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Non-vitamin K Antagonist Oral Anticoagulant, Warfarin, and ABC Pathway Adherence on Hierarchical Outcomes: Win Ratio Analysis of the COOL-AF Registry

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Abstract

Background Atrial fibrillation (AF) Better Care (ABC) pathway adherence is associated with improved outcomes. Clinical trials have shown that non-vitamin K antagonist oral anticoagulants (NOACs) are as least as effective as warfarin for stroke prevention in AF patients. The Win Ratio method, analyzing hierarchical composite outcomes considering event timing and severity, has limited data on its use in Asians.

Objectives We aim to apply Win Ratio in a registry to access the comparative effectiveness of NOACs versus warfarin and ABC adherence versus nonadherence in Asian patients with AF.

Methods Our study included nonvalvular AF patients from the nationwide prospective COOL-AF registry in Thailand. The NOAC-treated group was compared with the warfarin-treated group using the Win Ratio, with the following order: all-cause death, intracranial hemorrhage (ICH), ischemic stroke/transient ischemic attack/systemic embolism, non-ICH major bleeding, and myocardial infarction or heart failure. ABC pathway adherence versus nonadherence was also compared. A Win Ratio greater than 1.00 indicating a better outcome.

Results The analysis included 2,568 patients, with 228 in the NOAC group and 2,340 in the warfarin group. The NOAC group had more wins than the warfarin group, with an unmatched Win Ratio of 1.64 (95% confidence interval [CI]: 1.22–2.20; $p < 0.001$). When compared with nonadherence, ABC pathway adherence was associated with a Win Ratio of 1.57 (95% CI: 1.33–1.85; $p < 0.001$).

Conclusion This Win Ratio analysis demonstrates the significant benefits of NOACs over warfarin and ABC pathway adherence over nonadherence in reducing the composite outcome in patients with AF.

Keywords
- hierarchical composite outcome
- atrial fibrillation
- anticoagulants
- ABC pathway
- thrombosis

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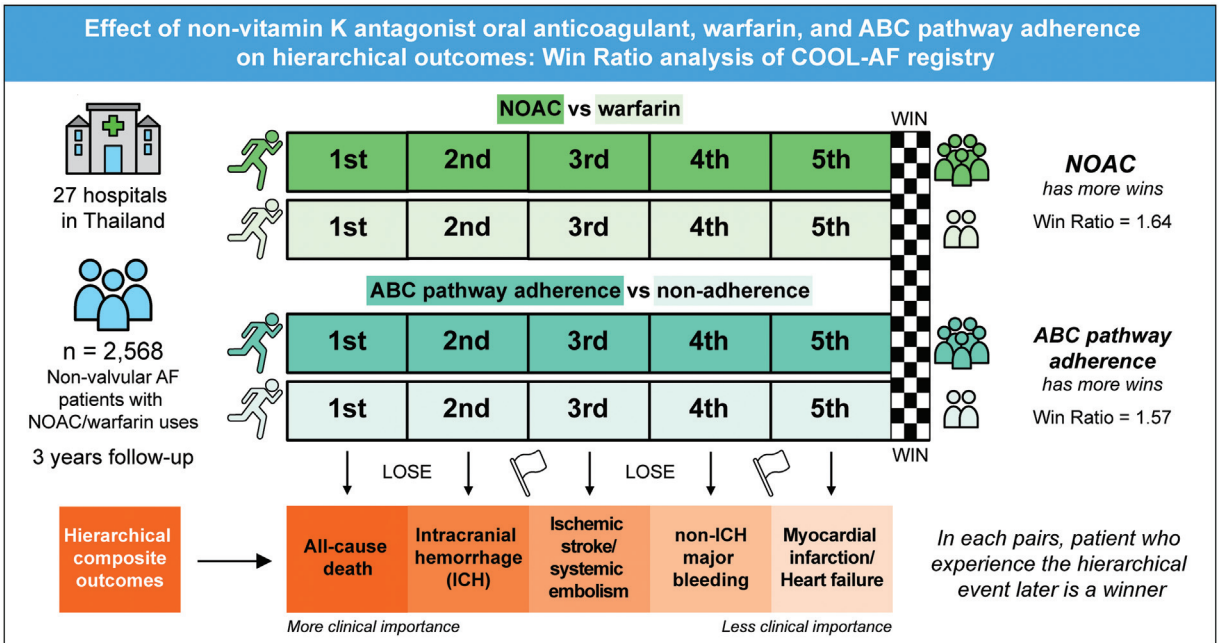

Visual summary. Win Ratio analysis comparing NOAC vs warfarin and ABC pathway adherence vs non-adherence in AF patients.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and remains a significant global health burden. The Global Burden of Diseases database estimates that AF affects over 37.5 million people worldwide in 2017, with a rising prevalence and incidence.[1] AF is associated with an increased risk of stroke, systemic embolism, and mortality.[2] To improve patients' outcome, current guidelines recommend the use of a holistic or integrated care approach based on the AF Better Care (ABC) pathway, which includes the pillars of AF care, as follows: "Anticoagulation to avoid stroke," "Better symptom control," and "Cardiovascular risk and comorbidity management."[3,4] Adherence with the ABC pathway has been associated with improved clinical outcomes.[5]

The standard choice of oral anticoagulants (OACs) has been vitamin K antagonists (VKAs), including warfarin; however, warfarin possesses several limitations, such as narrow therapeutic range, frequent international normalized ratio (INR) monitoring, and drug–drug/drug–food interaction.[6] From recent trials and meta-analyses, non-VKA oral anticoagulants (NOACs), such as dabigatran, rivaroxaban, apixaban, and edoxaban, have emerged as an alternative therapeutic option for stroke prevention with noninferior efficacy, better safety profile, and more convenient use.[7,8]

In cardiovascular trials, a primary composite endpoint is often used to evaluate the efficacy of randomized treatment, which often consists of two or more types of clinical events (i.e., cardiovascular death, stroke, hospitalization). This conventional composite endpoint analysis focuses on time-to-first event, neglecting severity or clinical importance of events. The effect size of time-to-first event analysis was mainly contributed by less severe events that occurred earlier than more severe events, including death.[9] Pocock et al proposed the "Win Ratio" as a new approach to analyze composite outcome in the way that account for both clinical priorities and timing of the events.[10] In recent years, the Win Ratio analysis has gained attention in many cardiovascular trials and post-hoc analysis of trials,[11–14] especially from Western population; however, its application in disease registries and Asian cohorts remains scarce.

