IJC Heart & Vasculature 23 (2019) 100367

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: http://www.journals.elsevier.com/ijc-heart-and-vasculature

Comparative effectiveness of rivaroxaban versus a vitamin K antagonist in patients with renal impairment treated for non-valvular atrial fibrillation in Germany — A retrospective cohort study☆

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ARTICLE INFO

Article history:
Received 7 November 2018
Received in revised form 2 April 2019
Accepted 22 April 2019
Available online 9 May 2019

Keywords:
Non-valvular atrial fibrillation
Phenprocoumon
RELOAD study
Renal impairment
Rivaroxaban

ABSTRACT

Background: The risk of thromboembolic events is increased in patients with non-valvular atrial fibrillation (NVAF) and renal impairment. The risk of bleeding events is increased if these patients are treated with anticoagulants and further increased in those with active cancer.
Methods: RELOAD, a retrospective database study, assessed the outcomes of patients with NVAF prescribed rivaroxaban versus phenprocoumon. Here, we present a subgroup analysis evaluating effectiveness and safety of rivaroxaban versus phenprocoumon in patients with NVAF and renal impairment. Analyses were additionally stratified by patients with and without evidence of cancer at baseline.
Results: When using the 'one tablet per day' definition of estimating drug exposure time, the incidence of the primary endpoint of ischaemic stroke was significantly lower in patients (without evidence of cancer at baseline) receiving rivaroxaban 15 mg or 20 mg once daily versus those receiving phenprocoumon (2.40 vs 3.51 events per 100 patient-years, respectively; hazard ratio [HR] = 0.72, 95% confidence interval [CI] 0.55–0.94, $p = 0.015$); with the incidence of the primary safety outcome of intracranial haemorrhage being numerically lower (0.57 vs 0.89 events per 100 patient-years, respectively; HR = 0.66, 95% CI 0.38–1.14, $p = 0.14$). Similar results were observed when using the 'empirical defined daily dose' definition to estimate drug exposure time and when including patients with evidence of cancer.
Conclusion: The prescription of rivaroxaban in patients with NVAF and renal impairment was associated with a lower incidence of ischaemic stroke and intracranial haemorrhage versus phenprocoumon in patients without evidence of cancer.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is a major risk factor for ischaemic stroke [1]. To reduce the risk of stroke, patients with one or more additional risk factors for stroke can be treated with a non-vitamin K antagonist (VKA) direct oral anticoagulant (DOAC; e.g. apixaban, dabigatran, edoxaban or rivaroxaban), which are recommended as alternatives to, or preferred to, VKAs [2]. DOACs are renally cleared to varying degrees; for example, dabigatran and edoxaban are ≥ 50% renally cleared, whereas apixaban and rivaroxaban are ≤ 36% renally cleared [3]. Renal impairment, which leads to decreased drug clearance, prolonged half-life and increased total drug exposure, is common in patients with AF [3]. Rivaroxaban has been shown to have a slower clearance in patients with renal impairment than in those that are healthy, which affects its pharmacodynamics [4]. The risk of thromboembolic events is increased in patients with renal impairment and non-valvular AF (NVAF), and the risk of bleeding events is increased if these patients are treated with anticoagulants [5–7].

The non-inferiority of rivaroxaban 20 mg once daily (od) to warfarin for the prevention of stroke or systemic embolism in patients with NVAF was demonstrated in the phase III, randomised ROCKET AF study [8]. A subanalysis of this study demonstrated the efficacy and safety of a

Abbreviations: AF, atrial fibrillation; $CHADS_2$, Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke or transient ischaemic attack (2 points); CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes mellitus, Stroke or transient ischaemic attack (2 points), Vascular disease, Age 65–74, Sex category (female); CI, confidence interval; DOAC, direct oral anticoagulant; eDDD, empirical defined daily dose; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalised ratio, Elderly, Drugs/alcohol concomitantly; HR, hazard ratio; ICD-10, International Classification of Diseases Tenth Revision; ICH, intracranial haemorrhage; NVAF, non-valvular atrial fibrillation; od, once daily; VKA, vitamin K antagonist; pPDD, personalised prescribed daily dose; PY, patient-years; TIA, transient ischaemic attack.

☆ Authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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https://doi.org/10.1016/j.ijcha.2019.100367

reduced rivaroxaban dose of 15 mg od in patients with NVAF and moderate renal impairment [9]. However, there is limited evidence available regarding patient characteristics and the effectiveness and safety of rivaroxaban in patients with NVAF and renal impairment in routine care.

Patients with cancer are at increased risk of thrombotic and bleeding complications relative to those without cancer [10]. Furthermore, cancer is more common among older individuals, with these patients more likely to have other ageing-related co-morbidities such as AF [11]. However, data on the use of DOACs in patients with AF and active cancer is generally limited [11]. In this study, patients with AF, with or without renal impairment, were stratified at baseline and the outcomes of patients prescribed either rivaroxaban or phenprocoumon assessed. A subsequent subanalysis considered patients with evidence of cancer within the baseline period of this study.

