

STATE-OF-THE-ART PAPER

Antithrombotics in Acute Coronary Syndromes

Marc P. Bonaca, MD,* Philippe Gabriel Steg, MD,† Laurent J. Feldman, MD,† John F. Canales, MD,‡ James J. Ferguson, MD,‡§ Lars Wallentin, MD, PhD,|| Robert M. Califf, MD,¶ Robert A. Harrington, MD,¶ Robert P. Giugliano, MD, SM*

Boston, Massachusetts; Paris, France; Houston, Texas; Uppsala, Sweden; and Durham, North Carolina

Antithrombotic agents are an integral component of the medical regimens and interventional strategies currently recommended to reduce thrombotic complications in patients with acute coronary syndromes (ACS). Despite great advances with these therapies, associated high risks for thrombosis and hemorrhage remain as the result of complex interactions involving patient comorbidities, drug combinations, multifaceted dosing adjustments, and the intricacies of the care environment. As such, the optimal combinations of antithrombotic therapies, their timing, and appropriate targeted subgroups remain the focus of intense research. During the last several years a number of new antithrombotic treatments have been introduced, and new data regarding established therapies have come to light. Although treatment guidelines include the most current available data, subsequent findings can be challenging to integrate. This challenge is compounded by the complexity associated with different efficacy and safety measures and the variability in study populations, presenting syndromes, physician, and patient preferences. In this work we review recent data regarding clinically available antiplatelet and anticoagulation agents used in the treatment of patients with ACS. We address issues including relative efficacy, safety, and timing of therapies with respect to conservative and invasive treatment strategies. In specific cases we will highlight remaining questions and controversies and ongoing trials, which will hopefully shed light in these areas. In addition to reviewing existing agents, we take a look forward at the most promising new antithrombotics currently in late-stage clinical development and their potential role in the context of ACS management. (J Am Coll Cardiol 2009;54:969-84) © 2009 by the American College of Cardiology Foundation

The large number of recent studies investigating various antithrombotic treatments necessitates a re-review of their role in managing patients with acute coronary syndromes (ACS). In this review, we focus on new data with clinically available antiplatelet and anticoagulation agents (Table 1) and also take a look forward at promising new antithrombotics in late-stage clinical development.

Part I: Antiplatelets

Glycoprotein IIb/IIIa inhibitors (GPIs). Intravenous GPIs are potent antiplatelet agents that inhibit fibrinogen-mediated platelet-platelet binding, the final common pathway of platelet aggregation. Guideline recommendations from the American College of Cardiology (ACC)/American Heart

From the *TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts; †Centre Hospitalier Bichat-Claude Bernard, Université Paris VII-Denis Diderot, Paris, France; ‡Texas Heart Institute at St. Luke's Episcopal Hospital, Baylor College of Medicine, Houston, Texas; §The University of Texas Health Science Center at Houston, Houston, Texas; ||Uppsala Clinical Research Centre at Uppsala University, Uppsala, Sweden; and the ¶Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina. Dr. Feldman has received research grant support from Sanofi-Aventis and Servier and consulting fees from Boehringer Ingelheim, Eli Lilly, and GlaxoSmithKline. Dr. Steg has received research grant support from Sanofi-Aventis; has participated in Speaker's Bureaus supported by AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, Nycomed, Sanofi-Aventis, Servier, and The Medicines Company; and is a member of consulting/advisory board for Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Endotis, GlaxoSmithKline, Medtronic, Merck-Sharp-Dohme, Nycomed, Sanofi-Aventis, Servier, and The Medicines Company. Dr. Ferguson has received research grant support from Eisai, The Medicines Company, and Sanofi-Aventis; has a consulting relationship with Astellas, AstraZeneca, Bristol-Myers Squibb, Daiichi-Sankyo, Eisai, Eli Lilly & Co., GlaxoSmithKline, Johnson & Johnson, Sanofi-Aventis, Schering-Plough, Takeda, The Medicines Company, and Therox; and is a member of the Speakers' Bureaus for Bristol-Myers Squibb, Sanofi-Aventis, and Schering-Plough. Dr. Ferguson is currently an employee of The Medicines Company. Dr. Wallentin has

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**Abbreviations
 and Acronyms**

- ACC** = American College of Cardiology
- ACS** = acute coronary syndromes
- ADP** = adenosine diphosphate
- AHA** = American Heart Association
- CABG** = coronary artery bypass grafting
- CrCl** = creatine clearance
- DTI** = direct thrombin inhibitor
- ESC** = European Society of Cardiology
- GPI** = glycoprotein IIb/IIIa inhibitor
- LMWH** = low molecular weight heparin
- MI** = myocardial infarction
- NSTE-ACS** = non-ST-segment elevation acute coronary syndromes
- PCI** = percutaneous coronary intervention
- STEMI** = ST-segment elevation myocardial infarction
- UFH** = unfractionated heparin

Association (AHA) (1–3) and European Society of Cardiology (ESC) (4–6) regarding the use of GPIs in patients with ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation acute coronary syndromes (NSTE-ACS), and percutaneous coronary intervention (PCI) are summarized in Table 2.

NSTE-ACS. Use of an IV GPI or clopidogrel prior to angiography is a Class I recommendation in conjunction with aspirin and an anti-coagulant (1,5). In patients managed conservatively, the use of eptifibatid or tirofiban is a Class IIa recommendation if high-risk features are present (and Class IIb otherwise) (1,5). New data available since the guidelines include studies with GPIs: 1) on a background of 600 mg of clopidogrel; 2) comparing early versus late initiation; and 3) compared with bivalirudin (see the section “Direct thrombin inhibitors”).

Abciximab was evaluated in 2,002 patients with NSTE-ACS pre-treated (>2 h) with clopidogrel 600 mg before PCI in the placebo-controlled ISAR-

REACT 2 (Intracoronary Stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment) trial (7). Abciximab reduced the relative risk of the primary composite of death, myocardial infarction (MI), or urgent target vessel revascularization at 30 days by 25% (95% confidence interval [CI]: 3% to 42%, $p = 0.03$); however, all of this early benefit was observed in patients with increased levels of baseline troponin (29% relative risk ratio, treatment-subgroup interaction $p = 0.07$). The use of abciximab did not increase the rate of major bleeding (1.4% in both groups). The 1-year results of ISAR-REACT 2 (8) showed sustained benefit in the primary end point (23.3% vs. 28%, $p = 0.012$) regardless of age, sex, diabetes, or timing of clopidogrel (>3 or <3 h) and was present even among patients with baseline negative troponin (in contrast to the 30-day results).

The ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial randomized 13,819 patients with moderate- or high-risk ACS who were managed with angiography within 72 h to open-label heparin with GPI, bivalirudin with GPI, or bivalirudin without GPI (9). In the ACUITY Timing Trial (subnested within the main trial), the 9,207 patients in the 2 GPI arms underwent a second randomization to either early (at randomization) GPI or

deferred selective GPI (at time of PCI) (10). At 30 days, deferred GPI administration was associated with a nonsignificant greater rate of composite ischemia (7.9% vs. 7.1%, $p = 0.13$ superiority), which did not satisfy the criteria for noninferiority compared with early GPI administration. However, major bleeding was reduced with deferred GPI (4.9% vs. 6.1%, $p < 0.001$ for noninferiority, $p = 0.009$ superiority), whereas the rates of ischemic and bleeding events (net clinical outcome) were identical (11.7%). Notable limitations of the ACUITY trial include its open-label and noninferiority design, use of various heparins and GPIs, lower risk profile of patients compared with other contemporary studies, and short upstream infusion of GPI before PCI (4 h compared with approximately 24 h in a recent U.S. registry) (11,12).

The EVEREST (Randomized comparison of upstream standard dose tirofiban VERSUS downstream high-dose Tirofiban or abciximab in high-risk ACS treated with PCI) trial compared the effects of upstream standard-dose tirofiban (0.4 $\mu\text{g}/\text{kg}/\text{min}$ for 30 min followed by an infusion of 0.10 $\mu\text{g}/\text{kg}/\text{min}$ for up to 12 h after PCI) to downstream high-dose bolus tirofiban (25 $\mu\text{g}/\text{kg}$ over 3 min, 10 min before PCI followed by 0.15 $\mu\text{g}/\text{kg}/\text{min}$ for 12 h) or standard-dose abciximab on tissue perfusion and biomarker levels in 93 patients with high-risk NSTE-ACS treated with PCI (13). Overall upstream tirofiban was associated with improved tissue-level perfusion (lower frequency of poor perfusion [Thrombolysis In Myocardial Infarction [TIMI] myocardial perfusion grade 0/1], greater myocardial contrast echo score index before and after PCI) and less frequent elevation in cardiac troponin-I after PCI. The EARLY-ACS (Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndrome) trial (14) randomized 9,492 patients with NSTE-ACS planned for invasive management to a strategy of either early, routine administration of eptifibatid versus delayed, provisional use. There was no difference between strategies in the primary outcome (death, myocardial infarction, recurrent ischemia requiring urgent revascularization, or thrombotic bailout at 96 h), which occurred in 9.3% of patients in the early-eptifibatid group compared with 10.0% in the delayed-eptifibatid group (odds ratio [OR]: 0.92, 95% CI: 0.80 to 1.06, $p = 0.23$), or key secondary end point (death or myocardial infarction at 30 days) 11.2% versus 12.3% (OR: 0.89, 95% CI: 0.79 to 1.01, $p = 0.08$). In addition, since there was more bleeding and transfusion with early routine use of eptifibatid, these data do not support the use of routine upstream GPI in NSTE-ACS.

