Anticoagulation in percutaneous coronary intervention

Balancing safety and efficacy of anticoagulation strategies is a fundamental goal in the performance of percutaneous coronary interventions. The ideal anticoagulant in the catheterization laboratory should effectively prevent thrombosis, yield a low bleeding risk, be titratable to individual clinical needs, be reversible when clinically indicated and be administered without the need for complicated infusions or routine monitoring. Despite its many drawbacks, unfractionated heparin continues to be the most commonly used anticoagulant in percutaneous coronary intervention. Nevertheless, anticoagulation options in the catheterization laboratory have grown substantially over the past 20 years and now include direct thrombin inhibitors, low-molecular-weight heparin molecules and Factor X inhibitors. Additional options are anticipated in the near future with novel agents targeting upstream factors in the coagulation cascade. The availability of multiple anticoagulation options allows for a tailored approach based on the individual patient's risk of thrombosis and bleeding. However, multiple anticoagulant choices add complexity in the catheterization laboratory because anticoagulants differ in the mode of administration, monitoring and duration of action. We present a review of current anticoagulation options, novel agents in development and practical issues such as monitoring, switching agents and importance of site access choice.

KEYWORDS: **anticoagulant** ▪ **coronary artery disease** ▪ **percutaneous coronary intervention** ▪ **thrombosis**

Brian P O'Neill[1], Eric Scot Shaw[1] & Mauricio G Cohen[†]

[1]*Cardiovascular Division, Miller School of Medicine University of Miami, Miami, FL, USA*

[†]*Author for correspondence: University of Miami Hospital, 1400 NW 12th Avenue, Suite 1179, Miami, FL 33136, USA*

Tel.: +1 305 243 5050

Fax: +1 305 243 5578

mgcohen@med.miami.edu

Over the past 20 years, the search for the ideal anticoagulant has become synonymous with a search for the holy grail. The ideal anticoagulant, besides maximizing efficacy and safety, would be conveniently administered without the need for constant monitoring. It would be easily titratable to each particular clinical situation or patient undergoing percutaneous coronary interventions (PCI) and finally, it would be easily reversible should the patient develop complications such as bleeding or coronary perforation. Table 1 presents the major characteristics of currently available agents. The main struggle throughout the past several decades has been the achievement of a balance between efficacy and safety, as both bleeding and recurrent ischemia have been shown to affect patient outcomes.

Patients with acute coronary syndromes (ACS) and thrombotic lesions are at a particularly increased risk of ischemic complications during PCI and therefore need potent and effective procedural anticoagulation. The presence of a large visible thrombus has been identified as an independent predictor of mortality, acute and subacute stent thrombosis and other major adverse cardiovascular events in patients undergoing PCI [1,2]. In addition, distal embolization, a thrombotic complication that may occur in up to 15% of patients undergoing primary PCI, is associated with increased reinfarction and long-term mortality rates [3].

Bleeding has also been shown to adversely affect outcomes. In a large international registry including 24,045 patients, major bleeding occurred in almost 4% of patients and was associated with a significantly increased risk of in-hospital death (18.6 vs 5.1%; $p < 0.001$) [4]. Registry data demonstrated that major bleeding occurs in approximately 5% of patients and minor bleeding in 12% of patients [5]. Independent risk factors for bleeding after PCI include older age, female gender, renal function, presence of anemia, use of balloon pumps, use of low-molecular-weight heparin (LMWH) prior to PCI and use of glycoprotein IIb/IIIa inhibitors (GPIs). A recent analysis from the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial demonstrated that bleeding and acute myocardial infarction (MI) have a similar and independent association with 30-day and 1-year mortality in moderate- to high-risk ACS patients managed with an invasive strategy, as depicted in Figure 1 [6].

Current available anticoagulation choices in PCI include unfractionated heparin (UFH), LMWH, direct thrombin inhibitors (DTIs)

Table 1. Principal characteristics of currently available anticoagulants.

Characteristic	UFH	LMWH	Fondaparinux	Bivalirudin
Anticoagulation target	IIa, Xa, IXa, XIa and XIIa	IIa and Xa	Xa	IIa
Labeled for PCI	Yes	Yes	No	Yes
Plasma half-life	30–60 min (iv.; longer at doses)	3–6 h (sc.)	17–21 h (sc.)	25 min (iv.)
ACC/AHA guideline recommendation for non-ST-elevation ACS undergoing initial invasive management	I (LOE: A)	I (LOE: A)	I (LOE: B)	I (LOE: B)
Need for iv. infusion	Yes	No	No	Yes
Elimination	Cellular mechanisms and renal	Renal	Renal	Renal (20%)
Need for monitoring	Yes	Yes	No	No
Test	ACT (during PCI)	Anti-Factor Xa level	Anti-Factor Xa level	ACT (not ideal)
Widely available point-of-care monitoring	Yes	No	No	No
Reversibility	Yes: protamine (1 mg/100 IU of UFH)	Partial: protamine (1 mg/1 mg of enoxaparin)	No	No

ACC: American College of Cardiology; ACS: Acute coronary syndrome; ACT: Activated clotting time; AHA: American Heart Association; iv.: Intravenous; LMWH: Low-molecular-weight heparin; LOE: Level of evidence; PCI: Percutaneous coronary intervention; sc.: Subcutaneous; UFH: Unfractionated heparin.

and Factor Xa inhibitors (Figure 2). Recent data from the Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) registry indicate that in a general catheterization laboratory population with a majority of cases (60%) undergoing PCI for positive stress test results or stable coronary disease, bivalirudin alone was used in 35% of cases, UFH combined with GPI in 34% and UFH alone in 19%. However, the anticoagulant choice changes significantly in patients with unstable coronary artery disease [7]. According to a recent analysis of the National Cardiovascular Data Registry (NCDR®) – Acute Coronary Treatment and Intervention Outcomes Network (ACTION®) registry, anticoagulation strategies used in non-ST-elevation ACS patients undergoing PCI were UFH in combination with GPI in 63% of cases, bivalirudin alone in 16%, UFH alone in 12.3% and bivalirudin in combination with GPI in 8% of cases [8]. The following sections address each individual anticoagulation strategy.

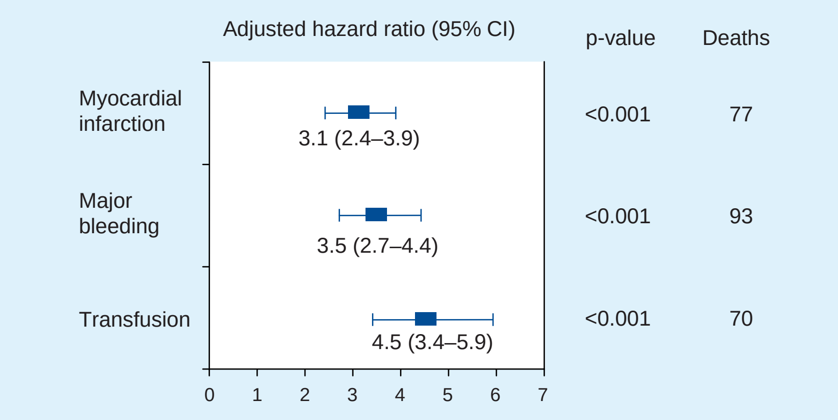

Figure 1. Adjusted 1-year mortality rates according to the occurrence of myocardial infarction, major bleeding and non-coronary artery bypass graft transfusion rates within 30 days of randomization in the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial. Indicates a similar mortality rate after recurrent ischemic and bleeding events in patients treated for acute coronary syndromes.
Adapted with permission from [6].

Unfractionated heparin

The anticoagulant of choice for the prevention of ischemic complications has been UFH since the inception of PCI in the late 1970s. Heparin is a heterogeneous mixture of highly sulfated polysaccharide chains ranging in molecular weight from approximately 3000 to 30,000 Da and manufactured from porcine intestine or bovine lung. Approximately a third of UFH molecules have the unique pentasaccharide sequence responsible for the interaction with anti-thrombin (AT) and most of its anticoagulant effect [9]. The pentasaccharide fraction causes a conformational change in AT, a naturally occurring α-globulin, which inactivates Factor Xa. Thrombin inhibition is mediated by the formation of a ternary complex, UFH–AT–thrombin. UFH binds to AT through its pentasaccharide sequence and to thrombin in a nonspecific charge-dependent fashion. In addition, the complex UFH–AT inactivates factors IXa, XIa and XIIa.

In the catheterization laboratory, UFH is administered intravenously. Once in the bloodstream, UFH binds to plasma proteins, which reduces its anticoagulant activity and explains the variability of its anticoagulant response. UFH has complex clearance kinetics through a double mechanism by binding to endothelial cells and macrophages responsible for most of the clearance and renal excretion [10]. UFH interacts with platelets and can either induce or inhibit platelet activation. Platelet activation has been observed within or in the vicinity of a well-formed thrombus, an effect that becomes relevant in the setting of ACS [11]. Additional limitations of UFH include the need for frequent intraprocedural monitoring, inability to bind to clot-bound thrombin, heparin-induced thrombocytopenia (HIT) and HIT and thrombosis syndrome (HITTS). Finally, rebound thrombin generation has been documented after UFH discontinuation with ACS reactivation and recurrent myocardial ischemia [12].

The concomitant use of GPI has proved useful as adjuvant therapy in decreasing ischemic complications of PCI. A meta-analysis of 12 clinical trials conducted between 1980 and 2002 in more than 20,000 patients undergoing PCI demonstrated a significant 23% relative reduction in 30-day mortality associated with GPI use [13]. However, increased bleeding is a serious tradeoff of GPI use. Therefore, careful patient selection, taking into consideration individual risks of ischemia versus bleeding and increased costs, should be emphasized before deciding to use these agents.

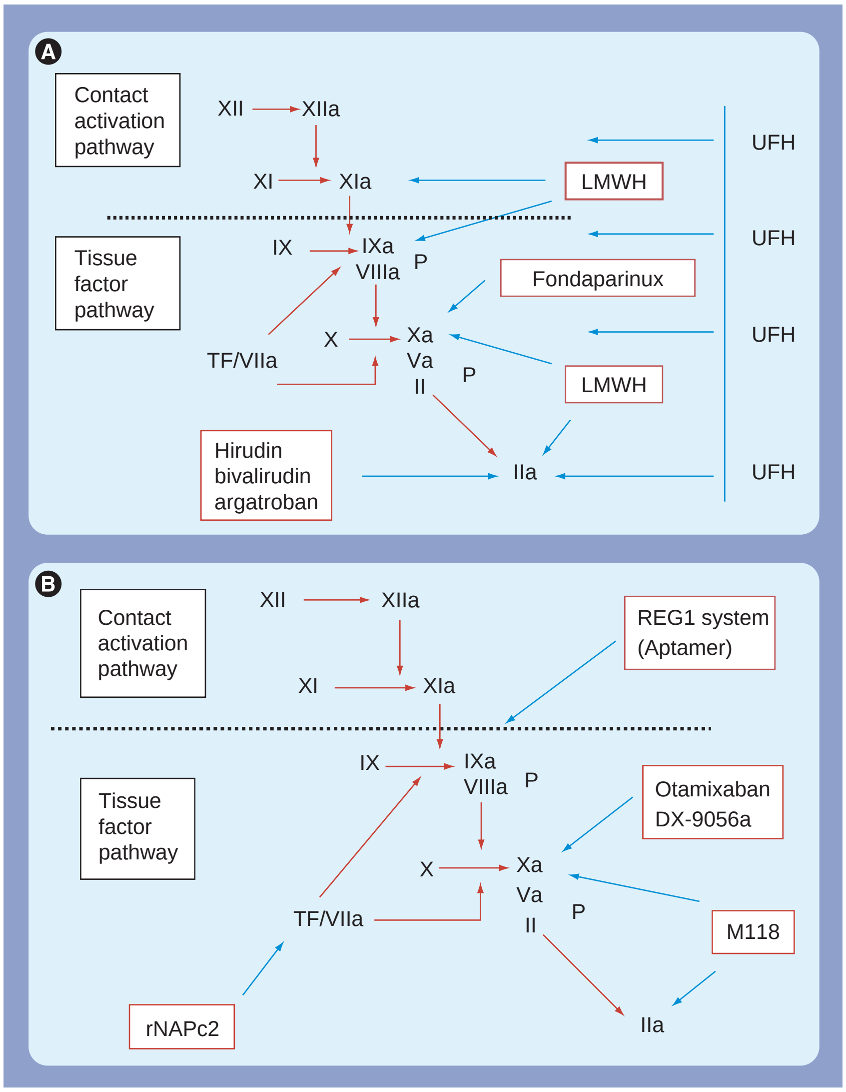

Figure 2. Anticoagulation targets of (A) current agents and (B) agents in development. Unfractionated heparin targets several factors in the contact and tissue factor pathways. By contrast, low-molecular-weight heparin and fondaparinux target factors in the tissue factor pathway. Agents in development exert target upstream factors in the coagulation cascade.
LMWH: Low-molecular-weight heparin; P: Phospholipid surface; rNAPc2: Recombinant nematode anticoagulant protein c2; TF: Tissue factor; UFH: Unfractionated heparin.
Adapted with permission from [88].