Recent German database studies evaluating the outcomes of patients who have been prescribed oral anticoagulants in a real-world setting have produced inconsistent results [12–14]. For example, one new-user cohort approach suggested that DOACs are associated with a favourable effectiveness and safety profile compared with phenprocoumon, the most frequently prescribed VKA for stroke prevention in patients with NVAF in Germany [12]. However, another new-user study found that the DOACs tested performed differently when compared with phenprocoumon (e.g. there was a similar incidence of bleeding events requiring hospitalisation and ischaemic stroke with rivaroxaban, a reduced incidence of bleeding and similar incidence of ischaemic stroke with dabigatran, and a reduced incidence of bleeding but an increased incidence of ischaemic stroke with apixaban) [14]. In a study that included VKA-experienced patients, it was concluded that VKA therapy was more effective and safer than DOAC therapy in a real-world setting [13]. These studies indicated that it might be useful to have a more detailed view on specific subgroups and subpopulations to better understand the effectiveness and safety of DOACs in routine care.

The RELOAD study, a retrospective database study based on German insurance claims data from the Health Risk Institute's research database, assessed the outcomes of patients with NVAF and renal impairment who were prescribed rivaroxaban versus phenprocoumon [15]. The 110–130-hour elimination half-life of phenprocoumon is not significantly affected by renal impairment [16,17]. Here, we present the results from a detailed assessment of a subgroup analysis of the RELOAD study. The subanalysis assessed the outcomes associated with patients with NVAF and renal impairment, with evidence of cancer within the baseline period, who were prescribed rivaroxaban versus those prescribed phenprocoumon.

2. Methods

2.1. Study design

The study included new users of rivaroxaban or phenprocoumon and assessed related effectiveness (ischaemic stroke) and safety (intracranial haemorrhage [ICH]) in patients with NVAF and renal impairment, utilising claims data between January 2012 and December 2016 (Fig. 1).

