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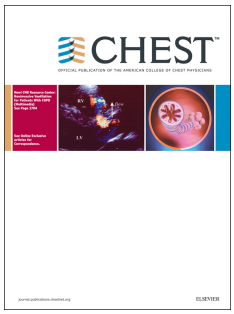


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# Effectiveness and Safety of Non-Vitamin K Antagonist Oral Anticoagulants in Atrial Fibrillation Patients with Hypertrophic Cardiomyopathy: A Nationwide Cohort Study

**Short title:** Effectiveness and safety of NOAC in AF with HCM

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**Conflicts of interest**

The authors have reported to CHEST the following: G.Y.H.L. has served a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo, and speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees were directly received personally. None of the other authors have any disclosures to make.

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**Abbreviations list**

**AF** = Atrial Fibrillation

**$CHA_2DS_2$-VASc** = congestive heart failure, hypertension, age ≥75, diabetes, stroke, vascular disease, age between 65-74, and female sex

**HCM** = hypertrophic cardiomyopathy

**ICD-10** = International Classification of Disease 10th Revision

**MI** = myocardial infarction

**NHIS** = National Health Insurance Service

**NOACs** = Non–vitamin K antagonist oral anticoagulants

**OAC** = oral anticoagulant

**PS** = Propensity Score

**ABSTRACT**

**BACKGROUND:** Chronic anticoagulation is recommended in patients with hypertrophic cardiomyopathy (HCM) and atrial fibrillation (AF). Non-vitamin K antagonist oral anticoagulants (NOACs) are an alternative to warfarin, but there are limited data to support their use in patients with HCM and AF. We sought to compare thromboembolic events, bleeding, and mortality between NOAC and warfarin in patients with HCM and AF.

**METHODS:** From the Korean National Health Insurance Service (NHIS) database during the period from January 1, 2011 to December 31, 2016, we identified a warfarin-treated group of patients with HCM and AF (n = 955) who were compared with a 1:2 propensity-matched NOAC treated group (n = 1,504).

**RESULTS:** After a median follow-up of 15 months, the incidence rates of ischemic stroke and major bleeding were similar between NOAC- and warfarin-treated patients with HCM and AF. NOAC-treated patients had lower incidence rates for all-cause mortality (5.11 and 10.13 events per 100 person-years for NOAC and warfarin groups) and the composite of fatal cardiovascular events (0.77 and 1.80 events per 100 person-years). Compared with warfarin, use of NOACs was associated with a significantly lower risk of all cause-mortality (hazard ratio [HR]: 0.43, 95% confidence interval [CI]: 0.32-0.57) and composite fatal cardiovascular events (HR: 0.39, 95% CI: 0.18-0.82).

**CONCLUSIONS:** Compared with warfarin, patients with HCM and AF on NOACs had similar stroke and major bleeding risks, but lower all-cause mortality and composite fatal cardiovascular events. Our data suggest that patients with HCM and AF can be safely and effectively treated with NOACs.

***Keywords***: Atrial fibrillation, hypertrophic cardiomyopathy, stroke, non-vitamin K antagonist oral anticoagulants.

## Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the general population,[1] and stroke prevention is the principal management priority in patients with AF, given its association with a five-fold increase in stroke risk.[1-3] Patients with hypertrophic cardiomyopathy (HCM) have a four- to six-fold greater likelihood of developing AF compared with the general population.[4-7] AF is the most common arrhythmia in HCM and has been known to be associated with a high risk of stroke and systemic embolic events as well as heart failure-related mortality.[4,5,7]

Currently, the $CHA_2DS_2$-VASc [congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65 to 74, female] score[8] is widely used in most guidelines for stroke prevention in patients with AF, with oral anticoagulants (OACs) being generally recommended for those with a $CHA_2DS_2$-VASc score of ≥ 2.[9] However, lifelong OAC therapy to prevent stroke is recommended in HCM patients who develop AF regardless of the patient's $CHA_2DS_2$-VASc score.[9-11] Non–vitamin K antagonist oral anticoagulants (NOACs) may be reasonable alternatives to warfarin, but there are limited data to support their use, since few patients with HCM were included in existing NOACs trials.[11,12] Therefore, large observational studies may offer an opportunity to examine the effectiveness and safety outcomes of NOAC use in these patients. In this nationwide cohort study, we sought to describe the pattern of use, occurrence of thromboembolic events and bleeding, and mortality in patients with HCM and AF treated with NOACs.

## Materials and Methods

This study is based on the national health claims database established by the National

Health Insurance Service (NHIS) of the Republic of Korea.[2,3,13] Details of Korean NHIS database are summarized in e-Appendix 1. This study was approved by the Institutional Review Board of the Yonsei University Health System (4-2016-0179), and informed consent was waived.

***Study population***

From the Korean NHIS database, 10,020 patients with HCM and AF who were aged 18 years or older were identified during the period from January 1, 2011 to December 31, 2016. The following were exclusion criteria: (i) those with valvular AF, such as mitral valve stenosis or prosthetic valve disease (n=576), (ii) those who had undergone radiofrequency ablation for AF (n=239), (iii) those with end-stage renal disease (n=97), (iv) those with no OAC use during the study period (Jan 2011 to Dec 2016) (n=3,667), (v) those with OAC use of less than 30 days (n=1,821), and (vi) those with OAC use for acute coronary syndrome or deep vein thrombosis prophylaxis (n=130). Finally, a total of 3,490 patients who took warfarin (n=1,188) or NOACs (n=2,302) were enrolled (Fig 1). After propensity score (PS) matching, we identified a warfarin-treated group of patients with HCM and AF (n=958) who were compared with a 1:2 propensity-matched NOAC treated group (n=1,514).

AF was diagnosed using the International Classification of Disease 10th Revision (ICD-10) codes I48, I48.0, and I48.1. Moreover, patients were defined as having AF only when they were given AF as a discharge diagnosis, or when this diagnosis was confirmed more than twice in the outpatient department, to ensure diagnostic accuracy. ICD-10 codes were used when diagnosing HCM (I42.1, I42.2) and obstructive HCM (I42.1). The validation of AF and HCM diagnosis is summarized in e-Appendix 1.

***Baseline comorbidities and outcome events***

Comorbidities were defined according to ICD-10 codes, prescription medication use using medical claim records. The definitions of comorbidities are presented in e-Table 1. The presence of comorbidities was assessed at the time of OAC initiation.

Primary outcome events were the first occurrence of all-cause death, any ischemic stroke, major bleeding, and any acute myocardial infarction (MI). Secondary outcome events were the occurrence of fatal ischemic stroke, fatal bleeding, fatal acute MI, and the composite of these fatal cardiovascular events. Any event that led to death within one month of its occurrence was considered a fatal event. Detailed information on outcomes is summarized in e-Appendix 1.

***Statistical analysis***

The detailed methods of statistical analysis are described in e-Appendix 1.

**Results**

Within the NOAC group (n=2,302), 890 patients were receiving rivaroxaban (38.7%), 705 dabigatran (30.6%), 585 apixaban (25.4%), and 122 edoxaban (5.3%). Table 1 shows the baseline characteristics of the study population before and after PS-matching. Before PS-matching, 55% of the NOAC group were male (vs. 57% in the warfarin group; p=0.32) and the mean age was higher in the NOAC group compared with the warfarin group (70.9 ± 10.2 vs. 67.0 ± 12.5 years; p<0.001). All comorbidities, including previous transient ischemic attack / ischemic stroke, hemorrhagic stroke, atherosclerotic disease, hypertension, diabetes, heart failure, malignant neoplasm, chronic kidney disease, dyslipidemia and chronic

obstructive pulmonary disease, were more prevalent in patients on NOACs than in those on warfarin (all p<0.05). e-Table 2 shows that the baseline medications were also different between the two groups, with a higher use of antiplatelet therapy (aspirin or P2Y12 inhibitor) in the warfarin group (all p<0.05). Covariates had significant imbalances in the pre-matched cohort but were well balanced after PS-matching. Absolute standardized mean differences in all measured covariates were less than 0.1, suggesting substantial covariate balance across the groups after PS-matching.

***Primary outcome events***

During a median follow-up of 16 months (interquartile range: 8-24 months), when considering the NOAC and warfarin groups together before PS-matching, ischemic stroke / systemic embolism and major bleeding occurred in 9.7% (339 of 3,490) and 6.3% (219 of 3,490) of AF patients with HCM, respectively. Overall, 315 out of 3,490 patients (9.0%) died. (e-Table 3).

In the PS-matched groups, the incidence rates for ischemic stroke or systemic embolism were similar between NOAC- and warfarin-treated patients (8.33 vs. 7.96 events per 100 person-years, respectively; p=0.725) (Fig 2). Major bleeding, gastrointestinal bleeding, intracranial hemorrhage, and acute MI were also similar between NOAC- and warfarin-treated patients. The incidence rate for all-cause death was significantly lower in NOAC-treated than in warfarin-treated patients (5.11 vs. 10.13 events per 100 person-years, respectively; p<0.001). Compared with warfarin, use of NOACs was associated with a significantly lower risk of all cause-mortality (HR) of 0.43 (95% confidence interval [CI]: 0.32-0.57; p<0.001) (Fig 2). Both standard- (HR 0.40; 95% CI 0.27-0.60) and reduced-dose NOACs (HR 0.45; 95% CI 0.32-0.63) were associated with significantly lower risk of all-

cause mortality with reference to warfarin (e-Table 4).

Fig 3 shows the Kaplan–Meier curves for clinical events in NOAC- and warfarin-treated patients after PS-matching. NOAC use was associated with significantly better event free survival from all-cause death than warfarin-treated patients (log-rank p<0.001).

***Secondary outcome events***

We compared the fatal cardiovascular events between PS-matched NOAC- and warfarin-treated patients. The incidence rates of fatal ischemic stroke (0.40 vs 0.48 events per 100 person-years, respectively; HR 0.87; 95% CI: 0.25-2.98, p=0.819) were similar between NOAC- and warfarin-treated patients. However, use of NOACs was associated with lower risks of fatal bleeding (0.33 vs 1.02 events per 100 person-years, respectively; HR 0.33; 95% CI: 0.11-0.99, p=0.047) and fatal MI (0.06 vs 0.39 events per 100 person-years, respectively; HR 0.06; 95% CI: 0.00-0.92, p=0.043) compared to warfarin-treated patients. Consequentially, the incidence rate for the composite of these fatal cardiovascular events was significantly lower in NOAC-treated patients compared to warfarin-treated patients (0.77 vs. 1.80 events per 100 person-years, respectively; HR: 0.39; 95% CI: 0.18-0.82; p=0.013) (Fig 4).

