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Abstract

Keywords
► atrial fibrillation
► anticoagulation
► dabigatran
► renal function
► stroke
► bleeding

Objective Anticoagulation management in patients with atrial fibrillation (AF) and impaired renal function is challenging. This study aimed to evaluate anticoagulation prescription patterns in relation to renal function and to describe 2-year clinical outcomes among dabigatran users.

Methods Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) is an international, prospective, and observational study program involving patients with newly diagnosed AF at risk for stroke. Prescription patterns were assessed by creatinine clearance (CrCl) at enrollment. Dabigatran users were followed for 2 years. Clinical outcomes were standardized for stroke and bleeding risk, based on CHA_2DS_2-VASc and HAS-BLED scores, with missing values imputed.

Results Baseline CrCl values were available for 12,056 of 15,308 eligible patients (79%). With declining renal function, prescriptions increased for vitamin K antagonists (VKAs) and decreased for dabigatran (30–47% and 34–12%, respectively). The prescription of other non-vitamin K antagonists remained similar across CrCl groups (14–19%). In 4,873 dabigatran users, standardized stroke rates were low across all CrCl groups; 0.58/100 patient-years (95% confidence interval [CI]: 0.30–0.90) in CrCl ≥80 mL/min, 0.85 (95% CI: 0.48–1.21) in CrCl 50 to 79 mL/min, and 0.33 (95% CI: 0.06–1.11) in CrCl 30 to 49 mL/min. Similarly, major bleeding rates were low and numerically increased with declining renal function (0.68/100 patient-years, 95% CI: 0.39–1.03; 0.92, 95% CI: 0.58–1.32; and 1.26, 95% CI: 0.66–1.97, respectively).

Conclusion In patients with AF, VKA prescriptions increased and dabigatran prescriptions decreased with declining renal function. Rates of stroke and major bleeding in dabigatran patients remained low across the categories of renal impairment.

Introduction

Some degree of renal impairment is estimated to be present in approximately 35% of patients with atrial fibrillation (AF) and is associated with increased risk of both thromboembolic and bleeding events.[1–3] Consequently, oral anticoagulation management is challenging and often requires dose adjustment. Suboptimal use of vitamin K antagonists (VKAs) or non-vitamin K antagonists (NOACs) increase the risk of stroke and systemic embolism.[4–6] How renal function affects anticoagulation prescription practice is unclear.

All NOACs undergo some degree of renal clearance. Consequently, diminished renal function could lead to drug accumulation and increase the risk of bleeding complications. Clinical practice guidelines recommend caution regarding NOAC use in patients with renal dysfunction.[7,8] Rivaroxaban, apixaban, and edoxaban, but not dabigatran, are approved in Europe for use in patients with severe renal impairment (i.e., a creatinine clearance [CrCl] of <30 mL/min).[8] This differs for the United States, where dabigatran is only contraindicated below a CrCl of 15 mL/min due to the available dose of 75 mg twice daily.[9] Moreover, in the United States, no contraindications exist for rivaroxaban and apixaban based on renal function. Lower doses, however, are recommended for CrCl ≤50 mL/min (rivaroxaban) and serum ≥1.5 mg/dL (apixaban).[10,11]

A meta-analysis demonstrated fewer thromboembolic and major bleeding events in patients with mild or moderate renal impairment (CrCL = 30–79 mL/min) treated with NOACs than with VKAs, although there is considerable heterogeneity across studies.[12] Moreover, the effectiveness and safety of NOACs in patients with a CrCl <30 mL/min has not been established.

The purposes of this study were to evaluate anticoagulation prescription patterns in relation to baseline renal function for patients with AF enrolled in phase II of the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) study and to describe clinical outcomes over 2 years in patients who received dabigatran etexilate.

Methods

Patients and Study Design

The study design and baseline characteristics of patients enrolled in the GLORIA-AF Registry Program have been described previously.[13,14] In short, GLORIA-AF is an international, prospective, observational and study program, run in three phases, enrolling consecutive adult patients with nonvalvular AF who were newly diagnosed in a variety of clinical settings between 2010 and 2017. The study excluded patients with mechanical heart valves, previous VKA therapy for >60 days, AF due to a generally reversible cause, and life expectancy <1 year. During phase II of the program (patient enrollment from 2011 to 2014), cross-sectional data were collected, regardless of treatment, and patients prescribed dabigatran were followed for up to 2 years, with visits scheduled around 3, 6, 12, and 24 months. Dabigatran was prescribed at the discretion of treating physicians in available doses (150, 110, and 75 mg twice daily, depending on the country and local label). Patients who took at least one dose of dabigatran were included in the outcome event analysis. Final phase II results have been recently been published.[15] In the present report, phase II data were evaluated in relation to baseline renal function. GLORIA-AF was a noninterventional study; hence, prescription requirements were not stipulated in the protocol.

