Thrombosis and Bleeding Outcomes with Warfarin Conversion to Rivaroxaban during the COVID-19 Pandemic

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A research report (in the format of a "submissible" paper) submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Haematology

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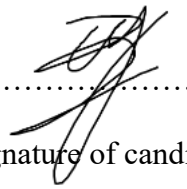
Declaration

I, Ching-Yu Wang, declare that this research report in the format of a “submissible” paper is my own, unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Haematology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



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Abbreviations

AF	Atrial fibrillation
Anti-FXa	Anti-factor Xa
ALT	Alanine aminotransferase
AST	Aspartate transaminase
BMI	Body mass index
CI	Confidence interval
CMJAH	Charlotte Maxeke Johannesburg Hospital
COVID-19	Coronavirus Disease of 2019
CRNMB	Clinically relevant non-major bleeding
DOACs	Direct oral anticoagulants
DVT	Deep vein thrombosis
ECG	Electrocardiograph
FIR	Frequency in therapeutic range
g/L	Grams per litre
HIV	Human immunodeficiency virus
HR	Hazard ratio
INR	International normalised ratio
IQR	Interquartile range
ISTH	International Society of Thrombosis and Haemostasis
kg/m^2	Kilograms per square meter
Ltd	Limited
mg/L	Milligrams per litre
MI	Myocardial infarction
n	Numbers
ng/mL	Nanograms per millilitre
NVAF	Non-valvular atrial fibrillation
OR	Odds ratio
PE	Pulmonary embolism

Pty	Proprietary
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
UK	United Kingdom
U/L	Units per litre
USA	United States of America
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
WHO	World Health Organisation

“Submissible” format of a paper

Title page

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Abstract

Introduction

In 2020, during the coronavirus disease 2019 (COVID-19) outbreak, eligible patients were converted from warfarin to rivaroxaban to limit the transmission of COVID-19 infection.

Methods

A retrospective audit was performed which identified 190 participants with venous thromboembolism (VTE) and 112 participants with non-valvular atrial fibrillation (NVAF) at the Anticoagulation Clinic Service at Charlotte Maxeke Johannesburg Academic Hospital, South Africa. Participants were converted to rivaroxaban 20mg [Xarelto®, Bayer (Pty) Ltd, South Africa] for a median [interquartile range] period of 4 [2] months between April and October 2020. Follow-up was conducted telephonically and face-to-face on conversion back to warfarin. Rates of COVID-19 infections, bleeding and thrombosis were objectively confirmed.

Results

The rates of COVID-19 infection were 3.3% (n=10) [95% confidence interval (CI), 1.6 to 6.0] with 5 (1.7%) related hospital admissions and 2 (0.7%) related deaths (1 on rivaroxaban and 1 after switching back to warfarin). One-week after conversion to rivaroxaban, the rates of clinically relevant non major bleeding were 0.7% (95% CI, 0.02 to 2.54), and minor bleeding rates were 9.2% (95% CI, 6.16 to 13.40). There were no major bleeds. The bleeding rate was not significantly higher on rivaroxaban as compared to warfarin. There were 2 (0.7%) myocardial infarctions (1 on rivaroxaban and 1 after switching back to warfarin) and 1 (0.3%)

venous thrombosis presenting as a newly diagnosed first episode pulmonary embolism of a participant in the VTE group initially on enoxaparin and switched to rivaroxaban.

Conclusion

Conversion of eligible participants from warfarin to rivaroxaban during the first wave of the COVID-19 pandemic was associated with a low rate of recurrent thrombosis, major bleeding as well as COVID-19 infection.

Running title: An Audit of Warfarin to Rivaroxaban Conversion

Keywords: rivaroxaban; warfarin; thrombosis; bleeding; COVID-19

1. Introduction

In March 2020, the World Health Organisation declared the coronavirus disease 2019 (COVID-19) outbreak a global pandemic [1]. South Africa'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 minimizing the risk of viral spread within these settings [3-4]. These measures included infection control protocols, such as mandatory mask-wearing, meticulous hand hygiene, as well as measures to facilitate social distancing among patients attending healthcare facilities. Furthermore, alternative approaches were explored to minimize the necessity for in-person visits, such as telemedicine consultations and home delivery of medications. However, for outpatients attending the Anticoagulation Clinic Services in South Africa 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 to 4 weeks, depending on the stability of the INR.

VKA are the predominant oral anticoagulant utilized in resource-limited settings [5]. Despite the widespread use of direct oral anticoagulants (DOACs) in high-income settings, in 2020, warfarin (Cipla/Aspen®, Cape Town, South Africa) was the only oral anticoagulant accessible in the public sector in South Africa. DOACs have predictable pharmacodynamics which obviates the need for regular laboratory monitoring and thus reduces the frequency of face to face clinic visits [6]. While the use of DOACs in the public sector has been proposed, their high

