REVIEW ARTICLE

JORNAL **VASCULAR** BRASILEIRO
ISSN 1677-7301 (Online)

Bleeding risk assessment for venous thromboembolism prophylaxis

Avaliação do risco de sangramento na profilaxia do tromboembolismo venoso

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Abstract

Venous thromboembolism (VTE) is one of the main preventable causes of morbidity and mortality in hospitalized patients and fatal pulmonary embolism (PE) may be its first manifestation. Several national and international guidelines recommend using risk assessment models for prescription of VTE prophylaxis in hospitalized patients. Despite evidence and guidelines supporting VTE prevention, use of VTE prophylaxis in hospitalized patients remains suboptimal, which may be because of low awareness of the benefits of VTE prophylaxis, but might also reflect fear of bleeding complications in these patients, since this constitutes one of the main reasons for underutilization of thromboprophylaxis worldwide. Bleeding risk assessment is therefore necessary for adequate prophylaxis prescription and should be carried out concurrently with assessment of the risk of thrombosis. The purpose of this review is to highlight the importance of jointly assessing risk of VTE and risk of bleeding in hospitalized patients.

Keywords: venous thrombosis; pulmonary embolism; prophylaxis; hemorrhage; patient safety; risk assessment.

Resumo

O tromboembolismo venoso (TEV) é uma das principais causas preveníveis de morbimortalidade em pacientes hospitalizados, sendo a embolia pulmonar (EP) fatal possivelmente a sua primeira manifestação. Diretrizes nacionais e internacionais recomendam o uso de modelos de avaliação de risco para a prescrição de profilaxia do TEV em pacientes hospitalizados. Apesar das evidências e diretrizes de apoio, o uso da tromboprofilaxia permanece abaixo do ideal, o que pode resultar da baixa conscientização dos benefícios da profilaxia, mas também pode refletir o medo de complicações hemorrágicas, justificando a subutilização da tromboprofilaxia em todo o mundo. A avaliação do risco de sangramento é, portanto, necessária para a adequação de profilaxia e deve ser realizada de forma concomitante à avaliação do risco de trombose. O objetivo desta revisão é salientar a importância da avaliação conjunta do risco de TEV e do risco de sangramento em pacientes hospitalizados.

Palavras-chave: trombose venosa; embolia pulmonar; profilaxia; hemorragia; segurança do paciente; avaliação de risco.

How to cite: Chindamo MC, Marques MA. Bleeding risk assessment for venous thromboembolism prophylaxis. J Vasc Bras. 2021;20:e20200109. https://doi.org/10.1590/1677-5449.200109

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Financial support: None.
Conflicts of interest: Authors are speakers at Sanofi.
Submitted: June 17, 2020. Accepted: October 13, 2020.

The study was carried out at Hospital Barra D'Or - Rede D'Or São Luiz, Rio de Janeiro, RJ, Brasil.

INTRODUCTION

Venous thromboembolism (VTE) is a major preventable cause of morbidity and mortality in hospitalized patients.[1,2] The first manifestation of VTE is often fatal pulmonary embolism (PE), which can be responsible for up to 10% of all in-hospital mortality.[2,3] Hospitalized patients can be at risk of VTE because of acquired or hereditary factors, such as obesity, cancer, previous VTE, thrombophilias, trauma, surgery, acute myocardial infarction, stroke, advanced age, congestive heart failure, acute infection, immobility, and admission to intensive care, among other factors.[4-6]

National and international guidelines recommend use of risk assessment models (RAM) for selection of pharmacological or mechanical prophylaxis in clinical,[7-14] surgical,[8,15,16] or obstetric patients,[10] targeting better prevention strategies. However, VTE risk cannot be assessed in isolation. The risk of bleeding must also be assessed concurrently when the appropriate thromboprophylaxis strategy is being evaluated, since it can be induced or exacerbated by anticoagulants.[6,7,9]

Even though many studies have reported low rates of bleeding related to pharmacological prophylaxis,[11,17,18] fear of hemorrhagic events is one of the main reasons for its underutilization worldwide.[6] Identification of conditions involving a potential risk of bleeding and implementation of RAM are therefore essential to ensure correct use of thromboprophylaxis.[19]

The objective of this review is to highlight the importance of concurrent assessment of VTE risk and bleeding risk in hospitalized patients.

ASSESSMENT OF THROMBOSIS RISK *VS.* BLEEDING RISK

There are many different VTE RAMs available, both for clinical and surgical patients, providing guidance on the principal thromboprophylaxis recommendations, based on risk stratification.[7-16] The best assessment model has not yet been defined.[19] When conducting VTE risk stratification, a model should be used that has been validated for the population in question and should be applied systematically at the key stages of care: hospital admission, transfer between sectors, and hospital discharge. This last assessment is particularly important in patients who still have risk factors for VTE at discharge, such as, for example, prolonged immobility.[2] Choice of the best thromboprophylaxis strategy should simultaneously consider risk of VTE and the potential risk of bleeding.[20,21]

The following are considered absolute contraindications to anticoagulants: severe or potentially fatal active bleeding, or active bleeding that is irreversible with medical or surgical intervention, including any active bleeding at critical sites (intracranial, pericardiac, retroperitoneal, intraocular, intraarticular, and intraspinal), malignant uncontrolled arterial hypertension, uncompensated severe coagulopathy, platelet dysfunction or severe primary hemostasis disorders, persistent thrombocytopenia (< 20,000/mm^3), and high-risk invasive procedures in critical areas, such as lumbar puncture and spinal anesthesia in patients whose surgical procedures are scheduled for the next 6 to 12 hours.[20] Other factors associated with increased risk of bleeding include heparin-induced thrombocytopenia (HIT), concomitant use of platelet antiaggregants and/or nonsteroidal anti-inflammatories, and renal dysfunction, particularly when anticoagulants subject to renal clearance are used (low molecular weight heparin [LMWH] and fondaparinux).[15] For patients with creatinine clearance < 30 mL/min, it is recommended that the LMWH dose be reduced, anticoagulant activity be monitored, or unfractionated heparin (UFH) be used as a substitute.[4] Regular reviews of both risks, especially when there are changes in clinical status, facilitate choice of the best prophylaxis strategy[21] (Figure 1).

