Addendum 1. Low molecular weight heparins for the treatment of Acute Coronary Syndromes

Background

Cardiovascular diseases (CVD) are currently the leading cause of death in industrialized countries and are expected to become so in emerging countries by 2020 (1,2). Among CVD, coronary artery disease (CAD) is the most prevalent manifestation and is associated with high mortality and morbidity. Acute coronary syndromes (ACS) represents the major clinical manifestation of CAD, along with silent ischemia and stable angina pectoris. ACS share a common pathophysiological substrate, represented by acute complications of atherosclerotic plaque, with differing degrees of superimposed thrombosis and distal embolization. Patients with acute chest pain may show persistent ST-segment elevation at EKG, that generally reflects an acute total coronary occlusion, ultimately leading to ST-elevation myocardial infarction (STEMI). Alternatively, patients may present with acute chest pain without persistent ST-segment elevation; EKG may show ST-segment depression or T-wave inversion, flat T waves, pseudo-normalization of T waves, or no EKG changes. These clinical presentations of non-ST-elevation ACS may be further categorized into non-ST-elevation myocardial infarction (NSTEMI) or unstable angina (UA), based on troponins release (3,4).

Data from a large registry on a 10-year timeframe (1999-2008) show that NSTE-ACS is more frequent than STEMI, accounting for 66.1% and 33.1% of cases, respectively (5). The annual incidence is about 3 per 1000 inhabitants and it seems to be declining for STEMI (from 1.21 to 0.77 per 1000/year), but increasing for NSTEMI (from 1.26 to 1.32 per 1000/year) (4). In-hospital mortality is higher in patients with STEMI than in those with NSTE-ACS (7% vs. 3 – 5%, respectively), but at 6 months the mortality rates are very similar between the two conditions (12% and 13%, respectively) (5,6). Coronary heart disease causes approximately 1 of every 6 deaths in the United States and accounts for 49.9% of cardiovascular mortality (7).
Worldwide, over seven million people every year die from ischemic heart disease, accounting for 13.2% of all deaths (2).

Comparison of LMWH versus UFH

Anticoagulation with intravenous unfractionated heparin (UFH) has been a cornerstone of therapy for patients with UA and NSTEMI for over two decades, based on the results of several trials that showed a reduction of death or myocardial infarction (MI) in patients treated with UFH alone or in combination with aspirin compared with aspirin alone (8-10). However, the desired anticoagulant effect of UFH is difficult to achieve in a non-negligible proportion of patients, due to the difficulties of dose titration, and this has been associated with a significant increase in bleeding or reinfarction in the presence of overtherapeutic or subtherapeutic activated partial thromboplastin time, respectively (OR 2.11, 95% CI 1.27-3.53, and OR 2.19, 95% CI 0.98-4.91, respectively) (11).

When low molecular weight heparin (LMWH) became available for clinical use, their potential advantages over UFH prompted studies to investigate their efficacy and safety in various clinical contexts, including acute coronary syndromes. Initially, the results of two trials performed in the 1990s showed a significant reduction in the rate of death or reinfarction in patients with UA or NSTEMI treated with subcutaneous dalteparin in addition to aspirin as compared to aspirin alone, with the benefit being evident within the first month (12,13). Subsequently, several trials directly compared LMWH (enoxaparin in particular) with UFH for the prevention of death or myocardial infarction after UA or NSTEMI. A meta-analysis of these trials, enrolling more than 21,000 patients, showed a significant reduction in the combined endpoint of death or MI at 30 days in favour of enoxaparin vs. UFH (10% vs. 11.0%; OR 0.90; 95% CI 0.81 – 0.996) (14). No significant difference in major bleeding was observed (4.7% vs. 4.5%; OR 1.13; 95% CI 0.84 – 1.54). Based on the available evidence, the guidelines from the European Society of Cardiology (ESC) on the management of UA and NSTEMI recommend the
use of anticoagulant therapy for all patients in addition to antiplatelet therapy. In particular, enoxaparin is preferred over UFH or other LMWHs (3).

With regards to STEMI, prompt coronary reperfusion with either thrombolysis or percutaneous coronary intervention (PCI) is the recommended strategy. The use of heparin is considered an adjunctive therapy to fibrinolysis or a treatment option in patients ineligible for any kind of reperfusion therapy.

In patients undergoing fibrinolysis, LMWH has been compared to UFH as adjunctive therapy in several trials. In this clinical context, heparin has been usually administered for at least 48 hours or for the duration of hospital stay, up to 8 days. A systematic review and meta-analysis of six trials found a statistically significant reduction of the composite outcome of death or non-fatal MI associated with enoxaparin compared to UFH (OR 0.78, 95% CI 0.67-0.91)(14). This meta-analysis also found that enoxaparin was associated with an increased risk of major bleeding (OR 1.45, 95% CI 1.23-1.72), but the net clinical benefit was significantly lower with enoxaparin (11.2% vs. 12.9%; OR 0.84, 95% CI 0.73-0.97). Based on the available evidence, the ESC guidelines on the management of STEMI recommend anticoagulation in patients treated with thrombolytics until revascularization (if performed) or for the duration of hospital stay up to 8 days. The guidelines recommend intravenous enoxaparin followed by subcutaneous enoxaparin (preferred over UFH) or UFH given as a weight-adjusted intravenous bolus and infusion (4).

In the context of primary PCI for STEMI, LMWH was compared to UFH only in one randomized open-label trial (ATOLL). The results of this trial showed a 17% reduction in the primary composite endpoint of 30-day death, complications of MI, procedural failure and major bleeding associated with LMWH, although this difference was not statistically significant (p=0.063) (15). Significant reductions were found in the main secondary composite endpoints. Based on the results of the ATOLL trial and of several non-randomized studies showing benefits of LMWH over UFH in primary PCI (16-18) and on the considerable clinical
experience with enoxaparin in other PCI settings (19-21), the latest version of ESC guidelines suggest the use of enoxaparin over UFH in the context of primary PCI (4). Finally, in patients ineligible for reperfusion, a randomized, double-blind trial compared enoxaparin versus UFH, finding a comparable efficacy ad safety profile (22).

Conclusions

LMWH offer several pharmacological advantages over UFH, including an almost complete absorption after subcutaneous administration, less protein binding, and, thereby, a more predictable dose – effect relationship. In the context of acute coronary syndromes, LMWH, and enoxaparin in particular, have shown substantial superiority over UFH, thus resulting the treatment of choice for most patients.
Table 1. Efficacy and safety of LMWH versus UFH

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>LMWH</th>
<th>UFH</th>
<th>Relative effect OR (95% CI)</th>
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<tbody>
<tr>
<td>Death or non-fatal myocardial infarction</td>
<td>Unstable angina or NSTEMI</td>
<td>10% 11%</td>
<td>0.90 (0.81-0.996)</td>
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<tr>
<td></td>
<td>STEMI</td>
<td>9.6% 11.7%</td>
<td>0.78 (0.67-0.91)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>Unstable angina or NSTEMI</td>
<td>6.3% 5.4%</td>
<td>1.13 (0.84-1.54)</td>
</tr>
<tr>
<td></td>
<td>STEMI</td>
<td>2.6% 1.8%</td>
<td>1.45 (1.23-1.72)</td>
</tr>
<tr>
<td>Net clinical benfit</td>
<td>Unstable angina or NSTEMI</td>
<td>14.1% 14.3%</td>
<td>0.97 (0.86-1.09)</td>
</tr>
<tr>
<td></td>
<td>STEMI</td>
<td>11.1% 12.9%</td>
<td>0.84 (0.73-0.97)</td>
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References


