Clinical Kidney Journal, 2023, vol. 16, no. 5, 835–844

https://doi.org/10.1093/ckj/sfad004
Advance Access Publication Date: 5 January 2023
Original Article

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ORIGINAL ARTICLE

Direct oral anticoagulants versus warfarin in patients with non-valvular atrial fibrillation and CKD G3–G5D

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ABSTRACT

Background. The use of direct oral anticoagulants (DOAC) in patients with non-valvular atrial fibrillation (NVAF) and advanced chronic kidney disease (CKD) including dialysis is growing. Several studies have shown favorable results of DOAC compared with warfarin regarding bleeding risk but no difference in stroke protection. However, these studies had poor time in therapeutic range (TTR), in the warfarin comparison group.

Methods. This was a Swedish national cohort study investigating the risk of ischemic stroke and major bleeding on DOAC compared with warfarin in patients with NVAF, glomerular filtration rate category 3–5D (G3–G5D), kidney transplant recipients excluded, between 2009 and 2018. Data extracted from high-quality national healthcare registries including the Swedish Renal Registry, AuriculA (the Swedish national quality register for AF and anticoagulation) and The Stroke Register.

Results. At enrolment, of 2453 patients 59% were treated with warfarin (mean TTR 67%) and 41% with DOAC. Overall, 693 (28.3%) had G3, 1113 (45.4%) G4, 222 (9.1%) G5 and 425 (17.3%) G5D. DOAC compared with warfarin showed lower hazard of major bleeding [hazard ratio 0.71 (95% confidence interval 0.53–0.96)] but no difference in ischemic stroke risk. Mortality was increased during DOAC treatment [1.24 (1.01–1.53)], presumably not a causal association since fewer fatal bleedings occurred on DOAC.

Conclusions. DOAC treatment, compared with warfarin, is associated with almost 30% lower risk of bleeding in patients with NVAF and CKD G3–G5D. The stroke risk is comparable between the treatments. This is the first study comparing DOAC and well-managed warfarin (TTR 67%) in advanced CKD. Ongoing and planned randomized controlled trials need to confirm the possible benefit of DOAC.

LAY SUMMARY

The arrythmia atrial fibrillation leads to an increased risk of stroke. Anticoagulants reduce the stroke risk in the general population. Direct oral anticoagulants (DOAC) have been proven to be equally (or more) effective and safe as the traditional warfarin. Whether this also applies in patients with chronic kidney disease is poorly investigated. This Swedish observational study compares DOAC and well-managed warfarin regarding the risk of stroke and bleeding in patients with chronic kidney disease. A total of 2453 patients with atrial fibrillation and moderate to advanced chronic

Received: 11.9.2022; Editorial decision: 21.12.2022

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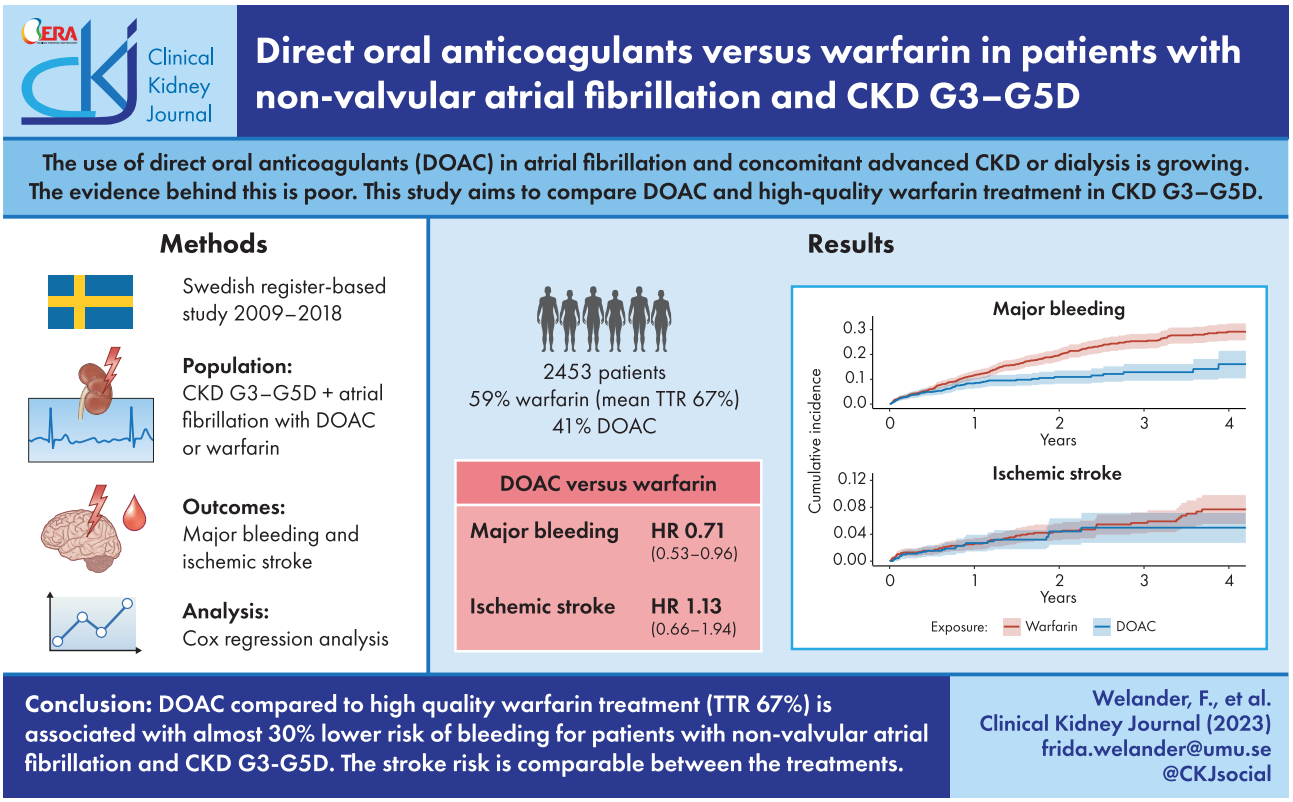
kidney disease, including patients on dialysis, are included. DOAC and warfarin treatment are compared using regression models. DOAC treatment is associated with 30% lower risk of major bleeding compared with warfarin. The stroke risk is comparable between the treatments. This reiterates the results of previous studies, for the first time with a well-managed warfarin comparison group. Randomized controlled studies are needed to confirm the results.