costs have precluded 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, South Africa with venous thromboembolism (VTE) and/or non-valvular atrial fibrillation (NVAF) from warfarin therapy to rivaroxaban 20mg (Xarelto®, Bayer (Pty) Ltd, South Africa) 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. Among patients with NVAF, DOACs showed a lower risk of stroke or systemic embolism [Pooled Odds Ratio (OR) 0.76, 95% Confidence Interval (CI) (0.68–0.84)] and a lower risk of major bleeding (OR 0.85, 95% CI 0.74–0.97). The risk for gastrointestinal bleeding, however, was higher (OR 0.1.26, 95% CI 1.06–1.48) [8]. Among patients with VTE, DOACs showed a lower risk of recurrent VTE (OR 0.88, 95% CI 0.75–1.03), a lower risk of major bleeding (OR 0.64, 95% CI 0.47–0.87) and a similar risk of gastrointestinal bleeding (OR 1.09, 95% CI 0.60–1.97) [8]. There is limited data to guide the selection of DOACs such as dabigatran, apixaban, rivaroxaban, and edoxaban. Retrospective analyses, however, have demonstrated similar efficacy and safety among the DOAC agents. The results from the randomized controlled trial comparing apixaban and rivaroxaban (COBRRA: NCT03266783) are awaited [9-10].

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 (20mg); 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.

2. Methods

2.1 Study design and population

A retrospective study was conducted at the combined Anticoagulation Clinic at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in Johannesburg, South Africa. Approximately 1300 patients attend this clinic per month of which 50% of patients 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 (20mg once daily) between April 15, 2020 and October 15, 2020 were reviewed. During the study period, 302 clinical records of eligible consenting patients were identified. The study included 112 patients with NVAF (of which 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, known renal impairment (estimated glomerular filtration rate < 60 ml/min), known liver impairment, known hypersensitivity to rivaroxaban, < 18 years, pregnancy 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. Patients without a baseline documented renal function or liver function test, where there was clinical indication to perform these tests, were included in the study. The study was approved by the Wits Human Research Ethics Committee, Medical (M-200551).

2.2 Study protocol

2.2.1 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 by dividing the total number of INRs in the therapeutic range by the total number of INR tests performed in the study cohort 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, D-dimers and anti-Factor Xa (anti-FXa) tests performed at 2 to 3 months after the initiation of rivaroxaban and pre-conversion back to warfarin; INR test 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 throughout the period from switching to rivaroxaban and conversion back to warfarin with the follow-up visit.

2.2.2 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 two to four months (subject to availability of stock). During this period there was no anticoagulation activity monitoring and no scheduled clinic visits. Management of patients with INR > 3 and/or bleeding was individualised. This included omitting warfarin prior to initiating rivaroxaban and the use of oral/IV vitamin K. Patients were supplied with a 24-hour emergency contact number. Patients were followed up

telephonically within a week of conversion. One week prior to completion of rivaroxaban therapy, patients were followed-up at the Anticoagulation Clinic. Patients who required ongoing anticoagulation were converted back to their prior warfarin dose which was overlapped with seven-days of rivaroxaban 20mg [11].

2.2.3 Outcomes

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

2.2.4 Laboratory methods

To assess the safety and efficacy of the anticoagulation therapy using rivaroxaban and assurance of medication adherence, venous blood for anti-FXa measurement was collected in 3.2% sodium citrate (Becton-Dickinson®, Oxford, 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®, Marburg, Germany) analyser with the chromogenic rivaroxaban anti-FXa reagants (Innovance, reference interval 189-419 ng/mL). Testing for D-dimer (on the STA-R Max®, Diagnostica Stago, Asnières sur Seine, France), full blood count (on the Sysmex XN-9000®, Sysmex, Kobe, Japan) as well as liver and renal function tests (on the Cobas ISE®, Sysmex, Kobe, 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® (Diagnostica Stago, Asnières sur Seine, France) at the CMJAH laboratory.

2.3 Statistical methods

Data was analysed using Statistica® 13.2 software (Palo Alto, California, USA). Statistical comparisons were performed between participants with VTE and NVAF using the parametric paired t test and non-parametric Mann–Whitney test. Categorical variables were compared using chi-square 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 value of <0.05.

3. Results

3.1 Patient characteristics

A total of 302 participants were eligible for inclusion (Fig 1.). 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 which 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 the age, gender and ethnicity between the VTE and NVAF group was observed. NVAF participants were older as compared to the VTE participants ($p<0.001$). In the VTE group, there was a higher proportion of female participants ($p<0.001$). The majority of this cohort comprised of African participants (n=217, 72%). In the NVAF group, there was a higher proportion of Caucasian participants (n=39, 35%) as compared to the VTE group (n=22, 12%) ($p<0.001$).

The number of comorbidities was higher in participants with NVAF as compared to VTE ($p<0.001$). Significant comorbidities in the NVAF group included hypertension, heart failure and cancer, whereas human immunodeficiency virus (HIV) infection was a significant comorbidity in the VTE group ($p<0.001$). There were no significant differences in body mass index (BMI) between the participants with NVAF or VTE.

A subgroup of participants with cancer was analysed and included: breast (n=12, 4%), prostate (n=2, 1%), ovarian (n=1, <1%), cervical (n=1, <1%), vulva (n=1, <1%), lung (n=1, <1%), multiple myeloma (n=2, <1%) and Kaposi sarcoma (n=1, <1%).

