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Two novel risk factors for postoperative venous thromboembolism: A reconsideration of standard risk assessment and prophylaxis

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ABSTRACT

Background: Postoperative venous thromboembolism (VTE) is usually preventable with adequate prophylaxis. In an institutional study, patients with emergency operations (EO), multiple operations (MO), and perioperative sepsis (PS) were more likely to develop VTE despite standard prophylaxis.
Methods: General surgery patients in the NSQIP database from 2011 to 2014 were stratified into VTE and non-VTE groups, and statistical analyses were performed.
Results: Among 1,610,086 patients, 13,673 (0.8%) were diagnosed with VTE. The VTE odds ratios for patients with EO, MO and PS were 1.4 (95%CI:1.3–1.5), 1.9 (95%CI:1.7–2.0), and 2.4 (95%CI:2.2–2.5), respectively. VTE odds ratios increased with concurrence of two factors (EO+PS: 2.0 (95%CI:1.9–2.2)) (EO+MO: 2.3 (95%CI:1.9–2.7)) (MO+PS: 2.5 (95%CI:2.2–2.7)) and further still for patients with all three factors (2.7, 95%CI:2.4–3.0).
Conclusion: General surgery patients with EO, MO, or PS have a greater likelihood of developing postoperative VTE. These factors are not necessarily captured in contemporary risk assessment models that guide chemoprophylaxis, and so these high-risk patients may receive insufficient prophylaxis.

Introduction

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is a serious and potentially devastating condition.[1,2] With adequate prophylaxis, VTE may be prevented, and yet it continues to cost the US healthcare system as much as $7–10 billion and contributes to over 100,000 deaths each year.[3,4] Although chemical prophylaxis effectively reduces the likelihood of VTE, this prevention strategy may be underutilized.[5–8] Risk stratification and risk-based prophylaxis are essential to the successful implementation and effectiveness of VTE prevention protocols.[9,10]

While VTE is prevalent in both medical and surgical patient populations, heightened risk following operations has prompted efforts to curtail these complications through targeted mechanical (e.g., sequential compression devices and early post-operative ambulation) and pharmacologic prophylaxis.[11,12] The Caprini risk assessment model utilizes established hazards to stratify patients into risk-based levels that direct appropriate therapy.[13,14] Individualized risk assessment leads to adequate prophylaxis for high-risk patients and the avoidance of overtreatment among low-risk patients.

Individualized risk assessment and chemoprophylaxis protocols have successfully reduced VTE rates at numerous institutions.[15,16] In 2011, a postoperative VTE prevention protocol was implemented at Boston Medical Center, an urban, safety net, academic medical center.[10] Mandatory Caprini risk calculations were integrated into the electronic medical record workflow, automatically generating recommendations for appropriate perioperative VTE prophylaxis on the general surgery and vascular surgery services. This protocol was eventually extended to other services, including plastic surgery, thoracic surgery, urology, and otolaryngology. From 2009 to 2018, the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) risk-adjusted likelihood (observed/expected ratios early in the series and odds ratios more recently) of VTE events in general surgery at our institution

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steadily declined from 3.02 (10th decile) in 2009 to 0.72 (1st – most desirable - decile) in calendar year 2018.

In an effort to prevent VTE as much as safely possible and achieve a "zero" incidence, all VTE events during the first three years of this new protocol (2011–2014) were investigated for patterns of prophylaxis "failure".[17] Despite good overall compliance with the Caprini protocol, three factors emerged as being strongly associated with VTE. These include emergency operations, multiple operations, and the presence of a perioperative infection. Although sepsis during the one month before an operation is captured as a hazard in the Caprini model, the two additional risk factors are not. Furthermore, the presence of sepsis and an elevated Caprini score guide administration of an "extended" course of VTE prophylaxis beyond discharge, whereas most of the prophylaxis "failures" after implementation of mandatory Caprini assessments occurred during the initial hospital stay, when extended prophylaxis could not yet have been implemented. The goal of the current study is to assess the relationship of emergency operations, multiple operations and perioperative sepsis with VTE within the large NSQIP database.