GRAPHICAL ABSTRACT



Keywords: anticoagulants, atrial fibrillation, chronic kidney disease, dialysis

INTRODUCTION

The significant burden of non-valvular atrial fibrillation (NVAF) affecting >20% of patients with advanced chronic kidney disease (CKD) and patients on dialysis provides a possible target for intervention—the possibility to reduce morbidity and mortality caused by thromboembolic stroke [1]. Oral anticoagulants (OAC) reduce the risk of thromboembolic stroke by approximately two-thirds in a general NVAF population [2]. The pivotal studies of direct oral anticoagulants (DOAC) in atrial fibrillation (AF) have shown equal, or even better, efficacy and safety than warfarin [3–6]. It is not known whether this also applies to patients with CKD glomerular filtration rate (GFR) category 4–5 (G4–G5) or patients on dialysis (G5D) since these patients were excluded (or included in a small number) in these trials. Even so, clinical experience of OAC in advanced CKD is continuously growing. American guidelines suggest warfarin or apixaban treatment to stable dialysis patients with NVAF, while European guidelines do not have this recommendation [7, 8]. DOAC is an appealing choice due to a set dose and the possible benefit of avoiding the dreaded complication of calciphylaxis, which is associated with vitamin K antagonists in particularly dialysis patients [9].

A meta-analysis including both available data from the pivotal DOAC trials as well as large observational studies favors the use of DOAC compared with warfarin in G3–G4 regarding the risk of ischemic stroke and intracranial bleeding [10]. Data on DOAC versus warfarin in CKD G5, end-stage kidney disease not on dialysis, is limited. Weir *et al.* showed no difference in the risk of stroke or major bleeding in G4–G5 when comparing rivaroxaban and warfarin [11]. More data are available on DOAC versus warfarin in dialysis patients. One small randomized controlled trial (RCT) (n = 132) showed favorable results of rivaroxaban compared with warfarin regarding a cardiovascular composite endpoint and bleeding, while another RCT (n = 154) comparing apixaban and warfarin in patients on hemodialysis was underpowered to draw conclusions on safety and efficacy [12, 13]. The largest conducted observational trial on apixaban versus warfarin in dialysis patients showed no difference in stroke rate but favored DOAC for avoiding major bleeding [14]. Another observational study comparing dabigatran or rivaroxaban with warfarin showed increased risk of bleeding with DOAC [15].

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Existing data are difficult to compare since the quality of warfarin treatment, measured as time in therapeutic range (TTR) is either poor or not disclosed [11–14]. Also, the stroke-preventing effect of OAC in G5 and G5D is yet to be proven [16–18].

The present study aims to investigate the risk of ischemic stroke and major bleeding of DOAC compared with well-managed warfarin treatment in patients with NVAF and CKD G3–G5D, hypothesizing that DOAC confers lower risk of major bleeding but is non-inferior to warfarin regarding the risk of ischemic stroke.

MATERIALS AND METHODS

This was a register-based study with a Swedish cohort adhering to the Declaration of Helsinki, approved by the Swedish Ethical Review Authority (registration number 2019-03289). Personal consent was not needed due to the register-based design.

Data sources

All Swedish inhabitants are provided with a unique identity number making it possible to link personal registry data [19]. The included registers are as follows. The Swedish Renal Registry (SRR), a quality register including patients from 98% of all nephrology clinics in Sweden monitoring CKD and kidney replacement therapy (KRT) care where estimated glomerular filtration rate (eGFR) is reported at least yearly. Patients are registered from G3b (some from G3a) through dialysis. Over 80% of CKD patients are registered before start of KRT and >90% of all dialysis patients are included [20]. The Swedish National Patient Register (NPR) governed by the National Board of Health and Welfare with almost complete coverage of all hospital admissions providing information on International Classification of Diseases, Tenth Revision (ICD-10) and surgical procedure codes, as well as admission and discharge dates. The register has high validity and the positive predictive value of AF is 97% [21]. The Stroke Register, a national Swedish quality register with high validity of the stroke diagnosis, monitoring the care of 94% of all acute stroke in Sweden [22]. The Stroke Register provides the correct date of the index stroke, in comparison with NPR where diagnoses are reported *a posteriori* at discharge from the hospital. AuriculA, a national Swedish quality register for atrial fibrillation and oral anticoagulation. The register was active between 2006 and 2018 including whole regions, with no evident selection bias. AuriculA provides data on the dosage and treatment periods of OAC as well as the information on International Normalized Ratio (INR) for warfarin users. The Swedish Prescribed Drug Register (PDR) has 100% coverage of all dispenses at Swedish pharmacies since 2006. The Cause of Death Register (CDR) includes date of death of all deceased in Sweden.

Inclusion

Adult patients with concomitant AF in NPR and CKD G3–G5D in SRR were included. Exclusion criteria were valvular AF due to mitral stenosis or mechanical heart valve replacement (ICD-10 codes Z952, I050, I342, Q232), kidney transplant recipients in SRR or Z940 (ICD-10) and V42A (ICD9) in NPR and long-term OAC users (any OAC prescription 3–4 years prior t0). A patient is censored if kidney transplanted or diagnosed with valvular AF during follow-up. A patient's individual start date (t0) occurred when the criterions for AF, G3–G5D and a treatment period of OAC was fulfilled after study start (1 January 2009), stop date if censored or at the end of the study (31 December 2018). Baseline data were obtained from NPR, AuriculA and SRR. Sources of included variables can be found in Supplementary data, Table S1. Baseline data were used to score CHA_2DS_2-VASc for stroke risk assessment [23].

Kidney function status

eGFR from SRR was categorized according to KDIGO guidelines (eGFR 30–59 mL/min/1.73 m^2, G3; eGFR 15–29, G4; eGFR <15, G5; on dialysis, G5D) [24]. eGFR could decline during the study; G3 could turn to G4 and G5 and G5D while the patient remained in the study. Increasing eGFR was ignored. Dialysis start date was provided by SRR.

