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# The effectiveness of interventions for the implementation of thromboprophylaxis in hospitalized patients at risk for venous thromboembolism: an abridged Cochrane systematic review and meta-analysis of Randomized Controlled Trials (RCT).

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## ABSTRACT

**Objective:** To assess the effectiveness of system-wide interventions designed to increase the implementation of thromboprophylaxis and decrease the incidence of venous thromboembolism (VTE) in hospitalized medical and surgical patients at risk for VTE.

**Design:** Systematic review and meta-analysis of randomised controlled trials (RCTs)

**Data sources:** We searched Medline, PubMed, Embase, BIOSIS, CINAHL, Web of Science, CENTRAL, DARE, EED, LILACS, and clinicaltrials.gov without language restrictions from inception to 7 January 2017, as well as the reference lists of relevant review articles.

**Eligibility criteria for selecting studies:** RCTs that evaluated the effectiveness of system-wide interventions such as alerts, multifaceted, education, and pre-printed orders as compared to no intervention, an existing policy, or another type of intervention.

**Results:** We included 13 RCTs involving 35,997 participants, of which 11 RCTs had data available for meta-analysis. Compared to control, we found absolute risk increases in the prescription of prophylaxis associated with alerts (21% risk difference) and multifaceted interventions (4% risk difference), absolute risk increase in the prescription of appropriate prophylaxis associated with alerts (16% risk difference), and relative risk reductions (64% risk ratio) in the incidence of symptomatic VTE associated with alerts. Computer alerts were found to be more effective than human alerts, and multifaceted interventions with an alert component appeared to be more effective than multifaceted interventions that did not involve an alert, although comparative pooled analyses were not feasible. The quality of evidence for improvement in outcomes was judged to be low to moderate-certainty of evidence.

**Conclusions:** Alerts increased the proportion of patients who received prophylaxis and appropriate prophylaxis, and decreased the incidence of symptomatic VTE. Multifaceted interventions increased the proportion of patients who received prophylaxis but were found to be less effective than alerts interventions.

**Keywords:** venous thromboembolism, deep venous thrombosis, pulmonary embolism, system-wide interventions, thromboprophylaxis.

**Systematic review protocol registration:** CD008201

## WHAT IS ALREADY KNOWN ON THIS TOPIC

- Previous systematics reviews and meta-analyses have reported that the use of alerts, multifaceted interventions, and educational interventions significantly increase the prescription of thromboprophylaxis or appropriate thromboprophylaxis, and the use of computer alerts such as computer-based clinical decision support system was also associated with a significant decrease of post-operative VTE.
- However, the comparative effectiveness of different types of system-wide interventions in increasing the prescription of appropriate thromboprophylaxis and reducing the rate of VTE was still uncertain.
- In general, previous systematic reviews and meta-analyses were mostly based on observational studies.

## WHAT THIS REVIEW ADDS

- This updated Cochrane review and meta-analysis included 13 RCTs involving a large number of participants (N = 35,997 participants).
- This updated review identifies the most effective system-wide intervention, focusing on the high quality evidence of randomized study designs to increase the appropriate use of thromboprophylaxis in hospitals and therefore decrease the rate and the burden of VTE
- Alerts and multifaceted interventions were found to be associated with significant improvements in the prescription of prophylaxis; however, multifaceted interventions appeared to be less effective overall than alerts interventions. The risk of symptomatic VTE was also significantly reduced with the use of alerts interventions.
- These findings support the use of alerts interventions to help clinicians and other healthcare professionals improve the use of appropriate thromboprophylaxis in hospitalized medical and surgical patients at risk of VTE, and thereby reduce the morbidity and mortality associated with VTE in hospital.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- This review was conducted following the *Cochrane Handbook for Systematic Reviews of Interventions.*
- We included all RCTs relevant to our research question.
- We preferentially accounted for clustering designs using the intraclass correlation coefficient (ICC) where available. ICCs were not provided in many study reports, leading to confidence intervals that may be narrower than if clustering had been accounted for.
- The quality of the evidence in this updated review was limited by the methodological quality of included trials.

## INTRODUCTION

Hospitalized medical and surgical patients are at high risk of developing venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism (PE). VTE that occurs during or within three months after hospitalization underlies more than 50% of all cases of the population burden of VTE.[1-3] VTE is a frequent complication in hospitalized medical and surgical patients, a leading cause of mortality and morbidity in hospitalized patients, a leading cause of increased hospital costs and length of hospital stay, and the leading cause of preventable death and disability in hospital.[4-8]

The appropriate use of thromboprophylaxis in hospitalized patients at risk for VTE has been shown to be safe, effective and cost-effective. Therefore, many international clinical practice guidelines have recommended the use of thromboprophylaxis (eg, pharmacologic and/or mechanical modalities) in targeted groups of hospitalized medical and surgical patients at risk for VTE.[9-18] The prevention of VTE was ranked as the number one of 79 strategies aimed to improve patient safety in hospitals,[19] and interventions to increase thromboprophylaxis prescriptions have been classified as a strongly encouraged patient safety practice.[20, 21] Nonetheless, a clear gap exists between the available evidence and the implementation of the appropriate use of thromboprophylaxis into day to day clinical practice.[22-30] System-wide interventions, by reaching the health care system as a whole, could help to improve prescription of thromboprophylaxis and ultimately reduce the risk of VTE in hospitalized medical and surgical patients at risk of VTE.[31]

In our previous Cochrane systematic review, we assessed the effectiveness of various system-wide interventions designed to increase the implementation of thromboprophylaxis in hospitalized medical and surgical patients at risk for VTE.[32] We identified various system-wide interventions such as simple distribution of guidelines, audit and feedback (eg, review of performance); preprinted orders (eg, written, predefined orders, which can be completed by the physician on paper or electronically); the use of automatic reminder systems that include alerts (eg, human alerts, by a trained nurse, pharmacist, or staff member; or computer, electronic alerts); multifaceted approaches that combine different types of interventions (eg, combination of education, audit and feedback, and alerts); and educational interventions, which focus on the teaching and learning process by organizing educational events (eg, grand rounds, self-administered courses).

This article presents the results of an update of our previous Cochrane review on the effectiveness of system-wide interventions designed to increase the use of thromboprophylaxis and decrease the incidence of VTE in hospitalized medical and surgical patients at risk for VTE. In this review, we focus exclusively on the higher level of evidence provided by randomized controlled trials (RCTs), whereas our previous review also included observational studies. The implementation of effective interventions could help clinicians and other health care professionals to improve the use of appropriate thromboprophylaxis in hospitalized medical and surgical patients at risk of VTE, and thereby reduce the morbidity and mortality associated with this preventable hospital complication.

## METHODS

This is an abridged version of an updated Cochrane systematic review.[33] The protocol and the previous Cochrane review can be accessed from the Cochrane Library.[32, 34]

### Inclusion criteria

Study type

We included all types of RCTs, namely RCTs with random or quasi-random (eg, pseudo-randomization such as even or odd date of birth) methods of allocation of interventions, which either randomized individuals (eg, parallel group, crossover, or factorial design RCTs) or groups of individuals (cluster RCTs (CRTs)), and whose interventions aimed to increase the use of prophylaxis and/or appropriate prophylaxis, and/or decrease the proportion of symptomatic or asymptomatic VTE in hospitalized adult patients. The control group comparison could be no intervention, an existing policy, or another type of intervention.
Studies were included if the study design, population, and intervention were clearly described if data were provided separately by intervention group, and for VTE outcomes, if VTE was diagnosed using objective, accepted criteria. Studies and abstracts could be in any language. We excluded observational studies, studies in which the intervention was a simple distribution of published guidelines, and studies whose interventions were not clearly described.

Participants
Participants included hospitalized adult medical or surgical inpatients, their physicians, residents or nurses, or, in the case of CRTs, the cluster unit (eg, ward, hospital, and physician practice).

Interventions
Any strategies targeted to individuals or to cluster units that aimed to increase the use of thromboprophylaxis in hospitalized patients at risk for VTE and/or decrease the rate of symptomatic or asymptomatic VTE. Examples of interventions include alerts (eg, computer alerts or human alerts), multifaceted interventions (eg, combination of education, audit and feedback, and alert), educational interventions (eg, grand rounds, self-administered course), and pre-printed orders interventions (eg, written predefined orders that can be completed by the physician on paper or electronically if they choose to).

Outcomes
The primary outcome of interest was the increase in the proportion of patients who received either pharmacologic or mechanical prophylaxis.

Secondary outcomes, described in the full Cochrane review, as summarized below:
1. Increase in the proportion of patients who received appropriate prophylaxis (defined by study authors as appropriate according to consensus, local, or international thromboprophylaxis guidelines);
2. Decrease in the proportion of patients who develop any, symptomatic, or asymptomatic VTE;
3. Decrease in the number of deaths;
4. Safety of the intervention.

**Search methods**
We did a systematic literature database search in Medline (Ovid), PubMed, Embase (Ovid), BIOSIS Previews (Ovid), CINAHL, Web of Science, Cochrane (including the Cochrane Central Register of Controlled Trials (CENTRAL), the Database of Abstracts of Reviews of Effects (DARE) and the NHS Economic Evaluation Database (EED)), Latin American and Caribbean Health Sciences Literature (LILACS) and clinicaltrials.gov from inception to 28 July 2015. After 28 July 2015, we updated the literature search monthly until 7 January 2017, when our database was closed. The search strategies comprised a combination of Medical Subject Headings (MeSH) or their equivalent (where available), keywords, truncations and Boolean operators (See Supplement). This search strategy is available in the full Cochrane review. We also hand searched the reference lists of relevant retrieved studies including narrative and systematic reviews to find additional potentially relevant articles from inception to 7 January 2017. Studies of any languages were searched.

**Study selection**
Two review authors independently reviewed titles, abstracts, and full-texts of each study and indicated on a Study Eligibility Form if it should be included, excluded, or undecided. Disagreements regarding study inclusion were resolved by discussion between the two review authors and, if necessary, by involving a third independent review author.

**Data extraction and handling of missing data**
Two review authors independently extracted data from the included articles. The data obtained for each study were entered in duplicate into two identical databases that were designed by Information Management Services of the Lady Davis Institute in Montréal, Canada. The two databases were compared for inaccuracies and any data entry errors were corrected. If agreement on the data entered for a given data field could not be reached between the two extractors, a third extractor was consulted. A third, final database was populated with the final corrected data.

**Time point of outcome assessment**
We used the end of trial follow-up for all outcomes as all included studies were CRTs or parallel group trials, and there were no cross-over trials. For withdrawals whether or not due to adverse events, we used the longest on-treatment follow-up data available. For studies with more than one time point of outcome assessment, we used the most recent follow-up data.

**Risk of bias of studies**
The methodological quality of included trials was independently assessed by two review authors based on the Cochrane Collaboration's tool for assessing the risk of bias.[35] Disagreements were resolved by discussion with co-authors. We assessed all seven domains that are potential sources of bias, and rated them as high, low, or unclear risk of bias (ROB). We assessed all items listed as other potential sources of bias including the design-specific risks of bias for CRTs, and multiple intervention studies.[35] We also assessed the overall ROB for each of the included studies (See supplement Table S1).

**Data analysis**
We evaluated the effectiveness of system-wide interventions by calculating pooled risk difference (RD) for the outcomes 'proportions of participants who received prophylaxis (RP)' and 'proportions of participants who received appropriate prophylaxis (RAP)' or relative ratio (RR) for outcomes with expected low events rates such as VTE, mortality, and safety based on the Cochrane Handbook recommendations for the choice of measure of effect.[35] We calculated a summary statistic for each intervention category (alerts, multifaceted interventions, educational interventions, and pre-printed orders) and associated outcome using a random effects model when there were sufficient studies to pool results (≥ 3 studies). We used Review Manager version 5.3 and SAS version 9.4 for all data analyses. We preferentially used effect estimates for which the variance had been adjusted to account for the clustered nature of the data. Adjustment for the clustered design was only feasible for the meta-analysis of multifaceted interventions. One of the included studies evaluated more than one intervention.[36] Meta-analysis was performed within the control group and each intervention group as recommended in the Cochrane Handbook. We did not use statistical methods to impute missing values or model missing data. Four original investigators were contacted for missing data;[37-40] only two of them were able to provide additional data.[38, 40]

**Quality of evidence (GRADE)**
We used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach to assess the quality of evidence for each outcome that we were able to

meta-analyzed, with the quality of evidence graded from high (best) to very low (worst).[41] The five GRADE considerations (risk of bias, indirectness of evidence, inconsistency of results, imprecision of results, and publication bias) were assessed according to the methods and recommendations in the Cochrane Handbook.[35]

### Patient involvement

No patients were involved in the development of this systematic review. However, we are planning to involve patients in the dissemination of results via interactive exchanges between healthcare providers, patient partners, clinicians and policy makers.

## RESULTS

### Included studies

From 12,920 records identified, 16 RCTs published up to 7 January 2017 were potentially relevant to our research question, of which 13 RCTs involving a total of 35,997 participants met our inclusion criteria (**Figure 1**). This included five new trials since our last review published in 2013.[32] Characteristics of included studies are reported in **Table 1**. Detailed characteristics of included and excluded studies are available in the full Cochrane review.[33]

The following type of interventions and comparisons were reported in the 13 trials:

- Six trials evaluated an alerts intervention compared to the standard of care. Of these, three used a computer alert,[38, 42, 43] and the other three, a person such as a trained nurse, a pharmacist or a hospital staff member as a human alert.[44-46]
- Six trials evaluated a multifaceted intervention that combined different types of interventions such as education, audit and feedback, and alert, compared to the standard of care,[36, 39, 40, 47, 48] or to another type of intervention (combination of educational session, dissemination of educational material, audit, and feedback).[49] Of these trials, only one included an alert component.[48]
- One trial evaluated a pre-printed orders intervention using predefined anticoagulant prescription forms as a passive reminder to use thromboprophylaxis, compared to the standard of care.[50]
- One trial reported a head-to-head comparison among interventions. This trial evaluated an educational intervention that used a hospital-administered course with self-assessment examinations compared to the standard of care and to a multifaceted intervention .[36]

Two of the 13 trials were not included in meta-analyses (one because of missing raw data on study outcomes,[39] and one was the only RCT to study a pre-printed orders intervention).[50] One type of comparison (educational intervention compared to the standard of care) was not included in meta-analyses due to the lack of studies assessing this intervention.[36]

**Table 1:** Characteristics of included studies

| Author | Study design | Study setting | Number of patients (centers) | Type of patients | Participants (gender, age) | System-wide intervention | Comparators | Follow-up (timing for outcome assessment) | Primary outcome | Secondary outcomes |
|---|---|---|---|---|---|---|---|---|---|---|
| **Anderson et al, 1994**[36] | Cluster RCT | Community, USA | 798 patients (15 centers) | Medical and surgical patients | Male 44% Mean 70.7 years | Multifaceted | No intervention vs educational vs multifaceted intervention | 3 months | RP | RAP, VTE, mortality, and safety outcomes not assessed |
| **Overhage et al, 1996**[43] | Cluster RCT | Academic, USA | 58 patients (1 center) | Medical patients | Male 50% Mean (SD), 51 years (18) | Alerts (computer alert) | No intervention (usual care) vs intervention | 6 months | RP | RAP, VTE, mortality, and safety outcomes not assessed |
| **Dexter et al, 2001**[38] | Cluster RCT | Academic, USA | 1,326 patients (1 center) | Medical patients | Male 50% Mean 53.2 years | Alerts (computer alert) | No intervention (standard care) vs intervention | 18 months | Not assessed | RAP assessed<br>VTE, mortality, and safety outcomes not assessed |
| **Kucher et al, 2005**[42] | Parallel group, quasi-RCT | Academic, USA | 2,506 patients (1 center) | Medical and surgical patients | Male 52.9% Median (range) 62.5 years (18-99) | Alerts (computer alert) | No intervention (usual care) vs intervention | 90 days | RP | RAP not assessed.<br>VTE, mortality, and safety outcomes assessed |
| **Fontaine et al, 2006**[50] | Cluster RCT | Academic, France | 719 patients (30 centers) | Medical patients | Male 51.5% Mean 72 years | Pre-printed orders | No intervention (usual practices) vs intervention; baseline vs post intervention | 1 day | RP | RAP described in a figure (raw data not available)<br>VTE, mortality, and safety outcomes not assessed |
| **Labarere et al, 2007**[49] | Cluster RCT | Academic/ Community, France | 812 patients (50 centers) | Medical patients | Male 34.2% Median (range) 82 years (75–90) | Multifaceted | Intervention targeted at physicians only vs multifaceted intervention targeted at physicians and nurses | Not clearly reported | RP | RAP and mortality outcomes not assessed.<br>VTE and safety outcomes assessed |
| **Piazza et al, 2009**[46] | Parallel group RCT | Academic/ Community USA | 2,493 patients (25 centers) | Medical and surgical patients | Male 53.7% Mean (SD), 68.8 years (15.2); Median (range) | Alerts (human alert) | No intervention (usual care) vs intervention | 90 days | RP | RAP and safety outcomes not assessed.<br>VTE and mortality assessed |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 72.5 years (19 to 103) | | | | | |
| **Garcia et al, 2009**[45] | Cluster, quasi-RCT | Academic, USA | 140 patients (1 center) | Medical patients | Male 50.7%<br>Mean (range) 59.5 years (20-97) | Alerts (human alert) | No intervention (usual care) vs intervention | 36 hours | Not assessed | RAP assessed.<br>VTE, mortality and safety outcomes not assessed. |
| **Hinchey et al, 2010**[39] | Cluster, quasi-RCT | Academic/ Community, USA | 2,071 patients (16 centers) | Medical patients | Male 50.1%<br>Mean 70 years | Multifaceted including reminders (standard orders, pathways, protocols, standardized dysphagia screens, atrial fibrillation reminder stickers) | Control group (audit, feedback, and benchmark information) vs intervention | 6 months | RP (raw data not available) | RAP, VTE, mortality, and safety outcomes not assessed |
| **Chapman et al, 2011**[44] | Parallel group RCT | Hospital type reported, Australia | 354 patients (number of centers not reported) | Medical patients | Non available | Alerts (human alert) | Standard care vs intervention | 3 months | Not assessed | Symptomatic VTE assessed.<br>RAP, mortality, and safety outcomes not assessed |
| **Pai et al, 2013**[47] | Cluster RCT | Academic/ Community, Canada | 2,611 patients (6 center) | Medical patients | Male 46.8%<br>Median (range) 72 (18-102) | Multifaceted | No intervention (usual care) vs intervention | 16 weeks | RP | RAP assessed.<br>VTE, mortality, and safety outcomes not assessed |
| **Cavalcanti et al, 2016**[40] | Cluster RCT | Academic/ Community, Brazil | 6761 patients (118 Intensive Care Units, number of centers not reported) | Medical patients | Male 54.2%<br>Mean (SD), 59.6 years (19) | Multifaceted including a general reminder (SMS messages) to complete checklists that targeted a broad spectrum of care processes including thromboprophylaxis | Standard care vs intervention | 60 days | RP | All-cause mortality assessed.<br>RAP, VTE, and safety outcomes not assessed |
| **Roy et al, 2016**[48] | Cluster RCT | Academic/ Community, France | 15,351patients (27 centers) | Medical patients | Male 50%<br>Median (range) 73.5 years (58-83) | Multifaceted including an alert component (computerized reminders) | No intervention (usual care) vs intervention | 3 months | RP | All secondary outcomes assessed |

**System-wide interventions** were categorized into four groups: alerts (eg, computer alerts or human alerts); multifaceted interventions (eg, combination of education, audit and feedback, and alert), educational interventions (eg, grand rounds, self-administered course), and pre-printed orders (eg, written predefined orders that can be completed by the physician on paper or electronically if they chose to). RCT: randomized controlled trials; RP: proportion of participants who received prophylaxis; RAP: proportion of participants who received appropriate prophylaxis; VTE: venous thromboembolism.