STEMI. The current ACC/AHA (2) and ESC (6) STEMI guidelines assign a Class IIa indication to the use of abciximab (Class IIb for eptifibatid and tirofiban) in patients treated with primary PCI and Class IIb recommendation for patients <75 years of age treated with GPI and half-dose fibrinolytic as part of a medical strategy (2,6). The authors of a recent European meta-analysis (15) reported long-term results with abciximab

Table 1 Major Recent Clinical Trials of Antiplatelet and Anticoagulants in NSTEMI-ACS

Trial	Agent	n	Primary Results	Note
NSTEMI-ACS				
ISAR-REACT 2 Kastrati et al. (7) JAMA 2006	GPI: abciximab vs. placebo	2,022	RRR of PE 25% at 30 days, $p = 0.03$ with sustained benefit at 1 yr $p = 0.012$	Benefit in patients with elevated cTn at 30 days and in all patients at 1 yr. Patients pre-treated with 600 mg of clopidogrel.
EVEREST Bolognese et al. (13) J Am Coll Cardiol 2006	GPI: upfront tirofiban vs. downstream GPI	93	TMPG 0/1 perfusion less frequent with upstream tirofiban vs. high-dose tirofiban or abciximab before PCI (28.1% vs. 66.7% vs. 71%, $p = 0.0009$)	Upstream tirofiban also associated with less frequent post-procedural cTnI elevation and lower cTnI levels after PCI
EARLY-ACS Giugliano et al. (14) N Engl J Med 2009	GPI: routine early vs. delayed provisional eptifibatide	9,492	No difference in PE (9.3% vs. 10.0%, $p = 0.23$) between early routine and delayed provisional groups	Trend toward fewer death/MI at 30 days (11.2% vs. 12.3%, $p = 0.08$), but more bleeding and transfusion with early routine eptifibatide.
ACUITY Stone et al. (9) N Engl J Med 2006	DTI: bivalirudin vs. bivalirudin and GPI vs. heparin and GPI	13,819	Bivalirudin alone noninferior for composite ischemic EP (7.8% vs. 7.3%, $p = 0.32$), reduced major bleeding (3.0% vs. 5.7%, $p < 0.001$) and net clinical outcome (10.1% vs. 11.7%, $p = 0.02$)	ACUITY Timing trial (10) showed more composite ischemic events with deferred GPI (7.9% vs. 7.1%, $p = 0.13$ superiority), which did not satisfy noninferiority
CURE Yusuf et al. (22) N Engl J Med 2001	Thienopyridine: clopidogrel vs. placebo	12,562	Reduced composite end point with clopidogrel (9.3% vs. 11.4%, $p < 0.001$)	Significantly more major bleeding with clopidogrel compared to placebo (3.7% vs. 2.7%, RR: 1.38, $p = 0.001$)
SYNERGY Ferguson et al. (63) JAMA 2004	LMWH: enoxaparin vs. UFH	10,027	No significant difference in PE with enoxaparin (14% vs. 14.5%, $p = 0.40$)	Significant increase in TIMI major bleeding with enoxaparin (9.1% vs. 7.6%, $p = 0.008$)
OASIS-5 Yusuf et al. (85) N Engl J Med 2006	LMWH: fondaparinux vs. enoxaparin	20,078	Fondaparinux noninferior in PE (5.8% vs. 5.7% $p = 0.007$ noninferiority)	Reduced major bleeding with fondaparinux (2.2% vs. 4.1%, $p < 0.001$)
STEMI				
FINESSE Ellis et al. (16) N Engl J Med 2008	GPI: \pm fibrinolytic Abciximab \pm half dose of reteplase vs. placebo	2,425	No difference in PE with combination (GPI and fibrinolytic) or GPI vs. placebo (9.8% vs. 10.5% vs. 10.7%, $p = 0.55$)	Non ICH TIMI major bleeding through discharge greater with combination (GPI and fibrinolytic) (14.5% vs. 10.1% vs. 6.9%, $p < 0.05$)
On-TIME 2 Van't Hof et al. (17) Lancet 2008	GPI: high-dose tirofiban vs. placebo before PCI	984	Significantly lower extent of mean ST-segment deviation after PCI with tirofiban (3.6 mm vs. 4.8 mm, $p = 0.003$)	On background of clopidogrel 600 mg
HORIZONS-AMI Stone et al. (78) N Engl J Med 2008	DTI: bivalirudin vs. UFH and GPI	3,602	Primary composite of ischemia and bleeding reduced with bivalirudin (9.2% vs. 12.1%, $p = 0.005$)	Reduction in bleeding with bivalirudin (4.9% vs. 8.3%), but increase in stent thrombosis (1.3% vs. 0.3%), both $p < 0.001$
CLARITY-TIMI 28 Sabatine et al. (24) N Engl J Med 2005	Thienopyridine: clopidogrel vs. placebo in patients planned for fibrinolytic	3,491	Significant reduction in PE with clopidogrel vs. placebo (15% vs. 21.7%, $p < 0.001$)	Similar rates of major bleeding and intracranial hemorrhage between the 2 groups
COMMIT/CCS-2 Chen et al. (25) Lancet 2005	Thienopyridine: clopidogrel vs. placebo	45,852	Significant reduction in PE with clopidogrel vs. placebo (9.2% vs. 10.1%, $p = 0.002$)	No significant increase bleeding (fatal, transfused, ICH) with clopidogrel
EXTRACT-TIMI 25 Antman et al. (68) N Engl J Med 2006	LMWH: enoxaparin vs. UFH in patients planned for fibrinolytic	20,506	Significant reduction in PE with enoxaparin vs. UFH (9.9% vs. 12.0%, $p < 0.001$)	Enoxaparin group was treated throughout the hospitalization. UFH group was treated for 48 h. Increased major bleeding was observed with enoxaparin (2.1% vs. 1.4%, $p < 0.001$).
OASIS-6 Yusuf et al. (86) N Engl J Med 2006	LMWH: fondaparinux vs. UFH or placebo	12,092	PE reduced with fondaparinux in total trial population (9.7% vs. 11.2%, $p = 0.008$)	Reduction in PE seen in Stratum I (no indication for UFH, randomized to fondaparinux or placebo), but not in Stratum II. Increased rate of catheter thrombosis in PCI group ($n = 0$ vs. 22, $p < 0.001$).
Across the spectrum of ACS (NSTEMI-ACS and STEMI)				
TRITON-TIMI 38 Wiviott et al. (43) N Engl J Med 2007	Thienopyridine: prasugrel vs. clopidogrel	13,608	Significant reduction in PE with prasugrel vs. clopidogrel (9.9% vs. 12.1%, $p < 0.001$)	More major bleeding with prasugrel (2.4% vs. 1.8%, $p = 0.03$)

cTn = cardiac troponin; DTI = direct thrombin inhibitor; GPI = glycoprotein IIb/IIIa inhibitor; ICH = intracranial hemorrhage; LMWH = low molecular weight heparin; NSTEMI-ACS = non-ST-segment elevation acute coronary syndromes; PCI = percutaneous intervention; PE = primary end point; RRR = relative risk ratio; STEMI = ST-segment elevation myocardial infarction; TMPG = Thrombolysis In Myocardial Infarction myocardial perfusion grade; UFH = unfractionated heparin.

Table 2 Current Guideline Recommendations for GPIIb/IIIa Inhibitors

	Early Invasive/PCI		Medical Management	
	ACC/AHA (1–3)	ESC (4–6)	ACC/AHA (1–3)	ESC (4–6)
STEMI (2,6)	Class IIa (abciximab) Class IIb (tirofiban, eptifibatide)	Class I (without stenting) Class IIa (with stenting)	Class IIIb (abciximab with half-dose lytic) Patients age <75 yrs	Class III
UA/NSTEMI (1,3–5)	Class I (either GPI or clopidogrel in addition to aspirin should be initiated before angiography) Class IIa (reasonable to initiate antiplatelet therapy with both GPI and clopidogrel)	Class I (high risk)	Class I (if subsequent recurrent symptoms/ischemia, heart failure, or serious arrhythmia occur angiography should be performed with upstream administration of either clopidogrel or GPI) Class IIa (if recurrent ischemic discomfort with clopidogrel, it is reasonable to add a GP IIb/IIIa antagonist before angiography) Class IIb (may be reasonable to add GPI to oral antiplatelet and anticoagulant therapy)	Class II (high risk)

ACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology; GP = glycoprotein; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; UA = unstable angina; other abbreviations as in Table 1.

in 1,101 patients with STEMI treated with primary stenting (rescue PCI was an exclusion) in 3 placebo-controlled trials. At 3-year follow-up, the use of abciximab significantly reduced the rate of death or reinfarction (12.9% vs. 19%, $p = 0.008$), with a trend toward lower rates of mortality (10.9% vs. 14.3%, $p = 0.052$). There was no significant difference in major bleeding risks between the 2 arms.

The FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial (16) was the largest study to date to investigate the strategy of facilitated PCI with GPI. A total of 2,452 patients were randomized in a double-blind, double dummy manner to 1 of 3 arms: abciximab with half dose reteplase ($n = 828$), abciximab alone ($n = 818$), or placebo ($n = 806$) before PCI. The last group received abciximab in the catheterization laboratory only if PCI was performed. There was no difference in the primary composite end point of mortality, ventricular fibrillation after 48 h, cardiogenic shock, or congestive heart failure within 90 days (9.8%, 10.5%, and 10.7% for the 3 treatment arms, respectively; $p = 0.55$) (Fig. 1A) despite greater rates of early ST-segment resolution with combination-facilitated PCI (43.9%, 33.1%, and 31.0%, respectively; $p = 0.01$ and $p = 0.003$, respectively). Moreover, the rates of nonintracranial TIMI major or minor bleeding through day 7/discharge were greater with combination facilitation (14.5%, 10.1%, 6.9%; both $p < 0.05$ compared with placebo).

In the ON-TIME 2 trial (17), 984 patients with STEMI who received aspirin, heparin, and 600 mg of clopidogrel were randomized to pre-treatment with high-dose tirofiban or placebo prior to PCI. The primary end point of the extent of mean residual ST-segment deviation 1 h after PCI was significantly lower in those receiving tirofiban versus those receiving placebo (3.6 mm vs. 4.8 mm, $p = 0.003$). In contrast to FINESSE, patients treated with GPI had lower rates of the composite of death, recurrent MI, urgent target vessel revascularization, or blinded bail-out use of tirofiban (26% vs. 32.9%, $p = 0.020$) with no significant increase in

TIMI major or TIMI minor bleeding (Fig. 1B). Patients in On-TIME 2 presented sooner after symptoms compared with those in FINESSE (median 76 min vs. 126 min, respectively), leading the authors to hypothesize that patients presenting late may not derive the same benefit from upstream GP IIb/IIIa inhibition as those presenting early.

SAFETY AND DOSING. The major risk of GPIs is primarily bleeding and to a lesser extent thrombocytopenia. Bleeding risks increase as multiple antithrombotic agents are combined, especially in certain vulnerable subgroups. In the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines) registry (18), 42% of patients received at least one initial dose of an antithrombotic drug outside of the recommended range, and 27% received an excess dose of GPI. Excess dosing was associated with older age, female sex, renal insufficiency, low body weight, diabetes mellitus, and congestive heart failure. Patient who received an excess dose of GPI had 36% (95% CI: 10% to 68%) greater odds of a major bleed. The authors estimated that 15% of major bleeding in the studied population could be attributed to excess dosing of antithrombotic therapies.

An analysis of 857 patients from the PROTECT (Randomized Trial to Evaluate the Relative PROTECTION against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia among Anti-Platelet and Anti-Thrombotic Agents)-TIMI 30 study with NSTEMI-ACS undergoing PCI treated with eptifibatide and either heparin or low molecular weight heparin (LMWH) also showed that older age was independently correlated with bleeding (19). Among patients with estimated creatinine clearance ($CrCl$) ≤ 50 ml/min, the maintenance infusion of eptifibatide was not properly adjusted downward (from 2 to 1 μ /kg/min) 45% of the time, leading to high rates of bleeding (20%) and transfusions (27%).

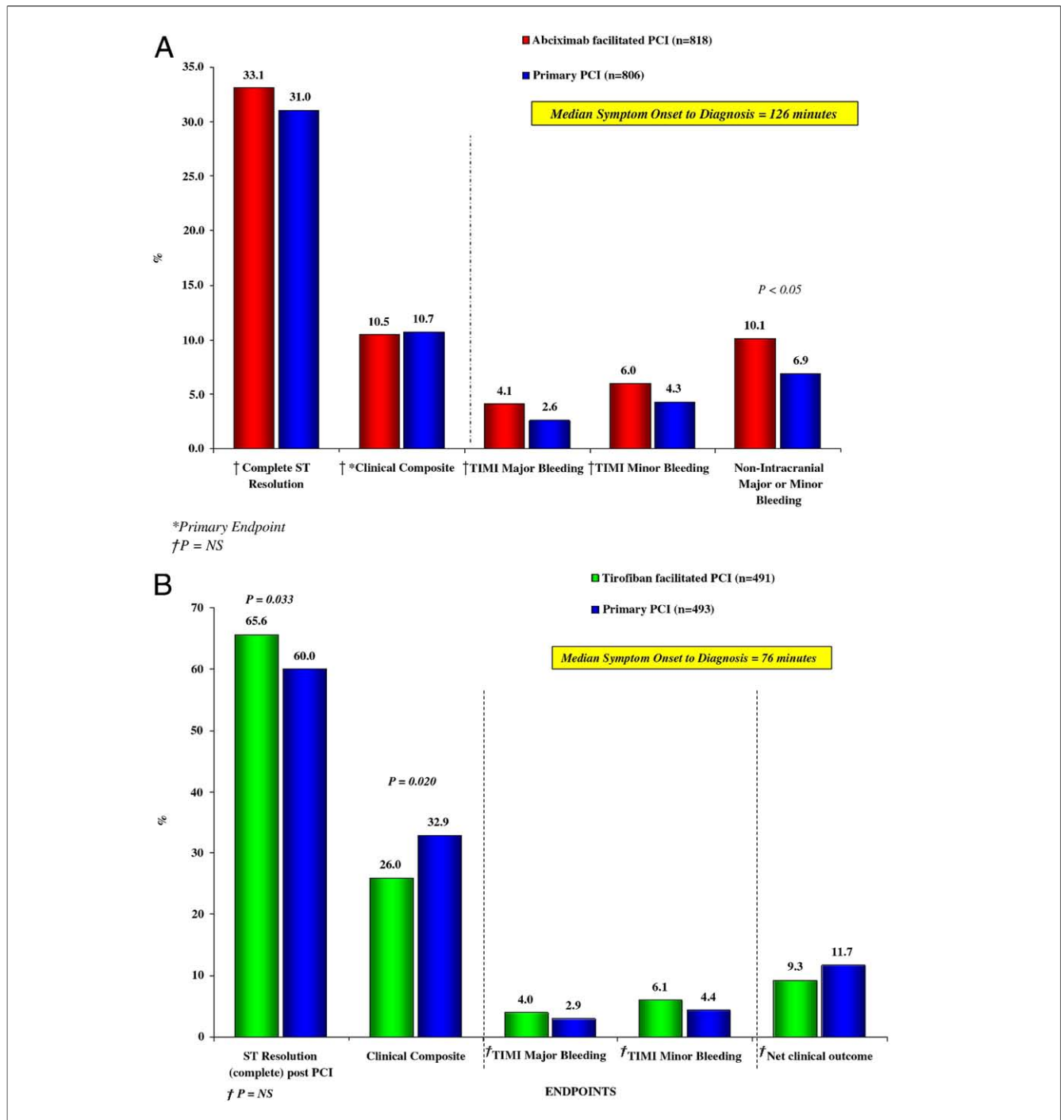


Figure 1 Major Trial Findings in FINESSSE and On-TIME 2

(A) Major findings in the FINESSSE trial (16). The rates of complete (>70%) ST-segment resolution at 60 to 90 min, primary composite (all-cause mortality, ventricular fibrillation >48 h, cardiogenic shock, congestive heart failure) through 90 days, Thrombolysis In Myocardial Infarction (TIMI) major bleeding, or TIMI minor bleeding were not significantly different between patients randomized to abciximab facilitated percutaneous coronary intervention (PCI) versus primary PCI. Abciximab did increase the combined rate of nonintracranial major or minor bleeding. (B) Major findings in the On-TIME 2 trial (17). The rate of complete ST-resolution after PCI was greater, and clinical composite of death, recurrent myocardial infarction, urgent target vessel revascularization, or blinded bail-out use of tirofiban at 30 days was lower in the tirofiban arm. There was no significant difference in TIMI major bleeding, TIMI minor bleeding, or net clinical outcome (death, recurrent myocardial infarction, urgent target vessel revascularization, or major bleeding). NS = not significant.