VTE risk assessment models

The main RAMs for VTE in clinical patients include the Brazilian VTE Prevention Guidelines for hospitalized clinical patients[9] and the Padua,[11] Geneva,[13] and IMPROVE (International Medical Prevention Registry on Venous Thromboembolism)[12] scores. The Caprini[15] and Rogers[16] scores are recommended for assessment of surgical patients, defining VTE risk on the basis of patient characteristics and the profile of each type of surgery. Women admitted to hospital during pregnancy, puerperium, or during the 6 weeks after a miscarriage or termination of pregnancy should be assessed for pharmacological prophylaxis.[21] The RAM most widely used for this patient profile was developed by the Royal College of Obstetricians and Gynecologists (RCOG).[10,21]

Although it is recommended that risk of VTE *vs.* risk of bleeding should be assessed concurrently as part of care for hospitalized patients, there are few RAMs for bleeding in the context of VTE prophylaxis.[19] Few RAMs combine these two characteristics[9,12,21] (Table 1).

This situation is very different to what is found in relation to bleeding risk assessment in the context of full anticoagulation for prevention of the thromboembolic phenomena of atrial fibrillation or for treatment of VTE. Ten bleeding RAMs

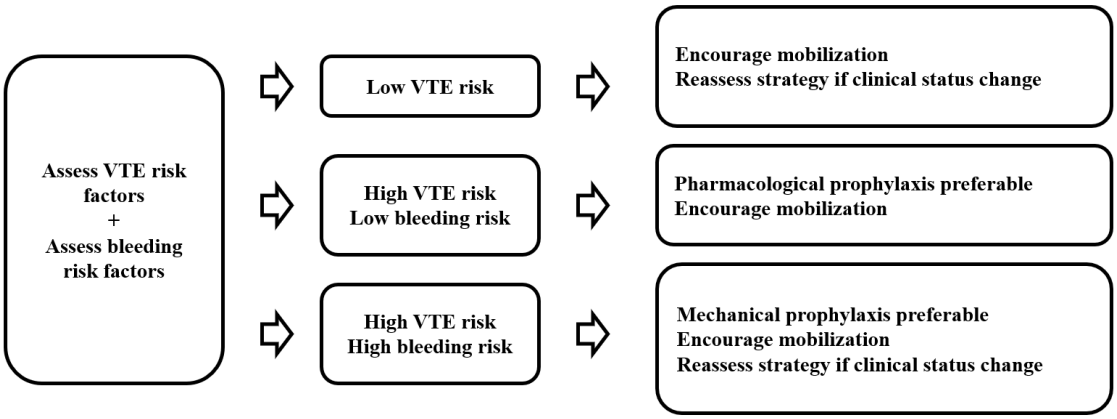

Figure 1. Recommendations for venous thromboembolism (VTE) prophylaxis by VTE risk *vs.* bleeding risk stratification. Adapted from: National Institute for Health and Care Excellence – NICE. NG89.[21]

Table 1. List of venous thromboembolism (VTE) and bleeding risk assessment models (RAM) according to study population.[9-16,21]

RAM	Types of patient	Risk of bleeding	Prophylaxis Recommendation
Caprini, 2005	Surgical	-	X
Geneva, 2006	Medical	-	X
Rogers, 2007	Surgical	-	X
Brazilian guidelines, 2007	Medical	X	X
Padua, 2010	Medical	-	X
IMPROVE, 2011	Medical	X	X
UK RCOG, 2015	Obstetric	-	X
NICE NG89, 2018	Medical/surgical	X	X

with this objective are available. Six of them are applicable to patients using oral anticoagulants for atrial fibrillation (ABC,[22] ORBIT,[23] ATRIA,[24] HAS-BLED,[25] HEMORR$_2$HAGES,[26] and Shireman[27]), three for anticoagulant VTE treatment (VTE-BLED,[28] Ruiz-Gimenez,[29] and Kuijer[30]), and one represents a mixed model (OBRI[31]). These scores identify situations of increased bleeding risk associated with full anticoagulation and support implementation of strategies that help to minimize the risk of hemorrhage by intervening in modifiable risk factors.[32]

RISK OF BLEEDING WITH PHARMACOLOGICAL PROPHYLAXIS

Assessment of bleeding risk in medical patients

IMPROVE *Bleeding Risk Score*

The principal RAM for bleeding associated with pharmacological prophylaxis in hospitalized medical patients is the IMPROVE Bleeding Risk Score.[6,7] Decousus et al.[6] used multivariate analysis to identify and score factors at hospital admission that were associated with risk of bleeding in acutely ill medical patients. Based on the IMPROVE data,[12] these authors conducted an observational multicenter study developed to assess VTE prophylaxis standards in more than 15,000 medical patients, determined the incidence of bleeding, and identified factors at admission that were associated with risk of bleeding.[6] Major bleeding was defined as fatal bleeding and/or symptomatic bleeding in a critical area or organ, and/or bleeding causing a $\geq$ 2 g/dL fall in hemoglobin or leading to transfusion of two or more units of packed red blood cells.[6] Bleeding was defined as not major but still clinically relevant if there was gastrointestinal hemorrhage, macroscopic hematuria with duration > 24 h, substantial epistaxis requiring intervention, epistaxis that was recurrent and/or with duration of at least 5 minutes, extensive hematoma (> 5 cm in diameter), intraarticular bleeding, menorrhagia or metrorrhagia, or other types of important bleeding requiring medical intervention.[6,33]

The cumulative incidence of hospital bleeding, defined as major and non-major bleeding up to 14 days after the admission, was 3.2% (1.2% major bleeding and 2.0% non-major, but clinically relevant bleeding).[6]

Risk factors at admission that were independently associated with risk of bleeding were:[6] active gastroduodenal ulcer, bleeding during the 3 months preceding admission, and platelet count < 50,000/mm.[3] Other risk factors for bleeding included advanced age, liver and/or kidney failure, admission to an intensive care unit, presence of a central venous catheter, rheumatic disease, cancer, and male sex, which were also factors related to increased risk of VTE.[6] Each of the factors above were included in the RAM with appropriate weighting (Table 2). The authors also developed an online resource that can be used to assess risk of bleeding.[34]

More than half of the episodes of major bleeding occurred in the 10% of hospitalized patients who had a bleeding risk score ≥ 7.[6] The authors therefore defined an IMPROVE Bleeding Risk Score of ≥ 7 as high risk of bleeding and scores < 7 as low risk. Rates of major bleeding, compared with rates of any bleeding (defined as major or not major but clinically relevant) in patients with scores < 7 were 0.4% and 1.5% respectively. Among those with scores ≥ 7, the rate of major bleeding was 4.1% and the any bleeding rate was 7.9%.[6]

Mechanical prophylaxis was used more in patients with a bleeding score ≥ 7, than in patients with scores < 7 (16.3% *vs.* 8.9%, respectively). In contrast, pharmacological prophylaxis was used in similar proportions of patients with risk scores of < 7 and ≥ 7 (48.9% *vs.* 49.3%, respectively).[6]

Table 2. IMPROVE Bleeding Risk Score.