While randomized controlled trials (RCTs) have demonstrated the efficacy and safety of NOACs,[15–18] real-world data from large registries are crucial to providing valuable insights into how anticoagulants perform in routine clinical practice, especially in clinically complex AF patients.[19,20] We therefore hypothesize that the Win Ratio method could be a novel tool in analyzing disease registry outcomes and providing a more comprehensive understanding of the treatment benefits when used in routine clinical practice.

In this study, we applied a Win Ratio analysis in the context of the COhort of antithrombotic use and Optimal INR Level in patients with nonvalvular Atrial Fibrillation in Thailand (COOL-AF) registry, a multicenter nationwide prospective cohort of patients with AF.[21] The objectives of our study are, firstly, to demonstrate the analysis and interpretation of Win Ratio in a disease registry in relation to clinical outcomes; secondly, to access the comparative efficacy of NOACs and warfarin in Asian patients with AF; and thirdly, we applied a Win Ratio analysis to AF patients who were ABC pathway adherence compared with those who were nonadherent.

Methods

Study Population

We utilized the data from the COOL-AF registry,[21] a nationwide prospective study that recruited nonvalvular AF (NVAF)

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patients aged 18 years or older from 27 hospitals in Thailand. Patients with rheumatic or severe valve disease, prosthetic valve or valve repair, AF from transient reversible cause, bleeding disorders, such as thrombocytopenia or myeloproliferative disorders, etc., ischemic stroke within 3 months, pregnancy, current participation in a clinical trial, life expectancy less than 3 years, or inability to attend follow-up were excluded from the registry. The protocol for the COOL-AF registry was approved by the Institutional Review Board of Central Research Ethics Committee (COA: CREC 003/2014). All patients provided written informed consent. The patients in the COOL-AF registry, who were treated with OACs at baseline, were included in the present analysis.

Study Protocol and Data Collection

The details of the COOL-AF registry protocol were previously published.[21] Clinical data were collected by investigators from the medical record and patient interview, which were recorded in the study case record form, entered in the web-based system, and verified via central data management. All participating hospitals underwent site monitoring and followed the good clinical practice. The data were collected at baseline, and at 6, 12, 18, 24, 30, and 36 months. The collected data included demographic data, vital signs, time after AF diagnosis, AF symptoms, type of AF, medical history, and medications.

Outcomes

The clinical outcomes were all-cause death, intracranial hemorrhage (ICH), ischemic stroke/transient ischemic attack (TIA)/systemic embolism (SSE), non-ICH major bleeding, and myocardial infarction (MI) or heart failure (HF). ICH was defined as bleeding within the cranium, such as intracerebral bleeding, subdural bleeding, and subarachnoid bleeding, but did not include microbleeds or hemorrhagic transformation.[22] Ischemic stroke was defined as an acute onset of a focal neurological deficit that lasted longer than 24 hours, whereas TIA had a similar definition but lasting less than 24 hours. Systemic embolism was defined as sudden loss of end-organ perfusion supported by both clinical and objective evidence. Major bleeding was defined using the International Society of Thrombosis and Hemostasis criteria.[23] The definition of MI was derived from the Fourth Universal Definition of Myocardial Infarction.[24] HF event was defined as either a hospitalization or an urgent or unscheduled visit to clinic, office, or emergency department due to symptoms and objective evidence of new or worsening HF. The definition also requires initiation or intensification of treatment specifically for HF.[25] All clinical events in the COOL-AF registry were adjudicated by the clinical event committee.

For hierarchical composite outcome analysis, we determined the order of the outcome based on clinical severity, prioritizing death, systemic embolism, and major bleeding events over MI or HF events. The hierarchical order was (1) all-cause death, (2) ICH, (3) SSE, (4) non-ICH major bleeding, and (5) MI or HF.

To compare adherence to the ABC pathway with nonadherence, we applied the unmatched Win Ratio to analyze the hierarchical composite outcome in the order mentioned above. Since the entirety of our patient cohort received OAC therapy, we conducted the Win Ratio analyses to compare (1) adherence to ABC pathway versus nonadherence, (2) adherence to component B versus nonadherence, and (3) adherence to component C versus nonadherence.

The definition of ABC pathway adherence was established based on the original definition.[26] Adherence to component A was achieved if patient received appropriate OAC strategy to their stroke risk at baseline. Component A adherence was met when male patients with CHA_2DS_2-VASc score ≥ 1 or ≥ 2 in females who received an OAC, and male patients with CHA_2DS_2-VASc score $= 0$ or ≤ 1 in females who did not receive an OAC. Component B adherence was fulfilled if patients had a European Heart Rhythm Association score ≤ 2. For component C, adherence was considered if patients had appropriate comorbidity management. This included (1) hypertension management with angiotensin-converting enzyme inhibitors (ACEi)/angiotensin (II) receptor blockers (ARB), calcium channel blockers, diuretics, and β-blockers (BBs), (2) coronary artery disease management with ACEi/ARB, BB, and statins, (3) ischemic stroke/TIA management with statins, (4) HF management with ACEi/ARB and BB, and (5) diabetes management with oral antidiabetics or insulin. Adherence to the ABC pathway was achieved when the patient met all three components.

Statistical Analysis

In this study, we conducted an analysis of all patients from the COOL-AF registry who were treated with NOACs or warfarin at baseline. The baseline characteristics of patients were presented as means ± standard deviation (SD), and frequency for continuous and categorical variable, respectively. The incidence rates of each clinical outcome were presented as rate per 100 person-years with a Poisson 95% confidence interval (95% CI) and a two-sided *p*-value.