## Methodological quality of included studies

The methodological quality of the included studies was variable (**Figure 2**). The overall ROB was high in two trials due to the existence of potential selection, performance, attrition, reporting, and other sources of bias.[39, 45] These trials were excluded from meta-analyses due to missing outcome data,[39] and as a sensitivity analysis.[45] The assessment of the certainty of the evidence for improvement in outcomes was limited by the incomplete reporting of study design features that did not allow proper scoring of relevant study design features such as sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. While we were able to account for clustering using the reported intraclass correlation coefficient (ICC) where available,[40, 47-49] in many cases the ICC was not provided,[36, 38, 39, 43, 45, 50] leading to confidence intervals (CIs); that may be narrower than if clustering had been adequately accounted for.

## Effects of interventions

Table 2 summarizes the results from the meta-analyses conducted for the primary and secondary outcomes, and **Figure 3** and **Figure 4** depict the forest plots for the meta-analyses. Additional tables summarizing the results of individual studies by intervention and by outcome when there were fewer than three studies to be able to pool results are reported in detail in the full Cochrane review.[33]

### Comparison of alerts with standard care

Alerts interventions were associated with three types of changes:

- A 21% absolute risk increase in the proportion of patients who received prophylaxis (RD 0.21, 95% CI 0.15 to 0.27; three studies; 5057 participants; $I^2$ = 75%; low-certainty evidence);
- A 16% absolute risk increase in the proportion of patients who received appropriate prophylaxis (RD 0.16, 95% CI 0.12 to 0.20; three studies; 1820 participants; $I^2$ = 0; moderate-certainty evidence);
- A 36% relative risk decrease in the risk of symptomatic VTE at 3-months post-intervention (RR 0.64, 95% CI 0.47 to 0.86; three studies; 5353 participants; $I^2$ = 15%; low-certainty evidence) (**Figure 3**).

Subgroup analyses to address statistical heterogeneity were not feasible as there were not enough studies to pool subgroup results and distinguish chance from subgroup differences.

### Comparison of multifaceted interventions with standard care or another intervention

Multifaceted interventions were associated with a small increase in the proportion of patients who received prophylaxis in the intervention groups, with no heterogeneity between individual studies when cluster design effect adjustment was performed (RD 0.04, 95%CI 0.02 to 0.06; five studies; 9198 participants; $I^2$ = 0%; moderate-certainty evidence) (**Figure 4**).

### Comparison of educational interventions with standard care

One study that compared the effectiveness of using educational and multifaceted interventions to control, reported that educational interventions were associated with a non- significant

decrease in the proportion of patients who received prophylaxis (RD -0.02, 95% CI -0.09 to 0.05; 1 study; 1,311 participants), but were less effective than a multifaceted intervention.[36]

Comparison of pre-printed orders with standard care

One study reported the use of written thromboprophylaxis prescription aids, which was associated with a non- significant decrease in the proportion of patients who received prophylaxis compared to the group that did not receive pre-printed orders (RD -0.05, 95% CI -0.12 to 0.02; one study; 719 participants).[50]

Head-to-head comparisons

One study reported comparisons between an educational intervention (continuing medical education) and a multifaceted intervention (continuing medical education in association with a quality assurance program), each compared to a control group (standard of care). The educational intervention was associated with a 2% decrease in the proportion of patients who received prophylaxis (RD -0.02, 95% CI -0.09 to 0.05) and the multifaceted intervention was associated with a 4% increase in the proportion of patients who received prophylaxis (RD 0.04, 95% CI -0.03 to 0.11).[36]

**Table 2:** Summary of main findings

| Intervention | Outcome | Number of Trials | Number of Patients | Comparative risk (Study population) | | Measure of association (95% CI), $I^2$ Statistic | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|---|---|
| | | | | Control | Intervention | | |
| Alerts Interventions | Received prophylaxis [a] | 3 studies | 5,057 participants | 18 % | 39 % | **RD** 0.21 [0.15, 0.27]; 75% | ⊕⊕⊖⊖ **Low**[1] |
| | Received appropriate prophylaxis [a] | 3 studies | 1,820 participants | 30 % | 46 % | **RD** 0.16 [0.12, 0.20]; 0% | ⊕⊕⊕⊖ **Moderate**[2] |
| | Symptomatic VTE | 3 studies | 5,353 participants | 6 % | 4 % | **RR** 0.64 [0.47, 0.86]; 15% | ⊕⊕⊖⊖ **Low**[3] |
| Multifaceted interventions | Received prophylaxis [b] | 5 studies | 9,198 | 47% | 51% | **RD** 0.04 [0.00, 0.06]; 0% | ⊕⊕⊕⊖ **Moderate**[4] |

[a] Clustered trials did not provide sufficient data (intra-class correlation (ICC) or adjusted confidence intervals) for us to pool cluster adjusted estimates.
[b] ICCs were available for 4/5 trials included in this meta-analysis. Adjustment for the cluster design effect was performed via reported ICCs and no ICC was applied to the one trial that did not report an ICC. Total patients are lower due to the cluster design effect applied to the numbers of events and participants.

**GRADE assessment**
[1] We downgraded the level of certainty of evidence from high to low based on the following reasons: serious study limitations and some inconsistency of pooled results.
[2] We downgraded the level of certainty of evidence from high to moderate based on the following reasons: serious study limitations.
[3] We downgraded the level of certainty of evidence from high to low based on the following reasons: serious study limitations and some imprecision of pooled results related to the small number of events.
[4] We downgraded the level of certainty of evidence from high to moderate based on the following reasons: serious study limitations

### Additional analyses

A sensitivity analysis removing the high ROB trial in the meta-analysis of studies with alerts interventions,[45] did not substantially impact the point estimate. A sensitivity analysis for the estimation of missing ICCs in the meta-analysis of studies with multifaceted interventions showed similar point estimates and similar variance. The sensitivity analyses using a fixed-effect approach did not change our point estimates. Results for the influence and sensitivity analyses are reported in detail in the full Cochrane review.[33]

### Planned analyses without sufficient data for meta-analysis

Mortality and safety outcomes such as major and minor bleeding did not appear to differ in frequency between interventions and control groups. However, we were unable to provide pooled effect estimates on the relative effectiveness of each type of intervention for all primary and secondary outcomes.

While not directly compared to each other, computer alerts seemed to be more effective than human alerts in increasing the proportion of patients who received appropriate prophylaxis and reducing the risk of symptomatic VTE at 3 months post intervention. Multifaceted interventions that included an alert component also appeared to be more effective than those without an alert component in increasing the proportion of patients who received prophylaxis and appropriate prophylaxis, although there were not enough studies to conduct a pooled analysis.

All outcomes and interventions subgroup categories without sufficient data for meta-analysis are reported in detail in the full Cochrane review.[33]

## DISCUSSION

### Summary of main results

The main new finding from our updated review which was focused on RCTs only, was that alerts interventions, whether computer alerts or human alerts, increased the absolute proportion of patients who received thromboprophylaxis by 21%, increased the absolute proportion of patients who received appropriate thromboprophylaxis by 16%, and decreased the relative incidence of symptomatic VTE at 3-month post treatment by 36%. Multifaceted interventions were associated with a modest 4% absolute increase in the prescription of thromboprophylaxis.

### Quality of evidence and study limitations

This updated review improves upon prior meta-analyses conducted in this area as it was restricted to RCTs only, thus providing a higher level of evidence, less widely differing estimates (i.e., heterogeneity in results) across studies, more precise (i.e., narrower confidence intervals) pooled effects due to the reduced between-study variance, lower ROB of included studies, and better quality of evidence for improvement in outcomes. Even if meta-analyses in our updated review were based on small numbers of studies, we included a large number of patients (N = 33,207 participants). We were able to account for clustering in one meta-analysis. The certainty of evidence for the improvement in outcomes was low or moderate in this updated review, as compared with very low in our previous review. We downgraded the level of certainty of the evidence from high to moderate or low because of methodological limitations in the included RCTs, and/or unexplained statistical heterogeneity in the pooled result, and/or imprecision of pooled results related to the small number of VTE events (less than 300). Despite the fact that

we could not assess for the presence of publication bias because all analyses were underpowered to distinguish chance from real asymmetry, there was a nearly symmetrical distribution of individual trials around the pooled estimate of effect in each meta-analysis.

Due to the lack of published trials, we were unable to provide quantitative estimates of the effects of the different types of system-wide interventions on the prescription of thromboprophylaxis and on key outcomes such as appropriate thromboprophylaxis, mortality, and safety outcomes.

### Agreements and disagreements with other reviews

Our findings are in agreement with other previous systematic reviews.[31, 32, 51-58] Only two of the previous reviews performed a meta-analysis.[32, 54] In our previous review, multifaceted interventions were found to be the most effective system-wide intervention in observational studies.[32] In the most recent systematic review and meta-analysis, the use of computer-based clinical decision support system in observational studies was associated with an increased rate of ordering appropriate thromboprophylaxis and a reduced rate of VTE in hospitalized surgical patients.[54] The additional findings from our updated review compared with other reviews are most likely due to the inclusion of the largest number of RCTs involving a large number of hospitalized medical and surgical patients at risk for VTE.

### Implications for practice

Our findings provided low- to moderate-certainty evidence to support the use of system-wide interventions to improve the prescription of thromboprophylaxis and decrease the incidence of symptomatic VTE in hospitalized adult medical and surgical patients at risk for VTE. Our results suggest that alerts interventions are associated with significant improvements in the prescription of prophylaxis. We also found that in individual studies that reported the outcome symptomatic VTE, the risk of symptomatic VTE was significantly reduced with alerts interventions, particularly with computer alerts. Multifaceted interventions were less effective overall than alerts interventions. Due to a lack of studies, we were not able to assess if multifaceted interventions that include an alert component were more effective than multifaceted interventions that did not include an alert.

### Implications for research

The effect of system-wide interventions on important clinical outcomes such as VTE, mortality and safety outcomes should be assessed in well-designed multicenter RCTs that ideally include university-affiliated and community hospitals of various sizes. In addition, rates of prescription of appropriate prophylaxis should be reported. Future research should also evaluate costs related to the implementation of various system-wide interventions. Finally, research should be conducted to better understand why such interventions do not have a larger effect on prescribing behaviours.

## FOOTNOTES

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Dr Kahn holds a Tier 1 Canada Research Chair in Venous Thromboembolism. Dr Kahn, Dr Tagalakis, Ms Emed, Dr Roussin, and Dr Geerts are investigators of the CanVECTOR Network (CIHR funding reference CDT-142654). Dr Klil-Drori is supported by a CanVECTOR fellowship award. Dr Filion is supported by a Junior II salary support award from the Fonds de recherche du Québec - Santé (Quebec Foundation for Health Research).

**Competing interests:** The authors of this review have not received any funding to undertake this review other than the peer-reviewed grant noted above. The authors report the following declarations of interest:

SK has received grant support from public granting agencies (CIHR) for research on the treatment of venous thrombosis. She participated in industry-sponsored advisory board meetings (Boehringer-Ingelheim, Servier Canada, one meeting for each entity), on the treatment of venous thrombosis and provided expert testimony for the Canadian Medical Protective Association. SK also reports that Sanofi Aventis has partnered with her institution to help create a center of excellence in thrombosis and anticoagulation.

AJK: AJK's institution has received funds from the Young Investigator Award from the American Society of Clinical Oncology Conquer Cancer Foundation. AJK reports receiving payments from Bristol Myers Squibb for lectures.

JD: JD reports receiving funds from board memberships of Bayer, Boehringer-Ingelheim, Bristol-Myers-Squibb, Daiichi-Sankyo, Pfizer, and Sanofi; consultancy fees from Actelion, Janssen Research, and Development; funds for speaking at educational activities; royalties from the Merck Manual, Up-to-Date; JD's institution has received a grant from Boehringer-Ingelheim.

JE: JE received an honorarium for participation in a single meeting (focus group) with LEO Pharma for work unrelated to the submitted review.

AR: AR reports board membership and consultancy activities for BMS, BI, Pfizer, and Bayer, and received payment for lectures from BMS, BI, Bayer, and Pfizer not related to this review. AR also reports that his institution has received a CIHR grant for AIDS vascular research, and payment for development of educational presentations from BI, Bayer, BMS, and Pfizer for the preparation of university-accredited symposiums and slide kits.

VT: VT has received, and currently holds grant support from the CIHR for research in venous thrombosis; has engaged in lectures sponsored by companies that manufacture anticoagulants (Leo Pharma, Bristol Myer Squibb, and Pfizer); has received a grant from a manufacturer of an anticoagulant (Sanofi Aventis).

MM: reports receiving funds from American Academy of Clinical Toxicology for creation of search strategies for systematic reviews, and from International Team for Implantology for peer reviewing of search strategy.

WG: WG reports consultancy (Bayer Healthcare, Pfizer, Sanofi) and payment for lectures (Bayer Healthcare, Leo Pharma, Sanofi). Other support has been received by his institution from Sanofi for clinical and quality of care initiatives in thromboembolism within and outside of his institution. WG reports that these relationships in no way impact on his involvement with this Cochrane review.

SK, JD, JE, AR, VT, and WG are investigators of the CanVECTOR Network; the Network receives grant funding from the Canadian Institutes of Health Research (Funding Reference: CDT-142654). AJK is a fellow of the CanVECTOR Network; the Network receives grant funding from the Canadian Institutes of Health Research (Funding Reference: CDT-142654).

GD, DM, AP, KBF: None declared.

**Ethics approval:** Not needed.

**Transparency declaration:** The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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**Data sharing:** No additional data available.

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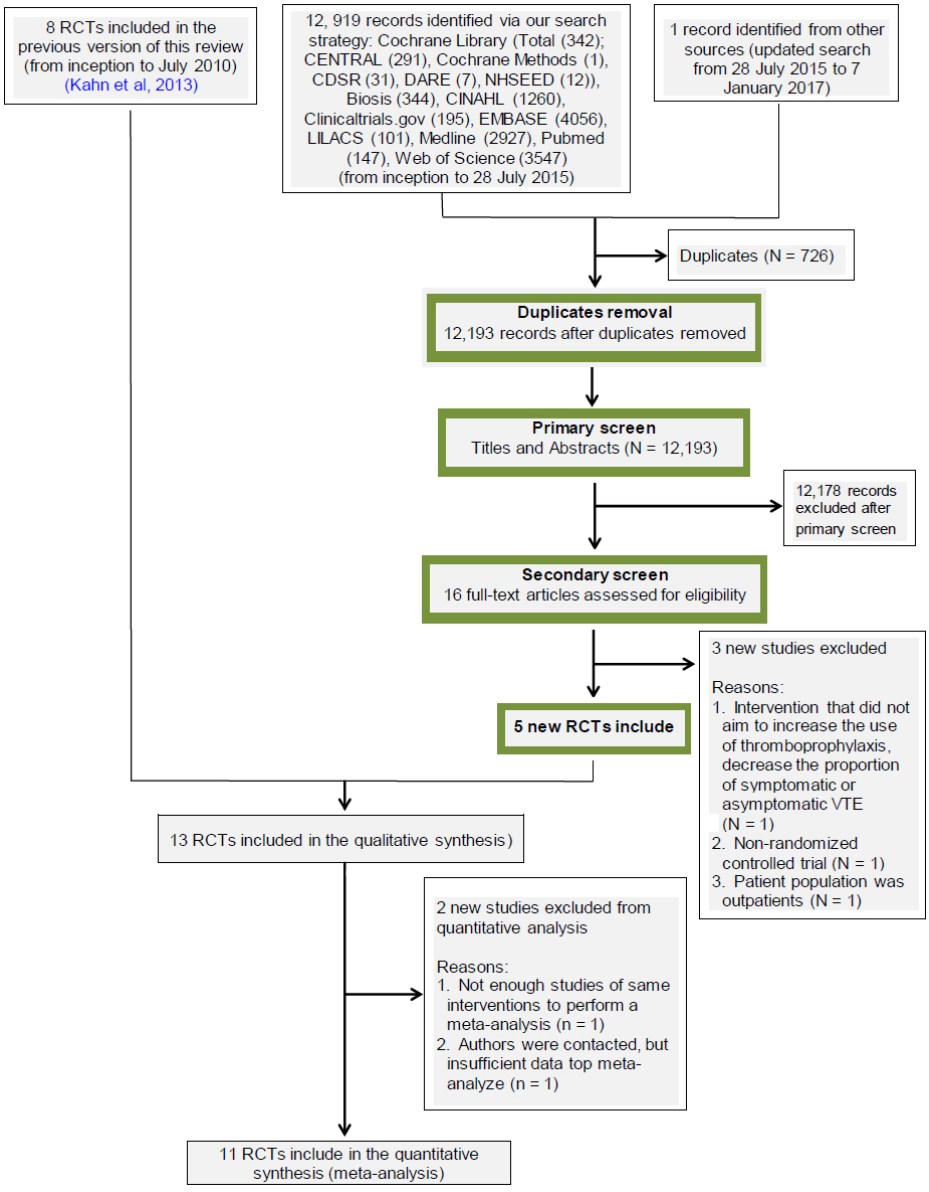


Figure 1. PRISMA flow diagram for Cochrane review updates demonstrating the outcomes of the search process, and the inclusion of studies in the updated Cochrane systematic review and meta-analysis
CDSR: Cochrane Database of Systematic Reviews
CENTRAL: Central Register of Controlled Trials
CINAHL: Cumulative Index to Nursing and Allied Health Literature
DARE: Database of Abstracts of Reviews of Effects
LILACS: Latin American and Caribbean Health Sciences Literature
NHSEED: NHS Economic Evaluation Database
RCT: Randomized Controlled Trial

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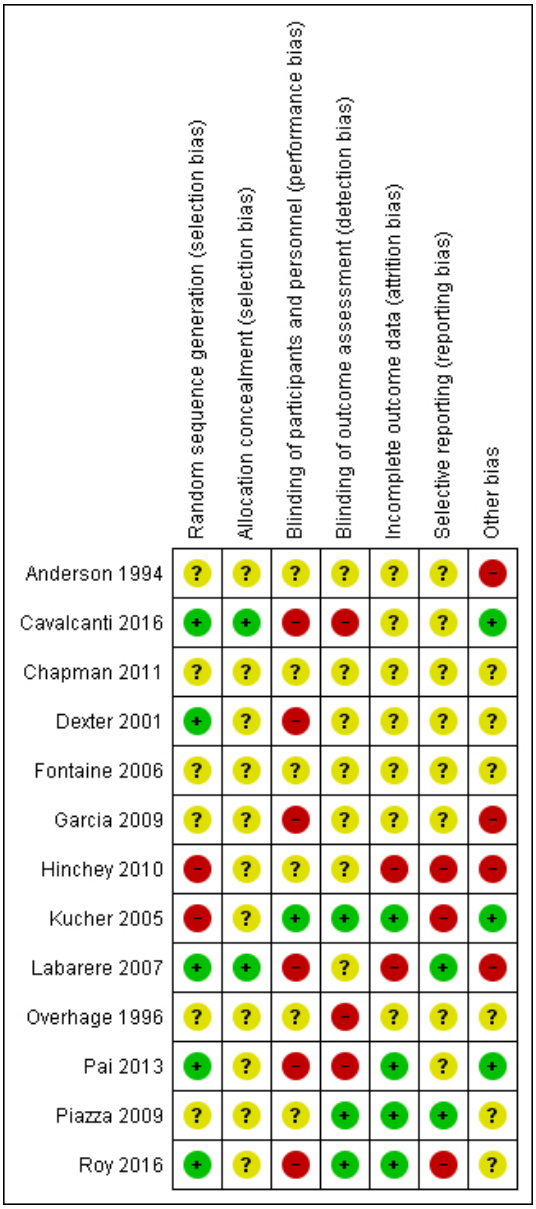


Figure 2. Methodological quality graph: review authors' judgments about each methodological quality item for each included study

85x193mm (96 x 96 DPI)

