**WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care**

<table>
<thead>
<tr>
<th>Worksheet author(s)</th>
<th>Date Submitted for review:</th>
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<tbody>
<tr>
<td>Arntz, Hans-Richard</td>
<td>28.01.10</td>
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<tr>
<td>Michelle Welsford</td>
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**Clinical question.**

In patients with suspected ST-elevation myocardial infarction in the prehospital and emergency department setting (P) to be treated with primary PCI, does the use of new anticoagulants i.e. pentasaccharide, enoxaparin, bivalirudin (I), compared with standard management (placebo, unfractionated heparin, other anticoagulant, or no anticoagulant) (C), improve outcome (e.g. mortality, reinfarction, revascularization, bleeding, stroke or other outcomes) (O)?

<table>
<thead>
<tr>
<th>Is this question addressing an intervention/therapy, prognosis or diagnosis?</th>
<th>Intervention</th>
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<tbody>
<tr>
<td>State if this is a proposed new topic or revision of existing worksheet:</td>
<td>New worksheet</td>
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**Conflict of interest specific to this question**

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet?  Lecture honoraria from Sanofi Aventis Daiichi Sankyo, Boehringer Ingelheim

**Search strategy (including electronic databases searched).**

*Acute coronary syndromes or myocardial infarction and PCI and enoxaparin and/or low molecular heparin and/or fondaparinux and/or pentasaccharide, and or bivalirudin.*

**State inclusion and exclusion criteria**

- Number of Articles Found
  - 394 reviewed by abstract
  - Exclusions
    - Criteria: letters, research animals, case reports, reviews. Hand search of abstracts as final step to exclude duplicate hits and exclude irrelevant articles according to the limitations cited above.
  - Number of Articles Finally Evaluated
    - 24
### Summary of evidence

#### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
<th>Study 4</th>
<th>Study 5</th>
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<tbody>
<tr>
<td><strong>Fair</strong></td>
<td>Yusuf, 2006 B, C, E, H</td>
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<tr>
<td><strong>Poor</strong></td>
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#### Level of evidence

- **A** = Enoxaparin
- **B** = Less cardiac events
- **C** = Decreased bleeding rate
- **D** = Increased intracranial bleeding rate
- **E** = Fondaparinux
- **F** = Bivalirudin
- **G** = Various LMWHs
- **H** = Other endpoint

#### Evidence Neutral to Clinical question

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<tr>
<td><strong>Fair</strong></td>
<td>Kim, 2006 C Sejersten, 2009 Labeque, 2006 A</td>
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<tr>
<td><strong>Poor</strong></td>
<td>Galeote, 2009 A Khoobiar, 2008 Abhyankar, 2008 A, H</td>
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#### Evidence Opposing Clinical Question

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**REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:**

There are various problems with transferring the study results into the situation as requested i.e. the viewpoint of the prehospital or ED setting since data comparing out of hospital/ED use of different antithrombins are scarce Thus principally conclusions can only be drawn by analogy. The first problem is, that only in 3 studies (Armstrong (2006) WEST-Study, which is a study on different reperfusion strategies, Welsh et al (2007) a WEST-substudy and Labeque et al (2006) who performed a small pilot trial without controls)and a small study with historical controls (Sejerstand et al, 200) treatment is initiated prehospitaly. Second, several studies combine one of the novel antithrombics with GP IIb/IIIa receptor blockers or clopidogrel (many of them leaving the use of these antplatelets at the discretion of the interventionalist performing PCI). Third some studies are performed in a broad spectrum of pts reaching from elective to urgent procedures in pts with STEMI i.e. primary PCI or PCI after primary reperfusion treatment with thrombolysis. Also in some studies non ST-elevation ACS pts and also STEMI pts were included. Fourth, some studies do not have an UFH control group and finally there are no data on head-to-head comparisons of the novel anticoagulants. There is some evidence from the studies to consider enoxaparin and to some extent also fondaparinux as least as effective as UFH with respect to major adverse cardiac events in pts with STEMI and planned PCI. With regard to safety (i.e. bleedings) enoxaparin is similar to UFH whereas bleeding rates with fondaparinux are lower compared to UFH, however there is some risk of catheter thrombus which requires additional UFH for fondaparinux treated patients when PCI is performed. Bivalirudin even with the restriction of an slightly increased risk of stent thrombosis within the first 24 hrs after PCI, leads to less bleedings compared to UFH plus a GPI and results in a lower cardiac and overall mortality (due to less bleedings?) but not total MACE in one study (HORIZONS-AMI) on a short and 1 year perspective (Stone 2008, Mehran 2009). The mortality differences, however, were not seen in a metaanalysis in which, however, pts with stable or unstable angina were also included in the analysis (De Luca 2009)