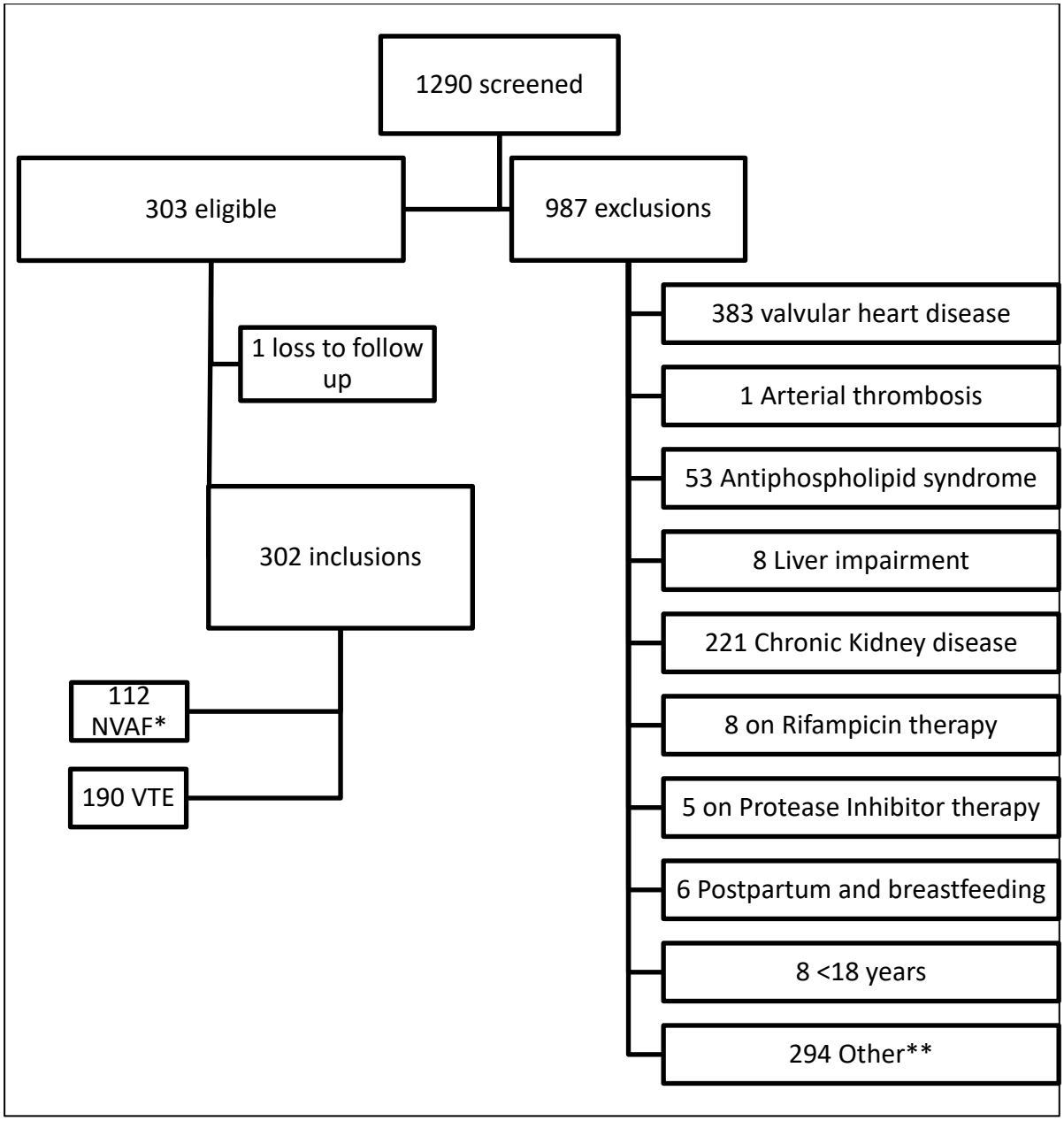

Figure 1. Flow diagram of study patients

Key: NVAF, non-valvular atrial fibrillation; VTE; venous thromboembolism.

*Including 4 patients with personal history of VTE

** Other comprised of patients discharged/transferred from the Anticoagulation Clinic; patients who followed up telephonically and patients not reviewed during the study period

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

Characteristic	NVAF (n = 112)	VTE (n = 190)	Total (n = 302)	p value
Demographics				
Age at study entry (years), mean ± SD	64 ± 14	51 ± 16	55 ± 16	<0.001
18-30 (n, %)	2, 2%	19, 10%	21, 7%	0.007
31-59 (n, %)	37, 33%	117, 62%	154, 51%	<0.001
>60 (n, %)	73, 65%	54, 28%	127, 42%	<0.001
Gender				
Male (n, %)	55, 49%	55, 29%	110, 36%	<0.001
Female (n, %)	57, 51%	135, 71%	192, 64%	<0.001
Ethnicity				
African (n, %)	64, 57%	153, 81%	217, 72%	<0.001
Caucasian (n, %)	39, 35%	22, 12%	61, 20%	<0.001
Indian (n, %)	3, 3%	7, 3%	10, 3%	0.750
Mixed (n, %)	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
Diabetes Mellitus (n, %)	21, 19%	24, 13%	45, 15%	0.149
Dyslipidaemia (n, %)	5, 4%	13, 7%	18, 6%	0.336
Epilepsy (n, %)	2, 2%	5, 3%	7, 2%	1.000
Heart Failure (n, %)	36, 32%	21, 11%	57, 19%	<0.001