Risk factors	Score
Active gastroduodenal ulcer	4.5
Hemorrhage 3 months before admission	4
Platelets < 50,000 mm^3	4
Age ≥ 85 years *vs.* < 40 years	3.5
Liver failure (INR* > 1.5)	2.5
Severe renal failure (GFR** < 30 *vs.* ≥ 60 mL/min)	2.5
Admission to intensive care unit	2.5
Central venous catheter	2
Rheumatological disease	2
Active cancer	2
Age 40-84 *vs.* < 40 years	1.5
Male	1
Moderate renal failure (GFR** 30-59 *vs.* ≥60 mL/min)	1

*INR: International normalized ratio; **GFR: glomerular filtration rate. Adapted from: Decousus et al.[6]

This RAM therefore helps to make decisions on pharmacological or mechanical prophylaxis in medical patients at high risk of VTE.[6] It can be used in combination with the IMPROVE score for VTE risk, enabling risk and benefit to be weighed up when choosing the best thromboprophylaxis strategy. This score has also been validated in other populations of medical patients.[35,36]

Assessment of bleeding risk in surgical patients

Bleeding rates associated with pharmacological prophylaxis in surgical patients vary according to the profile of the surgery involved. A meta-analysis of 52 randomized studies of pharmacological VTE prophylaxis in general surgery patients reported that minor bleeding events are common, including hematoma at the administration site (~7%), wound hematoma (~6%), bleeding at drain sites (~2%), and hematuria (~2%).[37] In contrast, major hemorrhagic complications were uncommon, including gastrointestinal (0.2%) or retroperitoneal bleeding (< 0.1%).[37] Prophylaxis was withdrawn in 2% of patients and subsequent reoperation because of bleeding was needed in less than 1%. Notwithstanding, patients with one or more individual bleeding risk factors were considered high risk during the postoperative period.[37]

Estimation of initial bleeding risk in surgical patients

The initial risk of bleeding has been poorly studied in non-orthopedic surgical patients. Major bleeding risk stratification was estimated according to the American College of Chest Physicians (ACCP) criteria in the following groups of surgical patients:[8] general/abdominal/pelvic (~1%), bariatric (< 1%), plastic/reconstructive (0.5 to 1.8%), vascular (0.4 to 1.8%), cardiac (~5% [high risk]), thoracic (1%), neurosurgery/craniotomy (1 to 1.5%), spinal column (<0.5%), and severe trauma (3.4 to 4.7% [high risk]).

In orthopedic surgeries, estimates of initial bleeding risk in the absence of prophylaxis vary widely because of the heterogeneous characteristics of the populations involved and the surgical techniques employed.[38] Risk of major bleeding is estimated in the range of 2 to 4% for orthopedic surgery with duration exceeding 45 minutes and in bilateral knee joint replacement. Non-major procedures, such as arthroscopies and shoulder, hand, and foot surgeries are considered lower bleeding risks (< 2%).[39] Rates of major bleeding among patients given VTE prophylaxis varied from 0.1% to 3.1% in studies of hip joint replacement and from 0.2% to 1.4% in studies of knee joint replacement,

suggesting that anticoagulants have little impact on risk of bleeding in these groups of patients.[40]

Risk of bleeding in special situations

Thrombocytopenia

Current VTE prophylaxis guidelines are based on randomized clinical trials that exclude people who have a high risk of potential bleeding, thereby limiting specific recommendations on pharmacological prophylaxis for patients with thrombocytopenia and/or platelet dysfunction.[41] These conditions are present in at least 25% of hospitalized individuals, represented by several pathologies, such as idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, antiphospholipid antibody syndrome (APS), HIT, disseminated intravascular coagulation, drug-induced thrombocytopenia, liver, kidney, and bone marrow failure, and cancer.[41] The minimum platelet levels recommended for pharmacological prophylaxis are also not uniform, ranging from 50,000 to 100,000/mm^3.[6,9,11,15,21] The IMPROVE Bleeding Risk Score[6] defines 50,000/mm^3 as the reference limit for platelets, whereas the NICE guidelines[21] set the cutoff point at 75,000/mm^3. The risk of spontaneous bleeding increases dramatically when platelet counts ranges from < 10,000 to 20,000/mm^3, varying according to the cause of thrombocytopenia.[41]

Chronic liver disease

Thrombocytopenia or platelet dysfunction combined with coagulation abnormalities are common in patients with liver cirrhosis.[41] However, these patients have a high incidence of portal and idiopathic venous thrombosis, showing that cirrhotic coagulopathy does not protect against thrombosis.[41] Situations associated with mild to moderate thrombocytopenia (> 50,000/mm^3) should not affect VTE prevention decisions. However, in patients with severe thrombocytopenia (< 50,000/mm^3), prophylaxis should be considered on a case-by-case basis.[41] Tufano et al.[41] conducted a systematic review of thromboprophylaxis and thrombocytopenia, proposing specific recommendations for use of pharmacological prophylaxis (Table 3).

Antiphospholipid Antibody Syndrome (APS)

In patients with both APS and thrombocytopenia, the tendency to thrombosis generally far outweighs the risk of bleeding.[41] In this population, VTE prophylaxis should be evaluated, especially for those considered high risk, such as, for example, patients positive for all three antiphospholipid antibodies: lupus anticoagulant, anticardiolipin, and anti ß2 glycoprotein I (triple-positive).[41] The Global APS Score (GAPSS) is a RAM that analyzes the antiphospholipid antibody profile and cardiovascular risk factors and could be useful for assessing risk of thrombotic events in patients with systemic lupus erythematosus, but it has not yet been validated.[42]

Up to 30% of patients with APS may have thrombocytopenia (< 100,000/ mm^3), but bleeding is rare and is normally associated with catastrophic APS, immune thrombocytopenia, or patients who produce antibodies against prothrombin or other coagulation factors.[42]

Table 3. Strategy for VTE prevention in patients with cirrhosis and/or thrombocytopenia.

