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## REVIEW

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# Anticoagulation control, outcomes, and associated factors in long-term-care patients receiving warfarin in Africa: a systematic review

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## Abstract

**Background:** Oral anticoagulation therapy with warfarin requires frequent monitoring level of anticoagulation by the international normalized ratio (INR). In Africa, studies that explore anticoagulation control, treatment outcomes, and associated factors are reported in various ways in long-term patients receiving warfarin therapy to generate concrete scientific evidence.

**Methods:** The literature search was conducted in PubMed, Cochrane Library, African Journal of Online databases, Google Scholar, and Google. An advanced search strategy was computed to retrieve relevant studies related to anticoagulation control and outcomes. Duplication, title and abstract screening, and full-text assessment were conducted in Covidence software. Study quality was assessed using the Joanna Briggs Institute Critical appraisal quality assessment tool. The systematic review is registered in PROSPERO (CRD42021260772) and performed based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline.

**Results:** Out of 298 identified articles, 18 articles were eligible for the final review and analysis. The mean of $39.4 \pm 8.4\%$ time in therapeutic range (TTR) (29.4 to 57.3%), $36.7 \pm 11.5\%$ TTR (range 25.2–49.7%) and 46% TTR (43.5–48.5%) was computed from studies that determined TTR by Rosendaal, direct and cross-section-of-the-files methods, respectively. In this review, the lowest percentage of TTR was 13.7%, while the highest was 57.3%. The highest percentage of patients (32.25%) who had TTR $\geq$ 65% was reported in Tunisia, but the lowest percentages were in Namibia (10%, TTR $\geq$ 65%) and Kenya (10.4%, TTR $\geq$ 70%). Most of the included studies (11 out of 18) used Rosendaal's method while the direct method was employed by three studies. Generally, 10.4–32.3% of study participants achieved desired optimal anticoagulation level. Regarding secondary outcomes, 1.6–7.5% and 0.006–59% of patients experienced thromboembolic complications and bleeding events, respectively. Having chronic comorbidities, taking more than two drugs, and presence of medications that potentially interact with warfarin, and patient-related factors (patients aged < 50 years old, female gender, lower education level, smoking history) were the frequently reported predictors of poor anticoagulation therapy.

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**Conclusions:** Oral anticoagulation control was suboptimal in patients taking warfarin as evidenced by low TTR in Africa. Therefore, there is an urgent need for further improving oral anticoagulation management services.

**Keywords:** Anticoagulation control, Anticoagulation outcomes, Warfarin, Long-term care, Africa

## Background

Vitamin K-dependent anticoagulants (VKAs) continue to be the principal anticoagulants for the treatment and prevention of thromboembolism [1] despite the introduction of direct-acting oral anticoagulants (DOACs) [2, 3]. It is used for the prevention and treatment of thromboembolic events (TEEs) and their complications in patients with atrial fibrillation, pulmonary embolism, deep venous thromboembolism, and valvular heart diseases [4, 5]. However, oral anticoagulation therapy with warfarin requires frequent international normalized ratio (INR) monitoring [6]. In addition, warfarin therapy is complicated by its unpredictable pharmacokinetics and dynamics features, multiple drugs and food interactions, narrow therapeutic index, and life-threatening complications due to subtherapeutic or excessively elevated INRs [7–10].

The quality of anticoagulation control with warfarin is majorly reflected by the mean individual patients spend in the therapeutic range [11, 12]. Time in therapeutic range (TTR) estimates the percentage of time a patient's INR is within the desired treatment range or goal and is used as an indicator of anticoagulation control [13]. The fraction of INRs in range or the direct method, the Rosendaal linear interpolation method, and the cross section-of-the-files method were the three common methods of TTR determination [14].

To achieve the optimal clinical outcome, the TTR should be $\geq 65\%$ [15] and, the recent European Cardiac Society (ESC) guidelines suggested TTR of $\geq 70\%$ [16] whereby the rates of thromboembolic events/complications and major bleeding-related due to VKA are low [17]. However, various studies conducted globally reported suboptimal anticoagulation with warfarin therapy by documenting low TTRs ($< 65\%$ [13, 18–22]. The extent of anticoagulation control and outcome in patients receiving warfarin in long-term care vary in Africa as TTR ranges from 29 to 49.7% [7, 23]. Moreover, these studies reported anticoagulation control, and treatment outcomes, and associated factors inconsistently. In addition, there has been no aggregate data in patients receiving warfarin therapy to generate concrete scientific evidence in Africa. Therefore, this systematic review was conducted to summarize anticoagulation control, treatment outcomes, and associated factors in patients taking warfarin for its various indications in Africa in long-term care by synthesizing and providing robust evidence.