Win Ratio is an emerging concept for analyzing composite outcome in clinical trials, which focuses on the severity of the outcome and timing of occurrence instead of solely relying on time-to-first event in conventional analysis. There are two approaches for analyzing hierarchical composite outcome using Win Ratio—unmatched-pair and matched-pair approaches.[10,11]

In the unmatched approach, all patients from the NOAC group were paired with all patients from the warfarin group. In each pair, the NOAC group was counted as a winner when a patient in the warfarin group developed all-cause death before the NOAC group. In contrast, the NOAC group was considered a loser if a patient in this group developed all-cause death first. If neither of these conditions were met, we assessed the next outcome in the prespecified hierarchical order until we determined the winner or loser. If the winner or loser could not be determined, the pair was a tie. The Win Ratio was calculated by dividing the number of win pairs by the number of lose pairs. The value of win ratio greater than 1.00 indicated that the treatment group (NOACs) had better outcomes compared with the control group (warfarin). Win Ratio, 95% CI, two-sided *p*-value, and numbers of wins, losses, and ties were calculated with WINS package in R.[27]

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In the matched-pair approach, we aim to compare the outcomes of the similar-risk patients between two groups. Our study employed propensity score matching by nearest neighbor method with logistic regression from the MatchIt package in R.[28] Each NOAC patient was matched with four warfarin patients based on all variables, including age, sex, body mass index, duration after AF diagnosis, AF symptoms, type of AF, history of congestive HF, history of revascularization, implanted cardiac device, peripheral arterial disease, carotid occlusive disease, ischemic stroke or TIA, hypertension, dyslipidemia, diabetes mellitus, smoking, renal replacement therapy, dementia, history of bleeding, and antiplatelet use. Win ratio, 95% CI, and two-sided *p*-value were calculated as described by Pocock et al.[10]

Because our study utilized data from a prospective registry, it is possible that there are some differences in the baseline characteristics between the NOACs and the warfarin group. Therefore, we created a propensity-matched population to minimize the differences and conducted a conventional win ratio analysis as a secondary analysis. The propensity-matched population was generated based on the same method as described in the matched-pair approach. Then we conducted an analysis, in which all patients from the NOAC group were paired with all patients from the warfarin group, to determine the Win Ratio, 95% CI, two-sided *p*-value, and numbers of wins, losses, and ties of the propensity-matched population.

For sensitivity analysis, we analyzed hierarchical composite outcome in the order of (1) ICH, (2) SSE, (3) non-ICH major bleeding, and (4) MI or HF, using the unmatched win ratio approach.

As demonstrated by Oakes and Finkelstein and colleagues, Win Ratio and win proportion could vary over the follow-up time.[29,30] Specifically, the beneficial effect of the treatment that contributes to wins may be driven by different outcomes at each time point in the study period. The win proportion of a group was defined as the number of wins for that group divided by the total number of pairs.[31] We used WIN package to calculate Win Ratio and win proportion for each group over the follow-up time to investigate the changes in the contribution to wins by each outcome. All analyses were done using R version 4.2.3 (www.r-project.org), IBM SPSS Statistics version 28.0 (IBM Corp., Armonk, New York, United States), and MedCalc Statistical Software version 20 (MedCalc Software Ltd., Ostend, Belgium).

Results

Study Population

Of the total cohort of 3,461 patients from the COOL-AF registry, follow-up data were unavailable for 50 patients, and 837 patients did not receive OACs. Therefore, a total of 2,568 patients (mean age: 68.8 ± 10.7 years; 43.4% female) were included in this analysis. The flow diagram of the study population is illustrated in ►**Fig. 1**.

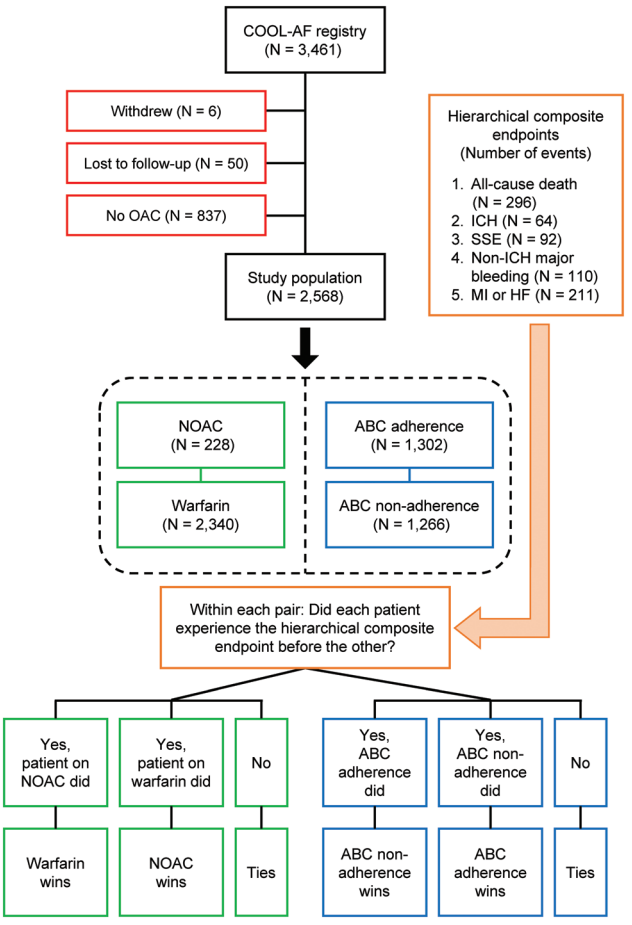

Fig. 1 Flow diagram of study population and hierarchical of composite endpoints. ABC, Atrial fibrillation Better Care; HF, heart failure; ICH, intracranial hemorrhage; MI, myocardial infarction; OAC, oral anticoagulants; SSE, ischemic stroke or transient ischemic attack or systemic embolism.

Baseline Characteristics

The number of patients receiving warfarin and NOACs was 2,340 (91.1%) and 228 (8.9%), respectively. The median follow-up time was 35.9 months, with an interquartile range of 34.7 to 36.0. Among the study population, 1,302 (50.7%) patients adhered to the ABC pathway, with adherence to components B and C observed in 1,942 (75.6%) and 1,787 (69.6%) patients, respectively.

►**Table 1** shows the baseline characteristics of the study population. Permanent AF was the majority of the warfarin group (52.7%), while paroxysmal AF was prominent in the NOAC group (50.0%). The NOAC group had more patients with a cardiovascular implantable electronic device. Patients in the warfarin group had more of the following characteristics: history of HF, history of ischemic stroke/TIA, hypertension, chronic kidney disease, anemia, and receiving antiplatelet. There were no statistically significant differences in other baseline factors between the two groups.

