A safer way to prevent VTE recurrence. *J Fam Pract*. 2012;61:673-674.

Potential PURL Review Form: Randomized controlled trials

SECTION 1: IDENTIFYING INFORMATION

1. Citation	Becattini C, Agnelli G, Schenone A, et al; for the WARFASA Investigators. Aspirin for preventing the recurrence of venous thromboembolism. *N Engl J Med*. 2012;366:1959-1967
2. Hypertext link to PDF of full article	http://www.ncbi.nlm.nih.gov/pubmed/22621626
3. First date published study available to readers	May 24, 2012
4. PubMed ID	22621626
5. Nominated By	Jim Stevermer
6. Institutional Affiliation of Nominator	University of Missouri
7. Date Nominated	May 24, 2012
8. Identified Through	InfoPOEMs
9. PURLS Editor Reviewing Nominated Potential PURL	Kate Rowland
10. Nomination Decision Date	May 31, 2012
11. Potential PURL Review Form (PPRF) Type	Randomized controlled trials
12. Other comments, materials or discussion	
13. Assigned Potential PURL Reviewer	Sonia Oyola
14. Reviewer Affiliation	University of Chicago
15. Date Review Due	July 5, 2012
16. Abstract	**BACKGROUND:** About 20% of patients with unprovoked venous thromboembolism have a recurrence within 2 years after the withdrawal of oral anticoagulant therapy. Extending anticoagulation prevents recurrences but is associated with increased bleeding. The benefit of

aspirin for the prevention of recurrent venous thromboembolism is unknown.

METHODS: In this multicenter, investigator-initiated, double-blind study, patients with first-ever unprovoked venous thromboembolism who had completed 6 to 18 months of oral anticoagulant treatment were randomly assigned to aspirin, 100 mg daily, or placebo for 2 years, with the option of extending the study treatment. The primary efficacy outcome was recurrence of venous thromboembolism, and major bleeding was the primary safety outcome.

RESULTS: Venous thromboembolism recurred in 28 of the 205 patients who received aspirin and in 43 of the 197 patients who received placebo (6.6% vs. 11.2% per year; hazard ratio, 0.58; 95% confidence interval [CI], 0.36 to 0.93) (median study period, 24.6 months). During a median treatment period of 23.9 months, 23 patients taking aspirin and 39 taking placebo had a recurrence (5.9% vs. 11.0% per year; hazard ratio, 0.55; 95% CI, 0.33 to 0.92). One patient in each treatment group had a major bleeding episode. Adverse events were similar in the two groups.

CONCLUSIONS: Aspirin reduced the risk of recurrence when given to patients with unprovoked venous thromboembolism who had discontinued anticoagulant treatment, with no apparent increase in the risk of major bleeding.

(Funded by the University of Perugia and others; WARFASA ClinicalTrials.gov number, NCT00222677.).

SECTION 2: CRITICAL APPRAISAL OF VALIDITY

1. Number of patients starting each arm of the study?	205 received aspirin and 197 received placebo.
2. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?	Mean age was 61±15 years; >60% were male; >98.9% were white; >54% had VKA treatment for 12 months before being randomized.
3. Intervention(s) being investigated?	Aspirin for prevention of recurrent VTE
4. Comparison treatment(s), placebo, or nothing?	Placebo
5. Length of follow-up? Note specified end points, e.g., death, cure, etc.	2 years
6. What outcome measures are used? List all that assess effectiveness.	The primary efficacy outcome was recurrence of venous thromboembolism; the primary safety outcome was major bleeding.
7. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CI, p-values, etc.	Venous thromboembolism recurred in 28 of the 205 patients who received aspirin and in 43 of the 197 patients who received placebo (6.6% vs. 11.2% per year; hazard ratio, 0.58; 95% confidence interval [CI], 0.36 to 0.93) (median study period, 24.6 months). During a median treatment period of 23.9 months, 23 patients taking aspirin and 39 taking placebo had a recurrence (5.9% vs. 11.0% per year; hazard ratio, 0.55; 95% CI, 0.33 to 0.92).

