An alternative to warfarin for patients with PE. *J Fam Pract*. 2012;61:751-752.

Potential PURL Review Form: Randomized controlled trials

SECTION 1: IDENTIFYING INFORMATION

1. Citation	EINSTEIN–PE Investigators; Büller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366:1287-1297.
2. Hypertext link to PDF of full article	http://www.nejm.org/doi/full/10.1056/NEJMoa1113572
3. First date published study available to readers	April 5, 2012
4. PubMed ID	22449293
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 trial
12. Other comments, materials or discussion	
13. Assigned Potential PURL Reviewer	Umang Sharma
14. Reviewer Affiliation	University of Chicago
15. Date Review Due	July 5, 2012
16. Abstract	**BACKGROUND:** A fixed-dose regimen of rivaroxaban, an oral factor Xa inhibitor, has been shown to be as effective as standard anticoagulant therapy for the treatment of deep-vein thrombosis, without the need for laboratory monitoring. This approach may also simplify the

treatment of pulmonary embolism.

METHODS: In a randomized, open-label, event-driven, noninferiority trial involving 4832 patients who had acute symptomatic pulmonary embolism with or without deep-vein thrombosis, we compared rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) with standard therapy with enoxaparin followed by an adjusted-dose vitamin K antagonist for 3, 6, or 12 months. The primary efficacy outcome was symptomatic recurrent venous thromboembolism. The principal safety outcome was major or clinically relevant nonmajor bleeding.

RESULTS: Rivaroxaban was noninferior to standard therapy (noninferiority margin, 2.0; *P*=0.003) for the primary efficacy outcome, with 50 events in the rivaroxaban group (2.1%) versus 44 events in the standard-therapy group (1.8%) (hazard ratio, 1.12; 95% confidence interval [CI], 0.75 to 1.68). The principal safety outcome occurred in 10.3% of patients in the rivaroxaban group and 11.4% of those in the standard-therapy group (hazard ratio, 0.90; 95% CI, 0.76 to 1.07; *P*=0.23). Major bleeding was observed in 26 patients (1.1%) in the rivaroxaban group and 52 patients (2.2%) in the standard-therapy group (hazard ratio, 0.49; 95% CI, 0.31 to 0.79; *P*=0.003). Rates of other adverse events were similar in the two groups.

CONCLUSIONS: A fixed-dose regimen of rivaroxaban alone was noninferior to standard therapy for the initial and long-term treatment of pulmonary embolism and had a potentially improved benefit-risk profile.

(Funded by Bayer HealthCare and Janssen Pharmaceuticals; EINSTEIN-PE ClinicalTrials.gov number, NCT00439777.)

SECTION 2: CRITICAL APPRAISAL OF VALIDITY

1. Number of patients starting each arm of the study?	2420 rivaroxaban, 2413 standard therapy
2. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?	Inclusion: confirmed symptomatic pulmonary embolism (PE) with or without concurrent deep vein thrombosis (DVT). Exclusion: receiving another medication/treatment for significant period of time, specific other indication for warfarin, CrCl <30 mL/min, liver disease, endocarditis, active bleed or risk for it, systolic blood pressure (BP) <180 mm Hg or a diastolic BP >110 mm Hg, pregnant or breastfeeding.
3. Intervention(s) being investigated?	Rivaroxaban 15 mg bid for 3 weeks then 20 mg qd.
4. Comparison treatment(s), placebo, or nothing?	Standard warfarin therapy with enoxaparin bridge.
5. Length of follow-up? Note specified end points, eg, death, cure, etc.	3, 6, or 12 months based on local factors and judgment of investigator (based on things like whether event was provoked or unprovoked) at time of randomization, then all followed by a 30-day observation period.
6. What outcome measures are used? List all that assess effectiveness.	Prespecified noninferiority margin: hazard ratio as high as 2.0 (upper limit of 95% CI) for recurrent symptomatic venous thromboembolism (VTE) (PE or DVT)—primary outcome. Occurred in 20/2419 in rivaroxaban group (2.1%) and 44/2413 of standard therapy group (1.8%), hazard ratio (HR) 1.12 (95% CI, 0.75-1.68), *P*=.003 for noninferiority and *P*=.57 for superiority. Primary safety outcome (bleeding): 249/2412 in rivaroxaban group (10.3%), 274/2405 of standard group (11.4%), HR 0.9 (95% CI, 0.76-1.07), *P*=.23 presumably for noninferiority.

7. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CI, p-values, etc.	*P* values not significant so ARR and NNT not relevant. HRs as above.
8. What are the adverse effects of intervention compared with no intervention?	Primary safety concern was bleeding—as above.
9. Study addresses an appropriate and clearly focused question - ***select one***	Well covered.
10. Random allocation to comparison groups	Well covered.
11. Concealed allocation to comparison groups	Well covered.
12. Subjects and investigators kept "blind" to comparison group allocation	Comments: Unblinded due to warfarin therapy.
13. Comparison groups are similar at the start of the trial	
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. Comments: no
15. Were all relevant outcomes measured in a standardized, valid, and reliable way?	Well covered. Comments: DVT diagnosis described in online protocol.
16. Are patient oriented outcomes included? If yes, what are they?	Yes, recurrent VTE and significant bleeds.
17. What percent dropped out, and were lost to follow-up? Could this bias the results? How?	Discontinuation of therapy (for any reason, including adverse event, consent withdrawal, loss to follow-up) was noted in 10.7% of rivaroxaban group, 12.3% of standard therapy group (*P*=.07). The dropout level was modest and similar in both groups. More dropped from standard therapy due to consent withdrawal.
18. Was there an intention-to-treat analysis? If not, could this bias the results?	Yes.

How?

19. If a multi-site study, are results comparable for all sites?	Multisite, but comparability among sites was not discussed.
20. Is the funding for the trial a potential source of bias? If yes, what measures were taken to insure scientific integrity?	Funded by Janssen Pharmaceuticals (rivaroxaban manufacturer) and Bayer.
21. To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized.	Patients with acute symptomatic PE.
22. In what care settings might the findings apply, or not apply?	Emergency departments, inpatient settings.
23. To which clinicians or policy makers might the findings be relevant?	Any clinicians working in the above settings.

SECTION 3: REVIEW OF SECONDARY LITERATURE

1. DynaMed excerpts

2. DynaMed citation/access date	Anticoagulant therapy for venous thromboembolism. In: DynaMed [database online]. Available at: www.DynamicMedical.com. Last updated June 6, 2012. Accessed July 17, 2012.
3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)	Midlevel evidence that rivaroxaban is equivalent to warfarin.

4. UpToDate excerpts

5. UpToDate citation/access date	Valentine et al. Anticoagulation in acute PE. In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2012. Available at: http://www.uptodate.com. Last updated April 20, 2012. Accessed July 17, 2012.
6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)	This trial was summarized and the unblinding noted.
7. PEPID PCP excerpts www.pepidonline.com username: fpinauthor	n/a

pw: pepidpcp

8. PEPID citation/access data	
9. PEPID content updating	
10. Other excerpts (USPSTF; other guidelines; etc.)	n/a
11. Citations for other excerpts	n/a
12. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)	n/a

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)	5
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?	Completely unblinded. There were more suspected events in the rivaroxaban group (491 vs 453) yet a similar number of confirmed events, suggesting a bias in intensity of follow-up, initial counseling, or patient responsiveness. While this particular piece of information may seem to strengthen the finding of equivalnce (presumably counseling was equivalent), lack of blinding remains a concern.
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)	3
4. If 4.3 was coded as 4, 5, 6, or 7, please provide an explanation.	Applicable to those doing ER or inpatient work.
5. Practice changing potential: If the findings of the study are both valid and relevant, does the practice that would be based on these	1

findings represent a change from current practice? Give one number on a scale of 1 to 7 (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.	Not a common practice per secondary literature review. In November 2012, the FDA approved rivaroxaban for the prevention and treatment of PE and DVT.
7. Applicability to a Family Medical Care Setting: 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)	2
8. If you coded 4.7 as a 4, 5, 6 or 7, please explain.	See 4.4 above.
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	1

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)	
10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.	Not yet FDA approved for this indication.
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).	3

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	
14. Comments on your response in 4.13	Validity concern relates to blinding. Relevant to full-scope FPs only, and warfarin use may be somewhat idealized (ie, higher bleeds?) than the real world, that is, warfarin may be safer in real life than in this study in terms of number of bleeds.