For the propensity-matched population, 228 patients from the NOAC group were matched to 912 patients from the warfarin group, resulting in a total of 1,140 patients. The mean age (±SD) of the patients was 67.7 ± 11.1 years, and 43.0% were female. There were no statistically significant differences of baseline variables between NOACs and warfarin groups. The baseline characteristics are displayed in

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Table 1 Baseline characteristics of the study population

Characteristics	All ($N = 2,568$)	Warfarin ($n = 2,340$)	NOACs ($n = 228$)	*p*-Value
Age (y)	68.8 ± 10.7	68.8 ± 10.7	68.5 ± 10.6	0.701
Female sex	1,115 (43.4%)	1,017 (43.5%)	98 (43.0%)	0.889
Body mass index (kg/m^2)	25.2 ± 4.8	25.2 ± 4.8	25.3 ± 4.4	0.748
Time after diagnosis of AF (y)	3.5 ± 4.4	3.5 ± 4.4	3.6 ± 4.7	0.755
Atrial fibrillation				
Paroxysmal	778 (30.3%)	664 (28.4%)	114 (50.0%)	<0.001
Persistent	482 (18.8%)	443 (18.9%)	39 (17.1%)	
Permanent	1,308 (50.9%)	1,233 (52.7%)	75 (32.9%)	
Symptomatic AF	1,974 (76.9%)	1,797 (76.8%)	177 (77.6%)	0.775
History of heart failure	702 (27.3%)	660 (28.2%)	42 (18.4%)	0.002
History of coronary revascularization	416 (16.2%)	378 (16.2%)	38 (16.7%)	0.841
History of PAD	32 (1.2%)	31 (1.3%)	1 (0.4%)	0.250
History of ischemic stroke/TIA	538 (21.0%)	502 (21.5%)	36 (15.8%)	0.045
History of bleeding	273 (10.6%)	252 (10.8%)	21 (9.2%)	0.466
Diabetes mellitus	690 (26.9%)	637 (27.2%)	53 (23.2%)	0.196
Hypertension	1,862 (72.5%)	1,710 (73.1%)	152 (66.7%)	0.039
Smoking	473 (18.4%)	434 (18.5%)	39 (17.1%)	0.592
Dyslipidemia	1,507 (58.7%)	1,373 (58.7%)	134 (58.8%)	0.977
Renal replacement therapy	22 (0.9%)	21 (0.9%)	1 (0.4%)	0.715
CHA_2DS_2-VASc score				
Low risk	102 (4.0%)	81 (3.5%)	21 (9.2%)	<0.001
Intermediate risk	348 (13.5%)	310 (13.2%)	38 (16.7%)	
High risk	2,118 (82.5%)	1,949 (83.3%)	169 (74.1%)	
HAS-BLED score				
0	336 (13.1%)	286 (12.2%)	50 (21.9%)	<0.001
1–2	1,818 (70.8%)	1,653 (70.7%)	165 (72.4%)	
≥3	414 (16.1%)	401 (17.1%)	13 (5.7%)	
Dementia	25 (1.0%)	21 (0.9%)	4 (1.8%)	0.273
CIED	270 (10.5%)	230 (9.8%)	40 (17.5%)	<0.001
Antiplatelet	309 (12.0%)	294 (12.6%)	15 (6.6%)	0.008

Abbreviations: AF, atrial fibrillation; CIED, cardiac implantable electronic device; CKD, chronic kidney disease; PAD, peripheral arterial disease; TIA, transient ischemic attack.

►**Supplementary Material** (►**Supplementary Table S1** [available in the online version]).

Incidence Rate of Outcomes

The warfarin group exhibited greater event rates (events per 100 person-years) than the NOAC group consistently across all outcomes; however, statistically significant differences were observed only in all-cause death and MI or HF outcome. Specifically, patients who received warfarin had an all-cause death rate of 4.51 (95% CI: 3.99–5.07), while the rate in NOAC group was 2.86 (95% CI: 1.69–4.52; $p = 0.025$). The event rates for all other outcomes are summarized in ►**Supplementary Material** (►**Supplementary Table S2** [available in the online version]).

Principal Composite Outcome

Two approaches of principal hierarchical outcome analysis were conducted as described in the Methods section. In the unmatched approach, all patients in the NOAC group were paired with all patients in the warfarin group, resulting in $228 \times 2,340 = 533,520$ matched pairs. The NOAC group had a total of 108,571 wins (20.3%), while experiencing 66,109 losses (12.4%) and 358,840 ties (67.3%). The Win Ratio was 1.64 (95% CI: 1.22–2.20; $p < 0.001$), with all-cause death as a major contributor to wins (52.9%). There were more wins than losses for the NOAC group in every outcome except for ICH events, which yielded 4,714 wins and 7,314 losses. The comprehensive breakdown of the hierarchical analysis is illustrated in ►**Fig. 2**.

