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Original Article

ORIGINAL ARTICLE

Risk factors for major bleeding in patients with atrial fibrillation and CKD G3–G5D on oral anticoagulants

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ABSTRACT

Background. Patients with chronic kidney disease (CKD) and atrial fibrillation (AF) on oral anticoagulants (OACs) are at high risk of bleeding. Determinants of major bleeding risk in OAC users with AF and CKD are not well established and available bleeding score systems do not perform well in CKD. This study aims to present risk factors associated with major bleeding in a Swedish cohort of OAC-treated patients with CKD G3–5D.

Methods. We conducted a Swedish register-based cohort study including patients with AF and CKD G3–5D on warfarin or direct OACs (DOACs) between 2009 and 2018. Data were collected from high-quality registers including the Swedish Renal Registry and Auricula, a register for AF and OACs. Risk factors for major bleeding were investigated with Cox regression analysis.

Results. Of 2453 included patients, 59% were on warfarin (time in therapeutic range 67%) and 41% on DOACs. Major bleeding rates were 8.9/100 patient-years. Factors associated with increased bleeding risk were glomerular filtration rate category, G5/5D versus G3 {hazard ratio [HR] 1.92 [95% confidence interval (CI) 1.43–2.56]}, previous gastrointestinal bleeding [HR 1.77 (95% CI 1.39–2.25)], previous other bleeding [HR 1.33 (95% CI 1.09–1.62)], congestive heart failure [HR 1.36 (95% CI 1.11–1.68)], male sex [HR 1.28 (95% CI 1.03–1.60)] and vascular disease [HR 1.35 (95% CI 1.01–1.79)].

Conclusion. Patients with AF and G3–5D on OACs are at a high risk of bleeding. Previous major bleeding and kidney failure are strongly associated with major bleeding. The present study also shows an association between OAC-associated bleeding and male sex, congestive heart failure and vascular disease. Knowledge about determinants of bleeding in advanced CKD is essential when deciding on when to anticoagulate or not.

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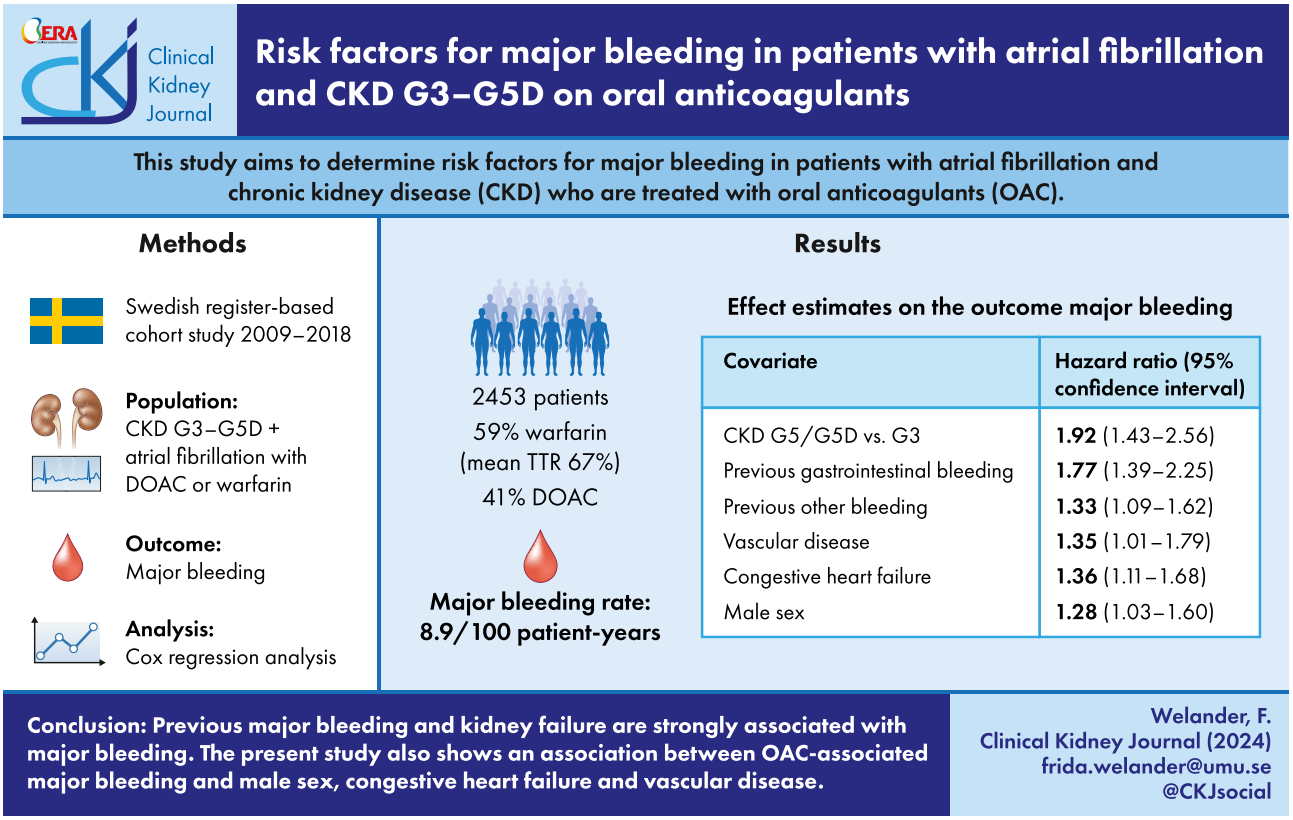
GRAPHICAL ABSTRACT