Treatment

Warfarin treatment periods were collected from AuriculA. DOAC treatment periods were calculated by dispensation dates from PDR assuming standard pill usage plus a grace period of 30 days (4 if they were dose dispensed). Undefined treatment was collected from PDR and was either a period of no OAC or a period with warfarin dispenses that did not match an AuriculA period. A warfarin dispense from PDR (P; warfarin) is counted as a 6-month treatment period + grace period of 30 days, possibly extended by a new dispensation. P; warfarin periods are necessary to label the OAC treatment new (no OAC treatment periods the last year) or old (OAC periods within a year). Quality of warfarin treatment was calculated as TTR by linear interpolation of available INR measurements according to Rosendaal *et al.* [25] .

Outcomes

Primary outcomes were ischemic stroke and major bleeding (requiring inpatient care). The stroke register and NPR were used for ischemic stroke diagnosis (ischemic strokes from NPR are disregarded the first 14 days after a preceding stroke diagnosis at inclusion if there was an ischemic stroke at t0 or 14 days prior, to avoid doublets of an index stroke). Major bleeding requiring inpatient care was collected from NPR and all-cause mortality from CDR. Death was a secondary outcome. After the occurrence of a primary outcome the patient was censored for this event but remained in the cohort for other outcomes. After death a patient was censored. A list of outcomes and sources is found in Supplementary data, Table S1.

Statistical analysis

Data was processed using R 4.2.0 (R Core Team, 2022). Outcomes were analysed according to ongoing treatment period (treatment was allowed to be switched during follow up) and presented with absolute numbers and rates with 95% confidence interval (CI), as well as with unadjusted Kaplan–Meier curves. Cox regression analysis with time dependent covariates was used to compare treatment periods of DOAC and warfarin in all patients (Model 1). Covariates adjusted for were age, sex, GFR category, years from study start and for any prior presence of the following: diabetes mellitus, hypertension, congestive heart failure, stroke or transient ischemic attack (TIA), vascular disease, major bleeding, myocardial infarction, percutaneous coronary intervention (PCI) and excessive alcohol use. Restricted cubic splines were used for quantitative variables. Adding GFR category as an interaction to Model 1 created Model 2 with G5/G5D merged, due to small sample size. Due to unexpected high hazard of death for DOAC

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compared with warfarin, an additional analysis was carried out *a posteriori*—cumulative incidence of death within 7 days after major bleeding (possible fatal bleeding).

A sensitivity analysis was performed comparing DOAC and warfarin among new treatments (i.e. patients with no treatment during the previous year) to assimilate a cohort of OAC-naïve patients. Balance primarily was sought on CKD category and age. Secondarily balance was sought on previous stroke or TIA, previous intracranial bleeding, previous gastrointestinal bleeding, diabetes mellitus and previous myocardial infarction. CKD category was unevenly distributed among warfarin ($n = 699$) and DOAC ($n = 457$) in this subset. Optimal matching was used, where we allowed comparison clusters containing up to 10 controls to a case, or up to 3 cases to a control (with each cluster always containing either exactly one case or exactly one control). Each case receives a weight of one, and controls receive a weight such that the clusters are balanced (i.e. a weight ranging from 1/10 to 3). These weights were then used in the Cox regression along with the clusters to obtain robust standard errors. Matching was done using Mahalanobis distance. Covariates were added as long as the overall balance seemed to improve and without looking at outcome data. This procedure resulted in using all but previous myocardial infarction as matching covariates, and 564 of the warfarin controls (weighted to 457).

Two more sensitivity analyses were performed, one including all patients G3–G5 (G5D excluded) comparing DOAC and warfarin and one with only correctly dosed apixaban compared with warfarin in G3–G5 (G5D excluded). G5D was excluded in both analyses due to the heterogenicity of the group with two dialysis modalities; also the correct DOAC dosage in G5 is not known. The cohort with correctly dosed apixaban included patients on apixaban in G3 if the dose was correctly reduced (2.5 mg twice daily) when fulfilling 2 of 3 criteria: age ≥80 years, body weight ≤60 kg and serum creatinine ≥133 µmol/L, or correctly prescribed standard dose (5 mg twice daily) if fulfilling ≤1 criteria. If missing values were present, making it impossible to know the correct dose, this time on apixaban was not included. Patients in G4–G5 were included if prescribed reduced-dose apixaban. The two sensitivity analyses used the same model and adjustments as in Model 1 described above (just different inclusion criteria).

RESULTS

Steps of inclusion

The registry outtake from SRR consisted of 15 218 patients with AF. Of these, 14 097 were candidates for inclusion (GFR category 3–5D). After the exclusion of valvular AF and kidney transplant recipients, 12 106 patients were eligible for inclusion. Of these, 8318 patients were excluded due to no treatment periods of OAC and 1335 were excluded due to long-term OAC use, leaving 2453 included patients. Total follow-up time was 5401.1 years; restriction to OAC treatment periods yielded 4462.1 years.

Cohort description

Altogether 2453 patients were included. Median age was 76.7 years and 31.9% were female (Table 1). At baseline 693 (28.3%) had G3, 1113 (45.4%) G4, 222 (9.1%) G5 and 425 (17.3%) G5D. At inclusion 59% were treated with warfarin and 41% with DOAC with a higher percentage of women on DOAC (35% females on DOAC compared with 30% on warfarin). There was an overweight of DOAC users compared with warfarin in G3 at inclusion (62.9% vs 37.1%). G4–G5D had higher percentage of warfarin users compared with DOAC (G4, 55.7% vs 44.3%; G5, 85.8% vs 14.2%; G5D, 91.6% vs 8.4%). Of the 1005 patients on DOAC, 81% had apixaban (77.7% reduced dose, 22.3% standard dose), 14.7% rivaroxaban (76.4% reduced dose, 23.6% standard dose), 2.8% dabigatran (78.6% reduced dose, 21.4% standard dose) and 1.4% edoxaban reduced dose. Mean TTR for warfarin treatment was 67.0% (71.4% in G3, 70.7% in G4, 67.7% in G5 and 60.9% in G5D). eGFR could worsen during follow-up—in total 1292 patients entered G4 and 427 G5 (Supplementary data, Table S2). Altogether 653 patients started or were on dialysis during follow-up (67% hemodialysis, 33% peritoneal dialysis). A total of 1156 patients had new OAC treatment (457 DOAC, 699 warfarin). These patients had no treatment periods of OAC for the last 365 days (as compared with the cohort with all patients containing both OAC-naïve patients as well as those on OAC the year before inclusion). The Supplementary data include a baseline table with characteristics sorted by GFR category at inclusion (Table S2), baseline data for the matched cohort (Table S3) and standardized differences before and after weighting (Fig. S1). Of 853 apixaban users in G3–G5 at inclusion (t0), 95 patients had correctly prescribed standard dose and 64 patients had incorrectly standard dose, 491 had correct reduced dose and 131 incorrect reduced dose. The correct apixaban dose could not be determined for 72 patients due to missing data. Altogether 715 patients had correctly dosed apixaban at some point during follow-up. The patients' characteristics from the first date of correctly dosed apixaban are presented in Table 1. Censoring by death occurred for 260 patients on DOAC and 757 patients on warfarin, while censoring due to new onset valvular heart disease occurred for 7 patients on DOAC and 14 patients on warfarin. Censoring due to kidney transplantation occurred for 1 patient on DOAC (dabigatran) and 53 patients on warfarin.

