Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: June 30, 2022

Citation Karasoy D, Torp-Pedersen C, et al., 2022. Cardiovascular Outcomes associated with Oral Anticoagulants, Antiplatelets and No-Treatment after Atrial Fibrillation Ablation: A Nationwide Cohort Study, Medical Research Archives, [online] 10(6). https://doi.org/10.18103/mra.v10i6.2837

DOI
https://doi.org/10.18103/mra.v10i6.2837

ISSN: 2375-1924

RESEARCH ARTICLE

Cardiovascular Outcomes associated with Oral Anticoagulants, Antiplatelets and No-Treatment after Atrial Fibrillation Ablation: A *Nationwide Cohort Study*

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ABSTRACT

Objective: We investigated the long-term cardiovascular outcomes associated with direct oral anticoagulants (DOACs), antiplatelets and No-Treatment compared to warfarin beyond 90-days after atrial fibrillation (AF) catheter ablation.
Methods: We identified 12,010 AF patients undergoing first-time ablation in Denmark (2002-2018) and analyzed stroke, serious bleeding, cardiovascular death and the composite of these three endpoints (MACE) by incidence rates (IR) per 1000 person-years and Cox proportional-hazard models.
Results: The median age was 62 years (interquartile range [IQR]: 54-68 years); 28.8% were female, 7225 (60.2%) patients were younger than 65-years, and 6927 (57.7%) patients had CHA_2DS_2-VASc score≥2. Over a total of 65,990 person-years follow-up commencing 90-days after first-time ablation, warfarin, DOACs, antiplatelets and 'No-treatment' exposures covered 30,877 (46.8%), 9,452 (14.3%), 6,003 (9.1%) and 19,657 (29.8%) person-years, respectively. There was no difference between DOACs vs warfarin (HR 1.04 [0.77-1.42]$_{95\%CI}$) while antiplatelets (HR 1.50 [1.11-2.05]$_{95\%CI}$) and No-Treatment (HR 1.50 [1.15-1.94]$_{95\%CI}$) were associated with a significantly higher rate of stroke. DOACs (HR 0.70 [0.54-0.92]$_{95\%CI}$), antiplatelets (HR 0.58 [0.41-0.82]$_{95\%CI}$) and No-Treatment (HR 0.52 [0.39-0.69]$_{95\%CI}$) were associated with a significantly lower rate of serious bleeding compared with warfarin. We found no difference between DOACs and warfarin (HR 0.87 [0.61-1.25]$_{95\%CI}$) while Antiplatelets (HR 1.42 [1.04-1.94]$_{95\%CI}$) and No-treatment (HR 2.77 [2.16-3.56]$_{95\%CI}$) were associated with a significantly higher rate of cardiovascular death. We observed no difference with DOACs (HR 0.86 [0.70-1.05]$_{95\%CI}$), antiplatelets (HR 1.04 [0.84-1.27]$_{95\%CI}$) or No-Treatment (HR 1.10 [0.93-1.31]]$_{95\%CI}$) compared to warfarin in multivariable analyses regarding the composite endpoint of MACE.
Conclusions: Our study indicates a better bleeding risk profile associated with DOACs than warfarin in patients undergoing AF ablation, but no difference for the endpoints of stroke, cardiovascular death, or the composite endpoint of MACE. Despite the favourable bleeding risk, antiplatelets and No-Treatment compared with warfarin appear hazardous due to a higher rate of stroke and cardiovascular death.

Introduction

Catheter ablation with pulmonary vein isolation has become the standard of care for rhythm control in selected patients with symptomatic paroxysmal and persistent atrial fibrillation (AF).[1,2] Data from randomized clinical trials and meta-analyses consistently suggest that freedom from AF is significantly higher after ablation compared with antiarrhythmic drugs (AADs).[2–6] Still, surprisingly little is known about the risks and benefits of direct oral anticoagulants (DOACs) after AF ablation.

International guidelines and expert consensus reports recommend that oral anticoagulation should be maintained for at least 2-months post-ablation and continued indefinitely regardless of the success or failure of AF ablation in patients at high risk of stroke.[1,2] DOACs are now the first choice of stroke prevention in non-valvular AF patients, and are recommended in preference to warfarin due to a better risk-benefit profile, i.e. lower mortality, lower risk of intracranial haemorrhage and significantly reduced stroke or systemic embolic events.[7–11]

DOACs are commonly prescribed before, during, and after AF ablation, whereas this population is not well-represented in current risk stratification schemes in the contemporary era of DOACs. Limited data is available regarding the long-term safety and effectiveness of DOACs, antiplatelets, and No-treatment compared to warfarin after AF ablation. We investigated the risk of stroke, bleeding and cardiovascular mortality over a long-time follow-up long-term follow-up by comparing DOACs, antiplatelets and No-Treatment with warfarin beyond 90-days after catheter ablation of AF.

Methods

Databases

This is a retrospective study based on prospectively recorded data in national administrative registers. Every hospital admission in Denmark has been registered in The Danish National Patient Registry since 1977. Hospital admissions are coded with one primary diagnosis and, if appropriate, one or more secondary diagnoses at discharge according to the *International Classification of Diseases*; the 10th revision (ICD-10) since 1994. All RFA procedures performed in Denmark's public or private sector have been registered and coded according to The Nordic Medico-Statistical Committee Classification of Surgical Procedures (NCSP). The Danish Registry of Medicinal Product Statistics has kept accurate records of all prescriptions dispensed from Danish pharmacies according to the Anatomical Therapeutic Chemical (ATC) classification system, including information on the date, quantity, strength, formulation, and affiliation of the prescribing physician since 1995. The civil registration system keeps data on patients' age, sex, and vital status where all deaths are registered within 14 days of the incident. A personal and permanent civil registration number provided for each resident in Denmark enables cross-linkage between these administrative registries at the individual level nationwide.

Population

Using the Danish National Patient Registry, all patients with AF (ICD-10: I48) aged 18 years or older, without rheumatic mitral valve disease (ICD-10: I05) or previous mitral or aortic valve surgery (NCSP: KFK, KFM), undergoing first-time radiofrequency- or cryoablation (NCSP: BFFB04 or KFPB10) in Denmark (public or private) between 01-January-2002 and 31-October-2018 were identified and included from the discharge date following the first-time ablation. Patients aged below 18 (n=16), patients with valvular AF (n=169), and those who did not survive the first 90 days from first-time ablation due to non-cardiovascular causes (n=13) and cardiovascular causes (n=44) were excluded. This algorithm for identifying the AF patients undergoing the first-time ablation was previously validated, yielding 97% sensitivity.[12]

Exposure

Four different exposure category was used 90-days after discharge from the first-time ablation: warfarin, DOACs, antiplatelets and No-Treatment. Lexis-split algorithm was utilized to enable time-dependent exposure that facilitates potential changes in exposure category/dosage for the same patient. Exposure to warfarin was determined based on the number and strength of tablets received at prescription claims divided by the number of days until the next prescription claim. Warfarin dosage and exposure duration were estimated using validated five consecutive prescription claim periods. Warfarin exposure was considered sustained until residual warfarin tablets were consumed and no longer were available in patients' possession. Treatment with DOACs and antiplatelets (aspirin or clopidogrel) were managed consistently.[13] Periods with simultaneous exposure to warfarin and DOACs were omitted. No-Treatment was defined as interruption or discontinuation of anticoagulants/antiplatelets,

calculated as the number of days with no available treatment according to the estimated dosage.

Baseline Comorbidity & Medication

Baseline comorbidities were identified using discharge diagnoses during the past 10 years before inclusion. Concomitant medications were ascertained from prescriptions filled within 180 days before inclusion (Supplementary Table-S1).

Endpoints

The primary effectiveness endpoint was stroke defined as hospitalization for any type of stroke (i.e., hemorrhagic stroke, ischemic stroke, unspecified stroke, or transient ischemic attack). Ischemic stroke in the Danish National Patient Registry has a positive predictive value (PPV) of 97-100%, while PPV for unspecified stroke and transient ischemic attack (TIA) is 80.5-86% and 57.9-68.4%, respectively.[14]

The secondary safety endpoints were serious bleeding, cardiovascular death and major adverse cardiovascular events (MACE: composite of stroke, serious bleeding and cardiovascular death). Bleeding-related hospitalizations were validated and could distinguish specific bleeding sites with a PPV between 89% and 99%.[15] Solely primary hospitalization A-diagnoses were utilized for all endpoints (Supplementary Table-S2).

Follow-up was commenced 90 days after the first-time ablation, and patients were followed until the first endpoint of interest, otherwise censored at death from another cause, or at the end of the study period (31-January-2019).

Risk profiles

The CHA_2DS_2-VASc-score was utilized to assess the thromboembolic risk profile. The thromboembolic risk was considered low, intermediate, and high if the CHA_2DS_2-VASc score was 0, 1, and ≥2, respectively. Women without other risk factors were considered low risk (score=0).

The risk profile for serious bleeding was assessed by the HAS-BLED score. This score ranged from 0-8 points and possibly underestimated in patients using warfarin since no information on the labile international normalized ratio (INR) was available. The risk of major bleeding was considered low, intermediate, and high if the HAS-BLED score was ≤1, 2, and ≥3, respectively.

Recurrent AF

We defined recurrent AF as the earliest record of any hospitalization with a primary diagnosis for AF with or without direct-current cardioversion or re-ablation after 90-days from the first-time ablation. We validated this definition previously and found sensitivity, specificity and PPV of 99.3%, 95.2% and 98%, respectively.[16]

Predefined Sensitivity Analyses

We performed two pre-defined sensitivity analyses; (i) following the patients persisting with baseline exposure allocation until the endpoint of interest or end of follow-up, otherwise censored when treatment was changed/discontinued; (ii) the year of inclusion and the study period was restricted to 01-January-2012 and after to integrate the changes in international guidelines regarding the anticoagulation suggestions.

Statistical analyses

We reported categorical variables as numbers with percentages and continuous variables as medians with interquartile range (IQR), assessing the differences by chi-square test and Kruskal–Wallis test, respectively. Incidence rates (IR) were calculated as the number of new cases per 1000 person-years exposure (1000-PYE). Cox regression was applied to determine the effect of exposures on the outcomes reported by the hazard ratios (HR) with 95% confidence intervals (95%CI). Fine-Gray[17] competing-risk regression was used to illustrate the cumulative incidences, where death from another cause was considered the competing event. Marginal structural binomial regression model[18] with bootstrap 95%CIs were used to compute the standardized risk difference and relative risk comparing warfarin and DOACs. A two-sided significance level of 0.05 was used in evaluations. We used SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA) for data management and Stata statistical software, version 15.0 (Stata Corp LP, College Station, TX, USA) for analyses.

Ethics

The Danish Data Protection Agency has approved the present study (ref. no. 2007-58-0015/GEH-2014-013 I-Suite no: 02731). According to Danish regulations register-based retrospective studies do not require ethical approval. We used anonymized/encrypted data so that individuals could not be identified. Statistical packages were arranged via encrypted servers by Statistics Denmark.

Results

Population

We included 12,010 patients followed for a median of 4.5 years (IQR: 1.9–8.9). The median AF duration (first-time registration to first-time ablation) was 1.8 years (IQR: 0.5–5.0). Table-1 summarizes the baseline characteristics of the total

population and by exposure allocation 90-days after AF ablation. The median age was 62 years (IQR: 54–67), 7225 (60.2%) patients were younger than 65-years, and 6927 (57.7%) patients had CHA_2DS_2-VASc score≥2. Antiplatelet and No-Treatment patients were younger than anticoagulant users, while comorbidity burden was higher in antiplatelet- and lower for No-Treatment groups compared with anticoagulant users.

Table 1. Baseline characteristics of all patients and by the exposure allocation 90-days after AF ablation.

