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

Worksheet author(s)

<table>
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<tr>
<th>Arntz, Hans-Richard</th>
<th>Date Submitted for review:</th>
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<td>28.01.2010</td>
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Clinical question.
In patients with suspected ST-elevation myocardial infarction in the prehospital and emergency department setting (P) treated with fibrinolysis, 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)?

Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention

State if this is a proposed new topic or revision of existing worksheet: New Topic Revision

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

Search strategy (including electronic databases searched).

Acute coronary syndromes or myocardial infarction and thrombolysis and enoxaparin and/or low molecular heparin and/or fondaparinux and/or pentasaccharide or bivalirudin and/or UFH. Review of the AHA/ACC, the ESC and the ACCP guidelines.

Medline, Cochrane Library of controlled clinical trials, Cochrane Database of systematic reviews, Embase and Google scholar

Actual guidelines

State inclusion and exclusion criteria

<table>
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<tr>
<th>Number of Articles Found for abstract review</th>
<th>424</th>
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ExclusionsLetters, research in animals, case reports, reviews. Hand search of abstracts as final step to exclude duplicate hits and exclude irrelevant articles according to the limitations cited

Number of Articles Finally Evaluated39
## Summary of evidence

### Evidence Supporting Clinical Question

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<tr>
<th>Level of evidence</th>
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<tr>
<td>A = Enoxaparin</td>
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<tr>
<td>B = Less cardiac events</td>
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<td>C = Increase bleeding rate</td>
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<td>D = increased intracranial bleeding rate</td>
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<td>E = Fondaparinux</td>
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<td>F = Bivalirudin</td>
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<td>G = Other LMWH than enoxaparin</td>
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<td>H = Decreased bleeding rate</td>
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### Evidence Neutral to Clinical question

| Good | Ross, 2001 $^A$  
|      | Sinnaeve, 2004 $^A$  
|      | Wallentin, 2003 $^{A, B, C, D}$  
|      | White, 2001 $^{B, F}$ | White, 1997 $^F$ |
|      | Armstrong, 2006 $^A$  
|      | Fox, 2007 $^{A, B, C}$  
|      | Sinnaeve, 2006 $^{A, B, C}$  
|      | White, 2007 $^{A, B, C}$ |
| Fair | Coussement, 2001 $^F$  
|      | Despotovic, 2009 $^{A, B}$  
|      | {Wallentin, 2003} $^G$ | Peters, 2008 $^{B, E, H}$ |
|      | Dubois, 2003 $^A$  
|      | Welsh, 2005 $^A$ |
| Poor | Tatu-Chitoiu, 2003 $^A$ |

**Level of evidence**

A = Enoxaparin  
E = Fondaparinux  
B = Less cardiac events  
F = Bivalirudin  
C = Increase bleeding rate  
G = Other LMWH than Enoxaparin  
D = increased intracranial bleeding rate  
H = Decreased bleeding rate

### Evidence Opposing Clinical Question

| Good |
|      |

| Fair |
|      |

| Poor |
|      |

**Level of evidence**

A = Enoxaparin  
E = Fondaparinux  
B = Less cardiac events  
F = Bivalirudin  
C = Increase bleeding rate  
G = Other LMWH than Enoxaparin  
D = increased intracranial bleeding rate  
H = Decreased bleeding rate
One principal problem of answering the posed question is that the vast majority of trials did not (at least not explicitly) include patients in the prehospital or ED setting. There are only a few exemptions, i.e., Armstrong PW (2006), the WEST trial, and Wallentin et al. (2003) with ASSENT 3+. Furthermore, different thrombolytics (in partially variable doses) have been used, which may have inherent influence on outcomes as well as efficacy as safety is concerned. The same is true for several studies utilizing different Gp IIb/IIIa inhibitors, in addition to thrombolysis. Also, clopidogrel is used in some studies. Moreover, different doses of the anticoagulants have been used. Studies also differ in strategy, e.g., with regard to PCI following thrombolysis. Comprehensive data on direct comparison of the UFH—alternatives are missing. Finally, there are differences in duration of treatment, usually 48 hrs for UFH and up to 8 days (or discharge) for LMWH, fondaparinux, and bivalirudin. These major differences between the studies clearly do not allow considering even the LMWHs as equal in efficacy and safety and thus interchangeable not to mention fondaparinux or bivalirudin. There is, however, sufficient evidence to consider enoxaparin as being superior to UFH with regard to adverse cardiac events at the cost of an increased bleeding rate—the latter risk being depending mainly on renal function and age of the patient. This requires dose adjustment for elder pts > 75 years and those with impaired renal function. Moreover, according to the study results, a somewhat prolonged treatment with bivalirudin, enoxaparin, or other LMWH or fondaparinux up to 8 days (or to discharge) is requested. There is, however, no need for control of coagulation parameters with enoxaparin, bivalirudin, and fondaparinux, whereas even a 48 hrs treatment only with UFH needs a coagulation control. Fondaparinux—specifically if combined with streptokinase also results in better clinical outcome (death and MI) and has a lower bleeding risk. There are, however, problems (cath. thromboses) with fondaparinux. For the case of necessary e.g., rescue PCI there is no data on procedure available.