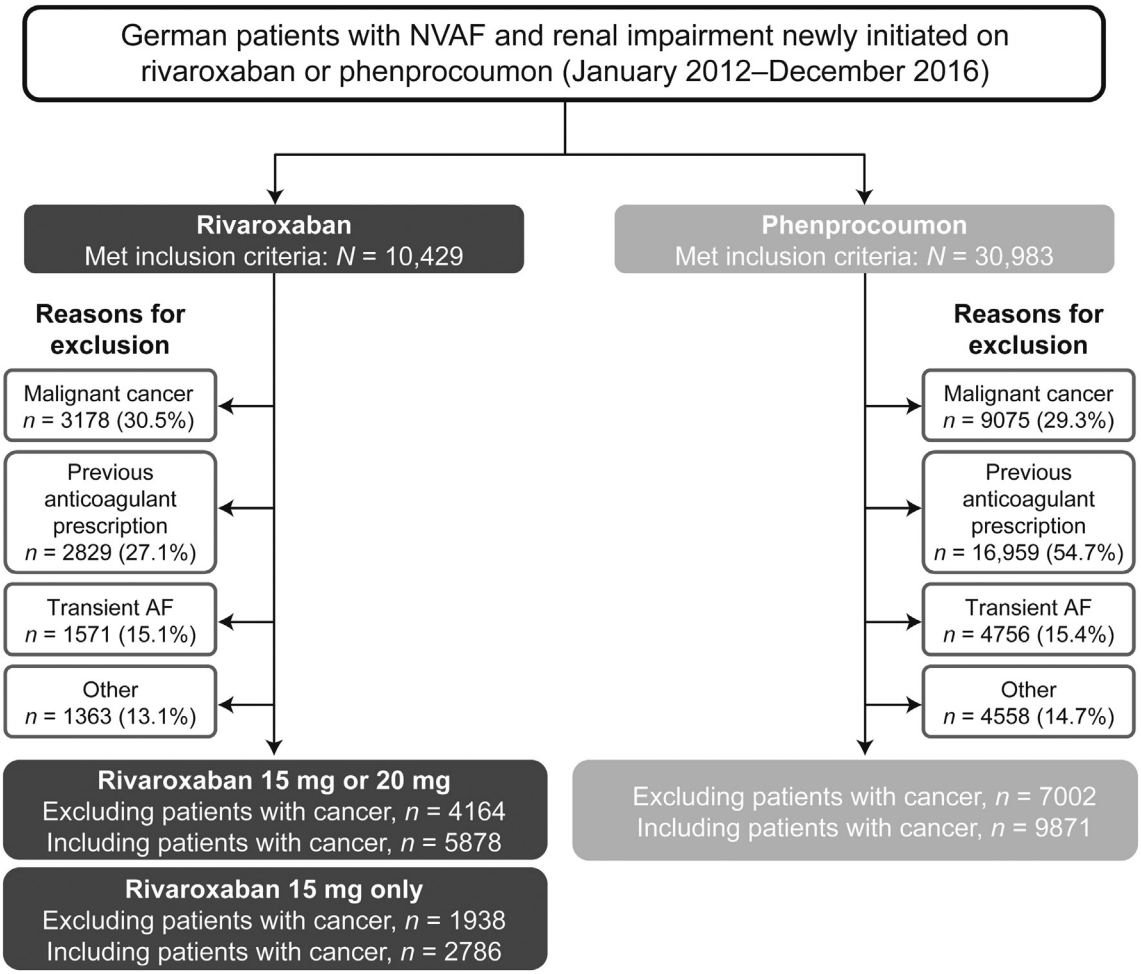


Fig. 1. Study design of the RELOAD renal impairment subanalysis. AF = atrial fibrillation, NVAF = non-valvular atrial fibrillation.

Table 1
Baseline demographics and clinical characteristics of patients with NVAF and renal impairment in the RELOAD study.

Characteristics*	Patients without evidence of cancer within the baseline period			Patients with evidence of cancer within the baseline period	
	Rivaroxaban 15 or 20 mg (n = 4164)	Rivaroxaban 15 mg (n = 1938)	Phenprocoumon (n = 7002)	Rivaroxaban 15 mg (n = 2786)	Phenprocoumon (n = 9871)
Age, years	76.9 ± 9.4	80.5 ± 7.8	77.2 ± 8.4	80.8 ± 7.6	77.7 ± 8.1
Male sex, %	47.7	40.9	50.8	45.0	54.1
CHA_2DS_2-VASc score	4.4 ± 1.7	4.9 ± 1.6	4.5 ± 1.6	4.9 ± 1.5	4.5 ± 1.6
$CHADS_2$ score	2.9 ± 1.4	3.2 ± 1.3	2.9 ± 1.3	3.2 ± 1.3	2.9 ± 1.3
Modified HAS-BLED score	3.4 ± 1.1	3.6 ± 1.1	3.4 ± 1.1	3.6 ± 1.1	3.5 ± 1.1
Modified HAS-BLED score, %					
< 3	22	13	18	13	17
≥ 3	78	87	82	87	83
Modified Charlson Comorbidity Index score	3.0 ± 2.0	3.5 ± 2.0	3.0 ± 1.9	3.9 ± 2.4	3.4 ± 2.2
Co-morbidities, %					
Myocardial infarction	7.6	8.4	11.6	8.1	11.3
Hypertension	91.4	92.0	93.0	92.5	93.1
Congestive heart failure	49.4	57.7	51.1	56.8	50.5
Coronary heart disease	46.9	50.9	54.7	52.1	55.5
Baseline stroke or TIA	14.8	16.9	13.8	16.6	13.5
Diabetes	47.1	50.2	48.6	49.9	47.8
Peripheral atherosclerosis	8.8	10.3	10.6	11.0	10.6
Obesity	28.5	25.2	29.3	25.0	28.0
Dementia	14.6	19.5	9.5	18.0	9.0
Number of unique medications	10.6 ± 5.5	11.3 ± 5.4	10.9 ± 5.4	11.7 ± 5.5	11.1 ± 5.4
Prescriptions, %					
Antiplatelet agents	33.3	38.6	35.3	38.2	35.5
Acetylsalicylic acid	26.3	30.1	27.4	30.3	27.7
Proton pump inhibitors	51.7	55.3	51.6	56.8	51.8
Interventions					
Coronary angioplasty	3.6	4.6	9.1	4.5	9.0

$CHADS_2$ = Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke or transient ischaemic attack (2 points), CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes mellitus, Stroke or transient ischaemic attack (2 points), Vascular disease, Age 65–74, Sex category (female), HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalised ratio, Elderly, Drugs/alcohol concomitantly, NVAF = non-valvular atrial fibrillation, TIA = transient ischaemic attack.

* All values are mean ± standard deviation unless stated otherwise.

2.2. Patient population

Patients ≥ 18 years of age diagnosed with NVAF and renal impairment were eligible (see Online Resource 1 for full inclusion and exclusion criteria). Renal impairment was defined using a published approach based on the International Classification of Diseases, Tenth Revision (ICD-10) codes D61.3, E08.22, E09.22, E10.2, E11.2, I12, I13, I95.3, N02, N03, N04, N05, N07, N11, N14, N18, N19, O10, Q61 or R88.0 [18]. Patients with evidence of cancer within the baseline period were excluded from the overall analysis that stratified according to renal function. A second subanalysis was then performed, for which patients with evidence of cancer within the baseline period were 'reincluded' into the overall population. Patients with evidence of cancer within the baseline period were identified using ICD-10 codes (ICD-10-GM C00–C97) [18].

