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ORIGINAL ARTICLE
Arrhythmia and electrophysiology

Reduced dose direct oral anticoagulants and time-in-therapeutic-range defined warfarin in new-onset atrial fibrillation: a report from the nationwide FinACAF study

Alex Luojus [1,*], Mika Lehto [1,2], Olli Halminen [3,4], Ossi Lehtonen [4], Mikko Niemi [5,6], Konsta Teppo [7], Jaana Kuoppala [8], Jari Haukka [8], Jukka Putaala [9], Miika Linna [3,4], Pirjo Mustonen [7], Aapo Aro [1], Juha Hartikainen [10], Gregory Yoke Hong Lip [11,12,13], and Kari Eino Juhani Airaksinen [7]

[1]Heart and Lung Center, Helsinki University Hospital and University of Helsinki, Helsinki, Finland; [2]Department of Internal Medicine, Jorvi Hospital, Helsinki and Uusimaa Hospital District, Espoo, Finland; [3]Aalto University, Espoo, Finland; [4]University of Eastern Finland, Kuopio, Finland; [5]Department of Clinical Pharmacology and Individualized Drug Therapy Research Program, University of Helsinki, Helsinki, Finland; [6]Department of Clinical Pharmacology, HUS Diagnostic Center, Helsinki University Hospital, Helsinki, Finland; [7]Turku University Hospital and University of Turku, Finland; [8]University of Helsinki, Helsinki, Finland; [9]Department of Neurology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland; [10]Kuopio University Hospital and University of Eastern Finland; [11]Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, UK; [12]Danish Center for Health Services Research, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; and [13]Medical University of Bialystok, Bialystok, Poland

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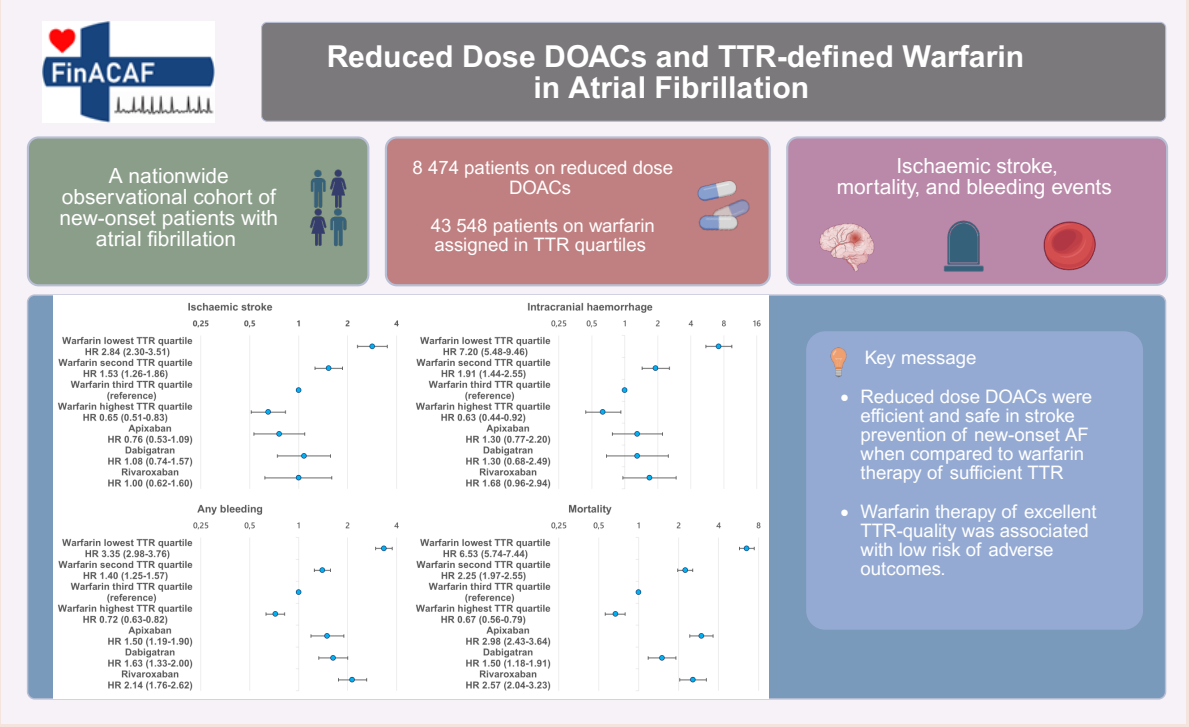
Aims Direct oral anticoagulants (DOACs) at reduced dosage regimens are the first choice of ischaemic stroke (IS) prevention for patients with atrial fibrillation (AF) and elevated bleeding risk or renal insufficiency. We compared the outcomes of reduced dose DOACs and warfarin.

Methods and results We included all new-onset patients with AF in Finland from 2011 to 2018. Adjusted hazard ratios (HRs) for IS, intracranial haemorrhage (ICH), bleeding, and mortality were calculated for dabigatran ($n = 2\,672$), rivaroxaban ($n = 1\,866$), apixaban ($n = 3\,936$), and warfarin ($n = 43\,548$). Patients on warfarin were grouped into quartiles by their individual time-in-therapeutic range (TTR), with the second best TTR quartile as a reference group for comparisons. Risk of IS was highest in the low TTR quartiles of warfarin, lowest in the best TTR quartile (0.65 95% confidence interval, 0.51–0.83), and did not differ for dabigatran, rivaroxaban, and apixaban compared with the second best TTR quartile. Risk of ICH was highest in low TTR quartiles of warfarin (HRs 7.20, 5.48–9.46 and 1.91, 1.44–2.55), and was not different in patients on dabigatran, rivaroxaban, and apixaban. Risk of all-cause death and bleeding were lowest in the two best TTR quartiles, and highest in the poorest TTR group. Mortality was higher for dabigatran, rivaroxaban, and apixaban, compared with the second best TTR quartile of warfarin.

Conclusion DOACs with reduced doses are efficient and safe stroke prevention therapy in high-risk patients with AF when compared with warfarin therapy of sufficient TTR. In this comparison, warfarin therapy of excellent TTR-quality was associated with the lowest risk of bleeding and mortality.

* Corresponding author. Tel: +358400728983, Email: alex.luojus@helsinki.fi.

