Chapter

Methodological Quality of Clinical Practice Guidelines for Pharmacological Prophylaxis of Venous Thromboembolism in Hospitalized Adult Medical and Surgical Patients and Summary of the Main Categories of Recommendations Included in High-Quality CPGs: A Systematic Review

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Abstract

Venous thromboembolism (VTE) is a complex multifactorial disease with an average annual incidence of approximately 1 per 1000 in the adult population. Recommendations about pharmacological prophylaxis of VTE in adult hospitalized surgical and medical patients are available in clinical practice guidelines (CPGs) to optimize healthcare delivery and improve patient outcomes. The aim of this study was to examine the methodological quality of CPGs for pharmacological prophylaxis of VTE in adult hospitalized medical and surgical patients and to summarize the main categories to contextualize the recommendations included in high-quality CPGs. Methodology: The study used the ADAPTE to contextualize in categories the main recommendations of the high-quality CPGs assessed by the Appraisal of Guidelines for Research and Evaluation (AGREE II). Results: Fourteen CPGs were screened for assessment of quality methodology by AGREE II instrument. Seven of fourteen CPGs were selected as high-quality (>60%) across domains 3 and 6 to contextualize the recommendations in categories. Conclusion: Seven CPGs evaluated by AGREE had

scores above 60% in domains 3 and 6. The scope addressed by the high-quality CPGs included important aspects of pharmacological prophylaxis of VTE in hospitalized patients.

Keywords: venous thromboembolism, practice guidelines, high-quality, adaptation, systematic review

1. Introduction

Venous thromboembolism (VTE) is a complex multifactorial disease influenced by acquired or inherited predispositions to thrombosis, environmental exposures, and the interaction between them, and can manifest as deep vein thrombosis (DVT) or pulmonary thromboembolism (PTE) [1].

The average annual incidence is approximately 1 per 1000 in the adult population, with a higher incidence rate in men than in women. The incidence increases after the age of 45, reaching a rate of 5 or 6 per 1000 inhabitants annually in the elderly over 80 years [1–3].

Approximately 50% of thrombotic events occur during or shortly after hospitalization, with 24% in surgical patients and 22% in medical patients [1]. PTE accounts for 5-10% of hospitalized patient deaths, making VTE the most common cause of preventable deaths in hospitalized patients, and thromboprophylaxis is an important strategy to improve patient safety in hospitals [4].

Clot formation during hospitalization, surgical procedure, or health care is known as hospital-acquired thrombosis and can occur during hospitalization and up to 90 days after discharge [4]. In addition, VTE is associated with recurrence, post-thrombotic syndrome, chronic pulmonary hypertension, and bleeding due to anticoagulation [1, 5, 6]. These complications substantially contribute to patient morbidity and the cost of management [4].

Although national and international consensus is available, studies show that 50% of at-risk patients do not receive adequate prophylaxis [7]. According to these consensuses for the prevention of VTE induced in hospitals, should take into account the risk factors for the occurrence of an event, the benefits of available prophylactic agents, possible complications, and the cost of treatment, information that should be part of a formal hospital strategy supporting the decision of the professionals involved [8, 9].

Clinical Practice Guidelines (CPGs) are tools that contain recommendations on clinical health interventions, with the aim of improving patient care, based on a systematic review of evidence to assess the benefits and harms of different therapeutic alternatives in health care [10, 11].

The Institute of Medicine (IOM) defines CPGs as “statements that included recommendations, intended to optimize patient care, informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options”. CPGs are underpinned by systematic review evidence and are usually formulated by groups of stakeholders with relevant domain expertise [12].

One way to obtain the CPGs is through adaptation. The ADAPTE Collaboration, an international collaboration of researchers, guideline developers, and guideline implementers, has developed a systematic approach tool for adapting guidelines considering the organizational and cultural environment to application in a different context. In this way, it is possible to take advantage of existing guidelines and produce high-quality adaptation [13].

The use of an instrument to assess the quality of guidelines, the Appraisal of guidelines research and Evaluation (AGREE II), is recommended during the guidelines decision and selection tasks that take place within the adaptation process by the ADAPTE methodology. From the selected CPGs, summaries of recommendations are created, allowing the visualization of whether the recommendations from different CPGs are similar or different, verifying which of these have strong evidence and providing the clinical importance of each one of them [14, 15].

Therefore, the aim of this study was to analyze the methodological quality of CPGs for pharmacological VTE prophylaxis in adult hospitalized medical and surgical patients; and to summarize the main categories of the recommendations included in high-quality CPGs.

1.1 Adaptation of clinical practice guidelines

Adaptation of guidelines is a systematic approach to modify guidelines produced in a cultural place and organizational setting to be applicable in another context [16]. The adaptation is an alternative to the development of a new guideline preserving the principle of evidence-based practice [17].