Fig 5 shows the Kaplan–Meier curves for fatal clinical events in NOAC-treated and warfarin-treated patients. NOAC was associated with significantly better event free survival from fatal bleeding (log-rank p=0.023), fatal MI (log-rank p=0.037) and composite fatal cardiovascular events (log-rank p=0.010) than warfarin.

***Subgroup analysis***

The mortality benefit of NOACs compared to warfarin in AF patients with HCM was consistent across most subgroups although it could not be assessed in patients with $CHA_2DS_2$-VASc scores ≤ 1 or in those without hypertension because of the small number of subjects (Fig 6). Compared with warfarin, use of NOAC was associated with significantly lower risk of all-cause mortality, regardless of sex, heart failure, diabetes mellitus previous transient ischemic attack / ischemic stroke, and CKD. NOACs were associated with a significantly lower all-cause mortality than warfarin in those aged ≥ 65 years, those without previous MI, those with dyslipidemia, those with non-obstructive HCM, those with $CHA_2DS_2$-VASc score ≥ 2 and those with hypertension.

There was no significant difference in the number of events, incidence, and risk of various events among apixaban, dabigatran and rivaroxaban in AF patients with HCM (e-Table 5).

**Discussion**

The principal finding of this study was that the incidences of stroke or major bleeding were similar between NOAC- and warfarin-treated AF patients with HCM. Second, use of NOAC was associated with significantly lower all-cause mortality than warfarin. Moreover, the composite of fatal cardiovascular events was lower amongst NOAC-treated patients, compared to warfarin-treated patients. The lower all-cause mortality in NOAC-treated patients was evident across most subgroups. Our data suggest that AF patients with HCM can be safely and effectively treated with NOACs.

***Oral anticoagulant for in AF patients with HCM***

AF is the most common arrhythmia in patients with HCM. Prospective data show that after 10 years of follow-up, 22% to 30% of HCM patients develop AF.[4,5,14] AF has a strong impact on the clinical course of HCM and on patients' quality of life. Due to the very high embolic risk, life-long OAC treatment is recommended in all HCM patients with AF. This recommendation is based on observational studies showing that warfarin-treated HCM patients with AF presented with about one half the number of embolic events (18% vs. 31%, respectively) and strokes (10% vs. 39%, respectively) compared to those not receiving OAC treatment.[4]

While HCM patients were not formally excluded from NOAC trials, the number of HCM patients included in these studies is unknown, and was presumably low because these patients tend to be younger (the mean age of patients included in NOAC trials was >70 years) and often do not exhibit the traditional $CHADS_2$ factors required to participate in NOAC studies. Therefore, few data currently support the use of NOACs in patients with HCM and AF despite the notion that NOACs could represent a valid alternative to warfarin treatment in this younger, active population.

The latest guidelines state that NOACs are broadly preferable to warfarin in the vast majority of patients with non-valvular AF,[9] based on clinical trials that have shown equivalent efficacy compared with warfarin, as well as better safety and a lower occurrence of intracranial hemorrhage.[15] Furthermore, recent studies have observed that NOACs are more cost effective than adjusted dose warfarin,[16] and that non-valvular AF patients are generally more satisfied with medical care when treated with NOACs.

The comparison of comorbidities and outcome events with other studies is discussed in e-Appendix 2.

***NOACs, mortality, and fatal outcomes***

The annual rates of ischemic stroke, systemic embolism, or major bleeding were similar between NOAC- and warfarin-treated patients. Our data show that usage of NOACs was associated with significantly lower all-cause mortality compared with warfarin, especially by reducing the composite of fatal cardiovascular events. In prior randomized clinical trials of NOAC vs. warfarin, there was no reduction in mortality except in apixaban trial. However, in Danish nationwide databases, the annual risk of death was significantly lower with apixaban and dabigatran compared with warfarin.[17] In real-world data from Asians with non-valvular AF, NOACs were associated with reduced risk for all-cause mortality compared to warfarin.[18] This finding was well explained by lower risk of composite of fatal cardiovascular events associated with NOAC use in this study.

A recent studies suggested that patients with HCM and AF could be safely treated with NOACs.[12,19] However, these studies were probably underpowered in terms of the number of individuals needed to concretely demonstrate the superiority of NOACs over warfarin in patients with HCM and AF. The results of our study, which used the largest sample of subjects with HCM published thus far, favor the use of NOACs as an alternative to warfarin when OAC treatment is needed for patients with HCM and AF.

In the subgroup analyses, the mortality reduction associated with NOAC treatment was observed across most subgroups. The prevalence of hypertension was over 95% in both PS-matched NOAC- and warfarin-treated groups. Because NOAC treatment is fully reimbursed only in Korean AF patients with $CHA_2DS_2$-VASc scores ≥ 2, the number of patients using NOACs was low amongst those with $CHA_2DS_2$-VASc scores ≤ 1. Therefore, the benefit of NOAC treatment was not adequately assessed in patients with $CHA_2DS_2$-VASc scores ≤ 1, and in those without hypertension.

Major and GI bleeding was more prevalent in reduced dose NOAC than standard dose users. This finding is consistent with previous studies.[20,21] In real-world studies, the choice of dosage of NOAC was obviously not due to random chance, but rather a complex mixture of physician experience, patient preferences, and clinical characteristics.

***Study limitations***

The present study has several limitations. Although administrative databases are increasingly used for clinical research, studies using such databases are potentially susceptible to errors arising from coding inaccuracies. To minimize this problem, we applied the definitions that we had already validated in previous studies that used a Korean NHIS sample cohort.[2,3,22] Although we validated the accuracy of our definition of HCM, we cannot exclude the possibility that hypertensive heart disease was included in our study population. Second, we were unable to define the type of AF (paroxysmal vs. persistent) in this study. In addition, we relied on billing codes for determination of patient characteristics and outcomes. As such, we lacked data on clinical characteristics, such as mitral valve dysfunction, left atrial enlargement, left ventricular dysfunction, and other factors that may predispose patients to cardioembolism. The information on family history of HCM and family history of sudden death was also unavailable. Third, more than half the NOAC treated patients in this study were receiving reduced doses of NOACs. This finding is consistent with the previous study that Asian physicians tend to prescribe low-dose NOACs to patients with AF for a number of reasons including the lower average body mass index of Asian adults and the concern for higher risk of ICH.[23] Finally, we had no data on time in therapeutic range (TTR) for the warfarin group due to the limitations of the national health claim database. Poor TTR status has generally been observed in Asian cohorts,[24,25] and may have affected the favorable

mortality outcomes seen in the NOAC group. A single-center study in which warfarin therapy was managed by a formal anticoagulation clinic showed that the TTR in AF-related stroke patients was 57.5%.[26] A recent multicentre retrospective study reported that the mean TTR of individual patients was 49.1% in Korean AF patients.[27]

Nonetheless, these observational data provide a glimpse of real-world clinical outcomes associated with NOAC use in patients with HCM and AF, a group not well studied in previously published or ongoing clinical trials.

## Conclusions

Compared with those on warfarin, AF patients with HCM on NOACs had similar stroke and major bleeding risks, but was associated with lower all-cause mortality and the composite of fatal cardiovascular events. Our data suggest that patients with HCM and AF can be safely and effectively treated with NOACs.



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**Table 1.** Baseline characteristics before and after propensity score matching by treatment group (NOAC vs. warfarin).

| | Before propensity score matching | | | After propensity score matching | | |
|---|---|---|---|---|---|---|
| | **Warfarin (n = 1,188)** | **NOAC (n = 2,302)** | **ASMD** | **Warfarin (n = 955)** | **NOAC (n = 1,504)** | **ASMD** |
| Age, years | 67.0 ± 12.5 | 70.9 ± 10.2 | 0.336 | 68.6 ± 11.6 | 69.3 ± 10.5 | 0.067 |
| <65 | 444 (37.4) | 545 (23.7) | | 314 (32.9) | 438 (29.1) | |
| 65-74 | 385 (32.4) | 795 (34.5) | | 316 (33.1) | 524 (34.8) | |
| ≥75 | 359 (30.2) | 962 (41.8) | | 325 (34.0) | 542 (36.0) | |
| Men | 675 (56.8) | 1,267 (55.0) | 0.036 | 530 (55.5) | 838 (55.7) | 0.004 |
| $CHA_2DS_2$-VASc score | 4.36 ± 2.14 | 5.20 ± 1.84 | 0.419 | 4.67 ± 2.08 | 4.82 ± 1.84 | 0.079 |
| Previous ischemic stroke / TIA | 480 (40.4) | 1,262 (54.8) | 0.292 | 437 (45.8) | 728 (48.4) | 0.053 |
| Previous hemorrhagic stroke | 38 (3.2) | 120 (5.2) | 0.100 | 30 (3.1) | 63 (4.2) | 0.056 |
| Previous MI | 237 (19.9) | 497 (21.6) | 0.040 | 204 (21.4) | 320 (21.3) | 0.002 |
| PAD | 218 (18.4) | 537 (23.3) | 0.123 | 199 (20.8) | 307 (20.4) | 0.011 |
| Vascular disease | 402 (33.8) | 879 (38.2) | 0.091 | 353 (37.0) | 541 (36.0) | 0.021 |
| Hypertension | 1,078 (90.7) | 2,247 (97.6) | 0.273 | 909 (95.2) | 1,452 (96.5) | 0.068 |
| Diabetes mellitus | 339 (28.5) | 784 (34.0) | 0.119 | 290 (30.4) | 463 (30.8) | 0.009 |
| Heart failure | 740 (62.3) | 1,755 (76.2) | 0.306 | 641 (67.1) | 1,069 (71.1) | 0.086 |
| History of cancer | 301 (25.3) | 747 (32.5) | 0.157 | 263 (27.5) | 435 (28.9) | 0.031 |
| CKD | 128 (10.8) | 281 (12.2) | 0.045 | 109 (11.4) | 171 (11.4) | 0.001 |
| Dyslipidemia | 1,032 (86.9) | 2,176 (94.5) | 0.266 | 864 (90.5) | 1,387 (92.2) | 0.062 |
| COPD | 475 (40.0) | 1042 (45.3) | 0.107 | 408 (42.7) | 652 (43.4) | 0.013 |
| Obstructive HCM | 191 (16.1) | 327 (14.2) | 0.053 | 154 (16.1) | 210 (14.0) | 0.061 |

Values are expressed as n (%) or mean ± SD. ASMD = absolute standardized mean di□erence; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; HCM = hypertrophic cardiomyopathy; MI = myocardial infarction; NOAC = non–vitamin K antagonist oral anticoagulant; PAD = peripheral artery disease; TIA = transient ischemic attack; Vascular disease = previous MI, PAD, or aortic plaque.