2.3. Outcomes

The primary outcomes were ischaemic stroke (effectiveness) and ICH (safety). A secondary outcome was the cerebral benefit as the combined endpoint of ischaemic stroke and ICH.

2.4. Statistical methods

Incidence rates and unadjusted incidence rate ratios were calculated, and comparative analyses were conducted using Cox proportional hazard regression models to estimate adjusted hazard ratios (HRs) as well as corresponding 95% confidence intervals (CIs). Overall, > 40 covariates collected at baseline were used to adjust for potential differences between the two groups by means of propensity score matching, multivariate adjustment and inverse probability of treatment weighting. A list of important patient characteristics can be found in Table 1. For phenprocoumon, a 'one tablet per day' (equal to 3 mg) definition was used to estimate a patient's drug exposure time. As a sensitivity analysis, an 'empirical defined daily dose' (eDDD) definition based on actual observed phenprocoumon prescription patterns was used. The eDDD accounted for the fact that the number of days of phenprocoumon supply did not correspond directly to the amount of drug prescribed — unlike rivaroxaban, which had a fixed daily dose. To calculate the eDDD for phenprocoumon, the amount of active ingredient dispensed to each patient per prescription was used to calculate a personalised prescribed daily dose per patient (pPDD). The eDDD is the median of the distribution of the pPDD across all patients treated with only phenprocoumon during the study period.

Patients with evidence of cancer within the baseline period were excluded from the overall analysis that stratified patients according to renal function. Given that rivaroxaban is the only DOAC without a warning for use in patients with cancer, however, it was also possible to stratify outcomes by patients with evidence of cancer within the baseline period [19]. To perform this second subanalysis, patients with evidence of cancer within the baseline period were added to the overall study population. Patients were also stratified by limiting the rivaroxaban group to those receiving 15 mg od.

3. Results

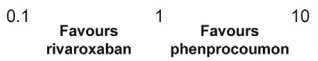
A total of 4164 patients with NVAF and renal impairment (excluding those with cancer) were prescribed rivaroxaban 15 or 20 mg od and 7002 patients (excluding those with cancer) were prescribed phenprocoumon (Fig. 1). Patients prescribed rivaroxaban 15 or 20 mg od or phenprocoumon were of similar age (mean 76.9 and 77.2 years old, respectively), had similar CHA_2DS_2-VASc (4.4 and 4.5, respectively),

$CHADS_2$ (2.9 in both groups) and modified HAS-BLED (3.4 in both groups) scores, and received similar baseline medications (Table 1). Prior myocardial infarction was more frequent in patients prescribed phenprocoumon compared with those prescribed rivaroxaban (11.6% vs 7.6%, respectively), as was prior coronary angioplasty (9.1% vs 3.6%, respectively; Table 1). Overall, chronic renal insufficiency, hypertension, congestive heart failure, coronary heart disease, diabetes mellitus and obesity were frequent co-morbidities in both groups (Table 1). Patients receiving rivaroxaban 15 mg od, were slightly older, were more likely to be female and had slightly higher CHA_2DS_2-VASc, $CHADS_2$ and modified HAS-BLED scores, regardless of cancer diagnosis (Table 1).

For all endpoints in patients receiving rivaroxaban 15 mg or 20 mg od (excluding those with evidence of cancer in the baseline period), the adjusted HRs indicated a potential benefit associated with rivaroxaban use compared with phenprocoumon (Fig. 2a). When using the 'one tablet per day' definition to estimate the drug exposure times for phenprocoumon, the mean follow-up for the primary effectiveness outcome was 381 days for rivaroxaban and 221 days for phenprocoumon. The incidence and related risk of ischaemic stroke was significantly lower for patients prescribed rivaroxaban versus phenprocoumon (2.40 vs 3.51 events per 100 patient-years, respectively; adjusted HR = 0.72, 95% CI 0.55–0.94, $p = 0.015$). The incidence and related risk of the primary safety outcome of ICH was numerically lower, but statistically not significant, in patients prescribed rivaroxaban compared with those prescribed phenprocoumon (0.57 vs 0.89 events per 100 patient-years, respectively; adjusted HR = 0.66, 95% CI 0.38–1.14, $p = 0.14$). When using the eDDD definition of drug exposure time, which corresponded to a daily dose of 1.96 mg, the mean follow-up for the primary effectiveness outcome was 381 days for patients prescribed rivaroxaban and 419 days for those prescribed phenprocoumon. All adjusted HRs using this definition indicated a consistent protective effect associated with rivaroxaban use compared with phenprocoumon (Fig. 2a). The occurrence and relative risk of the combined endpoint of ischaemic stroke and ICH was significantly lower in patients prescribed rivaroxaban versus phenprocoumon (2.88 vs 4.35 events per 100 patient-years, respectively; adjusted HR = 0.69, 95% CI 0.54–0.88, $p < 0.01$; Fig. 2a). When patients with a diagnosis of cancer in the baseline period were included, the adjusted HRs for all endpoints, regardless of the exposure time definition,

