Comparative effectiveness of warfarin management strategies: a systematic review and network meta-analysis

Teerapon Dhippayom,[a,*] Kansak Boonpattharatthiti,[a,b] Warittakorn Kategeaw,[c] Heeseung Hong,[c] Nathorn Chaiyakunapruk,[c,d] Geoffrey D. Barnes,[e] and Daniel M. Witt[c,**]

[a]The Research Unit of Evidence Synthesis (TRUES), Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok, Thailand
[b]Faculty of Pharmaceutical Sciences, Burapha University, Chon buri, Thailand
[c]Department of Pharmacotherapy, University of Utah College of Pharmacy, Salt Lake City, UT, USA
[d]IDEAS Center, Veterans Affairs Salt Lake City Healthcare System, Salt Lake City, UT, USA
[e]Frankel Cardiovascular Center, University of Michigan, Ann Arbor, MI, USA

eClinicalMedicine 2024;74: 102712
Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.102712

Summary

Background The management of warfarin therapy presents clinical challenges due to its narrow therapeutic index. We aimed to evaluate the comparative effectiveness of different management strategies in patients using warfarin.

Methods PubMed, Embase, Cochrane CENTRAL, CINAHL, and EBSCO Open Dissertation were searched from inception to 8 May 2024. Randomized controlled trials that compared the following interventions: patient self-management (PSM), patient self-testing (PST), anticoagulation management services (AMS), and usual care in patients prescribed warfarin for any indication were included. Risk ratios (RR) with 95% confidence interval (CI) were estimated using a random-effects model. Surface under the cumulative ranking curves (SUCRA) were used to rank different interventions. The certainty of evidence was assessed using the Confidence in Network Meta-Analysis (CINeMA) online platform. This study is registered with PROSPERO (CRD42023491978).

Findings Twenty-eight trials involving 8100 participants were included, with follow-up periods of 1–24 months. Mean warfarin dosages were 4.9–7.2 mg/day. Only PSM showed a significant reduction of major TE risk compared with usual care (RR = 0.41; 95% CI: 0.24, 0.71; I^2 = 0.0%) with moderate certainty of evidence. The 97.6% SUCRA also supported the beneficial effects of PSM over other interventions. The combined direct and indirect evidence showed significantly higher TTR in PSM compared with usual care (MD = 7.39; 95% CI: 2.39, 12.39), with very low certainty. However, direct evidence showed non-significant TTR improvement (MD = 6.49; 95% CI: −3.09, 16.07, I^2 = 96.1%). No differences across various strategies were observed in all-cause mortality, major bleeding, stroke, transient ischemic attack, and hospitalization.

Interpretation PSM reduces the risk of major TE events compared with usual care, tends to improve anticoagulation control, and should be considered where appropriate.

Funding Agency for Healthcare Research and Quality (grant ID 5R18HS027960).

Keywords: Anticoagulation management service; Self-management; Self-testing; Self-monitoring; Warfarin

Introduction

Vitamin K antagonists are one of the main anticoagulants used in the treatment and prevention of thrombosis in various medical conditions, such as venous thromboembolism, atrial fibrillation, and mechanical heart valve replacement. Warfarin is the most widely used VKA in many countries globally,[1] although there has been a declining trend in its use following the availability of direct oral anticoagulants (DOACs) since 2010.[2] However, warfarin continues to be a vital therapeutic option worldwide.[3] In addition to its relatively low cost, warfarin is associated with lower risk of gastrointestinal bleeding[4] and all-cause mortality[5] compared to some DOACs. Furthermore, warfarin is superior to DOACs in patients with antiphospholipid syndrome,[6] mechanical heart valves, and valvular AF.[7] However, to

*Corresponding author. Faculty of Pharmaceutical Science, Naresuan University, Phitsanulok 65000, Thailand.
**Corresponding author. University of Utah College of Pharmacy, Salt Lake City, UT, USA.
E-mail addresses: teerapond@nu.ac.th (T. Dhippayom), dan.witt@pharm.utah.edu (D.M. Witt).

Research in context

Evidence before this study

Warfarin remains the main anticoagulant used in the treatment and prevention of thrombosis in various medical conditions, especially in patients with antiphospholipid syndrome, mechanical heart valves, and valvular atrial fibrillation (AF), where it has been shown to be more advantageous than direct oral anticoagulants. Several previous studies have highlighted the beneficial effects on anticoagulation control and clinical outcomes of anticoagulation management services (AMS), patient self-testing (PST), and patient self-management (PSM) when compared with usual care. Although a previous network meta-analysis (NMA) has shown the advantageous effects of certain types of self-care on anticoagulation control, it did not consider AMS care separately from usual care. Hence, there is currently a lack of comparative evidence on the effectiveness of different warfarin management strategies.

Added value of this study

This is the first study to compare the effects of different warfarin management strategies on clinically important outcomes, using both direct and indirect evidence. Our findings have added to the current knowledge regarding the beneficial effects of PSM, demonstrating that it not only reduces the risk of thromboembolic (TE) events when compared with usual care, but also proves to be more effective than AMS. The certainty of evidence generated in our study, together with findings from sensitivity analyses, has supported the robustness of the beneficial effects of PSM program for patients using warfarin.

Implications of all the available evidence

PSM should be considered for patients who are on warfarin and capable of performing self-management, provided that they receive appropriate support and monitoring from healthcare providers. Further research is needed to gain insight into the adoption of PSM among warfarin users and healthcare providers, and to evaluate the cost-effectiveness of different warfarin management strategies, which could support successful implementation of PSM in practice.

achieve the benefits of warfarin, patients require careful and frequent monitoring with dose adjustment due to warfarin's narrow therapeutic index.

Warfarin management encompasses several approaches tailored to optimize treatment outcomes and ensure patient safety.[8] Usual care typically involves regular in person clinic visits for International Normalized Ratio (INR) monitoring, with dose adjustments made by healthcare providers based on test results and patient factors. Anticoagulation management services (AMS), or anticoagulation clinics, offer a more specialized approach where trained healthcare professionals (often nurses and/or pharmacists) provide comprehensive management, including INR testing, education, and dose adjustments using a systematic approach.[9] Patient self-testing (PST) empowers patients to conduct their own INR tests, with results reported to healthcare providers for dose advice. To ensure successful self-monitoring, appropriate patient education on how to accurately perform and interpret these tests is essential. Patient self-management (PSM) goes a step further, enabling patients to adjust their own warfarin dose based on self-testing results and dosing decision aids, which requires further education on effectively managing dosages.[10] The proportion of patients receiving different types of warfarin management varies by region, healthcare system, and patient preference. Generally, most patients are managed by usual care or AMS, with about 4% managed by PST.[11] The proportion of patients managed by PSM is expected to be significantly smaller than those managed by PST.

Several previous studies have shown the beneficial effects on anticoagulation control and clinical outcomes of AMS,[12] PST, and PSM,[13] when compared with usual care. However, there is a lack of comparative evidence on the effectiveness of these warfarin management strategies. A previous network meta-analysis (NMA) assessing warfarin care strategies did not consider AMS care separately from usual care.[14] This is a major limitation considering that AMS have become the standard of care in many healthcare centers given their central role in the broader mission of antithrombotic stewardship.[15,16] Therefore, we conducted this study to evaluate the comparative effectiveness of different management strategies in patients using warfarin.

