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

Worksheet author(s)
Michelle Welsford
Hans-Richard Arntz

Date Submitted for review: 27Jan2010

Clinical question.
ACS-017-3 In patients with suspected non St-elevation ACS in prehospital and emergency department settings (P), does the use of new anticoagulants i.e. pentasaccharide, enoxaparin, bivalirudin (I), compared with standard management (placebo, unfractionated heparin or 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?
Therapy

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

Conflict of interest specific to this question
Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet?
MW: NO
HRA: lecture honoraria from Sanofi Aventis

Search strategy (including electronic databases searched).

Medline (OVID):
[Heparin/ OR Low molecular weight heparin/,OR Enoxaparin.mp. OR Pentasaccharide.mp. OR Bivalirudin.mp. OR Unfractionated heparin.mp. OR Dalteparin.mp. OR Fondaparinux.mp. OR Nadroparin.mp OR Reviparin.mp OR Tinzaparin,mp OR Fraxaparin.mp] AND [Myocardial infarction/ OR Angina, Unstable/ OR acute coronary syndrome.mp. OR STEMI.mp.]; limit to human; limit to: (1980 to 1987 & 1988 to 1995 & 1996 to November week 3 2008) repeated search up to Feb 2009 week 3 = 2327 articles repeated search to September 2009, week 2 (> 200 additional articles reviewed; 13 final articles added

EMBASE (OVID):
[as above] AND [Myocardial infarction/ OR myocardial ischemia/ or Angina, Unstable/ OR coronary thrombosis/ OR myocardial reperfusion/ OR chest pain/ OR acute coronary syndrome.mp. OR STEMI.mp. OR angioplasty.mp. OR heart catheterization.mp. OR percutaneous coronary intervention.mp. OR primary angioplasty.mp.]; limit to human; (1980 to 2009 week 3)
= 7954 articles

COCHRANE Central Register of Controlled Trials (OVID):
As above (4th quarter 2008)
= 586 articles (205 for further review)

ECC EndNote Library 24Mar08: search for title contains: “heparin” = 176; or “enoxaparin” (65), or “bivalirudin” (3), or “dalteparin” (6) or “fondaparinux” (2), Nadroparin (3), “reviparin” (1), “tinzaparin” (1) or “fraxaparin” (0)

And hand searches of review articles and key articles
And ACC/AHA/ESC guidelines for non-STE ACS

State inclusion and exclusion criteria

Inclusion:
P: Patients with suspected acute (< 24 hours) ACS, Non-STEMI MI
I: new anticoagulants (LMWH or other): enoxaparin, dalteparin, nadroparin, reviparin, tinzaparin, fraxaparin and pentasaccarides: fondaparinux, and direct thrombin inhibitors: hirudin, bivalirudin, argatroban, and others
C: standard management (unfractionated heparin, other LMWH, or no anticoagulant)
O: mortality, reinfarction, revascularization, bleeding, stroke or other outcome
Type of study: Therapy trials or meta-analyses

Exclusion:
Abstract only, narrative reviews, no comparison group, comparison to placebo, animal studies, and articles reporting economic outcomes only.

Number of articles/sources meeting criteria for further review:

2327 + 7954 + 586 + 176 + 65 + 3 + 6 + 2 + 3 + 1 + 1 = 11,124

From 11, 124: 3,281 met criteria for further review;
85 final references included in this worksheet.
# Summary of evidence

## Evidence Supporting Clinical Question

**Question 3** – Non-STEMI ACS; *Enoxaparin, Dalteparin, Fondaparinux, Bivalirudin, Nadroparin, various*

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**Level of evidence**

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<th>Composite: death, reinfarction, stroke</th>
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## Evidence Neutral to Clinical Question

**Question 3** – Non-STEMI ACS; *Enoxaparin, Dalteparin, Fondaparinux, Bivalirudin, Nadroparin, various*

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Note: The table structure and content are designed to present the summary of evidence in a clear and organized manner, with clear separation between evidence supporting and neutral to clinical questions. The level of evidence is categorized into A to E, with A being the highest level of evidence. The research studies are listed with their respective years, and the level of evidence is indicated in the table.
A = Survival/mortality hospital discharge  C = Composite: death, reinfarction, stroke  E = Other clinical outcome
B = Survival/mortality 30 days  D = Other composite outcome  F = Platelet activity

Evidence Opposing Clinical Question

Question 3 – Non-STEMI ACS; Enoxaparin, Dalteparin, Fondaparinux, Bivalirudin, Nadroparin

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REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

The evidence for the use of LMWH rather than the standard UFH is agent specific. It is better to do a separate analysis based upon each agent rather than consider them as a class. The only class effect is to cause less HIT (heparin induced thrombocytopenia) than UFH.

Due to the broad spectrum of different strategies (i.e. conservative vs invasive) and comparisons of different combination of treatments and even dosing of the different UFH alternatives it is quite difficult to extract data which may fulfill criteria which may lead to substantiated recommendations. According to the study results recommendations for an invasive strategy will differ from those with a conservative approach. Also it seems to be reasonable to take the individual bleeding risks into account. Different strategies (i.e. conservative vs invasive) often are also combined with different additional medications which may explain the results partially. For example many interventionalists prefer to perform PCI with Gp IIb/IIIa receptor blockers (according to the guidelines). These substances however increase inherently bleeding risk, and thus may explain the results e.g. of the ACUITY trial (Stone et al 2006). The situation becomes even more complicated when Gp IIb/IIIa receptor blockers (of different kinds (mostly eptifibatide in the present studies) and potentially different risk) were “allowed” i.e. not used in a randomized manner for PCI. Finally the composite endpoints are frequently difficult to compare due to variable definitions and sometimes insufficiently controllable endpoints e.g. “necessity of urgent revascularization” or “unplanned revascularization” which is of major concern about all in open label studies. A general problem or all studies available is that no study was investigating early i.e. prehospital or ED initiation of treatment allowing only conclusions by analogy for these situations.