The ADAPTE collaboration is a group of researchers, guideline developers, and guideline implementers who proposed a systematic approach to adapting guidelines that ensure the elaboration of final recommendations and that address specific health issues adapted to the context of use, meeting local needs, priorities, legislation, policy, and resources [16].

The process is divided into 3 main phases, set up, adaptation and finalization, with 24 steps divided into 9 modules [13]. **Figure 1** demonstrates a summary of the processes.

The Set-up phase is described in 6 steps. At this stage, it must be verified whether the adaptation is feasible, tracking the availability of guidelines in specific repertoires to proceed with the adaptation process. A working group must also be defined with the activities to be developed by each member for the selected topic. All members must have their tasks well described and must sign the conflict-of-interest term. At this stage, it must also be defined how the consensus for decision-making among the members will be carried out, which must be described in the final document. All stages of the set-up phase must be described in the adaptation plan [11, 13, 16].

In the adaptation phase, the clinical questions that guide the search for CPGs must be defined. The search must be carried out with the elaboration of the clinical question. For this purpose, an acronym can be used, for example, PIPOH: Population, Intervention, Professional, Outcome and Health care setting, which allows for defining the clinical question by addressing the aspects necessary for the development of a well-defined search strategy, being able to identify relevant guidelines in databases and guideline-specific repositories, websites of guideline development organizations and specialized societies [11, 13, 16]. **Table 1** describes the components of the acronym.

The quality of the selected guidelines can be evaluated by the AGREE II (http://www.agreetrust.org)instrument,through the 23 items that make up the tool, and evaluate the guideline development method. In addition to quality, experts should be aware of the guidelines' update dates and check whether the recommendations have undergone changes that may impact the adaptation of the CPGs [11, 13].

Another factor to be evaluated is the content of the guidelines, through the extraction of recommendations, with their levels of evidence that must compose the matrices and can be grouped by guideline or by similarity [13].

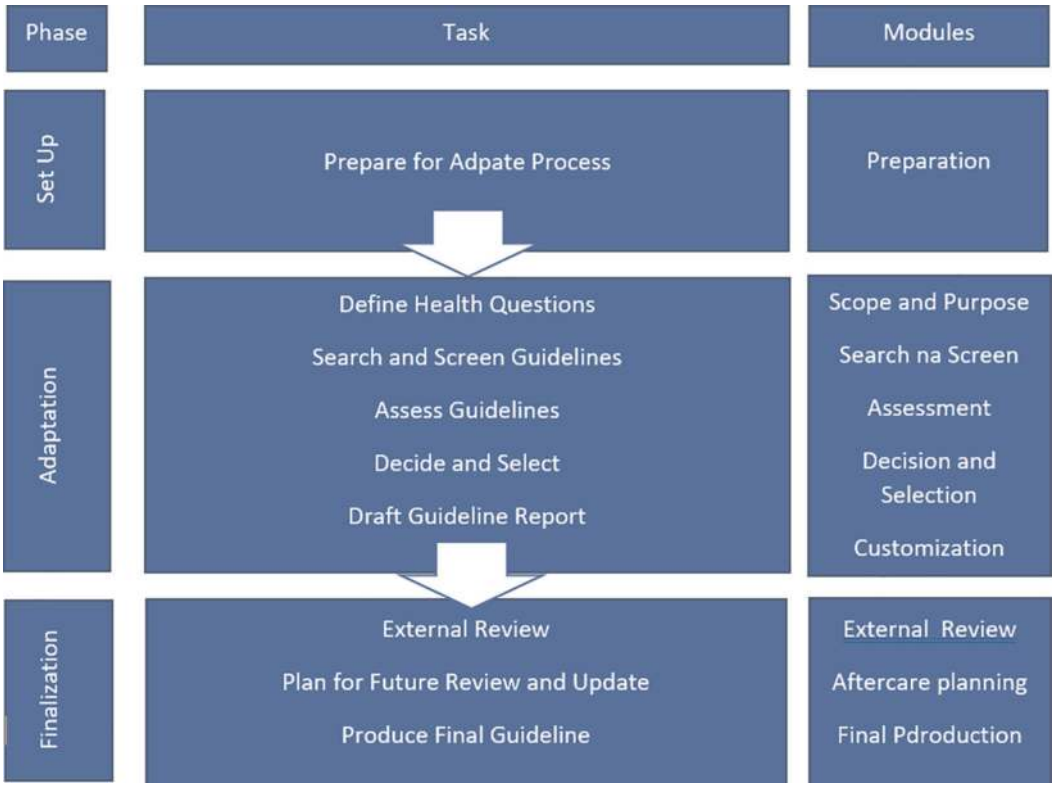

Figure 1.
Summary of the adaptation process from the description of the ADAPTE tool. ADAPTE collaboration (2009) was prepared and adopted by the author [13].

PIPOH	Description
Population	Characteristics of the disease or condition for the population of interest
Intervention	Intervention of interest
Professional	Professionals targeted by the guideline
Outcome	Expected outcomes
Health system	Location where the guideline will be implemented

Table 1.
Description of the PIPOH acronym for the elaboration of the clinical question ADAPTE collaboration (2009) prepared and adapted by the author [13].

