CLINICAL GUIDELINES

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American Society of Hematology, ABHH, ACHO, Grupo CAHT, Grupo CLAHT, SAH, SBHH, SHU, SOCHIHEM, SOMETH, Sociedad Panamena de Hematología, Sociedad Peruana de Hematología, and SVH 2023 guidelines for diagnosis of venous thromboembolism and for its management in special populations in Latin America

Ignacio Neumann,[1] Ariel Izcovich,[2] Ricardo Aguilar,[3] Guillermo León Basantes,[4] Patricia Casais,[5,6] Cecilia C. Colorio,[7] María Cecilia Guillermo Esposito,[8] Pedro P. García Lázaro,[9,10] Jaime Pereira,[11] Luis A. Meillon García,[12] Suely Meireles Rezende,[13] Juan Carlos Serrano,[14] Mario L. Tejerina Valle,[15] Diana Altuna,[16] Pamela Zúñiga,[11] Felipe Vera,[17] Lorena Karzulovic,[18] and Holger J. Schünemann[19]

[1]School of Medicine, Universidad San Sebastian, Santiago, Chile; [2]Hospital Alemán, Buenos Aires, Argentina; [3]Servicio de Hematología, Complejo Hospitalario Dr. Arnulfo Arias Madrid, Panama City, Panama; [4]Clínica Universitaria Colombia, Bogotá, Colombia; [5]Epidemiología Clínica y Evidencia, Instituto de Investigaciones en Salud Pública, Universidad de Buenos Aires, Buenos Aires, Argentina; [6]Centro de Hematología Pavlovsky, Buenos Aires, Argentina; [7]Fundación Favaloro, Buenos Aires, Argentina; [8]Hospital de Clínicas Dr. Manuel Quintela, Montevideo, Uruguay; [9]Faculty of Medicine, Universidad Privada Antenor Orrego, Trujillo, Peru; [10]Hospital Especializado Víctor Lazarte Echegaray, Trujillo, Peru; [11]Department of Hematology and Oncology, Pontificia Universidad Católica de Chile, Santiago, Chile; [12]The ABC Medical Center, Mexico City, Mexico; [13]Department of Internal Medicine, Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; [14]Unidad Hematológica Especializada IPS, Cúcuta, Colombia; [15]Caja Petrolera de Salud, La Paz, Bolivia; [16]Pediatric Oncology and Hematology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; [17]School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom; [18]Department of Pediatrics, Pontificia Universidad Católica de Chile, Santiago, Chile; and [19]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada

Background: Implementation of international guidelines in Latin American settings requires additional considerations (ie, values and preferences, resources, accessibility, feasibility, and impact on health equity).

Objective: The purpose of this guideline is to provide evidence-based recommendations about the diagnosis of venous thromboembolism (VTE) and its management in children and during pregnancy.

Methods: We used the GRADE ADOLOPMENT method to adapt recommendations from 3 American Society of Hematology (ASH) VTE guidelines (diagnosis of VTE, VTE in pregnancy, and VTE in the pediatric population). ASH and 12 local hematology societies formed a guideline panel comprising medical professionals from 10 countries in Latin America. Panelists prioritized 10 questions about the diagnosis of VTE and 18 questions about its management in special populations that were relevant for the Latin American context. A knowledge synthesis team updated evidence reviews of health effects conducted for the original ASH guidelines and summarized information about factors specific to the Latin American context.

Results: In comparison with the original guideline, there were significant changes in 2 of 10 diagnostic recommendations (changes in the diagnostic algorithms) and in 9 of 18 management recommendations (4 changed direction and 5 changed strength).

Conclusions: This guideline ADOLOPMENT project highlighted the importance of contextualizing recommendations in other settings based on differences in values, resources, feasibility, and health equity impact.

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The full-text version of this article contains a data supplement.

Introduction

Aim of these guidelines and specific objectives

Current evidence-based recommendations are informed not only by different evidence sources, such as randomized trials evaluating the health effects of interventions, but also by studies assessing patients' values and preferences, resource use, accessibility, feasibility, and impact on health equity.[1-3] Some of these factors are likely variable in different settings (eg, costs and equity). Although the American Society of Hematology (ASH) guidelines for management of venous thromboembolism (VTE) were developed for a global audience, recommendations were influenced by the perspectives of high-income countries. Therefore, implementation of some of these recommendations may not be straightforward in other contexts and may require additional considerations. In addition, developing evidence-based recommendations is a lengthy and resource-intensive process. This is mainly due to the difficulty of identifying and summarizing the relevant evidence necessary to develop trustworthy recommendations. Thus, the whole process cannot be easily replicated when local recommendations are needed, and adaptation is an efficient approach.

The purpose of this guideline is to provide evidence-based recommendations for the Latin American context about the diagnosis of VTE in the general population and its management during pregnancy and in pediatric patients. The recommendations included in this document complement the previously published guidelines about the management of VTE in adults and its prevention in surgical and medical patients, as well as in long-distance travelers.[4]

This article refers to the adaptation of the following ASH guidelines: diagnosis of VTE,[5] management of VTE in pregnant women,[6] and management of VTE in children.[7]

Methods

The recommendations presented in this guideline were adapted to the context of Latin America following the GRADE ADOLOPMENT method[8] (GRADE: Grading of Recommendations, Assessment, Development, and Evaluation) and according to the principles outlined by the Institute of Medicine[3] and the Guideline International Network.[2]

The detailed methods used in this effort are described elsewhere.[9]

Organization, panel composition, planning, and coordination

This project was a collaboration of ASH and 12 hematology/thrombosis and hemostasis societies in Latin America: Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular (ABHH), Asociación Colombiana de Hematología y Oncología (ACHO), Grupo Cooperativo Argentino de Hemostasia y Trombosis (Grupo CAHT), Grupo Cooperativo Latinoamericano de Hemostasia y Trombosis (Grupo CLAHT), Sociedad Argentina de Hematología (SAH), Sociedad Boliviana de Hematología y Hemoterapia (SBHH), Sociedad Chilena de Hematología (SOCHIHEM), Sociedad de Hematología del Uruguay (SHU), Sociedad Mexicana de Trombosis y Hemostasia (SOMETH), Sociedad Panameña de Hematología, Sociedad Peruana de Hematología, and Sociedad Venezolana de Hematología (SVH). Project coordination was provided by ASH. Project supervision was provided by the ASH Guideline Oversight Subcommittee, which reported to the ASH Committee on Quality, and by the executive boards of the Latin American partner societies.

The partner societies nominated individuals to serve on the guideline panel.

The McMaster University GRADE Centre recommended methodologists to conduct systematic evidence reviews and facilitate the GRADE ADOLOPMENT process. ASH vetted all nominated individuals, including for conflicts of interest, and formed the panel to include 2 methodologists (I.N. and A.I.) and 13 hematologists from 10 countries: Argentina, Bolivia, Brazil, Chile, Colombia, Mexico, Panama, Peru, Uruguay, and Venezuela. The partner societies were represented as follows: Suely Meireles Rezende representing ABHH, Guillermo León Basantes representing ACHO, Patricia Casais representing Grupo CAHT, Cecilia C. Colorio and Diana Altuna representing SAH, Mario L. Tejerina Valle representing SBHH, Jaime Pereira and Pamela Zúñiga representing SOCHIHEM, Ricardo Aguilar representing the Sociedad Panameña de Hematología; Pedro P. García Lázaro representing the Sociedad Peruana de Hematología, María Cecilia Guillermo Esposito representing SHU and Grupo CLAHT, Juan Carlos Serrano representing SVH, and Luis Meillón-García representing SOMETH. In October 2019, representation of Grupo CLAHT was transferred from Patricia Casais to María Cecilia Guillermo Esposito.

The McMaster University GRADE Centre formed a knowledge synthesis team that included individuals based in Chile and Argentina. The team determined methods, prepared meeting materials, updated the evidence reviews conducted for the source ASH guidelines, and searched for regional information about values and preferences, resources, accessibility, feasibility, and impact on health equity. Methodologists from the knowledge synthesis team (I.N. and A.I.) facilitated discussions and guided the panel through decision making.

The panel's work was done using web-based tools (www.surveymonkey.com and www.gradepro.org) and face-to-face and online meetings. These meetings were conducted mostly in Spanish.

The membership of the panel and the knowledge synthesis team is described in Supplement 1.