Methods

Following receipt of institutional review board approval, we queried the NSQIP Participant Use Files (PUF) for all general surgery patients for calendar years 2011–2014. This date range matches the institutional study by Cassidy et al., during which the high-risk factors were originally identified.[17] Subjects were included in our analysis if they underwent a general surgery operation, as defined by the specialty of the operating surgeon.

The NSQIP PUF contain scores of variables including preoperative, intraoperative, postoperative data. Importantly, the NSQIP PUF lack some information about VTE risk such as prior diagnoses of thrombophilia, personal and family history of VTE, and all pharmaceutical data, including usage of oral contraceptives, estrogen replacement therapy and VTE prophylaxis. Likewise, information on mechanical VTE prophylaxis is unavailable in this dataset. The variables collected in this series are listed in Tables 1 and 2. We utilized the term "perioperative sepsis" to reflect the group of patients who had preoperative sepsis or developed postoperative sepsis. In the PUF, sepsis is recorded if a patient has clinical signs and symptoms of systemic inflammatory response syndrome (SIRS) in addition to a positive blood culture or documentation of a positive culture or purulence from a relevant site, or alternatively if the patient has symptoms of SIRS with principal operative findings such as confirmed resection of infarcted bowel, purulence in the operative site, enteric contents in the operative site or positive intraoperative cultures.[18] Patients defined as having sepsis present at the time of surgery (PATOS) are a subset of those who meet the above criteria and for whom the data are highly suggestive of sepsis before or during the operation.

Subjects were stratified into VTE and non-VTE cohorts. The VTE group includes patients who developed a pulmonary embolism or deep vein thrombosis within 30 days of an operation. In NSQIP, pulmonary embolism is recorded for patients with a new diagnosis based on an imaging study such as a ventilation-perfusion scan, computed tomography (CT), transesophageal echocardiography, pulmonary arteriogram, or CT-angiogram. A vein thrombosis is recorded in NSQIP if a new thrombus is identified in the deep or superficial venous system by duplex, venogram, or CT scan, and if the patient requires therapy, including anticoagulation, placement of a vena cava filter, or clipping of the vena cava.[18] The patients who did not meet the above criteria within 30 days of an operation comprise the non-VTE group. Patients were included in the "multiple operations" subgroup if they underwent any additional operations within 30 days of the index operation. Additional operations were not exclusive to general surgery, and could include subspecialties of gynecology, neurosurgery, orthopedic, otolaryngology, plastics, thoracic, urology, vascular or interventional radiology. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). Summary statistics (e.g., proportions, median, quartiles) were obtained. Bivariate analyses were conducted using Chi-square and Kruskal Wallis tests for categorical and continuous variables, respectively. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were obtained from multivariable logistic regressions assessing the relationship of emergency operations, multiple operations and perioperative sepsis with the development of VTE, adjusting for age, sex, comorbidities, functional status, blood loss, transfusions, and operative time. Statistical significance was defined as a two-sided $p < 0.05$.

Results

In calendar years 2011–2014, 3,274,413 patient records were included in NSQIP, of whom 1,610,086 (49.2%) underwent general surgery operations. Among these patients, 13,673 developed VTE within 30 days of their operations, a rate of 0.8%. The distribution of demographic, perioperative, and operative variables were compared between VTE and non-VTE subgroups. Patients who manifested VTE were older, had a higher ASA classification, were more likely to have a partially or totally dependent functional status, and had more comorbidities (Table 1). Patients with VTE also had longer OR times, had a higher proportion of elective surgery, and were more likely to have received postoperative blood transfusions relative to the non-VTE group (Table 2).

Overall, 237,486 patients (14.7%) had emergency operations, 47,077 (2.9%) had multiple operations, and 158,526 (9.8%) had perioperative sepsis. Patients who developed VTE were more likely to have had an emergency operations, multiple operations, or perioperative sepsis than were those who did not (Fig. 1). Patients who had any one of these high-risk factors had higher rates of VTE (1.4%, 5.0%, and 2.8%, respectively) than did those without the factors (0.7%, 0.7% and 0.6%, respectively). The VTE risk associated with the concurrence of specific infectious complications was obtained from multivariate analysis with a 95% confidence interval (Table 3). The odds ratios for VTE were as much as 50% lower for the subset of patients in whom sepsis was recorded as PATOS compared to the aggregate group of patients with perioperative sepsis. Patients who required ventilatory support beyond 48 h also had an increased likelihood of developing VTE (Table 3).