Risk of spontaneous bleeding	Recommendations
Low (platelets < 90,000 mm^3)	Pharmacological prophylaxis*
Intermediate (platelets from 50,000 to 90,000 mm^3)	Pharmacological prophylaxis*
High (platelets < 50,000 mm^3)	Pharmacological prophylaxis in selected cases *
	Mechanical prophylaxis preferable**

*VTE prophylaxis should be administered if the patient has one or more additional VTE risk factors; **Graduated elastic compression stockings, intermittent pneumatic compression devices and venous foot pumps. Adapted from: Tufano et al.[41]

Cancer patients

Cancer is an important independent risk factor for development of VTE.[43] On the other hand, patients with cancer are also prone to bleeding, associated with complications of tumors, increased frequency of surgical procedures, and thrombocytopenia associated with systemic chemotherapy, making VTE prevention a major challenge in this population. Venous thromboembolism prophylaxis should be considered in hospitalized cancer patients even when they have thrombocytopenia, especially for those who have multiple VTE risk factors.[43,44] Pharmacological prophylaxis is recommended at the standard dose for patients with platelet levels > 80,000/mm^3.[43,44] If platelet counts are below 80,000/mm,^{3} management should be decided individually.[43,44] Careful monitoring of the undesirable effects of anticoagulant use *vs.* the risk of VTE is recommended.[43,44] In cases in which pharmacological prophylaxis is contraindicated, use of mechanical prophylaxis should be optimized.

Chronic Renal Failure (CRF)

From the point of view of coagulation state, CRF is a paradoxical disease. Although it increases the risk of VTE because of endothelial injury/dysfunction, initial platelet hyperreactivity, increased fibrin formation, and

reduced fibrinolytic system activity, it also increases the risk of major hemorrhage as renal function progressively deteriorates and platelet aggregation and adhesion reduce as a consequence.[45] While the IMPROVE Bleeding Risk Score[6] assesses CRF according to its severity (1 point for moderate CRF and 2.5 points for severe CRF), the VTE RAMs for medical patients (Brazilian VTE Prevention Guidelines,[9] and the Padua,[11] Geneva,[13] and IMPROVE[12] scores) and for surgical patients (Caprini[15] and Rogers[16] scores) do not include CRF as a risk factor for thrombosis. The fragile equilibrium between increased risk of VTE and risk of hemorrhage makes pharmacological prophylaxis of VTE a particular challenge, especially in those with advanced CRF (creatinine clearance of 15-29 mL/min) or end-stage kidney failure (creatinine clearance < 15 mL/min), for a variety of reasons including the fact that there is no specific RAM for this group of patients.[45]

With regard to pharmacological prophylaxis, current evidences are insufficient to conclude that the use of UFH at a dose of 5,000 UI three times / day increases the risk of major and minor hemorrhagic events in patients with creatinine clearance <30 ml / min compared to patients without severely impaired kidney function, as well as enoxaparin significantly increase the risk of major bleeding compared to UFH in this patient profile.[44]

How to proceed with patients at increased risk of bleeding

In the case of hospitalized patients who have a high risk of VTE associated with a high risk of bleeding or have contraindications for the use of anticoagulants, mechanical methods of preventing VTE, such as intermittent pneumatic compression, graduated compression stockings and venous foot pump, are recommended.[6] When mechanical prophylaxis options are used, the transition to a pharmacological agent should be considered as soon as the risk of bleeding becomes low or is reversed.

CONCLUSIONS

Appropriate use of pharmacological prophylaxis should be aligned with minimization of bleeding risk so that patients classified as at high risk of development of VTE may obtain real clinical benefit from thromboprophylaxis.

Several VTE prevention guidelines provide guidance on the main factors involved in the risk of bleeding. However, to date, the only validated RAM that enables identification at hospital admission of medical patients at risk of bleeding is the IMPROVE Bleeding Risk Score.[6,36] Patients with scores < 7 can safely be given pharmacological prophylaxis.[6] In contrast, prophylaxis decisions on patients at high risk of bleeding (scores ≥ 7) who also simultaneously have a high risk of VTE should be taken individually and dynamically over the course of the hospital stay, up to hospital discharge. In patients undergoing surgery, it is necessary to consider the procedure's potential risk of bleeding in conjunction with individual risk factors to define the best VTE prevention strategy.

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Author contributions
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Analysis and interpretation: MCC, MAM
Data collection: MCC
Writing the article: MCC, MAM
Critical revision of the article: MCC, MAM
Final approval of the article*: MCC, MAM
Statistical analysis: MCC
Overall responsibility: MCC
*All authors have read and approved of the final version of the article submitted to J Vasc Bras.

ARTIGO DE REVISÃO

JORNAL **VASCULAR** BRASILEIRO
ISSN 1677-7301 (Online)

Avaliação do risco de sangramento na profilaxia do tromboembolismo venoso

Bleeding risk assessment for venous thromboembolism prophylaxis

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Resumo

O tromboembolismo venoso (TEV) é uma das principais causas preveníveis de morbimortalidade em pacientes hospitalizados, sendo a embolia pulmonar (EP) fatal possivelmente a sua primeira manifestação. Diretrizes nacionais e internacionais recomendam o uso de modelos de avaliação de risco para a prescrição de profilaxia do TEV em pacientes hospitalizados. Apesar das evidências e diretrizes de apoio, o uso da tromboprofilaxia permanece abaixo do ideal, o que pode resultar da baixa conscientização dos benefícios da profilaxia, mas também pode refletir o medo de complicações hemorrágicas, justificando a subutilização da tromboprofilaxia em todo o mundo. A avaliação do risco de sangramento é, portanto, necessária para a adequação de profilaxia e deve ser realizada de forma concomitante à avaliação do risco de trombose. O objetivo desta revisão é salientar a importância da avaliação conjunta do risco de TEV e do risco de sangramento em pacientes hospitalizados.

Palavras-chave: trombose venosa; embolia pulmonar; profilaxia; hemorragia; segurança do paciente; avaliação de risco.

Abstract

Venous thromboembolism (VTE) is one of the main preventable causes of morbidity and mortality in hospitalized patients and fatal pulmonary embolism (PE) may be its first manifestation. Several national and international guidelines recommend using risk assessment models for prescription of VTE prophylaxis in hospitalized patients. Despite evidence and guidelines supporting VTE prevention, use of VTE prophylaxis in hospitalized patients remains suboptimal, which may be because of low awareness of the benefits of VTE prophylaxis, but might also reflect fear of bleeding complications in these patients, since this constitutes one of the main reasons for underutilization of thromboprophylaxis worldwide. Bleeding risk assessment is therefore necessary for adequate prophylaxis prescription and should be carried out concurrently with assessment of the risk of thrombosis. The purpose of this review is to highlight the importance of jointly assessing risk of VTE and risk of bleeding in hospitalized patients.