Graphical Abstract



Keywords Atrial fibrillation • Oral anticoagulation • Ischaemic stroke • Reduced dose direct oral anticoagulants

Introduction

The world-wide prevalence of atrial fibrillation (AF) is increasing due to improved diagnostic screening and prolonged life-expectancy, and increase especially in octogenarians is expected.[1,2] Patients with AF are at elevated risk of ischaemic stroke (IS), even though the risk between individuals varies considerably depending on their characteristics and comorbidities.[3] Oral anticoagulation (OAC) therapy reduces the risk of IS in patients with AF, either with direct oral anticoagulants (DOACs), or vitamin K antagonists (VKAs), such as warfarin. In the last decade, both randomized controlled trials (RCTs) and observational studies have shown DOACs to be the first choice of stroke prevention over VKAs in non-valvular AF, even though some patients still continue on warfarin therapy.[4–10]

While OAC therapy effectively reduces the risk of stroke in AF, it also increases the risk of adverse bleeding events such as intracranial haemorrhage (ICH). In particular, the risks are elevated for patients with AF who are elderly, who suffer from multiple comorbidities, or use multiple concomitant medications.[11] The attributes associated with increased risk of IS are also often the same increasing the risk of adverse bleeding,[12] and in clinical decision-making tools, such as CHA_2DS_2-VASc and HAS-BLED scores, have previously been used to estimate the net benefit of OAC therapy in AF patients.[3,13] The European guidelines for stroke prevention in AF suggest the use of DOACs for patients with moderate or high risk of IS, and DOACs in reduced doses for patients with elevated risk of bleeding, who are elderly, pose low body weight, and have either severe renal dysfunction or concomitant medication with possible adverse interactions.[14] (see Supplementary material online, table *S3*).

The landmark RCTs and initial large observational studies of DOACs did not include large number of patients eligible for dose-reduction criteria of DOACs, and patients with reduced dose DOACs were not formally studied with sufficient statistical power in the pivotal apixaban and rivaroxaban RCTs, where patients on DOACs were mostly younger than the average AF patient in real-world studies.[15] A meta-analysis of RCTs, revealed that patients with reduced dose DOACs had higher thromboembolic and bleeding rates than patients with standard dose DOACs, but the benefit-harm profile of appropriately adjusted reduced dose DOACs remained consistently better than warfarin, whether patients met the dose reduction criteria or not.[16] Similar results have been published from a handful of observational studies, where reduced dose DOACs were mainly associated with lower risk of IS than warfarin,[17–19] while indicating similar or mostly DOAC favouring rates of adverse events.[18,19]

With the increasing prevalence of elderly AF patients in the general population, need for dose-reduction assessment of DOACs will likely increase. Some patients also continue on warfarin therapy, where the outcomes are associated with the quality of care measured by individual time-in-therapeutic range (TTR).[20] In a recent RCT of frail patients with AF, switching from international normalized ratio (INR)—guided VKA therapy to DOAC therapy, was also associated with increased bleeding risk, and no significant change in thromboembolic events.[17]

In this study, we assessed the effectiveness and safety of reduced dose DOACs and warfarin treatment patients with new-onset AF in a real-world setting covering all levels of care, while considering the individual TTR information of patients using warfarin.

Methods

Study design and data

The Finnish AntiCoagulation in Atrial Fibrillation Study (FinACAF) (ClinicalTrials Identifier: NCT04645537; ENCePP Identifier: EUPAS 29845) is a nationwide registry study with comprehensive data on all recorded patients with AF between 1 January 2004 and 31 December 2018 in Finland. The study links individual patient health records and laboratory data from primary, secondary, and tertiary care as well as data regarding education, socio-economic status, income, taxing, and place of domicile. The study rationale and design have been reported previously.[18]

In this observational retrospective study of unselected patients with AF, patients were identified by International Classification of Diseases (ICD-10) diagnosis code I48 by using all national registries: The Care Register of Health Care (HILMO) for hospitalizations and secondary care outpatient visits, the Care Register of Health Care (AvoHILMO) for primary health care visits, and the National Reimbursement Register maintained by the Social Insurance Institution (KELA) for filled drug prescriptions. Data of patient comorbidities, diagnoses, cause of death, socio-economic status and place of domicile, registry data was obtained from National Prescription register, National Causes of Death Register, National Cancer Registry, six regional laboratory databases, Finnish population register, Finnish Tax register, Social HILMO, and The Register of Completed Education and Degrees (see Supplementary material online, *Table S1*).

Study population and baseline characteristics

All Finnish patients with new-onset non-valvular AF between years 2011 and 2018 who had not received prior OAC therapy, and who had laboratory data available for analysis were studied. Study patients were grouped by the initiated OAC: warfarin, dabigatran 110 mg, rivaroxaban 15 mg, apixaban 2.5 mg, or edoxaban 30 mg. Patients on warfarin were further divided into quartiles according to their individual TTR values.

Patients with previous OAC use, who either had filled an OAC prescription between 2004 and 2006 or within 1 year before the AF diagnosis were excluded from study. Patients with mitral stenosis or mechanical prosthetic heart valves were also excluded. Furthermore, patients without any OAC purchases and patients who initiated standard dose DOAC after AF diagnosis were excluded from analysis. Patient selection process is detailed in Supplementary material online, *Figure S1*.

Baseline comorbidities preceding AF diagnosis were identified by either ICD-10 codes, medication purchases, or laboratory data (see Supplementary material online, *Table S2*). Glomerular filtration rates were also included for analysis. Income quintiles were formed to minimize confounding by socio-economic factors. Baseline medication was defined as a purchase during the year prior diagnosis of AF, with purchases 30 days prior to AF diagnosis excluded to avoid confounding.

Exposure to oral anticoagulation and time-in-therapeutic range

The follow-up for outcomes and exposure to OAC therapy begun at the first OAC drug purchase after AF diagnosis of AF and were continued until the end of drug exposure or for maximum of 730 days if no other criteria for termination of exposure were met.

The drug consumption was estimated by manufacturers recommended reduced dose regimens of each DOAC as follows: One pill per day for rivaroxaban 15 mg and edoxaban 30 mg, and two pills per day for apixaban 2.5 mg, and dabigatran 110 mg. The exposure to DOACs ended 30 days after the calculated depletion of the purchased drugs unless subsequent purchases were made to continue the exposure. Crossover to another OAC or change in dosage also terminated the exposure.

For warfarin, subsequent INR-measurements of 60-day intervals were also required in addition to subsequent purchases. Exposure to warfarin was terminated also if 180 days passed without a new warfarin purchase, or at the purchase of any other OAC. For both DOACs and warfarin, exposure was terminated at the occurrence of any study outcome. A detailed description of OAC exposure in the study is visualized in Supplementary material online, *Figure S2*.