**Figure legends**

**Figure 1.** Flowchart of study population. ACS = acute coronary syndrome; AF = atrial fibrillation; DVT = deep vein thrombosis; ESRD = end-stage renal disease; HCM = hypertrophic cardiomyopathy; NOAC = non–vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; RFCA = radiofrequency catheter ablation.

**Figure 2.** The number of events, incidence, and risk of primary outcomes in propensity score matched NOAC- and warfarin-treated patients with HCM and AF. CI = confidence interval. Other abbreviations are as in Figure 1.

**Figure 3.** Kaplan-Meier curves for the crude cumulative incidence of primary outcomes. (A) Ischemic stroke, (B) major bleeding, (C) acute myocardial infarction, and (D) all-cause death in propensity score matched warfarin- and NOAC-treated patients with HCM and AF. NOAC-treated patients showed significantly better event free survival from all-cause death than warfarin-treated patients. Abbreviations are as in Figure 1.

**Figure 4.** The number of events, incidence, and risk of fatal cardiovascular events in propensity score matched NOAC- and warfarin-treated patients with HCM and AF. CI = confidence interval. Other abbreviations are as in Figure 1.

**Figure 5.** Kaplan–Meier curves for fatal cardiovascular events. (A) Fatal ischemic stroke, (B) fatal bleeding, (C) fatal acute MI, and (D) composite of these fatal cardiovascular events in propensity score matched NOAC- and warfarin-treated patients with HCM and AF. A fatal event is defined as an event in which the patient dies within 30 days of the event. MI =

myocardial infarction. Other abbreviations are as in Figure 1.

**Figure 6.** Forest plot displaying the hazard ratio for all-cause death for the NOAC-treated patients with HCM and AF compared with the warfarin-treated patients among various subgroups. CI = confidence interval; TIA = transient ischemic attack. Other abbreviations are as in Figure 1.

**Figure 1.**

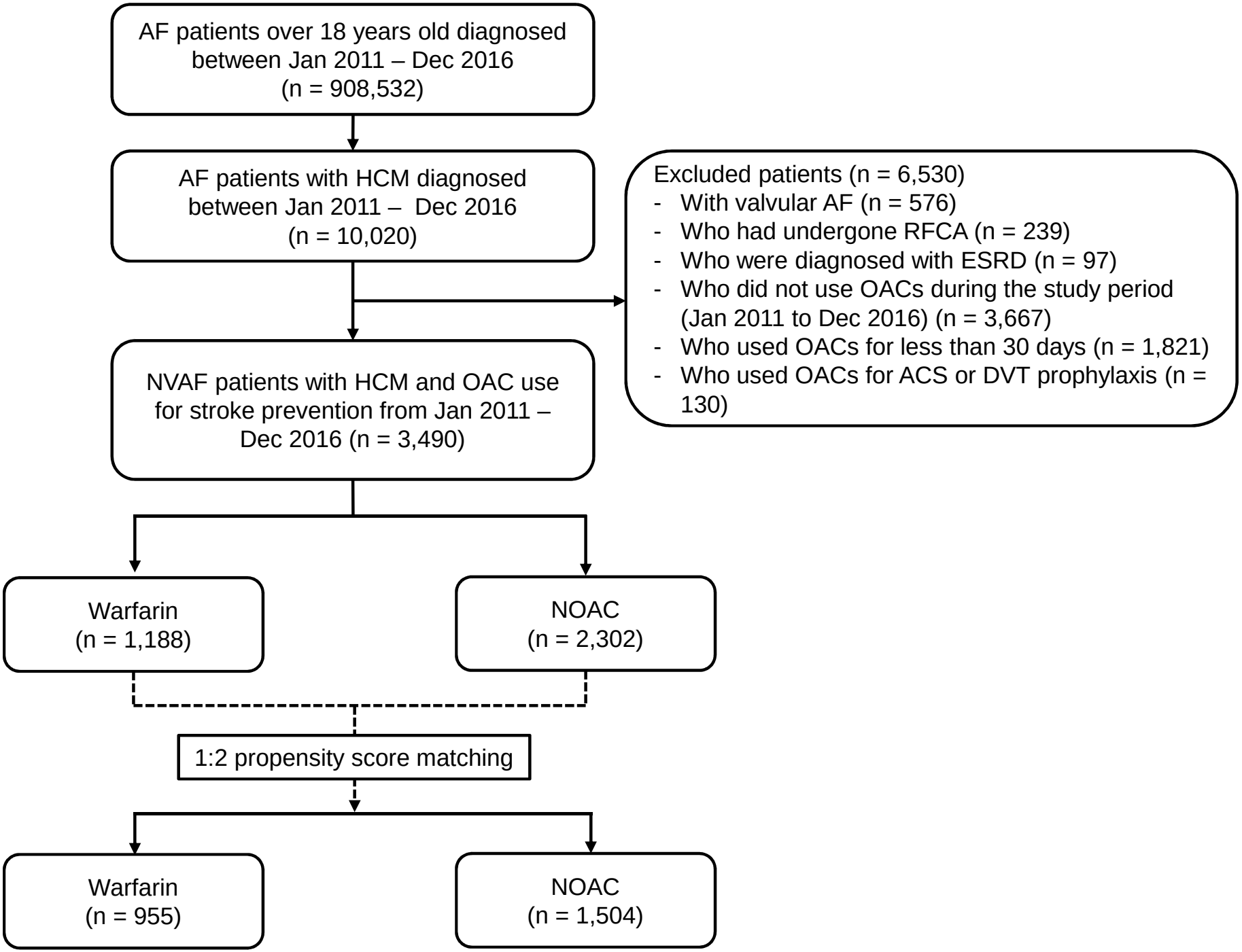

AF patients over 18 years old diagnosed between Jan 2011 – Dec 2016 (n = 908,532)
AF patients with HCM diagnosed between Jan 2011 – Dec 2016 (n = 10,020)
Excluded patients (n = 6,530)
- With valvular AF (n = 576)
- Who had undergone RFCA (n = 239)
- Who were diagnosed with ESRD (n = 97)
- Who did not use OACs during the study period (Jan 2011 to Dec 2016) (n = 3,667)
- Who used OACs for less than 30 days (n = 1,821)
- Who used OACs for ACS or DVT prophylaxis (n = 130)
NVAF patients with HCM and OAC use for stroke prevention from Jan 2011 – Dec 2016 (n = 3,490)
Warfarin (n = 1,188)
NOAC (n = 2,302)
1:2 propensity score matching
Warfarin (n = 955)
NOAC (n = 1,504)

**Figure 2.**

| | Patients, n | Events, n | Incidence (95% CI) | Hazard ratio* (95% CI) | p-value |
|---|---|---|---|---|---|
| Death from all causes | | | | | |
| Warfarin | 955 | 158 | 10.13 (8.61-11.83) | Reference | - |
| NOAC | 1,504 | 80 | 5.11 (4.05-6.36) | 0.43 (0.32-0.57) | <0.001 |
| Ischemic stroke or systemic embolism | | | | | |
| Warfarin | 955 | 115 | 7.96 (6.57-9.55) | Reference | - |
| NOAC | 1,504 | 124 | 8.33 (6.93-9.93) | 0.94 (0.72-1.23) | 0.672 |
| Major bleeding | | | | | |
| Warfarin | 955 | 78 | 5.19 (4.11-6.48) | Reference | - |
| NOAC | 1,504 | 82 | 5.41 (4.30-6.71) | 0.97 (0.70-1.34) | 0.838 |
| GI bleeding | | | | | |
| Warfarin | 955 | 61 | 4.03 (3.08-5.17) | Reference | - |
| NOAC | 1,504 | 67 | 4.40 (3.41-5.59) | 0.99 (0.69-1.44) | 0.985 |
| Intracranial hemorrhage | | | | | |
| Warfarin | 955 | 14 | 0.90 (0.49-1.51) | Reference | - |
| NOAC | 1,504 | 10 | 0.64 (0.31-1.18) | 0.70 (0.29-1.68) | 0.421 |
| Acute myocardial infarction | | | | | |
| Warfarin | 955 | 31 | 2.01 (1.37-2.86) | Reference | - |
| NOAC | 1,504 | 44 | 2.85 (2.07-3.83) | 1.32 (0.81-2.16) | 0.263 |