The recommendations help the end-user of the CPGs by describing what should be done to make an appropriate decision in certain situations and optimize patient care to improve the health outcome both individually and collectively [13].

The acceptability and applicability of recommendations to the target context depend on the adaptation to variables such as availability and organization of health services, resources, beliefs, and values of the population. All details of the process must be recorded in a draft document [11, 13].

In the finalization phase, the external review process by users must take place. Thus, all comments received must be evaluated by the elaboration group that proceeds with the modification of the guideline, if pertinent. Every process must also be

documented. At this stage, the guideline update plan should also be considered. With all the prerequisites defined, the final version can be produced and deployed [13].

1.2 Quality assessment of clinical practice guidelines

Adaptation involves the step of critically evaluating the methodological quality of the CPGs for the selection of high-quality guidelines, determined by confidence in how potential biases in the elaboration process were addressed and by verifying the validity of recommendations for clinical practice considering the risks, benefits, and costs [11, 13].

The first version of the Appraisal of Guidelines Research and Evaluation (AGREE) was published in 2003 by the AGREE collaboration, a group of international guidelines developers and researchers, with the aim of obtaining a tool for assessing the quality of CPGs. The evaluation included a judgment of the methods used to develop the guidelines, the components of the final recommendations, and the factors that are linked to their implementation. The instrument was translated into several languages and quickly became accepted as a gold standard tool for guideline evaluation. It has been tested in 11 countries in more than 100 guidelines and with more than 200 evaluators, being endorsed by the World Health Organization, the Council of Europe, and the Guideline International Network (GIN). The revised version was published in 2009 [15].

All 23 items on the instrument are scored on a Likert scale from one to seven, where one is "strongly disagree" and seven is "strongly agree". Scores between 2 and 6 are assigned when the item does not meet all criteria and considerations [15]. In this way, each domain is scored according to the dimension of quality addressed as described in **Table 2**.

The quality score is calculated for each of the six domains independently, which receives a score ranging from 0 to 100%. The calculation is performed by adding the

Domain	Definition
Scope and purpose	In this domain, the objective of the CPG, the correct elaboration of clinical questions, and the description of the target population of the guideline are evaluated (items 1-3)
Stakeholder involvement	Concerns about the professionals involved in the development process, addressing patient preferences, and defining target users (items 4-6)
Rigor of development	The evidence search strategy, classification of the level of evidence of the selected studies, mechanisms for formulating recommendations, whether there was an external review, and whether there are plans to update the GPC are evaluated (item 7-14)
Clarity of presentation	In this domain, it is evaluated whether the recommendations are clearly described, whether the guide considers different possibilities for managing the disease and whether the key recommendations are easily located (item 15 – 17)
Applicability	It addresses the description of barriers and facilitators that impact the applicability of the guideline and brings suggestions of tools and resources spent to apply the GPC and monitoring indicators (item 18-21)
Editorial independence	Evaluates the description of the financing funds and their impact on the preparation of the guideline and the existence of the conflict-of-interest policy (item 22-23)

Table 2.
Domains of the AGREE II instrument. AGREE next steps consortium (2017), prepared and adapted by the author [15].

scores of the individual items and calculating the maximum and minimum scores that the domain could receive depending on the number of evaluators, with at least two being indicated [15]. The calculation of the score for each domain does not indicate that one domain is more relevant than the other. The AGREE II manual also does not set a limit to distinguish between high- and low-quality CPGs [18, 19].

2. Methodology

The study involves a systematic search for CPGs for pharmacological prophylaxis of VTE in adult hospitalized orthopedic and non-orthopedic surgical patients and pharmacological prophylaxis of VTE in adult hospitalized patients with acutely ill medical. To summarize the main topics in the recommendations of the high-quality CPGs the ADAPTE methodology was used.

2.1 Selection criteria

The first step was formulating the clinical question grounded on the acronym PIPOH as described in **Table 3**.

The clinical question guided the search for CPGs through the definition of descriptors and inclusion criteria. The following items were outside the scope of this study: pregnant and postpartum women, pediatric patients, outpatients, patients being treated for VTE, and patients suspected or diagnosed with COVID-19. The search included CPGs defined by the IOM [12] open access, in updated versions in English, Portuguese and Spanish, published between 2011 and 2021. The study was registered on the protocol registration portal, International Register of Systematic Review (PROSPERO), under number CRD42021232578.

