Thrombosis and bleeding outcomes with warfarin conversion to rivaroxaban during the COVID-19 pandemic

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Background. In 2020, during the coronavirus disease 2019 (COVID-19) outbreak, eligible patients were converted from warfarin to rivaroxaban therapy to limit the transmission of COVID-19 infection.
Objective. To assess the thrombosis and bleeding outcomes associated with converting patients on warfarin therapy to rivaroxaban during the COVID-19 pandemic.
Methods. A retrospective audit was performed that identified 190 participants with venous thromboembolism (VTE) and 112 participants with non-valvular atrial fibrillation at the anticoagulation clinic service at Charlotte Maxeke Johannesburg Academic Hospital, South Africa. Participants were converted to rivaroxaban 20 mg for a median (interquartile range) period of 4 (2) months between April and October 2020. Follow-ups were conducted telephonically and face-to-face on conversion back to warfarin. Rates of COVID-19 infections, bleeding and thrombosis were objectively confirmed.
Results. The COVID-19 infection rate among participants was 3.3% (95% confidence interval (CI) 1.6 - 6.0), with five (1.7%) hospital admissions and two (0.7%) COVID-19-related deaths. The deaths occurred in one participant on rivaroxaban, and in another after switching back to warfarin. One week after switching to rivaroxaban, the rate of clinically relevant non-major bleeding was 0.7% (95% CI 0.02 - 2.54), while minor bleeding occurred at a rate of 9.2% (95% CI 6.16 - 13.40). No major bleeding events were reported, and bleeding rates on rivaroxaban were not significantly higher compared with warfarin. Additionally, two (0.7%) myocardial infarctions were recorded. One occurred on rivaroxaban and the other after switching back to warfarin. A single (0.3%) VTE presenting as a newly diagnosed pulmonary embolism was reported in a participant on rivaroxaban.
Conclusion. This study provides practical insights regarding the conversion of eligible participants from warfarin to rivaroxaban during the first wave of COVID-19, with the aim of informing future public health interventions in similar crisis settings.

Keywords: COVID-19, anticoagulation, venous thromboembolism, bleeding

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In March 2020, the World Health Organization declared the coronavirus disease 2019 (COVID-19) outbreak a global pandemic.[1] South Africa (SA)'s first case was reported on March 5, 2020.[2] As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continued to expand, hospital authorities were confronted with the concern that routine patient visits to outpatient clinical services and pharmacies could potentially serve as focal points for the transmission of COVID-19 infection. The challenges were compounded by the fact that such patients might already be vulnerable due to chronic health conditions. To address this concern, hospital authorities implemented various preventive measures aimed at minimising the risk of viral spread within these settings.[3,4] These measures included infection control protocols, such as mandatory mask-wearing and meticulous hand hygiene, as well as measures to facilitate social distancing among patients attending healthcare facilities. Furthermore, alternative approaches were explored to minimise the necessity for in-person visits, such as telemedicine consultations and home delivery of medications. However, for outpatients attending anticoagulation clinic services in SA for vitamin K antagonist (VKA) therapy, which necessitates regular international normalised ratio (INR) monitoring, such alternatives were not viable. The frequency of clinic visits ranged between 1 and 4 weeks, depending on the stability of the INR.

VKAs are the predominant oral anticoagulants utilised in resource-limited settings.[5] Despite the widespread use of direct oral anticoagulants (DOACs) in high-income settings, in 2020, warfarin was the only oral anticoagulant accessible in the public sector in SA. DOACs, unlike VKAs, have predictable pharmacodynamics.[6] This obviates the need for regular laboratory monitoring, and thus reduces the frequency of face-to-face clinic visits. While the use of DOACs in the public sector has been proposed, their high costs preclude their use in resource-limited settings.[7] In an attempt to safeguard patients and healthcare workers and to limit the transmission of the virus, a clinical decision was made to convert eligible patients attending the anticoagulation clinic services in Johannesburg, SA, with venous thromboembolism (VTE) and/or non-valvular atrial fibrillation (NVAF) from warfarin therapy to rivaroxaban 20 mg for a period ranging from 2 to 4 months, contingent upon the availability of drug supplies. Pooled efficacy and safety data of DOACs have demonstrated non-inferiority to standard of care anticoagulant therapy in patients with VTE and NVAF.[8-10]

We conducted an audit to assess the thrombosis and bleeding outcomes associated with converting patients with VTE and/or NVAF

on warfarin therapy to rivaroxaban (20 mg) during the COVID-19 pandemic. The secondary objective was to assess the impact of minimising outpatient clinic visits on the rates of COVID-19 infections during the study period.

