COLUMBIA UNIVERSITY MEDICAL CENTER

DIVISION OF GENERAL MEDICINE

Senior Medicine Rotation: Evidence-Based Medicine Project

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Case: 52 yo man with no significant past medical history presents with right calf swelling and 10/10 left sided pleuritic chest pain developing over several days prior to admission. CT angio revealed bilateral PE. He denies recent surgery, lengthy travel, personal or family history of cancer or clotting disorders. Plan was to initiate heparin and warfarin, maintain therapeutic PTT until warfarin was therapeutic for 48 hours (INR >2), and then discontinue heparin.

Clinical Question: What options other than warfarin and LMWH are available for long-term treatment of VTE?

ACCP Guidelines for Antithrombotic and Thrombolytic Therapy (2008)

Acute treatment of VTE:

1) Use LMWH, UFH, or fondaparinux for at least 5 d (1C) with INR>2 for 24 hrs (1A)
2) If DVT without PE, use LMWH (1C)
3) If nonmassive PE, use LMWH (1A)
4) If massive PE, concern about subcutaneous admin, or possible thrombolysis, use IV UFH (2C)
5) If renal failure, use UFH over LMWH (2C)

Treatment duration:

1) VTE with reversible risk factor*→ vitamin K antagonist (VKA) for 3 m (1A)
2) Unprovoked VTE→ VKA for at least 3 m (1A), then reconsider (1C):
    a. Proximal DVT or PE w/o bleeding RFs and can be monitored→ VKA long-term (1A)
3) Recurrent VTE→ VKA long-term (1A)
4) VTE with cancer → LMWH for 3-6 m (1A) then VKA/LMWH (1C)
5) For all, INR goal = 2-3 (1A)

***** Major RFs inc surgery, hospitalization, immobilizing cast w/in past month; minor RF inc estrogen therapy, pregnancy, prolonged travel (> 8 h), or major RF w/in past 1 to 3 months

LMWH:

Meta-analysis of 1,379 patients with VTE showed non-significant reduction in risk of VTE and major bleeding with 3 m of LMWH vs. VKA. No difference in total mortality.

Limitations of warfarin/LMWH:

Warfarin: monitoring at least every 4 weeks (2C), need to manage therapy in a systematic and coordinated fashion (1B), interactions with food/drugs

LMWH: no routine monitoring (1C), but not recommended in severe renal insufficiency or failure (2C), may have issues with insurance coverage and SC administration.

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Pubmed search criteria: venous thromboembolism, treatment, warfarin
Limits: randomized controlled trial, published in last 2 years, English language
Results: 8

Schulman et al (RE-COVER Study Group). Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *NEJM*. 2009; 361 (24): 2342-52.

Dabigatran etexilate = orally available direct thrombin inhibitor

- Converted to active drug by ubiquitous esterases
- Excreted by the kidney, $t_{1/2}$ = 12 to 17 hours
- Similar efficacy/safety as enoxaparin for prevention of VTE after hip/knee arthoplasty

RE-COVER study: double-blind RCT by Boehringer Ingelheim at 228 sites in 29 countries

Group	Criteria or definition	n
Population screened	18+	N/A
Inclusion criteria	Proximal DVT or PE for which 6 m anticoag deemed appropriate	2564
Exclusion criteria	Symptoms > 14 d, PE with hemodynamic instability, PE requiring thrombolysis, another indication for warfarin, recent unstable CV disease, high risk of bleeding, liver disease with AST/ALT > twice normal, CrCl<30 mL/min, life expectancy <6 m, contraindication to heparin or radiographic contrast, pregnancy, long term antiplatelet > 100 mg ASA	N/A
Treatment group	6 m dabigatran (150 mg BID)	1273
Control group	6 m warfarin (dosed to INR 2-3)	1266

