Cohort Study
Potential PURL Review Form
PURL Jam Version
Version #12 Sept 20, 2010

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

1. Citation	Full Citation: Larsen TB, Skjøth F, Nielsen PB, Kjældgaard JN, Lip GY. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. BMJ. 2016 Jun 16; 353:i3189. doi: 10.1136/bmj.i3189. PubMed PMID: 27312796
2. Hypertext link to PDF of full article	http://www.ncbi.nlm.nih.gov/pubmed/27312796
3. First date published study available to readers	06/16/2016
4. PubMed ID	27312796
5. Nominated By	Other Other: Kate Rowland
6. Institutional Affiliation of Nominator	Other Other: NorthShore
7. Date Nominated	7/5/2016
8. Identified Through	Other Other: TOC
9. PURLS Editor Reviewing Nominated Potential PURL	Kate Rowland
10. Nomination Decision Date	7/8/2016
11. Potential PURL Review Form (PPRF) Type	Cohort Study
12. Other comments, materials or discussion	
13. Assigned Potential PURL Reviewer	Corey Lyon
14. Reviewer Affiliation	Other Other: Colorado
15. Date Review Due	10/6/2016

16. Abstract

OBJECTIVE:
To study the effectiveness and safety of the non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) dabigatran, rivaroxaban, and apixaban compared with warfarin in anticoagulant naïve patients with atrial fibrillation.
DESIGN:
Observational nationwide cohort study.
SETTING:
Three Danish nationwide databases, August 2011 to October 2015.
PARTICIPANTS:
61 678 patients with non-valvular atrial fibrillation who were naïve to oral anticoagulants and had no previous indication for valvular atrial fibrillation or venous thromboembolism. The study population was distributed according to treatment type: warfarin (n=35 436,

57%), dabigatran 150 mg (n=12 701, 21%), rivaroxaban 20 mg (n=7192, 12%), and apixaban 5 mg (n=6349, 10%).
MAIN OUTCOME MEASURES:
Effectiveness outcomes defined a priori were ischaemic stroke; a composite of ischaemic stroke or systemic embolism; death; and a composite of ischaemic stroke, systemic embolism, or death. Safety outcomes were any bleeding, intracranial bleeding, and major bleeding.
RESULTS:
When the analysis was restricted to ischaemic stroke, NOACs were not significantly different from warfarin. During one year follow-up, rivaroxaban was associated with lower annual rates of ischaemic stroke or systemic embolism (3.0% v 3.3%, respectively) compared with warfarin: hazard ratio 0.83 (95% confidence interval 0.69 to 0.99). The hazard ratios for dabigatran and apixaban (2.8% and 4.9% annually, respectively) were non-significant compared with warfarin. The annual risk of death was significantly lower with apixaban (5.2%) and dabigatran (2.7%) (0.65, 0.56 to 0.75 and 0.63, 0.48 to 0.82, respectively) compared with warfarin (8.5%), but not with rivaroxaban (7.7%). For the combined endpoint of any bleeding, annual rates for apixaban (3.3%) and dabigatran (2.4%) were significantly lower than for warfarin (5.0%) (0.62, 0.51 to 0.74). Warfarin and rivaroxaban had comparable annual bleeding rates (5.3%).
CONCLUSION:
All NOACs seem to be safe and effective alternatives to warfarin in a routine care setting. No significant difference was found between NOACs and warfarin for ischaemic stroke. The risks of death, any bleeding, or major bleeding were significantly lower for apixaban and dabigatran compared with warfarin.

17. Pending PURL Review Date: 10/6/2016

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]

1 The study addresses an appropriate and clearly focused question.

☒ Well covered ☐ Not addressed
☐ Adequately addressed ☐ Not reported
☐ Poorly addressed ☐ Not applicable
Comments: This comparative effectiveness cohor study eamines the effectiness and safety of 4 NOACs versus warfarin in anticoagulant naïve pts with atrial fibrillation.

2 The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.

☒ Well covered ☐ Not addressed
☐ Adequately addressed ☐ Not reported
☐ Poorly addressed ☐ Not applicable
Comments:

3 The study indicates how many of the people asked to take part did so, in each of the groups being studied

☐ Well covered ☐ Not addressed
☐ Adequately addressed ☐ Not reported
☐ Poorly addressed ☒ Not applicable
Comments: This is an observational cohort study. Data is based upon a several Danish nationwide databases.

4 The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.

☒ Well covered ☐ Not addressed
☐ Adequately addressed ☐ Not reported
☐ Poorly addressed ☐ Not applicable
Comments: Time to event analysis was used to compare the risk of an endpoint between treatment groups.

