Online Supplement for:

Flaws in anticoagulation strategies in patients with atrial fibrillation at hospital discharge

Kartas et al.

Supplemental Data

Contents

Supplemental Table 1. Stroke and bleeding risk score definitions

Risk score	Points if present
CHA_2DS_2-Vasc *	
Congestive heart failure or Left Ventricular Dysfunction	1
Hypertension	1
Age ≥65 years	1
Age ≥75 years	1
Diabetes Mellitus	1
Stroke (ischemic stroke, transient ischemic disease or systemic embolism)	2
Vascular Disease (myocardial infarction, peripheral arterial disease, or aortic plaque)	1
Sex Category (female)	1
HAS-BLED †	
Hypertension	1
Abnormal renal function	1
Abnormal hepatic function	1
Stroke (ischemic stroke or transient ischemic attack)	1
Bleeding	1
Labile international normalized ratio ‡	1
Elderly age (≥65 years)	1
Drugs (aspirin, clopidogrel, or non-steroidal anti-inflammatory drugs)	1
Alcohol intake (≥8 drinks/week)	1

* Reflects stroke risk in atrial fibrillation patients not in anticoagulant therapy[1]

† Reflects bleeding risk in atrial fibrillation patients undergoing anticoagulant therapy[2]

‡ We defined Labile INR when at least two out of three last known INR measurements on or before admission were out of range. In case of missing INR values or newly diagnosed patient, we assigned zero points to the score

Supplemental Table 2. Categorization of patients according to stroke risk

Stroke risk	Low	Moderate	High
Non-gender related stroke risk factors	0	1	≥2
CHA_2DS_2-Vasc score	0 for males or 1 for females	1 for males or 2 for females	≥ 2 for males or ≥ 3 for females
Indication for OAC	contraindicated	should be considered	recommended
Class of recommendation, Level of evidence	III B	IIa B	I A

OAC, oral anticoagulant

Stratification of our study's sample in stroke risk strata, as dictated by the number of CHA_2DS_2-Vasc score non-gender related risk factors. Adapted from current ESC Guideline recommendations[3]

Supplemental Table 3. Evaluation of discharge OAC regimens

TTR prediction score for VKA regimens	Points if present
SAMe-TT_2R_2 *	
Sex (female)	1
Age <60 years	1
Medical history (more than 2 comorbidities) †	1
Treatment (drugs for rhythm control, e.g. amiodarone)	1
Tobacco use (within 2 years)	2
Race (non-white) ‡	2

Dose reduction of NOAC regimens according to European labelling

Drug	Dose reduction criteria §		Reduced dose
Dabigatran	CrCl <50 ml/min and HAS-BLED≥3 age ≥80 years concomitant verapamil use		110mg bid
Rivaroxaban	CrCl <50 ml/min		15mg qd
Apixaban	Two of three criteria (or CrCl <30ml/min):	age ≥80 years weight ≤60 kg serum Cr ≥1.5	2.5mg bid

OAC, oral anticoagulant; VKA, Vitamin-K antagonist; NOAC, non-Vitamin K Oral Anticoagulant; Cr, creatinine; CrCl, creatinine clearance

* A SAMe-TT_2R_2 score >2 discerns patients expected to achieve poor anticoagulation control (i.e., TTR <70%) from patients expected to achieve adequate anticoagulation control (i.e., score 0-2 and TTR ≥70%), when on VKA treatment

† Defined as more than two of the following: hypertension, diabetes, coronary artery disease/ myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease

‡ Our population was essentially white, thus race contributed zero points to the score

§ Concurrent antiplatelet therapy (due to acute coronary syndrome or elective percutaneous coronary intervention during hospitalisation/ previous 12 months) was also accepted as an indication for reduced NOAC dosing

Supplemental Table 4. Clinical characteristics of discharged AF patients, according to stroke risk and OAC use