Guideline funding and management of conflicts of interest

The source guidelines and these adapted guidelines were wholly funded by ASH, a nonprofit medical specialty society that represents hematologists, and the ASH Foundation. ASH staff supported panel appointments and coordinated meetings but had no role in choosing the guideline questions or determining the recommendations. Staff and members of the partner Latin American societies who did not serve on the guideline panel also had no such role.

Members of the guideline panel received travel reimbursement for attendance at in-person meetings but received no other payments. Through the McMaster GRADE Centre, some researchers who contributed to the systematic evidence reviews received salary or

grant support. Other researchers participated to fulfill the requirements of an academic degree or program.

Conflicts of interest of all participants were managed according to ASH policies, which are based on recommendations of the Institute of Medicine (IOM 2009) and the Guidelines International Network.[10] On appointment, all panelists agreed to avoid direct conflicts of interest with companies that could be affected by the guidelines. Participants disclosed all financial and nonfinancial interests relevant to the guideline topic. ASH staff reviewed the disclosures and made judgments about conflicts. Greatest attention was paid to direct financial conflicts with for-profit companies that could be directly affected by the guidelines. In consideration of regional economic factors in Latin America, ASH adjusted the conflict-of-interest policy for this panel to allow direct payment from affected companies to panelists for travel to attend educational meetings. Four panelists reported receiving travel support to attend educational meetings from companies that could be affected by the guidelines. ASH and the partner societies agreed to manage such support through disclosure. In addition, 5 panelists reported receiving direct payments from pharmaceutical companies that market products addressed by these guidelines. These conflicts were also managed through disclosure. None of the other panelists reported direct financial conflicts with for-profit companies that could be directly affected by the guidelines. None of the researchers who contributed to the systematic evidence reviews or who supported the guideline development process had any direct financial conflicts with for-profit companies that could be affected by the guidelines.

Supplement 2 provides the complete disclosure-of-interest forms of all panel members. In part A of the forms, individuals disclose direct financial interests for 2 years prior to appointment; in part B, indirect financial interests; and in part C, not mainly financial interests. Part D describes new interests disclosed by individuals after appointment. Part E summarizes ASH decisions about which interests were judged to be conflicts and how they were managed. Supplement 3 provides the complete disclosure-of-interest forms of the researchers who contributed to these guidelines.

Selecting clinical questions for adaptation

From all the clinical questions addressed by the source guidelines, the guideline panel prioritized those most relevant to the Latin American setting. First, through an online survey, panelists rated the clinical questions using a 9-point scale ranging from not relevant to highly relevant. Then, clinical questions were ranked based on the median score from all the panelists. Finally, in an in-person meeting, panelists reviewed the scores and selected the final clinical questions based on the results of the survey, while also ensuring the consistency and comprehensiveness of the guideline as a whole (Table 1).

Table 1. Clinical questions adapted

Diagnosis of VTE
Diagnosis of PE
Diagnosis of PE in individuals with low pretest probability (≤5%) of a first PE
Diagnosis of PE in individuals with low pretest probability (≤5%) of recurrent PE
Diagnosis of PE in individuals with intermediate pretest probability (~20%) of a first PE
Diagnosis of PE in individuals with high pretest probability (≥50%) of a first PE
Diagnosis of PE in individuals with high pretest probability (≥50%) of recurrent PE
Diagnosis of DVT
Diagnosis of DVT in individuals with low pretest probability (≤10%) of a first DVT
Diagnosis of DVT in individuals with low pretest probability (≤10%) of recurrent DVT
Diagnosis of DVT in individuals with intermediate pretest probability (~25%)
Diagnosis of DVT in individuals with high pretest probability (≥50%) of a first DVT
Diagnosis of DVT in individuals with high pretest probability (≥50%) of recurrent DVT
Management of VTE during pregnancy
Treatment of acute VTE and superficial venous thrombosis
Anticoagulation with LMWH vs no anticoagulation in superficial venous thrombosis
Use once-daily vs twice-daily LMWH in VTE
Thrombolytic therapy vs anticoagulation alone in PE and hemodynamic failure
Thrombolytic therapy vs anticoagulation alone in PE and right ventricular dysfunction
Home treatment vs hospital treatment DVT or PE and low risk of complication
Management of anticoagulants around the time of delivery
Scheduled delivery vs spontaneous labor for women receiving therapeutic-dose LMWH
Scheduled delivery vs spontaneous labor for women receiving prophylactic-dose LMWH
Anticoagulant use for breastfeeding women
One specific drug to be used vs others
Prevention of VTE
Antepartum prophylaxis vs no prophylaxis for women with previous VTE
Postpartum prophylaxis vs no prophylaxis for women with previous VTE
Antepartum prophylaxis vs no prophylaxis for women with thrombophilia
Postpartum prophylaxis vs no prophylaxis for women with thrombophilia
Management of VTE in children
Anticoagulation vs no anticoagulation in asymptomatic VTE
Thrombolytic therapy vs anticoagulation alone in PE and hemodynamic failure
Removal vs no removal of functioning central access in symptomatic associated VTE
LMWH vs VKAs as maintenance therapy for VTE
Anticoagulation vs no anticoagulation in cerebral sinus venous thrombosis

Evidence reviews and inclusion of local data

The original ASH VTE guidelines included an evidence-to-decision (EtD) framework for each of the questions addressed.[1] The knowledge synthesis team updated the electronic search of randomized trials and observational studies of the original guidelines and conducted a comprehensive search of regional evidence about patients' values and preferences, resource use, accessibility, feasibility, and impact on health equity in English, Spanish, and Portuguese (Supplement 4). For each EtD framework, researchers from the knowledge synthesis team summarized the data used in the original guideline as well as all relevant regional information identified using the GRADEpro guideline development tool (McMaster University, Hamilton, ON, Canada, and Evidence Prime, Inc, Kraków, Poland). To estimate the absolute effect of the interventions, we calculated the risk difference by multiplying the pooled risk ratio by the baseline risk of each outcome. We used as the baseline risk the median of the risks observed in the control groups of the included trials. In addition, when possible, the

researchers used the baseline risk observed in large observational studies.

We assessed the certainty in the body of evidence (also known as the quality of the evidence or confidence in the estimated effects) following the GRADE approach.[11,12] We made judgments regarding the risk of bias, precision, consistency, directness, and likelihood of publication bias and categorized the certainty in the evidence into 4 levels ranging from very low to high.

In the case of questions about VTE diagnosis, explicit and a priori thresholds were used to rank alternative diagnostic pathways. Panelists agreed that a false-negative risk of ≤2% and a misdiagnosis (false-negative + false-positive) risk of ≤5% were acceptable.

Development of recommendations

During an in-person meeting that took place in Lima, Peru, on 4 April 2019, the panel developed recommendations based on the evidence summarized in the EtD tables.

The panel agreed on the direction and strength of recommendations through group discussion and deliberation. In rare instances when consensus was not reached, voting took place. In such circumstances, the result of the voting was recorded on the respective EtD table. The direction of the recommendation was decided by a simple majority, whereas an 80% majority was required to issue a strong recommendation.

Although, as in the case of the original VTE guidelines, panels defined the direction and strength of every recommendation and made judgments on every relevant domain included in the EtD, Latin American panelists were not aware of those decisions and judgments.

Document review

Draft recommendations were reviewed by all members of the panel, revised, and then made available online for external review by stakeholders, including members of the Latin American partner societies, allied organizations, medical professionals, patients, and the general public. Recommendations for special populations were made available from 20 January to 20 February 2022; recommendations for diagnosis were made available from 10 May to 30 May 2022. Notifications were made via email and social media and at in-person meetings. The recommendations were presented in 3 languages (English, Portuguese, and Spanish). Fourteen individuals submitted comments about the special population recommendations, and 12 individuals submitted comments about the diagnosis recommendations. The document was revised to address pertinent comments, but no changes were made to the recommendations. The 12 Latin American societies described earlier approved the guidelines in July 2022. On 26 January 2023, the ASH Guideline Oversight Subcommittee and the ASH Committee on Quality agreed that the defined guideline development process was followed, and on 1 February 2023, the officers of the ASH Executive Committee approved the submission of the guidelines for publication under the imprimatur of ASH and the partner societies. The guidelines were then subjected to peer review by *Blood Advances*.

