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ORIGINAL RESEARCH

The Value of Anticoagulation Management Combining Telemedicine and Self-Testing in Cardiovascular Diseases: A Meta-Analysis of Randomized Controlled Trials

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Purpose: No consensus has been established on the safety and effectiveness of out-of-hospital management of Vitamin K antagonists (VKA) therapy combining portable coagulometers and telemedicine. The present meta-analysis investigated the safety and effectiveness of this hybrid anticoagulants management model.

Methods: The PubMed, Embase, Cochrane, and Web of Science databases were searched for papers published before May 1, 2022. To reduce bias, only randomized controlled trials were included. RevMan 5.3 (Cochrane) software was used to evaluate and analyze clinical outcomes, including the effectiveness and safety of patient management approaches, determined by the time in the therapeutic range (TTR) and occurrence of thrombotic and bleeding events.

Results: Eight studies, comprising 3853 patients, were selected. The meta-analysis showed that anticoagulant management combining portable coagulometers and telemedicine significantly improved frequency of testing (mean difference [MD]= 12.95 days; 95% CI, 8.77–17.12; I^2= 92%; P< 0.01) and TTR (MD= 9.50%; 95% CI, 3.16–15.85; I^2= 87%; P< 0.01). Thromboembolism events were reduced (RR= 0.72; 95% CI, 0.51–1.01; I^2= 0%; P= 0.05), but the results were not statistically significant. And no significant differences in major bleeding events, rehospitalization rate, mortality, or overall treatment cost existed between the two groups.

Conclusion: Although the safety of remote cardiovascular disease management is not superior to that of conventional outpatient anticoagulant management, it provides a more stable monitoring of coagulation status.

Keywords: VKA therapy, warfarin, telemedicine, self-testing, randomized controlled studies, meta-analysis

Introduction

Cardiovascular diseases are the leading cause of death worldwide,[1–3] and the incidence is increasing as populations age.[4] Oral anticoagulation drugs, which play a pivotal role in preventing the formation of blood clots, are used in cardiovascular diseases, such as venous thromboembolism and atrial fibrillation, and in patients who have undergone artificial valve surgery.[5,6] Warfarin is an anticoagulant that is widely used worldwide and recommended in guidelines for the treatment of cardiovascular diseases owing to its effectiveness and low cost.[7,8] However, the balance between the effectiveness and safety of anticoagulant therapy requires improvement. The narrow therapeutic window of warfarin, the need for frequent-dose adjustment, and drug and food interactions pose challenges for the maintenance of adequate anticoagulant levels.[9] Specifically, inconvenient testing methods and inefficient dose adjustment consistently place patients at risk of complications, such as bleeding and thrombosis. Similar challenges occur in the long-term treatment of patients with diabetes; however, portable blood glucose meter acts a tool to improve ease of testing, which helps increase the frequency of testing to some extent.[10–12]

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Recent advances in testing and communication technologies have facilitated the application of self-testing and self-management in clinical practice.[13–15] Similar to the advantages of portable glucose meters, the popularization of portable coagulometers is gradually addressing problems with anticoagulant therapy management. Such devices enable patients to determine their coagulation parameters in few minutes using fingertip blood samples, without the need to visit to fixed testing sites.[16] Studies have confirmed that there are no significant differences between the results from portable coagulometers and those from hospital laboratories.[17,18] Simultaneously, telemedicine—by telephone, the internet, and other remote networks—promotes doctor–patient communication, facilitates drug monitoring, and provides higher versatility to post-discharge anticoagulant management approaches.[19–22]

Although remote anticoagulation monitoring theoretically facilitates warfarin detection, there is disagreement among researchers as to whether the hybrid model is safer and more effective than hospital-based anticoagulant management. The international normalized ratio (INR) is a standardized measure of the time taken for blood to clot and is used to monitor coagulation status. When the INR is assumed to change linearly from the last INR until the INR at next check, the time in therapeutic range (TTR) refers to the number of days with an INR between 2.0 and 3.0 over total day counts using these integrated numbers and is typically calculated by the Rosendaal method.[23] TTR is thought to correlate with the quality and clinical outcome of Vitamin K antagonists (VKA) therapy; a high TTR implies a stable coagulation state and an increase in mean TTR is associated with a significant decrease in the incidence of major bleeding and thromboembolic events.[24] Clinical guidelines recommend that individuals have a TTR≥65% in the management of atrial fibrillation.[25] Common clinical factors affecting TTR have been used to develop SAMe-TT2R2 scores, and the use of portable coagulometers is encouraged.[25,26] In addition, it is recommended that anticoagulant medications are changed when the INR cannot be maintained in the effective range.[25,26] Randomized trials have shown anticoagulant therapy management by self-testing and telemedicine can increase TTR and reduce the incidence of complications.[27–31] In contrast, other studies suggested that there are differences in the effectiveness and outcomes of these two anticoagulant management models.[32,33] However, most of these studies are based on small sample single-center investigations and lack systematic evaluation of treatment outcomes. Therefore, a comprehensive and systematic meta-analysis could further contribute to our understanding of this field.

