ABSTRACT

Introduction Orthopaedic trauma patients are at high risk of venous thromboembolism (VTE). As VTE prophylaxis has gradually raised public concerns, guidelines related to this topic have increased over time. However, the existing recommendations of thromboprophylaxis guidelines in orthopaedic trauma patients are still inconsistent, and the quality of the guidelines and recommendations for the topic still lacks comprehensive assessments. This review aims to critically appraise clinical practice guidelines for thromboprophylaxis in orthopaedic trauma patients.

Methods and analysis We will conduct a comprehensive literature search up to 31 October 2022 in databases (PubMed, EMBASE, CINAHL, Web of Science, the Cochrane Library, etc), academic websites and guideline repositories. The quality of the guidelines and recommendations will be assessed by five reviewers independently using the Appraisal of Guidelines Research and Evaluation II (AGREE-II) and the AGREE - Recommendation EXcellence (AGREE-REX). We will summarise the characteristics of the guidelines and compare the differences between these recommendations.

Ethics and dissemination This study will follow the Declaration of Helsinki and has received approval from the Ethics Committee on Biomedical Research, West China Hospital, Sichuan University (ethics approval no. 2021-989). The results will be summarised as a paper, disseminated through peer-reviewed journals, and will help guide further research in the future.

Protocol registration number CRD42021273405.

INTRODUCTION

Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is the third most common cause of cardiovascular-related death and results in a mass of disability-adjusted life-years lost in hospitalised patients. More than 500,000 VTE-related deaths occur in the USA and cost US$7–US$10 billion for healthcare annually. As an avoidable in-hospital complication, each case of VTE will take an excess of 5.4 hospitalisation days and increase the mortality rate by 6.6 times. About 6% of patients with DVT and 12% of patients with PE die within 1 month after diagnosis. Various factors can lead to the occurrence of VTE, such as major surgery, trauma, plaster fixation, tumours, etc. Orthopaedic trauma patients are at high risk of VTE due to multiple risk factors. The incidence of VTE in orthopaedic trauma patients can vary from 4.78% to 40.25%, depending on the location of the injury, VTE monitoring method, ethnicity, etc.

Thromboprophylaxis has been proven able to reduce the occurrence of VTE effectively. Both chemical and mechanical prophylaxis strategies have shown their effects in orthopaedic trauma patients. At present, the most widely used VTE prevention clinical practice
guideline (CPG) in orthopaedic surgery is the ninth edition of the VTE prevention guideline presented by the American College of Chest Physicians (ACCP) in 2012. However, its recommendations for patients with orthopaedic trauma are insufficient, covering only patients with hip fractures, isolated lower leg injuries and knee arthroscopy. And no specific recommendations for the dose and frequency of chemoprophylaxis are mentioned in the above ACCP guideline. Recently, several updated CPGs for VTE prevention have been published, but many have been formed based on expert consensus. In addition, there are still many issues to be determined, such as the timing, duration and best practice protocol for VTE prevention in patients with different types of orthopaedic trauma. It is still necessary to explore further construction of a VTE prevention programme that fits the clinical situation of orthopaedic trauma patients based on guidelines.

Currently, the Appraisal of Guidelines for Research & Evaluation II instrument (AGREE-II) is widely accepted to evaluate the methodological quality of the guidelines. However, this tool does not assess the specific recommendations provided in the guidelines and cannot guarantee their applicability in clinical practice. The AGREE-Recommendation EXcellence (AGREE-REX) tool mainly evaluates the quality and applicability of the guideline recommendations, which is a powerful supplement to AGREE-II. We hope to use the AGREE-II and AGREE-REX tools to critically appraise the current CPGs for VTE prevention in orthopaedic trauma and understand both the methodological and recommendation quality of the current guidelines, which help guide the selection of reliable recommendations following the clinical situation.

METHODS AND ANALYSIS

Objectives

We plan to systematically collect VTE prophylaxis CPGs in the field of orthopaedic trauma and use AGREE-II and AGREE-REX tools to conduct a rigorous quality appraisal to answer the following questions:

1. What is the methodological quality of the VTE prophylaxis CPGs in orthopaedic trauma?
2. What similarities and differences are the recommendations provided in the current CPGs for VTE prophylaxis in orthopaedic trauma?
3. What is the strength and quality of the evidence provided in the current CPGs for VTE prophylaxis in orthopaedic trauma?

Protocol and registration

This report follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol statement (see online supplemental appendix 1) and has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42021273405.

Patient and public involvement

Patients and/or the public will not be involved in the design, conduct, reporting or dissemination plans of this research.

Eligibility criteria

See details in table 1. We will only include openly published literature in the study and grey literature will be excluded.