Primary and secondary outcomes

There was no difference between DOAC and warfarin regarding rates of ischemic stroke or death. DOAC conferred a lower bleeding rate than warfarin for all patients (Table 2 and Fig. 1). The adjusted material displays lower hazard of major bleeding for DOAC compared with warfarin for all patients [hazard ratio (HR) 0.71 (0.53–0.96)] and G4 [0.61 (0.40–0.92)] but no significant difference in G3 and G5/5D (Fig. 2). After adjustments there was no significant difference in risk of ischemic stroke between DOAC and warfarin in all patients [HR 1.13 (95% CI 0.66–1.94)], or in separate GFR categories [G3, 2.23 (0.78–6.36); G4, 1.01 (0.50–2.04); G5–G5D, 0.73 (0.10–5.52)]. The hazard of death was slightly increased for DOAC compared with warfarin after adjustments for all patients [1.24 (1.01–1.53)] and G4 [1.46 (1.11–1.90], but not in G3 and G5/5D.

Due to the higher hazard of death for DOAC treatment an additional analysis was carried out to investigate whether DOAC was associated with more fatal major bleedings. Thirteen patients on warfarin died within 7 days after a major bleeding compared with only one death on DOAC.

Sensitivity analyses

A first sensitivity analysis was performed including only patients on new OAC treatment (no OAC treatment the last year), thus excluding patients on long-time stable OAC treatment. Higher rates of all primary outcomes were found in this group, compared with the main cohort (Table 2). New DOAC treatment

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Table 1: Baseline characteristics for 2453 patients at the time of first treatment with either warfarin or DOAC, as well as the corresponding treatments restricted to only new treatments (no OAC within 12 months prior); baseline characteristics for patients exclusively on correctly dosed apixaban restricted to G3–G5 is also presented[a]

Characteristics	Total (*N* = 2453)	First DOAC (*N* = 1095)	First warfarin (*N* = 1495)	New DOAC (*N* = 463)	New warfarin (*N* = 699)	Correctly dosed apixaban G3–G5 (*N* = 715)
Demographics						
Age, years	76.7 (70.9–81.8)	77.4 (72.0–82.4)	76.4 (70.1–81.4)	78.5 (72.7–83.6)	76.2 (69.3–81.6)	79.1 (73.5–83.6)
Female	783 (31.9)	383 (35.0)	448 (30.0)	169 (36.5)	197 (28.2)	267 (37.3)
CKD G3	693 (28.3)	471 (43)	264 (17.7)	193 (41.7)	80 (11.4)	216 (30.2)
CKD G4	1113 (45.4)	541 (49.4)	650 (43.5)	238 (51.4)	263 (37.6)	470 (65.7)
CKD G5	222 (9.1)	37 (3.4)	195 (13)	13 (2.8)	101 (14.4)	29 (4.1)
CKD G5D	425 (17.3)	46 (4.2)	386 (25.8)	19 (4.1)	255 (36.5)	-
Medical history						
Diabetes mellitus	1180 (48.1)	525 (47.9)	724 (48.4)	209 (45.1)	362 (51.8)	345 (48.3)
Hypertension	2288 (93.3)	1023 (93.4)	1395 (93.3)	440 (95.0)	663 (94.8)	671 (93.8)
Stroke	507 (20.7)	225 (20.5)	309 (20.7)	96 (20.7)	170 (24.3)	148 (20.7)
TIA	230 (9.4)	99 (9.0)	144 (9.6)	43 (9.3)	73 (10.4)	177 (24.8)
COPD	364 (14.8)	188 (17.2)	199 (13.3)	73 (15.8)	80 (11.4)	128 (17.9)
Cancer	704 (28.7)	278 (25.4)	459 (30.7)	123 (26.6)	227 (32.5)	202 (28.3)
Congestive heart failure	1326 (54.1)	597 (54.5)	810 (54.2)	223 (48.2)	335 (47.9)	416 (58.2)
Myocardial infarction	832 (33.9)	352 (32.1)	527 (35.2)	152 (32.8)	259 (37.1)	232 (32.4)
Anaemia	911 (37.1)	423 (38.6)	545 (36.5)	184 (39.7)	263 (37.6)	287 (40.1)
Dementia	20 (0.82)	10 (0.91)	14 (0.94)	3 (0.65)	6 (0.86)	7 (0.98)
Liver disease	92 (3.8)	45 (4.1)	51 (3.4)	17 (3.7)	22 (3.1)	31 (4.3)
Excessive alcohol use	88 (3.6)	49 (4.5)	45 (3)	20 (4.3)	20 (2.9)	22 (3.1)
History of falls	289 (11.8)	146 (13.3)	164 (11.0)	66 (14.3)	91 (13.0)	103 (14.4)
Any previous major bleeding	979 (39.9)	450 (41.1)	590 (39.5)	190 (41)	296 (42.3)	307 (42.9)
Gastrointestinal bleeding	338 (13.8)	173 (15.8)	189 (12.6)	76 (16.4)	90 (12.9)	124 (17.3)
Intracranial bleeding	94 (3.8)	61 (5.6)	38 (2.5)	28 (6)	23 (3.3)	39 (5.5)
CHA2DS2-VASC	5 (4–6)	5 (4–6)	5 (4–6)	5 (4–6)	5 (4–6)	5 (4–6)

