

BMJ Open Effectiveness of interventions for the implementation of thromboprophylaxis in hospitalised patients at risk of venous thromboembolism: an updated abridged Cochrane systematic review and meta-analysis of randomised controlled trials

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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 hospitalised medical and surgical patients at risk of 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 preprinted orders when compared with 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 with control, we found absolute increase 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.

Strengths and limitations of this study

- This review was conducted following the *Cochrane Handbook for Systematic Reviews of Interventions*.
- We included all randomised controlled trials relevant to our research question.
- We preferentially accounted for clustering designs using the intracluster 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.

Trial registration number CD008201.

INTRODUCTION

Compared with persons in the community, hospitalised 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 3 months after hospitalisation underlies >50% of all cases of the population burden of VTE.^{3–5} VTE is a frequent complication in hospitalised medical and surgical patients, a leading cause of mortality and morbidity in hospitalised 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 third leading cause of preventable death and disability in hospital.^{7–11}

The appropriate use of thromboprophylaxis in hospitalised patients at risk of 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 hospitalised medical and surgical patients at risk of VTE.^{12–21} The prevention of VTE was ranked as the number 1 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 healthcare system as a whole, could help to improve prescription of appropriate thromboprophylaxis and ultimately reduce the risk of VTE in hospitalised 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 hospitalised medical and surgical patients at risk of VTE.³⁵ 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 organising 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 hospitalised medical and surgical patients at risk of VTE. In this updated review, we focus exclusively on the higher level of evidence provided by randomised controlled trials (RCTs), whereas our previous review also included observational studies. The implementation of effective interventions could help clinicians and other healthcare professionals to improve the use of appropriate thromboprophylaxis in hospitalised 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-randomisation such as even or odd date of birth) methods of allocation of interventions, which either randomised 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 hospitalised 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 hospitalised 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 hospitalised patients at risk of 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 preprinted 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, ie, 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), the Database of Abstracts of Reviews of Effects and the NHS Economic Evaluation Database, Latin American and Caribbean Health Sciences Literature 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 or their equivalent (where available), keywords, truncations and Boolean operators (see online 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 the following:

1. Description of study design: parallel-group, cross-over, cluster or factorial design, including cluster unit and intracluster correlation (ICC) if available.
2. Description of the randomisation procedure (unit of randomisation 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 centre characteristics): number of centres, university-affiliated hospital, community hospital, physician practice, type of healthcare system (public vs 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 (eg, age, sex, cancer patient and 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: pharmacological (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 (ROB).

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 ROB.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 ROB. We assessed all items listed as other potential sources of bias such as trial design biases (eg, 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 online supplementary 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 risk 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 preprinted 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 with multifaceted interventions that did not include an alert component.

We used Review Manager V.5.3 and SAS V.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 feasible only 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 (ie, chance).

Quality of evidence (GRADE)

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the quality of evidence for each outcome that we were able to meta-analyse, with the quality of evidence graded from high (best) to very low (worst).⁴⁴ The five GRADE considerations (ROB, 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 searched through conference abstracts and congress communications. Original investigators of included trials were also contacted to request missing and unpublished data. We examined funnel plots centred 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 the 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 alert intervention compared with 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 with 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 computerised 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 2 of the 14 intervention group centres. Thus, the overall effect of this multifaceted intervention might have been smaller than expected.
- ▶ One trial evaluated a preprinted orders intervention using predefined anticoagulant prescription forms as a passive reminder to use thromboprophylaxis, compared with 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 with the standard of care and with 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 preprinted orders intervention).⁵³ One type of comparison (educational intervention compared with the standard of care) was not included in meta-analyses due to a lack of studies assessing this intervention.³⁹