Enoxaparin: numerous studies have shown benefit (with a few that are neutral) in patient oriented outcomes (combined mortality, infarction, revascularization, etc) as well as cost effectiveness, but with increased evidence of minor bleeding. There does not appear to be increase in life-threatening bleeding. The studies that have shown the greatest benefit are those with primarily a conservative approach (lower rates of PCI, eg: ESSENCE). Those that are neutral in outcome have a greater interventional approach (AtoZ and SYNERGY). It may be that PCI neutralizes the benefit of enoxaparin by decreasing the combined endpoint through intervention. Additional anticoagulants may be required during an interventional approach – it is common to add UFH during a PCI procedure. Enoxaparin is renally excreted (non-saturable), therefore, patients in renal failure should have dosing adjusted or use another agent. Dosing may need to be adjusted, or another agent chosen for patients with renal dysfunction. Pre-hospital administration of Enox: ASSENT-3Plus showed increased bleeding in elderly, which led to new dosing recommendations for elderly patients.

Bivalirudin: all of the studies on this direct thrombin inhibitor for ACS patients managed with an invasive strategy are consistent in showing neutral outcomes compared to UFH, with less bleeding risk. Uncertain outcomes compared to the other LMWHs. Not enough evidence on its value in patients managed with a conservative strategy, mostly evaluated on patients undergoing an interventional approach. Likely safe in renal insufficiency without need for dose adjustment. Does not cause HIT (Heparin induced thrombocytopenia).

Fondaparinux: there are a few studies on this agent that have shown superiority or neutral outcomes in comparison to enoxaparin (a new standard treatment). The OASIS trial showed benefit primarily in patients treated with a conservative
approach. For those patients managed with PCI, an additional anticoagulant (UFH) or thrombin inhibitor needs to be added. Fonda also appears to have less bleeding risk than enoxaparin. Fonda is also renally excreted but does not appear to have increased bleeding risk in renal failure patients (at dose of 2.5) making this medication a good choice in these patients.

There is not enough evidence to make recommendations on the use of the other LMWH agents.

Only UFH has been regularly used in the prehospital or ED setting for treatment of patients presenting with signs and symptoms of non-STEMI ACS although early antithrombin treatment is recommended for these pts. There are no reliable data on the ED or prehospital use of alternatives until now. Furthermore, the optimal antithrombin treatment depends on the need and on the urgency of invasive procedures. This has to be taken into account in decision making. For pts with urgent indication for invasive procedures UFH, enoxaparin or bivalirudin may be considered.

For pts with delayed angiography or a principally conservative approach fondaparinux should be preferred due to its low bleeding risk over UFH and enoxaparin.

Antithrombins should not be switched for PCI specifically not UFH and enoxaparin.

 Patients treated with fondaparinux, however, should receive additional UFH (50 – 100 min/kg bolus) for intervention to avoid catheter thrombi.

For fondaparinux and enoxaparin dose adjustment is necessary in renal impairment.

Acknowledgements:
None

Citation List

(1-50)(51-85)


Prospective meta-analysis of 1 year follow-up data of TIMI 11B and ESSENCE trials. Hypothesis: Treatment effect of enoxaparin given in the acute phase for unstable angina/Non-STEMI would be sustained at 1 year. N=6646 available for follow-up of 7081 originally enrolled in the 2 trials (94%). However TIMI 11B study included prolonged treatment and not just acute. Outcomes: Individual events of death, MI, urgent revascularisation, and composite of death and MI, and triple composite. Patients with 0–2 risk factors were combined into a low risk stratum (32%), those with 3–4 risk factors into an intermediate risk stratum (56%), and 5–7 risk factors into a high risk stratum (12%), based on the following TIMI Risk Factors
- Age >65 y
- Documented prior coronary artery stenosis >50%
- Three or more conventional cardiac risk factors (eg, age, sex, family history, hyperlipidemia, diabetes, smoking, hypertension, obesity)
- Use of aspirin in the preceding 7 d
- Two or more anginal events in the preceding 24 h
- ST-segment deviation (transient elevation or persistent depression)
- Increased cardiac biomarkers

The 8 day benefit of enoxaparin was sustained at 1 year for the triple composite outcome and increased as the baseline risk for heart disease increased. A statistically significant treatment benefit of enoxaparin was observed in the intermediate (hazard ratio 0.87; 95% CI 0.77, 0.99; P=0.04) and high risk (hazard ratio 0.80; 95% CI 0.65, 0.98; P=0.03) groups.

Level of Evidence: 1; Quality of Evidence: Excellent design and methodology, appropriateness to ED setting is Good. Direction of Evidence: Supportive of LMWH over UFH (enoxaparin) in terms of efficacy for intermediate and high risk UA/NSTEMI.

LOE 1, supportive, good

Meta-analysis of ESSENCE and TIMI 11B trials. Trials selected for intervention with enoxaparin as the LMWH intervention group. Minor hemorrhage was not defined in this trial.
Level of Evidence: 1
Quality of Evidence: Good
Direction of Evidence: Supportive for efficacy of LMWH (Enoxaparin) v UFH, with treatment effect occurring within 48 hours and persisting out to day 43. No increase in major bleeding; only minor bleeding increased significantly with LMWH.
LOE 1; supportive, good quality


TIMI 8
RCT bivalirudin ACS vs UFH
stopped very early (133 instead of > 5000) b/c of sponsorship
primary outcome 14-day composite death or MI much less in Bivalirudin, but not powered to find a difference is such a small number: non significant less major bleeding
LOE 1, neutral, poor(study stopped very early)


TIMI 11B Trial. Multicentre, double blind, randomised controlled trial
Hypothesis: to test if LMWH (Enoxaparin) was superior to UFH in patients with unstable angina/Non-STEMI. Drug company sponsored the trial (declared).
P= ACS with prior history (removed after study half complete to focus on higher risk), ECG changes or positive biomarkers. excluded if planned revascularization within 24 hours.
I/C= Enoxaparin given as initial 30mg IV bolus, them 1mg/kg subcutaneously) in the acute phase (first 8 days or d/c) versus UFH > or = 3 days; and an extended outpatient course (additional 35 days) . ignore the extended course because this was compared against placebo.
O=Primary end points: For efficacy were a composite of all cause mortality, recurrent MI, or urgent revascularisation at 8 days. For safety, major hemorrhage. Secondary end points: Looked at the individual elements of the primary outcomes and minor hemorrhage. Also compostie of death or nonfatal MI. Outcomes at 48hrs and 14 days.
N=3910 pts, groups were similar. Time from qualifying symptom (>5 mins ischaemic discomfort at rest) to first dose of study medication: median 11 hours (5.8, 18.9).
Enoxaparin found to be superior in acute phase (combined endpoint), max benefit at 48 hrs, with no increase in major hemorrhage, but an increase in incidence of minor hemorrhage (injection site or sheath site hematoma). No statistical benefit in mortality. No continued benefit in outpatient phase but an increased incidence of major hemorrhage.

