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Antithrombotic Medication and the Risk of Vitreous Hemorrhage in Atrial Fibrillation: Korean National Health Insurance Service National Cohort

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Purpose: Antithrombotic therapy could be related with nuisance bleeding. This study investigated whether vitreous hemorrhage (VH) is associated with specific types of antithrombotic medication in patients with atrial fibrillation (AF).

Materials and Methods: In the Korean National Health Insurance Service National Sample Cohort, we identified 9352 antiplatelet/anticoagulant-treated AF patients. The occurrence of VH was compared between warfarin (n=1493) and a propensity score (PS)-matched antiplatelet group (n=1493) and between warfarin (n=1493) and a PS-matched warfarin+antiplatelet group (n=1493).

Results: The outcomes of VH were lower in the warfarin than in the matched antiplatelet (1.45 vs. 3.72 events/1000 patient-years) and matched warfarin+antiplatelet groups (1.45 vs. 6.87 events/1000 patient-years). Compared with warfarin, the risk of VH increased with antiplatelet [adjusted hazard ratio (aHR) 3.90; 95% confidence interval (CI) 1.22–12.4, p=0.022] and warfarin+antiplatelet agents (aHR 4.39, 95% CI 1.74–11.2, p=0.002). Compared with warfarin only, warfarin+antiplatelet agents increased the risk of VH in patients ≥65 years, regardless of gender and hypertension. The risk of VH was significantly higher with dual antiplatelet therapy (aHR: 5.02, 95% CI: 1.56–16.2, p=0.007) or in dual (aHR: 5.02, 95% CI: 1.74–14.5, p=0.003) or triple therapy using warfarin and antiplatelet agents than with warfarin monotherapy (aHR: 6.12, 95% CI: 1.76–21.3, p=0.004).

Conclusion: Dual antiplatelet or triple therapy increased the risk of VH significantly, compared to warfarin monotherapy. Considering the low efficacy of preventing ischemic stroke and high risk of bleeding, dual or triple therapy using warfarin and antiplatelet agents should be avoided to prevent VH in AF patients.

Key Words: Vitreous hemorrhage, antiplatelet, anticoagulant, atrial fibrillation

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, occurring in 1–2% of the general population.[1,2] AF confers a five-fold risk of stroke, and one in five of all strokes is attributed to this arrhythmia.[3] Therefore, the administration of antithrombotic (antiplatelet or anticoagulant) medication is critical for the prevention of thromboembolic events in patients with AF. According to recent worldwide data, the number of patients taking antithrombotic medication is expected to rise with an increase in the number of AF patients.[4] Although major bleeding, including intracranial hemorrhage or gastrointestinal bleeding, has been evaluated intensively, minor bleeding events (nuisance bleedings), including ocular bleeding, have not been well

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investigated. Recently, however, the importance of surveillance and adequate management for nuisance hemorrhagic complications arising from using these medications has been highlighted.[5] Nuisance bleedings is common among patients with AF on oral anticoagulants (OACs). However, nuisance bleedings was not associated with a higher risk of major bleeding or stroke/systemic embolism over the next 6 months, suggesting its occurrence should not lead to changes in anticoagulation treatment strategies.

Vitreous hemorrhage (VH) is a potential intraocular hemorrhagic complication associated with oral antiplatelet or anticoagulant medication, such as aspirin, clopidogrel bisulfate, and warfarin sodium.[6-12] Although VH can be absorbed spontaneously, it can also result in more serious complications threatening vision, such as intraocular pressure increase and proliferative vitreoretinopathy, leading to invasive surgical intervention. Moreover, many AF patients discontinue antiplatelet or anticoagulant medication after VH and might experience thromboembolic events during this period. Therefore, the association between VH and antiplatelet or anticoagulant medication is important for both ophthalmologists and cardiologists.

Previous clinical studies have reported varying degrees of associations between VH and oral antiplatelet or anticoagulant use.[6-12] However, most studies were performed on populations with specific retinal diseases or patients undergoing intraocular interventions. Epidemiological data are limited for generalizing the impact of antiplatelet or anticoagulation medication on VH risk. In this regard, we investigated the effects of antiplatelet and anticoagulation medication on VH development and non-pharmacological risk factors of VH in patients with AF using the Korean National Health Insurance Service (NHIS) database.

