

# Cohort Study Potential PURL Review Form PURL Jam Version

## PURLs Surveillance System Family Physicians Inquiries Network

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

- A. Citation: Ray WA, Chung CP, Murray KT, Smalley WE, Daugherty JR, Dupont WD, Stein CM. Association of Proton Pump Inhibitors With Reduced Risk of Warfarin-Related Serious Upper Gastrointestinal Bleeding. *Gastroenterology*. 2016 Dec;151(6):1105-1112.e10. doi: 10.1053/j.gastro.2016.08.054. PubMed PMID: 27639805; PubMed Central PMCID: PMC5124401.
- B. Link to PDF of full article: 27639805
- C. First date published study available to readers:08/2016
- D. PubMed ID: 27639805
- E. Nominated By: Janice Benson
- F. Institutional Affiliation of Nominator: University of Chicago NorthShore
- G. Date Nominated: 9/27/2016
- H. Identified Through: Gastroenterology
- I. PURLs Editor Reviewing Nominated Potential PURL: Corey Lyons
- J. Nomination Decision Date: 10/4/2016
- K. Potential PURL Review Form (PPRF) Type: Cohort Study
- L. Assigned Potential PURL Reviewer: Laura Morris
- M. Reviewer Affiliation: University of Missouri
- A. Abstract: BACKGROUND & AIMS:

Proton pump inhibitors (PPIs) might reduce the risk of serious warfarin-related upper gastrointestinal bleeding, but the evidence of their efficacy for this indication is limited. A gastroprotective effect of PPIs would be particularly important for patients who take warfarin with antiplatelet drugs or nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), which further increase the risk of gastrointestinal bleeding.

#### METHODS:

This retrospective cohort study of patients beginning warfarin treatment in Tennessee Medicaid and the 5% National Medicare Sample identified 97,430 new episodes of warfarin treatment with 75,720 person-years of follow-up. The study end points were hospitalizations for upper gastrointestinal bleeding potentially preventable by PPIs and for bleeding at other sites.

#### RESULTS:

Patients who took warfarin without PPI co-therapy had 119 hospitalizations for upper gastrointestinal bleeding per 10,000 person-years of treatment. The risk decreased by 24% among patients who received PPI co-therapy (adjusted hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.63-0.91). There was no significant reduction in the risk of other gastrointestinal bleeding hospitalizations (HR, 1.07; 95% CI, 0.94-1.22) or non-gastrointestinal bleeding hospitalizations (HR, 0.98; 95% CI, 0.84-1.15) in this group. Among patients concurrently using antiplatelet drugs or NSAIDs, those without PPI co-therapy had 284 upper gastrointestinal bleeding hospitalizations per 10,000 person-years of warfarin treatment. The risk decreased by 45% (HR, 0.55; 95% CI, 0.39-0.77) with PPI co-therapy. PPI co-therapy had no significant protective effect for warfarin patients not using antiplatelet drugs or NSAIDs (HR, 0.86; 95% CI,

0.70-1.06). Findings were similar in both study populations.

#### CONCLUSIONS:

In an analysis of patients beginning warfarin treatment in Tennessee Medicaid and the 5% National Medicare Sample, PPI co-therapy was associated with reduced risk of warfarin-related upper gastrointestinal bleeding; the greatest reduction occurred in patients also taking antiplatelet drugs or NSAIDs.

B. Pending PURL Review Date: 2/15/2017

### **SECTION 2: Critical Appraisal of Validity**

#### **[to be completed by the Potential PURL Reviewer]**

- A. The study address an appropriate and clearly focused question. Adequately addressed  
Comments: ok—Does use of PPI co therapy decrease hospitalization for UGI bleeds in patients on warfarin?
- B. The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation. Well covered  
Comments: Demographics of Medicaid and Medicare groups were similar.
- C. The study indicates how many of the people asked to take part in it in each of the groups being studied. Not applicable  
Comments: data on subjects pulled from registries
- D. The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis. Adequately addressed  
Comments: recent GI bleed and predisposing related illness was part of exclusion criteria. Cannot account for possible undiagnosed H Pylori infection
- E. What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?  
unclear/ N/a: individuals could meet criteria, then be excluded, then rejoin. Article does not provide exact numbers but does state that sensitivity analysis accounted for this and excluded patients who would affect validity.
- F. Comparison is made between full participants and those lost to follow up, by exposure status.  
Not applicable  
Comments: not applicable to this study design, but see sensitivity analysis discussion above
- G. The outcomes are clearly defined. Adequately addressed  
Comments: clearly defined outcome of risk of hospitalization for upper GI bleed for patients on warfarin with PPI co-therapy vs no PPI. Did not clearly state intent to divide into subgroups of concurrent NSAID/antiplatelet agent or not
- H. The assessment of outcome is made blind to exposure status. Not applicable  
Comments: Assessment of exposure status may introduce bias—PPI and NSAIDs available OTC and may not have captured all exposures. But, Medicaid patients may be more likely to obtain these meds by prescription compared to Medicare patients.

- I. Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome. Not applicable

Comments:

- J. What are the key findings of the study?

50% of patients took warfarin for a. fib. Demographics were similar for Medicaid and medicare cohorts.