HIV infection (n, %)	4, 4%	52, 27%	56, 19%	<0.001
Hypertension (n, %)	73, 65%	55, 29%	128, 42%	<0.001
Cancer (n, %)	19, 17%	2, 1%	21, 7%	<0.001
Medications				
Aspirin (n, %)	7, 6%	6, 3%	13, 4%	0.244
Clopidogrel (n, %)	3, 3%	0, 0%	3, 1%	0.050
Dual antiplatelet therapy (n, %)	0, 0%	0, 0%	0, 0%	-
Laboratory tests				
eGFR (ml/min)				
<50 (n, %)	0, 0%	0, 0%	0, 0%	-
50-60 (n, %)	5, 5%	6, 3%	11, 4%	0.431
>60 (n, %)	73, 65%	146, 77%	219, 72%	0.897
No baseline available (n, %)	34, 30%	38, 20%	72, 24%	-

Key: BMI, Body mass index; eGFR, estimated glomerular filtration rate; HIV, Human immunodeficiency virus; n, numbers; NVAF, non-valvular atrial fibrillation; VTE, venous thromboembolism.

*Comorbidities include asthma, chronic obstructive pulmonary disease, dyslipidaemia, diabetes mellitus, epilepsy, gout, human immunodeficiency virus, hypothyroidism, malignancy.

3.2 Anticoagulation characteristics

At baseline 291 (96%) participants were receiving warfarin, the majority (65%) of whom were on long-term therapy. The median [IQR] % FIR in 265 participants was 63 [41] %, with a mean of 11± 3 INR values per participant. 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, easy bruising and/or

epistaxis in 9 (3). The baseline mean INR (SD) was 2.7 ± 1.6 with an INR >2.5 in 40%, which was not significantly different between the NVAF and VTE groups. The mean duration of the initial in-person outpatient visit (SD) 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%) of the 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 BMI and anti-FXa levels (r=0.083) and notably, 36% of the anti-FXa levels (n=66) were below the reference range (see Table 2).

At the follow-up visit prior to conversion back to warfarin, the mean exposure time was 26 ± 8 minutes, which was significantly shorter than at the 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 at the 1st follow-up visit, 75 (28%) were in the therapeutic range at a mean 8 ± 10 days. At the 2nd follow-up visit, an additional 43 (of 105 who returned for testing) (41%) achieved a therapeutic INR at a mean of 16 ± 19 days. At the 2nd follow-up visit 34 (32.4%) were sub-therapeutic.

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

Characteristic	NVAF (n = 112)	VTE (n = 190)	Total (n = 302)

Baseline characteristics			
Warfarin (n, %)	108, 96%	183, 96%	291, 96%
Duration at Anticoagulation Clinic <1 month (n, %) 1-3 months (n, %) >3 months (n, %)	 7, 6% 3, 3% 102, 91%	 27, 14% 22, 12% 141, 74%	 34, 11% 25, 8% 243, 81%
Duration of anticoagulation Short-term (3-12 months) (n, %) Long-term (>12 months) (n, %)	 1, 1 % 111, 99%	 105, 55% 85, 45%	 106, 35% 196, 65%
Frequency in range (%), median [IQR]	50 [25]	42 [33]	50 [34]
Past history of minor bleeding on warfarin (n, %)	4, 4%	7, 4%	11, 4%
Past history of CRNMB on warfarin (n, %)	0, 0%	0, 0%	0, 0%
Past history of major bleeding on warfarin (n, %)	0, 0%	0, 0%	0, 0%
Past history of recurrent VTE on warfarin (n, %)	0, 0%	0, 0%	0, 0%
Past history of recurrent arterial thromboembolism on warfarin (n, %)	0, 0%	0, 0%	0, 0%
International normalized 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 (n, %) <189 (n, %) >419 (n, %)	 36, 49% 23, 32% 14, 19%	 57, 51% 43, 39% 11, 10%	 93, 51% 66, 36% 25, 13%

ALT (U/L), mean ± SD (ref: 10-40) AST(U/L), mean ± SD (ref: 15-40)	17 ± 9 22 ± 8	19 ± 10 24 ± 11	19 ± 9 23 ± 10
White cell count (x 10^9/L), mean ± SD (ref: 3.9-12.6) Haemoglobin (g/L), mean ± SD (ref: 116-164) Platelet count (x 10^9/L), mean ± SD (ref: 186-454)	7 ± 3 14 ± 2 262 ± 85	6 ± 2 13 ± 2 309 ± 126	6.4 ± 2 13.6 ± 2 291 ± 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 (n, %)	101, 90%	172, 91%	273, 90%
International normalized ratio 1st follow-up, mean ± SD (ref:2-3)	2.0 ± 0.9	1.8 ± 1	1.9 ± 0.9
Key: ALT, Alanine transaminase; AST, Aspartate transaminase; anti-FXa, anti-factor Xa; CRNMB, clinically relevant non-major bleeding; IQR, interquartile range; NVAF, mg, milligram; n, number; non-valvular atrial fibrillation; ref, reference range; SD, standard deviation; VTE, venous thromboembolism *of 184 participants			