Acknowledgement

Martina Weiland for preparing the worksheet
Citation List


Randomized comparison of 6065 STEMI pts (symptoms < 6 hrs) assigned to weight adjusted tenecteplase + enoxaparin (initially 30 mg i.v. followed by 1 mg/kg s.c. and 1 mg/kg s.c. every 12 hours for max. 7 days (group A) or tenecteplase and UFH (60 U/kg bolus, max. 4000 U followed by infusion to achieve an aPPT of 50-70 sec. for 48 hrs, group B) or half dose tenecteplase + 40 U/kg bolus UFH followed by 70 kg/hr + abciximab 0,25 mg/kg bolus followed by 0,125µg/kg/min infusion for 48 hrs (group C). Primary efficacy endpoint was 30 day composite of mortality re-MI or refractory ischemia. primary efficacy and safety endpoint was the above + intracranial and major bleeding. Efficacy and efficacy and safety endpoint showed equal significantly superiority of A+C over group B for the whole cohort as well as in nearly all subgroups. Also specific bleeding rates including intracranial bleedings were identical in all groups. Superiority of enoxaparin vs UFH and combination Tx

**LOE** 1  Supporting  Good


Randomized 4-arm study (n=483) comparing UFH (n=82) and enox (n=160) plus full dose TNK and the combination of ½ TNK + abciximab and UFH and enox resulting in less deaths at 30 days (p=0.003) and the composite of deaths and re-MI in the full dose TNK groups and comparable bleeding rates (not differences with ½ TNK + abciximab)

**LOE1**  Supporting  Good


Large randomized blinded double dummy study in 20506 pts (20479 intervention to treat) with STEMI (symptoms 6 hrs) and planned fibrinolysis (streptokinase, tenecteplase, alteplase or Reteplase) comparing antithrombin treatment with enoxaparin (adjusted to age and renal function < 75 years i.v. bolus of 30 mg followed by 1 mg/kg after 15 min and then every 12 hrs, > 75 years 0,75 mg/kg s.c. every 12 hrs only) for patients with a creatinin clearance < 30 mmol/min 1 mg/kg one daily) to discharge (max. 8 days) or UFH (60 U/kg initially max. 4000 U followed by an infusion of 12 U/kg/hr, target aPPT 1,5-2 times ULN) for 48 hrs. PCI could be performed at any time, deferring to at least 48 hrs was recommended. Use of clopidogrel (beside aspirin) was left to the discretion of the investigators. Primary endpoint was death or re-MI within 30 days, secondary endpoint was primary endpoint plus recurrent ischemia requiring revascularisation plus stroke. Net clinical endpoint major (TIMI) non-fatal bleedings. Primary efficacy endpoint occurred in 9,9 % of pts with enoxaparin and 12,0 % with UFH (RR 0.83 (0.77-0.90), p=0.001) (significant difference for re-MI, trend for death), secondary endpoint in 11,7 % vs 14,5 % of pts respectively (RR 0.81 (0.75-0.87) p< 0.001). Major bleeding were 2,1 & with enoxaparin and 1,4 % with UFH (p<0.001) resulting in a net clinical benefit of event reduction of 14-18 % (p<0.001) for all comparison and all subgroups. Intracranial bleedings were not different between groups. Major criticism is on fact that benefit for enoxaparin was most pronounced after 48 hrs (after stopping UFH).