This study used meta-analysis to provide high-level evidence on the effectiveness and safety of the management model combining portable coagulometers and telemedicine with VKA therapy. Only randomized controlled trials (RCTs) were included in this investigation, and treatment-related parameters, including test frequency, TTR, major bleeding events, thromboembolic events, rehospitalization rate, mortality, and cost, were analyzed.

Materials and Methods

Search Strategy and Study Selection

PubMed, Embase, Cochrane Library, Web of Science, and other databases were searched systematically, in combination with retrospective literature retrieval. The search keywords were "oral anticoagulation therapy", "warfarin therapy", "oral anticoagulation management", "mHealth", "Internet", "telemedicine", "self-testing", and "self-management". The screening criterion was "clinical trials". Details of search strategies are available in Supplementary Figure 1. PICO (population, intervention, comparator, outcomes) was defined as: (1) population: patients followed VKA therapy; (2) intervention: management models combining portable coagulometers and telemedicine; (3) comparator: clinical-based anticoagulant management; and (4) outcomes: test frequency, TTR, thromboembolic events, major bleeding events, rehospitalization rate, mortality, and cost.

Papers published before May 1, 2022 were included. Randomized controlled research reports written in English were considered. The titles and abstracts of all references were initially screened by Huang Yu and Xie Yilian independently; when these researchers expressed uncertain or divergent views regarding a report, a third person, Huang Lei, provided an opinion and helped in reaching a consensus. The full texts of selected studies were independently evaluated against the inclusion criteria by the same two reviewers. Similarly, if any differences in opinion emerged, Huang Lei offered a third opinion to facilitate a judgement.

Data Extraction

Data were extracted by Huang Yu, and Han Zhen confirmed their accuracy and authenticity. The use of INR self-testing combined with telemedicine was defined as the intervention, and patients using such measures were referred to as the intervention group. Patients undergoing outpatient anticoagulant management were assigned to the control group. The primary outcome was TTR. Secondary outcomes were thromboembolic events, major bleeding events, rehospitalizations, mortality, test frequency and cost. Major bleeding was overt bleeding that led to the loss of at least 2.0 units of blood in 1 week or less or was otherwise life-threatening including intracranial bleeding, gastrointestinal bleeding, pulmonary bleeding or other serious bleeding conditions that require urgent medical attention. Extracted information included 1) basic research information, such as article title, author(s), research area, and publication date; 2) basic characteristics of the study sample, such as sample size, primary disease, average age, and sex ratio of patients; 3) detail of portable coagulometer, telemedicine method and follow-up time; 4) effectiveness and safety information following intervention, including TTR, bleeding and thromboembolic events (such as venous thromboembolism, stroke, and pulmonary embolism.); and 5) other outcome measures, including frequency of testing, rehospitalization, mortality and overall treatment cost.

Inclusion Criteria

This study had five inclusion criteria. First, the study should have been an RCT. Second, patients must have had a history of thromboembolic diseases, including atrial fibrillation, deep vein thrombosis, or heart valve replacement, that required VKA therapy. Third, patients in the intervention group should have been treated by telemedicine with combined use of portable coagulometers for anticoagulation management. The intervention measures for the control group included ordinary outpatient anticoagulation management and drug dose adjustment according to the INR of each patient. Fourth, outcomes included the effectiveness and safety of telemedicine combined with a portable coagulometer for the anticoagulation management. Effectiveness was represented by the TTR and thromboembolic events, and safety was represented by bleeding events. Fifth, the studies were published in English.

Exclusion Criteria

The exclusion criteria were 1) single use of telemedicine or portable coagulometer; 2) nonrandomized and observational studies or unavailable full-text publication; 3) studies without a control group; 4) repeated reports; and 5) review articles, editorials, guides, case reports, and conference literature.

