45 yo TR diagnosed with proximal Rt leg DVT. ACCP guidelines recommendations state all the following EXCEPT:

1. Warfarin therapy should begin within 1-2 days of starting therapy with UFH or LMWH
2. Therapy with UFH or LMWH can be discontinued after an overlap of at least 5 days and when the international normalized ration is greater than or equal to 2 for 2 values (ie within 24 hours)
3. Systematic follow-up (i.e., anticoagulation clinics) of warfarin therapy should be initiated
4. Warfarin therapy should be postponed until the patient is stable
ROAD MAP

Treatment:
1. Treatment options for VTE
   ▫ LMWH, IV UFH, SQ UFH monitored, SQ UFH unmonitored,
   ▫ Cancer patients
2. Thrombolysis for DVT and PE
3. Lower INR’s?
4. Upper extremity DVT
5. Superficial thrombophlebitis
6. Pharmacy Pearls
   ▫ Obesity/max dose/rounding

Prophylaxis/Prevention:
1. Prophy in special populations
   ▪ Surgery (q8h) vs medical (q12h=q8)
   ▪ Cancer patients – (q8h)
2. IVC/IPC’s when and where
3. Statins for prophylaxis? – what is that all about?

Which statement is True regarding acute **treatment** of VTE?

1. SQ UHF > LMWH
2. UFH < LMWH
3. All forms of UFH = LMWH
4. Antisteroidal agents = UFH
ACCP 2008 Recommendations for Treatment of VTE

1.1 Initial Anticoagulation of Acute DVT of the Leg

1.1.1. For patients with objectively confirmed DVT, we recommend short-term treatment with SC LMWH (Grade 1A), IV UFH (Grade 1A), monitored SC UFH (Grade 1A), fixed-dose SC UFH (Grade 1A), or SC fondaparinux (Grade 1A) rather than no such short-term treatment.

IV UFH vs LMWH for treatment of VTE

• ACCP 2008– guidelines
  ▪ Therapies are Grade 1 A level of evidence over no such short term therapies
  ▪ BUT in comparison, meta-analysis have indicated LMWH to be statistically associated with:
    • Fewer thrombotic complications (32% reduction)
    • Less bleeding (43%)
    • Fewer deaths (24%) – with this mortality benefit being confined to patients with cancer

Therefore ACCP recommendations state:
“In patients with acute DVT, we recommend initial treatment with LMWH SC once or twice daily, as an outpatient if possible (Grade 1C), or as an inpatient if necessary (Grade 1A), rather than treatment with IV UFH.”
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>▫ LMWH is more effective than UFH for the initial treatment of VTE.</td>
<td>▫ LMWH significantly reduces the occurrence of major hemorrhage during initial treatment</td>
</tr>
<tr>
<td>▪ 30% less thrombotic complications (3.6% vs 5.3% CI: 0.57-0.85)</td>
<td>▪ occurred in 1.1% of participants treated with LMWH compared with 1.9% treated with UFH (OR 0.58; 95% CI 0.40 to 0.83).</td>
</tr>
<tr>
<td>▪ Thrombus sized reduced in 31% of participants (53% vs 43% CI:0.59-0.81)</td>
<td>▪ Significantly lower in participants treated with LMWH (OR 0.77; 95% CI 0.63 to 0.93). – <em>again appears statistically limited to patients with cancer</em></td>
</tr>
</tbody>
</table>

**Limitations of the Cochrane Review**

- **primarily DVT, only 25% with primary PE**
  - Recommendation for PE is to use IVUFH
- Concealment issues
- Assessment of individual patient groups
SQ UFH Treatment Options (Chest 2008)

• Standard SQ dosing with monitoring (Grade 1A)
  ▪ Dose:
    • 17,500 units divided q12h OR
    • 250 units/kg SQ q12h
  ▪ Monitoring
    • Mid-interval aPTT – targeted at 0.3-0.7 U/ml anti-xa activity

• SQ dosing NO monitoring (Grade 1A) (Kearon et al 2006)
  ▪ Dose
    • 333 units/kg bolus then 250 units/kg SQ q12h
    • Unmonitored

SQ UFH versus “standard therapies”

Cochrane Review – October 2009

• SQ UFH
  ▪ Monitored
  ▪ Unmonitored UFH SQ

vs

• Standard therapies as “Control”
  ▪ IV UFH or LMWH
# Cochrane Review October 2009