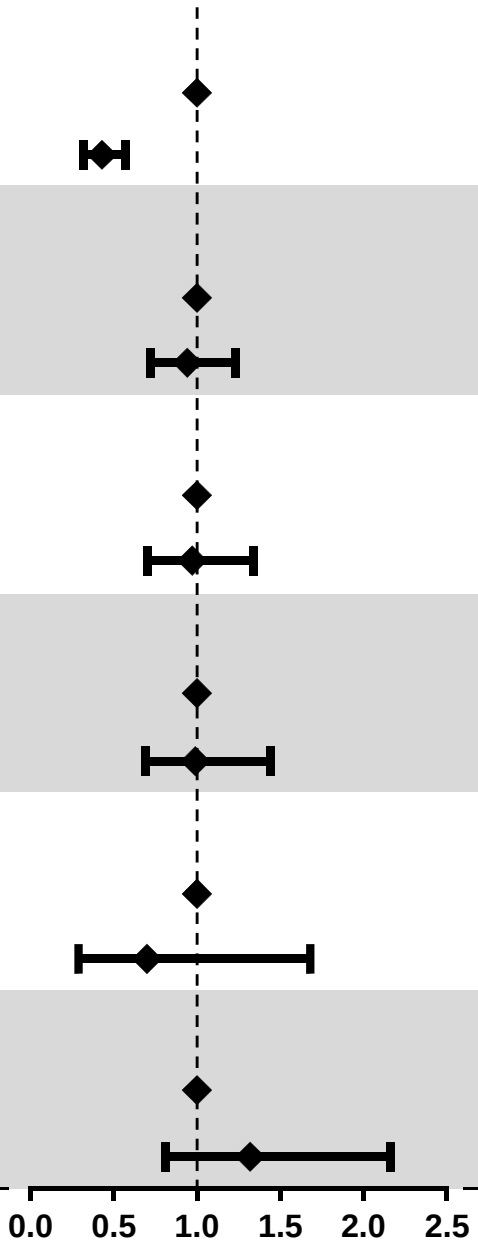


**Figure 3.**

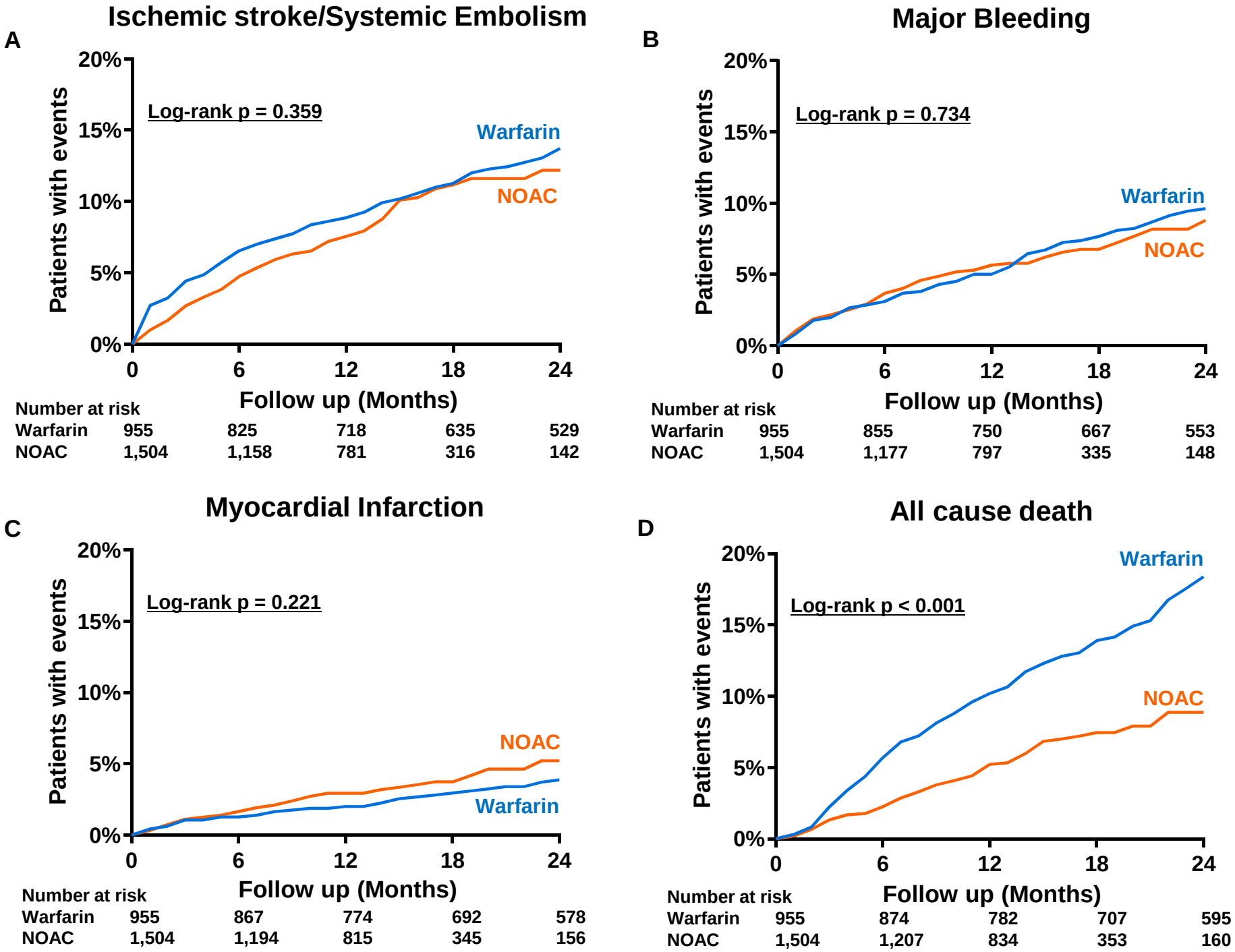

A
Ischemic stroke/Systemic Embolism
Log-rank p = 0.359
Warfarin
NOAC
Patients with events
20%
15%
10%
5%
0%
0
6
12
18
24
Follow up (Months)
Number at risk
Warfarin 955 825 718 635 529
NOAC 1,504 1,158 781 316 142
B
Major Bleeding
Log-rank p = 0.734
Warfarin
NOAC
Patients with events
Follow up (Months)
Number at risk
Warfarin 955 855 750 667 553
NOAC 1,504 1,177 797 335 148
C
Myocardial Infarction
Log-rank p = 0.221
NOAC
Warfarin
Patients with events
Follow up (Months)
Number at risk
Warfarin 955 867 774 692 578
NOAC 1,504 1,194 815 345 156
D
All cause death
Log-rank p < 0.001
Warfarin
NOAC
Patients with events
Follow up (Months)
Number at risk
Warfarin 955 874 782 707 595
NOAC 1,504 1,207 834 353 160

**Figure 4.**

| | Patients, n | Events, n | Incidence (95% CI) | Hazard ratio* (95% CI) | p-value |
|---|---|---|---|---|---|
| Fatal ischemic stroke | | | | | |
| Warfarin | 955 | 7 | 0.48 (0.19-0.98) | Reference | - |
| NOAC | 1,504 | 6 | 0.40 (0.15-0.87) | 0.87 (0.25-2.98) | 0.819 |
| Fatal bleeding | | | | | |
| Warfarin | 955 | 15 | 1.02 (0.57-1.69) | Reference | - |
| NOAC | 1,504 | 5 | 0.33 (0.11-0.78) | 0.33 (0.11-0.99) | 0.047 |
| Fatal acute myocardial infarction | | | | | |
| Warfarin | 955 | 6 | 0.39 (0.14-0.85) | Reference | - |
| NOAC | 1,504 | 1 | 0.06 (0.00-0.36) | 0.06 (0.00-0.92) | 0.043 |
| Composite of fatal cardiovascular events | | | | | |
| Warfarin | 955 | 25 | 1.80 (1.17-2.66) | Reference | - |
| NOAC | 1,504 | 11 | 0.77 (0.38-1.38) | 0.39 (0.18-0.82) | 0.013 |

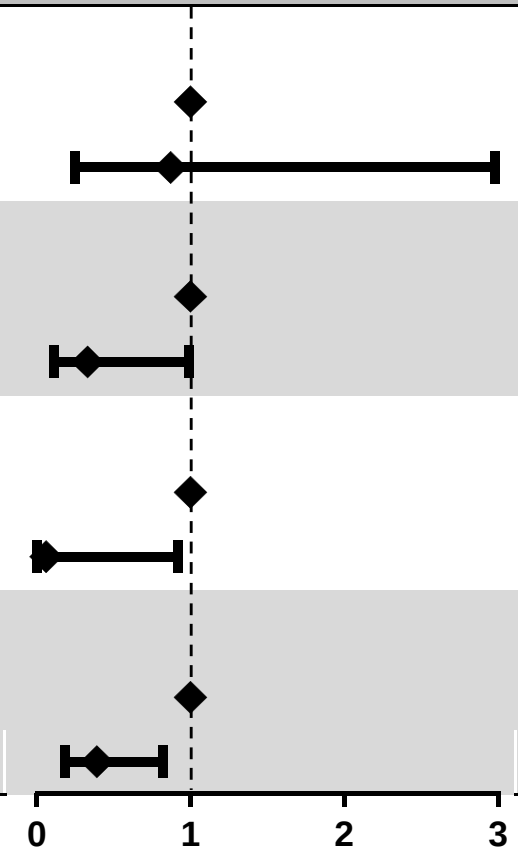


Figure 5.