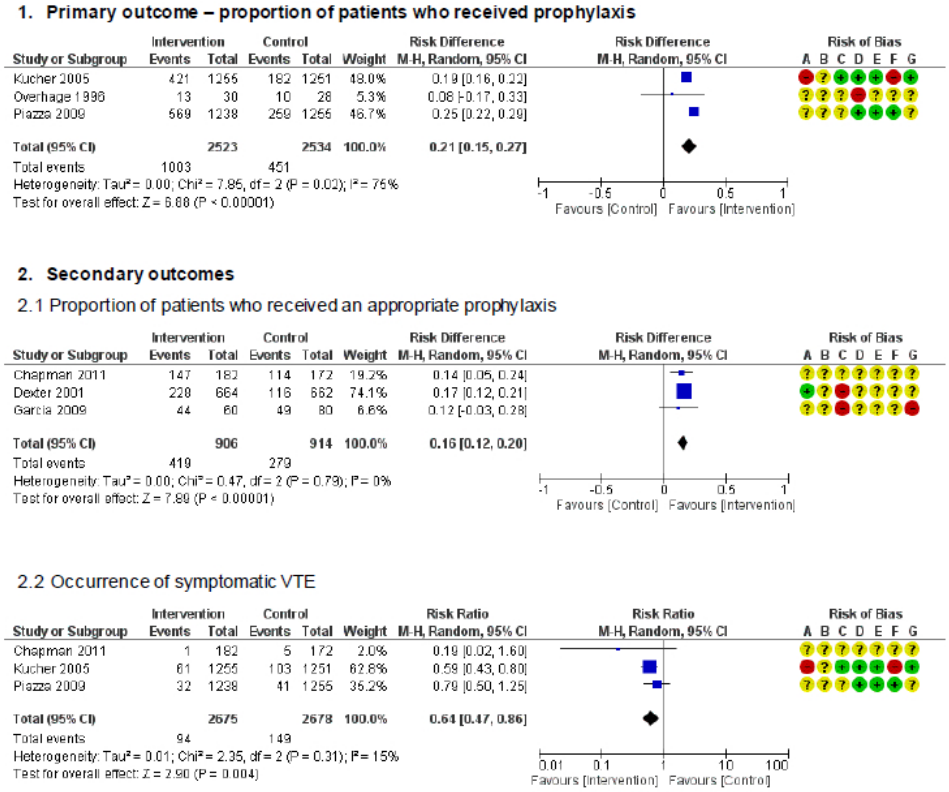


Figure 3. Forest plot and risk of bias assessment - comparison of alerts intervention with no intervention (standard care)

Risk of bias legend:

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

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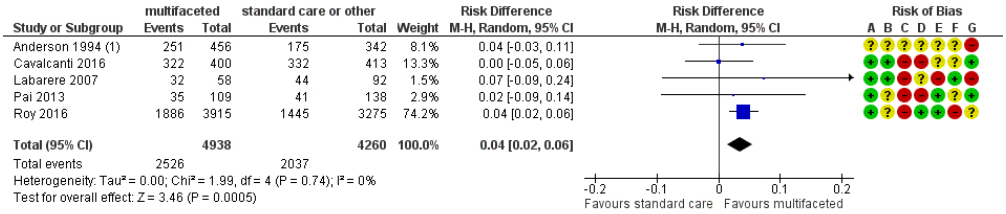


Figure 4. Forest plot and risk of bias assessment - comparison of multifaceted intervention with no intervention (standard care) or another intervention for the primary outcome 'Proportion of patients who received prophylaxis'

(1) Intraclass correlation coefficient not reported

Risk of bias:

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

252x56mm (96 x 96 DPI)

## SUPPLEMENTAL MATERIAL

# The effectiveness of interventions for the implementation of thromboprophylaxis in hospitalized patients at risk for venous thromboembolism: an abridged Cochrane systematic review and meta-analysis of Randomized Controlled Trials (RCT).

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## Search Criteria

### 1. MEDLINE Ovid and Cochrane

1. exp Thrombosis/pc
2. exp Embolism/pc
3. (thrombosis or thrombotic or thrombus or thrombi or thromboembol*).tw.
4. (emboli* or embolus).tw.
6. clot?.tw.
7. (DVT or VTE or PE).tw.
8. or/1-7
9. exp Anticoagulants/
10. anticoagulant*.tw.
11. (hydroxycoumarins or acenocoumarol or acenocoumar* or minisintrom or nicoumalone or s?nc?umar or sintrom or s?nthrom* or ancrod or ancrod or arvin or venacil or agkistrodon or arwinor or (blood adj3 coagulat* adj3 inhibit*) or "citric acid" or uralyt or dalteparin or tedelparin or fr-860 or fr860 or dalteparin or kabi2165 or kabi-2165 or fragmin* or "dermatan sulfate" or chondroitin or dextran or dextrans or hemodex or promit or macrodex or saviosol or rheodextran or polyglucin or hyskon or rheomacrodex or infukoll or rheopolyglucin or rheoisodex or rondex or dic?umarol or dicoumarin or bishydroxycoumarin or edetic or tetracemate or calcitetracemate or edta or ethylenedinitrilotetraacetic or edetate or (calcium adj3 tetacine) or versenate or coprin or edathamil or versene or dinitrilotetraacetate or "chelaton 3" or enoxaparin* or pk10169 or "pk 10169" or emt-967 or emt96* or clexane or lovenox or emt-966 or (ethyl adj3 biscoumacetate) or ethyldicoumarol or pelentan or tromexan or carbethoxydicoumarol or foy or gabexate or heparin* or at?eroid* or liquaemin or nadroparin* or fraxiparin* or cy-216 or cy216 or "pentosan sulfuric polyester" or "pentosan sulphuric polyester" or ((polysulfate or polysulphate) adj sodium adj pentosan*) or ((sulfuric or sulphuric) adj polyester adj pentosan*) or fibrocid or ((hoe or bay or hoe-bay) adj "946") or ((pentosan* or polypentose or xylan) adj (sulphate or sulfate or sp54 or sp-54 or polysulfate* or polysulphate*)) or pz68 or pz-68 or elmiron or hemoclar or phenindione or pindione or phenyline or fenilin or phenylindanedione or dindevan or phenprocoumon or falithrom or phenprogramma or phenprocoumalol or marcumar or phenylpropylhydroxycumarinum or phenprocoumarol or liquamar or marcoumar or "protein c" or "protein s" or warfarin marevan or coumadin* or warfant or aldocumar or tedicumar or "beta 2-glycoprotein i" or apo-h or anticardiolipin or "apoliprotein h" or ec-vmfa or "endothelial cell viability maintaining factor" or "beta(2)gpi").tw.
12. exp Stockings, Compression/
13. exp Intermittent Pneumatic Compression Devices/
14. ((compression* or thromboembolism-deterrent or anti-embolism or TED) adj3 (stocking* or hose or hosiery or device*)).tw.
15. (prophylaxis or prophylactic).tw.
16. pc.fs.
17. (prevent* or reduce or reduction or diminish or decrease* or inhibit*).tw.
18. or/9-17
19. exp Medical Order Entry Systems/
20. exp Reminder Systems/
21. exp Drug Therapy, Computer-Assisted/
22. (("computeri?ed physician" or system) adj5 "order entry").tw.
23. CPOE.tw.
24. ((computeri?ed or automat* or medicat* or electronic*) adj5 (alert* or reminder*)).tw.

25. sticker?.tw.
26. prescription aid?.tw.
27. exp Decision Support Systems, Clinical/
28. decision support.tw.
29. CDS.tw.
30. e-iatrogenesis.tw.
31. alert fatigue.tw.
32. electronic tool?.tw.
33. exp Guideline/
34. exp Guidelines as Topic/
35. exp Guideline Adherence/
36. exp Clinical Protocols/
37. protocol*.tw.
38. guideline*.tw.
39. adhere*.tw.
40. (comply or compliance).tw.
41. or/19-40
42. exp Inpatients/ or exp Hospitalization/ or exp Hospitals/
43. (inpatient* or "in?patient*").tw.
44. exp Adolescent, Hospitalized/ or exp Child, Hospitalized/
45. (hospitali?e* or hospitali?ation).tw.
46. (admitted adj3 (hospital or patient*)).tw.
47. ("high risk" or "at risk").tw.
48. or/42-47
49. thromboprophyla*.mp.
50. 8 and 18 and 41 and 48
51. 48 and 49
52. 50 or 51
53. limit 52 to yr="1980 -Current"

**2. Embase Ovid**

1. exp thrombosis prevention/
2. exp embolism prevention/
3. (thrombosis or thrombotic or thrombus or thrombi or thromboembol*).tw.
4. (emboli* or embolus).tw.
5. (phlebothrombo* or phlebitis).tw.
6. exp blood clotting/
7. clot.tw.
8. (DVT or VTE or PE).ti,ab.
9. or/1-8
10. exp *anticoagulant agent/
11. anticoagulant*.tw.
12. (hydroxycoumarins or acenocoumarol or acenocoumar* or minisintrom or nicoumalone or s?nc?umar or sintrom or s?nthrom* or ancrod or ancrod or arvin or venacil or agkistrodon or arwinor or (blood adj3 coagulat* adj3 inhibit*) or "citric acid" or uralyt or dalteparin or tedelparin or fr-860 or fr860 or dalteparin or kabi2165 or kabi-2165 or fragmin* or "dermatan sulfate" or chondroitin or dextran or dextrans or hemodex or promit or macrodex or saviosol or rheodextran or polyglucin or hyskon or rheomacrodex or infukoll or rheopolyglucin or rheoisodex or rondex or dic?umarol or dicoumarin or bishydroxycoumarin or edetic or tetracemate or calcitetracemate

or edta or ethylenedinitrilotetraacetic or edetate or (calcium adj3 tetacine) or versenate or coprin or edathamil or versene or dinitrilotetraacetate or "chelaton 3" or enoxaparin* or pk10169 or "pk 10169" or emt-967 or emt96* or clexane or lovenox or emt-966 or (ethyl adj3 biscoumacetate) or ethyldicoumarol or pelentan or tromexan or carbethoxydicoumarol or foy or gabexate or heparin* or at?eroid* or liquaemin or nadroparin* or fraxiparin* or cy-216 or cy216 or "pentosan sulfuric polyester" or "pentosan sulphuric polyester" or ((polysulfate or polysulphate) adj sodium adj pentosan*) or ((sulfuric or sulphuric) adj polyester adj pentosan*) or fibrocid or ((hoe or bay or hoe-bay) adj "946") or ((pentosan* or polypentose or xylan) adj (sulphate or sulfate or sp54 or sp-54 or polysulfate* or polysulphate*)) or pz68 or pz-68 or elmiron or hemoclar or phenindione or pindione or phenyline or fenilin or phenylindanedione or dindevan or phenprocoumon or falithrom or phenprogramma or phenprocoumalol or marcumar or phenylpropylhydroxycumarinum or phenprocoumarol or liquamar or marcoumar or "protein c" or "protein s" or warfarin marevan or coumadin* or warfant or aldocumar or tedicumar or "beta 2-glycoprotein i" or apo-h or anticardiolipin or "apoliprotein h" or ec-vmfa or "endothelial cell viability maintaining factor" or "beta(2)gpi").tw.
13. exp compression stocking/
14. ((compression* or thromboembolism-deterrent or anti-embolism or TED) adj3 (stocking* or hose or hosiery)).tw.
15. (prophylaxis or prophylactic).tw.
16. pc.fs.
17. (prevent* or reduce or reduction or diminish or decrease* or inhibit*).tw.
18. or/10-17
19. exp hospital information system/
20. exp reminder system/
21. exp computer assisted drug therapy/
22. (("computeri?ed physician" or system) adj5 "order entry").tw.
23. CPOE.tw.
24. ((computeri?ed or automat* or medicat* or electronic*) adj5 (alert* or reminder*)).tw.
25. sticker*.tw.
26. prescription aid*.tw.
27. exp decision support system/
28. "decision support".tw.
29. CDS.tw.
30. e-iatrogenesis.tw.
31. alert fatigue.tw.
32. electronic tool*.tw.
33. exp practice guideline/
34. exp clinical protocol/
35. (protocol* or guideline* or adhere*).tw.
36. (comply or compliance).tw.
37. or/19-36
38. exp hospital patient/ or exp hospitalization/ or (*exp * hospital/ and exp patient/)
39. (inpatient* or "in?patient").tw.
40. (hospitali?e* or hospitali?ation).tw.
41. (admitted adj3 (hospital or patient*)).tw.
42. ("high risk" or "at risk").tw.
43. or/38-42
44. thromboprophyla*.mp.
45. 9 and 18 and 37 and 43
46. 43 and 44

47. 45 or 46
48. limit 47 to yr="1980 -Current"

**3. BIOSIS previews Ovid**

1. (thrombosis or thrombotic or thrombus or thrombi or thromboembol*).mp.
2. (emboli* or embolus).mp.
3. (phlebothrombo* or phlebitis).mp.
4. clot*.mp.
5. (DVT or VTE or PE).tw.
6. or/1-5
7. anticoagulant*.mp.
8. (hydroxycoumarins or acenocoumarol or acenocoumar* or minisintrom or nicoumalone or s?nc?umar or sintrom or s?nthrom* or ancrod or ancrod or arvin or venacil or agkistrodon or arwinor or (blood adj3 coagulat* adj3 inhibit*) or "citric acid" or uralyt or dalteparin or tedelparin or fr-860 or fr860 or dalteparin or kabi2165 or kabi-2165 or fragmin* or "dermatan sulfate" or chondroitin or dextran or dextrans or hemodex or promit or macrodex or saviosol or rheodextran or polyglucin or hyskon or rheomacrodex or infukoll or rheopolyglucin or rheoisodex or rondex or dic?umarol or dicoumarin or bishydroxycoumarin or edetic or tetracemate or calcitetracemate or edta or ethylenedinitrilotetraacetic or edetate or (calcium adj3 tetacine) or versenate or coprin or edathamil or versene or dinitrilotetraacetate or "chelaton 3" or enoxaparin* or pk10169 or "pk 10169" or emt-967 or emt96* or clexane or lovenox or emt-966 or (ethyl adj3 biscoumacetate) or ethyldicoumarol or pelentan or tromexan or carbethoxydicoumarol or foy or gabexate or heparin* or at?eroid* or liquaemin or nadroparin* or fraxiparin* or cy-216 or cy216 or "pentosan sulfuric polyester" or "pentosan sulphuric polyester" or ((polysulfate or polysulphate) adj sodium adj pentosan*) or ((sulfuric or sulphuric) adj polyester adj pentosan*) or fibrocid or ((hoe or bay or hoe-bay) adj "946") or ((pentosan* or polypentose or xylan) adj (sulphate or sulfate or sp54 or sp-54 or polysulfate* or polysulphate*)) or pz68 or pz-68 or elmiron or hemoclar or phenindione or pindione or phenyline or fenilin or phenylindanedione or dindevan or phenprocoumon or falithrom or phenprogramma or phenprocoumalol or marcumar or phenylpropylhydroxycumarinum or phenprocoumarol or liquamar or marcoumar or "protein c" or "protein s" or warfarin marevan or coumadin* or warfant or aldocumar or tedicumar or "beta 2-glycoprotein i" or apo-h or anticardiolipin or "apoliprotein h" or ec-vmfa or "endothelial cell viability maintaining factor" or "beta(2)gpi").tw.
9. ((compression* or thromboembolism-deterrent or anti-embolism or TED) adj3 (stocking* or hose or hosiery)).mp.
10. (prophylaxis or prophylactic).mp.
11. (prevent* or reduce or reduction or diminish or decrease* or inhibit*).mp.
12. or/7-11
13. (("computeri?ed physician" or system) adj5 "order entry").tw.
14. CPOE.tw.
15. ((computeri?ed or automat* or medicat* or electronic*) adj5 (alert* or reminder*)).tw.
16. sticker*.tw.
17. prescription aid*.tw.
18. "decision support".tw.
19. CDS.tw.
20. e-iatrogenesis.tw.
21. alert fatigue.tw.
22. electronic tool*.tw.

23. (guideline* or protocol* or adhere*).tw.
24. (comply or compliance).tw.
25. or/13-24
26. (inpatient* or "in?patient").tw.
27. (hospitali?e* or hospitali?ation).tw.
28. (admit* adj3 (hospital or patient*)).tw.
29. ("high risk" or "at risk").tw.
30. or/26-29
31. thromboprophyla*.mp.
32. 6 and 12 and 25 and 30
33. 30 and 31
34. 32 or 33

**4. CINAHL**

S46 S44 OR S45
S45 S42 AND S43
S44 S8 AND S15 AND S32 AND S42
S43TI thromboprophyla* OR AB thromboprophyla*
S42 S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41
S41TI ("high risk" OR "at risk") OR AB ("high risk" OR "at risk")
S40TI (admitted N3 (hospital or patient*)) OR AB (admitted N3 (hospital or patient*))
S39TI (hospitali?e* OR hospitali?ation) OR AB (hospitali?e* OR hospitali?ation)
S38(MH "Child, Hospitalized")
S37(MH "Adolescent, Hospitalized")
S36TI (inpatient* OR in?patient*) OR AB (inpatient* OR in?patient*)
S35(MH "Hospitals+")
S34(MH "Hospitalization+")
S33(MH "Inpatients")
S32 S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31
S31TI (protocol* or guideline* OR adhere*) OR AB (protocol* or guideline* OR adhere*)
S30(MH "Practice Guidelines")
S29TI electronic tool* OR AB electronic tool*
S28TI alert fatigue OR AB alert fatigue
S27TI e-iatrogenesis OR AB e-iatrogenesis
S26TI CDS OR AB CDS
S25TI decision support* OR AB decision support*
S24(MH "Decision Support Systems, Clinical")
S23TI prescription aid* OR AB prescription aid*
S22TI sticker* OR AB sticker*
S21TI ((computeri?ed or automat* or medicat* or electronic*) N5 (alert* or reminder*)) OR AB ((computeri?ed or automat* or medicat* or electronic*) N5 (alert* or reminder*))
S20TI CPOE OR AB CPOE
S19TI (("computeri?ed physician" or system) N5 "order entry") OR AB (("computeri?ed physician" or system) N5 "order entry")
S18(MH "Drug Therapy, Computer Assisted")
S17(MH "Reminder Systems")
S16(MH "Electronic Order Entry")

S15 S9 OR S10 OR S11 OR S12 OR S13 OR S14
S14TI (prevent* or reduce or reduction or diminish or decrease* or inhibit*) OR AB (prevent* or reduce or reduction or diminish or decrease* or inhibit*)
S13TI (prophylaxis or prophylactic) OR AB (prophylaxis or prophylactic)
S12TI ((compression* or thromboembolism-deterrent or anti-embolism or TED) N3 (stocking* or hose or hosiery or device*)) OR AB ((compression* or thromboembolism-deterrent or anti-embolism or TED) N3 (stocking* or hose or hosiery or device*))
S11(MH "Compression Garments")
S10TI anticoagulant* OR AB anticoagulant*
S9(MH "Anticoagulants+")
S8 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7
S7TX (DVT OR VTE OR PE) OR AB (DVT OR VTE OR PE)
S6TX (clot or clots) OR AB (clot or clots)
S5TX (phlebothrombo* or phlebitis) OR AB (phlebothrombo* or phlebitis)
S4TX (emboli* OR embolus) OR AB (emboli* or embolus)
S3TX (thrombosis or thrombotic or thrombus or thrombi or thromboembol*) OR AB (thrombosis or thrombotic or thrombus or thrombi or thromboembol*)
S2(MH "Embolism+/PC")
S1(MH "Thrombosis+/PC")