Low-molecular-weight heparin

Low-molecular-weight heparins are produced from UFH by chemical or enzymatic depolimerization processes, which result in a molecular weight of approximately 5000 Da. Enoxaparin is the most widely studied and used LMWH in the setting of PCI. LMWH uses AT as a cofactor to exert its effect primarily through indirect inhibition of Factor Xa. Although it also causes some inhibition of Factor IIa, its anti-Factor Xa:anti-Factor IIa ratio of 4:1 is greater than that of standard heparin (1:1), accounting for its powerful anti-thrombotic effect [14]. In general, LMWHs offer several advantages over standard UFH. Having less affinity for plasma proteins, LMWH offers a more predictable anticoagulant effect, thereby decreasing the need for intraprocedural monitoring [15]. A decreased incidence of HIT is observed with LMWH compared with standard heparin [16]. LMWH's longer half-life affords a more sustained anticoagulant effect, obviating the need for continuous infusions, such as with heparin. In addition, there is less von Willebrand factor release and no rebound ischemia [17]. Two early trials comparing enoxaparin versus UFH in ACS patients, the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) and Thrombolysis In Myocardial Infarction (TIMI)-11B trials [18] demonstrated a significant reduction in serious ischemic events with enoxaparin that persisted at 1 year of follow-up. Given these findings, as well as the convenience of LMHW, subsequent studies examined LMHW as an anticoagulant in PCI [19–21]. The nonrandomized National Investigators Collaborating on Enoxaparin (NICE) studies assessed the use of enoxaparin with and without GPI during PCI. NICE 1 studied intravenous enoxaparin 1 mg/kg and NICE 4 studied intravenous enoxaparin 0.75 mg/kg in combination with a GPI. In-hospital and 30-day bleeding and ischemic events post-PCI were infrequent in both studies [22]. NICE 3 evaluated 671 patients with non-ST-elevation ACS managed with upstream subcutaneous enoxaparin. A large proportion of patients (94%) were concomitantly treated with GPI [23]. Bleeding and ischemic outcomes were low and comparable with previous studies of UFH and GPI.

The Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial enrolled 10,027 high-risk patients with non-ST-segment elevation ACS to an early invasive strategy with either heparin or enoxaparin. This trial demonstrated that enoxaparin was not inferior to heparin as an alternative anticoagulant in this higher-risk population. The use of enoxaparin was associated with a significantly elevated risk of TIMI major bleeding [24]. A substudy of this trial examined those patients undergoing PCI and again found similar rates of death and MI at 30 days with a higher rate of TIMI major bleeding in the LMWH group [25]. A summary of selected studies assessing the use of enoxaparin in PCI is presented in Table 2.

A meta-analysis including 13 trials with 7318 patients compared LMWH with UFH in the setting of PCI. Intravenous enoxaparin was administered at a dose of 0.5 mg/kg in two trials, 0.75 mg/kg in seven trials and 1 mg/kg in four trials. The use of LMWH was associated with a significant reduction in major bleeding (odds ratio [OR]: 0.57; 95% CI: 0.40–0.82; p = 0.002) and no differences in the composite end point of death and MI (OR: 0.99; 95% CI: 0.79–1.24; p = 0.93) [26].

Despite these encouraging results, the use of LMWH in the catheterization laboratory is encumbered with logistical issues. The lack of universal availability of LMWH anticoagulation monitoring in the catheterization laboratory is seen as a disadvantage by many interventional cardiologists, in particular for patients previously treated with subcutaneous LMWH, in whom there is either a risk of over- or under-dosing. Dosing for obese patients or those with renal insufficiency is less well-defined. Current guidelines recommend no additional anticoagulation if the last subcutaneous dose of enoxaparin was given 0–8 h prior to PCI and the patient had received three or more subcutaneous doses and achieved a steady state. If the last dose was given between 8 and 12 h prior to PCI, an additional intravenous bolus of 0.3 mg/kg is recommended. If the last dose was administered more than 12 h prior to PCI, conventional full anticoagulation is recommended [27].

Timing of sheath removal is another issue that varies according to dose and route of LMWH administration. The general recommendation is

Table 2. Selected studies comparing enoxaparin with unfractionated heparin in patients undergoing percutaneous coronary intervention.

Study (year)	n	Study population	Anticoagulation regimen		Outcomes (enoxaparin vs UFH)		Ref.
			Enoxaparin	*UFH*	*Ischemic end point*	*Major bleeding (non-CABG)*	
Rabah *et al.* (1999)	60	Stable angina	1 mg/kg iv. bolus	10,000 IU bolus to ACT > 300 s	0 vs 3 patients (p = NS)	1 vs 0 patients (p = NS)	[19]
ACTION (2005)	200	Elective PCI	0.75 mg/kg iv. bolus plus GPI	60 IU/kg bolus plus GPI	8.0 vs 14.0% (p = NS)	0% in both arms	[20]
CRUISE (2003)	261	Elective or urgent PCI	0.75 mg/kg iv. bolus plus GPI	60 IU/kg bolus plus GPI	8.5 vs 7.6% (p = 0.82)	0 vs 2.6% (p = 0.44)	[21]
SYNERGY (2004)	10,027	High-risk ACS with early invasive strategy	1 mg/kg sc. every 12 h	60 IU/kg bolus to ACT > 250 s	14.0 vs 14.5% (p = 0.40)	2.4 vs 1.8% (p = 0.03)	[24]
STEEPLE (2006)	3528	Elective PCI	0.5 or 0.75 mg/kg iv.	70–100 IU/kg to ACT 300–350 s	Enoxaparin 0.5 mg/kg: 6.2% Enoxaparin 0.75 mg/kg: 6.8% UFH: 5.8% (p = NS)	Enoxaparin 0.5 mg/kg: 1.2% Enoxaparin 0.75 mg/kg: 1.2% UFH: 2.8% (p < 0.01)	[28]

ACS: Acute coronary syndrome; ACT: Activated clotting time; ACTION: Assessment of Combination Therapy In Obstructed Native Coronary Arteries; CABG: Coronary artery bypass graft; CRUISE: Coronary Revascularization Using Integrilin and Single Bolus Enoxaparin; GPI: Glycoprotein IIb/IIIa inhibitor; iv.: Intravenous; NS: Not significant; PCI: ; Percutaneous coronary intervention; sc.: Subcutaneous; STEEPLE: Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients; SYNERGY: Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors; UFH: Unfractionated heparin.

to wait 8 h after the last subcutaneous dose and 4–6 h after an intravenous dose of 0.75–1.0 mg/kg. In clinical trials, the femoral sheaths have been safely removed within 1 h after an intravenous dose of 0.5 mg/kg [28].

Finally, the SYNERGY trial demonstrated increased bleeding rates among patients in whom anticoagulants were switched from UFH to LMWH and *vice versa* [24]. Hence, the issues of monitoring, sheath management and the need for consistent anticoagulation (without switching) can pose logistical challenges to the catheterization laboratory staff, highlighting the need for precise communication and documentation of LMWH dosing and timing to avoid dosing errors that can result in adverse outcomes. As a matter of fact, an analysis of the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines (CRUSADE) registry including 10,687 ACS patients demonstrated underdosing or overdosing of LMWH in approximately 50% of patients. Overdosing was associated with a significantly higher risk of bleeding and underdosing was associated with a trend towards increased mortality [29].

Table 3 displays some practical aspects in the management of PCI patients treated with enoxaparin. The use of LMWH in ACS patients undergoing either an invasive or a conservative management has a class Ia recommendation level by current ACS guidelines [30].

Direct thrombin inhibitors

Direct thrombin inhibitors are an appealing option for anticoagulation during PCI. Thrombin has procoagulant and prothrombotic properties that are mediated through the conversion of fibrinogen to clot-formable fibrin [31,32]. DTIs bind directly to thrombin and block its enzymatic activity without the need for a plasma cofactor, as opposed to the indirect anticoagulants UFH, LMWH and fondaparinux (GlaxoSmithKline, UK). Owing to their relatively small size, DTIs are also active against clot-bound thrombin and do not have any natural inhibitors, such as platelet Factor 4 in the case of heparin [33].

Available DTIs include bivalent agents such as deshirudin, lepirudin and bivalirudin and the monovalent agent argatroban. Bivalent agents bind to thrombin's active site and exosite 1. The hirudins irreversibly bind to the thrombin's active site through a covalent interaction. Similarly, bivalirudin initially binds covalently to thrombin's active site, but in contrast with the hirudins, once bound, bivalirudin is cleaved by thrombin, which recovers its activity with time. Argatroban reversibly binds to thrombin's active site [10]. Lepirudin is approved for the treatment of thrombotic complications associated with HIT. Desirudin is approved in Europe for venous thromboprophylaxis. Argatroban is approved for the treatment and prevention of HIT-associated thrombosis and for anticoagulation during PCI when UFH or LMWH are contraindicated owing to a previous history of HIT.

There is vast experience with DTIs in the ACS setting. A meta-analysis including 11 trials with 35,970 patients demonstrated that initial treatment with DTIs for at least 7 days was associated with a significant reduction in death and/or MI at 30 days in comparison with UFH (7.4 vs 8.2%; OR: 0.91; 95% CI: 0.84–0.99; p = 0.02). This effect was observed with the bivalent agents hidurin and bivalirudin but not with monovalent agents that were associated with a slight increase in death and/or MI. Major

Table 3. Management of enoxaparin during percutaneous coronary intervention.

Enoxaparin sc. 1 mg/kg every 12 h	Additional enoxaparin prior to PCI
Last dose <8 h[†]	Not needed
Last dose 8–12 h	0.3 mg/kg iv.
Last dose >12 h	Conventional anticoagulation as per standard of care
Additional glycoprotein IIb/IIIa inhibitors	At discretion of the operator. Increased bleeding risk
De novo anticoagulation in catheterization laboratory	0.75 mg/kg iv.
Timing of sheath removal	
After 1 sc. dose	4 h
After 2 sc. doses	6 h
After 3 sc. doses	8 h
After 0.75 mg/kg iv. dose	4–6 h

[†]If at least three doses had been administered, or if treatment included an initial iv. bolus of 30 mg.
iv.: Intravenous; PCI: Percutaneous coronary intervention; sc.: Subcutaneous.

bleeding during treatment was also reduced with the use of DTIs (1.9 vs 2.3%; OR: 0.75; 95% CI: 0.65–0.87; p < 0.001) [34].

