINA/NON-ST-ELEVATION MYOCARDIAL INFARCTION.^{1,2}

ST-segment-elevation myocardial infarction

→ **With thrombolytic strategy**

Antiplatelet therapy: aspirin and clopidogrel

Anticoagulation: unfractionated heparin, or enoxaparin for index hospitalization up to 8 days or until revascularization, or fondaparinux for index hospitalization up to 8 days or until revascularization

→ **With primary percutaneous coronary intervention**

Antiplatelet therapy: aspirin and either clopidogrel, prasugrel, or ticagrelor for at least 1 year

Anticoagulation: bivalirudin or unfractionated heparin

Medication doses: **aspirin** 162–325 mg at initial contact, then 81 mg or 162–325 mg daily; **bivalirudin** 0.75 mg/kg intravenous (IV) bolus, then 1.75 mg/kg/h infusion (1 mg/kg/h if creatinine clearance < 30 mL/min), with or without prior unfractionated heparin; bivalirudin is preferred over unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor in patients at high risk of bleeding; **clopidogrel** (with primary percutaneous coronary intervention) 600 mg, then 75 mg once daily; **clopidogrel** (with thrombolytic strategy) first dose 300 mg if age < 75, 75 mg or do not give if age ≥ 75; then 75 mg for at least 14 days and up to 1 year; **enoxaparin** if age < 75, 30 mg intravenous bolus and 1 mg/kg twice a day subcutaneously 15 minutes after bolus; if age ≥ 75: no bolus, 0.75 mg/kg twice a day subcutaneously (maximum 75 mg for first 2 doses); for creatinine clearance less than 30 mL/min, 1 mg/kg every 24 hours subcutaneously; **fondaparinux**, for index hospitalization, up to 8 days or until revascularization: 2.5 mg IV bolus, then 2.5 mg subcutaneously every 24 hours; contraindicated if creatinine clearance is < 30 mL/min; **prasugrel** 60 mg, then 10 mg once daily; **ticagrelor** 180 mg, then 90 mg twice daily; **unfractionated heparin** (with primary percutaneous coronary intervention) with glycoprotein IIb/IIIa inhibitor, 50–70 IU/kg IV bolus; target activated clotting time 200–250 seconds; without GP IIb/IIIa inhibitor, 70–100 IU/kg IV bolus; target activated clotting time 250–300 seconds; **unfractionated heparin** (with thrombolysis) 60 IU/kg IV bolus and 12 IU/kg infusion to achieve 1.5–2 times control for 48 hours or until revascularization

FIGURE 2. Suggested algorithm for antiplatelet and anticoagulant therapy in the management of ST-elevation myocardial infarction

BASED ON THE AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION 2013 GUIDELINES FOR MANAGEMENT OF ST-ELEVATION MYOCARDIAL INFARCTION⁷ AND 2011 GUIDELINES FOR PERCUTANEOUS CORONARY INTERVENTION.⁶

Clopidogrel, a prodrug

Clopidogrel has a half-life of 8 hours and a time to peak concentration of 4 hours. Eighty-five percent of a dose is inactivated by gut esterases. The remainder is metabolized primarily by the cytochrome P450C19 enzyme system into its active metabolite.

How to use. The recommended dosage is a 600-mg bolus early in the course of ACS. This is associated with a lower rate of cardiovascular events than a 300-mg dose,^{2,15} although no trial has rigorously compared 300-mg vs 600-mg

doses using major clinical end points. In patients presenting with ACS who cannot tolerate aspirin because of hypersensitivity or major gastrointestinal contraindication, clopidogrel is an alternative.¹

The **CURE trial**¹⁶ randomized 12,526 patients with non-ST-elevation ACS to receive clopidogrel or placebo in addition to standard therapy. Clopidogrel was associated with a 20% lower rate of cardiovascular death, myocardial infarction, or stroke in both low- and high-risk patients regardless of whether an invasive or conservative strategy was pursued.