Level of Evidence: 1; Quality of Evidence: Excellent in design and methodology, Excellent in terms of appropriateness to ED setting. Also included arm of enox by EMS (vs placebo)
Direction of Evidence: Supportive of LMWH (enoxaparin) over UFH in terms of efficacy and neutral for safety in the acute phase. (Commencing treatment within 24 hours symptom onset)
LOE 1, supportive, good

Subset of ESSENCE study, looking at hemorrhagic complications after treatment with LMWH (Enoxaparin) or UFH for unstable angina/NonSTEMI. Prospective, randomised, double-blinded controlled study. Concludes that enoxaparin is at least as safe as UFH with regard to major hemorrhage in this setting with no statistical difference between the two groups (although there was a non-statistical trend to increased rate of major hemorrhage while on treatment) With regard to minor hemorrhage there was an increased incidence injection site hematoma associated with LMWH).

Level of Evidence: 2
Quality of Evidence: Excellent design and methods, appropriate to ED/Prehospital setting as addresses safety concerns.
Direction of Evidence: Neutral for major hemorrhagic complications, opposing for minor hemorrhagic complications defined as increased rates of injection site hematoma.

LOE 2, neutral, fair


enox vs UFH; ACS; open-label;
LOE 2, neutral, good


RCT in 4098 patients
PCI for unstable or postinfarction angina (mixed group)
heparin vs bivalirudin.
primary end point: death in the hospital, myocardial infarction, abrupt vessel closure, or rapid clinical deterioration of cardiac origin.
Results: In the prospectively stratified subgroup of 704 patients with postinfarction angina, bivalirudin therapy resulted in a lower incidence of the primary end point (9.1 percent vs. 14.2 percent. P = 0.04) and a lower incidence of bleeding (3.0 percent vs. 11.1 percent, P < 0.001), but no diff at 6 moths. Bivalirudin, as compared with heparin, reduced the risk of immediate ischemic complications in patients with postinfarction angina, but this difference was no longer apparent after six months.; less bleeding with similar other outcomes means neutral but might be good option for patients with higher bleeding risks or an alternative if costs are similar
LOE 1; neutral, good


A to Z Trial (A phase). Prospective, open-label randomized trial of patients with NSTEMI receiving aspirin and G2b/3a inhibitor (tirofiban) comparing treatment with LMWH (enoxaparin) or UFH. Patients were randomized within 24 hours of symptom onset. Primary end points: combined outcome of death, recurrent myocardial infarction, or refractory ischemia at 7 days (efficacy) and major bleeding (safety).
This study is key in the finding that enox is safe when used with IIb inhibitors (noninferior) However enrollment not immediate and some patients (approx 35%) received prerandomized anticoagulants - therefore also dealing with the risks of switching anticoagulants.

Level of Evidence: 1  
Quality of Evidence: Fair (Good design and methods, moderate sample size, non-blinded.)  
Direction of Evidence: Neutral for efficacy and safety of LMWH (enoxaparin) compared to UFH in the setting of GIIb/IIIa inhibitor (tiropiban) use.  
LOE 1, neutral, fair


Post-hoc analysis of bleeding rates and link to mortality in OASIS-5 (RCT fond vs enox, ACS) found statistically significant fatal bleeding, major bleeding, need for transfusion, and minor bleeding. Major bleeding was associated with increase mortality, MI or stroke.  
LOE 5; supportive, good


Article in Spanish; translation into English obtained for C2005  
Prospective randomized controlled trial in Mexican patients with UA/NSTEMI, randomized within 48 hours of qualifying symptom onset. Compares a lower dose of LMWH (enoxaparin 0.8mg/kg/dose) to UFH. N=203.  
Primary outcome measures: Therapeutic serum levels of anti-Xa and major complications that included death, AMI, emergency coronary revascularization, refractory angina, and total hemorrhages.  
Level of Evidence: 1  
Quality of Evidence: fair  
Direction of Evidence: Supportive of lower dose LMWH (enoxaparin) in terms of safety and efficacy.  
LOE 1, supportive, fair


Randomized comparison of Enoxaparin vs UFH in 966 pts (283 with NSTE-ACS) 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 in ACS not STEMI  
enox vs UFH in stable CAD and ACS/NSTEMI undergoing angiography +/- PCI;  
LOE 5, neutral, fair


ESSENCE Trial. Prospective, double-blind, randomised, placebo controlled trial of patients with ACS/NSTEMI. Enox vs UFH; ESSENCE trial N=3171. Hypothesis: To demonstrate the superiority of LMWH (enoxaparin) over UFH with respect to safety and efficacy. Primary outcome measures: Composite of death, MI or recurrent angina at 14 days. Major and minor hemorrhage. Patients were randomised within 24 hours of symptoms (recent onset rest angina lasting >10 minutes) and 96% received the study medication within 12
hours of randomisation (no median reported for time from qualifying symptom to when study drug was given.) approx 50% underwent PCI.

Level of Evidence: 1; supportive

Quality of Evidence: Excellent design and methods. With respect to appropriateness to ED setting, patients were given the drug up to 36 hours from qualifying symptom.

