



# Elucidating the use of enoxaparin in non-ST-elevation acute coronary syndromes (NSTE-ACS)

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## The guidelines

The new joint guidelines from the American Heart Association (AHA) and the American College of Cardiology (ACC) for non-ST-elevation acute coronary syndromes (NSTE-ACS) represent the culmination of a massive undertaking to synthesise a large body of evidence, and the guideline writing committee is to be applauded for their efforts in preparing these guidelines.<sup>1,2</sup> As is the current standard, the online version of these guidelines was published ahead of print, and review of the electronic publication ahead of print revealed that the handling of enoxaparin was problematic.<sup>1</sup> The problem concerned the discussion of giving an initial 30 mg intravenous loading dose of enoxaparin prior to administering 1 mg/kg of enoxaparin subcutaneously every 12 h (q12h) when enoxaparin is selected as the anticoagulant. The electronic version published ahead of the print version simply stated "An initial intravenous loading dose is 30 mg." (ref. 1, p.42). This or similar phrasing appeared on page 43 in the text and in table 7 as well. These statements are accompanied by a grade of A for level of evidence.

However, although the final guideline now says the initial 30 mg intravenous loading dose "has been used in selected patients" (ref. 2, pp.164–5), and thus does seem to make it clear that the loading dose is not mandatory, the guideline still does not adequately convey the details of the literature with respect to use of enoxaparin in NSTE-ACS.<sup>2</sup> Guideline documents are plagued by space limitations in the setting of endeavours to summarise a large body of evidence, and this certainly may have contributed to the limited discussion of the data pertaining to the use of enoxaparin, but the details in this instance are important for clinicians to bear in mind when selecting enoxaparin as the anticoagulant when managing NSTE-ACS.

## Pursuing the evidence

The only randomised controlled trial (RCT) that reports results of an initial 30 mg intravenous loading dose of enoxaparin in addition to 1 mg/kg of enoxaparin subcutaneously q12h in NSTE-ACS is the TIMI (Thrombolysis in Myocardial Infarction) 11B trial, where the comparator anticoagulant was unfractionated heparin (UFH).<sup>3</sup> Five other RCTs have also investigated enoxaparin versus UFH in NSTE-ACS, including ESSENCE<sup>4</sup> and SYNERGY,<sup>5</sup> the other two RCTs cited in the discussion of enoxaparin versus UFH in the 2014 NSTE-ACS guidelines; however, all five of these RCTs studied 1 mg/kg of enoxaparin subcutaneously q12h without an initial loading dose.<sup>4–8</sup> TIMI 11B<sup>3</sup> and ESSENCE<sup>4</sup> were double-blind, whereas SYNERGY<sup>5</sup> was open-label. ACUTE II,<sup>6</sup> INTERACT<sup>7</sup> and A to Z<sup>8</sup> are the three other RCTs investigating enoxaparin versus UFH in NSTE-ACS, and all three of these trials involved all

patients receiving a glycoprotein IIb/IIIa inhibitor in addition to other standard therapies; two<sup>6,7</sup> were relatively small, and two<sup>7,8</sup> were open-label, but none used a loading dose of enoxaparin.

Importantly, there has never been a head-to-head trial comparing an initial 30 mg intravenous loading dose of enoxaparin added to 1 mg/kg of enoxaparin subcutaneously q12h versus 1 mg/kg of enoxaparin subcutaneously q12h without a loading dose, and there is also nothing in the TIMI 11B data compared to the other available data that even indirectly suggests an initial 30 mg intravenous loading dose of enoxaparin yields superior outcomes in NSTE-ACS compared to a regimen of 1 mg/kg of enoxaparin subcutaneously q12h without an initial intravenous loading dose. In other words, while TIMI 11B compared the anticoagulant regimens of a 30 mg intravenous loading dose of enoxaparin + 1 mg/kg enoxaparin subcutaneously q12h versus UFH in NSTE-ACS for the outcomes of death, myocardial infarction (MI) and urgent revascularisation, there is nothing in the TIMI 11B data compared to the other relevant RCT data that suggests an initial 30 mg intravenous loading dose of enoxaparin improves any of these outcomes compared to giving enoxaparin 1 mg/kg subcutaneously q12h without a loading dose. In addition to viewing the original trial publications just described, appraising the 43-day and 1-year data for TIMI 11B and ESSENCE is also instructive in this regard.<sup>9,10</sup>