2.2 Bibliographic databases

An electronic database search was conducted in April 2021 by CPGs for pharmacological prophylaxis in adult hospitalized patients published between January 1, 2011, and March 31, 2021. A search strategy was developed using the keywords “venous thromboembolism” and “guideline” in the following databases: Medline (via Pubmed), Cochrane Library (via CENTRAL), Embase, and Lilacs, and on specific CPG repositories and organization websites: Australian Clinical Practice guidelines

PIPOH	Inclusion criteria
Population	Adults (> 18 years) and hospitalized (> 24 hours)
Intervention	Pharmacological prophylaxis for venous thromboembolism (VTE)
Professional	Multi-professional team of a hospital
Outcome	Prophylaxis of VTE in 1) orthopedic and non -orthopedic surgical patients; 2) acutely ill medical patients
Health system	Hospital

Table 3.
Description of the PIPOH acronym for the elaboration of the clinical question for pharmacological prophylaxis of VTE in adult hospitalized patients.

(clinicalguidelines.gov.au), Canadian Agency for Drugs and Technologies in Health (cadth.ca), International Guidelines Network (gin.net), ECRI Guidelines Trust (guidelines.ecri.org), Scottish Intercollegiate Guidelines Network (sign.ac.uk), Queensland Health (health.qld.gov.au), American Society of Hematology (hematology.org), American College of physicians (acponline.org), American College of chest physicians (chestnet.org), International Union of Angiology (angiology.org), National Institute

Databases	Strategy search
Medline (via Pubmed)	("Practice Guidelines as Topic"[MeSH Terms] OR ("Practice Guidelines as Topic"[MeSH Terms] OR ("practice"[All Fields] AND "guidelines"[All Fields] AND "topic"[All Fields]) OR "Practice Guidelines as Topic"[All Fields] OR ("clinical"[All Fields] AND "guidelines"[All Fields] AND "topic"[All Fields])) OR ("Practice Guidelines as Topic"[MeSH Terms] OR ("practice"[All Fields] AND "guidelines"[All Fields] AND "topic"[All Fields]) OR "Practice Guidelines as Topic"[All Fields] OR ("best"[All Fields] AND "practices"[All Fields]) OR "best practices"[All Fields]) OR ("Practice Guidelines as Topic"[MeSH Terms] OR ("practice"[All Fields] AND "guidelines"[All Fields] AND "topic"[All Fields]) OR "Practice Guidelines as Topic"[All Fields] OR ("best"[All Fields] AND "practice"[All Fields]) OR "best practice"[All Fields]) OR ("Practice Guideline"[Publication Type] OR ("Practice Guideline"[Publication Type] OR "Practice Guidelines as Topic"[MeSH Terms] OR "clinical practice guideline"[All Fields]) OR (("ambulatory care facilities"[MeSH Terms] OR ("ambulatory"[All Fields] AND "care"[All Fields] AND "facilities"[All Fields]) OR "ambulatory care facilities"[All Fields] OR "clinic"[All Fields] OR "clinics"[All Fields] OR "clinical"[All Fields] OR "clinically"[All Fields] OR "clinicals"[All Fields] OR "clinics"[All Fields]) AND ("Guideline"[Publication Type] OR "guidelines as topic"[MeSH Terms] OR "guidelines"[All Fields]))) OR "Guideline"[Publication Type]) AND ("Venous Thromboembolism"[MeSH Terms] OR ("Venous Thromboembolism"[MeSH Terms] OR ("venous"[All Fields] AND "thromboembolism"[All Fields]) OR "Venous Thromboembolism"[All Fields] OR ("thromboembolism"[All Fields] AND "venous"[All Fields]) OR "thromboembolism venous"[All Fields]))
Embase	('practice guideline'/exp./mj OR 'clinical practice guidelines'/mj OR 'guidelines'/mj OR 'guidelines as topic'/mj OR 'practice guideline'/mj OR 'practice guidelines'/mj OR 'practice guidelines as topic'/mj) AND ('venous thromboembolism'/exp. OR 'thromboembolism, venous' OR 'vein thromboembolism' OR 'venous thromboembolism') AND [2011–2021]/py AND [embase]/lim
Cochrane	#1 Mesh descriptor: [Venous Thromboembolism] explode all trees
	#2 (Thromboembolism, Venous)
	#3 #1 OR #2
	#4 MeSH descriptor: [Practice Guidelines as Topic] explode all trees
	#5 Clinical Guidelines as Topic) OR (Best Practices) OR (Best Practice) OR (Practice Guideline) OR (Clinical Guidelines) OR (Guideline)
	#6 #4 OR #5
	#7 #3 AND #6
LILACS	"TROMBOEMBOLISMO" or "TROMBOEMBOLISMO VENOSO" [Palavras] and (("GUIDELINE" or "GUIDELINE/PROTOCOL" or "GUIDELINES AS TOPIC" or "GUIDELINES/CONSENSUS") or "GUIA DE PRATICA CLINICA" or "GUIA DE PRATICA MEDICA") or "DIRETRIZ" or "DIRETRIZ DE PRATICA MEDICA" or "DIRETRIZ PARA A PRATICA CLINICA" or "DIRETRIZ PARA A PRATICA MEDICA" or "DIRETRIZ/PROTOCOLO" [Palavras]

Table 4.
Search strategy used in PubMed, Cochrane library, Embase, and Lilacs databases.

for Health and care Excellence (nice.org.uk), National Guidelines Clearing House (guidelines.gov), European Society of Anesthesiology and intensive care (esaic.org), Thrombosis Canada (thrombosiscanada.ca). Search strategies are described in **Table 4**.