Literature Quality Evaluation and Analysis

In accordance with the literature evaluation criteria of the Cochrane Systematic Review Manual, the Cochrane risk of bias tool was used to evaluate the risk of bias in randomized controlled trials (RCTs).[34] Funnel plots for assessing the potential publication bias for the reported effect estimates were not constructed due to the small number of included studies ($n<10$).

Statistical Analysis

RevMan 5.3 software (Cochrane) was used for meta-analysis. Heterogeneity was assessed using a chi-square test, and quantitative analysis was performed using I^2. $P<0.05$ was considered statistically significant. $P \geq 0.05$ and $I^2 \leq 50\%$ were considered to represent no heterogeneity, in which case a fixed-effect model was used. Otherwise, a random effect model was used to analyze the combined effect of each risk factor and calculate 95% CIs. In this meta-analysis, a sensitivity analysis was conducted to determine the stability and reliability of the results. Subgroup analyses were conducted explore the between-study heterogeneity.

All procedures followed the PRISMA 2020 statement guidelines (Supplementary Table 1).

Results

Retrieved Articles

A total of 345 articles were screened. After screening the titles and abstracts and eliminating duplicate references, 42 papers were retrieved for full-text evaluation. Based on the inclusion and exclusion criteria described above, 8 studies including 3853 patients were selected for meta-analysis.[35–43] The literature screening flow chart is shown in Figure 1.

Basic Characteristics and Evaluation of Study Quality

The intervention group comprised 1941 patients, whereas the control group comprised 1912 patients. The basic characteristics of the studies, such as total number of patients, mean age, sex, primary indication, and intervention measures, chosen for analysis are presented in Table 1. The quality of the RCTs was evaluated using the Cochrane