3.3 Outcomes

Outcomes were assessed telephonically one-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 to 4.01) on rivaroxaban and 1.0% (95% CI, 0.00 to 2.10) on follow-up on warfarin (p=0.340). Minor bleeding was reported in 28 (9%) participants one-week after conversion to rivaroxaban. Fourteen (5%) participants reported ongoing minor bleeding symptoms for the duration of the rivaroxaban therapy. There were 2 (0.7%) CRNMB reported one-week after conversion to rivaroxaban and at conversion

back to warfarin: A 48-year-old female with recurrent right leg DVT and no comorbidities 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 the gynaecology. A 74-year-old female with NVAF and hypertensive heart disease, who reported a 10-day history of postmenopausal bleeding. These symptoms were previously 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 (n=30, 10%) was higher as compared to during the study period on rivaroxaban (n=16, 5%) (p=0.016). The bleeding rate during the study period was not significantly higher on rivaroxaban (n=16, 5%) as compared to warfarin prior to the study (n=11, 4%) and on follow-up (n=12, 4%[1]) (p=0.325 and p =0.766 respectively).

The survival curve and estimates of median survival time for the study population are depicted in Figure 2. There were 5 (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 MI who had a personal history of NVAF on long-term anticoagulation and 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). She was

switched from enoxaparin to rivaroxaban and demised three days later. There were also 2 deaths on conversion back to warfarin with the following contributory comorbidities: A 50-year-old female who presented with a MI. She had a personal history of a PE on long-term anticoagulation. An 81-year-old male who developed a COVID-19 infection after conversion back to warfarin. He had a personal history of a DVT, was on long-term anticoagulation, and epilepsy.

In addition, the following 2 COVID-19 infections were documented in the study cohort (Table 4): An 81-year-old female 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). A 37-year-old female presented with COVID-19 infection whilst on rivaroxaban. She had a personal history of a DVT, on short-term anticoagulation. A 28-year-old male was admitted with COVID-19 infection whilst on rivaroxaban. He had a personal history of a recurrent DVT and PE, was on long-term anticoagulation, and epilepsy.

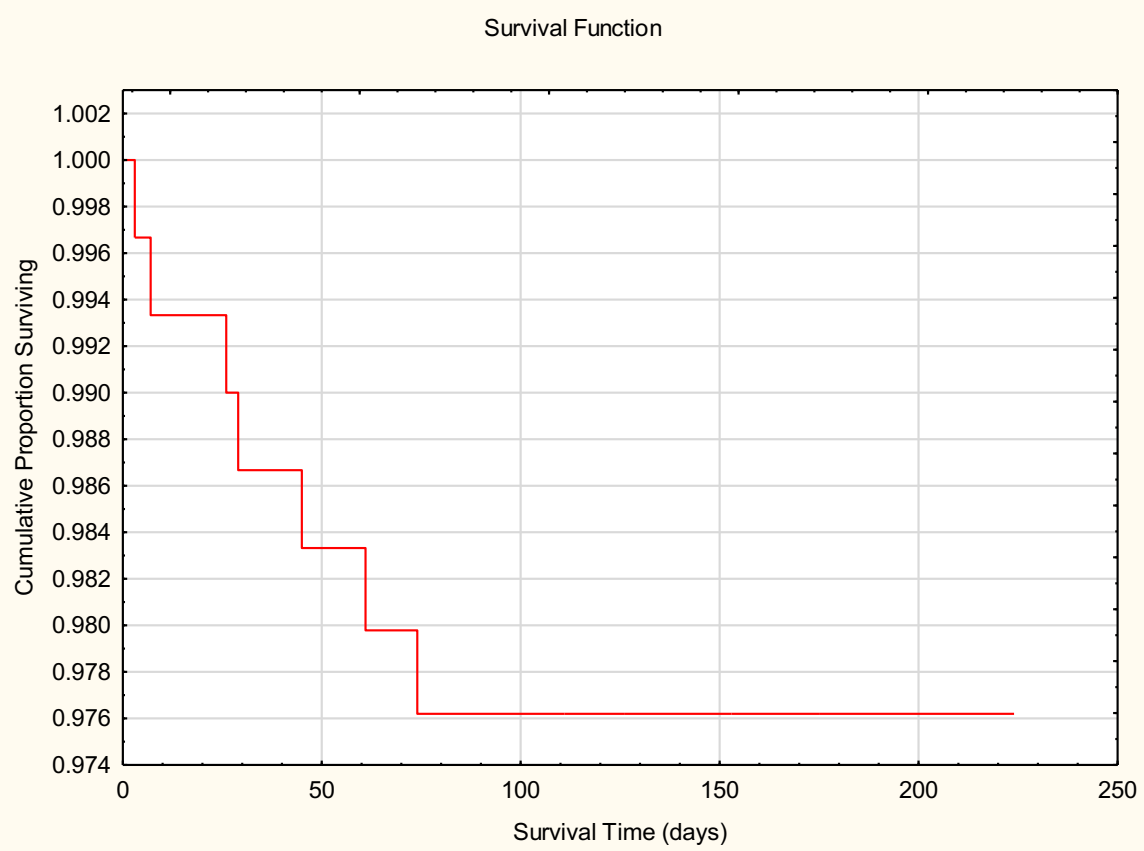

Figure 2. Kaplan–Meier survival curve in the overall study period

There were 3 participants with VTE who conceived on rivaroxaban. The first had a first trimester miscarriage whilst on rivaroxaban, 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 foetal or neonatal abnormalities.