Large study favouring enoxaparin vs UFH compared by several substudies dealing with relevant questions regarding elevated bleeding risk

**LOE** 1  Supporting  Good


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


Metaanalysis of ASSENT 3 and ASSENT 3 Plus data in the enoxaparin and UFH groups. Efficacy was significantly superior with enoxaparin as was the efficacy + safety endpoint for the whole cohort, greatest benefit present in patients urgently revascularized / (the increased bleeding rate with enoxaparin was confirmed to pts without or before revascularisation). Intracranial bleeding rates were the whole cohorts were similar but an excess intracranial bleeding rate was observed specifically among women > 75 years of age in the ASSENT 3 Plus trial.


Small randomized study (partially treating pts in the prehospital setting) comparing enox and UFH with fibrinolysis. Study resulted in a significant (p=0.04) less incidence of the triple endpoint of death, re-MI or readmission with UAP. No differences in major hemorrhages.


Randomized pilot study in 333 pts with STEMI (symptoms < 6 hrs) treated with alteplase and standard dose UFH for 48 – 72 hrs or fondaparinux (dose varying stratified by body weight between 4 to 12 mg initially i.v. followed by s.c. injections) for 5 to 7 days. TIMI flow grades were principal primary endpoints and were equal in all groups at 90 min and on day 5 to 7, as were bleedings (trend to increased bleeding rates with higher dose of fondaparinux). A trend to less reocclusions was observed with fondaparinux in pts who did not undergo PCI.


Metaanalysis on 8 randomized trials including 13940 STEMI pts treated with LMWH or UFH and thrombolysis. Showing a trend to reduction in mortality by LMWH vs UFH (6,6 % vs 7,2 % OR 0.92 (0.84-1.01) p=0.008) a significant reduction in re-MI but also a significantly higher rate of major bleedings (but not intracranial bleedings).


Small (n=64) randomized study utilizing streptokinase as thrombolitics comparing enoxaparin (initial 30 mg bolus followed by 80 mg daily for 3 days) or UFH (continuous infusion 1000 U/h for 3 days) as antithrombin. Study resulted in a non-significant trend favouring enoxaparin with regard to re-ischemia and heart failure.

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 5 Neutral Fair


Metaanalysis on 25280 pts with STEMI treated by thrombolysis (all lytics) studies compared UFH vs no heparin or placebo and LMWH vs UFH. Enoxaparin – in contrast to UFH – reduced the rate of deaths and reinfarctions if compared to placebo. If directly compared enoxaparin reduced reinfarction but not death at a cost of increased minor bleeding rates.
LOE 1 Supporting Good


ExTRACT TIMI 25 substudy showing a decreasing efficacy (death and MI) of enoxaparin over UFH with decreasing creatinine and an increasing major bleeding rate (including intracranial bleedings) most pronounced in patients with a clearance < 30 ml/min but also noticeable with minor renal impairment. Net clinical benefit for enoxaparin could only observed in pts with a creatinine clearance > 60-90 ml/Min underlining the necessity of a more stringent dosing adjustment for enoxaparin (anti Xa level ?) with renal impairment.
Additional information regarding bleeding risks
LOE 5 Neutral Good


Small randomized double blind study to compare UFH/Dalteparin for STEMI pts receiving thrombolysis with streptokinase with a trend to better TIMI flow at ~24 hrs and less signs of ischemia in Holter ECG.
LOE 1 Supporting Fair


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
LOE 2 Supporting Good


ExTRACT TIMI 25 substudy showing that efficacy of the used enoxaparin regimen (up to 8 days) is superior to UFH (for 48 hrs) irrespective whether streptokinase (n=4139) or a fibrin specific thrombolytic (n=16283) was used. Whereas total major bleeding rates were somewhat higher with streptokinase compared to fibrin specific
thrombolitics, intracranial bleeding rates did not differ significantly between thrombolitics and antithrombins. Net clinical benefit for enoxaparin was significant for fibrin specific lytics but showed only a trend for streptokinase. Risk reduction could be observed on pts on fibrin specific thrombolitics also in the first two days of treatment with enoxaparin. Favouring enoxaparin compared to UFH

LOE 2      Supporting     Good


Extension of the EXTRACT-TIMI 25 substudy by Giraldez et al 2007 pointing out the finding that enoxaparin with streptokinase used as thrombolytic results in similar outcomes as with use of fibrin-.specific lytic. This may reduce costs.