Bivalirudin, with its favorable pharmacokinetic profile, including a short plasma half-life of 25 min after intravenous injection and a 20% renal excretion, as well as a lack of a stimulatory effect on platelets, is by far the most widely studied DTIs in the PCI setting (Table 4) [35–40]. Initial trials studying bivalirudin in PCI were conducted in the early 1990s. The Bivalirudin Angioplasty Trial (BAT) was a large double blind, randomized trial that compared bivalirudin with UFH in 4312 patients undergoing angioplasty for unstable or postinfarction angina. Results demonstrated a 65% relative reduction in the incidence of bleeding (3.8 vs 9.8%; p < 0.0001) and a 22% reduction in death, MI, vessel closure or revascularization at 7 days (6.2 vs 7.9%; p = 0.012) [35,41]. The results of this trial led to the US FDA approval of bivalirudin in 2000 as an alternative to heparin in PCI. However, this trial antecedes the routine use of thienopyridines and stents and is therefore not representative of current practice. More recently, the second Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) trial compared bivalirudin and provisional GPI (used only in 7.2% of patients) with UFH and GPI in 6010 patients undergoing elective or urgent PCI [37]. All patients received aspirin and a thienopyridine for 30 days after the procedure. The 'quadruple' primary end point included efficacy and safety measures (death, MI, urgent repeat revascularization and major bleeding). Although there was a trend towards a higher rate of non-Q-wave MI at 30 days in the bivalirudin group, this did not translate into a higher 1-year mortality rate; instead, there was a trend towards lower 1-year mortality in the bivalirudin group. In addition, there was a statistically significant lower major bleeding rate

Table 4. Use of direct thrombin inhibitors in patients undergoing percutaneous coronary intervention.

Study	n	Study population	Anticoagulation regimen		Outcomes (bivalirudin vs UFH)		Ref.
			Bivalirudin	*UFH*	*Ischemic end point*	*Major bleeding (non-CABG)*	
BAT	4098	Unstable or post-MI angina	Bolus: 1.0 mg/kg Infusion: 2.5 mg/kg/h for 4 h and 0.2 mg/kg/h for 14–20 h	Bolus: 175 IU/kg, Infusion: 15 IU/kg/h for 18–24 h	6.2 vs 7.9% (p = 0.039)	3.5 vs 9.3% (p < 0.001)	[35]
CACHET	268	Elective PCI	Bolus: 0.5–1.0 mg/kg Infusion: 1.75–2.5 mg/kg/h for 4 h Planned or provisional GPI	Bolus: 70 IU/kg Planned GPI use	Bivalirudin + GPI: 0% Bivalirudin + provisional GPI: 0–4.7% UFH: 6.4% (p = NS)	Bivalirudin + GPI: 3.3% Bivalirudin + provisional GPI: 0–2.4% UFH: 4.3% (p = NS)	[36]
REPLACE-2	6010	Elective or urgent PCI	Bolus: 0.75 mg/kg Infusion: 1.75 mg/kg/h during PCI	Bolus: 65 IU/kg	7.6 vs 7.1% (p = 0.40)	2.4 vs 4.1% (p < 0.001)	[37]
ISAR-REACT 3	4570	Elective PCI	Bolus: 0.75 mg/kg Infusion: 1.75 mg/kg/h during PCI	Bolus: 140 IU/kg	5.9 vs 5.0% (p = 0.23)	3.1 vs 4.6% (p < 0.05)	[38]
ACUITY	13,819	Moderate- to high-risk ACS	Bolus: 0.1 mg/kg Infusion: 0.25 mg/kg/h before PCI Bolus: 0.5 mg/kg Infusion: 1.75 mg/kg/h (stopped after PCI)	Bolus: 60 IU/kg Infusion: 12 U/kg/h (stopped after PCI) planned GPI use Enoxaparin: sc. 1 mg/kg every 12h	Bivalirudin: 3.0% Bivalirudin + GPI: 5.3% UFH + GPI: 5.7% (p < 0.001, for bivalirudin vs UFH + GPI)	Bivalirudin: 7.8% Bivalirudin + GPI: 7.7% UFH + GPI: 7.3% (p = NS)	[39]
HORIZONS-AMI	3602	ST-elevation MI	Bolus: 0.75 mg/kg Infusion: 1.75 mg/kg/h during PCI	Bolus: 60 IU/kg Planned GPI use	5.4 vs 5.5% (p = 0.95)	4.9 vs 8.3% (p < 0.001)	[40]

ACS: Acute coronary syndrome; ACUITY: Acute Catheterization and Urgent Intervention Triage Strategy; BAT: Bivalirudin Angioplasty Trial; CABG: Coronary artery bypass graft; CACHET: Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial; GPI: Glycoprotein IIb/IIIa inhibitor; HORIZONS-AMI: Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; ISAR-REACT: Intracoronary Stenting and Anti-thrombotic Regimen – Rapid Early Action for Coronary Treatment; MI: Myocardial infarction; NS: Not significant; PCI: Percutaneous coronary intervention; REPLACE: Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events; sc.: Subcutaneous; UFH: Unfractionated heparin.

with bivalirudin (2.4 vs 4.1%; $p < 0.001$). These trials were designed primarily to show bivalirudin's noninferiority to heparin in the PCI setting [37,42]. The ACUITY trial enrolled patients with moderate- to high-risk ACS who were to undergo an early invasive strategy to one of three anticoagulation arms:

- Unfractionated heparin or enoxaparin plus a GPI;
- Bivalirudin plus a GPI;
- Bivalirudin alone.

Bivalirudin alone was noninferior compared with the two other strategies in terms of death, MI and unplanned revascularization and was associated with decreased rates of bleeding in comparison with heparin plus GPI and bivalirudin plus GPI (3.0 vs 5.7 vs 5.3%; $p < 0.001$) [39]. The Intracoronary Stenting and Anti-thrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT)-3 trial enrolled 4570 patients with stable or unstable angina with negative cardiac markers who were then pretreated with clopidogrel 600 mg and randomized to UFH or bivalirudin. There were no significant differences in the composite primary quadruple end point (8.3 vs 8.7%; p = not significant); however, treatment with bivalirudin was associated with a 34% relative reduction in bleeding risk (3.1 vs 4.6%; $p = 0.008$). It must be noted that the dose of UFH in this trial was 140 IU/kg, much higher than the dose of 70–100 IU/kg routinely used in practice [38].

The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial studied bivalirudin in a broad population of patients undergoing primary PCI for acute ST-elevation MI. This open-label study randomly assigned 3602 patients to UFH and GPI or bivalirudin alone. There was a lower 30-day net rate of adverse clinical events (death, stroke, reinfarction, unplanned revascularization or major bleeding) with bivalirudin (9.2 vs 12.1%; $p = 0.005$), which was driven by a reduction in major bleeding (4.9 vs 8.3%; $p < 0.001$). Bivalirudin was also associated with an unexpected reduction in 30-day cardiac mortality (1.8 vs 2.9%; $p = 0.03$), which was attributed to decreased bleeding. Conversely, the rate of stent thrombosis within the first 24 h after PCI was greater in the bivalirudin group (1.3 vs 0.3%; $p < 0.001$) [40]. In addition to randomized clinical trials, 'real world' registry data have also supported the use of bivalirudin [43,44]. Given the ease of administration, stable anticoagulation, short duration of action and safe bleeding risk profile, bivalirudin will continue to be a widely used anticoagulant agent during PCI.

Fondaparinux

Fondaparinux is a synthetic derivative of the natural pentasaccharide sequence that mediates the interaction of heparins with AT. The anticoagulant effect of fondaparinux is mediated through its binding with AT, which catalyzes the selective inhibition of Factor Xa, an appealing anticoagulation target and the link between the intrinsic and extrinsic coagulation pathways. Fondaparinux is a short molecule unable to bridge AT to thrombin and therefore does not increase the rate of thrombin inhibition by AT. Fondaparinux is attractive for use in PCI as it has predictable pharmacokinetics with a half-life of approximately 15 h after subcutaneous injection that allows a single, fixed, daily dose administration with little interpatient variability, thus eliminating the need for constant monitoring. Fondaparinux is excreted unchanged through renal elimination and therefore contraindicated in patients with severe chronic kidney disease (creatinine clearance <30 ml/min) [45]. Prior studies have demonstrated that fondaparinux prevents venous thrombosis particularly in patients undergoing orthopedic surgery, the current labeled indication for this agent [46]. An early trial studying fondaparinux in PCI, the Arixtra Study in Percutaneous Coronary Intervention: A Randomized Evaluation Pilot Trial (ASPIRE), randomized 350 patients undergoing elective or urgent PCI to UFH or intravenous fondaparinux 2.5 or 5.0 mg [47]. The results demonstrated similar rates of bleeding in all groups with no difference in all-cause mortality, MI, urgent target vessel revascularization or need for bailout GPI use. In addition, measurements of prothrombin fragment F1.2, a marker of thrombin generation, were lower at 6 and 12 h with fondaparinux, suggesting a more sustained anticoagulant effect. Bleeding rates among the two doses of fondaparinux were lower with the 2.5 mg group versus the 5.0 mg group (3.4 vs 9.6%; $p = 0.06$). The Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS) 5 and 6 trials compared fondaparinux with enoxaparin or UFH in patients with non-ST-elevation and ST-elevation ACS, respectively [48]. In OASIS 5, 20,078 patients were randomized to fondaparinux 2.5 mg subcutaneously once daily or enoxaparin 1 mg/kg subcutaneously twice daily. Patients undergoing PCI received additional intravenous doses of fondaparinux prior to the procedure. In the OASIS 6 trial with 12,092 patients, control therapy consisted of either enoxaparin or UFH per standard of care. A pooled analysis of the OASIS 5 and 6 trials including 26,512 patients (72% invasively managed), demonstrated that fondaparinux was associated with a significant 9% relative reduction in the composite end point of 30-day death, MI or stroke and a 33% relative reduction in major bleeding in comparison with heparin. Interestingly, fondaparinux was associated with a significant reduction in 6-month death rates (7.3 vs 6.5%, hazard ratio [HR]: 0.89; 95% CI: 0.81–0.98; p = 0.01). However, a major concern raised in these studies was the significantly higher occurrence of catheter-related thrombus in the fondaparinux arm of patients undergoing PCI (0.89 vs 0.22%; HR: 3.98; 95% CI: 1.74–9.09). Catheter thrombosis had serious clinical implications as it was associated with a substantially increased incidence of MI (27 vs 4.2%; RR: 6.51; 95% CI: 3.78–11.20) and stroke (5.4 vs 0.6%; RR: 9.48; 95% CI: 2.37–38.0) (Figure 3). This major concern was mitigated with a trial amendment that allowed the administration of a low dose of UFH prior to PCI within the course of the OASIS 5 trial [48]. The mechanism of catheter thrombosis is through the contact activation pathway of the coagulation cascade. *In vitro* studies demonstrated that in comparison with UFH, selective Factor Xa inhibition by fondaparinux has little action against the blood flow disturbances and foreign catheter surfaces that initiate clotting [49]. Current ACC/AHA guidelines support the use of fondaparinux for the management of non-ST-elevation ACS with a class I indication, level of evidence B. In case of PCI, the addition of an anticoagulant with AT activity is recommended [30]. However, this strategy needs prospective validation in a larger number of patients.