	All patients	Warfarin	DOACs	Antiplatelets	No-treatment	P-value
Number of patients, n (%) *	12.010 (100)	8959 (74.6)	1959 (16.3)	150 (1.3)	942 (7.8)	<0.0001
Total exposure, years (%) *	65,990 (100)	30,877.1 (46.8)	9,452.4 (14.3)	6,003.2 (9.1)	19,657.2 (29.8)	<0.0001
The median age in years (IQR)	62 (54-67)	62 (57-68)	63 (56-68)	59 (54-64)	58 (51-64)	<0.0001
The median AF duration, years (IQR)	1.8 (0.5-5.0)	2.5 (0.9-5.7)	1.8 (0.6-5.0)	2.0 (0.7-5.2)	1.9 (0.6-5.0)	<0.0001
Age ≤65, n (%)	7225 (60.2)	5571 (62.2)	998 (50.9)	82 (54.7)	576 (61.1)	<0.0001
Age 65-74, n (%)	4045 (33.7)	2916 (32.6)	784 (40.0)	48 (32.0)	297 (31.5)	<0.0001
Age ≥75, n (%)	738 (6.0)	472 (5.3)	177 (9.0)	20 (13.3)	69 (7.3)	<0.0001
Female, n (%)	3454 (28.8)	2504 (27.9)	646 (33.0)	45 (30.0)	259 (27.5)	<0.0001
Comorbidity, n (%)						
Congestive Heart Failure	1897 (15.8%)	1393 (15.5)	326 (16.6)	32 (21.3)	148 (15.7)	0.172
Arterial hypertension	8100 (67.4)	6100 (68.1)	1331 (67.9)	112 (74.7)	557 (59.1)	<0.0001
Vascular disease	2524 (21.0)	1859 (20.7)	378 (19.3)	81 (54.0)	206 (21.9)	<0.0001
Previous AMI	667 (5.5)	460 (5.1)	114 (5.8)	29 (19.3)	64 (6.8)	<0.0001
Ischemic Heart Disease	1852 (15.4)	1373 (15.3)	250 (12.8)	74 (49.3)	155 (16.5)	<0.0001
Peripheric Artery Disease	112 (0.9)	80 (0.9)	18 (0.9)	5(3.3)	9 (0.1)	0.023
Previous Stroke	753 (6.3)	551 (6.2)	143 (7.3)	16 (10.7)	43 (4.6)	0.004
Previous bleeding	675 (5.6)	482 (4.8)	128 (6.5)	14 (9.3)	51 (5.4)	0.046
Renal failure	251 (2.1)	173 (1.9)	46 (2.4)	4 (2.7)	28 (3.0)	0.135
Diabetes Mellitus	688 (5.7)	519 (5.8)	101 (5.2)	19 (12.7)	49 (5.2)	0.002
Alcohol abuse	363 (3.0)	256 (2.9)	57 (2.9)	6 (4.0)	44 (4.7)	0.017
Liver disease	89 (0.7)	65 (0.7)	18 (0.9)	≤4	≤4	0.412
CHA_2DS_2-VASc score, n (%)						
Low risk (Score=0)	2143 (17.9)	1592 (17.7)	300 (15.3)	12 (8.0)	239 (25.4)	<0.0001
Intermediate risk (Score=1)	2940 (24.4)	2280 (25.5)	403 (20.6)	24 (16.0)	233 (24.7)	<0.0001
High risk (Score ≥ 2)	6927 (57.7)	5087 (56.8)	1256 (64.1)	114 (76.0)	470 (49.9)	<0.0001
HAS-BLED score, n (%)						
Low risk (Score ≤ 1)	6595 (54.9)	4890 (54.5)	1078 (55.0)	44 (29.3)	583 (61.9)	<0.0001
Intermediate risk (Score=2)	3823 (31.8)	2846 (31.8)	650 (33.2)	63 (42.0)	264 (28.0)	<0.0001
High risk (Score ≥ 3)	1592 (13.3)	1223 (13.7)	231 (11.8)	43 (28.7)	95 (10.1)	<0.0001
Medication at baseline, n (%)						
Aspirin	1316 (11.0)	1089 (12.1)	48 (2.5)	140 (93.3)	41 (4.4)	<0.0001
Clopidogrel	143 (1.2)	62 (0.7)	19 (1.0)	21 (14.0)	41 (4.4)	<0.0001
Dual anti-platelet therapy	127 (1.1%)	71 (0.8)	19 (1.0)	9 (6.0)	28 (3.0)	<0.0001
Warfarin	9603 (80.0%)	8756 (97.7)	333 (17.0)	57 (38.0)	457 (48.5)	<0.0001
Direct oral anticoagulants (DOACs)	1959 (16.4)	≤4	1959 (100)	≤4	9 (1.0)	<0.0001
β-blockers	8630 (71.9)	6440 (71.9)	1519 (77.5)	87 (58.0)	584 (62.0)	<0.0001
Digoxin	2175 (18.1)	1738 (19.4)	264 (13.5)	29 (19.3)	144 (15.3)	<0.0001
Calcium antagonists (non-dihydropyridine)	1315 (11.0)	1038 (11.6)	159 (8.1)	18 (12.0)	100 (10.6)	<0.0001
Class 3-AADs	2681 (22.3)	2018 (22.5)	448 (22.8)	28 (18.7)	187 (19.9)	0.169
Class 1c-AADs	1945 (16.2)	1568 (17.5)	254 (13.0)	11 (7.3)	112 (11.9)	<0.0001
Renin-Angiotensin inhibitors	4745 (39.5)	3516 (39.3)	863 (44.1)	64 (42.7)	302 (32.6)	<0.0001
Statins	3818 (31.8)	2865 (32.0)	633 (32.3)	79 (52.7)	241 (25.6)	<0.0001
Diuretics	3001 (25.0)	2225 (24.9)	536 (27.4)	39 (26.0)	201 (21.3)	0.005
NSAIDs	1186 (9.9)	940 (10.5)	158 (8.1)	12 (8.0)	76 (8.1)	0.002

AADs: anti-arrhythmic drugs; AMI: acute myocardial infarction; IQR: interquartile range; NSAIDs: non-steroid anti-inflammatory drugs.
* Row percentages were used to report the number of patients and exposure in person-years for the total population and by the exposure allocation. The column percentages were used to report and compare the distribution of categorical variables by the exposure allocation at baseline.

Exposure

Exposure allocation on day-90 for warfarin, DOACs, antiplatelets and No-therapy were 8959 (74.6%), 1959 (16.3%), 150 (1.3%) and 942 (7.8%), comprising 30,877 (46.8%), 9,452 (14.3%), 6,003 (9.1%) and 19,657.2 (29.8%) person-years follow-up, respectively. Figure 1 illustrates antiplatelets overuse and No-Treatment both in all patients (A) and in patients with MACE (B), without significant differences in exposure

allocation regardless of the AF recurrence status across all risk groups with (supplementary Table-S3). Figure 2 depicts temporal trends in exposure status after 2011 since Dabigatran was introduced in Denmark in August 2011 and 80% of all patients with CHA_2DS_2-VASc score≥1 were anticoagulated with warfarin. During follow-up, 29 (0.2%) DOAC users shifted to warfarin and 2415 (20.1%) warfarin users shifted to DOACs. We excluded 643 person-years for cross-over exposure (warfarin+DOACs), involving 2 cardiovascular deaths, 2 strokes and 1 serious bleeding events.

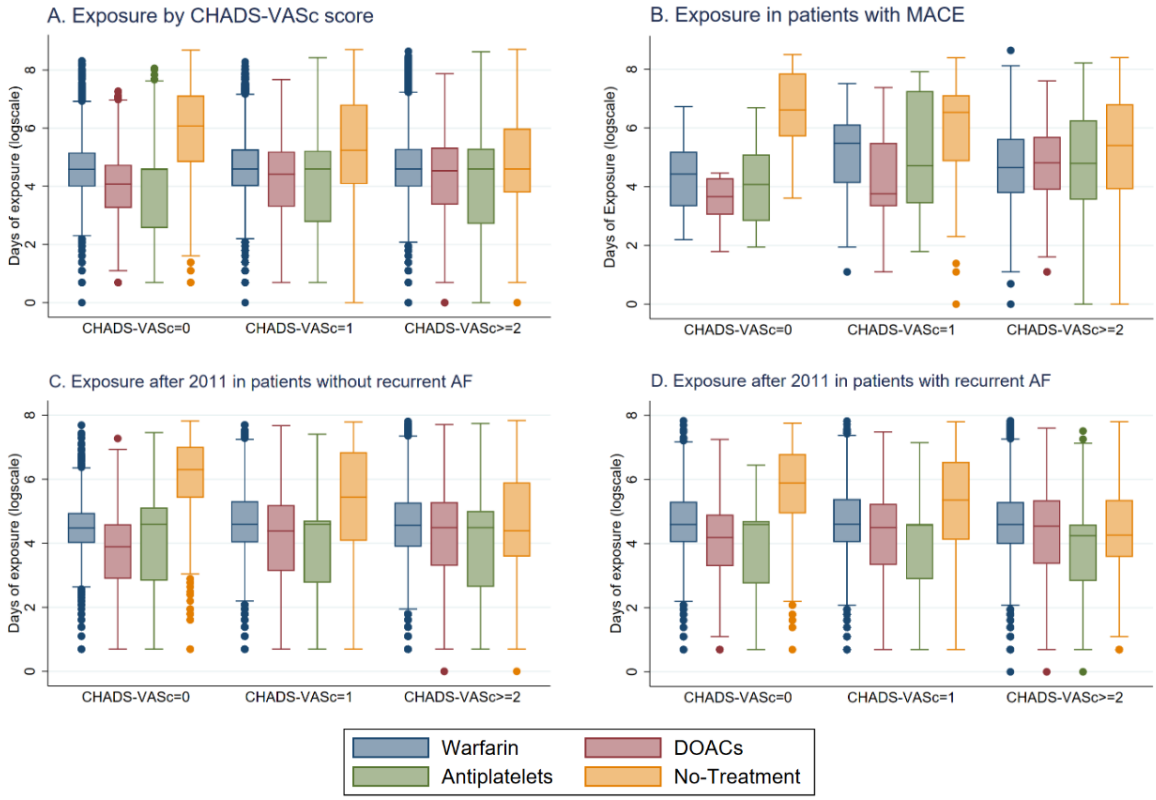

Figure 1. Exposure status depicting the duration for oral anticoagulants (DOACs and warfarin), antiplatelets and No-Treatment in days (log scale due to log distribution) according to the risk profile by the CHA_2DS2-VASc score. A) in all patients, B) in patients with MACE, C) in patients without recurrent AF after 2011 and D) in patients with recurrent AF after 2011.

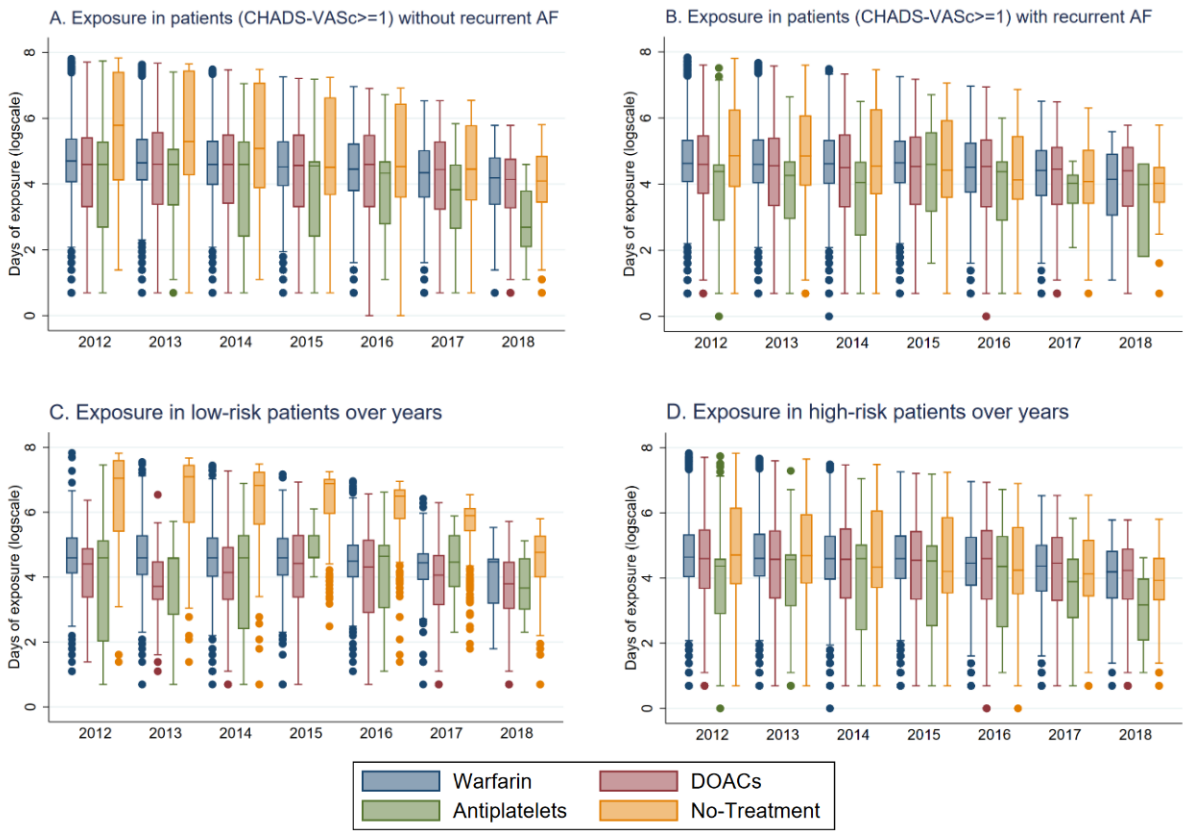

Figure 2. Exposure status depicting the duration for oral anticoagulants (DOACs and warfarin), antiplatelets and No-Treatment in days (log scale due to log distribution) according to the time trends after 2011. A) in patients (CHA_2DS_2-VASc score≥1) without recurrent AF, B) in patients (CHA_2DS_2-VASc score≥1) with recurrent AF, C) in low-risk patients (CHA_2DS_2-VASc score=0) and D) in high-risk patients (CHA_2DS_2-VASc score≥2).

Cardiovascular outcomes

Table-2 portrays the incidence rates per 1000 person-years according to exposure allocation and multivariable analyses (warfarin as the reference). We observed no difference between DOACs vs. warfarin (HR 1.04 [0.77–1.42]95%CI) while antiplatelets (HR 1.50 [1.11–2.05]95%CI) and No-Treatment (HR 1.50 [1.15–1.94]95%CI) were associated with a significantly higher rate of stroke. DOACs (HR 0.70 [0.54–0.92]95%CI), antiplatelets (HR 0.58 [0.41–0.82]95%CI), and No-Treatment (HR 0.52 [0.39–0.69]95%CI) were associated with a significantly lower rate of serious bleeding compared with warfarin. We detected no difference between DOACs and warfarin (HR 0.87 [0.61–1.25]95%CI) while antiplatelets (HR 1.42 [1.04–1.94]95%CI) and No-Treatment (HR 2.77 [2.16–3.56]95%CI) were associated with a significantly higher rate of cardiovascular death. We found no difference among the groups regarding MACE. Figure 3 illustrates the cumulative incidences by exposure allocation and the results of the ultivariable analyses.