## Summary of Findings for the Main Comparison

### Subgroup: Uncontrolled Hepatos

**Outcome:** Treatment allocation - clinical efficacy

**Patient population:** Year of treatment/clinical efficacy

### Subgroup: Uncontrolled Hepatos

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Outcome</th>
<th>Comparator</th>
<th>Risk Estimate</th>
<th>No of Participants</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
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<tbody>
<tr>
<td>Overall</td>
<td>Effect</td>
<td>Mean difference (95% CI)</td>
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<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>0.00</td>
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<td></td>
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</tr>
<tr>
<td>Other treatment modalities</td>
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</tr>
</tbody>
</table>

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**Notes:** *The basis for the assessed risk (e.g., median control group risk across studies) is provided in parentheses. The corresponding risk (and its 95% confidence interval) is based on the assumptions in the comparator group and the relative effect of the intervention (and its 95% CI).*

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>No of studies</th>
<th>Quality of the evidence (GRADE)</th>
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<td>0.00</td>
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<td></td>
</tr>
</tbody>
</table>

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**References:**

Cochrane Review  October 2009

- SQ UFH **can not be considered non-inferior** to other treatment modalities in terms of recurrent DVT/PE at 3 months
  - It does seem safe and effective in regards to rates of major bleeding and death

**Conclusion/recommendation:**
- If SQ UFH used, it is recommended you monitor (target aPTT 1.5-2 x) therapy rather than not.
- Assure a bolus dose is provided.

ACCP 2008 ......

- Mortality benefit of LMWH over UFH appears to be confined to patients with cancer.......

- So how do we treat cancer associated thrombosis (CAT)?
ACCP 2008 Guidelines: VTE Treatment and Cancer

2.1.3. For patients with DVT and cancer, we recommend LMWH for the first 3 to 6 months of long-term anticoagulant therapy (Grade 1A). For these patients, we recommend subsequent anticoagulant therapy with VKA or LMWH indefinitely or until the cancer is resolved (also, see Section 2.4) [Grade 1C].

Cancer and VTE - CLOT Trial

Control Group
- dalteparin 200 IU/kg OD
- oral anticoagulant (INR 2.0 to 3.0) x 6 mo

Experimental Group
- dalteparin 200 IU/kg OD x 1 mo then ~150 IU/kg OD x 5 mo

5 to 7 days 1 month 6 months

Conclusions from CLOT

In cancer patients with acute VTE,

- Long-term dalteparin therapy substantially reduced the risk of symptomatic, recurrent VTE by 52% compared to OAC therapy
- Risk of bleeding similar between dalteparin and OAC therapy
- No difference in overall mortality between dalteparin and OAC therapy
- Patients on warfarin were in target range only 42% of time

Caveat: once daily dosing (1.5mg/kg) enoxaparin not studied, post-hoc data by Merli et al suggested this dose may not be as effective in cancer patients
Thrombolysis - DVT

- Catheter directed Thrombolysis (CDT)
  - Grade 2B – selected patients

- Systemic
  - Grade 2C – highly selected patients when CDT not available
Thrombolysis - PE

4.3.1. All PE patients should undergo rapid risk stratification (Grade 1C). For patients with evidence of hemodynamic compromise, we recommend use of thrombolytic therapy unless there are major contraindications owing to bleeding risk (Grade 1B). Thrombolysis in these patients should not be delayed because irreversible cardiogenic shock may ensue. In selected high-risk patients without hypotension who are judged to have a low risk of bleeding, we suggest administration of thrombolytic therapy (Grade 2B). The decision

TR is a 44 yo patient with idiopathic VTE/PE, who has difficulty with compliance with appointments. He wants to discuss alternative options for treatment on warfarin for VTE. He has been on warfarin 1 yr.

1. He has completed 1 yr of therapy – he could stop therapy
2. He should continue therapy as is and try to be compliant.
3. Target INR could be lowered to 1.5-1.9, with less monitoring.
4. Discontinue warfarin and begin LMWH life long
Treatment of VTE: Intensity and Duration

• INTENSITY
  Ridker and Kearon – clarified this question with the PREVENT and ELATE trials published in NEJM, 2003.