However, patients who underwent coronary artery bypass grafting (CABG) had a 53% higher risk of bleeding (an absolute risk of 3.3%) if they received clopidogrel within 5 days of the surgery. This has led to the practice in some centers of delaying giving clopidogrel until after the coronary anatomy has been defined. This deprives the patient of the anti-ischemic benefits conferred by giving clopidogrel early and remains a contentious issue, with most suggesting that the risk-benefit ratio still favors giving clopidogrel early, before angiography, unless there is a high likelihood that surgery will ultimately be required.¹⁷ Alternatively, one could consider using a shorter-acting intravenous glycoprotein IIb/IIIa inhibitor such as eptifibatid as a “bridge” until a definitive reperfusion strategy is chosen.

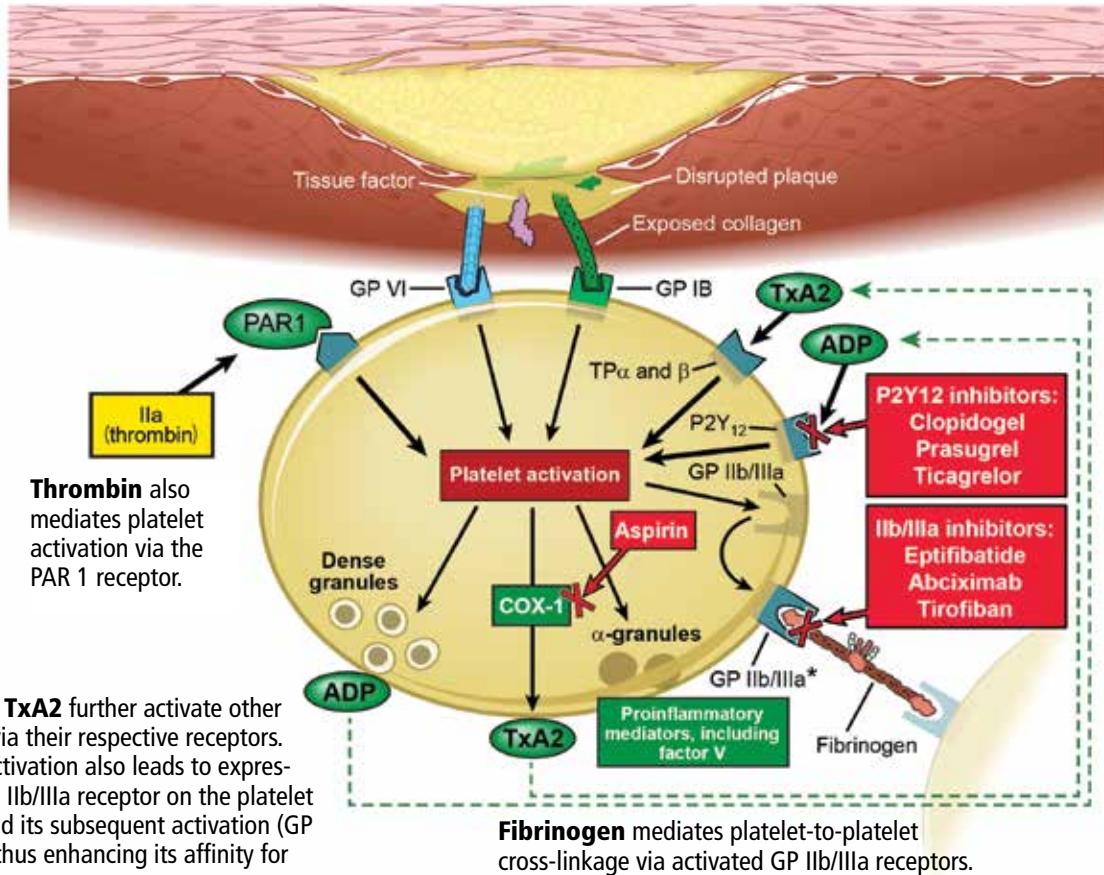
Effect of CYP2C19 variants. The **CLOVIS-2 study**¹⁸ assessed the effects of genetic variants on the clopidogrel concentration in 106 patients who had had a myocardial infarction. The study confirmed that patients who carry certain variants of the **CYP2C19** gene attain lower plasma concentrations of clopidogrel after receiving this drug.¹⁹ This accounts for its delayed onset of action as well as its variability in response in patients who have reduced expression or inhibition of this enzyme system. Doubling the standard dose in patients who carry these variants does not appear to provide clinical benefit.²⁰

Thus, the thought is emerging that one should consider using prasugrel or ticagrelor instead of clopidogrel in patients who have these polymorphisms, though this is yet to be backed by robust clinical evidence.