Table 2. Cardiovascular outcomes (stroke, serious bleeding, cardiovascular death and MACE) *according to exposure allocation.*

	Warfarin (reference)	DOACs		Antiplatelets		No-Treatment	
	IR (95%CI)	IR (95%CI)	HR (95%CI)	IR (95%CI)	HR (95%CI)	IR (95%CI)	HR (95%CI)
Stroke	6.8 (5.9-7.8)	6.2 (4.8-8.0)	1.04 (0.77-1.42)	9.5 (7.3-12.3)	1.50 (1.11-2.05)	6.3 (5.3-7.5)	1.50 (1.15-1.94)
Serious Bleeding	11.9 (10.7-13.2)	7.5 (5.9-9.5)	0.70 (0.54-0.92)	6.5 (4.7-8.9)	0.58 (0.41-0.82)	3.8 (3.0-4.7)	0.52 (0.39-0.69)
Cardiovascular death	6.2 (5.4-7.1)	3.9 (2.8-5.3)	0.87 (0.61-1.25)	8.7 (6.6-11.4)	1.42 (1.04-1.94)	6.3 (5.3-7.5)	2.77 (2.16-3.56)
MACE	20.1 (18.6-21.8)	14.5 (12.2-17.3)	0.86 (0.70-1.05)	19.2 (15.9-23.2)	1.04 (0.84-1.27)	12.7 (11.2-14.4)	1.10 (0.93-1.31)

IR (Incidence rate per 1000 person-years exposure with 95% Confidence Intervals). MACE: Major Adverse Cardiovascular Events including stroke, serious bleeding and Cardiovascular Death.
The reference is warfarin for all treatment allocations in Cox multivariable analyses adjusted for year of inclusion, time-dependent age, sex, hypertension, heart failure, diabetes mellitus, vascular disease, renal disease, alcohol abuse, liver disease, previous stroke, previous bleeding and recurrent AF.

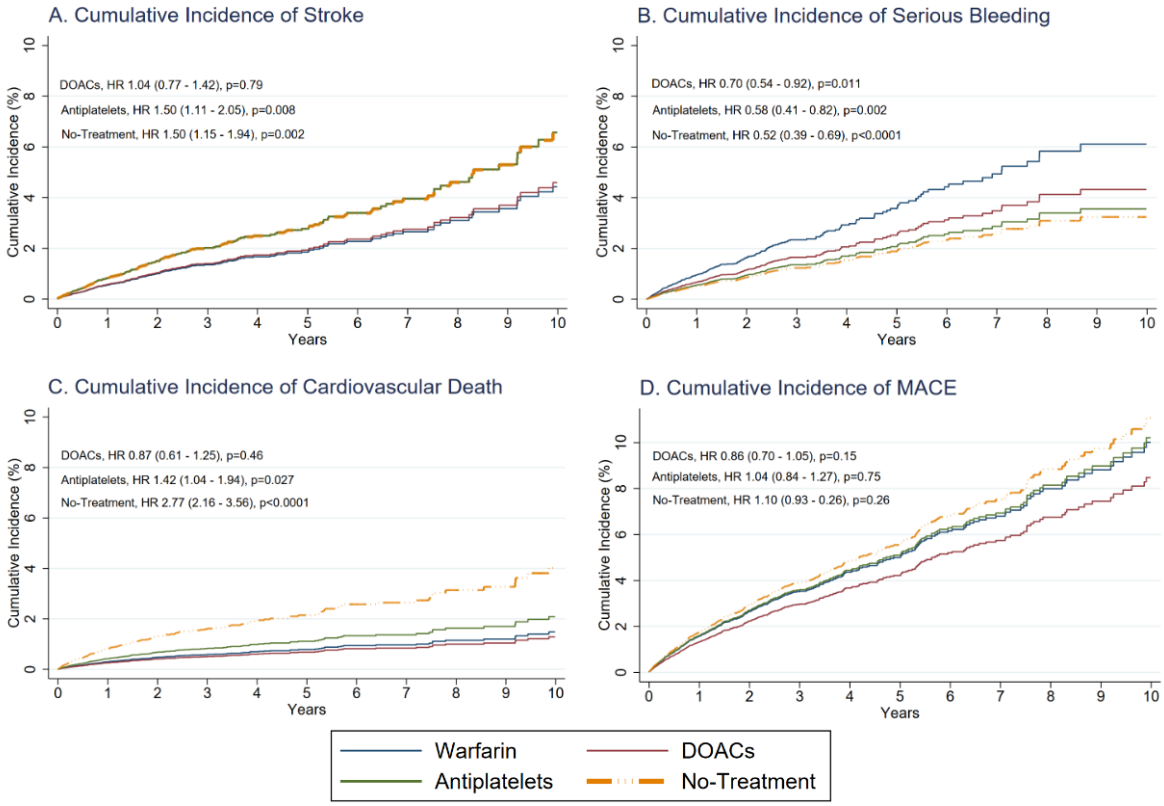

Figure 3. The cumulative incidence of stroke (A), serious bleeding (B), cardiovascular death (C) and MACE (D) over 10-years follow-up according to treatment allocation based on Fine and Gray competing risk regression adjusted for time-dependent age, sex, hypertension, heart failure, diabetes mellitus, vascular disease, renal disease, alcohol abuse, liver disease, previous stroke, previous bleeding and recurrent AF.

Stroke

In total, 491 (4.1%) patients had a stroke after discharge from first-time ablation; 54 (0.4%, IR:20/1000-PYE) events emerging within 90-days were censored from further analyses. Stroke occurred in 204 (1.7%, IR:6.8), 57 (0.5%, IR:6.2), 55 (0.5%, IR:9.5) and 121 (1%, IR:6.3) patients among warfarin, DOACs, antiplatelets and No-Treatment groups, respectively. In multivariable analyses, we observed no difference between DOACs vs warfarin while antiplatelets and No-Treatment were associated with a significantly higher rate of stroke (Table-3). No-Treatment was associated with a significantly higher rate of fatal (HR 2.22[1.20–4.13] $_{95\%CI}$) and thrombotic stroke (HR 1.82[1.26–2.63]$_{95\%CI}$). Event rates were higher among patients with recurrent AF, and amplified with increasing CHA_2DS_2-VASc scores. Ad hoc analysis of patient characteristics at stroke events revealed that compared with warfarin DOAC users were older with more comorbidity while the No-Treatment group was younger with less comorbidity and longer follow-up duration (Supplementary Table-S4). We found no difference between DOACs and warfarin in stratified sub-group analyses, standardized absolute risk difference (Table-6) or sensitivity analyses (Supplementary Table-S8, Table-S9).

Table 3. Stroke events with subtypes according to exposure allocation during follow-up and stroke events according to AF recurrences by CHA_2DS_2-VASc score

	All events	Warfarin (reference)	DOACs		Antiplatelets		No-Therapy	
	N / PYE IR (95%CI)	N / PYE IR (95%CI)	N / PYE IR (95%CI)	HR (95%CI) p-value	N / PYE IR (95%CI)	HR (95%CI) p-value	N / PYE IR (95%CI)	HR (95%CI) p-value
Stroke (All events)	**437 / 64,327 6.8 (6.2-7.5)**	**204 / 30,098 6.8 (5.9-7.8)**	**57 / 9,197 6.2 (4.8-8.0)**	**1.04 (0.77-1.42) p=0.79**	**55 / 5,815 9.5 (7.3-12.3)**	**1.50 (1.11-2.05) P=0.008**	**121 / 19,216 6.3 (5.3-7.5)**	**1.50 (1.15-1.94) p=0.002**
Fatal stroke	68 / 65,908 1.0 (0.8-1.3)	35 / 30,926 1.1 (0.8-1.6)	≤4 / 9,597 0.4 (0.2-1.1)	0.44 (0.15-1.27) p=0.13	9 / 5,966 1.5 (0.8-2.9)	1.42 (0.67-3.00) p=0.36	20 / 19,420 1.0 (0.7-1.6)	2.22 (1.20-4.13) p=0.01
Hemorrhagic stroke	73 / 65,744 1.1 (0.9-1.4)	46 / 30,909 1.5 (1.1-2.0)	7 / 9,546 0.7 (0.3-1.5)	0.47 (0.20-1.08) p=0.07	≤4 / 5,930 0.5 (0.2-1.6)	0.39 (0.12-1.27) p=0.12	17 / 19,359 0.9 (0.5-1.4)	0.97 (0.51-1.86) p=0.94
Thrombotic stroke	212 / 65,106 3.3 (2.8-3.7)	88 / 30,496 2.9 (2.3-3.6)	28 / 9,377 3.0 (2.1-4.3)	1.18 (1.76-1.83) p=0.47	28 / 5,903 4.7 (3.3-6.9)	1.84 (1.19-2.86) p=0.006	68 / 19,330 3.5 (2.8-4.5)	1.82 (1.26-2.63) p=0.001
Unspecified stroke	56 / 65,680 0.9 (0.7-1.1)	24 / 30,799 0.8 (0.6-1.2)	7 / 9,531 0.7 (0.4-1.5)	1.06 (0.44-2.54) p=0.89	14 / 5,936 2.4 (1.4-4.0)	2.70 (1.38-5.29) p=0.004	9 / 19,415 0.5 (0.3-0.9)	1.30 (0.58-2.94) p=0.51
TIA	127 / 65,438 1.9 (1.6-2.3)	58 / 30,632 1.9 (1.5-2.5)	19 / 9,492 2.0 (1.3-3.1)	1.25 (0.73-2.14) p=0.40	19 / 5,939 3.2 (2.0-5.0)	1.80 (1.05-3.06) p=0.03	31 / 19,375 1.6 (1.0-2.3)	1.29 (0.78-2.11) p=0.32
Incident Stroke in patients WITHOUT registered recurrent Atrial Fibrillation								
Stroke	**114 / 21,125 5.4 (4.5-6.5)**	**44 / 7,388 6.0 (4.4-8.0)**	**15 / 3,551 4.2 (2.5-7.0)**	**0.91 (0.49-1.71) p=0.78**	**18 / 2,040 8.8 (5.5-14.0)**	**1.47 (0.84-2.61) p=0.18**	**37 / 8,145 4.5 (3.3-6.3)**	**1.50 (0.88-2.53) p=0.13**
CHA_2DS_2-VASc=0	14 / 4,419 3.2 (1.9-5.3)	≤4 / 501 6.0 (1.9-18.5)	≤4 / 162 6.2 (0.9-43.9)	1.19 (0.10-14.3) p=0.90	≤4 / 236 4.2 (0.9-30.1)	0.78 (0.07-8.23) p=0.84	9 / 3,514 2.5 (1.3-4.9)	0.22 (0.04-1.05) p=0.06
CHA_2DS_2-VASc=1	11 / 4,165 2.6 (1.4-4.8)	≤4 / 1,202 3.3 (1.2-8.9)	≤4 / 1,202 5.0 (1.6-15.5)	0.86 (1.17-4.48) p=0.86	0 / 466 0.0	N/A	≤4 / 1,899 2.1 (0.8-5.6)	0.68 (0.14-3.29) p=0.63
CHA_2DS_2-VASc=2	27 / 5,441 4.9 (3.4-7.2)	7 / 2,080 3.4 (1.6-7.1)	≤4 / 1,046 1.0 (0.1-6.8)	0.33 (0.04-2.90) p=0.32	8 / 612 13.1 (6.5-26.1)	3.68 (1.22-11.1) p=0.02	11 / 1,704 6.5 (3.6-11.6)	2.06 (0.73-5.79) p=0.17
CHA_2DS_2-VASc=3	21 / 4,028 5.2 (3.4-8.0)	12 / 1,915 6.3 (3.6-11.1)	≤4 / 1,049 2.9 (0.9-8.8)	0.53 (0.15-2.05) p=0.37	≤4 / 423 4.7 (1.2-18.8)	0.58 (0.12-2.83) p=0.51	≤4 / 640 6.2 (2.3-16.6)	1.12 (0.32-3.91) p=0.85
CHA_2DS_2-VASc>=4	41 / 3,077 13.3 (9.8-18.1)	18 / 1,691 10.6 (6.7-16.9)	7 / 696 10.1 (4.8-21.2)	1.62 (0.62-4.26) p=0.33	7 / 303 23.1 (10.9-48.4)	2.17 (0.87-5.37) p=0.09	9 / 388 23.2 (12.1-44.6)	2.83 (1.17-6.86) p=0.02
Incident Stroke WITH registered recurrent Atrial Fibrillation								
Stroke	**323 / 43,202 7.5 (6.7-8.3)**	**160 / 22,710 7.0 (6.0-8.2)**	**42 / 5,645 7.4 (5.5-10.1)**	**1.09 (0.77-1.55) p=0.62**	**37 / 3,775 9.8 (7.1-13.5)**	**1.48 (1.03-2.14) p=0.03**	**84 / 11,072 7.6 (6.2-9.4)**	**1.51 (1.11-2.04) p=0.007**
CHA_2DS_2-VASc=0	39 / 6,568 5.9 (4.3-8.1)	11 / 2,119 5.2 (3.0-9.4)	≤4 / 378 10.6 (3.9-28.2)	2.30 (0.72-7.37) p=0.16	5 / 496 10.1 (4.2-24.2)	1.78 (0.61-5.22) p=0.29	19 / 3,575 5.3 (3.4-8.3)	1.87 (0.82-4.27) p=0.14
CHA_2DS_2-VASc=1	55 / 8,729 6.3 (4.8-8.2)	27 / 3,938 6.9 (4.7-10.0)	5 / 945 5.3 (2.2-12.7)	1.05 (0.40-2.81) p=0.91	≤4 / 828 4.8 (1.8-12.8)	0.64 (0.22-1.86) p=0.42	19 / 3,017 6.3 (4.0-9.9)	0.86 (0.44-1.68) p=0.65
CHA_2DS_2-VASc=2	75 / 11,750 6.4 (5.1-8.0)	35 / 6,439 5.4 (3.9-7.6)	9 / 1,520 5.9 (3.1-11.4)	1.07 (0.50-2.30) p=0.87	11 / 1,199 9.2 (5.1-16.6)	1.69 (0.87-3.40) p=0.14	20 / 2,592 7.7 (5.0-12.0)	1.56 (0.85-2.84) p=0.15
CHA_2DS_2-VASc=3	69 / 9,062 7.6 (6.0-9.6)	39 / 5,588 7.0 (5.1-9.6)	9 / 1,436 6.3 (3.3-12.0)	0.94 (0.45-2.00) p=0.88	7 / 782 8.9 (4.3-18.8)	1.51 (0.66-3.43) p=0.33	14 / 1,256 11.1 (6.6-18.8)	2.48 (1.31-4.69) p=0.005
CHA_2DS_2-VASc>=4	85 / 7,094 12.0 (9.7-14.8)	48 / 4,625 10.4 (7.8-13.7)	15 / 1,366 11.0 (6.6-18.2)	1.10 (0.60-2.01) p=0.76	10 / 471 21.3 (11.4-39.5)	2.18 (1.09-4.37) p=0.03	12 / 632 19.0 (10.8-33.4)	1.94 (1.00-3.77) p=0.049

Antiplatelets: Aspirin or Clopidogrel. DOACs: Direct Oral Anticoagulants. HR: Hazard ratio vs. Warfarin as the reference with 95% Confidence Intervals (95% CI). IR: Incidence rates per 1000 Person-years of exposure (PYE). TIA: Transient Ischemic Attack.
The abbreviations and multivariable analyses as in Table 2.