Study Aim

The aims of the study were to evaluate anticoagulation prescription patterns in patients with different CrCl categories and to describe 2-year incidence rates of stroke, major bleeding, and death for patients treated with dabigatran according to CrCl. The CrCl was calculated according to Cockcroft-Gault formula: CrCl (mL/min) = (140 − age) × weight (kg) × (0.85 if female)/(72 × serum creatinine concentration). Renal impairment was categorized according to international guidelines as no impairment (CrCl ≥ 80 mL/min), mild impairment (CrCl = 50–79 mL/min), moderate impairment (CrCl = 30–49 mL/min), and severe impairment (CrCl < 30 mL/min).[16,17]

Outcomes

Only patients taking dabigatran were followed for the occurrence of clinical outcomes. Stroke was defined as the acute onset of a focal neurologic deficit of presumed vascular origin 24 hours or more or resulting in death. Stroke type was categorized as ischemic, hemorrhagic, or uncertain (based on computed tomography or magnetic resonance scanning, or autopsy). Major bleeding was defined according to criteria of the International Society on Thrombosis and Haemostasis.[18] Deaths were classified as vascular (including bleeding) and nonvascular due to other specified causes (e.g., malignancy) or unknown cause.

Statistical Analysis

Baseline characteristics of patients were examined by categories of renal function. Continuous variables are presented as the means ($\pm$standard deviation [SD]) or medians (with interquartile range [IQR]) and categoric variables as frequency (n) and percent (%).

For the derivation of incidence rates of dabigatran outcome incidence rates, the risk period began with treatment initiation and ended with permanent dabigatran discontinuation, which was defined by treatment stop $+3$ days, substitution of another anticoagulant treatment, or study completion. Incidence rates were calculated based on time to first event of interest. Patients prescribed dabigatran who did not take at least one dose ($n = 14$) were excluded.

To adjust for potential confounding, incidence rates were standardized by HAS-BLED score using two categories, less than 2 or ≥ 2, and CHA$_2$DS$_2$-VASc scores using three categories, < 3, 3, and ≥ 4, for a total of six categories when stratifying by both variables. Standardization was accomplished by obtaining a weighted average of the stratum-specific incidence rates, using weights equal to the total number of patient years for all patients in that stratum. Because only a small number of patients had a CrCl <30 mL/min, rates were not reported for that category. HAS-BLED and CrCl had noticeable proportions of patients taking dabigatran with missing data (10 and 23%, respectively); multiple imputation using chained equations was applied to address this.[19] The imputation model was constructed upon 54 clinically relevant baseline patient characteristic variables and the number of imputation is 20. The CIs of the standardized incidence rates were constructed using the bootstrap method.[20]

Results

Patient Population

Baseline characteristics by CrCl for both the entire population as well as dabigatran users are displayed in ►Table 1. Baseline creatinine levels were available for 12,056 of 15,308 eligible patients (79%). For the entire population, a total of 5,116 of 15,308 patients (33%) had CrCl ≥ 80 mL/min; 4,714 (31%) had CrCl 50 to 79 mL/min; 1,805 (12%) had CrCl 30 to 49 mL/min, 430 (3%) had CrCl <30 mL/min; and 3,243 (21%) had missing values. Patients with a CrCl ≥ 80 mL/min were younger (63 ± 10 years) than those with CrCl 50 to 79; 30 to 49; or <30 mL/min (74 ± 8, 80 ± 7, 80 ± 11, respectively), or those

with unknown CrCl values (71 ± 11 years). Most patients had paroxysmal AF (51–56%, depending on CrCl category), followed by persistent (35–37%) and permanent AF (8–14%). As expected, the mean CHA$_2$DS$_2$-VASc score increased with declining renal function, ranging from 2.6 (SD = 1.3) in patients with a CrCl ≥ 80 mL/min to 4.7 (1.5) in patients with a CrCl <30 mL/min. A similar trend was observed for the mean HAS-BLED score, ranging from 1.1 (SD = 0.9) to 2.0 (1.0).