After adjusting for patient characteristics and comorbidities, the ORs of VTE were 1.4 (95%CI: 1.3–1.5) for emergency operations, 1.9 (95%CI: 1.7–2.0) for multiple operations, and 2.4 (95%CI: 2.2–2.5) for perioperative sepsis. Patients with any two of the high-risk factors (multiple operations, emergency operations or perioperative sepsis) had ORs at least 2.0, and patients with all three high-risk factors had an OR of 2.7 (95%CI: 2.4–3.0) (Table 4).

Discussion

Upon analysis of more than 1.6 million patient records, all three institutional high-risk factors were found to confer a heightened risk of postoperative VTE. Emergency operations, multiple operations, and perioperative sepsis are independently associated with VTE, after adjusting for confounding (OR of 1.4, 1.9 and 2.4, respectively). The combination of any two risk factors elevates the OR to 2.0 or higher, and patients with all three high risk factors have an OR of 2.7 (Table 4).

Evidence-based prophylaxis is essential in the prevention of postoperative VTE, and yet over 40% of surgical patients may not

Table 1
Distribution of patient characteristics among VTE and Non-VTE patients.

Variable Name	Patients with VTE	Patients without VTE	P Value
	n = 13,673 (0.8)	n = 1,596,413 (99.2)	
Age (years)	n (column %)		**< 0.0001**
18-39	1225 (9.0)	344,556 (21.6)	
40-59	4108 (30.0)	615,212 (38.5)	
60-79	6383 (46.7)	531,817 (33.3)	
80+	1693 (12.4)	91,824 (5.8)	
Sex			**< 0.0001**
Male	6641 (48.6)	669,356 (41.9)	
Female	7028 (51.4)	926,549 (58.0)	
ASA			**<0.0001**
1 No disturbances	229 (1.7)	157,918 (9.9)	
2 Mild disturbances	3109 (22.7)	746,134 (46.7)	
3 Severe disturbances	7724 (56.5)	608,285 (38.1)	
4 Life threatening disturbances	2453 (17.9)	77,321 (4.8)	
5 Moribund	133 (1.0)	3338 (0.2)	
Not Assigned	25(0.2)	3414 (0.2)	
Functional status			**<0.0001**
Independent	12,476 (91.2)	1,550,819 (97.1)	
Partially dependent	812 (5.9)	27,793 (1.7)	
Totally dependent	294 (2.2)	8369 (0.5)	
Current (within 1 year) smoker	2308 (16.9)	279,418 (17.5)	0.0563
Comorbidities			
Diabetes			**< 0.0001**
Insulin	1174 (8.6)	87,008 (5.5)	
Non-insulin	1531(11.2)	143,723 (9.0)	
Ventilator dependent	522 (3.8)	7742 (0.5)	**< 0.0001**
COPD	1194 (8.7)	61,934 (3.9)	**< 0.0001**
CHF	306 (2.2)	11,466 (0.7)	**< 0.0001**
Hypertension requiring medication	7447 (54.5)	660,768 (41.4)	**< 0.0001**
Current dialysis	322 (2.4)	22,005 (1.4)	**< 0.0001**
Disseminated cancer	1396 (10.2)	44,304 (2.8)	**< 0.0001**
Bleeding disorder	1324 (9.7)	55,198 (3.5)	**< 0.0001**
Preoperative factors			
Transfusion (1+ units within 72h of operation)	902 (6.6)	18,108 (1.1)	**< 0.0001**
Open wound/wound infection	908 (6.6)	40,586 (2.5)	**< 0.0001**
Chronic steroid usage	1387 (10.1)	60,724 (3.8)	**< 0.0001**
Recent weight loss (>10% of body weight)	948 (6.9)	30,476 (1.9)	**<0.0001**

N.B.: Numbers in some groups do not add up to the total "n" due to missing data in the NSQIP PUF. COPD = chronic obstructive pulmonary disease. CHF = congestive heart failure.

receive the standard of care.[19] Paramount to VTE prevention protocols is the stratification of patients based upon calculated risk. The three factors analyzed in this series were identified in an institutional study of patients who manifested VTE despite receiving prophylaxis in accordance with the Caprini risk assessment model.[17] These factors therefore represent situations in which VTE risk may be underestimated and those patients consequently receive insufficient prophylaxis.