Serious bleeding

In total, 585 (4.9%) patients suffered serious bleeding after discharge from first-time ablation; 53 (0.4%, IR:18/1000-PYE) events occurring within 90-days were censored from further analyses. Serious bleeding occurred in 354(2.9%, IR:11.9), 69 (0.6%, IR:7.5), 37 (0.3%, IR:6.5) and 72 (0.6%, IR:3.8) patients among warfarin, DOACs, antiplatelets and No-Treatment groups, respectively. In multivariable analyses, DOACs, antiplatelets and No-Treatment were associated with a significantly lower rate of serious bleeding compared with warfarin (Table-4). We detected this effect primarily in patients with registered AF recurrences. Standardized annual absolute risk difference and relative risk were significantly lower with DOACs vs warfarin (Table-6), while there was no difference between warfarin and DOACs in sensitivity analyses. We observed a non-significant trend for lower intracranial bleeding with DOACs (HR 0.47 $[0.20\text{-}1.08]_{95\%CI}$, p=0.07). Ad hoc analysis of patient characteristics at bleeding events (Supplementary Table-S5) showed that DOAC users were significantly older with fewer registered AF recurrences than warfarin users. Fatal bleeding occurred in 27 (0.2%) cases (18 intracranial, 9 gastro-intestinal) without any events with DOACs, and no difference between the groups.

Table 4. Serious Bleeding with subtypes according to exposure allocation during follow-up and stroke events according to AF recurrences by HAS-BLED score

	All events	Warfarin (reference)	DOACs		Antiplatelets		No-Therapy	
	N / PYE IR (95%CI)	N / PYE IR (95%CI)	N / PYE IR (95%CI)	HR (95%CI) p-value	N / PYE IR (95%CI)	HR (95%CI) p-value	N / PYE IR (95%CI)	HR (95%CI) p-value
Serious Bleeding	**532 / 63,800 8.3 (7.7-9.1)**	**354 / 29,840 11.9 (10.7-13.2)**	**69 / 9,193 7.5 (5.9-9.5)**	**0.70 (0.54-0.92) p=0.011**	**37 / 5,719 6.5 (4.7-8.9)**	**0.58 (0.41-0.82) p=0.002**	**72 / 19,049 3.8 (3.0-4.7)**	**0.52 (0.39-0.69) p<0.0001**
Fatal	27 / 65,958 0.4 (0.3-0.6)	15 / 30,950 0.5 (0.3-0.8)	0 / 9,602 0.0	N/A	≤4 / 5,975 0.7 (0.3-1.8)	1.24 (0.40-3.87) p=0.71	8 / 19,430 0.4 (0.2-0.8)	1.68 (0.63-4.44) p=0.29
Intracranial	73 / 65,744 1.1 (0.9-1.4)	46 / 30,909 1.5 (1.1-2.0)	7 / 9,546 0.7 (0.3-1.5)	0.47 (0.20-1.08) p=0.07	≤4 / 5,930 0.5 (0.2-1.6)	0.39 (0.12-1.27) p=0.12	17 / 19,359 0.9 (0.5-1.4)	0.97 (0.51-1.86) p=0.94
Gastro-Intestinal	218 / 65,146 3.4 (3.0-3.8)	133 / 30,528 4.4 (3.7-5.2)	31 / 9,435 3.3 (2.3-4.7)	0.77 (0.51-1.16) p=0.22	24 / 5,891 4.1 (2.7-6.1)	1.11 (0.71-1.73) p=0.64	30 / 19,291 1.5 (1.1-2.2)	0.68 (0.44-1.05) p=0.09
Urogenital	123 / 65,444 1.9 (1.6-2.2)	84 / 30,687 2.7 (2.2-3.4)	18 / 9,508 1.9 (1.2-3.0)	0.75 (0.44-1.28) p=0.29	9 / 5,903 1.5 (0.8-2.9)	0.55 (0.27-1.10) p=0.09	12 / 19,346 0.6 (0.4-1.1)	0.33 (0.17-0.63) p=0.001
Serious Bleeding events in patients WITHOUT registered recurrent Atrial Fibrillation								
Serious Bleeding	139 / 20,973 6.6 (5.6-7.8)	73 / 7,316 10.0 (7.9-12.6)	23 / 3,545 6.5 (4.3-9.8)	0.79 (0.47-1.31) p=0.36	12 / 2,054 5.8 (3.3-10.3)	0.60 (0.32-1.11) p=0.11	31 / 8,058 3.8 (2.7-5.5)	0.85 (0.52-1.40) 0.53
HAS-BLED=0	8 / 3,710 2.2 (1.1-4.3)	≤4 / 432 6.9 (2.2-21.5)	0 / 179 0.0	N/A	0 / 134 0.0	N/A	5 / 2,964 1.7 (0.7-4.1)	0.35 (0.05-2.26) p=0.27
HAS-BLED=1	24 / 6,195 3.9 (2.6-5.8)	12 / 1,834 6.5 (3.7-11.5)	≤4 / 1,056 2.8 (0.9-8.8)	0.35 (0.09-1.36) p=0.13	≤4 / 473 8.5 (3.2-22.5)	1.09 (0.31-3.76) p=0.89	5 / 2,833 1.8 (0.7-4.2)	0.47 (0.15-1.46) p=0.19
HAS-BLED=2	56 / 7,193 7.8 (6.0-10.1)	30 / 3,152 9.5 (6.7-13.6)	11 / 1,539 7.1 (4.0-12.9)	1.14 (0.53-2.46) p=0.73	≤4 / 876 3.4 (1.1-10.6)	0.30 (0.09-1.02) p=0.054	12 / 1,625 7.4 (4.2-13.0)	1.01 (0.48-2.11) p=0.97
HAS-BLED=3	39 / 3,078 12.7 (9.3-17.3)	19 / 1,470 12.9 (8.2-20.3)	7 / 610 11.5 (5.5-24.1)	1.00 (0.39-2.59) p=0.98	5 / 475 10.5 (4.4-25.3)	0.96 (0.35-2.67) p=0.94	8 / 522 15.3 (7.7-30.6)	1.98 (0.79-4.97) p=0.14
HAS-BLED>=4	12 / 797 15.1 (8.5-26.5)	9 / 428 21.1 (11.0-40.4)	≤4 / 160 12.5 (3.1-50.0)	1.18 (0.16-8.31) p=0.86	0 / 95 0.0	N/A	≤4 / 114 8.8 (1.2-62.3)	1.01 (0.12-8.71) p=0.99
Incident Serious Bleeding events in patients WITH registered recurrent AFLI								
Serious Bleeding	393 / 42,827 9.2 (8.3-10.1)	281 / 22,524 12.5 (11.1-14.0)	46 / 5,648 8.1 (6.1-10.9)	0.70 (0.50-0.97) p=0.03	25 / 3,665 6.8 (4.6-10.1)	0.56 (0.37-0.86) P=0.007	41 / 10,991 3.7 (2.7-5.1)	0.42 (0.29-0.60) P<0.0001
HAS-BLED=0	18 / 5,125 3.5 (2.2-5.6)	14 / 1,621 8.6 (5.1-14.6)	≤4 / 312 3.2 (0.5-22.7)	0.32 (0.04-2.66) P=0.29	0 / 322 0.0	N/A	≤4 / 2,869 1.0 (0.3-3.2)	0.11 (0.02-0.48) P=0.003
HAS-BLED=1	78 / 12,811 6.1 (4.9-7.6)	52 / 6,124 8.5 (6.5-11.1)	10 / 1,515 6.6 (3.5-12.3)	0.80 (0.39-1.65) P=0.55	6 / 986 6.1 (2.7-13.5)	0.68 (0.29-1.62) P=0.39	10 / 4,187 2.4 (1.3-4.4)	0.26 (0.13-0.55) P<0.0001
HAS-BLED=2	143 / 15,507 9.2 (7.8-10.9)	100 / 8,930 11.2 (9.1-13.6)	17 / 2,338 7.3 (4.5-11.7)	0.76 (0.45-1.28) P=0.31	9 / 1,376 6.5 (3.4-12.6)	0.58 (0.29-1.16) p=0.12	17 / 2,863 5.9 (3.7-9.6)	0.61 (0.35-1.06) p=0.08
HAS-BLED=3	127 / 7,807 16.3 (13.6-19.4)	94 / 4,775 19.7 (16.1-24.1)	17 / 1,240 13.7 (8.5-22.0)	0.80 (0.47-1.37) p=0.43	10 / 839 11.9 (6.4-22.2)	0.67 (0.35-1.31) p=0.24	6 / 953 6.3 (2.8-14.0)	0.34 (0.15-0.80) p=0.014
HAS-BLED>=4	27 / 1,578 17.1 (11.7-25.0)	21 / 1,074 19.6 (12.8-30.0)	≤4 / 242 4.1 (0.6-29.3)	0.15 (0.02-1.16) p=0.07	0 / 142 0.0	N/A	5 / 120 41.8 (17.4-100)	2.29 (0.82-6.40) p=0.11

The abbreviations and multivariable analyses as in Table 2.

Cardiovascular death

We identified 447 (3.7%) cardiovascular death after discharge from first-time ablation; 44 (0.3%, IR:16.3/1000-PYE) events occurring within 90-days were censored from further analyses (Supplementary Table-S10). Cardiovascular death occurred in 192 (1.6%, IR:6.2), 37 (0.3%, IR:3.9), 52 (0.4%, IR:8.7), 122 (1%, IR:6.3) patients among warfarin, DOACs, antiplatelets and No-Treatment groups, respectively (Table-5). We observed no difference between DOACs and warfarin in multivariable analyses, consistent with standardized absolute risk difference and sensitivity analyses. Antiplatelets and No-Treatment were associated with a significantly higher rate of cardiovascular death. Patients using DOACs and antiplatelets had comparable age and they were older than other groups, whereas DOAC users had longer follow-up, more AF recurrences and more patients with CHA_2DS_2-VASc score≥2 (Supplementary Table-S6).

Major Adverse Cardiovascular Events (MACE)

We detected 1206 (10%) MACE cases; 142 (1.2%, IR 51) events occurring within 90-days were censored from further analyses. MACE occurred in 586 (4.9%, IR:20.1), 129 (1.1%, IR:14.5), 108 (0.9%, IR:19.2) and 241 (2%, IR:12.7) patients among warfarin, DOACs, antiplatelets and No-Treatment groups, respectively (Table-5). We observed no difference among the groups or between DOACs and warfarin in multivariable analyses, consistent with standardized absolute risk

and sensitivity analyses. Ad-hoc analyses showed that DOAC users were older and comprised more patients with CHA_2DS_2-VASc score≥2, whereas No-Treatment group was younger with the least comorbidity and longest follow-up (Supplementary Table-S7).

Table 5. Cardiovascular death and MACE *according to exposure allocation during follow-up and events by AF recurrences.*

	All population	Warfarin (reference)	DOACs		Antiplatelets		No-Treatment	
	N / PYE IR (95%CI)	N / PYE IR (95%CI)	N / PYE IR (95%CI)	HR (95%CI) p-value	N / PYE IR (95%CI)	HR (95%CI) p-value	N / PYE IR (95%CI)	HR (95%CI) p-value
Cardiovascular death	403 / 65,958 6.1 (5.5-6.7)	192 / 30,950 6.2 (5.4-7.1)	37 / 9,602 3.9 (2.8-5.3)	0.87 (0.61-1.25) p=0.46	52 / 5,975 8.7 (6.6-11.4)	1.42 (1.04-1.94) p=0.027	122 / 19,403 6.3 (5.3-7.5)	2.77 (2.16-3.56) p<0.0001
without registered recurrent AF	161 / 21,402 7.5 (6.5-8.8)	73 / 7,515 9.7 (7.7-12.2)	8 / 3,625 2.2 (1.1-4.4)	0.44 (0.21-0.96) p=0.038	29 / 2,088 13.8 (9.6-20.0)	1.48 (0.95-2.30) p=0.082	51 / 8,174 6.2 (4.7-8.2)	2.62 (1.76-3.91) p<0,0001
with registered recurrent AF	242 / 44,556 5.4 (4.8-6.2)	119 / 23,435 5.1 (4.3-6.1)	29 / 5,977 4.8 (3.4-7.0)	1.15 (0.76-1.75) p=0.49	23 / 3,887 5.9 (3.9-8.9)	1.29 (0.82-2.03) p=0.26	71 / 11,257 6.3 (5.0-8.0)	2.89 (2.01-3.98) p<0,0001
MACE	1064 / 62,486 17.0 (16.0-18.1)	586 / 29,087 20.1 (18.6-21.8)	129 / 8,882 14.5 (12.2-17.3)	0.86 (0.70-1.05) p=0.148	108 / 5,611 19.2 (15.9-23.2)	1.04 (0.84-1.27) p=0.75	241 / 18,905 12.7 (11.2-14.4)	1.10 (0.93-1.31) p=0.26
without registered recurrent AF	322 / 20,749 15.5 (13.9-17.3)	150 / 7,210 20.8 (17.7-24.4)	38 / 3,488 10.9 (7.9-15.0)	0.78 (0.53-1.14) p=0.207	44 / 2,012 21.9 (16.3-29.4)	1.11 (0.79-1.58) p=0.54	90 / 8,038 11.2 (9.1-13.8)	1.35 (1.00-1.84) p=0.053
with registered recurrent AF	742 / 41,737 17.7 (16.5-19.1)	436 / 21,876 19.9 (18.1-21.9)	91 / 5,393 16.8 (13.7-20.7)	0.93 (0.73-1.17) p=0.53	64 / 3,599 17.7 (13.9-22.7)	0.97 (0.75-1.27) p=0.85	151 / 10,868 13.9 (11.8-16.3)	1.03 (0.84-1.28) p=0.79

MACE: Major Adverse Cardiovascular Events including stroke, serious bleeding and Cardiovascular Death. The abbreviations and multivariable analyses as in Table 2.