2.3 Selection process

Two reviewers independently screened the retrieve titles and abstracts. After the first screening two reviewers screened the full text independently and a third reviewer resolves disagreements when there was no consensus. All screenings were conducted by importing the search results into the Rayyan ® reference manager.

2.4 Clinical practice guideline quality assessment

Three reviewers trained in the AGREE II instrument, conduct an independently quality assessment of each eligible CPG. The instrument consists of 23 items grouped in six domains. Each item receives three grades one from each reviewer directly on the online platform My AGREE Plus (http://www.agreetrust.org). The grades were considered discrepant when there was a difference of two or more points between the reviewers' grades. Discrepancies in the scoring were resolved by group discussions. For defining a high-quality CPG was used the AGREE II domain scores and a cut-off of 60% or more for 3 (rigor of development) and 6 (editorial independence) AGREE II domains [19].

2.5 Summary of the recommendations in categories included in the clinical practice guidelines

After the quality assessment of each eligible CPGs, those who scored higher than 60% in 3 (rigor of development) and 6 (editorial independence) AGREE II domains were used to summarize the recommendations in categories included in the CPGs.

Two reviewers independently read each CPG to gain an overall knowledge of content and identify topics covered by the guidelines. The topics with the same theme were defined through constant comparison and were grouped within categories to contextualize the recommendations for pharmacological VTE prophylaxis. Generic recommendations were not included within the categories.

3. Results

3.1 Identification of CPGs

The bibliographic search identified 4698 records from databases of which 478 were duplicates. It was screened 4220 remaining references by title and abstract and excluded 4064 that were not in the selection criteria. It was reviewed, 156 documents in full text, and excluded 142 documents. Fourteen CPGs were included. **Figure 2** displays the selection process through the PRISMA statement flow diagram [20].

3.2 Methodological quality of clinical practice guidelines

The AGREE II standardized domain ratings are summarized in **Table 5**.

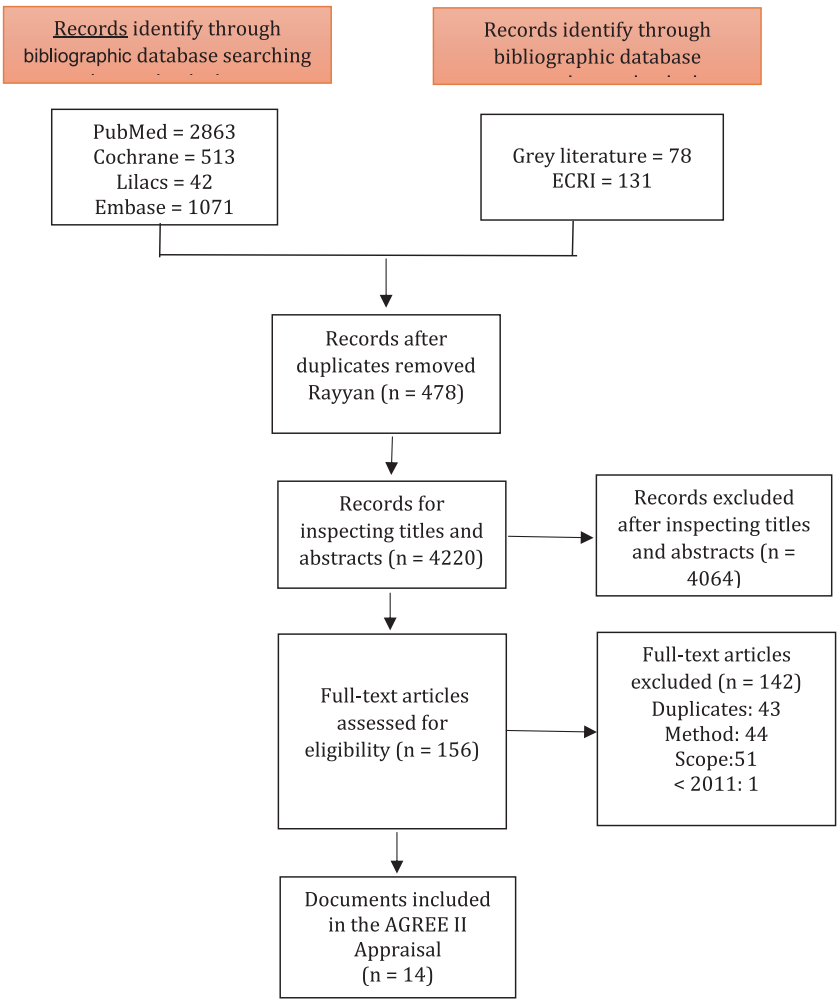

Figure 2.
PRISMA flow diagram of study selection.