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

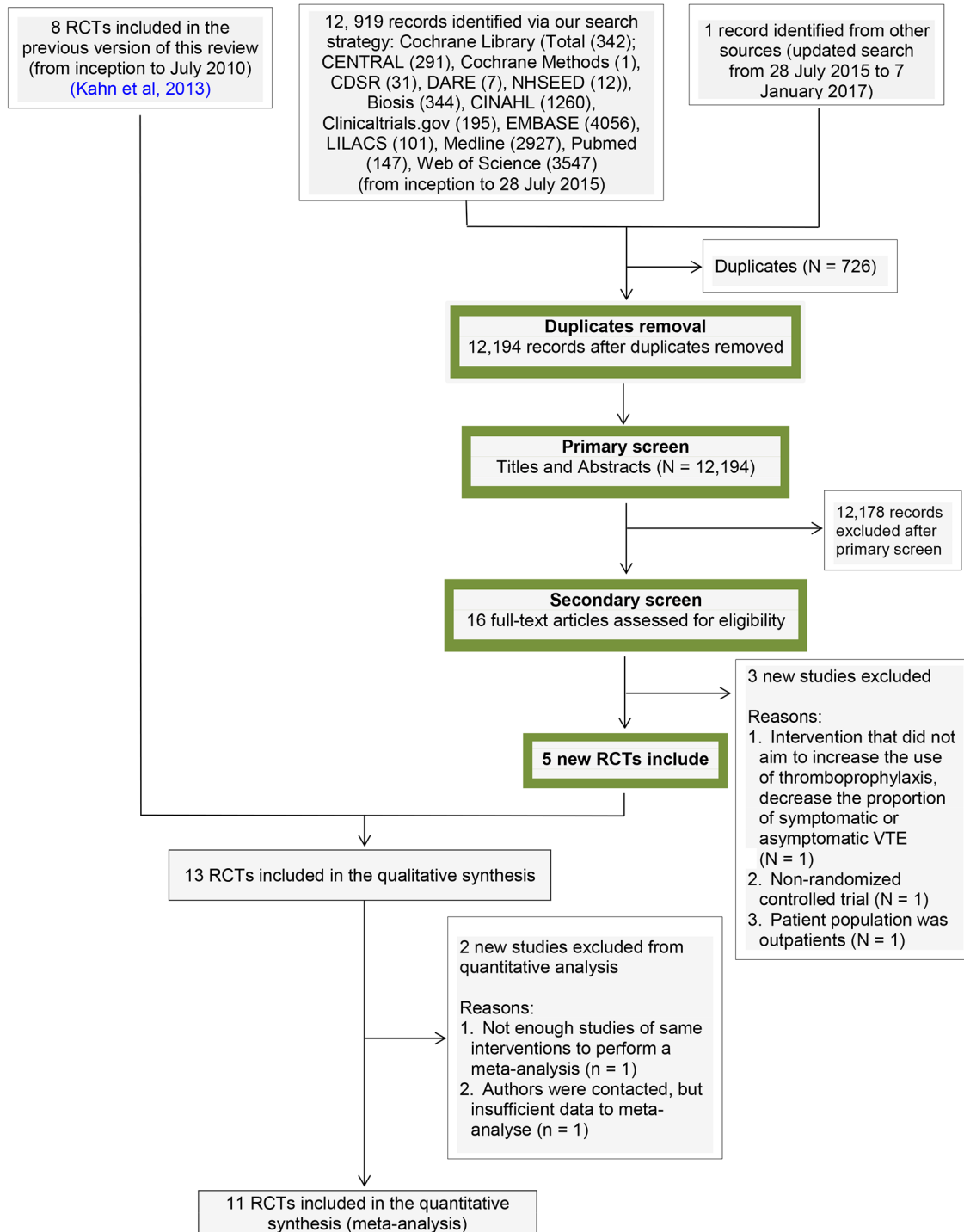


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for Cochrane review updates demonstrating the outcomes of the search process, and the inclusion of studies in the updated Cochrane systematic review and meta-analysis. CDSR, Cochrane Database of Systematic Reviews; 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, randomised controlled trial; VTE, venous thromboembolism.