Possible interaction with proton pump inhibitors. Controversy exists about whether

Platelet activation and site of action of various antiplatelet agents

Upon exposure of injured endothelium, platelets bind to von Willebrand factor (vWF) and exposed collagen via glycoprotein (GP) VI and GP IB alpha, leading to platelet activation. This causes a conformational change in the platelet shape and degranulation of dense and alpha granules, leading to release of adenosine diphosphate (ADP), thromboxane A2 (TxA2), and various proinflammatory mediators.



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Medical Illustrator: David Schumick ©2014

FIGURE 3

ADAPTED FROM STOREY RF. NEW DEVELOPMENTS IN ANTIPLATELET THERAPY. EUR HEART J SUPPL 2008; 10(SUPPL D):D30-D37.

proton pump inhibitors inhibit clopidogrel's action. Although the US Food and Drug Administration continues to warn against the concurrent use of omeprazole and clopidogrel,²¹ an analysis of the PLATO trial²² concluded that patients with ACS who were taking proton pump inhibitors were at higher risk of ischemic events regardless of whether they had been randomized to clopidogrel or ticagrelor (a drug that acts independently of the cytochrome P450 system). This observation suggests that patients on proton pump inhibitors are generally sicker and at higher risk of ischemic events regardless of the choice of antiplatelet therapy.

The use of other gastroprotective agents did not appear to mitigate these risks.

Prasugrel: Faster metabolism to active drug

Prasugrel is an irreversible P2Y₁₂ receptor antagonist (FIGURE 3) that is metabolized into its active metabolite faster and in a more predictable fashion than clopidogrel.²³

The TRITON-TIMI 38 study²⁴ included 13,608 ACS patients in whom an early invasive strategy was planned and who were pretreated with prasugrel or clopidogrel in addition to standard treatment. The rate of the primary efficacy end point of death, myocar-

Aspirin reduces morbidity and mortality rates by as much as 50% in patients with ACS

dial infarction, or stroke was 19% lower in the prasugrel group. In those who underwent percutaneous coronary intervention, the incidence of in-stent thrombosis was more than 50% lower in the prasugrel group regardless of whether bare metal stents or drug-eluting stents were used.

Greater platelet inhibition came at the price of a higher incidence of serious bleeding, particularly in the subgroups of patients who were over age 75, had a history of stroke or transient ischemic attack, or weighed less than 60 kg. Prasugrel is therefore contraindicated in patients with a history of transient ischemic attack or stroke. Some suggest that a 5-mg dose can be used with caution (rather than the usual 10-mg dose) in patients over age 75 years or those who have low body weight.

The **TRILOGY-ACS trial**²⁵ compared prasugrel and clopidogrel in medically managed patients with high-risk non-ST-elevation ACS. It found no difference in the rates of the primary end points of cardiovascular death, myocardial infarction, or stroke at 1 year. In the prespecified subset of patients over age 75 years, the rate of bleeding end points was no higher with prasugrel 5 mg once daily than with clopidogrel.

Prasugrel's half-life is 7 hours, and its peak antiplatelet effect is within 30 minutes after an oral dose, compared with 4 hours with clopidogrel. Therefore, if a patient with non-ST-elevation ACS is going to go to the catheterization laboratory soon, he or she should not receive prasugrel beforehand, and should receive it later only if the results of angiography indicate that CABG will not be needed urgently. This is an important consideration when using prasugrel, as the rate of surgery-related bleeding was four times higher than with clopidogrel. If possible, this drug should be withheld for at least 7 days before CABG.

Ticagrelor, a direct P2Y12 receptor inhibitor

Ticagrelor, a reversible direct inhibitor of the P2Y12 receptor, inhibits adenosine diphosphate-mediated activation and aggregation (FIGURE 3). It has a median time to peak concentration of 1.3 to 2 hours and a half-life of 9 hours.