Direction of Evidence: Supportive of LMWH (enoxaparin) over UFH in terms of efficacy at 14 days and 30 days and neutral for safety (major bleeding). (Commencing treatment within 24 hours symptom onset)

LOE 1, supportive, good


Substudy of the SYNERGY trial looking deeper in the subgroup of pts receiving pre-randomization antithrombin treatment. The 30 days rate of death and MI was of borderline significant increase with crossover at randomisation. Rate increased for crossover and enoxaparin only for bleedings. With consistent treatment rate of death and MI was significantly lower with enoxaparin (unadjusted for basic risks p=0.001, adjusted 0.041) and severe bleeding rates were slightly elevated compared to UFH 2.9% vs 2.6 % p=0.0465) respectively. substudy underlying the risk of switching between enoxaparin + UFH

LOE 5 neutral, good


ACUTE II study.
Prospective, randomised, double-blinded trial in patients with UA/NSTEMI. N=525. Patients had symptoms of UA within 24 hours of randomisation. Patients were all treated with ASA and a G2b3a inhibitor. Primary outcomes: Incidence of bleeding complications (safety).

Level of Evidence: 1

Quality of Evidence: Fair.

Direction of Evidence: Supportive evidence for decreased incidence of refractory ischemia requiring PCI and readmission with ACS (although study not adequately powered). Neutral for safety from major bleeding events (no difference found as not powered). Opposing with regard to minor cutaneous and oral bleeding events.

LOE 1, supportive, fair


Strategy study on timing of Enoxaparin before PCI

LOE 5 Neutral Fair


Substudy of the A to Z trial in non-STEMI ACS comparing the results of pts treated conservatively and receiving UFH (n=872) or enox (n= 906) resulting in less MACE with enox after 7 days.

LOE2 Supporting Fair

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


Reduced dose of Enoxaparin (0,5 mg/kg every 12 hours, last dose 10,8 hrs (mean) before PCI) + aspirin + clopidogrel before PCI followed by additional eptifibatide during and for 24 hrs after PCI (+ 0,3 – 0,5 mg Enoxaparin every 12-24 after PCI until discharge) proved to be safe and effective.

LOE 4 Neutral Fair


Observational study on 493 pts with stable or unstable angina undergoing PCI who were treated with i.v. enox (with an additional dose of 0,3 mg/kg before PCCI (n=222) or UFH (n=271) both groups + ASS + eptifibatide. There were less bleedings with enox and less cardiac enzyme elevation.

   LOE 2 Supporting Fair


Meta-analysis of 12 randomised trials comparing UFH to LMWH (or one or the other to placebo) in patients with UA/NSTEMI. Total of 17157 patients. Primary outcomes: Composite of death or MI (efficacy), major bleeding (safety); secondary outcomes: recurrent ischemia, need for revascularisation.

   Level of Evidence: 1
   Quality of Evidence: Excellent
   Direction of Evidence: Neutral for safety and neutral for efficacy of LMWH compared to UFH.
   LOE 1, neutral, good


Analysis of a REPLACE II subgroup of pts receiving provisional Gp IIb/IIIa receptor blockers: group with Bivalirudin to small for evaluation

   LOE 5 Neutral Fair

Substudy in 3852 patients with diabetes from the ACUITY trial. Rates of ischemia were higher in those pts compared to the main study. The principal result however was similar to the main study: similar (higher) rates of ischemia with the combo enox/UFH + GPI and bivalirudin + GPI or bivalirudin alone but less bleedings were less frequent with bivalirudin alone (in planned PCI).

LOE2 Neutral Good


Retrospective analysis of a case series of stable and unstable angina pts (n=1184) with planned PCI and bivalirudin as antithrombin of which a group of 156 pts received bail-out GPI treatment. MACE rates were similar in the bivalirudin alone group and the group with additional GPI but a higher rate of bleedings with additional GPI. Authors conclude that the preferred strategy should be with bivalirudin alone.

LOE4 Neutral Fair


Bivalirudin; LOE 2 (cohort) neutral, fair


Non randomized comparison of enoxaparin plus Gp IIb/IIIa (Tirofiban, eptifibatide, or abciximab) in 628 pts (n=283 also PCI) with results from other studies utilizing UFH + Gp IIb/IIIa which showed principally similar results.
Enox in ACS with historical controls;
LOE 2, neutral, fair


SYNERGY trial. Randomised controlled single-blinded trial comparing UFH to LMWH (enoxaparin) in patients with NSTEMI. N=4993. Patients received treatment within 24 hours of symptom onset (median 14 hours) and an early invasive strategy. Many patients received other anticoag prior to randomization and PCI. Approx 92% underwent PCI. Similar outcomes.; non-inferior. Nearly 800 patients received post-randomization cross-over; presumably the interventionalist was not comfortable with enox alone for PCI. The lack of benefit of enox might be related to the high use of PCI and the increased risk by switching and having more than one anticoagulant.
Level of Evidence: 1
Quality of Evidence:fair
Direction of Evidence: Neutral in terms of efficacy (and opposing/neutral in terms of safety).
LOE 1, neutral, fair


INTERACT substudy; enox vs UFH unblinded RCT; this substudy was long-term follow-up but only some sites were involved in this follow-up; incomplete f/u makes level 2; benefit of combined endpoint sustained LOE 2 (subgroup) supportive, good


Post-hoc analysis of 2 trials (ESSENCE and TIMI 11B), of patients with UA/NSTEMI randomised to UFH or LMWH (enoxapirin) who then had PCI. Outcomes: Composite of death/MI/recurrent angina or Major bleeding. Level of Evidence: 2
Quality of Evidence: fair, small numbers, results seem to duplicate original studies. PCI not randomised.
Direction of Evidence: Positive for enox; Neutral with regard to safety of major bleeding event for on treatment or in-hospital PCI (no difference found between LMWH and UFH).
LOE 2, supportive, fair


post-hoc analysis of EXTRACT - TIMI 25; RCT UFH vs Enox
this analysis looked at renal dysfunction and outcomes (combined endpoint and bleeding)
the benefit of enox was greatest in those with the best renal function; no benefit in those with the worse renal function; increased bleeding in those with renal dysfunction
LOE 2; neutral, fair