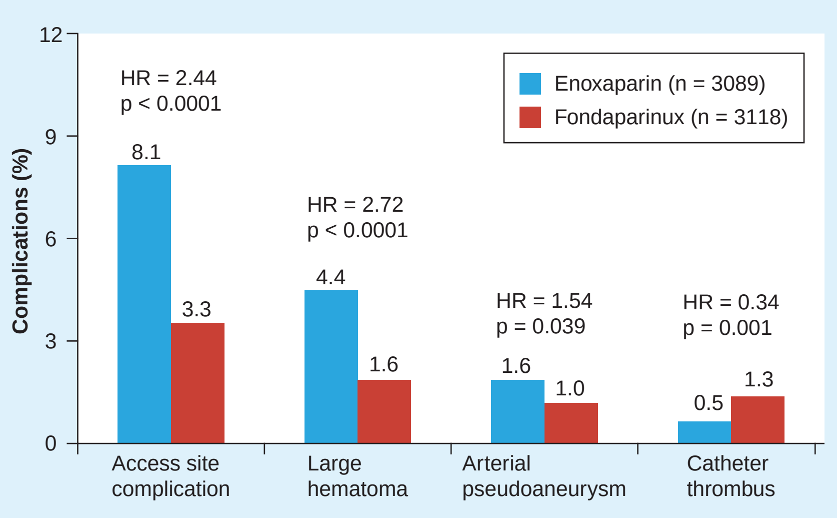

Figure 3. Summary of the percutaneous coronary intervention complications seen in the Organization for the Assessment of Strategies for Ischemic Syndromes 5 trial. This graph shows decreased complications with fondaparinux versus enoxaparin for most complications with the exception of catheter thrombus, for which there was a small but statistically significant higher incidence in the fondaparinux arm.
HR: Hazard ratio.
Adapted with permission from [89].

New anticoagulation targets & platforms

A number of agents in development with different anticoagulation targets have been tested in Phase II PCI trials (Figure 2B). Otamixaban and DX-9065 are direct selective Factor Xa inhibitors. The recombinant nematode anticoagulant protein c2 (rNAPc2) inhibits the complex tissue factor (TF)–Factor VIIa. The REG1 system is a regulatable anticoagulant:control agent RNA-based aptamer pair that inhibits Factor IXa. M118 is an engineered LMWH that inhibits Factor Xa and Factor IIa with an anti-Factor Xa:anti-Factor IIa ratio of 1.8:1, and its anticoagulant activity that can be monitored with the activated clotting time (ACT) and reversed with protamine.

■ Otamixaban

This is a fast-acting, synthetic, direct Factor Xa inhibitor that inhibits free and prothrombinase-bound Factor Xa. Otamixaban appears to have several advantages over the anticoagulants that are currently used. Unlike heparin, otamixaban has little affinity for plasma proteins, thereby possessing a more predictable dose–response relationship. In addition, otamixaban is excreted through both the biliary tract and the kidney. Preliminary trials in patients with mild renal insufficiency have shown no effect on systemic clearance of the drug, thus offering an advantageous pharmacokinetic profile compared with other LMWHs. Otamixaban plasma concentration falls within 30 min after cessation of the infusion, an advantageous pharmacokinetic feature in the event of unforeseen bleeding [50]. The Phase II trial Otamixaban in Comparison to Heparin in Subjects Undergoing Non-Urgent Percutaneous Coronary Intervention (SEPIA-PCI) demonstrated that otamixaban-supported PCI was safe and feasible. The study enrolled 947 patients and assigned them to one of five weight-adjusted regimens of otamixaban or UFH with or without GPI prior to elective PCI. Primary end points were change in prothrombin fragment F1.2 and anti-Factor Xa activity. Secondary end points were TIMI bleeding at day 3 or hospital discharge and 30-day ischemic events. Otaximaban reduced F1.2 more than UFH at the highest dose regimen (-0.3 vs -0.2 ng/ml; p = 0.008) with no significant difference in incidence of TIMI bleeding [51]. SEPIA-ACS 1 TIMI 42 was a Phase II double-blind trial that examined the use of otamixaban in 3241 non-ST-elevation ACS patients [52]. Patients were randomized to one of five regimens of otamixaban versus UFH and eptifibatide. Almost all patients were managed invasively within 48–72 h of admission and 63% of patients underwent PCI. The primary efficacy end point in this trial was the composite of death, MI, urgent revascularization or bailout GPI use at 7 days. The primary safety end point was non-coronary artery bypass graft TIMI major or minor bleeding. The results of this trial demonstrated that otamixaban infusions of 0.10–0.14 mg/kg/h might reduce ischemic events and have similar rates of TIMI major or minor bleeding compared with heparin and eptifibatide. A limitation of this study is that the control group (UFH and eptifibatide) is no longer representative of current practice. Early upstream administration of GPI is not routine and has not been shown to be superior to UFH alone with background thienopyridine therapy [53]. Further testing in Phase III trials will better define the efficacy and safety of otamixaban as an alternative anticoagulant in PCI.

■ DX-9065a

This small synthetic molecule is a highly selective and competitive direct inhibitor of free and prothrombinase-bound Factor Xa. The Xa Neutralization for Atherosclerotic Disease Understanding (XaNADU) Phase II studies tested DX-9065a in elective PCI and non-ST-elevation ACS. In XaNADU-PCI, a total of 175 patients were randomized to UFH or four different regimens of DX-9065a prior to elective PCI. Most patients received GPIs and clinical events were rare. One patient in the lowest dose DX-9065a regimen developed a large intracoronary thrombus that resulted in MI [54]. In XaNADU-ACS, 402 patients with non-ST-elevation ACS were randomized to UFH and two regimens of DX-9065a. Almost all patients underwent coronary angiography within 24 h of enrollment. DX-9065a had a more consistent and predictable anticoagulation effect but had no effect on the primary end points of death, MI, urgent revascularization or ischemia on continuous ST monitoring [54]. The role of DX-9065a is yet to be defined in larger studies.

■ M118

This is a new variant LMWH currently undergoing evaluation for potential use in PCI. M118 is a rationally engineered product that shares strengths of both UFH and LMWH; it can be administered intravenously or subcutaneously and exerts its anticoagulant effect primarily through the inhibition of Factor Xa, using AT as a cofactor in a similar fashion to LMWH. However, unlike LMWH, M118 also retains thrombin inhibition with an anti-Factor Xa:anti-Factor IIa activity ratio of 1.8:1. M118 has predictable subcutaneous and intravenous pharmacokinetics, is easily monitored via current assays including ACT and activated partial thromboplastin time (APTT) and is reversible with protamine [55]. The Evaluation of M118 in Percutaneous Coronary Intervention (EMINENCE) Phase II multicenter trial randomized 503 patients undergoing PCI to treatment with 50, 75 or 100 IU/kg of M118 or 70 IU/kg of UFH. The primary end point was the combined incidence of stroke, death, MI, repeat revascularization, bleeding, bailout GPI use and catheter thrombus formation. The results showed no statistically significant differences in the primary end point between UFH and M118 (31.1 vs 28.4%; p = not significant). In addition, there was a similar rate of bleeding between the two groups and a lower rate of bailout GPI in the M118 arms. In summary, the results of the EMINENCE trial were reassuring and demonstrated the feasibility and tolerability of M118 as an anticoagulant during PCI [56].

■ Recombinant nematode anticoagulant protein c2

After endothelial disruption, either by spontaneous plaque rupture or angioplasty balloon inflation, the initiation of coagulation takes place on tissue factor-bearing cells such as monocytes, macrophages and endothelial cells. In the presence of the complex TF–Factor VIIa, activation of Factor IX and Factor X generates a small but sufficient amount of thrombin to activate platelets, Factor V, Factor XI and Factor VIII. Therefore, targeting the initial coagulation response to vascular injury while leaving the downstream factors intact appears to be a sensible option. The 85-amino acid serine protease inhibitor rNAPc2 is isolated from the saliva of the hookworm parasite *Ancylostoma caninum*; it interferes with the TF coagulation pathway by binding to Factor Xa or Factor X before formation of a quarternary inhibitory complex with TF–Factor VIIa. A Phase II placebo-controlled trial randomized 154 patients undergoing elective PCI to placebo or four escalating subcutaneous doses of rNAPc2 administered 4–6 h prior to PCI. UFH was administered before femoral access to achieve an ACT of greater than 250 s. Clinical events were infrequent and minor bleeding events occurred more often in the highest rNAPc2 group. Assessment of F1.2 levels demonstrated continued suppression of thrombin generation in all rNAPc2-treated patients in contrast with placebo-treated patients [57]. The Anticoagulation With rNAPc2 to Help Eliminate Major Adverse Cardiac Events – TIMI (ANTHEM-TIMI)-32 study randomized 203 ACS patients in a dose-ranging trial to placebo versus four different dose regimens of rNAPc2 [58]. Subsequently, 52 ACS patients were included in an open-label pilot arm testing the feasibility of UFH de-escalation. This involved the administration of the highest dose of rNAPc2 (10 µg/kg) with either half-dose or no heparin with the goal of simplifying antithrombotic treatment and to investigate whether or not rNAPc2 could support PCI as a standalone agent. There were no differences in ischemic clinical end points among patients treated with background UFH therapy in the randomized part of the study. Treatment with rNAPc2 effectively suppressed thrombin generation and was associated with a significant reduction of ischemia on continuous ECG monitoring. However, in the UFH de-escalation part of the study, four out of 14 patients treated with rNAPc2 without UFH who underwent PCI had intraprocedural coronary thrombus formation with need for bail-out open-label anticoagulation. There were four major bleeding events that occurred with the highest rNAPc2 dose, mostly related to coronary artery bypass grafting. Therefore, rNAPc2 may be useful as an adjunct to reduce ischemic events when added to background heparin therapy in ACS patients, but not sufficient to support PCI as a standalone anticoagulant [58].

■ REG1 system & Factor IXa inhibition

Most targets of anticoagulation have focused on Factor Xa inhibition; however, a novel anticoagulant system, REG1, exerts its effect through the inhibition of Factor IXa. Factor IXa plays a key role in the propagation of the coagulation cascade and is initially activated by the TF–VIIa complex, which occurs when injured endothelial cells expose TF. Factor IXa forms a complex with Factor VIIIa, which then binds to platelets. This complex activates Factor Xa, which, in the presence of Va, catalyzes the formation of thrombin [59]. The REG1 anticoagulation system is an RNA-based aptamer pair (aptamer derives from the Latin word *aptus*, meaning 'to fit') that consists of two synthetic compounds RB006, the anticoagulant and RB007, the control agent. RB006 is an injectable single-stranded RNA oligonucleotide that binds selectively to Factor IXa, thus inhibiting the Factor VIIIa/Factor IXa-catalyzed conversion of Factor X to Factor Xa, a critical component of the prothrombinase complex. The control agent RB007 is a complementary oligonucleotide that binds to RB006 by Watson–Crick base pairing, neutralizing more than 95% of its anti-Factor IXa activity within minutes. Therefore, RB007 is administered in a separate injection from RB006 when either complete or partial reversal of anticoagulation is desired on completion of PCI. The RB006–RB007 complex is stable, biologically inactive and cleared rapidly from the circulation by endogenous endonucleases. Three completed Phase I studies with a total of 172 patients demonstrated the tolerability and safety of the REG1 system [60]. In a small Phase IIa study including 26 patients undergoing elective PCI, RB006 at a dose of 1 mg/kg was administered intravenously prior to PCI and achieved stable anticoagulation with a median APTT of 151 s. After completion of the procedure, RB007 was administered in the first 14 patients in two steps: 0.2 mg/kg to achieve 50% partial reversal of anticoagulation immediately after the procedure and 1.8 mg/kg to achieve 100% reversal at 4 h after the procedure. In the second group of 12 patients, a RB007 dose of 2.0 mg/kg was administered after PCI to achieve complete 100% reversal of anticoagulation. There were no acute thrombotic events among patients treated with the REG1 system. An ongoing Phase IIb trial is testing the REG1 system in the non-ST-elevation ACS patients undergoing invasive management. If clinical data confirm its efficacy and safety, the REG1 system has the potential to overcome many of the limitations of current anticoagulants by virtue of its reversibility and nonrenal clearance.