[a]Data are presented as count (percentage) for categorical variables and as median (Q1–Q3) for numerical variables. Note: patients are allowed to switch treatment during follow-up; consequently, first/new warfarin and first/new DOAC treatment periods do not represent unique patients.

displayed lower event rates/100 years of major bleeding than new warfarin [9.1 (95% CI 6.3–12.9) vs 14.5 (12.0–17.4)] but comparable rates of stroke and death. Due to differences in distribution of exposure (DOAC and warfarin) depending on GFR category (7% of DOAC users in G5/5D compared with 51% of warfarin users in G5/5D), matching was carried out. Matching yielded 1021 individuals and 994.5 years of follow-up. Comparison of new DOAC and warfarin treatment in the matched and weighted cohort showed comparable hazards of major bleeding, stroke and death [HR 0.96 (95% CI 0.58–1.59), 0.70 (0.27–1.78) and 0.86 (0.56–1.32), respectively] (Fig. 3).

A second sensitivity analysis was performed using the main analysis (Model 1 with the same adjustments) but excluding patients on dialysis. The results presented in Fig. 3 are very similar to the results in the main analysis of all patients in Fig. 2, with reduction of major bleedings [HR 0.67 (0.49–0.93)], no significant difference of ischemic stroke [1.39 (0.77–2.51)] but higher hazard of death [1.38 (1.10–1.74)].

A final sensitivity analysis investigated exclusively patients on correctly dosed apixaban in G3–G5 using Model 1 (same adjustments). Unadjusted rates are presented in Table 2 where DOAC confers a lower rate of bleeding, but a higher rate of death compared with warfarin. The adjusted model demonstrates lower risk of major bleeding [HR 0.58 (0.39–0.86)], no difference in risk of ischemic stroke [0.89 (0.42–1.92)] and higher hazard of death [1.40 (1.08–1.82)] (Fig. 3).

DISCUSSION

To our knowledge, this is the first observational study comparing DOAC and well-managed warfarin (mean TTR 67%) in NVAF, including the whole spectrum of moderate to advanced CKD, G3–G5D.

Compared with warfarin, DOAC is associated with lower risk of major bleeding but no difference in stroke risk in this cohort of patients with G3–G5D, a majority with G4 and G5/5D. The possible favorable bleeding profile of DOAC in CKD was also seen in recent meta-analyses [26, 27]. Like several other studies including mainly G4–G5D, there is no difference in stroke protection comparing DOAC and warfarin [12, 14, 26]. Our findings contribute to improved understanding of the role of DOAC in CKD, due to the well-managed warfarin comparison group, since a poor TTR has given previous studies less credibility [11, 12].

When adding the eGFR interaction, the favorable bleeding profile of DOAC compared with warfarin is only seen in the largest group, G4. The smaller G3 and G5/5D show similar bleeding risks between the treatments. The Valkyrie study showed a favorable bleeding profile of DOAC (rivaroxaban) compared with warfarin in 132 dialysis patients. Noteworthy is that this study had a poor TTR (48%) in the warfarin group, maybe affecting the comparison in favor of DOAC. More evidence is needed to confirm the possible benefit of DOAC compared with well-managed warfarin treatment in G5D.

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Table 2: Number of events, exposed time (years) and event rates per 100 years for warfarin and DOAC (all treatment periods), sorted by GFR category[a]; event rates for patients with new treatment (no OAC 12 months prior), before matching and weighting, are also presented

		Warfarin ($n = 1448$)[b]			DOAC ($n = 1005$)[b]		
Event	GFR category[c]	Time (100 years)	Events (n)	Rate (95% CI) (n/100 years)	Time (100 years)	Events (n)	Rate (95% CI) (n/100 years)
Major bleeding	All	28.3	275	9.7 (8.6–10.9)	12.2	77	6.3 (5.0–7.8)
	G3	5.0	29	5.8 (4.0–8.2)	5.7	34	6.0 (4.2–8.2)
	G4	12.7	104	8.2 (6.7–9.9)	5.9	33	5.6 (3.9–7.8)
	G5/5D	10.6	142	13.4 (11.3–15.7)	0.57	10	17.4 (8.9–31.3)
	New treatment[d]	7.5	109	14.5 (12.0–17.4)	3.3	30	9.1 (6.3–12.9)
	Correctly dosed apixaban[e]	20.9	177	8.5 (7.3–9.8)	6.8	39	5.7 (4.1–7.8)
Ischemic stroke	All	31.0	63	2.0 (1.6–2.6)	12.5	28	2.2 (1.5–3.2)
	G3	5.1	5	0.98 (0.4–2.2)	5.9	14	2.4 (1.4–3.9)
	G4	13.3	30	2.3 (1.6–3.2)	6.0	13	2.2 (1.2–3.6)
	G5-G5D	12.5	28	2.2 (1.5–3.2)	0.58	1	1.7 (0.1–8.5)
	New treatment[d]	8.0	21	2.6 (1.7–3.9)	3.4	8	2.4 (1.1–4.5)
	Correctly dosed apixaban G3–G5[e]	22.0	41	1.9 (1.4–2.5)	7.0	11	1.6 (0.8–2.7)
All-cause mortality	All	31.9	422	13.2 (12.0–14.5)	12.8	166	13.0 (11.1–15.1)
	G3	5.3	33	6.2 (4.4–8.6)	6.0	58	9.7 (7.4–12.4)
	G4	13.7	149	10.9 (9.2–12.7)	6.1	97	15.8 (13.0–19.3)
	G5/5D	12.9	240	18.6 (16.4–21.1)	0.61	11	18.0 (9.5–31.3)
	New treatment[d]	8.12	127	15.6 (13.1–18.5)	3.4	41	12.0 (8.8–16.2)
	Correctly dosed apixaban[e]	22.6	243	10.7 (9.5–12.2)	7.1	102	14.4 (11.8–17.4)

[a]Treatment time (time) presented as years. Events presented as number of events occurred. Event rate (rate) presents events per 100 person years with 95% CI. Only the first type of every outcome is counted. After the occurrence of an event a patient is censored for this event but remains in the cohort for other outcomes.
[b]Numbers (n) at risk at baseline.
[c]CKD G3 ($n = 693$), G4 ($n = 1292$), G5–G5D ($n = 904$), at risk at baseline for all outcomes.
[d]New DOAC ($n = 457$), new warfarin ($n = 699$).
[e]Correctly dosed apixaban G3–G5 ($n = 715$), warfarin G3–G5 ($n = 1066$); numbers (n) at risk at baseline.