Table 6. Comparison of warfarin and DOACs by standardized absolute risk difference and relative risk with bias-corrected bootstrap 95% confidence intervals

	Standardized Absolute Risk Difference per year	p-value	Relative Risk	Bias-corrected Bootstrap 95% Confidence Intervals*
Stroke	0.05% (-0.08% to 0.17%)	0.43	1.14	0.82-1.57
Serious Bleeding	-0.15% (-0.27% to -0.03%)	0.017	0.75	0.56-0.97
Cardiovascular Death	-0.16% (-0.12% to 0.09%)	0.76	0.95	0.75-1.49
MACE	-0.08% (-0.28% to 0.13%)	0.46	0.92	0.77-1.25

MACE: Major Adverse Cardiovascular Events including stroke, serious bleeding and Cardiovascular Death.
The reference is warfarin for standardized absolute risk difference and relative risk analyses adjusted for year of inclusion, time-dependent age, sex, hypertension, heart failure, diabetes mellitus, vascular disease, renal disease, alcohol abuse, liver disease, previous stroke, previous bleeding and recurrent AF. *500 repetitions.

Discussion

We compared DOACs, antiplatelets and No-Treatment to warfarin regarding the long-term cardiovascular outcomes in a nationwide cohort of 12,010 patients undergoing first-time AF ablation in Denmark. Our data showed that (i) overall stroke rates were low, higher with recurrent AF and escalating with increasing CHA_2DS_2-VASc scores; (ii) DOACs were comparable to warfarin regarding stroke, cardiovascular death and MACE, with a significantly lower rate of serious bleeding than warfarin; (iii) Antiplatelets and No-Treatment were associated with a significantly lower rate of serious bleeding and a significantly higher rate of stroke and cardiovascular death than warfarin.

The available literature on long-term outcomes with oral anticoagulants in ablated AF patients predominantly pertains to warfarin, with a large evidence gap regarding DOACs. The CABANA trial reported low stroke rates (0.1% vs 0.7%) with catheter ablation and drug therapy over a 4-year follow-up, respectively, and the corresponding bleeding rates were higher (3.0% vs 3.7%).[3]

Stroke

We found low stroke rates on long-term follow-up after AF ablation similar to the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement and previous observational studies.[18–24] Our data enriches this by showing that the stroke rate remains low on long-term follow-up and without a significant difference between DOACs and warfarin, while antiplatelets and No-Treatment expectedly pose significantly higher stroke rates, particularly with AF recurrences, even in younger patients with less comorbidity. Phase 3 randomized trials[8–11] revealed higher stroke rates (1.10% to 2.10% annually) over a shorter median follow-up (1.8 to 2.8 years) in older AF patients, in which ablated AF patients were not involved. Further, a recent meta-analysis[4] demonstrated that AF ablation significantly reduced the stroke risk compared to the medically treated AF population; HR 0.63 $(0.56\text{-}0.70)_{95\%CI}$. The low stroke rates in our data possibly reflect a relatively young and healthy population, besides the aptly anticoagulated majority post-ablation.

Stroke rates with DOACs and warfarin were virtually similar with lower crude rates of fatal and hemorrhagic stroke with DOACs, without a statistical difference, compelling careful interpretation, equally for the marginally higher stroke rates among patients with recurrent AF than those without (Table-3). Further, the stroke rates among anticoagulated post-ablation patients with

CHA_2DS_2-VASc score<5 was markedly lower than that considered by current guidelines, among unselected AF patients, suitable for oral Anticoagulation(1). In addition, escalating stroke rates with increasing scores reflect that the CHA_2DS_2-VASc score may sufficiently discriminate the truly low-risk patients and could consequently serve as a proper measure of risk stratification tool for stroke after AF ablation.

Serious bleeding

In Phase-3 trials, the major and clinically relevant non-major bleeding annual rates ranged from 3.09% to 14.5% with warfarin and 1.61% to 14.9% for DOACs, with a significantly lower bleeding risk with Apixaban and Edoxaban than warfarin. In the CABANA trial, this risk was 3.0% for ablated AF patients, where 52%, 23% and 43% of the patients were using warfarin, dabigatran and Factor Xa-inhibitors, respectively. Our results displayed lower serious bleeding rates, i.e. 0.75% for DOACs and 1.2% for warfarin annually; the latter is comparable to our previous findings regarding warfarin.[16] In the CABANA and the Phase-3 trials, the average age was 68-years and 70-73 years, respectively. Our study comprised younger patients whilst we defined serious bleeding based on hospital admissions, potentially underestimating the event rates, which suggests a probable explanation for the lower bleeding rates.

Our results expectedly indicated that serious bleeding rates were significantly lower for antiplatelets and No-Treatment. Moreover, DOACs was also associated with a significantly lower standardized annual absolute risk and relative risk, acknowledging the low event rates. Although the sensitivity analyses did not sustain these main results regarding DOACs vs warfarin, DOAC users at the time of the event were significantly older with a higher comorbidity burden than warfarin users (e.g. previous bleeding and vascular diseases), offering a plausible justification (Supplementary Table-8a, Table-9a).

Cardiovascular death and MACE

The CABANA trial revealed that the primary endpoint (cumulative risk of death, disabling stroke, bleeding or cardiac arrest) occurred in 8% of the ablation group over a median follow-up of 48.5 months. The annual risk of cardiovascular death and MACE in our data were 0.6% and 1.7%, respectively, lower than that of the CABANA trial, presumably rendered by the younger population with less comorbidity despite similar median follow-up. There was no significant difference between DOACs and warfarin, although DOAC users were older and had longer follow-up duration until both endpoints (Supplementary Tables S-6, S-7). Both antiplatelets and No-Treatment, as expected, were associated with a significantly higher rate of cardiovascular death compared to warfarin. However, we found no difference in the composite endpoint of MACE in these groups, most probably driven primarily by the lower cumulative bleeding risk.

Anticoagulation

Recurrent AF post-ablation is well recognized[1,2] and the anticoagulation suspension is not safe in high-risk patients.[19–21] In addition to antiplatelet overuse across all risk strata, we observed low-risk patients' overexposure and high-risk patients' underexposure to oral anticoagulation. Although we detected a trend toward international recommendations in recent years, evident inconsistency between real-life practice and the guidelines requires vigilance. Whilst oral anticoagulants are associated with higher bleeding risk and lower quality of life, our population is not naïve to anticoagulants, representing experienced users proven to have tolerated the treatment in terms of bleeding risk, thereby selecting for a low-risk population possibly leading to underestimated bleeding rates.

In our previous study,[16] we summarized the existing literature until 2014, and we recapitulated the multiple recent reports comparing On-OAC vs. Off-OAC in Supplementary table s11. Although these studies provide consistent conclusions regarding the increased bleeding risk associated with warfarin use, the safety of whether to discontinue OAC remains contradictory in terms of risk of stroke or thromboembolism, including the results from most recent four meta-analyses. Atti et al. studied 3,436 patients after an apparently successful AF ablation in patients with CHA_2DS_2-VASc ≥2 and concluded that OAC discontinuation appears to be safe in highly selected and closely monitored patients.[22] Proietti et al. investigated 25,177 patients and found that the risk-benefit ratio favoured the suspension of OAC after successful AF ablation even in patients at moderate-high risk patients.[23] Liu et al. analyzed 11,148 patients from prospective studies and deduced that it may be safe to discontinue OAC therapy in patients after successful AF ablation.[24] However, Romero et al. found in 3956 patients that the continuation of OAC in patients with CHA_2DS_2-VASc ≥2 is associated with a significantly decreased thromboembolic risk and a favourable net clinical benefit while continued

OAC offers no benefit with CHA_2DS_2-VASc ≤1.[25] Of note, the most recent consensus statement on catheter ablation of atrial fibrillation from 2017 suggest either frequent or continuous ECG monitoring to screen for AF recurrences if discontinuation of anticoagulation is considered based on patient values and preferences.[2]

The current guidelines for the management of Atrial fibrillation states that low-risk patients (CHA_2DS_2-VASc score of 0 for males or score of 1 for females) should not be offered antithrombotic therapy due to consistently low rates of ischaemic stroke or mortality (<1%/year). Our results support these statements in that the annual rates of stroke or cardiovascular death are lower than 1% for low-risk patients 90-days beyond AF ablation, and thereby no antithrombotic treatment is indicated. These guidelines recommend oral anticoagulants for stroke prevention in AF patients with CHA_2DS_2-VASc score ≥2 in men or ≥3 in women, advising DOACs preferred to warfarin except for patients with moderate-to-severe mitral stenosis or mechanical heart valves. Likewise, the CHA_2DS_2-VASc stroke risk factors should determine whether to continue oral anticoagulants beyond two months following AF ablation rather than rhythm status. DOACs, given the safety and effectiveness in Phase-3 trials as well as our results, remain a more convenient anticoagulation choice, also in light of the ease of use compared to warfarin. Thus, DOACs are probably a better alternative than warfarin in the long term among post-ablation AF patients with oral anticoagulation indication.

Limitations & strengths

The main limitation of our data pertains to its retrospective observational nature with potential confounders. Essential data such as the AF nature (paroxysmal vs persistent) or the clinical decision to choose DOACs or warfarin was missing. Here, we could not identify the motivation behind why some high-risk patients discontinued treatment or received antiplatelets or some low-risk patients overused anticoagulants. No information about INR values, the quality of warfarin therapy (i.e., time in therapeutic range) or DOAC compliance were available. Although we had previously validated the recurrent AF definition, we probably underestimated the numbers because the definition combined AF related hospitalizations and re-ablation procedures. Similarly, the lack of blood pressure or blood glucose levels possibly has resulted in missing the cases with undiagnosed hypertension and diabetes mellitus. Further, we could not detect bleeding events treated either by practitioners or in emergency-care settings without hospital admissions, or events not registered as the primary diagnoses, probably generating underestimated bleeding rates. Although we used age was as a time-dependent variable, long follow-up duration exposed this population to a higher burden of risk factors developing over time. Whilst the epidemiological method involves such shortcomings, our study demonstrates real-life clinical practice on a large cohort of nationwide scale with an unselected ablation population over a long-term follow-up investigated with previously validated methodology and endpoints. Besides, we studied only the primary diagnoses to reinforce our certainty so that the hospital admissions were due to our endpoints and not a record of a previous registry or secondary complication. Further, the Danish registries incorporate all residents regardless of participation in the labour market and are therefore not influenced by selection bias related to the inclusion of chosen age groups, hospitals, or insurance systems.

Conclusions

Our data indicate a better bleeding risk profile with DOACs than with warfarin but no difference for the endpoints of stroke, cardiovascular death, or the composite endpoint of MACE. Antiplatelets and No-Treatment compared with warfarin appear hazardous due to higher rates of stroke and cardiovascular death. We suggest a cautious interpretation of our findings due to lower-than-expected event rates regarding the predicted impact among treatment groups.

Funding

This work was supported by the Danish Heart Foundation (grant number 12-04-R90-A3820-22711).

Conflict of interest: none declared. G.H.G. is supported by an independent research grants from Boehringer Ingelheim and Bristol Myers Squibb. M.A. is consultant for Biosense Webster and receives educational grants from Abbott.

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SUPPLEMENTARY MATERIAL

Table S1. Definition of comorbidity and concomitant medication.