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 ICC where available,^{43 50–52} in many cases the ICC was not provided,^{39 41 42 46 48 53} leading to CIs that may be narrower than if clustering had been adequately accounted for. The units of clusters were

Table 1 Characteristics of the included studies

Author	Study design	Study setting	Number of patients (centres)	Type of patients	Participants (gender, age)	System-wide intervention	Comparators	Follow-up (timing for outcome assessment)	Primary outcome	Secondary outcomes
Anderson <i>et al.</i> ³⁹	Cluster RCT (unit of cluster: hospitals)	Community, USA	798 patients (15 centres)	Medical and surgical patients	Male 44% Mean 70.7 years	Multifaceted	No intervention versus educational versus multifaceted intervention	3 months	RP	RAP, VTE, mortality and safety outcomes not assessed
Overhage <i>et al.</i> ⁴⁵	Cluster RCT (unit of cluster: medical wards/departments)	Academic, USA	58 patients (1 centre)	Medical patients	Male 50% Mean (SD), 51 years (18)	Alerts (computer alert)	No intervention (usual care) versus intervention	6 months	RP	RAP, VTE, mortality and safety outcomes not assessed
Dexter <i>et al.</i> ⁴¹	Cluster RCT (unit of cluster: medical teams)	Academic, USA	1326 patients (1 centre)	Medical patients	Male 50% Mean 53.2 years	Alerts (computer alert)	No intervention (standard care) versus intervention	18 months	Not assessed	RAP assessed. VTE, mortality and safety outcomes not assessed
Kucher <i>et al.</i> ⁴⁵	Parallel group, quasi-RCT	Academic, USA	2506 patients (1 centre)	Medical and surgical patients	Male 52.9% Median (range) 62.5 years (18–99)	Alerts (computer alert)	No intervention (usual care) versus intervention	90 days	RP	RAP not assessed. VTE, mortality and safety outcomes assessed
Fontaine <i>et al.</i> ⁵³	Cluster RCT (unit of cluster: medical wards/departments)	Academic, France	719 patients (30 centres)	Medical patients	Male 51.5% Mean 72 years	Preprinted orders	No intervention (usual practices) versus intervention; baseline versus post intervention	1 day	RP	RAP described in a figure (raw data not available) VTE, mortality and safety outcomes not assessed
Labarere <i>et al.</i> ⁵²	Cluster RCT (unit of cluster: medical wards/departments)	Academic/Community, France	812 patients (50 centres)	Medical patients	Male 34.2% Median (range) 82 years (75–90)	Multifaceted	Intervention targeted at physicians only versus multifaceted intervention targeted at physicians and nurses	Not clearly reported	RP	RAP and mortality outcomes not assessed. VTE and safety outcomes assessed
Piazza <i>et al.</i> ⁴⁹	Parallel group RCT	Academic/Community, USA	2493 patients (25 centres)	Medical and surgical patients	Male 53.7% Mean (SD), 68.8 years (15.2); Median (range) 72.5 years (19–103)	Alerts (human alert)	No intervention (usual care) versus intervention	90 days	RP	RAP and safety outcomes not assessed. VTE and mortality assessed
Garcia <i>et al.</i> ⁴⁸	Cluster, quasi-RCT (unit of cluster: medical teams)	Academic, USA	140 patients (1 centre)	Medical patients	Male 50.7% Mean (range) 59.5 years (20–97)	Alerts (human alert)	No intervention (usual care) versus intervention	36 hours	Not assessed	RAP assessed. VTE, mortality and safety outcomes not assessed.