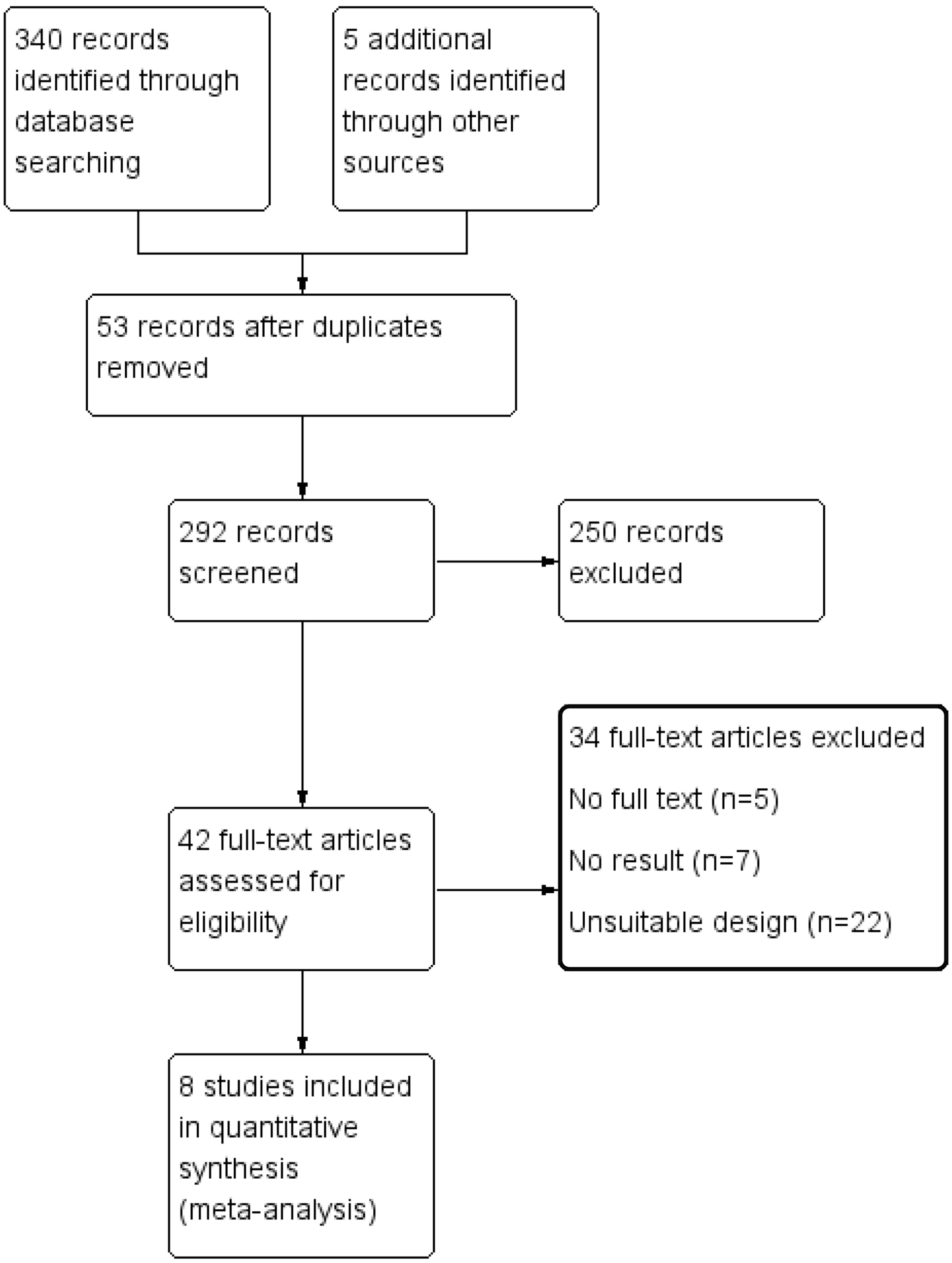

Figure 1 Study flow chart.

Table 1 Summary of Study Characteristics

Study	Location	Dates of Recruitment	Study Duration (Months)	Age /in Years (Mean)	Total Number of Patients	Female	Primary Indication	Type of Anticoagulation	Prosthetic Heart Valves	AF (%)	DVT/PE (%)	Telemedicine	Self- Testing
F. Ryan et al[35,36]	Ireland	2006.7–2007.4	9	58.7	132	42 (31.8)	AF Prosthetic heart valve DVT/PE	Warfarin	49 (37.1)	43 (32.6)	29 (22.0)	Internet web page	CoaguChek XS
Henry et al[37]	Denmark	2006–2008	6	63.6	123	31 (25.2)	AF Prosthetic heart valve DVT/PE Cardiomyopathy Cerebral infarct/ cerebral ischemia	Warfarin	23 (18.7)	71 (57.7)	25 (20.3)	Computer system	CoaguChek XS
Beyth et al[38]	USA	1992.9–1995.10	6	75	325	184 (56.6)	Venous thromboembolism AF Cerebrovascular disease Prosthetic heart valve Peripheral vascular disease	Warfarin	36 (11.1)	54 (29.3)	124 (67.4)	Phone	Coumatrak Protime
Verret et al[39]	Canada	2009.11–2010.01	4	57.7	114	36 (31.6)	AF Prosthetic heart valve	Warfarin	48 (42.1)	58 (50.9)	-	Voicemail message	CoaguChek XS
Chan et al[40]	Hong Kong	2002.11–2004.6	24	59	137	75 (54.7)	AF Prosthetic heart valve DVT/PE	Warfarin	24 (17.5)	72 (52.6)	26 (19.0)	Telephone	CoaguChek Pro DM
Soliman et al[41]	Netherlands	2005.01–2007.06	12	56	58	-	Mechanical aortic valve replacement	Not mentioned	58 (100)	-	-	Website	CoaguChek
David et al[42]	USA	2003.08–2006.05	24	67.0	2922	51 (1.75)	AF mechanical heart valve replacement	Warfarin	684 (23.4)	2229 (76.3)	-	Telephone response system	ProTime Microcoagulation System
Khan et al[43]	UK	Before 2004.03	6	74	79	34 (43.0)	AF	Warfarin	-	79 (100)	-	Telephone	Coaguchek

Abbreviations: AF, atrial fibrillation; DVT, deep vein thrombosis; PE, pulmonary embolism.

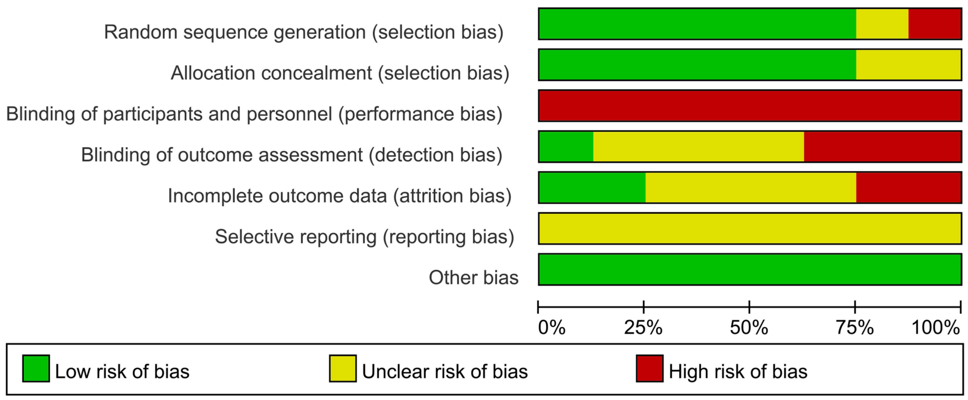

Figure 2 Risk of bias analysis.

systematic review method. The overall quality of the chosen literature was good (Figure 2). In these RCTs, bias was most common in blinding of participants and personnel followed by blinding of outcome assessment and incomplete outcome data.

