

Journal Club: 4/28/08
 Eastern Virginia Medical School
 Alex Yeats, MD

Clinical Scenario: A 67 y/o male w/ normal vital signs was sent to the ED after receiving an outpatient PVL which showed a right leg DVT. In your interview you ask about any shortness of breath and the patient noted slight decrease in exercise tolerance. You decide to order a CT scan which showed A PE. With this result you administer 1mg/kg of subcutaneous enoxaparin and call the hospitalist for admission and are told that you should have started UFH.

P: In patients with documented PE
 I: Does the use of UFH infusion
 C: Compared to LMWH
 O: Associated with better clinical outcomes?

1. A comparison of LMWH with UFH for Acute PE

Simonneau, NEJM, vol 337,1997

Methods	Multicenter Unblinded RCT: 57 centers, France, Belgium, Switzerland
Patients	>18y/o clinically suspected PE. Documented PE (high prob V/Q) or Indeterminate +documented DVT. 1482, enrolled 766 excluded.
Exclusion	Opinion of MD if embolectomy or thrombolytics, bleeding disorders, anticoagulant tx in last 24hrs, life expectancy <3months, organ failure, pregnancy
Intervention	Intervention: Tinzaparin 175 antifactor Xa units/kg. vs UFH 50IU/kg bolus + 500IU/day adjusted for APTT 2-3 times normal. Oral anticoagulant started day 1-3.
Outcome Measures	Superiority trial: Primary: 1. Reduction of recurrent VTE, 2. Major bleeding. 3. Death Secondary: Scintigraphic improvement scores in pulmonary vasc/Angiography Obstruction. DVT improvement. Days 1-8 + day 90. Evaluators blinded to tx.
Results	1482 patients: 766 excluded, 104 declined participation. 308 UFH 304 Tinzaparin 1. Death (all causes) Causes of death similar. 3PE in both groups. Days 1-8 UFH: 3 (1%) Tinza: 4 (1.3%) Day 9-90 UFH 11 (3.5%) Tinza 12 (2.6%) Days 1-90: absolute diff: 14vs12 0.1% 95CI -2.7-2.6 2. Recurrent VTE Total: UFH 6 Tinza 5 Diff: 0.3% (-1.8-2.4) 3. Major Bleeding: Transfusion of >2Units hem drop >2, intra cranial/retroperit Days 1-8 : UFH 5(1.6%) 1death 2/5 supra Tinza 3(1%) (0deaths) Days 9-90 UFH 6 Tinza 4 Overall UFH 8(2.6%) Tinza 6(2%) A. Diff 0.6% (-1.8-2.4) Minor Bleeding: Slight nonsignificant increase with LMWH. Overall Difference 0.6%(95%CI -.18-2.4) 4. Perfusion Lung Scans Days 1-8 UFH Improved 81% Unchanged 17% worsened 0.3% LMWH Improved 80% Unchanged 17% Worsened 0.7% 5. HIT 1 for UFH 0 Tinza Days 1-8: Total End points: 9UFH (2.9%) 9(3.0%) Tinza *patients w/ events in days 1-8 + 9-90 counted once
Conclusions	Tinzaparin: safe and effective. Similar rates for all end points for both. Combining all outcome measures: non significant trend favoring tinza: 5.9%vs 7.1%

Strengths	Symptomatic PEs. PE documented. 28% had signs of major PE(syncope, shock, R. Ventric failure, cyanosis) That subgroup analysis: trend favoring tinza. Patients at start of trial are similar.
Weaknesses	Physicians unblinded.Did not comment on therapeutic level of APTT of pts w/ recurrent VTE in UFH group. Low rate of outcome events reduced power to detect difference. Would have needed 10,000 patients to detect statistically significant difference. About 2/3s of pts in both groups received UFH before randomization 18+-6 hours average.

2. LMWH vs. Heparin in Tx of Pts w/ PE

Russell D. Hull et. Al Archives of Internal Medicine 2000;160:229-236

Methods	MC RCT DB US + Canada
Patients	Patients with DVT enrolled. Perfusion lung Scans done. High Prob patients included.
Exclusion	Bleeding, allergies to heparin, pregnancy, >2 previous DVT/PE, organ failure, heparin or other anticoags within 7days.
Interventions	UFH: 5000Unit bolus followed by infusion 40,320 U q 24hrs/29760 U for patients with a risk factor for bleeding (surgery within previous 14 days,h/oPUD/platelets<150,000. Dose adjusted to 1.5-2.5 normal. Tinzaparin: 175 International Factor Xa/kg once every 24hours. Both were DCd at 6days. All pts given warfarin for 3 months. UFH pts given placebo subcu injection Tinzaparin Pts given placebo infusion. APTTs reported to MD not involved in assessing outcomes.
Outcome Measures	s/s recurrent DVT/PE or bleeding, death. Documented by new perfusion defect or if DVT suspected impedance plethysmography or venography. 3month follow up. Bleeding = major or minor. 1.Recurrent VTE 2.Bleeding 3.Death 4.Thrombocytopenia
Results	432 patients with DVT enrolled. 419 pts got lung scan: 200(47.7%) high prob. 103pts UFH/97pts Tinzaparin. Treatment group characteristics except for age. Logistic regression analysis showed no effect in outcome. 1. Recurrent VTE UFH 7(6.8%) 4PE vs. 3DVT APTT therapeutic in 6/7 Tinzaparin: 0 2. Bleeding Major(during initial or right after immediate therapy): UFH 2(1.9%) (not supratherapeutic)Tinzaparin 1 (1%) Minor: UFH 3(2.9%) (2/3 (supratherapeutic) Tinza 1(1%) 3. Death UFH 6 (1 from PE) Tinzaparin 6 (0 from PE) 4. Thrombocytopenia UFH 1 (1%) Tinza 3(3.1%)
Conclusions	Tinzaparin: No less effective and probably more effective than UFH for preventing recurrent VTE.
Strengths	Double blinded. High measures to ensure this. Removes diagnostic suspicion bias. High prob scans.
Weakness	18.5% had h/o previous dVT or PE.(Did not differentiate UFHvs Tinza there) Different levels of UFH if risk factor.