	Overall (N=768)	Low stroke risk (N=34, 4.4%)			Moderate stroke risk (N=41, 5.3%)			High stroke risk (N=693, 90.2%)		
		OAC prescribed (N=23)	OAC not prescribed (N=11)	p	OAC prescribed (N=35)	OAC not prescribed (N=6)	p	OAC prescribed (N=592)	OAC not prescribed (N=101)	p
Age (Years)	73.6 ±11	57 ±8.1	46 ±13.1	**0.02**	59.5 ±9.4	53.3 ±4.1	**0.008**	75.2 ±9.2	77.2 ±9	**0.04**
Gender (male)	53.9% (414)	69.6% (16)	72.7% (8)	1.00	48.6% (17)	83.3% (5)	0.19	51.3% (304)	64% (64)	**0.02**
BMI (kg/m^2)	28.8 ±5.4	28.4 ±4.5	25.6 ±9.6	0.30	29.3 ±7.4	27.3 ±6	0.49	29.1 ±5.3	27.6 ±5.2	**0.01**
Smoker (ever)	48% (369)	64.7% (11)	63.6% (7)	1.00	48.6% (17)	66.7% (4)	0.66	45.7% (271)	58% (58)	**0.02**
Admitted for AF	47.5% (365)	88.2% (15)	100% (11)	0.51	85.7% (30)	50% (3)	0.06	45% (265)	41% (41)	0.46
AF										
First diagnosed	18.2% (140)	47.1% (8)	54.5% (6)	0.70	17.1% (6)	50% (3)	0.12	17.3% (101)	25,3% (25)	0.06
Paroxysmal	35.7% (274)	75% (12)	90.9% (10)	0.62	68.6% (24)	66.7% (4)	1.00	41.2% (244)	63% (63)	**<0.001**
Persistent or permanent	46.1% (354)	25% (4)	9.1% (1)	0.62	28.6% (10)	33.3% (2)	1.00	58.4% (342)	36% (36)	**<0.001**
History of Stroke/ TIA	14.2% (109)	-	-	-	-	-	-	16.8% (99)	9% (9)	**0.048**
History of Stroke under OAC	6.6% (51)	-	-	-	-	-	-	8.1% (48)	4% (4)	0.12
History of Major Bleeding	15.9% (122)	5.9% (1)	9.1% (1)	1.00	11.4% (4)	16.7% (1)	1.00	15.3% (91)	24% (24)	**0.03**
CHA_2DS_2-Vasc	4.4 ±1.9	0.3 ±0.5	0.3 ±0.5	0.85	1.5 ±0.5	1.2 ±0.4	0.06	4.9 ±1.6	4.6 ±1.4	0.09
HAS-BLED	1.9 ±1.1	0.6 ±0.4	0.1 ±0.3	0.26	1 ±0.7	1.2 ±0.8	0.74	1.9 ±1	2.2 ±1	**0.02**
Hypertension	79.6% (611)	-	-	-	48.6% (17)	33.3% (2)	0.66	84.7% (502)	85% (85)	0.93
Diabetes mellitus	34.6% (266)	-	-	-	2.9% (1)	-	1.00	38.1% (226)	38% (38)	0.98
Dyslipidemia	47.5% (365)	17.6% (3)	9.1% (1)	1.00	34.3% (12)	50% (3)	0.65	48.6% (288)	54% (54)	0.32
Coronary Artery Disease	44.8% (344)	-	-	-	5.7% (2)	50% (3)	**0.02**	47.9% (284)	54% (54)	0.26
Heart Failure	48.8% (375)	-	-	-	14.3% (5)	16.7% (1)	1.00	55.2% (327)	42% (42)	**0.01**
Chronic Kidney Disease	15% (115)	-	-	-	8.6% (3)	-	1.00	14.2% (84)	27% (27)	**0.001**
CrCl (mL/min)	67.9 ±34	102.1 ±40	141.4 ±59	**0.03**	90.1 ±42	91.3 ±49	0.99	65.4 ±30	56.2 ±33	**0.07**
CrCl <30 mL/min	8.8% (68)	-	-	-	5.7% (2)	16.7% (1)	0.42	7.3% (43)	22% (22)	**<0.001**
Rhythm control	22.4% (172)	47.1% (8)	27.3% (3)	0.44	31.4% (11)	16.7% (1)	0.57	21.2% (126)	20% (20)	0.78
Rate control	85% (653)	52.9% (9)	9.1% (1)	**0.04**	82.9% (29)	100% (6)	0.57	88.7% (526)	77% (77)	**0.001**
Antiplatelet use	22.9% (176)	-	9.1% (1)	0.39	5.7% (2)	50% (3)	**0.009**	19.4% (115)	58% (58)	**<0.001**

Values are % (*n*) or mean ± standard deviation of valid cases

AF, atrial fibrillation; BMI, body mass index; CrCl, creatinine clearance; OAC, oral anticoagulant; TIA, transient ischemic attack