**5. WEB OF SCIENCE**

#1 TS=(thrombosis or thrombotic or thrombus or thrombi or thromboembol* OR emboli* OR embolus OR phlebothrombo* or phlebitis OR clot OR DVT OR VTE OR PE)
#2 TS=(anticoagulant* OR hydroxycoumarins or acenocoumarol or acenocoumar* or minisintrom or nicoumalone or s?nc?umar or sintrom or s?nthrom* or ancrod or ancrod or arvin or venacil or agkistrodon or arwinor or (blood NEAR/3 coagulat* NEAR/3 inhibit*) or "citric acid" or uralyt or dalteparin or tedelparin or fr-860 or fr860 or dalteparin or kabi2165 or kabi-2165 or fragmin* or "dermatan sulfate" or chondroitin or dextran or dextrans or hemodex or promit or macrodex or saviosol or rheodextran or polyglucin or hyskon or rheomacrodex or infukoll or rheopolyglucin or rheoisodex or rondex or dic?umarol or dicoumarin or bishydroxycoumarin or edetic or tetracemate or calcitetracemate or edta or ethylenedinitrilotetraacetic or edetate or (calcium NEAR/3 tetacine) or versenate or coprin or edathamil or versene or dinitrilotetraacetate or "chelaton 3" or enoxaparin* or pk10169 or "pk 10169" or emt-967 or emt96* or clexane or lovenox or emt-966 or (ethyl NEAR/3 biscoumacetate) or ethyldicoumarol or pelentan or tromexan or carbethoxydicoumarol or foy or gabexate or heparin* or at?eroid* or liquaemin or nadroparin* or fraxiparin* or cy-216 or cy216 or "pentosan sulfuric polyester" or "pentosan sulphuric polyester" or ((polysulfate or polysulphate) NEAR/1 sodium NEAR/1 pentosan*) or ((sulfuric or sulphuric) NEAR/1 polyester NEAR/1 pentosan*) or fibrocid or ((hoe or bay or hoe-bay) NEAR/1 "946") or ((pentosan* or polypentose or xylan) NEAR/1 (sulphate or sulfate or sp54 or sp-54 or polysulfate* or polysulphate*)) or pz68 or pz-68 or elmiron or hemoclar or phenindione or pindione or phenyline or fenilin or phenylindanedione or dindevan or phenprocoumon or falithrom or phenprogramma or phenprocoumalol or marcumar or phenylpropylhydroxycumarinum or phenprocoumarol or liquamar or marcoumar or "protein c" or "protein s" or warfarin marevan or coumadin* or warfant or aldocumar or tedicumar or "beta 2-glycoprotein i" or apo-h or anticardiolipin or "apoliprotein h" or ec-vmfa or "endothelial cell viability maintaining factor" or "beta(2)gpi" OR ((compression* or thromboembolism-deterrent or anti-embolism or TED) NEAR/3 (stocking* or hose or hosiery)) OR prophylaxis or prophylactic or prevent* or reduce or reduction or diminish or decrease* or inhibit*)

#3 TS=((("computeri?ed physician" or system) NEAR/5 "order entry") OR CPOE OR ((computeri?ed or automat* or medicat* or electronic*) NEAR/5 (alert* or reminder*)) or sticker* OR "prescription aid*" OR "decision support" OR CDS OR e-iatrogenesis OR "alert fatigue" OR "electronic tool*" OR guideline* or protocol* OR adhere* OR comply or compliance)
#4 TS=(inpatient* OR "in-patient*" or hospitali?e* or hospitali?ation or (admitted NEAR/3 (hospital* or patient*)) OR "high risk" or "at risk")
#5 TS=(thromboprophyla*)
#6 #4 AND #3 AND #2 AND #1
#7 #5 AND #4
#8 #7 OR #6

**6. LILACS**

((thrombosis or thrombotic or thrombus or thrombi or thromboembol* or phlebothrombo* or phlebitis or clot* or DVT or VTE) AND (prophylaxis or prophylactic or prevent* or reduce or reduction or diminish or decrease* or inhibit*)) OR thromboprophyla*

**7. PubMed**

#65,"Search #64 NOT medline[sb]"
#64,"Search #62 OR #63"
#63,"Search #60 AND #61"
#62,"Search #15 AND #27 AND #52 AND #60"
#61,"Search thromboprophyla*[tw]"
#60,"Search #52 OR #53 OR #54 OR #55 OR #56 OR #58 OR #59"
#59,"Search high risk[tw] or at risk[tw]"
#58,"Search admitted[tw] AND (hospital[tw] or patient[tw] or patients[tw])"
#56,"Search hospitalise*[tw] or hospitalisation[tw] or hospitalize*[tw] or hospitalization[tw]"
#55,"Search Adolescent, Hospitalized[Mesh] or Child, Hospitalized[Mesh]"
#54,"Search inpatient[tw] or inpatients[tw] or in-patient[tw] or in-patients[tw]"
#53,"Search Inpatients[Mesh] or Hospitalization[Mesh] or Hospitals[Mesh]"
#52,"Search #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51"
#51,"Search comply[tw] or compliance[tw]"
#50,"Search adhere*[tw]"
#49,"Search guideline*[tw]"
#48,"Search protocol*[tw]"
#47,"Search Clinical Protocols[Mesh]"
#46,"Search Guideline Adherence[Mesh]"
#45,"Search Guidelines as Topic[Mesh]"
#44,"Search Guideine[Mesh] Schema: all"

#43,"Search Guideine[Mesh]"
#42,"Search electronic tool*[tw]"
#41,"Search alert fatigue[tw]"
#40,"Search e-iatrogenesis[tw]"
#39,"Search CDS[tw]"
#38,"Search decision support[tw]"
#37,"Search ""Decision Support Systems, Clinical""[Mesh]"
#36,"Search prescription aid*[tw]"
#35,"Search sticker*[tw]"
#34,"Search ((computerised or computerized or automat* or medicat* or electronic*) AND (alert* or reminder*))[tw]"
#33,"Search CPOE[tw]"
#32,"Search (((""computerised physician"" or ""computerized physician"" or system) AND ""order entry"")[tw]"
#31,"Search ""Drug Therapy, Computer-Assisted""[Mesh]"
#30,"Search ""Reminder Systems""[Mesh]"
#29,"Search ""Medical Order Entry Systems""[Mesh]"
#27,"Search #16 OR #17 OR #19 OR #21 OR #23 OR #24 OR #25 OR #26"
#26,"Search prevent*[tw] or reduce[tw] or reduction[tw] or diminish[tw] or decrease*[tw] or inhibit*[tw]"
#25,"Search prophylaxis[tw] or prophylactic[tw]"
#24,"Search ((compression* or thromboembolism-deterrent or anti-embolism or TED) AND (stocking* or hose or hosiery or device*))[tw]"
#23,"Search ""Intermittent Pneumatic Compression Devices""[Mesh]"
#21,"Search ""Stockings, Compression""[Mesh]"

#19,"Search hydroxycoumarins[tw] or acenocoumarol[tw] or acenocoumar*[tw] or minisintrom[tw] or nicoumalone[tw] or syncumar[tw] or sintrom[tw] or sinthrom*[tw] or synthrom*[tw] or ancrod[tw] or arvin[tw] or venacil[tw] or agkistrodon[tw] or arwinor[tw] or blood coagulation inhibitor[tw] or blood coagulation inhibitors[tw] or citric acid[tw] or uralyt[tw] or dalteparin[tw] or tedelparin[tw] or fr-860[tw] or fr860[tw] or dalteparin[tw] or kabi2165[tw] or kabi-2165[tw] or fragmin*[tw] or ""dermatan sulfate""[tw] or chondroitin[tw] or dextran[tw] or dextrans[tw] or hemodex[tw] or promit[tw] or macrodex[tw] or saviosol[tw] or rheodextran[tw] or polyglucin[tw] or hyskon[tw] or rheomacrodex[tw] or infukoll[tw] or rheopolyglucin[tw] or rheoisodex[tw] or rondex[tw] or dicumarol[tw] or dicoumarol[tw] or dicoumarin[tw] or bishydroxycoumarin[tw] or edetic[tw] or tetracemate[tw] or calcitetracemate[tw] or edta[tw] or ethylenedinitrilotetraacetic[tw] or edetate[tw] or (calcium AND tetacine)[tw] or versenate[tw] or coprin[tw] or edathamil[tw] or versene[tw] or dinitrilotetraacetate[tw] or ""chelaton 3""[tw] or enoxaparin*[tw] or pk10169[tw] or ""pk 10169""[tw] or emt-967[tw] or emt96*[tw] or clexane[tw] or lovenox[tw] or emt-966[tw] or ""ethyl biscoumacetate""[tw] or ethyldicoumarol[tw] or pelentan[tw] or tromexan[tw] or carbethoxydicoumarol[tw] or foy[tw] or gabexate[tw] or heparin*[tw] or ateroid*[tw] or atheroid*[tw] or liquaemin[tw] or nadroparin*[tw] or fraxiparin*[tw] or cy-216[tw] or cy216[tw] or ""pentosan sulfuric polyester""[tw] or ""pentosan sulphuric polyester""[tw] or ((polysulfate or polysulphate) AND sodium AND pentosan*)[tw] or ((sulfuric or sulphuric) AND polyester AND pentosan*)[tw] or fibrocid[tw] or ((hoe or bay or hoe-bay) AND ""946"")[tw] or ((pentosan* or polypentose or xylan)[tw] AND (sulphate or sulfate or sp54 or sp-54 or polysulfate* or polysulphate*))[tw] or pz68[tw] or pz-68[tw] or elmiron[tw] or hemoclar[tw] or phenindione[tw] or pindione[tw] or phenyline[tw] or fenilin[tw] or phenylindanedione[tw] or dindevan[tw] or phenprocoumon[tw] or falithrom[tw] or phenprogramma[tw] or phenprocoumalol[tw] or marcumar[tw] or phenylpropylhydroxycumarinum[tw] or phenprocoumarol[tw] or liquamar[tw] or marcoumar[tw] or ""protein c""[tw] or ""protein s""[tw] or

""warfarin marevan""[tw] or coumadin*[tw] or warfant[tw] or aldocumar[tw] or tedicumar[tw] or ""beta 2-glycoprotein i""[tw] or apo-h[tw] or anticardiolipin[tw] or ""apoliprotein h""[tw] or ec-vmfa[tw] or ""endothelial cell viability maintaining factor""[tw] or ""beta(2)gpi""[tw]"

#17,"Search anticoagulant*[tw]"
#16,"Search ""Anticoagulants""[Mesh]"
#15,"Search #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #14"
#14,"Search DVT[tiab] OR VTE[tiab] OR PE[tiab]"
#12,"Search clot[tw]
#11,"Search phlebothrombo*[tw] or phlebitis[tw]"
#10,"Search emboli[tw] or embolus[tw]"
#9,"Search thrombosis[tw] or thrombotic[tw] or thrombus[tw] or thrombi[tw] or thromboembol*[tw]"
#8,"Search ""Embolism/prevention and control""[Mesh]"
#7,"Search ""Thrombosis/prevention and control""[Mesh]"

**Table S1. Summary of study quality**

| Trial | Quantitative scores | Overall ROB |
|---|---|---|
| Anderson 1994 | -1 | Unclear |
| Overhage 1996 | -1 | Unclear |
| Dexter 2001 | 0 | Unclear |
| Kucher 2005 | +2 | Low |
| Fontaine 2006 | 0 | Unclear |
| Labarere 2007 | 0 | Unclear |
| Piazza 2009 | +3 | Low |
| Garcia 2009 | -2 | High |
| Hinchey 2010 | -4 | High |
| Chapman 2011 | 0 | Unclear |
| Pai 2013 | +1 | Unclear |
| Cavalcanti 2016 | +1 | Unclear |
| Roy 2016 | +1 | Unclear |

For each of the seven ROB domains, a negative score (-1) was assigned for each high ROB response, a score of zero was assigned for each unclear ROB response, and a positive score was assigned for each low ROB response.

Summary scores of less than -1 were considered as high ROB, summary scores of zero were considered as unclear ROB, and summary scores of greater than +1 were considered low ROB. Only two of the included studies were of low quality. High ROB was mainly related to selection, performance, attrition, reporting, and other biases.

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | **Page 0** |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | **Page 0** |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | **Page 1** |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | **Page 1** |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | **Page 1** |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | **Page 2** |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | **Page 2** |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | **Page 2** |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | **Page 3** |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | **Page 3** |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | **Page 3** |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | **Page 3** |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | **Page 3** |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | **Page 3** |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | **Page 3** |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | **Page 3 and 10** |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | **Page 4** |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | **Page 4-6** |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | **Page 7** |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | **Page 7-9** |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | **Page 7-9** |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | **Page 7** |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | **Page 10** |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | **Page 10** |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | **Page 10-11** |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | **Page 11** |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | **Page 12** |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

# The effectiveness of interventions for the implementation of thromboprophylaxis in hospitalized patients at risk for venous thromboembolism: an updated abridged Cochrane systematic review and meta-analysis of Randomized Controlled Trials (RCT).



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| | |

# The effectiveness of interventions for the implementation of thromboprophylaxis in hospitalized patients at risk for venous thromboembolism: an updated abridged Cochrane systematic review and meta-analysis of Randomized Controlled Trials (RCT).

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Number of tables: 3
Supplemental material: 1

## ABSTRACT

**Objective:** To assess the effectiveness of system-wide interventions designed to increase the implementation of thromboprophylaxis and decrease the incidence of venous thromboembolism (VTE) in hospitalized medical and surgical patients at risk for VTE.

**Design:** Systematic review and meta-analysis of randomised controlled trials (RCTs).

**Data sources:** Medline, PubMed, Embase, BIOSIS, CINAHL, Web of Science, CENTRAL, DARE, EED, LILACS, and clinicaltrials.gov without language restrictions from inception to 7 January 2017, as well as the reference lists of relevant review articles.

**Eligibility criteria for selecting studies:** RCTs that evaluated the effectiveness of system-wide interventions such as alerts, multifaceted, education, and pre-printed orders as compared to no intervention, existing policy, or another intervention.

**Results:** We included 13 RCTs involving 35,997 participants. Eleven RCTs had data available for meta-analysis. Compared to control, we found absolute increases in the prescription of prophylaxis associated with alerts (21% increase, 95% CI [15% to 275]) and multifaceted interventions (4% increase, 95% CI [3% to 11%]), absolute increase in the prescription of appropriate prophylaxis associated with alerts (16% increase, 95% CI [12% to 20%]), and relative risk reductions (risk ratio 64%, 95% CI [47% to 86%]) in the incidence of symptomatic VTE associated with alerts.. Computer alerts were found to be more effective than human alerts, and multifaceted interventions with an alert component appeared to be more effective than multifaceted interventions without, although comparative pooled analyses were not feasible. The quality of evidence for improvement in outcomes was judged to be low to moderate-certainty.

**Conclusions:** Alerts increased the proportion of patients who received prophylaxis and appropriate prophylaxis, and decreased the incidence of symptomatic VTE. Multifaceted interventions increased the proportion of patients who received prophylaxis but were found to be less effective than alerts interventions.



**Keywords:** venous thromboembolism, deep venous thrombosis, pulmonary embolism, system-wide interventions, thromboprophylaxis.

**Systematic review protocol registration:** CD008201

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- This review was conducted following the *Cochrane Handbook for Systematic Reviews of Interventions.*
- We included all RCTs relevant to our research question.
- We preferentially accounted for clustering designs using the intraclass correlation coefficient (ICC) where available. ICCs were not provided in many study reports, leading to confidence intervals that may be narrower than if clustering had been accounted for.
- The quality of the evidence in this updated review was limited by the methodological quality of included trials.

## INTRODUCTION

Compared to persons in the community, hospitalized medical and surgical patients are at approximately 50% higher risk of developing venous thromboembolism (VTE), which includes deep venous thrombosis (DVT),[1, 2] and pulmonary embolism (PE). VTE that occurs during or within three months after hospitalization underlies more than 50% of all cases of the population burden of VTE.[3-5] VTE is a frequent complication in hospitalized medical and surgical patients, a leading cause of mortality and morbidity in hospitalized patients (60,000-100,000 deaths per year),[6] a leading cause of increased hospital costs (at least $600 million per year) and length of hospital stay, and PE is the 3rd leading cause of preventable death and disability in hospital.[7-11]

The appropriate use of thromboprophylaxis in hospitalized patients at risk for VTE has been shown to be safe, effective and cost-effective. Therefore, many international clinical practice guidelines have recommended the use of thromboprophylaxis (eg, pharmacologic and/or mechanical modalities) in targeted groups of hospitalized medical and surgical patients at risk for VTE.[12-21] The prevention of VTE was ranked as the number one of 79 strategies aimed to improve patient safety in hospitals,[22] and interventions to increase thromboprophylaxis prescriptions have been classified as a strongly encouraged patient safety practice.[23, 24] Nonetheless, a clear gap exists between the available evidence and the implementation of the appropriate use of thromboprophylaxis into day to day clinical practice.[25-33] System-wide interventions, by reaching the health care system as a whole, could help to improve prescription of appropriate thromboprophylaxis and ultimately reduce the risk of VTE in hospitalized medical and surgical patients at risk of VTE.[34]

In our previous Cochrane systematic review, we assessed the effectiveness of various system-wide interventions designed to increase the implementation of thromboprophylaxis in hospitalized medical and surgical patients at risk for VTE.[35] We identified various system-wide interventions such as simple distribution of guidelines, audit and feedback (eg, review of performance); preprinted orders (e.g. written, predefined orders, which can be completed by the physician on paper or electronically); the use of automatic reminder systems that include alerts (eg, human alerts, by a trained nurse, pharmacist, or staff member; or computer, electronic alerts); multifaceted approaches that combine different types of interventions (eg, combination of education, audit and feedback, and alerts); and educational interventions, which focus on the teaching and learning process by organizing educational events (eg, grand rounds, self-administered courses).

This article presents the results of an update of our previous Cochrane review on the effectiveness of system-wide interventions designed to increase the use of thromboprophylaxis and decrease the incidence of VTE in hospitalized medical and surgical patients at risk for VTE. In this updated review, we focus exclusively on the higher level of evidence provided by randomized controlled trials (RCTs), whereas our previous review also included observational studies. The implementation of effective interventions could help clinicians and other health care professionals to improve the use of appropriate thromboprophylaxis in hospitalized medical and surgical patients at risk of VTE, and thereby reduce the morbidity and mortality associated with this preventable hospital complication.

## METHODS

This is an abridged, stand-alone version of an updated Cochrane systematic review.[36] The protocol and the previous Cochrane review can be accessed from the Cochrane Library.[35, 37]

**Inclusion criteria**

Study type

We included all types of RCTs, namely RCTs with random or quasi-random (eg, pseudo-randomization such as even or odd date of birth) methods of allocation of interventions, which either randomized individuals (eg, parallel group, crossover, or factorial design RCTs) or groups of individuals (cluster RCTs (CRTs), and whose interventions aimed to increase the use of prophylaxis and/or appropriate prophylaxis, and/or decrease the proportion of symptomatic or asymptomatic VTE in hospitalized adult patients. The control group comparison could be 'no intervention', an existing policy, or another type of intervention.

Studies were included only if the following characteristics were met: 1) the study design, population, and intervention were clearly described; 2) study data were provided separately by intervention group, and for VTE outcomes; and 3) VTE was diagnosed using objective and accepted criteria. Studies and abstracts could be in any language. We excluded observational studies, studies in which the intervention was a simple distribution of published guidelines, and studies whose interventions were not clearly described.

Participants

Participants included hospitalized acutely and critically ill adult medical or surgical inpatients (age range, 18-99 years), their physicians, residents or nurses, or, in the case of CRTs, the cluster unit (eg, ward, hospital, and physician practice).

Interventions

Any strategies targeted to individuals or to cluster units that aimed to increase the use of thromboprophylaxis in hospitalized patients at risk for VTE and/or decrease the rate of symptomatic or asymptomatic VTE. Examples of interventions include alerts (eg, computer alerts or human alerts), multifaceted interventions (eg, combination of education, audit and feedback, and alert), educational interventions (eg, grand rounds, self-administered course), and pre-printed orders interventions (eg, written predefined orders that can be completed by the physician on paper or electronically if they choose to).

Outcomes

The primary outcome of interest was the increase in the proportion of patients who received either pharmacologic or mechanical prophylaxis.

