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Outcomes of real-world patients with non-valvular atrial fibrillation on anticoagulants ineligible for Phase III trials of direct oral anticoagulants

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Abstract

Aims: To compare the outcomes of real-world Japanese patients with nonvalvular atrial fibrillation who are ineligible for phase III trials of direct oral anticoagulants with those of eligible patients. Methods: In retrospective cohort design, consecutively registered patients with nonvalvular atrial fibrillation who had taken warfarin were followed up and assessed eligibility of patients for phase III trials of direct oral anticoagulants. The effects of the ineligibility of patients on outcomes were estimated using Cox proportional hazards models to calculate the hazard ratio (HR) and 95% confidence interval. Results: We registered 7826 Japanese patients with nonvalvular atrial fibrillation from 71 hospitals. Nearly half (48.2%, n=3772) of these patients were ineligible for phase III trials of direct oral anticoagulants, mainly because of low CHADS2 scores (26.4%), renal dysfunction (9.5%), anemia (6.4%), and chronic treatment with nonsteroidal anti-inflammatories (4.0%). After excluding patients with a CHADS2 score <2 (n=2064, 26.4%) from total ineligible patients, the remaining ineligible patients (n=1708) exhibited significantly greater risks of major bleeding (unadjusted hazard ratio 2.00, 95% confidence interval 1.63–2.44, p<0.0001), stroke/systemic embolism (unadjusted hazard ratio 1.53, 95% confidence interval 1.17–1.98, p=0.0016), and all-cause mortality (unadjusted hazard ratio 2.84, 95% confidence interval 2.36–3.43, p<0.0001) compared to the eligible patients. Conclusions: The benefits and risks of direct oral anticoagulants suggested by phase III trials may not necessarily apply to patients ineligible for Phase III trials. This gap between evidence and practice is an issue in the real-world safety and efficacy of anticoagulants.

Outcomes of real-world patients with non-valvular atrial fibrillation on anticoagulants ineligible for Phase III trials of direct oral anticoagulants

Running title: Real-world patients with NVAF

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Keywords: non-valvular atrial fibrillation, anticoagulation, Phase III trial, eligibility

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Key Points

What is already known about this subject

- Phase III trials for regulatory approval typically have conducted under strict eligibility criteria that exclude certain patients.
- These ineligible patients often receive the approved drugs post-trial.
- The balance of risks and benefits for these ineligible patients remains unclear.

What this study adds

Patients ineligible for Phase III trials of direct oral anticoagulants, yet receiving anticoagulants for non-valvular atrial fibrillation, exhibited worse outcomes compared to eligible patients.

The study points to a potential discrepancy between clinical evidence and real-world practice regarding the safety and effectiveness of anticoagulants.

ABSTRACT

Aim: To compare the outcomes of real-world Japanese patients with nonvalvular atrial fibrillation who are ineligible for Phase III trials of direct oral anticoagulants with those of eligible patients.

Methods: In retrospective cohort design, consecutively registered patients with nonvalvular atrial fibrillation who had taken warfarin were followed up and assessed patients' eligibility for Phase III trials of direct oral anticoagulants. The effects of the ineligibility of patients on outcomes were estimated using Cox proportional hazards models to calculate the hazard ratio (HR) and 95% confidence interval.

Results: We registered 7826 Japanese patients with nonvalvular atrial fibrillation from 71 hospitals. Approximately half (48.2%, n=3772) of these patients were ineligible for Phase III trials of direct oral anticoagulants, mainly because of low $CHADS_2$scores (26.4%), renal dysfunction (9.5%), anaemia (6.4%), and chronic treatment with nonsteroidal anti-inflammatories (4.0%). After excluding patients with a $CHADS_2$ score <2 (n=2064, 26.4%) from total ineligible patients, the remaining ineligible patients (n=1708) exhibited significantly greater risks of major bleeding (unadjusted hazard ratio 2.00, 95% confidence interval 1.63–2.44, p <0.0001), stroke/systemic embolism (unadjusted hazard ratio 1.53, 95% confidence interval 1.17–1.98,p =0.0016), and all-cause mortality (unadjusted hazard ratio 2.84, 95% confidence interval 2.36–3.43, p <0.0001) compared to the eligible patients.

