

## Anticoagulant agents for Acute Coronary Syndromes



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The classical recommendations for efficient and safe use of fibrinolytic agents have been described in detail in The Bangkok Medical Journal; February 2012, Volume 3. This article is an up to date description of how to use anticoagulant agents in acute coronary syndrome.

### Intravenous and subcutaneous anticoagulants

It is generally agreed that short-time administration of an anticoagulant in the acute phase of an acute coronary syndrome (ACS) is beneficial. There is however ongoing debate about the best choice of intravenous or subcutaneous anticoagulant therapy for acute-phase management of ACS patients. Current recommendations for the use of unfractionated heparin (UFH), enoxaparin, fondaparinux, or bivalirudin vary depending on whether or not patients are undergoing fibrinolysis, Percutaneous Coronary Intervention (PCI), or surgical revascularization, and on individual patient characteristics, including ischemic and bleeding risk.

UFH is still widely used, but a systematic overview of enoxaparin studies involving non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS) patients (with or without PCI) showed a statistically significant reduction in the composite endpoint of death or nonfatal myocardial infarction (MI) at 30 days with enoxaparin compared with UFH.<sup>1</sup> Furthermore, individual responses to UFH vary considerably, necessitating careful monitoring of activated clotting times.<sup>2</sup> In ST-segment elevation myocardial infarction (STEMI) populations, trials showed that enoxaparin reduced cardiovascular event rates compared with UFH in patients receiving fibrinolysis<sup>3</sup> or undergoing primary PCI (ATOLL trial)<sup>4</sup> but not in those who were unsuitable for revascularization (TETAMI trial).<sup>5</sup> There is also evidence of an increased risk of bleeding with enoxaparin compared with UFH (e.g. ExTRACT-TIMI253, TIMI 11B-ESSENCE meta-analysis, and SYNERG).<sup>6,7</sup> It should be noted that pre-randomization anticoagulation treatment in these trials may have led to an excess of bleeding in some cases. Nevertheless, careful dose adjustment of enoxaparin and other low molecular weight heparins (LMWHs) is necessary in patients who are older, underweight, or have renal failure. Both UFH and LMWHs carry a potential risk of 'heparin rebound' after stopping treatment, resulting in increased thrombin generation (i.e., above baseline levels), but this tends not to be a serious clinical issue. Heparin-induced thrombocytopenia is an uncommon but serious complication.<sup>2</sup>

The selective Factor Xa inhibitor fondaparinux has been shown to achieve a comparable reduction in cardiovascular events to that achieved with enoxaparin in patients with NSTEMI-ACS, with a significant reduction in major bleeding, leading to improved long-term

mortality and morbidity in the fondaparinux group (OASIS-5 trial).<sup>8</sup> Although the bleeding rates due to dose choice of enoxaparin were higher than in previous studies with this agent, similar results were seen in a secondary analysis of patients in this study who underwent PCI.<sup>9</sup> However, guiding catheter thromboses were more common in the fondaparinux group (0.9% vs. 0.4%), except in those who also received open-label UFH after fondaparinux.<sup>9</sup> In a study in STEMI patients, fondaparinux was found to reduce cardiovascular endpoints compared with placebo in those without an indication for heparin, and compared with UFH in those with an indication for heparin, with no differences in major bleeding between the treatment groups (OASIS-6 trial).<sup>10</sup> It should be noted that most patients who did not undergo primary PCI in this study were treated with streptokinase, and only a minority with fibrin-specific agents. As in the OASIS-5 trial, there was an increased rate of guiding catheter thrombosis with fondaparinux compared with UFH in patients undergoing PCI. A Cochrane Database systematic review of fondaparinux randomized controlled trials (RCTs) in patients with ACS found that it was associated with a reduced risk of all-cause mortality at 90-180 days compared with UFH or enoxaparin, and with a reduced incidence of major and minor bleeding compared with enoxaparin (but not UFH).<sup>11</sup>