Secondary outcomes

1. Increase in the proportion of patients who received appropriate prophylaxis (defined by study authors as appropriate according to consensus, local, or international thromboprophylaxis guidelines) (note: "appropriate prophylaxis" signifies that the patient received the proper treatment whether or not he/she received prophylaxis, i.e. received prophylaxis in an at-risk patient, or did not receive prophylaxis in a low risk patient);
2. Decrease in the proportion of patients who develop any, symptomatic, or asymptomatic VTE;
3. Decrease in the number of deaths;
4. Safety of the intervention.

**Search methods**

We did a systematic literature database search in Medline (Ovid), PubMed, Embase (Ovid), BIOSIS Previews (Ovid), CINAHL, Web of Science, Cochrane (including the Cochrane Central Register of Controlled Trials (CENTRAL), the Database of Abstracts of Reviews of Effects (DARE) and the NHS Economic Evaluation Database (EED), Latin American and Caribbean Health Sciences Literature (LILACS) and clinicaltrials.gov from inception to 28 July 2015. After 28 July 2015, we updated the literature search monthly until 7 January 2017, when our database was closed. The search strategies comprised a combination of Medical Subject Headings (MeSH) or their equivalent (where available), keywords, truncations and Boolean operators (See Supplement). We also hand searched the reference lists of relevant retrieved studies including narrative and systematic reviews to find additional potentially relevant articles from inception to 7 January 2017. Studies of any languages were searched.

**Study selection**

Two review authors independently reviewed titles, abstracts, and full-texts of each study and indicated on a Study Eligibility Form if it should be included, excluded, or undecided. Disagreements regarding study inclusion were resolved by discussion between the two review authors and, if necessary, by involving a third independent review author.

**Data extraction and handling of missing data**

Two review authors independently extracted data from the included articles. The data obtained for each study were entered in duplicate into two identical databases that were designed by Information Management Services of the Lady Davis Institute in Montréal, Canada. The two databases were compared for inaccuracies and any data entry errors were corrected. If agreement on the data entered for a given data field could not be reached between the two extractors, a third extractor was consulted. A third, final database was populated with the final corrected data.

The data abstraction form included:

1. Description of study design: parallel group, cross-over, cluster, or factorial design, including cluster unit and intra cluster correlation (ICC) if available
2. Description of the randomization procedure (unit of randomization and analysis)
3. Description of study period, years of enrolment, year of publication, duration and completeness of follow-up
4. Description of study setting (hospital, or center characteristics): number of centers, university-affiliated hospital, community hospital, physician practice, type of healthcare system (public versus private), departments included
5. Description of physicians: number of physicians, physician specialties
6. Description of patients: patient types (medical, surgical, trauma, other), inclusion and exclusion criteria, number of patients screened and included, average age, percent male, comorbidities and individual VTE risk profile; (e.g. age, sex, cancer patient, cardiac patient)
7. Description of study intervention (active and control arms): type of intervention (alerts, multifaceted interventions, educational interventions, preprinted orders, other), intervention components (alert, no alert), type of alert (computer alert, human alert), timing of intervention (before or concurrent with intervention group)
8. Description of VTE prophylaxis: pharmacologic (type, dose), mechanical, appropriateness (definition and assessment)
9. Method of VTE screening and diagnosis
10. Description of study outcomes (raw data and effect estimates)
11. Risk of bias

**Time point of outcome assessment**

We used the end of trial follow-up for all outcomes as all included studies were CRTs or parallel group trials, and there were no cross-over trials. For withdrawals whether or not due to adverse events, we used the longest on-treatment follow-up data available. For studies with more than one time point of outcome assessment, we used the most recent follow-up data.

**Risk of bias of studies**

The methodological quality of included trials was independently assessed by two review authors based on the Cochrane Collaboration's tool for assessing the risk of bias.[38] Disagreements were resolved by discussion with co-authors. We assessed all seven domains that are potential sources of bias, and rated them as high, low, or unclear risk of bias (ROB). We assessed all items listed as other potential sources of bias such as trial design biases (e.g. carry-over in cross-over trials, selective reporting bias in multiple intervention studies, and recruitment bias in CRT); early study stopping for benefit; severe baseline imbalances; and inappropriate influence of study funders that may compromise the internal validity of the study.[38] We also assessed the overall ROB for each of the included studies (See supplement Table S1).

**Data analysis**

We evaluated the effectiveness of system-wide interventions by calculating pooled risk difference (RD) for the outcomes 'proportions of participants who received prophylaxis (RP)' and 'proportions of participants who received appropriate prophylaxis (RAP)' or relative ratio (RR) for outcomes with expected low events rates such as VTE, mortality, and safety based on the Cochrane Handbook recommendations for the choice of measure of effect.[38] We calculated a summary statistic for each intervention category (alerts, multifaceted interventions, educational interventions, and pre-printed orders) and associated outcome using a random effects model when there were sufficient studies to pool results (≥ 3 studies). To account for potential synergistic effects of multiples interventions, multifaceted interventions with an alert component (either computer alert or human alert) were compared to multifaceted interventions that did not include an alert component.

We used Review Manager version 5.3 and SAS version 9.4 for all data analyses. We preferentially used effect estimates for which the variance had been adjusted to account for the clustered nature of the data. Adjustment for the clustered design was only feasible for the meta-analysis of multifaceted interventions. One of the included studies evaluated more than one intervention.[39] Meta-analysis was performed within the control group and each intervention group as recommended in the Cochrane Handbook. We did not use statistical methods to impute missing values or model missing data. Four original investigators were contacted for missing data;[40-43] only two of them were able to provide additional data.[41, 43] To assess heterogeneity, we estimated the $I^2$ statistic which determines the percentage of variability between studies in the effect estimate that is above and beyond what is expected through sampling error (i.e. chance).

**Quality of evidence (GRADE)**

We used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach to assess the quality of evidence for each outcome that we were able to meta-analyzed, with the quality of evidence graded from high (best) to very low (worst).[44] The five GRADE considerations (risk of bias, indirectness of evidence, inconsistency of results, imprecision of results, and publication bias) were assessed according to the methods and recommendations in the Cochrane Handbook.[38] To mitigate publication bias, unpublished data were also search though conference abstracts and congress communications. Original

investigators of included trials were also contacted to request missing and unpublished data. We examined funnel plots centered around the pooled studies effect (either RD or RR) to assess the potential for publication bias.

**Patient and public involvement**

Patients and the public were not involved in the development or conduct of this systematic review. However, we are planning to involve patients in the dissemination of results via interactive exchanges between healthcare providers, patient partners, clinicians and policy makers.

## RESULTS

### Included studies

From 12,920 records identified, 16 RCTs published up to 7 January 2017 were potentially relevant to our research question, of which 13 RCTs involving a total of 35,997 participants met our inclusion criteria (**Figure 1**). This included five new trials since our last review published in 2013.[35] Characteristics of included studies are reported in **Table 1**.

The following type of interventions and comparisons were reported in the 13 trials (detailed descriptions of study interventions are shown in **Table 2**):

- Six trials evaluated an alerts intervention compared to the standard of care. Of these, three used a computer alert[41, 45, 46] and the other three, a person such as a trained nurse, a pharmacist or a hospital staff member as a human alert.[47-49]
- Six trials evaluated a multifaceted intervention that combined different types of interventions such as education, audit and feedback, and alert, compared to the standard of care[39, 42, 43, 50, 51] or to another type of intervention (combination of educational session, dissemination of educational material, audit, and feedback).[52] Of these trials, only one included an alert component.[51] This study evaluated a computer alert (computer-based clinical decision support system and computerized reminders) along with educational lectures, posters, and pocket cards compared with no intervention. However, the computer alert component of the intervention was implemented in only two of the 14 intervention group centers. Thus, the overall effect of this multifaceted intervention might have been smaller than expected.
- One trial evaluated a pre-printed orders intervention using predefined anticoagulant prescription forms as a passive reminder to use thromboprophylaxis, compared to the standard of care.[53]
- One trial reported a head-to-head comparison among interventions. This trial evaluated an educational intervention that used a hospital-administered course with self-assessment examinations compared to the standard of care and to a multifaceted intervention .[39]

Two of the 13 trials were not included in meta-analyses (one because of missing raw data on study outcomes,[42] and one was the only RCT to study a pre-printed orders intervention).[53] One type of comparison (educational intervention compared to the standard of care) was not included in meta-analyses due to a lack of studies assessing this intervention.[39]

**Table 1:** Characteristics of included studies

| Author | Study design | Study setting | Number of patients (centers) | Type of patients | Participants (gender, age) | System-wide intervention | Comparators | Follow-up (timing for outcome assessment) | Primary outcome | Secondary outcomes |
|---|---|---|---|---|---|---|---|---|---|---|
| **Anderson et al, 1994**[39] | Cluster RCT (unit of cluster: hospitals) | Community, USA | 798 patients (15 centers) | Medical and surgical patients | Male 44%<br>Mean 70.7 years | Multifaceted | No intervention vs educational vs multifaceted intervention | 3 months | RP | RAP, VTE, mortality, and safety outcomes not assessed |
| **Overhage et al, 1996**[46] | Cluster RCT (unit of cluster: medical wards/departments) | Academic, USA | 58 patients (1 center) | Medical patients | Male 50%<br>Mean (SD), 51 years (18) | Alerts (computer alert) | No intervention (usual care) vs intervention | 6 months | RP | RAP, VTE, mortality, and safety outcomes not assessed |
| **Dexter et al, 2001**[41] | Cluster RCT (unit of cluster: medical teams) | Academic, USA | 1,326 patients (1 center) | Medical patients | Male 50%<br>Mean 53.2 years | Alerts (computer alert) | No intervention (standard care) vs intervention | 1 months | Not assessed | RAP assessed<br>VTE, mortality, and safety outcomes not assessed |
| **Kucher et al, 2005**[45] | Parallel group, quasi-RCT | Academic, USA | 2,506 patients (1 center) | Medical and surgical patients | Male 52.9%<br>Median (range) 62.5 years (18-99) | Alerts (computer alert) | No intervention (usual care) vs intervention | 90 days | RP | RAP not assessed.<br>VTE, mortality, and safety outcomes assessed |
| **Fontaine et al, 2006**[53] | Cluster RCT (unit of cluster: medical wards/departments) | Academic, France | 719 patients (30 centers) | Medical patients | Male 51.5%<br>Mean 72 years | Pre-printed orders | No intervention (usual practices) vs intervention; baseline vs post intervention | 1 day | RP | RAP described in a figure (raw data not available)<br>VTE, mortality, and safety outcomes not assessed |
| **Labarere et al, 2007**[52] | Cluster RCT (unit of cluster: medical wards/departments) | Academic/ Community, France | 812 patients (50 centers) | Medical patients | Male 34.2%<br>Median (range) 82 years (75–90) | Multifaceted | Intervention targeted at physicians only vs multifaceted intervention targeted at physicians and nurses | Not clearly reported | RP | RAP and mortality outcomes not assessed. |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | VTE and safety outcomes assessed |
| **Piazza et al, 2009[49]** | Parallel group RCT | Academic/ Community USA | 2,493 patients (25 centers) | Medical and surgical patients | Male 53.7%<br>Mean (SD), 68.8 years (15.2);<br>Median (range) 72.5 years (19 to 103) | Alerts (human alert) | No intervention (usual care) vs intervention | 90 days | RP | RAP and safety outcomes not assessed.<br>VTE and mortality assessed |
| **Garcia et al, 2009[48]** | Cluster, quasi-RCT (unit of cluster: medical teams) | Academic, USA | 140 patients<br>(1 center) | Medical patients | Male 50.7%<br>Mean (range) 59.5 years (20-97) | Alerts (human alert) | No intervention (usual care) vs intervention | 30 hours | Not assessed | RAP assessed.<br>VTE, mortality and safety outcomes not assessed. |
| **Hinchey et al, 2010[42]** | Cluster, quasi-RCT (unit of cluster: hospitals) | Academic/ Community, USA | 2,071 patients (16 centers) | Medical patients | Male 50.1%<br>Mean 70 years | Multifaceted including reminders (standard orders, pathways, protocols, standardized dysphagia screens, atrial fibrillation reminder stickers) | Control group (audit, feedback, and benchmark information) vs intervention | 6 months | RP (raw data not available) | RAP, VTE, mortality, and safety outcomes not assessed |
| **Chapman et al, 2011[47]** | Parallel group RCT | Hospital type reported, Australia | 354 patients (number of centers not reported) | Medical patients | Non available | Alerts (human alert) | Standard care vs intervention | 3 months | Not assessed | Symptomatic VTE assessed.<br>RAP, mortality, and safety outcomes not assessed |
| **Pai et al, 2013[50]** | Cluster RCT (unit of cluster: hospitals) | Academic/ Community, Canada | 2,611 patients<br>(6 center) | Medical patients | Male 46.8%<br>Median (range) 72 (18-102) | Multifaceted | No intervention (usual care) vs intervention | 16 weeks | RP | RAP assessed.<br>VTE, mortality, and safety outcomes not assessed |
| **Cavalcanti et al, 2016[43]** | Cluster RCT (unit of cluster: ICU) | Academic/<br>Community, Brazil | 6761 patients | Medical patients | Male 54.2%<br>Mean (SD), 59.6 years (19) | Multifaceted including a general reminder (SMS messages) to complete checklists | Standard care vs intervention | 60 days | RP | All-cause mortality assessed. |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | (118 Intensive Care Units, number of centers not reported) | | | that targeted a broad spectrum of care processes including thromboprophylaxis | | | | RAP, VTE, and safety outcomes not assessed |
| **Roy et al, 2016[51]** | Cluster RCT (unit of cluster: hospitals) | Academic/ Community, France | 15,351 patients (27 centers) | Medical patients | Male 50%<br>Median (range) 73.5 years (58-83) | Multifaceted including an alert component (computerized reminders) | No intervention (usual care) vs intervention | 3 months | RP | All secondary outcomes assessed |

Notes: ICU: intensive care units; RCT: randomized controlled trials; RP: proportion of participants who received prophylaxis; RAP: proportion of participants who received appropriate prophylaxis; VTE: venous thromboembolism.

**Table 2:** Description of study interventions

| Author | Type of Intervention | Description |
|---|---|---|
| Anderson et al, 1994[39] | Multifaceted | • Aimed at doctors<br>• Use of two interventions: educational and multifaceted intervention<br>• Educational component: exam component + hospital-administered course<br>• Distribution of guidelines<br>• Audit and feedback<br>• Multiple intervention study: 1 control group (group 1), 1 continuing medical education group (CME; group 2), 1 CME + quality assurance group (QA; group 3)<br>• Comparator: no intervention vs. CME only vs. CME + QA |
| Overhage et al, 1996[46] | Alert (computer) | • Aimed at doctors<br>• Use of reminders: electronic alert<br>• Computer reminder program analyzed electronic medical records, reminders appeared on printed daily reports and at work station when entering order, suggestions for orders provided<br>• Comparator: physicians who received the intervention (electronic alert) vs. controls (reminders were not printed or displayed) |
| Dexter et al, 2001[41] | Alert (computer) | • Aimed at doctors and medical students<br>• Use of reminders: electronic alert<br>• Reminder generated when patient's electronic medical recorder included at least one indication for one of the selective preventative therapies, no evidence of contraindications to therapies, and no active orders for the therapy. Physicians could accept or reject the reminders with one or two keystrokes on the computer<br>• Comparator: no intervention (computer does not display the reminder) vs. intervention |
| Kucher et al, 2005[45] | Alert (computer) | • Aimed at doctors<br>• Use of reminders: electronic alert<br>• Computer program that identified patients at risk for VTE; if patient at risk then computer reviews orders to identify current medications and then alerts responsible physician to patient's risk of VTE. MD required to acknowledge the alteration then withheld or ordered prophylaxis |

| | | |
|---|---|---|
| | | • Comparator: no intervention (no specific prompt was provided to use guidelines for the prevention of VTE) vs. intervention (computer alert) |
| Fontaine et al, 2006[53] | Pre-Printed Order | • Aimed at doctors<br>• Use of reminders: preprinted orders<br>• All physicians in intervention group were required to use specific anticoagulant prescription forms featuring the recommended prescription criteria<br>• 4 groups: baseline control (group 1), baseline intervention (group 2), post-intervention control (group 3), post-intervention intervention (group 4).<br>• In January, baseline survey was performed. Intervention was implemented over the next 3 months, and the post-intervention survey was carried out in April.<br>• Comparator: no intervention (usual practices) vs. intervention; baseline vs. post-intervention |
| Labarere et al, 2007[52] | Multifaceted | • Aimed at doctors and nurses<br>• Use of multifaceted intervention<br>• Educational component: 1 hour on-site educational session re: prophylaxis against VTE, pocket size card of guidelines, posters, mailed data re: prophylaxis use in the department<br>• Development and distribution of guidelines<br>• Audit and feedback<br>• Comparator: group 1 = intervention targeted at physicians only vs. group 2 = intervention targeted at physicians and nurses |
| Piazza et al, 2009[49] | Alert (human) | • Aimed at doctors<br>• Use of reminders: human alert<br>• Responsible physicians alerted by another staff member if his or her patient was at high risk for VTE, and that VTE prophylaxis was recommended, based on point scale of VTE risk factors<br>• Comparator: doctors were either alerted or not alerted |
| Garcia et al, 2009[48] | Alert (human) | • Aimed at doctors<br>• Use of reminders: human alerts<br>• Pharmacist used history and physical exam available to determine VTE risk score. Pharmacist determined if VTE prophylaxis had been ordered for at-risk patient. Pharmacist notified admitting physician |

| | | |
|---|---|---|
| | | • Comparator: no intervention (usual care) vs. intervention |
| Hinchey et al, 2010[42] | Multifaceted | • Aimed at doctors<br>• Use of multifaceted interventions<br>• Reminders (standard orders (including for VTE prophylaxis), pathways, protocols, standardized dysphagia screens, atrial fibrillation reminder stickers), written information, face-to-face interview, audit and feedback<br>• Comparator: control group (audit, feedback, and benchmark information) vs. intervention group (audit, feedback, and benchmark information plus a multifaceted intervention) |
| Chapman et al, 2011[47] | Alert (human) | • Did not report who the intervention was aimed at<br>• Use of reminders: human alerts<br>• A trained nurse assessed participants and if necessary requested prophylaxis or ceased prophylaxis to reflect the guidelines. The type of guidelines (local, consensus, international) was not stated<br>• Comparator: standard care vs. intervention |
| Pai et al, 2013[50] | Multifaceted | • Aimed at medical wards<br>• Use of multifaceted intervention<br>• Education sessions, standardized risk assessment algorithm and physicians' orders, audit, and feedback<br>• Comparator: no intervention (no active or passive knowledge-translation strategies to improve thromboprophylaxis) vs. intervention |
| Cavalcanti et al, 2016[43] | Multifaceted | • Aimed at team<br>• Use of multifaceted intervention<br>• Daily multidisciplinary rounds to include the use of a checklist and discussion of goals of care, reminder via SMS messages one to three times a week to ensure follow-through with checklist adherence and goals of care that targeted a broad spectrum of care processes including thromboprophylaxis<br>• The checklist was developed based on the clinical practice guideline development cycle<br>• Comparator: routine care and no pre-intervention training vs. intervention |
| Roy et al, 2016[51] | Multifaceted | • Aimed at doctors and residents<br>• Use of multifaceted intervention that included an alert component |

| | | |
|---|---|---|
| | | • Educational lectures, posters and pocket cards, computerized clinical decision support systems and computerized reminders<br>• Comparator: no intervention vs. intervention |

CME: continuing medical education

DVT: deep vein thrombosis

MD: medical doctor

QA: quality assurance

VTE: venous thromboembolism

## Methodological quality of included studies

The methodological quality of the included studies was variable (**Figure 2**). The overall ROB was high in two trials due to the existence of potential selection, performance, attrition, reporting, and other sources of bias.[42, 48] These two trials were excluded from meta-analyses. The assessment of the certainty of the evidence for improvement in outcomes was limited by the incomplete reporting of study design features that did not allow proper scoring of relevant study design features such as sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. While we were able to account for clustering using the reported intraclass correlation coefficient (ICC) where available,[43, 50-52] in many cases the ICC was not provided,[39, 41, 42, 46, 48, 53] leading to confidence intervals (CIs); that may be narrower than if clustering had been adequately accounted for. The unit of clusters were intensive care units (ICU) (1/10 CRTs), [43] medical teams (2/10 CRTs), [41 48] medical wards/departments (3/10 CRTs), [46, 52, 53] and hospitals (4/10 CRTs). [39, 42, 50, 51]

## Effects of interventions

**Table 3** summarizes the results from the meta-analyses conducted for the primary and secondary outcomes, and **Figure 3** and **Figure 4** depict the forest plots for the meta-analyses. Funnel plots are shown in Supplement as **Figures S1, S2, and S3**. There was a near symmetrical distribution of individual trials around the pooled estimate of effect in each meta-analysis, particularly for the alerts interventions (outcome RAP) and the multifaceted interventions (outcome RP).