Supplemental Table 5. Clinical characteristics of discharged AF patients, divided by OAC type and its quality assessment

	VKA (N=203)			NOAC (N=408)		
	SAMe-TT2R2 ≤2 (N=101, 49.8%)	**SAMe-TT2R2 >2 (N=102, 50.2%)**	**p**	**Dosing consistent with labelling (N=290, 71.1%)**	**Potential off-label dosing (N=118, 28.9%)**	**p**
Age (Years)	77.3 ±8.4	71.8 ±11.3	**<0.001**	72.2 ±11.2	76.5±8.1	**<0.001**
Gender (male)	37.6% (38)	71.6% (73)	**<0.001**	52.1% (151)	49.2% (58)	0.59
BMI (kg/m^2)	29.1±5.5	29.0±4.8	0.93	29.2 ±5.2	29.0±5.9	0.75
Smoker (ever)	8.9% (9)	88.2% (90)	**<0.001**	45.8% (131)	50.8% (60)	0.36
Admitted for AF	36.0% (36.0)	35.3% (36)	0.92	55.4% (158)	56.8% (67)	0.81
AF						
First diagnosed	11.9% (12)	13.7% (14)	0.69	24.9% (70)	16.5% (19)	0.07
Paroxysmal	29.7% (30)	40.2% (41)	0.12	48.8% (139)	49.2% (58)	0.95
Persistent or permanent	70.3% (71)	59.8% (61)	0.12	51.1% (145)	50.8% (60)	0.97
History of Stroke/ TIA	16.8% (17)	20.8% (21)	0.47	11.2% (32)	22% (26)	**0.01**
History of Stroke under OAC	8.2% (8)	12.1% (12.1)	0.36	7.7% (9)	4.3% (12)	0.17
History of Major Bleeding	15.8% (16)	20.6% (21)	0.38	10.8% (31)	16.9% (20)	0.09
CHA_2DS_2-Vasc	5.1±1.9	4.7±1.8	0.14	4.1±1.9	4.9±1.8	**<0.001**
HAS-BLED	2.1±1.1	2.2±1.1	0.68	1.6±1	2.0±1.0	**<0.001**
Hypertension	74.3% (75)	80.4% (82)	0.30	80.8% (231)	82.2% (97)	0.74
Diabetes mellitus	40.6% (41)	36.3% (37)	0.53	34.6% (99)	33.9% (40)	0.89
Dyslipidemia	46.5% (47)	54.9% (56)	0.23	46.2% (132)	43.2% (51)	0.59
Coronary Artery Disease	56.4% (57)	69.6% (71)	0.05	34.8% (100)	41.5% (49)	0.21
Heart Failure	66.3% (67)	66.7% (68)	0.96	42.8% (122)	50.8% (60)	0.14
Chronic Kidney Disease	24.8% (25)	21.6% (22)	0.59	8% (23)	11% (13)	0.34
CrCl (mL/min)	56.0±23.6	66.9±34.5	**0.01**	75.7±33.8	60.0±23.4	**<0.001**
CrCl <30 mL/min	12.9% (13)	13.9% (14)	0.84	3.5% (10)	4.2% (5)	0.77
Rhythm control	10.9% (11)	34.3% (35)	**<0.001**	26.2% (76)	17.8% (21)	0.07
Rate control	84.2% (85)	91.2% (93)	0.13	86.2% (250)	88.1% (104)	0.60
Antiplatelet use	30.7% (31)	38.2% (39)	0.26	12.8% (37)	1.7% (2)	**0.001**

Values are % (*n*) or mean ± standard deviation of valid cases

AF, atrial fibrillation; BMI, body mass index; CrCl, creatinine clearance; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; TIA, transient ischemic attack; VKA, vitamin K antagonist

Multiple imputation for missing data

The overall missing rate was low (1.5%). The degree of missingness for individual variables used in the regression models prior to the imputation procedure was 2.1% (see Supplemental Table 6). In the models, 9/12 of variables had missing data and 86 of 768 cases (11.2%) had missing data for at least one variable. Missing values of certain variables (e.g., HAS-BLED, antiplatelet use, NOAC appropriateness) were more, and could pose restrictions in our analyses if left unaddressed. We avoided simpler methods (e.g., replacement with mean values), so as not to distort the multivariate inferences.[4]