Continued

Table 1 Continued

Author	Study design	Study setting	Number of patients (centres)	Type of patients	Participants (gender, age)	System-wide intervention	Comparators	Follow-up (timing for outcome assessment)	Primary outcome	Secondary outcomes
Hinchey <i>et al</i> ⁴²	Cluster, quasi-RCT (unit of cluster: hospitals)	Academic/Community, USA	2071 patients (16 centres)	Medical patients	Male 50.1% Mean 70 years	Multifaceted including reminders (standard orders, pathways, protocols, standardised dysphagia screens, atrial fibrillation reminder stickers)	Control group (audit, feedback and benchmark information) versus intervention	6 months	RP (raw data not available)	RAP, VTE, mortality and safety outcomes not assessed
Chapman <i>et al</i> ⁴⁷	Parallel group RCT	Hospital type reported, Australia	354 patients (number of centres not reported)	Medical patients	Not available	Alerts (human alert)	Standard care versus intervention	3 months	Not assessed	Symptomatic VTE assessed. RAP, mortality and safety outcomes not assessed
Pai <i>et al</i> ⁵⁰	Cluster RCT (unit of cluster: hospitals)	Academic/Community, Canada	2611 patients (6 centres)	Medical patients	Male 46.8% Median (range) 72 years (18–102)	Multifaceted	No intervention (usual care) versus intervention	16 weeks	RP	RAP assessed. VTE, mortality and safety outcomes not assessed
Cavalcanti <i>et al</i> ⁴³	Cluster RCT (unit of cluster: ICU)	Academic/Community, Brazil	6761 patients (118 ICUs, number of centres not reported)	Medical patients	Male 54.2% 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 versus intervention	60 days	RP	All-cause mortality assessed. RAP, VTE and safety outcomes not assessed
Roy <i>et al</i> ⁵¹	Cluster RCT (unit of cluster: hospitals)	Academic/Community, France	15 351 patients (27 centres)	Medical patients	Male 50% Median (range) 73.5 years (58–83)	Multifaceted including an alert component (computerised reminders)	No intervention (usual care) versus intervention	3 months	RP	All secondary outcomes assessed

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

Table 2 Description of study interventions

Author	Type of intervention	Description
Anderson <i>et al</i> ³⁹	Multifaceted	<ul style="list-style-type: none"> ▶ Aimed at doctors ▶ Use of two interventions: educational and multifaceted intervention ▶ Educational component: exam component+hospital administered course ▶ Distribution of guidelines ▶ Audit and feedback ▶ Multiple intervention study: 1 control group (group 1), 1 CME group (group 2), 1 CME+QA group (group 3) ▶ Comparator: no intervention versus CME only versus CME+QA
Overhage <i>et al</i> ⁴⁶	Alert (computer)	<ul style="list-style-type: none"> ▶ Aimed at doctors ▶ Use of reminders: electronic alert ▶ Computer reminder programme analysed electronic medical records, reminders appeared on printed daily reports and at work station when entering order, suggestions for orders provided ▶ Comparator: physicians who received the intervention (electronic alert) versus controls (reminders were not printed or displayed)
Dexter <i>et al</i> ⁴¹	Alert (computer)	<ul style="list-style-type: none"> ▶ Aimed at doctors and medical students ▶ Use of reminders: electronic alert ▶ 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 ▶ Comparator: no intervention (computer does not display the reminder) versus intervention
Kucher <i>et al</i> ⁴⁵	Alert (computer)	<ul style="list-style-type: none"> ▶ Aimed at doctors ▶ Use of reminders: electronic alert ▶ Computer program that identified patients at risk of VTE; if a patient is 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) versus intervention (computer alert)
Fontaine <i>et al</i> ⁵³	Preprinted order	<ul style="list-style-type: none"> ▶ Aimed at doctors ▶ Use of reminders: preprinted orders ▶ All physicians in intervention group were required to use specific anticoagulant prescription forms featuring the recommended prescription criteria ▶ Four groups: baseline control (group 1), baseline intervention (group 2), post-intervention control (group 3), post-intervention intervention (group 4). ▶ In January, baseline survey was performed. Intervention was implemented over the next 3 months, and the post-intervention survey was carried out in April. ▶ Comparator: no intervention (usual practices) versus intervention; baseline versus post intervention
Labarere <i>et al</i> ⁶²	Multifaceted	<ul style="list-style-type: none"> ▶ Aimed at doctors and nurses ▶ Use of multifaceted intervention ▶ Educational component: 1 hour on-site educational session addressing prophylaxis against VTE; provision of pocket-sized guidelines card ;distribution of posters and mailed data on prophylaxis use in the department ▶ Development and distribution of guidelines ▶ Audit and feedback ▶ Comparator: group 1=intervention targeted at physicians only versus group 2=intervention targeted at physicians and nurses
Piazza <i>et al</i> ⁴⁹	Alert (human)	<ul style="list-style-type: none"> ▶ Aimed at doctors ▶ Use of reminders: human alert ▶ Responsible physicians alerted by another staff member if his or her patient was at high risk of VTE, and that VTE prophylaxis was recommended, based on point scale of VTE risk factors ▶ Comparator: doctors were either alerted or not alerted
Garcia <i>et al</i> ⁴⁸	Alert (human)	<ul style="list-style-type: none"> ▶ Aimed at doctors ▶ Use of reminders: human alerts ▶ 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) versus intervention
Hinchey <i>et al</i> ⁴²	Multifaceted	<ul style="list-style-type: none"> ▶ Aimed at doctors ▶ Use of multifaceted interventions ▶ Reminders (standard orders [including for VTE prophylaxis], pathways, protocols, standardised dysphagia screens, atrial fibrillation reminder stickers), written information, face-to-face interview, audit and feedback ▶ Comparator: control group (audit, feedback and benchmark information) versus intervention group (audit, feedback and benchmark information plus a multifaceted intervention)