Keywords: venous thrombosis; pulmonary embolism; prophylaxis; hemorrhage; patient safety; risk assessment.

Como citar: Chindamo MC, Marques MA. Avaliação do risco de sangramento na profilaxia do tromboembolismo venoso. J Vasc Bras. 2021;20:e20200109. https://doi.org/10.1590/1677-5449.200109

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Fonte de financiamento: Nenhuma.
Conflito de interesse: Os autores são palestrantes da Sanofi.
Submetido em: Junho 17, 2020. Aceito em: Outubro 13, 2020.

O estudo foi realizado no Hospital Barra D'Or - Rede D'Or São Luiz, Rio de Janeiro, RJ, Brasil.

INTRODUÇÃO

O tromboembolismo venoso (TEV) é uma das principais causas preveníveis de morbimortalidade em pacientes hospitalizados[1,2]. A embolia pulmonar (EP) fatal é frequentemente a primeira manifestação de TEV e pode representar até 10% de todas as mortes hospitalares[2,3]. Os pacientes hospitalizados apresentam risco de TEV devido à presença de fatores adquiridos ou hereditários, como obesidade, câncer, TEV prévio, trombofilias, trauma, cirurgia, infarto agudo do miocárdio, acidente vascular cerebral, idade avançada, insuficiência cardíaca congestiva, infecção aguda, imobilidade e admissão em unidades de terapia intensiva, entre outros[4-6].

Diretrizes nacionais e internacionais recomendam o uso de modelos de avaliação de risco [*risk assessment model* (MAR)] para a profilaxia farmacológica ou mecânica em pacientes clínicos[7-14], cirúrgicos[8,15,16] ou obstétricos[10], visando à melhor estratégia de prevenção. Contudo, o risco de TEV não pode ser avaliado isoladamente. O risco de sangramento, induzido ou potencializado pelos anticoagulantes, também deve ser avaliado simultaneamente quando se considera a adequação da tromboprofilaxia[6,7,9].

Embora diversos estudos reportem baixas taxas de sangramento relacionadas à farmacoprofilaxia[11,17,18], o medo de eventos hemorrágicos é uma das principais justificativas da sua subutilização em todo o mundo[6]. A identificação de condições com potencial risco de sangramento e a implementação de MAR são, portanto, fundamentais para o uso adequado da tromboprofilaxia[19].

O objetivo desta revisão é salientar a importância da avaliação conjunta do risco de TEV e do risco de sangramento em pacientes hospitalizados.

AVALIAÇÃO DE RISCO TROMBÓTICO *VERSUS* RISCO DE SANGRAMENTO

Inúmeros MARs de TEV estão disponíveis, tanto para pacientes clínicos quanto cirúrgicos, e direcionam as principais recomendações de tromboprofilaxia com base na estratificação de risco[7-16]. O modelo mais adequado de avaliação ainda não está definido[19]. Na estratificação de risco de TEV, devemos utilizar um modelo validado para a população em questão aplicado de forma sistemática nas principais etapas de assistência: admissão hospitalar, transição entre setores e alta hospitalar. Essa última avaliação é particularmente importante nos pacientes que mantêm fatores de risco para TEV na alta, como, por exemplo, a imobilidade prolongada[2]. A escolha da melhor estratégia de tromboprofilaxia deve considerar, simultaneamente, o risco de TEV e o risco potencial de sangramento[20,21].

São consideradas contraindicações absolutas ao uso de anticoagulantes o sangramento ativo, grave ou potencialmente fatal, não reversível com intervenção médica ou cirúrgica, incluindo qualquer sangramento ativo em local crítico (intracraniano, pericárdico, retroperitoneal, intraocular, intra-articular e intraespinhal), hipertensão arterial maligna não controlada, coagulopatia grave não compensada, disfunção plaquetária ou distúrbios primários de hemostasia graves, trombocitopenia persistente (< 20.000/mm^3) e procedimentos invasivos de alto risco em local crítico, como punção lombar e raquianestesia em pacientes cujo procedimento cirúrgico é planejado no período de 6 a 12 horas seguintes[20]. Outros fatores associados ao risco aumentado de sangramento são a trombocitopenia induzida pela heparina (TIH), o uso concomitante de antiagregantes plaquetários e/ou anti-inflamatórios não hormonais e a disfunção renal, principalmente quando utilizados anticoagulantes de eliminação renal [heparina de baixo peso molecular (HBPM) e fondaparinux][15]. Em pacientes que apresentam *clearance* de creatinina < 30 mL/min, recomenda-se a redução da dose de HBPM, monitoramento da ação anticoagulante ou substituição por heparina não fracionada (HNF)[4]. A revisão periódica de ambos os riscos, principalmente nas mudanças de quadro clínico, ajuda a orientar a melhor estratégia para a profilaxia[21] (Figura 1).

Modelos de avaliação de risco de TEV

Entre os principais MARs de TEV em pacientes clínicos, estão a Diretriz Brasileira de Prevenção de TEV em pacientes clínicos hospitalizados[9] e os escores de Padua[11], Genebra[13] e IMPROVE (*International Medical Prevention Registry on Venous Thromboembolism*)[12]. Para a avaliação de pacientes cirúrgicos, são recomendados os escores de Caprini[15] e Rogers[16], que definem o risco de TEV com base nas características dos pacientes e no perfil de cada cirurgia. Mulheres hospitalizadas durante a gravidez, no puerpério ou no período de até seis semanas após aborto espontâneo ou interrupção da gravidez, devem ser avaliadas quanto à necessidade de farmacoprofilaxia[21]. O MAR mais utilizado nesse perfil de pacientes foi desenvolvido pelo *Royal College of Obstetricians and Gynecologists* (RCOG)[10,21].

Apesar da recomendação de avaliação concomitante do risco de TEV *versus* risco de sangramento durante o cuidado do paciente hospitalizado, são escassos os MARs de sangramento no contexto da profilaxia de TEV[19]. Poucos são os modelos que associam essas duas características[9,12,21] (Tabela 1).