### Comparison of alerts with standard care

Alerts interventions were associated with three types of changes:

- A 21% absolute increase in the proportion of patients who received prophylaxis (RD 0.21, 95% CI 0.15 to 0.27; three studies; 5057 participants; $I^2$ = 75%; low-certainty evidence);
- A 16% absolute increase in the proportion of patients who received appropriate prophylaxis (RD 0.16, 95% CI 0.12 to 0.20; three studies; 1820 participants; $I^2$ = 0; moderate-certainty evidence);
- A 36% relative risk decrease in the risk of symptomatic VTE at 3-months post-intervention (RR 0.64, 95% CI 0.47 to 0.86; three studies; 5353 participants; $I^2$ = 15%; low-certainty evidence) (**Figure 3**).

Subgroup analyses to address statistical heterogeneity were not feasible as there were not enough studies to pool subgroup results and distinguish chance from subgroup differences.

### Comparison of multifaceted interventions with standard care or another intervention

Multifaceted interventions were associated with a small increase in the proportion of patients who received prophylaxis in the intervention groups, with no heterogeneity between individual studies when cluster design effect adjustment was performed (RD 0.04, 95%CI 0.02 to 0.06; five studies; 9198 participants; $I^2$ = 0%; moderate-certainty evidence) (**Figure 4**).

### Comparison of educational interventions with standard care

One study that compared the effectiveness of using educational and multifaceted interventions to control, reported that educational interventions were associated with a non- significant decrease in the proportion of patients who received prophylaxis (RD -0.02, 95% CI -0.09 to 0.05; 1 study; 1,311 participants), but were less effective than a multifaceted intervention.[39]

Comparison of pre-printed orders with standard care

One study reported the use of written thromboprophylaxis prescription aids, which was associated with a non- significant decrease in the proportion of patients who received prophylaxis compared to the group that did not receive pre-printed orders (RD -0.05, 95% CI -0.12 to 0.02; one study; 719 participants).[53]

Head-to-head comparisons

One study reported comparisons between an educational intervention (continuing medical education) and a multifaceted intervention (continuing medical education in association with a quality assurance program), each compared to a control group (standard of care). The educational intervention was associated with a 2% decrease in the proportion of patients who received prophylaxis (RD -0.02, 95% CI -0.09 to 0.05) and the multifaceted intervention was associated with a 4% increase in the proportion of patients who received prophylaxis (RD 0.04, 95% CI -0.03 to 0.11).[39]

**Table 3:** Summary of main findings

| Intervention | Outcome | Number of Trials | Number of Patients | Comparative risk (Study population) | | Measure of association (95% CI), $I^2$ Statistic | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|---|---|
| | | | | Control | Intervention | | |
| Alerts Interventions | Received prophylaxis [a] | 3 studies | 5,057 participants | 18 % | 39 % | **RD** 0.21 [0.15, 0.27]; 75% | ⊕⊕⊖⊖ **Low**[1] |
| | Received appropriate prophylaxis [a] | 3 studies | 1,820 participants | 30 % | 46 % | **RD** 0.16 [0.12, 0.20]; 0% | ⊕⊕⊕⊖ **Moderate**[2] |
| | Symptomatic VTE | 3 studies | 5,353 participants | 6 % | 4 % | **RR** 0.64 [0.47, 0.86]; 15% | ⊕⊕⊖⊖ **Low**[3] |
| Multifaceted interventions | Received prophylaxis [b] | 5 studies | 9,198 participants | 47% | 51% | **RD** 0.04 [0.00, 0.06]; 0% | ⊕⊕⊕⊖ **Moderate**[4] |

[a] Clustered trials did not provide sufficient data (intra-class correlation (ICC) or adjusted confidence intervals) for us to pool cluster adjusted estimates.
[b] ICCs were available for 4/5 trials included in this meta-analysis. Adjustment for the cluster design effect was performed via reported ICCs and no ICC was applied to the one trial that did not report an ICC. Total patients are lower due to the cluster design effect applied to the numbers of events and participants.

**GRADE assessment**
[1] We downgraded the level of certainty of evidence from high to low based on the following reasons: serious study limitations and some inconsistency of pooled results.
[2] We downgraded the level of certainty of evidence from high to moderate based on the following reasons: serious study limitations.
[3] We downgraded the level of certainty of evidence from high to low based on the following reasons: serious study limitations and some imprecision of pooled results related to the small number of events.
[4] We downgraded the level of certainty of evidence from high to moderate based on the following reasons: serious study limitations

**Additional analyses**

A sensitivity analysis removing the high ROB trial in the meta-analysis of studies with alerts interventions[48] did not substantially impact the point estimate. A sensitivity analysis for the estimation of missing ICCs in the meta-analysis of studies with multifaceted interventions showed similar point estimates and similar variance. A sensitivity analysis was done removing the multifaceted intervention study that included an alert component, and was associated with a decrease in the pooled RD (RD 0.02, 95% CI -0.02 to 0.06) with the result no longer statistically significant, indicating that alerts might play a role in the estimate effect of multifaceted interventions. A sensitivity analysis to ensure there was not contamination between intervention groups where the one multifaceted intervention including an alert[51] was added to the alerts (RP) analysis did not substantially change the significance of the result (RD of 0.15 [0.02,0.27]). The sensitivity analyses using a fixed-effect approach did not change our point estimates.

**Planned analyses without sufficient data for meta-analysis**

Mortality and safety outcomes such as major and minor bleeding did not appear to differ in frequency between interventions and control groups. However, we were unable to provide pooled effect estimates on the relative effectiveness of each type of intervention for all primary and secondary outcomes.

While not directly compared to each other, computer alerts seemed to be more effective than human alerts in increasing the proportion of patients who received appropriate prophylaxis and reducing the risk of symptomatic VTE at 3 months post intervention. Multifaceted interventions that included an alert component also appeared to be more effective than those without an alert component in increasing the proportion of patients who received prophylaxis and appropriate prophylaxis, although there were not enough studies to conduct a pooled analysis.

All outcomes and interventions subgroup categories without sufficient data for meta-analysis are reported in detail in the full Cochrane review.[36]

## DISCUSSION

**Summary of main results**

The main new finding from our updated review which was focused on RCTs only was that alerts interventions, whether computer alerts or human alerts, increased the absolute proportion of patients who received thromboprophylaxis by 21%, increased the absolute proportion of patients who received appropriate thromboprophylaxis by 16%, and decreased the relative incidence of symptomatic VTE at 3-month post treatment by 36%. Multifaceted interventions were associated with a modest 4% absolute increase in the prescription of thromboprophylaxis.

**Quality of evidence and study limitations**

This updated review improves upon prior meta-analyses conducted in this area as it was restricted to RCTs only, thus providing a higher level of evidence, less widely differing estimates (i.e., heterogeneity in results) across studies, more appropriate comparisons (i.e., narrower confidence intervals) of pooled effects due to the reduced between-study variance, lower ROB of included studies, and better quality of evidence for improvement in outcomes. Even if meta-analyses in our updated review were based on relatively small numbers of studies, we included a large number of patients (N = 33,207 participants). We were able to account for clustering in one meta-analysis. The certainty of evidence for the improvement in outcomes was low or moderate in this updated review, as compared with very low in our previous review. The level of

certainty of the evidence was downgraded from high to moderate or low because of methodological limitations in the included RCTs, and/or unexplained statistical heterogeneity in the pooled result, and/or imprecision of pooled results related to the small number of VTE events (less than 300). Despite the fact that we could not assess for the presence of publication bias because all analyses were underpowered to distinguish chance from real asymmetry, there was a nearly symmetrical distribution of individual trials around the pooled estimate of effect in each meta-analysis. A number of factors could contribute to the perfect symmetry of the funnel plots, including selective outcome reporting, differences in methodological quality among studies, poor methodological quality leading to spuriously inflated effects in smaller studies, true heterogeneity, artefact, and chance.[38]

Due to the lack of published trials, we were unable to provide quantitative estimates of the effects of the different types of system-wide interventions on the prescription of thromboprophylaxis and on key outcomes such as appropriate thromboprophylaxis, mortality, and safety outcomes.

### Agreements and disagreements with other reviews

Our findings are in agreement with other previous systematic reviews.[34, 35, 54-61] Only two of the previous reviews performed a meta-analysis.[35, 57] In our previous review, multifaceted interventions were found to be the most effective system-wide intervention in observational studies.[35] In the most recent systematic review and meta-analysis, the use of computer-based clinical decision support system in observational studies was associated with an increased rate of ordering appropriate thromboprophylaxis and a reduced rate of VTE in hospitalized surgical patients.[57] The additional findings from our updated review compared with other reviews are most likely due to the inclusion of the largest number of RCTs involving a large number of hospitalized medical and surgical patients at risk for VTE.

### Implications for practice

Our findings provided low- to moderate-certainty evidence to support the use of system-wide interventions to improve the prescription of thromboprophylaxis and decrease the incidence of symptomatic VTE in hospitalized adult medical and surgical patients at risk for VTE. Our results suggest that alerts interventions are associated with significant improvements in the prescription of prophylaxis. We also found that in individual studies that reported the outcome symptomatic VTE, the risk of symptomatic VTE was significantly reduced with alerts interventions, particularly with computer alerts. Multifaceted interventions were less effective overall than alerts interventions. Due to a lack of studies, we were not able to assess if multifaceted interventions that include an alert component were more effective than multifaceted interventions that did not include an alert.

### Implications for research

The effect of system-wide interventions on important clinical outcomes such as VTE, mortality and safety outcomes should be assessed in well-designed multicenter RCTs that ideally include university-affiliated and community hospitals of various sizes. In addition, rates of prescription of appropriate prophylaxis should be reported. Future research should also evaluate costs related to the implementation of various system-wide interventions. Finally, research should be conducted to better understand why such interventions do not have a larger effect on prescribing behaviours.

## CONCLUSION

This systematic review assessed the effectiveness of various system-wide interventions aimed to increase the use of VTE prophylaxis and decrease the incidence of VTE in hospitalized patients. Alerts interventions (e.g. computer alerts or human alerts) increased the prescription of appropriate thromboprophylaxis and decreased the incidence of symptomatic VTE in hospitalized medical and surgical patients at risk for VTE. This updated systematic review helps to identify the most effective system-wide interventions that could help healthcare providers to improve the use of appropriate VTE prophylaxis and thereby reduce the morbidity and the mortality associated with VTE in hospital.

## FIGURE LEGENDS

**Figure 1.** PRISMA flow diagram for Cochrane review updates demonstrating the outcomes of the search process, and the inclusion of studies in the updated Cochrane systematic review and meta-analysis.
CDSR: Cochrane Database of Systematic Reviews
CENTRAL: Central Register of Controlled Trials
CINAHL: Cumulative Index to Nursing and Allied Health Literature
DARE: Database of Abstracts of Reviews of Effects
LILACS: Latin American and Caribbean Health Sciences Literature
NHSEED: NHS Economic Evaluation Database
RCT: Randomized Controlled Trial

**Figure 2.** Methodological quality graph: review authors' judgments about each methodological quality item for each included study

**Figure 3.** Forest plot and risk of bias assessment - comparison of alerts intervention with no intervention (standard care).
Risk of bias legend:
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

**Figure 4.** Forest plot and risk of bias assessment - comparison of multifaceted intervention with no intervention (standard care) or another intervention for the primary outcome 'Proportion of patients who received prophylaxis'
(1) Intraclass correlation coefficient not reported
Risk of bias:
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## FOOTNOTES

**Contribution:** All authors contributed to the original Cochrane review and have approved this abridge Cochrane review article.

1. Article reviewers: Dr Susan Kahn (SK), Gisèle Diendéré (GD), David R Morrison (DM)

2. Drafting the manuscript: SK, GD, DM

3. Resolving disputes: SK, GD, DM

4. Statistical expertise: Alexandre Piché (AP), Dr Kristian B Filion (KF)

5. Content expertise: SK, KF, James D. Douketis (JD), Jessica Emed (JE), Dr André Roussin (AR), Dr Vicky Tagalakis (VT), Dr William Geerts (WG)

6. Administrative coordination: GD

7. Literature searches: DM, Dr Adi J Klil-Drori (AK), Martin Morris (MM)

8. Revising the manuscript: All authors

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SK has received grant support from public granting agencies (CIHR) for research on the treatment of venous thrombosis. She participated in industry-sponsored advisory board meetings (Boehringer-Ingelheim, Servier Canada, one meeting for each entity), on the treatment of venous thrombosis and provided expert testimony for the Canadian Medical Protective Association. SK also reports that Sanofi Aventis has partnered with her institution to help create a center of excellence in thrombosis and anticoagulation.

AK: AK's institution has received funds from the Young Investigator Award from the American Society of Clinical Oncology Conquer Cancer Foundation. AJK reports receiving payments from Bristol Myers Squibb for lectures.

JD: JD reports receiving funds from board memberships of Bayer, Boehringer-Ingelheim, Bristol-Myers-Squibb, Daiichi-Sankyo, Pfizer, and Sanofi; consultancy fees from Actelion, Janssen Research, and Development; funds for speaking at educational activities; royalties

from the Merck Manual, Up-to-Date; JD's institution has received a grant from Boehringer-Ingelheim.

JE: JE received an honorarium for participation in a single meeting (focus group) with LEO Pharma for work unrelated to the submitted review.

AR: AR reports board membership and consultancy activities for BMS, BI, Pfizer, and Bayer, and received payment for lectures from BMS, BI, Bayer, and Pfizer not related to this review. AR also reports that his institution has received a CIHR grant for AIDS vascular research, and payment for development of educational presentations from BI, Bayer, BMS, and Pfizer for the preparation of university-accredited symposiums and slide kits.

VT: VT has received, and currently holds grant support from the CIHR for research in venous thrombosis; has engaged in lectures sponsored by companies that manufacture anticoagulants (Leo Pharma, Bristol Myer Squibb, and Pfizer); has received a grant from a manufacturer of an anticoagulant (Sanofi Aventis).

MM: reports receiving funds from American Academy of Clinical Toxicology for creation of search strategies for systematic reviews, and from International Team for Implantology for peer reviewing of search strategy.

WG: WG reports consultancy (Bayer Healthcare, Pfizer, Sanofi) and payment for lectures (Bayer Healthcare, Leo Pharma, Sanofi). Other support has been received by his institution from Sanofi for clinical and quality of care initiatives in thromboembolism within and outside of his institution. WG reports that these relationships in no way impact on his involvement with this Cochrane review.

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**Ethics approval:** Not needed.

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**Data sharing:** No additional data available.