Some might wonder if the 30 mg intravenous loading dose could be to address concern about whether patients were adequately anticoagulated when an early invasive strategy is being employed. However, this is fortunately not a valid concern when one considers the currently available evidence or standards. If such a situation arises and the provider elects to use enoxaparin, it is standard to deliver 0.5–0.75 mg/kg of enoxaparin intravenously if the patient has not received any prior anticoagulant therapy or 0.3 mg/kg of enoxaparin intravenously at the time of percutaneous coronary intervention (PCI) if the last subcutaneous dose of enoxaparin was administered between 8 and 12 h earlier or if less than two therapeutic subcutaneous doses of enoxaparin have been administered. The current AHA/ACC guidelines address this clearly.<sup>2</sup> The open-label SYNERGY trial is also of relevance here, as it sought to investigate enoxaparin (n=4993) versus UFH (n=4985) in high-risk patients who were intended to be managed with an early invasive strategy in the era of contemporary antiplatelet therapy.<sup>5</sup> In SYNERGY, there was no significant benefit of enoxaparin over UFH in terms of the primary composite outcome of all-cause mortality or non-fatal MI at 30 days (14.0% vs 14.5%, respectively, if rounding to a single decimal point; HR 0.96; 95% CI, 0.86 to 1.06; p=0.40). Outcomes at 48 h and 14 days were also not significantly different, and follow-up assessment at

6 and 12 months had similar results.<sup>5 11</sup> Rates of ischaemic events during PCI were also reported to be similar between the enoxaparin and UFH groups, including abrupt closure (1.3% vs 1.7%), threatened abrupt closure (1.1% vs 1.0%), PCI failure (3.6% vs 3.4%) or emergent coronary artery bypass grafting (0.3% in both groups), though no statistical tests were reported for these outcomes.<sup>5</sup> However, in-hospital TIMI major bleeding was significantly greater in the enoxaparin group compared to the UFH group (9.1% vs 7.6%; number needed to treat to harm (NNT<sub>H</sub>), 66 to 67;  $p=0.008$ ).<sup>5</sup> GUSTO (Global Utilisation of Streptokinase and t-PA for Occluded Arteries) severe bleeding occurred in 2.7% of the enoxaparin recipients and 2.2% of the UFH recipients ( $p=0.08$ ), and 17% and 16% of enoxaparin and UFH recipients required a transfusion, respectively ( $p=0.16$ ).<sup>5</sup> Importantly, SYNERGY excluded patients with a creatinine clearance  $<30$  mL/min, the point at which there is a labelling indication to adjust enoxaparin to 1 mg/kg subcutaneously daily if enoxaparin is still used in a patient with this severity of renal insufficiency. Thus, while one must still bear in mind the open-label design of SYNERGY, it still leads one to question the selection of enoxaparin as the anticoagulant if one has original intent to pursue an early invasive strategy with contemporary antiplatelet therapy (realising that management strategies evolve accordingly with the patient's status and preferences, which sometimes leads to changing from a conservative strategy to an early invasive strategy).