Switching anticoagulants

In most cases, the choice of the initial anticoagulation strategy in patients with high-risk ACS referred for an early invasive approach is not under the control of the operator who will perform the procedure. Instead, the anticoagulation strategy is determined at first patient contact, either in the ambulance or the emergency department. With the multiple anticoagulation choices available in current practice, issues of safety and efficacy of switching anticoagulants becomes relevant.

Enoxaparin has become a popular anticoagulation choice in emergency departments. It is easy to administer and its use is supported by a class Ia guideline indication in ACS [30]. Pharmacodynamic data have demonstrated improved outcomes when anti-Factor Xa levels are in the range of 0.5–1.8 IU/ml, which is achieved in more than 90% of patients receiving a subcutaneous dose of 1 mg/kg twice daily [61,62]. Additional doses of intravenous enoxaparin 0.3 mg/kg administered to patients who had received their last subcutaneous dose between 8 and 12 h previously helps to achieve optimal anti-Factor Xa levels that are needed to support PCI [27]. Given the long history of UFH use and its familiarity among the interventional community, a common scenario could be the administration of enoxaparin in the emergency department with subsequent UFH given prior to the procedure or 'stack-on' UFH. The time interval for which UFH can safely be given after enoxaparin to maintain a therapeutic level of anticoagulation is not well defined. The Stack-on to Enoxaprin (STACKENOX) study was a Phase I trial that included 72 healthy subjects who received enoxaparin 1 mg/kg subcutaneously every 12 h for 2.5 days [63]. At the end of this period, enrollees were randomized to receive a 70 IU/kg bolus of UFH at 4, 6 or 10 h. Levels of ACT, Factors Xa and IIa, as well as endogenous thrombin potential were measured. After the initial dose of enoxaparin, endogenous thrombin potential levels fell by 40%, but the ACT remained unchanged. UFH at all three time points caused a complete abolition of thrombin generation with a 4-h lag prior to returning to normal. During this time, the ACT level remained in the range expected after only being given UFH without any effect from enoxaparin. Anti-Factor Xa activity increased significantly at all three time points ($p < 0.001$) to levels that were associated with hemorrhage in the TIMI 11A trial, even 10 h after of the last dose of enoxaparin [64]. As a clinical example, in the OASIS 5 trial, a 'stack-on' dose of UFH was administered to patients undergoing PCI 6 h after of the last subcutaneous dose of enoxaparin. Most likely, these patients achieved supratherapeutic anticoagulation levels, which may explain the excessive bleeding observed with enoxaparin in this trial (Figure 4).

In the SYNERGY trial, 75% of patients received anticoagulation therapy prior to randomization. Crossover rates from UFH to enoxaparin occurred in 12% of patients and from enoxaparin to UFH in 4% of patients. Adverse outcomes were significantly higher among patients who switched anticoagulants after randomization. Patients maintained on consistent therapy had 30-day death/MI and transfusion rates of approximately 14 and 15%, respectively, whereas patients who switched anticoagulants had 30-day death and/or MI and transfusion rates of approximately 20 and 32%, respectively (Figure 5) [24]. Therefore, it is important to maintain consistent anticoagulation in patients initially treated with LMWH to avoid the 'stack-on' effect of UFH, which is clearly associated with worse ischemic and bleeding outcomes.

In the case of DTIs, the ACUITY trial demonstrated that switching from either UFH or LMWH to bivalirudin was not associated with adverse outcomes [65]. As a matter of fact, the 2078 ACS patients enrolled in the ACUITY trial who were pretreated with heparin (UFH or enoxaparin) and subsequently switched to bivalirudin had similar ischemic outcomes and less major bleeding compared with the 2137 patients who received consistent therapy with heparin and GPI (Figure 6). In the HORIZONS trial, approximately two-thirds of patients received UFH before primary PCI in patients assigned to bivalirudin. Pretreatment with UFH prior to bivalirudin use was associated with a significant reduction in major adverse cardiovascular events (7.2 vs 4.6%) and had similar bleeding rates (5.6 vs 5.2%) in comparison with patients not pretreated with UFH [40]. In addition, pretreatment with UFH in the bivalirudin arm was independently associated with a 73% reduction in acute stent thrombosis (HR: 0.27; 95% CI: 0.12–0.60; $p = 0.002$) [66].

The Switching from Enoxaparin to Bivalirudin in Patients with ACS without ST-Segment Elevation Undergoing Percutaneous Coronary Intervention (SWITCH) trial prospectively

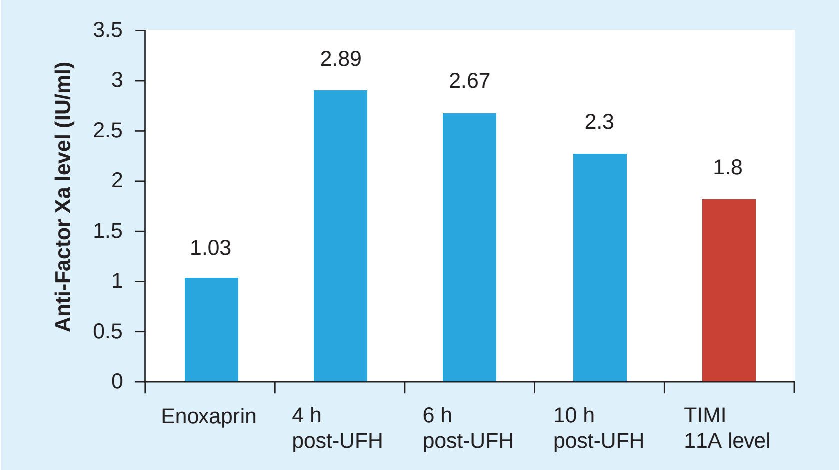

Figure 4. Measured anti-Factor Xa levels were higher in all groups administered heparin after enoxaparin, even 10 h after the previous dose of enoxaparin. The anti-Factor Xa levels are higher than those associated with a higher rate of major bleeding in the TIMI 11A trial.
TIMI: Thrombolysis In Myocardial Infarction; UFH: Unfractionated heparin.
Adapted from [63].

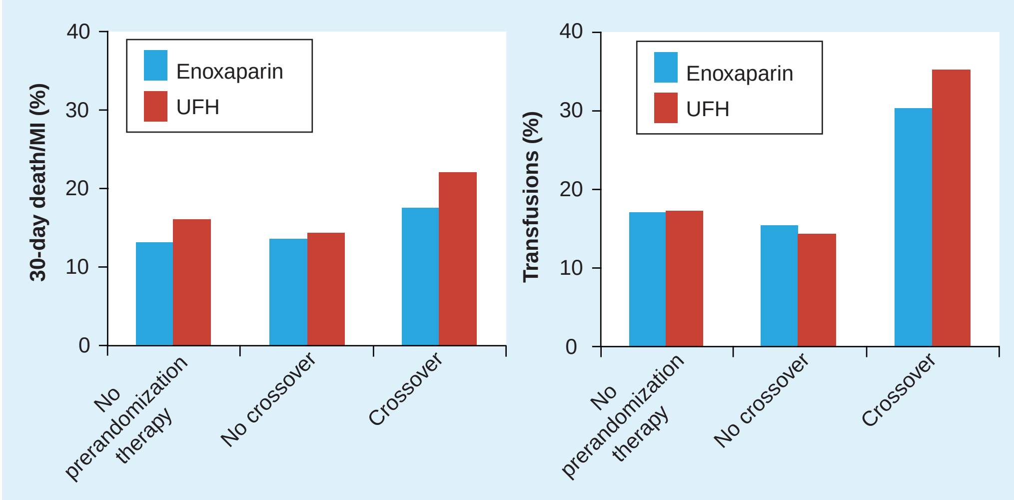

Figure 5. The Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial highlighted the importance of maintaining consistent anticoagulant therapy in acute coronary syndrome patients. Death and/or MI as well as transfusion rates were significantly higher in patients treated with either enoxaparin or UFH prior to randomization and were crossed over after randomization to a different anticoagulant.
MI: Myocardial infarction; UFH: Unfractionated heparin.
Adapted from [24].

studied the efficacy of switching between enoxaparin and bivalirudin in ACS patients undergoing catheterization. A total of 91 patients were categorized into three groups according to the timing of their last enoxaparin dose prior to PCI (0–4 h, 4–8 h and 8–12 h). Major bleeding occurred in four patients in the 0–4 h group, in two patients in the 4–8 h group and in two patients in 8–12 h group. Even though the difference was not statistically significant, this study was underpowered and the interventionalist should be cautious in administering bivalirudin in close proximity to the most recent dose of enoxaparin [67]. The ongoing SWITCH III trial (NCT00464087) is comparing bivalirudin with UFH prior to PCI in ACS patients initially treated with fondaparinux.

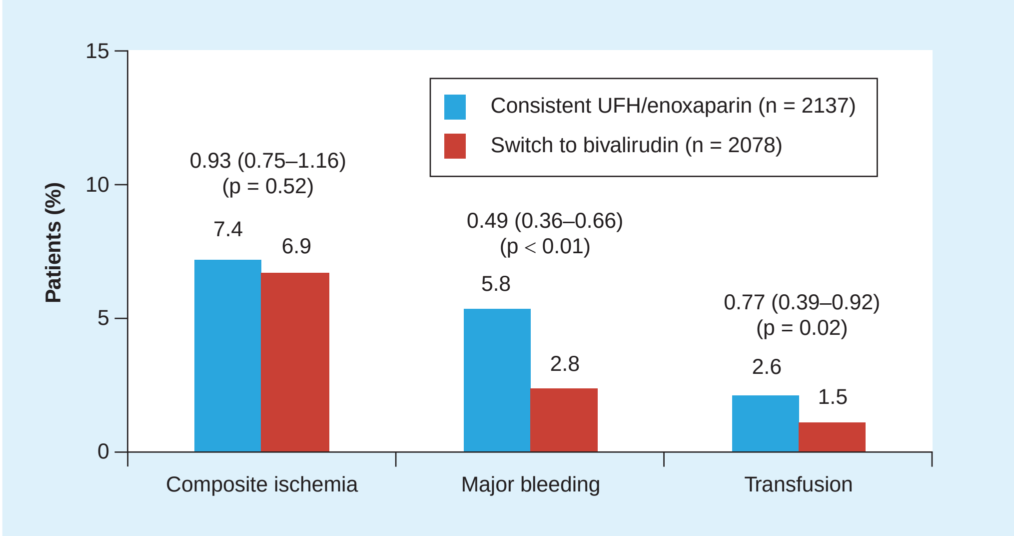

Figure 6. Results of the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial for patients who received either unfractionated heparin or enoxaparin prior to randomization and were switched to bivalirudin. Patients switched to bivalirudin had similar 30-day ischemic outcomes (death, myocardial infarction or unplanned revascularization), but significantly lower rates of major bleeding and transfusions in comparison with patients maintained on consistent heparin therapy. The numbers above the bars represent risk ratios (95% CI).
UFH: Unfractionated heparin.
Adapted with permission from [65].

The results of these studies not only emphasize the challenges of using multiple anticoagulation strategies during PCI but also highlight the need for further prospective investigations that could provide data for first-line clinicians who might modify their initial anticoagulation strategy based on an assessment of their patient's chance for a possible PCI, thus potentially improving patient care and outcomes. Excellent documentation, standardized processes and optimal communication between the emergency department, in-patient units and the catheterization laboratories are needed to avoid dosing errors and maintain optimal anticoagulation levels with consistent therapy.