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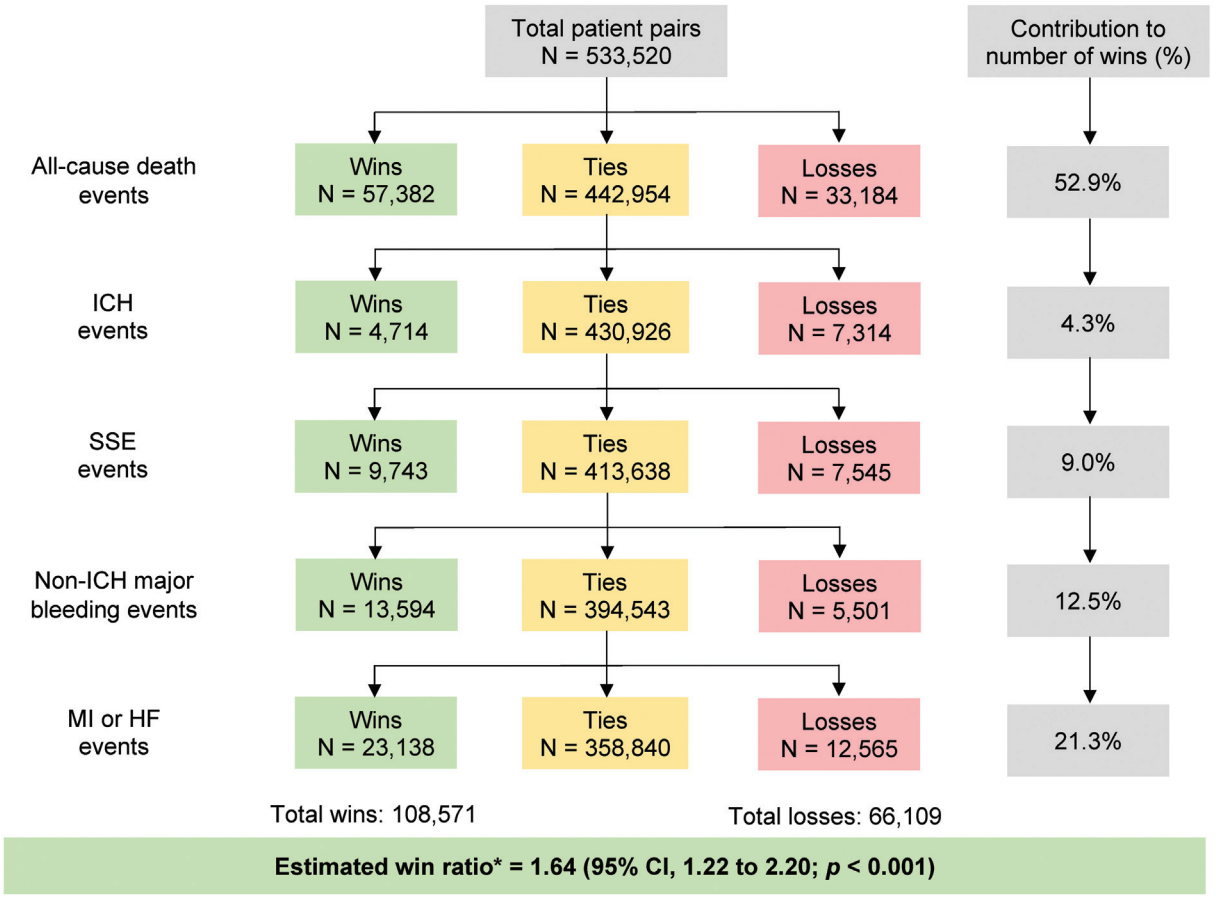

Fig. 2 Unmatched Win Ratio for the hierarchical composite outcome analysis of all-cause death, ICH, SSE, non-ICH major bleeding, and MI or HF in NOACs versus warfarin group. HF, heart failure; ICH, intracranial hemorrhage; MI, myocardial infarction; NOACs, non-vitamin K antagonist oral anticoagulants; SSE, ischemic stroke or transient ischemic attack or systemic embolism.

In matched pairs, each patient in the NOAC group was matched to four patients in the warfarin group as previously described, yielding 912 pairs. The total number of wins for the NOAC group was 156 (17.1%), the total number of losses was 117 (12.8%), and the number of ties was 639 (70.1%). The Win Ratio for matched pairs was 1.33 (95% CI: 1.17–1.52; $p = 0.017$) with all-cause death accounted for a half of the total wins. Similar to the unmatched approach, the NOAC group encountered a greater number of wins than losses in all outcomes, with the exception of ICH events, which had 11 wins and 16 losses. The details of the hierarchical analysis are shown in ►**Fig. 3**.

Conventional Win Ratio analysis was also conducted on a propensity-matched population, resulting in 207,936 pairs from 228 patients in the NOAC group and 912 patients in the warfarin group. The Win Ratio for this analysis was 1.42 (95% CI: 1.02–1.99; $p = 0.039$), which is consistent with both previous analyses. The comprehensive details of this analysis are displayed in Supplementary Material (►**Supplementary Fig. S1** [available in the online version]).

Win Ratio and Win Proportion Changes over Follow-Up

The unmatched Win Ratio showed an initial increase, reaching its peak at around 200 days of follow-up time, which was then followed by a decrease and plateau for the remainder of the study period (►**Fig. 4A**). The NOAC group had a higher total win proportion than the warfarin group, with all-cause death and MI or HF outcomes being the main contributors to the determination of wins and losses in both groups during the entire follow-up time. Interestingly, all outcomes contributed to the win proportion of the NOAC group since the beginning of the study. In contrast, only all-cause death and MI or HF outcomes contributed to the win proportion of the warfarin group in the early stage, as depicted in ►**Figs. 4(B, C)**.

Sensitivity Analysis

The unmatched Win Ratio for the hierarchical outcome analysis in the order of ICH, SSE, non-ICH major bleeding, and MI or HF event was 1.84 (95% CI: 1.32–2.57; $p < 0.001$), which was consistent with the primary analyses. The NOAC group achieved a total of 82,367 wins (15.4%), 44,716 losses (8.4%), and 406,437 ties (76.2%). The NOAC group achieved more wins than losses in all outcomes, including ICH events with 12,339 wins and 10,067 losses (see ►**Supplementary Material**: ►**Supplementary Fig. S2** [available in the online version]).

Win Ratio Analysis in ABC Pathway Adherence

The Win Ratio comparing adherence to the ABC pathway with nonadherence was 1.57 (95% CI: 1.33–1.85; $p < 0.001$). ►**Fig. 5**