Continued

Table 2 Continued

Author	Type of intervention	Description
Chapman <i>et al</i> ⁴⁷	Alert (human)	<ul style="list-style-type: none"> ▶ Did not report who the intervention was aimed at ▶ Use of reminders: human alerts ▶ 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 ▶ Comparator: standard care versus intervention
Pai <i>et al</i> ⁵⁰	Multifaceted	<ul style="list-style-type: none"> ▶ Aimed at medical wards ▶ Use of multifaceted intervention ▶ Education sessions, standardised risk assessment algorithm and physicians' orders, audit and feedback ▶ Comparator: no intervention (no active or passive knowledge-translation strategies to improve thromboprophylaxis) versus intervention
Cavalcanti <i>et al</i> ⁴³	Multifaceted	<ul style="list-style-type: none"> ▶ Aimed at team ▶ Use of multifaceted intervention ▶ 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 ▶ The checklist was developed based on the clinical practice guideline development cycle ▶ Comparator: routine care and no preintervention training versus intervention
Roy <i>et al</i> ⁵¹	Multifaceted	<ul style="list-style-type: none"> ▶ Aimed at doctors and residents ▶ Use of multifaceted intervention that included an alert component ▶ Educational lectures, posters and pocket cards, computerised clinical decision support systems and computerised reminders ▶ Comparator: no intervention versus intervention

CME, continuing medical education; MD, medical doctor; QA, quality assurance; VTE, venous thromboembolism.

intensive care units (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 summarises 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 online supplementary figure 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; one study; 1311 participants), but were less effective than a multifaceted intervention.³⁹

Comparison of preprinted 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 with the group that did not receive preprinted orders (RD -0.05, 95% CI -0.12 to 0.02; one study; 719 participants).⁵³

	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	+	?	-	+	+	-	?