  An INR of 2-3 results in a > 90% decrease in the risk of recurrent VTE, without an apparent increased risk of bleeding

Ridker PM et al. NEJM 2003;348(15):1425-34
Duration of therapy

A community-based cohort study followed 1719 patients after short-term anticoagulation for a first DVT. The overall cumulative incidence of first VTE recurrence at 30 days, 90 days, 180 days, 1 year, and 10 years was 5.2%, 8.3%, 10.1%, 12.9%, and 30.4%, respectively. While VTE recurrence is highest in the months immediately following diagnosis, the cumulative risk of recurrence continued to increase over time; it is therefore suggestive of a role for extended therapy.

ACCP Recommendations for Duration

- three months if secondary to a transient risk factor (grade 1A recommendation)
- at least 3 months if unprovoked and consideration for long-term if the VTE is a first episode that is unprovoked and proximal (grade 1A recommendation)
- long-term for a second unprovoked episode (grade 1A recommendation)
Risk factors associated with recurrence

- Obesity – BMI $\geq 30$ kg/m$^2$
- Male sex
- IBS
- Neurologic disease with paresis
- Thrombophilia
- Post-thrombotic syndrome
- Unprovoked nature of VTE

Intensity of anticoagulant effect

- PREVENT Trial
  - Idiopathic
  - 3 months tx then: Placebo or warfarin 1.5-1.9

- 64% RR reduction in recurrent VTE (intention to treat analysis)

Ridker PM et al. NEJM 2003;348(15):1425-34
ACCP Guidelines 2008
Alternative management option ***

- After 3 months of INR = 2-3, you can ↓ frequency of monitoring, in preference to discontinuing therapy.
  - Lowering intensity of therapy (INR=1.5-1.9)
  - Less monitoring
    - Q 8 weeks

Grade 1A

SC is a 62 yo female patient. The doctors comes to you for your recommendation of treating her superficial thrombophlebitis. What would be your recommendation to the MD?

1. Naprosyn 500 mg po BID
2. Full dose LMWH bridging to warfarin, target INR=2-3 x 3 months
3. Enoxaparin 40 mg qday x 4 weeks
4. UFH 5000 units SQ q12h
ACCP Guidelines 2008
Superficial Thrombophlebitis

- Prophylactic (Grade 2B)
  - LMWH
  - Or
  - Intermediate (Grade 2B)
    - LMWH
    - UFH
    - Traditional bridging with LMWH/UFH w/ warfarin, INR=2-3 (Grade 2C)

For 4 weeks!

Superficial Thrombophlebitis

- In cases where the thrombus is located at less than 2 cm from the saphenofemoral junction, then
  - warfarin (target INR 2.4; range 2.0 to 3.0) overlapped with 4 days of treatment dose (weight-adjusted) LMWH or UFH
  - for at least 3 months.
  - Treatment duration more than 3 months may be appropriate in certain cases, especially in patients with a history of VTE
Should patients with upper extremity DVT due to PICC line, be treated with anticoagulation therapy if PICC removed?

1. YES
2. NO

ACCP Guidelines 2008

Upper Extremity (UE) Thrombosis

- Account for approx 5% of VTE events
- Primary: (spontaneously – Paget-Schroetter syndrome)
  - As for leg DVT (Grade 1C)
  - Treatment at least 3 months, long-term if bleeding risk low
- Secondary: catheter related
  - As per leg DVT, and as a provoked event
  - Do not remove functional catheter, if needed
    - If catheter kept in – treat while catheter indwelling and for up to at least 3 months (Grade 2C)
    - If catheter removed, treat at least 3 months (Grade 2C)
TR is a 47 yo male patient admitted to hospital for Dx of DVT/PE. MD desires to use fondaparinux. Patients weight is 199 kg, Est Cl=66 ml/min. Provide the appropriate recommendation.

1. Fondaparinux 10 mg sq qday
2. Fondaparinux should not be used due to obesity
3. Use UFH, as dose can be monitored more closely
4. Use Fragmin 200 IU/kg sq qday represents an alternative in obese patients
Effect of obesity on outcomes after fondaparinux, enoxaparin, or heparin treatment for acute venous thromboembolism in the Matisse trials

Does your institution recommend a dose or weight “cap” on LMWH’s?

1. Yes
2. No
Obesity and LMWH Dosing for Treatment

- Use ABW to dose all LMWH products, regardless of body size.