Esse cenário é bastante distinto daquele encontrado na avaliação de risco de sangramento aplicada à anticoagulação plena na prevenção dos fenômenos tromboembólicos da fibrilação atrial ou no tratamento

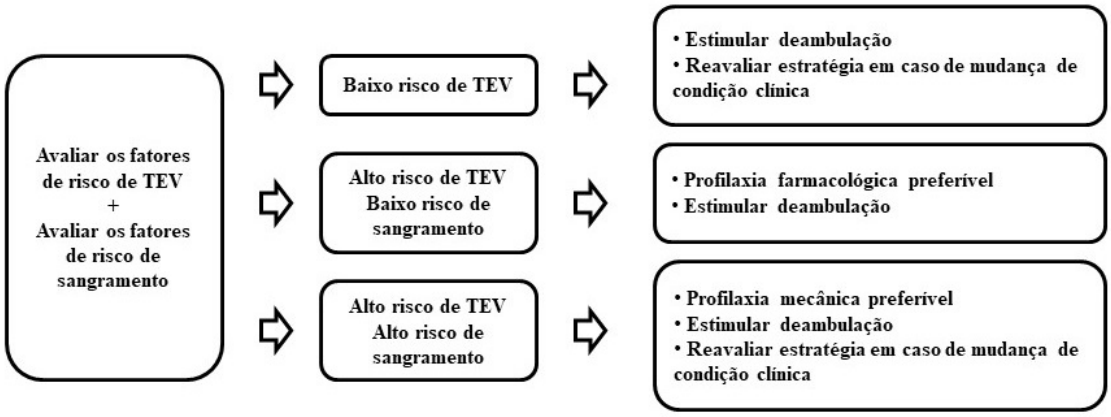

Figura 1. Recomendações de profilaxia de tromboembolismo venoso (TEV) segundo estratificação do risco de TEV ***versus*** risco de sangramento. Adaptado de: National Institute for Health and Care Excellence – NICE. NG89[21].

Tabela 1. Lista de modelos de avaliação de risco (MAR) de tromboembolismo venoso (TEV) e de sangramento de acordo com a população estudada[9-16,21].

MAR	Tipo de paciente	Risco de sangramento	Recomendação de profilaxia
Caprini, 2005	Cirúrgico	-	X
Geneva, 2006	Clínico	-	X
Rogers, 2007	Cirúrgico	-	X
Diretriz brasileira, 2007	Clínico	X	X
Padua, 2010	Clínico	-	X
IMPROVE, 2011	Clínico	X	X
UK RCOG, 2015	Obstétrico	-	X
NICE NG89, 2018	Clínico/cirúrgico	X	X

de TEV. Dez MARs de sangramento estão disponíveis com esse objetivo. Seis deles são aplicáveis aos casos dos pacientes que fazem uso de anticoagulantes orais na fibrilação atrial (ABC[22], ORBIT[23], ATRIA[24], HAS-BLED[25], HEMORR$_2$HAGES[26], Shireman[27]), três no tratamento anticoagulante de TEV (VTE-BLED[28], Ruiz-Gimenez[29], Kuijer[30]) e um misto (OBRI[31]). Esses escores evidenciam situações de aumento do risco de sangramento associado à anticoagulação plena e auxiliam na aplicação de estratégias que ajudam a minimizar o risco de hemorragia por meio da intervenção em fatores de risco modificáveis[32].

RISCO DE SANGRAMENTO NA FARMACOPROFILAXIA

Avaliação de risco de sangramento em pacientes clínicos

IMPROVE *Bleeding Risk Score*

O principal MAR de sangramento associado à farmacoprofilaxia em pacientes clínicos hospitalizados é o IMPROVE *Bleeding Risk Score*[6,7]. Decousus et al.[6] utilizaram uma análise multivariada para identificar e pontuar fatores na admissão hospitalar associados ao risco de sangramento em pacientes clínicos agudamente doentes. Com base nos dados do IMPROVE[12], um estudo observacional multicêntrico desenvolvido para avaliar os padrões de profilaxia de TEV em mais de 15.000 pacientes clínicos, os autores verificaram a incidência de sangramento e identificaram os fatores, na admissão, associados ao risco de sangramento[6]. O sangramento maior foi definido como sangramento fatal e/ou sintomático em uma área ou órgão crítico e/ou sangramento que resultou em queda de hemoglobina ≥ 2 g/dL ou levou à transfusão de dois ou mais concentrados de hemácias[6]. O sangramento não maior, mas clinicamente relevante, foi caracterizado como hemorragia gastrointestinal, hematúria macroscópica de duração > 24 h, epistaxe substancial com necessidade de intervenção, epistaxe recorrente e/ou de duração de pelo menos cinco minutos, hematomas extensos (> 5 cm de diâmetro), sangramento intra-articular, menorragia ou metrorragia ou ainda outro sangramento importante que necessitasse de intervenção médica[6,33].

A incidência cumulativa de sangramentos hospitalares descritos como maiores e não maiores até 14 dias após a internação foi de 3,2% (1,2% de sangramento maior e 2,0% de sangramento não maior clinicamente relevante)[6].

Os fatores de risco, na admissão, independentemente associados ao risco de sangramento foram[6]: úlcera gastroduodenal ativa, sangramento nos três meses anteriores à admissão e contagem de plaquetas < 50.000/mm^3. Outros fatores de risco de sangramento incluíram idade avançada, insuficiência hepática e/ou renal, permanência em unidade de terapia intensiva, presença de cateter venoso central, doença reumática, câncer e sexo masculino, fatores que também estão relacionados ao aumento do risco de TEV[6]. Cada um dos fatores acima, com ponderação apropriada, foi inserido neste MAR (Tabela 2). Os autores também elaboraram um recurso *on-line* no qual o risco de sangramento pode ser avaliado[34].

Mais da metade dos episódios de sangramento maior ocorreu em 10% dos pacientes hospitalizados que tiveram escore de risco de sangramento ≥ 7[6]. Desse modo, os autores consideraram como alto risco de sangramento a pontuação no IMPROVE *Bleeding Risk Score* ≥ 7 e como baixo risco a pontuação < 7. As taxas de sangramento maior, em comparação às taxas de qualquer sangramento (definido como maior ou não maior clinicamente relevante) nos pacientes com escore < 7 foram respectivamente 0,4% e 1,5%. Naqueles com escore ≥ 7, a taxa de sangramento maior foi de 4,1% e a de qualquer sangramento, 7,9%[6].