In a similar vein, OASIS-5 was a double-blind, double-dummy RCT that studied enoxaparin without any intravenous loading dose ( $n=10\,021$ ) versus fondaparinux ( $n=10\,057$ ) in NSTEMI-ACS.<sup>12</sup> OASIS-5 had no pre-specified intent regarding whether management was to be invasive or conservative, but OASIS-5 had a dual antiplatelet therapy utilisation rate similar to that of SYNERGY. In OASIS-5, fondaparinux was non-inferior to enoxaparin with respect to the primary composite efficacy outcome (death, MI or refractory ischaemia at 9 days; 5.7% for enoxaparin vs 5.8% for fondaparinux; HR 1.01; 95% CI 0.90 to 1.13;  $p$  for non-inferiority=0.007) with similar rates for all individual components of the outcome (death, 1.9% vs 1.8%; MI, 2.7% vs 2.6%; refractory ischaemia, 1.9% vs 1.9%). The primary safety outcome of major bleeding at 9 days was significantly better with fondaparinux than with enoxaparin (4.1% for enoxaparin vs 2.2% for fondaparinux; number needed to treat to benefit (NNT<sub>B</sub>), 52 to 53; HR 0.52; 95% CI 0.44 to 0.61;  $p$  for superiority  $<0.001$ ). Furthermore, the primary composite efficacy outcome data at 180 days strongly suggest fondaparinux is not just non-inferior, but indeed as effective as, enoxaparin (13.2% for enoxaparin vs 12.3% for fondaparinux; HR 0.93; 95% CI 0.86 to 1.00;  $p$  for superiority=0.06). The individual components for enoxaparin versus fondaparinux at 180 days are encouraging as well: death, 6.5% vs 5.8%; MI, 6.6% vs 6.3%; refractory ischaemia, 2.4% vs 2.3%). The superiority of fondaparinux for major bleeding also persisted at 180 days (5.8% for enoxaparin vs 4.3% for fondaparinux; HR 0.72; 95% CI 0.64 to 0.82;  $p$  for superiority  $<0.001$ ). OASIS-5 also accounted for renal function, but instead of excluding patients with a

creatinine clearance  $<30$  mL/min as SYNERGY did, the dose of enoxaparin was simply downwardly adjusted to 1 mg/kg subcutaneously daily in such patients; surprisingly, although fondaparinux has a labelled contraindication if creatinine clearance is  $<30$  mL/min, it was still administered without any adjustment to patients with such levels of renal insufficiency in OASIS-5. This makes the bleeding outcomes in favour of fondaparinux even more noteworthy. As a pre-specified secondary outcome, fondaparinux also resulted in lower total mortality compared to enoxaparin at 30 days (3.5% for enoxaparin vs 2.9% for fondaparinux; HR 0.83; 95% CI 0.71 to 0.97;  $p$  for superiority=0.02), and this seemed to persist, albeit somewhat attenuated, at 180 days (6.5% for enoxaparin vs 5.8% for fondaparinux; HR 0.89; 95% CI 0.80 to 1.00;  $p$  for superiority=0.05); however, although certainly reassuring with respect to fondaparinux use, this was not a primary outcome, and there were multiple hypothesis tests for the secondary outcomes without any measure of statistical adjustment for such. Finally, it must be noted that if one were to elect to use fondaparinux over enoxaparin simply for the reduction in major bleeding, one must also be cognisant of the need to administer additional anticoagulant (eg, UFH) at the time of PCI to prevent catheter thrombosis, a matter addressed in FUTURA/OASIS-8 and the current AHA/ACC guidelines.<sup>2 13</sup>

## Conclusions

In summary, when considering the data surrounding the use of enoxaparin in NSTEMI-ACS, it seems rather clear there is no evidence-based justification for giving or considering an initial 30 mg intravenous loading dose of enoxaparin, as there are no data clearly showing or even indirectly suggesting superior outcomes of such an approach compared to giving 1 mg/kg of enoxaparin subcutaneously q12h without an initial intravenous loading dose. Additionally, as outlined above, enoxaparin may not actually offer benefit over UFH or fondaparinux depending on the specifics of the management strategy, and bleeding risks need to be considered as well. Certainly, NSTEMI-ACS is an incredibly important matter to treat with the utmost diligence, but it is also imperative that we select interventions carefully and avoid overtreatment, and a rather eloquent and insightful statement from a critical care textbook seems instructive in this instance:

As with many therapeutic interventions in critical illness [and in many other areas of medicine], too much can cause harm [or simply offer no further benefit], so it is helpful to define the goal of each intervention and then use the mildest intervention to achieve that goal. (ref. 14, p.245, parenthetical elements added)

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