SUMMARY. Extensive data support the use of intravenous GPIs in the setting of moderate- or high-risk NSTEMI-ACS, particularly if an early invasive strategy is planned. Patients

who present with STEMI who are undergoing primary PCI also appear to benefit; however, the benefit is less evident, in part because of the difficulty of diagnosing reinfarction early

after STEMI due to increased (and often still increasing) cardiac markers. In the setting of low-risk ACS, GPIs may not be useful, and are potentially harmful, in troponin-negative patients in whom a conservative management strategy is planned, or if the bleeding risk is elevated. Although these agents have been available for more than a decade, and they have been studied extensively, open questions remain, including the timing of initiation, their clinical utility in combination with and compared with newer antithrombotics, and optimal dosing in certain patient populations (i.e., the elderly, patients with renal insufficiency).

Adenosine diphosphate (ADP) antagonists. Clopidogrel bisulfate is a thienopyridine derivative, which is an antagonist for the P2Y₁₂ receptor. It is a pro-drug that first must be absorbed and metabolized by the liver cytochrome P450 enzymes into an active metabolite, which then binds irreversibly to the receptor (20). The combination of clopidogrel and aspirin has become the standard adjunctive regimen in prevention of thrombotic events after intracoronary stenting (21).

CLOPIDOGREL AS AN ANTIPLATELET AGENT IN ACS. In the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial, dual antiplatelet therapy with clopidogrel (300-mg load, then 75 mg/day) for an average of 9 months in addition to aspirin was found to be superior to aspirin alone in preventing the composite end point of cardiovascular death, MI, and stroke in >12,500 patients with NSTEMI-ACS (22). This benefit also was observed in the large subset of patients who underwent PCI in the first weeks of therapy, most of whom had received open-label clopidogrel for four weeks after PCI (23).

More recently, both the CLARITY (Clopidogrel as Adjunctive Reperfusion Therapy)-TIMI 28 angiographic trial (24) and the COMMIT/CCS-2 (Clopidogrel and Metoprolol in Myocardial Infarction Trial/Chinese Cooperative Study) mortality trial (25) provided solid evidence of the benefit of the combination of aspirin and clopidogrel in patients with STEMI. Overall, in these trials, the safety profile of combination therapy appeared good, as there was no significant increase in major bleeding rates compared with the addition of clopidogrel. No loading dose was used in the COMMIT/CCS-2 trial, whereas in the CLARITY-TIMI 28 trial a 300-mg load was used. Patients >75 years of age (who are at greater risk of intracerebral bleeding) were excluded from CLARITY-TIMI 28. Therefore, it is important to stress that there are no safety data with a loading dose of clopidogrel in elderly patients receiving fibrinolytics or in patients with STEMI managed without reperfusion therapy (at any age).

NEED FOR PRE-TREATMENT. The authors of several studies have established the clinical benefit of pre-treatment with a loading dose of 300 mg of clopidogrel on clinical outcomes after PCI. A post-hoc analysis of the CREDO (Clopidogrel for the Reduction of Events During Observation) trial has demonstrated that for clopidogrel to be fully effective, the

loading dose of 300 mg of clopidogrel should be given at least 15 h before intervention (26). Although this dose can be readily implemented in patients undergoing elective PCI, it is problematic when unplanned intervention is required in an urgent setting.

The authors of recent studies have highlighted that a greater loading dose of 600 mg clopidogrel achieves quicker and greater platelet inhibition (27) and may result in better clinical outcomes (28). In the recently completed CURRENT-OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events-Optimal Antiplatelet Strategy for InterventionS 7) study, researchers compared the safety and efficacy of a high-dose regimen (600-mg load, followed by 150 mg/day for a week, then 75 mg/day for 3 weeks) versus a standard dose regimen (300-mg load, then 75 mg/day) of clopidogrel in approximately 14,000 patients with NSTEMI-ACS and PCI planned within the next 24 h (29). Results are expected to be reported this year.

Early pre-loading with clopidogrel may result in a greater rate of perioperative bleeding if surgery is performed <5 days after clopidogrel withdrawal (22). This concern has led some to advocate withholding clopidogrel in ACS patients until the coronary anatomy is defined at least when early coronary angiography is planned. However, the early phase of ACS is the period of greatest risk, and if patients are not receiving GPIs, there is a concern that they may be left with high residual platelet activation when receiving aspirin alone. The ESC guidelines (5), on these grounds as well as the merit of simplicity, recommend against postponing the administration of clopidogrel until after angiography. Recent observational data from the CRUSADE registry in patients undergoing coronary artery bypass surgery (30), the majority of whom received clopidogrel within 5 days of surgery, suggests that the modest increase in bleeding and blood transfusion in those patients is not associated with a detectable impact on the “hard” outcomes of death, reinfarction and stroke.

VARIABILITY IN RESPONSE TO CLOPIDOGREL. The authors of several studies have demonstrated that there is a wide interindividual variability in the response to clopidogrel, at least in terms of inhibition of platelet response to ADP (31). Part of this variability may be genetically determined (32), dependent upon clinical patient characteristics (33), and/or result from interactions with commonly used drugs such as proton pump inhibitors (34), although the latter remains controversial as detailed in a recent ACC/AHA/American College of Gastroenterology joint statement (35). The predictive value of an impaired response to clopidogrel is debated. Although a few studies (36,37) suggest that patients experiencing a stent thrombosis have suboptimal inhibition of platelet aggregation on clopidogrel, the post hoc nature of many of these studies makes it difficult to clarify whether abnormal response to clopidogrel is the cause or the consequence of stent thrombosis. A prospective

study (38) performed in 804 patients (the majority with ACS) who underwent drug-eluting stent implantation demonstrated for the first time that poor responders to clopidogrel had a ~3-fold increased risk of definite/probable stent thrombosis and cardiac death.

Emerging studies suggest that greater, repeated doses of clopidogrel may be effective to reduce complications in patients with impaired response to clopidogrel (39). However, there is also wide variability in terms of assays used, experimental conditions, timing of assessment, and definitions used for defining poor responders (40). In addition, the optimal level of *ex vivo* platelet inhibition to have an impact on clinical outcomes *in vivo* is unclear. Given these uncertainties, it is premature to embark on widespread testing of the response of patients to clopidogrel or other antiplatelet agents, particularly given the modest amount of data regarding the proper clinical course of action if a poor response is identified.

PRASUGREL. New P2Y₁₂ receptor antagonists are under clinical development, and one (prasugrel) has been approved by the U.S. Food and Drug Administration. Prasugrel is a third-generation thienopyridine derivative that provides quicker, greater, and more consistent inhibition of platelet activation than clopidogrel (41,42). In the TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel)–TIMI 38 trial, 13,608 patients with moderate-to-high-risk NSTEMI-ACS or STEMI who were scheduled to undergo PCI were randomly assigned to receive prasugrel (60-mg load then 10 mg/day) or clopidogrel (300-mg load then 75 mg/day) for a mean duration of 14.5 months (43). The major efficacy end point (a composite of cardiovascular death, nonfatal MI, or nonfatal stroke) was significantly reduced from 12.1% in patients receiving clopidogrel to 9.9% in patients receiving prasugrel.

Importantly, the protective effect of prasugrel was observed across the full spectrum of ACS and was already apparent 3 days after treatment start. Stent thrombosis also was reduced (2.4% and 1.1%, respectively). However, the reduction of ischemic events with prasugrel was achieved at the expense of a 32% increase in TIMI major bleeding not related to coronary artery bypass grafting (CABG) (1.8% and 2.4%, respectively), including life-threatening bleeding. Exploratory subgroup analysis indicate that the safety/efficacy balance of prasugrel might be particularly unfavorable in patients with a history of stroke or transient ischemic attack, in elderly patients (age ≥75 years), and in those with a body weight <60 kg.

Novel antiplatelet agents. Given the importance of the platelet in the response to vascular injury and the clinical benefit observed with a variety of approaches to interfering with platelet function, there have been multiple attempts to further improve upon both the safety and efficacy of antiplatelet therapy. Current antiplatelet therapies typically are used in combination (for example, aspirin plus clopidogrel and/or GP

IIB/IIIa inhibitors) for better efficacy with the recognition that such an approach creates the possibility of additional bleeding. Several ADP P2Y₁₂ inhibitors that achieve a high degree of platelet inhibition (>70%) are under clinical investigation. These agents aim to overcome some of the potential limitations of clopidogrel, namely, delayed onset of action, modest level of platelet inhibition, wide variability in interpatient pharmacodynamic response (“hyporesponders” and “hyperresponders”), and irreversible platelet inhibition (see also the previous section “Prasugrel”).