Methods

Study design and population

A retrospective study was conducted at the combined anticoagulation clinic at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in Johannesburg, SA. Approximately 1 300 patients attend this clinic per month, of whom 50% have NVAF and VTE. Patients are managed by specialised nursing staff trained in anticoagulation therapy and monitoring, supported by haematologists. The clinical records of consecutive eligible patients who were converted from warfarin to rivaroxaban (20 mg once daily) between 15 April 2020 and 15 October 2020 were reviewed. During the study period, 302 clinical records of eligible consenting patients were identified. The study included 112 patients with NVAF (of whom 4 had a personal history for VTE) and 190 patients with VTE. The VTE group included patients with deep vein thrombosis (DVT) and/or pulmonary embolism (PE). The following exclusion criteria were applied (n=987): valvular heart disease; arterial thrombosis; anti-phospholipid syndrome; renal impairment (estimated glomerular filtration rate <60 mL/min), known hypersensitivity to rivaroxaban; ≤18 years of age; pregnant or breastfeeding; drug interactions, e.g. anti-tuberculous therapy containing rifampicin, anti-retroviral therapy containing protease inhibitors; non-adherence to medication; bleeding disorder; and patients who could not be contacted for follow-up.

Study protocol

Data collection

At initiation of rivaroxaban, demographics, medical history, comorbidities and concomitant medications, anticoagulant characteristics and baseline renal function tests were recorded. The frequency in therapeutic range (FIR) was calculated as using the total number of INRs that fall within the therapeutic range and dividing it by the total number of INR tests performed on anticoagulation therapy. Signs and symptoms of thrombosis, bleeding, hospital admission and adverse events were recorded on follow-up (telephonic call within a week of conversion, prior to conversion back to warfarin and after conversion back to warfarin). In addition, the following laboratory investigations were recorded: liver function tests; renal function tests; full blood count; and anti-Factor Xa (anti-FXa) performed at 2 and 3 months after initiation of rivaroxaban; INR after conversion back to warfarin at a mean (standard deviation (SD)) of 2.0 (1.0) weeks, and subsequently after a mean of 4.6 (3.1) weeks; and testing for COVID-19. Written informed consent was obtained from all study participants, and the study was approved by the University of the Witwatersrand Human Research Ethics Committee, Medical (ref. no. M-200551).

Management

At initiation of rivaroxaban, patients were advised to discontinue warfarin (irrespective of the INR, in order to limit contact time of the in-person visit), and rivaroxaban 20 mg once daily was commenced on the following day at 07h00 for 2 - 4 months (subject to availability of stock). During this period there was no anticoagulation activity monitoring and no scheduled clinic visits. Patients were supplied with a 24-hour emergency contact number. Patients were contacted by telephone within 1 week of initiating rivaroxaban to assess self-reported adherence. Additionally, 1 week before completing rivaroxaban therapy, patients were followed up at the anticoagulation clinic, where self-reported adherence over the preceding 2 - 4 months was evaluated. Patients who required ongoing anticoagulation were converted back to their prior warfarin dose, which was overlapped with 7 days of rivaroxaban 20 mg.[11]

Outcomes

Symptomatic PE was confirmed by computed tomography pulmonary angiogram. Myocardial infarction was confirmed by laboratory and radiological findings, e.g. serum troponin T, electrocardiograph and angiogram, in conjunction with clinical history. Major bleeding, clinically relevant non-major bleeding (CRNMB) and minor bleeding events were confirmed by independent adjudication (CW, ES and SL).[12] COVID-19 infection was confirmed with a positive real-time polymerase chain reaction from the upper respiratory tract (nasopharyngeal or oropharyngeal swab). Death was classified as due to thrombosis, bleeding, COVID-19, or other established causes.

