Gastrointestinal-Bleeding between NOACs and VKAs

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Non-vitamin K antagonist oral anticoagulants (NOACs) are more commonly used to prevent atrial fibrillation (AF) patients from thromboembolic events than vitamin K antagonists (VKAs). However, the gastrointestinal bleeding (GIB) risk in the Asian AF patients associated with NOACs in comparison with VKAs remained unaddressed.

Keywords: gastrointestinal bleeding ; Asian ; non-vitamin K antagonist oral anticoagulants ; NOAC ; warfarin ; vitamin K antagonist ; atrial fibrillation

1. Introduction

The overall atrial fibrillation (AF) prevalence is about 1% worldwide, and nearly 10% in populations older than 80 years old [1]. Stroke prevention in the AF patients is an important issue because patients with AF have an approximately five times higher risk of stroke than those without AF [2][3]. The resulting mortality and bed-ridden status bring plenty of problems in terms of medical expenditure and long-term care [4].

Non-vitamin K antagonist oral anticoagulants (NOACs) involve dabigatran, which inhibits thrombin, and rivaroxaban, apixaban, and edoxaban, which inhibit factor Xa. NOACs have some advantages, such as minor drug-food or drug-drug interactions and no need for laboratory monitoring. Besides, Asian AF patients under vitamin K antagonists (VKAs, warfarin) use easily encountered bleeding events and would seldom reach an optimal international normalized ratio control when taking VKAs.

Moreover, Asian AF patients have more risks of stroke/systemic embolism, ischemic stroke, and hemorrhagic stroke than non-Asians under VKAs use [5]. Therefore, NOAC use is recommended in non-Asia areas [6][7][8]. However, the gastrointestinal safety remains an essential concern of NOAC use.

Gastrointestinal bleeding (GIB) resulting from NOACs is potentially life-threatening [9][10]. However, the current non-Asia meta-analyses are controversial. According to the meta-analysis performed by Holster et al., a 1.6- and 1.5-fold increased GIB risk among dabigatran and rivaroxaban users was reported, respectively [11]. A subsequent meta-analysis by Rong et al. discovered no increased GIB risk associated with NOACs [12]. On the other hand, a meta-analysis by Wang et al. [13] mentioned that with VKAs use, Asian patients had similar GIB to non-Asian patients, and the risk of GIB with standard-dose NOACs was higher than that with warfarin. However, such the observation might be modified by races. The hypothesis is that the concomitant antiplatelet therapy and the use of proton pump inhibitors might be independent factors to influence the GIB risk. As time goes on, further studies including the GIB risk of the Asian AF patients taking different NOACs (rivaroxaban, dabigatran, apixaban, and edoxaban) compared with VKAs are being published. Therefore, this study aimed to apply the up-to-date trials and real-world studies to investigate the GIB risk in the Asian AF population using NOACs and VKAs. The GI safety of different NOACs versus VKAs was also evaluated.

2. Discussion

This study was the first meta-analysis investigating the GIB risk associated with NOACs in Asian AF patients. It highlighted the real situations of GIB resulting from NOACs use in Asia. Our study recruited more than 200,000 patients. We used the rigorous article appraisal tools such as ROB 2.0 for RCTs and ROBINS-I for retrospective studies.

According to this study, overall, NOACs cause less risk of GIB than conventional VKAs. Among them, apixaban seemed to bring about the lowest risk of GIB compared with VKAs, though we could not evaluate the publication bias due to the limited number of enrolled studies. Rivaroxaban was noted with the highest risk of GIB in current analyses.

We set the primary outcome of “any” GIB instead of “major” GIB because clinical decision making is often affected by the GIB signs related to NOACs and VKAs. A major GIB analysis was also performed and the result was similar to any GIB (Figure S4). Except for major GIB, physicians usually hold NOACs or VKAs if the other GIB conditions were suspected,

not only focusing on major GIB. Therefore, our study was close to the real-world circumstances. Additionally, we excluded the studies which probably used the identical database or the same population to increase the validity of the meta-analysis. We recruited only Asian patients to emphasize the clinical practicality when physicians prescribe NOACs.

Our study revealed NOACs GI safety versus VKAs and presented different NOACs versus VKAs for the Asian AF population. Previous systematic reviews and meta-analyses reported mainly non-Asians and did not separate AF from the other diseases that also need NOACs treatment. One systematic review and meta-analysis revealed a similar risk of major GIB between NOACs and conventional anticoagulants [14]. However, it included patients with AF and venous thromboembolism (VTE). Among the AF patients, they were almost all non-Asians. The other systematic review and meta-analysis enrolling data from RCTs and real-world studies reported no significant difference in the risk of major GIB between the patients receiving NOACs and conventional anticoagulants. Rivaroxaban users had a 39% increase in the risk for major GIB [15]. However, the recruited patients were nearly from the non-Asia regions. Furthermore, they did not focus on the AF population and not consider the dosage difference between the enrolled studies. Another large-scale network meta-analysis showed that apixaban and edoxaban had the most favorable major GIB safety profile, while rivaroxaban and dabigatran were the least safe [16]. Although the primary outcome was similar to our study and the population was large, it did not focus on Asian AF population and might cause selection bias. We used a more precise statistical method such as HRs, which can represent instantaneous risk over the study period time, or some subset thereof. HRs suffer somewhat less from selection bias concerning the endpoints chosen and can indicate the risks that happen before the endpoint. Therefore, our study could offer a significant and favorable choice of NOACs for clinicians and give patients medical advice about the real GIB risk data.