Acknowledgements:

Martina Weiland for preparing the worksheet

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**Citation List**


*Small observational non randomized study on 100 pts receiving enox in the ED before PCI compared with a similar group of 100 pts receiving UFH in the cath-lab. Study revealed slight improvement with TIMI flow before and after PCI with pre-treatment but no differences in clinical outcome (abstract only). LOE 2 Supporting Poor*


*Randomized prehospital open label feasibility study in 304 STEMI pts (symptoms < 6 hrs comparing thrombolysis with tenecteplase (TNK) and usual care, TNK followed by angiography < 24 hrs and primary PCI with 300 mg clopidogrel loading dose. All patients received enoxaparin 1 mg/kg s.c. initially followed by 0.3-0.5 mg/kg for pts with planned primary PCI before angiography (abciximab recommended for PCI). In the other groups further enoxaparin treatment was left to the attending physician. Primary endpoint was death + re-MI+refractory ischemia, congestive heart failure, cardiogenic shock and major ventricular arrhythmia. Secondary endpoint was ST-resolution. The primary endpoint was observed with a similar rate in all groups (23 – 25 %) however the combination of death and re-MI was more frequent (13 %) in the TNK only group compared to primary PCI (4,0 %) p=0.021. ST-resolution tended to be greater in the TNK+PCI group, whereas persisting ST elevation (Selvester Score) was greatest in the primary PCI group. Study supports the idea of early thrombolysis combined with early rescue PCI as an alternative to primary PCI. Primary a comparison of reperfusion strategies LOE 5 Neutral Fair*

Retrospective evaluation of registry data on pts with cardiogenic shock undergoing PCI receiving bivalirudin + GPI or heparin + GPI. There were less deaths with bivalirudin but no difference in bleedings.

LOE 4 Supporting Fair


Retrospective study on 899 consecutive STEMI patients receiving bivalirudin (n=566) or UFH (n=333) for PCI without additional Gp IIb/IIIa receptor blockers. Outcomes with respect to bleeding rates and MACE rates were similar with bivalirudin and UFH.

LOE 4 Neutral Good


Randomized comparison of enoxaparin vs UFH in 966 pts (283 with NSTEMI) for planned PCI. Enoxaparin was given at a dose of 1 mg/kg every 12 hrs at least twice before PCI (performed 1-8 hrs after the lost dose) 25 mg UFH was given before angiography, another 65 mg was given if PCI was performed. Anti Xa level was measured 1 – 8 hrs after enoxaparin. Enoxaparin proved to be equally safe and effective as did UFH.

Strategy of dosing enoxaparin before PCI

LOE 5 Neutral Fair


Non randomized study comparing UFH (n=456) 40 U/kg bolus followed by infusion to achieve a target ACT of 250 – 300 sec or bivalirudin (n=216) 0.75 mg/kg bolus followed by 1.65 mg/kg/hr in STEMI pts with planned PCI. No significant difference in bleeding or MACES was observed

LOE 2 Neutral Good


Metaanalysis on studies comparing UFH vs bivalirudin for PCI on pts with stable angina, non ST elevation ACS and STEMI. There was no difference in mortality (without relation to basic risk or major bleeding complications) but a significant reduction in major bleedings and a trend to an increased risk for re-infarction with bivalirudin.

