Research Review™
STUDY REVIEW

Thromboembolism, bleeding, and vascular death in nonvalvular atrial fibrillation patients with type 2 diabetes receiving rivaroxaban or warfarin

Making Education Easy 2021

Independent expert commentary provided by Associate Professor John Amerena

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While still actively researching in hypertension, his focus has changed to research in antithrombotic/antiplatelet therapies, particularly in the context of acute coronary syndromes and atrial fibrillation. Heart failure is also a major interest, and he is also the Director of the Heart Failure Programme at Barwon Health. He is well published in these areas, as well as in many other areas of cardiovascular medicine.

Abbreviations used in this review:

CI = confidence intervals;
CRBN = clinically relevant nonmajor;
EHR = electronic health record; **HR** = hazard ratio;
ISTH = International Society of Thrombosis and Haemostasis; **NVAF** = nonvalvular atrial fibrillation;
RRR = relative risk reduction;
SSE = stroke/systemic embolism;
T2DM = type 2 diabetes mellitus ;
TTR = time in therapeutic range.

This study review summarises data from a cohort analysis that evaluated the effectiveness and safety of rivaroxaban versus warfarin in patients with nonvalvular atrial fibrillation and with comorbid type 2 diabetes mellitus.[1] Data from the US Optum® De-Identified electronic health record were used to perform this analysis.[1] The study found that rivaroxaban, compared with warfarin, was associated with a reduced risk of stroke/systemic embolism or vascular death, and fewer bleeding-related hospitalisations in this patient group.

Study background

Patients with type 2 diabetes mellitus (T2DM) have an increased risk of developing nonvalvular atrial fibrillation (NVAF), which in turn increases their risk of stroke/systemic embolism (SSE) and vascular death compared with individuals without diabetes.[2-5] Studies have shown that rivaroxaban is at least as effective and safe as warfarin in preventing SSE in patients with NVAF and T2DM.[6-8]

The study reviewed herein sought to assess the incidence rates of SSE/vascular death and major or clinically relevant nonmajor (CRNM) bleeding complications resulting in hospitalisation in NVAF patients with T2DM who were treated with either rivaroxaban or warfarin.[1]

Study methods

Design

The study analysed US Optum® De-Identified electronic health record (EHR) data from November 1, 2010 through to December 31, 2019.[1] The Optum® EHR data set includes longitudinal patient-level medical record data for over 91 million patients seen at over 700 hospitals and over 7000 clinics across the US.[1, 9] This database includes records of prescriptions and over-the-counter medications (as prescribed or self-reported by patients), laboratory results, vital signs, anthropometrics, other clinical observations, diagnoses, and procedures codes.

Patients

Eligible patients were aged ≥18 years with NVAF and comorbid T2DM.[1] Further details of key inclusion and exclusion criteria for this study are shown in **Table 1**.[1]

The presence of a code for T2DM was considered sufficient to indicate its presence regardless of glycated haemoglobin (HbA1c) value, given the high specificity (>98%) of billing codes for identifying T2DM.[10] Due to the moderate sensitivity of billing codes for detecting T2DM (~60–70%), patients without a billing code for diabetes but with HbA1c >6.5% and receiving a non-insulin antihyperglycaemic medication were also considered to have T2DM.[10]

Table 1. Key inclusion and exclusion criteria[1]

Inclusion criteria	Exclusion criteria
• Aged ≥18 years with NVAF and comorbid T2DM	• Patients with valvular heart disease (defined as any rheumatic heart disease, mitral stenosis, or mitral valve repair/replacement)
• Oral anticoagulant-naïve	• Any prior oral anticoagulant use per written prescription or patient self-report during the 12-month pre-index period
• Newly initiated on rivaroxaban or warfarin after November 1, 2011 (defined as the index date)	• Receiving rivaroxaban doses other than 15 mg once daily or 20 mg once daily
• Active in the data set for at least 12-months prior to the index date	• Patients with venous thromboembolism as an alternative indication for oral anticoagulant use
• Documented care in the EHR from at least one provider in the 12-months prior to the index date	• Patients who underwent recent orthopaedic knee or hip replacement
	• Patients who were pregnant