Non randomized post-hoc substudy of the OASIS-5 trial; RCT of ACS fond vs enox
This analysis looked at renal dysfunction and association with outcome and bleeding. Bleeding rates increased for both substances according to the degree of renal impairment. Average bleeding rates with enoxaparin were two times higher than with fondaparinux. Differences between treatment arms most pronounced with a GFR < 58 ml/min/1,73 m2.
Additional information on bleeding risk with fondaparinux and enoxaparin with regard to impaired renal function
found persistent benefit on fonda in renal dysfunction, with widening bleeding rates favoring fonda
LOE 2, supportive, fair


Prospective randomized study on 857 non STE ACS pts and planned PCI comparing the influence of bivalirudin or reduced dose of UFH + eptifibatide or reduced dose of enoxaparin + eptifibatide on coronary and myocardial perfusion/ischemia. Clinical outcome did not differ between groups eptifibatide improved myocardial perfusion (at the cost of higher bleeding rates) and coronary flower reserve i.e. epicardial flow was increased with bivalirudin. These were not-patient oriented outcomes, but mostly secondary outcomes.
LOE 5 neutral, good

REPLACE 2 substudy showing that antithrombin pre-treatment is not associated with increased bleeding risk with bivalirudin but with UFH + Gp IIb/IIIa.
no increased bleeding risk with Bivalirudin but with UFH

LOE 5; neutral; fair


ESSENCE substudy. Prospective, randomised, double-blinded controlled trial in patients with UA/NSTEMI, applying ST segment monitoring. Hypotheses well stated. Problems with relatively small number of patients and not accounting for all patients. Some relevance to the ED setting as randomisation and treatment took part in the first 24 hours from symptom onset for the initial 48 hour monitoring period, but the outcomes from this part of the trial showed no significant difference in rates or total duration of ischemia between LMWH (enoxaparin) and UFH.

Level of Evidence: 2
Quality of Evidence: Fair design and Methods.
Direction of Evidence: Supportive for efficacy of LMWH over UFH for the prevention of rebound ischemia as per ST monitoring.
LOE 2, supportive, fair


ESSENCE(4) Trial – Retrospective one year follow-up results. Primary outcome: Composite triple endpoint at one year.
Level of Evidence: 1
Quality of Evidence: Good
Direction of Evidence: Supportive of efficacy of LMWH (Enoxaparin) compared to UFH in patients with UA/NSTEMI to one year.


INTERACT Trial.
Prospective randomised, open-label trial in 746 patients with NSTEMI ACS treated with aspirin and G2b3a inhibitor (eptifibatide) comparing the addition of LMWH (enoxaparin) or UFH. Primary outcome: Non CABG major hemorrhage (safety) and rate of recurrent ischemia (efficacy). Secondary outcomes: Composite double or triple endpoints at 30 days. Intervention was initiated after randomisation, which occurred within 24 hours of qualifying symptoms, median 4.4 hours (2.8, 7.7).
Level of Evidence: 1;
Quality of Evidence: Good, appropriate to ED setting but non blinded
Direction of Evidence: Supportive for LMWH (enoxaparin) over UFH in combination with G2b3a Inhibitor and aspirin for NSTEMI.
LOE 1, supportive, good


Prospective randomised, single-blinded trial of patients with UA, all had the qualifying symptom of ischemic rest pain within the previous 24 hours (mean time to randomisation 6.17 hrs). Hypothesis: LMWH may lessen the severity of ischemic events in patients with UA. N=219. Endpoints as in abstract. Limitations: Study terminated early by data committee due to significant results.

Level of Evidence: 1
Quality of Evidence: Fair. Small number and single blinding of heparin only (no placebo subcutaneous injections, so possibly biased. Relevant to PH/ED Setting.

Direction of Evidence: Supportive of LMWH (Nadroparin) over UFH in terms of efficacy (Recurrent angina, silent ischemia and combined major events) and safety (minor bleeding).
LOE 1, supportive, fair


Registry data comparing outcome with enox + clopidogrel + aspirin to treatment with UFH + aspirin. After adjustment for basline variables MACE rate was lower with enox + clopidogrel + aspirin but a slight trend to increase in major bleeding and more minor bleeding with the combo of enox, clopidogrel and aspirin was observed.

LOE 4 Supporting Fair


Subgroup analysis of OASIS 5 showing benefit of fondaparinux exists whether or not the patient received non-randomized IIb/IIa and/or thienopyridines

LOE 2, fair quality, supportive


post-hoc analysis of OASIS-5 (RCT ACS to fonda vs enox stratified patients by GRACE score and found consistent non-inferiority of fonda across all groups with statistically significant less bleeding in each group.

LOE 2; neutral, fair


Bivalirudin vs UFH stable and unstable angina (no NSTEMI and neg trop) prior to PCI small number are ACS
RCT, double-blind; 4570 patients; all pretreated with clopidogrel 600 mg PO; then randomized to UFH or bivalirudin

primary end-point: composite death, MI, revascularization due to MI within 30 d, or major bleeding during hospitalization; secondary end-point: composite death, MI, revascularization;
neutral benefit, significant reduction in major bleeding; MACE rate similar, bleeding reduced
LOE: 5 (mostly non-ACS); neutral; good


Non-randomized pilot comparison trial of UFH vs enox IV/SC prior to PCI in 83 patients
Not powered to look at efficacy but little difference in mortality, MACE, and NACE (net adverse cardiac events); trend toward more moderate and severe GUSTO bleeding and major TIMI bleeding with UFH
LOE 2; neutral; poor quality (not a good control group, small numbers so not powered to show small benefit/harm)