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Conclusion: The benefits and risks of direct oral anticoagulants suggested by Phase III trials may not necessarily apply to patients ineligible for Phase III trials. This gap between evidence and practice is an issue in anticoagulants' real-world safety and efficacy.

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I. Introduction

Direct oral anticoagulants (DOACs) have been increasingly prescribed to patients with non-valvular atrial fibrillation (NVAF) following regulatory approval and guideline recommendations following successful Phase III trials demonstrating their non-inferiority and superiority to warfarin.[1-5] However, the results from pivotal trials should be interpreted with caution because of the strict inclusion and exclusion criteria to ensure participant safety and provide clear results for regulatory approval. The Food and Drug Administration recommends that enrolling participants with a wide range of baseline characteristics may create a trial population that more accurately reflects the patients who are likely to take the drug if it is approved and may allow evaluation of the impact of these characteristics on the trial drug's safety and efficacy.[6] The ICH Steering Committee has also stated that as drug development progresses, the study population should be expanded to reflect the target population.[7]

These recommendations aim to ensure that the results of Phase III trials can be used for a broader range of patients; however, several studies have attempted to assess the generalizability of the results from Phase III trials of DOACs to the extent to which real-world patients with NVAF can be enrolled in Phase III trials. The proportion of real-world patients eligible for the trials varied widely, ranging from 35% to 72%.[8-13] There were trends towards low eligibility for ROCKET-AF and high eligibility for ARISTOTLE and RE-LY, presumably because of the $CHADS_2$ score as an inclusion criterion. However, there have been few comparisons of outcomes between eligible and ineligible patients in Phase III trials. This study aimed to determine the proportion of real-world Japanese patients with NVAF eligible for Phase III trials and compare the characteristics and outcomes of ineligible and eligible patients.

II. Methods

Study design

We conducted a historical registry study of patients with NVAF taking warfarin at 71 centres in Japan. We registered patients in Japan on February 26, 2013, and followed them until February 25, 2017.

Ethics

The ethics committees of all 71 participating centres approved the study following the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. The requirement for individual written informed consent was waived.

Patients

Consecutive patients with NVAF who had already received warfarin on February 26, 2013, were retrospectively registered. Patients with mechanical heart valves and previous pulmonary or deep vein thrombosis diagnoses were excluded from the study.

Data Collection and Definitions

Trained clinical research coordinators reviewed and collected relevant clinical information, including patient characteristics, laboratory data, risk of ischemic stroke ($CHADS_2$ score), and major bleeding (HAS-BLED score) at baseline and relevant medications directly from medical charts at baseline and at 1, 2, 3, and 4 years of follow-up. Definitions of the baseline characteristics have been previously described.[14] The $CHADS_2$score was developed to estimate the stroke risk in patients with NVAF,[15] and the HAS-BLED score was developed to predict major bleeding in patients receiving anticoagulation therapy.[16]

Assessment of our registered patients' eligibility for Phase III trials of DOACs

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We scrutinised the most frequently used inclusion and exclusion criteria of the four DOACs Phase III trials (Table 1).[1,2,4,5]Baseline data collected at registration for all patients (medical history, background, and laboratory values) were checked against the developed inclusion and exclusion criteria to assess eligibility. Regarding the CHADS2 score, two trials used [?]2 as a criterion, and the others used [?]1. We used [?]2 as our criterion. Therefore, ineligible patients included those with a $CHADS_2$ score of <2. In addition, we checked the baseline data against each Phase III trial's inclusion and exclusion criteria.

Comparison of outcomes between eligible and ineligible patients with $CHADS_2$ score [?]2

We compared the outcomes between eligible and ineligible patients after excluding patients with a $CHADS_2$ score of <2. A comparison between eligible and ineligible patients, including those with a $CHADS_2$ score of <2, was also performed for sensitivity analysis.