Study endpoints

The co-primary outcomes of the study included the incidence rates (%/year) of developing the composite of SSE/vascular death (effectiveness) and major/CRNM bleeding resulting in hospitalisation (safety).[1]

Individual components of the composite outcomes were also assessed.[1]

Vascular death was defined as primary diagnosis/procedure code for acute coronary syndrome, venous thromboembolism, aortic plaque, carotid stenosis, carotid stenting, heart failure, hypertension, intracranial haemorrhage, ischaemic heart disease, stroke, major adverse limb event, myocardial infarction, peripheral artery disease, systemic embolism, ventricular fibrillation/arrest, or revascularisation associated with a hospital admission or emergency room visit within 365 days of the date of death.[1]

The major bleeding component was intended to approximate the International Society of Thrombosis and Haemostasis (ISTH) definition of major bleed, and was defined as an intracranial haemorrhage, critical organ bleed per ISTH, or other bleed associated with a fall in haemoglobin level of ≥2 g/dL or requiring transfusion of ≥2 units of whole blood or cells.[11]

Statistical analysis

Propensity scores based upon multivariable logistic regression were used to adjust for potential confounding between the rivaroxaban and warfarin cohorts. Covariates included in the propensity score model included demographics, comorbidities, laboratory and vital signs, and concurrent outpatient co-medication use.[1] Estimated propensity scores were subsequently used to weight patients for analysis using an overlap weighting approach.[1] Propensity score-overlap weighted Cox proportional hazards regression models were used to calculate hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) for all outcomes.

Study results

A total of 32,078 rivaroxaban- and 83,971 warfarin-treated patients with NVAF and comorbid T2DM were identified.[1]

Patient characteristics

Key characteristics of the patients are shown in **Table 2**.[1] A total of 99% patients had a diagnostic code for T2DM.[1] A total of 31% patients treated with rivaroxaban were initiated on the 15 mg dose, and the remainder were prescribed the 20 mg dose.[1] The rivaroxaban and warfarin cohorts were identical after propensity score overlap weighting. Using an estimated glomerular filtration rate cut-off of 50 mL/min/1.75m^2, 6.4% of rivaroxaban patients were overdosed and 21.0% underdosed.[1] Patients started on rivaroxaban were followed for a mean 1048 days (2.9 years). Warfarin patients were followed for a mean 1044 days (2.9 years).

Table 2. Key demographic and clinical characteristics at baseline[1]

	Unweighted		Propensity score overlap weighted	
	Rivaroxaban (N=32,078)	Warfarin (N=83,971)	Rivaroxaban (N=32,078)	Warfarin (N=83,971)
Mean age, years	70	73	71	71
Female, % pts	39.9	40.8	40.5	40.5
Most common baseline comorbidities, % pts (>20%)				
Haemoglobin A1c				
<7%	52.1	54.7	52.9	52.9
7-8%	23.3	22.8	23.0	23.0
>8%	24.6	22.5	24.0	24.0
BMI, % pts				
30 to <40 kg/m^2	45.0	41.8	43.8	43.8
≥40 kg/m^2	26.3	22.7	25.1	25.1
Chronic obstructive pulmonary disease	24.0	27.4	25.2	25.2
Gastroesophageal reflux disease	25.3	25.7	25.5	25.5
Heart failure	33.6	45.8	37.3	37.3
Haemoglobin <13 g/dL in men or <12 g/dL in women (anaemia)	40.5	57.6	45.8	45.8
Hyperlipidaemia	82.7	80.6	82.2	82.2
Hypertension	91.3	90.2	90.8	90.8
Major surgery in prior 90 days	40.6	44.6	41.8	41.8
Osteo- or rheumatoid arthritis	23.3	22.3	23.2	23.2
Revascularization (CABG or PCI)	20.8	26.3	22.7	22.7
Sleep apnoea	24.7	22.4	23.6	23.6
Vascular disease (prior MI, PAD or aortic plaque)	26.8	33.1	28.7	28.7
Haemorrhagic and thrombotic scores				
Mean CHA_2DS_2VASc score	4.2	4.6	4.3	4.3
Mean modified HAS-BLED score	1.5	1.7	1.5	1.5
Mean $CHADS_2$ score	3.1	3.4	3.2	3.2
Mean time in therapeutic INR range, %		46		47
Anti-hyperglycaemic medications, % pts (>10%)				
Dipeptidyl peptidase-4 inhibitor	11.5	9.3	10.7	10.7
Insulin	29.2	36.6	31.0	31.0
Metformin	51.5	38.6	47.8	47.8
Sulfonylurea or glinide	25.9	28.1	26.8	26.8
Other medications, % pts (>10%)				
Amiodarone	11.8	15.4	13.1	13.1
ACE inhibitor or ARB	70.7	65.1	69.3	69.3
Aspirin	28.5	29.4	29.0	29.0
Beta blocker	73.2	74.0	73.3	73.3
Diltiazem	20.0	17.7	19.3	19.3
Loop diuretic	38.1	52.0	43.0	43.0
Nonsteroidal anti-inflammatory drug	23.4	16.7	21.0	21.0
Proton pump inhibitor	35.6	38.2	36.2	36.2
SSRI or SNRI	22.2	22.3	22.2	22.2
Statin	70.0	69.7	70.0	70.0
Thiazide diuretic	30.5	26.2	29.2	29.2