Laboratory methods

Venous blood for anti-FXa measurement was collected in 3.2% sodium citrate (Becton-Dickinson, UK) 3 - 4 hours after the rivaroxaban dose. The platelet-poor plasma was separated, frozen at −80°C and transported to Lancet Laboratory. The samples were processed on the Atellica COAG 360 (Siemens Healthineers, Germany) analyser with the chromogenic rivaroxaban anti-FXa reagents (Innovance, reference interval 189 - 419 ng/mL). Testing for D-dimer (on the STA-R Max, Diagnostica Stago, France), full blood count (on the Sysmex XN-9000, Sysmex, Japan) and liver and renal function tests (on the Cobas ISE, Sysmex, Japan) were performed at the CMJAH laboratory prior to conversion back to warfarin. Venous blood for INR measurement was collected in 3.2% sodium citrate after conversion back to warfarin and processed on the STA-R Max at the CMJAH laboratory.

Statistical methods

A sample size was estimated, assuming a 2.0% incidence of major bleeding or VTE on rivaroxaban, and considering a maximum incidence of 15%, at a confidence interval (CI) of 95% (Epi Info v7.2.0.1, USA).[8] Data were analysed using Statistica 13.2 software (TIBCO, USA). Statistical comparisons were performed between participants with VTE and NVAF using the parametric unpaired t-test and non-parametric Mann-Whitney U-test. Categorical variables were compared using the χ^2 test or Fisher's exact test where necessary. Univariate Cox proportional hazard regression analysis was used to identify predictors of bleeding events by calculating hazard ratios (HR; with 95% CI). The median survival time was estimated using the Kaplan-Meier method. Statistical significance was set at p<0.05.

Results

Patient characteristics

A total of 302 participants were eligible for inclusion. Indications for warfarin in the VTE group included: PE (n=93, 49%), DVT (n=74, 39%), internal jugular vein thrombosis (n=2, 1%), mesenteric vein thrombosis (n=2, 1%), portal vein thrombosis (n=2, 1%), venous sinus thrombosis (n=4, 2%), renal vein thrombosis (n=1, 0.5%), cardiac mural thrombus (n=11, 6%) and retinal vein thrombosis (n=1, 0.5%). Of these, 29 (15%) had a history of recurrent VTE defined as recurrent thrombosis that occurred once anticoagulation had been discontinued. The baseline demographics, clinical and laboratory characteristics of the 112 (37%) participants with NVAF and 190 (63%) participants with VTE are described in Table 1. A significant difference in age, gender and ethnicity between the VTE and NVAF group was observed. The number of comorbidities was

Table 1. Baseline characteristics of participants with non-valvular atrial fibrillation and venous thromboembolism

Characteristic, *n* (%)*	NVAF (*n*=112)	VTE (*n*=190)	Total (*N*=302)	*p*-value
Age at study entry (years), mean (SD)	64 (14)	51 (16)	55 (16)	<0.001
18 - 30	2 (2)	19 (10)	21 (7)	0.007
31 - 59	37 (33)	117 (62)	154 (51)	<0.001
≥60	73 (65)	54 (28)	127 (42)	<0.001
Gender				
Male	55 (49)	55 (29)	110 (36)	<0.001
Female	57 (51)	135 (71)	192 (64)	<0.001
Ethnicity				
Black African	64 (57)	153 (81)	217 (72)	<0.001
White	39 (35)	22 (12)	61 (20)	<0.001
Indian	3 (3)	7 (3)	10 (3)	0.750
Mixed	6 (5)	8 (4)	14 (5)	0.778
BMI (kg/m^2), mean (SD)	29.6 (7.1)	30.3 (7.4)	30.1 (7.3)	0.421
Medical history				
Comorbidities per participant, mean (SD)	1.6 (0.9)	1.2 (0.8)	1.4 (0.9)	<0.001
HIV infected	4 (4)	52 (27)	56 (19)	<0.001
Hypertension	73 (65)	55 (29)	128 (42)	<0.001
Diabetes mellitus	21 (19)	24 (13)	45 (15)	0.149
Epilepsy	2 (2)	5 (3)	7 (2)	1.000
Heart failure	36 (32)	21 (11)	57 (19)	<0.001
Malignancy	19 (17)	2 (1)	21 (7)	<0.001
Medications				
Aspirin	7 (6)	6 (3)	13 (4)	0.244
Clopidogrel	3 (3)	0 (0)	3 (1)	0.050
Dual antiplatelet therapy	0 (0)	0 (0)	0 (0)	-
Estimated glomerular filtration rate (mL/min)				
<50	0 (0)	0 (0)	0 (0)	-
50 - 60	5 (5)	6 (3)	11 (4)	0.431
>60	73 (65)	146 (77)	219 (72)	0.897
No baseline available	34 (30)	38 (20)	72 (24)	-