LOE2      Supporting     Fair


Substudy from ExTRACT TIMI 25 showing again a generally higher mortality risk for women compared to men nearly irrespective of age. Bleeding rates and net clinical benefit however did not differ significantly between sexes. Specifically intracranial bleeding rates did not differ between sexes after adjustment for age.

Additional information regarding bleeding risks

LOE 5      Supporting     Good


Substudy of ExTRACT TIMI 25 on diabetics showing an even larger clinical benefit (specifically mortality) for enoxaparin compared to UFH in patients with diabetics compared.

Additional information on risk/benefit relation

LOE 5      Supporting     Good


Metaanalysis on 12 studies on 49088 pts with STEMI and non STEMI ACS which investigates enox vs UFH with respect to the net clinical endpoint of death, MI or major bleeding by 30 days. The net clinical endpoint overall was reduced with enox be relative 10 % (12,5 vs 13,5 %) but in STEMI pts by 16 % (p = 0.015). Major bleeding was more frequent with enox (4,3 vs 3,4 % compared to UFH.

LOE1      Supporting     Good


Substudy of the OASIS-6 trial investigating the results of 5436 STEMI pts receiving thrombolysis in that study (4415 pts did have an indication for UFH, 1021 did not). In all groups the risk of bleeding was reduced with fondaparinux irrespective of stratum, fibrinolytic used or delay to treatment. Moreover the risk of stroke was reduced with fondaparinux and the composite 30 days composite endpoint of death or MI specifically in those 4415 pts of the stratum with no indication for UFH of whom 3829 were treated with streptokinase.

LOE2      Neutral     fair


Extended metaanalysis by adding the EXTRACT TIMI 25 (2006) and the papararin study by Wang (2006) to an earlier metaanalysis on the role of LMWH compared to UFH with thrombolysis in STEMI. The results are similar to the original work (Eikelboom, 2005): LMWH treatment for 1 week compared to UFH results in less reinfarctions but not deaths at the costs of an increased rate of minor and major bleedings.
**LOE1**  Supporting  Good


Randomized study in 400 STEMI pts, < 12 hrs symptomatic comparing enoxaparin or UFH on angiographic outcome with thrombolysis with accelerated tPA (enoxaparin 30 mg bolus followed by 1 mg/kg s.c. every 12 hrs, UFH initially 4000 – 5000 U (weight adjusted) and followed by infusion to achieve a target aPPT 1.5 – 2 x ULN for 72 hrs). Angiography being performed after 90 Min and after 5 – 7 days. Bleeding rates were identical in both groups, initial TIMI flow grades 2 + 3 were 80.1 % with enoxaparin and 75.1 with UFH. Reocclusion at days 5 to 7 or TIMI flow o/1) showed a trend to better results with enoxaparin. Neutral regarding angiography and clinical outcomes

**LOE 1**  Neutral  Good


Analysis of 12 randomized on 26800 pts treated with thrombolysis and LMWH compared to placebo or UFH (LMWH: dalteparin, enoxaparin and reviparin). Dalteparin was not superior to placebo in clinical outcome. Enoxaparin and reviparin compared to placebo reduced mortality and re-MI rates without increased stroke rate. Bleeding rates with LMWH were comparable to UFH but higher compared to placebo (exemption higher rates of intracranial bleedings in ASSENT 3 plus). Authors conclude that several problems (elderly pts ranal impairment, edition of Gp IIb/IIIa) should be solved before general recommendation of LMWH.

Metaanalysis on different LMWH vs UFH or placebo (with thrombolysis) showing superiority of enoxaparin and reviparin compared to UFH

**LOE 1**  Supporting  Good


Non-randomized substudy of the CLARITY TIMI 28 trial on pts receiving LMWH (n=1429) or UFH (n=1431) on angiographic and clinical outcome (angiography performed after 48 hrs). The primary endpoint of CLARITY (death or MI or TIMI flow 0/1 at angiography) was more frequent with UFH (22,5%) compared to LMWH (13.5 %) p=0.027. TIMI flow 3 more frequent with LMWH (69.9 %) compared to UFH (59.8%) p=0.002. By 30 days pts in LMWH had a low rate of death and MI (6,9 %) compared to UFH (11.5 %) p=0.03 regard of age gender, infarct localisation or use of clopidogrel. There were no significant differences in bleedings (including intracranial).