SELECTION OF STUDIES

Data sources

The following databases and websites from inception to 31 October 2022 will be searched:


Tabla 1. Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Guidelines published in English or Chinese.</td>
<td>1. Evidence summary, editorials, letters, consensus statements, policy statements or standards, or just a quick reference guide which do not involve the evaluation of evidence and the description of the method of forming recommendations.</td>
</tr>
<tr>
<td>2. The guideline has clearly stated that it is a ‘guideline’ in the context.</td>
<td>2. The previous version of the updated guideline.</td>
</tr>
<tr>
<td>3. The content includes statements and recommendations for the prevention of VTE in orthopaedic trauma patients.</td>
<td>3. Repeated publication.</td>
</tr>
<tr>
<td>5. The latest complete version of the guideline and any partial revisions or updates published afterward.</td>
<td>5. Only included one or more of the following: spinal fractures, craniocerebral or maxillofacial fractures, rib fractures, or skin and soft tissue injuries.</td>
</tr>
<tr>
<td>6. Unable to get the full text.</td>
<td></td>
</tr>
</tbody>
</table>

VTE, venous thromboembolism.
Box 1  Sample research strategy for PubMed

| #1 (orthopedics[MeSH Terms]) OR (traumatology[MeSH Terms]) OR (wounds and injuries[MeSH Terms]) |
| #2 (((((fracture[Title/Abstract]) OR (limb trauma[Title/Abstract])) OR (extremity trauma[Title/Abstract])) OR (musculoskeletal injur*[Title/Abstract])) OR (musculoskeletal trauma[Title/Abstract])) OR (limb immobility*[Title/Abstract])) OR (skeletal fixation[Title/Abstract])) OR (“orthopedic”[Title/Abstract] AND “trauma”[Title/Abstract]) |
| #3 ((venous thromboembolism[MeSH Terms]) OR (venous thrombosis[MeSH Terms]) OR (pulmonary embolism[MeSH Terms]) |
| #4 ((((venous thromboembolism[Title/Abstract]) OR (venothromboembolism[Title/Abstract])) OR (venous thrombosis[Title/Abstract])) OR (vein thrombosis[Title/Abstract])) OR (DVT[Title/Abstract]) OR (VTE[Title/Abstract]) OR (pulmonary embolism[Title/Abstract])) OR (lung embolism[Title/Abstract])) OR (PE[Title/Abstract]) OR (thromboembolism[Title/Abstract]) OR (embolism[Title/Abstract])) OR (blood clot[Title/Abstract]) |
| #5 ((thromboprophylaxis[Title/Abstract]) OR (prophylaxis*[Title/Abstract])) OR (prevent*[Title/Abstract]) |
| #6 (((((heparin[MeSH Terms]) OR (heparin, low-molecular-weight[MeSH Terms])) OR (anticoagulants[MeSH Terms])) OR (warfarin[MeSH Terms]) OR (aspirin[MeSH Terms]) OR (vena cava filters[MeSH Terms]) OR (stockings, compression[MeSH Terms]) OR (intermittent pneumatic compression devices[MeSH Terms]) |
| #7 ((pentasaccharide*[Title/Abstract]) OR (ondaparinux[Title/Abstract])) OR (LMWH[Title/Abstract]) |
| #8 (guideline[Publication Type]) OR (consensus development conference[Publication Type]) |
| #9 (guidelines as topic[MeSH Terms]) OR (consensus[MeSH Terms]) OR (consensus development conferences as topic[MeSH Terms]) |
| #10 (((guideline[Title/Abstract]) OR (guidance[Title/Abstract])) OR (recommendation[Title/Abstract]) OR (consensus[Title/Abstract])) OR (best practice[Title/Abstract]) |
| #11 #1 OR #2 |
| #12 #3 OR #4 |
| #13 #5 OR #6 OR #7 |
| #14 #8 OR #9 OR #10 |
| #15 #11 AND #12 AND #13 AND #14 |

**Determination of eligibility**

Two reviewers (LH and J-YX) will independently screen and select the literature. First, they will determine whether the documents meet the inclusion criteria based on the titles and abstracts. After that, the reviewers will obtain the full texts of the documents, then read and filter out the eligible guidelines. Any disagreement between the two reviewers will be resolved through consensus or by the third reviewer (Z-KZ).

**DATA EXTRACTION**

We will extract the following information of CPGs: (1) title; (2) year of publication; (3) authors; (4) country of development; (5) objective of CPG; (6) target users; (7) method used to collect the evidence; (8) grading methods for the evidence; (9) recommendation formulation method; (10) guideline validation methods; (11) intended users and (12) the specific content of the recommendations given, including the method of thromboprophylaxis, the timing of initiation, dose and duration, and target patients. In addition, we will record each score of items in AGREE-II and AGREE-REX with their reasons.