## Methods

### Protocol and reporting

This systematic review is registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42021260772. In addition, the review was prepared based on PRISMA guidelines [24].

### Data source and search strategy

The literature search was conducted in PubMed/Ovid, Cochrane Library, African Journal of Online databases (AJOL), Google Scholar, and Google from database inception to November 2021. The reference lists of all included studies were also reviewed. The search strategy used Medical Subject Heading (MeSH) and keywords; anticoagulant agents, treatment outcome, bleeding, thromboembolism, TTR, time in therapeutic range, international normalized ratio, INR, Africa, and long-term care. These keywords were combined using "AND" and/ "OR" Boolean operators. They were combined as follows: [Anticoagulant OR (anticoagulant agents) OR (agents anticoagulation) OR (anticoagulation agents) OR (anticoagulant drugs) OR (warfarin) OR (Coumadin) OR (warfarin therapy) OR (warfarin potassium) OR (warfarin sodium) OR (vitamin K antagonist) OR (oral anticoagulant)] AND [treatment outcome OR (outcome treatment) OR (patient-related outcome) OR (clinical effectiveness) OR (treatment effectiveness) OR (treatment efficacy) OR (clinical) OR (efficacy) OR (bleeding) OR (bleeding events) OR (hemorrhage) OR (hemorrhagic events) OR (stroke) OR (ischemic stroke) OR (thromboembolism) OR (thromboembolic events) OR (hospitalization) OR (emergency department visit) OR (mortality) OR (intracranial hemorrhage) OR (intracranial bleeding)] AND [international normalized ratio OR (INR)) OR (monitoring) OR (time in therapeutic range) OR (TTR)] AND [long term care OR (long-term care) OR (outpatient) OR (outpatient department) OR (cardiac clinic) OR (hematology clinic) OR (anticoagulation clinic) OR (anticoagulation management service) OR (anticoagulation management quality)] AND [Africa OR (sub-Saharan Africa) OR (Africa central) OR (Africa eastern) OR (Africa southern) OR (Africa western) OR (Africa northern) OR (low-income country) OR (developing country)] OR (middle-income country)].

Tadesse *et al. Thrombosis Journal*     (2022) 20:58

Page 3 of 12

### Inclusion and exclusion criteria

Observational studies that reported on warfarin use, anticoagulation control, and outcomes among adult patients in long term care in African countries (monitoring of international normalized ratio and time in therapeutic range); or warfarin therapy-related adverse outcomes among these patient groups (bleeding events, thromboembolic events, stroke (ischemic stroke), hospitalization, emergency room visit and mortality) were included. In addition, only studies published in English were considered. Animal studies, studies conducted on admitted and emergency patients, and pharmacogenomics studies were also excluded. Furthermore, studies that reported merely other anticoagulation outcomes (patients' knowledge, adherence, satisfaction, quality of life, economic outcomes, adverse drug events other than bleeding, warfarin drug interactions) were excluded. Further, qualitative studies, review articles, unpublished works (thesis), case reports, case series, case–control studies, letters to the editor with incomplete information, author perspective, abstract proceedings, and expert opinions were excluded from the review.

### Article screening process

Articles identified from various electronic databases were exported to ENDNOTE reference software version 9 (Thomson Reuters, Stamford, CT, USA) with compatible formats. Then, they were imported to Covidence software [25] for screening, full-text analysis, and extraction. Duplicate records were identified, recorded, and removed with Covidence. Title and abstract screening were performed by the two reviewers (TAT and GTT). Three categories (yes, no, maybe) were used during the selection process. The full text of studies reported as "yes" or "maybe" during the initial screening process were evaluated based on the eligibility criteria by two authors (TAT and GTT). Any discrepancy in the screening processes was resolved by discussion.

### Data extraction

Data were extracted by TA using a standardized data abstraction format prepared in Microsoft Excel. This tool contains data related to study characteristics (country and study setting, first author, publication year, study design, population characteristics, and sample size) and the result of studies (percentage of time in therapeutic range and warfarin-related adverse effects).

### Quality assessment

Studies' methodological quality was assessed using Joanna Briggs Institute Prevalence Critical Appraisal Tool (JBI) for cross-sectional study [26]. It is an 8-item rating scale developed for prevalence studies. Sampling, data collection, reliability, and validity of study tools, case definition, and prevalence periods were included in the tool. The rating scale was categorized as having a low risk of bias ("yes" answers to domain questions) or a high risk of bias ("no" answers to domain questions) for each article. Each study was assigned a score of 1 (Yes) or 0 (No) for each domain, and these scores were summed to provide an overall study quality score. Studies with less than 50% scores were considered as high studies. For the final risk of bias classification, disagreements between the reviewers were resolved via consensus. Two independent authors (TAT and GTT) assessed the quality of included studies. Discrepancies between the two reviewers were resolved through discussion. The mean score of 2 authors was taken for scaling studies.