Outcome measure

The primary outcome was major bleeding. Major bleeding was defined following the International Society on Thrombosis and Hemostasis criteria.[17,18] Other outcomes were stroke, including transient ischemic attack, systemic embolism (Stroke/SE), and all-cause mortality.

Statistical Analyses

Descriptive Statistics

The eligibility proportions of all patients were described. The proportion of patients who met each inclusion criterion and conflicted with each exclusion criterion was described.

Clinical characteristics were described and compared between the eligible and the ineligible patients with $CHADS_2$ scores [?]2. Categorical variables were presented as numbers and percentages. Continuous variables were expressed as means ± standard deviation (SDs), median value, or interquartile range. The Student's t-test or Wilcoxon rank-sum test was performed for continuous variables to evaluate differences in characteristics between the two groups. The chi-square test was used for categorical variables.

Survival Analysis

The incidence rates of outcomes are presented as cases per 100 patient-years. The cumulative incidence of outcomes was estimated using the Kaplan–Meier method. The difference between eligible and ineligible patients with $CHADS_2$ scores [?]2 was assessed using the log-rank test. The effects of the ineligibility of patients on outcomes were estimated using Cox proportional hazards models to calculate the hazard ratio (HR) and 95% confidence interval. Statistical significance was set at P <0.05 for all analyses. We presented only unadjusted HR because the effects of ineligibility on the outcomes reflected the integrated impact of many variables in ineligible patients.

In addition, we added patients with $CHADS_2$ scores <2 to the group of ineligible patients and compared them with the eligible patients regarding baseline characteristics and outcomes as part of the sensitivity analysis.

III. Results

We registered 7826 Japanese patients with NVAF and followed them for four years; the median age was 74 (66–80) years old; 3755 (48.0%) patients were at least 75 years old, 2552 (33%) were female; the mean $CHADS_2$ score was 2.44.

Eligibility of all registered patients

Following our inclusion/exclusion criteria derived from Phase III trials of DOACs (Table 1), 4054 (51.8%) patients with NVAF were classified as the eligible group, whereas the remaining patients (n=3772, 48.2%) were classified as the ineligible group mainly because of $CHADS_2$ score <2 (26.4%), renal dysfunction (9.5%), anaemia (6.4%), and chronic treatment with nonsteroidal anti-inflammatories (NSAIDs (4.0%) (**Table 2**).[14]

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Comparisons of Baseline Characteristics between Eligible and Ineligible Patients with $CHADS_2$ Score [?]2

Figure 1 presents the flow diagram of the study. We excluded patients with $CHADS_2$ <2 (n=2063, 26.4% of all registered patients) from comparing outcomes. **Table 3** presents the baseline characteristics of the eligible and ineligible patients with $CHADS_2$ [?]2. Ineligible patients were more likely to be elderly, female, and have comorbidities such as stroke, heart failure, coronary artery disease, chronic liver disease, and kidney disease than the eligible patients. The $CHADS_2$ score after excluding patients with <2 and the HAS-BLED score were significantly higher in ineligible patients than in eligible patients.

Comparisons of Outcomes between Eligible and Ineligible Patients with $CHADS_2$ Score[?]2

At 4 years, 59% of patients had completed follow-up, and the median follow-up duration was 3.9 years. The cumulative incidence of major bleeding at 4 years in the eligible and ineligible groups was 7.0% and 13.4%, respectively (**Figure 2a**). The risk of major bleeding in ineligible patients with $CHADS_2$ score [?]2 was almost double that of eligible patients and statistically significantly higher (**Table 4**). The 4-year cumulative stroke and systemic embolism incidence in the eligible and ineligible groups was 5.5% and 7.5%, respectively (**Figure 2b**). Notably, both groups had a $CHADS_2$ score of [?]2; however, the risk of stroke/SE was significantly higher in ineligible patients than in eligible patients (**Table 4**). At 4 years, the cumulative incidence of death from any cause in the eligible and ineligible groups was 7.3% and 17.6%, respectively (**Figure 1c**). The risk of death from any cause in ineligible patients was approximately three times higher than that in eligible patients (**Table 4**).