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

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 programme), each compared with 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

Additional analyses

A sensitivity analysis removing the high ROB trial in the meta-analysis of studies with alerts interventions⁴⁸ 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 no contamination between intervention groups where the one multifaceted intervention including an alert⁵¹ 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 with 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

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*	Three studies	5057 participants	18	39	RD 0.21 (0.15 to 0.27); 75%	⊕⊕⊕⊖ Low‡
	Received appropriate prophylaxis*	Three studies	1820 participants	30	46	RD 0.16 (0.12 to 0.20); 0%	⊕⊕⊕⊖ Moderate§
	Symptomatic VTE	Three studies	5353 participants	6	4	RR 0.64 (0.47 to 0.86); 15%	⊕⊕⊕⊖ Low¶
Multifaceted interventions	Received prophylaxis†	Five studies	9198 participants	47	51	RD 0.04 (0.00 to 0.06); 0%	⊕⊕⊕⊖ Moderate§

*Clustered trials did not provide sufficient data (ICC or adjusted confidence intervals) for us to pool cluster-adjusted estimates.

†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

‡ 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.

§ We downgraded the level of certainty of evidence from high to moderate based on the following reason: serious study limitations.

¶ 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.

GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICC, intracluster correlation coefficient; RD, risk difference; RR, relative ratio; VTE, venous thromboembolism.

by 16% and decreased the relative risk of symptomatic VTE at 3 months 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 on 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 (ie, heterogeneity in results) across studies, more appropriate comparisons (ie, 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 (<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.

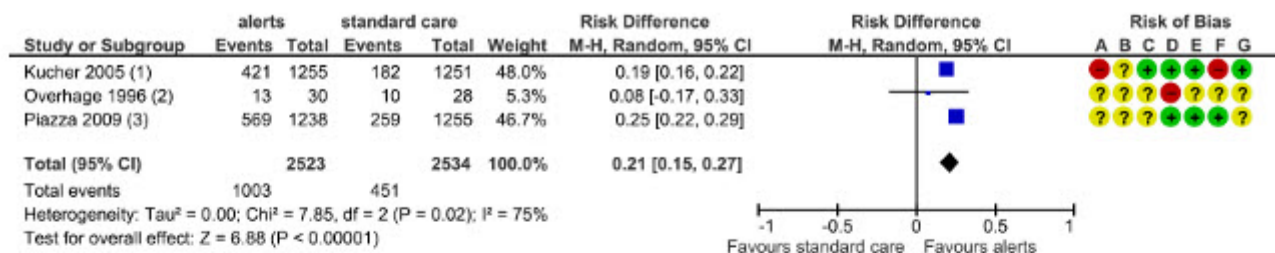
Agreements and disagreements with other reviews

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 hospitalised 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 hospitalised medical and surgical patients at risk of VTE.

Implications for practice

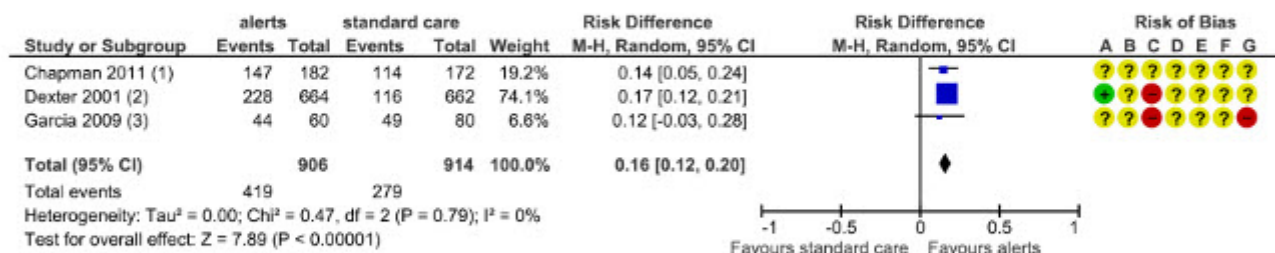
Our findings provide low-to-moderate certainty evidence to support the use of system-wide interventions to improve the prescription of thromboprophylaxis and decrease the incidence of symptomatic VTE in hospitalised adult medical and surgical patients at risk of VTE. Our results suggest that alerts interventions are associated