BMI = body mass index; **$CHADS_2$** = congestive heart failure, hypertension, age, diabetes, previous stroke/transient ischaemic attack; **CHA_2DS_2VASc** = congestive heart failure, hypertension, age ≥75 years – diabetes mellitus, previous stroke/transient ischaemic attack – vascular disease, age 65-74 years, female sex; **HAS-BLED** = hypertension, abnormal renal and liver function, stroke – bleeding tendency, labile International Normalised Ratio, elderly, drugs or alcohol; **INR** = international normalised ratio; **pts** = patients.

Outcomes

Co-primary outcomes: Rivaroxaban was associated with a reduced risk of SSE or vascular death (HR=0.91, 95% CI 0.88, 0.95), driven by a reduction in vascular death (HR=0.90, 95% CI 0.86, 0.95) and systemic embolism (HR=0.82, 95% CI 0.66, 1.02; **Table 3**).[1]

The Kaplan–Meier curve for SSE and vascular death is shown in **Figure 1**.[1]

Table 3. Efficacy outcomes

Efficacy outcomes, no. (%/year)	Rivaroxaban (N=32,078)	Warfarin (N=83,971)	Hazard ratio[a] (95% CI)
Stroke, systemic embolism, vascular death	3497 (3.79)	10,077 (4.19)	0.91 (0.88, 0.95)
Ischaemic stroke	1026 (1.10)	2519 (1.05)	1.05 (0.97, 1.14)
Systemic embolism	128 (0.13)	420 (0.16)	0.82 (0.66, 1.02)
Myocardial infarction	898 (0.99)	2267 (0.95)	1.04 (0.96, 1.14)
Vascular death	2598 (2.81)	7641 (3.18)	0.90 (0.86, 0.95)

[a] Propensity score overlap weighted.

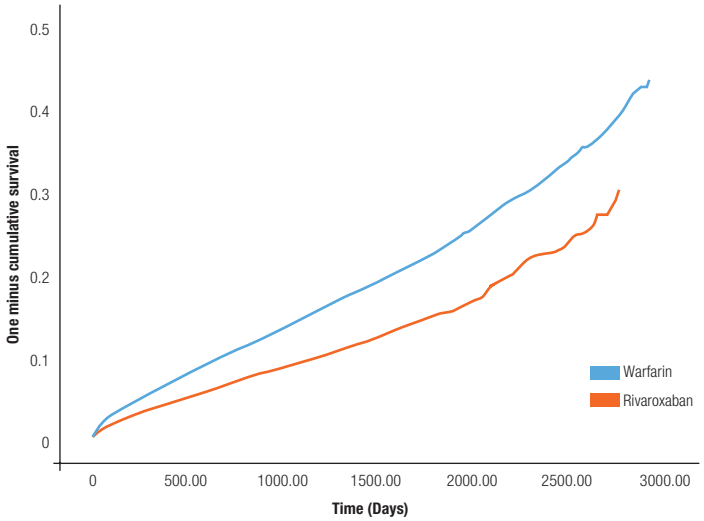

Figure 1. Kaplan–Meier rates of stroke, systemic embolism, or vascular death (primary efficacy outcome)[1]

Adapted from Coleman CI, et al. Cardiovasc Diabetol. 2021;20(1):52.