Comparisons of Characteristics and Outcomes between Eligible and Ineligible Patients, including those with $CHADS_2$ score <2

The baseline characteristics of eligible and ineligible patients, including those with a $CHADS_2$ score <2, are presented in **Table 5** . By putting low-risk patients back into the ineligible group, it appears that there were more elderly patients and patients with comorbidities in the eligible group, contrary to what is shown in Table 3. Regarding outcomes, unlike the main analysis after excluding patients with $CHADS_2$ score <2, there was no difference in stroke/SE risk between the groups, and the effect of ineligibility on the risk of major bleeding was smaller and did not reach statistical significance, although the risk of all-cause mortality remained significantly higher in ineligible patients with an unadjusted HR (95% CI) of 1.54 (1.29–1.83).

IV. Discussion

Using a registry of Japanese patients with NVAF, we examined their eligibility for Phase III trials comparing DOACs with warfarin. Approximately 50% of our "real world" registered patients with NVAF were ineligible following the inclusion and exclusion criteria we derived from reports of Phase III trials. Further comparative analysis of outcomes strongly suggested that eligibility may affect the outcomes in our patients, with significantly higher risks of major bleeding, stroke/systemic embolism, and all-cause death in ineligible patients.

Eligibility

Our inclusion and exclusion criteria, which were derived from the most commonly used criteria of four DOACs Phase III trials, were considered valid for assessing eligibility and comparing outcomes between eligible and ineligible patients because the proportion of eligible patients using our criteria did not differ significantly from those using the criteria of the individual Phase III trials (**Table S1**).

Notably, several studies have reported the proportion of "real-world" patients with NVAF eligible for Phase III trials. In a UK general practice database study,[8] 68% of patients would be eligible for RE-LY, compared with 65% and 51% for ARISTOTLE and ROCKET-AF, respectively. A retrospective cross-sectional database analysis at the University Hospital Stroke Unit in Belgium[11] found that 47.6% of patients were eligible for RE-LY, 45.5% for ARISTOTLE, and 39.3% for ROCKET-AF. A study of patients with a discharge diagnosis of AF in a large public hospital network in Melbourne, Australia, showed that 60.5%, 52.6%, and 35.8% of

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patients would have been eligible for the ARISTOTLE, RE-LY, and ROCKET-AF trials, respectively.[12] Of the patients with NVAF in the MAQI2 registry in Michigan, USA, 54.5% would meet the selection criteria used in RE-LY, 39.1% for ROCKET-AF, and 59.9% for ARISTOTLE.[13] The reported proportions of patients eligible for Phase III trials of DOACs in real-world practice, including our results, were consistently around 50%, although there were some differences among studies.

The ineligible patients were mainly characterised by low $CHADS_2$ scores, renal dysfunction, anaemia, and chronic NSAID use. The latter three are well-known risk factors for major bleeding in patients with NVAF treated with anticoagulation. However, elderly patients with these risk factors are often encountered in real-world clinical practice, and anticoagulation should be considered in the presence of atrial fibrillation. The studies cited above also reported a high risk of bleeding, poor renal function, and concomitant use of aspirin and antiplatelet agents as reasons for not enrolling in the Phase III trial, despite taking anticoagulants in actual practice.[12,13]

Comparisons of Basic Characteristics and Outcomes between Eligible and Ineligible Patients

We found that the risk of major bleeding, stroke and systemic embolism, and all-cause death in ineligible patients with $CHADS_2$score [?]2 was significantly higher than those in eligible patients. The poor prognosis of these ineligible patients may be explained by more comorbidities such as anaemia, heart failure, coronary artery disease, renal insufficiency, liver disease, or more concomitant medications such as antiplatelet agents or NSAIDs than those in eligible patients. Therefore, ineligibility for Phase III trials can be considered a variable summarising these factors and indicating worse outcomes.