Meta-Analysis

Time in Therapeutic Range (TTR)

TTR was calculated with the Rosendaal method[23] though Chan[40] also calculated the expanded therapeutic INR range which defined as the therapeutic range INR±0.2 method. Three studies mentioned TTR but the standard deviation was not obtained directly or indirectly and were therefore not included in the analysis. TTR was evaluated in 3305 patients from 5 studies selected, which included 1664 patients in the intervention group and 1641 patients in the control group. The mean TTR values in the intervention group control group of these 5 RCTs were 72% vs 59%,80% vs 75.5%,72.9% vs 53.9%,66.2% vs 62.4% and 71.1% vs 63.2%. And the TTR was significantly higher than that of the control group (mean difference [MD] = 9.50%; 95% CI, 3.16–15.85; I^2 = 87%; P = 0.003) (Figure 3). The results of the subgroup analysis suggest that the study area may be the source of heterogeneity (Supplementary Figure 2).

Major Bleeding Events

Out of these 8 papers, 2 papers gave too vague data or not reported control group data on bleeding events.6 papers reported major bleeding events in the intervention group and control group: 8/163 vs 17/162, 1/68 vs 2/69,147/1465 vs 143/1457, 0/72 vs 1/60, 1/29 vs 1/29, 2/58 vs 1/56. Fixed-effects models were used for meta-analysis of these 6 RCTs. As shown in Figure 4, less bleeding events were recorded in the intervention group, but the difference was no statistically significant (RR =0.96; 95% CI, 0.78–1.18; I^2 = 0%; P =0.68).

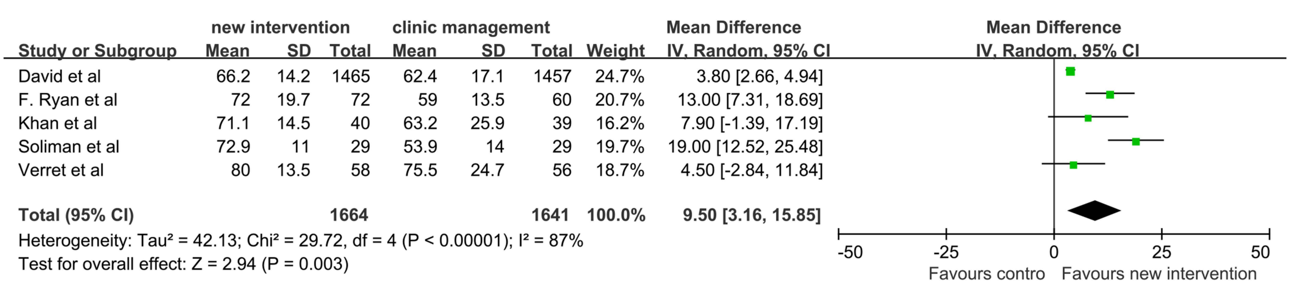

Figure 3 Time in therapeutic range (TTR).

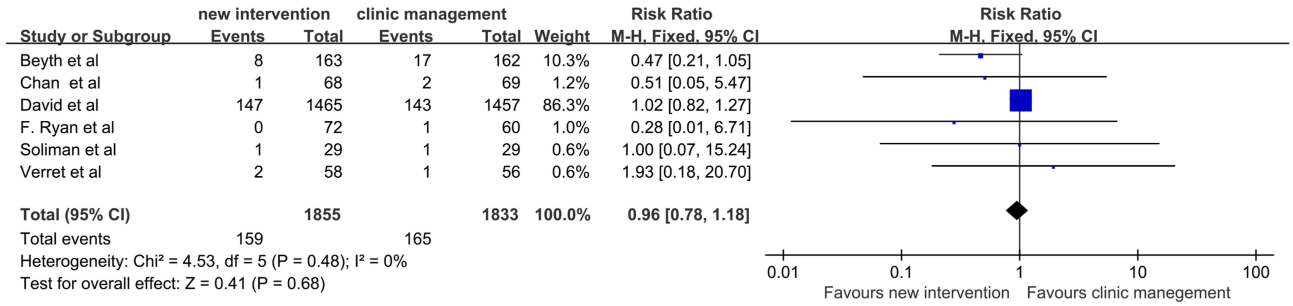

Figure 4 Major bleeding events.