However..................

Is there a “Maximum Dose” for Treatment?

- Enoxaparin (Lovenox™)
  - ACS Trials have data up to 154 kg & VTE treatment trials up to 159 kg
  - Package insert does not suggest a max dose or “dose capping”, and clinical data suggests the same

“Clinical” recommendation:
1. there is data to support dosing up to 159 kg
2. thereafter, it has been suggested to obtain anti-Xa levels (peak – yes trough=not clear) to assess effect and toxicity
   - Peak target: 0.5 – 1 U/ml (drawn 4 hrs post SQ dose)
   - Trough target: 0.2-0.3 U/ml (if done at all)

Annals of Pharmacotherapy, June 2009;43:1064-1083)
Max Dosing cont....

- Dalteparin (Fragmin™)
  - Package insert caps dose at 90 kg........therefore:

  - **Dose for treating ACS** is 120 IU/Kg SQ q12h
    - Not to exceed 20,000 units per day (10,000 units SQ q12h)

  - **Dose for treatment of DVT** (cancer patients) 200 IU/kg SQ qday
    - Not to exceed 18,000 units/day (or if given SQ 12 – not to exceed 9,000 units SQ q12)

---

### Dalteparin
Pharmacokinetics In Obesity

<table>
<thead>
<tr>
<th>Dose: 200 U/kg qd Duration: 5 Days</th>
<th>&lt;20% of IBW</th>
<th>20-40% of IBW</th>
<th>&gt; 40% of IBW</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>13</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Mean Dose (U)</td>
<td>14.030</td>
<td>17.646</td>
<td>23.565</td>
</tr>
<tr>
<td>Ant-Xa Activity (u/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3 Peak</td>
<td>1.01</td>
<td>0.97</td>
<td>1.12 NS</td>
</tr>
<tr>
<td>Day 3 Trough</td>
<td>0.12</td>
<td>0.11</td>
<td>0.11 NS</td>
</tr>
</tbody>
</table>

Conclusion: Body mass does not appear to have an important effect on the response to LMWH up to a weight of 190kg in patients with normal renal function.

Max Dosing Dalteparin cont...

Clinical recommendation:
1. Package insert “caps dose” – most institutions will not violate this

- However study by Wilson et al in Haemostasis 2001 suggests safety with full dosing in patients up to 190 kg for DVT indication w/ Nl renal function as dose Al-Yaseen et al study data.

- If dosing > than package insert recommends, the following is suggested:
  1. obtaining anti-Xa levels to assess effect and toxicity

- Peak target: 1-2 U/ml (remember as dalteparin is dosed Qday for treatment of DVT)
- Trough: 0.2-0.3 U/ml

Annals of Pharmacotherapy, June 2009;43:1064-1083

Obesity and LMWH’s

| Obesity                  | Anti-Xa monitoring and treatment dose adjustments are generally not necessary for pts. weighing ≤190 kg. Anti-Xa monitoring can be considered in pts. with morbid obesity (BMI >40 kg/m²). |

Annals of Pharmacotherapy, June 2009;43:1064-1083
What about “Dose Rounding”?

- **Enoxaparin (Lovenox™)**
  - Available as prefilled syringes:
    - 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, 120 mg, 150 mg
    - Can round does a bit to minimize errors in dosing, try to limit round to 5 mg to 10 mg
  - Also available as multidose vial (MDV) – 300 mg/3 ml

- **Dalteparin (Fragmin™)**
  - Available as prefilled syringes:
    - 2,500 units, 5,000 units, 7,500 units, 10,000 units, 12,500 units, 15,000 units, 18,000 units
    - Can round does a bit to minimize errors in dosing.
    - Refer to institution specific recommendations
  - Also available as multidose vial (MDV) – 95,000 units/3.8 ml and 95,000 units/9.5 ml
Postthrombotic Syndrome

Symptoms
- chronic leg swelling
- (or waxing) pain
- diffuse aching
- leg heaviness
- leg tiredness
- hardening of the skin
- skin dryness
- skin ulcer (stasis ulcer)
- leg cramping
- dark skin
- pigmentation (= post-thrombotic pigmentation; figure)
- formation of varicose veins
Incidence of Syndrome

• Lower extremity DVT
  • 60% of patients post DVT will NOT have residual symptoms
  • 40% can have varying degrees
  • Occurs typically in first 6 months, up to 2 years post event