Comorbidity	**Definition**	**Specification (ICD-10* and ATC**)**
Heart failure	Previous discharge diagnosis and treatment with loop diuretics at baseline	**ICD-10:** I11, I13, I42, I50 **ATC:** C03C
Hypertension	Discharge diagnosis or combination treatment with two different antihypertensive medications at baseline	**ICD-10:** I10-13, I15 Adrenergic α-antagonists [**ATC:** C02A, C02B, C02C], Non-loop-diuretics [**ATC:** C02L, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52], vasodilators [**ATC:** C02DB, C02DD, C02DG, C04, C05], Beta- blockers excluding sotalol [**ATC:** C07] Calcium channel blockers [**ATC:** C07F, C08, C09BB, C09DB], Renin-angiotensin system inhibitors [**ATC:** C09].
Vascular disease	Discharge diagnosis	Coronary artery disease, previous periphery artery disease, or cerebrovascular disease
Previous AMI	Discharge diagnosis	**ICD-10:** I21-23
Ischemic Heart Disease	Discharge diagnosis	**ICD-10:** I20, I24-25
Cerebrovascular disease	Discharge diagnosis	**ICD-10:** I60-69
Peripheric Artery Disease	Discharge diagnosis	**ICD-10:** I70, I74
Previous Stroke	Discharge diagnosis	**ICD-10:** I61, I63-64
Transient Ischemic Attack	Discharge diagnosis	**ICD-10:** G458-459
Previous Bleeding	Discharge diagnosis	**ICD-10:** D500, D62, E078B, E274B, G951A, H052A, H113, H313, H356, H431, H450, I312, I60-I62, I692, I850, I864A, J942, K228F, K250, K252, K254, K256, K260, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K298A, K625, K638B, K638C, K661, K838F, K868G, K920-922, N02, R04, R31, R58
Renal failure	Discharge diagnosis	**ICD-10:** E102, E112, E132, E142, I12-13, M319, M321B, N03-N08, N11-19, N158-159, N26, R34, Q612-613, Q615-619, Z992
Chronical Obstructive Pulmonary Disease	Discharge diagnosis	**ICD-10:** J44
Diabetes mellitus	Glucose lowering medication at baseline	**ATC:** A10
Alcohol abuse	Discharge diagnosis and reported unfavourable alcohol consumption	**ICD-10:** E244, E52, F1, G312, G621, G721, I426, K292, K70, K860, O354, T51, Z714, Z721
Liver disease	Discharge diagnoses of liver cancer, chronic liver disease, cirrhosis, or hepatitis	**ICD-10:** B150, B160, B190, K70-77
Concomitant medication**		
Oral anticoagulants	Warfarin	B01AA03
Oral anticoagulants	DOACs	B01AF0
Dabigatran		B01AE07
Rivaroxaban		B01AE01
Apixaban		B01AE02
Edoxaban		B01AE03
Aspirin	Acetylsalicylic acid	B01AC06
Clopidogrel		B01AC04
Ticagrelor		B01AC24
Class Ic AADs	Flecainide & Propafenone	C01BC0
Class III AADs	Amiodarone & Dronedarone	C01BD0
Amiodarone		C01BD01
Dronedarone		C01BD07
Sotalol		C07AA07
Beta-blockers	Excluding Sotalol	C07
Calcium Channel Blocker		C08D
Anti-diabetics		A10
Renin-Angiotensin system inhibitors		C09
Spironolactone		C03D
Thiazide diuretics		C03A
Loop diuretics		C03CA01

Statins	C10A
NSAID	M01A

AADs, anti-arrhythmic drugs; **NSAID,** Non-steroidal anti-inflammatory drugs.
ICD-10: The International Classification of Diseases system, 10. Revision
ATC: Anatomical Therapeutic Chemical system

*The discharge diagnoses were considered valid if registered within 10 years before inclusion.
** Baseline use of medication was considered valid if prescriptions were claimed within 180 days before inclusion.

Table S2. Definition of primary effectiveness and secondary safety endpoints.

Primary endpoint	**Definition**	***Specification (ICD-10)***
Stroke	Discharge diagnosis of hemorrhagic, ischemic, or unspecified stroke or transient ischemic attack (TIA) resulting in hospitalization recorded only as a primary discharge diagnosis.	Hemorrhagic Stroke: I61-62; Thrombotic Stroke: I63; Unspecified Stroke: I64; TIA: G458, G459
Secondary endpoints		
Serious bleeding	Discharge diagnosis of intracranial, intraocular, gastrointestinal, urinary or respiratory tract bleeding resulting in hospitalization recorded only as a primary discharge diagnosis.	**ICD-10:** D500, D62, E078B, E274B, G951A, H052A, H113, H313, H356, H431, H450, I312, I60-I62, I692, I850, I864A, J942, K228F, K250, K252, K254, K256, K260, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K298A, K625, K638B, K638C, K661, K838F, K868G, K920-922, N02, R04, R31, R58
Cardiovascular death (CVD)	Death due to any cardiovascular event resulting in hospitalization and death recorded in the National Causes of Death registry only as a primary ICD-10 diagnosis.	**ICD-10:** I00-99
Major adverse cardiovascular events (MACE)	Composite of stroke, serious bleeding or cardiovascular death.	Any discharge diagnosis enclosed above within primary or secondary endpoints

Table S3. The median duration (25%-75% Interquartile range) of exposure by treatment allocation according to CHA_2DS_2-VASc score

All population	**Warfarin**	**DOACs**	**Antiplatelets**	**No-Treatment**	**p-value***
CHA_2DS_2-VASc =0	2.3 (0.9-6.8)	0.8 (0.3-2.0)	4.7 (2.4-6.6)	3.3 (1.2-6.3)	0.0001
CHA_2DS_2-VASc =1	4.9 (2.2-8.9)	1.9 (1.0-3.9)	4.5 (2.7-7.0)	2.5 (0.7-5.2)	0.0001
CHA_2DS_2-VASc ≥2	6.2 (3.4-9.6)	2.2 (1.1-4.0)	4.8 (2.4-8.0)	1.2 (0.3-3.9)	0.0001
Patients without registered recurrent AF					
CHA_2DS_2-VASc =0	0.4 (0.2-1.5)	0.5 (0.1-1.2)	5.1 (2.4-6.9)	2.2 (0.9-6.9)	0.0001
CHA_2DS_2-VASc =1	3.4 (1.0-6.0)	1.5 (0.8-3.0)	5.4 (3.4-8.0)	2.2 (0.6-5.0)	0.0001
CHA_2DS_2-VASc ≥2	4.7 (2.1-7.6)	1.6 (0.8-3.0)	6.0 (2.9-9.2)	0.9 (0.2-3.3)	0.0001
Patients with registered recurrent AF					
CHA_2DS_2-VASc =0	3.2 (1.4-8.0)	1.2 (0.6-3.1)	4.6 (2.5-7.0)	4.1 (1.8-7.1)	0.0001
CHA_2DS_2-VASc =1	5.8 (2.7-9.4)	2.2 (1.2-4.0)	4.2 (2.2-6.8)	2.9 (0.9-6.0)	0.0001
CHA_2DS_2-VASc ≥2	6.9 (4.0-10.0)	2.6 (1.5-4.5)	4.2 (2.0-7.0)	1.4 (0.4-4.3)	0.0001

*Kruskal-Wallis' equality-of-populations test.

Table s4. Baseline characteristics of patients with stroke by respective treatment allocation at the time of the event.

	All patients	Warfarin	DOACs	Antiplatelets	No-Therapy	p-value
Number of patients, n (%) *	437 (3.6)	204 (46.7)	57 (13)	55 (12.6)	121 (27.7)	<0.0001
Median age at the time of the event, years (IQR) †	67 (62-74)	68 (62-74)	70 (65-76)	66 (62-72)	64 (57-71)	0.0008
Median follow-up duration, years (IQR) †	4.0 (2.0-7.0)	3.9 (1.8-6.1)	3.7 (1.7-8.0)	3.7 (2.2-6.1)	4.7 (2.3-8.2)	<0.0001
Median AF duration, years (IQR) †	2.3 (0.7-5.9)	2.5 (0.9-5.7)	2.6 (0.8-8.1)	1.3 (0.4-5.4)	2.2 (0.6-5.8)	<0.0001
Recurrent AF, n (%)	323 (73.9)	160 (78.4)	42 (73.7)	37 (67.3)	84 (69.4)	0.20
Age <65, n (%)	169 (38.7)	70 (34.3)	13 (22.8)	19 (34.5)	67 (55.3)	<0.0001
Age 65-74, n (%)	180 (41.2)	90 (44.1)	26 (45.6)	26 (47.3)	38 (31.4)	0.07
Age ≥75, n (%)	88 (20.1)	44 (21.6)	18 (31.6)	10 (18.2)	16 (13.2)	0.03
Female, n (%)	115 (26.3)	60 (29.4)	12 (21.1)	17 (30.9)	26 (21.5)	0.27
Comorbidity, n (%)						
Congestive Heart Failure	73 (16.7)	32 (15.7)	11 (19.3)	12 (21.8)	18 (14.9)	0.63
Arterial hypertension	316 (72.3)	164 (80.4)	40 (70.2)	41 (74.5)	71 (58.7)	<0.0001
Diabetes Mellitus	29 (6.6)	11 (5.4)	8 (14.0)	6 (10.9)	≤4	0.02
Previous Stroke	58 (13.3)	31 (15.2)	10 (17.4)	≤4	13 (10.7)	0.27
Vascular disease	127 (29.6)	67 (32.8)	20 (35.1)	19 (34.5)	21 (17.4)	0.01
Previous bleeding	34 (7.8)	16 (7.8)	7 (12.3)	≤4	8 (6.6)	0.52
Renal failure	13 (3.0)	5 (2.5)	≤4	≤4	≤4	0.70
Liver disease	≤4	≤4	≤4	≤4	≤4	0.484
Alcohol abuse	20 (4.6)	7 (3.4)	≤4	≤4	9 (7.4)	0.27
CHA_2DS_2-VASc score, n (%)						
Low risk (Score=0)	53 (12.1)	14 (6.9)	5 (8.8)	6 (10.9)	28 (23.1)	<0.0001
Intermediate risk (Score=1)	66 (15.1)	31 (15.2)	8 (14.0)	≤4	23 (19.1)	0.24
High risk (Score ≥ 2)	318 (72.8)	159 (77.9)	44 (77.2)	45 (81.8)	70 (57.8)	<0.0001

* Row percentages. The abbreviations and multivariable analyses as in Table2.

Table s5. Baseline characteristics of patients with serious bleeding by respective treatment allocation at the time of the event.

	All patients	Warfarin	DOACs	Antiplatelets	No-Therapy	P-value
Number of patients, n (%) *	532 (4.4)	354 (66.5)	69 (13)	37 (5.9)	72 (13.5)	<0.0001
Median age at the time of the event, years (IQR) †	69 (63-74)	68 (62-74)	73 (69-78)	68 (63-73)	68 (60-72)	<0.0001
Median follow-up duration, years (IQR) †	3.8 (1.4-6.9)	3.3 (1.2-6.6)	4.6 (2.0-8.3)	3.4 (1.7-6.6)	4.9 (2.0-7.7)	0.02
Median AF duration, years (IQR) †	3.0 (0.9-6.5)	3.3 (1.0-6.5)	3.2 (1.1-7.7)	2.1 (0.7-5.0)	2.8 (0.8-5.0)	0.19
Recurrent AF, n (%)	393 (73.8)	281 (79.4)	46 (66.7)	25 (67.6)	41 (56.9)	<0.0001
Age ≤65, n (%)	168 (31.6)	123 (34.7)	8 (11.6)	11 (29.3)	26 (36.1)	0.002
Age 65-74, n (%)	249 (46.8)	162 (45.8)	34 (49.3)	19 (51.4)	34 (47.2)	0.88
Age ≥75, n (%)	115 (21.6)	69 (19.5)	27 (39.1)	7 (18.9)	12 (16.7)	0.002
Female, n (%)	138 (25.9)	93 (26.2)	17 (24.6)	9 (24.3)	19 (264)	0.98
Comorbidity, n (%)						
Congestive Heart Failure	95 (17.8)	65 (18.4)	13 (18.8)	≤4	13 (18.1)	0.71
Arterial hypertension	417 (78.4)	287 (81.0)	56 (81.2)	30 (81.1)	44 (61.1)	0.002
Diabetes Mellitus	43 (8.1)	28 (7.9)	≤4	5 (13.5)	7 (9.7)	0.39
Previous Stroke	51 (9.6)	41 (11.6)	≤4	≤4	6 (8.3)	0.10
Vascular disease	150 (28.2)	103 (29.1)	18 (26.1)	10 (27.0)	19 (26.4)	0.93
Previous bleeding	72 (13.5)	50 (14.1)	11 (15.6)	0 (0)	11 (15.3)	0.09
Renal failure	16 (3.0)	10 (2.8)	≤4	≤4	≤4	0.13
Liver disease	8 (1.5)	5 (1.4)	≤4	≤4	≤4	0.14
Alcohol abuse	19 (3.6)	15 (4.2)	≤4	≤4	≤4	0.66
HAS-BLED score, n (%)						
Low risk (Score ≤ 1)	128 (34,5)	81 (22.8)	14 (20.3)	10 (27.0)	23 (31.9)	0.32
Intermediate risk (Score=2)	199 (37.4)	130 (36.7)	28 (40.6)	12 (32.4)	29 (40.3)	0.80
High risk (Score ≥ 3)	205 (38.5)	143 (40.4)	27 (39.1)	15 (40.5)	20 (27.8)	0.25

* Row percentages. The abbreviations and multivariable analyses as in Table2.

Table s6. Baseline characteristics of patients with cardiovascular death by respective treatment allocation at the time of the event.