To determine the quality of warfarin therapy, individual TTR values for eligible patients were calculated by using Rosendaal's method.[19] The percentage of times observed INR-values fell between 2.0 (≥) and 3.0 (≤) was calculated if a patient had at least three subsequent INR-measurements within a maximum interval of 60 days between each measurement. Patients with warfarin were then assigned into quartiles according to their respective TTR values.[21]

Eligibility for direct oral anticoagulant dose reduction

The eligibility criteria for DOAC dose reduction were applied according to the European Society of Cardiology (ESC) guidelines[14] and the European Heart Rhythm Association (EHRA) practical guide,[22] derived from manufacturer- given criteria on dose adjustment of each DOAC (see Supplementary material online, *Table S3*).

Study outcomes

IS was set as the primary outcome of treatment efficacy, defined as the first ICD-10 diagnosis I63 to occur during follow-up. Similarly, ICD-10 diagnosis codes for ICH—both non-traumatic and traumatic, as well as any bleeding as a composite outcome of intra- and extracranial bleeding, were studied to assess safety of treatment. All-cause mortality under OAC exposure was studied, and additionally gastrointestinal (GI) bleeding was studied as a secondary study outcome.

The events of IS, ICH, and any bleeding were acquired from the hospital care register, and the dates of death from the National Cause of Death register. For IS, ICH, or bleeding, both new and recurrent event were accepted as an outcome, if the recurrent episode fulfilled the following criteria: (i) event was the main diagnosis of hospitalization, (ii) a minimum of 90 days had elapsed since the previous diagnosed event and (iii) The event occurred under the exposure of the first initiated OAC after diagnosis of AF. Further definitions of outcomes are given in Supplementary material online, *Table S2*.

To assess possible bias of inadequate dose reduction in our reduced dose DOAC groups, we analysed the prevalence of available dose-lowering criteria in all treatment groups. The most common causes of death in treatment groups were also analysed to further assess if the differences in mortality as an outcome could be explained by the choice of OAC therapy.

Statistical analysis

Patient characteristics are reported as counts and percentages, or as means and medians with standard deviations (SD) or interquartile ranges, respectively. Counts and crude rates of outcomes (IS, ICH, any bleeding, and mortality) per 100 patient years (py) are reported for each treatment group.

An inverse probability of treatment weighted analysis (IPTW) was applied to obtain balanced treatment populations that represent the average treatment effect for the population.[23] These treatment weights were derived by generalized boosted model with 10 000 regression trees, and the underlying covariates in the propensity model included age, sex, vascular disease, previous stroke or transient ischaemic attack, diabetes, hypertension, cancer, use of statin or antithrombotic medication, CHA_2DS_2-VASc, and HAS-BLED scores. During the study period CHA_2DS_2-VASc and HAS-BLED scores were widely used, hence CHA_2DS_2-VASc, and a modified HAS-BLED-score were calculated.[24] The balance between the studied groups was obtained by examining the standardized mean differences between each treatment group. A threshold of 0.1 was used in the analysis to obtain a sufficient balance between the weighted groups.

To estimate hazard ratios (HRs) of outcomes with 95% confidence intervals between treatment groups, a Cox-regression analysis was used. As applied previously,[21] the second best (3rd) TTR quartile of warfarin was selected as a reference group for risk estimation, it being the closest representative with the DOAC groups on visual inspection, and to give DOACs a point of comparison with warfarin treatment of reasonably good quality. A significance threshold of 0.05 was considered for the *P*-values. The statistical analyses were conducted using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

In total, 52 384 patients with new-onset non-valvular AF (46.1% male, mean age 75.7 years) between years 2011 and 2018 who initiated

reduced dose DOAC, or warfarin were analysed (*Table 1*). Altogether 43 548 (83.7%) patients initiated warfarin, 2672 (5.1%) low dose dabigatran, 1866 (3.6%) rivaroxaban, 3936 (7.6%) apixaban, and 182 (0.3%) edoxaban. The mean and median TTR values for patients with warfarin as whole were 66% and 72%, respectively. The mean TTR values (range) warfarin quartiles were 32% (0–52%) in the lowest TTR quartile, 65% (52–72%) in the second TTR quartile, 77% (72–83%) in the third TTR quartile, and 90% (83–100%) in the highest TTR quartile. The mean exposure length for all treatment groups was 408 days overall and varied between 235 days (lowest warfarin quartile) and 512 days (4th warfarin quartile). Patients with edoxaban were excluded from the main analyses due to the small numbers of patients with insufficient exposure time. Supplementary material online, *Table S4*, illustrates the incidence of the study endpoints IS, ICH, and all-cause mortality, with edoxaban included.

The mean ages in warfarin quartiles (73.6–75.3 years) were lower than in DOAC groups, with mean age of 80.5 years for dabigatran, 79.6 years for rivaroxaban, and 84.2 years for apixaban. The most common comorbidities in treatment groups were hypertension (77.7–87.0%) and dyslipidaemia (53.3–65.6%). In general, patients with DOACs had a higher baseline prevalence of dyslipidaemia, coronary heart disease, dementia, any vascular disease, and cancer than patients with warfarin. Patients with apixaban had the highest mean CHA_2DS_2-VASc score of 4.78 (1.45), and the highest 12.2% prevalence of renal dysfunction. In turn, patients in the highest TTR quartile of warfarin had the lowest CHA_2DS_2-VASc-score 3.50 (1.67), and the lowest prevalence of renal dysfunction (2.5%). Patients on DOACs were less likely to use beta blocker medication than those on warfarin but were more likely to have preceding antithrombotic or statin medication compared with warfarin. The baseline differences were reduced to <0.1 in standardized differences at maximum, after the study populations were analysed with IPTW.

Ischaemic stroke and intracranial haemorrhage

A total of 875 events of IS, and 452 events of ICH were recorded during the follow-up. Among patients on warfarin, the rates of IS were 3.45/100 patient years (py), 1.79/100 py, 1.18/100 py, and 0.74/100 py from the lowest to the highest TTR quartile, respectively (*Table 2*). Among patients on DOAC, the rates of IS were 1.63/100py for dabigatran, 1.49/100py for rivaroxaban, and 1.63/100 py for apixaban. The weighted rates of IS in warfarin quartiles were 3.70, 1.87, 1.21, and 0.79/100 py from the highest to the lowest TTR quartile. Similarly, the weighted rates of IS for reduced dose DOAC users were 1.34/100 py for dabigatran, 1.25/100 py for rivaroxaban, and 0.96/100 py for apixaban. The cumulative incidence curves for IS and ICH in OAC groups are observed in *Figure 1*.