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

INTRODUCTION

The experience of oral anticoagulants (OACs) as stroke prevention in patients with atrial fibrillation (AF) and advanced chronic kidney disease (CKD) or dialysis is continuously growing. The traditional treatment warfarin is being replaced step by step by direct oral anticoagulants (DOACs) [1]. Both small randomized controlled trials (RCTs) and large observational cohorts have shown an association of a lower risk of bleeding on DOACs compared with warfarin and other vitamin K antagonists (VKAs) in advanced CKD or dialysis, similar to data from the pivotal DOAC trials [2–5]. An important distinction between CKD and non-CKD cohorts is that the ischaemic stroke–reducing effect of OACs in advanced CKD or dialysis is yet to be proven. Also, patients with CKD have a non-negligible risk of major bleeding. Uraemic platelet dysfunction is thought to be the most important reason for bleeding in patients with advanced CKD. Platelets in uraemic patients have displayed lower levels of platelet activators in the alfa-granulae; lower reaction to adenosine diphosphate, epinephrine and collagen; altered arachidonic acid metabolism and disturbed calcium mobilization leading to dysfunctional aggregation and activation [6–8]. The platelet–vessel wall interaction is altered by anaemia due to disturbances of the laminar flow of the erythrocytes, which normally pushes the platelets close to the vessel wall. Also, reduced expression of the platelet receptor GP1b has been observed, leading to insufficient binding of von Willebrand factor in uraemic patients [8]. Furthermore, dialysis-related repeated cannulation and frequent invasive procedures can contribute to an increased risk of bleeding. Several recent studies have shown an up to 10 times higher risk of major bleeding than ischaemic stroke in patients on OACs with advanced CKD or on dialysis [2, 4, 9]. Subsequently, the stroke and bleeding risk in patients with AF and advanced CKD must be carefully evaluated when deciding on whether to prescribe oral anticoagulants or not. Unfortunately, available stroke and bleeding scoring systems are often no better than tossing a coin in advanced CKD [10, 11]. There is a knowledge gap regarding who will benefit from OACs and who might not. This study aims to present risk factors associated with major bleeding in a Swedish cohort of OAC-treated patients with CKD G3–5, including patients on dialysis (G5D).

MATERIALS AND METHODS

We conducted a Swedish register-based cohort study adhering to the Declaration of Helsinki and approved by the Swedish Ethical Review Authority (registration 2019-03289). Due to the register-based design, personal consent was waived.

Data sources

The Swedish unique personal identity number makes it possible to link Swedish health care and quality registers. Included

KEY LEARNING POINTS

What was known:

- The experience of oral anticoagulants (OACs) as stroke prevention in patients with atrial fibrillation (AF) and chronic kidney disease (CKD) is growing. However, the ischaemic stroke–reducing effect of OACs in advanced CKD or dialysis is yet to be proven and there is a substantial risk of major bleeding.
- The uraemic platelet dysfunction is thought to be the most important reason for bleeding in patients with advanced CKD.
- Determinants of bleeding risk in OAC users with AF and CKD are not well established. Guidelines recommend using stroke- and bleeding scoring systems when initiating OACs, but these are often no better than tossing a coin in the setting of CKD.

This study adds:

- Patients with non-valvular AF and CKD G3–5D on OACs are at high risk of bleeding.
- This study confirms the previous described association between the risk of OAC-related major bleeding and kidney failure as well as a history of previous major bleeding.
- There is an association between major bleeding and the non-modifiable risk factors of male sex, congestive heart failure and vascular disease.
- A previous tolerated dual antiplatelet therapy might indicate lower bleeding risk.