	All patients	Warfarin	DOACs	Antiplatelets	No-Therapy	P-value
Number of patients, n (%) *	403 (3.4)	192 (47.6)	37 (9.2)	52 (12.9)	122 (30.3)	<0.0001
Median age at the time of the event, years (IQR)	71 (65-77)	70 (64-76)	74 (71-80)	74 (68-81)	70 (63-76)	0.005
Median follow-up duration, years (IQR)	4.8 (2.1-7.4)	4.4 (2.1-7.2)	6.5 (2.7-9.0)	4.1 (2.0-6.1)	5.5 (2.1-7.5)	0.04
Median AF duration, years (IQR)	2.8 (0.8-5.8)	3.0 (0.8-6.9)	3.9 (0.9-6.5)	1.9 (0.5-4.4)	2.8 (1.0-4.9)	0.14
Recurrent AF, n (%)	242 (60.0)	119 (62.0)	29 (78.4)	23 (44.3)	71 (58.2)	0.01
Age ≤65, n (%)	102 (25.3)	52 (27.1)	≤4	10 (19.2)	37 (30.3)	0.03
Age 65-74, n (%)	175 (43.4)	87 (45.3)	18 (48.6)	20 (38.5)	50 (41.0)	0.68
Age ≥75, n (%)	126 (31.3)	53 (27.6)	16 (43.2)	22 (42.3)	35 (28.7)	0.07
Female, n (%)	102 (25.3)	50 (26.0)	12 (32.4)	12 (23.1)	28 (23.0)	0.67
Comorbidity, n (%)						
Congestive Heart Failure	147 (36.5)	73 (38.0)	12 (32.4)	19 (36.5)	43 (35.3)	0.91
Arterial hypertension	359 (89.1)	177 (92.2)	33 (89.2)	47 (90.4)	102 (83.6)	0.12
Diabetes Mellitus	45 (11.2)	20 (10.4)	≤4	7 (13.5)	15 (12.3)	0.83
Previous Stroke	40 (9.9)	17 (8.9)	≤4	7 (13.5)	12 (9.8)	0.80
Vascular disease	173 (42.9)	83 (43.2)	17 (46.0)	26 (50.0)	47 (38.5)	0.54
Previous bleeding	46 (11.4)	23 (12.0)	5 (13.5)	9 (17.3)	9 (7.4)	0.26
Renal failure	30 (7.4)	14 (7.3)	≤4	8 (15.4)	7 (5.7)	0.09
Liver disease	10 (2.5)	≤4	≤4	≤4	≤4	0.14
Alcohol abuse	26 (6.5)	12 (6.3)	5 (13.5)	≤4	7 (5.7)	0.29
CHA_2DS_2-VASc score, n (%)						
Low risk (Score=0)	9 (2.2)	≤4	≤4	≤4	7 (5.7)	0.02
Intermediate risk (Score=1)	35 (8.7)	15 (7.8)	≤4	≤4	16 (13.1)	0.14
High risk (Score ≥ 2)	359 (89.0)	175 (91.2)	36 (97.3)	49 (94.2)	99 (81.2)	0.005
HAS-BLED score, n (%)						
Low risk (Score ≤ 1)	62 (15.4)	30 (15.6)	≤4	≤4	26 (21.3)	0.04
Intermediate risk (Score=2)	149 (37.0)	78 (40.6)	12 (32.4)	14 (26.9)	45 (36.9)	0.30
High risk (Score ≥ 3)	192 (47.6)	84 (43.8)	23 (62.2)	34 (65.4)	51 (41.8)	0.006

* Row percentages. The abbreviations and multivariable analyses as in Table2.

Table s7. Baseline characteristics of patients with MACE by respective treatment allocation at the time of the event.

	All patients	Warfarin	DOACs	Antiplatelets	No-Therapy	P-value
Number of patients, n (%) *	1064 (8.9)	586 (55.1)	129 (12.1)	108 (10.2)	241 (22.6)	<0.0001
Median age at the time of the event, years (IQR) †	69 (62-74)	68 (62-74)	72 (68-77)	68 (63-75)	65 (59-72)	<0.0001
Median follow-up duration, years (IQR) †	3.8 (1.7-7.0)	3.3 (1.3-6.3)	4.4 (1.9-8.2)	4.0 (2.2-6.1)	5.0 (2.1-7.6)	<0.0001
Median AF duration, years (IQR) †	2.7 (0.8-5.9)	2.9 (0.9-6.2)	3.2 (1.0-7.3)	1.9 (0.5-5.2)	2.3 (0.8-4.7)	0.01
Recurrent AF, n (%)	742 (69.7)	436 (74.4)	91 (70.5)	64 (59.3)	151 (62.7)	0.001
Age ≤65, n (%)	378 (35.5)	205 (35.0)	22 (17.1)	34 (31.5)	117 (48.6)	<0.0001
Age 65-74, n (%)	454 (42.7)	263 (44.9)	63 (48.8)	48 (44.4)	80 (33.2)	0.007
Age ≥75, n (%)	232 (21.8)	118 (20.1)	44 (34.1)	26 (24.1)	44 (18.3)	0.002
Female, n (%)	276 (25.9)	162 (27.7)	31 (24.0)	26 (24.1)	57 (23.7)	0.58
Comorbidity, n (%)						
Congestive Heart Failure	248 (23.3)	133 (22.7)	28 (21.7)	26 (24.1)	61 (25.3)	0.83
Arterial hypertension	834 (78.4)	484 (82.6)	99 (76.7)	89 (82.4)	162 (67.2)	<0.0001
Diabetes Mellitus	87 (8.2)	47 (8.0)	12 (9.3)	10 (9.3)	18 (7.5)	0.90
Previous Stroke	105 (9.9)	63 (10.8)	12 (9.3)	9 (8.3)	21 (8.7)	0.75
Vascular disease	326 (30.6)	190 (32.4)	36 (27.9)	41 (38.0)	59 (24.5)	0.04
Previous bleeding	118 (11.1)	69 (11.8)	19 (14.7)	9 (8.3)	21 (8.7)	0.24
Renal failure	45 (4.2)	23 (3.9)	≤4	9 (8.3)	10 (4.2)	0.12
Liver disease	16 (1.5)	8 (1.4)	≤4	≤4	≤4	0.44
Alcohol abuse	51 (4.8)	26 (4.4)	6 (4.7)	≤4	15 (6.2)	0.67
CHA_2DS_2-VASc score, n (%)						
Low risk (Score=0)	91 (8.6)	37 (6.3)	6 (4.7)	9 (8.3)	39 (16.2)	<0.0001
Intermediate risk (Score=1)	142 (13.4)	71 (12.1)	15 (11.6)	11 (10.2)	45 (18.7)	0.047
High risk (Score ≥ 2)	831 (78.1)	478 (81.6)	108 (83.7)	88 (81.5)	157 (65.2)	<0.0001
HAS-BLED score, n (%)						
Low risk (Score ≤ 1)	286 (26.9)	140 (23.9)	31 (24.0)	23 (21.3)	92 (38.2)	<0.0001
Intermediate risk (Score=2)	392 (36.8)	223 (38.1)	42 (32.6)	35 (32.4)	92 (38.2)	0.48
High risk (Score ≥ 3)	386 (36.3)	223 (38.1)	56 (43.4)	50 (46.3)	57 (23.7)	<0.0001

* Row percentages. The abbreviations and multivariable analyses as in Table2.

Table s8. Sensitivity analyses following the patients persisting with baseline exposure allocation until the endpoint of interest or end of follow-up, otherwise censored when treatment was changed/discontinued.

	All population	Warfarin (reference)	DOACs		Antiplatelets		No-Therapy	
	N / PYE IR (95%CI)	N / PYE IR (95%CI)	N / PYE IR (95%CI)	HR (95%CI) p-value	N / PYE IR (95%CI)	HR (95%CI), p-value	N / PYE IR (95%CI)	HR (95%CI) p-value
Stroke	130 / 23,371 5.6 (4.7-6.6)	107 /18,201 5.9 (4.9-7.1)	10 /2,326 4.3 (2.3-8.0)	0.80 (0.4-1.60) p=0.54	≤4 / 835 2.4 (0.6-9.6)	0.42 (0.10-1.70) 0.22	11 / 2,008 5.5 (3.0-9.9)	1.18 (0.54-2.58) p=0.67
Serious Bleeding	195 / 23,002 8.5 (7.4-9.8)	167 / 17,929 9.3 (8.0-10.8)	15 / 2,261 6.6 (4.0-11.0)	0.91 (0.51-1.61) p=0.75	≤4 / 814 4.9 (1.8-13.1)	0.52 (0.19-1.41) p=0.20	9 / 1,997 4.5 (2.3-8.7)	0.92 (0.43-1.98) p=0.84
CVD	113/ 23,808 4.8 (3.9-5.7)	88 / 18,551 4.7 (3.8-5.8)	7 / 2,372 3.0 (1.4-6.2)	0.85 (0.38-1.92) p=0.70	7 / 866 8.1 (3.9-16.9)	1.90 (0.86-4.18) p=0.11	11 / 2,018 5.5 (3.0-9.8)	2.84 (1.35-5.96) P=0.006
MACE	330 / 22,656 14.6 (13.1-16.2)	275 / 17,642 15.6 (13.9-17.5)	24 / 2,230 10.8 (7.2-16.0)	0.86 (0.55-1.35) p=0.53	7 / 797 8.8 (4.2-18.4)	0.58 (0.27-1.23) p=0.16	24 / 1,987 12.1 (8.1-18.0)	1.30 (0.79-2.14) p=0.30

* Row percentages. The abbreviations and multivariable analyses as in Table2.

Table S8a. Baseline characteristics of patients with serious bleeding by respective treatment allocation at the time of the event-based on the subset of data as in Table S8.

	All patients	Warfarin	DOACs	Antiplatelets	No-Therapy	p-value
Number of patients, n (%) *	195 (1.6)	167 (85.6)	15 (7.7)	≤4 (2.1)	9 (4.6)	<0.0001
Median age at the time of the event, years (IQR)	69 (62-74)	69 (63-74)	75 (72-81)	69 (63-77)	58 (49-67)	0.0008
Median follow-up duration, years (IQR)	2.7 (1.4-6.0)	2.7 (1.4-6.1)	4.1 (2.4-6.0)	1.7 (1.1-1.8)	1.2 (0.4-6.0)	0.027
Median AF duration, years (IQR)	3.1 (1.1-6.3)	3.3 (1.2-6.5)	1.8 (0.8-4.3)	2.4 (1.0-3.1)	2.0 (0.9-4.7)	0.29
Recurrent AF, n (%)	136 (69.7)	124 (74.2)	7 (46.7)	≤4	≤4	0.008
Age <65, n (%)	63 (32.3)	54 (32.3)	≤4	≤4	6 (66.7)	0.06
Age 65-74, n (%)	88 (45.1)	78 (46.7)	5 (33.3)	≤4	≤4	0.67
Age ≥75, n (%)	44 (22.6)	35 (21)	8 (53.5)	≤4	≤4	0.012
Female, n (%)	65 (33.3)	53 (31.7)	≤4	≤4	7 (77.8)	0.02
Comorbidity, n (%)						
Congestive Heart Failure	37 (19)	36 (21.6)	≤4	≤4	≤4	0.15
Arterial hypertension	161 (82.6)	142 (85)	13 (86.7)	≤4	≤4	0.005
Diabetes Mellitus	15 (7.7)	13 (7.7)	≤4	≤4	≤4	0.23
Previous Stroke	21 (10.8)	19 (11.4)	≤4	≤4	≤4	0.52
Vascular disease	55 (28.2)	47 (28.1)	7 (46.7)	≤4	≤4	0.11
Previous bleeding	34 (17.4)	29 (17.4)	≤4	≤4	≤4	0.57
Renal failure	≤4	≤4	≤4	≤4	≤4	0.25
Liver disease	≤4	≤4	≤4	≤4	≤4	0.91
Alcohol abuse	8 (4.1)	7 (4.2)	≤4	≤4	≤4	0.58
HAS-BLED score, n (%)						
Low risk (Score ≤ 1)	37 (9)	29 (17.4)	≤4	≤4	≤4	0.075
Intermediate risk (Score=2)	82 (42.1)	71 (42.5)	6 (40)	≤4	≤4	0.91
High risk (Score ≥ 3)	76 (39)	67 (40.1)	7 (46.7)	≤4	≤4	0.29

* Row percentages. The abbreviations and multivariable analyses as in Table2.

Table s9. Sensitivity analyses in patients undergoing atrial fibrillation ablation from 01-January-2012 or later.

	All population	Warfarin (reference)	DOACs		Antiplatelets		No-Therapy	
	N / PYE IR (95%CI)	N / PYE IR (95%CI)	N / PYE IR (95%CI)	HR (95%CI) p-value	N / PYE IR (95%CI)	HR (95%CI), p-value	N / PYE IR (95%CI)	HR (95%CI) p-value
Stroke	113 / 21,195 5.3 (4.4-6.4)	52 / 9,402 5.5 (4.2-7.3)	29 / 5,653 5.1 (3.5-7.4)	1.05 (0.65-1.69) p=0.82	≤4 / 382 10.5 (3.9-27.9)	1.87 (0.66-5.24) p=0.23	28 / 5,758 4.9 (3.4-7.0)	1.69 (1.002-2.85) p=0.049
Serious Bleeding	152 / 21,114 7.2 (6.1-8.4)	84 / 9,346 9.0 (7.3-11.1)	37 / 5,671 6.5 (4.7-9.0)	0.78 (0.52-1.17) p=0.23	6 / 383 15.7 (7.0-34.9)	1.91 (0.83-4.43) p=0.13	25 / 5,715 4.4 (2.9-6.5)	0.90 (0.54-1.49) p=0.67
CVD	72 / 21,411 3.4 (2.6-4.2)	38 / 9,491 4.0 (2.9-5.5)	10 / 5,749 1.7 (0.9-3.2)	0.56 (0.27-1.16) p=0.12	5 / 399 12.5 (5.2-30.1)	2.70 (1.04-7.00) p=0.04	19 / 5,772 3.3 (2.1-5.2)	3.11 (1.72-5.63) p<0.0001
MACE	275 / 20,928 13.1 (11.7-14.8)	145 / 9,259 15.6 (13.3-18.4)	62 / 5,591 11.1 (8.6-14.2)	0.79 (0.58-1.08) p=0.14	12 / 373 32.2 (18.3-56.7)	2.12 (1.16-3.85) p=0.01	56 / 5,706 9.8 (7.6-12.8)	1.23 (0.86-1.75) p=0.24

* Row percentages. The abbreviations and multivariable analyses as in Table2.