Methods

We conducted this study in accordance with the Cochrane Collaboration guidelines for systematic review of interventions[17] and followed the PRISMA 2020 statement[18] as well as the PRISMA extension statement for reporting of systematic reviews incorporating NMA of health care interventions.[19] Our study protocol was registered in PROSPERO (CRD42023491978).

Search strategy

We searched the following bibliographic databases: PubMed, EMBASE, the Cochrane Central Register of clinical trials (CENTRAL), and CINAHL from the inception of each database to August 2023, with an update on 8 May 2024. We also searched grey literature using EBSCO Open Dissertation. Our search strategy

comprised both free text and thesaurus to cover possible synonyms of the following key domains: 1) warfarin; 2) warfarin management strategies; and 3) randomized controlled trial (RCT). The complete search terms for each database are presented in Appendix 1. We also performed other searching techniques in addition to database searches.

Selection criteria

We included RCTs that met the following criteria: 1) conducted in patients who use warfarin for any indication and at any dose, with a study duration of at least one month; 2) compared the effect of at least two of the following warfarin management strategies: AMS, PSM, PST, and usual care; and 3) measured one of the following outcomes: all-cause mortality, fatal stroke, fatal pulmonary embolism, major bleeding, major thromboembolic events, stroke, myocardial infarction, hospitalization, and time in therapeutic INR range (TTR). Three reviewers (KB, WK, and HH) were paired and independently screened the titles and abstracts of the search results. Full-text articles that passed the title/abstract screening process were subsequently assessed independently by a pair of reviewers (KB, WK, and HH). Disagreements and uncertainties about inclusion were discussed and resolved by TD.

Data extraction

KB and WK independently extracted data using a data extraction form modified from the Cochrane Effective Practice and Organization of Care Group (EPOC) guidelines.[20] Data extracted included: study design and duration; study aim; setting; number of participants and their characteristics; treatment stage (initiation vs maintenance); inclusion criteria; characteristics of the intervention and comparator; outcome measurement; and funding sources. Data extraction was randomly verified by TD.

Risk of bias assessment

We assessed risk of bias for each outcome using the EPOC risk of bias tool.[21] Each study was classified as being of low risk, high risk, or unclear risk. KB and WK independently performed the quality assessment, with any disagreements resolved through discussion or by consulting a third reviewer, TD.

Statistics

We drew a network geometry to explore the comparative relationship among different types of warfarin management strategies for each comparable outcome. We performed global network inconsistency tests to evaluate the extent of disagreement between direct and indirect effects.[22] Statistical heterogeneity between studies with direct evidence was assessed using the Chi-squared test and I^2. We also conducted transitivity assessments to explore the distribution of clinical variables that might affect the outcomes of interest.

We conducted NMAs with a random-effects model in the frequentist framework[23] to compare the effect of different warfarin management strategies, using usual care as a common comparator in each NMA model. Direct and indirect evidence were incorporated into the NMAs when direct comparisons between management strategies were available. We reported the effect estimates alongside the corresponding 95% confidence intervals (CI). Effect measures for dichotomous data were presented as risk ratios (RR), whereas mean differences (MD) illustrated the effects of TTR.

We estimated the probability of which warfarin management strategies are best by using the surface under the cumulative ranking (SUCRA).[24] SUCRA values range from 0 to 100%; the larger the SUCRA value, the better the treatment's rank.[25] We conducted sensitivity analyses by excluding: small trials (<25th percentile of sample size); and trials with high risk of bias.[26] Subgroup analyses were based on the country of origin (US vs others); duration of study (less than 12 months and 12 months or more); warfarin treatment status (initiation and maintenance); proportion of warfarin treatment for AF indication (less than 50% and 50% or more); and warfarin dose (high dose of more than or equal to 50 mg/week vs non-high dose of less than 50 mg/week). Publication bias was evaluated for small study effects using a comparison-adjusted funnel plot and Egger's test. A p-value of <0.05 was considered statistically significant. All analyses were conducted using STATA 17 (College Station, TX).

We assessed the certainty of evidence using the Confidence in Network Meta-Analysis (CINeMA) online platform.[27] Judgements were summarized into four levels of confidence for each relative treatment effect according to the standard Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment[28]: high (the true effect closely matches the estimated effect), moderate (the estimate is likely accurate but may differ substantially), low (limited confidence with potential substantial difference from the estimate), and very low (very little confidence in the estimate, with the true effect likely being substantially different).

Ethics

Due to the nature of the present study, informed consent or approval by local ethical committees was not required.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the study.

Results

Search results

We identified 2656 articles from bibliographic databases search after duplicates were removed (Fig. 1). Of these, 75 full-text articles passed title/abstract screening, were retrieved, and reviewed for eligibility. A total of 52 articles were excluded after full text review (see the complete list in Appendix 2). Five additional RCTs, identified from previous relevant systematic reviews and other search techniques, were included, resulting in a total of 28 trials[29–56] included in our study. Two 3-arm trials divided their intervention groups based on different INR measurement frequencies[35] and PSM algorithms.[47] However, in our analysis exploring the broad types of warfarin management, we combined the groups with the same management type in each trial.

Study characteristics

Of the 28 included trials, 8 were conducted in the United States[29,30,34,46,49,51,52,54] (Table 1); 5 in Canada[55]; 4 each in the UK[39–41,43] and Denmark[31,35,36,47]; 2 in Ireland[50]; and 1 each in Australia,[37] Brazil,[45] Germany,[38] Hong Kong,[33] and Turkey.[56] The study duration ranged from 1 month to 24 months (interquartile range: 6–12), with 16 trials lasting less than 12 months.[30–32,34,39,41–44,47,49,51–55] In total, these 28 trials involved 8100 warfarin users, with mean age ranging from 48.5 to 74.7 years. Mean daily warfarin doses among the included studies varied between 4.9 and 7.2 mg. Race/ethnicity and socioeconomic status were not well reported among the included trials. The proportion of participants prescribed warfarin for AF ranged from 16.1% to 84.1%. The majority of included trials (19) were conducted in patients on maintenance warfarin therapy.[29,31,32,35–37,39–43,45,46,48,50,51,53,56]

Warfarin management strategies

Twenty-two trials compared usual care with other warfarin management strategies.[29,30,32–40,42,44,45,47,49–53,55,56] The practice of usual care appeared similar across these trials, although some details of the protocols varied. These variations ranged from physicians adjusting the warfarin dose based on INR readings and dosing algorithms to practices where physicians managed INR monitoring and warfarin dosing adjustments without the support of an anticoagulation protocol (Appendix 3). Healthcare providers in the 12 AMS trials were pharmacists (6 trials),[32–34,44,48,49] a multidisciplinary team (1 trial),[45] nurses (1 trial),[54] and unspecified healthcare providers (4 trials).[29,43,46,52,55] In 9 PST trials, patients performed their own INR tests during the maintenance phase at the following frequencies: once a week (5 trials),[31,35,43,46,52] every two weeks (3 trials),[35,41,48] every month (1 trial),[30] or at an unknown frequency (1 trial).[54] Warfarin dosing instruction was received from various sources, including computer application/software guiding healthcare providers (4 trials),[35,46,48,52] physicians (2 trials),[31,54] and unspecified healthcare providers (3 trials).[30,41,43] The frequency of INR measurements by patients in the 13 PSM trials were as follows: once a week

