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 intervention thrombosis coronary artery disease percutaneous coronary intervention

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 inhospital 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)
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.

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 α2-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, Xa and XIIa.

In the catheterization laboratory, UFH is administered intravenously. Once in the bloodstream, UFH binds to plasma proteins, which

### Table 1. Principal characteristics of currently available anticoagulants.

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

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.

![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.](image)

Indicates a similar mortality rate after recurrent ischemic and bleeding events in patients treated for acute coronary syndromes. Adapted with permission from [6].
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 (HITT) 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.

**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 LMWH 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.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>n</th>
<th>Study population</th>
<th>Anticoagulation regimen</th>
<th>Outcomes (enoxaparin vs UFH)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabah et al. (1999)</td>
<td>60</td>
<td>Stable angina</td>
<td>1 mg/kg iv. bolus</td>
<td>10,000 IU bolus to ACT &gt; 300 s</td>
<td>0 vs 3 patients (p = NS) 1 vs 0 patients (p = NS)</td>
</tr>
<tr>
<td>ACTION (2005)</td>
<td>200</td>
<td>Elective PCI</td>
<td>0.75 mg/kg iv. bolus plus GPI</td>
<td>60 IU/kg bolus plus GPI</td>
<td>8.0 vs 14.0% (p = NS) 0% in both arms</td>
</tr>
<tr>
<td>CRUISE (2003)</td>
<td>261</td>
<td>Elective or urgent PCI</td>
<td>0.75 mg/kg iv. bolus plus GPI</td>
<td>60 IU/kg bolus plus GPI</td>
<td>8.5 vs 7.6% (p = 0.82) 0 vs 2.6% (p = 0.44)</td>
</tr>
<tr>
<td>SYNERGY (2004)</td>
<td>10,027</td>
<td>High-risk ACS with early invasive strategy</td>
<td>1 mg/kg sc. every 12 h</td>
<td>60 IU/kg bolus to ACT &gt; 250 s</td>
<td>14.0 vs 14.5% (p = 0.40) 2.4 vs 1.8% (p = 0.03)</td>
</tr>
<tr>
<td>STEEPLE (2006)</td>
<td>3528</td>
<td>Elective PCI</td>
<td>0.5 or 0.75 mg/kg iv.</td>
<td>70–100 IU/kg to ACT 300–350 s</td>
<td>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 &lt; 0.01)</td>
</tr>
</tbody>
</table>

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 desirudin, 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>
<thead>
<tr>
<th>Enoxaparin sc. 1 mg/kg every 12 h</th>
<th>Additional enoxaparin prior to PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last dose &lt;8 h†</td>
<td>Not needed</td>
</tr>
<tr>
<td>Last dose 8–12 h</td>
<td>0.3 mg/kg iv.</td>
</tr>
<tr>
<td>Last dose &gt;12 h</td>
<td>Conventional anticoagulation as per standard of care</td>
</tr>
<tr>
<td>Additional glycoprotein IIb/IIia inhibitors</td>
<td>At discretion of the operator. Increased bleeding risk</td>
</tr>
<tr>
<td>De novo anticoagulation in catheterization laboratory</td>
<td>0.75 mg/kg iv.</td>
</tr>
</tbody>
</table>

### Timing of sheath removal

<table>
<thead>
<tr>
<th>Timing of sheath removal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>After 1 sc. dose</td>
<td>4 h</td>
</tr>
<tr>
<td>After 2 sc. doses</td>
<td>6 h</td>
</tr>
<tr>
<td>After 3 sc. doses</td>
<td>8 h</td>
</tr>
<tr>
<td>After 0.75 mg/kg iv. dose</td>
<td>4–6 h</td>
</tr>
</tbody>
</table>