### Outcome measurement

The primary outcome of the review was a time in the therapeutic range while bleeding, thromboembolic events/complications, hospitalization, emergency department visit, and mortality were the secondary outcomes. According to the criteria of International Society on Thrombosis and Haemostasis (ISTH), major bleeding is defined as fatal bleeding and/ or symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular resulting in vision changes, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome; and/ or bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells. All non-major bleeds will be considered minor bleeds. Minor bleeds will be further divided into those that are clinically relevant and those that are not [27].

### Data management and analysis

The mean and/or median percentages of TTR or percentages of TTR were extracted in all included studies. Secondary outcomes were reported by mean, percentage, or frequency. Factors contributing to primary and secondary outcomes were reported as described by studies.

## Results

### Literature identification and search findings

A total of 298 articles were obtained from different electronic databases. 59 articles were removed due to duplication. Title and abstract screening were performed on 239 articles and, 188 articles were irrelevant. The full-text screening was then conducted on 47 articles, and 29 articles were excluded due to their ineligibility (e.g., absence of the outcome of interest). Finally, 18-articles were eligible and included in the systematic review (Fig. 1).

**Fig. 1** PRISMA Flow diagram for study selection for systematic review
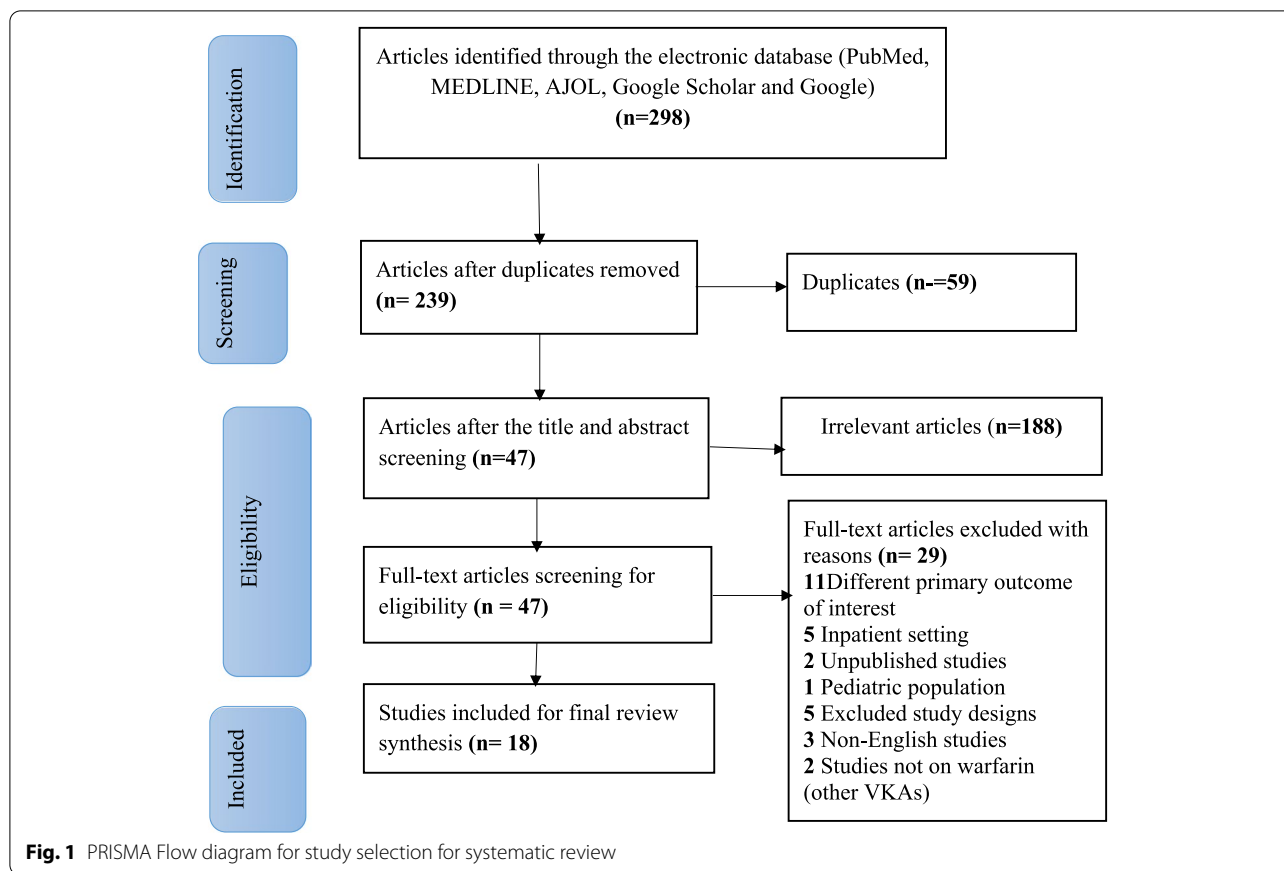
The included studies were published between 2006 to 2021. The majority of them (15 out of 18) were conducted using retrospective study designs [7, 23, 28–40]. Pre-post intervention [41] and prospective study designs [42, 43] were employed by one and two studies, respectively. Five studies were conducted in South Africa [7, 28, 33, 37, 38], 3 in Ethiopia [23, 31, 40], 2 in Sudan [32, 41], 2 in Kenya [36, 42], 2 in Tunisia [29, 43] and 2 in Botswana [39, 44]. One study was included from Namibia [35] and the remaining one study was conducted both in South Africa and Uganda. A total of 4,730 study participants were included in 18 studies. The smallest and the largest sample size was 21 [32] and 915 [45], respectively. In addition, the minimum cohort follow-up period was 4 months [46], and the maximum was 19 years [28]. All studies were conducted in outpatient settings (cardiology clinic anticoagulation clinic, INR testing clinic, warfarin clinic, cardiac, hemato-oncology, and cardiothoracic clinics, etc.). Except for one study [32], all studies were conducted in government health facilities. Various indications of warfarin were reported in the included studies (Table 1).

