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Major bleeding and intracranial hemorrhage risk prediction in patients with atrial fibrillation: Attention to modifiable bleeding risk factors or use of a bleeding risk stratification score? A nationwide cohort study

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ABSTRACT

Background: While modifiable bleeding risks should be addressed in all patients with atrial fibrillation (AF), use of a bleeding risk score enables clinicians to 'flag up' those at risk of bleeding for more regular patient contact reviews. We compared a risk assessment strategy for major bleeding and intracranial hemorrhage (ICH) based on modifiable bleeding risk factors (referred to as a 'MBR factors' score) against established bleeding risk stratification scores ($HEMORR_2HAGES$, HAS-BLED, ATRIA, ORBIT).

Methods: A nationwide cohort study of 40,450 AF patients who received warfarin for stroke prevention was performed. The clinical endpoints included ICH and major bleeding. Bleeding scores were compared using receiver operating characteristic (ROC) curves (areas under the ROC curves [AUCs], or c-index) and the net reclassification index (NRI).

Results: During a follow up of 4.60 ± 3.62 years, 1581 (3.91%) patients sustained ICH and 6889 (17.03%) patients sustained major bleeding events. All tested bleeding risk scores at baseline were higher in those sustaining major bleeds. When compared to no ICH, patients sustaining ICH had higher baseline $HEMORR_2HAGES$ ($p = 0.003$), HAS-BLED ($p < 0.001$) and MBR factors score ($p = 0.013$) but not ATRIA and ORBIT scores. When HAS-BLED was compared to other bleeding scores, c-indexes were significantly higher compared to MBR factors ($p < 0.001$) and ORBIT ($p = 0.05$) scores for major bleeding. C-indexes for the MBR factors score was significantly lower compared to all other scores (De long test, all $p < 0.001$). When NRI was performed, HAS-BLED outperformed all other bleeding risk scores for major bleeding (all $p < 0.001$). C-indexes for ATRIA and ORBIT scores suggested no significant prediction for ICH.

Conclusion: All contemporary bleeding risk scores had modest predictive value for predicting major bleeding but the best predictive value and NRI was found for the HAS-BLED score. Simply depending on modifiable bleeding risk factors had suboptimal predictive value for the prediction of major bleeding in AF patients, when compared to the HAS-BLED score.

1. Introduction

Stroke prevention is the principal initial objective of management in patients with atrial fibrillation (AF) [1,2]. Effective stroke prevention means oral anticoagulation (OAC) therapy, which requires a balance between stroke risk reduction and the risk of major bleeding, particularly intracranial hemorrhage (ICH).

Similar to stroke risk, the risks of serious bleeding in patients with AF are not homogeneous, and depend on the presence of various bleeding risk factors [3]. The more common and validated bleeding risk factors have been used to formulate bleeding risk stratification scores [4]. The latter have varying complexity and incorporation of bleeding risk factors, and have been subject to inappropriate use and misconceptions. Thus, recent guidelines have de-emphasized the use or value of bleeding risk scores but instead directed focus on modifiable bleeding risk factors [5].

However, bleeding risk is simply not dependent on modifiable bleeding risk factors determined at baseline, and the bleeding endpoint

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ascertained years later, as bleeding risk is highly dynamic and many reasons for bleeding can be modified [3]. The use of bleeding risk scores has also been subject to misconceptions and misuse, and a high bleeding risk score is not an excuse to withhold OAC [6]. While modifiable bleeding risks should be addressed in all patients, a high bleeding risk score 'flags up' those at risk of bleeding for more regular patient contact reviews [6].

In this study, we compared a risk assessment strategy for major bleeding and ICH based on *modifiable bleeding risk factors* promoted by the 2016 European Society of Cardiology (ESC) guidelines [5] (referred to as a 'MBR factors score') against established bleeding risk stratification scores.

2. Methods

This study used the "National Health Insurance Research Database (NHIRD)" released by the Taiwan National Health Research Institutes. The National Health Insurance (NHI) system is a mandatory universal health insurance program that offers comprehensive medical care coverage to all Taiwanese residents. NHIRD consists of detailed health care data from >23 million enrollees, representing >99% of Taiwan's population. In this cohort dataset, the patients' original identification numbers have been encrypted to protect their privacy, but the encrypting procedure was consistent, so that a linkage of the claims belonging to the same patient was feasible within the NHI database and can be followed continuously.

2.1. Study cohort and study design

The study protocol of the present study was similar to our previous studies [7–12]. From January 1, 1998 to December 31, 2011, a total of 327,373 AF patients aged ≥20 years were identified from the NHIRD. AF was diagnosed using the International Classification of Diseases (ICD), Ninth Revision, Clinical Modification (ICD-9-CM) codes (427.31). To ensure the accuracy of diagnosis, we defined patients with AF only when it was a discharge diagnosis or confirmed for at least 2 times in the outpatient department. The diagnostic accuracy of AF using this definition in NHIRD has been validated previously [13]. Among 327,373 AF patients, 40,450 patients who received warfarin for stroke prevention were identified as the study population. The clinical endpoints included ICH and major bleeding, defined as ICH or bleeding from gastrointestinal or genitourinary or respiratory tract requiring hospitalization and blood transfusion. The flowchart of patient enrollment is shown in Supplemental Fig. 1.