3. LMWH vs. UFH in Tx of Pts w/ Acute Pulmonary Thromboembolism

Serha, Findik. Respiration: International Journal of Thoracic Medicine Vol 69, No 5, 2002

Methods	RCT
Patients	Consecutive Pts >18y/o with clinically suspected PE. High Prob VQ/Indeterminate w/ DVT (Compression US)
Exclusion Criteria	Massive PE thrombolytics/embolectomy, sbp <90, +1 of following high prob VQ, acute right ventric. Hypokinesia, leftward shift of septum, bleeding, anticoags in previous 24hours. Life expectancy <3months.
Interventions	UFH: 5,000IU bolus then 1000IU/h adjusted APTT 1.5-2.5. Enoxaparin: 1mg/kg BID. Study Drug for 5 days. Oral anticoags started on day 2.
Outcomes	Pts. Examined daily for s/s of recurrent VTE. Day 8 +90 All pts received V/Q + compression US. Patients with new symptoms. New perfusion defect. If not conclusive angiography done. DVT change on Compression US from first test. 1. Recurrent VTE Perfusion LS 2. Major Bleeding Decrease in hemoglobin >2, transfusion of >2units PRBC, retroperitoneal or intracranial. 3. Death 4. Thrombocytopenia
Results	87 patients enrolled. 28 excluded. Of 59 30 received UFH 29 Enox. 1. Recurrent VTE Days 1-8: UFH 1 (3.3%) Enox: 0 Difference Not statistically significant. Perfusion LS: UFH: Improved 22 (73%) Same 7(23%) Worsened 1(3%) Perfusion LS: Enox: Improved 21(72%) Same 8 (28%) Worsened 0 Day 9-90: UFH 3(10%) Enox: 1 (3.4%). Odds ratio 0.32. Perfusion LS: UFH All except two. Developed new VTE on day 86+88 Perfusion LS: Improved in all. Bleeding+Death: None
Conclusions	Treatment of patients w/ non-massive PE can be used safely + effectively.
Strengths	All patients received perfusion LS.
Weaknesses	Low # of patients, No mention of blinding. Sponsored by maker of heparin+enoxaparin.

4. LMWH Copared to IV UFH for Tx of Pulmonary Emoblism: A Meta-analysis of RCTs

Daniel Quinian, Andrew McQuilan, John W. Eikelboom. Annals of Internal Medicine. 2004;140:175-183.

Purpose	Compare Efficacy +Safety of subcutaneous fixed doses LMWH vs. UFH for PE
Data Sources	Medline, EMBASE, Cochrane. Through 2003. Also contacted pharm companies for unpublished data.
Inclusion Criteria	RCT, Blinded. Pts w/ nonmassive PE symptomatic +asymptomatic. Objectively documented PE. Any type of LMWH
Outcome Measures	1. Symptomatic VTE at end of heparin tx +3month follow up. 2. Mortality 3. Bleeding
Results	1. Symptomatic VTE. End of heparin TX. UFH: 2.4% LMWH: 1.4% OR 0.63 (95%CI 0.33-1.18) Not significant 3months: LMWH 3.0% vs UFH 4.4% OR 0.68 (CI 0.42-1.09) 2. Mortality. End hep tx. LMWH 1.4% vs. UFH 1.2% OR 1.2 (0.59-2.45) 3. Bleeding Major. End hep tx. LMWH 1.4% of 1023 UFH 2.3% of 928. OR 0.67 (CI 0.36-1.59). Minor Bleeding LMWH 6.8% vs UFH 5.5% OR 1.0 (0.73-1.59)

Conclusions	LMWH: as effective as UFH in non-massive PE. Superior convenience
Strengths	Objective criteria for PE, Removed studies one at a time looking to detect disproportionate influence on results(none found). Ensured similar time frames of studies. Excluded ones with poor follow up.
Weaknesses	Retrospective, Low # of outcome events diminished power, unable to excluded publication bias. Not able to look at individual pts, cancer, double counting etc.. Not able to look at causes of mortality.

Clinical Bottom Line: In the setting of documented pulmonary embolism where thrombolytics and embolectomy are not employed, the use of low molecular weight heparin should be used instead of unfractionated heparin due to its overall effectiveness, safety profile and the ease of use and administration.