Patients treated with dabigatran had baseline characteristics similar to the overall GLORIA-AF population. Of 4,873 patients prescribed dabigatran, 3,759 (77%) had creatinine measurements available at baseline. A total of 1,743 of 4,873 (36%) had CrCl ≥ 80 mL/min, 1,488 (31%) had CrCl 50 to 79 mL/min, 476 (10%) had CrCl 30 to 49 mL/min, and 52 (1%) had CrCl <30 mL/min.

Anticoagulation Prescription

At baseline, of all patients with CrCl ≥ 80 mL/min ($n = 5,116$), most were prescribed dabigatran ($n = 1,743$; 34%) or a VKA ($n = 1,534$; 30%), followed by rivaroxaban ($n = 647$; 13), antiplatelet therapy ($n = 592$; 12%), no antithrombotic treatment ($n = 389$; 8%) and apixaban ($n = 188$; 3.7%). With declining renal function, prescription rates increased for VKA and decreased for dabigatran (30–47% and 34–12%, respectively; ►Fig. 1). Of the 52 patients taking dabigatran with CrCl <30 mL/min, 41 (79%) were treated with the 150 or 110 mg twice daily dosage, and 11 (21%) received a 75 mg twice-daily dose. Eleven patients receiving the 75 mg twice-daily dose were all located in the United States. Among all dabigatran patients, 0.9% ($n = 41$) received dabigatran 150 and 110 mg BID and had a CrCl <30 mL/min, constituting a contraindication. Prescription rates for other NOACs were similar across renal function strata (9.3–13% for rivaroxaban and 3.5–6.5% for apixaban, depending on CrCl). As renal function decreased, prescription of other NOAC standard doses decreased and use of low doses increased, although contraindications due to CrCl were not further assessed. The dabigatran standard dose (150 mg twice daily) was prescribed more frequently in patients with normal renal function (72%) than for those with CrCl 50 to 79 (45%) or 30 to 49 mL/min (20%) (►Table 2). The prescription rate of antiplatelet or no treatment was consistent across the renal function strata (19–23%, depending on CrCl).

Clinical Outcomes

Clinical outcomes in dabigatran-treated patients are shown in ►Table 3. The standardized incidence rates for stroke were 0.58/100 patient-years (95% confidence interval [CI]: 0.30–0.90) for CrCl ≥ 80 mL/min, 0.85/100 patient-years (95% CI: 0.51–1.2) for CrCl 50 to 79 mL/min, and 0.33/100 patient-years (95% CI: 0.06–1.1) for CrCl 30 to 49 mL/min. The incidence rates for major bleeding were 0.68/100 patient-years (95% CI: 0.39–1.0) for CrCl ≥ 80 mL/min, 0.92/100 patient-years (95% CI: 0.58–1.3) for CrCl 50 to 79 mL/min, and 1.26 (95% CI: 0.66–2.0) for CrCl 30 to 49 mL/min. The rates for all-cause death were highest in patients with a CrCl 30 to 49 mL/min (4.5/100 patient-years; 95% CI: 3.1–6.3), followed by patients with CrCl 50 to 79 mL/min (2.6/100 patient-years; 95% CI: 2.0–3.3) and patients with CrCl ≥ 80 mL/min (1.6/100 patient-years; 95% CI: 1.1–2.2).

Table 1 Baseline characteristics of the entire GLORIA-AF population and the subset of patients treated with dabigatran according to creatinine clearance