The weighted risk of IS in OAC groups was compared with the 3rd quartile of warfarin (mean TTR 77%) as a reference group, and a significantly higher risk of IS was observed in the two lowest quartiles of warfarin. In turn, patients in the highest TTR quartile, and patients on dabigatran, rivaroxaban, and apixaban had a similar or non-significantly lower risk of IS when compared with the 3rd TTR quartile, with HRs of 0.65 (0.51–0.83), 1.08 (0.74–1.57), 1.00 (0.62–1.60), and 0.76 (0.53–1.09), respectively (*Figure 2*).

The ICH rates among warfarin quartiles were 3.60, 0.99, 0.51, and 0.32/100 py from the lowest to the highest TTR quartile. The corresponding rates of ICH were 0.68/100py for dabigatran, 1.06/100 py for rivaroxaban, and 1.09/100 py for apixaban. After balancing baseline characteristics with IPTW, the weighted rate of ICH was highest in the lowest TTR quartile of warfarin (*Table 2*). The risk of ICH was highest in the lowest quartiles of warfarin, and similar or non-significantly elevated in other groups, when compared with the second best TTR quartile of warfarin (*Figure 2*). Frequencies for subclasses of spontaneous ICHs are given in Supplementary material online, *Table S6*.

Bleeding

The rates of overall bleeding events (both intra- and extracranial combined) were highest in the 1st and 2nd TTR quartiles of warfarin, and the lowest in 3rd and 4th quartiles of warfarin, with rates of 14.8, 5.4 3.7, and 2.7/100 py. For DOACs the rates of bleeding events were 6.6/100py for dabigatran, 9.8/100 py for rivaroxaban, and 6.7/100 py for apixaban. Weighted rates of any bleeding for reduced dose DOACs were 6.7 for dabigatran, 8.9 for rivaroxaban, and 6.4 for apixaban.

After IPTW analysis, the risk of bleeding was lowest in the best quartile of warfarin with HR 0.72 (0.63–0.82) when compared with 3rd TTR quartile, and significantly ($P < 0.001$) higher in every other treatment group (*Figure 2*).

Gastrointestinal bleeding

The rates of GI bleeding were 4.97, 1.66, 0.85, and 0.43/100 py from the lowest to the highest TTR quartile of warfarin, respectively. For reduced dose DOACs, the rates were 2.52/100py for dabigatran, 3.70/100 py for rivaroxaban, and 2.06/100 py for apixaban, see cumulative rates in Supplementary material online, *Figure S4*. The respective weighted rates were 5.21, 1.73, 0.89, and 0.45/100 py from the lowest to the highest TTR quartile of warfarin, and 2.30/100 py for dabigatran, 3.47/100 py for rivaroxaban, and 1.76/100 py for apixaban (*Table 2*). HRs are given in Supplementary material online, *Figure S5*.

All-cause mortality

The observed mortality rates in warfarin quartiles were 16.45, 5.33, 2.31, and 1.53/100 py, from the lowest to the highest TTR quartile, respectively. The mortality rates in DOAC groups were 4.31/100 py for dabigatran, 8.11/100 py for rivaroxaban, and 11.40/100 py for apixaban. After balancing the baseline characteristics with IPTW method, the corresponding weighted mortality rates for warfarin quartiles were 18.08, 5.86, 2.58, and 1.73/100 py from lowest to the highest TTR quartile, respectively. The weighted mortality rates for reduced dose DOACs were 3.97/100 py for dabigatran, 6.78/100 py for rivaroxaban, and 7.97/100 py for apixaban (*Figure 2*).

Patient eligibility for direct oral anticoagulant dose reduction

The most prominent measure of any dose-reduction criteria with reduced dose DOACs was Age ≥ 80, which was factual for 67.8% of dabigatran, 60.8% of rivaroxaban, and 83.1% of apixaban using patients. The least frequent dose-reduction criterion in all treatment groups was the use of verapamil, ranging from 0.6% to 1.3% in the treatment groups (*Table 3*).

At least one dose reduction criterion was met in 82.5% of patients with dabigatran, 83.1% of rivaroxaban, and 93.5% of apixaban. The corresponding percentages for warfarin were 53.7%, 54.6%, 50.1%, and 44.7% from the lowest to the highest TTR quartile, respectively.

Cause of death analysis

The most common causes of death in reduced dose DOAC and warfarin groups were chronic ischaemic heart disease (19.8% and 19.8%, respectively), Alzheimer disease (9.3% and 9.0%, respectively), and hypertensive heart disease (7.8% and 5.3%, respectively) see Supplementary material online, *Table S5*. When comparing the proportion of deaths associated with our study outcomes, IS, ICH, and bleeding, we observed no proportional increase of these causes for reduced dose DOACs in comparison to warfarin (see Supplementary material online, *Figure S3*).

Discussion

In a comprehensive on-treatment analysis of all patients with AF in Finland, reduced dose DOACs were efficient and safe in stroke

Table 1 Baseline characteristics of patients with new-onset atrial fibrillation stratified by time-in-therapeutic range (TTR) quartiles of warfarin and direct oral anticoagulant type. Standardized mean differences (SMD) of treatment groups before and after weighting, as well as mean risk scores of HAS-BLED and CHA_2DS_2-VASc given