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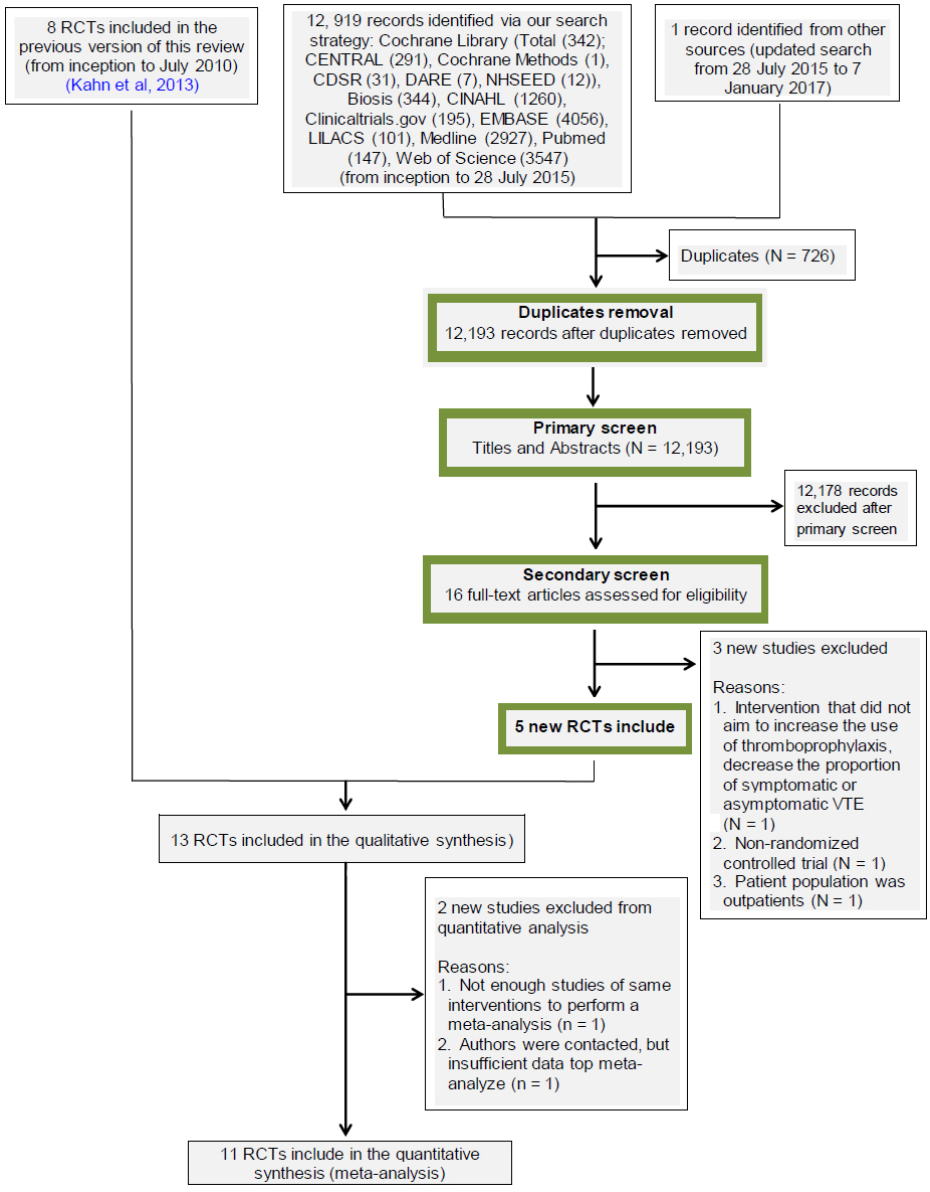
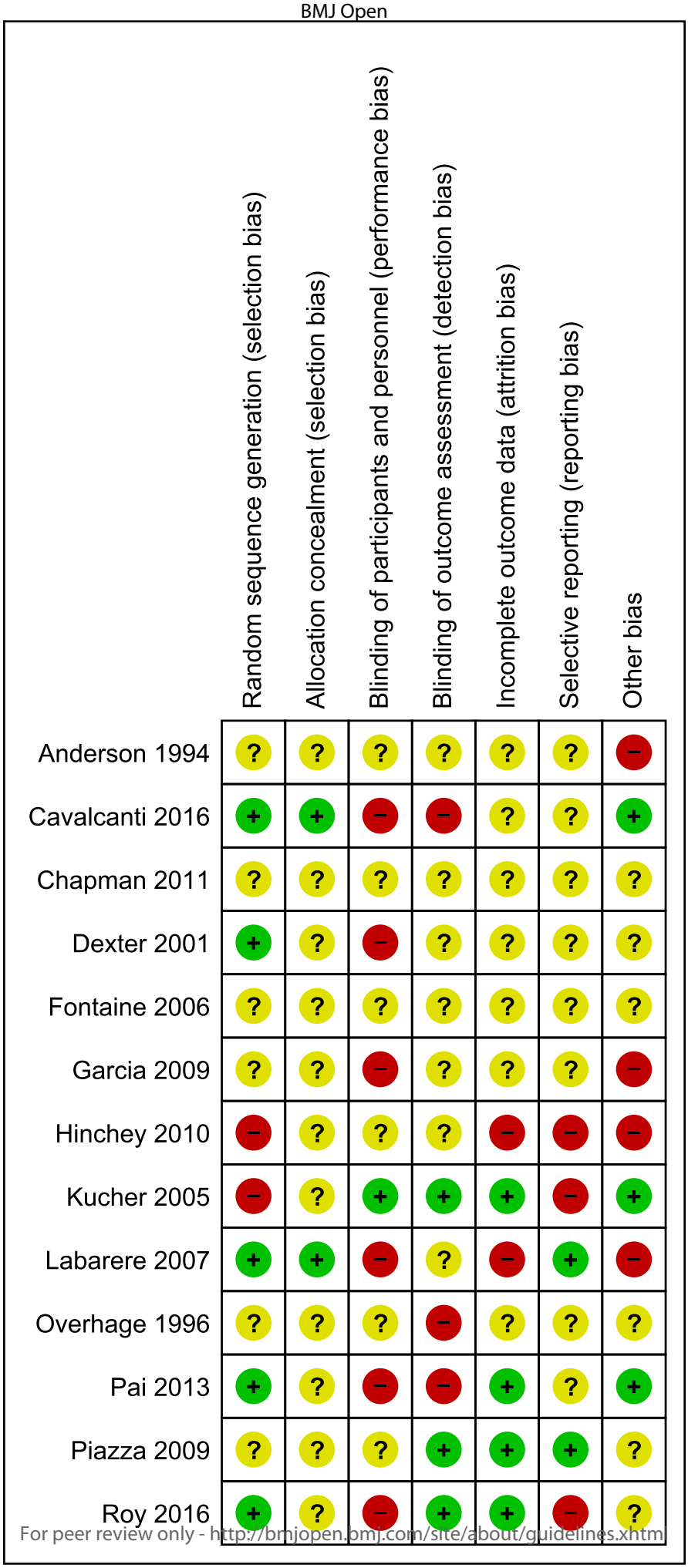
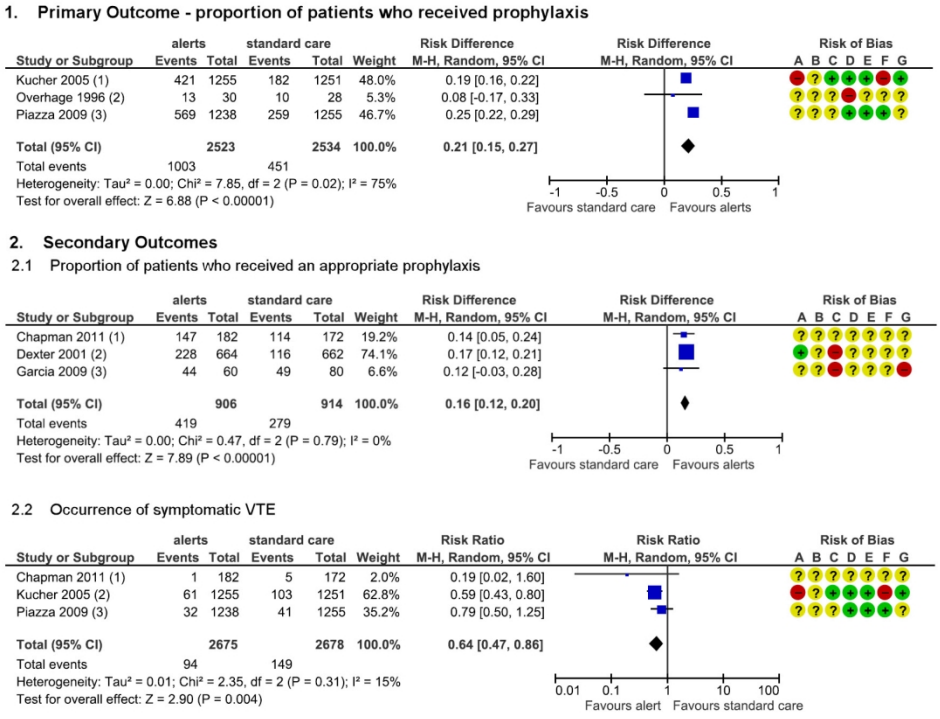



Figure 1. PRISMA flow diagram for Cochrane review updates demonstrating the outcomes of the search process, and the inclusion of studies in the updated Cochrane systematic review and meta-analysis
CDSR: Cochrane Database of Systematic Reviews
CENTRAL: Central Register of Controlled Trials
CINAHL: Cumulative Index to Nursing and Allied Health Literature
DARE: Database of Abstracts of Reviews of Effects
LILACS: Latin American and Caribbean Health Sciences Literature
NHSEED: NHS Economic Evaluation Database
RCT: Randomized Controlled Trial

246x315mm (96 x 96 DPI)


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Anderson 1994
Cavalcanti 2016
Chapman 2011
Dexter 2001
Fontaine 2006
Garcia 2009
Hinchey 2010
Kucher 2005
Labarere 2007
Overhage 1996
Pai 2013
Piazza 2009
Roy 2016

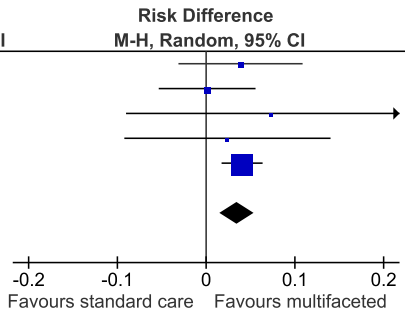



Forest plot and risk of bias assessment - comparison of alerts intervention with no intervention (standard care) Risk of bias legend: (A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias) (C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias) (E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias) (G) Other bias

493x394mm (96 x 96 DPI)

| Study or Subgroup | multifaceted Events | Total | standard care or other Events | Total | Weight | Risk Difference M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Anderson 1994 (1) | 251 | 456 | 175 | 342 | 8.1% | 0.04 [-0.03, 0.11] |
| Cavalcanti 2016 | 322 | 400 | 332 | 413 | 13.3% | 0.00 [-0.05, 0.06] |
| Labarere 2007 | 32 | 58 | 44 | 92 | 1.5% | 0.07 [-0.09, 0.24] |
| Pai 2013 | 35 | 109 | 41 | 138 | 2.9% | 0.02 [-0.09, 0.14] |
| Roy 2016 | 1886 | 3915 | 1445 | 3275 | 74.2% | 0.04 [0.02, 0.06] |
| **Total (95% CI)** | | **4938** | | **4260** | **100.0%** | **0.04 [0.02, 0.06]** |
| Total events | 2526 | | 2037 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 1.99, df = 4 (P = 0.74); I² = 0%
Test for overall effect: Z = 3.46 (P = 0.0005)





Footnotes
(1) ICC not reported

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

## SUPPLEMENTAL MATERIAL

# The effectiveness of interventions for the implementation of thromboprophylaxis in hospitalized patients at risk for venous thromboembolism: an updated abridged Cochrane systematic review and meta-analysis of Randomized Controlled Trials (RCT).

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[7]Department of Nursing, Jewish General Hospital, Montreal, Canada
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[9]Schulich Library of Physical Sciences, Life Sciences and Engineering, McGill University, Montreal, Canada
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Jewish General Hospital
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## Search Criteria

### 1. MEDLINE Ovid and Cochrane

1. exp Thrombosis/pc
2. exp Embolism/pc
3. (thrombosis or thrombotic or thrombus or thrombi or thromboembol*).tw.
4. (emboli* or embolus).tw.
6. clot?.tw.
7. (DVT or VTE or PE).tw.
8. or/1-7
9. exp Anticoagulants/
10. anticoagulant*.tw.
11. (hydroxycoumarins or acenocoumarol or acenocoumar* or minisintrom or nicoumalone or s?nc?umar or sintrom or s?nthrom* or ancrod or ancrod or arvin or venacil or agkistrodon or arwinor or (blood adj3 coagulat* adj3 inhibit*) or "citric acid" or uralyt or dalteparin or tedelparin or fr-860 or fr860 or dalteparin or kabi2165 or kabi-2165 or fragmin* or "dermatan sulfate" or chondroitin or dextran or dextrans or hemodex or promit or macrodex or saviosol or rheodextran or polyglucin or hyskon or rheomacrodex or infukoll or rheopolyglucin or rheoisodex or rondex or dic?umarol or dicoumarin or bishydroxycoumarin or edetic or tetracemate or calcitetracemate or edta or ethylenedinitrilotetraacetic or edetate or (calcium adj3 tetacine) or versenate or coprin or edathamil or versene or dinitrilotetraacetate or "chelaton 3" or enoxaparin* or pk10169 or "pk 10169" or emt-967 or emt96* or clexane or lovenox or emt-966 or (ethyl adj3 biscoumacetate) or ethyldicoumarol or pelentan or tromexan or carbethoxydicoumarol or foy or gabexate or heparin* or at?eroid* or liquaemin or nadroparin* or fraxiparin* or cy-216 or cy216 or "pentosan sulfuric polyester" or "pentosan sulphuric polyester" or ((polysulfate or polysulphate) adj sodium adj pentosan*) or ((sulfuric or sulphuric) adj polyester adj pentosan*) or fibrocid or ((hoe or bay or hoe-bay) adj "946") or ((pentosan* or polypentose or xylan) adj (sulphate or sulfate or sp54 or sp-54 or polysulfate* or polysulphate*)) or pz68 or pz-68 or elmiron or hemoclar or phenindione or pindione or phenyline or fenilin or phenylindanedione or dindevan or phenprocoumon or falithrom or phenprogramma or phenprocoumalol or marcumar or phenylpropylhydroxycumarinum or phenprocoumarol or liquamar or marcoumar or "protein c" or "protein s" or warfarin marevan or coumadin* or warfant or aldocumar or tedicumar or "beta 2-glycoprotein i" or apo-h or anticardiolipin or "apoliprotein h" or ec-vmfa or "endothelial cell viability maintaining factor" or "beta(2)gpi").tw.
12. exp Stockings, Compression/
13. exp Intermittent Pneumatic Compression Devices/
14. ((compression* or thromboembolism-deterrent or anti-embolism or TED) adj3 (stocking* or hose or hosiery or device*)).tw.
15. (prophylaxis or prophylactic).tw.
16. pc.fs.
17. (prevent* or reduce or reduction or diminish or decrease* or inhibit*).tw.
18. or/9-17
19. exp Medical Order Entry Systems/
20. exp Reminder Systems/
21. exp Drug Therapy, Computer-Assisted/
22. (("computeri?ed physician" or system) adj5 "order entry").tw.
23. CPOE.tw.
24. ((computeri?ed or automat* or medicat* or electronic*) adj5 (alert* or reminder*)).tw.
25. sticker?.tw.
26. prescription aid?.tw.

27. exp Decision Support Systems, Clinical/
28. decision support.tw.
29. CDS.tw.
30. e-iatrogenesis.tw.
31. alert fatigue.tw.
32. electronic tool?.tw.
33. exp Guideline/
34. exp Guidelines as Topic/
35. exp Guideline Adherence/
36. exp Clinical Protocols/
37. protocol*.tw.
38. guideline*.tw.
39. adhere*.tw.
40. (comply or compliance).tw.
41. or/19-40
42. exp Inpatients/ or exp Hospitalization/ or exp Hospitals/
43. (inpatient* or "in?patient*").tw.
44. exp Adolescent, Hospitalized/ or exp Child, Hospitalized/
45. (hospitali?e* or hospitali?ation).tw.
46. (admitted adj3 (hospital or patient*)).tw.
47. ("high risk" or "at risk").tw.
48. or/42-47
49. thromboprophyla*.mp.
50. 8 and 18 and 41 and 48
51. 48 and 49
52. 50 or 51
53. limit 52 to yr="1980 -Current"

**2. Embase Ovid**

1. exp thrombosis prevention/
2. exp embolism prevention/
3. (thrombosis or thrombotic or thrombus or thrombi or thromboembol*).tw.
4. (emboli* or embolus).tw.
5. (phlebothrombo* or phlebitis).tw.
6. exp blood clotting/
7. clot.tw.
8. (DVT or VTE or PE).ti,ab.
9. or/1-8
10. exp *anticoagulant agent/
11. anticoagulant*.tw.
12. (hydroxycoumarins or acenocoumarol or acenocoumar* or minisintrom or nicoumalone or s?nc?umar or sintrom or s?nthrom* or ancrod or ancrod or arvin or venacil or agkistrodon or arwinor or (blood adj3 coagulat* adj3 inhibit*) or "citric acid" or uralyt or dalteparin or tedelparin or fr-860 or fr860 or dalteparin or kabi2165 or kabi-2165 or fragmin* or "dermatan sulfate" or chondroitin or dextran or dextrans or hemodex or promit or macrodex or saviosol or rheodextran or polyglucin or hyskon or rheomacrodex or infukoll or rheopolyglucin or rheoisodex or rondex or dic?umarol or dicoumarin or bishydroxycoumarin or edetic or tetracemate or calcitetracemate or edta or ethylenedinitrilotetraacetic or edetate or (calcium adj3 tetacine) or versenate or coprin or edathamil or versene or dinitrilotetraacetate or "chelaton 3" or enoxaparin* or pk10169 or "pk

10169" or emt-967 or emt96* or clexane or lovenox or emt-966 or (ethyl adj3 biscoumacetate) or ethyldicoumarol or pelentan or tromexan or carbethoxydicoumarol or foy or gabexate or heparin* or at?eroid* or liquaemin or nadroparin* or fraxiparin* or cy-216 or cy216 or "pentosan sulfuric polyester" or "pentosan sulphuric polyester" or ((polysulfate or polysulphate) adj sodium adj pentosan*) or ((sulfuric or sulphuric) adj polyester adj pentosan*) or fibrocid or ((hoe or bay or hoe-bay) adj "946") or ((pentosan* or polypentose or xylan) adj (sulphate or sulfate or sp54 or sp-54 or polysulfate* or polysulphate*)) or pz68 or pz-68 or elmiron or hemoclar or phenindione or pindione or phenyline or fenilin or phenylindanedione or dindevan or phenprocoumon or falithrom or phenprogramma or phenprocoumalol or marcumar or phenylpropylhydroxycumarinum or phenprocoumarol or liquamar or marcoumar or "protein c" or "protein s" or warfarin marevan or coumadin* or warfant or aldocumar or tedicumar or "beta 2-glycoprotein i" or apo-h or anticardiolipin or "apoliprotein h" or ec-vmfa or "endothelial cell viability maintaining factor" or "beta(2)gpi").tw.
13. exp compression stocking/
14. ((compression* or thromboembolism-deterrent or anti-embolism or TED) adj3 (stocking* or hose or hosiery)).tw.
15. (prophylaxis or prophylactic).tw.
16. pc.fs.
17. (prevent* or reduce or reduction or diminish or decrease* or inhibit*).tw.
18. or/10-17
19. exp hospital information system/
20. exp reminder system/
21. exp computer assisted drug therapy/
22. (("computeri?ed physician" or system) adj5 "order entry").tw.
23. CPOE.tw.
24. ((computeri?ed or automat* or medicat* or electronic*) adj5 (alert* or reminder*)).tw.
25. sticker*.tw.
26. prescription aid*.tw.
27. exp decision support system/
28. "decision support".tw.
29. CDS.tw.
30. e-iatrogenesis.tw.
31. alert fatigue.tw.
32. electronic tool*.tw.
33. exp practice guideline/
34. exp clinical protocol/
35. (protocol* or guideline* or adhere*).tw.
36. (comply or compliance).tw.
37. or/19-36
38. exp hospital patient/ or exp hospitalization/ or (*exp * hospital/ and exp patient/)
39. (inpatient* or "in?patient").tw.
40. (hospitali?e* or hospitali?ation).tw.
41. (admitted adj3 (hospital or patient*)).tw.
42. ("high risk" or "at risk").tw.
43. or/38-42
44. thromboprophyla*.mp.
45. 9 and 18 and 37 and 43
46. 43 and 44
47. 45 or 46
48. limit 47 to yr="1980 -Current"

**3. BIOSIS previews Ovid**

1. (thrombosis or thrombotic or thrombus or thrombi or thromboembol*).mp.
2. (emboli* or embolus).mp.
3. (phlebothrombo* or phlebitis).mp.
4. clot*.mp.
5. (DVT or VTE or PE).tw.
6. or/1-5
7. anticoagulant*.mp.
8. (hydroxycoumarins or acenocoumarol or acenocoumar* or minisintrom or nicoumalone or s?nc?umar or sintrom or s?nthrom* or ancrod or ancrod or arvin or venacil or agkistrodon or arwinor or (blood adj3 coagulat* adj3 inhibit*) or "citric acid" or uralyt or dalteparin or tedelparin or fr-860 or fr860 or dalteparin or kabi2165 or kabi-2165 or fragmin* or "dermatan sulfate" or chondroitin or dextran or dextrans or hemodex or promit or macrodex or saviosol or rheodextran or polyglucin or hyskon or rheomacrodex or infukoll or rheopolyglucin or rheoisodex or rondex or dic?umarol or dicoumarin or bishydroxycoumarin or edetic or tetracemate or calcitetracemate or edta or ethylenedinitrilotetraacetic or edetate or (calcium adj3 tetacine) or versenate or coprin or edathamil or versene or dinitrilotetraacetate or "chelaton 3" or enoxaparin* or pk10169 or "pk 10169" or emt-967 or emt96* or clexane or lovenox or emt-966 or (ethyl adj3 biscoumacetate) or ethyldicoumarol or pelentan or tromexan or carbethoxydicoumarol or foy or gabexate or heparin* or at?eroid* or liquaemin or nadroparin* or fraxiparin* or cy-216 or cy216 or "pentosan sulfuric polyester" or "pentosan sulphuric polyester" or ((polysulfate or polysulphate) adj sodium adj pentosan*) or ((sulfuric or sulphuric) adj polyester adj pentosan*) or fibrocid or ((hoe or bay or hoe-bay) adj "946") or ((pentosan* or polypentose or xylan) adj (sulphate or sulfate or sp54 or sp-54 or polysulfate* or polysulphate*)) or pz68 or pz-68 or elmiron or hemoclar or phenindione or pindione or phenyline or fenilin or phenylindanedione or dindevan or phenprocoumon or falithrom or phenprogramma or phenprocoumalol or marcumar or phenylpropylhydroxycumarinum or phenprocoumarol or liquamar or marcoumar or "protein c" or "protein s" or warfarin marevan or coumadin* or warfant or aldocumar or tedicumar or "beta 2-glycoprotein i" or apo-h or anticardiolipin or "apoliprotein h" or ec-vmfa or "endothelial cell viability maintaining factor" or "beta(2)gpi").tw.
9. ((compression* or thromboembolism-deterrent or anti-embolism or TED) adj3 (stocking* or hose or hosiery)).mp.
10. (prophylaxis or prophylactic).mp.
11. (prevent* or reduce or reduction or diminish or decrease* or inhibit*).mp.
12. or/7-11
13. (("computeri?ed physician" or system) adj5 "order entry").tw.
14. CPOE.tw.
15. ((computeri?ed or automat* or medicat* or electronic*) adj5 (alert* or reminder*)).tw.
16. sticker*.tw.
17. prescription aid*.tw.
18. "decision support".tw.
19. CDS.tw.
20. e-iatrogenesis.tw.
21. alert fatigue.tw.
22. electronic tool*.tw.
23. (guideline* or protocol* or adhere*).tw.
24. (comply or compliance).tw.
25. or/13-24
26. (inpatient* or "in?patient").tw.
27. (hospitali?e* or hospitali?ation).tw.