5 What percentage of individuals or clusters recruited into each arm of the study dropped out before the

This information was not reported in the study. What was reported was the types of analysis conducted for possible drop out of loss to follow up. Time to event analysis was used to compare the risk of an endpoint between treatment group. This measured risk time from the initial prescription to the relevant event, emigration, death or end of follow up. An intention to treat approach was used for

study was completed?	all endpoints. Continuous treatment analysis was conducted which censored or removed follow-up if a patient was prescribed another treatment than what was initiated.
6 Comparison is made between full participants and those lost to follow up, by exposure status.	☒ Well covered ☐ Not addressed ☐ Adequately addressed ☐ Not reported ☐ Poorly addressed ☐ Not applicable Comments: Intent to treat analysis completed
7 The outcomes are clearly defined.	☒ Well covered ☐ Not addressed ☐ Adequately addressed ☐ Not reported ☐ Poorly addressed ☐ Not applicable Comments: Outcomes were to compate the effectiveness and safety of dabigatran, rivaroxaban, and apixaban compared with warfarin for patients with atrial fibrillation who were naïve to oral anticoagulants. Maon outcome measures were ischaelmic stroke, a composite of ischaemic stroke or systemic embolism, death, and a composite of ischaemic stroke, systemic embolism or death. Safety outcomes were any bleeding, intracranial bleeding and major bleeding.
8 The assessment of outcome is made blind to exposure status	☐ Well covered ☐ Not addressed ☐ Adequately addressed ☐ Not reported ☐ Poorly addressed ☒ Not applicable Comments: Observation cohort study
9 Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	☐ Well covered ☐ Not addressed ☐ Adequately addressed ☐ Not reported ☐ Poorly addressed ☒ Not applicable Comments:
10 What are the key findings of the study?	All NOACS (Dabigatran, rivaroxaban, and apixaban) are safe and effective alternatives to warfarin. There is no difference in risk for these NOACS versus warfarin for ischaemic stroke. Rivaroxaban was associated with a lower risk of ischaelmic stroke or systemic embolism than warfarin (hazard ratio [HR] 0.83; 95% CI, 0.69-0.99), but with comparable major bleeding rates. Bleeding events (defined as intracranial, major gastrointestinal, and traumatic intracranial) were lower in the apixaban group (HR 0.63; 95% CI, 0.53-0.76) and dabigatran group (HR 0.61; 95% CI, 0.51-0.74) compared to warafarin. There was no difference between rivaroxaban and warfarin.
11 How was the study funded? Any conflicts of interest? Any reason to believe that the results may be influenced by other interests?	The study was partly funded by a family foundation grant. The study was free from industry sponsorships. Authors disclosed relationships with pharmaceutical companies. No obvious influences due to the nature of the study design.

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]

Citation Instructions	For UpTo Date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS as editor & current year as publication year.

EXAMPLE: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert dated modified if given.} Accessed February 12, 2009. {whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:
Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at: http://www.DynamicMedical.com. Last updated February 4, 2009. {Insert dated modified if given.} Accessed June 5, 2009.{search date}

1. DynaMed excerpts

2. DynaMed citation/access date

Title. Thromoembolic prophylaxis in atrial fibrillation Author. Kramer, D.B, Epstein, L. In: DynaMed [database online]. Available at: www.DynamicMedical.com Last updated: 7/15/16. Accessed

3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)

American, European and Canadian guidelines suggest the use of novel oral anticoagulants over warfarin (ACCP Grade 2B, ESC Class IIa, Level A; CCS Strong recommendation, High quality evidence. Options include dabigatran (ACCP Grade 2B), rivaroxaban, and apixaban.

4. UpToDate excerpts

We prefer one of the non-vitamin K antagonist oral anticoagulants, sometimes abbreviated NOAC, (eg, dabigatran, rivaroxaban, apixaban, or edoxaban) to warfarin for most patients in whom oral anticoagulant therapy is chosen. However, without blinded head-to-head trial comparisons between these newer agents, it is difficult to assert that any of the NOAC agents is clearly superior. We suggest that each practitioner become familiar with and comfortable using at least one or two NOAC agents.

5. UpToDate citation/access date

Always use Basow DS as editor & current year as publication year.
Title. Atrial fibrillation: Anticoagulant therapy to prevent ebolization. Author. Manning, W.J., Singer, D.E., Lip, G YH In: UpToDate [database online]. Available at: http://www.uptodate.com. Last updated: 7/6/16. Accessed

6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)

In patients with nonvalvular AF for whom anticoagulant therapy is chosen, we suggest an oral direct thrombin inhibitor or a factor Xa inhibitor rather than warfarin (Grade 2B). The evidence does not allow for us to prefer one non-vitamin K antagonist oral anticoagulant (NOAC) agent to another. Thus, we suggest that practitioners become familiar with and comfortable using at least one NOAC agent.