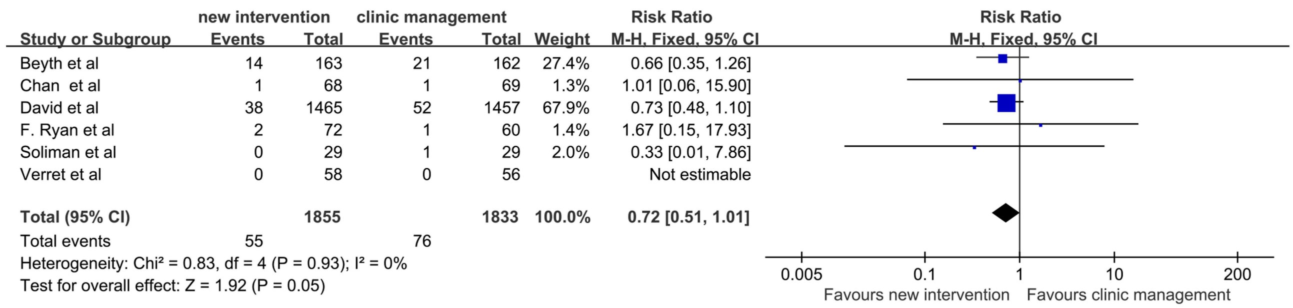

Figure 5 Thromboembolic events.

Thromboembolic Events

A total of 3688 patients from 6 studies were assessed. The thromboembolic events in two groups were: 14/163 vs 21/162, 1/68 vs 1/69, 38/1456 vs 52/1457, 2/72 vs 1/60, 0/29 vs 1/29, 0/58 vs 0/56. A fixed-effects model was used for meta-analysis. Fewer thromboembolic events were recorded in the intervention group than in the control group and the risk ratio suggested a trend toward a better outcome in the intervention group than the control one, but the difference was not statistically significant (RR=0.72; 95% CI, 0.51–1.01; I^2=0%; P=0.05) (Figure 5).

Frequency of INR Testing

Among 3140 patients from 3 studies, comprising 1583 patients in the intervention group and 1557 patients in the control group, the frequency of INR testing was 7.6±5.4 days vs 23.1±18.1 days, 4.6±8 days vs 19.6±6.6 days, 7.4±2.7 days vs 15.3±8.8 days, indicating significant difference between two groups (MD = 12.95 days; 95% CI, 8.77–17.12; I^2 = 92%; P <0.0001) (Figure 6).

Other Results

Rehospitalization

Rehospitalization was described in 2 studies involving 251 patients. As shown below, the difference was not statistically significant (RR=1.39; 95% CI, 0.56–3.46; I^2=0%; *P*=0.48) (Figure 7).

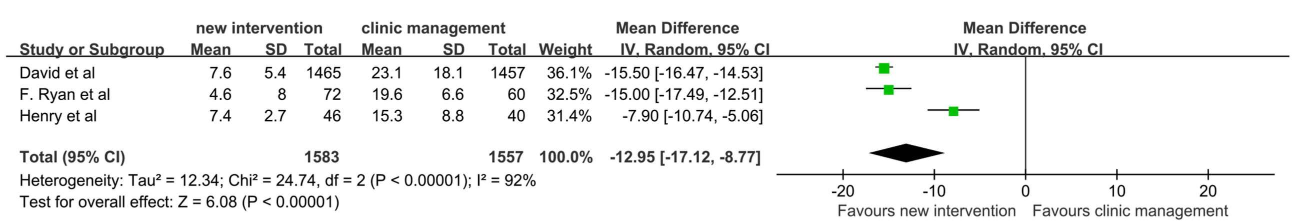

Figure 6 Frequency of testing.

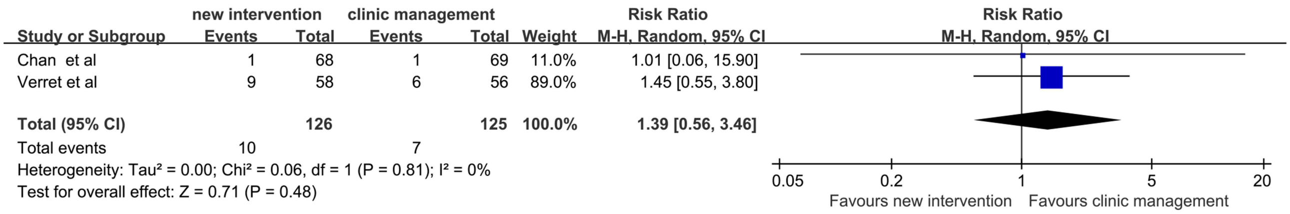

Figure 7 Rehospitalization.