Characteristic	Entire GLORIA-AF population (n = 15,308)					Patients treated with dabigatran (n = 4,873)				
	CrCl ≥ 80 mL/min (n = 5,116)	CrCl 50–79 mL/min (n = 4,714)	CrCl 30–49 mL/min (n = 1,805)	CrCl < 30 mL/min (n = 430)	Missing CrCl (n = 3,243)	CrCl ≥ 80 mL/min (n = 1,743)	CrCl 50–79 mL/min (n = 1,488)	CrCl 30–49 mL/min (n = 476)	CrCl < 30 mL/min (n = 52)	Missing CrCl (n = 1,114)
Age (y), mean ± SD	63 ± 10	74 ± 8	80 ± 7	80 ± 11	71 ± 11	64 ± 10	74 ± 8	80 ± 7	78 ± 12	71 ± 10
Gender (male), n (%)	3290 (64)	2343 (50)	1091 (60)	166 (39)	1827 (56)	1149 (66)	707 (48)	184 (39)	21 (40)	650 (58)
BMI (kg/m^2), mean ± SD	31 ± 6.7	27 ± 4.7	25 ± 4.6	25 ± 5.2	29 ± 6	32 ± 6.3	27 ± 4.4	25 ± 3.9	25 ± 4.4	29 ± 6
Missing, n (%)	7 (0.14)	15 (0.32)	9 (0.50)	0	175 (5.4)	0	3 (0.20)	2 (0.42)	0	43 (3.9)
Type of atrial fibrillation, n (%)										
Paroxysmal	2,828 (55)	2,476 (53)	915 (51)	205 (48)	1,735 (54)	922 (53)	762 (51)	234 (49)	23 (44)	587 (53)
Persistent	1,821 (36)	1,719 (37)	632 (35)	166 (39)	1,118 (35)	633 (36)	516 (35)	162 (34)	21 (40)	387 (35)
Permanent	467 (9.1)	519 (11)	258 (14)	59 (14)	390 (12)	188 (11)	210 (14)	80 (17)	8 (15)	140 (13)
CHADS2VASC2 score										
1, n (%)	1,237 (24)	366 (7.8)	26 (1.4)	16 (3.7)	485 (15)	345 (20)	82 (5.5)	4 (0.84)	6 (12)	155 (14)
≥ 2, n (%)	3,879 (76)	4,348 (92)	1,779 (99)	414 (96)	2,758 (85)	1,398 (80)	1,406 (95)	472 (99)	46 (89)	959 (86)
Mean ± SD	2.6 ± 1.3	3.3 ± 1.7	4.3 ± 1.7	4.7 ± 1.5	3.0 ± 1.4	2.7 ± 1.3	3.6 ± 1.4	4.3 ± 1.4	3.9 ± 1.8	3.1 ± 1.4
HAS-BLED score										
< 3, n (%)	4,255 (83)	3,740 (79)	1,351 (75)	287 (67)	2,475 (76)	1,475 (85)	1,240 (83)	378 (79)	39 (75)	903 (81)
≥ 3, n (%)	329 (6.4)	506 (11)	263 (15)	107 (25)	191 (5.9)	99 (5.7)	121 (8.1)	48 (10)	10 (19)	52 (4.7)
Mean ± SD	1.1 ± 0.9	1.5 ± 0.8	1.7 ± 0.8	2.0 ± 1.0	1.3 ± 0.8	1.0 ± 0.9	1.4 ± 0.8	1.6 ± 0.8	1.7 ± 0.9	1.2 ± 0.8
Missing, n (%)	532 (10)	468 (9.9)	191 (11)	36 (8.4)	577 (18)	169 (10)	127 (8.5)	50 (11)	3 (5.8)	159 (14)
Medications (%)										
Antiplatelet	1,382 (27)	1,234 (26)	536 (30)	124 (29)	798 (25)	274 (16)	245 (17)	89 (19)	11 (21)	159 (14)