NVAF = non-valvular atrial fibrillation; VTE = venous thromboembolism; SD = standard deviation; BMI = body mass index.
*Unless otherwise indicated.

higher in participants with NVAF than VTE (p<0.001). In particular, malignancy was increased in participants with NVAF compared with VTE (p<0.001). Subgroup analysis identified breast cancer (n=12), prostate cancer (n=2), genitourinary cancers (n=3), lung cancer (n=1), multiple myeloma (n=2) and Kaposi sarcoma (n=1).

Anticoagulation characteristics

At baseline, 291 (96%) participants were receiving warfarin, the majority (65%) of whom were on long-term therapy (Table 2). The median (interquartile range (IQR)) % FIR in 265 participants, with a mean (standard deviation (SD)) of 11 (3) INR values per participant, was 63%. There were no reports of previous warfarin-associated recurrent thrombosis, major bleeding or CNRMB events. Minor bleeding events on warfarin included heavy menstrual bleeding in 2 (1%), gum bleeding and easy bruising and/or epistaxis in 9 (3%). The baseline mean (SD) INR was 2.7 (1.6), which was not significantly different between the NVAF and VTE groups. The mean (SD) duration of the initial in-person outpatient visit was 52 (30) minutes. The study participants were converted to rivaroxaban for a median (IQR) of 4 (2) months. Anti-FXa testing was performed in 284 (94%) participants on rivaroxaban at the follow-up visit prior to conversion back to warfarin. Testing was performed after 4 hours in 100 (35%) of the samples tested, which were excluded due to delayed sample collection. Ninety-three (51%) of the remaining 184 samples collected within 4 hours of taking rivaroxaban were in the laboratory reference range. There was no correlation between body mass index (BMI) and anti-FXa levels (r=0.083)

At the follow-up visit prior to conversion back to warfarin, the mean (SD) exposure time was 26 (8) minutes, which was significantly shorter than baseline visit (p<0.001). There were 273 (90%) study participants who were converted back to warfarin, and 29 (10%) who discontinued anticoagulation at the end of the study period. On follow-up post conversion back to warfarin, in 265 participants with INR testing performed after 1 month, 75 (28%) were in the therapeutic range at a mean (SD) 8 (10) days. At the second follow-up visit, an additional 43 (of 105 tested) (41%) achieved a therapeutic INR at a mean (SD) of 16 (19) days.

Outcomes

Outcomes were assessed telephonically 1 week after conversion to rivaroxaban, face to face at conversion back to warfarin and face to face on follow-up on warfarin for INR testing (Table 3). The rates of COVID-19 infection were 2.3% (95% CI 0.62 - 4.01) on rivaroxaban and 1.0% (95% CI 0.00 - 2.10) on follow-up on warfarin (p=0.340). Minor bleeding was reported in 28 (9%) participants 1 week after conversion to rivaroxaban. Fourteen (5%) participants reported ongoing minor bleeding symptoms on rivaroxaban at the conversion back to warfarin visit. There were 2 (0.7%) CRNMB reported 1 week after conversion to rivaroxaban and at conversion back to warfarin: a 48-year-old female with recurrent right leg DVT and no comorbidities

Table 2. Anticoagulant characteristics at baseline and follow-up of participants with non-valvular atrial fibrillation and venous thromboembolism