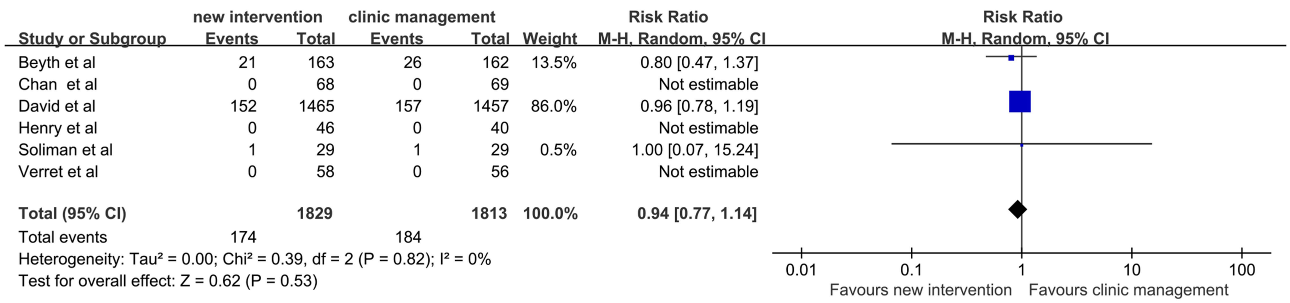

Figure 8 Mortality.

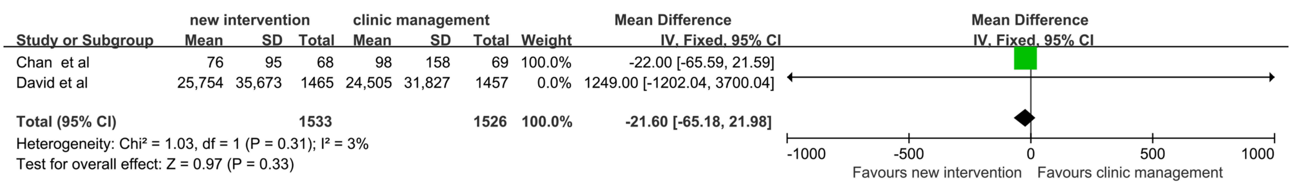

Figure 9 Cost of management.

Mortality

Six studies, comprising 3642 patients, reported patient deaths. Fewer deaths were recorded in the intervention group than in the outpatient management group; however, the difference was not statistically significant (RR= 0.94; 95% CI, 0.77–1.14; I2 = 0%; P= 0.53) (Figure 8).

Costs

Three studies reported findings on medical costs. Because one of these studies reported incomplete data, data from the remaining two studies, comprising 3059 patients, were used for analysis. Cost calculations included health care expense but Ryan[36] included laboratory test cost and medical service provider cost in anticoagulation management service and point of care (POC) devices related costs in patient self-testing group. And Chan[40] assessed the total direct cost per patient: medication, laboratory and diagnostic tests, clinic visits, emergency room visits and hospitalization. No difference in testing costs was recorded between the control group and intervention group (MD= 21.60; 95% CI, –65.18–21.98; I^2 = 3%; *P*=0.33) (Figure 9).

Discussion

Our analysis showed that a management model using portable coagulometers combined with telemedicine was significantly superior to the traditional model in increasing test frequency and improving TTR. And no significant differences in major bleeding events, thrombotic events, rehospitalization rate, mortality, and costs existed between these modalities. The hybrid model improved the stability of treatment but had minimal effect in improving the safety or other outcomes of VKA therapy.