Ticagrelor (formerly AZD6140) is an orally active, non-thienopyridine, reversible, P2Y₁₂ receptor antagonist (44). Contrary to clopidogrel or prasugrel, it is active without the requirement for metabolic activation and results in a high level of inhibition of ADP-induced platelet aggregation (45). It was recently compared with clopidogrel in DISPERSE-2 (Dose confirmation Study assessing anti-Platelet Effects of AZD6140 vs. clopidogrel in non-ST-segment Elevation myocardial infarction) (46), a phase 2 study in patients with ACS and demonstrated no increase in major bleeding and favorable trends in rates of MI or the composite end point of cardiovascular death, MI, or stroke. Of note, the use of this agent is associated with an increase in 2 adverse events: dyspnea and ventricular pauses. Although these side effects were of mild-to-moderate intensity and also were observed in patients treated with clopidogrel, it will be important to assess their clinical impact in future studies. A very large clinical trial, PLATO (PLATElet inhibition and patient Outcomes), compared ticagrelor with clopidogrel in approximately 18,000 ACS patients, with a primary end point of cardiovascular death, MI, and stroke at 12 months. Top-line results announced in a press release (47) reported that ticagrelor reduced the primary composite of vascular death, nonfatal myocardial infarction, or nonfatal stroke compared with clopidogrel, while achieving a similar safety profile as in the DISPERSE-2 phase 2 study (46).

Cangrelor (formerly AR-C69931 MX) is a parenteral direct P2Y₁₂ receptor antagonist. It has a rapid onset of action and a plasma half-life of 5 to 9 min. After withdrawal of therapy, platelet function returns to normal in approximately 20 min (48). The agent has linear kinetics, with no interference with renal or hepatic function. These characteristics make it a potentially attractive agent for use in PCI (49,50). Two large randomized clinical trials tested cangrelor in PCI (CHAMPION PCI [Cangrelor versus standard therapy to achieve optimal management of platelet inhibition] and CHAMPION PLATFORM), with a composite primary end point of death, MI, and urgent target vessel revascularization at 48 h. Recently, a press release reported that both CHAMPION trials were terminated early due to lack of efficacy with cangrelor (51).

Therapeutic approaches that have incremental efficacy while minimizing additional bleeding liability would be especially desirable. Such a concept might be possible through agents that inhibit the platelet thrombin receptor also known as PAR. Recently, Becker *et al.* (52) published

the TRA-PCI (Thrombin Receptor Antagonist Percutaneous Coronary Intervention) study, in which they tested a novel PAR-1 inhibitor, also known as a thrombin receptor antagonist. These data suggested that high levels of thrombin-induced platelet aggregation inhibition could be obtained in patients undergoing elective percutaneous intervention while adding minimal bleeding risk to a regimen of aspirin, clopidogrel, and a parenteral anticoagulant. This novel antiplatelet agent is now being studied in 2 large phase 3 clinical trials (TRA 2P [Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events]–TIMI 50 and TRACER [Thrombin Receptor Antagonist for Clinical Event Reduction in acute coronary syndrome]).

Part 2: Anticoagulants

Heparin and LMWHs. The LMWHs are fragments of unfractionated heparin (UFH) with a mean molecular weight of approximately 5,000 Daltons (53). Similar to UFH, LMWHs exert their anticoagulant effect indirectly via antithrombin. However, with shorter chain lengths, LMWHs have less of an effect on thrombin (factor IIa) and a more preferential effect on factor Xa, along with less plasma protein binding, better bioavailability, less platelet activation, lower risk of immune-mediated thrombocytopenia (54), and significantly less activity on osteoclasts and risk of bone loss than with UFH (55).

Although the bioavailability of LMWH is sustained when given subcutaneously, there are uncertainties regarding the onset of effective anticoagulation, as well as an inability to monitor or titrate drug levels. Although anti-Xa activity can be measured in the laboratory, there is no clearly established “therapeutic” range for the degree of anticoagulation that should be targeted, particularly in the setting of PCI. The LMWHs also are cleared renally; thus, in patients with renal insufficiency, a dose adjustment may be necessary to avoid excessive bleeding complications. In a recent substudy of ExTRACT (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment)–TIMI 25, multivariate analysis revealed that with every 30 ml/min stratum decrease in CrCl, the risk of major and minor bleeding increased by 50% (56). Thus, adjusting the dose of LMWH by one-half may be necessary in patients with CrCl <30 ml/min, and its use in the presence of overt renal failure requires further evaluation. Finally, in the presence of bleeding, reversal with protamine only appears to neutralize approximately 60% of the antifactor Xa activity of LMWH. The recommended dose is 1 mg of protamine per 100 antifactor Xa units (1 mg enoxaparin = approximately 100 antifactor Xa units) if LMWH was given within 8 h (57).

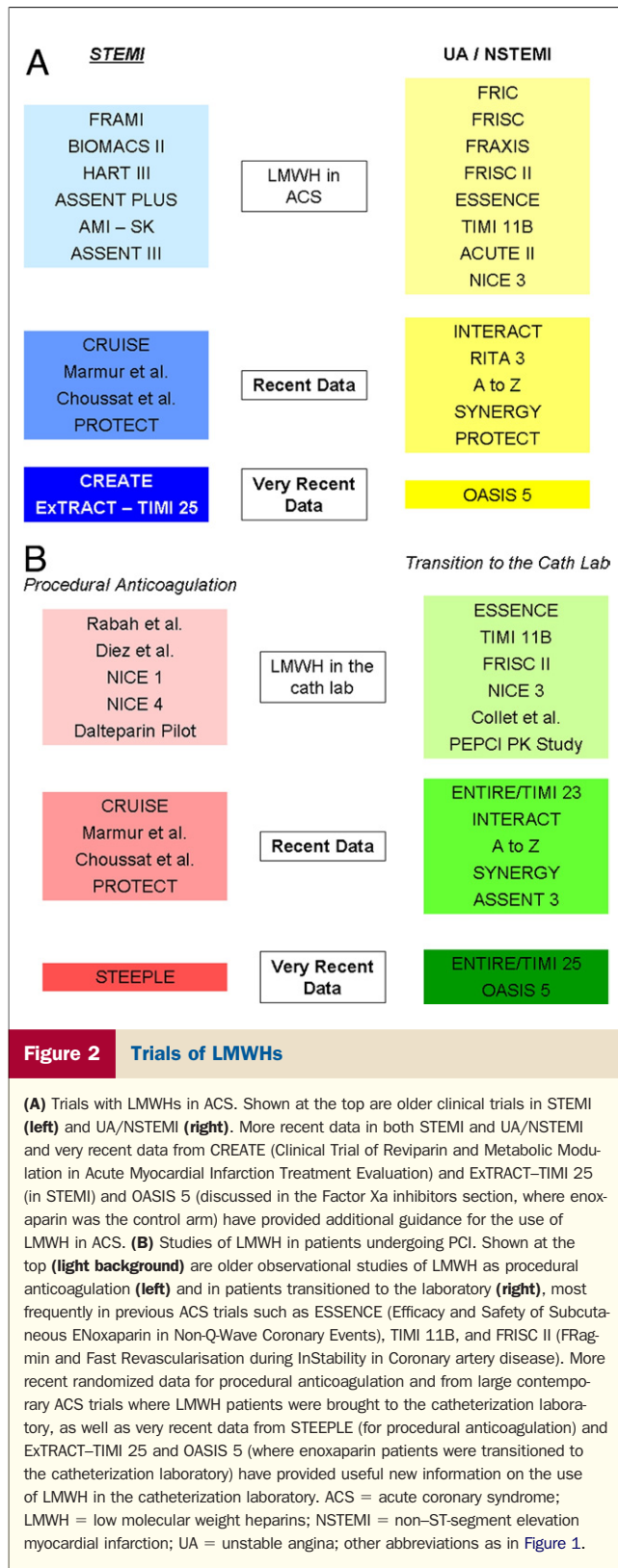
Although numerous studies have been performed that demonstrate the benefit (reduction in death and MI) of short-term UFH over placebo (58) in the setting of ACS, numerous pharmacokinetic limitations of UFH have necessitated the study of more effective anticoagulants. A number of trials have demonstrated the superiority of LMWH over

UFH in the conservative management of patients with NSTEMI-ACS (54,58). Although there have been several studies evaluating LMWHs in the setting of additional adjunctive pharmacologic therapies (59–61), further questions remain regarding the use of LMWHs in other settings, including in an early invasive strategy, in rapid transitions to the catheterization laboratory, for procedural anticoagulation, and in conjunction with fibrinolytic therapy for patients STEMI.

LMWH IN THE INVASIVE MANAGEMENT OF NSTEMI-ACS. Previous trials (ESSENCE and TIMI 11B) (54) suggested that medically managed patients with NSTEMI-ACS treated with LMWH had no increase in bleeding complications if they were transferred to the catheterization laboratory, although in older studies this was relatively infrequent and these transfers did not proceed rapidly (Figs. 2A and 2B). The authors of other studies (60,61) have provided evidence on patients receiving LMWH transferred to the catheterization laboratory with a supplemental intravenous dose of LMWH at the time of PCI. Additional larger studies have investigated LMWH in the context of an earlier invasive approach. The A to Z (Aggrastat to Zocor) study showed that in high-risk ACS patients managed with aspirin, tirofiban, and PCI the use of enoxaparin (1 mg/kg subcutaneous twice a day) was noninferior to UFH with no significant differences in TIMI major and minor bleeding (62).

The SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors) study (63) included 10,027 high-risk patients with NSTEMI-ACS destined for an early invasive approach who were randomized to subcutaneous enoxaparin (1 mg/kg twice a day) or weight-based UFH in addition to guideline-recommended aspirin, clopidogrel, and GPI. Patients randomized to enoxaparin who arrived to the catheterization laboratory >8 h after the last subcutaneous dose received an additional intravenous dose of 0.3 mg/kg before PCI. The primary end point (death or MI at 30 days) was not significantly different between the 2 groups (14% with enoxaparin, 14.5% with UFH, $p = 0.40$). However, there was a significant increase in TIMI major bleeding with enoxaparin (9.1% vs. 7.6% with UFH, $p = 0.008$) and, slightly, although not significantly, greater rates of GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) major bleeding (2.7% vs. 2.2% with UFH, $p = 0.08$) and transfusion (17% vs. 16% with UFH, $p = 0.16$).

In patients already receiving UFH or LMWH who were switched at randomization under controlled, protocol-driven algorithms, there was no significant difference in bleeding between enoxaparin and UFH. Finally, patients randomized to enoxaparin who crossed over (off protocol) to UFH had significantly greater bleeding rates. Thus, adding UFH to enoxaparin in an uncontrolled fashion (“stacking” therapy), as opposed to a controlled, protocol-driven transition (Fig. 3), may result in increased bleeding complications. This issue was further highlighted in the recently



LMWH DURING PCI. The authors of several early studies (65,66) examined the use of intravenous LMWH as an alternative to UFH as procedural anticoagulation for PCI and found that LMWH in a nonemergent procedural PCI setting was as efficacious as UFH, with similar bleeding risk (Fig. 2B). Researchers from the STEEPLE (Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients, an International Randomized Evaluation) trial (67) examined the use of procedural intravenous enoxaparin in 3,528 patients undergoing nonurgent PCI. Patients were randomized to IV enoxaparin (0.5 or 0.75 mg/kg) or intravenous (IV) UFH (50 to 70 U/kg or 70 to 100 U/kg) with or without a GPI. The primary end point, non-CABG-related major plus minor bleeding at 48 h, occurred in 6%, 6.6%, and 8.7% of the 0.5 mg/kg IV enoxaparin group, 0.75 mg/kg IV enoxaparin group, and IV UFH group, respectively ($p = 0.014$ for 0.5 mg/kg enoxaparin vs. UFH and $p = 0.052$ for 0.75 mg/kg enoxaparin vs. UFH). There was no statistically significant difference in death, nonfatal MI, or urgent target vessel revascularization at 30 days. By multivariate analysis, assignment to the enoxaparin group was an independent predictor of reduced major plus minor bleeding.

LMWH IN STEMI. The EXTRACT-TIMI 25 trial (68) involved 20,506 patients with STEMI who were randomized to enoxaparin (30 mg IV, then 1 mg/kg twice a day until hospital discharge; in patients >75 years of age, no bolus was given, and the subcutaneous dose was reduced to 0.75 mg/kg twice a day) or UFH (weight-based, activated partial thromboplastin time-adjusted) for at least 48 h. The primary end point of death/nonfatal MI at 30 days was significantly lower in the enoxaparin group (9.9% vs. 12% with UFH, $p = 0.001$), primarily driven by a significant reduction in reinfarction. In the overall study there was a significant increase in TIMI major bleeding (2.1% vs. 1.4% with UFH; $p < 0.001$) with no differences in ICH. It is important to note that treatment durations were, by design, not equivalent in the 2 groups (mean 7 days with enoxaparin, 48 h with UFH); therefore, the question of the impact of variable duration of therapy remains unanswered.

The treatment benefits of enoxaparin appeared to emerge by 48 h (while both groups were receiving active therapy), with a nonsignificant trend in death or nonfatal MI (4.7% vs. 5.2% with UFH; $p = 0.08$) and a significant difference in death, nonfatal MI, or urgent revascularization (5.3% vs. 6.1% with UFH; $p = 0.02$) through 48 h. These reductions, however, were relatively small in comparison with the overall reductions at 30 days, suggesting that continued in-hospital therapy with enoxaparin provided substantial additional benefit. In a recent analysis of 4,676 patients from EXTRACT undergoing PCI within 30 days of randomization, there was a significant reduction in death/MI, urgent revascularization, and stroke in the enoxaparin group, whereas TIMI major and minor bleeding was similar to the UFH group (69).

presented STACKENOX (STACK-on ENOXaparin) study (64), which showed that adding UFH on top of previous enoxaparin resulted in dramatic and prolonged increases in coagulation parameters.

SYNERGY – Protocol for Switching at Randomization

Enoxaparin → UFH (unfractionated heparin)

If ≤ 8 hours after the last enoxaparin dose – start UFH infusion at 12 U/kg/hr (no bolus, 1000 U/hr maximum) 8 hours after the last enoxaparin dose

If > 8 but ≤ 12 hours after the last enoxaparin dose – start UFH infusion at 12 U/kg/hr (1000 U/hr maximum) after a 30 U/kg bolus (5000 U maximum)

If > 12 hours after the last enoxaparin dose – start UFH infusion at 12 U/kg/hr (1000 U/hr maximum) after a 60 U/kg bolus (5000 U maximum)

UFH → Enoxaparin

Turn off UFH, give subcutaneous enoxaparin right away

Figure 3 Antithrombotic Protocol Used in SYNERGY

The SYNERGY trial (63) used a pre-specified protocol to transition patients in a controlled fashion to/from UFH and LMWH. UFH = unfractionated heparin; other abbreviations as in Figure 2.

REAL-WORLD CONCLUSIONS. In numerous clinical trials, including a recent meta-analysis of $>22,000$ patients (70), the use of LMWH appears to be a viable treatment option across a wide clinical spectrum of patients presenting with ACS. The use of LMWH appears safe and effective in patients undergoing a controlled transition to the catheterization laboratory (SYNERGY), during PCI (STEEPLE), and in fibrinolytic-treated STEMI (ExTRACT-TIMI 25), including those going on to elective or urgent PCI (ExTRACT PCI). As LMWH becomes integrated into more broad-based ACS treatment strategies, it must be investigated in the future for potential use in other settings such as primary PCI for acute MI.

Direct thrombin inhibitors (DTIs). Increasingly, thrombin is viewed as functioning at the complex interface of tissue injury, hemostasis, and platelet response (71). The DTIs act by binding to thrombin and blocking its interaction with substrates in this multifaceted, redundant, and interactive biological system. Not only can DTIs directly block the formation of fibrin from fibrinogen by the action of thrombin, but they also can block the feedback activation of coagulation factors by thrombin (72) and inhibit the thrombin-induced component of platelet aggregation (73). The dual activity on fluid-phase thrombin and fibrin-bound thrombin gives DTIs a conceptual advantage over indirect upstream inhibitors in that the accretion of thrombi may be more effectively inhibited. The conceptual disadvantage is the risk that upstream prothrombotic elements may accumulate during DTI activity, leading to the risk of rebound. Currently, 3 DTIs are available for use in the setting of arterial thrombosis: lepirudin, argatroban, and bivalirudin;

however, this state-of-the-art review will focus on the latter given the more promising recent data with bivalirudin in ACS.

Bivalirudin is a synthetic bivalent inhibitor that consists of 20 amino acids that are slowly cleaved by thrombin at the active site, permitting gradual recovery of some of thrombin's functionality (74). When initially administered, it therefore begins as a noncompetitive thrombin inhibitor but gradually becomes a competitive inhibitor because of this return of thrombin functionality. It is cleared predominately by proteolytic cleavage but also has a significant component of renal clearance with a half-life of 25 min. Bivalirudin has been widely studied in conjunction with percutaneous coronary revascularization and may soon be available for treatment of NSTEMI-ACS when the aggressive interventional approach is used.

Interestingly, although no DTIs are currently approved for use in ACS, the largest mass of clinical trial data concerning DTIs was acquired in the setting of ACS. The authors of a key systematic overview (75) used patient-level data pooled across multiple trials comparing DTIs with UFH in $>35,000$ patients with either STEMI or NSTEMI-ACS. The primary result was that, overall, the DTIs reduced the composite of death and nonfatal MI by 15% on the relative scale and 0.8% on the absolute scale; however, there was no significant reduction in total mortality compared with UFH, and there was a modest increase in bleeding. However, significant heterogeneity was observed in 2 aspects: the bivalent inhibitors (hirudin and bivalirudin) were more effective versus UFH than were the univalent inhibitors (which actually appeared to be detrimental rela-

tive to UFH); and bivalirudin led to a markedly lower rate of bleeding than UFH, while the other DTIs had more bleeding.

