Reviewer’s report

Title: Ischemic stroke risk estimation in patients without oral anticoagulation: an observational cohort study based on secondary data from Germany

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Reviewer: Gautam Shroff

Reviewer's report:

Wicke et al performed a retrospective observational cohort study in the contemporary era (2015-2016) using a large health insurance registry comprising 3.8 million individuals. They identified those with "non-valvular" AF (excluding RHD, prosthetic valves); and used ICD codes to determine CHADS-VASC score. They identified a total prevalence of AF of about 3%; of which 27% did not receive anticoagulation. The primary outcome of ischemic stroke was 2.2/100-person-years and secondary endpoint of hospitalization for thromboembolic event was 3.6 per 100-person years. The authors conclude that the performance of the CHADSVASC score differs in the German population with an overall lower risk of ischemic stroke in non-anticoagulated patients with AF.

Comments:

1. This is an important topic and merits attention. Particularly the point about the differing populations that were used to determine the CHADSVASC score is well stated as well as the variation in incidence of ischemic stroke. The study has implications regarding the threshold of selection of anticoagulation.

2. The definition of SSE (stroke and systemic embolism) has been systematically utilized in the literature for all major randomized trials. The authors have broken up this outcome into primary vs secondary outcome in this paper -- I worry that this may be will be confusing to the audience. Is it possible for the authors to also report a composite SSE outcome, to match comparators to randomized studies?

3. Agree with the authors about the confounding by indication being a major limitation. There must have been strong reasons why the clinician decided against anticoagulation in these patients, and this could therefore possibly represent a higher risk population. As an example, in table 1, it is noted that about 31% of these patients had kidney disease (no definition provided), 19% had dementia, and 15% had liver disease. It is possible, the risk of bleeding may be too high in this population. Similar to the ischemic stroke risk by CHADSVASC score, is it possible for the authors to provide the incidence of bleeding too?
4. Would suggest that table 1 include the characteristics of patients who did undergo anticoagulation also - as emphasized in point #3, it would be beneficial for the differences between these two populations to be described.

5. Minor error in results - page 6, line 143.

6. It may also be worth emphasizing in background that the cohorts used to derive the current CHADS-VASC score were not contemporary. There has been an overall reduction in the population risk of stroke since those initial observational cohorts were established. This would support the authors contention that overall actual ischemic stroke risks are lower than conventionally estimated. (Asinger RW et al, PMID: 28893833).

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

No

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

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