The present study shows comparable rates of all-cause mortality between all DOAC as a group and warfarin but after adjustment the risk of death seems higher for DOAC. Correctly dosed apixaban displays both higher unadjusted rate and adjusted HR of all-cause mortality compared with warfarin. This is not in line with previous studies showing no difference or lower mortality for DOAC compared with warfarin in advanced CKD [14, 28, 29]. However, the present study showed fewer fatal bleedings on DOAC compared with warfarin, thus the association is not likely causal. More likely, there are bias and unmeasured confounders present that we were unable to adjust for. Since DOAC was a novelty during the study in 2009–18, there might be an overrepresentation of patients on warfarin with an older, more stable treatment who have already been proven to tolerate the treatment. When comparing only patients with new OAC treatment there is no difference in the risk of death. Also, there could be indication bias contributing to the higher mortality in DOAC since patients waiting for a kidney transplant during the time of the study were almost exclusively on warfarin. These patients are usually healthier and less likely to die. Patients censored due to kidney transplantation were warfarin users in 53 of the 54 cases, which also might contribute to informative censoring. Since the unadjusted Kaplan–Meier curves in the main analysis show similar cumulative incidence of death between the treatments, there might also be overadjustment present. Of note is that a small recent RCT ($n = 154$) comparing apixaban and warfarin in patients on hemodialysis demonstrated numerically more deaths on apixaban. This study was inadequately powered to draw conclusions on efficacy or safety, but this still calls for the need of further studies [13].

The sensitivity analysis comparing patients with new OAC treatments shows no difference in risk of stroke or bleeding when comparing DOAC and warfarin. This method of comparison is probably more accurate, since it excludes patients who have already been proven to tolerate the treatment. However, this analysis should be interpreted with caution since the number of included patients is few. Investigating only patients on correctly dosed apixaban G3–G5 as well as all patients in G3–G5, excluding the heterogenous group of patients on dialysis, shows very similar results as the main analysis. Adding these results to the main analysis, DOAC seems comparably (or more) safe and comparably effective to well-managed warfarin. DOAC is an easy treatment and seems like a compelling alternative to warfarin in NVAF and moderate to advanced CKD.

This study has limitations. The retrospective design is, naturally, the main issue. This leads to multiple bias and confounders, many of which are difficult to compensate for. Patients with G5/5D were prescribed DOAC off-label since this indication is not yet recommended in Europe. These patients are few and probably carefully selected, therefore it is difficult to generalize from such a selected group. Also, there is an uncertainty in the DOAC treatment periods derived from dispensing data from PDR (compared with registered warfarin treatment periods from AuriculA), leading to uncertainty over whether an event occurred on- or off-treatment. Retaining the treatment periods from two different sources is also likely to confound the results. The DOAC group was dominated by apixaban followed

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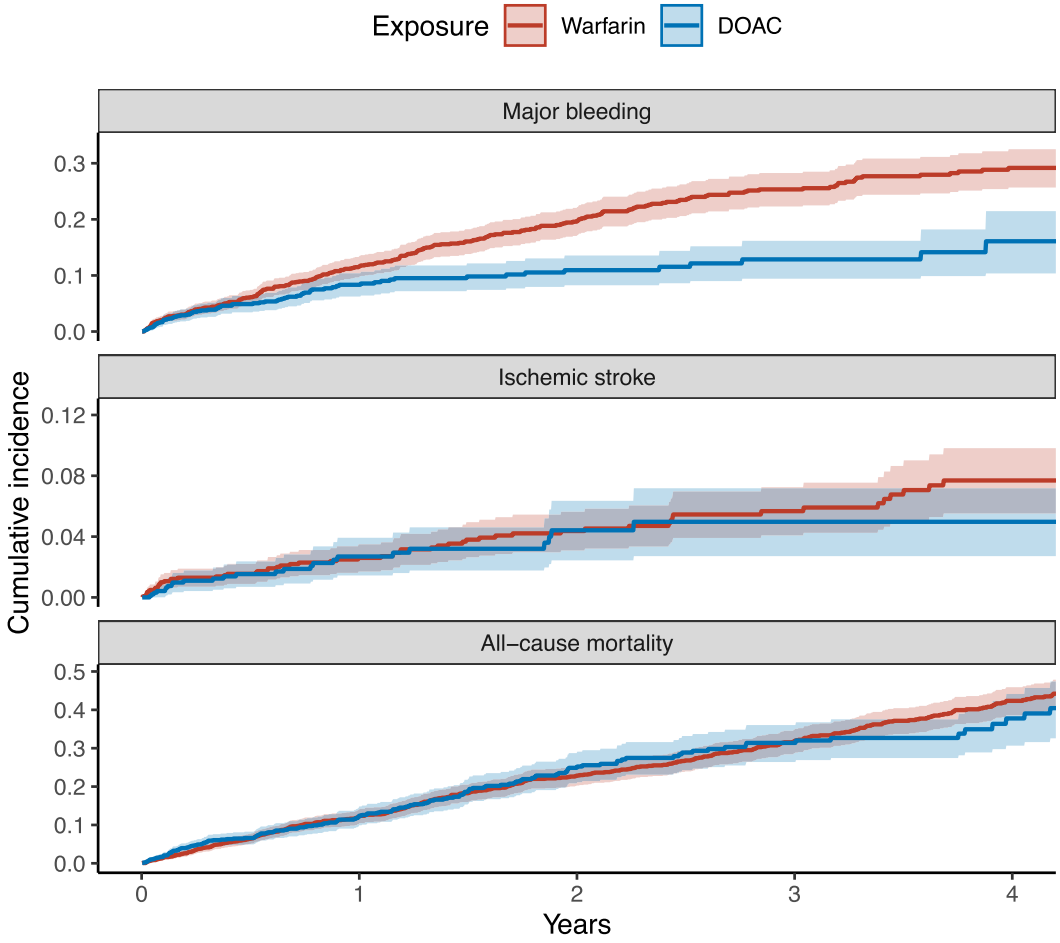