In this analysis, all variables directly used in the regression analyses that contained missing values were imputed and served as predictors with multiple imputation. In addition to the rest of the variables presented in the main article, we incorporated extra variables as predictors into the imputation model. These variables are only present in the original MISOAC-AF dataset of the principal prospective trial. In this way, we aimed to minimize bias and maximize certainty of the model. These, auxiliary variables, were: length of hospitalization (days), systolic/ diastolic blood pressure, place of living (urban, city), physical exercise, laboratory values (high-sensitive cardiac troponin T, N-terminal pro b-type natriuretic peptide, C-reactive protein, hemoglobin) and all admission counterparts of the variables used in the main analysis (e.g., CHA_2DS_2-Vasc score on admission).

We allowed the software to choose the best imputation method, dictated by scanning the patterns of missingness (i.e., monotonicity) of the data. The Fully Conditional Specification (iterative Markov-chain Monte Carlo algorithm) method was eventually applied.

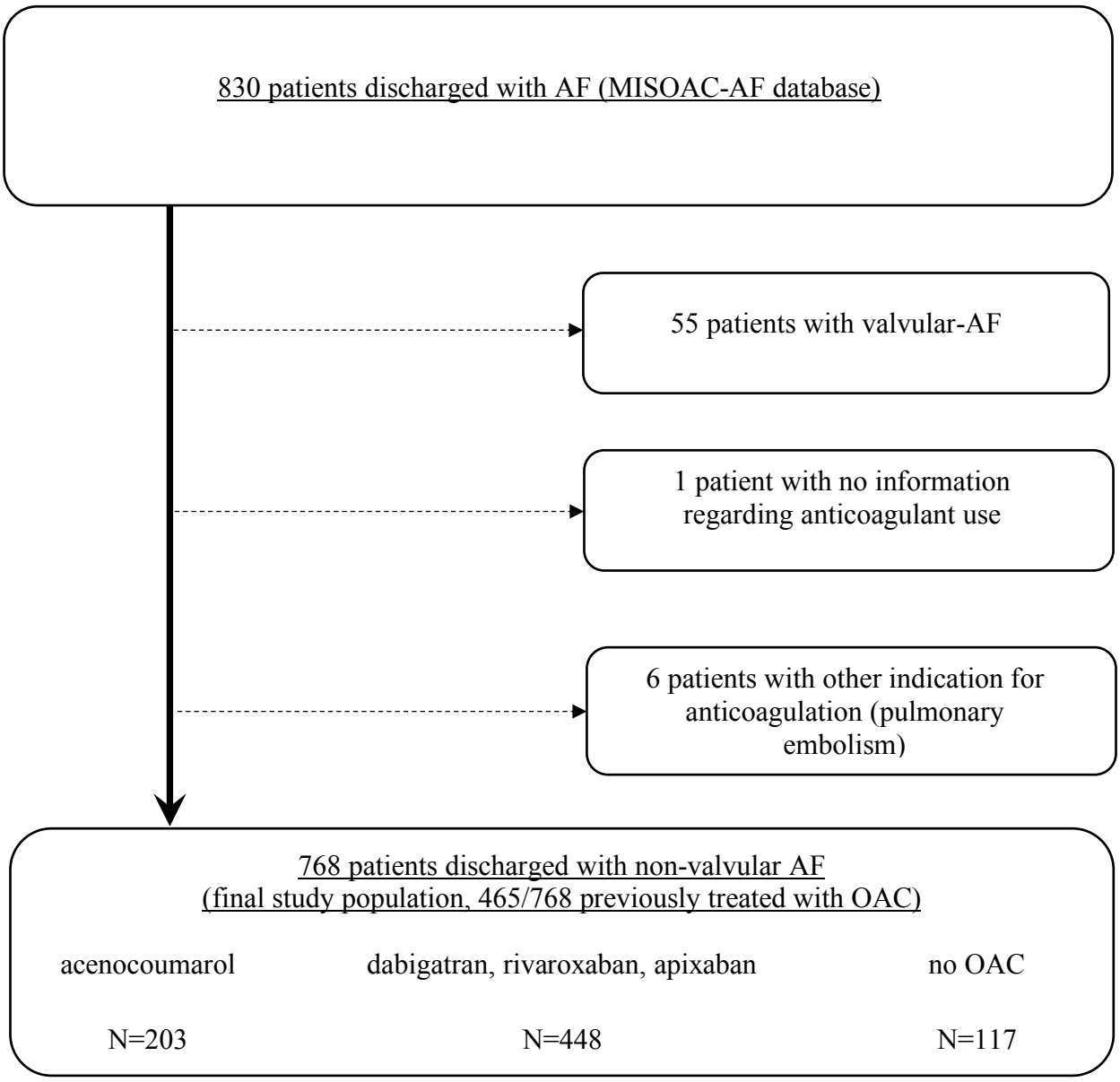
In our study, imputed values compare reasonably to observed values, and results using listwise deletion were broadly similar to MI. Thus, pooled results from 5 datasets, after using Rubin's combination rules are presented.[5]