Considerable interest has developed in the use of bivalirudin for ACS and PCI. Multiple trials have firmly established that bivalirudin is a reasonable therapy in both clinical conditions, although the clinical and expert communities remain divided in their interpretation of how extensively the results of these trials should be applied in practice. The authors of the REPLACE II (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events) study (76) compared a regimen of bivalirudin and GPI for “bailout” with a regimen of UFH and GPI with a primary end point of noninferiority for a triple composite end point of death, nonfatal MI, and major bleeding (77). The trial has been interpreted by its advocates to demonstrate that bivalirudin is noninferior to a combination of UFH and GPI in PCI; however, others believe that the study design prevents definitive interpretation: the noninferiority margins were borderline, the patient population was low-risk, the end point definitions emphasized small differences in bleeding (in favor of bivalirudin) and deemphasized differences in markers of cardiac necrosis (again in favor of bivalirudin), and the use of the comparator treatments was suboptimal.

Similarly, in the ACUTY trial (9) bivalirudin with GPI was noninferior in terms of the 30-day composite ischemia end point (7.7% vs. 7.3% $p = 0.39$), major bleeding (5.3% vs. 5.6% $p = 0.38$), and the net clinical end point (11.8% vs. 11.7% $p = 0.93$) when compared with heparin with GPI. Bivalirudin alone was associated with a noninferior rate of the ischemia end point and significantly lower rates of major bleeding (3.0% vs. 5.7%, $p < 0.001$) as well as the net clinical end point (10.1% vs. 11.7%, $p = 0.02$). At 1 year, the rates of composite ischemia and mortality remained similar in patients treated with bivalirudin alone when compared with heparin (unfractionated or enoxaparin) plus GPI regardless of patient risk. The mortality benefit was independent of the timing of clopidogrel administration. In addition, switching to bivalirudin from unfractionated heparin or enoxaparin also appeared to be associated with similar benefits of reduced bleeding and protection for the composite or ischemia and death at one year.

In the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial (78), 3,602 patients with STEMI undergoing primary PCI were randomized to either open-label bivalirudin monotherapy or heparin and GPI. Bivalirudin monotherapy reduced the primary composite of ischemic events or bleeding by 24% (9.2% vs. 12.1%, $p = 0.005$), driven entirely by a 40% reduction in bleeding (4.9% vs. 8.3%, $p < 0.001$) (Fig. 4). There was a 1% absolute excess in acute stent thrombosis with bivalirudin monotherapy (1.3% vs. 0.3%, $p < 0.001$), which possibly was related to insufficient antiplatelet effect in the first 24 h despite a load of 600 mg of clopidogrel. Nonetheless, death from cardiac

causes were reduced with bivalirudin (1.8% vs. 2.9%, $p = 0.03$).

Again, concerns about the specifics of the comparator regimens, patient populations, and definitions have led to healthy debate about the pragmatic interpretation of these trials. However, the pattern of effective reduction in ischemic events compared with putative placebo and a very favorable profile for bleeding is consistent throughout these trials. In summary, bivalirudin is established as a viable monotherapy in the setting of “nonhigh-risk” PCI (79) and may soon be available for ACS in situations in which an aggressive, angiographically driven strategy is planned. The profile supports use of bivalirudin particularly in patients at high risk of bleeding, except in the case of MI treated with fibrinolytic agents, in which an appropriate dose has not yet been developed (80).

The future may bring expanded use of DTIs. The development of an effective, safe, orally available DTI has been a major challenge for the pharmaceutical industry. Ximelagatran was a highly touted, orally administered DTI that, despite many favorable characteristics, was not approved by the U.S. Food and Drug Administration and was withdrawn from the market in Europe because of evidence of hepatotoxicity combined with questions about the demonstrated benefit compared with warfarin (81). Currently, at least 7 DTIs are being examined in clinical trials that are evaluating their use in deep venous thrombosis, ischemic heart disease, and atrial fibrillation. The oral DTI dabigatran (82) is farthest along the path of development, with major trials underway in all 3 arenas.

Factor Xa inhibitors. Fondaparinux is a synthetic analog of the pentasaccharide sequence in heparin that has a reversible binding to antithrombin but induces irreversible conformational changes, leaving the antithrombin activated also after dislocation of fondaparinux (83,84). As with LMWH, fondaparinux has complete subcutaneous availability and a longer half-life, allowing its administration as a once-daily dose for all indications. Fondaparinux has been tested in daily fixed doses ranging from 2.5 mg up to 7.5 mg. Surprisingly, the lowest dose of 2.5 mg was tested and documented to be efficacious in NSTEMI-ACS and STEMI, as outlined in the next section. Beside the expected side effects of bleeding, the treatment is associated with very few side effects.

FONDAPARINUX IN NSTEMI-ACS. The efficacy and safety of subcutaneous fondaparinux 2.5 mg daily was compared with routine treatment with enoxaparin 1 mg/kg body weight for 8 days or until hospital discharge in the OASIS-5 trial (85). In this study, 20,078 patients with NSTEMI-ACS were randomized to either of these 2 treatments within 24 h after start of symptoms. The primary objective of showing noninferiority concerning the efficacy outcome of death, MI, or refractory ischemia at 9 days was fulfilled ($p = 0.007$) with 5.8% events in the fondaparinux compared with 5.7% in the enoxaparin group. However, major bleeds were

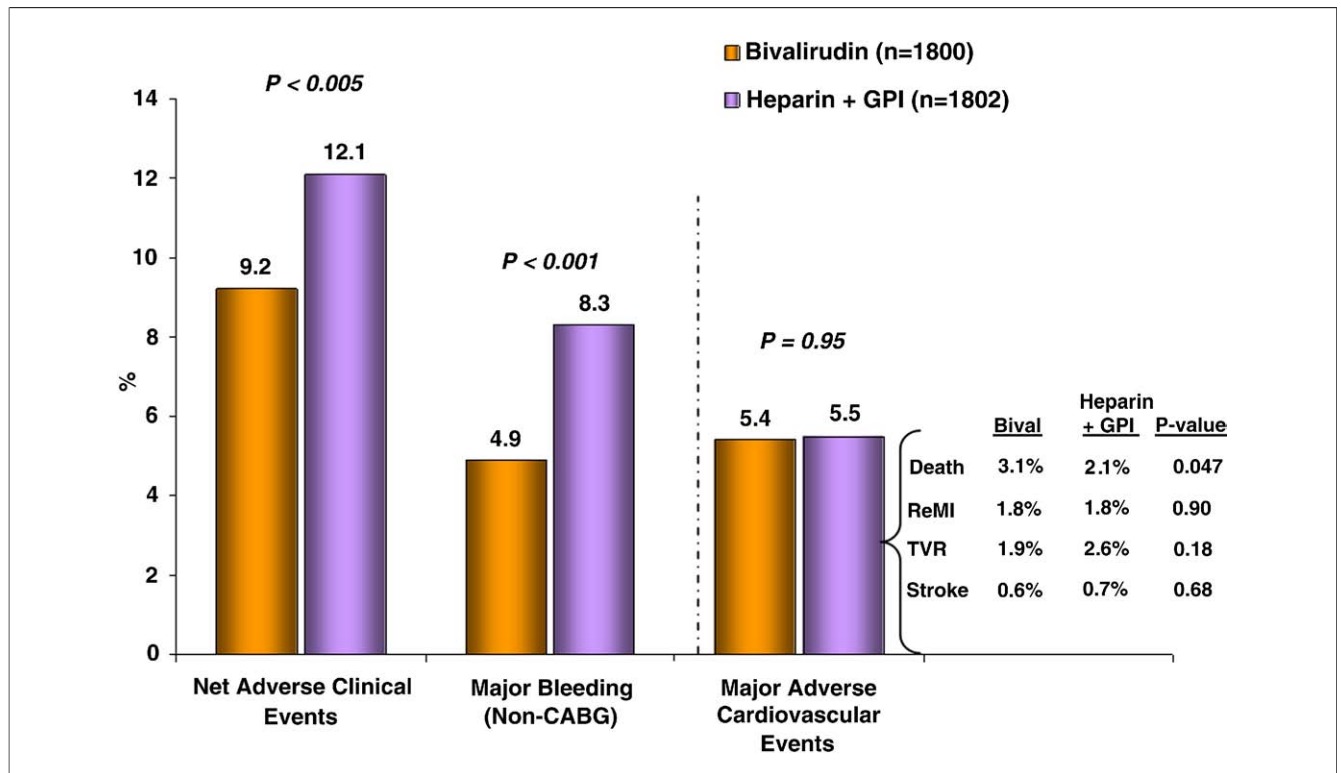


Figure 4 Main Results From HORIZONS-AMI

In HORIZONS-AMI (78), bivalirudin (Bival) was reduced the primary end point of net adverse clinical events (composite of major non-coronary artery bypassing grafting (CABG) bleeding and major adverse cardiovascular events) and major non-coronary artery bypassing grafting (CABG) bleeding compared to heparin and glycoprotein IIb/IIIa inhibitor (GPI). There was no difference in the composite of major adverse cardiovascular events (composite of death, reinfarction [ReMI], target vessel revascularization for ischemia [TVR], or stroke).

halved (2.2% with fondaparinux compared with 4.1% with enoxaparin, $p < 0.001$). Accordingly, the net clinical outcome of the composite of death, MI, refractory ischemia, or major bleeding was lower with fondaparinux (7.3% compared with 9.0% with enoxaparin, $p < 0.001$). Importantly, long-term mortality after 6 months was lower with fondaparinux 5.8% compared with 6.5% with enoxaparin ($p = 0.05$). Also, at this time point the net clinical benefit of the composite of death, MI, or stroke was reduced with fondaparinux (11.3% compared with 12.5% with enoxaparin, $p = 0.007$). Interestingly, long-term mortality was associated with the occurrence of earlier major bleeding, thereby emphasizing the importance of the reduced bleeding rate with fondaparinux as compared with enoxaparin.