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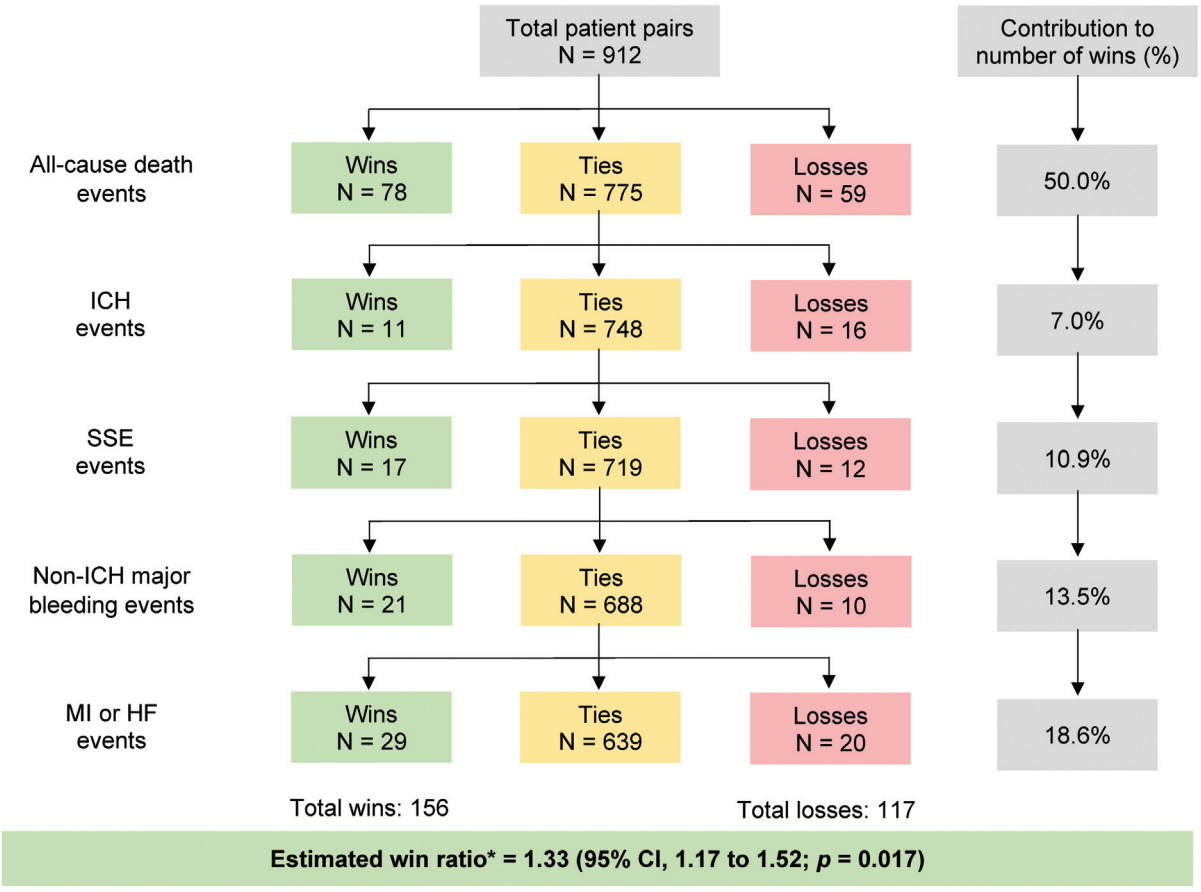

Fig. 3 Matched pairs Win Ratio for the hierarchical composite outcome analysis of all-cause death, ICH, SSE, non-ICH major bleeding, and MI or HF in NOACs versus warfarin group. HF, heart failure; ICH, intracranial hemorrhage; MI, myocardial infarction; NOACs, non-vitamin K antagonist oral anticoagulants; SSE, ischemic stroke or transient ischemic attack or systemic embolism.

presents comprehensive results for each outcome. In terms of adherence to components B and C individually, the corresponding Win Ratios were 1.76 (95% CI: 1.45–2.13; $p < 0.001$) and 1.46 (95% CI: 1.22–1.71; $p < 0.001$), respectively.

When examining the Win Ratio over the course of the study, we noted a slight increase during the initial 150 days of follow-up, followed by a stable trend throughout the follow-up period. Notably, the ABC adherence group exhibited a higher total win proportion in comparison to the nonadherence group, with all-cause death and MI or HF as the major contributors to wins (►**Fig. 4D–F**).

Discussion

First, our study demonstrates that NOACs have more beneficial effects than warfarin in patients with NVAF in reducing a hierarchical composite outcome that includes all-cause death, ICH, ischemic stroke/TIA or SSE, non-ICH major bleeding, and MI or HF. Second, the Win Ratio and the win proportion change over follow-up, which might suggest the time-dependent benefits of NOACs compared with warfarin, and the extent of these benefits varied across each outcome. Third, adherence to the ABC pathway was associated with favorable win outcomes compared with nonadherence.

By using the Win Ratio method, we simultaneously considered both clinical priorities and timing of the events when comparing the composite outcome between two groups. Specifically, this method enables us to focus more on severe events, for example, all-cause death, over nonfatal and less important events.

According to a meta-analysis of RCTs, NOACs was associated with over 50% greater reduction in ICH compared with warfarin.[7,32] In our primary analysis, we performed Win Ratio analysis by first considering all-cause death, followed by ICH, ischemic stroke/TIA or SSE, non-ICH major bleeding, and MI or HF. The results show that the NOAC group had more wins than the warfarin group in every hierarchical outcome except for ICH events; however, by analyzing in this hierarchical order, the benefits of NOACs over warfarin in the ICH outcome could be obscured by all-cause death. This hypothesis was confirmed by the sensitivity analysis, in which the NOAC group also had more wins than the warfarin group in ICH events.

The recommendation of anticoagulation for stroke prevention in AF of current guidelines favors NOACs over warfarin due to its efficacy and safety profile.[3,4] Recently published patient-level meta-analysis of four pivotal trials demonstrated that NOAC use was associated with an 8% significant reduction of all-cause death, a 51% significant reduction of