Multiple operations and emergency operations are not commonly regarded as being independent hazards for VTE and are not included in contemporary risk assessment models. The performance of multiple operations has been associated with VTE in some studies, but those series have lacked statistical power to declare it an independent hazard.[20,21] However, this factor is now corroborated by the large NSQIP series.

Of the three high-risk factors analyzed in this cohort, perioperative sepsis was associated with the greatest odds of VTE. Infection is an established risk factor for the development of VTE.[22–24] In the Caprini model, the presence of sepsis during the month prior to operation confers a one-point increase in a patient's VTE risk score, but this risk may still be underestimated. Infection within 92 days has been identified as an independent hazard for VTE in another study, with an OR 2.37 (95%CI: 1.77–3.17).[25] Infections may increase VTE risk because cytokine release and endothelial cell activation produce a pro-inflammatory effect that persists for many months.[26] In a population-based case control study of more than 1.8 million medical and surgical patients in Northern Denmark, a history of infection within the past year was found to confer an elevated risk of VTE.[27] The VTE risk was greatest during the first two weeks after onset of infection (OR 5.6) and declined to 2.5 by weeks 3 and 4.

In this study, subsets of patients with sepsis recorded as PATOS have lower VTE odds ratios than the overall perioperative sepsis groups that include both pre- and postoperative sepsis. However, many of the odds ratios for the sepsis PATOS subgroups in this analysis were not statistically significant (Table 3). Although VTE risk may vary within the time course of an infection, the data in this series cannot adequately assess any temporal effect because sepsis PATOS comprises a small subset of the overall perioperative sepsis group. The temporal relationship between VTE and infection is difficult to reconcile, particularly because many VTE events can go unnoticed until incidental discovery, leaving this measure particularly susceptible to surveillance bias.[28] Additional studies are needed to elucidate the timing between the onset and duration of infection and the manifestation of VTE events.

Two of the three high-risk VTE factors (multiple operations and emergency operations) identified in this series are not typically included in VTE risk calculators. Furthermore, risk assessment

Table 2
Distribution of Perioperative Variables among VTE and non-VTE Patients.

Perioperative Variable	Patients with VTE		Patients without VTE	P Value
	n = 13,673 (0.8)		n = 1,596,413 (99.2)	
OR time (minutes, median)	*143*		*75*	**< 0.0001**
Anesthesia technique		n (column %)		**< 0.0001**
Epidural	15 (0.1)		902 (0.06)	
General	13,519 (98.9)		1,517,430 (95.1)	
Local	4 (0.03)		3951 (0.2)	
Monitored anesthesia care/IV sedation	98 (0.7)		64,535 (4.0)	
None	2 (0.01)		137 (0.01)	
Other	5 (0.04)		633 (0.04)	
Regional	5 (0.04)		1783 (0.1)	
Spinal	23 (0.2)		6741 (0.4)	
Operation type				
Elective operation	7148 (52.3)		1,169,335 (73.2)	**< 0.0001**
Emergency operation	3400 (24.9)		234,086 (14.7)	**< 0.0001**
Multiple operations				
1 return to OR	2359 (17.3)		44,718 (2.8)	**< 0.0001**
2 returns to OR	424 (3.1)		4457 (0.3)	**< 0.0001**
3 or more returns to OR	136 (1.0)		1090 (0.1)	**< 0.0001**
Postoperative transfusion requirement	3396 (24.8)		68,537 (3.7)	**< 0.0001**
Length of stay (median days)	11		1	**< 0.0001**
Discharge destination				**< 0.0001**
Home	8964 (65.6)		1,496,514 (93.7)	
Facility that had been home	169 (1.2)		11,144 (0.7)	
Rehabilitation facility	992 (7.3)		16,200 (1.0)	
Acute care facility	317 (2.3)		6545 (0.4)	
Skilled care facility	2280 (16.7)		47,033 (2.9)	
Unskilled care facility	47 (0.3)		1301 (0.1)	
Expired	790 (5.8)		14,221 (0.9)	
Readmission	5138 (5.8)		93,510 (5.9)	**< 0.0001**
Number of days from discharge to readmission	15		13	**< 0.0001**