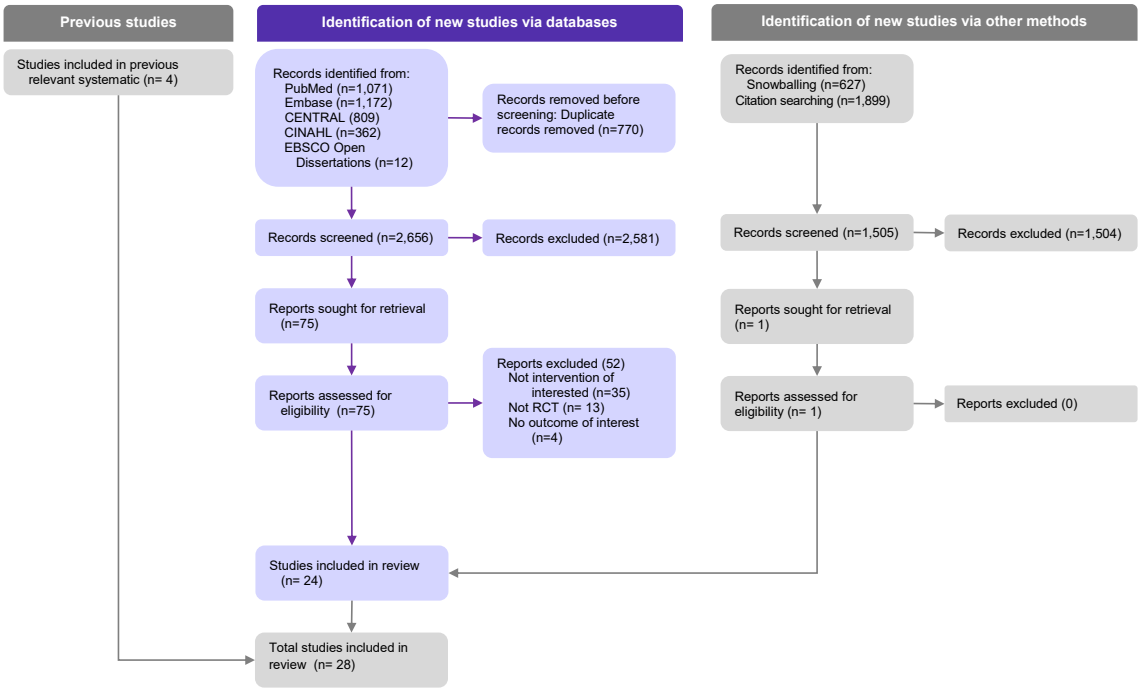

Fig. 1: PRISMA flow diagram of selected articles.

Study (Year)	Country	Setting	Total participants (No.)	Mean age (SD)	Male (%)	AF Indication (%)	Warfarin treatment phase	Duration of study (months)	Outcomes	Funding
Banet (2003)[29]	USA	Eight health care centers	231	72 (NR)	AMS (55.3) UC (45.3)	AMS (56.3) UC (42.1)	Maintenance	18	Major bleeding	Public funding
Beyth (2000)[30]	USA	Hospital	325	74.7 (6.66)	PST (45.4) UC (41.4)	PST (17.0) UC (17.0)	Initiation	6	All-cause mortality; Hospitalization; Major bleeding; Major TE	Public funding
Brasen (2018)[31]	Denmark	Anticoagulation Clinic	87	69.39 (NR)	PSM (79.5) PST (79.1)	PSM (65.9) PST (62.7)	Maintenance	10	All-cause mortality; Major bleeding; TTR (NR)	Not received funding
Bungard (2012)[32]	Canada	Anticoagulation Clinic and primary care practice	62	NR (NR)	AMS (62.5) UC (60.0)	AMS (75.0) UC (83.0)	Maintenance	6	Hospitalization; Major bleeding; Stroke; Major TE; TIA; TTR (Rosendaal's methods)	University funding
Chan (2006)[33]	China (Hong Kong)	Anticoagulation Clinic in Hospital	137	59.01 (14)	AMS (35.3) UC (55.1)	AMS (54.0) UC (51.0)	Initiation	24	All-cause mortality; Hospitalization; Major bleeding; Major TE; TIA; TTR (Rosendaal's methods)	Public funding
Chenella (1983)[34]	USA	Hospital	81	48.89 (16)	AMS (45.2) UC (41.0)	NR	Initiation	6	All-cause mortality; Major bleeding	Not reported
Christensen (2006)[36]	Denmark	Hospital	100	48.55 (13.76)	PSM (74.0) UC (60.0)	PSM (34.3) UC (34.3)	Maintenance	14	All-cause mortality; Major bleeding; Major TE	Public funding
Christensen (2011)[35]	Denmark	Anticoagulation Clinic in Hospital	140	63.54 (NR)	PST (68.7) UC (87.5)	PST (53.6) UC (67.5)	Maintenance	12	All-cause mortality; TTR (Rosendaal's methods)	Hospital funding
Dignan (2013)[37]	Australia	Hospital	310	59.71 (11.76)	PSM (67.3) UC (70.7)	PSM (43.1) UC (40.8)	Maintenance	12	All-cause mortality; Major bleeding; Major TE	Industrial funding
Eitz (2008)[38]	Germany	Health care center	765	58.71 (8.04)	PSM (73.0) UC (63.1)	PSM (28.0) UC (32.0)	Initiation	24	Major bleeding; Major TE	Not reported
Fitzmaurice (2002)[39]	UK	Six general practices	49	66.18 (NR)	PSM and UC (75.5)	PSM and UC (55.1)	Maintenance	6	All-cause mortality; Major bleeding; TTR (NR)	Industrial funding
Fitzmaurice (2005)[40]	UK	Primary care centers	617	65 (NR)	PSM and UC (64.8)	NR	Maintenance	12	All-cause mortality; Stroke; TIA; TTR (Rosendaal's methods)	Public funding
Gardiner (2006)[41]	UK	Anticoagulant clinic	104	NR (NR)	PSM (60.0) PST (61.2)	PSM (41.8) PST (38.7)	Maintenance	6	TTR (Rosendaal's methods)	Public funding
Grunau (2011)[42]	Canada	Family practice	11	72.29 (NR)	PSM (66.7) UC (80.0)	PSM (33.3) UC (60.0)	Maintenance	8	Major bleeding; Major TE	Not received funding
Khan (2004)[43]	UK	Anticoagulation clinic	125	NR (NR)	PST (65.0) AMS (48.7)	PST (100) AMS (100)	Maintenance	6	Major TE; TTR (Rosendaal's methods)	Public funding
Lalonde (2008)[44]	Canada	Hospital	250	65.42 (11.6)	AMS (49.2) UC (53.3)	AMS (58.6) UC (60.6)	Initiation or maintenance	6	All-cause mortality; Major TE	Public and Industrial funding
Martins (2023)[45]	Brazil	Hospital	280	56.8 (13.1)	AMS (43.4) UC (47.0)	AMS (66.7) UC (60.9)	Maintenance	12	All-cause mortality; TTR (Rosendaal's methods)	Public funding
Matchar (2010)[46]	USA	28 Health care centers	2922	67 (9.41)	PST (98.4) AMS (98.6)	PST (82.1) AMS (84.1)	Maintenance	24	All-cause mortality; Major TE; Major bleeding; Stroke; TTR (Rosendaal's methods)	Public funding
Rasmussen (2012)[47]	Denmark	Hospital	54	NR (NR)	PSM (57.0) UC (59.0)	NR	Initiation	7	TTR (Rosendaal's methods)	Public funding
Ryan (2009)[48]	Ireland	Anticoagulation Clinic in Hospital	132	58.7 (14.3)	PST and AMS (60.6)	PST and AMS (32.6)	Maintenance	12	TIA; TTR (Rosendaal's methods)	Public and Industrial funding
Schillig (2011)[49]	USA	Hospital	500	66.05 (14.98)	AMS (54.0) UC (56.4)	AMS (54.4) UC (66.4)	Transition after discharge	1	Major bleeding; Major TE	Industrial funding
Sidhu (2001)[50]	Ireland	NA	100	60.902 (NR)	PSM (52.9) UC (38.8)	NR	Maintenance	24	All-cause mortality; Major bleeding; Stroke; Major TE; Hospitalization; TTR (Rosendaal's methods)	Industrial funding
Sunderji (2004)[51]	USA	Tertiary care center	139	59.96 (NR)	PSM (64.0) UC (77.0)	PSM (29) UC (39)	Maintenance	8	Major bleeding; Major TE; TTR (Rosendaal's methods)	Public funding