MATERIALS AND METHODS

Data source

This study was conducted using the NHIS-National Sample Cohort (NSC).[13] The NHIS database represents the nationwide population of South Korea.[1-3] The NHIS is a single insurer managed by the Korean government that covers 97% of the entire population; other programs, such the Medical Assistance Program, cover the remaining 3%. The National Health Insurance Claim database stores data on the entire Korean population, including all demographic and medical information. Based on this database, the NHIS-NSC was created and released in 2014.[13] It contains medical claims for 2.2% (n=1025340) of the total Korean population (about 50 million); individuals were randomly selected from January 1, 2002. NHIS-NSC data provide information on healthcare utilization based on the National Health Insurance claims from medical institutions to the NHIS for inpatient and outpatient clinic visits.[1-3] The database is open to researchers once their study protocol has been approved by an official review committee. The Institutional Review Board of Severance Hospital at Yonsei University College of Medicine approved our study (4-2014-0996). Since we used anonymous data, the requirement to obtain informed consent was waived.

Study population

The current study included patients aged 19 years or older who were diagnosed with AF from January 2002 to December 2008. Patients with AF were identified using the International Classification of Disease, Tenth Revision (ICD-10): I480, I481, I482, I484, and I489. AF was validated in previous studies with a positive predictive value of 94.1%.[1-3] To ensure diagnostic accuracy, we defined patients with AF only when they had a discharge diagnosis or were confirmed more than twice in the outpatient department.[1-3] We excluded patients without a history of antiplatelet/anticoagulant use before enrollment. Among 9352 patients who were followed from January 2009 to December 2013, we identified 6074 antiplatelet agent-treated patients, 1493 warfarin-treated patients, and 1785 warfarin+antiplatelet agent-treated patients. The occurrence of VH was compared between warfarin (n=1493) and a 1:1 propensity score (PS)-matched antiplatelet group (n=1493) and between warfarin (n=1493) and a 1:1 PS-matched warfarin+antiplatelet group (n=1493) (Fig. 1).

We obtained information on selected comorbid conditions from inpatient and outpatient hospital diagnoses. Baseline comorbidities were defined using the medical claims and prescription medication prior to the index date. In order to ensure diagnostic accuracy, patients were considered to have comorbidities when the condition was a discharge diagnosis or was

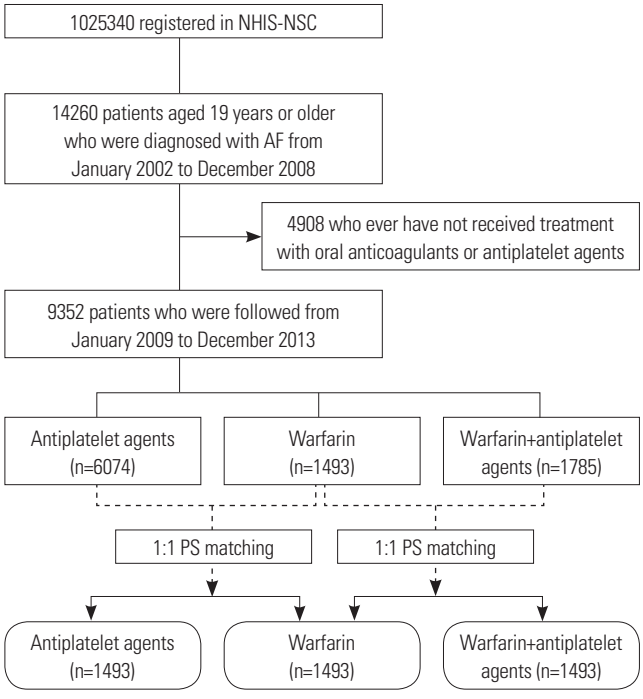

Fig. 1. Study cohort. NHIS-NSC, National Health Insurance Service-National Sample Cohort. AF, atrial fibrillation; PS, propensity score.

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confirmed at least twice in an outpatient setting, which was similar to previous studies with NHIS (Supplementary Table 1, only online).[14-17] Also CHA_2DS_2-VASc [congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, prior stroke or transient ischemic attack (TIA) (doubled), vascular disease, age 65 to 74, female] score and HAS-BLED [hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history, labile INR (left out because of data are unavailable), elderly (>65 years), concomitant drug (1 point each)] score were evaluated.[1]

Exposure of antiplatelet and anticoagulation agents

The exposure to antiplatelet and anticoagulation agents was identified based on filled antiplatelet or anticoagulant medication prescriptions over the follow-up period between January 2009 and December 2013. We used the most common medications for stroke prevention in patients with AF: aspirin and P2Y12 inhibitors (clopidogrel bisulfate, prasugrel, and ticagrelor) for antiplatelet medication and warfarin sodium for anticoagulation medication. The index date was defined as the date of first prescription of antiplatelet, warfarin, and warfarin + antiplatelet agents in antiplatelet, warfarin, and warfarin + antiplatelet groups, respectively.