Patients prescribed PPI co-therapy tended to have more risk factors for GI bleeding (eg, history of PUD) than patients not prescribed PPI

1. Current PPI co-therapy (but not former PPI therapy) reduced hospitalization rates for serious upper GI bleed.

Overall HR 0.76; 95% CI (XX-XX)

29 fewer hospitalizations per 10,000 patient years (10-44)

2. PPI co-therapy decreased risk of serious upper GI bleed for patients concurrently on antiplatelet agents or NSAIDs/ASA, but there was no statistically significant decrease in risk for patients who were not also on antiplatelets/NSAIDs/ASA

For patients on concurrent NSAID/ASA, HR 0.55; 95% CI,

Further subgroup analysis of patients on concurrent NSAID/warfarin PLUS additional GI risk factors

With subgroup analysis, the group that remained statistically significant is patients taking concurrent NSAID/ASA plus risk factors

- K. How was the study funded? Any conflicts of interest? Any reason to believe that the results may be influenced by other interests?  
grant funded, data via government bureaus

### **SECTION 3: Review of Secondary Literature**

**[to be completed by the Potential PURL Reviewer]**

**[to be revised by the Pending PURL Reviewer as needed]**

#### **Citation Instructions:**

For up-to-date citations, use style modified from [http://www.uptodate.com/home/help/faq/using\\_UTD/index.html#cite](http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite) & AMA style. Always use Basow DS on 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 date 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 date modified if given.} Accessed June 5, 2009. {search date}

- A. DynaMed excerpts    did not find recommendations for GI bleed prophylaxis for patients on warfarin
  
- B. DynaMed citation/    Title. Author. In: DynaMed [database online]. Available at: access date [www.DynamicMedical.com](http://www.DynamicMedical.com) Last Updated:Accessed [Click here to enter text.](#)
  
- C. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)  
[Click here to enter text.](#)
  
- D. UpToDate excerpts    did not find recommendations for this clinical question
  
- E. UpToDate citation/    Always use Basow DS as editor & current year as publication year. Access date Title. Author. In: UpToDate [database online]. Available at: <http://www.uptodate.com>. Last updated: Accessed [Click here to enter text.](#)
  
- F. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)  
[Click here to enter text.](#)
  
- G. Other excerpts (USPSTF; other guidelines; etc.)  
ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use:  
  
“The combination of [aspirin] and anticoagulant therapy [including . . . warfarin] is associated with a clinically meaningful and significantly increased risk of major . . . bleeding events, a large proportion from the upper GI tract. . . patients should receive concomitant PPIs as well.”
  
- H. Citations for other excerpts  
Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2008;52:1502-1517
  
- I. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)  
Consider PPIs for GI bleed prophylaxis in patients on aspirin + warfarin.

This potential PURL appears to be the best available evidence to answer this question at this time.

## SECTION 4: Conclusions

[to be completed by the Potential PURL Reviewer]

[to be revised by the Pending PURL Reviewer as needed]

- A. **Validity:** How well does the study minimize sources of internal bias and maximize internal validity?      2
- B. If **A** was coded 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?  
[Click here to enter text.](#)
- C. **Relevance:** Are the results of study generalizable to and relevant to the health care needs of patients cared for by “full scope” family physicians?      1 (extremely well)
- D. If **C** was coded 4, 5, 6, or 7, please provide an explanation.  
[Click here to enter text.](#)
- E. **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?  
2

F. If **E** 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.

Many family medicine patients are on warfarin. Many may already be on a PPI for other indications, but if not, consider starting a PPI as GI bleed prophylaxis. This is especially true if the patient also takes aspirin, other antiplatelet agents, or NSAIDs.

**G. 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, education or counseling a patient; or creating a system for implementing an intervention? 1 (definitely could be done in a medical care setting)

H. If **G** was coded as a 4, 5, 6, or 7, please explain.

[Click here to enter text.](#)

**I. 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? 1 (definitely could be immediately applied)

J. If **I** was coded 4, 5, 6, or 7, please explain why.

Caveats to implementation might include the growing body of evidence around long term PPI exposure—bone density, renal issues, etc

**K. Clinically meaningful outcomes or patient oriented outcomes:**

Are the outcomes measured in the study clinically meaningful or patient oriented?

1 (definitely clinically meaningful or patient oriented)

L. If **K** was coded 4, 5, 6, or 7 please explain why.

[Click here to enter text.](#)

M. In your opinion, is this a pending PURL? 2

1. Valid: Strong internal scientific validity; the findings appear to be true.  
yes

2. Relevant: Relevant to the practice of family medicine.  
yes

3. 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.  
yes

4. Applicability in medical setting.

yes

5. Immediacy of implementation

yes

N. Comments on your response for question M.

We have a few concerns—retrospective cohort methodology (in general less strength of conclusion vs a prospective cohort or RCT) and dwindling # of person-years in some subgroups that did not show statistically significant benefit. It is also unclear how many patients may be using OTC PPI or NSAIDS, ASA, etc., which could lead to misclassification bias. Medicaid patients may be more likely to obtain OTC meds by prescription. In theory, use of OTC PPI would bias the non-PPI group toward the null, and use of OTC NSAID would make the non-NSAID group more likely to bleed, so the conclusions would remain valid.

We advocate limiting the conclusions of the article to the population on concurrent NSAID/ASA