Abbreviations: BMI, body mass index; creatinine clearance; SD, standard deviation; TIA, transient ischemic attack; VTE, venous thromboembolism.
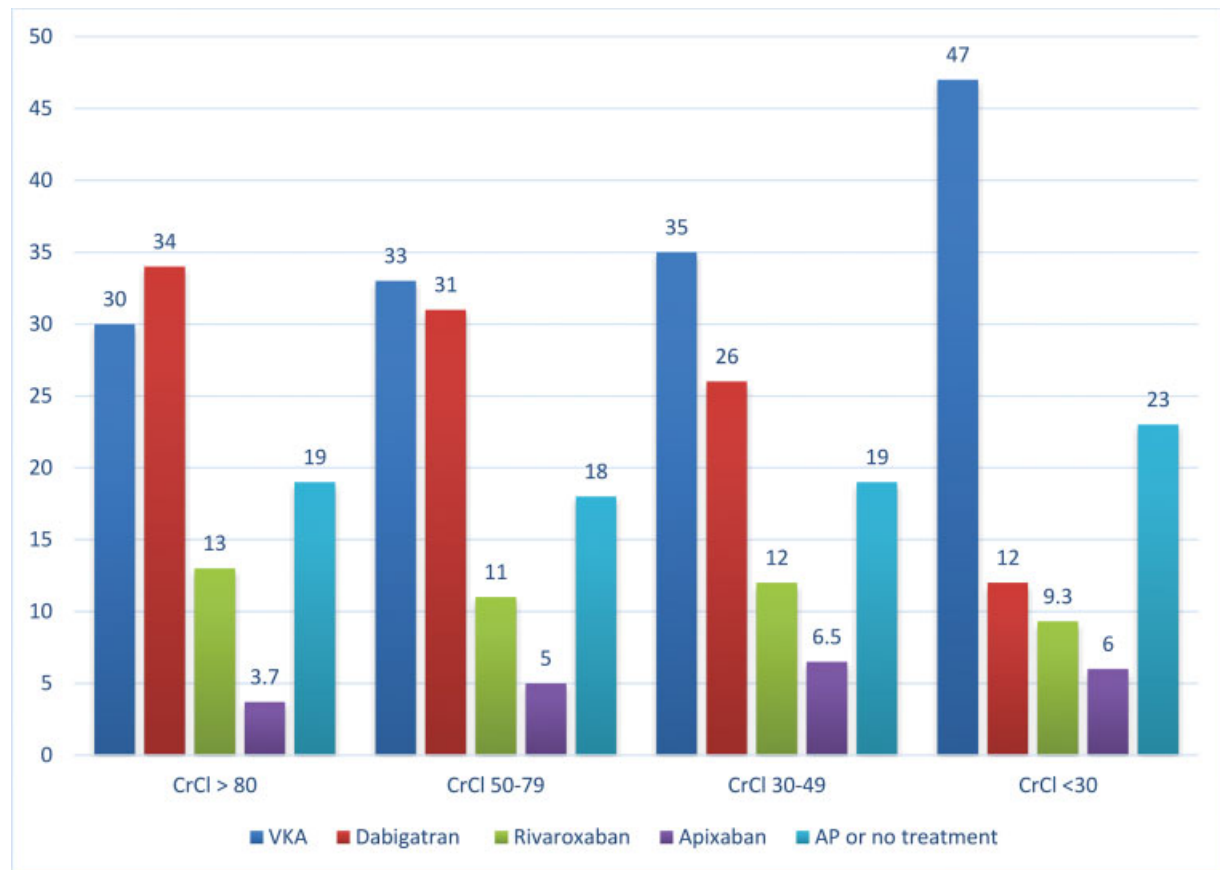
Fig. 1 Antithrombotic prescription patterns according to CrCl in GLORIA-AF. Numbers are percentages. CrCl in mL/min. AP, antiplatelet therapy; CrCl, creatinine clearance; VKA, vitamin K antagonist.

Discussion

The first main finding of this large global prospective study is that VKA prescription increased and dabigatran prescription decreased with declining renal function. No clear trend could be observed for the prescription of other NOACs and antiplatelet/ no treatment groups. Second, less than 1% of dabigatran users were prescribed the contraindicated 150 and 110 mg twice-daily dosages when their CrCl was <30 mL/min. Third, among dabigatran users, the estimated rates of stroke and major bleeding were low across all CrCl categories.

Consistent with the EURObservational Research Program: the Heart Failure Pilot Survey on patients with AF (EORP-AF Pilot), nearly 60% of enrolled patients had a CrCl 30 to 79 mL/min and 4% had a CrCl <30 mL/min.[21] Patients with declining renal function were older and had a higher risk of stroke (CHA2DS2-VASc score ≥ 2) and bleeding risk (HAS-BLED ≥ 3). This might have led to a decrease in dabigatran prescriptions, although both the 150 and 110 mg twice daily doses have been found to be safe in patients with a CrCl 30 to 79 mL/min.[22,23] Conversely, VKA prescriptions increased, with the highest incidence of 47% in patients with a CrCl <30 mL/min. Consistent with other studies, the use of the dabigatran 150 and 110 mg twice daily doses in patients with a CrCl <30 mL/min was less than 1%, indicating that contraindicated dabigatran use is rare in clinical practice.[24,25] For other NOACs, similar prescription rates were observed across

CrCl groups, which is probably related to label differences (i.e., <15 mL/min for rivaroxaban, edoxaban, and apixaban in the European Union, and no contraindications for rivaroxaban and apixaban in the United States). Moreover, the enrollment period must be taken into account. As dabigatran was the only NOAC approved in the European Union during the first year of study enrollment, higher number of dabigatran prescriptions are included in this assessed cohort as compared with other NOACs.