Study outcome

The study outcome was newly developed VH (ICD-10 code H43.1) during the follow-up period between 2009 and 2013. To evaluate the accuracy of our definition of VH, we conducted a validation study with 102 randomly chosen patients with the ICD-10 code H43.1. Fundus photos and ultrasonographic images were reviewed by two ophthalmologists (KEK and SJK). The patients were deemed to have VH if it was documented by fundus photos and ultrasonography examinations. The positive predictive value was 95.3%. To ensure diagnostic accuracy, we defined patients with VH only when they had a discharge diagnosis or were confirmed more than twice in the outpatient department. The follow-up period was defined as from the index date until the first occurrence of VH or the end date of the study period, whichever came first.

Statistical analysis

The PS method, which simulates the effect of a randomized clinical trial for observational cohort data, was used to study the effects of warfarin on the occurrence of VH in comparison to other groups. PS reflects the predicted probability of treatment conditional on selected covariates, including age, sex, baseline comorbidities, and CHA_2DS_2-VASc and HAS-BELD scores, using logistic regression. The balance of covariates at baseline among the study groups was assessed using the absolute standardized mean difference (SMD). An absolute SMD <0.1 indicates a negligible difference in potential confounders between two study groups.

Incidence rates were estimated using the total number of study outcomes during the follow-up period divided by person-years at risk. The 95% confidence interval (CI) of incidence rate was estimated using a Poisson distribution.[18] The risk of VH for warfarin versus other drugs was obtained using survival analysis: Kaplan-Meier method and log-rank test for univariate analysis and Cox proportional hazards regression for multivariate analysis. We adjusted for age, gender, heart failure, hypertension, diabetes, stroke/TIA, previous myocardial infarction, dyslipidemia, hemorrhagic stroke, valvular heart disease, malignancy, nonsteroidal anti-inflammatory drugs (NSAID), and corticosteroid medications. Statistical analyses were performed using Statistical Package for the Social Science version 19.0 for Windows (IBM Corp., Armonk, NY, USA) and MedCalc (v. 12.0; MedCalc Statistical software, Marakierke, Belgium). Statistical significance was defined as $p<0.05$.

RESULTS

Study subjects

Before PS matching, the warfarin group was younger, had lower CHA_2DS_2-VASc score, and had a lower proportion of comorbidities than other groups (Supplementary Table 2, only online). After PS matching, both of the two groups were well balanced with the warfarin group for all characteristics (all SMD <0.1). The warfarin group included more patients with valvular heart disease, including mitral stenosis or prosthetic mitral valve, than the other groups (20.4, 1.1, and 7.0%, $p<0.001$) (Table 1).

Primary study outcomes

The cumulative incidence of VH is shown in Fig. 2. Overall, cumulative incidence curves revealed a lower rate of VH with warfarin than in matched antiplatelet (log rank $p=0.003$) (Fig. 2A) or warfarin+antiplatelet groups (log rank $p<0.001$) (Fig. 2B). The cumulative incidence of VH in each group is shown in Supplementary Fig. 1 (only online).

The outcomes of VH were lower for warfarin than for matched antiplatelet (1.45 vs. 3.72 events/1000 patient-years) and matched warfarin+antiplatelet groups (1.45 vs. 6.87 events/1000 patient-years). Compared with warfarin, the risk of VH was increased with antiplatelet [adjusted hazard ratio (aHR) 3.90; 95% CI 1.22–12.4, $p=0.022$] and warfarin+antiplatelet agents (aHR 4.39, 95% CI 1.74–11.2, $p=0.002$) (Table 2).