Characteristic, *n* (%)*	NVAF (*n*=112)	VTE (*n*=190)	Total (*N*=302)
Baseline characteristic			
Warfarin	108 (96)	183 (96)	291 (96)
Duration at anticoagulation clinic			
<1 month	7 (6)	27 (14)	34 (11)
1 - 3 months	3 (3)	22 (12)	25 (8)
>3 months	102 (91)	141 (74)	243 (81)
Duration of anticoagulation			
Short term (3 - 12 months)	1 (1)	105 (55)	106 (35)
Long term (>12 months)	111 (99)	85 (45)	196 (65)
Frequency in range (%), median (IQR)	50 (25)	42 (33)	50 (34)
Past history of minor bleeding on warfarin	4 (4)	7 (4)	11 (4)
Past history of CRNMB on warfarin	0 (0)	0 (0)	0 (0)
Past history of major bleeding on warfarin	0 (0)	0 (0)	0 (0)
Past history of recurrent VTE on warfarin	0 (0)	0 (0)	0 (0)
Past history of recurrent arterial thromboembolism on warfarin	0 (0)	0 (0)	0 (0)
International normalised ratio at study entry, mean (SD) (ref: 2 - 3)	2.7 (1.4)	2.7 (1.7)	2.7 (1.6)
Conversion to rivaroxaban			
Duration of anticoagulation (months), median (IQR)	4 (2)	4 (2)	4 (2)
Anti-FXa (ng/mL) (ref: 189 - 419)†			
189 - 419	36 (49)	57 (51)	93 (51)
<189	23 (32)	43 (39)	66 (36)
>419	14 (19)	11 (10)	25 (13)
ALT (U/L), mean (SD) (ref: 10 - 40)	17 (9)	19 (10)	19 (9)
AST (U/L), mean (SD) (ref: 15 - 40)	22 (8)	24 (11)	23 (10)
White cell count ($\times 10^9$/L), mean (SD (ref: 3.9 - 12.6)	7 (3)	6 (2)	6.4 (2)
Haemoglobin (g/L), mean (SD) (ref: 116 - 164)	14 (2)	13 (2)	13.6 (2)
Platelet count ($\times 10^9$/L), mean (SD) (ref: 186 - 454)	262 (85)	309 (126	291 (115)
D-dimer (mg/L), mean (SD) (ref: <0.5)	0.4 (0.4)	0.5 (1.2)	0.4 (0.9)
Follow-up on warfarin			
Warfarin	101 (90)	172 (91)	273 (90)
INR at 1st follow-up, mean (SD) (ref: 2 - 3)	2.0 (0.9)	1.8 (1)	1.9 (0.9)

NVAF = non-valvular atrial fibrillation; VTE = venous thromboembolism; IQR = interquartile range; CRNMB = clinically relevant non-major bleeding; SD = standard deviation; anti-FXa = anti-Factor Xa; ALT = alanine transaminase; AST = aspartate transaminase; ref = reference; INR = international normalised ratio.
*Unless otherwise indicated.
†Of 184.

and no concomitant medications reported heavy menstrual bleeding. Her haemoglobin level was 94 g/L, and she was commenced on oral iron replacement therapy with referral to gynaecology. A 74-year-old female with NVAF and hypertensive heart disease reported a 10-day history of postmenopausal bleeding. These symptoms had previously been experienced on warfarin. She was prescribed oral tranexamic acid and referred to gynaecology. There were no major bleeds. The overall bleeding rate during the initial 7 days was higher than during the study period on rivaroxaban ($p<0.016$). The bleeding rate during the study period was not significantly higher on rivaroxaban than on warfarin prior to the study and on follow-up ($p=0.325$ and $p=0.766$, respectively).

There were five (1.7%) deaths on rivaroxaban: a 56-year-old female with COVID-19 infection and a personal history of a PE on long-term anticoagulation with significant comorbidities (type 2 diabetes mellitus, chronic obstructive pulmonary disease and pulmonary hypertension); a 63-year-old male with a myocardial infarction, and a personal history of NVAF on long-term anticoagulation, with significant comorbidities (chronic hypertension, heart failure and gout); an 83-year-old male with lung adenocarcinoma and a personal history of DVT on long-term anticoagulation; a 74-year-old female with septicaemia, who had a personal history of a NVAF on long-term anticoagulation and significant comorbidities (chronic hypertension, heart failure, dyslipidaemia and hypothyroidism and gout); a 68-year-old female with a newly diagnosed PE and significant comorbidities (chronic hypertension and dyslipidaemia), switched from enoxaparin to rivaroxaban, who died 3 days later. There were also two deaths on conversion back to warfarin with the following contributory comorbidities: A 50-year-old female who presented with a myocardial infarction. She had a personal history of a PE on long-term anticoagulation. An 81-year-old male with COVID-19 infection after conversion back to warfarin. He had a personal history of a DVT on long-term anticoagulation and epilepsy.