## Quality assessment of included studies

With the exception of two studies, the majority of the included studies have a low-risk methodological quality according to the modified the Joanna Briggs Institute (JBI) critical appraisal tool as is indicated in a supplementary table.

## Primary outcome: time in therapeutic range

Direct, Roosendaal's, cross-section of-the-files methods, or a mixture of direct and Roosendaal's methods were used to determine TTR in the included studies. Eleven studies used Rosendaal's method, while the direct method was employed by three studies. The direct method (the fraction of INRs in range) and the cross-section-of- the-files method were utilized by two studies [37, 47]. In the remaining two studies [32, 33, 35], TTR was calculated both by direct and Roosendaal's methods [32, 35]. The included studies reported TTR as mean and /or median TTR percentages or only percentages.

The lowest percentage of TTR was 13.7% (mean) which was reported by a study conducted in adult patients with prosthetic heart valves at the medical outpatient

Tadesse *et al. Thrombosis Journal*     (2022) 20:58

Page 5 of 12

**Table 1** Characteristics of included studies in the systematic review

| Author ID | Country | Study design | Study population | Sample size | Follow up time | Mean or Median age in years | Service setting | Indication of warfarin |
|---|---|---|---|---|---|---|---|---|
| Salaheldin A, 2019 [32] | Sudan | Retrospective | Private cardiology clinic attendants | 21 | 14 months | Mean: 64, Median: 62 | Cardiology Clinic | AF, VHD, DVT, PE, LVT |
| Karuri et al., 2019 [36] | Kenya | Retrospective | Adult outpatients | 406 | 2 years and 6 months | Mean: 42.7 (SD: 16.9) | Cardiac, hemato-oncology, and clinic | DVT, PE, Prosthetic valves, AF, VHD |
| Sana et al., 2020 [43] | Tunisia | Prospective | AF patients ≥ 20 years | 915 | 12 months | Mean: 64.27 | In- and outpatients setting | AF |
| Lauren et al., 2019 [35] | Namibia | Retrospective | Adult outpatients | 215 | 12 months | Median: 46 | Warfarin Clinic | DVT, PE, AF, CVA, AVR, LVT, DCM, MVR, DVR, Others |
| Sonuga et al., 2016 [37] | South Africa | Retrospective | Adult patients | 136 | 6 months | Mean: 62 (for male), Median: 66 (for female) | INR Clinic | VHD, mechanical heart valve replacement |
| Fenta et al., 2017 [23] | Ethiopia | Retrospective | Adults outpatients | 360 | 12 months | Mean: 35.3 | Cardiac and hematology clinics | AF, DVT, PE, VHD, MI, HVR, PVR |
| Semakula et al., 2020 [5] | South Africa and Uganda | Retrospective | Outpatients | 229 | 6 months | Median: 56 | Anti-coagulation clinic | VTE, AF, VHD |
| Prinsloo et al., 2021 [38] | South Africa | Retrospective | Adult patients | 191 | 12 months | Median: 56 | INR Clinic | AF, VTE, MPHV, APS, and LVT |
| Ahmed et al., 2017 [41] | Sudan | Pre-and post- Intervention | Adult patients | 135 | 12 months | Mean: 41.8 | Anticoagulation clinic | MVR, DVR, total valve replacement |
| Botsile et al., 2020 [39] | Botswana | Retrospective | Patients aged ≥ 18 years | 142 | 5 months | Mean: 42 | INR Clinic | MHV replacement |
| Masresha et al., 2021 [31] | Ethiopia | Retrospective | Adult outpatients | 202 | 2 years | Mean: 44.33 | Outpatient department | AF, VHD, DVT, and PE |
| Kizito et al., 2016 [47] | Kenya | Prospective | Adult outpatients | 147 | NA | Mean: 41 | Hemato-oncology and cardiothoracic clinics | Heart disease, VTE, HVR |
| Yimer et al., 2021 [40] | Ethiopia | Retrospective | Adult outpatients | 300 | 2 years | Mean: 56.4 | Anticoagulation Clinic | AF |
| Sadhabiriss and Brown, 2021 [33] | South Africa | Retrospective | Adult outpatients | 263 | 1 year | Mean age for AF patients: 64.68, mean age for PHV patients:41.83 | Outpatient adult medical department | non-valvular AF, PHV, venous thrombosis or embolism, arterial or left ventricle thrombus, valvular AF, HF |
| Ntlokotsi et al., 2018 [28] | South Africa | Retrospective | Adult patients | 95 | 19 years | Mean 39.7 (SD:18) | Academic hospital | HVR |
| Rejeb et al., 2019 [29] | Tunisia | Retrospective | Adult patients | 200 | 3 years | Mean: 58.8 ± 12 | Cardiac clinic | AF |
| Mwita et al., 2017 [30] | Botswana | Retrospective | Adult patients | 410 | 2 years | Median: 46(35–58 IQR) | Outpatient medical clinic | Mechanical valves, DVT, AF, intracardiac thrombosis, pulmonary hypertension |