Favouring enoxaparin over UFH (non randomized substudy of CLARITY).

**LOE 5**  Supporting  Good


Substudy of ExTRACT trial showing that the addition of clopidogrel to enox with thrombolysis results in less MACE at the cost of an slightly increased rate of non fatal bleedings compared to no clopidogrel. Superiority to UFH persists also in this subgroup of pts.

**LOE5**  Supporting  Good


Long time (1 year) results on mortality of ASSENT-3 showing similar results in all 3 groups

**LOE 1**  Neutral  Good

Study combining data from ASSENT-3 and ASSENT-3-Plus investigating the age dependent risks of adverse events (bleedings) with enox compared to UFH, study shows low risk of bleedings in pts < 65 years an offset of the clinical advantage of enox in the group aged > 65 < 75 years and an increased risk of adverse outcome in those > 75 years.

LOE5  Neutral  Good


Non-randomized study testing efficacy of modified dosing of streptokinase (accelerated) and different enoxaparin regimens in pts presenting with STEMI. Superior efficacy by accelerated streptokinase was shown by faster reductions of pain intensity and ST resolution as well as arrhythmias.

Mixture of modified streptokinase dose and different enoxaparin doses plus soft points.

LOE 5  Neutral  Poor


Metaanalysis on 4 smaller and 1 large study (ASSENT 3 representing ~ 70 % of the cohort) comparing UFH and enoxaparin with thrombolysis showing superior efficacy regarding important clinical endpoint but also revealed a higher rate of major bleeding (but not intracranial haemorrhages).

Metaanalysis with regard to superior efficacy of enoxaparin vs UFH regarding MACE at the price of elevated bleeding risks confirming the results of the main studies.

LOE 1  Supporting  Good


Prospective, randomised, single-blinded trial comparing the adjunctive treatment of LMWH (Dalteparin) to UFH in patients with STEMI, onset within 6 hours, receiving fibrinolysis. N=439 Primary end point: TIMI grade 3 flow at angiography at or after day4, clinical end points were death, recurrent MI, revascularization, stroke and major hemorrhage.

LOE1  Neutral  fair (dalteparin)


Randomized prehospital study in 1639 STEMI pts (symptoms < 6 hrs) treated with tenecteplase and enoxaparin (initially 30 mg i.v. followed by 2 x 1 mg/kg s.c. daily up to 7 days) or UFH (60 U/kg max. 4000 U followed by 12 U/kg/hr infusion for 48 hrs). Primary efficacy endpoint was 30 days mortality + re-MI+refractory ischemia and combined efficacy + safety endpoint was the above + intracranial hemorrhages + major bleeding. The primary efficacy endpoint tended to be lower with enoxaparin compared to UFH, mortality tended to be higher with enoxaparin stroke and intracranial hemorrhages were significantly more frequent with enoxaparin (2,9 % add 2,2 %) compared to UFH (1,3 % and 0,97 %) respectively. There increased rates were specifically high in pts > 75 years of age (predefined subgroup): total stroke 9,4 % with enoxaparin vs 2,3 with UFH and intracranial bleeding 6,7 % with enoxaparin vs 0,8 % with UFH. This study was reason to the reduced enoxaparin regimen in ExTRACT TIMI 28.

Trend to better primary and point for enoxaparin but higher intracranial hemorrhages (unspecific subgroup)

LOE 1  Neutral  Good


Small randomized study (n=186) comparing efficacy and safety of pamparin (4250 IU every 12 hrs for 7 days) with UFH (initiated 12 hrs after start of lysis, followed by APPT adjusted infusion for 3 days and UFH s.c. 7500 U every 12 hrs for another 4 days) in pts with STEMI < 70 years of age and a symptom duration of < 12 hrs utilizing
urokinase as a thrombolytic. Parnaparin treatment resulted in a significant lower rate of the composite endpoint of total death, first occurrence of not fatal AMI or first occurrence of need for urgent revasc at 5 days but not for the individual endpoints. Bleeding risk insignificantly tended to be lower with parnaparin.