• Upper extremity DVT
  • Occurs in approx 15% of cases
  • Catheter associated clots seem less likely to develop this complication

Risk Factors and Prevention for PPS

- Risk factors: not fully identified
  • DVT size - ? (ie proximal DVT)
  • DVT location – ?
  • Recurrent events, even in ipsilateral leg
  • Obesity
  • Deficient therapy first 3 months of therapy

- Prevention
  • Preventative maintenance ......
  • Prandoni et al (Ann Int Med 2004;141:249-256)
    • RCT (not double blind)
    • N=180
    • Elastic stockings (30-40 mmHg at ankle) BK vs control x2 years, final FU up to 5 years
PTS Prevention

49.1% vs 24.5%
HR=0.49 (P=0.011)

Compression stockings

- Grade 2 stocking
  - 35 mm Hg at ankle
  - 25 mm Hg at mid-calf
  - 18 mm Hg below knee

- Jobst stocking 30-40 mm Hg

- At least 2 yrs- longer if patient has symptoms

- Begin as soon as possible after diagnosis
UEDVT - PTS

- Prevention – (Grade 2C)
  - do not use elastic compression of venoactive medications

- Treatment (Grade 2C)
  - Elastic bandages or elastic compression sleeves

Prevention Roadmap

- Strategies
  - Medications
    - LMWH vs UFH
    - Q12 vs q8
      - Cancer and obesity prophylaxis
      - Extended duration
  - IPC/stockings
  - IVC filters

- Arterial - Venous disease
  - Ageno et al article – Circulation 2008; 117:93-102
  - Jupiter trial
Meta-analysis VTE Prophylaxis
UFH/LMWH/Fonda vs placebo


Approx 20,000 patients found pharmacologic prophylaxis decreased risk of symptomatic DVT/PE by 58%/53% and fatal PE by 64%
No increased bleeding

NNT= 345 to prevent 1 symptomatic PE
Medications - Medical Prophylaxis

conclusions

• LMWH vs UFH
  - LMWH=TID UFH
  - LMWH > UFH BID
• UFH - Q8 vs q12h?
  - ACCP 2008 –
    - “there is no compelling evidence that UFH should be administered TID over BID, although these two regimens have never been directly compared”
  - However, multiple meta-analysis indicate there is a difference but at the cost of higher bleeding.
  - Assessing patients at risk (ie moderate vs high) and balancing risk-benefit ratio is vital. For many cases the NNT > NNH.
Situations where q8h should be used

CANCER

**Table 2. VTE Prophylaxis Regimens for Patients With Cancer**

<table>
<thead>
<tr>
<th>Heparin Type</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin*</td>
<td>5000 units SC every 8 hours</td>
</tr>
<tr>
<td>LMWH*</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin 40 mg SC daily</td>
<td></td>
</tr>
<tr>
<td>Dalteparin 5000 units SC daily</td>
<td></td>
</tr>
<tr>
<td>Tinzaparin™ 4500 units (fixed dose) SC daily</td>
<td></td>
</tr>
<tr>
<td>Fondaparinux™ 2.5 mg SC daily</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SC, subcutaneous; CrCl, creatinine clearance; FDA, Food and Drug Administration; LMWH, low-molecular-weight heparin

* Monitor hemoglobin, hematocrit, and platelets as appropriate.
* Refer to package insert and guidelines for dosing recommendations based on age, weight, and renal function and monitoring recommendations.
* Use with caution in patients with renal dysfunction.
* Not FDA-approved for this indication.
* Avoid in patients >70 years with renal insufficiency.
* Contraindicated in patients with CrCl <30 mL/min. Use with caution in those with CrCl 30-50 mL/min, weight <50 kg, or age >75 years.

http://jpp.sagepub.com/content/23/4/294.full.pdf+html

Obesity

Complications of Prophylaxis

- **Bleeding**
  - Major bleeding rates
    - no different from placebo in major trials
    - enoxaparin, dalteparin, UFH and fondaparinux
    - Rates 0.2-1.7%

- **HIT/HITTs**
  - Potentially catastrophic- thrombosis rates as high as 60%.
  - Increased risk over LMWH/fondaparinux
    - Estimated to occur in 1.4% of medically ill pts exposed to preventive doses of UFH.
    - LMWH 8-10X’s less likely to cause HIT
    - No clinical cases of HITTS for fondaparinux
    - Has been used anecdotally in patients with HIT/HITTS