Similar findings were observed in a sensitivity analysis that compared rates of VH after excluding patients with valvular heart disease. In sensitivity analysis, the outcomes of VH were lower in the warfarin than in the matched antiplatelet (1.79 vs. 5.33 events/1000 patient-years) and matched warfarin + antiplatelet groups (1.79 vs. 7.21 events/1000 patient-years). The risk of VH was lower for warfarin than for antiplatelet (aHR 4.64, 95% CI 1.38–15.5, $p=0.013$) and warfarin+antiplatelet groups (aHR 4.15, 95% CI 1.57–11.0, $p=0.004$) (Table 3).

Table 1. Characteristics of Warfarin and Propensity Score-Matched Antiplatelet or Warfarin+Antiplatelet-Treated Patients with Atrial Fibrillation

	Warfarin (n=1493)	Antiplatelet (n=1493)	Warfarin+antiplatelet (n=1493)	SMD (warfarin vs. antiplatelet)	SMD (warfarin vs. warfarin+ antiplatelet)
Age (yr)	67 (56, 73)	66 (56, 74)	67 (57, 74)	-0.020	-0.098
Men	782 (52.4)	798 (53.4)	829 (55.5)	0.022	0.063
Congestive heart failure	559 (37.4)	539 (36.1)	516 (34.6)	0.028	0.060
Hypertension	1087 (72.8)	1057 (70.8)	1141 (76.4)	0.045	-0.081
Diabetes mellitus	231 (15.5)	228 (15.3)	289 (19.4)	0.006	-0.097
Ischemic stroke or TIA	333 (23.1)	356 (23.8)	345 (23.1)	0.019	-0.018
Previous MI	113 (7.6)	129 (8.6)	113 (9.8)	0.035	-0.041
PAD	104 (7.0)	104 (7.0)	131 (8.8)	0.049	-0.077
Dyslipidemia	639 (42.8)	626 (41.9)	717 (48.0)	0.018	-0.096
Hemorrhagic stroke	23 (1.5)	14 (0.9)	27 (1.8)	0.049	-0.022
Malignancy	233 (15.6)	215 (14.4)	238 (15.9)	0.032	-0.009
CHA_2DS_2-VASc score	3.00 (2.00, 4.00)	3.0 (1.0, 4.0)	3.0 (2.0, 5.0)	0.032	-0.067
HAS-BLED score	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	3.0 (2.0, 3.0)	0.011	-0.091
Propensity score-unmatched variables					
Valvular heart disease	305 (20.4)	16 (1.1)	104 (7.0)		
NSAID	586 (39.2)	721 (48.3)	676 (45.3)		
Steroid	122 (8.2)	148 (9.9)	154 (10.3)		

CHA_2DS_2-VASc, congestive heart failure, hypertension, age of ≥75 years (doubled), diabetes mellitus, prior stroke or TIA (doubled), vascular disease, age of 65 to 74 years, female sex; HAS-BLED, hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history, labile INR (left out because of data are unavailable), elderly (>65 years), concomitant drug (1 point each); MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drugs; PAD, peripheral artery disease; TIA, transient ischemic attack; SMD, standardized mean difference.
Values are presented as numbers (%) or medians (interquartile range).