Profilaxia mecânica foi mais utilizada em pacientes com escore de sangramento ≥ 7, comparada ao escore < 7 (16,3% *versus* 8,9%, respectivamente). Por outro lado, a profilaxia farmacológica foi utilizada em proporções semelhantes em pacientes com escore de risco de < 7 e ≥ 7 (48,9% *versus* 49,3%, respectivamente)[6].

Este MAR ajuda, portanto, a decidir sobre a profilaxia farmacológica ou mecânica em pacientes clínicos de alto risco de TEV[6]. Pode ser aplicado em associação com o escore IMPROVE para risco de TEV, permitindo a ponderação do risco e do benefício na escolha da melhor estratégia de tromboprofilaxia. Esse escore já foi validado em outras populações de pacientes clínicos[35,36].

Tabela 2. IMPROVE *Bleeding Risk Score*.

Fatores de risco	Pontuação
Úlcera gastroduodenal ativa	4,5
Hemorragia três meses antes da internação	4
Plaquetas < 50.000 mm^3	4
Idade ≥ 85 anos *versus.* < 40 anos	3,5
Insuficiência hepática (RNI* > 1,5)	2,5
Insuficiência renal severa (TFG** < 30 *versus.* ≥ 60 mL/min)	2,5
Internação em unidade de terapia intensiva	2,5
Cateter venoso central	2
Doença reumatológica	2
Câncer ativo	2
Idade 40-84 *versus* < 40 anos	1,5
Sexo masculino	1
Insuficiência renal moderada (TFG** 30-59 *versus* ≥60 mL/min)	1

*RNI: Razão Normalizada Internacional; **TFG: taxa de filtração glomerular. Adaptada de: Decousus et al.[6].

Avaliação de risco de sangramento em pacientes cirúrgicos

A taxa de sangramento associada à farmacoprofilaxia em pacientes cirúrgicos varia de acordo com o perfil da cirurgia. Uma metanálise de 52 estudos randomizados sobre farmacoprofilaxia de TEV em pacientes de cirurgia geral relatou que os sangramentos menores são comuns e abrangem hematomas no local de aplicação (~7%), hematoma da ferida (~6%), sangramento no local do dreno (~2%) e hematúria (~2%)[37]. As complicações hemorrágicas maiores, no entanto, foram incomuns e incluíram sangramento gastrointestinal (0,2%) ou retroperitoneal (< 0,1%)[37]. A descontinuação da profilaxia ocorreu em 2% dos pacientes e a reoperação subsequente por sangramento em menos de 1%. Da mesma forma, os pacientes com um ou mais fatores de risco individuais de sangramento foram considerados de alto risco no pós-operatório[37].

Estimativas do risco inicial de sangramento em cirurgia

O risco inicial de sangramento foi pouco estudado em pacientes cirúrgicos não ortopédicos. A estratificação de risco de sangramento maior foi estimada pelo *American College of Chest Physicians* (ACCP) nos seguintes grupos de pacientes cirúrgicos[8]: geral/abdominal/pélvica (~1%), bariátrica (< 1%), plástica/reconstrutiva (0,5 a 1,8%), vascular (0,4 a 1,8%), cardíaca [~5% (alto risco)], torácica (1%), neurocirurgia/craniotomia (1 a 1,5%), coluna vertebral (<0,5%) e trauma grave [3,4 a 4,7% (alto risco)].

Nas cirurgias ortopédicas, as estimativas de risco inicial de sangramento na ausência de profilaxia são heterogêneas devido às características distintas das populações e das técnicas cirúrgicas utilizadas[38]. Estima-se um risco de sangramento maior, variando de 2 a 4% nas cirurgias ortopédicas com duração acima de 45 minutos e na artroplastia bilateral de joelhos. Procedimentos menores, como artroscopias, cirurgias de ombro, mãos e pés, são considerados de menor risco de sangramento (< 2%)[39]. As taxas de sangramento maior em pacientes submetidos a

profilaxia de TEV variaram de 0,1% a 3,1% nos estudos de artroplastia de quadril e de 0,2% a 1,4% nos estudos de artroplastia de joelho, sugerindo haver pouca interferência dos anticoagulantes no risco de sangramento desses grupos de pacientes[40].

Risco de sangramento em situações especiais

Trombocitopenia

As diretrizes atuais sobre profilaxia de TEV são baseadas em ensaios clínicos randomizados que excluem os indivíduos de risco potencialmente alto de sangramento, limitando, portanto, as recomendações específicas sobre farmacoprofilaxia em pacientes com trombocitopenia e/ou disfunção plaquetária[41]. Essas condições estão presentes em pelo menos 25% dos indivíduos hospitalizados e são representadas por uma série de patologias, como púrpura trombocitopênica idiopática, púrpura trombocitopênica trombótica, síndrome do anticorpo antifosfolipídeo (SAF), TIH, coagulação intravascular disseminada, plaquetopenia induzida por medicamentos, insuficiência hepática, renal e medular e câncer[41]. Os valores mínimos de plaquetas para a utilização da farmacoprofilaxia também não são uniformes, variando entre 50.000 e 100.000/mm^3.[6,9,11,15,21]. O IMPROVE *Bleeding Risk Score*[6] considera como referência o limite de plaquetas de 50.000/mm^3, enquanto a diretriz NICE[21] estabelece o ponto de corte em 75.000/mm^3. O risco de sangramento espontâneo aumenta dramaticamente quando há contagens de plaquetas de < 10.000 a 20.000/mm^3 e varia de acordo com a causa da trombocitopenia[41].

Hepatopatia crônica

A trombocitopenia ou disfunção plaquetária associadas a anormalidades da coagulação são comuns em pacientes com cirrose hepática[41]. No entanto, esses pacientes apresentam alta incidência de trombose venosa portal e idiopática, o que significa que a coagulopatia da cirrose não protege contra a trombose[41]. As situações associadas à trombocitopenia leve/moderada (> 50.000/mm^3) não devem interferir nas decisões de prevenção de TEV. Na trombocitopenia grave (< 50.000/mm^3), no entanto, a profilaxia deve ser considerada individualmente[41]. Em uma revisão sistemática sobre tromboprofilaxia e trombocitopenia, Tufano et al.[41] propõem recomendações especificas para o uso de profilaxia farmacológica (Tabela 3).