**QUALITY ASSESSMENT OF CPGS**

We will assess the quality of CPGs by AGREE-II. The tool was released in 2009 and includes 23 items in 6 domains (scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence), with two additional assessments for the guideline’s overall quality and whether it is recommended to use.

The quality of recommendations is evaluated using AGREE-REX. The tool was released in 2019 and included nine items in three domains (clinical applicability, values and preferences, and implementability). Each item has two assessment questions, one for quality evaluation (required) and another for suitability for use (optional). Overall judgement for all recommendations in CPG has two additional assessments: (1) I would recommend these recommendations for use in the appropriate context (required) and (2) I would recommend these recommendations for use in my context (optional).

Both AGREE-II and AGREE-REX quality evaluation items adopt a Likert scale of one to seven scores. The standardised scores for each domain are calculated according to the user manual, ranging from 0% to 100%. The higher the score obtained, the better the quality of the guideline in the relevant field. Considering that the method for evaluating the overall quality of the guideline remains controversial, we will not use a cut-off value to rate the overall quality but directly present the reviewers’ subjective judgement results.

Five reviewers (LH, J-YX, JL, HL and NN) conducted quality appraisals after systematically learning how to use AGREE-II and AGREE-REX. Reviewers use the online platform MY AGREE PLUS to use AGREE-II independently.
and blindly (https://www.agreetrust.org/my-agree/), while the AGREE-REX assessment is performed offline.

DESCRIPTION AND COMPARISON OF THE RECOMMENDATIONS

We plan to compare the recommendations included in the CPG, which will be extracted independently by two reviewers (D-BL and GL-W). The recommendations will be expectancy classified according to risk assessment, screening strategies, mechanical prophylaxis, chemical prophylaxis and other interventions to evaluate their scopes and differences in different CPGs. Discrepancies will be highlighted when there are conflicts between some recommendations.

DATA ANALYSIS AND PRESENTATION

All the data will be saved with Excel (Microsoft 365, Microsoft, Redmond, Washington, USA) and analysed with SPSS statistical software (.26, IBM). For each domain of AGREE II and AGREE-REX, we will calculate the score by the following formula:

\[
\text{The scaled domain score} = \frac{\text{Obtained score} - \text{Minimum possible score}}{\text{Maximum possible score} - \text{Minimum possible score}}
\]

Scores for guidelines and recommendations will be described using the mean (SD) and median (IQR) (if needed). The intraclass correlation coefficient (ICC) will be used to evaluate the degree of agreement between reviewers. Based on Landis and Koch, an ICC value of 0.00–0.20 indicates slight agreement, 0.21–0.40 indicates fair agreement, 0.41–0.61 indicates moderate agreement, 0.61–0.80 indicates substantial agreement, 0.81–1.00 indicates almost perfect agreement. Differences in domain scores between CPGs will be compared using the Kruskal-Wallis H test. Significance level \(a=0.05\) (two tailed).

Our study is expected to begin in November 2022 and complete in April 2023. We will explain any methodological changes in the study. The results are intended to be published in a peer-reviewed open journal.

DISCUSSION

Thromboprophylaxis in orthopaedic trauma patients is complicated due diverse risk factors. It is challenging to choose appropriate prevention methods for patients with coagulation abnormalities, lower limb injuries, etc. The use of anticoagulants may increase the risk of bleeding and wound complications in trauma patients, especially in the early postoperative period. Research in this field is scattered and controversial, and more work is needed to form conclusions. There is still no consensus on evaluating evidence and recommendations between different guidelines, which increases the uncertainty of clinical decision making. Even in the relatively large number of hip fracture patients studied, physicians still believe that there is a lack of adequate clinical guidelines. We hope to evaluate the relevant guidelines for VTE prevention in orthopaedic trauma and critically appraise the quality of the guidelines and recommendations. To the best of our knowledge, there is currently no systematic review on the quality of English and Chinese orthopaedic trauma thromboprophylaxis guidelines.

It is a long process that costs plenty of workforce and resources for planning, formulating and disseminating a CPG, especially for high-quality CPGs. Rigorous methodology and regular updates play essential roles in maintaining the quality of the guidelines and practical application. Identifying high-quality recommendations will help us to prescribe appropriate thromboprophylaxis in the trauma population. It will also help discover knowledge gaps and new points for further research. We plan to summarise the divergent recommendations in such guidelines, which will be the main focus of future thromboprophylaxis research.

Our research may still have shortcomings. First, although we will adopted a comprehensive search strategy, only openly published documents will be obtained, and some grey literature may miss during the process. Second, we will only include CPGs published in Chinese and English, which may lead to an underestimation of the overall number of guidelines. Third, to obtain as comprehensive information as possible, we will not limit the start time for the publication of the guidelines. Those recommendations from earlier CPGs may not be consistent with current evidence.

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