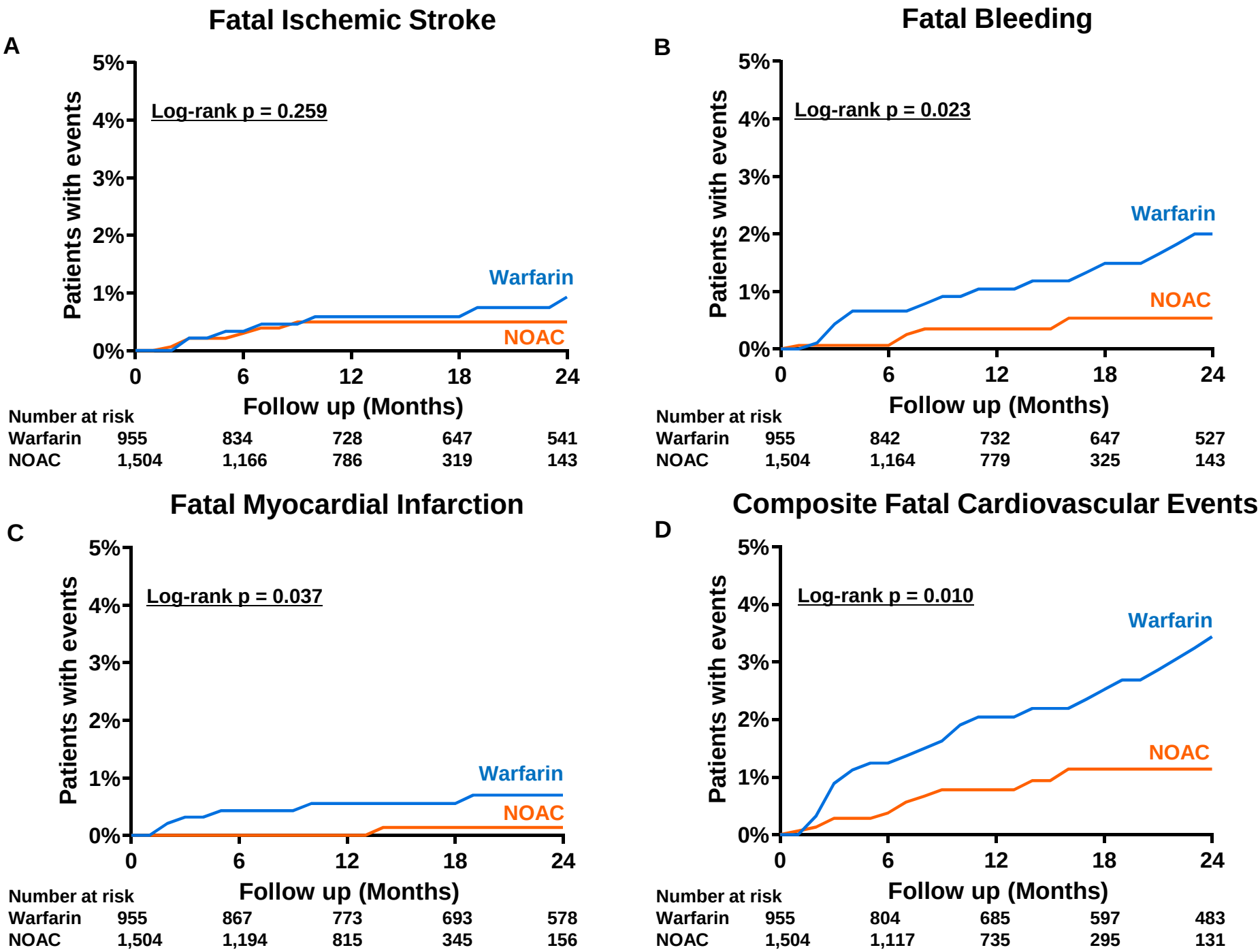
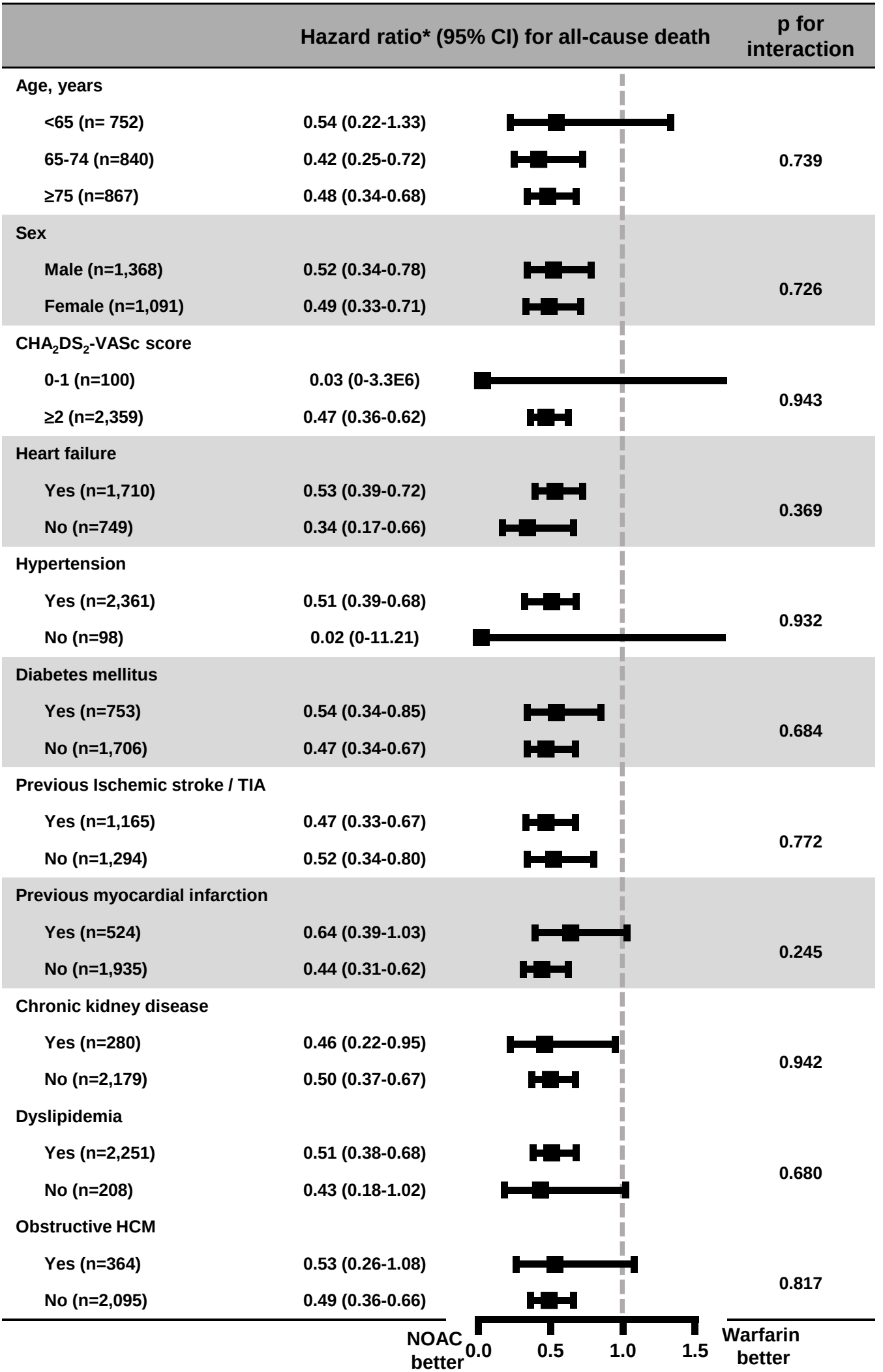

A
Fatal Ischemic Stroke
Log-rank p = 0.259
Patients with events
5%
4%
3%
2%
1%
0%
Warfarin
NOAC
0
6
12
18
24
Follow up (Months)
Number at risk
Warfarin 955 834 728 647 541
NOAC 1,504 1,166 786 319 143
B
Fatal Bleeding
Log-rank p = 0.023
Patients with events
Warfarin
NOAC
Follow up (Months)
Number at risk
Warfarin 955 842 732 647 527
NOAC 1,504 1,164 779 325 143
C
Fatal Myocardial Infarction
Log-rank p = 0.037
Patients with events
Warfarin
NOAC
Follow up (Months)
Number at risk
Warfarin 955 867 773 693 578
NOAC 1,504 1,194 815 345 156
D
Composite Fatal Cardiovascular Events
Log-rank p = 0.010
Patients with events
Warfarin
NOAC
Follow up (Months)
Number at risk
Warfarin 955 804 685 597 483
NOAC 1,504 1,117 735 295 131

**Figure 6.**


Hazard ratio* (95% CI) for all-cause death
p for interaction
Age, years
<65 (n= 752)
0.54 (0.22-1.33)
65-74 (n=840)
0.42 (0.25-0.72)
0.739
≥75 (n=867)
0.48 (0.34-0.68)
Sex
Male (n=1,368)
0.52 (0.34-0.78)
0.726
Female (n=1,091)
0.49 (0.33-0.71)
CHA2DS2-VASc score
0-1 (n=100)
0.03 (0-3.3E6)
0.943
≥2 (n=2,359)
0.47 (0.36-0.62)
Heart failure
Yes (n=1,710)
0.53 (0.39-0.72)
0.369
No (n=749)
0.34 (0.17-0.66)
Hypertension
Yes (n=2,361)
0.51 (0.39-0.68)
0.932
No (n=98)
0.02 (0-11.21)
Diabetes mellitus
Yes (n=753)
0.54 (0.34-0.85)
0.684
No (n=1,706)
0.47 (0.34-0.67)
Previous Ischemic stroke / TIA
Yes (n=1,165)
0.47 (0.33-0.67)
0.772
No (n=1,294)
0.52 (0.34-0.80)
Previous myocardial infarction
Yes (n=524)
0.64 (0.39-1.03)
0.245
No (n=1,935)
0.44 (0.31-0.62)
Chronic kidney disease
Yes (n=280)
0.46 (0.22-0.95)
0.942
No (n=2,179)
0.50 (0.37-0.67)
Dyslipidemia
Yes (n=2,251)
0.51 (0.38-0.68)
0.680
No (n=208)
0.43 (0.18-1.02)
Obstructive HCM
Yes (n=364)
0.53 (0.26-1.08)
0.817
No (n=2,095)
0.49 (0.36-0.66)
NOAC better
0.0
0.5
1.0
1.5
Warfarin better

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**e-Appendix 1.**

## Methods

### *Database Description*

The National Health Insurance Service (NHIS) is a single insurer managed by the Korean government, and the majority (97.1%) of the Korean population are mandatory subscribers, with the remaining 3% of the population being medical aid subjects. The NHIS database also contains information on the medical aid subjects, and is therefore based on the *entire* Korean population.[1] The following medical information is provided: the patients' sociodemographic information, their use of inpatient and outpatient services, their pharmacy dispensing claims, and mortality data. Every person in the NHIS database is linked to their information by their Korean social security numbers. In this study, all social security numbers were deleted after constructing the cohort by assigning each individual a serial number to prevent the leakage of personal information. These databases are open to researchers, whose study protocols are approved by the official review committee.