7. PEPID PCP excerpts
www.pepidonline.com
username: fpinauthor
pw: pepidpcp

8. PEPID citation/access data

Author. Title. In: PEPID [database online]. Available at: http://www.pepidonline.com. Last updated: . Accessed

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
☐ No, this topic is current, accurate and up to date.
If yes, which PEPID Topic, Title(s):

2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon (EB) that should be updated on the basis of the review?
☐ Yes, there is important evidence or recommendations that are missing
☐ No, this topic is current, accurate and up to date.
If yes, which Evidence Based Inquiry(HelpDesk Answer or Clinical Inquiry), Title(s):

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
[to be completed by the Potential PURL Reviewer; Revised by the Pending PURL Reviewer as needed]

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)
☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7

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?

No data on INRs for pts on warfarin.
The study design leads to concern with balancing of unmeasured confounders that come with randomization; however, the gain is that this data comes from actual sources of care instead of artifical trial enviroments.

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 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7

4. If 4.3 was coded as 4, 5, 6, or 7, lease provide an explanation.

Primary limitation is the results apply to a white european population

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=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice)
☐1 ☐2 ☒3 ☐4 ☐5 ☐6 ☐7

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.

NOACs can be a safe and effective alternative to warfarin for patients with atrial fibrillation. Apixaban and dabigatran have a lower risk for death, any bleeding or major bleeding compared to warfarin.
Individual trials have shown comparible effectivness of these agents and some providers are most likely using, but we are not sure all are using this as an option; this trial shows all are effective and providers can chose any agent. Some providers may need this info to be convinenced.

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)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

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 ☐2 ☒3 ☐4 ☐5 ☐6 ☐7

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

Cost could be a barrier; insurance coverage may be an issue, especially for hihg deductable plans or pts in the "donut hole"

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 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

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?
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

Give one number on a scale of 1 to 7
(1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL)
☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7

14. Comments on your response in 4.13

NOACs from this study are safe and effective alternative to warfarin for patients with atrial fibrillation.

SECTION 4.1: Diving for PURLs
[optional for the potential PURL reviewer -if you wish to be the author on the summary]

1. Study Summary- Please summarize the study in 5-7 sentences

2. Criteria- note yes or no for those which this study meets

RELEVENT -
VALID -
CHANGE IN PRACTICE-
MEDICAL CARE SETTING -

IMMEDIATELY APPLICABLE -
CLINICALLY MEANINGFUL -

3. Bottom Line- one –two sentences noting the bottom line recommendation

4. Title Proposal

SECTION 5: Editorial Decisions
[to be completed by the FPIN PURLs Editor or Deputy Editor]

1. FPIN PURLs editorial decision (select one)

☐1 Pending PURL Review—Schedule for Review
☐ 2 Drop
☐ 3 Pending PURL

3. Follow up issues for Pending PURL Reviewer

3. FPIN PURLS Editor making decision

☐1 Bernard Ewigman
☐2 John Hickner
☐3 Sarah-Anne Schumann
☐4 Kate Rowland

4. Date of decision

5. Brief summary of decision

SECTION 6: Survey Questions for SERMO, PURLs Instant Polls and Other Surveys
[To be completed by the PURLs Survey Coordinator and PURLs Editor]

1. Current Practice Question for Surveys

2. Barriers to Implementation Question for Surveys

3. Likelihood of Change Question for Surveys

4. Other Questions for Surveys

SECTION 7: Variables for Secondary Database Analyses

1. Population: Age, gender, race, ethnicity

2. Diagnoses

3. Drugs or procedures

SECTION 8: Pending PURL Review Assignment
[to be completed by PURLs Project Manager

1. Person Assigned for Pending PURL Review

2. Date Pending PURL Review is due

SECTION 9: Pending PURL Review
[to be completed by the Pending PURL Reviewer]

1. Did you address the follow up issues identified at the PURL Jam (Section 5.2). Add comments as needed.

☐ Yes
☐ No
☐ Not applicable
Comments:

2. Did you review the Sermo poll & Instant Poll results (if available)? Add comments as needed.

☐ Yes
☐ No
☐ Not applicable
Comments:

3. Did you modify Sections 2, 3, or 4? Add comments as needed.

☐ Yes
☐ No
☐ Not applicable
Comments:

SECTION 10: PURL Authoring Template
[to be completed by the assigned PURL Author]

Author Citation Information (Name, Degrees, Affiliation)

1. Practice Changer

2. Illustrative Case

3. Background/
Clinical Context/Introduction/Current Practice/

4. Study Summary

5. What's New

6. Caveats

7. Challenges to Implementation

8. Acknowledgment Sentence

The PURLs Surveillance System is supported in part by Grant Number UL1RR024999 from the National Center For Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Research Resources or the National Institutes of Health.

If using UHC data:
We acknowledge Sofia Medvedev of University HealthSystem Consortium (UHC) in Oak Brook, IL for analysis of the National Ambulatory Medical Care Survey data.

9. References