(Table 1 continues on next page)

Study (Year)	Country	Setting	Total participants (No.)	Mean age (SD)	Male (%)	AF Indication (%)	Warfarin treatment phase	Duration of study (months)	Outcomes	Funding
(Continued from previous page)										
Thompson (2013)[52]	USA	Health care clinic	200	NR (NR)	PST (77.9) UC (64.5)	NR	Initiation	3	Major bleeding; Major TE; TIA; TTR (NR)	Industrial funding
Verret (2012)[53]	Canada	Tertiary care center	114	57.71 (10.63)	PSM (39) UC (39)	PSM (43.1) UC (58.9)	Maintenance	4	All-cause mortality; Hospitalization; Major TE; TTR (Rosendaal's methods)	Industrial funding
White (1989)[54]	USA	Hospital	46	49.52 (15.01)	PST (50.0) AMS (62.5)	NR	Initiation	2	Hospitalization; Major bleeding; Stroke; Major TE	Industrial funding
Wilson (2003)[55]	Canada	3 Hospitals	221	61 (15)	AMS (52.7) UC (63.3)	AMS (16.1) UC (21.1)	Initiation or maintenance	3	All-cause mortality; Major bleeding; Stroke; Major TE	Public funding
Yildrim (2020)[56]	Turkey	Hospital	36	62.27 (12.36)	PSM (44.4) UC (50.0)	NR	Maintenance	12	Stroke; TTR (NR)	Public funding

AMS = Anticoagulation management service; Ctrl = Control; Int = Intervention; NR = Not reported; PSM = Patient self-management; PST = Patient self-testing; TE = Thromboembolism; TIA = Transient ischemic attack; TTR = Time in therapeutic range; UC = Usual care.

Table 1: **General characteristics of included studies.**

(6 trials),[31,36,37,47,50,53] every two weeks (4 trials),[39–41,56] at patient's discretion (2 trials),[38,51] or at unspecified intervals (1 trial).[42]

Risk of bias of included trials

Since the risk of bias may vary for certain steps in RCTs across different outcomes, the risk of bias in the included trials was assessed and reported separately for each outcome (see Appendix 4). Among the 15 trials reporting all-cause mortality, 9 were justified as having a low risk of bias,[33,35,36,39,40,44,45,53,55] 4 an unclear risk,[30,31,34,46] and 2 a high risk of bias.[37,50] For other outcomes, a higher proportion of trials exhibited an overall unclear risk of bias. This was attributed to the need for clearer reporting of outcome assessments. For example, 14 out of 18 trials, and 12 out of 17 trials were justified as having unclear risk of bias for major bleeding[29–34,36,38,39,42,46,49,51,54] and major TE.[30,32,33,36,38,42,43,46,49,51,53,54]

Effects on all-cause mortality

There were 15 trials, involving a total of 5631 patients, that reported all-cause mortality. Direct evidence was present in almost all treatment comparisons, except between PSM and AMS (Fig. 2A). There were no significant differences in all-cause mortality among the four different types of warfarin management strategies, as shown in Table 2 and Appendix 5, with the certainty of evidence ranging from very low to moderate (Appendix 6).

Effects on TE events

A network geometry for TE events was constructed from 17 trials (6180 patients), although direct evidence between PSM vs AMS, and PSM vs PST was lacking (Fig. 2B). Among the four warfarin management strategies, only PSM demonstrated a significantly lower risk of TE events compared to AMS and usual care, RRs (95% CI) of 0.42 (0.18, 0.99) and 0.41 (0.24, 0.71), with low and moderate certainty of evidence, respectively (Table 2). There was no direct evidence comparing PSM and AMS. The RR from direct evidence of PSM compared with usual care was identical with the network meta-analysis findings without heterogeneity (0.41; 95% CI: 0.24, 0.71; I^2 = 0.0%). The cumulative probability of reducing the risk of TE events, as indicated by SUCRA, also supported these findings, showing PSM with the highest SUCRA of 97.6%, followed by PST at 52.6% (see Appendix 5). This means PSM is most likely to be better than PST, AMS, and usual care.

Effects on major bleeding

Eighteen trials involving 6185 participants reported data on major bleeding. The network geometry had direct evidence in all treatment comparisons, except for PSM vs AMS (Fig. 2C). No significant differences were