**Table 1** (continued)

| Author ID | Country | Study design | Study population | Sample size | Follow up time | Mean or Median age in years | Service setting | Indication of warfarin |
|---|---|---|---|---|---|---|---|---|
| Ebrahim et al., 2018 [7] | South Africa | Retrospective | Adult out patients | 363 | 6 years | Median: 55(IQR 44—64) | Warfarin anticoagulation Clinic | AF, VHD, PE VTE, SLE, hypercoagulable states |

*AF* Atrial fibrillation, *VHD* Valvular heart disease, *DVT* Deep vein thrombosis deep, *PE* Pulmonary embolism, *CVA* Cerebrovascular accident, *AVR* Atrial valve replacement, *LVT* Left ventricular thrombus, *DCM* Dilated cardiomyopathy, *DVR* Double valve replacement, *MVR* Mitral valve replacement, *MI* Myocardial infarction, *SLE* Systemic lupus erythematosus, *HF* Heart failure, *APS* Antiphospholipid syndrome, *MHV* Mechanical heart valve, *HVR* Heart valve replacement, *MPHV* Mechanical prosthetic heart valve, *IQR* Interquartile range, *SD* Standard deviation, *INR* International normalized ratio

department in KwaZulu-Natal, South Africa [33]. However, a mean TTR of 44.5% was reported in this South African study among AF patients. The highest (57.3%) was observed in a study conducted in Tunisia [29]. In another way, a higher mean TTR of 68.3% was also documented in the post-interventional study from Sudan [41]. The mean of $39.4 \pm 8.4\%$ TTR (29.4 to 57.3%), $36.7 \pm 11.5\%$ TTR (range 25.2–49.7%) and 46% TTR (43.5–48.5%) was computed from studies that determined TTR by Rosendaal, direct and cross-section-of-the-files methods, respectively.

The percentage of patients with optimal anticoagulation (TTR ≥ 65%) or above as indicated by studies was documented by 13 studies. Accordingly, the highest percentage of patients (32.25%) who had TTR ≥ 65% was reported in studies conducted in Tunisia [43] and lowest percentages i.e. 10% (TTR ≥ 65%) [35] and 10.4% (TTR ≥ 70%) [36] were obtained in studies conducted in warfarin anticoagulation clinic at Windhoek Central Hospital in Namibia and Kenyatta National Hospital (KNH), Kenya, respectively (Table 2).