LOE1 Supporting Fair


ASSENT 3 Plus substudy showing that presence of a physician at prehospital initiation of treatment led to some time delays but somewhat greater protocol adherence, did however not have a principal influence on quality of care.

LOE 5 Neutral Fair


Large randomized study in 17073 STEMI pts comparing thrombolysis with streptokinase and 0,25 mg/kg bivalirudin as bolus followed by 0,5 mg/kg/h infusion for 12 hrs and 0,25 mg/kg/h for 36 hrs (reduced dose if aPPT was prolonged at 18 hrs > 150 sec) or IFH (5000 U bolus followed by 1000 U/h in pts > 80 kg and 800 U/h in pts < 80 kg for 48 hrs, target aPPT 50 – 75 sec). The primary endpoint of total mortality was equal (10,8 % for bivalirudin, 10,9 % for UFH) in both group, but at 96 hrs significantly fewer reinfarctions occurred with bivalirudin (1,6 % with bivalirudin vs 2,5 with UFH (CI 0.56-0.87 p= 0,00)1 and also during the whole hospital stay (2,8 % vs 3,6 % (CI 0.66-0.93, p= 0.005). Stroke and intracranial bleeding rates were low in both group, severe bleeding rates revealed on slightly increased trend in favour of UFH. Mild and moderate bleedings occurred significantly more often with bivalirudin

LOE 1 Neutral Good


Prospective randomized dose finding study in 412 STEMI pts comparing SK lysis and 60 hrs UFH (standard dose) or 0,125 mg/kg hirulog bolus i.v. followed by 0,125 mg/kg/h or 0,25 mg/kg bolus followed by 0,5 mg/kg/h. Primary efficacy outcome of TIMI grade 3 flow 90-120 min was significantly better with both doses of hirulog compared to UFH, there was no difference in clinical outcome by 35 days (death, cardiogenic shock or re MI and significantly less bleeding (specifically with low dose hirulog). Dose finding study.

LOE 2 Neutral Good


ExTRACT TIMI 25 substudy comparing results in elderly (>75 years) and younger patients. Interestingly the bleeding rates with the reduced enoxaparin regimen in the elderly were equal with UFH (even if absolutely higher compared to the younger groups) but were relatively higher with "full dose" enoxaparin in the younger group (1,1 % with UFH, 1,9 % with enoxaparin p<0.0001). Clinical benefit (Death and MI) tended only to be less frequent in the elderly (24,8 % with enoxaparin, 26,3 wit UFH) as did net clinical benefit. The number needed to treat for net clinical benefit of enoxaparin was 59 for younger pts and 67 for the elderly. Additional information bleeding risks and efficacy.

LOE 5 Neutral Good


Large randomized complex study (n=12092) comparing fondaparinux (2,5 mg/day for up to 8 days) with UFH (bolus 60 U/kg followed by 12 U/kg/hr for 24-48 hrs). Randomization was stratified for indication of UFH e.g. planned use fibrin-specific lytics or PPCI or no indication for UFH. Patients fared specifically better with fondaparinux in the subgroups with thrombolysis and no reperfusion Tx but tended to have a worse outcome with
PCI. Bleeding risk was lower in all subgroups with fondaparinux.

LOE1 Supporting Fair


Large randomised study comparing reviparin (weight adjusted for 7 days) or placebo in 15570 pts presenting with STEMI and a symptom duration of < 12 hrs. Primary efficacy outcome was combination of death, re-MI or stroke at 7 and 30 days, which occurred in 11 % of the placebo group and 9.6 % with reviparin (HR 0.87, CI 0.79-0.96; p=0.005) at 7 days persisting to days 30 compared to placebo (significant reduction) in death and re-MI but not stroke. There was an increase in life threatening bleeding at days 7 with reviparin (0.2%) vs placebo (0.1 %) p=0.07. Best results with early (< 2hrs) treatment with additional PCI UFH was given. LMWH product generally not (if at all) on the market study in favour of reviparin compared to placebo

LOE1 Supporting Good


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