(a)

Description	Rivaroxaban 15 mg or 20 mg (*n* = 4164)				Phenprocoumon (*n* = 7002)				HR (95% CI)	HR (95% CI)	*p*-value
	Events (*n*)	Days of follow-up		Events/ 100 PY	Events (*n*)	Days of follow-up		Events/ 100 PY			
		Mean	Median			Mean	Median				
Exposure time estimated with 'one tablet per day' definition											
Ischaemic stroke (effectiveness)	104	380.82	275	2.40	149	221.29	148	3.51		0.72 (0.55–0.94)	0.015
ICH (safety)	25	386.98	281	0.57	38	222.46	149	0.89		0.66 (0.38–1.14)	0.14
Combined endpoint	125	380.38	275	2.88	184	220.95	147	4.35		0.69 (0.54–0.88)	<0.01
Exposure time estimated with eDDD definition											
Ischaemic stroke (effectiveness)	104	380.82	275	2.40	198	419.15	313.0	2.47		0.86 (0.67–1.09)	0.22
ICH (safety)	25	386.98	281	0.57	67	424.45	318.6	0.82		0.59 (0.37–0.94)	0.03
Combined endpoint	125	380.38	275	2.88	254	418.35	311.33	3.17		0.80 (0.64–0.99)	0.04



(b)

Description	Rivaroxaban 15 mg or 20 mg (*n* = 5878)				Phenprocoumon (*n* = 9871)				HR (95% CI)	HR (95% CI)	*p*-value
	Events (*n*)	Days of follow-up		Events/ 100 PY	Events (*n*)	Days of follow-up		Events/ 100 PY			
		Mean	Median			Mean	Median				
Exposure time estimated with 'one tablet per day' definition											
Ischaemic stroke (effectiveness)	168	377.3	269	2.8	201	219.6	148	3.4		0.84 (0.68–1.05)	0.13
ICH (safety)	39	384.1	278.5	0.63	59	220.8	149	0.99		0.67 (0.43–1.03)	0.07
Combined endpoint	201	376.4	269	3.3	255	219.2	148	4.3		0.79 (0.65–0.97)	0.02
Exposure time estimated with eDDD definition											
Ischaemic stroke (effectiveness)	168	377.3	269	2.8	276	415.4	308	2.5		0.98 (0.81–1.20)	0.87
ICH (safety)	39	384.1	278.5	0.63	98	420.5	312	0.86		0.67 (0.46–0.97)	0.04
Combined endpoint	201	376.4	269	3.3	357	414.5	306.6	3.2		0.92 (0.77–1.10)	0.34

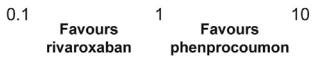


Fig. 2. Multiple regression analysis (adjusted hazard ratios) of the primary effectiveness and safety outcomes in patients with NVAF and renal impairment receiving rivaroxaban 15 or 20 mg od versus those receiving phenprocoumon in patients with evidence of cancer within the baseline period excluded (a) or included (b). CI = confidential interval, eDDD = empirical defined daily dose, HR = hazard ratio, ICH = intracranial haemorrhage, NVAF = non-valvular atrial fibrillation, od = once daily, PY = patient-years.

indicated that there was a potential benefit associated with the use of rivaroxaban 15 or 20 mg od compared with phenprocoumon (Fig. 2b).

In the group of patients receiving rivaroxaban 15 mg od only (excluding those with evidence of cancer within the baseline period), when using the 'one tablet per day' definition of drug exposure time, the mean follow-up for the primary effectiveness outcome was 354 days for patients prescribed rivaroxaban and 221 days for those prescribed phenprocoumon (Fig. 3a). The incidence and related risk of the primary endpoint of ischaemic stroke was lower in patients receiving rivaroxaban versus those receiving phenprocoumon (2.77 vs 3.51 events per 100 patient-years, respectively; adjusted HR = 0.63, 95% CI 0.44–0.90, $p = 0.0105$; Fig. 3a), as was the incidence and related risk of the primary safety outcome of ICH (0.68 vs 0.89 events per 100 patient-years, respectively; adjusted HR = 0.54, 95% CI 0.27–1.08, $p = 0.0811$; Fig. 3a). The occurrence and related risk of the combined endpoint (ischaemic stroke and ICH) was significantly lower in patients prescribed rivaroxaban versus phenprocoumon (3.36 vs 4.35 events per 100 patient-years, respectively; adjusted HR = 0.60, 95% CI 0.44–0.83, $p = 0.0017$; Fig. 3a). When considering eDDD data in patients without evidence of cancer in the baseline period, a numerically higher event rate was observed for ischaemic stroke in patients receiving rivaroxaban 15 mg od versus those receiving phenprocoumon (2.77 vs 2.47 events per 100 patient-years, respectively; adjusted HR = 0.79, 95% CI 0.57–1.09, $p = 0.1499$; Fig. 3a). Rates of ICH were significantly lower in patients receiving rivaroxaban 15 mg od versus phenprocoumon (0.68 vs 0.82 events per 100 patient-years, respectively; adjusted HR = 0.53, 95% CI 0.29–0.99, $p = 0.0468$; Fig. 3a). These results suggest a potential safety benefit for ICH events associated with the use of rivaroxaban 15 mg od over phenprocoumon in patients without cancer. The rates of the combined endpoint were significantly higher in patients without evidence of cancer within the baseline period receiving rivaroxaban 15 mg od versus phenprocoumon (3.36 vs 3.17 events per 100 patient-years, respectively; adjusted HR = 0.73, 95% CI 0.55–0.98, $p = 0.0343$; Fig. 3a).