The **PLATO trial**²⁶ enrolled 18,624 patients with ACS who were given either ticagrelor or clopidogrel in addition to standard therapy. At

12 months, the composite primary end point of myocardial infarction, death, or stroke had occurred in 16% fewer patients receiving ticagrelor than in the clopidogrel group. Analyzed separately, there were 16% fewer myocardial infarctions, 21% fewer cardiovascular deaths, and 22% fewer deaths from any cause, regardless of whether an invasive or conservative strategy was used, and with or without prior clopidogrel use. Fewer cases of stent thrombosis occurred in the ticagrelor group, and the rate of major bleeding was the same.

In a prospectively defined subgroup analysis,²⁷ ticagrelor was beneficial only in patients who received lower doses of aspirin (< 100 mg daily): the hazard ratio for the primary end point was 0.79 (95% confidence interval [CI] 0.71–0.88) in ticagrelor recipients who received low-dose aspirin and 1.45 (95% CI 1.01–2.09) in those who received high-dose aspirin.

Although this analysis is underpowered and controversial, the current evidence suggests that when used in combination with ticagrelor, the aspirin dose should be 81 mg.

Ticagrelor was also associated with a 19% higher incidence of non-CABG- or procedure-related major bleeding, more nonfatal and fatal intracranial bleeding, a higher incidence of dyspnea, and significantly more ventricular pauses.

Although ticagrelor carries no black-box warning about its use in patients with prior stroke or transient ischemic attack, the number of such patients in PLATO was small. Thus, caution should still be used in these patients.²⁸

Ticagrelor should preferably be discontinued 5 days before CABG.

Glycoprotein IIb/IIIa inhibitors: Eptifibatide, tirofiban, abciximab

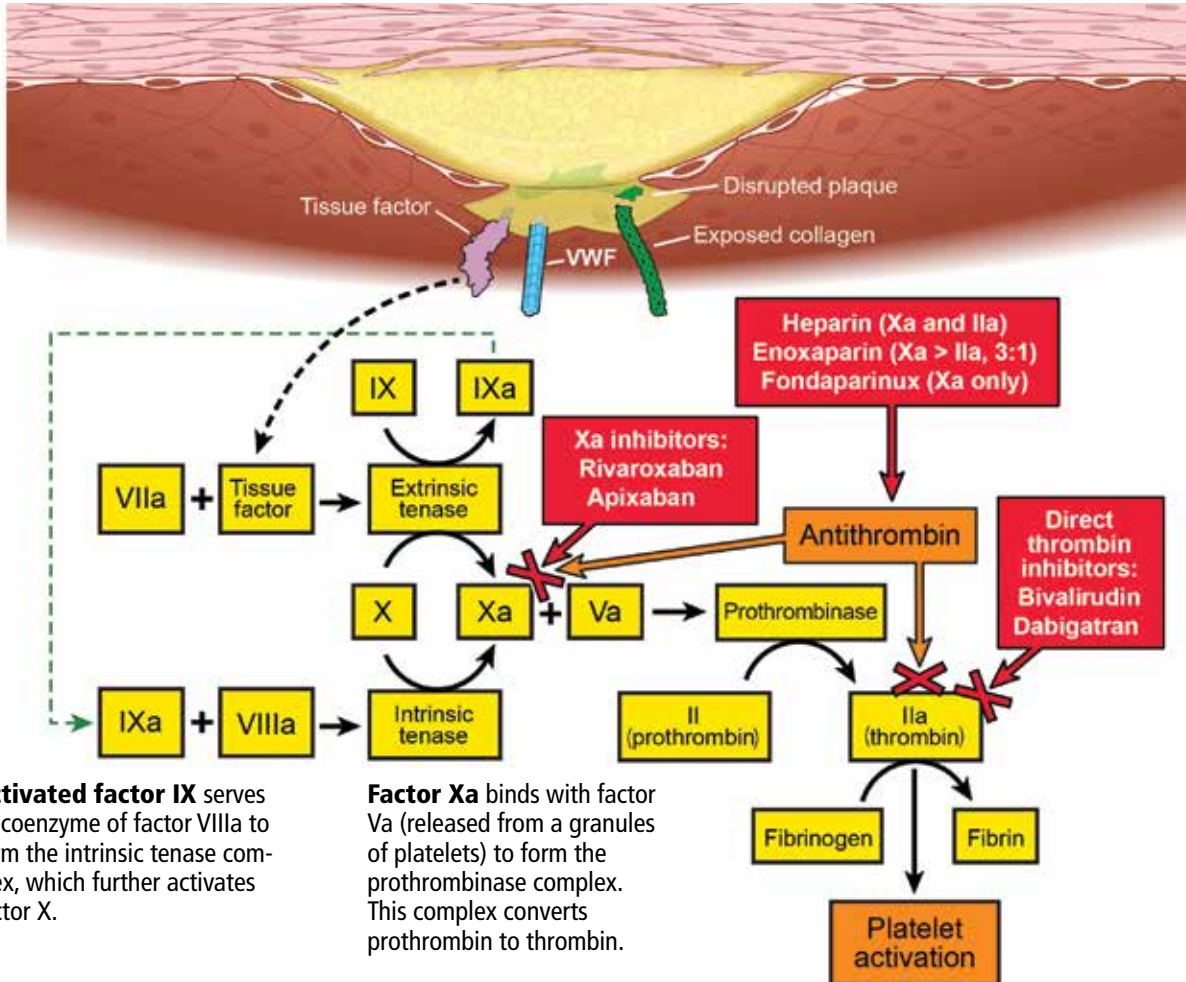
Glycoprotein IIb/IIIa inhibitors are intravenous agents that act by inhibiting fibrinogen- and von Willebrand factor-mediated platelet-to-platelet cross-linkage, the final pathway of platelet aggregation (FIGURE 3).