2.2. Bleeding scores

The HAS-BLED score was calculated by assigning 1 point each for hypertension, abnormal renal or liver function, stroke, bleeding history, age 65 years or older, and antiplatelet drug or alcohol use [14]. Since the information of international normalized ratio (INR) of warfarin was not available in the Taiwan registry database, the component of "labile INR," was excluded from the scoring in the present study, consistent with prior registry studies. Other bleeding scores, including HEMORR$_2$HAGES, ATRIA and ORBIT scores, were calculated for each patient based on his/her original calculation rules with some modifications owing to the limitations of the registry database [15–17]. Specifically, the components of "genetic factors (CYP2C9 single nucleotide polymorphism)" and "excessive fall risk" were excluded from the HEMORR$_2$HAGES score. Also, abnormal liver function, anemia, renal insufficiency, and reduced platelet count were defined by the ICD-9-CM codes rather than laboratory data.

The MBR factors score was defined as the cumulative number of modifiable bleeding risk factors of each patient according to the 2016 ESC guideline [5], including hypertension, medication predisposing to bleeding (e.g. concomitant antiplatelet drugs and non-steroidal anti-inflammatory drugs [NSAIDs]) and excess alcohol. The MBR factors score of each patient would range from 0 to 3.

2.3. Statistical analysis

Data are presented as the mean value (standard deviation [SD]) for continuous variables and proportions for categorical variables. The differences between normally distributed continuous values and nominal variables were assessed using an unpaired 2-tailed t-test and Chi-square test, respectively. The risks of ICH and major bleeding were assessed using the Cox regression analysis. The diagnostic accuracies of the bleeding schemes in predicting ICH and major bleeding were assessed by calculating c-indexes, based on the receiver operating characteristic (ROC) curve. The areas under the ROC curves (AUCs, C-indexes) of these scorings were compared using DeLong's test. The net reclassification index (NRI) comparing HAS-BLED score and 'MBR factors score' to other scoring systems was also calculated. Decision curve analysis was performed to study the net benefits related to the use of HAS-BLED and MBR factors scores for the prediction of major bleeding [18]. All statistical significances were set at a $p < 0.05$.

3. Results

Among 40,450 patients with a follow up of 4.60 ± 3.62 years, 1581 (3.91%) patients sustained ICH and 6889 (17.03%) patients sustained major bleeding events (Supplemental Fig. 1).

Table 1 shows the baseline characteristics of study population and patients with or without major bleeding and ICH. When compared to no ICH, patients sustaining ICH were older ($p = 0.004$) and had more prevalent abnormal liver function ($p < 0.001$), stroke ($p < 0.001$), use of NSAIDs ($p = 0.012$) and higher baseline HEMORR$_2$HAGES ($p = 0.003$) and HAS-BLED scores ($p < 0.001$), and as expected, a higher MBR factors score ($p = 0.013$) [Table 1]. Baseline ATRIA and ORBIT scores were not significantly different between ICH and non-ICH patients.

Compared to patients without major bleeding, age and various comorbidities such as hypertension, abnormal renal or liver function, stroke, history of bleeding, anemia, and use of NSAIDs were higher in those sustaining major bleeds [Table 1]. All tested bleeding risk scores (HEMORR$_2$HAGES, HAS-BLED, ATRIA, ORBIT and MBR factors score) at baseline were higher in those sustaining major bleeds (all $p < 0.005$) [Table 1]. Fig. 1 summarizes the hazard ratios (HRs) for ICH and major bleeding *per point increment* of the respective bleeding risk scores; all scores showed a significant increased HR per point increase (all $p < 0.001$). The annual risk of major bleeding and ICH for patients stratified by HAS-BLED and MBR factors score is shown in Table 2. As expected, major bleeding and ICH rates increased with increasing points on the tested scores.

All the bleeding risk scores (HEMORR$_2$HAGES, HAS-BLED, ATRIA, ORBIT and MBR) had modest predictive value for predicting major bleeding (c-indexes approx. 0.55) with the highest c-index found for the HAS-BLED score [Table 3a]. When HAS-BLED score was compared to other bleeding scores, there were significantly higher c-indexes compared to MBR factors score ($p < 0.001$) and ORBIT score ($p = 0.05$) for major bleeding, but non-significant for HEMORR$_2$HAGES and ATRIA scores. C-index for the MBR factors score was significantly lower compared to all other bleeding scores (ie. HEMORR$_2$HAGES, HAS-BLED, ATRIA, ORBIT; De long test, all $p < 0.001$) [Table 3a].

Only HEMORR$_2$HAGES, HAS-BLED and MBR factors scores had significant but modest predictive value for predicting ICH, with the highest c-index found for the HAS-BLED score [Table 3a]. C-indexes for ATRIA and ORBIT scores suggested no significant prediction for ICH. When HAS-BLED score was compared to ATRIA and ORBIT scores, HAS-BLED had a significantly higher c-index for ICH (Delong test, all $p < 0.001$) [Table 3a]. C-indexes for the MBR factors score were non-significantly different for ICH compared to other scores (HEMORR$_2$HAGES, HAS-BLED, ATRIA) apart from ORBIT, which was significantly lower ($p = 0.043$) [Table 3a].

When NRI was performed, HAS-BLED outperformed all other bleeding risk scores for major bleeding (all $p < 0.001$), while for ICH, HAS-BLED outperformed the ATRIA ($p < 0.001$) and ORBIT scores ($p = 0.014$) [Table 3b].

Decision curve analyses for the HAS-BLED and MBR factors scores in predicting major bleeding are shown in Supplemental Fig. 2. This analysis shows the clinical usefulness of each score based on a continuum of potential thresholds for major bleeding (x axis) and the net benefit of using the model to stratify patients at risk (y axis) relative to assuming that no patient will have a major bleeding. The results showed that HAS-BLED had better net benefit of predicting major bleeding compared to the MBR factors score.

4. Discussion

As far as we are aware, this is the largest *nationwide* assessment of the various contemporary bleeding risk scores for patients with AF, assessing the endpoints of major bleeding and ICH. Our principal findings are as follows: (i) Baseline HEMORR$_2$HAGES, HAS-BLED and MBR