FRIC trial – open-label RCT dalteparin or UFH; Prospective, randomised trial of 1482 patients with UA/NSTEMI symptoms in the preceding 72 hours. 2 phases to trial, acute phase (day 1-6, unblinded, comparing LMWH, dalteparin to UFH) relevant for PH/ED setting although concern as some of the patients were not randomised until up to 72 hours after their last episode chest pain, and prolonged blinded phase, comparing dalteparin to placebo. Primary outcomes: composite of death, MI or recurrent angina in 2nd phase of study (efficacy) and major and minor hemorrhage and thrombocytopenia (safety). Secondary outcomes: Composite endpoints in 1st phase of study and requirement for revascularization. Trial finds no significant difference in 2nd phase of study in terms of efficacy, but an increased number of minor bleed in the 2nd phase, no difference in major or minor bleeds in the acute phase and no difference in composite end points. The single end point of death is higher in the acute phase in the LMWH group 11 (1.5%) compared to 3(0.4%) in the UFH group (p=0.05). This is discussed as a borderline increase in mortality and it is stated that the study was not powered to find differences in the acute phase.
Level of Evidence: 1
Quality of Evidence: Fair design and methods. (open label)
Direction of Evidence: Neutral for efficacy and safety of LMWH (Dalteparin) compared to UFH in the acute phase of treatment.
LOE 1, neutral, fair


Post hoc analysis of patients entered in GRACE (Global registry of Acute Coronary Events). Time between symptom onset and treatment initiation not reported. Enoxaparin was the LMWH 80% of the time.
Level of Evidence: 4 (registry data)
Quality of Evidence: fair design and methods.
Direction of Evidence: Supportive of LMWH compared to UFH in terms of efficacy and safety.
LOE 4, supportive, fair

meta-analysis bivalirudin ACS/ PCI
4603 patients for elective pci and 1071 with ACS
in those trials compared to UFH; found similar endpoints or reduction in MI/revascularization, not mortality;
much less bleeding
LOE 5 (mostly non-ACS); neutral, fair


Pre-specified subgroup analysis of ACUITY by gender. ACUITY studied randomized allocation of NSTE-ACS patients to bivalirudin or heparin (UFH or enox) +/- GPAIIa/IIIb
Found that ischemic outcomes were not different between the groups regardless of gender. Female gender had increased bleeding complications and there was a statistically significant reduction in this complication in the bivalirudin monotherapy group.
LOE 2 (non-randomized by subgroup), good quality, neutral outcome


A meta-analysis of LMWH compared to UFH in the early management of ACS. pts (n=13320). outcome: death, death + MI or death+MI+recurrent angina or major bleedings
14% risk reduction for Death and MI for LMWH versus UFH (p=0.06).
Level of Evidence: 1
Quality of Evidence: Good design and methods.
Direction of Evidence: Neutral with regard to efficacy and safety.
LOE 1, neutral, good


Prospective, randomised, double-blinded trial in patients with UA/NSTEMI. Primary outcome: cardiac death, myocardial infarction, refractory angina, or recurrence of unstable angina at day 14, secondary outcomes: above composite of cardiac events at 6 and 3 months and major hemorrhage. Same length of treatment between UFH and LMWH 6 group. 53% of patients were randomised <6 hours from their last episode of pain.
Level of Evidence: 1
Quality of Evidence: Excellent design and methods.
Direction of Evidence: Neutral for safety and efficacy of LMWH (Nadroparin) compared to UFH
LOE 1, neutral, good


REPLACE-2 INTERACT trial;
RCT double blind bivalirudin vs UFH
primary endpoints: 30 day composite: death MI or urgent revasc and major bleeding and composite without major bleeding; noninferior, less major bleeding
LOE 1, neutral, good quality

REPLACE-1, bivalirudin
Prospective randomized study in 1056 non STE ACS pts for elective or urgent PCI; randomized to UFH (60 – 70 U/kg) bolus, followed by a ACT adjusted infusion (target ACT 200 – 300 sec) or bivalirudin (bolus 0.75 mg/kg followed by infusion of 1.75 mg/kg/l) until sheath removal (at ACT < 175 sec. or aPPT < 250 sec). Use of thienopyridine was encouraged, use of Gp IIb/IIIA inhibitor left to the attending physician. The efficacy endpoint 48 h composite mortality, MI or repeat revascularization (death, MI defined as new Q waves or CK-MB > 3 times ULN) or repeat revascularisation within 48 hrs or hospital discharge occurred with bivalirudin (5.6 %) or UFH (6.9 %) p = 0.40 as did major bleedings. Neutral with respect to bleedings and MACE no difference, bleeding similar
LOE 1, neutral, good quality


REPLACE-2 1 year results showing an insignificant trend to a lower rate of death with bivalirudin compared to UFH + GP IIb/IIla. Incidence of MI and need for repeat revascularisation was similar in both groups
LOE 1, neutral, fair quality


Post-hoc analysis of ACUITY trial of bivalirudin investigating results when clopidogrel was preadministered or after PCI or not administered at all. Found that the results were not similar (with less bleeding) when preadministered, but the bivalirudin group had a trend towards worse outcomes if the administration of clopidogrel was delayed or eliminated.
LOE 5 fair quality, neutral


pre-specified analysis of ACUITY trial of NSTE-ACS patients (bivalirudin, enox, UFH and GP IIb/IIla); stratified by age. Found that the composite and individual outcomes (ischemia, MI, death, etc) were no different in all age groups but that bivalirudin was associated with a statistically significant reduction in minor and major bleeding for all patients 55 and older and that reduction was greatest in the 75 years and older group.
LOE 2 (wasn't separately randomized by age groups); good; neutral (combined end points) or supportive (less bleeding)


pre-specified subgroup analysis of SYNERGY
RCT open-label enox vs UFH in 9,977 high risk ACS patients (with age recorded)
This study looked at elderly patients > or = 75 and association with treatment
Found trend to greater bleeding in oldest group given enox, but not significant; similar efficacy; raises concern re greater bleeding risk.
LOE 2 (non-randomized by age); good quality; neutral;

meta-analyis of LMWH vs UFH; showed no benefit in mortality but benefit in MI and revascularization; however, quality fair because pooled at LMWHs together.
LOE 1, supportive, good

