Reviewer’s report

Title: Anticoagulant Use for the Prevention of Stroke in Patients with Atrial Fibrillation: Findings from a Multi-Payer Analysis

Version: 1 Date: 8 February 2014

Reviewer: Daniel E Singer

Reviewer’s report:

Lang et al report the application of a software tool they have developed, Anticoagulant Quality Improvement Analyzer (AQIA), to 2-year data from five large insurance databases. Anticoagulation for atrial fibrillation (AF) is the most effective preventive cardiology intervention and guidelines strongly recommended anticoagulation for higher stroke risk AF patients. Yet, surveys indicate that large fractions of AF patients are not on anticoagulants. Until recently, warfarin was the exclusive anticoagulant for AF. The quality of warfarin anticoagulation is highly variable although it can be quite high with careful INR testing and skilled dose adjustment. The AQIA tool is meant to facilitate health systems’ monitoring of use of anticoagulation in AF patients and frequency of INR testing for those on warfarin. Using administrative data and pharmacy claims, AQIA identifies patients with AF, categorizes their stroke risk by comorbidity and age, assesses their use of warfarin, frequency of INR tests, and stroke and bleed hospitalization outcomes. The authors report wide differences in patient demographic features across databases, variable and generally low percentage use of warfarin, low frequency of INR tests, and very low cumulative incidence of events. My concerns and questions follow. The authors should respond to these concerns and then choose whether they believe they need revisions in the analysis or text.

General:

Multiple reports from large databases have used administrative and pharmacy data to describe warfarin use in AF. The authors should make clearer what features and applications of the AQIA tool are distinctive. As detailed below, the findings of the current study strongly suggest that INR tests and outcome event, and perhaps warfarin use, are not being captured. The authors should address this concern in the Limitations section. Is this a problem with the AQIA tool or with the databases or both.

Specific:

1. Construction of AQIA. Table A1, stroke risk codes. Why did the authors use codes for deep vein thrombembolism, pulmonary embolism, and obstetrical embolism? These are not relevant “systemic embolism” events.

2. Construction of AQIA. The stroke rates are very low. Have the authors explored use of the “.x0” codes for ICD-9 codes 433 and 434 (i.e., without mention of infarction). Did the authors restrict ICD-9 stroke codes to the primary
position?

3. Databases. Can the authors comment on the comprehensiveness of the databases. AF is overwhelmingly a condition of the Medicare-eligible population. Is it possible that warfarin prescriptions, INR tests, and hospitalizations were paid out of standard Medicare and not recorded in the databases? If so, what is the magnitude of the effect?

4. Warfarin persistence is particularly challenging to measure via pharmacy claims since the dose is frequently changed. INR testing during gaps indicates ongoing warfarin use.

5. Hospitalization for bleeding is not the same as major hemorrhage. Many such hospitalizations do not meet ISTH criteria for “major.” Since the authors do not have access to use of transfusion or hemoglobin levels, they should describe their bleeding events simply as hospitalizations for bleeding not major bleeds. They could restrict use of “major” to events in critical anatomic areas.

6. Results, Anticoagulation Use. Were there outpatient INR tests in gaps? If so, MPR should include periods with such INR tests.

7. Results, outcome events. The 1-2% with strokes during the 2-yr period is very low and strongly suggests that events were missed. The bleeding event rates of 0-1% are even more impressively low strongly indicating that events were missed.

8. Table 3. Stroke events not on anticoagulant are reported. What is needed is an estimate of event rates on and off warfarin. These should be calculated in standard person-years fashion accounting for censoring. These can be reported as unadjusted or stratified by CHADS2 score.

9. Results and Table 4, INR Outcomes. Are the authors asserting that large fractions of patients receiving warfarin did not get even 1 INR test? In clinical practice, essentially everyone taking warfarin gets an INR test. They may not get enough INR tests but they all get at least one. If I am interpreting the results correctly, they indicate INR testing is not comprehensively captured in the databases or via the authors’ algorithms.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

My potential competing interests follow:
1. I have published in this area.
2. I am a member of the Executive Committee of the ROCKET AF trial of rivaroxaban for AF.
3. I am a member of the Steering Committee of the ORBIT registry to assess use of anticoagulants for AF in clinical care.
2. I have served as a consultant to all the manufacturers of the novel oral anticoagulants.
3. I have received research support related to use of anticoagulants for AF from Daiichi Sankyo, Bristol-Myers Squibb, and Johnson and Johnson.