SCIENTIFIC EDITORIAL

Anticoagulant for primary percutaneous coronary intervention—the last dance for unfractionated heparin?

Anticoagulation de l’angioplastie primaire—dernière danse pour l’héparine?

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Rates of short- and long-term mortality after an acute coronary syndrome (ACS) have been reduced dramatically through advances in percutaneous coronary intervention (PCI) techniques and the availability of new antithrombotic agents. This is particularly true for patients with ST-elevation myocardial infarction (STEMI) treated with primary PCI. On the antiplatelet side, we have, besides clopidogrel, two new P2Y12 inhibitors—prasugrel and ticagrelor—for which data and subset analyses have allowed a better understanding of which patients with an ACS would truly benefit from these drugs. On the anticoagulant side, besides unfractionated heparin (UFH), we have three newer anticoagulants that can be used in ACS: enoxaparin, fondaparinux and bivalirudin. In this competitive field, the past decade has provided a large flow of evidence-based information in terms of the safety and efficacy of these antithrombotic agents. This information needs to be implemented both in guidelines and in our daily clinical practice. As always, there is no simple rule or conclusion; rather, different options exist according to current practice and our own personal environment and experiences.

The efficacy of anticoagulation therapy is evaluated on the basis of ischaemic complications of ACS and sometimes the outcome of PCI itself, both of which have a real impact on short- and long-term mortality. The first goal of anticoagulation therapy during primary PCI of STEMI is therefore to avoid or control at all times the development of thrombus and in doing so obtain or maintain blood flow through the coronary circulation and protect the myocardium from harmful damage related to ischaemia and necrosis. If the drug efficacy translates into a mortality reduction, there is a good chance of recognition and acceptance of the new treatment by practising physicians.

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Safety is also a major issue of anticoagulation therapy: all of these drugs increase the risk of instrumental or spontaneous bleeding, leading to more transfusions and subsequently higher morbidity and mortality [1]. Lowering instrumental or procedure-related bleeding is very important; when interventional cardiologists are not sufficiently skilled to perform PCI through the radial approach, this reduced bleeding risk can be achieved with the use of a more stable anticoagulant and a lower level of anticoagulation.

The latest data on the efficacy (ischaemic and mortality endpoints) and safety (major bleeding endpoint) of the three newest anticoagulants—enoxaparin, fondaparinux, and bivalirudin—tested in primary PCI for patients with STEMI are provided in Table 1.

In the Harmonizing Outcomes with Revascularization and Stents (HORIZONS) trial [2], bivalirudin did not reduce the rate of the ischaemic endpoint compared with UFH (relative risk [RR] 0.99, 95% confidence interval [CI] 0.76–1.30); the trial involved 3602 patients with STEMI treated by primary PCI and had sufficient power to address this question. However, the main result of the trial was a 40% reduction in the safety endpoint (RR 0.60, 95% CI 0.46–0.77), corresponding to both procedure-related and spontaneous bleedings; the result was of such a magnitude that mortality was also reduced significantly (RR 0.66, 95% CI 0.44–1.00). This explanation of the mortality reduction is consistent with other trials that also reduced procedure-related major bleeding and mortality, with a radial approach rather than a femoral approach [3]. In the Radial Versus Femoral Investigation (RIFLE) trial, radial access reduced procedure-related major bleedings by 47% and subsequently mortality by 57%, without any impact on ischaemic endpoints [3]. These results highlight that safety is a serious issue and that improvement in safety can have a direct impact on mortality, especially when considering PCI performed via the femoral approach.

Fondaparinux was compared with UFH in the Optimal Antiplatelet Strategy for Interventions 6 (OASIS) trial [4]—a large trial of 12,092 STEMI patients. However, only 3789 patients were treated by primary PCI, and the results regarding this indication were in opposition to the group of patients treated medically or by fibrinolysis, with a significant P value for interaction (P = 0.04). Indeed, at 30 days the classic ischaemic endpoint of death or myocardial infarction was increased by 20% (RR 1.20, 95% 0.91–1.57), also with a trend towards a higher rate of severe bleeding, which was increased by 18% (RR 1.18, 95% CI 0.63–2.22); this led to a non-significant but worrying increase of 16% in all-cause mortality (RR 1.16, 95% CI 0.85–1.58). Therefore, with such results, fondaparinux cannot be recommended in primary PCI for STEMI patients.

Enoxaparin, when compared with UFH in the Acute STEMI Treated with primary angioplasty and intravenous enoxa-parin Or UFH to Lower ischemic and bleeding events at short- and Long-term follow-up (ATOLL) trial [5], reduced the classic ischaemic endpoint of death, recurrent myocardial infarction/ACS or urgent revascularization by 41% (RR 0.59, 95% CI 0.38–0.91), with even a trend towards a 40% mortality reduction (RR 0.60, 95% CI 0.33–1.07), which was significant when considering the combination of death and resuscitated cardiac arrest (P = 0.049). The rate of major bleeding did not differ between the two arms and the effect on mortality appeared, this time, to be in opposition to bivalirudin, driven by the reduction in the rate of ischaemic endpoints. The primary endpoint of the ATOLL trial combining ischaemic, bleeding and procedural events was also reduced, although the P value fell short of statistical significance (P = 0.06). The expected reduction in major bleeding with enoxaparin did not occur, most likely due to predominant use of the radial access, an unusual predominant approach in international trials of primary PCI.