Furthermore, all our patients were prescribed anticoagulants by their physicians, regardless of their eligibility for Phase III trials of DOACs. However, the outcomes of eligible and ineligible patients differed markedly, suggesting that the risks and benefits of anticoagulant therapy depend on patient eligibility. Our results showed that not only is the risk of stroke not sufficiently reduced by anticoagulation in ineligible patients, but the risk of major bleeding is almost double that of eligible patients, probably due to over-anticoagulation. Notably, some might assume that ineligible patients have a higher risk of stroke and that the benefit of anticoagulant treatment is greater; however, this is not the case, and our results suggest that the risk of bleeding with anticoagulation outweighs the benefit of stroke prevention in ineligible patients owing to various factors mentioned above. Patients who were deemed ineligible because of a low $CHADS_2$ score and were excluded from the outcome comparison had a low absolute risk of stroke, and the expected absolute risk reduction with anticoagulant therapy was small; therefore, the risk of bleeding was relatively high, making anticoagulants less advisable. The guidelines also state that anticoagulation is recommended for patients with NVAF and a $CHADS_2$ score of 1 or higher. Finally, the similar efficacy and safety demonstrated in Phase III trials of DOACs may be unlikely in ineligible patients.

As suggested by the ELDERCARE-AF study,[19] which included inappropriate elderly patients for oral anticoagulants at approved doses or recommended strengths for reasons such as decreased eGFR and chronic use of NSAIDs, lower doses of DOACs might be a solution to prevent major bleeding if lower doses successfully reduce the risk of stroke compared to no anticoagulation. However, the risk of major and clinically relevant minor bleeding remained significantly higher in patients who received a lower dose of edoxaban than in those who received a placebo in the ELDERCARE-AF study.[19]

Our retrospective cohort study has certain limitations that are distinctive to this type of study. The data used in this cohort were initially obtained from medical records and were not collected according to a study protocol. Furthermore, the study had a notable amount of missing data, particularly regarding relevant confounding factors, and many patients were lost to follow-up.

The criteria developed from the four trials are generally considered valid; however, it is essential to note that we were unable to assess specific exclusion criteria, such as patients who were planning to undergo ablation or major surgery or those with a life expectancy of less than one year at the time of enrollment. In addition, all patients within the cohort were receiving warfarin at the time of enrollment, and some transitioned to direct oral anticoagulants (DOACs). The effects of such transitions on outcomes and their potential relationship

with eligibility at enrollment were not evaluated.

Approximately half the real-world patients with NVAF on anticoagulants are ineligible for Phase III trials of DOACs. In particular, those with a high risk of stroke had significantly worse outcomes than eligible patients; that is, they had a higher risk of stroke and major bleeding and death. The benefits of DOACs presented in Phase III trials may not necessarily apply to the patients ineligible for such trials. This gap between evidence and practice[20] is an issue for anticoagulants' real-world safety and efficacy.

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Author Contributions

Mayumi Higa collected data from medical records, was involved in data management, performed statistical analysis, and wrote the draft manuscript. Takeshi Morimoto contributed to the study design, supervised statistical analysis as the study biostatistician, and revised the draft manuscript. Masayuki Ikeda contributed to the development of the study concept and study design. Shinichiro Ueda conducted this registry study as the principal investigator, contributed to the study concept and design, and revised the draft manuscript.

Conflict of interest

Dr Shinichiro Ueda reports a research grant from Bristol Myers Squibb and a lecturer's fee from Kowa. Dr Takeshi Morimoto reports lecturer's fees from AstraZeneca, Bristol-Myers Squibb, Daiichi Sankyo, Japan Lifeline, Kowa, Toray, and Tsumura; manuscript fees from Bristol-Myers Squibb and Kowa; advisory board for Novartis and Teijin.