*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.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Study population</th>
<th>Anticoagulation regimen</th>
<th>Outcomes (bivalirudin vs UFH)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAT</td>
<td>4098</td>
<td>Unstable or post-MI angina</td>
<td>Bivalirudin: Bolus: 1.0 mg/kg Infusion: 2.5 mg/kg/h for 4 h</td>
<td>Ischemic end point: 6.2 vs 7.9% (p = 0.039)</td>
<td>[35]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Planned or provisional GPI</td>
<td>Major bleeding (non-CABG): 3.5 vs 9.3% (p &lt; 0.001)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>UFH: Bolus: 175 IU/kg Infusion: 15 IU/kg/h for 18–24 h</td>
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<td></td>
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<tr>
<td>CACHET</td>
<td>268</td>
<td>Elective PCI</td>
<td>Bivalirudin: Bolus: 0.5–1.0 mg/kg Infusion: 1.75–2.5 mg/kg/h</td>
<td>Bivalirudin + GPI: 0%</td>
<td>[36]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>for 4 h Planned or provisional GPI</td>
<td>Bivalirudin: 3.3%</td>
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<td>GPI: 3%</td>
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<td>GPI: 0%</td>
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<td>GPI: 0–4.7%</td>
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<td></td>
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<td></td>
<td></td>
<td>UFH: 6.4%</td>
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<td>(p = NS)</td>
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<td></td>
<td></td>
<td>GPI: 0–2.4%</td>
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<td></td>
<td></td>
<td></td>
<td>UFH: 4.3%</td>
<td></td>
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<td></td>
<td></td>
<td>(p = NS)</td>
<td></td>
</tr>
<tr>
<td>REPLACE-2</td>
<td>6010</td>
<td>Elective or urgent PCI</td>
<td>Bivalirudin: Bolus: 0.75 mg/kg Infusion: 1.75 mg/kg/h during PCI</td>
<td>7.6 vs 7.1% (p = 0.40)</td>
<td>[37]</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Planned or provisional GPI</td>
<td>2.4 vs 4.1% (p &lt; 0.001)</td>
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<tr>
<td>ISAR-REACT 3</td>
<td>4570</td>
<td>Elective PCI</td>
<td>Bivalirudin: Bolus: 0.75 mg/kg Infusion: 1.75 mg/kg/h during PCI</td>
<td>5.9 vs 5.0% (p = 0.23)</td>
<td>[38]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Planned or provisional GPI</td>
<td>3.1 vs 4.6% (p &lt; 0.05)</td>
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<tr>
<td>ACUITY</td>
<td>13,819</td>
<td>Moderate- to high-risk ACS</td>
<td>Bivalirudin: Bolus: 0.1 mg/kg Infusion: 0.25 mg/kg/h before PCI</td>
<td>Bivalirudin: 3.0%</td>
<td>[39]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Planned or provisional GPI</td>
<td>Bivalirudin: 7.8%</td>
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<td>GPI: 7.7%</td>
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<td></td>
<td></td>
<td></td>
<td>UFH: 7.3%</td>
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<td>HORIZONS-AMI</td>
<td>3602</td>
<td>ST-elevation MI</td>
<td>Bivalirudin: Bolus: 0.75 mg/kg Infusion: 1.75 mg/kg/h during PCI</td>
<td>5.4 vs 5.5% (p = 0.95)</td>
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<td>Planned or provisional GPI</td>
<td>4.9 vs 8.3% (p &lt; 0.001)</td>
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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 [49]. 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.

### 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 (nNAPc2) inhibits the complex tissue factor (TF)–Factor VIIa. The REG1 system is a regulatable anticoagulant:control agent RNA 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 (SEP1A-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. Otamixaban 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 I 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 GPs 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.

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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 quaternary 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 that 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 anti-thrombotic 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 without UFH who underwent PCI had intraprocedural coronary thrombus formation with need for bailout 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 Ib 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 [60]. 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 return 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 9) [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 [60]. 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 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 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.](image-url)
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 [72,73].

As ACT is primarily a measurement of thrombin generation, it is not a reliable monitoring tool for fondaparinux, a selective Factor Xa 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 HemonoxTM 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 owing 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 [8]. 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...
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.

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].
**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.

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**Executive summary**

**Background**

- The ideal anticoagulant should 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 vascular 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.
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No writing assistance was utilized in the production of this manuscript.

Bibliography

Papers of special note have been highlighted as:

\* of interest

\(\Rightarrow\) of considerable interest


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

Anticoagulation in percutaneous coronary intervention

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


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


- Pivotal randomized clinical trial demonstrating safety of enoxaparin in PCI.


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


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


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


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


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