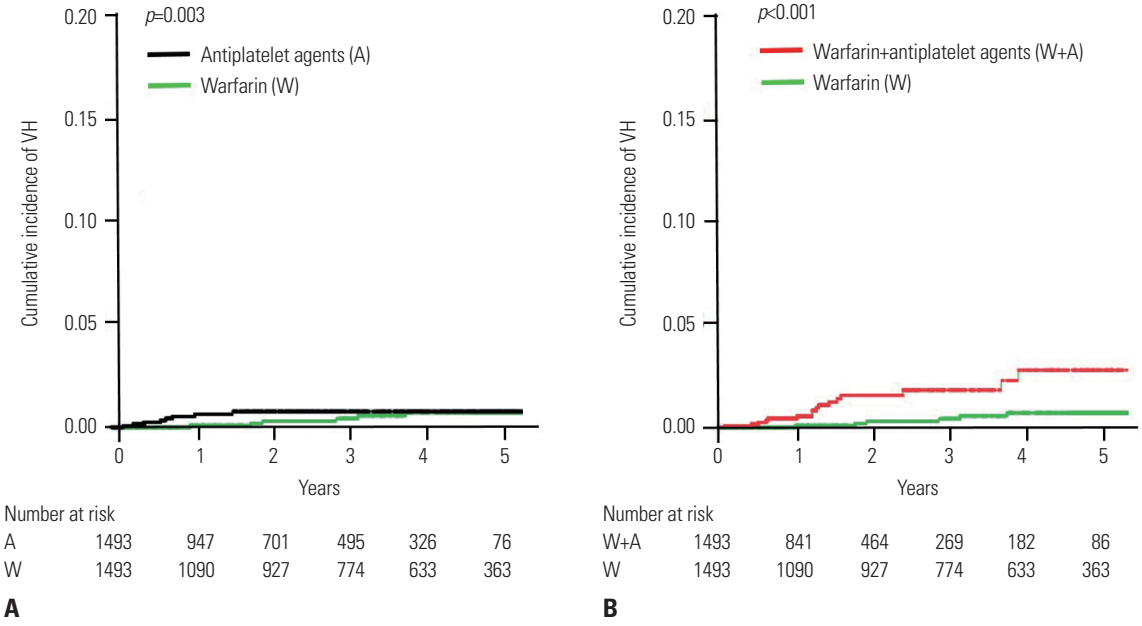

Fig. 2. Cumulative incidence of vitreous hemorrhage (VH). (A) Warfarin vs. antiplatelet agents. (B) Warfarin vs. warfarin+antiplatelet agents.

Outcomes according to different medications

Compared with warfarin, the risk of VH was significantly higher in dual antiplatelet therapy using aspirin and P2Y2 inhibitor (1.45 vs. 8.70 events/1000 patient-years; aHR: 5.02, 95% CI: 1.56–16.2, p=0.007), dual therapy using warfarin and aspirin (1.45 vs. 6.82 events/1000 patient-years; aHR: 5.02, 95% CI: 1.74–14.5, p=0.003), and also triple therapy using warfarin, aspirin, and P2Y2 inhibitor (1.45 vs. 8.91 events/1000 patient-years; aHR: 6.12, 95% CI: 1.76–21.3, p=0.004). However, P2Y2 inhibitor monotherapy or dual therapy using warfarin and P2Y2 inhibitors did not increase the risk of VH (Fig. 3).

Supplementary Fig. 2 (only online) shows the risk of VH ac-

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cording to warfarin, antiplatelet agents, and warfarin + antiplatelet agents in overall patients.

Outcomes by different subgroups

Compared with warfarin, antiplatelet agents significantly increased the risk of VH in patients with hypertension and stroke or TIA (Fig. 4A). The risk of VH was generally increased by warfarin+antiplatelet agents across most subgroups, except younger age, diabetes, heart failure, and previous history of stroke or TIA. The risk of VH was increased in patients equal or older than 65 years, but not in those younger than 65 years (Fig. 4B).

Compared with warfarin, the risk of VH was generally increased by dual antiplatelet agents, dual therapy warfarin and P2Y2 inhibitor, and triple therapy with warfarin, aspirin and P2Y2 inhibitor (Supplementary Fig. 3, only online).

DISCUSSION

The main findings of this study are a lower incidence of VH for warfarin than for antiplatelet or warfarin+antiplatelet treated individuals. Compared with warfarin, the risk of VH was increased with antiplatelet and warfarin+antiplatelet agents by 3.9 and 4.39 times, respectively. Second, compared with warfarin monotherapy, warfarin+antiplatelet agents increased the risk of VH in patients equal or more than 65 years, but not in those younger than 65 years. Finally, while combination treatment including aspirin (dual antiplatelet therapy, dual or

Table 2. Cox Proportional HR of the Risk of Different Types of Antiplatelet and Anticoagulant Medications for Vitreous Hemorrhage in Patients with Atrial Fibrillation

	Warfarin (n=1493)	Antiplatelet agents (n=1493)	Warfarin+antiplatelet agents (n=1493)
Events	7	12	18
Person years	4844	3230	2619
/1000 PYs (95% CI)	1.45 (0.63–2.86)	3.72 (2.01–6.32)	6.87 (4.20–10.7)
HR (95% CI), *p* value			
Unadjusted	1 (Reference)	5.11 (1.59–16.4), 0.002	5.19 (2.11–12.7), <0.001
Clinical variable-adjusted*	1 (Reference)	3.90 (1.22–12.4), 0.022	4.39 (1.74–11.2), 0.002

CI, confidence interval; HR, hazard ratio; PYs, person years.
*Adjusted by age, gender, heart failure, hypertension, diabetes, stroke/transient ischemic attack, previous myocardial infarction, dyslipidemia, hemorrhagic stroke, valvular heart disease, malignancy, nonsteroidal anti-inflammatory drugs and corticosteroid medications.