How to use these guidelines

The recommendations are labeled as "strong" or "conditional" according to the GRADE approach. The words "the ASH Latin American guideline panel recommends" are used for strong recommendations; the words "the ASH Latin American guideline panel suggests" are used for conditional recommendations. Table 2 provides GRADE's interpretation of strong and conditional recommendations by patients, clinicians, health care policy makers, and researchers.

These guidelines are intended primarily to help clinicians make decisions about diagnostic and treatment alternatives. Other purposes are to inform policy, education, and advocacy and to state future research needs. They may also be used by patients. These guidelines are not intended to serve or be construed as a standard of care. Clinicians must make decisions based on the clinical presentation of each individual patient, ideally through a shared process that considers the patient's values and preferences with respect to the anticipated outcomes of the chosen option. Decisions may be constrained by the realities of a specific clinical setting and local resources, including but not limited to institutional policies, time limitations, or the availability of treatments. These guidelines may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence becomes available, recommendations may become outdated. Following these guidelines cannot guarantee successful

Table 2. Interpretation of strong and conditional recommendations

Implications for	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients, and clinicians must help each patient arrive at a management decision consistent with the patient's values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or a performance indicator.	Policy making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help to identify possible research gaps.

outcomes. ASH and the partner societies do not warrant or guarantee any of the products described in these guidelines.

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are integral parts and serve to facilitate a more accurate interpretation. They should never be omitted when quoting or translating recommendations from these guidelines. The use of these guidelines is also facilitated by the links to the EtD frameworks and interactive summary of findings tables in each section.

Search results

In our comprehensive search, we found 2 observational studies published after the original guideline.[13,14] Those studies provided additional data for the question addressing the use of thrombolysis vs anticoagulation alone in children with pulmonary embolism (PE) and hemodynamic failure.

We also identified information about the cost of the interventions in different countries of the region as well as evidence of accessibility and potential impact on health equity.

Recommendations

Interpretation of strong and conditional recommendations

The strength of a recommendation is expressed as either strong ("the guideline panel recommends…") or conditional ("the guideline panel suggests…") and has the interpretation described in Table 2.

Diagnosis of VTE

Figures 1 and 2 summarize recommendations 1 to 10 in flow diagrams.

Diagnosis of PE

For a patient population with a low clinical probability of PE, what is the optimal diagnostic strategy to evaluate a suspected PE?

Recommendation 1

For a patient with a low pretest probability of a first episode of PE (≤5%), the ASH Latin American guideline panel *recommends* using D-dimer for excluding PE (strong recommendation based on high-certainty evidence about effects ⊕⊕⊕⊕), followed by computed tomography pulmonary angiography (CTPA) for patients with a positive D-dimer result (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

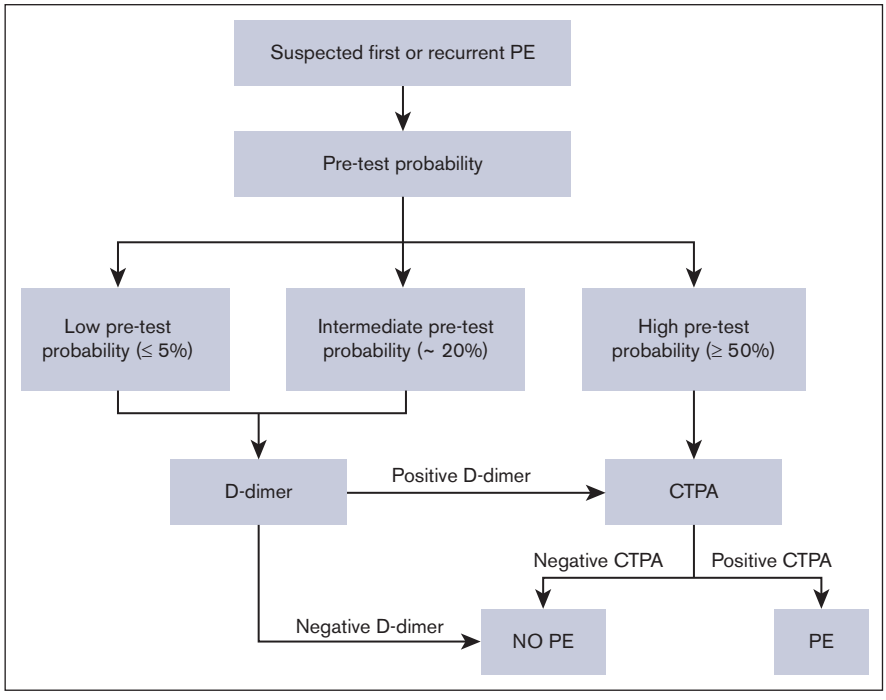
Recommendation 2

For a patient with a low pretest probability of recurrent PE (≤5%), the ASH Latin American guideline panel *suggests* using D-dimer for excluding PE (conditional recommendation based on low-certainty evidence about effects ⊕⊕◯◯), followed by CTPA for patients with a positive D-dimer result (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remark:

- If CTPA is not available, an alternative could be a ventilation-perfusion (VQ) scan followed by proximal compression ultrasound (CUS) if the VQ scan does not rule out or confirm PE (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Figure 1. Diagnosis of first or recurrent PE.



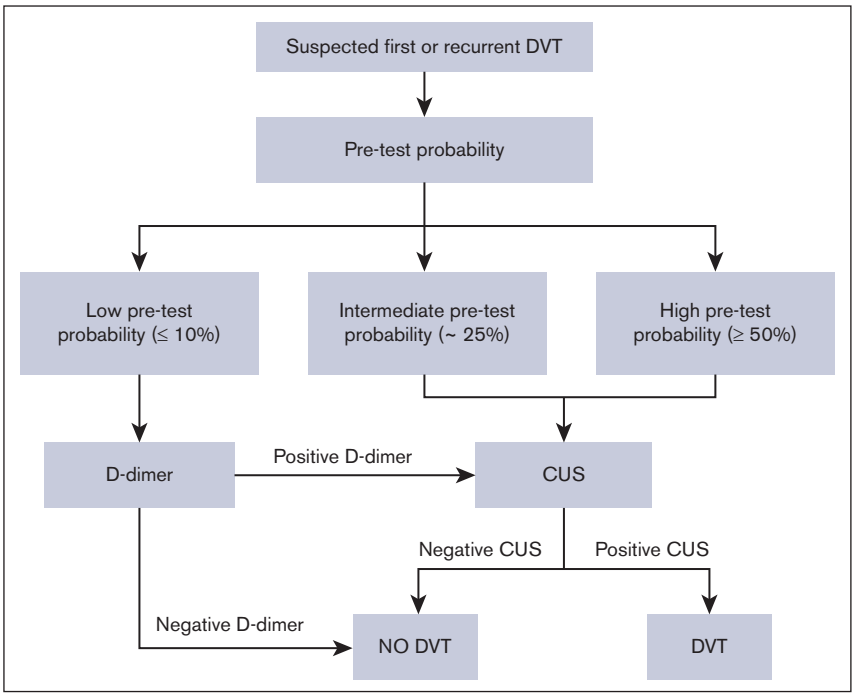


Figure 2. Diagnosis of first or recurrent DVT.

Summary of the evidence. No additional evidence was identified (https://dbep.gradepro.org/profile/e9600faf-99bc-4ade-9f2f-70bf6e078f9e and https://guidelines.gradepro.org/profile/dc56e5e0-1329-450a-882f-b7c96b1572ef).

Justification. These recommendations changed the preferred diagnostic pathways. The original panel selected D-dimer followed by a VQ scan or CTPA. The Latin American panel considered that D-dimer was affordable and generally available in the region; therefore, it was considered a reasonable first step to rule out PE. However, owing to the very limited availability of VQ scanning in Latin America, the panel opted for suggesting CTPA over VQ scan as a follow-up test to a positive D-dimer result.

Conclusion. Several clinical prediction rules estimating the probability of having a PE have been studied. Systematic reviews addressing the available models showed that all have a similar discriminative ability, with a high sensitivity (88%-96%) and a relatively low specificity (48%-53%).[15,16] Clinicians may therefore choose the prediction rule that best suits their specific setting. However, it is important to consider that the labels "low," "intermediate," and "high" probability may not refer to the same numbers and may not necessarily match how we categorized the probability in this guideline.

In individuals with a low pretest probability (≤5%), a negative D-dimer result effectively rules out the diagnosis in both a suspected first episode of PE and in recurrent PE. However, an abnormal D-dimer result can be observed in many clinical conditions apart from VTE and hence must be followed by a confirmatory test.