Table 3. Adverse events

	NVAF (n = 112)	VTE (n = 190)	Total (n = 302)
Telephonic follow up on rivaroxaban (week 1)			
COVID-19 infection (n, %)	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%
Clinically relevant non major bleeding	1, 0.9%	1, 0.5%	2, 0.7%
Major bleeding (n, %)	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 (n, %)	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%
Clinically relevant non major bleeding	0, 0%	0, 0%	0, 0%
Major bleeding (n, %)	0, 0%	0, 0%	0, 0%
Key: NVAF, non-valvular atrial fibrillation; VTE, venous thromboembolism; COVID-19, coronavirus disease 2019. *in 98 participants with NVAF, 155 with VTE and 253 in total.			

Table 4. COVID-19 infections during the study period

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

COVID-19 related death (n, %)	0, 0%	2, 1.1%	2, 0.7%
Key: NVAF, non-valvular atrial fibrillation; VTE, venous thromboembolism; COVID-19, coronavirus disease 2019			

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

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 Gender	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
Key: AF, atrial fibrillation; Anti-FXa, anti-factor Xa; CI, confidence interval; HR, hazard ratio; INR, international normalised ratio			

4. Discussion

During the first wave of the COVID-19 pandemic in South Africa, 23% (n=302) of patients attending the Anticoagulation Clinic at CMJAH were converted from warfarin to rivaroxaban for a median of 4 [2] months. Prior to conversion to rivaroxaban, the majority of participants were receiving warfarin, of whom 65% were on long-term therapy. Participants were predominantly of African ethnicity, reflecting the hospital's demographics. Participants with NVAF were significantly older and had more comorbidities as compared to 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 adverse events, safety outcomes or COVID-19 infection rates between the two groups.

During the period of 5 March to 26 December 2020, the country reported 59 622 350 COVID-19 infections, 33 679 hospital admissions for COVID-19 and 23212 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. The mean duration of this follow-up visit was significantly shorter 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 the INR. Guidelines, however, recommend switching from warfarin to DOAC treatment when the INR is less than 2.5 to limit bleeding [14]. This is based on the findings of the ARISTOTLE and RE-LY2 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 [15-16]. In contrast, in the ROCKET AF (rivaroxaban) a higher INR threshold of <3.0 was applied, which was associated with a higher bleeding rate of 4% during the first 7 days of rivaroxaban as compared to 3% in warfarin naïve patients [17]. As such guidelines recommend follow-up INR testing when the INR is >2.5, prior to switching to a DOAC [14]. The mean 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 one 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 as compared to during the 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. On univariate analysis, a baseline INR > 2.5 was not a significant predictor of bleeding. 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]. 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.

In this study, a 68-year-old female with a newly diagnosed PE demised three days after being switched from enoxaparin to rivaroxaban in the acute period. There were no recurrent VTE. However, two participants who had been on rivaroxaban and converted back to warfarin died as a result of MI. Risk factors included age, chronic hypertension, and heart failure. Nonetheless, owing to the small number of events, this study could not assess for predictors of thrombosis.

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 which 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 due to insufficient evidence to guide management

[19-20]. The updated guidance from the International Society of Thrombosis and Haemostasis (ISTH) 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 has several limitations too, 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 with possible sample degradation prior to testing. Furthermore, therapeutic targets for Anti-FXa levels have not been established, and assays calibrated for specific DOACs are limited in availability. Due 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 CRNMB, major bleeds or recurrent VTE. INR monitoring was performed and after approximately one 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 co-morbidities influence INR variability.

Several limitations of this study warrant consideration. Firstly, the study was not statistically powered for overall and subgroup analysis of bleeding and thrombotic events. Secondly, the study did not include information on participant adherence to warfarin or rivaroxaban during the study period. Thirdly, testing for COVID-19 infection on follow-up was not performed. During the study period testing was performed in only 34 (11.3%) symptomatic participants with NVAF and VTE respectively. This may in part explain the low rates of COVID-19 infection as compared to rest of the country (n=10, 3.3%). 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 for these participants to achieve a therapeutic INR beyond the study period.

In summary, this audit provides information on the safety profile of a protocol recommending rivaroxaban 20mg in participants with VTE and NVAF attending an Anticoagulation Clinic, irrespective of the INR during the COVID-19 pandemic. The switch of eligible participants from warfarin to rivaroxaban allowed participants to avoid in-person hospital visits and thereby reduce the rates of COVID-19 infection. Participants were safely converted back to warfarin after a median of 4 months. Moreover, the rates of thrombosis and bleeding were consistent with similar studies and can be used to guide management.

Author contributions

C Wang: protocol development, data analysis, manuscript writing

E Schapkaitz: data analysis, manuscript writing

S Louw: protocol development, manuscript writing

B Jacobson: protocol development, manuscript writing

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Conflict of Interests

The authors have declared no conflicts of interest with respect to the authorship and/or publication of this article.