The lack of power for hard endpoints in the comparison between enoxaparin and UFH in the ATOLL trial was solved by the publication of two recent meta-analyses from different research groups. The first study [6] focused on primary PCI, showing that low-molecular-weight heparin (in most cases enoxaparin) was superior in reducing mortality, by 49% (RR 0.51, 95% CI 0.41–0.64) and major bleeding by 32% (RR 0.68, 95% CI 0.49–0.94) when regrouping the data of 16,286 patients. The second meta-analysis [7] pooled more than 30,000 patients treated with enoxaparin only, and extended these results to all types of PCI, with a global reduction in mortality of 34% (RR 0.66, 95% CI 0.57–0.76) independently of the clinical presentation. The benefit was driven largely by the effect obtained in the 10,243 STEMI patients treated with primary PCI, with a reduction in mortality of 48% (RR 0.52, 95% CI 0.42–0.64), through a combined effect on the ischaemic endpoints (recurrent myocardial infarction or complication of myocardial infarction was reduced by 24%; RR 0.76, 95% CI 0.60–0.96) and bleeding endpoints, which were reduced by 28% (RR 0.72, 95% CI 0.56–0.93). These meta-analyses confirm and reinforce the ATOLL findings, with an improved safety and efficacy globally with enoxaparin compared with UFH.

Taking all of this information into account, what should we use for the anticoagulation of our patients in primary PCI? Should we prefer a reduction in the risk of major bleeding, translating into a reduction of mortality, or should we use drugs that decrease the risk of ischaemic endpoints (and bleeding in femoral primary PCI), with also a benefit on mortality? The next European guidelines should update the levels of recommendation for anticoagulants in primary PCI. The level of evidence for UFH in the current guidelines remains poor (level C). UFH could be downgraded, as at least two other options look superior (bivalirudin and enoxaparin) with a direct impact on mortality.

In selecting strategies, bivalirudin appears to be a valid choice in centres using both a femoral approach and glycoprotein IIb/IIIa inhibitors, with the idea of reducing bleeding with a glycoprotein IIb/IIIa-inhibitor—sparing strategy. In radial centres, this strategy is less attractive, radial access being a safety net for the use of glycoprotein IIb/IIIa inhibitors, which still have a good indication in primary PCI, especially when patients present early and need a transfer [8]. Whether the benefit of bivalirudin can be reproduced with radial primary PCI is unknown, but is currently being tested in the randomized international Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX (MATRIX) trial, which should include 6200 STEMI patients (NCT01436327). Enoxaparin is the alternative to UFH, with some major advantages: the drug is widely available worldwide, inexpensive, well known by all cardiologists, with a pharmacodynamic profile perfectly adapted to primary PCI, excellent clinical results in
primary PCI in terms of efficacy and safety, and can be used with or without glycoprotein IIb/IIIa inhibitors, the ischaemic benefit remaining consistent regardless of the arterial access.

While waiting for a trial comparing enoxaparin with bivalirudin in primary PCI, the main conclusion is that we are moving away from UFH in this procedure.

**Disclosure of interest**


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**Table 1** Main results trial and meta-analysis of anticoagulants compared to UFH in primary PCI for STEMI patients. The ischaemic endpoint (hazard ratio and 95% confidence interval) was the main ischaemic endpoint available in the study results at 30 days. It was the combination of death, recurrent myocardial infarction/acute coronary syndrome or urgent revascularization in ATOLL; the combination of death, recurrent MI, urgent target vessel revascularization and stroke in HORIZONS; and the combination of death and recurrent MI for OASIS-6. The bleeding endpoint was the main definition used for major/severe bleeding in each trial that was available.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study</th>
<th>Anticoagulant</th>
<th>Patients (n)</th>
<th>Ischaemic</th>
<th>Major bleeding</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silvain et al. [7]</td>
<td>Meta-analysis (primary PCI) ATOLL</td>
<td>Enoxaparin</td>
<td>10,243</td>
<td>0.76$^a$ (0.60—0.96)</td>
<td>0.72$^a$ (0.56—0.93)</td>
<td>0.52$^a$ (0.42—0.64)</td>
</tr>
<tr>
<td>Montalescot et al. [5]</td>
<td>ATOLL</td>
<td>Enoxaparin</td>
<td>910</td>
<td>0.59$^a$ (0.38—0.91)</td>
<td>0.92 (0.51—1.66)</td>
<td>0.60 (0.33—1.07)</td>
</tr>
<tr>
<td>Stone et al. [2]</td>
<td>HORIZONS</td>
<td>Bivalirudin</td>
<td>3602</td>
<td>1.00 (0.75—1.32)</td>
<td>0.60$^a$ (0.46—0.77)</td>
<td>0.66$^a$ (0.44—1.00)</td>
</tr>
<tr>
<td>Yusuf et al. [4]</td>
<td>OASIS 6 (primary PCI)</td>
<td>Fondaparinux</td>
<td>3789</td>
<td>1.20 (0.91—1.57)</td>
<td>1.18 (0.63—2.22)</td>
<td>1.16 (0.85—1.58)</td>
</tr>
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$^a$ P < 0.05.

**References**


