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Title	Anticoagulation reduces population risk of stroke and mortality in incident atrial fibrillation: a population-based cohort study
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Reviewer 1	Mary S Vaughan-Sarrazin
Institution	Internal Medicine, University of Iowa, Iowa City, Iowa, USA
General comments (author response in bold)	Anticoagulation reduces population risk of stroke and mortality in incident atrial fibrillation. This study used data for 10,745 patients with new atrial fibrillation diagnosis in Alberta, Canada. The investigators sought to determine whether anticoagulant use of effective and/or safe for stroke prevention in patients with atrial fibrillation, Outcomes assessed included ischemic stroke, mortality, and common complications (gastrointestinal hemorrhage, subdural hemorrhage, and hemorrhagic stroke). Overall, roughly two-thirds of patients received oral anticoagulation, of which most were warfarin recipients. Anticoagulant use was associated with significant reduction in relative hazard of ischemic stroke and death, but an increased likelihood of hemorrhagic stroke. The authors concluded that use of oral anticoagulation is effective and safe for stroke prevention and decreases mortality in patients with incident atrial fibrillation. Major comment: The paper is well written and methods are generally appropriate. My primary criticism of this paper is that I am not convinced that it provides new information. Anticoagulant use is widely recognized as an effective strategy for preventing stroke in AF, and the use of anticoagulants for patients at risk of stroke is already recommended by most professional clinical guidelines. Thus, the contribution of this work to existing knowledge is minimal. **RESPONSE:** Anticoagulation has been shown in prior trials to be an effective stroke prevention strategy. It is much less clear that it actually reduces mortality. Our study of a complete Canadian population of new-onset atrial fibrillation and high rates of anticoagulationis novel and complimentary to trial results. Further, we show that in Albertans who have atrial fibrillation and a prior stroke, over one in four patients who receive their first diagnosis of atrial fibrillation presented with a cerebrovascular event, a finding that has important implications for primary prevention of stroke. Minor comments: There are two sentences in 'Statistical Methods' that are confusing and potentially conflicting: (page 7): First, the authors status ""Patients were considered anticoagulated if they had been prescribed oral anticoagulants within the 6 months prior to an outcome or the last date of follow-up, whichever was first, and if they had at least one renewal of the prescription." Subsequently they state: "We assumed continuous anticoagulation use between the first dispensation date of oral anticoagulant to the day the prescription ends after the last dispensation date." This is confusing. In general, measurement of anticoagulant use was unclear. Was anticoagulation treated as time dependent? (e.g., suppose a patient initiates anticoagulant use 3 months after initial AF diagnosis. Does that patient's anticoagulant flag get turned 'on' only after the first prescription is filled?) **RESPONSE:** Thank you, we agree this was confusing. We have removed the subsequent statement and updated the 'Statistical Methods' section
Reviewer 2	Kuan Huei Ng
Institution	McMaster University, Stroke Department, Population Health Research Institute; David Braley Cardiac, Vascular and Stroke Institute, Hamilton, Ontario
General comments (author response in bold)	1. In Table 1, please provide an explaination how secondary prevention patients had a CHADS2 of 0 or 1 if by definition, they have had a stroke or TIA. It would be good to expand the analysis to better describe the groups on OAC and those not on OAC. The conclusions in the manuscript are invalid if the two groups above are distinctly different. **RESPONSE:** Thank you, we have specified in the text ('Methods', 3rd paragraph, last sentence) that some patients in the secondary prevention group had CHADS2 0 or 1 because of prior hemorrhagic strokes. Given the nature of thedata source – Alberta Health administrative data - we are unable to add further information in the anticoagulated versus non-anticoagulated than what is provided in Table 1. 2. In the analysis for Table 2 and 3, it would have been helpful to adjust for age in addition to Sex and CHADS2 score as OAC is often witheld in the frail elderly. The use of

	CHADS2 and sex alone is insufficient. Patients not anticoagulated would have been two distinct groups at both ends of the age spectrum i.e. the young with low risks and the very old thought to be too high risk for OAC. I note the age spread in your IQR in Table 1 confirms that. The mortality and morbidity difference could have been driven by the latter. **RESPONSE:** Thank you, we have adjusted for age as this is included in the CHADS2 score. 3. The penultimate sentence in the conclusion is superfluous. **RESPONSE:** Thank you, we have revised the 'Conclusions' accordingly. 4. We cannot state a causal relationship in an observational retrospective unrandomised analysis that OAC reduces mortality and strokes but is clearly associated with better outcomes. In the absence of a clear cause and effect, the concluding statement recommending widespread community screening for AF is premature. Finding AF and taking OAC for stroke prevention is another. **RESPONSE:** Thank you, we have revised the 'Conclusions' accordingly. 5. In the discussion, there should be some explanation for the higher rates of OAC in Alberta compared to previous observational population-wide studies e.g. in the UK. Is there a younger population in Alberta relative to other countries or provinces? **RESPONSES:** Thank you, we have described in the 'Interpretations' that there is a trend to improved care. The rates of oral anticoagulation have improved in both Alberta and other populations, such as the UK, but our rates were still observed to be higher. We do not have access to the UK data and do not know why Alberta rates (and by extension, Canadian rates) are higher. 6. The frail elderly are often not given OAC but the only trial to date of a direct acting OAC versus ASA, the AVERROES trial, suggests that apixaban is safe and effective in patients not suitable for VKA. Has this influenced prescribing patterns? Is this the explanation for the increased rates of OAC? **RESPONSES:** Thank you, the direct oral anticoagulant use was limited during our study period 2009-2010 (19.4%, and mainly dabigatran because this was the approved DOAC at the time). We cannotcomment on its use compared to vitamin K antagonists. It would be interesting to study this in a future study.
Reviewer 3	Philip Podrid
Institution	Cardiology, VA Boston Healthcare System-West Roxbury Division, West Roxbury, Massachusetts, USA
General comments (author response in bold)	The study of Yu and coworker is a large cohort study of anticoagulation in patients with AF. The results of this study are not surprising and are very much in keeping with a number of other population based studies. Therefore, there is nothing new or different about this trial, albeit the database is large. **RESPONSE:** Please see the response to review #1 above, regarding novelty. I do have two questions: 1.Why was not anticoagulation therapy identified by use of INR levels (in those using warfarin) rather than from pharmacy records? **RESPONSE:** Thank you, we used pharmacy prescription information as INR levels are not linked to the administrative data used and were unavailable to us. We do agree with the implication of your question, that a better measure of the effectiveness of anticoagulation is the time-in-the-therapeutic-range (TTR), but again, we did have access to these data. 2. Clarify the comments on page 8 line 49 and following in regard to double counting of patients. **RESPONSE:** Thank you, we have clarified under 'Results', 1st paragraph: the sum of warfarin and direct oral anticoagulant use is over 100% because a number of patients were prescribed both medication, serially, during the study period