Figure legends

Figure 1. Flow diagram of study participants

Figure 2. Kaplan–Meier survival curve in the overall study period

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Appendices

Appendix A: Ethics approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Dr C-Y Wang
School of Pathology
Department of Molecular Medicine and Haematology
Medical School
University

E-mail: cywang6@hotmail.com

CC: Supervisor: Profs B Jacobson & E Schapkaitz; Dr S Louw <clot@nhls.ac.za> and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2020/08/20

REF: *R14/49*

PROTOCOL NO: **M200551** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *Safety and efficacy of Warfarin conversion to a fixed dose Rivaroxaban during the Covid-19 pandemic*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

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UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr C-Y Wang

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200551

NAME: (Principal Investigator)	Dr C-Y Wang
DEPARTMENT:	School of Pathology Department of Molecular Medicine and Haematology Medical School University
PROJECT TITLE:	Safety and efficacy of Warfarin conversion to a fixed dose Rivaroxaban during the Covid-19 pandemic
DATE CONSIDERED:	2020/05/29
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Profs B Jacobson & E Schapkaitz; Dr S Louw
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/08/20

This clearance certificate is valid for 5 years from the date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

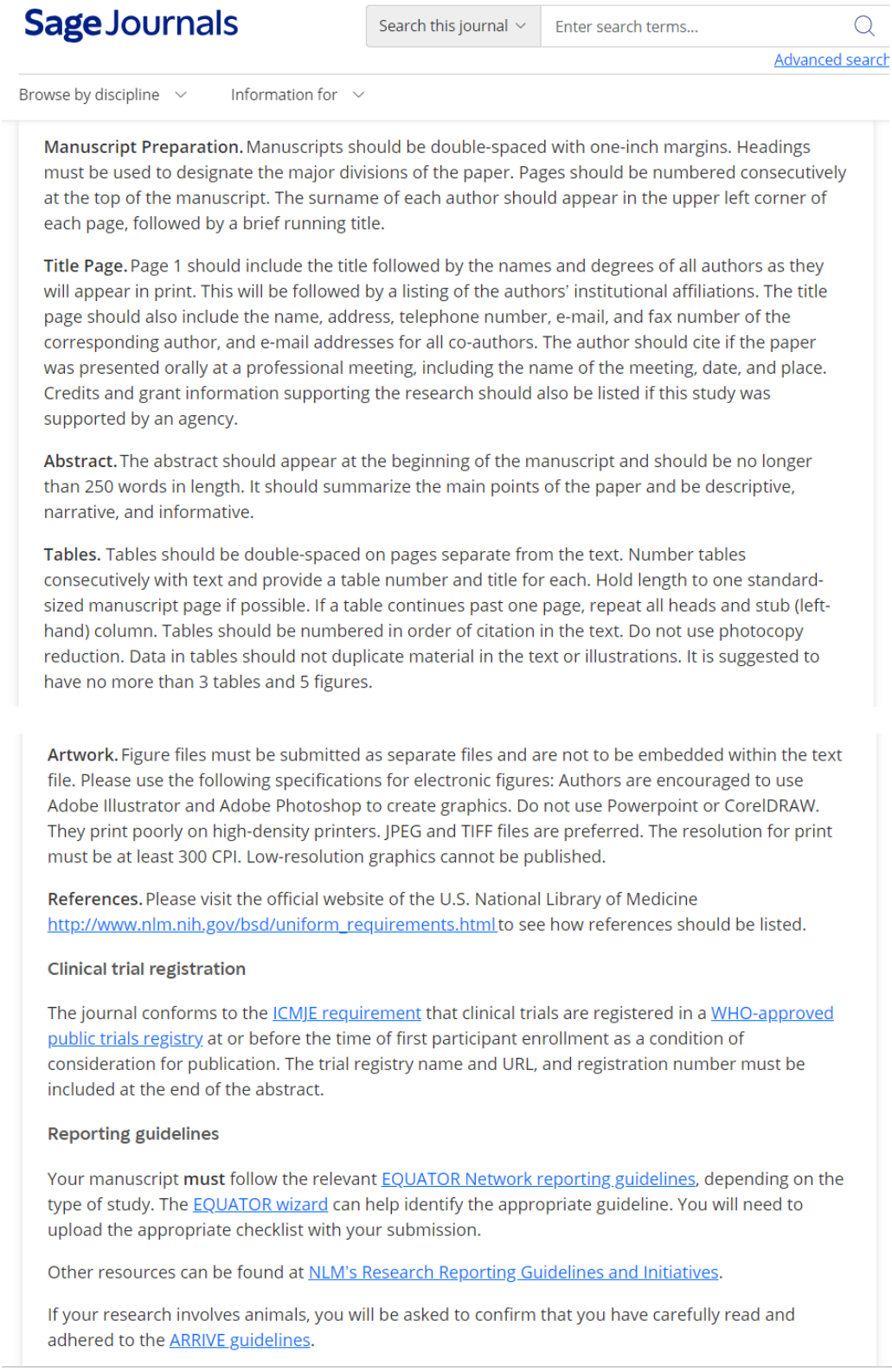
To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **May** and will therefore reports and re-certification will be due early in the month of **May** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

20-Aug-2020
Date

Appendix B: Journal article submission guidelines

The journal article submission guidelines were obtained from https://journals.sagepub.com/author-instructions/CAT



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Abstract. The abstract should appear at the beginning of the manuscript and should be no longer than 250 words in length. It should summarize the main points of the paper and be descriptive, narrative, and informative.