Supplemental Table 6. List of variables (of the regression models) imputed and amount of missing data at baseline

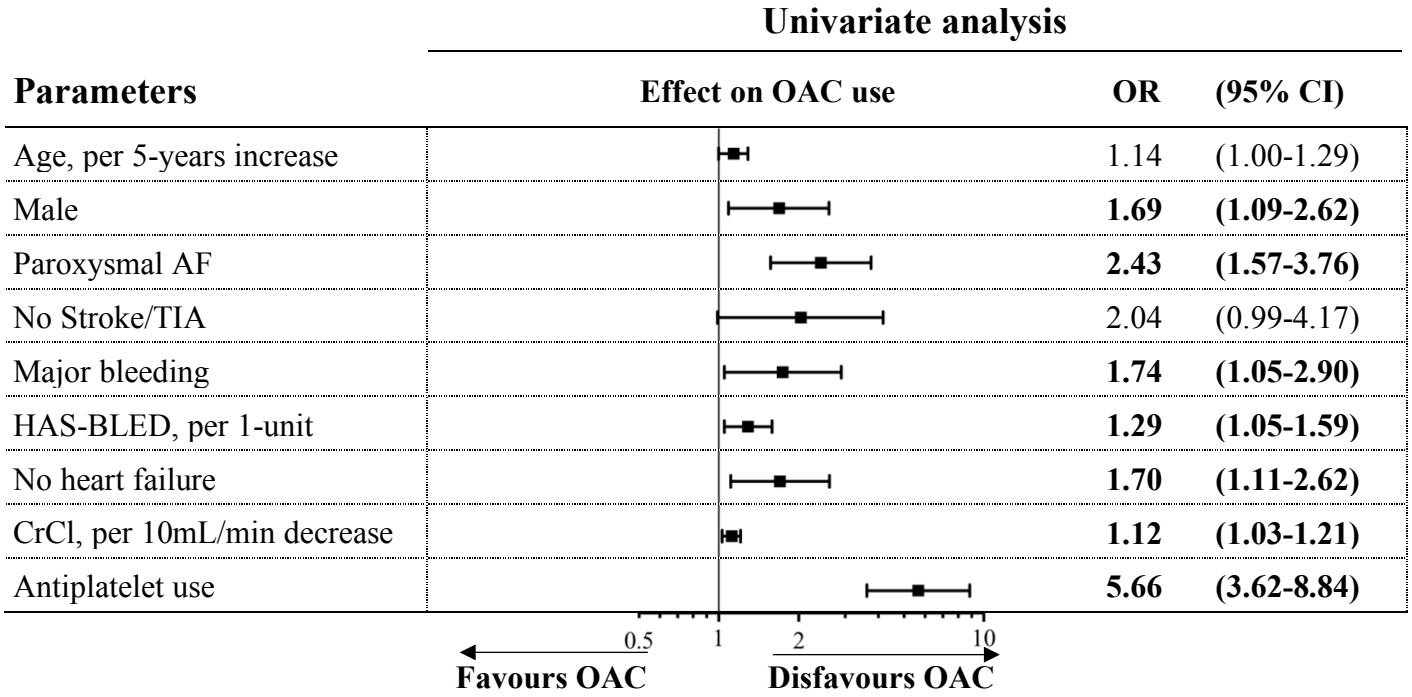
Variable imputed (and used as predictor)	**% missing data in regression models**
Age	1.2%
Gender	0%
AF type	2.1%
History of Stroke/ TIA	1.2%
History of Major Bleeding	0.9%
CHA_2DS_2-Vasc score	0%
HAS-BLED score	6.5%
Heart Failure	1 %
CrCl	2.1%
Rhythm control	0%
Antiplatelet use	4.4%
NOAC appropriateness	8.9%
Overall	**2.1%**