Potential impact:

- Patients on dialysis who had recent major bleeding are at high risk of a new bleeding event. Pros and cons of anticoagulants need to be evaluated carefully when deciding on appropriate treatment.
- Women are underrepresented in OAC prescription and randomized controlled studies of OACs. The present study suggests that women do not have higher risk of bleeding then men and treatment should not be withheld from women only because of their gender.

sources were the Swedish Renal Registry (SRR), Auricula, the Swedish Stroke Register, the Swedish National Patient Register (NPR), the Swedish Prescribed Drug Register (PDR) and the Cause of Death Register (CDR). The SRR includes information on CKD, dialysis and kidney transplantation reported from all Swedish nephrology departments [12]. More than 90% of all Swedish nephrology clinics report patients systematically to the SRR from CKD G4 (some from G3), registering the estimated glomerular filtration rate (eGFR) at least yearly. Auricula, a register for AF and OACs with coverage of >50% of all VKA-treated patients in Sweden, provides information of VKA treatment quality [13]. The Swedish Stroke Register is a national quality register with high validity of acute stroke diagnoses [14]. The Swedish NPR has nearly complete coverage and general high validity of inpatient care with International Classification of Diseases, Tenth Revision (ICD-10) and surgical procedure codes [15]. The Swedish PDR provides 100% coverage of all drugs dispensed by Swedish pharmacies. The CDR provides information on the date of passing and cause of death.

Inclusion criteria

Patients ≥18 years of age were included if their eGFR was <60 ml/min/1.73 m^2 or on dialysis (according to the SRR), had a diagnosis of AF (according to the NPR) and were dispensed a DOAC in PDR (apixaban, rivaroxaban, edoxaban or dabigatran) or warfarin (according to Auricula) between 2009 and 2018. Kidney transplant recipients, patients with valvular AF (defined as mitral stenosis or mechanical heart valve replacement; ICD-10 codes Z952, I050, I342, Q232) and long-term OAC users (any OAC dispense 3–4 years prior) were excluded. Kidney transplantation or a diagnosis of valvular AF during follow-up led to censoring. Time zero (t0) occurred when all inclusion and no exclusion criteria were fulfilled. Baseline characteristics were collected from the NPR and SRR. Sources of included variables can be found in Supplementary Table S1.

Treatment periods

DOAC treatment periods were collected from the Swedish PDR, starting from the dispensing date (covering the assumed standard pill use) and an additional 3-day grace period. Warfarin treatment periods were collected directly from Auricula. These two types of treatment periods (DOAC and warfarin from Auricula) are defined as OAC treatment periods. Warfarin treatment quality, described as the time in therapeutic range (TTR), was calculated according to Rosendaal *et al.* [16]. Therapeutic range was defined as an international standardized ratio of 2–3. An undefined treatment was a period of no OAC or warfarin from the PDR not matching a treatment period in Auricula. Patients could switch between treatments (DOAC, warfarin or undefined) during follow-up but remained in the cohort. Outcomes were analysed with respect to ongoing treatment at the time of the event due to time updates.

Kidney function status

The SRR provided eGFR determined by the Modification of Diet in Renal Disease formula. eGFR was classified into categories 3–5D according to the Kidney Disease: Improving Global Outcomes guidelines [17]: G3, eGFR 30–59 ml/min/1.73 m^2; G4, eGFR 15–29 ml/min/1.73 m^2; G5, eGFR <15 ml/min/1.73 m^2; and G5D, on dialysis. eGFR could worsen during follow-up, as G3 could switch to G4, G4 to G5 and so on, but improved eGFR was disregarded.

Outcomes

The outcome of interest was major bleeding, defined as the first occurrence of an intracranial, gastrointestinal or other bleeding event requiring inpatient care. Bleeding rates of the first occurrence of every type of the three bleeding types were also reported. ICD-10 codes of included diagnoses are found in Supplementary Table S2.

Table 1: Baseline characteristics at inclusion of 2453 patients in total and sorted by treatment.