### *Outcome events*

Primary outcome events were the first occurrence of all-cause death, any ischemic stroke, major bleeding, and any acute myocardial infarction (MI). The mortality information along with date of death of the participants was included in NHIS database, obtained from the Korean National Statistical Office. Ischemic stroke was defined as any admission diagnosis of ischemic stroke (ICD-10 codes: I63, I64) with concomitant brain-imaging studies, including computed tomography or magnetic resonance imaging. The definition of ischemic stroke was validated in previous studies.[2-4] Major bleeding was defined as gastrointestinal bleeding (ICD-10 codes: K25-28 [subcodes 0-2 and 4-6 only], K92.0, K92.1, K92.2, K62.5, I85.0, I98.3) or a cerebral hemorrhage episode (ICD-10 codes: I60-I62) that required hospital admission and/or a blood transfusion. Acute MI was identified by any admission diagnosis of acute MI (ICD-10 codes: I21, I22) with prescription of dual antiplatelet therapy of aspirin and P2Y12 inhibitor during admission. The definition of acute MI was also validated in previous study.[5]

### *Validation of diagnosis*

In Korea, hypertrophic cardiomyopathy (HCM) patients are registered in the national registry for rare diseases and can receive large medical expense reductions. Therefore, HCM diagnostic code entry is very strictly controlled. To evaluate the accuracy of our definition of HCM, we conducted a validation study in two hospitals with 2,970 patients with the ICD-10 code (I42.1, I42.2). The patients' medical records and images including echocardiography were reviewed by two physicians (PSY and BYJ). Patients were ascertained to have HCM if it

was diagnosed by echocardiography and registered in the national registry for rare diseases to get insurance benefits. The positive predictive value was 90.7%. The diagnosis of AF has previously been validated in the NHIS database, with a positive predictive value of 94.1%.[2,3,6]

***Statistical analysis***

Descriptive statistics were used to characterize baseline characteristics and comorbidities. Continuous variables were expressed as the means ± standard deviations and categorical variables were reported as frequencies (percentages). We created a propensity score (PS)–matched warfarin versus non–vitamin K antagonist oral anticoagulants (NOACs) cohort, using 1:2 PS matching without replacement and with a caliper of 0.1 based on baseline characteristics, including age, sex, annual household income, individual components of the $CHA_2DS_2$2-VASc scores, history of cerebral hemorrhage, chronic kidney disease, chronic obstructive pulmonary disease, dyslipidemia and obstructive hypertrophic cardiomyopathy. We used Cox proportional hazards models to compare time to outcome events between groups. A multivariate-adjusted analysis was performed after adjusting for age, sex, hypertension, previous transient ischemic attack / ischemic stroke, previous hemorrhagic stroke, previous vascular disease, diabetes mellitus, heart failure, history of malignant neoplasm, chronic kidney disease, dyslipidemia, chronic obstructive pulmonary disease, obstructive hypertrophic cardiomyopathy, implantable cardioverter-defibrillator insertion, surgical myectomy and usage of medications including aspirin, P2Y12 inhibitor, statin, beta blocker, angiotensin converting enzyme inhibitor / angiotensin receptor blocker, diuretics, dihydropyridine calcium channel blocker, non-dihydropyridine calcium channel blocker, digoxin, class Ic antiarrhythmic drugs, amiodarone, dronedarone, rifampin, phenytoin, azole based antifungal agents and proton pump inhibitors. The patients were censored at the date when the endpoint events occurred, at the date of their death, or at end of follow-up. All tests were two-tailed, with a p-value of $<0.05$ considered significant. Statistical analyses were conducted with SAS version 9.3 (SAS Institute, Cary, NC, USA) and the SPSS version 23.0 statistical package (SPSS Inc., Chicago, IL, USA).

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**e-Appendix 2.**

**Discussion**

***Comorbidities and outcome events***

Because this study included only HCM patients on OAC, the direct comparison of comorbidities with other studies which included overall HCM patients is impossible. The high prevalence of comorbidities including hypertension and heart failure in HCM with OAC might be related to the fact that this study only included HCM with AF taking OAC. Although the prevalence of hypertension was above 90% in this study, it was only 68% in HCM without AF (e-Table 6). Moreover, because NOAC is not reimbursed in Korean AF patients with CHA2DS2-VASc scores less than 2, the NOAC group had even more stroke related comorbidities. Third, the mean age of HCM patients of this study was consistent with a large U.S. commercial insurance database,[7] but was older than those without AF in the Mayo Clinic report.[8]

Moreover, although the all-cause death in this study was around 12% at 1 year in warfarin treated patients, the incidence of all-cause death was 4.2% in overall patients with HCM with AF. This number was actually lower compared with the annual mortality rates of patients with HCM and AF in the Mayo Clinic series (6.9%).[8] Good anticoagulation control is associated with reductions in stroke and mortality in AF patients. If warfarin control is suboptimal this may be a contributory factor.

The stroke and bleeding rates in this study were higher or comparable with those found in the NOAC trials.[9,10] The rate of ischemic stroke/systemic embolism of Korean AF is reported 3.98 per 100 Person-Years. This rate is similar to the Denmark Nationwide Cohort of 5.29 per 100 Person-Years and is much higher than Euro Heart Survey of 2.3 per 100 Person-Years.[3,11] It is well known that individuals of Asian ethnicity are at a disproportionately high risk of stroke and have greater consequent mortality.[12] Moreover, the HCM patients with AF had higher risk of stroke compared to non-HCM AF patients. Even AF patients with HCM who were categorized as 'low risk' have an unadjusted rate of ischemic stroke of 3.38%.[13]

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**e-Table 1.** Definitions and ICD-10 codes used for defining comorbidities.

| Comorbidity | Definition | ICD-10 code or condition |
|---|---|---|
| Heart failure | Defined from diagnosis [a] | ICD-10: I11.0, I50, I97.1 |
| Hypertension | Defined from diagnosis [a] plus treatment | ICD-10: I10, I11, I12, I13, I15<br>Treatment: beta-blocker, ACEi, ARB, DHP CCB or diuretics |
| Diabetes mellitus | Defined from diagnosis [a] plus treatment | ICD-10: E10, E11, E12, E13, E14<br>Treatment: all kinds of oral antidiabetics and insulin |
| Ischemic stroke | Defined from diagnosis [a] | ICD-10: I63, I64 |
| TIA | Defined from diagnosis [a] | ICD-10: G45 |
| Previous MI | Defined from diagnosis [a] | ICD-10: I21, I22, I25.2 |
| Peripheral arterial disease | Defined from diagnosis [a] | ICD-10: I70.0, I70.1, I70.2, I70.8, I70.9 |
| CKD | Defined from diagnosis [a] | ICD-10: N18, N19 |
| ESRD | Defined from the national registry for severe illness. | Patients undergoing chronic dialysis or those who had received a kidney transplant. |
| Dyslipidemia | Defined from diagnosis [a] | ICD-10: E78 |
| Malignancy | Defined from diagnoses of cancer (non-benign) | ICD-10: C00-C97 |
| COPD | Defined from diagnosis [a] plus treatment | ICD-10: J42, J43(except J43.0), J44<br>Treatment: inhaled corticosteroid, inhaled bronchodilators, or oral methylxanthine (>1 months). |

ACEi = Angiotensin Converting Enzyme inhibitor; ARB = Angiotensin Receptor Blocker; DHP = Dihydropyridine; CCB = Calcium Channel Blocker; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; ESRD = end stage renal disease; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; TIA = transient ischemic attack.

[a] To ensure accuracy, comorbidities were established based on more than one inpatient or two outpatient records of ICD-10 codes in the database.

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**e-Table 2.** Prescription rate of medications before and after propensity score matching.

| | Before propensity score matching | | | After propensity score matching | | |
|---|---|---|---|---|---|---|
| | **Warfarin (n = 1,188)** | **NOAC (n = 2,302)** | **p-value** | **Warfarin (n = 955)** | **NOAC (n = 1,504)** | **p-value** |
| Aspirin | 492 (41.4) | 381 (16.6) | <0.001 | 321 (33.6) | 374 (24.9) | <0.001 |
| P2Y12 inhibitor | 235 (19.8) | 243 (10.6) | <0.001 | 160 (16.8) | 198 (13.2) | <0.001 |
| Statin | 680 (57.2) | 1383 (60.1) | 0.002 | 560 (58.6) | 879 (58.4) | 0.848 |
| Beta blocker | 890 (74.9) | 1555 (67.5) | <0.001 | 712 (74.6) | 1,047(69.6) | <0.001 |
| ACEi / ARB | 696 (58.6) | 1241 (53.9) | <0.001 | 554 (58.0) | 828 (55.1) | 0.003 |
| Diuretics | 775 (65.2) | 1359 (59.0) | <0.001 | 633 (66.3) | 856 (56.9) | <0.001 |
| Potassium sparing diuretics | 380 (32.0) | 609 (26.5) | <0.001 | 314 (32.9) | 386 (25.7) | <0.001 |
| DHP CCB | 307 (25.8) | 444 (19.3) | <0.001 | 243 (25.4) | 280 (18.6) | <0.001 |
| Non-DHP CCB | 290 (24.4) | 461 (20.0) | <0.001 | 228 (23.9) | 308 (20.5) | <0.001 |
| Verapamil | 66 (5.6) | 124 (5.4) | 0.677 | 61 (6.4) | 76 (5.1) | 0.005 |
| AAD Ic | 81 (6.8) | 142 (6.2) | 0.138 | 62 (6.5) | 93 (6.2) | 0.540 |
| AAD III | 364 (30.6) | 484 (21.0) | <0.001 | 282 (29.5) | 356 (23.7) | <0.001 |
| Amiodarone | 333 (28.0) | 428 (18.6) | <0.001 | 258 (27.0) | 317 (21.1) | <0.001 |
| Dronedarone | 34 (2.9) | 53 (2.3) | 0.045 | 28 (2.9) | 36 (2.4) | 0.103 |
| Digoxin | 220 (18.5) | 377 (16.4) | 0.002 | 185 (19.4) | 231 (15.4) | <0.001 |
| Rifampin | 11 (0.9) | 13 (0.6) | 0.014 | 11 (1.2) | 9 (0.6) | 0.003 |
| Phenytoin | 3 (0.3) | 6 (0.3) | 0.929 | 2 (0.2) | 3 (0.2) | 0.915 |
| Azole antifungals | 26 (2.2) | 29 (1.3) | <0.001 | 19 (2.0) | 19 (1.3) | 0.004 |
| PPI | 483 (40.7) | 856 (37.2) | <0.001 | 396 (41.5) | 561 (37.3) | <0.001 |
| ICD implantation | 49 (4.1) | 84 (3.6) | 0.487 | 37 (4.0) | 60 (4.0) | 0.775 |
| Surgical myectomy | 20 (1.7) | 6 (0.3) | <0.001 | 17 (1.8) | 5 (0.3) | <0.001 |
| Septal alcohol ablation | 0 | 0 | | 0 | 0 | |

Values are expressed as n (%) or mean ± SD. ACEi = Angiotensin Converting Enzyme inhibitor; ARB = Angiotensin Receptor Blocker; DHP = Dihydropyridine; CCB = Calcium Channel Blocker; AAD = Antiarrhythmic Drug; PPI = Proton Pump Inhibitor, ICD = Implantable Cardioverter-Defibrillator

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**e-Table 3.** The number of events, incidence, and risk of various events in NOAC- and warfarin-treated AF patients with HCM among baseline study population before propensity score matching.

