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Title	Comparative effectiveness and safety of direct oral anticoagulants compared to vitamin K antagonists in non-valvular atrial fibrillation: a multi-center observational cohort study
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Reviewer 1	Herbert Manosalva Alzate
Institution	Division of Neurology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alta.
General comments (author response in bold)	1) Important to have a clear definition of what was consider "major bleeding". Important that you give the criteria for this definition. **This study uses administrative healthcare databases. In these databases, we do not have accessibility to laboratory data (eg: hemoglobin) or transfusions, therefore we rely on ICD-9 and ICD-10 codes. The definition of major bleeding was added and now reads (p 10):** **"Major bleeding was defined as a composite of intracranial (including haemorrhagic stroke), gastrointestinal, ocular, and any other bleeding necessitating hospitalization or emergency room visit. The complete list of diagnostic codes used to define the secondary outcomes is available in supplementary appendix 2."** 2) Important to comment why there was no difference in the rate of GI bleedings between the NOAC group and warfarin. It would be very useful that you do a sub analysis between GI bleeding and dabigatran vs warfarin, rivaroxaban vs warfarin, and apixaban vs warfarin. This statistical analysis might offer an objective answer to this question. **This was not part of our original protocol and it has not been done. This study was conducted in multiple sites, with each individual site obtaining ethical approval based on the original protocol. Post hoc and additional analyses are not possible at this point but could be part of a new project.**
Reviewer 2	Max Levine
Institution	Faculty of Medicine and Dentistry, University of Alberta, Continuous Professional Learning, Edmonton, Alta.
General comments (author response in bold)	This is an observational study of the comparative effectiveness of DOACs compared to VKAs in NVAF in the Canadian population. The most important limitations are recognized by the authors, which includes the lack of data on the renal function at time of starting DOAC/VKA, which may drive clinicians to choose one agent over another, or the time in therapeutic range while on VKA, which is a major determinant of VKA efficacy. A further consideration may be given to the exposure to p-glycoprotein inhibitors and inducers, as these influence the efficacy/safety of DOAC's. If the data are granular enough, it would be beneficial to provide the rate of exposure to p-glycoprotein inhibiting/inducing medication beyond the list of medication exposures already listed in the Appendices. This may be done as an additional category in the appropriate Appendices. **Thank you for this important comment, which we take careful note of for future works. At this point, we cannot go back to all individual databases to**

	describe the use of p-glycoprotein inhibitors. While this is indeed a very interesting pharmacological question, we still believe that our work still gives a valid estimate of the real life safety and effectiveness to DOACs vs warfarin in the Canadian setting. Future work could specifically address this question.