Table 3. Cox Proportional HR of the Risk of Different Types of Antiplatelet and Anticoagulant Medications for Vitreous Hemorrhage in Patients with Non-Valvular Atrial Fibrillation

	Warfarin (n=1188)	Antiplatelet agents (n=1474)	Warfarin+antiplatelet agents (n=1389)
Events	6	17	17
Person years	3355	3192	2357
/1000 PYs (95% CI)	1.79 (0.72–3.72)	5.33 (3.20–8.35)	7.21 (4.34–11.31)
HR (95% CI), *p* value			
Unadjusted	1 (Reference)	4.58 (1.37–15.3), 0.013	4.17 (1.62–10.8), 0.003
Clinical variable-adjusted*	1 (Reference)	4.64 (1.38–15.5), 0.013	4.15 (1.57–11.0), 0.004

CI, confidence interval; HR, hazard ratio; PYs, person years.
*Adjusted by age, gender, heart failure, hypertension, diabetes, stroke/transient ischemic attack, previous myocardial infarction, dyslipidemia, hemorrhagic stroke, valvular heart disease, malignancy, nonsteroidal anti-inflammatory drugs and corticosteroid medications.

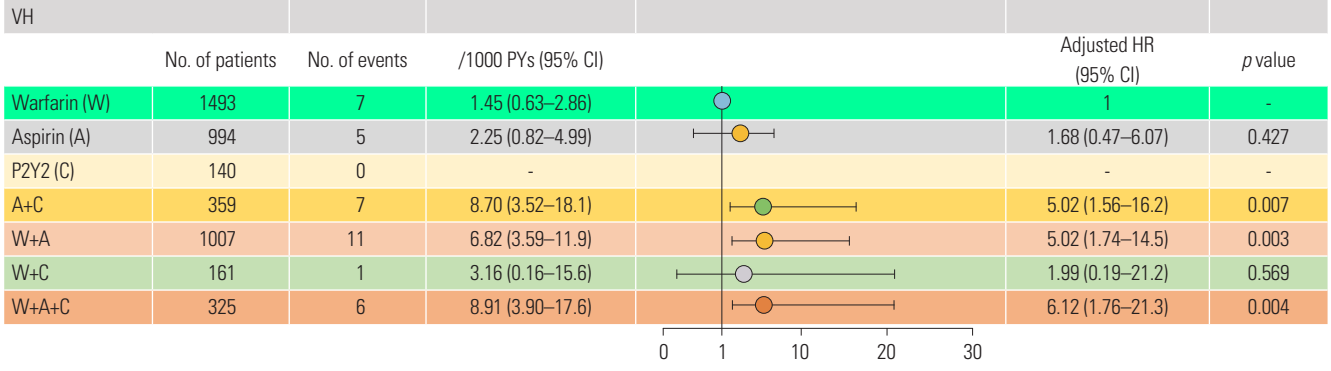

Fig. 3. Risk of VH according to different warfarin or antiplatelet agent combinations. VH, vitreous hemorrhage; CI, confidence interval; HR, hazard ratio.