Use of these agents in ACS has been decreasing, as evidence supporting their use was largely established before the era of dual antiplatelet therapy.

A **meta-analysis**²⁹ of 46,374 patients with non-ST-elevation ACS found that routinely adding a glycoprotein IIb/IIIa inhibitor “up-

Coagulation cascade and site of action of various anticoagulants

Exposed tissue factor from vascular injury binds to circulating activated factor VII to form the extrinsic tenase complex. This complex is a potent activator of factors IX and X.



Thrombin is a powerful stimulant of platelet activator (via PAR 1; see FIGURE 3), further propagating the platelet plug. It also converts soluble fibrinogen to insoluble fibrin, leading to clot formation, and it activates factor XIII, leading to cross-linking of fibrin and further stabilization of the clot.

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Medical Illustrator: David Schumick ©2014

FIGURE 4

stream” as a third agent in patients receiving dual antiplatelet therapy bought only a modest (11%) reduction in death or myocardial infarction at 30 days, at the price of a 23% increase in major bleeding and no decrease in the overall rate of death. Roughly 70% of the patients were receiving dual antiplatelet therapy before cardiac catheterization.

These agents can be considered in high-risk ACS patients, such as those with ST-segment changes or elevated troponin concentrations,

and in diabetic patients, on the assumption that these patients likely have a high intracoronary thrombus burden and are at higher risk of microvascular embolization.^{6,30} They can also be considered at the time of primary percutaneous coronary intervention in selected patients receiving heparin.⁷

Eptifibatide

Eptifibatide is a small-molecule, short-acting glycoprotein IIb/IIIa inhibitor with a half-life

of 2.5 hours. Its inhibition of platelet aggregation is reversible by stopping the drug infusion and is thought to be a result of dissociation of the drug from platelets.

The **PURSUIT trial**³¹ studied 10,948 patients presenting with non-ST-elevation ACS randomized to placebo, eptifibatide in a 180- $\mu\text{g}/\text{kg}$ bolus followed by a 2.0- $\mu\text{g}/\text{kg}/\text{min}$ infusion, or eptifibatide in a 180- $\mu\text{g}/\text{kg}$ bolus followed by a 1.3- $\mu\text{g}/\text{kg}/\text{min}$ infusion. Both eptifibatide groups had a 1.5% absolute reduction in the incidence of the primary end point of death or myocardial infarction, a benefit that was apparent at 96 hours and that persisted through 30 days. Bleeding was more common in the eptifibatide groups, but there was no increase in the rate of hemorrhagic stroke.

The **ACUITY trial**³² found that early use of eptifibatide or tirofiban had no effect on the primary outcome. (See the section below on bivalirudin for more information about the ACUITY trial.)