Anticoagulation monitoring during percutaneous coronary intervention

Both ACT and APTT are useful anticoagulation monitoring tools. However, with the larger doses of heparin needed for interventional procedures, the APTT becomes unreliable with a nonlinear response. For this reason and the availability of a point-of-care device in the catheterization laboratory, ACT has become the standard of care for monitoring anticoagulation with UFH [68,69]. Nevertheless, owing to the unpredictable biologic activity of UFH, the ACT levels are highly variable even with rigorous weight-based regimens. Early studies with balloon angioplasty and no thienopyridine use showed an inverse relationship between ACT levels and ischemic complications and determined a lower threshold of 300 s for anticoagulation during PCI [70,71]. However, a meta-analysis including seven PCI trials with universal stenting and GPI use showed no correlation between ACT levels and ischemic complications, but increased bleeding rates with higher ACT levels and UFH doses [72]. The American College of Chest Physicians (ACCP) and ACC/AHA guidelines recommend a targeted ACT of 250–350 s for patients not receiving GPI and an ACT of 200 s for those patients who do receive GPI. In general, the femoral arterial sheath can be safely removed when the ACT falls to 150–180 s [27,73].

As ACT is primarily a measurement of thrombin generation, it is not a reliable monitoring tool for fondaparinux, a selective Factor X inhibitor, or LMWH, given its higher Xa:IIa inhibition ratio [74]. The gold standard for assessment of therapeutic anticoagulation for LMWH is chromogenic anti-Factor Xa level determination with an accepted target range of 0.5–1.8 IU/ml. However, higher bleeding rates have been observed with anti-Factor Xa levels over 0.9 IU/ml. The test is costly and a point-of-care assessment device is not yet widely available. For this reason and owing to the predictable pharmacodynamic profile of LMWH, empiric dosing is recommended in patients undergoing PCI (Table 3). However, interventional cardiologists are not yet comfortable without real-time anticoagulation monitoring in the catheterization laboratory and it is mainly for this reason that LMWHs have not gained wide acceptance as a preferred anticoagulant for PCI. Moreover, from a safety standpoint, routine anticoagulation monitoring during PCI is an important reminder to nursing and medical staff to administer an anticoagulant before the procedure. It should be noted that subcutaneous or intravenous enoxaparin, regimens may not reach an optimal anti-Factor Xa activity greater than 0.5 IU/ml in up to 7% of patients with ACS and 11.7% of patients undergoing elective PCI (Figure 7). These patients are at higher risk of experiencing adverse ischemic events [61,75].

There have been efforts to develop point-of-care monitoring devices for LMWH that correlate well with anti-Factor Xa levels. An early device did not correlate with ischemic complications, but correlated well with higher rates of bleeding [76]. A recent study demonstrated that the Hemonox™ clotting time point-of-care device (International Technidyne Corp., NJ, USA) can identify patients on enoxaparin with inadequate anti-Factor Xa levels of less than 0.5 IU/ml before PCI with a sensitivity and a specificity of 95 and 74%, respectively [77].

In the case of DTIs, routinely used monitoring tests including ACT, APTT and thrombin time have not proved useful owning to the lack of a linear dose–response relationship over a broad range of DTI plasma concentrations [78]. In fact, ACT levels during PCI in patients anticoagulated with bivalirudin were not correlated with adverse ischemic events in a large randomized study [79]. Nonetheless, assessment of ACT levels after bivalirudin injection in the catheterization laboratory is a recommended safety measure to verify that the drug has been effectively administered.

Importance of the access site in the anticoagulant choice

In US medical practice, the femoral artery is the preferred and most common vascular access site [80]. However, this approach is not without complications, such as hematomas, pseudoaneurysms, arteriovenous fistulae and retroperitoneal hemorrhage. In fact, 60–70% of bleeding events post-PCI are access site-related [5]. As noted previously, bleeding control is of critical importance to optimize survival outcomes in ACS and PCI [6,81]. For this reason, the transradial approach has gained popularity, especially outside of the USA, owing

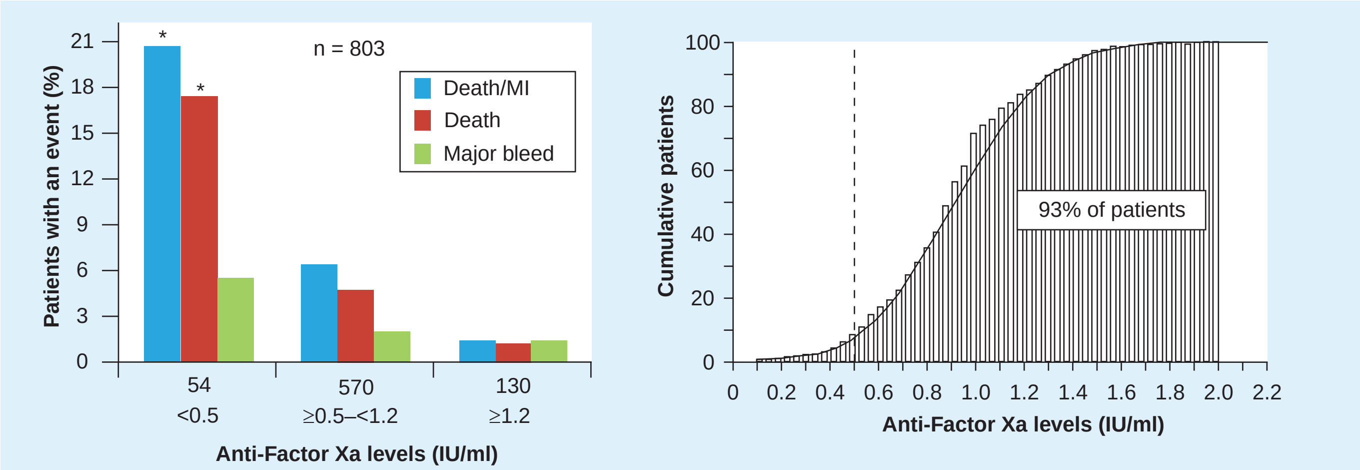

Figure 7. Significantly high rates of ischemic outcomes in acute coronary syndrome patients who achieve anti-Factor Xa levels of less than 5 IU/ml. These patients represented approximately 7% of the studied population.
*p < 0.05.
MI: Myocardial infarction.
Adapted with permission from [61].

to its easily compressible site, immediate sheath removal regardless of anticoagulation level and earlier patient mobilization postprocedure. A growing body of evidence indicates that routine transradial access is associated with a substantially greater reduction in bleeding complications than any of the safer contemporary anticoagulation strategies [82]. Moreover, the safety of transradial access may allow for more aggressive anti-thrombotic choices without paying the price of increased bleeding complications. In a subanalysis of 798 (6.2%) patients who underwent transradial catheterization within the ACUITY trial, the use of bivalirudin was not associated with the reduction in major bleeding noted in the general trial results. Major bleeding rates after transradial access were 4.2% with bivalirudin and 2.2% with UFH plus GPI (p = 0.19). By contrast, bleeding rates after transfemoral access were 3.0% with bivalirudin and 5.8% with UFH plus GPI (p < 0.0001) [83]. An observation from the Early Discharge After Transradial Stenting of Coronary Arteries (EASY) trial demonstrated lower rates of postprocedural troponin elevation in association with ACT levels greater than 330 s, without increased bleeding complications [84]. Registry data suggest that transradial access is even associated with a survival benefit secondary to the reduction in bleeding complications [85,86]. As more equipment specifically designed for transradial PCI is developed, the advantages of this technique are likely to continue to increase.

Dosing errors

The clinician should pay careful attention to patient history at the time of choosing the anticoagulant agent and its dose prior to PCI and should also calculate the creatinine clearance for all patients taken to the catheterization laboratory. According to an analysis of the CRUSADE registry, in a large sample of 46,492 ACS patients, the Cockcroft–Gault formula yielded lower creatinine clearance values and identified more patients with moderate chronic kidney disease than the modification of diet in renal disease (MDRD) formula. This difference translated into a higher need for anti-thrombotic dose adjustments and a lower risk of bleeding with the Cockcroft-Gault formula. Therefore, this formula should be the preferred method for creatinine clearance calculation for anti-thrombotic dosing in the catheterization laboratory [87].

Independent patient factors associated with increased bleeding in ACS include female gender, advanced age, prior history of bleeding and renal insufficiency [4]. Despite these known risk factors, in addition to careful monitoring and administration of anticoagulants, dosing errors remain an important problem in clinical practice. In a large ACS registry, at least 42% of patients on an anti-thrombotic agent received it at an excessive dose. Excessive dosing of LMWH and GPI was significantly associated with higher bleeding rates and longer lengths of stay. It is interesting that the factors associated with excess dosing, including older age, female sex, renal insufficiency, low bodyweight, diabetes mellitus and congestive heart failure, are almost identical to the factors associated with increased bleeding risk. Anticoagulant dosing errors may not be uncommon in the catheterization laboratory and may result in higher costs, longer hospitalizations and unfavorable outcomes, given the higher rates of bleeding.

Conclusion & future perspective

The development of novel agents will allow a more individualized approach to anticoagulation in the catheterization laboratory, but at the same time, will add complexity to the decision-making process. Excellent documentation, attention to detail and standardized processes across hospital departments, including the emergency room, coronary care unit and catheterization laboratory, are crucial to avoid dosing errors that expose patients to increased ischemic or bleeding complications. It is important that the clinician is aware of the advantages and disadvantages of currently available anticoagulants in order to individualize care, reduce ischemic complication and minimize bleeding risks. However, clinical trial data interpretation is challenged by the lack of uniform definitions of bleeding across major studies. It is now clear that continued adoption of transradial access for PCI will provide incremental safety to patients exposed to potent anti-thrombotic agents. Efforts should focus on the development of anticoagulants with wide therapeutic windows, stable pharmacodynamic profiles, lack of dependence on renal clearance, real-time monitoring and easy reversibility. Ideally, the anticoagulation strategy should be uniform throughout the care pathway of patients with acute or chronic coronary syndromes undergoing PCI, allowing an easy transition from the ambulance to the emergency room, catheterization laboratory and coronary care unit. Hopefully, the new classes of agents will fulfill current clinical needs.

Executive summary

Background

- The ideal anticoagulant hould maximize efficacy and safety, be conveniently administered without monitoring, be easily titratable to individual needs in percutaneous coronary intervention (PCI) and be easily reversible in case of bleeding or coronary perforation.

Current anticoagulants

- Heparin is limited by an unpredictable response, but continues to be the most widely used anticoagulant in the USA owing to its familiarity among cardiologists and ease of monitoring.
- Low-molecular-weight heparin provides stable anticoagulation and its use is associated with a lower bleeding risk in elective or urgent PCI; however, the use of enoxaparin in higher-risk patients undergoing PCI may be associated with an increased bleeding risk.
- Bivalirudin has gained wide acceptance in the catheterization laboratory owing to its predictable anticoagulation effect, short duration of action and decreased bleeding risk. Bivalirudin use was associated with decreased mortality in ST-segment elevation myocardial infarction.
- Fondaparinux is noninferior to low-molecular-weight heparin or unfractionated heparin (UFH) in the prevention of ischemic events and is associated with a lower bleeding risk in patients treated for acute coronary syndrome. However, additional administration of UFH is needed in patients undergoing PCI to prevent catheter thrombosis.

New anticoagulation targets & platforms

- New targets and anticoagulation platforms are being developed to meet current clinical needs, such as ease of administration without monitoring, ability to safely dose patients with impaired renal function and reversibility.

Switching anticoagulants

- Switching anticoagulants should be avoided, in particular in patients who have started on enoxaparin. Switching enoxaparin to UFH or *vice versa* is associated with an increased risk of bleeding and recurrent ischemia. Switching from UFH to bivalirudin appears to be safe.

Anticoagulation monitoring

- Monitoring identifies patients with insufficient anticoagulation levels who may be at risk of thrombotic coronary events. Monitoring is also a safety reminder to confirm that effective anticoagulation was administered.