### Secondary outcomes

Bleeding/hemorrhagic events were reported in three studies as both major and minor bleeding events [29, 39, 43], and the remaining studies that documented these events reported either of them. The highest percentage of bleeding incidence [(59%, (9.5% major bleeding, 49.5% minor bleeding)] was reported by studies carried out in Tunisia [29] and the lowers incidence (0.006% per patient-year) was reported from Dr. George Mukhari Academic Hospital [28] study in South Africa. During follow-up period, six studies [28, 31, 37, 43, 48, 49] reported that 0.002% per-patient year) [43] to 22.5% [39] of the patients developed thromboembolic events. Thromboembolic complications/events in range of 1.64 to 7.5% were occurred in four remaining studies [29, 31, 43, 50]. All-cause hospital admission during the study period was reported only by two studies with the incidence of 32.5% [38] and (10.4% before intervention vs 3.7% after intervention) [41], respectively. Emergency department visits and mortality during the study period were reported by studies conducted in Ethiopia and Tunisia in 1.5% [31, 51] and 5.6% [43] of patients, respectively (Table 2).

### Factors associated with optimal anticoagulation in patients receiving warfarin

There were various patients' sociodemographic and clinical characteristics (age, sex, hospitalization, mortality, disease, and medication-related factors) that contributed to poor TTR, and occurrences of bleeding and thromboembolic events. The most frequently reported factors were the presence of comorbidities (heart failure comorbidity [31, 36, 40, 43], renal dysfunction [36], pulmonary hypertension [7]), taking more than two drugs with warfarin [40], presence of potentially interacting medication with warfarin [31], patients' socio-demographic profile (age less than 50 years [38], female gender and lower education level [47] and smoking [39]). In addition, hospitalization [38] and frequent INR monitoring [7] were also reported as predictors of poor anticoagulation (lower TTR) in included studies. The detail on these associations and other associations with secondary outcomes is provided in Table 3. Only studies that reported significant association were included in the table.

## Discussion

This systematic review was conducted to assess the level of anticoagulation control, treatment outcome, and associated factors among patients receiving warfarin in long-term care in Africa. Suboptimal anticoagulation was reported in this review with TTR ranging from 13.7% to 57.3% as compared to the recommended TTR level (≥ 65%) [52] or ESC 2020TTR recommendation (≥ 70%) [16].

The lowest TTR level was observed in studies conducted in China (38.2%) [21], Lithuania (40%) [53], and Turkey (42.3%) [54]. On the other hand, a higher TTR values of 61.5% [52] and 65% [55] were reported by the FANTASIIA and ORBIT-A registries, respectively. Moreover, a huge variation in the percentage of TTRs was observed in patients receiving warfarin in different African countries. Similarly, TTR variation was seen among different studies conducted in Canada (TTR of 44.2 to 61%) [20, 56, 57], Saudi Arabia, Iran, Kuwait, and Brazil with the mean TTR of 52.6 to 59% [13, 58–60]. However, TTRs reported in this systematic review were lower as compared with reports from Canada (58.76%) [20], the USA (overall mean and median TTR of $65 \pm 20\%$ and 68% [IQR 53–79%] and South Africa ($58.1\% \pm 16\%$) [20, 61, 62]. The discrepancies might be due to the difference in method used to determine TTR, and sample size [14].

Higher TTR is the best indicator of good anticoagulation management service [63]. The lower TTR reported in Africa questioned the quality of anticoagulation service [2, 34]. Despite the presence of several risk factors, this might be partly explained by the limited and ineffective implementation of evidence-based AMS recommended by international guidelines. This includes the inappropriateness of the current setup for providing expected AMS (poorly developed structure in Africa), unavailability of working manuals e.g., functional protocols; resources (coagulation tests and anticoagulants); prescribing anticoagulation prescription with little or no monitoring. absence of specialty anticoagulation clinics/