	Warfarin 1st TTR quartile (lowest)	Warfarin 2nd TTR quartile	Warfarin 3rd TTR quartile	Warfarin 4th TTR quartile (highest)	Dabigatran	Rivaroxaban	Apixaban	SMD before weighting	SMD after weighting
N	10 883	10 877	10 893	10 895	2672	1866	3936	–	–
Demographics									
Mean age, years (SD)	73.6 (11.8)	75.3 (10.3)	75.0 (9.7)	73.7 (9.9)	80.5 (7.7)	79.6 (10.0)	84.2 (7.5)	0.511	0.046
Female sex	5305 (48.7)	5898 (54.2)	6044 (55.5)	6524 (51.6)	1549 (58.0)	1056 (56.6)	2572 (65.3)	0.126	0.007
Income quintiles								0.115	–
1st (lowest)	2307 (21.2)	2246 (20.6)	2096 (19.2)	1976 (18.1)	526 (19.7)	363 (19.5)	890 (22.6)	–	–
2nd	2146 (19.7)	2208 (20.3)	2100 (19.3)	2006 (18.4)	592 (22.2)	401 (21.5)	951 (24.2)	–	–
3rd	2012 (21.7)	2201 (20.2)	2210 (20.3)	2203 (20.2)	584 (21.9)	352 (18.9)	842 (21.4)	–	–
4th	2135 (19.6)	2154 (19.8)	2325 (21.3)	2349 (21.6)	449 (16.8)	368 (19.7)	624 (15.9)	–	–
5th (highest)	2282 (21.0)	2068 (19.0)	2162 (19.8)	2361 (21.7)	521 (19.5)	382 (20.5)	627 (15.9)	–	–
Comorbidities									
Renal insufficiency	702 (6.5)	453 (4.2)	349 (3.2)	275 (2.52)	86 (3.2)	207 (11.1)	479 (12.2)	0.183	–
Any vascular disease	3310 (30.4)	3191 (29.3)	3053 (28.0)	2693 (24.7)	936 (35.0)	712 (38.2)	1625 (41.3)	0.155	0.029
Cancer	2344 (21.5)	2480 (22.8)	2336 (21.4)	2172 (20.0)	731 (27.4)	527 (28.2)	1234 (31.4)	0.118	–
Dementia	560 (5.1)	502 (4.6)	426 (3.9)	325 (3.0)	159 (6.0)	133 (7.1)	374 (9.5)	0.112	–
Diabetes	2971 (27.3)	2981 (27.4)	2583 (23.7)	2333 (21.4)	710 (26.6)	560 (30.0)	1038 (26.4)	0.075	0.019
Dyslipidaemia	5870 (53.9)	6252 (57.5)	6108 (56.1)	5812 (53.3)	1669 (62.5)	1194 (64.0)	2582 (65.6)	0.123	–
Heart failure	2580 (23.7)	2338 (21.5)	1777 (16.3)	1382 (12.7)	413 (15.4)	421 (22.6)	998 (25.4)	0.148	–
Hypertension	8516 (78.3)	8780 (80.7)	8752 (80.3)	8461 (77.7)	2271 (85.0)	1606 (86.1)	3424 (87.0)	0.121	0.017
Prior bleeding	1277 (11.7)	1128 (10.4)	970 (8.9)	874 (8.02)	377 (14.1)	272 (14.5)	636 (16.1)	0.117	0.055
Prior IS or TIA	1783 (16.4)	1920 (17.7)	1866 (17.1)	1749 (16.0)	519 (19.4)	330 (17.7)	891 (22.6)	0.064	0.017
CAD	2814 (25.9)	2700 (24.8)	2643 (24.3)	2319 (21.3)	790 (30.0)	618 (33.1)	1411 (35.8)	0.141	–
COPD	860 (7.9)	707 (6.5)	438 (4.0)	332 (3.0)	126 (4.7)	90 (4.8)	214 (5.4)	0.086	–
Medications									
Statin	4113 (38.0)	4580 (42.1)	4597 (42.2)	4385 (40.2)	1183 (44.3)	869 (46.6)	1771 (45.0)	0.073	0.013
Antithrombotic	1095 (10.0)	1195 (11.0)	1077 (9.9)	948 (8.7)	324 (12.8)	258 (13.8)	623 (15.9)	0.093	0.015
Beta blocker	5016 (46.0)	5481 (50.4)	5300 (48.7)	5168 (47.4)	1145 (42.9)	729 (39.1)	1305 (33.2)	0.147	–
Risk scores									
Mean modified HAS-BLED score	2.38 (1.14)	2.42 (1.07)	2.34 (1.01)	2.21 (1.01)	2.54 (0.95)	2.77 (1.08)	2.82 (1.05)	0.260	0.042
Mean CHA_2DS_2-VASc score	3.68 (1.86)	3.88 (1.72)	3.76 (1.67)	3.50 (1.67)	4.36 (1.52)	4.35 (1.68)	4.78 (1.45)	0.337	0.036
Exposure time (days)	235 (191.0)	448 (248.6)	511 (243.8)	467 (243.8)	387 (261.5)	361 (270.0)	358 (242.3)	0.452	–

Abbreviations: SD, Standard Deviation, TTR, Time-in-therapeutic range; TIA, transient ischaemic attack; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease.

Table 2 Number of events, and both crude and weighted incidence rates of study outcomes per 100 patient years in new-onset atrial fibrillation atrial fibrillation stratified by time-in-therapeutic range (TTR) quartiles of warfarin and direct oral anticoagulant type

	Warfarin 1st TTR quartile (lowest)	Warfarin 2nd TTR quartile	Warfarin 3rd TTR quartile	Warfarin 4th TTR quartile (highest)	Dabigatran	Rivaroxaban	Apixaban
Ischaemic stroke							
Events (*n*)	238	236	178	102	43	24	54
Crude rate	3.45	1.79	1.18	0.74	1.63	1.49	1.63
Weighted rate	3.70	1.87	1.21	0.79	1.34	1.25	0.96
Intracranial haemorrhage							
Events (*n*)	249	131	78	44	18	17	36
Crude rate	3.60	0.99	0.51	0.32	0.68	1.06	1.09
Weighted rate	3.80	1.03	0.54	0.34	0.70	0.90	0.70
Any bleeding							
Events (*n*)	987	690	548	361	170	151	217
Crude rate	14.8	5.4	3.7	2.7	6.6	9.8	6.7
Weighted rate	15.5	5.5	3.8	2.8	6.7	8.9	6.4
All-cause mortality							
Events (*n*)	1147	709	351	211	114	131	378
Crude rate	16.45	5.33	2.31	1.53	4.31	8.11	11.40
Weighted rate	18.08	5.86	2.58	1.73	3.97	6.78	7.97
GI bleeding							
Events (*n*)	341	219	129	59	66	59	68
Crude rate	4.97	1.66	0.85	0.43	2.52	3.70	2.06
Weighted rate	5.21	1.73	0.89	0.45	2.30	3.47	1.76

Rates depict events per 100 patient years. Abbreviations: *n* = count, TTR, time-in-therapeutic range, GI, Gastrointestinal.

prevention of elderly patients with new-onset AF, when compared with warfarin therapy. For warfarin, the rates of IS, ICH, bleeding, and mortality were associated with the quality of treatment measured by TTR, and patients with suboptimal TTR had considerably higher risk of adverse outcomes when compared with other treatment groups.

To our knowledge, this is the first nationwide observational study of reduced dose DOACs and warfarin with the individual TTR measured quality of warfarin treatment available, and the first one to include patients from all levels of care, including primary care patients.