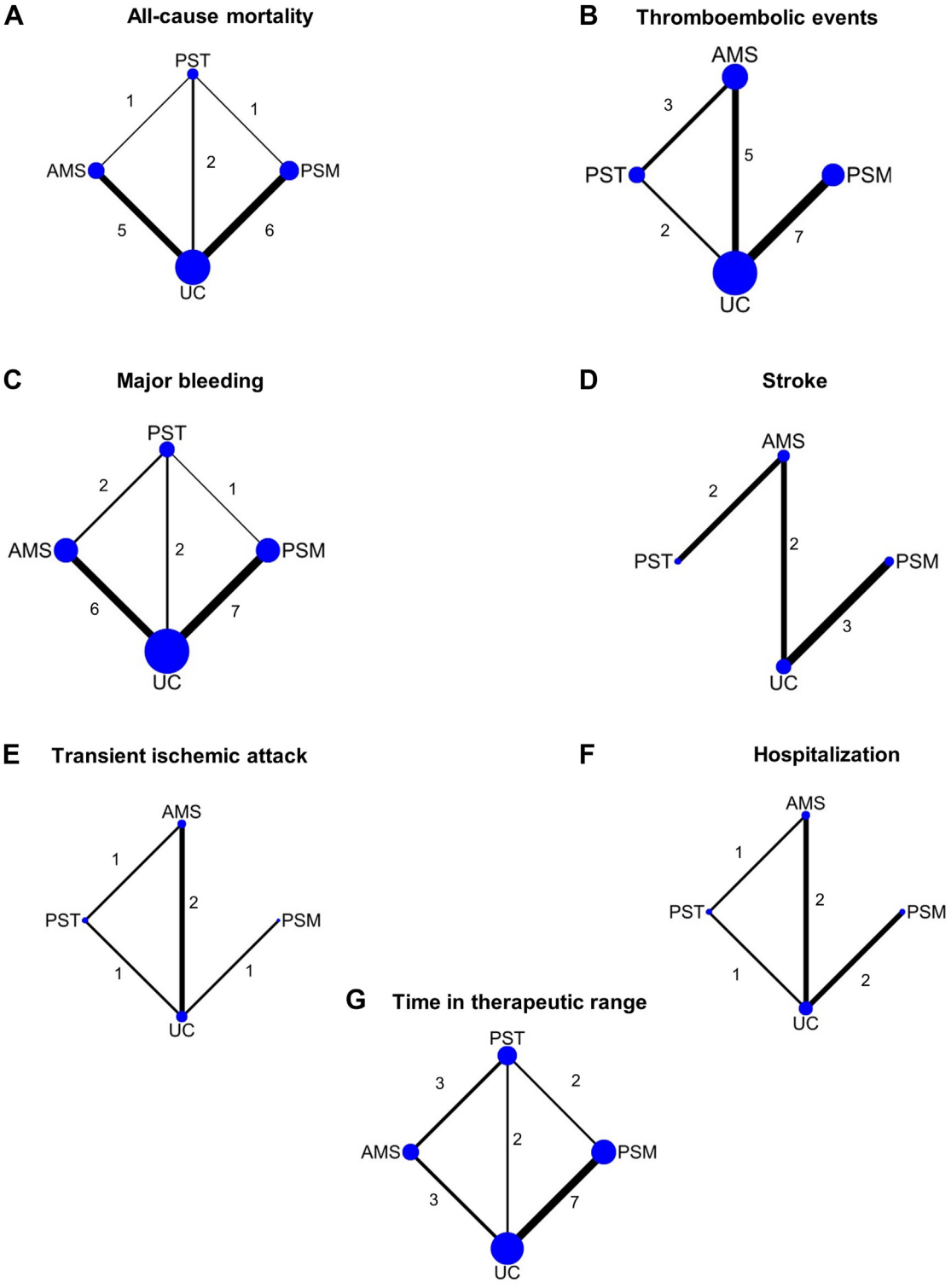

Fig. 2: Network geometry of treatment comparisons of warfarin self-care. Abbreviations: AMS = Anticoagulation management service; INR = International normalized ratio; PSM = Patient self-management; PST = Patient self-testing; UC = Usual care. The numbers along the connection lines in each network geometry indicate the number of studies for each direct comparison.

Outcomes	PSM vs UC	PST vs UC	AMS vs UC	PSM vs AMS	PST vs AMS	PSM vs PST
All-cause mortality (15 trials), RR	0.51 (0.21, 1.22) Certainty ⊕⊕⊕◯	0.79 (0.48, 1.30) Certainty ⊕⊕◯◯	0.75 (0.41, 1.35) Certainty ⊕◯◯◯	0.68 (0.23, 2.00) Certainty ⊕◯◯◯	1.05 (0.66, 1.67) Certainty ⊕◯◯◯	0.65 (0.24, 1.75) Certainty ⊕◯◯◯
Major TE events (17 trials), RR	**0.41 (0.24, 0.71)**[a] Certainty ⊕⊕⊕◯	0.82 (0.47, 1.45) Certainty ⊕◯◯◯	0.97 (0.51, 1.87) Certainty ⊕◯◯◯	**0.42 (0.18, 0.99)**[a] Certainty ⊕⊕◯◯	0.85 (0.55, 1.29) Certainty ⊕◯◯◯	0.50 (0.23, 1.10) Certainty ⊕⊕◯◯
Major bleeding (18 trials), RR	0.98 (0.65, 1.46) Certainty ⊕⊕⊕◯	0.90 (0.48, 1.67) Certainty ⊕◯◯◯	0.89 (0.48, 1.68) Certainty ⊕◯◯◯	1.09 (0.52, 2.29) Certainty ⊕◯◯◯	1.00 (0.81, 1.24) Certainty ⊕⊕⊕◯	1.09 (0.52, 2.26) Certainty ⊕◯◯◯
Stroke (7 trials), RR	0.50 (0.10, 2.44) Certainty ⊕◯◯◯	0.92 (0.09, 9.11) Certainty ⊕◯◯◯	0.95 (0.10, 8.94) Certainty ⊕◯◯◯	0.53 (0.03.8.26) Certainty ⊕◯◯◯	0.97 (0.59, 1.57) Certainty ⊕◯◯◯	0.55 (0.03, 8.92) Certainty ⊕◯◯◯
TIA (5 trials), RR	1.66 (0.06, 49.44) Certainty ⊕⊕◯◯	1.57 (0.20, 12.12) Certainty ⊕◯◯◯	2.01 (0.31, 12.82) Certainty ⊕◯◯◯	0.83 (0.02, 39.61) Certainty ⊕⊕◯◯	0.78 (0.08, 7.88) Certainty ⊕◯◯◯	1.06 (0.02, 55.42) Certainty ⊕◯◯◯
Hospitalization (6 trials), RR	1.32 (0.52, 3.31) Certainty ⊕⊕⊕◯	0.35 (0.10, 1.16) Certainty ⊕◯◯◯	1.41 (0.27, 7.31) Certainty ⊕◯◯◯	0.94 (0.14, 6.19) Certainty ⊕⊕◯◯	0.25 (0.04, 1.51) Certainty ⊕◯◯◯	3.78 (0.83, 17.25) Certainty ⊕◯◯◯
TTR (17 trials), MD (%)	**7.39 (2.39, 12.39)**[a] Certainty ⊕◯◯◯	**7.85 (1.82, 13.88)**[a] Certainty ⊕◯◯◯	2.08 (−4.26, 8.42) Certainty ⊕⊕⊕◯	5.31 (−2.20, 12.82) Certainty ⊕⊕◯◯	5.77 (−0.52, 12.06) Certainty ⊕⊕◯◯	−0.46 (−7.20, 6.28) Certainty ⊕◯◯◯

Certainty of evidence: ⊕◯◯◯ = Very low; ⊕⊕◯◯ = Low; ⊕⊕⊕◯ = Moderate; ⊕⊕⊕⊕ = High. AMS = Anticoagulation management service; INR = International normalized ratio; MD = Mean difference; PSM = Patient self-management; PST = Patient self-testing; RR = Risk ratio; UC = Usual care. [a]Statistically significant.

Table 2: **Effect estimates among treatment comparisons for studied outcomes.**

observed in major bleeding across the four warfarin management approaches, with very low to moderate certainty (Table 2).