■ PARENTERAL ANTICOAGULANTS

Unfractionated heparin: A declining role

Heparin binds to antithrombin and induces a conformational change, causing rapid inhibition of factor IIa (thrombin), factor IXa, and factor Xa, thus preventing further thrombus propagation (FIGURE 4). An intravenous bolus of 60 units/kg produces a time to peak of 5 to 10 minutes and a half-life of 30 to 60 minutes.

Heparin can be reversed by giving protamine sulfate (1 mg per 100 units of heparin). For ACS, it is given in a bolus of 60 units/kg not exceeding 4,000 units, followed by an infusion of 12 units/kg/hour, with monitoring of the activated partial thromboplastin time every 6 hours with a goal value of 50 to 70 seconds or 1.5 to 2.5 times control.

Side effects include thrombocytopenia, heparin-induced thrombocytopenia (a distinct condition), and bleeding.

The use of unfractionated heparin was tested in ACS in the early 1990s. Oler et al³³ performed a meta-analysis of six randomized trials and found a 33% lower rate of death in patients treated with heparin in addition to aspirin in ACS, as well less reported ischemic pain.

Advantages of unfractionated heparin are

that it has stood the test of time, is inexpensive, and can be rapidly reversed. The disadvantages are that it can have serious side effects, including heparin-induced thrombocytopenia, and is more likely to cause bleeding than the newer intravenous anticoagulants discussed below. Thus, its position as the main anticoagulant in ACS is being challenged.

Bivalirudin, a direct thrombin inhibitor

Bivalirudin is a synthetic direct thrombin inhibitor of fluid-phase and clot-bound thrombin (FIGURE 4). It also inhibits platelets directly.

The **ACUITY trial**³² randomized 13,819 patients with moderate to high-risk ACS scheduled for invasive treatment into three treatment groups:

- Heparin (either unfractionated heparin or enoxaparin) plus a glycoprotein IIb/IIIa inhibitor (either eptifibatide, tirofiban, or abciximab)
- Bivalirudin plus a glycoprotein IIb/IIIa inhibitor
- Bivalirudin alone.

The bivalirudin-alone treatment was associated with noninferior rates of composite ischemia end points and significantly lower rates of major bleeding, adding up to a significant reduction in the net clinical outcome end point. An important caveat is that bivalirudin's noninferiority was mostly in the group of patients already receiving a thienopyridine before angiography and percutaneous coronary intervention (RR 0.97 vs 1.27, $P = .054$). There was less major, nonmajor, minor, CABG-related, and non-CABG-related bleeding as well as need for transfusion in the bivalirudin-alone group, making bivalirudin monotherapy an attractive option in ACS patients with or without ST-segment elevation undergoing a percutaneous coronary intervention.^{1,31}

The **ISAR-REACT trial**³⁴ later compared bivalirudin alone vs unfractionated heparin and abciximab in patients with non-ST-elevation myocardial infarction undergoing percutaneous coronary intervention pretreated with aspirin and clopidogrel. The composite rate of ischemia was similar in the two treatment groups, with significantly lower rates of bleeding in the bivalirudin group.

HORIZONS-AMI³⁵ randomized 3,602 pa-

Patients taking aspirin daily should avoid concurrent use of NSAIDs

tients with ST-elevation myocardial infarction receiving aspirin and clopidogrel either to unfractionated heparin and a glycoprotein IIb/IIIa inhibitor or to bivalirudin. As in the ACUITY trial, there was no difference in ischemic end points and a 40% to 45% lower rate of major bleeding end points in the bivalirudin group, translating into an overall lower rate of death.

Enoxaparin, a low-molecular weight heparin

Enoxaparin is a low-molecular-weight heparin that inhibits factor IIa and factor Xa via antithrombin, roughly in a ratio of 1:3 (FIGURE 4). It has a time to peak effect of 10 minutes when given intravenously³⁶ and 3 to 5 hours when given subcutaneously.³⁷ Its half-life is 4.5 hours, but it is longer in patients with renal dysfunction, requiring dose adjustments in this population.

Its anticoagulant effect is partially reversible. If it is to be reversed between 0 and 8 hours after dosing, the recommended reversal regimen is 1 mg of protamine sulfate for every 1 mg of enoxaparin used. At 8 to 12 hours, it is 0.5 mg of protamine for every 1 mg of enoxaparin. After 12 hours, no protamine is required.