Characteristics	Total (N = 2453)	DOAC (n = 1005)	Warfarin (n = 1448)
Demographics			
Age (years), median (IQR)	76.7 (70.9–81.8)	77.3 (71.9- 82.4)	76.4 (70.1–81.5)
Female	783 (31.9)	351 (34.9)	432 (29.8)
CKD G3	693 (28.3)	436 (43.4)	257 (17.7)
CKD G4	1113 (45.4)	494 (49.2)	619 (42.7)
CKD G5	222 (9.1)	32 (3.2)	190 (13.1)
CKD G5D	425 (17.3)	43 (4.3)	382 (26.4)
Medical history			
Diabetes mellitus	1180 (48.1)	480 (47.8)	700 (48.3)
Hypertension	2288 (93.3)	937 (93.2)	1351 (93.3)
Stroke	507 (20.7)	205 (20.4)	302 (20.9)
TIA	230 (9.4)	90 (9.0)	140 (9.7)
COPD	364 (14.8)	172 (17.1)	192 (13.3)
Cancer	704 (28.7)	255 (25.4)	449 (31.0)
CHF	1326 (54.1)	546 (54.3)	780 (53.9)
Myocardial infarction	832 (33.9)	321 (31.9)	511 (35.3)
Anaemia	911 (37.1)	384 (38.2)	527 (36.4)
Dementia	20 (0.82)	8 (0.80)	12 (0.83)
Liver disease	92 (3.8)	45 (4.1)	51 (3.4)
Excessive alcohol use	88 (3.6)	45 (4.5)	43 (3.0)
History of falls	289 (11.8)	131 (13.0)	158 (10.9)
Any previous major bleeding	979 (39.9)	406 (40.4)	573 (39.6)
Gastrointestinal bleeding	338 (13.8)	155 (15.4)	183 (12.6)
Intracranial bleeding	94 (3.8)	58 (5.8)	36 (2.5)
CHA_2DS_2-VASc, median (IQR)	5 (4–6)	5 (4–6)	5 (4–6)

Data are presented as *n* (%) unless stated otherwise.
COPD: chronic obstructive pulmonary disease; CHF: congestive heart failure; CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischaemic attack (doubled), vascular disease, age 65–74, female.

Statistics

Data were processed using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Rates of major bleeding per 100 patient-years with 95% confidence intervals (CIs) were presented. All treatment periods were evaluated in a multivariate Cox regression model regarding the risk of the first occurrence of a major bleeding requiring inpatient care and presented with hazard ratios (HRs) and 95% CIs. The competing events death and kidney transplantation led to censoring. Time-dependent covariates adjusted for in the model were age, sex, years from study start, GFR category, congestive heart failure (CHF), diabetes mellitus, hypertension, excessive alcohol use, liver disease, vascular disease, previous gastrointestinal bleeding, intracranial bleeding, other bleeding, ischaemic stroke/transient ischaemic attack (TIA), myocardial infarction, percutaneous coronary intervention (PCI) and OAC treatment (DOAC, warfarin or undefined treatment). Continuous variables were modelled with splines, for these the HR for the third to first quartile is reported. A list of ICD-10 codes defining the covariates is found in Supplementary Table S1. A sensitivity analysis investigated risk factors of the three types of major bleeding—intracranial, gastrointestinal and other bleeding—with the same adjustments as described above. If a patient suffered from one type of bleeding, the patient was censored for this type of bleeding but remained in the cohort for the other two types of bleeding. Thus a patient could potentially contribute to three major bleedings, one of each type in the sensitivity analysis, as opposed to the primary analysis where only the first major bleeding of any type was counted.

RESULTS

Of 2453 included patients, 59% had warfarin (TTR 67%) and 41% had DOAC at inclusion. The predominant DOAC was apixaban [81% (77.7% reduced dose, 22.3% standard dose)], followed by rivaroxaban [14.7% (76.4% on reduced dose, 23.6% standard dose)], dabigatran [2.8% (78.6% reduced dose, 21.4% standard dose)] and edoxaban [1.4%, all reduced dose]. The mean age was 76.7 years and 68.1% were male, 28.3% were G3, 45.4% were G4, 9.1% were G5 and 17.3% were G5D (Table 1). The mean follow-up was 2.2 years. Patients were allowed to stop, restart and switch OACs during follow-up and the mean time on OAC per person in total was 1.8 years or 664.4 days (median 449 days, minimum–maximum 1–3651 days). The mean time on DOAC was 1.2 years or 425.6 days (median 298 days, minimum–maximum 1–2208 days). The mean time on warfarin was 2.1 years or 778.5 days (median 549 days, minimum–maximum 1–3651 days). The mean time on undefined treatment was 315.8 days (median 89 days, minimum–maximum 1–3007 days).

During follow-up, 424 major bleedings occurred yielding 8.9/100 patient-years (95% CI 8.1–9.8). When restricted to OAC treatment periods, 352 major bleedings occurred, corresponding to a bleeding rate of 8.7/100 patient-years (95% CI 7.8–9.6) (Table 2). If counting the first of every type of major bleeding during OAC treatment, there were 45 intracranial bleedings (1/100 patient-years), 158 gastrointestinal bleedings (3.7/100 patient-years) and 202 other bleedings (4.8/100 patient-years). Unadjusted Kaplan–Meier curves and at-risk numbers for major bleedings and the three types of bleedings during

Table 2: Time on OAC treatment, number of events and event rates/100 patient years.