**Table 2** Anticoagulation control, primary and secondary outcomes of included studies in the systematic review

| Author ID | Primary outcomes | | | % of patients with TTR ≥ 65% or indicated by a study | Secondary Outcomes | | |
|---|---|---|---|---|---|---|---|
| | Method to determine TTR | Percentage of TTR | % of patients within the therapeutic range | | Bleeding during warfarin therapy (%) | Major bleeding (%) | Thromboembolic events (%) |
| Salaheldin A, 2019 [32] | Rosendaal and Direct Method | Median 37% by Rosendaal method, and median TTR 42.9% by Direct Method | NA | 23% of patients with TTR > 72% | 9.50 | NA | NA |
| Karuri et al., 2019 [36] | Rosendaal method | Mean 31.1% (±26.7) | 82% of MVR (mech); 54% of patients with MVR (prosthetic) | 10.4% of pts (TTR ≥ 70%) | NA | NA | NA |
| Sana et al., 2020 [43] | Rosendaal method | Mean 48.87 ±28.69% in 341 patients | NA | 32.50 | 5.80 | 5.80 | 1.64 |
| Lauren et al., 2019 [35] | Rosendaal and Direct Method | Mean 29.4% by Rosendaal method and 25.2% by direct method | NA | 10 | NA | NA | NA |
| Sonuga et al., 2016 [37] | Cross-section-of-the-files method | 48.50% | 48 | NA | 14.00 | NA | 2.20 |
| Fenta et al., 2017 [23] | Direct Method | Mean 29% | NA | NA | NA | NA | NA |
| Semakula et al., 2020 [5] | Rosendaal method | Median 41% | NA | NA | NA | NA | NA |
| Prinsloo et al., 2021 [38] | Rosendaal method | Median 37.2% | NA | 17.80% | NA | NA | NA |
| Ahmed et al., 2017 [41] | Direct Method | BI mean 51.5% and AI 68.3% | BI mean 51.5% and AI 68.3% | NA | BI 37% of patients, AI 53 of patients | 0.00 | NA |
| Botsile et al., 2020 [39] | Rosendaal method | Median 29.8% | NA | 14.80 | 14.10 | 14.10 | 22.50 |
| Masresha et al., 2021 [31] | Rosendaal method | Mean 41% | NA | 29.20 | 4.50 | NA | 7.40 |
| Kizito et al., 2016 [47] | Cross-section-of-the-files method | Mean 43.5% | 43.50 | NA | NA | NA | NA |
| Yimer et al., 2021[40] | Rosendaal method | Mean 42.03% | NA | 12.67 | 20.67 | NA | NA |
| Sadhabiriss and Brown, 2021 [33] | Rosendaal method | Mean TTR for the AF group was 44.5% and for PHV was 13.7% | NA | 10.4% for the AF group had a range of more than 70% but none in the PHV group achieved this | 24.00 | NA | NA |
| Ntlokotsi et al., 2018 [28] | Direct method | 49.70% | NA | Cut-off TTR was ≥ 70% | 0.006% per patient-year | NA | 0.002% per patient-year |
| Rejeb et al., 2019 [29] | Rosendaal method | Mean 57.3% | NA | 24.5%; Cut-off TTR was ≥ 70% | 0.59 | 9.50 | 15 patients |
| Mwita et al.,2017 [30] | Rosendaal method | Median 30.8% | NA | 14.90 | NA | NA | NA |
| Ebrahim et al., 2018 [7] | Rosendaal method | Mean 47% | NA | 25.10 | NA | NA | NA |

*MVR* Mitral valve replacement, *PHV* Prosthetic heart valve, *BI* Before the intervention, *AI* After the intervention, *TTR* Time in therapeutic range, *NA* Not applicable

Tadesse *et al. Thrombosis Journal*      (2022) 20:58

Page 9 of 12

**Table 3** Factors associated with poor anticoagulation and other secondary outcomes in long term care in Africa

| Authors' name | Factors associated with poor anticoagulation outcomes (low TTR%) | Factors associated with bleeding events | Factors associated with Thromboembolism events | Factors associated with hospitalization events | Factors associated with mortality during warfarin therapy |
|---|---|---|---|---|---|
| Karuri et al., 2019 [36] | CHF, renal dysfunction | NA | NA | NA | NA |
| Sana et al., 2020 [43] | CHF, and nonvalvular AF type | Hypertension and antiplatelet use | obstructive sleep apnea and higher CHA2DS2VASc score | NA | CHF, and hypertension |
| Prinsloo et al., 2021 [38] | Patents aged < 50, hospitalization | NA | NA | NA | NA |
| Ahmed et al., 2017 [41] | Absence of pharmacists' intervention | NA | NA | clinical pharmacy intervention (-) | NA |
| Botsile et al., 2020 [39] | NA | Duration of warfarin use, Increased level of education | NA | NA | NA |
| Masresha et al., 2021 [31] | potential medication interaction, presence of co-morbid conditions | NA | NA | NA | NA |
| Kizito et al., 2016 [47] | female gender, lower education level | NA | NA | NA | NA |
| Yimer et al., 2021 [40] | Receiving > 2 drugs with warfarin, heart failure comorbidity | NA | NA | NA | NA |
| Rejeb et al., 2019 [29] | NA | Poor TTR (< 50%) | NA | NA | NA |
| Mwita et al.,2017 [30] | Smoking and pulmonary hypertension | NA | NA | NA | NA |
| Ebrahim et al., 2018 [7] | Frequent INR monitoring | NA | NA | NA | NA |

*CHF* heart failure, *NA* Not applicable, *TTR* Time in therapeutic range, *AF* Atrial fibrillation, *INR* International normalized ratio

services; lack of a multidisciplinary team in managing anticoagulation service in health facilities [2]. Application of evidence-based strategies should be settled, like implementing 'warfarin care bundles' that include process- and patient-centered activities [64], employing interventions that improve INR control [41, 65], decentralization of anticoagulation services, setting up of anticoagulation clinics, improving access to warfarin, improving access to laboratory testing and/or scaling up point-of-care INR testing, task-shifting of anticoagulation care to mid-level health care workers, staff training, and implementing locally validated dose initiation and dose adjustment algorithms [23].