Transradial vasular access to maximize treatment safety

- Transradial vascular access is associated with lower complication rates than transfemoral access. Observational data suggest that higher anticoagulation levels may be associated with lower rates of ischemic complications after transradial PCI without increased bleeding.

Dosing errors

- In an acute coronary syndrome registry, 42% of subjects received treatment at an excessive anti-thrombotic dose. Excessive dosing of low-molecular-weight heparin and glycoprotein IIb/IIIa inhibitors was significantly associated with higher bleeding rates and longer lengths of stay. Predictors of excess dosing include older age, female sex, renal insufficiency, low bodyweight, diabetes mellitus and congestive heart failure. These factors are almost identical to the predictors of increased bleeding risk.

Conclusion & future perspective

- Novel agents will allow a more individualized approach to anticoagulation, but introduce complexity to the decision-making process.
- Documentation, attention to detail and standardized processes are crucial to avoid dosing errors that expose patients to increased ischemic or bleeding complications.
- Clinical trial data interpretation is challenged by the lack of uniform definitions of bleeding across major studies.
- To enhance safety, anticoagulant therapy should be uniform throughout the care pathway of patients with chronic and acute coronary syndromes.

Financial & competing interests disclosure

Mauricio G Cohen is a consultant for Medtronic and Terumo Medical, and receives research support from Regado Biosciences. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Bibliography

Papers of special note have been highlighted as:
▪ of interest
▪▪ of considerable interest

1 Sianos G, Papafaklis MI, Daemen J *et al.*: Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden. *J. Am. Coll. Cardiol.* 50, 573–583 (2007).

2 Singh M, Berger PB, Ting HH *et al.*: Influence of coronary thrombus on outcome of percutaneous coronary angioplasty in the current era (the Mayo Clinic experience). *Am. J. Cardiol.* 88, 1091–1096 (2001).

3 Henriques JP, Zijlstra F, Ottervanger JP *et al.*: Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction. *Eur. Heart J.* 23, 1112–1117 (2002).

4 Moscucci M, Fox KA, Cannon CP *et al.*: Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur. Heart J.* 24, 1815–1823 (2003).

5 Kinnaird TD, Stabile E, Mintz GS *et al.*: Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. *Am. J. Cardiol.* 92, 930–935 (2003).

6 Mehran R, Pocock SJ, Stone GW *et al.*: Associations of major bleeding and myocardial infarction with the incidence and timing of mortality in patients presenting with non-ST-elevation acute coronary syndromes: a risk model from the ACUITY trial. *Eur. Heart J.* 30, 1457–1466 (2009).

▪ **Secondary data analysis demonstrating that bleeding and recurrent ischemia have similar impacts on mortality in acute coronary syndrome (ACS) patients.**

7 Lindsey JB, Marso SP, Pencina M *et al.*: Prognostic impact of periprocedural bleeding and myocardial infarction after percutaneous coronary intervention in unselected patients: results from the EVENT (Evaluation of Drug-Eluting Stents and Ischemic Events) registry. *JACC Cardiovasc. Interv.* 2, 1074–1082 (2009).

8 Alexander KP, Chen AY, Roe MT *et al.*: Anti-thrombotic strategy during percutaneous coronary intervention in NSTEMI: update from ACTION Registry-GWTG. *J. Am. Coll. Cardiol.* 53(Suppl. A), A398 (2009).

9 Linhardt RJ, Gunay NS: Production and chemical processing of low molecular weight heparins. *Semin. Thromb. Hemost.* 25(Suppl. 3), 5–16 (1999).

10 Hirsh J, Bauer KA, Donati MB, Gould M, Samama MM, Weitz JI: Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest* 133, S141–S159 (2008).

11 Xiao Z, Theroux P: Platelet activation with unfractionated heparin at therapeutic concentrations and comparisons with a low-molecular-weight heparin and with a direct thrombin inhibitor. *Circulation* 97, 251–256 (1998).

12 Bahit MC, Topol EJ, Califf RM *et al.*: Reactivation of ischemic events in acute coronary syndromes: results from GUSTO-IIb. Gobal use of strategies to open occluded arteries in acute coronary syndromes. *J. Am. Coll. Cardiol.* 37, 1001–1007 (2001).

13 Kong DF, Hasselblad V, Harrington RA *et al.*: Meta-analysis of survival with platelet glycoprotein IIb/IIIa antagonists for percutaneous coronary interventions. *Am. J. Cardiol.* 92, 651–655 (2003).

14 Samama MM, Bara L, Gerotziafas GT: Mechanisms for the anti-thrombotic activity in man of low molecular weight heparins (LMWHs). *Haemostasis* 24, 105–117 (1994).

15 Weitz JI: Low-molecular-weight heparins. *N. Engl. J. Med.* 337, 688–698 (1997).

16 Warkentin TE, Levine MN, Hirsh J *et al.*: Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N. Engl. J. Med.* 332, 1330–1335 (1995).

17 Montalescot G, Bal-dit-Sollier C, Chibedi D *et al.*: Comparison of effects on markers of blood cell activation of enoxaparin, dalteparin, and unfractionated heparin in patients with unstable angina pectoris or non-ST-segment elevation acute myocardial infarction (the ARMADA study). *Am. J. Cardiol.* 91, 925–930 (2003).

18 Antman EM, Cohen M, McCabe C, Goodman SG, Murphy SA, Braunwald E: Enoxaparin is superior to unfractionated heparin for preventing clinical events at 1-year follow-up of TIMI 11B and ESSENCE. *Eur. Heart J.* 23, 308–314 (2002).

19 Rabah MM, Premmereur J, Graham M *et al.*: Usefulness of intravenous enoxaparin for percutaneous coronary intervention in stable angina pectoris. *Am. J. Cardiol.* 84, 1391–1395 (1999).

20 Madan M, Radhakrishnan S, Reis M *et al.*: Comparison of enoxaparin versus heparin during elective percutaneous coronary intervention performed with either eptifibatide or tirofiban (the ACTION trial). *Am. J. Cardiol.* 95, 1295–1301 (2005).

21 Bhatt DL, Lee BI, Casterella PJ *et al.*: Safety of concomitant therapy with eptifibatide and enoxaparin in patients undergoing percutaneous coronary intervention: results of the Coronary Revascularization Using Integrilin and Single Bolus Enoxaparin Study. *J. Am. Coll. Cardiol.* 41, 20–25 (2003).

22 Kereiakes DJ, Grines C, Fry E *et al.*: Enoxaparin and abciximab adjunctive pharmacotherapy during percutaneous coronary intervention. *J. Invasive Cardiol.* 13, 272–278 (2001).

23 Ferguson JJ, Antman EM, Bates ER *et al.*: Combining enoxaparin and glycoprotein IIb/IIIa antagonists for the treatment of acute coronary syndromes: final results of the National Investigators Collaborating on Enoxaparin-3 (NICE-3) study. *Am. Heart J.* 146, 628–634 (2003).

24 Ferguson JJ, Califf RM, Antman EM *et al.*: Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. *JAMA* 292, 45–54 (2004).

▪▪ **Pivotal randomized clinical trial that demonstrated increased bleeding rates with enoxaparin in high-risk ACS patients undergoing percutaneous coronary intervention (PCI).**

25 White HD, Kleiman NS, Mahaffey KW *et al.*: Efficacy and safety of enoxaparin compared with unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndrome undergoing percutaneous coronary intervention in the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial. *Am. Heart J.* 152, 1042–1050 (2006).

26 Dumaine R, Borentain M, Bertel O *et al.*: Intravenous low-molecular-weight heparins compared with unfractionated heparin in percutaneous coronary intervention: quantitative review of randomized trials. *Arch. Intern. Med.* 167, 2423–2430 (2007).

▪ **Large meta-analysis demonstrating the efficacy and safety of low-molecular-weight heparins in PCI.**

27 Popma JJ, Berger P, Ohman EM, Harrington RA, Grines C, Weitz JI: Anti-thrombotic therapy during percutaneous coronary intervention: the Seventh ACCP Conference on Anti-thrombotic and Thrombolytic Therapy. *Chest* 126, 576S–599S (2004).

▪▪ **Guideline recommendations for management of anti-thrombotic therapies in PCI.**

28 Montalescot G, White HD, Gallo R *et al.*: Enoxaparin versus unfractionated heparin in elective percutaneous coronary intervention. *N. Engl. J. Med.* 355, 1006–1017 (2006).

▪▪ **Pivotal randomized clinical trial demonstrating safety of enoxaparin in PCI.**

29 LaPointe NM, Chen AY, Alexander KP *et al.*: Enoxaparin dosing and associated risk of in-hospital bleeding and death in patients with non ST-segment elevation acute coronary syndromes. *Arch. Intern. Med.* 167, 1539–1544 (2007).

30 Anderson JL, Adams CD, Antman EM *et al.*: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *Circulation* 116, E148–E304 (2007).

31 Furie B, Furie BC: Molecular and cellular biology of blood coagulation. *N. Engl. J. Med.* 326, 800–806 (1992).

32 Di Nisio M, Middeldorp S, Buller HR: Direct thrombin inhibitors. *N. Engl. J. Med.* 353, 1028–1040 (2005).

33 Eitzman DT, Chi L, Saggin L, Schwartz RS, Lucchesi BR, Fay WP: Heparin neutralization by platelet-rich thrombi. Role of platelet Factor 4. *Circulation* 89, 1523–1529 (1994).

34 Direct Thrombin Inhibitor Trialists' Collaborative Group: Direct thrombin inhibitors in acute coronary syndromes: principal results of a meta-analysis based on individual patients' data. *Lancet* 359, 294–302 (2002).

▪ **Large meta-analysis demonstrating the efficacy of direct thrombin inhibitors in ACS.**

35 Bittl JA, Strony J, Brinker JA *et al.*: Treatment with bivalirudin (Hirulog) as compared with heparin during coronary angioplasty for unstable or postinfarction angina. Hirulog Angioplasty Study Investigators. *N. Engl. J. Med.* 333, 764–769 (1995).

36 Lincoff AM, Kleiman NS, Kottke-Marchant K *et al.*: Bivalirudin with planned or provisional abciximab versus low-dose heparin and abciximab during percutaneous coronary revascularization: results of the Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial (CACHET). *Am. Heart J.* 143, 847–853 (2002).

37 Lincoff AM, Bittl JA, Harrington RA *et al.*: Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 289, 853–863 (2003).

38 Kastrati A, Neumann FJ, Mehilli J *et al.*: Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. *N. Engl. J. Med.* 359, 688–696 (2008).

39 Stone GW, McLaurin BT, Cox DA *et al.*: Bivalirudin for patients with acute coronary syndromes. *N. Engl. J. Med.* 355, 2203–2216 (2006).

▪ **Large randomized clinical trial demonstrating decreased bleeding rates in moderate-risk ACS patients.**

40 Stone GW, Witzenbichler B, Guagliumi G *et al.*: Bivalirudin during primary PCI in acute myocardial infarction. *N. Engl. J. Med.* 358, 2218–2230 (2008).

▪ **Large randomized clinical trial demonstrating decreased bleeding rates with bivalirudin as an adjunct to primary PCI.**

41 Bittl JA, Chaitman BR, Feit F, Kimball W, Topol EJ: Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina: final report reanalysis of the Bivalirudin Angioplasty Study. *Am. Heart J.* 142, 952–959 (2001).

42 Lincoff AM, Kleiman NS, Kereiakes DJ *et al.*: Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: REPLACE-2 randomized trial. *JAMA* 292, 696–703 (2004).

43 Gurm HS, Smith DE, Chetcuti SJ *et al.*: Temporal trends, safety, and efficacy of bivalirudin in elective percutaneous coronary intervention: insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. *J. Interv. Cardiol.* 20, 197–203 (2007).