In patients receiving rivaroxaban 15 mg od only (including those with evidence of cancer within the baseline period), when using the 'one tablet per day' definition of drug exposure time, the mean follow-up for the primary effectiveness outcome was 347 days for patients prescribed rivaroxaban and 220 days for those prescribed phenprocoumon (Fig. 3b). The incidence and related risk of ischaemic stroke was similar

(a)

Description	Rivaroxaban 15 mg (n=1938)				Phenprocoumon (n=7002)				HR (95% CI)	HR (95% CI)	*p*-value
	Events, n	Days of follow-up Mean	Days of follow-up Median	Events/ 100 PY	Events, n	Days of follow-up Mean	Days of follow-up Median	Events/ 100 PY			
Exposure time estimated with 'one tablet per day' definition											
Ischaemic stroke (effectiveness)	52	353.74	247	2.77	149	221.29	148	3.51		0.63 (0.44–0.90)	0.0105
ICH (safety)	13	359.59	251	0.68	38	222.46	149	0.89		0.54 (0.27–1.08)	0.0811
Combined endpoint	63	353.52	246	3.36	184	220.95	147	4.35		0.60 (0.44–0.83)	0.0017
Exposure time estimated with eDDD definition											
Ischaemic stroke (effectiveness)	52	353.74	247	2.77	198	419.15	313	2.47		0.79 (0.57–1.09)	0.1499
ICH (safety)	13	359.59	251	0.68	67	424.45	318.6	0.82		0.53 (0.29–0.99)	0.0468
Combined endpoint	63	353.52	246	3.36	254	418.35	311.33	3.17		0.73 (0.55–0.98)	0.0343

0.1 1 10

Favours rivaroxaban Favours phenprocoumon

(b)

Description	Rivaroxaban 15 mg (n=2786)				Phenprocoumon (n=9871)				HR (95% CI)	HR (95% CI)	*p*-value
	Events, n	Days of follow-up Mean	Days of follow-up Median	Events/ 100 PY	Events, n	Days of follow-up Mean	Days of follow-up Median	Events/ 100 PY			
Exposure time estimated with 'one tablet per day' definition											
Ischaemic stroke (effectiveness)	90	347.27	238.5	3.40	201	219.56	148	3.39		0.84 (0.64–1.10)	0.21
ICH (safety)	21	354.76	247	0.78	59	220.82	149	0.99		0.61 (0.35–1.06)	0.08
Combined endpoint	108	346.96	238	4.08	255	219.21	148	4.31		0.78 (0.61–1.00)	0.05
Exposure time estimated with eDDD definition											
Ischaemic stroke (effectiveness)	90	347.27	238.5	3.4	276	415.4	308	2.46		1.02 (0.79–1.31)	0.91
ICH (safety)	21	354.76	247	0.78	98	420.54	312	0.86		0.64 (0.39–1.04)	0.074
Combined endpoint	108	346.96	238	4.08	357	414.5	306.62	3.19		0.93 (0.74–1.17)	0.54

0.1 1 10

Favours rivaroxaban Favours phenprocoumon

Fig. 3. Multiple regression analyses (adjusted hazard ratios) of the primary effectiveness and safety outcomes in patients with NVAF and renal impairment receiving rivaroxaban 15 mg od versus those receiving phenprocoumon in patients with evidence of cancer within the baseline period excluded (a) or included (b). CI = confidential interval, eDDD = empirical defined daily dose, HR = hazard ratio, ICH = intracranial haemorrhage, NVAF = non-valvular atrial fibrillation, od = once daily, PY = patient-years.