01. National Institute for Health and Care Excellence (NICE, 2018): Venous thromboembolism in over 16 s Reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism; 02. American Society of Hematology (ASH, 2018): American Society of Hematology guidelines for the management of venous thromboembolism: Prevention of venous thromboembolism in surgical and medical hospitalized patients; 03. Scottish Intercollegiate Guidelines Network (SIGN, 2014): Prevention and management of venous thromboembolism; 04. German interdisciplinary, evidence- and consensus-based (S3, 2015): Clinical practice guideline: The prophylaxis of venous thromboembolism; 05. National Health and Medical Research Council (NHMRC, 2012): Clinical practice guideline for the prevention of venous thromboembolism in patients admitted to Australian hospitals; 06. American College of Chest Physicians (ACCP, 2012): Antithrombotic Therapy and Prevention of Thrombosis, 9th ed.: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines; 07. American College Physicians (ACP, 2011): Venous thromboembolism prophylaxis in hospitalized patients: A clinical practice guideline from the American College of Physicians; 08. Saudi Scientific Hematology Society and the Saudi Association for VTE (SAVTE, 2013): Saudi Arabian Handbook for Healthcare

	Clinical Practice Guidelines	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
		Scope and Purpose	Stakeholder Involvement	Rigor of Development	Clarity of Presentation	Applicability	Editorial Independence
01	NICE, 2018 [21]	93%	76%	86%	83%	64%	83%
02	ASH, 2018 [22, 23]	80%	74%	76%	81%	58%	86%
03	SIGN, 2014 [24]	81%	80%	72%	81%	61%	69%
04	S3, 2015 [25]	74%	65%	72%	74%	35%	83%
05	NHRMC, 2012 [26]	80%	78%	72%	78%	49%	61%
06	ACCP, 2012 [27–29]	80%	54%	67%	83%	38%	75%
07	ACP, 2011 [8]	76%	56%	65%	63%	28%	67%
08	SAVTE, 2013 [30]	67%	50%	54%	70%	58%	50%
09	IUA, 2013 [31]	59%	30%	47%	59%	33%	33%
10	Queensland Health, 2018 [32]	83%	52%	44%	72%	67%	44%
11	Mexicano, 2011 [33]	57%	31%	40%	65%	17%	8%
12	MOH, 2013 [34]	80%	54%	39%	76%	35%	61%
13	Argentina, 2013 [35]	50%	46%	35%	57%	18%	44%
14	JCS, 2011 [36]	44%	31%	19%	43%	17%	0%

Table 5.
AGREE II standardized domain scores for the 14 included CPGs for pharmacological prophylaxis of VTE in hospitalized adult surgical and medical patients.

Guideline Development; 09. International Union Angiology (IUA, 2013): Prevention and Treatment of Venous Thromboembolism; 10. Medication Services (Queensland Health, 2018): Guideline for the Prevention of Venous Thromboembolism (VTE) in Adult Hospitalized Patients; 11. Colégio Mexicano de Ortopedia y Traumatología (Mexicano, 2011): Declaración de posición conjunta del Colegio Mexicano de Ortopedia y Traumatología: Profilaxis de la enfermedad tromboembólica venosa en cirugía ortopédica de alto riesgo; 12. Ministry of Health of Malaysia (MOH, 2013): Clinical Practice Guidelines: Prevention and Treatment of Venous Thromboembolism; 13. Researchers Group (Argentina, 2013): Guía de recomendaciones para la profilaxis de la enfermedad tromboembólica venosa en adultos en la Argentina; 14. Japanese Circulation Society (JCS, 2011): Guidelines for the Diagnosis, Treatment, and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis;

The methodological quality of fourteen (14) CPGs was assessed by AGREE II instrument. Seven (50%) guidelines obtained scores equal to or greater than 60% in domains 3 or 6 being considered of high quality as described in **Table 6**. The mean scores for the domains were: scope and purpose 72%, stakeholder involvement 56%, rigor of development 56%, clarity of presentation 70%, applicability 41%, and editorial Independence 55%.

	Clinical practice guideline	Name	Organization	Country
01	NICE, 2018 [21]	Venous thromboembolism in over 16 s Reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism	National Institute for Health and Care Excellence	United Kingdom
02	ASH, 2018 [22, 23]	Guideline for management of venous thromboembolism: Prevention of venous thromboembolism in surgical and medical hospitalized patients	American Society of Hematology	United States
03	SIGN, 2014 [24]	Prevention and management of venous thromboembolism	Scottish Intercollegiate Guidelines Network	Scotland
04	S3, 2015 [25]	Clinical practice guideline: The prophylaxis of venous thromboembolism	German interdisciplinary, evidence- and consensus-based	German
05	NHRMC, 2012 [26]	Clinical practice guidelines for the prevention of venous thromboembolism in patients admitted to Australian hospitals	National Health and Medical Research Council	Australia
06	ACCP, 2012 [27–29]	Antithrombotic Therapy and Prevention of Thrombosis, 9th ed.: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines	American College of Chest Physicians	United States
07	ACP, 2011 [8]	Venous thromboembolism prophylaxis in hospitalized patients: A clinical practice guideline from the American College of Physicians	American College Physicians	United States

Table 6.
Clinical practice guidelines for pharmacological prophylaxis of VTE in hospitalized adult medical and surgical patients with high quality assessed by AGREE II.