For a patient population with an intermediate clinical probability of PE, what is the optimal diagnostic strategy to evaluate for a suspected first episode of PE?

Recommendation 3

For a patient with an intermediate pretest probability of a first episode of PE (~20%), the ASH Latin American guideline panel *suggests* using D-dimer for excluding PE (conditional recommendation based on high certainty in the evidence about effects ⊕⊕⊕⊕), followed by CTPA for patients with a positive D-dimer result (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- If CTPA is not available, an alternative could be a VQ scan followed by proximal CUS if the VQ scan does not rule out or confirm PE (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).
- If the pretest probability is estimated at >20% (intermediate to high pretest probability), D-dimer probably is no longer able to safely rule out PE. In such circumstances, the guideline panel suggests following recommendations 4 and 5.

Summary of the evidence. No additional evidence was identified (https://dbep.gradepro.org/profile/2d575b1d-8e36-43db-8805-713732e1508a).

Justification. This recommendation changed the preferred diagnostic pathway. The original panel selected D-dimer followed by a VQ scan or CTPA. As with recommendation 1, given the limited

availability of VQ scanning in the region, the Latin American panel opted for suggesting CTPA over VQ scanning as a follow-up test to a positive D-dimer result.

Conclusion. The ability of D-dimer to rule out PE decreases with higher pretest probabilities. The Latin American panel judged that at a 20% probability, D-dimer can still safely rule out a first episode of PE. However, patients with an intermediate probability of recurrent PE (~20%) may not be adequately categorized by D-dimer alone, and hence, the panel suggests following recommendation 5 in this situation.

As before, it should be noted that an abnormal D-dimer test result can be observed in many clinical conditions apart from VTE, and therefore, a positive D-dimer result should not be the sole basis for VTE diagnosis.

For a patient population with a high clinical probability of PE, what is the optimal diagnostic strategy to evaluate for suspected PE?

Recommendations 4 and 5

For a patient with a high pretest probability of a first episode (recommendation 4) or recurrent PE (recommendation 5) (≥50%), the ASH Latin American guideline panel *suggests* using a strategy starting with CTPA (both conditional recommendations based on very low certainty in the evidence about effects ⊕◯◯◯).

Remark:

- If the clinical suspicion of PE remains high after a negative CTPA result, following up with a CUS or D-dimer may help to rule out the diagnosis.

Summary of the evidence. No additional evidence was identified (https://dbep.gradepro.org/profile/6affa6fc-0c1c-44e0-a901-2558ee36032b and https://guidelines.gradepro.org/profile/dc56e5e0-1329-450a-882f-b7c96b1572ef).

Justification. These recommendations did not change the preferred diagnostic pathways.

Conclusion. A pretest probability of ≥50% means that for a particular patient, PE is the most likely diagnosis. In these circumstances, D-dimer is no longer able to safely rule out PE and therefore should not be used.

In many instances in the region, patients with a high probability of PE may need to be transferred to a medical center where CTPA is available. A crucial decision in this situation is whether to start anticoagulation empirically or wait for the test results. In making the decision, it may be important to consider the expected delay in obtaining CTPA, the bleeding risk, and the patients' values and preferences.

Diagnosis of DVT

For a patient population with a low clinical probability of lower extremity deep vein thrombosis (DVT), what is the optimal diagnostic strategy to evaluate for a suspected DVT?

Recommendation 6

For a patient with a low pretest probability of a first episode of DVT (≤10%), the ASH Latin American guideline panel *recommends* using D-dimer for excluding DVT (strong recommendation based on moderate-certainty evidence about effects ⊕⊕⊕◯), followed by CUS for patients with a positive D-dimer test result (both conditional recommendations based on very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 7

For a patient with a low pretest probability of a recurrent DVT (≤10%), the ASH Latin American guideline panel *suggests* using D-dimer for excluding DVT (conditional recommendation based on low-certainty evidence about effects ⊕⊕◯◯), followed by CUS for patients with a positive D-dimer test result (both conditional recommendations based on very low certainty in the evidence about effects ⊕◯◯◯).

Summary of the evidence. No additional evidence was identified (https://dbep.gradepro.org/profile/c039b042-6668-4b66-b2a8-cbd6e0397f9c and https://dbep.gradepro.org/profile/37638e9e-85a2-499b-8aed-44e2ef55806b).

Justification. These recommendations did not change the preferred diagnostic pathways.

Conclusion. The Latin American panel judged that both D-dimer and ultrasound were generally available and affordable in most settings in Latin America. Therefore, the original recommendations were considered applicable.

For a patient population with an intermediate clinical probability of lower extremity DVT, what is the optimal diagnostic strategy to evaluate for a suspected first episode of DVT?

Recommendation 8

For a patient with an intermediate pretest probability of a first episode of DVT (~25%), the ASH Latin American guideline panel *suggests* using CUS as the preferred diagnostic strategy (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- For most patients, a negative CUS result rules out DVT. However, if no other alternative diagnosis is identified and the clinical suspicion remains, serial CUS may be needed.
- This recommendation likely applies to patients with an intermediate clinical probability of recurrent lower extremity DVT.

Summary of the evidence. No additional evidence was identified (https://dbep.gradepro.org/profile/6e603c3b-fdf2-478b-9abb-bf09ea983839).

Justification. This recommendation did not change the preferred diagnostic pathway.

Conclusion. As with people with suspected PE, the ability of D-dimer to rule out DVT decreases as the pretest probability increases. The Latin American guideline panel judged that at an intermediate probability of DVT, D-dimer alone no longer safely rules out DVT. In addition, the panel considered that both D-dimer and CUS are generally available and affordable in most settings in Latin America; thus, a strategy based on CUS was preferred.

For a patient population with a high clinical probability of lower extremity DVT, what is the optimal diagnostic strategy to evaluate for a suspected DVT?

Recommendations 9 and 10

For a patient with a high pretest probability of a first episode (recommendation 9) or recurrent DVT (recommendation 10) (≥50%), the ASH Latin American guideline panel *suggests* using CUS as the preferred diagnostic strategy (both conditional recommendations based on very low certainty in the evidence about effects ⊕◯◯◯).

Remark:

- For most patients, a negative CUS result rules out DVT. However, if no other alternative diagnosis is identified and the clinical suspicion remains, serial CUS may be needed.

Summary of the evidence. No additional evidence was identified (https://dbep.gradepro.org/profile/514261d1-957b-4bd0-a137-74cb6878e1f1 and https://dbep.gradepro.org/profile/37638e9e-85a2-499b-8aed-44e2ef55806b).

Justification. These recommendations did not change the preferred diagnostic pathways.

Conclusion. When DVT is the most likely diagnosis for a patient with a suspected first or recurrent episode, D-dimer alone does not rule out the diagnosis, and therefore, it should not be used. As in individuals with a high probability of PE, a crucial decision in this situation is whether to start anticoagulation empirically or wait for the test results. Given the relatively lower risk of serious adverse outcomes of DVT compared with PE, most patients may be better off waiting for the test results. However, in some patients, it may be appropriate to start anticoagulation empirically if the potential benefits of early treatment are considered to outweigh the bleeding risk, especially for patients who may place a higher value on avoiding the complications of thrombotic events.

Prevention and management of VTE during pregnancy

Treatment of acute VTE and superficial venous thrombosis. *For pregnant women with proven acute superficial vein thrombosis of the lower extremity, should we use anticoagulation with low-molecular-weight heparin (LMWH)?*

Recommendation 11

For pregnant women with proven acute superficial venous thrombosis of the lower extremity, the ASH Latin American panel *suggests* anticoagulation with LMWH over no anticoagulation (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Remarks:

- Women with risk factors for progression to DVT (like extensive thrombosis or localized close to the saphenofemoral junction) may obtain a greater benefit from anticoagulation than women without these risk factors.
- There is no consensus regarding the optimal duration for the treatment of superficial thrombosis in pregnant women. A frequent approach is to use anticoagulants for 45 days.

SUMMARY OF THE EVIDENCE. No additional evidence on the intervention's efficacy or safety was identified. Regional data about epidemiology, resource use, and impact on health equity were added to the EtD framework (https://guidelines.ash.gradepro.org/staging/profiles/bmBhqE_rfkg).