8. What are the adverse effects of intervention compared with no intervention?	One patient in each treatment group had a major bleeding episode. Adverse events were similar in the 2 groups.
9. Study addresses an appropriate and clearly focused question - ***select one***	Well covered
10. Random allocation to comparison groups	Poorly addressed Comments: This is the only statement addressing randomization: "Eligible patients were randomly assigned to aspirin, 100 mg once daily, or placebo for 2 years, with the option of extending the study treatment."
11. Concealed allocation to comparison groups	Poorly addressed Comments: as above
12. Subjects and investigators kept “blind” to comparison group allocation	Adequately addressed Comments: "All suspected study outcome events were assessed by a central, independent adjudication committee whose members were unaware of the group assignments and who reviewed the imaging results.” No statement was made about whether the study participants were blinded.
13. Comparison groups are similar at the start of the trial	Well covered
14. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential source of bias.	Well covered
15. Were all relevant outcomes measured in a standardized, valid, and reliable way?	Well covered
16. Are patient-oriented outcomes included? If yes, what are they?	Yes: VTE and major bleeding.
17. What percent dropped out, and were lost to follow up? Could this bias the results? How?	17% dropped out of the aspirin arm and 15% dropped out of the placebo arm. If most of those who dropped out of the aspirin arm were very ill, it can bias the result toward aspirin therapy.
18. Was there an intention-to-treat analysis? If not, could this bias the results? How?	Yes.

19. If a multi-site study, are results comparable for all sites?	This was not addressed.
20. Is the funding for the trial a potential source of bias? If yes, what measures were taken to insure scientific integrity?	Yes. Bayer provided a grant and both the placebo and aspirin tablets, but was not involved with the study design, collection of data, or writing of final manuscript.
21. To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized.	Male caucasian patients ≥60 years of age, but I would generalize this to patients 45 to 65 years of age, sex, or race.
22. In what care settings might the findings apply, or not apply?	Outpatient primary care office settings.
23. To which clinicians or policy makers might the findings be relevant?	Any primary care physician caring for adult patients; inpatient doctors caring for someone being admitted into the hospital with a history of VTE, PE, or both.

SECTION 3: REVIEW OF SECONDARY LITERATURE

1. DynaMed excerpts

2. DynaMed citation/access date	Becattini C. Aspirin for preventing the recurrence of venous thromboembolism. Author. In: DynaMed [database online]. Available at: www.DynamicMedical.com Last updated June 25, 2012. Accessed July 2, 2012.
3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)	Aspirin may decrease VTE recurrence.

4. UpToDate excerpts

5. UpToDate citation/access date	Lip G. Treatment of lower extremity deep vein thrombosis. In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2012. Available at: http://www.uptodate.com. Last updated June 13, 2012. Accessed July 2, 2012.
6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)	Long-term anticoagulation is recommended for those at risk for recurrent VTE. What anticoagulation and the treatment length are still unclear.
7. PEPID PCP excerpts www.pepidonline.com username: fpinauthor pw: pepidpcp	Medications 1. Low-dose unfractionated heparin: 5000 U SC q 12h or 2. Enoxaparin: 40 mg (4000 U) SC qd 3. Warfarin • Effective for secondary prevention of VTEs for patients positive for antiphospholipid antibodies

8. PEPID citation/access data	Lyons M. Heart and vascular. In: PEPID [database online]. Available at: http://www.pepidonline.com.
9. PEPID content updating	1. Do you recommend that PEPID get updated on this topic? Yes, there is important evidence or recommendations that are missing If yes, which PEPID Topic, Title(s): Aspirin for Recurrent VTE?
10. Other excerpts (USPSTF; other guidelines; etc.)	
11. Citations for other excerpts	
12. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)	
SECTION 4: CONCLUSIONS	
1. Validity: How well does the study minimize sources of internal bias and maximize internal validity? Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly)	2
2. If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?	
3. Relevance: Are the results of this study generalizable to and relevant to the health care needs of patients cared for by "full scope" family physicians? Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly)	1
4. If 4.3 was coded as 4, 5, 6, or 7, please provide an explanation.	
5. Practice-changing potential: If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice? Give one number on a scale of 1 to 7	1

(1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice)

6. If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

7. Applicability to a Family Medical Care Setting: 1

Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an intervention? Give one number on a scale of 1 to 7 (1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting)

8. If you coded 4.7 as a 4, 5, 6 or 7, please explain.

9. Immediacy of Implementation: Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug or other essentials available on the market? Give one number on a scale of 1 to 7 (1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied) 1

10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.

11. Clinical meaningful outcomes or patient-oriented outcomes: Are the outcomes measured in the study clinically meaningful or patient oriented? Give one number on a scale of 1 to 7 (1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented)

1

12. If you coded 4.11 as a 4, 5, 6, or 7 please explain why.

13. In your opinion, is this a Pending PURL? Give one number on a scale of 1 to 7 (1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL)

2

Criteria for a Pending PURL:

- Valid: Strong internal scientific validity; the findings appears to be true.
- Relevant: Relevant to the practice of family medicine
- Practice changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
- Applicability in medical setting:
- Immediacy of implementation