Intermittent pneumatic compression (IPC)/Sequential compression device (SCD)

• How long to wear for efficacy?
  20 hrs per day
• Effective only for:
  ▫ Pts with contraindications
  ▫ In combo
  ▫ No longer an option for moderate risk patients
• What about graduated compression stockings (CGS)
  "Annals of Surgery • Volume 251, Number 3, March 2010"

ACCP 2008 IVC recommendations

1.13.1. For patients with DVT, we recommend against the routine use of a vena cava filter in addition to anticoagulants (Grade 1A).
1.13.2. For patients with acute proximal DVT, if anticoagulant therapy is not possible because of the risk of bleeding, we recommend placement of an inferior vena cava (IVC) filter (Grade 1C).
1.13.3. For patients with acute DVT who have an IVC filter inserted as an alternative to anticoagulation, we recommend that they should subsequently receive a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 1C).
IVC filters
The only widely accepted and validated indications for IVC filter placement are:

- Absolute contraindication to therapeutic anticoagulation

- Failure of anticoagulation when there is acute proximal venous thrombosis.

Controversial uses

- A compromised pulmonary vascular bed due to an embolic event, such that another embolic event would be poorly tolerated.
  - Examples include acute hemodynamically massive pulmonary embolism and chronic thromboembolic pulmonary hypertension
- Proximal venous thrombosis in a patient with poor cardiopulmonary reserve
- Venous thromboembolism in a patient who has a high risk of bleeding
- Prophylactically in patients at high risk of PE events
Efficacy – PREPIC study

- N=400 patients w/ proximal DVT’s
- The patients were followed up at:
  - day 12
    - there were fewer PEs in the group that received filters (OR 0.22, 95% CI, 0.05-0.90).
  - two years,
    - there was no significant difference in PE development in the filter group compared with the no-filter group (OR 0.50, 95% CI, 0.19-1.33).
    - Additionally, at year two, the filter group was more likely to develop recurrent DVT (OR 1.87, 95% CI, 1.10-3.20).
  - annually up to eight years following randomization
    - there was a significant reduction in the number of PEs in the filter group versus the no-filter group (6.2% vs. 15.1%, \( P=0.008 \)).
    - However, at eight-year followup, IVC filter use was associated with increased DVT (35.7% vs. 27.5%, \( P=0.042 \)).
    - There was no difference in mortality between the two groups.

Conclusion to PREPIC

- the use of IVC filters was associated with decreased incidence of PE at eight years, offset by higher rates of recurrent DVT and no overall mortality benefit.
- Importantly, the indications for IVC filter use in this study differ from the current ACCP guidelines; all patients were given concomitant anticoagulation for at least three months, which might not be possible in patients for whom the ACCP recommends IVC filters.
Complications of IVC Filters

- The incidence of complications related to IVC filter placement is 4% to 11%.
- Complications include:
  - Insertion-site thrombosis;
  - IVC thrombosis;
  - Recurrent DVT postphlebitic syndrome;
  - Filter migration;
  - Erosion of the filter through the vessel wall; and
  - Vena caval obstruction
- Although no head-to-head comparisons, complications seem less with retrievable filters

IVC filters Plus anticoagulation

- There are no randomized controlled trials to guide the use of concomitant anticoagulation after filter insertion,
- A meta-analysis of 14 studies evaluating the rates of VTE after IVC filter placement demonstrated a non-statistically significant trend toward fewer VTE events in the patients with an IVC filter and concomitant anticoagulation in comparison with those who solely had an IVC filter (OR 0.64, 95% CI, 0.35-1.2).
- The duration and degree of anticoagulation was not presented in all of the studies in the meta-analysis, therefore limiting the analysis
Relationship between arterials and venous thrombosis

- Prandoni et al showed an relationship between asymptomatic atherosclerotic lesions and spontaneous VTE of the legs.
  - Prandoni et al, NEJM 2003

- Cardiovascular risk factors are associated with an increased risk of VTE
  - Ageno et al NEJM 2009 – JUPITER Trial