Table S9a. Baseline characteristics of patients with serious bleeding by respective treatment allocation at the time of the event-based on the subset of data as in Table S9.

	All patients	Warfarin	DOACs	Antiplatelets	No-Therapy	p-value
Number of patients, n (%) *	152 (1.3)	84 (55.3)	37 (24.3)	6 (3.9)	≤4	<0.0001
Median age at the time of the event, years (IQR)	70 (61-74)	68 (60-73)	71 (68-76)	78 (75-80)	67 (58-72)	0.005
Median follow-up duration, years (IQR)	1.9 (0.7-3.7)	1.5 (0.4-2.8)	2.4 (0.8-3.9)	2.8 (2.4-4.5)	2.6 (1.3-4.5)	0.005
Median AF duration, years (IQR)	2.5 (0.8-6.7)	3.0 (0.8-6.6)	2.3 (0.6-7.7)	1.5 (0.1-5.3)	1.6 (0.8-3.2)	0.42
Recurrent AF, n (%)	91 (59.9)	53 (63.1)	24 (64.8)	≤4	11 (44)	0.30
Age <65, n (%)	51 (33.5)	33 (39.3)	8 (21.6)	≤4	10 (40)	0.07
Age 65-74, n (%)	69 (45.4)	38 (45.2)	18 (48.7)	≤4	12 (48)	0.52
Age ≥75, n (%)	32 (21.1)	13 (15.5)	11 (29.7)	≤4	≤4	<0.0001
Female, n (%)	41 (27)	21 (25)	10 (27)	≤4	8 (32)	0.89
Comorbidity, n (%)						
Congestive Heart Failure	33 (21.7)	19 (22.6)	8 (21.6)	≤4	5 (20)	0.98
Arterial hypertension	118 (77.6)	65 (77.4)	31 (83.8)	5 (83.3)	17 (68)	0.52
Diabetes Mellitus	16 (10.5)	8 (9.5)	≤4	≤4	≤4	0.29
Previous Stroke	19 (12.5)	14 (16.7)	≤4	≤4	≤4	0.20
Vascular disease	45 (29.6)	20 (23.8)	12 (32.4)	4 (66.7)	9 (36)	0.11
Previous bleeding	29 (19.1)	16 (19.1)	6 (16.2)	≤4	7 (28)	0.40
Renal failure	6 (4)	≤4	≤4	≤4	≤4	0.68
Liver disease	≤4	≤4	≤4	≤4	≤4	0.81
Alcohol abuse	5 (3.3)	≤4	≤4	≤4	≤4	0.53
HAS-BLED score, n (%)						
Low risk (Score ≤ 1)	46 (30.2)	28 (33.3)	10 (27)	≤4	7 (28)	0.77
Intermediate risk (Score=2)	53 (34.9)	28 (33.3)	15 (40.5)	≤4	9 (36)	0.68
High risk (Score ≥ 3)	53 (34.9)	28 (33.3)	12 (32.4)	≤4	9 (36)	0.41

* Row percentages. The abbreviations and multivariable analyses as in Table2.

Table S10. The primary cause of cardiovascular death registered among 44 cases within 90-days from first-time AF ablation

Cause of death	**Definition**	***Specification (ICD-10)***
9 cases	Chronic ischemic heart disease	I25
7 cases	Stroke	I63, I64
6 cases	Acute myocardial infarction	I21
3 cases	Congestive heart failure	I509
3 cases	Aortic stenosis	I350
2 cases	Intracranial bleeding	I619
2 cases	Atrial fibrillation	I48
1 case	Cardiogenic shock	R570
1 case	Acute coronary syndrome	I249
1 case	Rheumatic mitral stenosis with insufficiency	I052
1 case	Rheumatic aortic stenosis	I060
1 case	Disease in the pulmonary circulation	I28
1 case	Pericardial disease	I318
1 case	Infective endocarditis	I389
1 case	Non- Rheumatic mitral valve disease	I349
1 case	Dilated cardiomyopathy	I420
1 case	Arrhythmia	I499
1 case	Grown-Up with Congenital Heart defects	Q249
1 case	Marfan syndrome	Q874

Table S11. The existing literature published after 2013.

Authors	Study design	Objective	Population & Follow-up	Main results	Conclusions
Nademanee (2015)	Retrospective analysis of prospectively collected data	To evaluate the safety and efficacy, including long-term outcomes, of catheter ablation for maintaining normal sinus rhythm (NSR) in elderly patients with AF.	587 elderly patients (age≥75 years) with AF. 324 were eligible for ablation. 261 (group1) underwent ablation. 63 patients (group 2) either declined or were not suitable for ablation.	Warfarin therapy was discontinued in 169 of the 216 group 1 patients (78%) who maintained NSR and had only 3% 5-year stroke/bleeding rates compared to 16% in group 2 (P <.001).	After successful ablation, warfarin treatment can be safely discontinued without an increased risk of cerebrovascular accidents.
Jacobs (2017)	Retrospective observational study	To compare outcomes for cerebrovascular accidents and bleeding among patients receiving: none, aspirin, or warfarin as long-term therapies.	4124 patients. CHA_2DS_2-VASc scores 0: 1,143 (28%), 1: 1,588 (39%), and 2: 1,393 (34%). 1- and 3-years follow-up.	At 3 years, 238 (5.9%) patients were on warfarin, 743 (18.6) on aspirin, and 3,013 (75.5%) on no therapy; with occurrences of cerebrovascular events (1.4%, 3.0%, 3.9%, P < 0.0001, respectively). GI bleeding (0.8%, 1.9%, 1.1%, P=0.06, respectively), and GU bleeding (1.7%, 2.8%, 2.1%, P=0.008, respectively).	After catheter ablation, low-risk patients do not benefit from long-term aspirin therapy, but are at risk for higher rates of bleeding when compared to no therapy or warfarin.
Kawaji (2017)	Retrospective single-centre study	To investigate the very long-term outcomes after AF ablation in a large number of consecutive patients.	1206 consecutive patients undergoing their first AF ablation. Mean follow-up duration of 5.0±2.5 years.	Discontinuation rate of oral anticoagulation at 1-, 3-, and 10-year was 34.6%, 53.4%, 58.0%. The cumulative 10-year incidences of stroke and major bleeding were 4.2% and 3.5%, respectively, with annual rates of 0.3%.	The 10-year rates of stroke and major bleeding were low even with discontinuation of oral anticoagulation in a large proportion of patients.
Okumura (2019)	Registry-based observational study	To investigate the terminated anticoagulation after AF ablation and the relationship between discontinuation and the long-term incidences of stroke, major bleeding, cardiovascular events, and death.	3,451 consecutive patients (74.1% men; age, 63.3±10.3 years, mean CHA_2DS_2-VASc score was 2.1±1.5). OAC therapy was discontinued in 1,836 (53.2%) patients. Follow-up median of 20.7 [12.7–33.2] months.	The overall incidence of clinical adverse events, including stroke/TIA, major bleeding, cardiovascular events, and death was significantly lower in the OAC discontinuation group than in the OAC continuation group (P<0.05 for all).	The incidences of stroke/TIA, major bleeding, and death were relatively low among approximately half of our registry patients for whom OAC therapy was discontinued. Stroke/TIA occurrence was strongly associated with a high baseline stroke risk rather than with OAC status suggesting that OACs should be continued in high-risk patients.
Rong (2020)	Single-center, prospective	To determine the thromboembolic risk in patients with and without AF recurrence (RAF vs NRAF) post-ablation.	796 patients who discontinued OAC at 3 months after AF ablation. CHA_2DS_2-VASc score was 1.79 ± 1.50; 547 (68.7%) patients were at intermediate and high risk (i.e., CHA_2DS_2-VASc score ≥1 in male patients, or ≥2 in female patients); 169 (21.2%) had RAF. Follow-up 29.2±12.2 months.	The incidence rate of thromboembolism was 1.62 per 100 patient-year in RAF, 0.33 per 100 patient-year in NRAF (adjusted HR, 4.488; 95% CI, 1.381 to 14.586). The rate of thromboembolism was even higher in patients with intermediate and high risk (2.16 per 100 patient-year vs 0.38 per 100 patient-year, HR, 5.807; 95% CI, 1.631 to 20.671).	The cessation of OAC in NRAF may be reasonable; however, cessation of OAC appeared unsafe in RAF with a high-risk stroke profile because of the high incidence rate of thromboembolism.
Pothineni (2021)	Single-center, prospective	To evaluate a strategy of OAC discontinuation following AF ablation guided by continuous rhythm monitoring.	196 patients (mean age 64.7 ± 11.3 years, 66.8% male, 85.7% ICM, 14.3% CIEDs). The mean CHA_2DS_2-VASc score was 2.2 ± 1.5. Over 3-year follow-up, OAC was discontinued in 57 (33.7%) patients and restarted for AF recurrence in 9 (15.8%) patients.	This discontinuation protocol led to a 21.9% reduction in overall time exposed to OAC. There were no thromboembolic or major bleeding events.	OAC can be discontinued in a significant percentage of patients following AF ablation. When guided by continuous rhythm monitoring, this practice does not unacceptably increase the risk of thromboembolic events.

Inoue (2021)	Prospective registry study for patients on rivaroxaban or warfarin undergoing ablation	To evaluate long-term anticoagulation strategies and clinical outcomes.	975 patients (rivaroxaban, n=823; warfarin, n=152). Mean CHA_2DS_2-VASc score 1.9 ± 1.5. Mean follow-up period 28.7 ± 12.7 months.	Thromboembolism occurred in 3 patients, hemorrhagic stroke in 5, and major bleeding events in 9 (annualized event rate, 0.13%, 0.22%, and 0.40% per patient-year, respectively), bleeding between rivaroxaban and warfarin cohorts (0.53% and 0.55% per patient-year), respectively.	Long-term incidence of thromboembolism was extremely low in patients with AF treated with ablation, while that of major bleeding was not especially low.
Atti (2018)*	Meta-analyses [Yagishita (2011), Themistoclakis (2010), Winkle (2013), Uhm (2014), Gaita (2014), Riley (2014), Gallo (2016), Sjalander (2017), Liang (2018)]	To evaluate the safety and efficacy of continuation vs. discontinuation of OACs after an apparently successful AF ablation in patients with CHA_2DS_2-VASc score≥ 2.	3,436 patients of whom 1,815 continued OACs and1,621 discontinued OAC post–AF ablation.	There was no significant difference in risk of cerebrovascular events (RR: 0.85, 95%CI: 0.42 to 1.70, p= 0.64) and systemic thromboembolism (RR: 1.21, 95%CI: 0.66 to 2.23, p= 0.54) between the two groups. Continuation of OACs was associated with an increased risk of major bleeding (RR: 6.50, 95% CI: 2.53 to 16.74, p= 0.0001).	Discontinuation of oral anticoagulation 3 months after a successful AF ablation appears to be safe in highly selected closely monitored patients.
Romero (2019)*	A systematic review and meta-analysis.	To compare patients who were continued on OAC (ON-OAC) vs those in which OAC was discontinued (OFF-OAC).	3956 patients. Mean follow-up of 39.6 ± 11.7 months	OAC-continuation was associated with a significant decrease in the risk of TE in the high-risk cohort (CHA_2DS_2-VASc ≥ 2) (risk ratio [RR] 0.41, 95% CI: 0.21-0.82, P=.01) with a RR reduction of 59%. Intracranial bleeding was significantly higher in the ON-OAC group (RR, 5.78; 95% CI, 1.33-25.08; p=0.02).	Continuation of OAC after AF ablation with CHA_2DS_2-VASc ≥ 2 is associated with a significant decreased thromboembolic risk and a favourable net clinical benefit. The risk of intracranial bleeding significantly increased in the ON-OAC group. Continued OAC offers no benefit with CHA_2DS_2-VASC ≤ 1.
Proietti (2019)*	A systematic review and meta-analysis (10 prospective and 6 retrospective cohort studies)	To investigate cerebrovascular events after AF ablation and to compare patients on or off OAC.	25,177 patients: 13,166 off-OAC and 12,011 on-OAC.	No significant difference in the incidence of CVE emerged between on-OAC and off-OAC patients after AF ablation (risk ratio, 0.66; confidence interval [CI], 0.38, 1.15). Similar results were found after stratification by $CHADS_2$ and CHA_2DS_2-VASc scores. Off-OAC patients suffered significantly less bleeding than those on OAC (RR, 0.17; CI, 0.09, 0.34).	The risk-benefit ratio favoured the suspension of OAC after successful AF ablation even in patients at moderate-high risk.
Liu et al. (2021)*	Meta-analysis of prospective cohort studies [Oral (2006), Nademanee (2008), Saad (2011), Winkle (2013), Gaita (2014), Yang (2020), Yu (2020)]	To assess the safety and feasibility of discontinuing OAC therapy after successful AF ablation.	11,148 patients (7,160 in the off-OAC group and 3,988 in the on-OAC group).	No significant difference in thromboembolic events between both groups (OR, 0.73; 95%CI, 0.51-1.05). The risk of major bleeding in off-OAC group was significantly lower compared to the on-OAC group (OR, 0.18; 95%CI, 0.07-0.51; I2=51.7%).	It may be safe to discontinue OAC therapy in patients after successful AF ablation. Additionally, an increased risk of major bleeding was observed in patients on OAC.

Search strategy: "(catheter ablation OR ablation) AND (atrial fibrillation) AND (warfarin OR anticoagulation OR anticoagulants OR antiplatelet OR antithrombotic) AND (stroke OR thromboembolic OR thromboembolism) AND (bleeding) AND (discontinuation OR discontinuing OR cessation) NOT (uninterrupted OR periprocedural OR appendage)" published in English.
We excluded case reports/series, non-comparative studies and review articles after the abstract review.
* Studies included in systematic reviews and/or meta-analyses were not independently specified in this table.