Invited Commentary

Are We Really Supposed to Start Giving Venous Thromboembolism Prophylaxis for a Month After Outpatient Surgery?

Ira L. Leeds, MD, MBA, ScM; Elliott R. Haut, MD, PhD

Venous thromboembolism (VTE) remains a significant cause of postoperative morbidity, and inpatient postoperative VTE prophylaxis remains standard of care.[1] For select procedures, there is a well-recognized risk of VTE that extends beyond hospital discharge,[2] and numerous guidelines support extended prophylaxis for 4-6 weeks following discharge for high-risk surgical subgroups.[1,3]

In this issue, Caron and colleagues[4] report on the late diagnosis of VTE after surgical procedures in France's national administrative claims database. This large population-based retrospective case-control study has two dramatic findings: (1) the increased VTE risk following surgery extended to as long as six months for some procedures and (2) prolonged VTE risk is elevated in patients undergoing less complex surgery often done in an outpatient setting. These unique findings regarding the breadth and duration of VTE risk are underrecognized and should be addressed by evolving VTE prophylaxis recommendations.

Related article

The authors overcame many common limitations of administrative databases[5] because French claims data have longitudinal linkage for follow-up combined with the sophisticated case-crossover study design. Unlike other commonly used sources such as the US Health Care Utilization Project's National Inpatient Sample, the French data allow any VTE event to be linked to a prior surgical encounter. It also captures all initial surgical procedures and all subsequent emergency department visits and readmissions that occurred in any public or private French health care facility. These features substantially address the limitations that have hampered prior studies asking similar questions. We are jealous of the robust longitudinal data and suggest other databases expand upon their existing capabilities.

The findings of Caron et al[4] must be considered in light of 2 limitations. First, a plurality of surgical cases included were minor procedures (eg, endoscopic polypectomies and vein stripping). If VTE is commonly associated with minor procedures, should we use prophylaxis even more broadly? While the authors' concerns for statistical power are understandable, their decision to include these patients may limit generalizability. Second, it is difficult to interpret the absolute risk difference for VTE (as opposed to a relative increase). Postoperative VTE events occurring after discharge in large series are less than 1% for normal risk patients.[2] Efforts to reduce VTE in low prevalence populations may increase bleeding risk and may not provide an overall societal health benefit.[6] With a known low prevalence of VTE, are the absolute risk reductions clinically significant beyond their statistical significance?[7]

Outpatient VTE events continue to be a vexing and potentially preventable complication after surgery. Caron and colleagues[4] have reaffirmed that this risk continues longer and for a broader range of procedures than those typically deemed high risk. Existing guidelines may need to further consider the potential scope, target patient population, and duration of extended prophylaxis.

ARTICLE INFORMATION

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JAMA Surgery | Original Investigation

Risk of Pulmonary Embolism More Than 6 Weeks After Surgery Among Cancer-Free Middle-aged Patients

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IMPORTANCE The risk of postoperative pulmonary embolism has been reported to be highest during the first 5 weeks after surgery. However, how long the excess risk of postoperative pulmonary embolism persists remains unknown.

OBJECTIVE To assess the duration and magnitude of the late postoperative risk of pulmonary embolism among cancer-free middle-aged patients by the type of surgery.

DESIGN, SETTING, AND PARTICIPANTS Case-crossover analysis to compute the respective risks of pulmonary embolism after 6 types of surgery using data from a French national inpatient database, which covers a total of 203 million inpatient stays over an 8-year period between 2007 and 2014. Participants were cancer-free middle-aged adult patients (aged 45 to 64) with a diagnosis of a first pulmonary embolism.

EXPOSURES Hospital admission for surgery. Surgical procedures were classified into 6 types: (1) vascular surgery, (2) gynecological surgery, (3) gastrointestinal surgery, (4) hip or knee replacement, (5) fractures, and (6) other orthopedic operations.

MAIN OUTCOMES AND MEASURES Diagnosis of a first pulmonary embolism.

RESULTS A total of 60 703 patients were included (35 766 [58.9%] male; mean [SD] age, 56.6 [6.0] years). The risk of postoperative pulmonary embolism was elevated for at least 12 weeks after all types of surgery and was highest during the immediate postoperative period (1 to 6 weeks). The excess risk of postoperative pulmonary embolism ranged from odds ratio (OR), 5.24 (95% CI, 3.91-7.01) for vascular surgery to OR, 8.34 (95% CI, 6.07-11.45) for surgery for fractures. The risk remained elevated from 7 to 12 weeks, with the OR ranging from 2.26 (95% CI, 1.81-2.82) for gastrointestinal operations to 4.23 (95% CI, 3.01-5.92) for surgery for fractures. The risk was not clinically significant beyond 18 weeks postsurgery for all types of procedures.

CONCLUSIONS AND RELEVANCE The risk of postoperative pulmonary embolism is elevated beyond 6 weeks postsurgery regardless of the type of procedure. The persistence of this excess risk suggests that further randomized clinical trials are required to evaluate whether the duration of postoperative prophylactic anticoagulation should be extended and to define the optimal duration of treatment with regard to both the thrombotic and bleeding risks.