| | Warfarin (n = 1,188) | NOAC (n = 2,302) | p value |
|---|---|---|---|
| **Death from all causes** | | | |
| Number of events | 182 | 133 | |
| Incidence per 100 person-years (95% CI) | 9.37 (8.06-10.83) | 5.66 (4.74-6.71) | <0.001 |
| Hazard ratio [a] | Reference | 0.40 (0.31-0.51) | <0.001 |
| **Ischemic stroke or systemic embolism** | | | |
| Number of events | 144 | 195 | |
| Incidence per 100 person-years (95% CI) | 8.03 (6.77-9.46) | 8.71 (7.53-10.02) | 0.461 |
| Hazard ratio [a] | Reference | 0.95 (0.75-1.22) | 0.700 |
| **Major bleeding** | | | |
| Number of events | 98 | 121 | |
| Incidence per 100 person-years (95% CI) | 5.23 (4.25-6.38) | 5.31 (4.40-6.34) | 0.918 |
| Hazard ratio [a] | Reference | 0.95 (0.70-1.29) | 0.736 |
| **Gastrointestinal bleeding** | | | |
| Number of events | 73 | 98 | |
| Incidence per 100 person-years (95% CI) | 3.86 (3.03-4.86) | 4.28 (3.48-5.22) | 0.506 |
| Hazard ratio [a] | Reference | 1.01 (0.71-1.42) | 0.972 |
| **Intracranial hemorrhage** | | | |
| Number of events | 18 | 19 | |
| Incidence per 100 person-years (95% CI) | 0.93 (0.55-1.47) | 0.81 (0.49-1.27) | 0.674 |
| Hazard ratio [a] | Reference | 0.86 (0.41-1.82) | 0.698 |
| **Acute myocardial infarction** | | | |
| Number of events | 36 | 55 | |
| Incidence per 100 person-years (95% CI) | 1.88 (1.32-2.60) | 2.37 (1.78-3.08) | 0.280 |
| Hazard ratio [a] | Reference | 1.28 (0.80-2.06) | 0.303 |
| **Composite fatal cardiovascular events** | | | |
| Number of events | 32 | 20 | |
| Incidence per 100 person-years (95% CI) | 1.86 (1.27-2.62) | 0.92 (0.56-1.43) | 0.013 |
| Hazard ratio [a] | Reference | 0.34 (0.19-0.64) | 0.001 |

AF = atrial fibrillation; CI = confidence interval; HCM = hypertrophic cardiomyopathy; NOAC = Non–vitamin K antagonist oral anticoagulants.

[a] Multivariate-adjusted for age, sex, heart failure, hypertension, diabetes mellitus, previous transient ischemic attack / ischemic stroke, previous hemorrhagic stroke, previous vascular disease, malignant neoplasm, chronic kidney disease, dyslipidemia, chronic obstructive pulmonary disease, obstructive hypertrophic cardiomyopathy, implantable cardioverter-defibrillator insertion, surgical myectomy and medications (aspirin, P2Y12 inhibitor, statin, beta blocker, angiotensin converting enzyme inhibitor / angiotensin receptor blocker, diuretics, dihydropyridine calcium channel blocker, non-dihydropyridine calcium channel blocker, digoxin, class Ic antiarrhythmic drugs, amiodarone, dronedarone, rifampin, phenytoin, azole based antifungal agents and proton pump inhibitor).

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**e-Table 4.** The number of events, incidence, and risk of various events in patients with HCM and AF according to NOAC dose after propensity score matching.

| | Warfarin (n =955) | Reduced dose NOAC (n=751) | Standard dose NOAC (n=753) |
|---|---|---|---|
| **Death from all causes** | | | |
| Number of events | 158 | 49 | 31 |
| Incidence per 100 person-years (95% CI) | 10.13 (8.61-11.83) | 6.44 (4.77-8.52) | 3.85 (2.62-5.47) |
| Hazard ratio [a] | Reference | 0.45 (0.32-0.63) | 0.40 (0.27-0.60) |
| **Ischemic stroke or systemic embolism** | | | |
| Number of events | 115 | 58 | 66 |
| Incidence per 100 person-years (95% CI) | 7.96 (6.57-9.55) | 7.97 (6.05-10.30) | 8.67 (6.71-11.04) |
| Hazard ratio [a] | Reference | 0.84 (0.60-1.17) | 1.06 (0.77-1.45) |
| **Major bleeding** | | | |
| Number of events | 78 | 45 | 37 |
| Incidence per 100 person-years (95% CI) | 5.19 (4.11-6.48) | 6.11 (4.45-8.17) | 4.74 (3.34-6.54) |
| Hazard ratio [a] | Reference | 0.95 (0.64-1.39) | 0.99 (0.66-1.50) |
| **Gastrointestinal bleeding** | | | |
| Number of events | 61 | 38 | 29 |
| Incidence per 100 person-years (95% CI) | 4.03 (3.08-5.17) | 5.14 (3.64-7.06) | 3.70 (2.48-5.31) |
| Hazard ratio [a] | Reference | 0.97 (0.63-1.48) | 1.04 (0.65-1.65) |
| **Intracranial hemorrhage** | | | |
| Number of events | 14 | 6 | 4 |
| Incidence per 100 person-years (95% CI) | 0.90 (0.49-1.51) | 0.79 (0.29-1.72) | 0.50 (0.14-1.28) |
| Hazard ratio [a] | Reference | 0.81 (0.29-2.29) | 0.57 (0.18-1.85) |
| **Acute myocardial infarction** | | | |
| Number of events | 31 | 28 | 16 |
| Incidence per 100 person-years (95% CI) | 2.01 (1.37-2.86) | 3.73 (2.48-5.39) | 2.02 (1.15-3.27) |
| Hazard ratio [a] | Reference | 1.47 (0.85-2.54) | 1.13 (0.60-2.12) |
| **Composite fatal cardiovascular events** | | | |
| Number of events | 25 | 7 | 4 |
| Incidence per 100 person-years (95% CI) | 1.80 (1.17-2.66) | 1.00 (0.40-2.06) | 0.55 (0.15-1.40) |
| Hazard ratio [a] | Reference | 0.42 (0.18-1.01) | 0.33 (0.11-1.00) |

AF = atrial fibrillation; CI = confidence interval; HCM = hypertrophic cardiomyopathy; NOAC = Non–vitamin K antagonist oral anticoagulants.
[a] Multivariate-adjusted for age, sex, heart failure, hypertension, diabetes mellitus, previous transient ischemic attack / ischemic stroke, previous hemorrhagic stroke, previous vascular disease, malignant neoplasm, chronic kidney disease, dyslipidemia, chronic obstructive pulmonary disease, obstructive hypertrophic cardiomyopathy, implantable cardioverter-defibrillator insertion, surgical myectomy and medications (aspirin, P2Y12 inhibitor, statin, beta blocker, angiotensin converting enzyme inhibitor / angiotensin receptor blocker, diuretics, dihydropyridine calcium channel blocker, non-dihydropyridine calcium channel blocker, digoxin, class Ic antiarrhythmic drugs, amiodarone, dronedarone, rifampin, phenytoin, azole based antifungal agents and proton pump inhibitor).

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**e-Table 5.** The number of events, incidence, and risk of various events in patients with HCM and AF according to type of NOACs after propensity score matching.

| | Warfarin (n=955) | Apixaban (n=375) | Dabigatran (n=458) | Rivaroxaban (n=585) |
|---|---|---|---|---|
| **Death from all causes** | | | | |
| Number of events | 158 | 16 | 21 | 43 |
| Incidence per 100 person-years (95% CI) | 10.13 (8.61-11.83) | 4.29 (2.45-6.96) | 4.02 (2.49-6.14) | 6.73 (4.87-9.07) |
| Hazard ratio [a] | Reference | 0.39 (0.23-0.65) | 0.36 (0.22-0.57) | 0.53 (0.37-0.75) |
| **Ischemic stroke or Systemic embolism** | | | | |
| Number of events | 115 | 25 | 40 | 58 |
| Incidence per 100 person-years (95% CI) | 7.96 (6.57-9.55) | 7.01 (4.54-10.35) | 8.04 (5.74-10.94) | 9.61 (7.30-12.43) |
| Hazard ratio [a] | Reference | 0.79 (0.50-1.23) | 0.86 (0.59-1.24) | 1.16 (0.84-1.62) |
| **Major bleeding** | | | | |
| Number of events | 78 | 17 | 25 | 37 |
| Incidence per 100 person-years (95% CI) | 5.19 (4.11-6.48) | 4.72 (2.75-7.56) | 4.93 (3.19-7.27) | 5.98 (4.21-8.24) |
| Hazard ratio [a] | Reference | 0.85 (0.49-1.46) | 0.88 (0.55-1.40) | 1.09 (0.72-1.64) |
| **Gastrointestinal bleeding** | | | | |
| Number of events | 61 | 15 | 23 | 28 |
| Incidence per 100 person-years (95% CI) | 4.03 (3.08-5.17) | 4.15 (2.32-6.85) | 4.53 (2.87-6.79) | 4.50 (2.99-6.50) |
| Hazard ratio [a] | Reference | 0.93 (0.52-1.68) | 1.01 (0.62-1.67) | 1.04 (0.65-1.66) |
| **Intracranial Hemorrhage** | | | | |
| Number of events | 14 | 3 | 1 | 4 |
| Incidence per 100 person-years (95% CI) | 0.90 (0.49-1.51) | 0.81 (1.67-2.36) | 0.19 (0.00-1.07) | 0.63 (0.17-1.61) |
| Hazard ratio [a] | Reference | 0.94 (0.25-3.58) | 0.25 (0.03-1.98) | 0.60 (0.18-1.98) |
| **Acute myocardial infarction** | | | | |
| Number of events | 31 | 9 | 10 | 23 |
| Incidence per 100 person-years (95% CI) | 2.01 (1.37-2.86) | 2.44 (1.12-4.63) | 1.93 (0.92-3.55) | 3.67 (2.33-5.51) |
| Hazard ratio [a] | Reference | 1.28 (0.59-2.79) | 0.80 (0.39-1.67) | 1.81 (1.02-3.23) |
| **Composite fatal cardiovascular events** | | | | |
| Number of events | 25 | 0 | 2 | 9 |
| Incidence per 100 person-years (95% CI) | 1.80 (1.17-2.66) | 0 (0-1.07) | 0.42 (0.05-1.50) | 1.57 (0.72-2.97) |
| Hazard ratio [a] | Reference | N/A | 0.21 (0.05-0.90) | 0.85 (0.37-1.94) |

AF = atrial fibrillation; CI = confidence interval; HCM = hypertrophic cardiomyopathy; NOAC = Non–vitamin K antagonist oral anticoagulants. Edoxaban group was not shown in this table because the number of patients was small (n=86).