We found low rates of stroke (rate estimates range from 0.46 to 0.96/100 patient-years) and major bleeding (rate estimates range from 0.72 to 2/100 patient-years) across all CrCl categories with wide and overlapping confidence intervals. These rates are consistent with those observed in the EORP-AF Pilot registry in which the 1-year rates of stroke and major bleeding were similar across different renal groups.[21] However, although not directly comparable, the RE-LY trial reported increasing stroke, systemic embolism, and major bleeding incidences with declining renal function, with highest risk estimates in patients with a CrCL 30 to 49 mL/min and lowest in those with normal renal function, including patients using VKA.[23,26] Importantly, the RE-LY study was a randomized trial without specified dose reductions and thereby evaluated both dabigatran 150 and 110 mg twice daily doses, independent of CrCl. Conversely, in our study, dosing was individualized based on patient characteristics and physician and/or patient preferences, including the

Table 2 Anticoagulation dose prescription patterns according to creatinine clearance

Prescribed antithrombotic treatment	CrCl ≥ 80 mL/min (n = 5,116)	CrCl 50–79 mL/min (n = 4,714)	CrCl 30–49 mL/min (n = 1,805)	CrCl < 30 mL/min (n = 430)	Missing CrCl (n = 3,243)	Total (n = 15,308)
VKA	1,534 (30)	1,558 (33)	636 (35)	201 (47)	1,034 (32)	4,963 (32)
Dabigatran						
Total	1,743 (34)	1,488 (31)	476 (26)	52 (12)	1114 (34)	4,873 (32)
150 mg twice daily	1,252 (25)	675 (14)	93 (5.2)	15 (3.5)	629 (19)	2,664 (17)
110 mg twice daily	465 (9.1)	783 (17)	355 (20)	26 (6)	467 (14)	2,105 (14)
75 mg twice daily	18 (0.35)	21 (0.44)	21 (1.2)	11 (2.6)	16 (0.49)	87 (0.57)
Other	8 (0.16)	9 (0.19)	7 (0.38)	0	2 (0.06)	26 (0.17)
Rivaroxaban						
Total	647 (13)	531 (11)	218 (12)	40 (9.3)	319 (9.8)	1,755 (11)
20 mg once daily	590 (12)	388 (8.2)	88 (4.9)	10 (2.3)	236 (7.3)	1,312 (8.6)
15 mg once daily	47 (0.92)	138 (2.9)	128 (7.1)	30 (7.0)	82 (2.5)	425 (2.8)
Other	10 (0.20)	5 (0.11)	2 (0.11)	0	1 (0.031)	18 (0.012)
Apixaban						
Total	188 (3.7)	234 (5.0)	118 (6.5)	26 (6.0)	137 (4.2)	703 (4.6)
5 mg twice daily	180 (3.5)	192 (4.1)	48 (2.7)	6 (1.4)	117 (3.6)	543 (3.5)
2.5 mg twice daily	7 (0.14)	41 (0.87)	69 (3.8)	20 (4.7)	20 (0.62)	157 (1.0)
Other	1 (0.020)	1 (0.021)	1 (0.055)	0	0	3 (0.020)
Other						
Total	1,002 (20)	902 (19)	357 (20)	111 (26)	638 (20)	3,010 (20)
Antiplatelet treatment	613 (12)	543 (12)	242 (13)	63 (15)	379 (12)	1,840 (12)
No antithrombotic treatment	389 (7.6)	359 (7.6)	115 (6.4)	48 (11)	259 (8.0)	1,170 (7.6)

Abbreviations: CrCl, creatinine clearance; NOAC, non-vitamin K oral anticoagulant; VKA, vitamin K antagonist.
Note: All data are reported in numbers (percentages).