Hospitalisation due to major/CRNM bleeding was less frequent with rivaroxaban than with warfarin (HR=0.94, 95% CI 0.89, 0.99) due to decreased critical organ bleeding (including intracranial haemorrhage) (HR=0.63, 95% CI 0.55, 0.72; **Table 4**).[1] There was no between-group difference in extracranial bleeding, including gastrointestinal bleeding (**Table 4**).[1]

Table 4. Bleeding outcomes[1]

Bleeding outcomes, no. (%/year)	Rivaroxaban (N=32,078)	Warfarin (N=83,971)	Hazard ratio[a] (95% CI)
Hospitalisation for major or CRNM bleed	1989 (2.17)	5542 (2.31)	0.94 (0.89, 0.99)
Major or CRNM bleed	6416 (6.95)	16,710 (6.95)	1.00 (0.97, 1.03)
Major bleed	834 (0.90)	2687 (1.11)	0.80 (0.74, 0.97)
Critical organ bleed	321 (0.35)	1344 (0.54)	0.63 (0.55, 0.72)
Intracranial haemorrhage	257 (0.29)	1008 (0.40)	0.72 (0.62, 0.84)
Gastrointestinal bleeding	NA (1.50)	NA (1.42)	1.06 (0.99, 1.13)
Extracranial bleed	1732 (1.87)	4450 (1.86)	1.00 (0.95, 1.07)
CRNM bleed	5614 (6.09)	14,443 (6.00)	1.02 (0.98, 1.05)

[a] Propensity score overlap weighted. **CRNM** = clinically relevant non-major; **NA** = not available.

Sub-group analysis: In general, exploratory analyses did not show a statistically significant interaction across subgroups for either of the co-primary endpoints, including across patients with different baseline HbA1c levels.[1] However, rivaroxaban 20 mg compared with warfarin was more effective than rivaroxaban 15 mg compared with warfarin for reducing the risk of SSE/vascular death (p-interaction <0.05). In patients with a warfarin time in therapeutic range (TTR) ≥75% (11.6% of all warfarin users), warfarin was more effective than rivaroxaban for reducing the risk of SSE/vascular death (HR=1.33, 95% CI 1.22, 1.44; p-interaction <0.05).[1] Adjusting for confounding or applying a 2-year follow-up cap did not impact the SSE/vascular death or major/CRNM bleed analysis outcomes.

Expert's comment

We know that T2DM is a risk factor for stroke in patients with NVAF and that the risk of stroke is higher in diabetic than non-diabetic individuals. The ROCKET AF study showed that rivaroxaban was as effective as warfarin in reducing stroke in patients with NVAF at high risk of stroke, including those with T2DM, with similar major bleeding rates but much less intracranial haemorrhage.[7] These real-world data are concordant of the results of this large clinical trial, with a significantly lower rate of the combined endpoint of stroke, systemic embolism, and vascular death in patients who received rivaroxaban compared with warfarin, with vascular death the major contributor to this result. Overall, 30% of patients received the 15 mg dose of rivaroxaban in this real-world analysis, which is a greater proportion of patients that you would expect from the ROCKET AF study where patients with creatinine clearance between 30 and 49 mL/min received the lower dose (~20%).[7] It is likely that many patients in this cohort were inappropriately treated with the low dose, but this is common globally, as many patients who do not meet the dose reduction criteria for all the novel anti-coagulants are given an inappropriately low dose on the assumption it will reduce bleeding risk, but it is under appreciated that inappropriate under dosing may compromise stroke reduction efficacy. This use of low-dose rivaroxaban in inappropriate patients may have influenced the efficacy result in favour of warfarin, so it would be interesting to see if the results were stronger if only patients with appropriate dosing were evaluated.