MI utilizes the distributional property of each measured variable as well as intervariable correlations within the dataset to run iterated regression analyses, taking one variable as the outcome variable and the remaining variables in the dataset as the predictor variables. Doing this for all variables produces logical simulations (imputed values) of the missing data. Repeating this procedure multiple times yields multiple complete datasets which are pooled together to perform analyses.[6]

Supplemental Figure 1. Flowchart of the study population

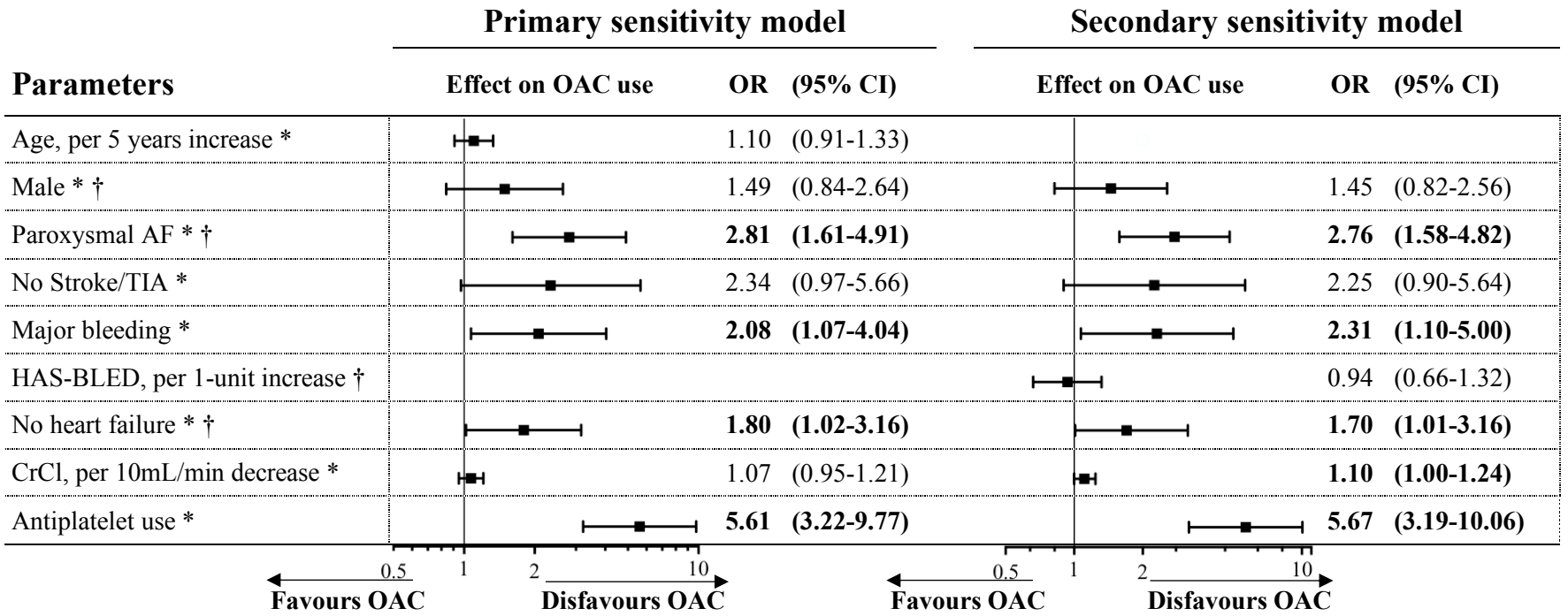


Supplemental Figure 2. Univariate analysis of factors related to non-prescribing of OAC to high stroke-risk AF patients