Effects on TTR

Comparative estimates from a network of 17 trials (5163 patients) showed that, when compared with usual care, higher TTR was observed in patients practicing PSM (MD 7.39%; 95% CI: 2.39, 12.39) and PST (MD 7.85%; 95% CI: 1.82, 13.88), although both evidence were graded as very low certainty. SUCRA findings also indicated that these two strategies were more likely to be better than others in anticoagulation control, having SUCRA of 79.1% for PSM, and 83.4% for PST (Appendix 5). According to SUCRA findings and the pooled estimates of these two strategies compared with usual care, it appears that PST is likely to be better than PSM for TTR improvement. However, the certainty of these estimates was rated as very low due to some concern for within-study bias and major concern for heterogeneity (Appendix 6).

In contrast to the pooled estimate from the network meta-analysis, the direct evidence showed no significant effect on TTR between PSM and usual care (MD 6.49; 95% CI: −3.09, 16.07). This finding was also accompanied by high heterogeneity (I^2 = 96.1%), which was one of the reasons for the very low certainty of evidence in this comparison. We explored the sources of heterogeneity by excluding trials with a baseline TTR greater than 65% and trials with a study duration of more than 12 months. The results indicated that trials involving participants with a baseline TTR over 65% were the source of heterogeneity. After eliminating trials with baseline TTR greater than 65%, the effects of PSM and PST remained significantly higher than usual care, with improved certainty of evidence from very low to low.

Effects on stroke, TIA, and hospitalization

A small number of included trials measured the effects of warfarin management strategies on stroke (7 trials), TIA (5 trials), and hospitalization (6 trials). None of the four strategies had a significant impact on these outcomes (Table 2).

Sensitivity and subgroup analyses

Sensitivity analyses revealed trends and effect sizes like those in the main analysis, although some were not statistically significant in analyses that excluded trials with small sample sizes and those with a high risk of bias (Appendix 7). Subgroup analyses based on the country of origin and study duration for all outcomes demonstrated comparable effect estimates across different subgroups (Appendix 8). However, the warfarin treatment phase and proportion of AF-treated patients presented contradictory findings among different subgroups, suggesting they might be potential effect modifiers. Notably, PSM significantly reduced the risk of TE events compared with usual care in studies lasting 12 months or longer (RR 0.41; 95% CI 0.23, 0.72), and among patients starting warfarin treatment (RR 0.42; 95% CI 0.22, 0.81). No significant effects were observed in other subgroups. It was not feasible to compare the effects of high dose warfarin with low dose warfarin since there was only one trial using high dose warfarin. However, the findings of non-high dose warfarin (less than 50 mg/week) were consistent with the main analysis.

Exploration for heterogeneity, inconsistency, transitivity, and publication bias

The pooled estimates from pairwise meta-analyses of direct evidence appeared similar to those calculated from network meta-analyses, which consider both direct and indirect evidence, across various comparisons for all

outcomes (see Appendix 5). No significant heterogeneity was observed among the majority of direct evidence in the pairwise meta-analyses. There were no effect estimate inconsistencies between direct and indirect evidence within the network for all outcomes (Appendix 5,7, and 8). Transitivity across treatment comparisons was assessed with an emphasis on effect modifiers identified from subgroup analyses. The findings indicated some concern in specific comparisons (Appendix 9), which in turn affected the certainty of evidence. The funnel plots for all-cause mortality, major TE events, major bleeding, and TTR outcomes appeared symmetrical, suggesting no risk of small-study effects as a proxy for publication bias (Appendix 10). This was confirmed by non-significant Egger's tests.

Discussion

Our study provides comparative evidence on the effects of different warfarin management strategies on clinically important outcomes. The strength of our study lies in the use of a network meta-analysis approach, which incorporates both direct and indirect evidence. This represents the first network meta-analysis to compare all types of warfarin management strategies. The certainty of evidence and findings from sensitivity analyses give us confidence that PSM significantly reduces the risk of TE events. This effect is likely due to its beneficial effects on coagulation control, as indicated by a higher TTR, compared to usual care. However, while PST improved TTR, effects on clinical outcomes were not observed. Compared with other interventions, usual care and AMS offered no advantages for any outcomes of interest.

The beneficial effect of PSM in reducing the risk of TE events, when compared with usual care, aligns with findings from a previous Cochrane review on self-monitoring and self-management of oral anticoagulant,[13] as well as our previous NMA on warfarin self-care strategies.[14] The effect of PSM in reducing the risk of major TE events was not much different between the current study and our previous one (RR 0.41; 95% CI 0.24–0.71 vs RR 0.39; 95% CI 0.20–0.77).[14] The current study has also shown a beneficial effect of PSM over AMS, which was not covered in our previous study. One plausible explanation is the improved coagulation control through PSM, possibly due to the enhanced ability of patients to monitor their INR and self-adjust warfarin dose accordingly. PSM was also shown to lower the risk of TE events in a subgroup of trials involving patients who were initiating warfarin therapy. This finding suggests that warfarin-naïve patients could benefit from PSM, provided they are capable of self-management. However, given the requirement for appropriate monitoring and support during the course of treatment, the additional workload on healthcare providers should be considered. Of note, the effectiveness of PSM observed in our study was derived from findings from RCTs where practice protocols were strictly followed. Successful implementation of a PSM program requires the following components: creating a dosing algorithm, providing comprehensive patient education materials, establishing standard operating procedures, and integrating PSM into clinic workflows with proper training sessions.[57]

Although the effect of PSM on TE was shown to be better than that of AMS, the certainty of this evidence was rated as low. Furthermore, a sensitivity analysis excluding trials with a high risk of bias failed to support this effect. Therefore, advocating for PSM over AMS based solely on its effect on TE events should be undertaken cautiously. The impact of reducing the risk of TE events between PSM and AMS requires further investigation through high-quality studies.

PSM and PST were shown to improve TTR when compared with usual care, aligning well with the findings from our previous study.[14] The certainty of this evidence has changed from very low to low after removing trials with participants' baseline TTR greater than 65%. It is plausible that there was not much room for significant improvement in this patient group. Accordingly, we suggest that PSM and PST could be useful for coagulation control and should be considered in patients with a baseline TTR of less than or equal to 65%. However, these approaches often require more frequent INR tests and support from healthcare providers, which may result in higher costs and require further investigation of cost-effectiveness. Additionally, this recommendation is based on low certainty of evidence and requires validation through further well-designed RCTs.

Unlike the previous Cochrane review by Heneghan et al.,[13] our findings showed no significant effects of PSM on all-cause mortality. The difference in findings could be attributed to the methodological variations and specific inclusion criteria between the studies, with our study focused solely on warfarin. Additionally, Heneghan et al. conducted a pairwise meta-analysis combining usual care or AMS as a comparator, whereas our study used an NMA approach that considers both direct and indirect evidence to enhance the precision of the pooled estimates and differentiate usual care from AMS, as these two management programs showed different effects on the outcomes. We have also updated the search to include more recent evidence up to May 2024, while the included trials in Heneghan et al.'s study were dated to July 2015. Study duration may also influence the treatment effects, as findings from subgroup analysis indicated that trials with a study duration longer than or equal to 12 months have narrower confidence intervals and only slightly cross the line of no effect compared to trials shorter than 12 months.