In addition, the following two COVID-19 infections were documented in the study cohort (Table 4). The first was an 81-year-old female who was admitted with COVID-19 infection after conversion back to warfarin. She had a personal history of a NVAF on long-term anticoagulation and significant comorbidities (type 2 diabetes mellitus, chronic hypertension and heart failure). The second was a 37-year-old female who presented with COVID-19 infection on rivaroxaban. She had a personal history of a DVT on short-term anticoagulation.

Table 3. Adverse events

Event, *n* (%)	NVAF (*n*=112)	VTE (*n*=190)	Total (*N*=302)
Telephonic follow-up on rivaroxaban (week 1)			
COVID-19 infection	0 (0)	1 (0.5)	1 (0.3)
Minor bleeding	10 (8.9)	18 (9.5)	28 (9.3)
Heavy menstrual bleeding	1 (0.9)	6 (3.2)	7 (2.3)
Gum bleeding alone	1 (0.9)	5 (2.6)	6 (2)
Epistaxis alone	4 (3.6)	2 (0.5)	6 (2)
Gum bleeding and epistaxis	2 (1.8)	1 (0.3)	3 (1)
Haematuria	0 (0)	3 (1.6)	3 (1)
Haemorrhoids	2 (1.1)	0 (0)	2 (0.7)
Bruising alone	0 (0)	1 (0.5)	1 (0.3)
CRNMB	1 (0.9)	1 (0.5)	2 (0.7)
Major bleeding	0 (0)	0 (0)	0 (0)
Visit – conversion of rivaroxaban to warfarin			
COVID-19 infection	0 (0)	6 (3.2)	6 (2)
Venous thromboembolism	0 (0)	1 (0.5)	1 (0.3)
Arterial thrombosis	1 (0.9)	1 (0.5)	2 (0.7)
Death	2 (1.1)	5 (2.6)	7 (2.3)
Minor bleeding	3 (2.7)	11 (5.8)	14 (4.6)
Clinically relevant non-major bleeding	1 (0.9)	1 (0.5)	2 (0.7)
Major bleeding	0 (0)	0 (0)	0 (0)
Visit – follow-up on warfarin*			
COVID-19 infection	2 (1.8)	1 (0.5)	3 (1)
Minor bleeding	3 (2.7)	9 (4.7)	12 (4)
CRNMB	0 (0)	0 (0)	0 (0)
Major bleeding	0 (0)	0 (0)	0 (0)

NVAF = non-valvular atrial fibrillation; VTE = venous thromboembolism; COVID-19 = coronavirus disease 2019; CRNMB = clinically relevant non-major bleeding.
*In 98 with NVAF, 155 with VTE and 253 in total.

A 28-year-old male was admitted with COVID-19 infection on rivaroxaban. He had a personal history of a recurrent DVT and PE on long-term anticoagulation and epilepsy.

There were 3 participants with VTE who conceived on rivaroxaban. The first had a first trimester miscarriage; the second was changed to enoxaparin on confirmation of pregnancy, and subsequently had a first trimester miscarriage; and the third was converted to enoxaparin and had a term delivery. She had been converted from rivaroxaban to warfarin, following completion of the rivaroxaban trial period, 2 weeks prior to confirmation of pregnancy. There were no fetal or neonatal abnormalities.

On univariate logistic regression analysis, a past history of bleeding on warfarin was an independent predictor of bleeding on rivaroxaban (Table 5). Due to the small number of events, the confidence intervals were very wide.

Discussion

During the first wave of the COVID-19 pandemic in SA, 23% of patients attending the anticoagulation clinic at CMJAH were converted from warfarin to rivaroxaban for a median (IQR) of 4 (2) months. Prior to conversion to rivaroxaban, the majority of participants were receiving warfarin, of whom 65% were on long-term therapy. Anticoagulation clinic visits ranged between 1 and 4 weeks apart for INR monitoring, and the FIR was >60%. Participants were predominantly of black African ethnicity, reflecting the hospital's demographics. Participants with NVAF were significantly older and had more comorbidities than those with VTE. In the NVAF group, the most common comorbidities were hypertension and heart failure, whereas in the VTE group, hypertension and HIV infection were the most prevalent. However, we did not observe a significant difference in safety outcomes or COVID-19 infection rates between the two groups.