Bivalirudin is a direct thrombin inhibitor that has demonstrated comparable efficacy to heparin (UFH or enoxaparin) plus a glycoprotein (GP) IIb/IIIa inhibitor in NSTEMI-ACS patients, including those undergoing PCI, with similar rates of major bleeding (ACUITY trial).<sup>12,13</sup> Bivalirudin was associated with a significant reduction in major bleeding compared with heparin and a GpIIb/IIIa inhibitor, with similar rates of ischemic endpoints. Subsequent analysis of PCI patients from the ACUITY trial suggested that timing of clopidogrel therapy was important in this context.<sup>14</sup> That is, bivalirudin without a GPIIb/IIIa inhibitor may actually be associated with worse outcomes than with heparin in patients who only received clopidogrel more than 30 minutes after PCI or not at all, as opposed to before or within 30 minutes of PCI. On the other hand, bivalirudin may be particularly suitable for elderly patients with NSTEMI-ACS because bleeding complications were significantly less frequent in patients aged 75 years or more treated with bivalirudin alone compared with heparin plus GPIIb/IIIa inhibitor, but with similar rates of ischemic outcomes.<sup>15</sup> In the recently published ISAR-REACT 4 studies in NSTEMI patients undergoing PCI, bivalirudin was also found to be associated with significantly less bleeding than heparin plus abciximab, with comparable ischemic event rates.<sup>16</sup>

A study evaluating bivalirudin in STEMI patients undergoing PCI also demonstrated comparable efficacy and reduced rates of major bleeding compared with UFH plus a GPIIb/IIIa inhibitor (HORIZONS-AMI trial).<sup>17</sup> Patients treated with a clopidogrel 600mg loading dose in this study had significantly reduced 30 days ischemic

adverse and bleeding event rates compared with those who received a clopidogrel 300mg loading dose.<sup>18</sup> The 3-year mortality was significantly less in bivalirudin-treated patients.<sup>19</sup>

### New oral anticoagulants

The oral factor Xa inhibitors rivaroxaban, apixaban, and darexaban have all been evaluated on top of standard therapy in ACS, with varying degrees of benefit and a consistent increase in bleeding risk versus placebo. Development of darexaban has actually been discontinued for all indications<sup>20</sup> following disappointing results in a phase II trial in ACS, which showed increased bleeding with no reduction of ischemic events with various darexaban regimens on top of dual antiplatelet therapy (RUBY-1 trial).<sup>21</sup>

A phase III trial with apixaban in ACS was terminated prematurely after enrollment of 7,392 patients (out of a planned 10,800) because of an increased bleeding risk with apixaban versus placebo, with no reduction in recurrent ischemic events (APPRAISE-2 trial).<sup>22</sup> A phase II Japanese study (NCT00852397) with apixaban has also been stopped.

The oral direct thrombin inhibitor dabigatran has also been evaluated in a phase II study in ACS patients, but showed a dose-related increase in major bleeding at 6 months without a convincing signal for a reduction in ischemic events (RE-DEEM trial).<sup>23</sup>

However, a phase III trial with rivaroxaban in ACS reported a statistically significant reduction in the primary composite endpoint of cardiovascular death, MI, and stroke compared with standard therapy plus placebo (ATLAS ACS 2-TIMI 51 trial).<sup>24</sup> The low-dose rivaroxaban arm (2.5mg twice a day (bid)) showed a significant reduction in total mortality. There was an increased risk of major and intracranial bleeding with rivaroxaban, but no increased risk of fatal bleeding.

### Implications for guidelines

The latest ESC (the European Society of Cardiology) guidelines for NSTEMI-ACS recommend the use of fondaparinux as a first-line anticoagulant, because it has the best efficacy-safety profile.<sup>25</sup> For patients undergoing PCI, they also recommend the use of a single bolus of UFH. Subsequent choices are enoxaparin and then UFH; although bivalirudin without a GPIIb/IIIa inhibitor is recommended as an alternative for patients with an early invasive strategy, particularly if the bleeding risk is high.<sup>25</sup> The current STEMI guidelines also recommend UFH or bivalirudin during primary PCI. Whether rivaroxaban on top of dual antiplatelet therapy will be recommended in future guidelines will depend on further analyses of the ATLAS ACS 2 study.

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