LOE 5 Neutral Good


Substudy of ASSENT 3 on urgent and elective PCI after thrombolysis with the two different lytic strategies, showing less need for urgent PCI after enoxaparin and abciximab but less favourable clinical outcome with abciximab (the results difficult to understand: every low event rates, by suspicion of patient selection by delayed PCI with enoxaparin and abciximab).

LOE 2 Neutral Fair


Small non randomized observational study on 191 pts with STEMI (< 12 hrs) to undergo PCI and who received UFH n=100 or enox (n=91). The UFH group tended to include more pts with a history of MI, otherwise groups were comparable. TIMI flow grades before and after PCI were not different as were clinical outcomes (death and bleedings) and other parameters (ejection fraction and peak troponin release).

LOE 2 Neutral Poor

*ExTRACT TIMI 25 non-randomised substudy on pts with additional PCI after thrombolysis (n=4676).* An additional dose of 0.3 mg/kg enoxaparin (or placebo) i.v. was given before PCI if the last dose was between 8 and 12 hrs before, no additional enoxaparin with shorter delay. UFH was dosed according to aPPT. Fewer patients with enoxaparin underwent PCI compared to those on UFH by 30 days (22.8 % vs 24.2) from beginning on death or re-MI occurred significantly less frequently with enoxaparin (10.7 % vs 13.8 %, p=0.001) also after adjustment for risk factors, bleeding was similar in both groups (e.g. major bleedings 1.4 % with enoxaparin vs 1.6 % with UFH) resulting in a superior net clinical benefit for enoxaparin.

In favour of enoxaparin compared to UFH.

LOE52 Supporting Good


*Non randomized study comparing UFH with dalteparin (+GPI each) in 140 high risk pts with STEMI to undergo PCI. There were no differences in any outcome category during hospitalisation and up to 4 years after the event.*

LOE 2 Neutral Fair


*Small non-randomized study comparing enox (partially started in the emergency room) according to the ExTRACT therapeutic scheme or UFH (total 83 pts) in pts with STEMI undergoing PCI. No difference was found in MACE but mor bleedings occurred with UFH.*

LOE 2 Neutral Poor


*Observational study in 143 STEMI pts receiving 0.5 mg/kg enoxaparin and 1 mg/kg s.c. in the prehospital setting before transportation for primary PYI. Anti-Xa level was > 0.5 UK/ml in 99 % of pts at PCI (Clopidogrel given after PCI, nearly all pts received abciximab). TIMI flow 2/3 was observed in 40.6 % of pts before PCI, bleedings were rare as were MACES (death 2.8 %, ReMI 3.5 % and need for revascularisation 3.5 %). No control group.*

LOE 4 Neutral Fair


*Registry data on 3800 ACS pts of which 22 % had STEMI. ll were treated with bivalirudin and had a lower rate of MACE and bleedings.*

LOE 4 Supporting Poor


1 year term results from the HORIZONS-AMI confirm the short term results: no difference in MACE, but significant difference in cardiac (2.1 vs 3.8 %, p=0.005) and consecutive all cause mortality (3.5 vs 4.8 %, p=0.037) favouring bivalirudin over UFH + an GPI

LOE1 Supporting Good

Randomised pilot study on 350 pts undergoing elective or urgent PCI (including pts with STEMI) randomized to receive UFH, 2.5 mg or 5.0 mg fondaparinux i.v. and additional Gp IIb/IIIa antagonists according to local standards (UFH without Gp IIb/IIIa initially 100U/kg, with Gp IIb/IIIa 65 mg/kg). Primary safety endpoint was bleeding (fatal, symptomatic intracranial, retroperitoneal, intraocular or Hb fall > 3 g/dl) occurring in 7.7 % of pts on UFH and 6.4 % on fondaparinux [HR 0.81 (0.35-1.84)] (3.4 % with lower, 9.6 % with high dose fondaparinux [HR 0.33 (0.1 – 1.04)]. Efficacy endpoint (death, MI, urgent revasc., bailout Gp IIb/IIIA) occurred in 6 % in each group. Thus fondaparinux was comparable to UFH regarding safety and efficacy outcomes.