The safety and effectiveness of VKA therapy have been a continual concern for clinicians. Maintaining a stable plasma concentration and reducing bleeding and thrombotic complications are important criteria for evaluating the safety and effectiveness of anticoagulant management models. For warfarin treatment, the TTR is the standard measure to evaluate its quality and effectiveness.[44,45] In fact, genetic characteristics and patient adherence to treatment are important factors in maintaining low TTR.[7,9] Moreover, in 1 study, a TTR < 70 was associated with a switch from VKA to non-VKA oral anticoagulants.[46] However, the implications of our results for clinical practice may be more focused on patients with warfarin, as seven of the included studies were based on patients treated with warfarin. Consistent with the conclusions of most of the research reports,[47–49] patients using portable coagulometers had higher testing frequencies and better TTR than those receiving conventional clinical management. This finding was expected because patients using the hybrid model avoided travel time and medical procedures and could easily perform self-testing at any time. Furthermore, the advantages of increased test frequency are reflected in the improvement in TTR stability, as regular multiple testing can detect trends in coagulation changes sooner, allowing timely implementation of effective intervention. This advantage is more obvious in patients with unstable INR values.[47] Xia et al[49] analyzed the management models used for 16,915 patients receiving anticoagulant therapy and showed that no difference in TTR existed between online and hospital management. However, only one randomized controlled study was included in that analysis. Hence, the evidence level was not high. Consistent with published findings, the reported incidence of thrombosis in patients managed using hospital-based models was more than that of those using the hybrid model,[50–54] but our analysis shows there is no statistically significance in the analysis of major bleeding events and thrombotic events. However, Samsa et al[55] reported patients who underwent remote management had fewer thrombotic events and pointed that better TTR suggests stable hemodynamics, and the thrombosis process is not easily initiated. In our analysis, the hybrid model contributed fewer bleeding events though without the difference between the models while David et al[42] showed difference in reported minor bleeding episode which included 540 and 401 in self-testing group and clinic test group, which was probably due to the more frequent contact between investigators and patients in self-testing group. In fact, due to loss of regular contact, some patients may forget about less serious complications.[47,56] Zhu et al[53] argued that bleeding events had a lower frequency in the internet-based group than in the conventional group. In the future, a more rigorous and standardized study spanning several years will be necessary to address this issue.

Notably, consistent with previous findings,[35,49,57] patients managed using the hybrid model had slightly higher rehospitalization and mortality rates; this finding was, however, not statistically significant. It may likely be due to the low rehospitalization rate and overall mortality caused by warfarin treatment, as well as the relatively small sample sizes of the studies. Therefore, the effects of the two management approaches on mortality events warrant further study with longer follow-up. Our results do not establish that self-testing and telemedicine are significantly superior to traditional outpatient management, regarding safety, but do provide evidence of improved TTR. Given the obvious shortcomings of routine outpatient management, we recommend that patients with barriers adherence with outpatient visits including disabilities and those suffered from work schedule, longer distances or from transportation should consider self-testing. This recommendation is equally important for patients who may be forced into isolation because of the COVID-19 pandemic.

In this meta-analysis study, the total cost of outpatient therapy was not lower than that of the traditional model. Since most of the patients in the included studies were followed up for ≤24 months, the results of this analysis may not be representative of those from longer treatment times. Considering the cost of transportation and absenteeism for outpatient visits, then telemedicine will be more cost-effective over a long enough period of time. If the hybrid model would result in fewer complications, then the spending gap would be further widened.[58–61] Therefore, INR self-testing and online consulting may be more economical in the long term.[43,62]

Our study had some limitations. First, only studies published in English were included in the meta-analysis. Therefore, the analysis did not consider all studies published worldwide, incurring a possible language bias. Second, no new RCTs were reported in the past 3 years. Therefore, our findings may not fully reflect current progress in the application of telemedicine and portable coagulometers for VKA therapy. Third, there was approximately 120 patients in most studies. The small sample sizes were not conducive for further analysis and interpretation of heterogeneity among studies, especially in TTR analysis. Fourth, only three papers classified bleeding events, and two of these reported meaningful minor bleeding events. If a distinction was made between the severity of adverse events, it might reduce potential bias and provide the reader with a more comprehensive understanding of adverse events. Therefore, a large population study could strongly influence these results. High-quality randomized trials are recommended to better assess the advantages and disadvantages of telemedicine interventions in anticoagulation management.

Conclusions

This meta-analysis demonstrated that the management model combining self-testing and telemedicine significantly improved TTR compared, with the traditional intervention. Additionally, no significant differences within the incidence of major bleeding events, thromboembolic events, mortality, and rehospitalizations existed. Nevertheless, studies reported to date were small sample single-center investigations; therefore, multi-center studies with larger sample sizes are needed to further define the safety and effectiveness of this new management approach.

Abbreviations

VKA, vitamin K antagonists; TTR, time in therapeutic range; INR, international normalized ratio; POC, point of care; RCT, randomized controlled trial.

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Disclosure

The authors declare that they have no conflicts of interest in relation to this work.

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