Our study has some limitations. Firstly, the details of warfarin management among the included trials were not uniform, with variations in management protocols such as testing frequency, patient education, and support from healthcare providers. Further study is required to investigate the impact of these variations on treatment outcomes. Secondly, while our study highlighted significant effects in certain comparisons, most of the evidence was rated as having low or very low certainty, largely due to within-study bias. Thirdly, we focused solely on warfarin self-care, not all vitamin K antagonists (VKAs). This decision was made to avoid heterogeneity from different VKAs with varying pharmacokinetic properties, which have been shown to significantly impact TTR in patients who conducted anticoagulant self-management.[58] Therefore, the findings from this study cannot be generalized to other VKAs. Lastly, not all interventions were available for all outcomes, forcing us to rely solely on indirect evidence to estimate treatment effects. This approach may reduce the precision of our findings. We suggest further research to measure and report all relevant clinical outcomes, to provide a comprehensive understanding of the effects of warfarin management.

Further well-designed RCTs on PSM could enhance the certainty of evidence, strengthen the recommendations, and provide important insights into key implementation elements. We also encourage research to understand the adoption of PSM among warfarin users and healthcare providers, to refine its implementation, and to evaluate the cost-effectiveness of different warfarin management strategies.

Our study highlights the potential of PSM in reducing TE events compared to usual care and AMS. PSM and PST also demonstrated improving coagulation control in patients treated with warfarin. The moderate certainty of evidence regarding the effects of PSM on reducing the risk of TE events supports the beneficial impacts of PSM. We suggest healthcare providers and policymakers consider adopting and promoting PSM in appropriate patient populations.

Contributors

TD contributed to the conceptualization, development of methodology including data collection, data validation, and analysis, and writing the original draft. KB did data collection, data analysis, and verified the underlying data. WK and HH contributed to data collection. NC managed and coordinated responsibility for the research activity planning and execution, contributed to formulation of overarching research goals and aims. GDS contributed to the conceptualization and data interpretation. DMW is responsible for the acquisition of the financial support for the project leading to this publication and contributed to the conceptualization. All authors contributed to edits of the manuscript and had read and approved the final version of the manuscript.

Data sharing statement

Data will be made available upon request made to the corresponding author.

Declaration of interests

Geoffrey D. Barnes received grants from Boston Scientific and consulting fees from Pfizer, Bristol-Myers Squibb, Janssen, Bayer, AstraZeneca, Sanofi, Anthos, Abbott Vascular, and Boston Scientific. The other authors have no conflicts of interest to declare.

Acknowledgements

This study received financial support as a subaward recipient from Agency for Healthcare Research and Quality for the main project titled "Overcoming Barriers to Warfarin Patient Self-Management in the US Healthcare System" (grant ID 5R18HS027960).

During the preparation of this work the authors used ChatGPT in order to check and correct grammar. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102712.

References

1 Haas S, Ten Cate H, Accetta G, et al. Quality of vitamin K antagonist control and 1-year outcomes in patients with atrial fibrillation: a global perspective from the GARFIELD-AF registry. *PLoS One*. 2016;11(10):e0164076.
2 Costa LSD, Alsultan MM, Hincapie AL, Guo JJ. Trends in utilization, reimbursement, and price for DOACs and warfarin in the US Medicaid population from 2000 to 2020. *J Thromb Thrombolysis*. 2023;55(2):339–345.
3 Lippi G, Mattiuzzi C, Adcock D, Favaloro EJ. Oral anticoagulants around the world: an updated state-of-the art analysis. *Ann Blood*. 2018;3(49):10–21037.
4 Abraham NS, Singh S, Alexander GC, et al. Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study. *BMJ*. 2015;350:h1857.
5 Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. *BMJ*. 2018;362:k2505.
6 Lee YH, Song GG. Direct oral anticoagulants versus warfarin in patients with antiphospholipid syndrome: a meta-analysis of randomized controlled trials. *Lupus*. 2022;31(11):1335–1343.
7 Chen A, Stecker E, B AW. Direct oral anticoagulant use: a practical guide to common clinical challenges. *J Am Heart Assoc*. 2020;9(13):e017559.
8 Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl):e44S–e88S.
9 Woodill L, Bodnar A. A novel model of care in anticoagulation management. *Healthc Manage Forum*. 2020;33(6):247–252.
10 Keeling D, Baglin T, Tait C, et al. Guidelines on oral anticoagulation with warfarin - fourth edition. *Br J Haematol*. 2011;154(3):311–324.
11 Van Beek A, Moeyaert M, Ragheb B, et al. Outcomes of warfarin home INR monitoring vs office-based monitoring: a retrospective claims-based analysis. *J Gen Intern Med*. 2023;39(7):1127–1134.
12 Zhou S, Sheng XY, Xiang Q, Wang ZN, Zhou Y, Cui YM. Comparing the effectiveness of pharmacist-managed warfarin anticoagulation with other models: a systematic review and meta-analysis. *J Clin Pharm Ther*. 2016;41(6):602–611.
13 Heneghan CJ, Garcia-Alamino JM, Spencer EA, et al. Self-monitoring and self-management of oral anticoagulation. *Cochrane Database Syst Rev*. 2016;7:Cd003839.
14 Dhippayom T, Boonpattharatthiti K, Thammathuros T, Dilokthornsakul P, Sakunrag I, Devine B. Clinical outcomes of different warfarin self-care strategies: a systematic review and network meta-analysis. *Thromb Haemost*. 2022;122(4):492–505.
15 Barnes GD, Kline-Rogers E, Graves C, et al. Structure and function of anticoagulation clinics in the United States: an AC forum membership survey. *J Thromb Thrombolysis*. 2018;46(1):7–11.
16 Burnett AE, Barnes GD. A call to action for anticoagulation stewardship. *Res Pract Thromb Haemost*. 2022;6(5):e12757.