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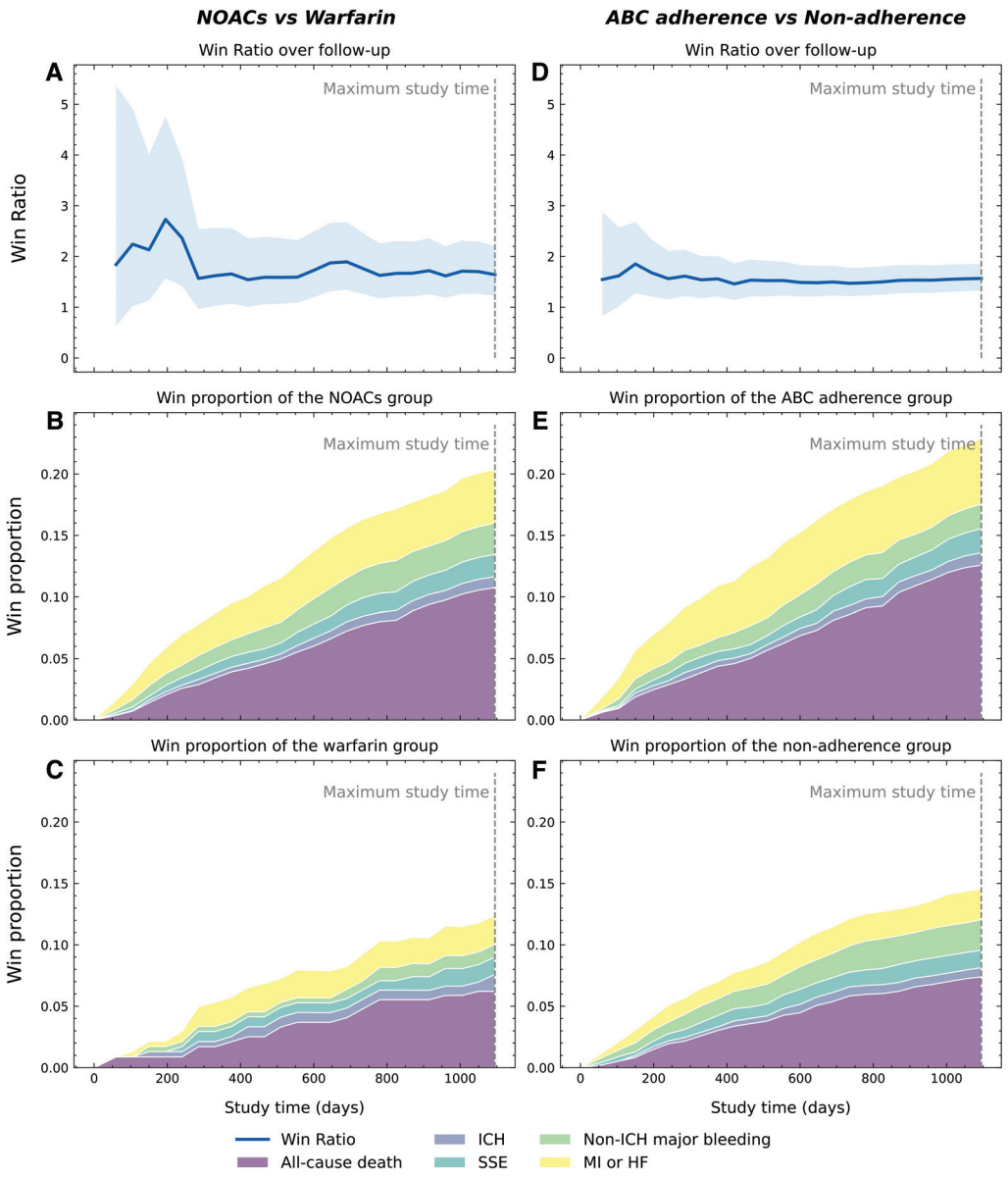

Fig. 4 Changes over the course of follow-up of: the unmatched Win Ratio with 95% confidence interval in NOACs versus warfarin group (**A**) and ABC pathway adherence versus nonadherence group (**D**), win proportion of the NOAC group (**B**), win proportion of the warfarin group (**C**), win proportion of the ABC pathway adherence group (**E**), and win proportion of the ABC pathway nonadherence group (**F**). ABC, Atrial fibrillation Better Care; HF, heart failure; ICH, intracranial hemorrhage; MI, myocardial infarction; SSE, ischemic stroke or transient ischemic attack or systemic embolism; TIA, transient ischemic attack.

ICH, and a 19% significant reduction of stroke or systemic embolism.[32] Our findings concur with those of the meta-analyses in that the NOAC group had larger win proportions over the entire study time, which might suggest a better effectiveness than warfarin in reducing the hierarchical outcome. When considering only ICH, SSE, and non-ICH major bleeding, we found that the win proportions of the NOAC group were also greater than those of the warfarin group during the whole follow-up period. This finding is consistent with data from previous studies that showed the greater benefits of NOACs over warfarin with significant reduction in ICH, ischemic stroke, SSE. Regarding major bleeding risk, a reduction was observed but its statistical significance was inconclusive among previous publications.[7,32–35]

Asian patients with AF who are taking warfarin were reported to have a greater risk for ICH than non-Asians.[36] Meta-analyses of RCTs showed that standard dose of NOACs use in Asians was associated with a greater reduction in risk for stroke or systemic embolism, ICH, and major bleeding than non-Asians, when compared with warfarin. The reduction of all-cause mortality risk was also observed with no significant difference between Asians and non-Asians, while the reduced risk of MI being nonsignificant.[37,38] However, some analysis of real-world data found significant reductions in MI risk in patients taking NOACs versus warfarin.[39,40]

In our study, the win proportion of MI or HF in the NOAC group was larger than the warfarin group, and the contribution to wins of MI or HF was greatest among nonfatal events.