SYNERGY trial - >10,000 UFH vs Enoxaparin in non-STE ACS (mod to high risk); completed in era of clopidogrel (62-63%) and IIb/IIIa(56-58%) (but these were not mandated, but optional). Primary outcome: composite of death, nonfatal MI at 30 d. Secondary outcomes: 1. combined mortality, nonfatal MI, stroke or recurrent ischemia requiring revascularization at 14 and 30 days; individual components of these composites; composite of death or nonfatal MI at 14 days and 6 months; and mortality at 6 months and 1 year. Safety end points: major bleeding or stroke through 30 days. This study allowed randomization even if patient had already received one of these agents and there was a high incidence of this occurring. Similarly, there was post-randomization crossover during PCI. Found non significant difference in outcomes with statistically significant increased major bleeding in enox group.
LOE 1, fair quality, neutral

Substudy of the 1 year results of the SYNERGY trial intending to define risk factors for 30 days and 1 year mortality surviving 30 days: Risk factors for 1 year mortality known at baseline were: age, male, sex, low weight, having ever smoked, decreased creatin cleaance, ST segment depression, diabetes, CABG, composite heart failure, increased heart rate, rales, increased hematocrit, haemoglobin and higher platelet count, for 30 days mortality decreased weight, atrial fibrillation, no use of β-blockers and not receiving reperfusion treatment.
LOE 5 Neutral Fair

Prospective, randomised single-blinded trial in patients with UA with symptoms occurring within 72 hours. N=93. Enoxaparin was given as1mg/kg subcutaneously, without an initial IV bolus. Primary outcome: composite of death, MI, recurrent angina or revascularisation (efficacy) and major and minor bleeding complications (safety) within 7 days. A cumulative cost analysis was also done. (feasibility). The composite end point of myocardial infarction, cardiac death, recurrent angina and need for intervention was observed in 62% of patients treated with UFH and in 37% of patients treated with enoxaparin (RR 1.7, 95% CI 0.75 to 3.71, p = 0.04).
Level of Evidence: 1
Quality of Evidence: Poor (open label, small)
Direction of Evidence: Supportive in terms of efficacy for LMWH (enoxaparin) compared to UFH. Neutral for safety and total cost.
LOE 1, supportive, poor


Meta-analysis of trials comparing LMWH (other than enoxaparin) to UFH in patients with UA/NSTEMI. Includes 5 trials. Primary outcome: composite of death, MI, recurrent angina or revascularisation (efficacy), major and minor bleeding complications (safety). Results as above. Problem: Tests for trial heterogeneity positive for efficacy end point.
Level of Evidence: 1
Quality of Evidence: Fair
Direction of Evidence: Neutral for comparison of LMWHs other than enoxaparin in terms of efficacy and safety.
LOE 1, neutral, fair


Non randomized comparison of high risk pts with non-STEMI ACS undergoing PCI treated with bivalirudin (+ GPI in 14 %) or UFH (+ GPI in 72 %). Bleeding rates and clinical outcome was similar in both groups; pre-and post-PCI TIMI flow was in favour of bivalirudin.
LOE2 Neutral Fair


Prospective, randomised, non-blinded pilot study of "OP 200" patients with UA symptoms within 60 hours of commencement of either UFH or very LMWH. N=120. Primary end points as described in abstract. Trial was terminated early after interim analysis showed a significant reduction in composite of major events and recurrent angina in the very LMWH group compared to the UFH group.
Level of Evidence: 1
Quality of Evidence: Fair design and methods.
Direction of Evidence: Supportive of a very LMWH compared to UFH in terms of efficacy, neutral in terms of safety.
LOE 1, supportive, fair


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.
LOE 2, supportive, good

Non-randomized substudy from OASIS 5 regarding 6238 NSTE-ACS pts undergoing PCI (~ 30 % of the original sample of 20028 pts). Bleeding rates were halved with fondaparinux (2.4 %) versus enoxaparin (5.1 %) whereas MACE (death, MI, stroke) were identical at 9/30 days and 6 months, resulting in a net clinical benefit for fondaparinux. Additional information on efficacy and risks in the PCI subgroup of OASIS 5

LOE 2 (prospectively planned substudy), neutral, good


ASPIRE, fonda 2.5, 5 mg or UFH;
Randomised pilot study on 350 pts undergoing elective or urgent PCI (NSTEMI ACS) 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. Trend to less bleeding but a concern regarding increased stent thrombosis
Fonda LOE 5 neutral, fair
different study populations (18% elective, 80% NSTEMI ACS < 2% STEMI/PCI)


Substudy of the ACUITY trial (planned PCI in ACS) being admitted to the hospital after presenting at the ED. This subgroup at pts shows similar results as the main and other substudies.

LOE5 Neutral Poor


RCT (nonblinded) of enox vs UFH in 60 NSTEMI-ACS patients.
showed statistical benefit of reduction in recurrent ischemia, reinfarction, and a trend to decrease in heart failure, strokes, and death and a trend to increase in minor bleeding. However, the rate of PCI was 90% in the enox group and 33.3% in the UFH group. This key difference in these two groups could be a confounder and thus the outcomes may not be solely due to the enox but rather the PCI. confounder makes it impossible to determine true effect of enox
LOE 1; poor quality; neutral

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 by 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. For non-STEMI ACS group, found no significant benefit for STEMI-lysis, found benefit.

LOE 1, supportive (STEMI-lysis); quality good
LOE 1; neutral (nonSTEMI ACS); quality good (subgroup was NSTEMI)


Key article
Systematic review with meta-analysis of the data from 6 RCTs comparing the LMWH Enoxaparin to UFH in patients with ACS. Comparison of overall population and population receiving no prerandomisation antithrombin therapy. End points: All-cause death and the combined end point of death and nonfatal MI (efficacy) at 30 days, transfusion, and major bleeding (safety) at 7 days. N=21946.

Level of Evidence: 1
Quality of Evidence: Good design and methods
Direction of Evidence: Neutral for mortality, but benefit for MI; Supportive in terms of efficacy of LMWH (Enoxaparin) compared to UFH in ACS, neutral in terms of safety.

LOE 1, supportive, good


Comparison of outcomes of stable vs unstable pts in the REPLACE-2 trial. There were no differences in outcome overall and also not in subgroups treated with bivalirudin or UFH + GPI.