28. (admit* adj3 (hospital or patient*)).tw.
29. ("high risk" or "at risk").tw.
30. or/26-29
31. thromboprophyla*.mp.
32. 6 and 12 and 25 and 30
33. 30 and 31
34. 32 or 33

**4. CINAHL**

S46 S44 OR S45
S45 S42 AND S43
S44 S8 AND S15 AND S32 AND S42
S43TI thromboprophyla* OR AB thromboprophyla*
S42 S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41
S41TI ("high risk" OR "at risk") OR AB ("high risk" OR "at risk")
S40TI (admitted N3 (hospital or patient*)) OR AB (admitted N3 (hospital or patient*))
S39TI (hospitali?e* OR hospitali?ation) OR AB (hospitali?e* OR hospitali?ation)
S38(MH "Child, Hospitalized")
S37(MH "Adolescent, Hospitalized")
S36TI (inpatient* OR in?patient*) OR AB (inpatient* OR in?patient*)
S35(MH "Hospitals+")
S34(MH "Hospitalization+")
S33(MH "Inpatients")
S32 S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31
S31TI (protocol* or guideline* OR adhere*) OR AB (protocol* or guideline* OR adhere*)
S30(MH "Practice Guidelines")
S29TI electronic tool* OR AB electronic tool*
S28TI alert fatigue OR AB alert fatigue
S27TI e-iatrogenesis OR AB e-iatrogenesis
S26TI CDS OR AB CDS
S25TI decision support* OR AB decision support*
S24(MH "Decision Support Systems, Clinical")
S23TI prescription aid* OR AB prescription aid*
S22TI sticker* OR AB sticker*
S21TI ((computeri?ed or automat* or medicat* or electronic*) N5 (alert* or reminder*)) OR AB ((computeri?ed or automat* or medicat* or electronic*) N5 (alert* or reminder*))
S20TI CPOE OR AB CPOE
S19TI (("computeri?ed physician" or system) N5 "order entry") OR AB (("computeri?ed physician" or system) N5 "order entry")
S18(MH "Drug Therapy, Computer Assisted")
S17(MH "Reminder Systems")
S16(MH "Electronic Order Entry")
S15 S9 OR S10 OR S11 OR S12 OR S13 OR S14
S14TI (prevent* or reduce or reduction or diminish or decrease* or inhibit*) OR AB (prevent* or reduce or reduction or diminish or decrease* or inhibit*)
S13TI (prophylaxis or prophylactic) OR AB (prophylaxis or prophylactic)
S12TI ((compression* or thromboembolism-deterrent or anti-embolism or TED) N3 (stocking* or hose or hosiery or device*)) OR AB ((compression* or thromboembolism-deterrent or anti-embolism or TED) N3 (stocking* or hose or hosiery or device*))

S11(MH "Compression Garments")
S10TI anticoagulant* OR AB anticoagulant*
S9(MH "Anticoagulants+")
S8 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7
S7TX (DVT OR VTE OR PE) OR AB (DVT OR VTE OR PE)
S6TX (clot or clots) OR AB (clot or clots)
S5TX (phlebothrombo* or phlebitis) OR AB (phlebothrombo* or phlebitis)
S4TX (emboli* OR embolus) OR AB (emboli* or embolus)
S3TX (thrombosis or thrombotic or thrombus or thrombi or thromboembol*) OR AB (thrombosis or thrombotic or thrombus or thrombi or thromboembol*)
S2(MH "Embolism+/PC")
S1(MH "Thrombosis+/PC")

**5. WEB OF SCIENCE**

#1 TS=(thrombosis or thrombotic or thrombus or thrombi or thromboembol* OR emboli* OR embolus OR phlebothrombo* or phlebitis OR clot OR DVT OR VTE OR PE)
#2 TS=(anticoagulant* OR hydroxycoumarins or acenocoumarol or acenocoumar* or minisintrom or nicoumalone or s?nc?umar or sintrom or s?nthrom* or ancrod or ancrod or arvin or venacil or agkistrodon or arwinor or (blood NEAR/3 coagulat* NEAR/3 inhibit*) or "citric acid" or uralyt or dalteparin or tedelparin or fr-860 or fr860 or dalteparin or kabi2165 or kabi-2165 or fragmin* or "dermatan sulfate" or chondroitin or dextran or dextrans or hemodex or promit or macrodex or saviosol or rheodextran or polyglucin or hyskon or rheomacrodex or infukoll or rheopolyglucin or rheoisodex or rondex or dic?umarol or dicoumarin or bishydroxycoumarin or edetic or tetracemate or calcitetracemate or edta or ethylenedinitrilotetraacetic or edetate or (calcium NEAR/3 tetacine) or versenate or coprin or edathamil or versene or dinitrilotetraacetate or "chelaton 3" or enoxaparin* or pk10169 or "pk 10169" or emt-967 or emt96* or clexane or lovenox or emt-966 or (ethyl NEAR/3 biscoumacetate) or ethyldicoumarol or pelentan or tromexan or carbethoxydicoumarol or foy or gabexate or heparin* or at?eroid* or liquaemin or nadroparin* or fraxiparin* or cy-216 or cy216 or "pentosan sulfuric polyester" or "pentosan sulphuric polyester" or ((polysulfate or polysulphate) NEAR/1 sodium NEAR/1 pentosan*) or ((sulfuric or sulphuric) NEAR/1 polyester NEAR/1 pentosan*) or fibrocid or ((hoe or bay or hoe-bay) NEAR/1 "946") or ((pentosan* or polypentose or xylan) NEAR/1 (sulphate or sulfate or sp54 or sp-54 or polysulfate* or polysulphate*)) or pz68 or pz-68 or elmiron or hemoclar or phenindione or pindione or phenyline or fenilin or phenylindanedione or dindevan or phenprocoumon or falithrom or phenprogramma or phenprocoumalol or marcumar or phenylpropylhydroxycumarinum or phenprocoumarol or liquamar or marcoumar or "protein c" or "protein s" or warfarin marevan or coumadin* or warfant or aldocumar or tedicumar or "beta 2-glycoprotein i" or apo-h or anticardiolipin or "apoliprotein h" or ec-vmfa or "endothelial cell viability maintaining factor" or "beta(2)gpi" OR ((compression* or thromboembolism-deterrent or anti-embolism or TED) NEAR/3 (stocking* or hose or hosiery)) OR prophylaxis or prophylactic or prevent* or reduce or reduction or diminish or decrease* or inhibit*)
#3 TS=((("computeri?ed physician" or system) NEAR/5 "order entry") OR CPOE OR ((computeri?ed or automat* or medicat* or electronic*) NEAR/5 (alert* or reminder*)) or sticker* OR "prescription aid*" OR "decision support" OR CDS OR e-iatrogenesis OR "alert fatigue" OR "electronic tool*" OR guideline* or protocol* OR adhere* OR comply or compliance)
#4 TS=(inpatient* OR "in-patient*" or hospitali?e* or hospitali?ation or (admitted NEAR/3 (hospital* or patient*)) OR "high risk" or "at risk")
#5 TS=(thromboprophyla*)
#6 #4 AND #3 AND #2 AND #1

#7 #5 AND #4
#8 #7 OR #6

**6. LILACS**

((thrombosis or thrombotic or thrombus or thrombi or thromboembol* or phlebothrombo* or phlebitis or clot* or DVT or VTE) AND (prophylaxis or prophylactic or prevent* or reduce or reduction or diminish or decrease* or inhibit*)) OR thromboprophyla*

**7. PubMed**

#65,"Search #64 NOT medline[sb]"
#64,"Search #62 OR #63"
#63,"Search #60 AND #61"
#62,"Search #15 AND #27 AND #52 AND #60"
#61,"Search thromboprophyla*[tw]"
#60,"Search #52 OR #53 OR #54 OR #55 OR #56 OR #58 OR #59"
#59,"Search high risk[tw] or at risk[tw]"
#58,"Search admitted[tw] AND (hospital[tw] or patient[tw] or patients[tw])"
#56,"Search hospitalise*[tw] or hospitalisation[tw] or hospitalize*[tw] or hospitalization[tw]"
#55,"Search Adolescent, Hospitalized[Mesh] or Child, Hospitalized[Mesh]"
#54,"Search inpatient[tw] or inpatients[tw] or in-patient[tw] or in-patients[tw]"
#53,"Search Inpatients[Mesh] or Hospitalization[Mesh] or Hospitals[Mesh]"
#52,"Search #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51"
#51,"Search comply[tw] or compliance[tw]"
#50,"Search adhere*[tw]"
#49,"Search guideline*[tw]"
#48,"Search protocol*[tw]"
#47,"Search Clinical Protocols[Mesh]"
#46,"Search Guideline Adherence[Mesh]"
#45,"Search Guidelines as Topic[Mesh]"
#44,"Search Guideine[Mesh] Schema: all"
#43,"Search Guideine[Mesh]"
#42,"Search electronic tool*[tw]"
#41,"Search alert fatigue[tw]"
#40,"Search e-iatrogenesis[tw]"
#39,"Search CDS[tw]"
#38,"Search decision support[tw]"
#37,"Search ""Decision Support Systems, Clinical""[Mesh]"
#36,"Search prescription aid*[tw]"
#35,"Search sticker*[tw]"
#34,"Search ((computerised or computerized or automat* or medicat* or electronic*) AND (alert* or reminder*))[tw]"
#33,"Search CPOE[tw]"
#32,"Search (((""computerised physician"" or ""computerized physician"" or system) AND ""order entry"")[tw]"
#31,"Search ""Drug Therapy, Computer-Assisted""[Mesh]"
#30,"Search ""Reminder Systems""[Mesh]"

#29,"Search ""Medical Order Entry Systems""[Mesh]"
#27,"Search #16 OR #17 OR #19 OR #21 OR #23 OR #24 OR #25 OR #26"
#26,"Search prevent*[tw] or reduce[tw] or reduction[tw] or diminish[tw] or decrease*[tw] or inhibit*[tw]"
#25,"Search prophylaxis[tw] or prophylactic[tw]"
#24,"Search ((compression* or thromboembolism-deterrent or anti-embolism or TED) AND (stocking* or hose or hosiery or device*))[tw]"
#23,"Search ""Intermittent Pneumatic Compression Devices""[Mesh]"
#21,"Search ""Stockings, Compression""[Mesh]"

#19,"Search hydroxycoumarins[tw] or acenocoumarol[tw] or acenocoumar*[tw] or minisintrom[tw] or nicoumalone[tw] or syncumar[tw] or sintrom[tw] or sinthrom*[tw] or synthrom*[tw] or ancrod[tw] or arvin[tw] or venacil[tw] or agkistrodon[tw] or arwinor[tw] or blood coagulation inhibitor[tw] or blood coagulation inhibitors[tw] or citric acid[tw] or uralyt[tw] or dalteparin[tw] or tedelparin[tw] or fr-860[tw] or fr860[tw] or dalteparin[tw] or kabi2165[tw] or kabi-2165[tw] or fragmin*[tw] or ""dermatan sulfate""[tw] or chondroitin[tw] or dextran[tw] or dextrans[tw] or hemodex[tw] or promit[tw] or macrodex[tw] or saviosol[tw] or rheodextran[tw] or polyglucin[tw] or hyskon[tw] or rheomacrodex[tw] or infukoll[tw] or rheopolyglucin[tw] or rheoisodex[tw] or rondex[tw] or dicumarol[tw] or dicoumarol[tw] or dicoumarin[tw] or bishydroxycoumarin[tw] or edetic[tw] or tetracemate[tw] or calcitetracemate[tw] or edta[tw] or ethylenedinitrilotetraacetic[tw] or edetate[tw] or (calcium AND tetacine)[tw] or versenate[tw] or coprin[tw] or edathamil[tw] or versene[tw] or dinitrilotetraacetate[tw] or ""chelaton 3""[tw] or enoxaparin*[tw] or pk10169[tw] or ""pk 10169""[tw] or emt-967[tw] or emt96*[tw] or clexane[tw] or lovenox[tw] or emt-966[tw] or ""ethyl biscoumacetate""[tw] or ethyldicoumarol[tw] or pelentan[tw] or tromexan[tw] or carbethoxydicoumarol[tw] or foy[tw] or gabexate[tw] or heparin*[tw] or ateroid*[tw] or atheroid*[tw] or liquaemin[tw] or nadroparin*[tw] or fraxiparin*[tw] or cy-216[tw] or cy216[tw] or ""pentosan sulfuric polyester""[tw] or ""pentosan sulphuric polyester""[tw] or ((polysulfate or polysulphate) AND sodium AND pentosan*)[tw] or ((sulfuric or sulphuric) AND polyester AND pentosan*)[tw] or fibrocid[tw] or ((hoe or bay or hoe-bay) AND ""946"")[tw] or ((pentosan* or polypentose or xylan)[tw] AND (sulphate or sulfate or sp54 or sp-54 or polysulfate* or polysulphate*))[tw] or pz68[tw] or pz-68[tw] or elmiron[tw] or hemoclar[tw] or phenindione[tw] or pindione[tw] or phenyline[tw] or fenilin[tw] or phenylindanedione[tw] or dindevan[tw] or phenprocoumon[tw] or falithrom[tw] or phenprogramma[tw] or phenprocoumalol[tw] or marcumar[tw] or phenylpropylhydroxycumarinum[tw] or phenprocoumarol[tw] or liquamar[tw] or marcoumar[tw] or ""protein c""[tw] or ""protein s""[tw] or ""warfarin marevan""[tw] or coumadin*[tw] or warfant[tw] or aldocumar[tw] or tedicumar[tw] or ""beta 2-glycoprotein i""[tw] or apo-h[tw] or anticardiolipin[tw] or ""apoliprotein h""[tw] or ec-vmfa[tw] or ""endothelial cell viability maintaining factor""[tw] or ""beta(2)gpi""[tw]"

#17,"Search anticoagulant*[tw]"
#16,"Search ""Anticoagulants""[Mesh]"
#15,"Search #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #14"
#14,"Search DVT[tiab] OR VTE[tiab] OR PE[tiab]"
#12,"Search clot[tw]
#11,"Search phlebothrombo*[tw] or phlebitis[tw]"
#10,"Search emboli[tw] or embolus[tw]"
#9,"Search thrombosis[tw] or thrombotic[tw] or thrombus[tw] or thrombi[tw] or thromboembol*[tw]"
#8,"Search ""Embolism/prevention and control""[Mesh]"
#7,"Search ""Thrombosis/prevention and control""[Mesh]"

**Table S1. Summary of study quality**

| Trial | Quantitative scores | Overall ROB |
|---|---|---|
| Anderson 1994 | -1 | Unclear |
| Overhage 1996 | -1 | Unclear |
| Dexter 2001 | 0 | Unclear |
| Kucher 2005 | +2 | Low |
| Fontaine 2006 | 0 | Unclear |
| Labarere 2007 | 0 | Unclear |
| Piazza 2009 | +3 | Low |
| Garcia 2009 | -2 | High |
| Hinchey 2010 | -4 | High |
| Chapman 2011 | 0 | Unclear |
| Pai 2013 | +1 | Unclear |
| Cavalcanti 2016 | +1 | Unclear |
| Roy 2016 | +1 | Unclear |

For each of the seven ROB domains, a negative score (-1) was assigned for each high ROB response, a score of zero was assigned for each unclear ROB response, and a positive score was assigned for each low ROB response.

Summary scores of less than -1 were considered as high ROB, summary scores of zero were considered as unclear ROB, and summary scores of greater than +1 were considered low ROB. Only two of the included studies were of low quality. High ROB was mainly related to selection, performance, attrition, reporting, and other biases.

## Figure S1

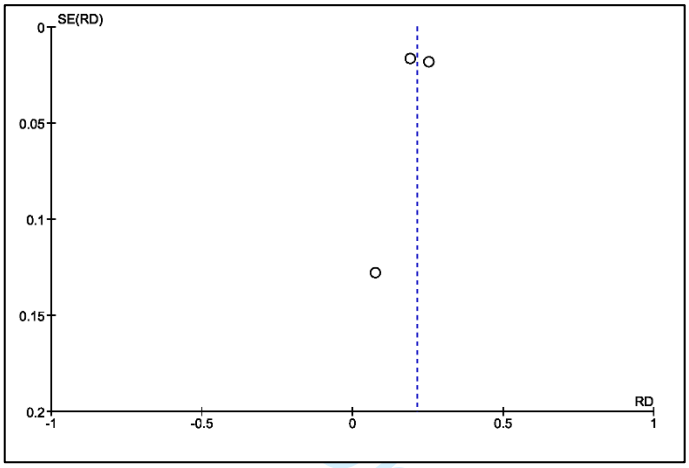


Figure S1, legend: Funnel plot of comparison: Alerts versus standard care, outcome: Received prophylaxis.

## Figure S2

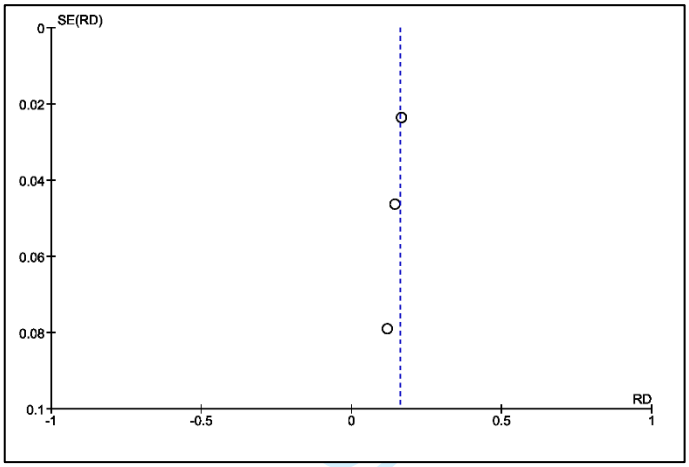


Figure S2, legend: Funnel plot of comparison: Alerts versus standard care, outcome: Received appropriate prophylaxis.

## Figure S3

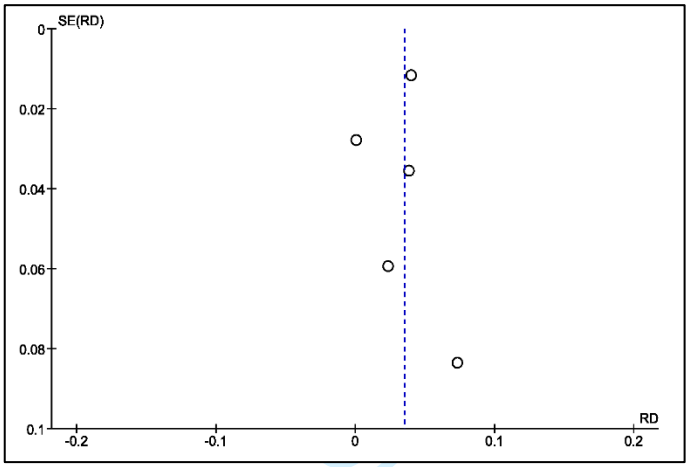


Figure S3, legend: Funnel plot of comparison: Multifaceted interventions versus standard care or another intervention, outcome: Received prophylaxis (adjusted)

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | **Page 0** |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | **Page 0** |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | **Page 1** |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | **Page 1** |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | **Page 1** |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | **Page 2** |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | **Page 2** |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | **Page 2** |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | **Page 3** |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | **Page 3** |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | **Page 3** |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | **Page 3** |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | **Page 3** |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | **Page 3** |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | **Page 3** |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | **Page 3 and 10** |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | **Page 4** |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | **Page 4-6** |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | **Page 7** |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | **Page 7-9** |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | **Page 7-9** |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | **Page 7** |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | **Page 10** |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | **Page 10** |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | **Page 10-11** |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | **Page 11** |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | **Page 12** |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.