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Data Access, Responsibility, and Analysis

Dr Shinichiro Ueda had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

Data Availability statement

Data in our registry will be available upon request after evaluating the proposal based on scientific rationale and methodology, experience and relevant qualifications of the research team, presence of a robust statistical analysis plan, publication plan, and conflict of interests.

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Tables

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Table 1 Developed Inclusion /exclusion criteria for the assessment of eligibility of our registered patients and criteria of 4 Phase III trials of DOACs

	Our study	RE-LY[a][1]	ROCKET-AF[b][2]	ARISTOTLE[c][4]	ENGAGE TIMI48[d][5]
Inclusion					
Age	[?] 18 years	[?] 18 years	[?] 18 years	[?] 18 years	[?] 21 years
AF	Non-valvular atrial fibrillation	Atrial fibrillation	Non-valvular atrial fibrillation	Atrial fibrillation or atrial flutter	Paroxysmal, persistent, or permanent AF
$CHADS_2$ Score	$CHADS_2$ score [?] 2	One of the following: 1. Prior stroke, TIA or SE 2. EF<40% 3. HF 4. Age[?]75. 5. 65[?]age<75&(DM or HT or CAD)	$CHADS_2$ score [?] 2	$CHADS_2$ score [?] 1	$CHADS_2$ score [?] 2
Exclusion					
Bleeding Risk	History of major bleeding	History of major bleeding	History of major bleeding	N/A	History of major bleeding
Uncontrolled hypertension	SBP >180mmHg or DBP >100mmHg	SBP > 180mmHg and/or DBP > 100mmHg	SBP [?] 180mmHg or DBP [?] 100mmHg	SBP >180mmHg or DBP > 100mmHg	SBP > 170mmHg or DBP > 100mmHg
Renal function	Calculated CLCR < 30 mL/min	Calculated CLCR [?] 30 mL/min	Calculated CLCR < 30 mL/min	Serum creatinine > 2.5 mg/dL or a calculated CLCR < 25	Calculated CLCR < 30 mL/min
Hepatic function	ALT or AST > 2x the ULN, or TBL [?] 1.5x the ULN	Active liver disease, including but not limited to a. persistent ALT, AST, Alk Phos > 2x the ULN	Known significant liver disease, or ALT > 3x the ULN	ALT or AST > 2x the ULN, or a Total Bilirubin [?] 1.5x the ULN	Active or persistent liver disease, positive hepatitis B to C test, in: ALT or AST [?] 2x the ULN TBL [?] 1.5x the ULN
Haemoglobin & platelet count	Hgb < 10 g/dL or platelet count < 100,000 cells/mL	Hgb < 10 g/dL or platelet count < 100,000 cells/mL	Hgb < 10 g/dL or platelet count < 90,000 cells/mL	Hgb < 9 g/dL or platelet count [?] 100,000 cells/mL	Hgb < 10 g/dL or platelet count < 100,000 cells/mL or WBC < 3000cell/mL
Antiplatelet therapy	Aspirin in combination with thienopyridines	N/A	Aspirin > 100 mg/day or Aspirin in combination with thienopyridines	Aspirin > 165 mg/day or Aspirin in combination with thienopyridines	Aspirin in combination with thienopyridines

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	Our study	RE-LY[a][1]	ROCKET-AF[b][2]	ARISTOTLE[c][4]	ENGAGE TIMI48[d][5]
Anti-inflammatory agents	Chronic treatment with NSAIDs	N/A	Anticipated need for chronic treatment with NSAIDs	N/A	Chronic treatment with NSAIDs
Concomitant Therapy		N/A	CYP3A4 inducer CYP3A4 inhibitor	CYP3A4 inhibitor Macrolide antibiotics	Cox-2 inhibitor
Drug or alcohol dependence	Alcohol dependence	N/A	Drug addiction or alcohol dependence	Drug addiction or alcohol dependence	Drug addiction or alcohol dependence

[a] The Randomised Evaluation of Long-term Anticoagulation Therapy.

[b] The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

[c] The Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation.

[d] Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation.

Table 2 Proportion of eligible and ineligible patients according to inclusion and exclusion criteria.