Statistical analysis: Noninferiority trial

- Primary endpoint = symptomatic VTE or death associated with VTE
- Secondary endpoints = safety (bleeding, adverse events, etc)
- Hazard ratio (Cox model) and risk difference (Kaplan-Meier)
- Noninferiority by 95% confidence interval, if noninferior test for superiority
- Sample size calculation = 2250
- Modified intention to treat (patients who did not receive any study drug excluded)

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Results (dabigatran, warfarin)

- N 1273, 1266 | Age 55.0, 54.4 | Female 42.0%, 41.1%
  White 95.2%, 94.4% | BMI 28.9, 28.4 | Est CrCl 105.8, 104.4
  DVT 69.1%, 68.6% | PE 21.2%, 21.4% | DVT&PE 9.5%, 9.8%
  Neither 0.2%, 0.2% | Cancer 5.0%, 4.5% | Parenteral days 10, 10
  UFH 11.3%, 13.0% | LMWH 89.4%, 90.7% | Fondaparinux 3.9%, 2.8%
  Study days 163.4, 163.9 | Adherence 98.0%, 97.5% | Drug stopped 16.0%, 14.5%
  Observ stopped 7.9%, 7.7% | RE-MEDY 506, 541

- Warfarin INR: therapeutic 59.9%, sub 21%, supra 19%

- Recurrent VTE or death from VTE: 2.4% vs. 2.1%
  Risk diff 0.4% (95% CI -0.8 to 1.5); hazard ratio 1.10 (95% CI 0.65 to 1.84)
  Noninferiority achieved, superiority was not

- Major bleed: 1.6% vs. 1.9% (hazard ratio 0.82; 95% CI 0.45 to 1.48)
  Dabigatran sites: GI (9), GU (5), intraarticular (1), IM (1), other (6)
  Warfarin sites: GU (6), GI (5), intraarticular (4), intracranial (3), IM (3), other (4)

- Major or clinically relevant nonmajor bleed: 5.6% vs. 8.8%
  Hazard ratio 0.63, ***95% CI 0.47 to 0.84***

- Other AEs
  AE → discontinue: 9.0%, 6.8% (hazard ratio 1.33, 95% CI 1.01 to 1.76, p=0.05)
  Death, ACS, elevated AST/ALT did not differ between the groups
  Only significant difference in freq of AE was dyspepsia: 2.9% vs. 0.6% (P<0.001)

For treatment of acute VTE, fixed dose dabigatran is as effective as warfarin, has a similar safety profile, and does not require lab monitoring

Limitations in general

- Inherent to study (noninferiority, power, applicability, acute role, conflict of interest)
- Some evidence that patients on dabigatran would benefit from monitoring
- Anticipated cost of dabigatran is 4 to 5 times cost of warfarin despite cost of monitoring

Applicability to our patient

- Patient meets all inclusion and none of the exclusion criteria
- Close to mean age, however he is Hispanic (95% study population white, no Hispanic category)
- Medication is not approved in the US!
- If this medication were available in the US, it *might* be a good option for our patient

References

1. Hirsh et al. Executive Summary: ACCP Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008; 133: 71S-109S.

2. Hirsh et al. Antithrombotic and Thrombolytic Therapy: ACCP Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008; 133: 110S-112S.

3. Weitz, Hirsh, and Samama. New Antithrombotic Drugs: ACCP Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008; 133: 234S-256S.

4. Kearon et al. Antithrombotic Therapy for Venous Thromboembolic Disease: ACCP Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008; 133: 454S-545S.

5. Iorio, Guercini, Pini. LMWH for the long-term treatment of symptomatic venous thromboembolism: meta-analysis of the randomized comparisons with oral anticoagulants. *J Thromb Haemost.* 2003*;* 1:1906-1913.

6. Schulman et al (RE-COVER Study Group). Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *NEJM*. 2009; 361 (24): 2342-52.

7. Correspondence re: Dabigatran versus Warfarin for Venous Thromboembolism. *NEJM*. 2010; 362:1050-1051