	Major bleedings[a]				Intracranial bleedings[d]			Gastrointestinal bleedings[d]			Other bleedings[d]		
Treatment	100 years	Events	Rate/100 patient-years (95% CI)	Treatment	100 years	Events	Rate/100 patient-years (95% CI)	100 years	Events	Rate/100 patient-years (95% CI)	100 years	Events	Rate/100 patient years (95% CI)
Warfarin	28.3	275	9.7 (8.6–10.9)	Warfarin	31.7	37	1.2 (0.8–1.6)	30.4	122	4.0 (3.3–4.8)	29.5	160	5.4 (4.6–6.3)
DOAC	12.2	77	6.3 (5.0–7.9)	DOAC	12.7	8	0.6 (0.3–1.2)	12.5	36	2.9 (2.0–3.9)	12.4	41	3.3 (2.4–4.5)
Any OAC[b]	40.4	352	8.7 (7.8–9.7)	Any OAC	44.4	45	1.0 (0.7–1.3)	42.9	158	3.7 (3.1–4.3)	42.0	202	4.8 (4.2–5.5)
Undefined[c]	7.1	72	10.2 (8.0–12.7)	Undefined	9.0	14	1.56 (0.9–2.5)	8.3	32	3.9 (2.7–5.4)	8.1	43	5.3 (3.7–7.1)

[a]The first major bleeding of any type (intracranial, gastrointestinal or other).
[b]Any OAC: total time with either warfarin or DOAC, undefined treatment excluded.
[c]Undefined treatment: a period of no OAC or a dispense of warfarin from the Swedish PDR not matching a treatment period in Auricula. This time, and the bleedings occurring within this time, is not included in the regression analysis.
[d]The first of every type of the three bleedings (intracranial, gastrointestinal, other) counted in contrast to the definition 'major bleeding', where only the first bleeding of any type is counted.

OAC treatment periods are found in Fig. 1. Censoring by death occurred for 1017 patients, by new-onset valvular heart disease for 21 patients and by kidney transplantation for 54 patients.

Covariates, besides warfarin, associated with an increased risk of major bleeding were GFR category G5/5D versus G3 [HR 1.92 (95% CI 1.43–2.56)], previous gastrointestinal bleeding [HR 1.77 (95% CI 1.39–2.25)] and previous other bleeding [HR 1.33 (95% CI 1.09–1.62)] (Table 3). Other factors associated with major bleeding were CHF [HR 1.36 (95% CI 1.11–1.68)], male sex [HR 1.28 (95% CI 1.03–1.60)] and vascular disease [HR 1.35 (95% CI 1.01–1.79)]. Previous PCI was associated with a lower risk of major bleeding [HR 0.71 (95% CI 0.53–0.96)].

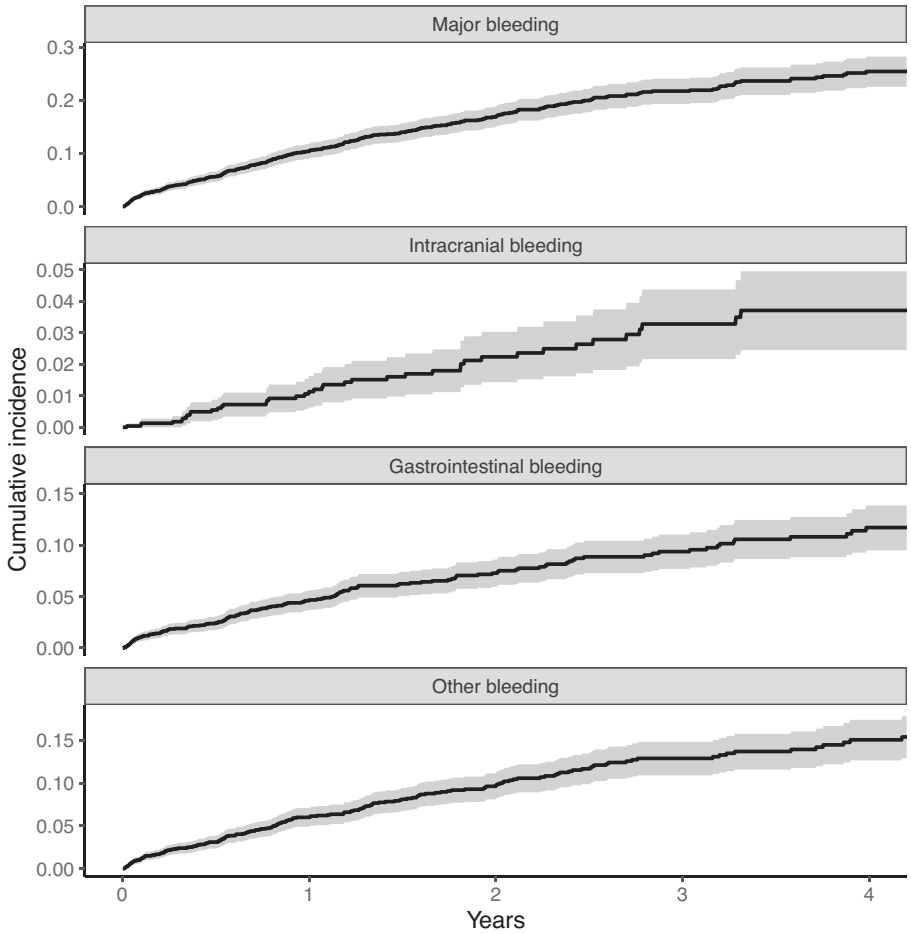
A sensitivity analysis for each type of bleeding shows that a history of a specific bleeding is associated with a new event of this type of bleeding (Table 4). A previous intracranial bleeding is associated with a greater hazard of a new intracranial bleeding [HR 5.70 (95% CI 2.74–11.88)], and the same association was seen regarding gastrointestinal bleeding [HR 2.64 (95% CI 1.91–3.65)] and other bleedings [HR 1.89 (95% CI 1.46–2.45)]. Diabetes mellitus and excessive alcohol use was associated with greater hazard of gastrointestinal bleeding [HR 1.60 (95% CI 1.18–2.17) and HR 2.00 (95% CI 1.07–3.73), respectively]. CHF and male sex were associated with a greater hazard of other bleedings [HR 1.48 (95% CI 1.12–1.95) and HR 1.46 (95% CI 1.08–1.97), respectively].