44 Rassen JA, Mittleman MA, Glynn RJ, Alan Brookhart M, Schneeweiss S: Safety and effectiveness of bivalirudin in routine care of patients undergoing percutaneous coronary intervention. *Eur. Heart J.* 31, 561–572 (2010).

45 Samama MM, Gerotziafas GT: Evaluation of the pharmacological properties and clinical results of the synthetic pentasaccharide (fondaparinux). *Thromb. Res.* 109, 1–11 (2003).

46 Turpie AG, Gallus AS, Hoek JA: A synthetic pentasaccharide for the prevention of deep-vein thrombosis after total hip replacement. *N. Engl. J. Med.* 344, 619–625 (2001).

47 Mehta SR, Steg PG, Granger CB *et al.*: Randomized, blinded trial comparing fondaparinux with unfractionated heparin in patients undergoing contemporary percutaneous coronary intervention: Arixtra Study in Percutaneous Coronary Intervention: a Randomized Evaluation (ASPIRE) Pilot Trial. *Circulation* 111, 1390–1397 (2005).

48 Mehta SR, Boden WE, Eikelboom JW *et al.*: Anti-thrombotic therapy with fondaparinux in relation to interventional management strategy in patients with ST- and non-ST-segment elevation acute coronary syndromes: an individual patient-level combined analysis of the Fifth and Sixth Organization to Assess Strategies in Ischemic Syndromes (OASIS 5 and 6) randomized trials. *Circulation* 118, 2038–2046 (2008).

49 Montalescot G, Walenga JM: Catheter-related thrombosis: biological and clinical evidence for risk with currently available anticoagulants. *Clin. Appl. Thromb. Hemost.* 15, 183–196 (2009).

50 Paccaly A, Frick A, Rohatagi S *et al.*: Pharmacokinetics of otamixaban, a direct Factor Xa inhibitor, in healthy male subjects: pharmacokinetic model development for Phase II/III simulation of exposure. *J. Clin. Pharmacol.* 46, 37–44 (2006).

51 Cohen M, Bhatt DL, Alexander JH *et al.*: Randomized, double-blind, dose-ranging study of otamixaban, a novel, parenteral, short-acting direct Factor Xa inhibitor, in percutaneous coronary intervention: the SEPIA-PCI trial. *Circulation* 115, 2642–2651 (2007).

52 Sabatine MS, Antman EM, Widimsky P *et al.*: Otamixaban for the treatment of patients with non-ST-elevation acute coronary syndromes (SEPIA-ACS1 TIMI 42): a randomised, double-blind, active-controlled, Phase II trial. *Lancet* 374, 787–795 (2009).

53 Giugliano RP, White JA, Bode C *et al.*: Early versus delayed, provisional eptifibatide in acute coronary syndromes. *N. Engl. J. Med.* 360, 2176–2190 (2009).

54 Alexander JH, Dyke CK, Yang H *et al.*: Initial experience with Factor-Xa inhibition in percutaneous coronary intervention: the XaNADU-PCI Pilot. *J. Thromb. Haemost.* 2, 234–241 (2004).

55 Volovyk Z, Monroe DM, Qi Y, Becker R, Hoffman M: A rationally designed heparin, M118, has anticoagulant activity similar to unfractionated heparin and different from Lovenox in a cell-based model of thrombin generation. *J. Thromb.* 28, 132–139 (2009).

56 Rao SV: Evaluation of a novel, rationally designed, low-molecular-weight heparin during elective PCI: results of the Phase II EMINENCE trial. Presented at: *Transcatheter Therapeutics (TCT) Conference 2009.* CA, USA, 21–25 September 2009.

57 Moons AH, Peters RJ, Bijsterveld NR *et al.*: Recombinant nematode anticoagulant protein c2, an inhibitor of the tissue factor/ Factor VIIa complex, in patients undergoing elective coronary angioplasty. *J. Am. Coll. Cardiol.* 41, 2147–2153 (2003).

58 Giugliano RP, Wiviott SD, Stone PH *et al.*: Recombinant nematode anticoagulant protein c2 in patients with non-ST-segment elevation acute coronary syndrome: the ANTHEM-TIMI-32 trial. *J. Am. Coll. Cardiol.* 49, 2398–2407 (2007).

59 Hoffman M, Monroe DM: Coagulation 2006: a modern view of hemostasis. *Hematol. Oncol. Clin. North Am.* 21, 1–11 (2007).

60 Becker RC, Povsic T, Cohen MG, Rusconi CP, Sullenger B: Nucleic acid aptamers as anti-thrombotic agents: opportunities in extracellular therapeutics. *Thromb. Haemost.* 103, 586–595 (2010).

61 Montalescot G, Collet JP, Tanguy ML *et al.*: Anti-Xa activity relates to survival and efficacy in unselected acute coronary syndrome patients treated with enoxaparin. *Circulation* 110, 392–398 (2004).

62 Martin JL, Fry ET, Sanderink GJ *et al.*: Reliable anticoagulation with enoxaparin in patients undergoing percutaneous coronary intervention: the Pharmacokinetics of Enoxaparin in PCI (PEPCI) study. *Catheter Cardiovasc. Interv.* 61, 163–170 (2004).

63 Drouet L, Bal dit Sollier C, Martin J: Adding intravenous unfractionated heparin to standard enoxaparin causes excessive anticoagulation not detected by activated clotting time: results of the STACK-on to ENOXaparin (STACKENOX) study. *Am. Heart J.* 158, 177–184 (2009).

- **Phase I study that explains the increased bleeding risk observed with the addition of unfractionated heparin to enoxaparin.**

64 Dose-ranging trial of enoxaparin for unstable angina: results of TIMI 11A. The Thrombolysis in Myocardial Infarction (TIMI) 11A Trial Investigators. *J. Am. Coll. Cardiol.* 29, 1474–1482 (1997).

65 White HD, Chew DP, Hoekstra JW *et al.*: Safety and efficacy of switching from either unfractionated heparin or enoxaparin to bivalirudin in patients with non-ST-segment elevation acute coronary syndromes managed with an invasive strategy: results from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. *J. Am. Coll. Cardiol.* 51, 1734–1741 (2008).

66 Dangas GD, Lansky AJ, Brodie BR *et al.*: Predictors of acute, subacute and late stent thrombosis after acute MI primary angioplasty in the Horizons AMI trial. Presented at: *American College of Cardiology 2009 Annual Scientific Sessions.* Orlando, FL, USA, 29–31 March 2009.

67 Waksman R, Wolfram RM, Torguson RL *et al.*: Switching from enoxaparin to bivalirudin in patients with acute coronary syndromes without ST-segment elevation who undergo percutaneous coronary intervention. Results from SWITCH – a multicenter clinical trial. *J. Invasive Cardiol.* 18, 370–375 (2006).

68 Dougherty KG, Gaos CM, Bush HS, Leachman DR, Ferguson JJ: Activated clotting times and activated partial thromboplastin times in patients undergoing coronary angioplasty who receive bolus doses of heparin. *Cathet. Cardiovasc. Diagn.* 26, 260–263 (1992).

69 Ferguson JJ: All ACTs are not created equal. *Tex. Heart Inst. J.* 19, 1–3 (1992).

70 Narins CR, Hillegass WB Jr, Nelson CL *et al.*: Relation between activated clotting time during angioplasty and abrupt closure. *Circulation* 93, 667–671 (1996).

71 Ferguson JJ, Dougherty KG, Gaos CM, Bush HS, Marsh KC, Leachman DR: Relation between procedural activated coagulation time and outcome after percutaneous transluminal coronary angioplasty. *J. Am. Coll. Cardiol.* 23, 1061–1065 (1994).

72 Brener SJ, Moliterno DJ, Lincoff AM, Steinhubl SR, Wolski KE, Topol EJ: Relationship between activated clotting time and ischemic or hemorrhagic complications: analysis of 4 recent randomized clinical trials of percutaneous coronary intervention. *Circulation* 110, 994–998 (2004).

73 Smith SC Jr, Feldman TE, Hirshfeld JW Jr *et al.*: ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to update 2001 guidelines for percutaneous coronary intervention). *Circulation* 113, E166–E286 (2006).

74 Henry TD, Satran D, Knox LL, Iacarella CL, Laxson DD, Antman EM: Are activated clotting times helpful in the management of anticoagulation with subcutaneous low-molecular-weight heparin? *Am. Heart J.* 142, 590–593 (2001).

75 Montalescot G, Cohen M, Salette G *et al.*: Impact of anticoagulation levels on outcomes in patients undergoing elective percutaneous coronary intervention: insights from the STEEPLE trial. *Eur. Heart J.* 29, 462–471 (2008)

76 Moliterno DJ, Hermiller JB, Kereiakes DJ *et al.*: A novel point-of-care enoxaparin monitor for use during percutaneous coronary intervention. Results of the Evaluating Enoxaparin Clotting Times (ELECT) study. *J. Am. Coll. Cardiol.* 42, 1132–1139 (2003).

77 Silvain J, Beygui F, Ankri A *et al.*: Enoxaparin anticoagulation monitoring in the catheterization laboratory using a new bedside test. *J. Am. Coll. Cardiol.* 55, 617–625 (2010).

78 Nowak G: Clinical monitoring of hirudin and direct thrombin inhibitors. *Semin. Thromb. Hemost.* 27, 537–541 (2001).

79 Bittl JA, Ahmed WH: Relation between abrupt vessel closure and the anticoagulant response to heparin or bivalirudin during coronary angioplasty. *Am. J. Cardiol.* 82, 50P–56P (1998).

80 Rao SV, Ou FS, Wang TY *et al.*: Trends in the prevalence and outcomes of radial and femoral approaches to percutaneous coronary intervention: a report from the National Cardiovascular Data Registry. *JACC Cardiovasc. Interv.* 1, 379–386 (2008).

- **Large registry data demonstrating the underuse of transradial access for PCI in the USA.**

81 Manoukian SV, Feit F, Mehran R *et al.*: Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY Trial. *J. Am. Coll. Cardiol.* 49, 1362–1368 (2007).

82 Jolly SS, Amlani S, Hamon M, Yusuf S, Mehta SR: Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials. *Am. Heart J.* 157, 132–140 (2009).

83 Hamon M, Rasmussen LH, Manoukian SV *et al.*: Choice of arterial access site and outcomes in patients with acute coronary syndromes managed with an early invasive strategy: the ACUITY trial. *EuroIntervention* 5, 115–120 (2009).

84 Bertrand OF, Rodes-Cabau J, Rinfret S *et al.*: Impact of final activated clotting time after transradial coronary stenting with maximal antiplatelet therapy. *Am. J. Cardiol.* 104, 1235–1240 (2009).

85 Chase AJ, Fretz EB, Warburton WP *et al.*: Association of the arterial access site at angioplasty with transfusion and mortality: the MORTAL study (Mortality Benefit Of Reduced Transfusion after Percutaneous Coronary Intervention via the Arm or Leg). *Heart* 94, 1019–1025 (2008).

86 Montalescot G, Ongen Z, Guindy R *et al.*: Predictors of outcome in patients undergoing PCI. Results of the RIVIERA study. *Int. J. Cardiol.* 129(3), 379–387 (2008).

87 Melloni C, Peterson ED, Chen AY *et al.*: Cockcroft–Gault versus modification of diet in renal disease: importance of glomerular filtration rate formula for classification of chronic kidney disease in patients with non-ST-segment elevation acute coronary syndromes. *J. Am. Coll. Cardiol.* 51, 991–996 (2008).

88 Hirsh J, O'Donnell M, Eikelboom JW: Beyond unfractionated heparin and warfarin: current and future advances. *Circulation* 116, 552–560 (2007).

89 Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators, Yusuf S, Mehta SR, Chrolavicius S *et al.*: Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N. Engl. J. Med.* 354(14), 1464–1476 (2006).