Major bleeding: Warfarin	1448	863	534	353	213
: DOAC	1005	412	209	104	45
Ischemic stroke: Warfarin	1448	919	597	402	241
: DOAC	1005	424	213	108	45
All–cause mortality: Warfarin	1448	933	613	419	255
: DOAC	1005	434	219	111	48

Figure 1: Unadjusted Kaplan–Meier curves for primary and secondary outcomes comparing all treatment periods of warfarin (red) and DOAC (blue). Graphs presented with years since entry (up to 4 years) on the x-axis and cumulative incidence on the y-axis.

by rivaroxaban; only a small number of patients on dabigatran and edoxaban were included. It would have been desirable to adjust for dosage or type of DOAC in the analysis. Due to small sample size this adjustment was not possible. Previous studies have shown more favorable results for apixaban than for example dabigatran [14, 15]. To compensate for the heterogenicity in the DOAC group a sensitivity analysis of exclusively correctly dosed apixaban was performed. This analysis showed similar results to the main analysis, implying robustness of the results. The stroke rate is low, with few events in G5–G5D, which calls for caution while interpreting the results, although very similar stroke rates were presented by Weir *et al.* [11]. The present study only includes patients at nephrology clinics. This selection might exclude stable patients with G3–G4 not yet referred to nephrology clinics, as well as frail patients in G5 with short expected survival, not suitable for kidney replacement therapy.

CONCLUSIONS

In the present study DOAC treatment, compared with warfarin, is associated with almost 30% lower risk of bleeding in patients with NVAF and CKD G3–G5D. The risk of ischemic stroke is comparable between the treatments. This reiterates the results of previous studies, but for the first time with a well-managed warfarin comparison group (TTR 67%). Ongoing and planned RCTs in this field are needed to confirm the possible benefit of DOAC (or OAC at all) in advanced CKD.

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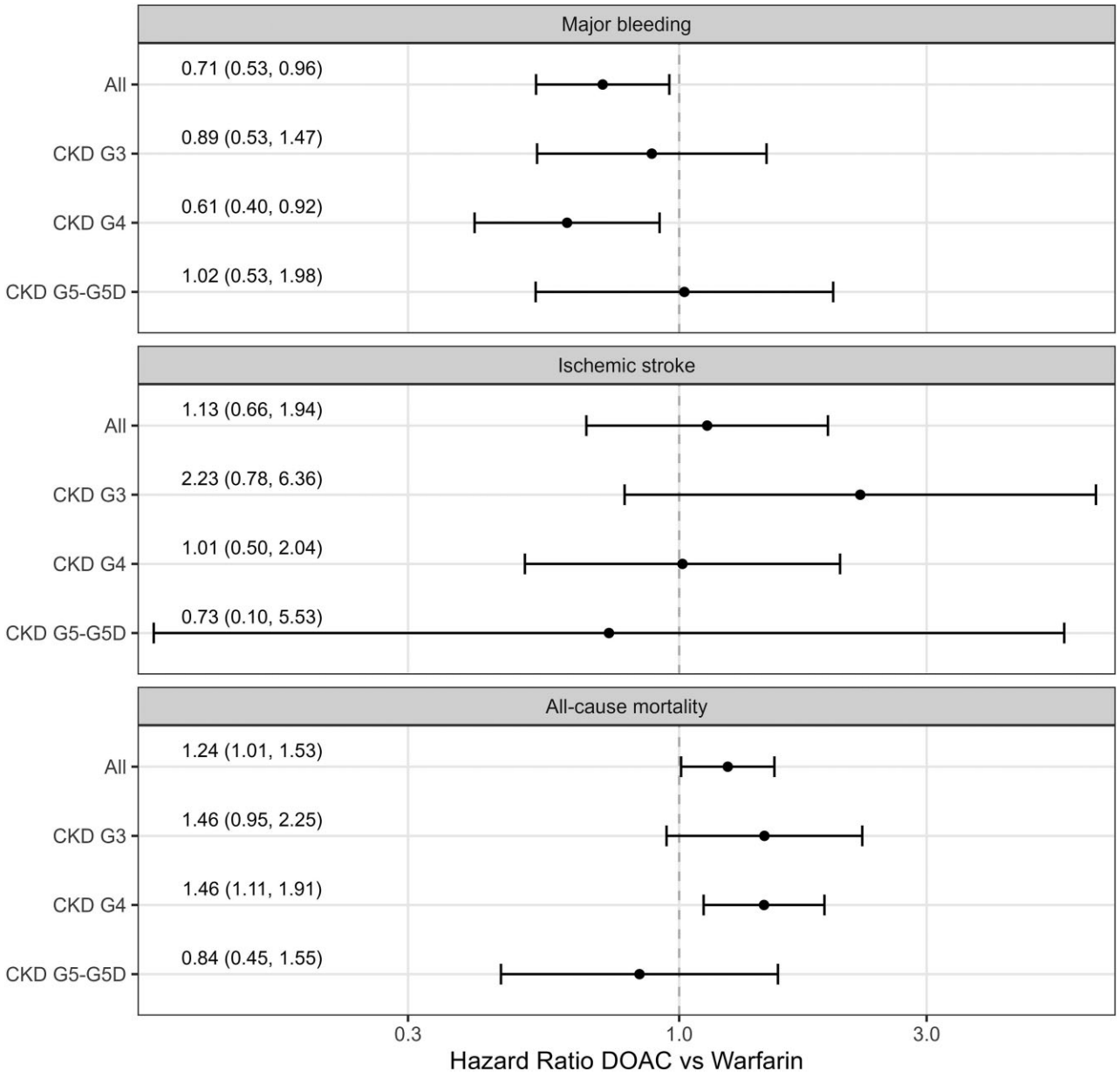

Figure 2: Adjusted models for DOAC vs warfarin. Data presented as HR (95% CI). 'All patients' with all 2453 patients (Model 1), and 'CKD G3–G5/5D' (Model 2) created by adding GFR category as an interaction to Model 1. Models 1 and 2 are adjusted for sex, age, GFR category, years from study start and for any prior presence of the following: congestive heart failure, diabetes mellitus, hypertension, stroke or TIA, vascular disease, major bleeding, myocardial infarction, PCI and excessive alcohol use.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

ACKNOWLEDGEMENTS

The study was approved by the Swedish Ethical Review Authority (registration number 2019-03289).