Different study populations (elective, urgent + PCI NSTEMI/STEMI)


Combo analysis of OASIS 5 (non STEMI ACS) and OASIS 6 (STEMI) with respect to PCI treatment. Fondaparinux resulted in an overall reduced major bleedings and an improved net outcome (death, MI, stroke and major bleeding) but not MACE alone. A recommendation to add UFH (50 -60 U/kg for PCI) is given regarding the fact that in 7 of 1000 procedures catheter thrombus was present with fondaparinux alone.


Small study comparing ambulance use of bivalirudin (n=102 bolus 1mg/kg followed by infusion) and UFH (n=72, 10000 U bolus pts = comparison group of pts stemming from the preceding year) in STEMI pts for whom PPCI was planned. There were no differences n clinical outcomes including bleedings.


Case series (n=91) of STEMI pts receiving bivalirudin alone (no Gp IIb/IIIa) for PCI with excellent outcome. No control group


Large randomized study comparing bivalirudin with UFH + Gp IIb/IIIa receptor blockers in 3602 pts presenting within 12 hrs after symptom onset with STEMI. The study resulted in a significant reduction of major bleeding, a lower rate of CV deaths and a combination of major adverse clinical events (=combination of major bleeding, death, re-infarction, target vessel. revasc or stroke). There was however an increased rate of stent thromboses within the first 24 hrs after PCI.

Randomized prospective study in 12092 pts with STEMI (symptoms 12 – 24 hrs) stratified in 2 groups. Group 1 (n=5638): no indication for UFH, Group 2 (n=6434): indication for UFH e.g. use of fibrinspecific lytics or primary PCI or other indication for UFH. Pts then were randomised to receive fondaparinux (group 1 2,5 mg fondaparinux daily s.c., Group fondaparinux initially 2,5 mg i.v. followed by 2,5 mg daily s.c.) up to 8 days or matching placebo and the controls 60 U/kg UFH initially i.v. followed by an infusion of 12 U/kg for 24-48 hrs with an adjustment of aPTT to 1,5 – 2,0 times normal value. Generally mortality and incidence of MI was reduced in the fondaparinux groups up to 180 days specifically in those treated by thrombolysis or not receiving reperfusion treatment, but not in the subgroup treated by PCI. With PCI a increased rate of catheter thrombus and more coronary complications were observed with fondaparinux, which could be avoided by UFH before intervention. Also there were less severe bleeds with fondaparinux. Complex study in a population not primarily selected for PPCI: results therefore not straightly transferable to ED or prehospital routine (what is no indication for UFH etc.) trend favouring fondaparinux because of reduced bleeding risk in general. Fondaparinux however is not suitable as alone standing antithrombin treatment in planned primary PCI.

LOE 1 Supporting fair


Registry data of 6299 pts with STEMI and symptoms < 12 hrs comparing enoxaparin (n=609) or UFH (n=5690) as Antithrombin treatment. A multivariate propensity score analysis revealed a reduction in the combined endpoint of death and re-MI in favour of enoxaparin in the entire cohort with fibrinolysis, primary PCI and those without early fibrinolysis without increased bleeding risk. In favour of enoxaparin compared to UFH.

LOE 4 Supporting Good


Retrospective analysis of registry data showing that (after adjustment in a propensity score) outcome in STEMI pts receiving enoxaparin + GPI for PCI had a lower MACE compared to UFH + GPI

LOE4 Supporting fair