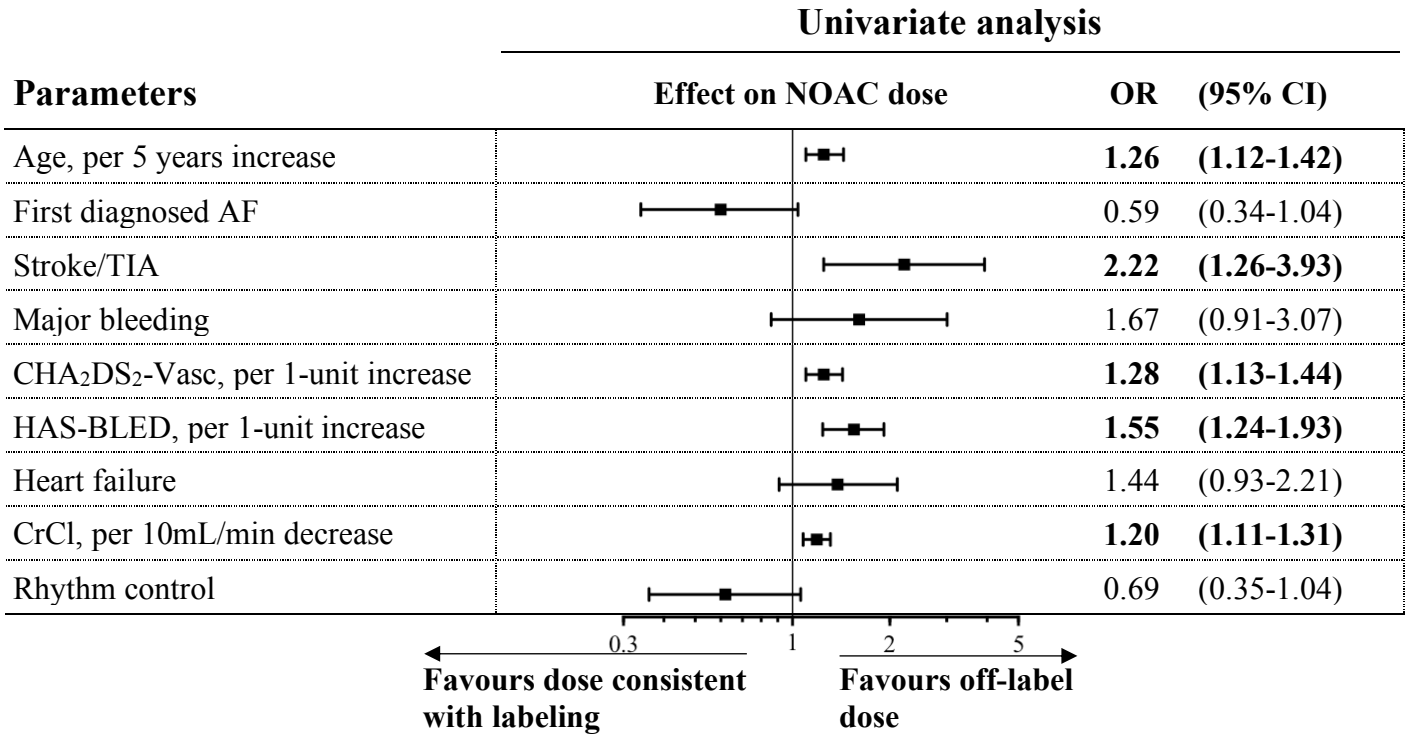
AF, atrial fibrillation; CI, confidence interval; CrCl, creatinine clearance; OAC, oral anticoagulant; OR, odds ratio; TIA, transient ischemic attack.

Supplemental Figure 3. Sensitivity analysis of factors related to non-prescribing of OAC to high stroke-risk patients (CrCl >30 ml/min)



Adjusted odds ratios of factors contained in the two final sensitivity models.
Variables forced into the first step of the primary and secondary model are marked as (*) and (†) respectively.
The remaining variables' contribution was assessed with backward regression.
AF, atrial fibrillation; CI, confidence interval; CrCl, creatinine clearance; OR, odds ratio; TIA, transient ischemic attack.

Supplemental Figure 4. Univariate analysis of factors related to prescribing an off-label dosed NOAC



AF, atrial fibrillation; CI, confidence interval; CrCl, creatinine clearance; NOAC, non-vitamin K antagonist oral anticoagulant; OR, odds ratio; TIA, transient ischemic attack.

References

1. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro Heart Survey on atrial fibrillation. *Chest*. 2010;137(2):263-272. doi:10.1378/chest.09-1584

2. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138(5):1093-1100. doi:10.1378/chest.10-0134

3. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37(38):2893-2962. doi:10.1093/eurheartj/ehw210

4. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res*. 2007;16(3):219-242. doi:10.1177/0962280206074463

5. Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley, 1987. 1989;31:131-132.

6. Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM. Review: A gentle introduction to imputation of missing values. *J Clin Epidemiol*. 2006;59(10):1087-1091. doi:10.1016/j.jclinepi.2006.01.014