DISCUSSION

In a setting of advanced CKD, where OAC-associated bleedings are possibly 10 times more common than ischaemic strokes, knowledge of determinants of major bleeding is fundamental. We have previously shown an association between the modifiable risk factors choice of anticoagulants and quality of treatment and the risk of major bleeding in AF and CKD G3–5D [4, 18]. DOAC compared with warfarin is associated with a lower risk of bleeding and a higher TTR during warfarin treatment. The present study adds information on non-modifiable risk factors and the patients for whom OAC prescription might be inappropriate.

Kidney failure (G5 and G5D) is strongly associated with major bleeding in OAC-treated patients and is an established risk factor in both the general population and in CKD [19–21]. G4 was not associated with a higher risk of bleeding compared with G3. In a meta-analysis by Dahal *et al.* [19] evaluating the risk of adverse events associated with warfarin in CKD, only G5/G5D, not G3–4, was associated with major bleeding. This association is reasonable since the most important cause of bleeding in CKD is thought to be the uraemic platelet dysfunction associated with kidney failure and the uraemic state [7, 8]. Previous major bleeding seems strongly associated with new major bleeding. This is well known in a general population and previous bleeding is included as a risk factor in most bleeding risk scores such as the HAS-BLED, ATRIA and ABC scores [22–24]. Data from the Dialysis Outcomes and Practice Patterns Study including 48 144 haemodialysis patients on OAC or antiplatelet agents showed that gastrointestinal bleeding in the past 12 months was highly predictive of new major bleeding, similar to our findings. The sensitivity analysis indicates that a previous major bleeding (intracranial, gastrointestinal or other bleeding) is associated with an increased risk of this specific type of bleeding. This is also in line with the previous literature [25].

The present study also shows an association between major bleeding and male sex, CHF and vascular disease.



Major bleeding	2453	1275	743	457	255
Intracranial bleeding	2453	1362	826	526	299
Gastrointestinal bleeding	2453	1330	795	501	282
Other bleeding	2453	1311	779	482	268

Figure 1: Unadjusted Kaplan–Meier curves for the outcome major bleeding as well as the three types of major bleeding (intracranial, gastrointestinal and other bleeding) during OAC treatment. Graphs presented with years since entry (up to 4 years) on the *x*-axis and cumulative incidence on the *y*-axis. At-risk numbers are provided.

Data from RCTs considering the impact of sex on bleeding outcomes in OAC-treated patients with AF in the general population are scarce. A post hoc analysis from the ARISTOTLE trial (NCT00412984) suggests less clinically relevant bleeding in women versus men, and similar findings were presented in a meta-analysis of the pivotal DOAC trials [26, 27]. Several Swedish cohorts have suggested the same association in VKA-treated patients [28, 29]. The present study reiterates this association. Female sex is underrepresented in anticoagulant RCTs as well as in OAC prescription, possibly related to a perception that females are more frail or have a higher bleeding risk than men. Our data point in the reverse direction. Female sex is a risk factor for stroke, and if women have lower (or at least not higher) bleeding risk than men, treatment should not be withheld.