Regarding patients with optimal anticoagulation (i.e., TTR ≥ 65%), a lower percentage of patients (10 to 32.25%) achieved this target. The maximum percentage (32.25%) was reported by Tunisia prospective study [43]. In the same way, the Lithuanian (20%) [53] and Brazilian studies (31%) [60] studies reported a similar range of patients who achieved TTR above 65%. However, a study that evaluated the TTRs in four European countries in AF patients found that 44.2 to 47.8% of patients achieved TTR above 70% and with a higher percentage (65.4%) in United Kingdom patients [66]. A higher percentage of

patients with optimal anticoagulation was also reported in Canada [19]. A lower percentage of patients in achieving recommended TTR may indicate a higher likelihood of suboptimal anticoagulation with warfarin in Africa countries which mandate a significant room for improvement of anticoagulation control in countries across low-income countries including Africa. Decentralization of anticoagulation care, together with expanded access to anticoagulants and monitoring, and enhanced support to practitioners and patients, developing and using initiation and maintenance/adjustment dosing protocols that developed by taking consideration of locally relevant factors into account is crucial to achieve better anticoagulation control in resource-limited settings [64].

Our review also explored factors associated with poor anticoagulation in patients receiving warfarin therapy. Having heart failure, renal dysfunction, and pulmonary hypertension comorbidities, taking more than two drugs along with warfarin, presence of interacting medication with warfarin, different socio-demographic characteristics, history of hospitalization, and frequent INR monitoring were identified as predictors of poor anticoagulation. A plethora of literature showed controversial results on the association of age with poor TTR.

Tadesse *et al. Thrombosis Journal*    (2022) 20:58

Page 10 of 12

This review study conducted by Prinsloo et al., in South Africa, showed patients less than 50 years had worsened INR control [38]. A Swedish study reported this correlation the other way round that is the presence of correlation between improved TTR and older age [67]. However, the quality of anticoagulation was minimal in the aged population, and there was a negative association between age and TTR levels in a study conducted in Turkey [54].

Having congestive heart failure as a comorbidity was reported as an independent predictor of poor control of anticoagulation in three studies included in this review [36, 40, 43]. This effect was also documented in patients with non-valvular atrial fibrillation in a private setting in Brazil among patients with atrial fibrillation, and in, Israel [68] among patients with non-valvular atrial fibrillation in primary care (Fantas-TIC Study) [69]. This might be due to abnormal blood flow in patients with left ventricular dysfunction (including regional areas of dyskinesis or aneurysm) resulted in the development of LV thrombus. While all the components of Virchow's triad may apply to HF patients, blood flow abnormalities are presumed to play the biggest role in imparting stroke risk [70]. This implies that having heart failure may be considered a double burden in managing/ controlling anticoagulation in these patient populations. Furthermore, patients with comorbidities require more drugs/polypharmacy for their management, which makes them more vulnerable to warfarin drug interactions which in turn, affect optimal anticoagulation [31, 40].

### Strength and limitation of study
This systematic review is the first to show anticoagulation control and outcome in different African countries by characterizing time in therapeutic range and other secondary outcomes. The review has some limitations. First, we included only articles reporting in the English language, which may result in the loss of some important studies and thereby underestimation of the findings. Second, the practice of AMS varies across the studies, which require further assessment of TTR pooled estimates. Third, some relevant data (e.g., the incidence of thrombotic and bleeding events) were not reported in most of the studies. Finally, the results of this systematic review may not be representative of all Africa countries as there might be studies that were not included and also due to a limited aspect of care provided in these regions.

### Conclusion and recommendations
Oral anticoagulation control was suboptimal in patients taking warfarin in Africa as evidenced by low TTR when compared with the recommended target by different international guidelines to achieve optimal anticoagulation. Special emphasis should be given to improving AMS in Africa region by working towards optimizing anticoagulation and decreasing harms (thromboembolic and bleeding events) in patients taking anticoagulation. Moreover, establishing dedicated anticoagulation clinics led by pharmacists or multidisciplinary teams using standardized approaches in Africa health care settings may achieve better anticoagulation control than routine models of care, where anticoagulation patients are seen as part of the general patient mix.

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Tadesse *et al. Thrombosis Journal*        (2022) 20:58

Page 11 of 12

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Page 12 of 12

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