Different from other areas of the world, NOACs are beneficial for the Asian population and result in less GIB risk. In the non-Asian population, the use of NOACs seems to cause a higher risk of GIB than the Asian population. Holster et al. revealed an increased risk of GIB among NOAC users compared with standard care (pooled OR = 1.45), although significant heterogeneity existed regarding the choice of drugs and the indications of anticoagulation. The other meta-analysis recruiting mainly studies from the USA, New Zealand, and Europe revealed a slightly higher risk of GIB with dabigatran compared with VKAs. In contrast, no significant difference was found between rivaroxaban and VKAs for GIB risk [17]. Another meta-analysis showed that rivaroxaban, high-dose dabigatran, and edoxaban should not be prescribed to patients with high GIB risk [18]. However, this study did not solely enroll Asians.

We disclosed that overall NOACs presented better than VKAs in GIB for the Asian AF population. Previously, a new score system which was named “SAMe-TT2R2” could predict the quality of anticoagulation control among patients with AF on VKAs [19]. Based on Chan’s study, the time in therapeutic range (TTR) decreased progressively with increasing SAMe-TT2R2 score (*p*: 0.016). When the cut-off value of SAMe-TT2R2 score was set at 2, the sensitivity and specificity to predict TTR < 70% were 85.7% and 17.8%, respectively [20]. In the Chinese AF patients, the SAMe-TT2R2 score has a good correlation with TTR. For example, a female Asian’s SAMe-TT2R2 score is at least three, high in the baseline. Then low TTR could cause VKA-related GIB. Therefore, NOACs are a better choice for Asians than VKAs.

We recruited two RCTs in this meta-analysis. Only one enrolled RCT showed some concerns in bias due to deviations from intended interventions because the selected group using NOACs might have less GIB risk. It also showed some concerns in bias in the selection of the reported result. Nevertheless, these two RCTs were very significant for this study because there were few RCTs about NOACs GIB in Asia. Although RCTs have advantages in the GRADE system, they may not reflect the real situations of the AF population in Asia. First, RCTs with limited follow-up can potentially underestimate the long-term benefits of treatment and may fail to detect delayed hazards. A post-trial follow-up of RCTs, which means extended follow-up starting after the end of the scheduled period of the original trial is needed. It is essential not only to define the impact of a long-term intervention but also to ascertain the safety profile. Moreover, potential hazards may not be obvious during the duration of trial follow-up [21]. Second, RCTs usually pay attention to major GIB only, which might lead to an underestimation of all GIB. Third, we need real-world data to distinguish GIB risk from different NOAC because it is impossible to perform head-to-head RCTs currently. In addition, the Asian AF patients only accounted for about 10% in the pivotal RCTs. Therefore, we need to recruit the postmarketing studies and the retrospective observational studies for more accurate data. Besides, physicians might avoid prescribing NOACs for the patients at high risk of GIB in the real-world clinical conditions. Our study contained two RCTs and four retrospective studies, which was close to the real-world practice situations. They were also strictly evaluated by the current appraisal tools from the Cochrane system. There were still some biases in our enrolled retrospective studies. They had serious performance in bias in the selection of participants into the study, which was probably due to ICD codes not precise in the diagnosis from the database. There was a low risk of bias in the classification of interventions and bias in missing data because the clinical setting was prominent while GIB happened and the database was intact in several Asian countries/regions (Taiwan, Korea, Japan, China/Hong Kong, etc.). A serious risk of bias due to deviations from intended

interventions was originated from unseen biases such as the methods of study design, patient's lifestyle and eating habits, body mass index, and alcohol/betel nut/smoking. A serious risk of bias in the measurement of outcomes happened because sometimes clinical conditions such as bloody sputum or food digestion color were mistaken as GIB. A moderate risk of bias in the selection of the reported result was evaluated because there might be some negative result data not reported. The definite conclusions could not be just based on these studies.

Recently, the FDA issued a renewed dabigatran safety announcement, which reported a higher GIB risk (HR = 1.28; 95% CI, 1.14 to 1.44) in contrast with warfarin [22][23]. Besides, the postmarketing pharmacovigilance studies showed adverse drug reactions of GIB in Japan, Australia, Canada, and the USA [24][25][26][27].

NOACs, mainly rivaroxaban and dabigatran, were considered more dangerous in GIB. However, the apixaban and the edoxaban observational studies re-defined the GIB risk. One study revealed the non-major bleeding (including GIB) was substantially less frequent in apixaban than in warfarin [28]. Another first head-to-head Korean study made a comparison of the effectiveness and safety between rivaroxaban and edoxaban and showed that edoxaban had a trend toward less GIB [29]. The results from these two studies were similar to our study. However, we still need more observational studies from other countries in Asia to establish the NOACs GI safety profile in the future.

Our studies had some limitations. First, not all Asian countries were included, and the results could not be applied to the whole Asian population. Second, the apixaban and the edoxaban head-to-head studies are still lacking because the marketed time was shorter than that of dabigatran and rivaroxaban. Third, we calculated the HR of GIB from different NOACs compared with VKAs, but our enrolled studies did not uniformly use the same definition of GIB event and did not describe the source of GIB at all. Finally, we did not focus on the meta-analyses of the different doses of NOACs versus VKAs for GIB risk because few studies included this concern. In our enrolled articles, only Yamashita et al. [49] and Chan et al. [51] had analyzed the GIB risk of standard-dose and low-dose NOACs compared with VKAs. The result of meta-analyses was shown in Figure S5, which suggested that low-dose NOACs was significantly associated with a lower risk of GIB than standard-dose NOACs compared with VKAs.

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