Síndrome anticorpo antifosfolipídeo (SAF)

Em pacientes com SAF e trombocitopenia, a tendência trombótica é geralmente muito superior ao risco de sangramento[41]. A profilaxia de TEV deve ser avaliada nessa população, especialmente naqueles considerados de alto risco, como, por exemplo, os pacientes positivos para os três anticorpos antifosfolipídios: anticoagulante lúpico, anticardiolipina e anti ß2 glicoproteína I (triplo-positivo)[41]. O *Global APS Score* (GAPSS) é um MAR que analisa o perfil dos anticorpos antifosfolipídios e fatores de risco cardiovascular e pode ser útil para avaliar o risco de eventos trombóticos em pacientes portadores de lúpus eritematoso sistêmico, porém ainda não foi validado[42].

Até 30% dos pacientes portadores de SAF podem apresentar trombocitopenia (< 100.000/ mm^3), porém o sangramento é raro e normalmente está associado à SAF catastrófica, trombocitopenia imune ou naqueles que desenvolvem anticorpos contra protrombina ou outros fatores da coagulação[42].

Tabela 3. Estratégia de prevenção do TEV em pacientes com cirrose e/ou trombocitopenia.

Risco de sangramento espontâneo	Recomendações
Baixo (plaquetas < 90.000 mm^3)	Profilaxia farmacológica*
Intermediário (plaquetas ente 50 e 90.000 mm^3)	Profilaxia farmacológica*
Alto (plaquetas < 50.000 mm^3)	Profilaxia farmacológica em casos selecionados* Profilaxia mecânica preferencial**

*A profilaxia do TEV deve ser realizada na presença de um ou mais fatores de risco adicionais para TEV; **Meias elásticas de compressão graduada, compressão pneumática intermitente e dispositivos e bombas podais. Adaptada de: Tufano et al.[41].

Pacientes oncológicos

O câncer é um fator de risco independente e importante para o desenvolvimento de TEV[43]. Por outro lado, pacientes com câncer são propensos a sangramentos, associados às complicações dos tumores, frequência aumentada de procedimentos cirúrgicos e trombocitopenia associada à quimioterapia sistêmica, tornando a prevenção do TEV um grande desafio nessa população. A profilaxia do TEV deve ser considerada em pacientes hospitalizados com câncer mesmo na presença de trombocitopenia, principalmente nos que têm múltiplos fatores de risco para TEV[43,44]. Nos pacientes que apresentam valores de plaquetas > 80.000/mm^3, recomenda-se o uso de farmacoprofilaxia em dose padrão[43,44]. Se a contagem de plaquetas estiver abaixo de 80.000/mm^3, a conduta deve ser considerada individualmente[43,44]. Recomenda-se monitoramento cuidadoso quanto a efeitos indesejáveis relacionados ao uso do anticoagulante *versus* risco de TEV[43,44]. No caso de contraindicação à profilaxia farmacológica, deve-se otimizar o uso da profilaxia mecânica.

Insuficiência Renal Crônica (IRC)

A IRC é uma doença de caráter paradoxal do ponto de vista da coagulação, pois, ao mesmo tempo em que aumenta o risco de TEV devido à injúria/disfunção endotelial, hiperreatividade plaquetária inicial, aumento da formação de fibrina e diminuição da atividade do sistema fibrinolítico, aumenta o risco de hemorragia maior com a piora progressiva da função renal e consequente decréscimo da adesão e agregação plaquetária[45]. Embora o IMPROVE *Bleeding Risk Score*[6] pontue a IRC de acordo com a sua gravidade (um ponto para IRC moderada e 2,5 pontos para IRC severa), os MARs de TEV para pacientes clínicos (Diretriz Brasileira de Prevenção-de TEV[9] e os escores de Padua[11], Genebra[13] e IMPROVE[12]) e pacientes cirúrgicos (escore de Caprini[15] e Rogers[16]) não incluem a IRC como fator de risco de trombose. Esse equilíbrio frágil entre o risco aumentado de TEV e o risco de hemorragia torna a farmacoprofilaxia do TEV um desafio particular especialmente naqueles com IRC avançada (*clearance* de creatinina 15-29 mL/min) ou falência renal terminal (clearance de creatinina < 15 mL/min), por várias razões, incluindo o fato de não haver um MAR específico para esse grupo de pacientes[45].

Com relaçao às opções de profilaxia farmacológica, as evidências são insuficientes para concluir que o uso de HNF na dose de 5.000 UI três vezes/dia aumente o risco de eventos hemorrágicos graves e menores em pacientes com *clearence* de creatinina < 30 mL/min em comparação a pacientes sem disfunção renal severa ou que a enoxaparina aumente significativamente o risco de sangramento maior em comparação a HNF nesse perfil de pacientes[46].

Como proceder no caso de pacientes com aumento do risco de sangramento

No caso dos pacientes hospitalizados que apresentam alto risco de TEV associado a alto risco de sangramento ou que têm contraindicação do uso de anticoagulantes, os métodos mecânicos de prevenção de TEV, como compressão pneumática intermitente, meias de compressão graduadas e bomba venosa plantar são recomendados[6]. Quando as opções de profilaxia mecânica são utilizadas, a transição para um agente farmacológico deve ser considerada assim que o risco de sangramento se tornar baixo ou for revertido.

CONCLUSÃO

A adequação do uso de farmacoprofilaxia deve estar alinhada com a minimização do risco de sangramento para que os pacientes classificados como de alto risco de desenvolvimento de TEV obtenham benefício clínico real da tromboprofilaxia.

Diversas diretrizes de prevenção de TEV orientam sobre os principais fatores implicados no risco de sangramento. No entanto, até o momento, o único MAR validado que permite a identificação dos pacientes clínicos na admissão hospitalar sob risco de sangramento é o IMPROVE *Bleeding Risk Score*[6,36]. Os pacientes com pontuação < 7 podem receber farmacoprofilaxia com segurança[6]. Por outro lado, pacientes com alto risco de sangramento (pontuação ≥ 7), mas que apresentam simultaneamente alto risco de TEV, devem ter as decisões relativas à profilaxia avaliadas de forma individualizada e dinâmica ao longo da internação, até a alta hospitalar. Nos pacientes submetidos à cirurgia, é necessário considerar o potencial risco de sangramento do procedimento em conjunto com os fatores de risco individuais para definir a melhor estratégia de prevenção de TEV.

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Coleta de dados: MCC
Redação do artigo: MCC, MAM
Revisão crítica do texto: MCC, MAM
Aprovação final do artigo*: MCC, MAM
Análise estatística: MCC
Responsabilidade geral pelo estudo: MCC

*Todos os autores leram e aprovaram a versão final submetida ao J Vasc Bras.