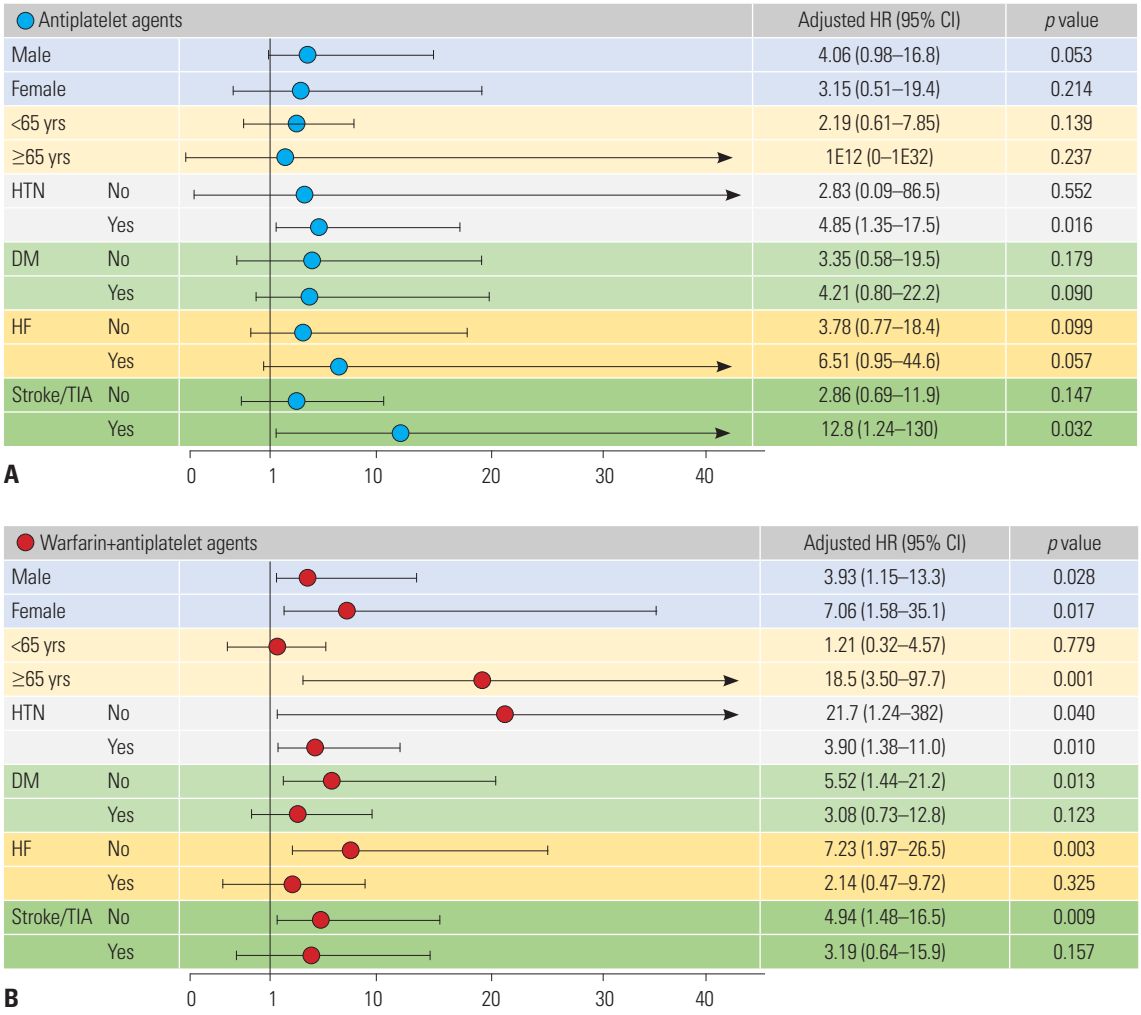

Fig. 4. Subpopulation analysis in patients with diverse comorbidities. The point estimates of vitreous hemorrhage risk in group with antiplatelet (A) or warfarin+antiplatelet combination (B) compared with reference (warfarin). HTN, hypertension; DM, diabetes mellitus; HF, heart failure; TIA, transient ischemic attack; HR, hazard ratio; CI, confidence interval.

triple therapy using warfarin and antiplatelet agents) increased the risk of VH, that without aspirin (dual therapy using warfarin and P2Y2 inhibitors) did not significantly increase the risk of VH. This finding suggests that a combination of antiplatelet and anticoagulation agents should be avoided, especially in older adult patients, and cautiously recommends the use of P2Y2 inhibitor instead of aspirin if combination therapy is needed.

Stroke prevention is the principal management priority in patients with AF. Compared to control or placebo, OAC therapy reduces the risk of stroke by 64% and the risk of death by 26%,[19] but also increases bleeding risk, which can be fatal. Despite the positive net clinical benefit of OACs in the majority of patients with AF, between 30% and 50% of patients meeting indications for OACs with AF are not on treatment.[20] The OAC rate of total AF in the Korean nationwide cohort remains very low at about 18%, while the usage rate of aspirin exceeds 35%.[4,14] The analysis of a prospective multicenter study performed in tertiary hospitals in Korea [COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation (CODE-AF) registry] showed the optimistic future of stroke prevention in patients with AF. The current OAC rate of AF patients with high stroke risk (CHA_2DS_2-VASc score ≥2) was about 83%.[21] Bleeding risk is commonly cited as a reason for stopping OAC therapy in high-risk patients.[22,23]