CHF and vascular disease are well known risk factors for ischaemic stroke, at least in a general AF population. These covariates were associated with major bleeding in the present study. This association has also been suggested previously in a general AF population [28, 30]. Structural vessel changes could be part of the explanation for this possible dual relationship and the presence of these risk factors might indicate vascular aging and frailty associated with both ischaemic stroke and bleeding.

Previous PCI seems protective of major bleeding. Patients who have undergone PCI routinely receive dual antiplatelet therapy. Perhaps this causes a selection bias. Patients who bled during dual platelet therapy might not be in this cohort of OAC-treated patients (since they were not offered OAC), whereas patients who tolerated the treatment already proved themselves not to bleed. Hence previous tolerated dual antiplatelet therapy might be a clue to if a patient will tolerate OAC treatment or not.

Table 3: Effect estimates on the outcome major bleeding.

Covariate	HR (95% CI)
Age (years)	1.16 (0.89–1.51)
Years from study start	1.14 (0.87–1.50)
CKD G4:G3	1.10 (0.83–1.46)
CKD G5/G5D:G3	1.92 (1.43–2.56)
CHF	1.36 (1.11–1.68)
Diabetes mellitus	1.22 (1.0–1.48)
Excessive alcohol use	1.33 (0.8–2.21)
Gastrointestinal bleeding	1.77 (1.39–2.25)
Hypertension	1.26 (0.78–2.04)
Intracranial bleeding	1.37 (0.87–2.18)
Ischaemic stroke or TIA	0.97 (0.78–1.21)
Liver disease	1.28 (0.8–2.05)
Male sex	1.28 (1.03–1.60)
Myocardial infarction	0.85 (0.63–1.16)
Other bleeding	1.33 (1.09–1.62)
PCI	0.71 (0.53–0.96)
DOAC versus warfarin	0.71 (0.53–0.96)
Undefined treatment[a] versus warfarin	1.11 (0.85–1.45)
Vascular disease	1.35 (1.01–1.79)

Continuous variables are modelled with splines. For these the HR for the third to first quartile is reported.

[a]Undefined treatment: a period of no OAC or a dispense of warfarin from the Swedish PDR not matching a treatment period in Auricula.

Age was not associated with a significant effect on the risk of bleeding in the present study. This might be surprising since age is an established risk factor in bleeding risk scores [21–24]. A reason for this could be the narrow age span of the patients included, with a median age 76.7 years (interquartile range 70.9–81.8). Another theory is that chronological age is a weaker risk factor for bleeding in CKD compared with the general population. Bleeding in advanced CKD might be more related to the uraemic state, with platelet dysfunction and biological aging due to, for example, CKD–mineral and bone disorder contributing to vascular calcification in young patients [31]. Hypertension is considered a general risk factor for major bleeding but was not associated with a significant effect on bleeding risk in the present study. In a population where >90% of patients have hypertension, hypertension per se will not be a helpful clue to the risk of bleeding. Uncontrolled hypertension would have been a better variable to investigate.

The sensitivity analysis indicates that there might be different risk factors associated with different types of bleeding, except previous bleedings. CHF and male sex were only associated with other bleedings, which might be, for example, haematuria. Excessive alcohol use and diabetes mellitus did not increase the hazard of major bleeding in the primary analysis, but in the sensitivity analysis these covariates were associated with a greater hazard of gastrointestinal bleeding. Excessive alcohol use is a previously known risk factor for gastrointestinal bleeding in the general population as well [22].

How can we navigate between ischaemic stroke and bleeding in AF and advanced CKD when the risk of bleeding is high, irrespective of anticoagulants? Pros and cons of OAC need to be carefully evaluated and an individual decision needs to be made for each patient. Kidney failure and a recent major bleeding might indicate a higher bleeding risk. In the choice of OAC, DOAC might be preferable. In all patient's, modifiable general risk factors for bleeding need to be overseen, such as compliance, anaemia, blood pressure, use of non-steroidal anti-inflammatory drugs and additional antiplatelet therapy/over-the-counter aspirin. Also, modifiable risk factors for ischaemic stroke, beyond OAC, need to be overseen, such as smoking habits, blood pressure and glycaemic control. Ongoing RCTs comparing OAC and no anticoagulant treatment in G5/G5D are anticipated and will hopefully give a clearer answer on their efficacy and safety and help clinicians decide when anticoagulants are warranted.

Limitations

The register-based design is the main limitation and with this follows the risk of selection bias, misclassification and confounding by indication. This study only reflects patients in specialized outpatient or inpatient nephrology care, not patients in primary care. The definition of major bleeding could possibly include minor clinically relevant bleeding, which is a drawback. All patients started on DOAC or warfarin, but since patients were allowed to switch or stop treatment and remain in the cohort, a minority of the major bleedings occurred off treatment (part of the undefined treatment), and this is a limitation.