1. Primary Outcome - proportion of patients who received prophylaxis



2. Secondary Outcomes

2.1 Proportion of patients who received an appropriate prophylaxis



2.2 Occurrence of symptomatic VTE

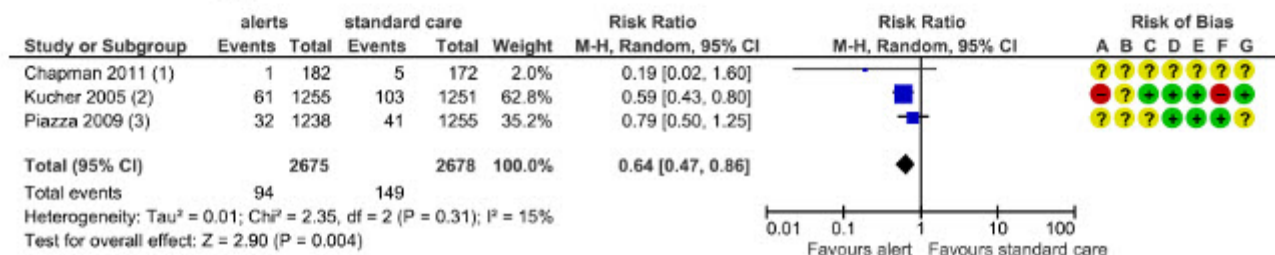


Figure 3 Forest plot and risk of bias assessment—comparison of alerts intervention with no intervention (standard care). Risk of bias: (A) random sequence generation (selection bias); (B) allocation concealment (selection bias); (C) blinding of participants and personnel (performance bias); (D) blinding of outcome assessment (detection bias); (E) incomplete outcome data (attrition bias); (F) selective reporting (reporting bias) and (G) other bias.

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

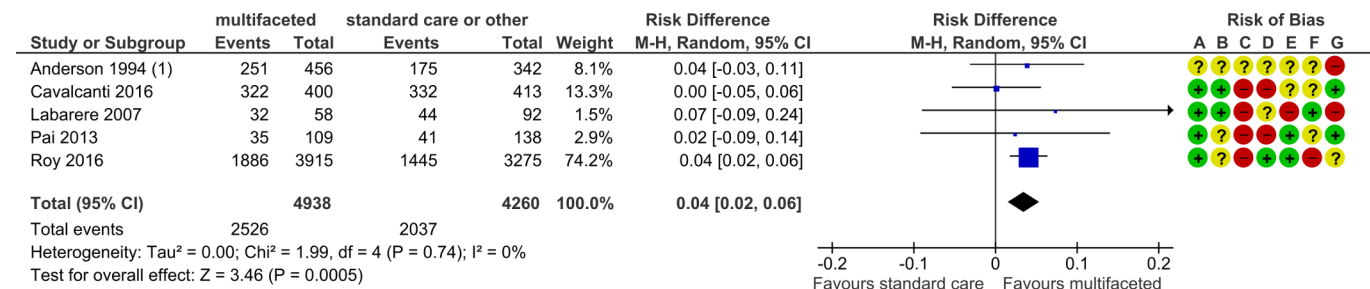


Figure 4 Forest plot and risk of bias assessment—comparison of multifaceted intervention with no intervention (standard care) or another intervention for the primary outcome 'Proportion of patients who received prophylaxis': (1) intraclass correlation coefficient not reported. Risk of bias: (A) random 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) and (G) other bias.

should be assessed in well-designed multicentre RCTs that ideally include university-affiliated and community hospitals of various sizes. In addition, rates of prescription of appropriate prophylaxis should also 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 hospitalised patients. Alerts interventions (eg, computer alerts or human alerts) increased the prescription of appropriate thromboprophylaxis and decreased the incidence of symptomatic VTE in hospitalised medical and surgical patients at risk of 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.

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