Compared with warfarin, patients on reduced dose DOACs were older and had higher prevalence of several comorbidities such as renal insufficiency, dementia, cancer, previous bleeding, or any vascular disease, including coronary artery disease, and they were also more likely to have a history of antithrombotic medication or statin use and were less likely to have history of beta blocker use. A finding mostly attributed to dose-reduction criteria of DOACs.[14,22]

The overall rate of IS varied between 0.74 and 3.45/100 py in warfarin TTR quartiles and between 1.49 and 1.63/100 py for reduced dose DOACs, For reduced dose DOACs, IS rates were lower than reported in a previous study of similar approach by Nielsen *et al.*[25] where the crude rate of IS for reduced dose DOACs varied between 2.77 and 6.44/100 py in a follow-up of 1–2.5 years, while in some other previous studies with reduced dose DOACs, no crude rates of IS were published.[26,27] When comparing the rates of IS between reduced dose and standard dose receiving patients, our results were mostly in accordance with previous studies.[9,28] Also, the risk of IS was very similar in reduced dose DOAC groups, when compared with warfarin therapy of good TTR. Slight variance in outcomes compared with previous studies could be explained by our inclusion of primary care patients, follow-up regimen, or the on-treatment analysis requiring continuous INR-measurements and/or uninterrupted drug-purchases from patients. Due to differences in baseline characteristics, however, the rates of IS for reduced dose DOACs were higher than observed in our previous study of standard dose DOACs.[21]

As expected, the poorest TTR quartiles had significantly elevated risk of ICH in our cohort, compared with the 3rd TTR quartile with the ICH rate varying 10-fold from 0.32 to 3.60/100 py from the highest to the lowest TTR group. For reduced dose DOACs, the rates of ICH ranged from 0.68/100 py of dabigatran to 1.09/100 py of apixaban, which were very similar to rates observed in standard dose DOAC receiving patients in this same study cohort.[21]

Previously, elevated risk for major bleeding has been observed for reduced dose rivaroxaban and high mean TTR-warfarin therapy.[27] Overall, the crude rates of bleeding for reduced dose DOACs were somewhat higher when compared with the previously mentioned study by Nielsen *et al.*[25] which presented varying bleeding rates from 4.76 to 6.60/100 py, which in this study ranged from 6.6 of dabigatran to 9.8/100 py of rivaroxaban, and as a result could be attributed to differences in study protocol.

Similarly to ICH, the lowest TTR quartiles had a significantly elevated risk of GI bleeding, compared with the third TTR quartile. Additionally, GI bleeding rates for reduced dose dabigatran, rivaroxaban, and apixaban support the hypothesis proposed by Vanassche *et al.*, suggesting that among DOACs, rivaroxaban, and dabigatran may be associated with a higher risk of GI bleeding than apixaban. This increased risk is likely due to the partial conversion of dabigatran into its active form within the GI tract, and the high intraluminal concentrations of

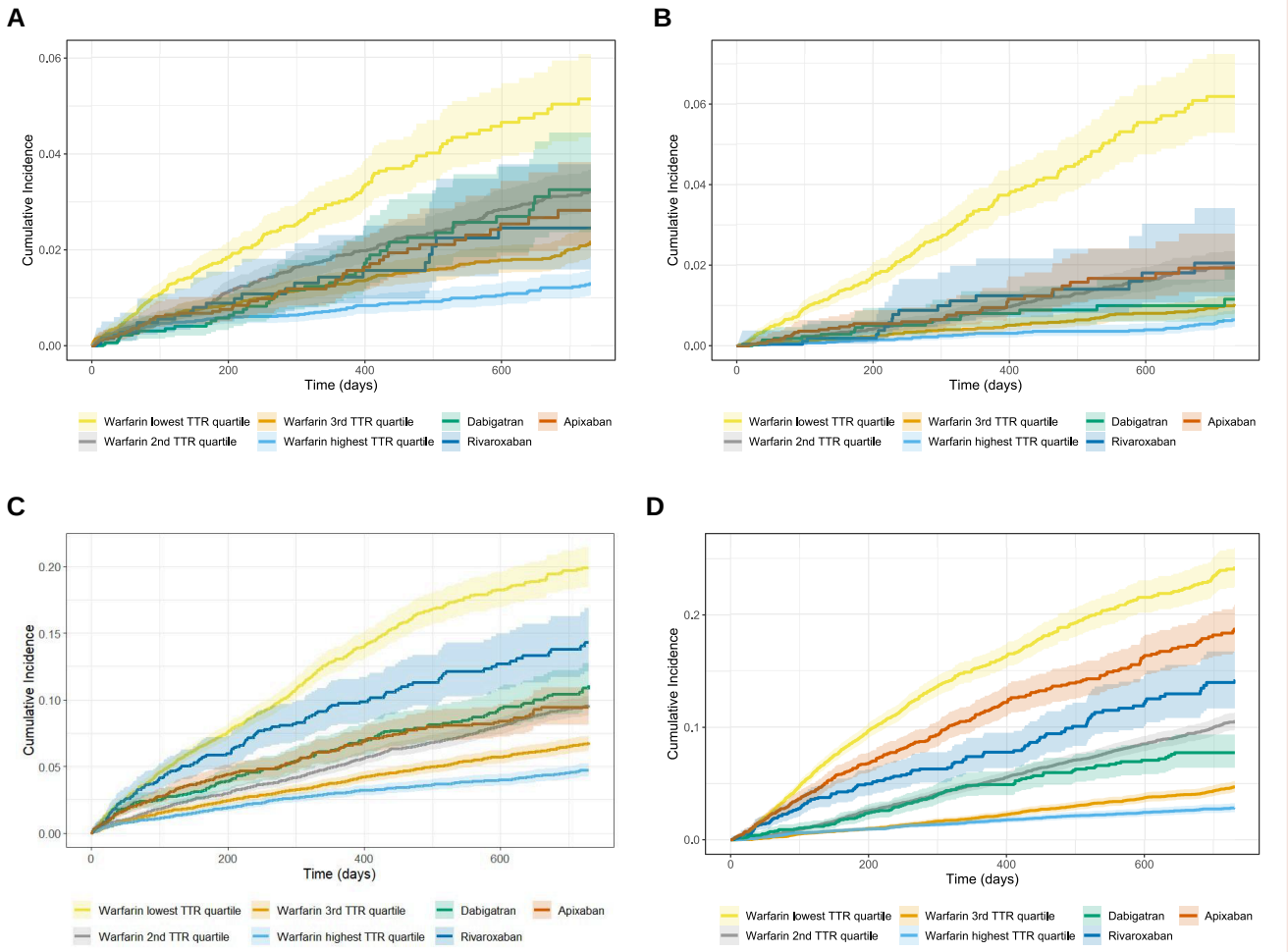


Figure 1 Crude cumulative incidence of (*A*) ischaemic stroke, (*B*) intracranial haemorrhage, (*C*) any bleeding, and (*D*) all-cause mortality in patients with new-onset atrial fibrillation, stratified by oral anticoagulation type and time-in-therapeutic range (TTR) quartiles of warfarin.