JUSTIFICATION. This recommendation did not change its direction or strength. The panel considered that the recommendation was feasible to implement in the region, given the general availability of LMWH.

CONCLUSION. Superficial venous thrombosis is a relatively infrequent complication of pregnancy in Latin America, although it is associated with significant discomfort.[17] The main concern with superficial venous thrombosis relates to its eventual progression to DVT, which is associated with significant morbidity.

Because pregnant women are at an increased risk of VTE given the effects of hormones, their risk of progression is likely higher than that of nonpregnant women, especially if other risk factors are present or the thrombosis extends close to the saphenofemoral junction.

For pregnant women with acute VTE, should we use once-daily or twice-daily LMWH?

Recommendation 12

For pregnant women with acute VTE, the ASH Latin American panel *suggests* either once-daily or twice-daily LMWH according to clinical circumstances and patients' values and preferences (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Remark:

- Theoretically, once-a-day LMWH might lead to a greater peak concentration and a lower trough level. The impact of these pharmacokinetics on patients' important outcomes is uncertain. Women who place a higher value on avoiding injections may prefer LMWH once daily. In contrast, women who place a higher value on the potential complications inferred from LMWH pharmacokinetics may prefer LMWH twice a day.

SUMMARY OF THE EVIDENCE. No additional evidence on the intervention's efficacy or safety was identified. Regional data about epidemiology, resource use, and impact on health equity were added to the EtD framework (https://guidelines.ash.gradepro.org/staging/profiles/8VhLH09uX88).

JUSTIFICATION. This recommendation did not change its direction or its strength. The panel considered that the recommendation was feasible to implement in the region, given the general availability of LMWH.

CONCLUSION. There is considerable uncertainty regarding the optimal frequency for LMWH for pregnant women. The rationale behind the different options is based mostly on pharmacokinetic knowledge, and it is unknown whether the expected differences translate into potential clinical benefits or harms. The guideline panel considered that both options were reasonable alternatives. Values and preferences and practical considerations may be the main factors in reaching the final decision. Women who place a higher value on convenience and avoiding a second injection may prefer once-a-day LMWH. However, in obese patients, it may not be feasible to reach the appropriate dose with 1 injection. In such circumstances, a twice-a-day scheme may be preferred.

For pregnant women with PE and hemodynamic failure, should we use thrombolytic therapy in addition to anticoagulation?

Recommendation 13

For pregnant women with PE and hemodynamic failure, the ASH Latin American panel *recommends* thrombolytic therapy in addition to anticoagulation (strong recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- For women with PE and hemodynamic failure, the potential benefit of thrombolytics in preserving life outweighs the risk of bleeding (maternal and fetal). Although the certainty in the evidence of the benefits of thrombolytic is very low, thrombolytic therapy may be a life-saving intervention in a condition of high mortality. This justifies a strong recommendation according to the ASH GRADE rules.
- The implementation of this recommendation may be hampered by the lack of appropriate facilities and human resources to provide critical care in some settings within the region. Given the potential life-saving effect of thrombolytics, local efforts may be made to ensure opportune access to specialized care for women with PE and hemodynamic failure.

SUMMARY OF THE EVIDENCE. No additional evidence on the intervention's efficacy or safety was identified. Regional data about resource use and impact on health equity were added to the EtD framework (https://guidelines.ash.gradepro.org/staging/profiles/OWD56Z9syss).

JUSTIFICATION. This recommendation changed its strength. The original panel made a conditional recommendation in favor of thrombolytic therapy, whereas the Latin American panel made a strong recommendation with the same directions. The evidence that informs this recommendation comes primarily from the general adult population; therefore, there is considerable uncertainty regarding the effect of thrombolytic therapy for pregnant women. The Latin American panel, however, considered that in a situation of high mortality, thrombolytic therapy may be a life-saving intervention and placed a higher value on preserving maternal life than on potential bleeding complications.

CONCLUSION. Pregnant women with massive PE and shock are at high risk of dying, given the ventilation/perfusion mismatch and the hemodynamic stress with an already overloaded heart in a hypercirculatory state. Although there is not much evidence of the effects of thrombolytics in pregnant women, the benefit in preventing death observed in the general adult population is probably generalizable. However, pregnant women likely have a higher risk of bleeding than the general adult population,[18] which can also affect fetal health.[19,20] Even so, the panel considered the potential benefit of preserving life to outweigh the risk of bleeding complications, which are often treatable and do not lead to permanent sequelae.

For pregnant women with PE and right ventricular dysfunction, should we use thrombolytic therapy in addition to anticoagulation?

Recommendation 14

For pregnant women with PE and right ventricular dysfunction (detected through ultrasonography or by biomarkers), the ASH Latin American panel *suggests* against thrombolytic therapy in addition to anticoagulation (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Remark:

- Women with deterioration of their condition or at high risk of dying may benefit from thrombolysis, especially if the bleeding risk is not increased. The final decision may consider the clinical circumstances, evolution of the right ventricular dysfunction, and patients' values and preferences.

SUMMARY OF THE EVIDENCE. No additional evidence on the intervention's efficacy or safety was identified. Regional data about resource use and impact on health equity were added to the EtD framework (https://guidelines.ash.gradepro.org/staging/profiles/tY9AGzgnllo).

JUSTIFICATION. This recommendation did not change its direction or strength. The panel considered that the recommendation was feasible to implement in the region.

CONCLUSION. In the general adult population, patients with PE and ultrasonographic or laboratory evidence of right ventricular disfunction have a relatively low risk of death or serious complications. Therefore, for most patients, the bleeding risk associated with thrombolytic therapy likely outweighs its potential benefits. For pregnant women, who have a higher risk of bleeding,[18] the use of thrombolytics may be even riskier.

However, the use of thrombolytics may be appropriate if the cardiovascular condition of the pregnant woman deteriorates and early signs of hemodynamic failure are observed. In such situations, it is

important to consider that thrombolytics should be administered only at hospitals in which there is appropriate expertise in providing intensive care to both the woman and the child.

In pregnant women with DVT or PE and low risk of complications, is home treatment preferable to hospital treatment?

Recommendation 15

For pregnant women with DVT or PE and low risk of complications (maternal and fetal), the ASH Latin American guideline panel *suggests* home treatment over hospital treatment (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Remarks:

- Women who place a higher value on the comfort of being treated at home probably will prefer not being admitted to the hospital. However, some pregnant women may feel safer at the hospital and may reject home treatment.
- In addition, providing LMWH or unfractionated heparin for home treatment may be difficult in some settings within the region. In such circumstances, hospital treatment may be the better option to ensure adherence with anticoagulation.

SUMMARY OF THE EVIDENCE. No additional evidence on the intervention's efficacy or safety was identified. Regional data about resource use and impact on health equity were added to the EtD framework (https://guidelines.ash.gradepro.org/staging/profiles/md9sUUVm2aY).

JUSTIFICATION. This recommendation did not change its direction or strength. The panel considered that the recommendation was generally feasible to implement in the region.

CONCLUSION. Evidence from the general adult population suggests that home treatment is safe for patients with either DVT or PE. The evidence for pregnant women is very limited; however, the same trend was observed. Key aspects to consider when reaching the final decision are costs and feasibility. Although the overall costs are probably reduced with home treatment, in some health systems, home treatment is not covered, and patients need to pay for it out of pocket. In addition, because of poor socioenvironmental conditions, home treatment may not always be feasible. If there are important barriers to providing appropriate home care, admission to the hospital may be the safer alternative for both the woman and the child.

Management of anticoagulants around the time of delivery. *For pregnant women receiving therapeutic-dose LMWH, should we offer scheduled delivery with prior discontinuation of LMWH or cessation of LMWH with spontaneous onset of labor?*

Recommendation 16

For pregnant women receiving therapeutic-dose LMWH, the ASH Latin American panel *suggests* scheduled delivery with prior discontinuation of LMWH over cessation of LMWH with spontaneous onset of labor (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remark:

- Scheduled delivery might reduce the risk of bleeding and may facilitate the use of peridural anesthesia. However, there is an important variation in what pregnant women may prefer. Thus, it is important to explore values and preferences and explain the potential benefits and risks of scheduled delivery vs spontaneous labor.

SUMMARY OF THE EVIDENCE. No additional evidence on the intervention's efficacy or safety was identified. Regional data about resource use and impact on health equity were added to the EtD framework (https://guidelines.ash.gradepro.org/staging/profiles/h3LpEQZT5F8).