FUNDING

Support for this study was provided by Unit for Research and Development, Region Västernorrland grant number LVN-FOU938547, www.rvn.se (FW), Agreement regarding research and education of doctors, Umeå university (HH), Swedish stroke fund (FW), The Swedish Kidney Foundation, grant nr F2022-0084 and F2021-0105 (FW), Njurstiftelsen (FW) and the Swedish Heart and Lung foundation, grant nr 20200766 (AS). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHORS' CONTRIBUTIONS

All authors were involved with study conception; study design was by F.W., H.R., E.D. and A.S.; Statistical analysis was carried out by H.R. Interpretation of data was performed by all authors. Drafting the article was made by F.W. and all authors revised the

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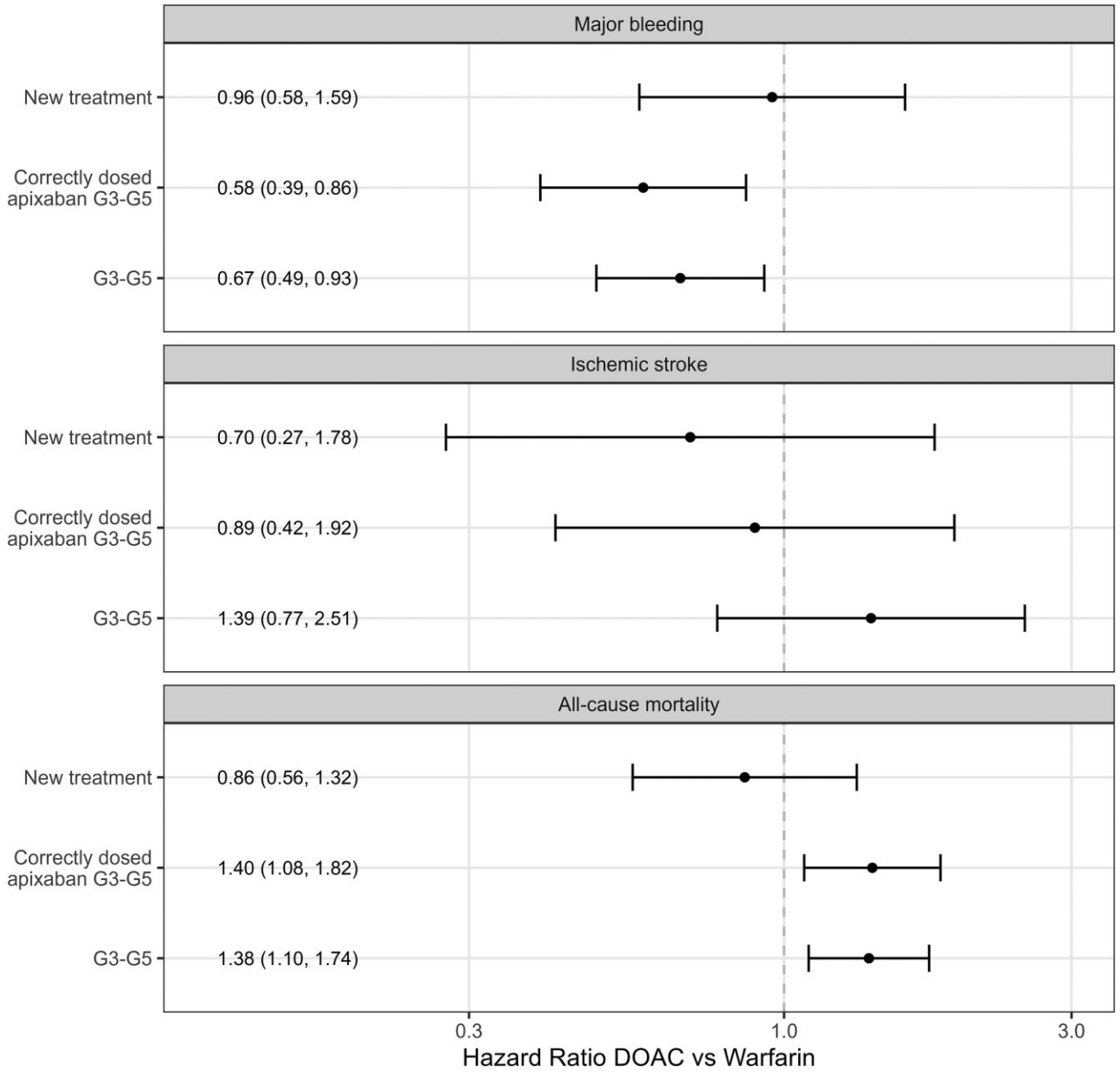

Figure 3: Sensitivity analyses with adjusted models for DOAC vs warfarin. Data presented as HR (95% CI). New treatment is a weighted model restricted to new treatments only with the 1021 matched patients, first treatment period only. Correctly dosed apixaban is Model 1 including only G3–G5 but the DOAC group is restricted to only correctly dosed apixaban ($n = 715$) compared with warfarin in G3–G5 ($n = 1066$). G3–G5 is Model 1 'all patients', but here G5D is excluded ($n = 2028$). The latter two analyses adjusted for sex, age, GFR category, years from study start and for any prior presence of the following: congestive heart failure, diabetes mellitus, hypertension, stroke or TIA, vascular disease, major bleeding, myocardial infarction, PCI and excessive alcohol use.

article. All authors provided with intellectual content of critical importance to the work described. All authors approved the final version to be published.

DATA AVAILABILITY STATEMENT

Because of the sensitive nature of the data that support the findings of this study, data cannot be shared publicly for ethical reasons. The data will be shared on reasonable request to the corresponding author after permission from the National Board of Health and Welfare managing the included registers.

CONFLICT OF INTEREST STATEMENT

A.S. has received consultancy or lecture fees from Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb and Pfizer. F.W., H.R., H.H. and E.D. have no conflicts of interests to declare.

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