LOE5 Neutral Fair


Comparison of bivalirudin and provisional GPI with UFH + mandatory GPI during PCI. Study on platelet activation an the coagulation cascade, showing that bivalirudin results in less platelet activation but lack of release of tissue factor pathway inhibitor.

LOE5 Neutral Good


in this post-hoc ESSENCE substudy of Enox vs UFH, looked at nonrandomized subgroups of ASA or no-ASA prior. Found benefit to enox regardless of prior ASA use.

LOE 5; supportive; quality fair

FONDUA study (Fondaparinux)
Dose finding study on ACS patients. Enox vs Fonda at 4 doses
Fonda at 2.5 mg showed improved outcomes compared to enox; similar bleeding
LOE 5 (dose finding study); supportive, fair quality


Bivalirudin meta-analysis
Metaanalysis on 5 larger studies (> 200 pts) on efficacy and safety of bivalirudin vs heparin (UFH and LMWH) in non STE ACS. No difference was found in cardiovascular endpoints (death, MI, revascularisation) between strategies however significant less major bleedings (RR 0.553 (0.4 (0.2 – 0.761)) with bivalirudin. Limitations: different doses of bivalirudin, use of GP IIb/IIIa receptor blocker and thienopyridines in some studies., UFH and LMWH representing comparison group
LOE 2, neutral, good


Post-hoc meta-analysis from ESSENCE and TIMI 11B trials in subgroup of patients who were obese or who had renal impairment. End points as in abstract. Renal impairment group very small, study not powered to show a difference in this subgroup. Mean time to first dose study drug (not clear if from randomisation or symptom onset) 10 – 11.4 hours.
Level of Evidence: 2
Quality of Evidence: Fair
Direction of Evidence: Supportive for LMWH (Enoxaparin) compared to UFH regardless of weight.
LOE 2, supportive, fair


Comparison of 602 pts with stable or unstable angina undergoing PCI and treated to an target activated clotting time of 250 sec. compared to 603 pts treated with bivalirudin. Bleedings and 6 months clinical outcomes was similar in the groups.
LOE5 Neutral Fair


ACUITY trail
large open-label randomized trial in ACS with early invasive strategy
13, 819 patients UFH or enox plus GP IIb or bivalirudin plus GP IIb or bivalirudin alone primary end point: 30 days death, MI or revascularization,
bivalirudin alone or with GP was noninferior; bleeding better alone and similar with; bivalirudin alone needs clopidogrel
LOE 1; neutral, good

Bivalirudin, ACUITY 1 year
1 year follow-up of the ACUITY trial showing no difference in primary efficacy endpoint (death, MI, unplanned resvascularisation) also after 1 year
LOE 1, neutral, good


Bivalirudin - subgroup analysis of ACUITY
LOE 2, neutral, fair


GUSTO IIb trial
ACS patients RCT UFH or hirudin (desirudin)
primary end point: death, nonfatal MI at 30 days showed trend, but not significant reduction; 24h death, nonfatal MI was reduced. moderate bleeding was increased by 1%
LOE 1; fair quality; neutral


Substudy of 6352 PCI pts in SYNERGY undergoing PCI within 48 hrs of admission study intending to define the best time point for PCI (best time window being within 6 hrs of admission in avoiding death and MI no effect beyond 30 hrs). No variations regarding bleeding rates and transfusion across time to PCI intervals.
Strategy substudy of SYNERGY
LOE 5 Neutral Fair


Small pilot study (n=91) showing that switching from enoxaparin to bivalirudin for PCI in Non STE ACS pts seems to be safe.
LOE 5 Neutral Fair

81. White HD, Chew DP, Hoekstra JW, Miller CD, Pollack CV, Jr., Feit F, et al. Safety and efficacy of switching from either unfractionated heparin or enoxaparin to bivalirudin in patients with non-ST-segment elevation acute coronary syndromes managed with an invasive strategy: results from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial.[see comment][erratum appears in J Am Coll
this study looked at what agent given prior to randomization eg: switched from enox/UFH
primary outcomes: composite ischemia, major bleeding at 30d
no difference in efficacy, but when switched from enox/UFH to bivalirudin alone, had less bleeding
LOE 2: neutral; fair


enox ACS SYNERGY PCI subgroup,
Subgroup analysis of 4687 pts from the SYNERGY trial undergoing PCI. The study confirms data from the main study: efficacy measured in terms of clinical outcome data and vascular complications was similar with enoxaparin (trend in favour of enoxaparin) where as bleeding rates were higher with enoxaparin and specifically higher for pts who had cross over at randomisation. Study confirms data from the main study in PCI pts
LOE 2, neutral, fair quality (subgroup)


1 year follow-up substudy of ACUITY: RCT of 3 treatments for ACS patients (high-risk); PCI substudy 3 arms: UFH or enox + IIb; bivalirudin + IIb; bivalirudin alone
primary endpoint: composite ischemia (death, MI, unplanned revascul) at 1 year; also looked at mortality
found: no difference in composite ischemia nor mortality
LOE 2; neutral; fair quality (subgroup)


meta-analysis of 11 RCTs; 35,970 ACS Patients (some STEMI);
direct thrombin inhibitors vs UFH in ACS; one of which is Bivalirudin;
looked at all studies and those without STEMI; found decrease in MI (reinfarction) but not mortality; increase in bleeding with hirudin compared to UFH; decreased bleeding with bivalirudin vs UFH
LOE 5, supportive, good


OASIS-5
fond vs enox; double-blind RCT of 20,078 ACS patients; fonda 2.5 mg sc daily vs enox 1 mg/kg BID (and adjusted for Cr); during PCI added additional fonda/UFH vs UFH
showed no difference in primary outcome of 9 day composite mortality, MI or refractory ischemia; improved mortality at 180 days and death/MI composite, less bleeding; more catheter thrombus formation with fond (0.9% vs enox (0.4%). ? need to add UFH during PCI to decrease thrombosis risk.
LOE 1, Positive, good quality