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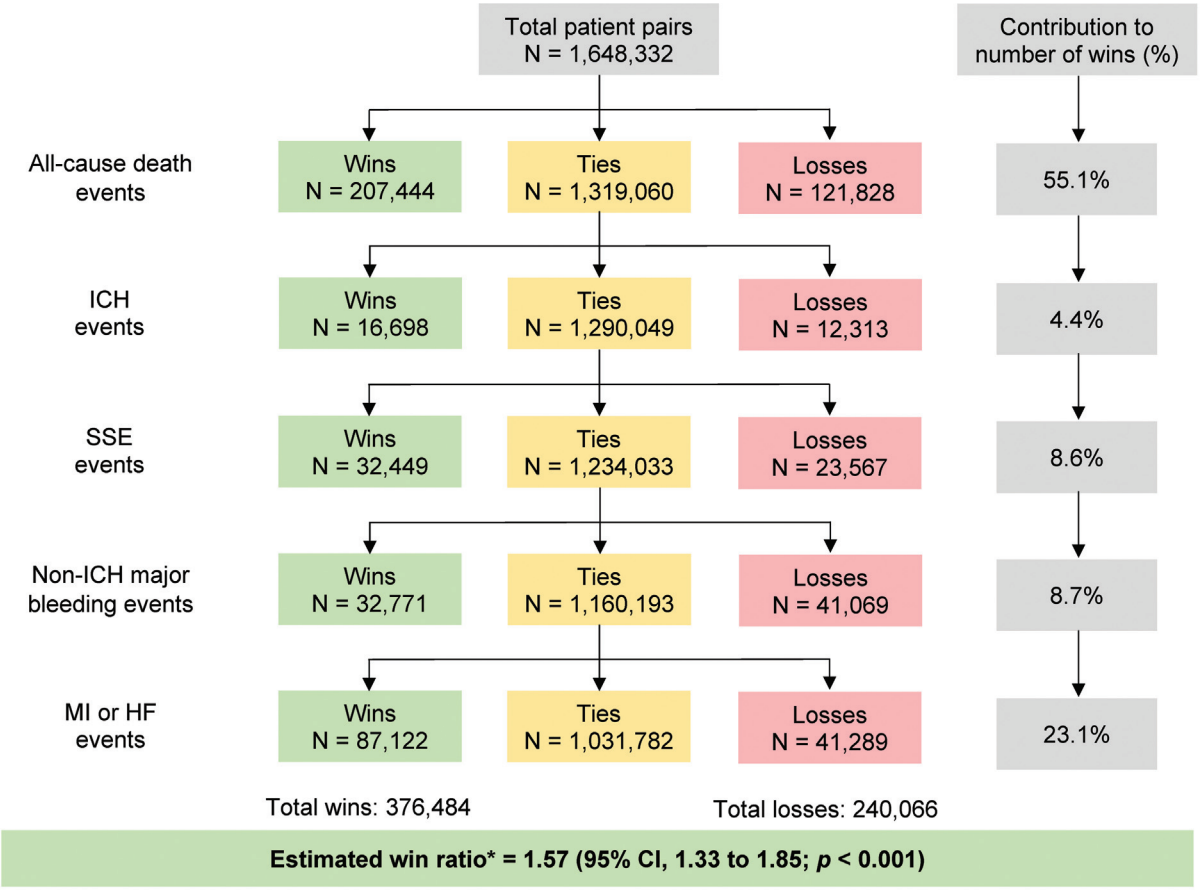

Fig. 5 Unmatched Win Ratio for the hierarchical composite outcome analysis of all-cause death, ICH, SSE, non-ICH major bleeding, and MI or HF in ABC pathway adherence versus nonadherence groups. ABC, Atrial fibrillation Better Care; HF, heart failure; ICH, intracranial hemorrhage; MI, myocardial infarction; NOACs, non-vitamin K antagonist oral anticoagulants; SSE, ischemic stroke or transient ischemic attack or systemic embolism.

This might suggest the possible benefit of NOACs over warfarin in the MI or HF outcome; however, further studies are needed to confirm the effect.

Regarding adherence to the ABC pathway, our study shows that the subgroup adherent to the ABC pathway was associated with greater win benefits compared with the nonadherent group in reducing the same hierarchical composite outcomes. These benefits are also observed when comparing adherence to component B and component C to the nonadherence group. Our findings are consistent with the results from a study that applied the Win Ratio method to a cluster randomized trial in Asians with AF, comparing the mobile-health application of the ABC pathway care to the usual care.[41]

To the best of our knowledge, this is the first study to apply Win Ratio analysis to a prospective registry. The concept of Win Ratio has gained more attention in analyzing composite outcome in cardiovascular trials in recent years,[11–14] whereas the application in cardiovascular registries is limited, and we are unaware of prior studies in an Asian cohort.

Previous studies utilized only matched pairs approach in the retrospective cohort analysis.[42,43] The rationale behind selectively applying the matched pairs approach might be the nature of the retrospective cohort that required matching to mitigate the bias from a nonrandomized design. We were also aware of this potential bias, so we employed three methods of Win Ratio application, which were unmatched approach, matched pairs approach, and conventional Win Ratio on propensity-matched population. The Win Ratio from all three approaches consistently showed the benefits of NOACs over warfarin in reducing the hierarchical composite endpoint of NVAF patients. Our approach could pave the way for further applications of a Win Ratio analysis in cohort studies.

Limitation

There are some limitations to this study. First, our study acquired the data from the COOL-AF registry, which were collected in Thailand where warfarin was the only OAC reimbursed by the National Health Security Office. Therefore, the sample size of the NOAC group was limited. Second, the Win Ratio method was initially designed for clinical trials, so the application in prospective registry and its interpretation might be subject to bias. We tried to account for the nonrandomized nature of the prospective cohort by employing different approaches, including the propensity-matched population. However, the concordance between our findings and previous results from meta-analyses and trials comparing NOAC and warfarin in AF may suggest that the unknown biases are likely to be limited.

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Conclusion

This Win Ratio analysis of the COOL-AF registry demonstrated the significant beneficial effects of NOACs over warfarin in reducing all-cause death, ICH, SSE, non-ICH major bleeding, and MI or HF in patients with AF. Furthermore, our findings highlight the association between adherence to the ABC pathway and a reduction in the hierarchical composite outcome. This study underscores the potential of employing the Win Ratio method as a novel approach for analyzing time-to-event outcomes in cardiovascular registry analyses.

What is known about this topic?

- When comparing to warfarin, NOAC use in Asians with AF was associated with a greater reduction in the risk of stroke, ICH, and major bleeding than non-Asians.
- AF Better Care (ABC) pathway adherence has been associated with improved outcomes in AF patients, but the data are limited in Asians.
- Win Ratio is a new approach for analyzing composite outcomes considering event timing and severity. It was developed and applied mainly in cardiovascular trials.

What does this paper add?

- In a real-world setting, adherence to the ABC pathway and the use of NOACs were associated with a greater reduction in the composite outcome of all-cause death, ICH, SSE, non-ICH major bleeding, and MI or HF compared with ABC pathway nonadherence and warfarin in Asians.
- The application of Win Ratio in a prospective AF registry may be a novel approach for analyzing time-to-event outcomes in cardiovascular registry.

Data Availability Statement

The data used in this analysis are available from the corresponding author upon reasonable request.

Authors' Contribution

All authors made substantial contributions to conception and design, data interpretation, and revising the manuscript critically for important intellectual content. S.T. and R.K. made contributions to drafting and acquisition of data. S.T. made contributions to data analysis and figure drawing. All authors approved the final version to be published and agree to be accountable for all aspects of the work.

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Conflict of Interest

G.Y.H.L.: consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Anthos, and Daiichi-Sankyo. No fees are directly received personally. G.Y.H.L. is co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No. 899871. Other authors hereby declare no personal or professional conflicts of interest relating to any aspect of this particular study.

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