	DOACs criteria	Eligible n (%)	Ineligible n (%)
Inclusion			
Age	age [?]18 years	7826 (100%)	
AF	non-valvular atrial fibrillation	7826 (100%)	
$CHADS_2$	$CHADS_2$ score [?] 2	5763 (73.6%)	2063 (26.4%)
Exclusion			
Haemorrhage Risk	History of major bleeding	7547 (96.5%)	279 (3.5%)
Uncontrolled hypertension	SBP $>$ 180mmHg or DBP $>$ 100mmHg	7701 (98.4%)	125 (1.6%)
Renal dysfunction	Calculated CLCR $<$ 30 mL/min	7085 (90.5%)	741 (9.5%)
Hepatic function	ALT or AST $>$ 2 times the ULN or TBL [?] 1.5 times the ULN	7608 (97.2%)	218 (2.8%)
Haemoglobin & platelet count	Hgb $<$ 10 g/dL or platelet count $<$ 100,000 cells/mL	7324 (93.6%)	502 (6.4%)
Antiplatelet therapy	Aspirin $>$ 100 mg daily or Aspirin in combination with thienopyridines	7550 (96.5%)	276 (3.5%)
Anti-inflammatory agents	chronic treatment with NSAIDs	7513 (96%)	313 (4.0%)

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	DOACs criteria	Eligible n (%)	Ineligible n (%)
Drug or alcohol dependence	alcohol dependence	7783 (99.5%)	43 (0.5%)
Overall		4054 (51.8%)	3772 (48.2%)

Table 3 Baseline Characteristics of eligible and ineligible patients with $CHADS_2$ score [?] 2.

	Eligible (n=4054)	Ineligible with $CHADS_2$ [?] 2 (n=1709)	*p*-value
Age [yr] Median (Interquartile range)	76 (69–81)	79 (73–85)	<.0001
Female sex no. (%)	1320 (32.6)	708 (41.4)	<.0001
Body Weight kg (mean)	62.9	57.5	<.0001
BMI, mean (SD)	24.7 (4.04)	23.43 (4.31)	<.0001
Systolic Blood pressure — mmHg Median	128	126	0.196
Paroxysmal atrial fibrillation no. (%)	1304 (36.9)	467 (32.0)	0.0011
$CHADS_2$ score Mean	2.96	3.24	<.0001
$CHADS_2$ Score 2-no. (%)	1711 (42.2)	508 (29.7)	<.0001
$CHADS_2$ Score [?] 3-no. (%)	2343 (57.8)	1201 (70.3)	<.0001
HASBLED Score	1.72	2.43	<.0001
Prior stroke or transient ischemic attack no. (%)	1270 (31.4)	599 (35.2)	0.0047
Age [?] 75yr – no. (%)	2324 (57.3)	1198 (70.1)	<.0001
Heart failure – no. (%)	2020 (50.1)	1074 (63.6)	<.0001
Diabetes mellitus– no. (%)	1642 (40.5)	707 (41.4)	0.546
Hypertension– no. (%)	3552 (87.7)	1497 (87.7)	0.989
CAD–no. (%)	1111 (27.5)	653 (38.4)	<.0001
ACS–no. (%)	422 (10.6)	308 (18.5)	<.0001
PCI	286 (7.2)	318 (19.1)	<.0001
CABG	125 (3.1)	101 (6.0)	<.0001
COPD	177 (4.4)	93 (5.5)	0.076
Chronic liver disease–no. (%)	290 (7.2)	183 (10.7)	<.0001
History of cancer–no. (%)	453 (11.2)	254 (14.9)	<.0001
History of RFCA–no. (%)	261 (6.5)	70 (4.1)	0.0004
CCr mean (SD)	63.68 (24.7)	44.59 (27.5)	<.0001
PT-INR mean (SD)	1.91 (0.38)	1.87 (0.41)	0.0006
TTR mean (SD)	74.69 (33.34)	68.91 (35.51)	<.0001
ASA–no. (%)	805 (19.9)	612 (35.9)	<.0001

Table 4 Outcomes of eligible and ineligible patients with $CHADS_2$ score [?] 2.

