Letters to the Editor

Effect and risk of novel oral anticoagulants versus warfarin in patients with non-valvular atrial fibrillation

I read the article by Bengtson et al. on the advantage and risk of novel oral anticoagulants (NOACS) versus warfarin in patients with non-valvular atrial fibrillation (NVAF) [1]. The authors adopted propensity score-adjusted Cox regression for calculating hazard ratio (HR) [95% confidence interval (CI)]. HRs (95% CIs) of dabigatran versus warfarin for ischemic stroke and myocardial infarction were 0.65 (0.52–0.82) and 0.72 (0.57–0.91), respectively. In addition, HRs (95% CIs) of dabigatran versus warfarin for intracranial bleeding (ICB) and gastrointestinal bleeding were 0.37 (0.20–0.67) and 1.04 (0.88–1.22), respectively. The authors concluded that there was an advantage for NOACs versus warfarin in patients with NVAF by preventing ischemic disease and ICB without increase of gastrointestinal bleeding. I have two concerns about their study.

First, Chan et al. reported that HRs (95% CIs) of dabigatran versus warfarin in patients with NVAF for ischemic stroke, myocardial infarction, ICB, and major gastrointestinal bleeding were 0.62 (0.52–0.73), 0.67 (0.43–1.05), 0.44 (0.32–0.60), and 0.99 (0.66–1.49), respectively. In addition, effect and risk differed by prescription dose of dabigatran [2]. Chan et al. also conducted subanalysis on the effect and risk by the change from warfarin to dabigatran, and the study outcomes were basically in concordance with those by Bengtson et al. Although there was no significant difference in the risk for gastrointestinal bleeding between dabigatran versus warfarin, further study is needed to verify their report.

Second, the authors did not adjust medication on depression in their study. Renoux et al. evaluated the risk of selective serotonin reuptake inhibitors (SSRIs) in patients with a history of stroke or transient ischemic attack for ICB with special reference to the concomitant use of antithrombotic drugs [3]. They set two levels of prescription dose of SSRIs in each antithrombotic drug, and adjusted relative risk (95%CI) of strong level of SSRIs versus weak level of SSRIs with concomitant use of anticoagulant was 4.99 (1.25–19.92). In addition, there is a review on the risk of gastrointestinal bleeding by SSRI medication, especially in patients with concurrent use of nonsteroidal anti-inflammatory or antithrombotic drugs [4]. Furthermore, Hackam and Mrkobrada reported that SSRIs were associated with an increased risk of ICB, although the absolute risk was low [5]. Depression is prevalent as comorbid disease in patients with physical disorders and I recommend Bengtson et al. considering psychiatric medication such as SSRIs for their analysis.

References


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Received 12 December 2016
Accepted 20 December 2016
Available online 13 February 2017

http://dx.doi.org/10.1016/j.jccd.2016.12.017

Author’s reply

Questions in the comparative effectiveness of dabigatran and warfarin in atrial fibrillation

Keywords:
Atrial fibrillation
Anticoagulation
Comparative effectiveness

We appreciate Dr Kawada’s letter to the editor regarding our manuscript assessing the comparative effectiveness of dabigatran and rivaroxaban versus warfarin in patients with non-valvular atrial fibrillation (AF) [1,2]. In the letter, Dr Kawada highlights the consistency of our results with those from a recent report by Chan and colleagues comparing outcomes in patients with AF receiving dabigatran to those receiving warfarin using data from the Taiwan National Health Insurance Research Database [3]. The similarity in
findings across diverse geographic regions should reassure both clinicians and patients about the effectiveness of dabigatran (and possibly other newer oral anticoagulants) in the prevention of stroke and systemic embolism in non-valvular AF.

Dr Kawada also mentions the previously reported association between use of selective serotonin reuptake inhibitors (SSRIs) and risk of intracranial bleeding, particularly among individuals taking oral anticoagulants [4]. Although we did not specifically adjust for SSRI or antidepressant use, our decision to use high-dimensional propensity score adjustment ensures that our analysis controlled for the most important measured confounders. If SSRIs, other antidepressants, or a diagnosis of depression confounded the associations being studied, these clinical covariates would have been incorporated into the calculation of high-dimensional propensity scores since our approach included both diagnostic codes from inpatient and outpatient claims and outpatient pharmacy claims, as has been recommended [5]. Future studies should explore whether SSRIs and other antidepressants interact with warfarin and non-vitamin K antagonists oral anticoagulants to modify the risk of bleeding in patients with non-valvular AF.

Disclosures: Dr Alonso is supported by grant R01 HL122200 from NIH and 16EIA26410001 from the American Heart Association and Dr Lutsey by grant R01 HL131579 from NIH. Dr Bengtson is an employee of Optum.

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Received 21 January 2017
Available online 18 March 2017

http://dx.doi.org/10.1016/j.jcc.2017.02.003