During the trial, there were observations of catheter-related thrombi occurring more frequently with the use of fondaparinux (0.9% compared with 0.4% with enoxaparin, $p < 0.001$). In addition, there tended to be more clinical PCI-related coronary complications with fondaparinux (9.5% compared with 8.6% with enoxaparin, $p = 0.21$). There was, however, a lower rate of puncture-related bleedings with fondaparinux (3.3% compared with 8.1% with enoxaparin, $p < 0.001$). Therefore, the composite of procedure-related complications including death, MI, or bleeding was significantly less frequent with fondaparinux

than with enoxaparin (16.6% compared with 20.6%, $p < 0.001$). The overall conclusions from the trial were that fondaparinux, as compared with the currently recommended routine treatment with enoxaparin, reduces the risk of bleeding and lowers long-term morbidity and mortality (5). Retrospectively, the investigators learned during the trial that the greater risk of catheter-related thrombi might be avoided by using UFH during the procedure without losing the advantage with regard to reduction in bleeding.

FONDAPARINUX IN STEMI. Fondaparinux also has been evaluated as an alternative to standard adjuvant anticoagulant treatment in STEMI (86). In the OASIS-6 trial, 12,092 patients were randomized to subcutaneous fondaparinux 2.5 mg daily during 8 days or until hospital discharge and compared with subjects who received standard treatment with UFH or no anticoagulant treatment. In Stratum I (no indication for UFH), 5,658 patients were randomly allocated to fondaparinux or placebo. In Stratum II, 6,434 patients were randomized to fondaparinux in comparison with an infusion of UFH for 48 h, followed by placebo for 8 days or until hospital discharge. Within both strata there were subgroups with and without reperfusion treatments. Among those in whom reperfusion therapy was administered, different modes were used. Thrombolysis was admin-

istered in 5,436 patients and was dominated by nonfibrin-specific lytics (84%). Primary PCI was used in 3,789 patients, of whom 99% were in Stratum II.

In the total trial population the composite primary end point of death or reinfarction at 30 days was reduced from 11.2% to 9.7% with the use of fondaparinux ($p = 0.008$). The reduction was only observed in Stratum I (without indication for UFH), with a reduction from 14.0% to 11.2% ($p < 0.001$) with fondaparinux. In Stratum II (with indication for UFH) there was no difference, with 8.3% in the UFH/placebo group versus 8.7% in the fondaparinux group. In the subgroup treated with primary PCI, there was a trend of harm with fondaparinux, with a 30-day rate of death or MI of 6.1% with fondaparinux compared with 5.1% in the UFH group ($p = 0.19$). In the fondaparinux group there was also a greater rate of catheter-related thrombosis ($n = 0$ vs. 22; $p < 0.001$) and more coronary complications ($n = 225$ vs. 270; $p = 0.04$). In the other 2,666 patients in Stratum II (with indication for UFH but without primary PCI), there was a trend to benefit with fondaparinux versus UFH/placebo, with a reduction from 13.8% to 11.5% in the composite of death or MI at 30 days ($p = 0.08$). There was also a trend toward fewer major bleeds with fondaparinux when combining both strata.

The conclusions of the trial were that in acute STEMI without indication for UFH, fondaparinux is more effective and as safe as no anticoagulant treatment, regardless of whether any reperfusion treatment with streptokinase is used (30). In other STEMI patients treated with thrombolytics with an indication for UFH (i.e., fibrin-specific agents such as alteplase), fondaparinux for 8 days (or until discharge) seems at least as effective and as safe as a UFH infusion for 48 h. In STEMI patients treated with primary PCI, fondaparinux appears to be associated with a risk of harm, on the basis of an increased rate of coronary complications.

ORAL FACTOR Xa INHIBITORS. Currently, a number of intravenous and oral direct factor Xa inhibitors have entered clinical development. In contrast to antithrombin-mediated inhibition, these compounds inhibit factor Xa both when free in the circulation and when bound within the prothrombinase complex. Some information on the initial clinical results and the development programs are currently available for at least 1 IV (otamixaban) (87) and several oral inhibitors of factor Xa: edoxaban (DU-176b) (88), apixaban (89), rivaroxaban (90), waroxaban (LY 5157117) (91), and YM 150 (92). The majority of the available clinical data are related to the efficacy and safety of the oral inhibitors of factor Xa in phase 2 to 3 studies on the prevention of venothromboembolism after major orthopedic surgery. In regard to otamixaban, results of a phase 2 study in the context of PCI have recently been published (87). Rivaroxaban, apixaban, and edoxaban are currently under evaluation in phase 3 studies of stroke prevention in atrial fibrillation and/or secondary prevention after ACS. To date, the hepatic safety profile reported with oral factor Xa

inhibitors compares favorably to that described with ximelagatran (see the section “Direct thrombin inhibitors”).

Novel anticoagulants. Both oral and parenteral anticoagulants under development seek to improve upon currently available therapeutic approaches. New anticoagulants can be divided into 3 groups based on their primary target in the coagulation cascade: 1) inhibitors of initiation of coagulation; 2) inhibitors of the propagation of coagulation; and 3) thrombin inhibitors (see the section “Direct thrombin inhibitors”) (93).

Inhibitors of the initiation of coagulation cascade include drugs that target tissue factor, the tissue factor-VIIa complex, and active site-blocked FVIIa. A monoclonal antibody to tissue factor demonstrated dose-related inhibition of coagulation parameters in patients with coronary artery disease, although unexpected mucosal bleeding occurred at greater doses (94). A parenteral recombinant protein (rNAPc2) derived from the hematophagous hookworm reduced new thrombin generation and recurrent ischemia in a phase 2 trial of patients with NSTEMI-ACS managed with multiple antithrombotics and early catheterization (95). Although the addition of rNAPc2 was generally well tolerated when added to UFH or enoxaparin, some heparin appears necessary to avoid procedure-related thrombosis (as was observed with fondaparinux in the OASIS 5 and 6 trials; see the section “Factor Xa inhibitors”).

Novel anticoagulants that inhibit propagation of coagulation by targeting factor IXa, Xa, or their respective cofactors (factors VIIIa, Va) are under development. As examples, consider the factor IXa-antidote combination recently described (96). These drugs are based upon aptamer technology, single-stranded nucleic acids that can be tailored for specific targets with a high affinity. Aptamer technology addresses the issue of control and reversibility when anticoagulants are used in an acute care setting (97). An initial study (97) with this unique approach to anticoagulation suggest that anticoagulation (as measured by the aPTT) can be readily and predictably achieved and that the effects can be immediately reversed when administering an appropriately designed/matched antidote that also relies upon aptamer technology. Such an approach may have value in acute care settings where reversibility is critical, such as during and after cardiopulmonary bypass for coronary surgery or in situations in which bleeding occurs.

Conclusions

The projection that cardiovascular disease will be the predominant cause of death for at least the next generation (98) has caught the attention of the public, media, and policy makers worldwide. Despite great advances in antithrombotic therapies, associated high risks remain as the result of multifaceted interactions among patient comorbidities, drug combinations, multifaceted dosing adjustments, and the complexity of the care environment. In undertaking efforts to develop novel antithrombotic drugs,

Table 3 Challenges in Anticoagulant Drug Development and Use

Acute Care Setting	Chronic Care Setting
Treating patients early	Bleeding/tolerability
Complexity of health systems	Adherence issues/costs
Length of stay	Events over time
Drug combinations	Patient comorbidities
Monitoring effects	Monitoring effects
Interplay with invasive strategy	Drug combinations
Patient comorbidities	Surgeries/procedures
Dosing; bleeding	Multiple providers
Pharmacodynamics/pharmacokinetics outcomes	Pharmacodynamics/pharmacokinetics outcomes

many challenges exist (Table 3). Furthermore, the level of evidence needed to achieve the safety and efficacy standards required for regulatory approval and eventual clinical acceptance necessitates long-term investments and takes time. Public and media expectations regarding the safety and efficacy of novel therapies also add pressure on developers, physicians, and regulators. As novel therapies come into use, rigorous application of evidence-based medicine will be essential to ensure improved patient care with both current and novel antithrombotics.

Reprint requests and correspondence: Dr. Robert P. Giugliano, SM, TIMI Study Group, 350 Longwood Avenue, 1st Floor Offices, Boston, Massachusetts 02115. E-mail: rgiugliano@partners.org.

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