Table 3 Crude and standardized incidence rates of dabigatran patients stratified by creatinine clearance

Event	Crude incidence rates, per 100 patient-years (95% CI)			Standardized incidence rates, per 100 patient-years (95% CI)		
	CrCl ≥ 80 (n = 1,738)	CrCl 50–79 (n = 1,483)	CrCl 30–49 (n = 475)	CrCl ≥ 80	CrCl 50–79	CrCl 30–49
Stroke						
Stroke[a]	0.53 (0.29–0.89)	0.96 (0.6–1.5)	0.46 (0.1–1.4)	0.58 (0.30–0.90)	0.85 (0.51–1.2)	0.33 (0.06–1.1)
Ischemic or hemorrhagic stroke	0.46 (0.24–0.8)	0.73 (0.42–1.2)	0.46 (0.1–1.4)	0.47 (0.23–0.75)	0.59 (0.33–0.88)	0.23 (0–0.53)
Death						
All cause	1.2 (0.83–1.7)	2.7 (2.1–3.5)	5.4 (3.8–7.5)	1.6 (1.1–2.2)	2.6 (2.0–3.3)	4.5 (3.1–6.3)
Vascular	0.49 (0.26–0.84)	0.78 (0.45–1.3)	1.7 (0.85–3.0)	0.69 (0.37–1.1)	0.81 (0.49–1.2)	1.8 (0.81–3.4)
Non-vascular	0.45 (0.23–0.79)	1.3 (0.85–1.9)	2.2 (1.2–3.6)	0.59 (0.30–0.96)	1.2 (0.74–1.6)	1.5 (0.77–2.3)
Major bleeding						
All major bleeding	0.72 (0.43–1.1)	1.1 (0.67–1.6)	2 (1.1–3.4)	0.68 (0.39–1.0)	0.92 (0.58–1.3)	1.26 (0.66–2.0)
Life-threatening	0.3 (0.13–0.6)	0.5 (0.25–0.9)	0.93 (0.34–2.0)	0.29 (0.11–0.53)	0.45 (0.22–0.72)	0.54 (0.19–1.0)

Abbreviations: CI, confidence interval; CrCl, creatinine clearance.
Note: Patients with CrCl <30 mL/min were omitted from this analysis due to low numbers. Standardized incidence rates were calculated with all missing HAS-BLED and CrCl values imputed.
[a]Includes hemorrhagic, ischemic strokes, and strokes of unknown origin.

perceived bleeding risk. Therefore, our findings emphasize that dabigatran can safely be used in patients with mild-to-moderate impairment. Of note, in the ongoing phase III of GLORIA-AF follow-up data will be collected from VKA-treated patients, allowing for future comparison of safety and effectiveness.[13]

Limitations

This study has several limitations. First, CrCl values were missing in 21% of patients and were imputed for the outcome analyses. Second, due to broad inclusion of many centers and countries in this global registry, slight differences in NOAC labels existed regarding CrCl, which might have influenced the prescription pattern. Third, while we standardized for CHADS-VASc and HAS-BLED scores, other differences in baseline characteristics CrCl groups may not adequately have been captured. Finally, we assessed renal function at baseline and did not assess changes in renal function over the follow-up period.

In conclusion, in contrast to VKA, dabigatran prescription decreased with declining renal function and was rare in patients with severe renal impairment. Further, in dabigatran-treated patients, the estimated rates of stroke and major bleeding were low across the categories of renal impairment.

Note

This study is registered with ClinicalTrials.gov with identifier no. NCT01468701 (http://www.clinicaltrials.gov).

Conflict of Interest

S.J.V declares no conflict of interest. H.C.D. has received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from Abbott, Allergan, AstraZeneca, Bayer Vital, Boehringer Ingelheim, Bristol-Myers Squibb, Covidien, Daiichi-Sankyo, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Knoll, Lilly, Merck Sharp & Dohme, Medtronic, Novartis, Pfizer, Sanofi-Aventis, Servier, St Jude, and WebMD Global. The Department of Neurology at the University Duisburg-Essen received research grants from the German Research Council (DFG), the German Ministry of Education and Research (BMBF), the European Union, the National Institutes of Health (NIH), the Bertelsmann Foundation, and the Heinz-Nixdorf Foundation. S.J.D. has received consultancy fees for serving as a steering committee member for Boehringer Ingelheim. He also holds research grants from Abbott (St Jude Medical). J.H. is currently conducting research sponsored by Boehringer Ingelheim as a member of the Executive Steering Committee for the GLORIA-AF Registry, and has received consulting fees from Bayer HealthCare, Janssen-Ortho-McNeil, and Pfizer for advisory activities involving the development of anticoagulant drugs. C.H.M. has received honoraria for presentations, as well as research grants from AstraZeneca, Bayer

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