There is potential residual confounding. We do not have knowledge of aspirin or other antiplatelet use, either as a prescription or over-the-counter use. Additional antiplatelet use with OAC is a well-known risk factor for bleeding [2, 29]. We do not think this missing information has affected the results significantly. We know from previous Swedish studies of a general AF population that ≈17% of patients on OAC have concurrent antiplatelet therapy; in patients with CKD we believe that this use is more rare. We do not have knowledge on low molecular weight heparin use (e.g. during dialysis) either. The use of time-dependent covariates entails a risk of introducing time-varying confounding by previous exposure.

TTR is not adjusted for in this analysis. It is possible that some of the effect seen in the analysis is a TTR effect not controlled for, although the warfarin treatment was very well managed with a high TTR of 67%.

CONCLUSION

Patients with non-valvular AF and CKD G3–5D on OAC are at high risk of bleeding. The most important risk factors for major bleeding are kidney failure and previous major bleeding. A previous tolerated dual antiplatelet therapy might indicate a lower bleeding risk. Treatment should not be withheld from women solely because of their gender. Patients with CKD and advanced vascular disease and CHF might be at high risk of both ischaemic stroke and bleeding. Knowledge about determinants of major bleeding on OAC in advanced CKD is essential when deciding whether to anticoagulate or not.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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Table 4: Sensitivity analysis: effect estimates of the different types of bleeding.

Covariate	Intracranial bleeding	Gastrointestinal bleeding	Other bleeding
Age (years)	2.37 (1.11–5.07)	0.81 (0.54–1.23)	1.21 (0.86–1.70)
Years from study start	0.77 (0.37–1.60)	0.94 (0.62–1.42)	1.34 (0.93–1.93)
CKD G4:G3	1.48 (0.62–3.53)	1.32 (0.86–2.02)	0.87 (0.60–1.27)
CKD G5/G5D:G3	2.42 (0.99–5.89)	1.99 (1.27–3.11)	1.79 (1.23–2.60)
CHF	1.28 (0.73–2.22)	1.05 (0.76–1.43)	1.48 (1.12–1.95)
Diabetes mellitus	0.95 (0.56–1.63)	1.60 (1.18–2.17)	1.18 (0.91–1.54)
Excessive alcohol use	0.87 (0.11–6.70)	2.00 (1.07–3.73)	1.12 (0.54–2.31)
Gastrointestinal bleeding	1.73 (0.96–3.10)	2.64 (1.91–3.65)	1.27 (0.92–1.74)
Hypertension	1.60 (0.38–6.70)	0.98 (0.49–1.94)	1.03 (0.58–1.83)
Intracranial bleeding	5.70 (2.74–11.88)	0.84 (0.39–1.83)	0.66 (0.31–1.42)
Ischaemic stroke or TIA	1.39 (0.80–2.40)	0.92 (0.66–1.27)	0.86 (0.64–1.15)
Liver disease	0.57 (0.074–4.38)	1.58 (0.87–2.88)	1.01 (0.51–2.01)
Male	1.07 (0.61–1.88)	0.95 (0.69–1.30)	1.46 (1.08–1.97)
Myocardial infarction	0.51 (0.23–1.14)	1.06 (0.67–1.68)	0.87 (0.58–1.32)
Other bleeding	1.07 (0.62–1.83)	0.96 (0.71–1.31)	1.89 (1.46–2.45)
PCI	0.92 (0.41–2.05)	0.70 (0.46–1.08)	0.79 (0.54–1.15)
DOAC versus warfarin	0.68 (0.28–1.63)	0.76 (0.49–1.18)	0.70 (0.47–1.05)
Undefined treatment[a] versus warfarin	1.14 (0.60–2.16)	1.13 (0.75–1.70)	1.01 (0.71–1.43)
Vascular disease	1.59 (0.79–3.20)	1.33 (0.86–2.06)	1.20 (0.82–1.76)

Data presented as HR (95% CI).
Continuous variables were modelled with splines. For these the HR for the third to first quartile is reported.
[a]Undefined treatment: a period of no OAC or a dispense of warfarin from the Swedish PDR not matching a treatment period in Auricula.

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AUTHORS' CONTRIBUTIONS

All authors were involved with the study conception and interpretation of data. F.W., H.R. and A.S. were responsible for the study design. H.R. was responsible for the statistical analysis. F.W. wrote the draft of the article. All authors revised the article, provided intellectual content of critical importance to the work described and 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 upon 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. and H.R. declare no conflicts of interest.

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