During the period of 5 March - 26 December 2020, the country reported 92 3274 COVID-19 infections, 13 3679 hospital admissions for COVID-19 and 23 212 COVID-19 related deaths.[13] In contrast, the rates of COVID-19 infection and hospital admission in the study population were low, at 3.3% and 1.7%, respectively. There were two deaths secondary to COVID-19 infection in the study period: one on rivaroxaban, and one after conversion back to warfarin. The switch to rivaroxaban allowed participants to avoid frequent in-person hospital visits for anticoagulation monitoring during this period. Instead, participants were followed up telephonically within a week of the conversion to assess for adverse events, including drug tolerability, bleeding and thrombosis. One week before completing rivaroxaban therapy, participants visited the anticoagulation clinic. The mean duration of this follow-up visit was significantly shorter than of the pre-COVID visit, thereby decreasing the risk of viral infection.

In addition, to reduce the mean exposure time at the baseline anticoagulation clinic visit, participants were started on rivaroxaban 20 mg irrespective of their INR. Guidelines, however, recommend switching from warfarin to DOAC treatment when the INR is <2.5, to limit bleeding.[14] This is based on the findings of the ARISTOTLE[15] and RE-LY2[16] clinical trials, which showed that initiating apixaban and dabigatran, respectively, when the INR was <2.0 were not associated with an increased risk of bleeding. In contrast, in the ROCKET AF (rivaroxaban) study,[17] a higher INR threshold of <3.0 was applied. This was associated with a higher bleeding rate of 4% during the first 7 days of rivaroxaban, compared with 3% in warfarin-naive patients. As such, guidelines recommend follow-up INR testing when the INR is >2.5, prior to switching to a DOAC.[14] The mean

Table 4. COVID-19 infections during the study period

Characteristic, *n* (%)	NVAF (*n*=112)	VTE (*n*=190)	Total (*N*=302)
COVID-19 positive	2 (1.8)	8 (4.2)	10 (3.3)
Hospital admission for COVID-19	2 (1.8)	3 (1.6)	5 (1.7)
COVID-19 related death	0 (0)	2 (1.1)	2 (0.7)

NVAF = non-valvular atrial fibrillation; VTE = venous thromboembolism; COVID-19 = coronavirus disease 2019.

Table 5. Univariate Cox proportional hazard regression analysis of predictors of bleeding on rivaroxaban

Variable	HR	95% CI	*p*-value
AF	1.79	0.58 - 5.58	0.313
Age >60 years	2.03	0.65 - 6.33	0.222
Female	1.71	0.55 - 5.31	0.352
Comorbidities >2	1.57	0.36 - 6.92	0.552
Past history of bleeding on warfarin	18.61	6.80 - 50.93	<0.001
Baseline INR >2.5	1.77	0.56 - 5.66	0.333
Anti-FXa >419	1.17	0.15 - 8.95	0.880

CI = confidence interval; AF = atrial fibrillation; INR = international normalised ratio; anti-Fxa = anti-factor Xa; HR = hazard ratio.

(SD) INR at study entry was 2.7 (1.6), with an INR >2.5 in 40%. Nonetheless, this protocol was not associated with any major bleeding events on telephonic follow-up after 1 week. Moreover, there were no gastrointestinal bleeding events on rivaroxaban. This contrasts with an earlier report of an increased risk within the first 90 days among NVAF patients switching to rivaroxaban.[18] Risk factors for gastrointestinal bleeding included older age and a higher number of comorbidities. We did, however, observe a significant increase in the overall bleeding rate in the first 7 days compared with the entire study period on rivaroxaban. This increase primarily involved minor bleeding, such as gum bleeding, epistaxis and bruising, as well as CRNMB, namely menorrhagia, which persisted during the study period on rivaroxaban. Notably, the overall bleeding rates during the study period on rivaroxaban were not significantly higher than those observed with warfarin, consistent with previous studies.[8] Bleeding outcomes with VKAs and DOACs are influenced by their distinct mechanisms of action and pharmacodynamic profiles. VKAs work by inhibiting the synthesis of vitamin K-dependent clotting factors. This mechanism results in a variable anticoagulant response that requires frequent monitoring and dose adjustments. In contrast, DOACs selectively target factor Xa, resulting in a more predictable and consistent anticoagulant effect. VKA-related bleeding is affected by factors such as the frequency of INR monitoring, dietary variations, genetic predisposition to altered warfarin metabolism and drug interactions. In contrast, the shorter half-life and selective inhibition of DOACs contribute to a lower incidence of bleeding complications than with VKAs.[19] Of note, a past history of bleeding on warfarin was a significant predictor of bleeding on rivaroxaban. Careful monitoring in this select patient group is necessary.