3.3 Summary of the recommendations in categories

Six major categories, included in high-quality CPGs, were considered important to contextualize the recommendations. There were: 1. patient involvement, 2. risk of VTE and bleeding, 3. indication and strategy of pharmacological prophylaxis in acute ill medical patients, 4. indication and strategy of pharmacological prophylaxis in orthopedic surgical patients, 5. indication and strategy of pharmacological prophylaxis in no-orthopedic surgical patients, 6. monitoring adverse effects.

3.3.1 Patient involvement

- Giving Information: Three [21, 24, 25] of the seven (43%) guidelines included recommendations for giving information to the patients about the importance of VTE prophylaxis on admission.

- Planning Discharge: Three [21, 24, 25] of the seven (43%) included recommendations for planning discharge.

3.3.2 Risk of VTE and bleeding

- Risk Assessment of VTE and bleeding: Five [8, 21, 24–26] of the seven (71%) guidelines included recommendations for identifying the risk of VTE and bleeding in medical and surgical patients admitted to the hospital.

- Reassessment of risk of VTE and bleeding: Two [21, 24] of the seven (29%) guidelines included recommendations about reassessment periodically of the risk of VTE and bleeding in medical and surgical patients admitted to the hospital.

- Risk Assessment Tools: Four [21, 24–26] of the seven (57%) guidelines included recommendations about risk assessment tools. The CPGs discuss assessment tools for VTE and bleeding to perform the risk factors. The factors are related to exposure (type of surgical procedure/trauma/acute disease, extent of immobilization) and disposition (individual inherited and acquired factors) [25] and to estimate the baseline risk for patients with low and high VTE risk, has been used data from risk assessment models (RAMs) [27–29]. These tools have limitations including lack of prospective validation, applicability only to high-risk subgroups, inadequate follow-up time, and excessive complexity [27–29].

3.3.3 Indication and strategy of pharmacological prophylaxis in acute ill medical patients

- Pharmacological prophylaxis: Six [8, 21, 24–26, 29] of the seven (86%) included guidelines with recommendations to pharmacological thromboprophylaxis. CPGs report that after individually assessing for risk of VTE and bleeding and the assessment favors the use of pharmacologic thromboprophylaxis, the use of pharmacological agents has been considered.

- Pharmacological agents: All guidelines [8, 21, 23–26, 29] contained recommendations related pharmacological agents for patients who receive pharmacological prophylaxis. Of these seven guidelines, three [21, 24, 25]

contained recommendations for pharmacological VTE prophylaxis for people with renal impairment or obesity.

- Duration of prophylaxis: Four [21, 24, 25, 29] of the seven (57%) contained recommendations related to the duration of prophylaxis in acute ill medical patients.

4. Indication and strategy of pharmacological prophylaxis in orthopedic surgical patients

ACCP, 2012 [27] classified hip arthroplasty, knee arthroplasty, and hip fracture surgery as major orthopedic surgery. ASH, 2019 [22] recommendations 1 to 8 for patients undergoing major surgery were not included (generic recommendations). ACP, 2011 [8] contained recommendations only for medical patients.

4.1 Hip Arthroplasty

- Pharmacological agents and duration of prophylaxis: Six [21, 22, 24–27] of the seven (86%) guidelines contained recommendations related to pharmacological prophylaxis strategy for surgical patients undergoing hip arthroplasty with high VTE risk determined after individually assess for risk of VTE and bleeding.

- Preoperatively and postoperatively: Only ACCP, 2012 [27] and S3, 2015 [25] contained recommendations for patients undergoing hip arthroplasty preoperatively and postoperatively.

4.2 Knee arthroplasty

- Pharmacological agents and duration of prophylaxis: Six [21, 22, 24–27] of the seven (86%) guidelines contained recommendations related to pharmacological prophylaxis for surgical patients undergoing knee arthroplasty whose risk of VTE outweighs the risk of bleeding determined after to individually assess for risk of VTE and bleeding.

- Preoperatively and postoperatively: Only ACCP, 2012 [27] and S3, 2015 [25] contained recommendations for patients undergoing knee arthroplasty preoperatively and postoperatively.

4.3 Fragility fractures of the pelvis, hip, and proximal femur

- Pharmacological agents and duration of prophylaxis: Five [21, 22, 25–27] of seven (71%) CPGs contained recommendations for patients undergoing surgery for fragility fractures in the absence of contraindications.