Compared with unfractionated heparin, enoxaparin has less plasma protein binding and a more consistent anticoagulant effect. Its high bioavailability also allows for subcutaneous dosing. Its greater anti-Xa activity inhibits thrombin generation more effectively, and it causes lower rates of thrombocytopenia and heparin-induced thrombocytopenia.

de Lemos et al³⁸ found that, in ACS patients in whom an early conservative approach of medical management was planned, enoxaparin was more efficacious than unfractionated heparin and caused a similar rate of bleeding.

Murphy et al,³⁹ in a meta-analysis of 12 trials in 49,088 ACS patients, also found that enoxaparin had a net clinical benefit compared with unfractionated heparin in reducing rates of myocardial infarction and death despite more bleeding.

The ESSENCE trial⁴⁰ compared enoxaparin vs unfractionated heparin in 3,171 patients with ACS. It found fewer ischemic events with enoxaparin in the early phase, more minor bleeding, but no increase in major bleeding.

The SYNERGY trial,⁴¹ in 10,027 patients with high-risk non-ST-elevation ACS undergoing percutaneous coronary intervention, compared subcutaneous enoxaparin with intravenous heparin. Enoxaparin was found to be noninferior to heparin but caused more bleeding, including major bleeding, drops in hemoglobin, and intracranial hemorrhage.

The EXTRACT-TIMI 25 trial.⁴² In patients with ST-elevation myocardial infarction, enoxaparin has been shown to be beneficial both in patients treated with fibrinolysis and in those who underwent primary percutaneous coronary intervention. The EXTRACT-TIMI 25 trial randomized 20,749 patients to receive either enoxaparin (an intravenous bolus and maintenance subcutaneous dosing based on renal function) or intravenous heparin in addition to thrombolysis within 6 hours of the diagnosis of ST-elevation myocardial infarction. Although the enoxaparin group had more bleeding end points, they had fewer primary and secondary efficacy end points, translating into an overall net clinical benefit in favor of enoxaparin.

The ATOLL trial⁴³ examined the use of enoxaparin (0.5 mg/kg intravenously) or unfractionated heparin in 910 patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention (via the radial artery in 66% to 69%). Although there was a trend towards benefit in terms of the primary end point of death, myocardial infarction complications, procedure failure, and major bleeding favoring enoxaparin, it was not statistically significant (95% CI 0.68–1.01, $P = .06$).

However, there was a 37% to 42% lower rate of the secondary end point of death, recurrent myocardial infarction or ACS, or urgent target-vessel revascularization in the enoxaparin group, with a 40% reduction in death from any cause, death from a cardiac cause, or shock. The safety profiles of the two drugs were similar, and the net clinical benefit significantly favored enoxaparin.

Fondaparinux, a factor Xa inhibitor

Fondaparinux is a synthetic pentasaccharide that indirectly inhibits factor Xa through the action of antithrombin (FIGURE 4). After a 2.5-mg subcutaneous dose, it has a time to peak

Patients who carry certain variants of CYP2C19 attain lower plasma concentrations of clopidogrel

concentration of 2 hours and a half-life of 17 to 21 hours.

The **OASIS-5 trial**⁴⁴ compared fondaparinux and enoxaparin in 20,078 patients treated for non-ST-elevation ACS. Although the rates of death, myocardial infarction, and refractory ischemia at 9 days were similar for both drugs, the fondaparinux group had a significantly (almost 50%) lower rate of bleeding at 30 days, translating into significantly fewer deaths at 30 days. However, patients receiving fondaparinux who underwent percutaneous coronary intervention had a threefold higher rate of catheter-related thrombosis.

The **OASIS-6 trial**⁴⁵ compared fondaparinux vs usual care (placebo in those in whom unfractionated heparin was not indicated or unfractionated heparin for up to 48 hours followed by placebo for up to 8 days) in 12,092 patients with ST-elevation myocardial infarction. There was a 1.5% absolute risk reduction in death and reinfarction without an increase in bleeding at 30 days, with trends persisting 6 months into the study. However, fondaparinux was not superior to heparin in the 3% of patients who underwent primary percutaneous coronary intervention. As in OASIS-5, there was more catheter-related thrombosis in the fondaparinux group.

