Peer Review File

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Reviewer Comments

Comment 1:

Introduction:

a. The assumption that NOAC are better than Vitamin-K-antagonists (VKA) derive mainly from trials, sponsored by the manufacturers of the NOAC (ref. 2-5). Independent data, although retrospectively collected, show a different aspect regarding safety and efficacy of NOAC compared with VKA. Two recently published examples are: Wang et al. TH Open. 2020 Jul 13;4(3):e145-e152. and Paschke et al. BMC Med. 2020 Aug 27;18(1):254. This issue should be mentioned in the introduction.

b. Most probably, there are differences in the pharmacology of these drugs, as discussed by Paschke et al. Is warfarin the only available VKA in China or are other drugs like phenprocoumon or acenocoumarol also available?

Reply 1:

a. We thanks the reviewer for constructive suggestion. We accordingly have revised the statements as follows: Based on randomised clinical trial (RCTs) results, current guidelines have adopted NOACs as the preferred treatment for the prevention of stroke in patients with AF (1-4). Meanwhile, the current evidence from RCTs and real-world studies suggest a variability across NOACs regarding bleeding risk, with a concern for rivaroxaban, but not for dabigatran and apixaban (5,6). In China, besides warfarin, NOACs, including Dabigatran, rivaroxaban, and edoxaban, have been approved by the National Medical Products Administration (NMPA) for stroke prevention in patients with AF.

b. Indeed, warfarin is the only vitamin K antagonist that has been approved for the anticoagulant treatment in China.

Comment 2:

Patients recruitment: The prevalence of AF and the stroke risk increases with age. The NOAC- investigating trials (ref. 2-5) have mainly included younger patients. Thus, it seems important that especially patients >75 years will be included in the trial – how will this be organized?

Reply 2:

We thank the reviewer for pointing out this issue. We accordingly have added the statements as

follows: Patients will be consecutively enrolled from 26 sites in seven geographical regions (East China, South China, North China, Central China, Northwest China, Southwest China, and Northeast China) from January 2021 to June 2021, using a competitive inclusion method. Given that AF patients aged ≥75 years is considered a risk factor in stroke risk-stratification tool (CHA2DS2-VASc score) and account for over 30% of AF patients in clinical setting (7), this study will included at least 30% of elderly patients to strengthen the representativeness of population.

Comment 3:

Data extraction:

a. Not only the weight but also the body mass index (BMI) should be registered because NOAC are not recommended in patients with a BMI>40: Martin et al. J Thromb Haemost. 2016; 14: 1308–1313.

b. I miss the list of potentially interacting drugs which will be collected. The drugs, listed in table 2 as “drug-drug interaction” is by far not complete! An attempt for a complete list has been made by Stöllberger Expert Rev Clin Pharmacol. 2017 Nov;10(11):1191-1202. In the list of drugs, herbal substances, which are used in China, should be added. I am not familiar with these substances, but I assume that

some of them might affect the activity of CYP3A4, p-Glycoprotein or CYP2C9.

c. The SAMe-TT2R2 score will be used to predict INR control. Has this score been validated in Chinese patients? Has this score been validated in NOAC-treated patients?

Reply 3:

a. We appreciate the Reviewer for pointing out this issue. We accordingly have added the body mass index (BMI) information in the data collection section.

b. We thank the reviewer for constructive suggestion. We accordingly added the drug-drug information in revised Table 2.

c. We thank the reviewer for constructive suggestion. The SAMe-TT2R2 score has been validated in a Hong Kong population cohort and a Singapore population cohort. We accordingly have revised the sentences as follows: "SAMe-TT_2R_2 scores will be used to predict INR control in warfarin users (8), which has been validated in two Asian population cohorts (9,10)."

Comment 4:

Quality control: Reference 20 is not available; thus, I cannot assess the appropriateness of quality control.

Reply 4:

We have added the reference 20, which is a Chinese article (Y Z, Z D. Expert Consensus on the Standard Operating Procedure for Anticoagulation (Antithrombotic) Clinic. Chinese Circulation Journal 2019;34:944-50.)

Comment 5:

Outcomes: It remains unclear how "inappropriate prescription" is defined.

Reply 5:

We are sorry for the vague expression about inappropriate prescription. We accordingly revised the sentences as follows: A prescription of NOACs will be defined as inappropriate based on indications, choices, or dosages. The appropriateness of antithrombotic therapy and NOAC prescriptions will be evaluated

according to the evaluation flow chart (**Figure 2**) and label recommendations for dabigatran, rivaroxaban, and edoxaban (**Table 2**). First, patients will be categorised into the antithrombotic therapy-appropriate and antithrombotic therapy-inappropriate groups according to the 2018 American College Chest Physicians recommendation for AF (8). Specifically, the recommendations state that (i) aspirin has no role in stroke prevention in patients with non-valvular AF; (ii) in patients with a "low risk" CHA2DS2-VASc score (i.e. 0 in males or 1 in females), no antithrombotic therapy is recommended; (iii) in patients with a CHA2DS2-VASc score ≥1 (beyond female sex alone), antithrombotic therapy should be considered, and NOACs are preferred over vitamin K antagonists (VKAs); and (iv) NOACs should not be used in patients with moderate-to-severe mitral stenosis or prosthetic heart valves.

In addition to the inappropriate indications and choices mentioned above, the appropriateness of NOAC dosing will be evaluated based on patient-specific factors such as age, renal and hepatic function, weight, bleeding risk, and concurrent medications according to the approved NMPA label. These patients will be categorised into four groups based on their NOAC dose: on-label standard dose, on-label reduced dose, underdosing, and overdosing. An overdosed prescription will be defined as a prescription for a standard dose of a NOAC despite the patient meeting the dose reduction criteria. An underdosed prescription will be defined as a prescription for a reduced dose of a NOAC despite the patient meeting the standard dose criteria.

References

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10. Chan PH, Hai JJ, Chan EW, et al. Use of the SAMe-TT2R2 Score to Predict Good Anticoagulation Control with Warfarin in Chinese Patients with Atrial Fibrillation: Relationship to Ischemic Stroke Incidence. PLoS One 2016;11:e0150674.