rivaroxaban measured in the intestinal lumen.[29] Overall, these results are comparable to findings from a Swedish cohort of AF patients.[27]

The all-cause mortality rate for reduced dose DOACs in this study (4.3–11.4/100 py) was somewhat lower than in the above-mentioned Danish cohort,[25] and in warfarin quartiles the mortality rate varied 10-fold according to TTR, from 16.45 to 1.53/100 py. When compared with the warfarin reference quartile, the mortality rate was significantly higher in all reduced dose DOACs. These differences in bleeding and mortality risk between reduced dose DOACs and warfarin are a novel finding compared with previous studies, which is, in part, is explained by comparison to higher TTR of warfarin treatment than previous studies.[20,27]

To further assess the overall mortality rate, especially for apixaban (11.40/100 py), and for rivaroxaban (9.11/100 py), we analysed the primary causes of death for both warfarin and reduced dose DOACs, in which no obvious difference was found in the most common causes of deaths nor in IS, ICH, or bleeding as a primary cause of death.

A recent meta-analysis of observational studies found no significant difference between outcomes of patients using reduced dose DOACs when comparing patient outcomes of both on-label and off-label dose reduction,[30] even though previous evidence points that inappropriate dosing of DOACs can increase patients' mortality and bleeding risk.[31–33] Although our study did not consider whether the dosing reduction of DOACs was appropriate or inappropriate, patients' eligibility for DOAC dose-reduction criteria was determined. The dose-reduction criteria for DOACs, except dabigatran, were set before the landmark RCTs, and differed for each DOAC. Therefore, the proportion of patients filling any available dose-reduction criterion was characterized. In our sensitivity analysis 82.5–93.5% of patients in reduced dose DOAC groups fulfilled at least one criterion of dose reduction, which indicates that most patients on reduced dose DOACs to be close with guideline recommended population for dose reduction. This finding is also supported by observing the baseline characteristics of both patients on reduced and standard dose DOACs in Finland.[21]

Differing from previous studies, we studied the treatment outcomes in all levels of care, while ensuring that warfarin treatment was investigated under optimal conditions with individual levels of TTR, since the outcomes of warfarin treated patients have improved up to very high TTR percentages of over 80%.[34] The rates of outcomes in this study were in line with previous studies, but for comparison of the risks of study outcomes between established TTR quartiles of warfarin and reduced dose DOACs, no published results of similar approach were available for comparison. Moreover, as known from previous studies of TTR as well as the pivotal DOAC RCTs, reporting of TTR may differ from study to study, and direct comparison of TTR values between

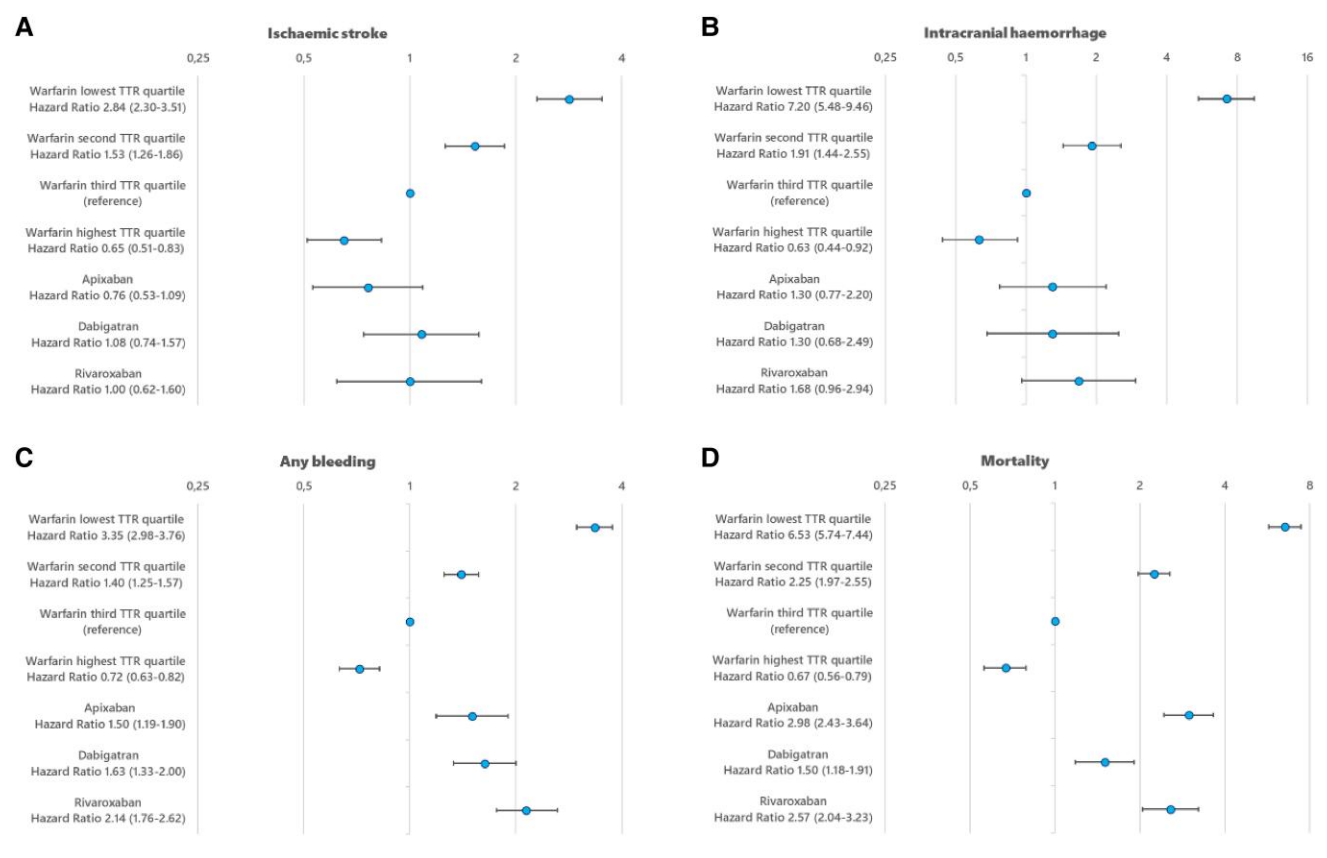


Figure 2 Hazard ratios (HRs) and 95% confidence intervals (CIs) from inverse probability of treatment weighted Cox-regression models for reduced dose direct oral anticoagulants and warfarin in time-in-therapeutic range (TTR)-quartiles. Hazard ratios are given for (*A*) ischaemic stroke, (*B*) intracranial haemorrhage, (*C*) any bleeding, and (*D*) mortality. Reference groups (1) = Warfarin patients of the second best (third) TTR -quartile.