Venous “verses” Arterial Thrombosis

<table>
<thead>
<tr>
<th>Arterial Disease</th>
<th>VTE no./total</th>
<th>No VTE no./total</th>
<th>OR (95%CI)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid plaque</td>
<td>72/183</td>
<td>48/150</td>
<td>2.3 (1.4-3.7)</td>
<td>62</td>
</tr>
<tr>
<td>Coronary artery calcification</td>
<td>46/69</td>
<td>25/69</td>
<td>4.3 (1.9-10.1)</td>
<td>63</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0.32/90000</td>
<td>0.20/12,040</td>
<td>1.1 (0.61-1.94)</td>
<td>64</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>96/118,037</td>
<td>362/166,657</td>
<td>1.18 (1.1-1.27)**</td>
<td>65</td>
</tr>
<tr>
<td>Stroke</td>
<td>1118/16,067</td>
<td>360/166,657</td>
<td>1.29 (1.21-1.38)**</td>
<td>65</td>
</tr>
<tr>
<td>Not Specified</td>
<td>16/151</td>
<td>0/151</td>
<td>2.86 (1.07-7.82)**</td>
<td>66</td>
</tr>
</tbody>
</table>

*rate/100 patient-years
**hazard ratio

Hematology 2009
## Occurrence of venous thromboembolism

<table>
<thead>
<tr>
<th>End point</th>
<th>Rosuvastatin (n=8901)</th>
<th>Placebo (n=8901)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with event, n</td>
<td>Events/100 person-years, n</td>
<td>Patients with event, n</td>
</tr>
<tr>
<td>Total VTE</td>
<td>34</td>
<td>0.18</td>
<td>60</td>
</tr>
<tr>
<td><em>Unprovoked</em></td>
<td>19</td>
<td>0.10</td>
<td>31</td>
</tr>
<tr>
<td><em>Provoked</em></td>
<td>15</td>
<td>0.08</td>
<td>29</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>17</td>
<td>0.09</td>
<td>22</td>
</tr>
<tr>
<td>DVT only</td>
<td>17</td>
<td>0.09</td>
<td>38</td>
</tr>
</tbody>
</table>

*Unprovoked VTE is defined as VTE occurring in the absence of a known malignancy condition, trauma, hospitalization, or surgery, whereas a provoked VTE occurs in patients with cancer, during or shortly after trauma, hospitalization, or surgery.*


## Occurrence of venous thromboembolism and cardiovascular events

<table>
<thead>
<tr>
<th>End point</th>
<th>Rosuvastatin (n=8901)</th>
<th>Placebo (n=8901)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with event, n</td>
<td>Events/100 person-years, n</td>
<td>Patients with event, n</td>
</tr>
<tr>
<td>VTE with no prior cardiovascular event</td>
<td>32</td>
<td>0.17</td>
<td>56</td>
</tr>
<tr>
<td>Cardiovascular event with no prior VTE</td>
<td>141</td>
<td>0.76</td>
<td>249</td>
</tr>
<tr>
<td>VTE after cardiovascular event</td>
<td>2</td>
<td>0.61</td>
<td>4</td>
</tr>
<tr>
<td>First cardiovascular event or VTE</td>
<td>173</td>
<td>0.93</td>
<td>305</td>
</tr>
</tbody>
</table>

JUPITER
Total Venous Thromboembolism

Glynn et al NEJM 2009

HR 0.57, 95% CI 0.37-0.86
P= 0.007

- 43%

Placebo 60 / 8901
Rosuvastatin 34 / 8901

JUPITER
Venous Thromboembolism – Unprovoked vs Provoked

Unprovoked Venous Thromboembolism
HR 0.61, 95% CI 0.35-1.09
P= 0.09

Provoked Venous Thromboembolism
HR 0.52, 95% CI 0.28-0.96
P= 0.03

Clear clinical benefit in the absence of any bleeding hazard
(hemorrhagic events: rosuvastatin 258, placebo 275, P=0.45)
VTE in JUPITER: Conclusions

VTE is a serious event that occurred about as often as MI and stroke in the JUPITER study.

Rosuvastatin was associated with a significant 43 percent reduction in risk of VTE with no increase in bleeding.

This benefit was comparable in magnitude and independent of the effect on arterial events.

Widening the treatment target to include prevention of VTE and death in addition to arterial thrombosis increases the estimated benefit of statin use.

THANK YOU!