JUSTIFICATION. This recommendation did not change its direction or strength. The panel considered that the recommendation was generally feasible to implement in the region.

CONCLUSION. Most pregnant women in Latin America may prefer spontaneous labor over a scheduled delivery.[21] Thus, a careful assessment of women's values and preferences should be carried out before applying this recommendation. A scheduled delivery with prior discontinuation of LMWH may reduce the risk of bleeding and facilitate the use of peridural anesthesia in a vaginal delivery. It may allow the use of regional anesthesia if a cesarean delivery is necessary.

In addition, a scheduled delivery may be particularly important for women at risk of maternal or fetal complications or for women who may not have expedited access to hospitals that can provide intensive care.

For pregnant women receiving prophylactic-dose LMWH, should we offer scheduled delivery with prior discontinuation of LMWH or cessation of LMWH with spontaneous onset of labor?

Recommendation 17

For pregnant women receiving prophylactic-dose LMWH, the ASH Latin American panel *suggests* scheduled delivery with prior discontinuation of LMWH over cessation of LMWH with spontaneous onset of labor (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remark:

- Although most women receiving prophylactic-dose LMWH may go through spontaneous labor safely, many women in Latin America have poor access to skilled birth attendance. In this scenario, a scheduled delivery conducted at a hospital may be safer for women receiving LMWH.

SUMMARY OF THE EVIDENCE. No additional evidence on the intervention's efficacy or safety was identified. Regional data about resource use and impact on health equity were added to the EtD

framework (https://guidelines.ash.gradepro.org/staging/profiles/B8wOYJahAug).

JUSTIFICATION. This recommendation changed its direction. The original panel made a recommendation in favor of cessation of LMWH with spontaneous onset of labor, whereas the Latin American panel made a recommendation in favor of a scheduled delivery.

The risk associated with going through labor and receiving prophylactic doses of LMWH is likely very small, and in most instances, it is a safe option. However, many women in Latin America have limited access to skilled birth attendance.[22] In such situations, a scheduled delivery conducted at hospitals may offer a safer environment for the woman and the child.

CONCLUSION. The use of prophylactic-dose LMWH probably does not pose an important risk for women in Latin America who have access to proper follow-up and professional birth attendance. For them, stopping anticoagulants once spontaneous labor begins may be the better option. In addition, most women in Latin America may prefer spontaneous labor over a scheduled delivery.[21]

However, Latin America is a very heterogeneous region. Countries such as Chile and Uruguay have a relatively low maternal mortality rate, close to the average of Organisation for Economic Co-operation and Development (OECD) countries. In contrast, countries such as Haiti and Bolivia exceed that number by 10 times.[23] This distribution closely correlates with the proportion of women who can access prenatal care and professional birth attendance.[24] In this scenario, women receiving prophylactic-dose LMWH may have an increased risk of maternal and fetal complications, and thus, a closer follow-up and a scheduled delivery may be the safer option.

Anticoagulant use in breastfeeding women. *In breastfeeding women receiving anticoagulation, should 1 specific drug be used over the others?*

Recommendation 18

For breastfeeding women who require anticoagulant treatment, the ASH Latin American guideline panel *recommends* using vitamin K antagonists (VKAs) or LMWH over direct oral coagulants (DOACs) (strong recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- Both VKAs and LMWH seem to be safe options for breastfeeding women. Given that VKAs are an oral medication, they may be preferred by most patients if follow-up and dose monitoring are feasible. In contrast, DOACs may be associated with an increased risk of bleeding in the infants and therefore should not be used.
- In this recommendation, there is certainty regarding the equivalence of the benefits of the different options, but DOACs may be associated with serious harm. This situation justifies a strong recommendation despite the very low certainty in the evidence according to the ASH GRADE rules.

SUMMARY OF THE EVIDENCE. No additional evidence on the intervention's efficacy or safety was identified. Regional data about resource use and impact on health equity were added to the EtD framework (https://guidelines.ash.gradepro.org/staging/profiles/DKMaCHdujnI).

JUSTIFICATION. This recommendation did not change its direction or strength. The panel considered that the recommendation was generally feasible to implement in the region.

CONCLUSION. The effects of DOAC exposure through breast milk are largely unknown because breastfeeding women have been systematically excluded from randomized trials. In addition, there are almost no observational data. The only information available suggests a significant concentration of DOACs in the breast milk.

VKAs and LMWH have been safely used in breastfeeding women for many years. Given that the breastfeeding period is limited in time, the inconvenience derived from follow-up and monitoring or injections may be an acceptable burden.

Prevention of VTE. *For women with previous VTE, should we use antepartum anticoagulant prophylaxis?*

Recommendation 19

For pregnant women with prior VTE, the ASH Latin American panel *suggests* antepartum anticoagulant prophylaxis over no prophylaxis (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Remarks:

- Pregnant women with a prior thrombotic event with a high risk of recurrence (unprovoked events or related to a chronic risk factor) or with a VTE related to pregnancy or estrogen use would probably obtain a larger benefit from antepartum prophylaxis.
- In contrast, for women with a previous VTE related with a transient risk factor different from estrogen exposure, the benefit of prophylaxis may be small. However, some of these women may prefer to receive prophylaxis, especially if they place a higher value on avoiding a new thrombosis. In this population, clinicians may consider exploring other risk factors for VTE and values and preferences regarding the risk of a new thrombosis, bleeding, and the burden of daily injections.

SUMMARY OF THE EVIDENCE. No additional evidence on the intervention's efficacy or safety was identified. Regional data about resource use and impact on health equity were added to the EtD framework (https://guidelines.ash.gradepro.org/staging/profiles/oW6dI-Grtpg).

JUSTIFICATION. The original panel made a strong recommendation in favor of prophylaxis for women at high risk and a conditional recommendation against prophylaxis for women at low risk. The Latin American panel unanimously agreed that all or almost all women with a previous VTE event and high risk of recurrence or related to estrogen exposure will be better off with anticoagulation. However, the ASH GRADE rules specified in our methods[9] prevented a strong recommendation in the context of low certainty in

the evidence regarding the benefits of prophylaxis (ie, uncertain benefit). In addition, the Latin American panel noted that most of the women at low risk of recurrence place a higher value on preventing a new VTE event than the daily injections of LMWH and thus prefer to receive prophylaxis.

CONCLUSION. The key aspects to consider when deciding whether to offer prophylaxis to pregnant women with previous VTE are the baseline risk of VTE recurrence and the women's values and preferences.

Women with a high risk of VTE recurrence, for example, with a previous unprovoked event, a VTE related to a chronic risk factor that is still present, or a VTE related to estrogen exposure, will probably obtain a larger benefit from prophylaxis.

In contrast, women with a low risk of recurrence, for example, with a VTE related to a transient risk factor different from estrogen exposure (eg, VTE related to surgery or a fracture), may not need prophylaxis because the benefit is small and likely balanced with the potential harms (bleeding).

However, studies assessing women's values and preferences show that even women at low risk of recurrence place a higher value on preventing a new VTE event than the daily injections of LMWH and thus prefer to receive prophylaxis.[25,26]

Therefore, to best implement this recommendation, clinicians may explore the baseline risk for VTE recurrence and, concomitantly, women's preferences.

For women with previous VTE, should we use postpartum anticoagulant prophylaxis?

Recommendation 20

For pregnant women with a prior VTE, the ASH Latin American panel *suggests* postpartum anticoagulant prophylaxis over no prophylaxis (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Remarks:

- Compared with the antepartum period, the baseline risk of thrombosis is higher in the postpartum period. Therefore, even women who choose not to use antepartum prophylaxis probably will benefit from receiving postpartum prophylaxis.
- A frequent scheme used is prophylaxis for 6 weeks. However, the duration of postpartum prophylaxis was not formally assessed in the guideline.

SUMMARY OF THE EVIDENCE. No additional evidence on the intervention's efficacy or safety was identified. Regional data about resource use and impact on health equity were added to the EtD framework (https://guidelines.ash.gradepro.org/staging/profiles/9Hwx9ARVQT8).

JUSTIFICATION. This recommendation changed its strength. The original panel made a strong recommendation in favor of prophylaxis, whereas the Latin American panel made a conditional recommendation with the same directions. The reason for the discrepancy is the uncertain benefit of the intervention (low certainty in the evidence). The ASH GRADE rules specified in our methods prevent a strong recommendation in such situations.[9] In addition, some women in the region may have significant barriers to accessing adequate follow-up and treatment.