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If you are including an Acknowledgements section, this will be published at the end of your article. The Acknowledgments section should include all contributors who do not meet the criteria for authorship. Per ICMJE recommendations, it is best practice to obtain consent from non-author contributors who you are acknowledging in your manuscript.

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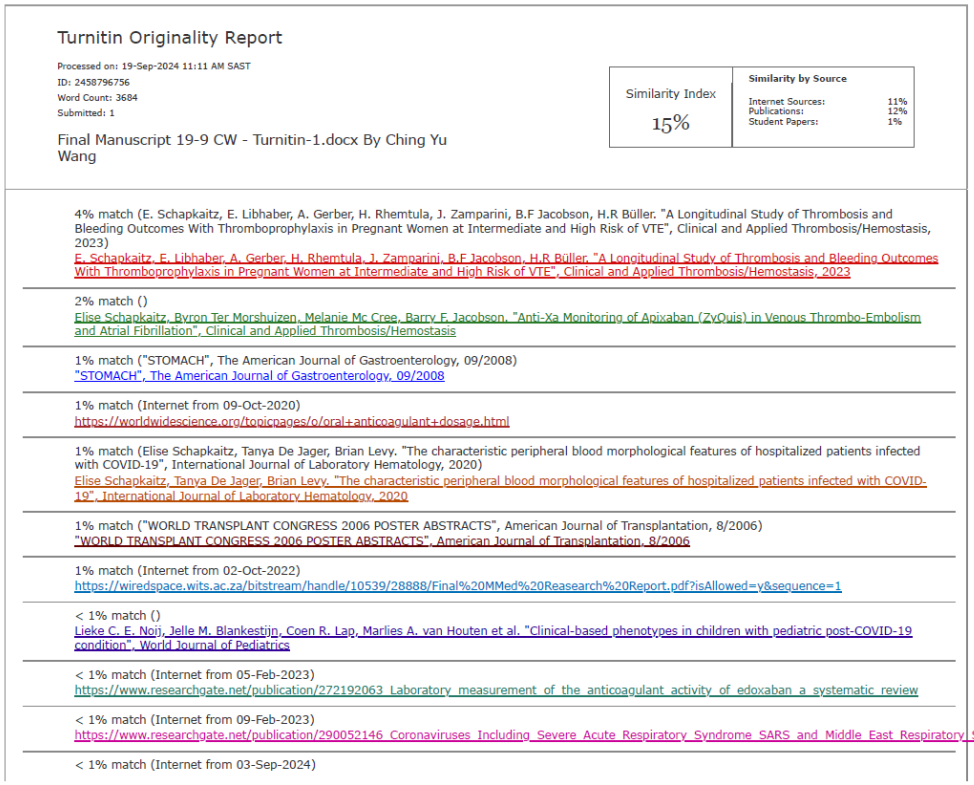

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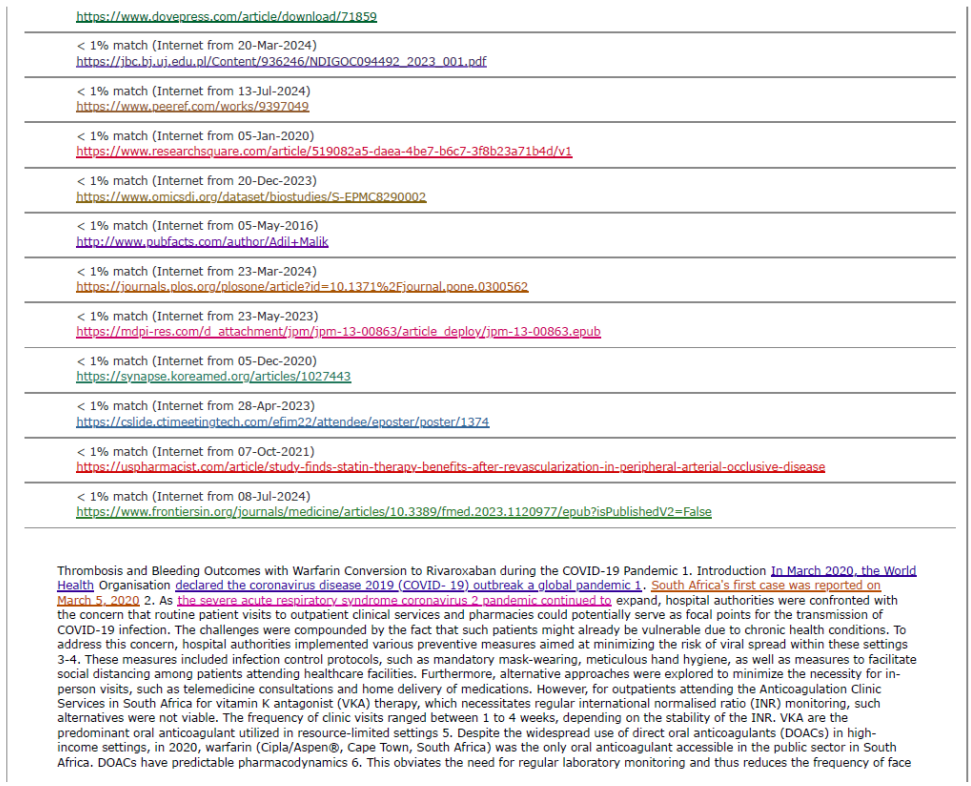

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