N.B.: Numbers in some groups do not add up to the total "n" due to missing data in the NSQIP PUF. OR = operating room.

models have historically selected candidates for extended courses of chemoprophylaxis following discharge rather than for modifications of inpatient prophylaxis. A previous report from our group indicated that VTE was not ordinarily associated with non-compliance with standardized prophylaxis. Instead, most VTE manifested during patients' initial hospital stays despite appropriately prescribed and administered prophylaxis, as has been reported by others.[29] As a result, most of the patients who developed VTE in spite of the implementation of the Caprini protocol did not have the opportunity to benefit from extended courses of outpatient prophylaxis. This experience has prompted us to consider the notion of "enhanced" prophylaxis, perhaps comprised of dosages greater than standard prophylaxis, during the initial postoperative period for patients with combinations of emergency operations, multiple operations, and perioperative sepsis.[17]

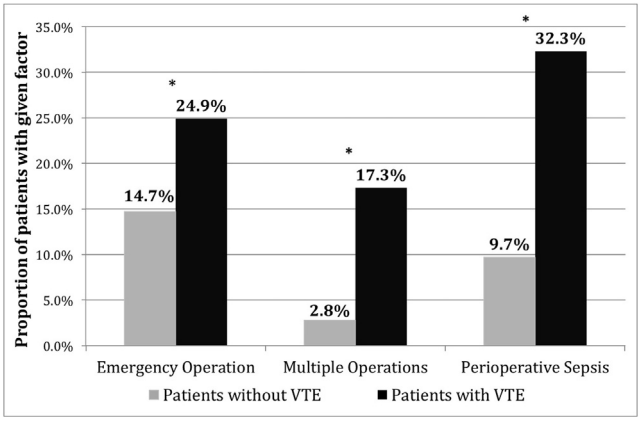

Fig. 1. Prevalence of each factor within the non-VTE and VTE groups (*p < 0.0001).

This study is not without limitations. The retrospective nature of a large database restricts available details. The NSQIP database does not record the usage of mechanical or pharmacologic VTE prophylaxis, and so we are unable to adjust for this significant protective factor in our analysis. When considering patients at high-risk of thromboembolic complications, details of VTE prophylaxis are essential to understanding outcomes, and these data are notably lacking. However, while prophylaxis likely differs between participating hospitals, variability among subgroups is expected to be minimal given the large number and presumed distribution of patients in this analysis. In addition, VTE events are not recorded beyond 30 days, even though high-risk patients remain vulnerable to this complication for a protracted period. The median time to a postoperative VTE may be as long as 51 days.[12] In fact, a large proportion of VTE events, particularly deep vein thromboses, are clinically occult or may be diagnosed only upon autopsy.[2] Without active screening, it is certain that the incidence of VTE is under-reported in this database, although the overall VTE rate of 0.8% is consistent with contemporary literature.[30,31] Lastly, the data used in this analysis were obtained through 2014 to correlate with our previously published local series.[17] Although more contemporary data might expand the ability to evaluate the novel risk factors, risk stratification and prophylaxis practices have not changed dramatically since the study period. Therefore, the association between the risk factors and VTE, identified in multivariable logistic regression models, is still valid.

In both our institutional experience and the large NSQIP database, multiple operations, emergency operations, or the presence of

Table 3
Results from multivariable logistic regression to assess the relationship of clinical factors with VTE[a].