studies has been proven to be methodologically challenging, even if using a well-established tool such as Rosendaal's method.[35]

Our study evaluated warfarin treatment when 'at its best' but also when poorest and compared the outcomes with reduced dose DOACs, with observed low rates of IS, ICH, overall bleeding and death in the highest TTR quartiles. Since no current clinical tool can be used to reliably predict the prospective TTR-level of an individual patient, the superior results of the highest TTR quartiles should not be interpreted as a suggestion to initiate warfarin therapy over reduced dose DOACs as a first drug of choice for new-onset AF patients.[21] Rather, it must be acknowledged that the highest TTR quartiles represent only a particular subgroup of warfarin using patients, and thus, the favourable outcomes in this group may be influenced by factors beyond OAC therapy. Secondly, the baseline characteristics of treatment groups differed significantly in certain aspects (i.e. mean age 84.2 years in apixaban group, vs. 73.7 years in the 4th TTR quartile of warfarin group), which may have effect on the outcomes despite the use of IPTW balancing. Nonetheless, given these considerations, it remains reasonable to assume that continuing warfarin therapy of excellent long-term TTR can be regarded as a viable treatment strategy for IS prevention.

Strengths and limitations

A major strength of our study is the large nationwide cohort of unselected patients from all levels of healthcare including comprehensive information of our patients. In Finland, the whole population is covered by taxation-based healthcare and drug reimbursement system, where it is ensured that treatments are accessible to all citizens, and that prescription drugs are reimbursed. In this study, we have covered all diagnosed patients with AF in Finland—including hospitalizations and primary, secondary, and tertiary outpatient clinics—while previous studies of similar approach may have been subject to selection or information bias due including patients only from hospital level.

We also acknowledge some limitations. This study was non-randomized and observational study and is a subject to both confounding bias and typical limitations of observational studies. Conclusions regarding causality are not to be drawn from the results. Our study relies on administrative data, which is limited by the quality of the registries used. Despite our comprehensive approach, there may remain a range of unmeasured or unknown confounders or errors that could have had an impact on our results. Also, some important information on other confounders such as bodyweight, smoking, alcohol, and substance abuse, ethnicity, use of aspirin, and hereditary information were not available in our data.

Conclusion

In this nationwide analysis with primary care patients included, reduced dose DOACs were efficient and safe in stroke prevention of new-onset AF, when compared with good quality warfarin. Within warfarin groups the risk of poor outcomes was associated with low TTR, while warfarin therapy of excellent TTR-quality was associated with the lowest risk of bleeding and mortality.

Table 3 Dose-reduction criteria of direct oral anticoagulants in patients with new-onset atrial fibrillation, stratified by time-in-therapeutic range (TTR) quartiles of warfarin and direct oral anticoagulant type

		Warfarin 1st TTR quartile (lowest)	Warfarin 2nd TTR quartile	Warfarin 3rd TTR quartile	Warfarin 4th TTR quartile (highest)	Dabigatran	Rivaroxaban	Apixaban
Age ≥ 80 years	Events (*n*)	3785	4356	4031	3479	1812	1135	3 272
	%	36.5	40.0	37.0	31.9	67.8	60.8	83.1
Verapamil use	Events (*n*)	70	78	66	88	15	25	27
bleeding	%	0.6	0.7	0.6	0.8	0.6	1.3	0.7
GFR <50	Events (*n*)	1933	1812	1456	1105	307	687	1 248
	%	19.9	18.4	14.8	11.8	15.5	47.7	38.7
Previous	Events (*n*)	1434	1252	1071	1001	436	322	727
bleeding	%	13.2	11.5	9.8	9.2	16.3	17.3	18.5
Any criteria	Events (*n*)	5470	5605	5145	4454	2059	1436	3 599
	%	53.7	54.6	50.1	44.7	82.5	83.1	93.5

Abbreviations: GFR, Glomerular filtration rate; TTR, Time-in-therapeutic range.

Lead author biography

Alex Luojus is a medical doctor and PhD student at the University of Helsinki, Finland. He serves both as a clinician and researcher, with research focus on cardiovascular medicine. His research is primarily conducted within the Finnish Anticoagulation in Atrial Fibrillation (FinACAF) study group, where he investigates atrial fibrillation and anticoagulation therapy in real-world populations. Dr. Luojus aims to bridge clinical practice and research to improve patient outcomes in cardiovascular care.

Data availability

The data underlying this article were provided by the Finnish institute for health and Welfare, the Population Register center and the social insurance institution (Kela) under license. Based on the contracts with the Finnish registries, restrictions apply to the public availability of these data. Data might be, however, available from the authors upon reasonable request and with permissions needed from the Finnish institute for health and Welfare, the Population Register centre, and the social insurance institution (Kela).

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Ethical approval

The protocol for this study received approval of the Ethics Committee of the Medical Faculty of Helsinki University, Helsinki, Finland (no. 15/2017 and 15/2024). The study was granted research permission by the Helsinki University Hospital (HUS/46/2018 and HUS/217/2024). Study permissions were also issued by separate Finnish register holders (THL 2101/5.05.00/2018; KELA 138/522/2018; Statistics Finland TK-53–1713–18/u1281; Population Register Centre VRK/1291/2019-3; and Tax Register VH/874/07.01.03/2019).

Patient consent was not obtained since the study was conducted without any direct patient contact or involvement, and according to Finnish legislation no patient consent is therefore required. To protect patient personal information, all individual patient data were encrypted by anonymized and individualized study ID's (SIDs). The study is compliant both with the Declaration of Helsinki (revised in 2013).

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