- Preoperatively and postoperatively: Only Nice, 2018 [21] and S3, 2015 [25] contained recommendations related to preoperatively and postoperatively in patients undergoing surgery for fragility fractures.

4.4 Foot and ankle orthopedic surgery

Only one guideline [21] considered recommendations for pharmacological prophylaxis in patients undergoing foot or ankle surgery after individually assessing for risk of VTE and bleeding.

4.5 Upper limb orthopedic surgery

Two [21, 25] of seven (29%) CPGs contained recommendations with pharmacological prophylaxis in patients undergoing surgery upper limb surgery.

4.6 Lower limb immobilization

Five [21, 24–27] of seven (71%) CPGs contained recommendations for patients with lower limb immobilization whose risk of VTE outweighs the risk of bleeding and are subject to prolonged immobility.

4.7 Knee arthroscopy

Four [21, 25–27] of seven (57%) CPGs contained recommendations for pharmacological prophylaxis in patients undergoing knee arthroscopy in longer arthroscopic procedures with no contraindications.

5. Indication and strategy of pharmacological prophylaxis no orthopedic surgical patients

5.1 Trauma patients

Five [21, 22, 25–27] of seven (71%) CPGs included recommendations about pharmacological prophylaxis in major trauma patients after assessment to identify the risk of VTE and bleeding.

5.2 General and abdominal-pelvic surgery

This group included patients undergoing gastrointestinal, urological, and gynecologic surgeries. Six [21, 22, 24–26, 28] of the seven (86%) CPGs included recommendations about pharmacological prophylaxis in patients undergoing general and pelvic abdominal surgery depending on the type of risk (low, moderate, or high) after an individual assessment.

5.3 Thoracic surgery

Five [21, 24–26, 28] of the seven (71%) CPGs included recommendations for thoracic surgery after an individual risk assessment. Not included recommendations in cardiac surgery.

5.4 Vascular surgery

This group included recommendations for patients undergoing a lower limb amputation and varicose vein surgery. Six [21, 22, 24–26, 28] of the seven (86%) CPGs included recommendations for pharmacological prophylaxis in patients whose risk of VTE outweighs the risk of bleeding.

5.5 Laparoscopic surgery

Laparoscopic surgery can include procedures ranging from a very short diagnostic laparoscopic procedure to lengthy major surgery, e.g., laparoscopic colectomy. Three [22, 24, 25] CPGs of the seven (43%) included recommendations about pharmacological prophylaxis for patients with risk factors for VTE.

6. Monitoring adverse effects

Heparin-induced thrombocytopenia (HIT) is a serious complication of heparin anticoagulant therapy and can cause thrombocytopenia, venous or arterial thrombosis, skin lesions, and rarely a systemic reaction that can be serious and fatal. HIT may occur in any patient who is receiving heparin [24]. Three [24–26] CPGs of the seven (43%) included recommendation to minimize the incidence of HIT, monitor the development of HIT, and therapeutic options for thrombotic event related to HIT. The ACCP, 2012 [37] and ASH, 2018 [38] have supplementary material that included recommendations about HIT and were not included in this study.

7. Conclusion

This systematic review analyzed the methodological quality and summarized the main recommendations of the CPGs for pharmacological prophylaxis of VTE in adult hospitalized surgical and medical patients.

Seven CPGs were considered with high-quality after assessment by AGREE II a tool accepted as a gold standard for guideline evaluation. The scores with a cut-off of 60% or more for domains 3 (rigor of development) and 6 (editorial independence) were used to identify high-quality CPGs in this study. Domain 3 indicates minimum bias and evidence-based guideline development and domain 6 indicates the relevance of conflict of guideline authors as a potential source of bias. Special attention should be directed to domain 5 (applicability) which indicates the description of barriers and facilitators that impact the applicability of the guideline and had an average score of a 41%. The findings, by presenting the weaknesses in the method's rigor, can also help developers to improve the quality of future CPGs.

Regarding the scope addressed by the guidelines, it was identified that the topics were included regarding important aspects in pharmacological prophylaxis of VTE in hospitalized patients. Most CPGs included recommendations about drug, dose, and duration of therapy that were summarized in the indication and strategy of pharmacological prophylaxis.

The high-quality CPGs discussed about the patient assessment to determine risk stratification for VTE and most CPGs agree that tools have limitations and an individual risk assessment was necessary to focus on patient-specific characteristics,

incorporating surgery-specific risk in addition to medical factors. These recommendations were summarized into the risk of VTE and bleeding risk categories.

Some high-quality CPGs included recommendations about the involvement of the patient and family in the management of the prophylaxis of VTE and monitoring adverse effects during the use of the pharmacological prophylaxis. These recommendations were summarized in the category of patient involvement and monitoring adverse effects respectively.

Thus, analyzing the methodological quality and summarizing the recommendations were important steps to support the process of adopting new guidelines for pharmacological prophylaxis of VTE in adult hospitalized surgical and medical patients.

Conflict of interest

Authors have a link only with the University of São Paulo.

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