Study interpretation

This study evaluated EHR data from more than 116,000 patients with NVAF and comorbid T2DM initiated on rivaroxaban or warfarin for a mean of about 2.9-years of follow-up. Rivaroxaban, compared with warfarin, was associated with a reduced risk of SSE/vascular death (co-primary efficacy outcome).[1] With regards to individual components of the composite primary co-endpoints, rivaroxaban use was associated with a reduced risk of vascular death (10% relative risk reduction [RRR]), critical organ bleeding (37% RRR), and intracranial haemorrhage (28% RRR).[1]

The primary efficacy and safety outcomes were consistent across most subgroups including baseline HbA1c levels.[1] Statistically significant interactions for the primary efficacy outcome only occurred when comparing the rivaroxaban 20 mg versus rivaroxaban 15 mg subgroups (an interaction based more on magnitude than direction of effect) and among patients with a well-controlled international normalised ratio (TTR ≥75%).[1]

The outcomes from this study are similar to those from the diabetes sub-analysis of the ROCKET AF trial,[6, 7] in which rivaroxaban, compared with warfarin, reduced the incidence rate of SSE/vascular death (4.23 vs 5.17%/year, HR=0.84, 95% CI 0.70, 1.00) and vascular death (2.83 vs 3.65%/year, HR=0.80, 95% CI 0.64, 0.99) in subjects with diabetes. The vascular mortality reduction with rivaroxaban compared to warfarin in ROCKET AF was observed in subjects with diabetes but not in those without diabetes (HR=1.08, 95% CI 0.89, 1.30; p-interaction=0.037 for diabetic vs non-diabetic subgroup comparison).[6, 7]

Other analyses of claims databases have indicated that rivaroxaban is at least as effective and safe as warfarin in patients with NVAF and comorbid T2DM.[8, 12]

The reduction in vascular mortality with rivaroxaban versus warfarin reported in this study was also supported by the outcomes of a meta-analysis of four randomised controlled trials that demonstrated a reduction in vascular mortality with direct oral anticoagulants versus a vitamin K antagonist in patients with comorbid NVAF and diabetes (4.97 vs 5.99%; relative reduction 0.83, 95% CI 0.72, 0.96).[13]

The study had a number of limitations including:

- The non-randomised, retrospective nature of this study, which may introduce bias. Although, the authors used propensity score overlap weighting to reduce the risk of confounding bias, residual confounding cannot be ruled out.
- The observational nature of the study meant that there was no control over warfarin dosing, or the target INR chosen. However, TTR observed in this study (mean 47%) was not dissimilar to that of the patients treated with warfarin in the ROCKET AF trial (mean 55%)[6] or in routine clinical practice (mean: 55%).[14]
- Time since diabetes diagnosis could not be accurately ascertained from the available HER data and could not be included in the propensity score model.
- Cause of death was not available in the database and so the authors used an algorithm consisting of hospitalisation due to vascular cause within 365 days of death to identify "vascular" mortality.
- The data only included US patients and so the outcomes may not be generalisable to other regions.
- The EHR database did not include information of persistence or adherence of oral anticoagulant use.

Take-home messages

- In NVAF patients with comorbid T2DM, rivaroxaban, compared with warfarin, was associated with:
  - A reduced risk of SSE/vascular death, mostly driven by the reduction in vascular mortality and systemic embolism; and
  - Fewer bleeding-related hospitalisations, which was largely driven by the decreased critical organ bleeding.

Expert's concluding remarks

This real-world analysis of using rivaroxaban for stroke reduction in patients with T2DM has its limitations (as do all real-world analyses) but the results are reassuring that the benefits seen in the large registration trial ROCKET AF were reproduced in a large number of patients treated outside a clinical trial environment. This gives us confidence that the benefits of stroke reduction with rivaroxaban compared with warfarin are not compromised by associated T2DM. The reduction in vascular death is interesting, as there was a signal for this in ROCKET AF, but it was not examined as to whether the presence of diabetes influenced this result. With the larger numbers in this study, the reduction in vascular death was significant, which lends further weight to consideration of using rivaroxaban for stroke reduction in patients who also have T2DM.

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