for patients prescribed rivaroxaban 15 mg od and for those prescribed phenprocoumon (3.40 vs 3.39 events per 100 patient-years, respectively; adjusted HR = 0.84, 95% CI 0.64–1.10, $p = 0.21$). The incidence and related risk of the primary safety outcome of ICH was lower, although not significantly, in patients prescribed rivaroxaban 15 mg od compared with those prescribed phenprocoumon (0.78 vs 0.99 events per 100 patient-years, respectively; adjusted HR = 0.61, 95% CI 0.35–1.06, $p = 0.08$). The incidence and related risk of the combined endpoint of ischaemic stroke and ICH was significantly lower in patients prescribed rivaroxaban 15 mg od versus phenprocoumon (4.08 vs 4.31 events per 100 patient-years, respectively; adjusted HR = 0.78, 95% CI 0.61–1.00, $p = 0.05$; Fig. 3b). Interestingly, considering the eDDD data for patients with evidence of cancer at baseline receiving rivaroxaban 15 mg od, the rates of ischaemic stroke events were numerically higher (3.40 vs 2.46 events per 100 patient-years, respectively; adjusted HR = 1.02, 95% CI 0.79–1.31, $p = 0.91$; Fig. 3b) and the rates of ICH were numerically lower compared with patients receiving phenprocoumon (0.78 vs 0.86 events per 100 patient-years, respectively; adjusted HR = 0.64, 95% CI 0.39–1.04, $p = 0.074$; Fig. 3b). Furthermore, the rates of the combined endpoint were numerically higher in patients with evidence of cancer at baseline receiving rivaroxaban 15 mg od versus those receiving phenprocoumon (4.08 vs 3.19 events per 100 patient-years, respectively; adjusted HR = 0.93, 95% CI 0.74–1.17, $p = 0.54$; Fig. 3b).

Unadjusted rate ratios for the primary and secondary endpoints of this study can be found in Online Resources 2 and 3.

4. Discussion

This subgroup analysis of the RELOAD study investigated the effectiveness and safety of rivaroxaban versus phenprocoumon in patients with NVAF and renal impairment. Adjusted HRs were calculated using Cox proportional hazard regression models, which considered > 40 confounding factors. Overall, the results showed a trend towards a reduced incidence and related risk of stroke and ICH associated with rivaroxaban use compared with phenprocoumon. However, the results also demonstrated how important it is to address uncertainties in calculating exposure time for VKA therapy in healthcare databases, because there was no strict dosing scheme in these patients (the effect of under-dosing of the VKA to reduce the risk of bleeding may in turn lead to an increased risk of stroke). In analyses of the RELOAD study, the defined daily dose using the 'one tablet per day' definition was 3 mg, whereas the eDDD was assessed using 1.96 mg. This means there was a potential for introducing a patient–time bias by only taking into consideration the prescription and package sizes for calculating exposure time. In addition, these results also highlighted the significance of considering cancer as an important subgroup. When using the 'one tablet per day' definition of drug exposure time, the risks associated with the occurrence of ischaemic stroke events and the combined endpoint were reduced by 28% and 31%, respectively, in patients initiating anticoagulation treatment with rivaroxaban 15 mg or 20 mg od (excluding those with evidence of cancer within the baseline period) compared with those prescribed phenprocoumon. The results suggest that there is an overall benefit associated with the use of rivaroxaban 15 mg or 20 mg od compared with phenprocoumon in patients with AF and renal impairment (excluding those with evidence of cancer within the baseline period). Similar trends were observed when using the eDDD definition of drug exposure time, when including patients with evidence of cancer within the baseline period and when the analysis was limited to patients receiving rivaroxaban 15 mg od only.

These results were consistent with the previously reported analyses of the full RELOAD study population, which included patients with or without renal impairment; a significant relative risk reduction of 23% in ischaemic stroke was observed among all patients prescribed rivaroxaban compared with those prescribed phenprocoumon (HR = 0.77, 95% CI 0.63–0.93, $p = 0.01$) [15].

Previous real-world studies have reported poor outcomes in patients with AF who have renal impairment compared with those without renal impairment. In the Global Anticoagulant Registry in the FIELD-AF (GARFIELD-AF) – an ongoing multinational, observational registry in patients newly diagnosed with NVAF and ≥ 1 additional risk factor for stroke – severe renal impairment was associated with an increased risk of death, stroke/systemic embolism and major bleeding [20]. Furthermore, in another observational study of patients receiving a diagnosis of AF at a four-hospital institution, renal failure was an independent risk factor for cardiovascular and non-cardiovascular death [21]. In a subanalysis of the phase III ROCKET AF study, patients with AF and moderate renal impairment were at increased risk of stroke and bleeding, whereas rivaroxaban treatment was associated with reduced stroke rates and similar bleeding rates compared with warfarin treatment, irrespective of renal function [9]. Subanalyses of phase III trials have demonstrated that treatment with other DOACs also reduced the risk of thromboembolic events compared with warfarin in patients with moderate renal impairment (creatinine clearance [CrCl] < 50 ml/min) and AF [22–25].