Nuisance bleeding events (e.g., bruising, epistaxis, intraocular bleeding) are substantially more common than more serious adverse bleeding events.[24] As an indicator of bleeding tendency, they may influence decisions regarding discontinuation of OAC therapy, especially in older patients.[25] Although it is considered a type of nuisance bleeding, intraocular hemorrhage is important and can lead to vision-threatening situations. The incidence of VH was reported as seven cases per 100000 person-years in the general population.[26] However, the incidence of VH in AF patients with antithrombotic medications has not been well identified. While some studies have reported that antiplatelet or anticoagulation medication increases the possibility of intraocular hemorrhage,[6-8] others

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had contrary findings.[9-12,27] In this study, while the incidence of VH was 1.45 cases per 1000 person-years in warfarin monotherapy, it increased to 8.91 cases per 1000 person-years by triple therapy. Dual antiplatelet therapy and dual therapy with aspirin and P2Y2 inhibitors significantly increased the risk of VH more than warfarin monotherapy. More importantly, aspirin monotherapy had an incidence of VH of 2.25 cases per 1000 person-years with the same bleeding risk as warfarin monotherapy. Therefore, considering the low efficacy of aspirin to prevent stroke and similar risk of bleeding, aspirin should be avoided in AF patients. However, the use of aspirin for stroke prevention in AF patients is more than 30% in Korean AF patients.[14]

Theoretically, triple therapy combining all drugs, including dual antiplatelet therapy and warfarin, may be a reasonable choice as an initial antithrombotic regimen. However, prolonged triple therapy has been shown to be associated with an increased risk of bleeding and even mortality.[28,29] Recent well-designed RCTs suggested dual therapy with a single antiplatelet agent and an OAC might be safer and show similar efficacy to triple therapy for preventing ischemic/thromboembolic events.[28,30-32] Dual therapy with clopidogrel and OAC was suggested to be a safe initial alternative regimen to triple therapy.[30,31] Consistently, this study showed that dual therapy with warfarin and P2Y2 inhibitor did not significantly increase the risk of VH.

Witmer and Cohen[7] reported that patients taking aspirin, clopidogrel, or warfarin who developed acute posterior vitreous detachment were more likely to present with VH. Their results showed that the number of eyes with VH was significantly larger in patients taking antithrombotic medications than in those not taking them (43% vs. 31%, p=0.034). Interestingly, P2Y2 inhibitors monotherapy or dual therapy using warfarin and P2Y2 inhibitors did not increase the risk of VH significantly.

Our study also showed that triple therapy increased the risk of VH in older adults equal or older than 65 years, but not in those younger than 65 years. Consistently, Biyik, et al.[8] reported that warfarin increased the frequency of ocular bleeding in patients with hypertension and older age. In patients who were diagnosed as neovascular age-related macular degeneration (AMD), arterial hypertension was a strong risk factor for large subretinal hemorrhages,[33] and antiplatelet or anticoagulant use was significantly associated with retinal or subretinal hemorrhage only in patients with hypertension.[34] Previously, a significant association was reported between diabetes and hypertension with macular hemorrhage (including VH) after intravitreal injection for neovascular AMD.[35] Consistently, our findings suggest the importance of cautious monitoring for VH risk in patients with AF on stroke prevention therapy with such clinical characteristics.

Several limitations should be considered when interpreting our results. First, since the present study was a retrospective study using NHIS-NSC database, it had the intrinsic limitations as a retrospective study. Second, we tried to determine the incidence of spontaneous VH from antithrombotic medication; however, the ICD-10 code was not specialized to spontaneous VH. It is possible that the incidence of VH is underestimated in patients who take anti-platelets/anti-coagulants based on database records, since the clinicians did not mention it in the medical record. However, because VH is a serious disease related with blindness, the possibility of underestimation is relatively low. Third, because the reason of discontinuation of anti-platelets/anti-coagulants was not available in the database, we could not present the number of patients who stopped taking anti-platelets/anti-coagulants due to VH. Finally, although we used PS matching among groups, uncontrolled covariates may exist. Despite these limitations, the strength of this study is that it included a large, population-based dataset to determine whether VH and the most commonly used antiplatelet and anticoagulation medications were associated.

In conclusion, dual antiplatelet or triple therapy including aspirin appears to increase the risk of VH, compared to warfarin monotherapy. This finding suggests that a combination of antiplatelet and anticoagulation agents should be avoided, especially in elderly patients, and recommends the use of P2Y2 inhibitor instead of aspirin if combination therapy is needed.

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