Although the use of supplemental unfractionated heparin appears to have mitigated this risk, fondaparinux remains a less-than-ideal option in the era of primary percutaneous coronary intervention for ST-elevation myocardial infarction and has therefore found limited use in this group of patients. It should, however, be considered in patients for whom a conservative strategy is planned, especially if bleeding risk is deemed to be high.

■ **ORAL ANTICOAGULANTS**

Oral anticoagulants provide ischemic benefit in selected patients with ACS—at the price of a higher risk of significant bleeding.

Warfarin

Warfarin was investigated after myocardial infarction in the WARIS II,⁴⁶ CARS,⁴⁷ and CHAMP⁴⁸ trials.

WARIS II⁴⁶ looked at the use of aspirin alone, warfarin alone, and aspirin and warfa-

rin in combination. The rates of the primary end points of stroke, nonfatal infarction, and death were lower in the warfarin group.

CARS⁴⁷ found no difference in the rate of the primary end point of fatal infarction, nonfatal ischemic stroke, or cardiovascular death with aspirin vs warfarin plus aspirin.

CHAMP⁴⁸ saw similar trends, ie, no difference in the rate of death, recurrent myocardial infarction, or stroke with warfarin plus aspirin vs aspirin alone.

All three studies showed increases in major bleeding with warfarin use.

Putting these trials into context, the significant net clinical benefit of dual antiplatelet therapy in the current era compared with the significant bleeding and questionable conflicting evidence supporting benefit with warfarin has limited its use in ACS patients.

Rivaroxaban, an oral factor Xa inhibitor

Rivaroxaban is a novel oral direct reversible factor Xa inhibitor.

The **ATLAS ACS 2-TIMI 51 trial**⁴⁹ found rivaroxaban 2.5 mg or 5 mg to yield a significantly lower rate of the primary outcome of cardiovascular death, myocardial infarction, ischemic stroke, and in-stent thrombosis compared with placebo, but significantly more major non-CABG bleeding and intracranial hemorrhage.

The dose used in this trial was much lower than the dose used in trials investigating the role of this drug in stroke prophylaxis in atrial fibrillation.

Apixaban, an oral factor Xa inhibitor

Apixaban is another direct factor Xa inhibitor.

The **APPRAISE-2 trial**⁵⁰ compared apixaban 5 mg twice daily vs placebo in ACS. There was no difference in the rate of cardiovascular death, myocardial infarction, or stroke, but there was significantly more bleeding in the apixaban group, prompting early termination of this study.

Dabigatran, an oral thrombin inhibitor

Dabigatran is an oral direct thrombin inhibitor.

The **RE-DEEM trial**⁵¹ compared four doses of dabigatran (50, 75, 110, and 150 mg twice daily) and placebo in ACS patients. The dabigatran groups had more major and

If possible, prasugrel should be withheld for at least 7 days before CABG

minor bleeding, and the higher the dose, the higher the incidence of bleeding. In addition, the rates of ischemic end points were no lower with dabigatran, although this trial was not powered to show differences in clinical events.

■ REDUCING THE RISK OF BLEEDING

In the treatment of ACS, the benefits of restoring perfusion by preventing further propagation of thrombus and platelet aggregation come at a significant price of higher bleeding risk. This in turn increases the risk of death through various mechanisms, including shock, worsening ischemia, discontinuation of antiplatelet and anticoagulation therapy causing stent thrombosis, and anemia leading to transfusion, which propagates the underlying inflammatory milieu.⁵²

Giugliano and Braunwald⁵³ provide practical suggestions to reduce this risk, advising physicians to:

- Avoid inappropriately high dosing, particularly in patients with renal insufficiency
- Preferentially use agents that cause less bleeding (eg, bivalirudin, fondaparinux) without compromising anti-ischemic efficacy
- Minimize the concomitant use of other drugs that cause bleeding (eg, NSAIDs)
- Use drugs that protect against bleeding (eg, proton pump inhibitors) in patients at high risk
- Prevent access-site bleeding by using the radial artery, smaller sheaths, and appropriate sheath and closure device management. Indeed, the use of radial interventions in ACS has been shown to reduce access-site-related bleeding, even in patients at high risk.⁵⁴

The reduction in bleeding risk may provide future trials the opportunity to increase anti-thrombotic efficacy of different agents with goals of reducing ischemic end points. ■

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