The results of this subanalysis are, therefore, consistent with the trends observed in the main RELOAD analysis [15] and previous studies; the effect of rivaroxaban in patients with renal impairment was generally independent of a diagnosis of cancer. Furthermore, the data demonstrate the consistent benefit of rivaroxaban compared with phenprocoumon in this very important subgroup of patients with renal impairment.

4.1. Limitations

There were several limitations to this analysis. Phenprocoumon is a VKA and requires dose adjustment. In this study, however, it was not possible to ascertain the actual extent of anticoagulation for patients who were prescribed phenprocoumon, because there was no information about the international normalised ratio or the time in therapeutic range. The phenprocoumon dose in this study was variable and had to be estimated. In addition, the assumption that patients always take the drug in accordance with the product label might not be accurate. To establish a best estimate of the drug exposure time, analyses were performed assuming different daily doses, using 'one tablet per day' and eDDD definitions. Similar approaches to define and estimate anticoagulant drug exposure time from claims databases have been used by Ujeyl et al. and Mueller et al. [13,14]. The use of claims databases does, however, introduces the potential for documentation bias, because claims were submitted for accounting rather than clinical purposes. In addition, the database used included only statutory health insurance data; therefore, privately insured patients were not represented. Furthermore, renal impairment was defined via a validated algorithm using ICD-10 codes. Although no laboratory values on glomerular filtration rate or CrCl were available for this study, these values would have been used to diagnose renal impairment and for the corresponding ICD-10 codes to be assigned (Online Resource 4). Data on organ-specific bleeding rates are not available because the ICD-10 codes were only used to calculate the modified HAS-BLED score at baseline. Furthermore, secondary endpoints such as systemic embolism were not reported because the event rates were too low to be meaningful in a subanalysis.

Choice of dosage is assumed to be based on rivaroxaban prescribing information, which states that patients with AF and without renal impairment (CrCl > 50 ml/min) receive a dose of 20 mg od taken with food to reduce the risk of stroke. Patients with AF and renal impairment (CrCl < 50 ml/min) receive a dose of 15 mg od taken with food to reduce the risk of stroke [19]. It would not be possible to assess whether alternative criteria were used by prescribing physicians given the data captured in the claims database. Lastly, although > 40 covariates were defined and used to adjust for potential baseline differences, we cannot rule out additional residual confounding caused by unmeasured factors. The results observed in patients with evidence of cancer within the

baseline period receiving rivaroxaban and phenprocoumon, though providing insight into numerical trends, become less statistically significant across both the 'one tablet per day' and 'eDDD' definition data sets, relative to the data sets for patients without evidence of cancer at baseline. This may be due to additional confounding factors, such as cancer severity, which were not considered in the Cox proportional hazard regression analysis model.

5. Conclusions

This subgroup analysis was the first of its kind in Germany comparing the use of rivaroxaban and phenprocoumon in patients with NVAF and renal impairment, with and without evidence of cancer within the baseline period. Although patient numbers in this subgroup were still low, the results of this analysis were generally consistent with the trends observed in the main RELOAD analysis, showing a reduced occurrence and associated reduction in the risk of the primary safety and effectiveness endpoints for patients prescribed rivaroxaban versus those given phenprocoumon. The area of anticoagulation is a very complex field. Where recent real-world evidence publications mainly focus on the overall evaluation of DOACs compared with VKAs, our results suggest that future studies focussing on detailed subgroups and subpopulations are warranted.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2019.100367.

Conflicts of interest

Hendrik Bonnemeier has received honoraria for lectures from Advanced Circulatory Systems, Bayer, Biotronik, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardiome, Daiichi Sankyo, Impulse-Dynamics, Jolife, NayaMed, Medtronic, Lilly, MSD, Physiocontrol, Pfizer, Sanofi, Servier, Sorin and St. Jude Medical; received honoraria for advisory board activities from Bayer, Boehringer Ingelheim, Biotronik, Biosense-Webster, Bristol-Myers Squibb, Boston Scientific, Daiichi Sankyo, Medtronic, MSD, NayaMed, Physiocontrol, Pfizer and Sanofi; and been involved with clinical trials for Biotronik, CVRx, Daiichi Sankyo, Impulse Dynamics, NayaMed, Novartis, Medtronic, MSD, Respicardia, Resmed, Sorin, St. Jude Medical and Sanofi. Maria Huelsebeck and Sebastian Kloss are employees of Bayer AG.

Funding

This work was supported by Bayer AG.

Acknowledgments

The authors would like to acknowledge Lizahn Zwart of Chameleon Communications International Ltd., who provided editorial support with funding from Bayer AG and Janssen Scientific Affairs, LLC.

Compliance with ethical standards

The study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the study.

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