Participants were closely monitored during the study to assess for efficacy of anticoagulation. Anti-FXa monitoring of rivaroxaban was performed within 3 - 4 hours of the dose in 184 (61%) participants, of whom 51% were within the reference range. Participants with an estimated glomerular filtration rate <60 mL/min, and/or significant drug interactions, were excluded. Those with a BMI >40 kg/m² comprised 10% of the study population. There was no significant correlation between increasing weight and decreasing anti-FXa levels. Current guidelines advise against routine peak anti-FXa testing owing to insufficient evidence to guide management.[19,20] The updated guidance from the International Society of Thrombosis and Haemostasis suggests that standard doses of rivaroxaban are appropriate for patients with high BMI without the need for regular anti-FXa testing.[21] Anti-FXa monitoring also has several limitations, particularly regarding the timing of the assay, which is necessary for accurate interpretation. In this study, testing was performed after 4 hours in 100 (35%) of the samples tested. Furthermore, therapeutic targets for anti-FXa levels have not been established, and assays calibrated for specific DOACs are limited in availability. Owing to the low incidence of recurrent thrombotic and/or bleeding events, this study could not confirm the efficacy and safety of anti-FXa monitoring. More data correlating anti-FXa levels with clinical outcomes are needed to determine the role of regular anti-FXa monitoring. On conversion back to warfarin, there were no CRNMBs, major bleeds or recurrent VTE. INR monitoring was performed, and after ~1 week only 28% of participants achieved a therapeutic INR. This highlights the challenges of warfarin in a real-world setting, where multiple factors, such as adherence, diet, drug-drug interactions and comorbidities, influence INR variability.

The study findings contribute to international published studies describing the impact of the COVID-19 pandemic on clinical practice.[21-23] In March 2020, the National Health Service in England issued guidance to support the management of outpatient anticoagulation, recommending that patients stable on warfarin be assessed for switching to DOACs. To enable this transition, procurement efforts were undertaken to secure an adequate supply of DOACs at reduced costs. Prescribing trends were analysed using the OpenSAFELY-TPP platform, which examined 20.5 million electronic health records between January 2018 and February 2023.[21,22] During this period, DOAC prescribing increased from 0.82% to 1.58%. Although a substantial number of patients were switched in line with national guidance, the rapid change raised safety concerns. Notably, 13.8% of patients with AF on a DOAC were prescribed a non-recommended dose based on their calculated creatinine clearance.[21] In addition, there were instances of concurrent prescribing of warfarin and a DOAC, which highlights the importance of anticoagulant monitoring.[22]

Several limitations of the current study warrant consideration. Firstly, the bleeding and thrombotic outcomes of participants (most of whom were on long-term anticoagulant therapy) were evaluated over a relatively short follow-up period of 4 months. Outcomes were

assessed over a short period owing to limited access to rivaroxaban. Secondly, testing for COVID-19 infection on follow-up was not performed, and the study did not aim to collect data on long-COVID outcomes. During the study period, testing was performed in only 34 (11.3%) symptomatic participants with NVAF and VTE. This may, in part, explain the low rates (n=10, 3.3%) of COVID-19 infection compared with those in the country overall. Thirdly, the study was conducted at a single tertiary care centre, which selected for a patient population with comorbidities, which limits the generalisability of the study findings. Lastly, on follow-up, post conversion to warfarin, 34 of 105 (32.4%) participants were sub-therapeutic on warfarin. The study, however, did not evaluate the time taken for these participants to achieve a therapeutic INR beyond the study period.

Conclusion

In summary, this audit provides information on the safety profile of a protocol recommending rivaroxaban 20 mg in participants with VTE and NVAF, irrespective of their INR, attending an anticoagulation clinic during the COVID-19 pandemic. This study provides insights into the practical implementation of converting from VKAs to DOACs during a public health crisis; clinical outcomes in a high-risk population with limited access to healthcare; and the use of AFXa monitoring in a real-world context. The findings of this study have the potential to inform future public health interventions in similar crisis settings.

Data availability. Data used for this study are available from the authors on request.

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