[a] Multivariate-adjusted for age, sex, heart failure, hypertension, diabetes mellitus, previous transient ischemic attack / ischemic stroke, previous hemorrhagic stroke, previous vascular disease, malignant neoplasm, chronic kidney disease, dyslipidemia, chronic obstructive pulmonary disease, obstructive hypertrophic cardiomyopathy, implantable cardioverter-defibrillator insertion, surgical myectomy and medications (aspirin, P2Y12 inhibitor, statin, beta blocker, angiotensin converting enzyme inhibitor / angiotensin receptor blocker, diuretics, dihydropyridine calcium channel blocker, non-dihydropyridine calcium channel blocker, digoxin, class Ic antiarrhythmic drugs, amiodarone, dronedarone, rifampin, phenytoin, azole based antifungal agents and proton pump inhibitor).

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**e-Table 6.** Baseline characteristics of overall HCM+AF in Korean NHIS and NHIS-HealS cohort.

| | Korean NHIS | Korean NHIS-HealS cohort | |
|---|---|---|---|
| | HCM+AF (n=10,020) | HCM (n=593) | HCM+AF (n=165) |
| **Age** | 65.1 ± 12.6 | 60.1 ± 9.7 | 62.4 ± 9.5 |
| **<65** | 4,354 (43.5) | 345 (58.2) | 93 (56.4) |
| **65-74** | 3,227 (32.2) | 205 (34.6) | 57 (34.5) |
| **≥75** | 2,439 (24.3) | 43 (7.3) | 15 (9.1) |
| **Men** | 5,492 (54.8) | 380 (64.1) | 103 (62.4) |
| **$CHA_2DS_2$-VASc score** | 3.53 ± 2.12 | 2.15 ± 1.67 | 2.56 ± 1.75 |
| **Previous ischemic stroke / TIA** | 2,596 (25.9) | 69 (11.6) | 20 (12.1) |
| **Previous hemorrhagic stroke** | 222 (2.2) | 5 (0.8) | 2 (1.2) |
| **Previous MI** | 1,567 (15.6) | 52 (8.8) | 23 (13.9) |
| **PAD** | 1,300 (13.0) | 26 (4.4) | 12 (7.3) |
| **Vascular disease** | 2,547 (25.4) | 72 (12.1) | 31 (18.8) |
| **Hypertension** | 8,224 (82.1) | 403 (68.0) | 128 (77.6) |
| **Diabetes mellitus** | 2,258 (22.5) | 67 (11.3) | 20 (12.1) |
| **Heart failure** | 4,540 (45.3) | 108 (18.2) | 52 (31.5) |
| **History of cancer** | 1,934 (19.3) | 72 (12.1) | 24 (14.5) |
| **CKD** | 696 (6.9) | 19 (3.2) | 11 (6.7) |
| **Dyslipidemia** | 7,108 (70.9) | 304 (51.3) | 96 (58.2) |
| **COPD** | 3,092 (30.9) | 117 (19.7) | 43 (26.1) |

Values are expressed as n (%) or mean ± SD. ASMD = absolute standardized mean difference; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; HCM = hypertrophic cardiomyopathy; HealS, Health Screening; MI = myocardial infarction; NHIS, National Health Insurance Service; NOAC = non–vitamin K antagonist oral anticoagulant; PAD = peripheral artery disease; TIA = transient ischemic attack; Vascular disease = previous MI, PAD, or aortic plaque.

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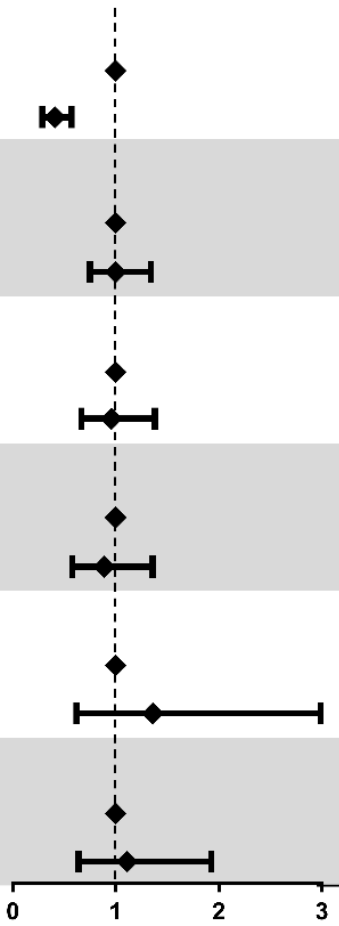
**e-Figure 1.** The number of events, incidence, and risk of primary outcomes in propensity score including including ASA, P2Y12 inhibitors and statin matched NOAC- and warfarin-treated patients with HCM and AF. CI = confidence interval. Other abbreviations are as in e-Table 2.

| | Patients, n | Events, n | Incidence (95% CI) | Hazard ratio* (95% CI) | p-value |
|---|---|---|---|---|---|
| Death from all causes | | | | | |
| Warfarin | 989 | 162 | 10.11 (8.61-11.79) | Reference | - |
| NOAC | 989 | 51 | 4.98 (3.71-6.55) | 0.41 (0.29-0.57) | <0.001 |
| Ischemic stroke or systemic embolism | | | | | |
| Warfarin | 989 | 115 | 7.75 (6.40-9.30) | Reference | - |
| NOAC | 989 | 89 | 9.10 (7.31-11.20) | 1.00 (0.75-1.34) | 0.996 |
| Major bleeding | | | | | |
| Warfarin | 989 | 80 | 5.17 (4.10-6.44) | Reference | - |
| NOAC | 989 | 55 | 5.55 (4.18-7.22) | 0.96 (0.67-1.38) | 0.826 |
| GI bleeding | | | | | |
| Warfarin | 989 | 60 | 3.85 (2.93-4.95) | Reference | - |
| NOAC | 989 | 39 | 3.91 (2.78-5.35) | 0.89 (0.58-1.36) | 0.588 |
| Intracranial hemorrhage | | | | | |
| Warfarin | 989 | 15 | 0.94 (0.53-1.55) | Reference | - |
| NOAC | 989 | 14 | 1.37 (0.75-2.31) | 1.36 (0.62-2.99) | 0.436 |
| Acute myocardial infarction | | | | | |
| Warfarin | 989 | 31 | 1.96 (1.33-2.78) | Reference | - |
| NOAC | 989 | 27 | 2.67 (1.76-3.89) | 1.11 (0.64-1.93) | 0.707 |




* Multivariate-adjusted for age, sex, heart failure, hypertension, diabetes mellitus, previous transient ischemic attack / ischemic stroke, previous hemorrhagic stroke, previous vascular disease, malignant neoplasm, chronic kidney disease, dyslipidemia, chronic obstructive pulmonary disease, obstructive hypertrophic cardiomyopathy, implantable cardioverter-defibrillator insertion, surgical myectomy and medications (aspirin, P2Y12 inhibitor, statin, beta blocker, angiotensin converting enzyme inhibitor / angiotensin receptor blocker, diuretics, dihydropyridine calcium channel blocker, non-dihydropyridine calcium channel blocker, digoxin, class Ic antiarrhythmic drugs, amiodarone, dronedarone, rifampin, phenytoin, azole based antifungal agents and proton pump inhibitor).

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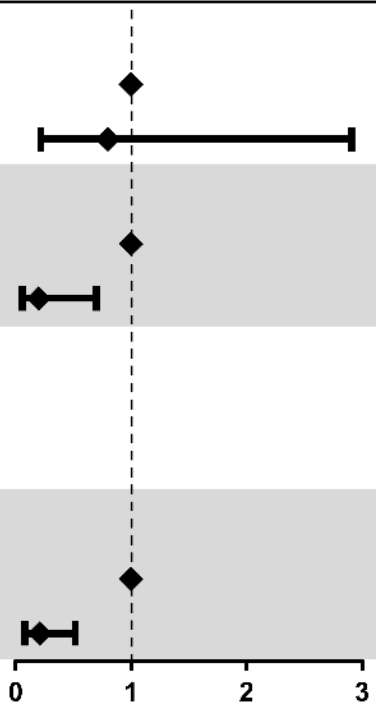
**e-Figure 2.** The number of events, incidence, and risk of fatal cardiovascular events in propensity score including ASA, P2Y12 inhibitors and statin matched NOAC- and warfarin-treated patients with HCM and AF. CI = confidence interval. Other abbreviations are as in e-Table 2.

| | Patients, n | Events, n | Incidence (95% CI) | Hazard ratio* (95% CI) | p-value |
|---|---|---|---|---|---|
| Fatal ischemic stroke | | | | | |
| Warfarin | 989 | 7 | 0.47 (0.19-0.96) | Reference | - |
| NOAC | 989 | 5 | 0.51 (0.17-1.19) | 0.80 (0.22-2.91) | 0.803 |
| Fatal bleeding | | | | | |
| Warfarin | 989 | 18 | 1.19 (0.71-1.88) | Reference | - |
| NOAC | 989 | 3 | 0.31 (0.06-0.89) | 0.20 (0.06-0.70) | 0.012 |
| Fatal acute myocardial infarction | | | | | |
| Warfarin | 989 | 6 | 0.38 (0.14-0.83) | Reference | - |
| NOAC | 989 | 0 | 0 (0-0.37) | N/A | |
| Composite of fatal cardiovascular events | | | | | |
| Warfarin | 989 | 28 | 1.97 (1.31-2.85) | Reference | - |
| NOAC | 989 | 6 | 0.64 (0.24-1.39) | 0.21 (0.08-0.52) | 0.001 |




* Multivariate-adjusted for age, sex, heart failure, hypertension, diabetes mellitus, previous transient ischemic attack / ischemic stroke, previous hemorrhagic stroke, previous vascular disease, malignant neoplasm, chronic kidney disease, dyslipidemia, chronic obstructive pulmonary disease, obstructive hypertrophic cardiomyopathy, implantable cardioverter-defibrillator insertion, surgical myectomy and medications (aspirin, P2Y12 inhibitor, statin, beta blocker, angiotensin converting enzyme inhibitor / angiotensin receptor blocker, diuretics, dihydropyridine calcium channel blocker, non-dihydropyridine calcium channel blocker, digoxin, class Ic antiarrhythmic drugs, amiodarone, dronedarone, rifampin, phenytoin, azole based antifungal agents and proton pump inhibitor).