CONCLUSION. Compared with the risk during the antepartum period, the risk of VTE during the postpartum period is considerably higher.[27] In addition, the risk of bleeding is less of a concern for both the mother and the child. Thus, for most women with prior VTE events, using postpartum prophylaxis may be the better course of action. Some women, however, may have difficult access to anticoagulants and proper follow-up, which may hamper the implementation of the recommendation.

For women with hereditary thrombophilia and no personal history of VTE, should we use antepartum anticoagulant prophylaxis?

Recommendation 21

For pregnant women with hereditary thrombophilia and no personal history of VTE, the ASH Latin American panel *suggests* against the use of antepartum anticoagulant prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- Women with a family history of thrombosis who are homozygotes for factor V Leiden or prothrombin G20210A mutation or have a combined thrombophilia (eg, double heterozygotes) may be at a higher risk of VTE during pregnancy. In this population, the benefits of using prophylaxis may outweigh the risk of bleeding.
- In contrast, women without family history or who are heterozygotes for factor V Leiden or prothrombin G20210A mutation may have a relatively low risk of thrombosis. Here, the risk of bleeding with prophylaxis likely outweighs the potential benefits.
- Between these 2 groups, there may be women at intermediate risk of thrombosis. In this case, clinicians and patients may want to consider additional risk factors for thrombosis before decision making.

SUMMARY OF THE EVIDENCE. No additional evidence on the intervention's efficacy or safety was identified. Regional data about resource use and impact on health equity were added to the EtD framework (https://guidelines.ash.gradepro.org/staging/profiles/FmkLB4o8_sU).

JUSTIFICATION. This recommendation did not change its direction or strength; however, important modifications were made to the text of the recommendation. The original panel made 3 separate recommendations for different groups: a recommendation against antepartum prophylaxis for women with low-risk thrombophilia, a second recommendation against prophylaxis for women with high-risk thrombophilia, and a recommendation in favor of prophylaxis for women with thrombophilia and previous VTE events.

The Latin American panel independently made the same recommendations for women with low- and high-risk thrombophilia, but they were merged into a single recommendation statement. In

addition, the Latin American panel did not make a specific recommendation for women with thrombophilia and previous VTE events because the management of this clinical situation was already addressed in recommendation 9.

CONCLUSION. It has been estimated that ~50% of VTE cases during pregnancy are associated with hereditary thrombophilia.[28] Although estimates for the contribution of each thrombophilia to the risk of VTE may not be accurate, given the limitation of the available data, there are some conditions that confer a higher risk than others. A systematic review of 9 observational studies (n = 2526)[29] found that homozygotes for factor V Leiden or prothrombin G20210A may increase 20 to 30 times the risk of VTE in comparison with women without thrombophilia. In contrast, the risk associated with heterozygotes for factor V Leiden or prothrombin G20210A, antithrombin deficiency, or protein C or S deficiency is substantially lower (around 3-6 times the risk of women without thrombophilia).

Despite the large increment in the risk of VTE associated with hereditary thrombophilia, VTE during pregnancy remains a rare event. Thus, even in conditions associated with a high risk of VTE, the absolute number of events in the antepartum period is relatively small. Therefore, for most women with hereditary thrombophilia, the use of prophylaxis may result in a very small benefit at the cost of an increase in the risk of bleeding and the inconvenience of daily injections. However, women with high-risk thrombophilia who place a higher value on avoiding a VTE event than on the risk of bleeding or the inconvenience may still choose to receive prophylaxis.

For women with hereditary thrombophilia and no personal history of VTE, should we use postpartum anticoagulant prophylaxis?

Recommendation 22

For pregnant women with hereditary thrombophilia and no personal history of VTE, the ASH Latin American panel *suggests* postpartum anticoagulant prophylaxis over no prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- Likely, the baseline risk of thrombosis increases in the postpartum period compared with the antepartum period. Hence, most women with a family history of thrombosis and thrombophilia may benefit from prophylaxis. However, for women who are heterozygotes for factor V Leiden or prothrombin G20210A mutation without a family history of VTE, the risk of thrombosis may be low enough to be safely managed without prophylaxis. In this case, clinicians and patients may want to consider additional risk factors for thrombosis to make the decision.
- A frequent scheme used is prophylaxis for 6 weeks.

SUMMARY OF THE EVIDENCE. No additional evidence on the intervention's efficacy or safety was identified. Regional data about resource use and impact on health equity were added to the EtD framework (https://guidelines.ash.gradepro.org/staging/profiles/_ch1N47OM74).

JUSTIFICATION. This recommendation partially changed its direction and strength. The original panel made 5 different recommendations: 2 conditional recommendations in favor of postpartum prophylaxis for women with a family history of VTE and protein C or S deficiency and for women with combined thrombophilias or who are homozygous for the factor V Leiden or prothrombin G20210A mutation; 1 strong recommendation in favor of postpartum prophylaxis for women with a family history of VTE who have antithrombin deficiency; and 2 recommendations against postpartum prophylaxis for women without a family history of VTE who are heterozygous for the factor V Leiden or prothrombin G20210A mutation or who have antithrombin, protein C, or protein S deficiency and for women with a family history of VTE who are heterozygous for the factor V Leiden or prothrombin G20210A mutation.

The Latin American panel took a different approach and considered that, given the higher risk of thrombosis during the postpartum period, most women may be better off with prophylaxis. They issued a single recommendation statement suggesting this course of action and made the contextualization to different clinical scenarios on the remarks.

CONCLUSION. Thrombophilia is a heterogeneous group of conditions with different thrombotic risks. However, postpartum increases substantially the risk of VTE, especially during the first week.[27] In addition, the use of anticoagulants is safer and more practical after delivery. Thus, most women with hereditary thrombophilia may be better off receiving prophylaxis, especially if they place a higher value on avoiding a VTE event, as most women do.[25,26]

Women with a particularly low risk of VTE, however, such as heterozygotes for factor V Leiden or prothrombin G20210A mutation without family history, may be managed safely without prophylaxis if there are no other risk factors for VTE.

Management of VTE in children

For children with asymptomatic VTE, should we use anticoagulation?

Recommendation 23

For children with asymptomatic VTE, the ASH Latin American guideline panel *suggests* against anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remark:

- Although for most children with asymptomatic VTE, the risk of anticoagulation likely outweighs the benefits, some patients at high risk of thrombosis recurrence or those who may require multiple central venous access devices (CVADs) during their lives might benefit from anticoagulation. The final decision should consider individual risk factors as well as parents and patients' values and preferences.

Summary of the evidence. No additional evidence on the intervention's efficacy or safety was identified. Regional data about resource use and impact on health equity were added to the EtD

framework (https://guidelines.ash.gradepro.org/staging/profiles/rH7IBtYKjts).

Justification. This recommendation changed its direction. The original guideline panel made a conditional recommendation for either anticoagulation or no anticoagulation. The Latin American panel considered that in most children with asymptomatic VTE, the risk of bleeding exceeds the potential benefits.

Conclusion. Asymptomatic VTE in children is usually detected in the context of a CVAD.[30,31] Given the provoked nature of the event, the risk of recurrence is generally small, and the use of anticoagulants may result in net harm. However, anticoagulation for a limited period may benefit children with other risk factors for VTE (ie, thrombophilia) or those who require multiple CVADs.

For children with PE and hemodynamic failure, should we use thrombolytic therapy?

Recommendation 24

For children with PE and hemodynamic failure, the ASH Latin American panel *recommends* thrombolytic therapy in addition to anticoagulation (strong recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Remark:

- There is considerable uncertainty regarding the effect of thrombolytics in children given the lack of appropriately designed and powered studies. However, the available evidence suggests a significant effect of thrombolytics in preserving life in a condition of high mortality. This scenario justifies a strong recommendation in favor of the intervention following the ASH GRADE rules.

Summary of the evidence. We found 2 observational studies published after the original guideline.[13,14] Both were too small to provide reliable estimates of the relative estimates. However, they did report a different estimate for the baseline risk of mortality: 22% vs 4.5% used in the original guideline. The results of these studies as well as regional data about resource use and impact on health equity were added to the EtD framework (https://guidelines.ash.gradepro.org/staging/profiles/Es4MarsRuKU).