Clinical Factors	Patients with VTE	Patients without VTE	OR (95% CI)
	n = 13,673 (0.8%)	n = 1,596,413 (99.2%)	
Surgery type	n (column %)		
Elective operation	7148 (52.3)	1,169,335 (73.2)	1.0[a]
Emergency operation	3400 (24.9)	234,086 (14.7)	1.4 (1.3, 1.5)
Multiple operations	2359 (17.3)	44,718 (2.8)	1.9 (1.7, 2.0)
Complications			
Perioperative Sepsis	4412 (32.3)	154,114 (9.7)	2.4 (2.2, 2.5)
Sepsis PATOS	571 (4.2)	17,112 (1.1)	1.2 (1.1, 1.3)
Septic shock	1603 (11.7)	19,026 (1.2)	1.2 (1.1, 1.3)
Superficial SSI	925 (6.8)	36,166 (2.3)	1.4 (1.3, 1.5)
Superficial SSI PATOS	52 (0.4)	2372 (0.1)	0.8 (0.6, 1.1)
Deep SSI	468 (3.4)	11,492 (0.7)	1.2 (1.1, 1.4)
Deep SSI PATOS	85 (0.6)	2471 (0.2)	0.9 (0.7, 1.2)
Organ space SSI	1814 (13.3)	29,290 (1.8)	1.7 (1.6, 1.9)
Organ space SSI PATOS	470 (3.4)	9138 (0.6)	0.9 (0.8, 1.0)
Pneumonia	1842 (13.5)	21,409 (1.3)	2.1 (1.9, 2.2)
Pneumonia PATOS	283 (2.1)	4156 (0.3)	0.7 (0.6, 0.8)
Unplanned intubation	1552 (11.4)	15,243 (1.0)	1.8 (1.7, 1.9)
Ventilator time > 48 h	2320 (17.0)	21,978 (1.4)	2.9 (2.6, 3.1)
On ventilator > 48 h prior to operation	359 (2.6)	4290 (0.3)	1.1 (1.0, 1.2)
Urinary tract infection	840 (6.1)	19,180 (1.2)	1.6 (1.5, 1.8)
Urinary tract infection PATOS	219 (1.6)	4190 (0.3)	0.9 (0.8, 1.1)
Postoperative acute renal failure	427 (3.1)	5257 (0.3)	1.2 (1.1, 1.3)
Wound disruption	395 (2.9)	7507 (0.5)	1.1 (1.0, 1.3)
Readmission	5138 (37.6)	93,510 (5.9)	5.7 (5.5, 6.0)

[a] The OR (95% CI) were obtained from multivariable logistic regression models that adjusted for age, sex, comorbidities, functional status, operative time, blood loss, and blood transfusions SSI = Surgical site infection. PATOS = Present at time of surgery.

Table 4
Combinations of emergency operation, multiple operations, and perioperative sepsis - multivariable regression[a].

Variable Name	Patients with VTE	Patients without VTE	OR (95% CI)
	n = 13,673 (0.8%)	n = 1,596,413 (99.2%)	
Perioperative Sepsis (PS) + Emergency Operations (EO)	1687 (12.3)	80,066 (5.0)	2.0 (1.9, 2.2)
Multiple Operations (MO) + Emergency Operations (EO)	542 (4.0)	7737 (0.5)	2.3 (1.9, 2.7)
Perioperative Sepsis (PS) + Multiple Operations (MO)	183 (1.3)	3583 (0.2)	2.5 (2.2, 2.7)
PS + MO + EO	477 (3.5)	5787 (0.4)	2.7 (2.4, 3.0)

[a] The ORs (95% CI) were obtained from multivariable logistic regression models that adjusted for age, sex, comorbidities, functional status, operative time, blood loss, and blood transfusions.

perioperative sepsis are associated with a significantly increased chance of a VTE event, often before patients might receive extended courses of prophylaxis. Moreover, the odds of VTE increase with a combination of any two factors, and even more for patients with all three factors. While the Caprini risk assessment model assigns a modest hazard to sepsis (one point), it does not include the impact of multiple or emergency operations. To our knowledge, this is the first study to identify emergency operations and multiple operations as independent hazards for VTE. Patients with these factors, as well as perioperative sepsis, may require more intensive chemoprophylaxis than is routinely prescribed. In that the large NSQIP database has corroborated our institutional experience, we recently developed an electronic medical record-embedded protocol for an enhanced VTE prophylaxis regimen among patients with two or more of the identified hazards. This involves an escalation of dosages of twice-daily low molecular weight heparin, based upon anti-Factor Xa levels.

Conclusion

Using the expansive NSQIP database, this study identifies multiple operations, emergency operations, and perioperative sepsis as independent risk factors for VTE, confirming prior institutional findings. These factors are not currently captured in common risk assessment models and represent subsets of patients with an elevated risk of VTE despite receiving standard prophylaxis regimens. Patients with any of these three risk factors, and especially with combinations of the factors, should be regarded as having a particularly increased risk of developing postoperative thromboembolic complications.

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Declaration of competing interest

The authors have no conflicts of interest to disclose.

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