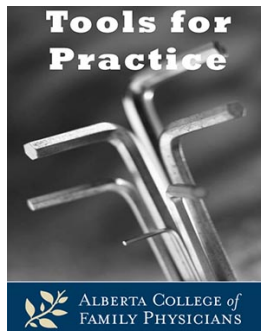


Tools for Practice is proudly sponsored by the Alberta College of Family Physicians (ACFP). ACFP is a provincial, professional voluntary organization, representing more than 3,900 family physicians, family medicine residents and medical students in Alberta. Established over fifty years ago, the ACFP strives for excellence in family practice through advocacy, continuing medical education and primary care research. www.acfp.ca

April 14, 2014



A pill for the second clot I do not want

Clinical Question: Are novel anti-coagulants as effective as warfarin in treating acute venous thromboembolism (VTE)?

Bottom-line: Studies show novel anti-coagulants are non-inferior to warfarin in the treatment of VTE and generally have less major bleeding. Regulatory approval, patient values, and drug costs should help in deciding which therapy to use.

Evidence:

- Five large, industry-funded, non-inferiority randomized clinical trials compared available novel oral anticoagulants to warfarin. Patients' mean age 55-58 years, ~60% men, ~20% with previous VTE, significant renal impairment excluded.
 - Rivaroxaban: 15mg bid x three weeks, then 20mg qd for three, six, or 12 months for 3,449 deep vein thrombosis (DVT)¹ and 4,832 pulmonary embolism (PE)² patients had:
 - Similar rates of: recurrent VTE (2-3%), major or clinically significant bleeding (8-11%), and death (2-3%).
 - Dabigatran: 150mg bid for six months in 5,107 DVT or PE patients^{3,4} had:
 - Similar rates of recurrent VTE: ~2-2.5%.
 - Statistically significantly less major or clinically relevant bleeding: 5.3% vs. 8.5%, Number Needed to Treat (NNT) 32.
 - More acute coronary syndromes (9 vs. 5) but statistics not reported.
 - Apixaban: 10mg bid x seven days, then 5mg bid x six months in 5,395 DVT or PE patients⁵ had:
 - Similar rates of recurrent VTE or VTE-related death: 2.2% vs. 2.6%.
 - Statistically significantly less major or clinically significant bleeding: 4.3% vs. 9.7%, NNT 19.
- Most patients receiving rivaroxaban or apixaban had initial LMWH treatment for <2 days,^{1,2,5} while dabigatran-treated patients had LMWH for a median of nine days.^{3,4}
- Statistical issues:
 - Non-inferiority margins set higher than clinically important differences:
 - Rivaroxaban considered non-inferior to warfarin if had ≤twice the number of recurrent VTEs. Dabigatran margins set higher, apixaban lower.

Context:

- Warfarin time in therapeutic range ~60%, lower earlier in studies.¹⁻⁵
- Compared to placebo, extending novel oral anticoagulant therapy decreases VTE recurrence which is partially offset by increased bleeding.^{1,6,7}
 - Extending treatment with aspirin also decreases VTE recurrence.⁸
- LMWH is recommended for treating VTEs in cancer patients.⁹
- Only rivaroxaban is currently approved in Canada for VTE treatment.¹⁰
 - Drug costs, six months (Alberta): rivaroxaban ~\$625, warfarin ~\$40.¹¹

Authors:

Michael R Kolber BSc MD CCFP MSc, Tammy Bungard BSP PharmD

Disclosure:

Michael R Kolber, no conflicts to disclose. Tammy Bungard, speaker with honoraria (Bayer, Boehringer Ingelheim) in the past two calendar years.

References:

1. EINSTEIN Investigators. *N Engl J Med.* 2010; 363:2499-510.
2. EINSTEIN-PE Investigators. *N Engl J Med.* 2012; 366:1287-97.
3. Schulman S, Kearon C, Kakkar AK, *et al.* *N Engl J Med.* 2009; 361:2342-52.
4. Schulman S, Kakkar AK, Goldhaber SZ, *et al.* *Circulation.* 2014; 129(7):764-72.
5. Agnelli G, Buller HR, Cohen A, *et al.* *N Engl J Med.* 2013; 369:799-808.
6. Schulman S, Kearon C, Kakkar AK, *et al.* *N Engl J Med.* 2013; 368:709-18.
7. Agnelli G, Buller HR, Cohen A, *et al.* *N Engl J Med.* 2013; 368:699-708.
8. Ference J, Allan GM. Tools for Practice, Alberta College of Family Physicians 2013 July 22. http://www.acfp.ca/Portals/0/docs/TFP/20130722_060542.pdf. Accessed April 7, 2014.
9. Lyman GH, Khorana AA, Kuderer NM, *et al.* *J Clin Oncol.* 2013; 31:2189-2204.
10. Drugs and Health Products. Health Canada. Available at <http://webprod5.hc-sc.gc.ca/noc-ac/info.do?no=14313&lang=eng>. Accessed April 7, 2014.
11. Kolber MR, Lee J, Nickonchuk T. Price Comparison of Commonly Prescribed Pharmaceuticals 2014. Available at <http://acfp.ca/Portals/0/docs/ACFPricingDoc2014.pdf>. Accessed April 7, 2014.

Tools for Practice is a biweekly article summarizing medical evidence with a focus on topical issues and practice modifying information. It is coordinated by G. Michael Allan, MD, CCFP and the content is written by practising family physicians who are joined occasionally by a health professional from another medical specialty or health discipline. Each article is peer-reviewed, ensuring it maintains a high standard of quality, accuracy, and academic integrity. If you are not a member of the ACFP and would like to receive the TFP emails, please sign up for the distribution list at <http://bit.ly/signupfortfp>. Archived articles are available on the ACFP website.

This communication reflects the opinion of the authors and does not necessarily mirror the perspective and policy of the Alberta College of Family Physicians.