Outcome	Eligible (n=4054)	Eligible (n=4054)	Ineligible & $CHADS_2$ [?] 2 (n=1709)	Ineligible & CHAD
	No. of events	Event rate, %/yr	No. of events	Event rate, %/yr
Major bleeding	224	1.83	163	3.67
Stroke/SE	156	1.27	87	1.93
Death from any cause	213	1.70	221	4.82

Table 5 Baseline characteristics of eligible and ineligible patients, including patients with $CHADS_2$<2.

	All	Eligible (n=4054)	Ineligible (n=3772)	*P*-value
Age yr Median (Interquartile range)	74 (66–80)	76 (69–81)	71 (64–80)	<.0001
Female sex no. (%)	2552 (33)	1320 (32.6)	1232 (32.7)	0.923
Body Weight kg, mean	62.3	62.9	61.6	<.0001
BMI, mean (SD)	24.4 (4.11)	24.7 (4.04)	24.0 (4.16)	<.0001
Systolic Blood pressure – mmHg Mean	126	127	126	0.0004
Paroxysmal atrial fibrillation no. (%)	2643 (38.7)	1304 (36.9)	1339 (40.6)	0.0016
$CHADS_2$ score Mean	2.44	2.96	1.89	<.0001
$CHADS_2$ Score 0-1-no. (%)	2063 (26.3)	0 (0)	1569 (41.6)	<.0001
$CHADS_2$ Score 2-no. (%)	2252 (28.8)	1711 (42.2)	541 (14.3)	<.0001
$CHADS_2$ Score [?] 3-no. (%)	3511 (44.9)	2343 (57.8)	1201 (31.8)	<.0001
HASBLED Score	1.73	1.73	1.73	0.976
Prior stroke or transient ischemic attack no. (%)	1903 (24.3)	1270 (31.4)	633 (16.8)	<.0001
Age [?] 75yr – no. (%)	3755 (48.0)	2324 (57.3)	1431 (37.9)	<.0001
Heart failure – no. (%)	3291 (42.4)	2020 (50.1)	1271 (34.1)	<.0001
Diabetes mellitus– no. (%)	2444 (31.2)	1642 (40.5)	802 (21.3)	<.0001
Hypertension– no. (%)	6119 (78.2)	3552 (87.7)	2567 (68.1)	<.0001
CAD–no. (%)	2075 (27)	1111 (27.5)	964 (25.7)	0.066
ACS–no. (%)	819 (10.6)	422 (10.6)	397 (10.7)	0.813
PCI–no. (%)	684 (8.9)	286 (7.2)	398 (10.7)	<.0001
CABG–no. (%)	246 (3.2)	125 (3.1)	121 (3.2)	0.767
COPD–no. (%)	330 (4.2)	177 (4.4)	153 (4.1)	0.496
Chronic liver disease–no. (%)	606 (7.8)	290 (7.2)	316 (8.4)	0.0425
History of cancer–no. (%)	875 (11.2)	453 (11.2)	422 (11.2)	0.972
History of RFCA–no. (%)	623 (8.0)	261 (6.5)	362 (9.7)	<.0001
CCr mean (SD)	63.03 (28.75)	63.68 (24.7)	62.34 (32.37)	0.0486
PT-INR mean (SD)	1.90 (0.38)	1.91 (0.38)	1.89 (0.39)	0.0110
TTR mean (SD)	73.35 (33.8)	74.69 (33.34)	71.91 (34.22)	0.0003
ASA–no. (%)	168 4(22)	805 (19.93)	879 (23.36)	0.0002

Figure legends

Figure 1. Flow diagram of registered patients

Figure 2. Cumulative incidence of major bleeding (panel a), stroke/systemic embolism (panel b), and all-cause death (panel c) in eligible and ineligible patients with $CHADS_2$ score [?] 2.

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