Justification. This recommendation changed its strength. The original guideline panel made a conditional recommendation in favor of thrombolytic therapy. The Latin American panel considered the baseline risk of mortality identified in the update (22% vs 4.5% used on the original guideline) and issued a strong recommendation.

Conclusion. PE with hemodynamic failure is a serious condition associated with a high mortality rate. In 1 cohort (n = 5654), the overall mortality of children with PE was 8.6%, with a bimodal distribution with a first peak in children younger than 1 year and a second peak at adolescents aged 16 to 17 years. The first peak in young children was largely explained by congenital conditions such as underlying cardiopathy.[19] Another cohort (n = 170) showed a similar overall mortality of 6% but also reported a mortality risk of 22% in children with PE and hemodynamic failure.[18]

Although there are no direct data from randomized trials conducted with children, indirect evidence from the adult population does suggest a potential benefit in preserving life. Given the high mortality observed in children with PE and hemodynamic failure, thrombolytic therapy should be routinely offered.

The implementation of this recommendation may be hampered by the lack of appropriate facilities and human resources to provide critical care in some settings within the regions. Local efforts may be made to ensure opportune access to specialized care for children with PE and hemodynamic failure.

For children with CVAD-related thrombosis, should we remove a functioning CVAD?

Recommendation 25

For children with symptomatic thrombosis related to a functioning CVAD who continue to require vascular access, the ASH Latin American guideline panel *suggests* maintaining the CVAD over removing it and inserting a new catheter (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Remarks:

- The potential benefits of removing a functioning CVAD might include preventing thrombosis progression and providing symptomatic relief. However, removing the CVAD and replacing it generally imply the use of anesthesia and may expose children to potential harms associated with the insertion procedure.
- Although, for most patients, maintaining the CVAD seems to be the better option, if the risk of thrombosis progression is considered too high or the symptoms experienced by the children are important, catheter removal may be a reasonable option.

Summary of the evidence. No additional evidence on the intervention's efficacy or safety was identified. Regional data about resource use and impact on health equity were added to the EtD framework (https://guidelines.ash.gradepro.org/staging/profiles/psXoCCFk9Dg).

Justification. This recommendation did not change its direction or strength. The panel considered that the recommendation was generally feasible to implement in the region.

Conclusion. The use of anticoagulation to treat symptomatic VTE related to a CVAD likely minimizes the risk of thrombus progression and provides symptomatic relief.[32,33] Therefore, maintaining a functioning CVAD seems to be the best course of action for most children, especially considering the potential harms and burden associated with the installation procedure of a new catheter. In addition, the clinical situation with an in situ CVAD can be monitored clinically, and replacement remains an alternative if anticoagulation alone proves to be insufficient.

For children with VTE, should we use LMWH or VKAs as maintenance therapy?

Recommendation 26

For children with VTE, the ASH Latin American guideline panel *suggests* either anticoagulation with VKAs or LMWH according to the age of the children, the clinical circumstances, access to follow-up, and the patients' values and preferences (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- Children aged <6 months with underlying cancer, limited oral tolerance, or important barriers to follow-up and monitoring may benefit from the use of LMWH. In contrast, children who can receive oral medication and adhere to strict follow-up may benefit from VKAs, especially if the children and family place a higher value on avoiding injections.
- The cost of LMWH may be an important barrier in settings with insufficient coverage from health insurance. In this scenario, VKAs may be an option for some patients but not for all. Therefore, local efforts should be made to provide access to both options for children with VTE.

Summary of the evidence. No additional evidence on the intervention's efficacy or safety was identified. Regional data about resource use and impact on health equity were added to the EtD framework (https://guidelines.ash.gradepro.org/staging/profiles/PXerXdrW8x4).

Justification. This recommendation did not change its direction or strength. The panel considered that the recommendation was generally feasible to implement in the region, although some gaps may exist in the availability of LMWH in some settings.

Conclusion. Likely, both LMWH and VKAs are equally effective for children with VTE.[32] Therefore, the key factors that finally influence the selection are the underlying clinical circumstances and the feasibility of the options. VKAs are widely available in the region, and they may be the better option for older children who can adhere to the daily schedule and have access to follow-up and monitoring.

Alternatively, children can also be treated with DOACs, although there is still limited evidence about their effects, and important accessibility and affordability barriers exist in the region.

For children with cerebral sinus venous thrombosis, should we use anticoagulation?

Recommendations 27 and 28

Recommendation 27: For children with cerebral sinus venous thrombosis without hemorrhagic transformation, the ASH Latin American panel *recommends* anticoagulation over no anticoagulation (strong recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 28: For children with cerebral sinus venous thrombosis with hemorrhagic transformation, the ASH Latin American panel *suggests* anticoagulation over no anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remark:

- For children with cerebral venous thrombosis, the potential benefit of anticoagulation in preserving life and avoiding permanent neurologic damage likely outweighs the risk of bleeding.

Summary of the evidence. No additional evidence on the intervention's efficacy or safety was identified. Regional data about resource use and impact on health equity were added to the EtD framework (https://guidelines.ash.gradepro.org/staging/profiles/clnLhRn8u_4 and https://guidelines.ash.gradepro.org/staging/profiles/hLlkXfsqoro).

Justification. These recommendations did not change its direction or strength. The panel considered that the recommendations were generally feasible to implement in the region.

Conclusion. Cerebral sinus venous thrombosis is a rare condition associated with significant mortality and the risk of permanent motor and cognitive sequelae.[34,35] Data regarding the effects of treatment with an anticoagulant are very limited. There are only 2 randomized trials available,[36,37] both conducted in adults. In these trials, participants were randomly assigned to anticoagulation vs no anticoagulation. Investigators observed a better prognosis in the treated group, although the differences were not statistically significant. Data regarding the effects on pediatric patients are even sparser. Nevertheless, there are multiple reports of observational series that showed that anticoagulation for children with cerebral sinus venous thrombosis, even for patients with hemorrhagic transformation, can be carried out safely.[38,39]

Given the high risk of death or serious neurologic sequelae in children without hemorrhagic transformation, anticoagulation should be offered routinely (despite the overall very low certainty in the evidence). Children with hemorrhagic transformation might have the worst outcome, especially if the hemorrhage is large. In this situation, the potential benefits of avoiding thrombosis progression should be balanced with the risk of further intracranial bleeding.

Strengths and limitations of these guidelines

As with the original guidelines, our recommendations are limited by the low and very low certainty in the underlying evidence. The pediatric population and pregnant women are typically underrepresented in research,[40] and thus there is considerable uncertainty in the management of many clinical issues. Evidence-based guidelines may prove even more important when only low-certainty or very low-certainty evidence is available because they may help clinicians make better decisions,[41] may pinpoint knowledge gaps, and may help raise awareness of neglected populations.

Our guidelines are also limited by the inclusion of panelists with conflicts of interest. Of note, a significant proportion of panelists had received travel support to attend educational meetings, which, given the scarcity of public funding, is a very widespread practice in Latin America. We balanced the inclusion of conflicted panelists by appointing unconflicted methodologists as panel leaders.

Finally, Latin America includes a variety of settings. Although we made efforts to represent them as much as possible (eg, by inviting experts from 10 countries), it is still possible that our recommendations may not be applicable to some scenarios.

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Authorship

Contribution: I.N. and H.J.S. developed the methods for this adaptation; I.N. and A.I. wrote the first draft of the manuscript and revised the manuscript based on authors' suggestions; guideline panel members (I.N., A.I., R.A., G.L.B., P.C., C.C.C., M.C.G.E., P.P.G.L., J.P., L.A.M.-G., S.M.R., J.C.S., and M.L.T.V.) critically reviewed the manuscript and provided suggestions for improvement; members of the knowledge synthesis team (I.N., A.I., F.V., L.K., and H.J.S.) contributed with evidence summaries to the guidelines; all authors approved the content; and I.N. and A.I. led panel meetings.

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ORCID profiles: A.I., 0000-0001-9053-4396; P.C., 0000-0002-0121-150X; J.P., 0000-0003-0481-328X; P.Z., 0000-0003-0467-7513; F.V., 0000-0001-9460-4101; H.J.S., 0000-0003-3211-8479.

Correspondence: Ignacio Neumann, Universidad San Sebastián, Lota 2465, 7510602 Providencia, Región Metropolitana, Santiago, Chile; email: ignacio.neumann@gmail.com.

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