17 Higgins JPT, Thomas J, Chandler J, et al. *Cochrane handbook for systematic reviews of interventions version 6.4 (updated August 2023)*. The Cochrane Collaboration; 2023 [cited 2023 Dec 14]. Available from: www.training.cochrane.org/handbook.
18 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
19 Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. 2015;162(11):777–784.
20 Cochrane Effective Practice and Organisation of Care. Good practice data extraction form oxford: Cochrane effective practice and organisation of care (EPOC). c2020 [cited 2023 Oct 15]. Available from: https://epoc.cochrane.org/sites/epoc.cochrane.org/files/public/uploads/Resources-for-authors2017/good_practice_data_extraction_form.doc.
21 Cochrane Effective Practice and Organisation of Care. Summary assessments of the risk of bias. EPOC resources for review authors c2020 [cited 2023 Oct 15]. Available from: https://epoc.cochrane.org/resources/epoc-resources-review-authors.
22 Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med*. 2010;29(7–8):932–944.
23 White IR. Network meta-analysis. *STATA J*. 2015;15(4):951–985.
24 Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods*. 2012;3(2):80–97.
25 Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One*. 2013;8(10):e76654.
26 Dechartres A, Altman DG, Trinquart L, Boutron I, Ravaud P. Association between analytic strategy and estimates of treatment outcomes in meta-analyses. *JAMA*. 2014;312(6):623–630.
27 Nikolakopoulou A, Higgins JPT, Papakonstantinou T, et al. CINeMA: an approach for assessing confidence in the results of a network meta-analysis. *PLoS Med*. 2020;17(4):e1003082.
28 Puhan MA, Schünemann HJ, Murad MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ*. 2014;349:g5630.
29 Banet GA, Waterman AD, Milligan PE, Gatchel SK, Gage BF. Warfarin dose reduction vs watchful waiting for mild elevations in the international normalized ratio. *Chest*. 2003;123(2):499–503.
30 Beyth RJ, Quinn L, Landefeld CS. A multicomponent intervention to prevent major bleeding complications in older patients receiving warfarin. A randomized, controlled trial. *Ann Intern Med*. 2000;133(9):687–695.
31 Brasen CL, Madsen JS, Parkner T, Brandslund I. Home management of warfarin treatment through a real-time supervised telemedicine solution: a randomized controlled trial. *Telemed J E Health*. 2019;25(2):109–115.
32 Bungard TJ, Ritchie B, Garg S, Tsuyuki RT. Sustained impact of anticoagulant control achieved in an anticoagulation management service after transfer of management to the primary care physician. *Pharmacotherapy*. 2012;32(2):112–119.
33 Chan FW, Wong RS, Lau WH, Chan TY, Cheng G, You JH. Management of Chinese patients on warfarin therapy in two models of anticoagulation service - a prospective randomized trial. *Br J Clin Pharmacol*. 2006;62(5):601–609.
34 Chenella FC, Klotz TA, Gill MA, et al. Comparison of physician and pharmacist management of anticoagulant therapy of inpatients. *Am J Hosp Pharm*. 1983;40(10):1642–1645.
35 Christensen H, Lauterlein JJ, Sørensen PD, Petersen ER, Madsen JS, Brandslund I. Home management of oral anticoagulation via telemedicine versus conventional hospital-based treatment. *Telemed J E Health*. 2011;17(3):169–176.
36 Christensen TD, Maegaard M, Sørensen HT, Hjortdal VE, Hasenkam JM. Self-management versus conventional management of oral anticoagulant therapy: a randomized, controlled trial. *Eur J Intern Med*. 2006;17(4):260–266.
37 Dignan R, Keech AC, Gebski VJ, Mann KP, Hughes CF. Is home warfarin self-management effective? Results of the randomised Self-Management of Anticoagulation Research Trial. *Int J Cardiol*. 2013;168(6):5378–5384.
38 Eitz T, Schenk S, Fritzsche D, et al. International normalized ratio self-management lowers the risk of thromboembolic events after prosthetic heart valve replacement. *Ann Thorac Surg*. 2008;85(3):949–954. ; discussion 55.
39 Fitzmaurice DA, Murray ET, Gee KM, Allan TF, Hobbs FD. A randomised controlled trial of patient self management of oral anticoagulation treatment compared with primary care management. *J Clin Pathol*. 2002;55(11):845–849.
40 Fitzmaurice DA, Murray ET, McCahon D, et al. Self management of oral anticoagulation: randomised trial. *BMJ*. 2005;331(7524):1057.
41 Gardiner C, Williams K, Longair I, Mackie IJ, Machin SJ, Cohen H. A randomised control trial of patient self-management of oral anticoagulation compared with patient self-testing. *Br J Haematol*. 2006;132(5):598–603.
42 Grunau BE, Wiens MO, Harder KK. Patient self-management of warfarin therapy: pragmatic feasibility study in Canadian primary care. *Can Fam Phys*. 2011;57(8):e292–e298.
43 Khan TI, Kamali F, Kesteven P, Avery P, Wynne H. The value of education and self-monitoring in the management of warfarin therapy in older patients with unstable control of anticoagulation. *Br J Haematol*. 2004;126(4):557–564.
44 Lalonde L, Martineau J, Blais N, et al. Is long-term pharmacist-managed anticoagulation service efficient? A pragmatic randomized controlled trial. *Am Heart J*. 2008;156(1):148–154.
45 Martins MA, Oliveira JA, Ribeiro DD, et al. Efficacy of an anticoagulation clinic in low-income Brazilian patients with heart disease: a randomized clinical trial. *Hemato*. 2023;4(3):227–239.
46 Matchar DB, Jacobson A, Dolor R, et al. Effect of home testing of international normalized ratio on clinical events. *N Engl J Med*. 2010;363(17):1608–1620.
47 Rasmussen RS, Corell P, Madsen P, Overgaard K. Effects of computer-assisted oral anticoagulant therapy. *Thromb J*. 2012;10(1):17.
48 Ryan F, Byrne S, O'Shea S. Randomized controlled trial of supervised patient self-testing of warfarin therapy using an internet-based expert system. *J Thromb Haemost*. 2009;7(8):1284–1290.
49 Schillig J, Kaatz S, Hudson M, Krol GD, Szandzik EG, Kalus JS. Clinical and safety impact of an inpatient pharmacist-directed anticoagulation service. *J Hosp Med*. 2011;6(6):322–328.
50 Sidhu P, O'Kane HO. Self-managed anticoagulation: results from a two-year prospective randomized trial with heart valve patients. *Ann Thorac Surg*. 2001;72(5):1523–1527.
51 Sunderji R, Gin K, Shalansky K, et al. A randomized trial of patient self-managed versus physician-managed oral anticoagulation. *Can J Cardiol*. 2004;20(11):1117–1123.
52 Thompson JL, Burkhart HM, Daly RC, et al. Anticoagulation early after mechanical valve replacement: improved management with patient self-testing. *J Thorac Cardiovasc Surg*. 2013;146(3):599–604.
53 Verret L, Couturier J, Rozon A, et al. Impact of a pharmacist-led warfarin self-management program on quality of life and anticoagulation control: a randomized trial. *Pharmacotherapy*. 2012;32(10):871–879.
54 White RH, McCurdy SA, von Marensdorff H, Woodruff DE Jr, Leftgoff L. Home prothrombin time monitoring after the initiation of warfarin therapy. A randomized, prospective study. *Ann Intern Med*. 1989;111(9):730–737.
55 Wilson SJ, Wells PS, Kovacs MJ, et al. Comparing the quality of oral anticoagulant management by anticoagulation clinics and by family physicians: a randomized controlled trial. *CMAJ*. 2003;169(4):293–298.
56 Yıldırım JG, Bayık Temel A. The effect of nurse home-support program on self-management of patients receiving oral anticoagulation (warfarin) therapy. *Florence Nightingale J Nurs*. 2020;28(1):13–22.
57 Fleming RP, Vazquez SR, Witt DM. Implementation and evaluation of a warfarin patient self-management (PSM) program among experienced patients in a U.S. academic health system. *J Thromb Thrombolysis*. 2023;56(4):511–513.
58 Jensen CF, Christensen TD, Maegaard M, Hasenkam JM. Quality of oral anticoagulant therapy in patients who perform self management: warfarin versus phenprocoumon. *J Thromb Thrombolysis*. 2009;28(3):276–281.