Invited Commentary

Supplemental content

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Venous thromboembolism (VTE) is associated with considerable clinical and economic burden. The annual incidence is estimated to range from 1 to 1.8 per 1000, and pulmonary embolism (PE) remains the most common preventable cause of in-hospital death.[1,2] The health care costs associated with PE are estimated to be more than $1.5 billion each year in the United States alone.[3]

Surgery is defined as a major transient risk factor of VTE, and almost 25% of all cases can be attributed to a recent surgery.[4] For more than 25 years, evidence-based guidelines worldwide have recommended active strategies for preventing VTE in at-risk patients undergoing surgery.[5] The implementation of these guidelines is facilitated by quality improvement strategies (eg, the Agency for Healthcare Research and Quality prevention guide).[6] The risk of postoperative PE is highest during the first 5 weeks postsurgery and is associated with the type of surgery.[7-9] Current international guidelines recommend prophylactic anticoagulation treatment for up to 5 weeks postsurgery.[7,10]

Although the risk of thrombosis has been studied for a limited number of very high-risk surgical procedures, it is not clear how long the excess risk of thrombosis persists after the 5-week postoperative period. Most randomized clinical trials have a short follow-up period and low statistical power for the assessment of adverse events.[11] Results of population-based studies in some contexts (eg, hip or knee replacement) have provided conflicting evidence.[9,12] At present, we lack large studies of the duration of the excess risk of PE, particularly beyond 6 weeks, for all types of surgery. Hence, the objective of the present study was to assess the duration and the magnitude of the late postoperative risk of PE among cancer-free middle-aged patients by the type of surgery.

Key Points

Question What is the duration and the magnitude of the late postoperative risk of pulmonary embolism among cancer-free middle-aged patients by the type of surgery?

Findings In this case-crossover analysis of 60 703 patients aged 45 to 64 years without cancer from the French national inpatient database, the postoperative risk of pulmonary embolism extended beyond 6 weeks for 6 types of surgery. The excess risk of postoperative pulmonary embolism remained significantly elevated between 7 and 12 weeks after surgery.

Meaning Further randomized clinical trials are required to evaluate whether the duration of postoperative prophylactic anticoagulation should be extended and to define its optimal duration.

Methods

Setting and Study Design

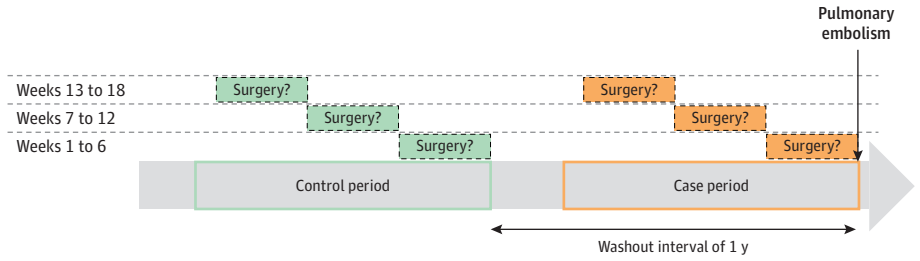
In this retrospective case-crossover study, we performed an analysis of data from the French national inpatient database (Programme de Médicalisation des Systèmes d'Information [PMSI]). This medical and administrative database contains information on 203 million inpatient stays in French public and private-sector hospitals over an 8-year period (from January 1, 2007, to December 31, 2014). The database is described in detail in the eMethods in the Supplement. Risk was computed in a case-crossover analysis, a study design in which the patient (the case) serves as his or her own control. We compared the likelihood of surgery during the period preceding the outcome of interest (PE) with the likelihood during the same period exactly 1 year earlier (**Figure 1**). This design is appropriate when a brief exposure (such as a surgical procedure) causes a transient rise in the risk of an outcome. Hence, all unmeasured time-constant confounding factors (sex, age, and lifestyle pattern) are controlled for by this study design.[13] We restricted our analysis to a population of middle-aged adults aged 45 to 64 because the higher probability of death in older patients prevented us from applying a case-crossover design.

According to French legislation, retrospective registry-based studies do not require approval by an independent ethics committee. The data were structured so that individual patients could not be identified by name. The study database was registered with the French national data protection commission (Commission Nationale de l'Informatique et des Libertés; registration number 1754053). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for case-control studies and its Reporting of Studies Conducted Using Observational Routinely-collected Health Data (RECORD) extension.

Eligibility Criteria

The participants were cancer-free middle-aged adults (aged from 45 to 64) admitted to the emergency department or hospital for PE between January 1, 2009, and December 31, 2014.

Figure 1. Schematic Representation of the Case-Crossover Design



The likelihood of surgery during the case period immediately preceding the onset of pulmonary embolism (in orange) is compared with the likelihood during the control period exactly 1 year earlier (in green). Case and control periods are divided into 6-week (42-day) intervals. Each interval in the case period is compared with the corresponding interval in the control period.

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For patients having experienced 2 or more PEs, we considered the first stay only and discarded any subsequent admissions. The date of diagnosis allowed us to define the case period immediately preceding the onset of PE. The corresponding control period ended 12 months before the date of diagnosis. The year between the control and case periods was considered as a washout interval (ie, far from the occurrence of the event), ensuring that the patient's risk has returned to baseline. Data were available from January 1, 2007. We therefore included patients hospitalized for PE from January 1, 2009, onward, to allow analyses of both the case and the control periods. By definition, each included patient had a period free of the outcome of at least 2 years during which any hospital admissions were recorded. This period could therefore be searched for noninclusion and exclusion criteria.

We excluded patients with a history of thrombosis, myocardial infarction,[14] and ischemic stroke according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* (eTable 1 in the Supplement).[15] We also excluded patients with a history of cancer (as defined in the French National Cancer Institute guidelines; the full algorithm and the corresponding *ICD-10* diagnostic codes are available at http://www.e-cancer.fr) because the risk of VTE remains elevated in this population. Under these circumstances, the case-crossover design would have been unsuitable because the supposedly transient risk would not have returned to baseline. Unless specified otherwise, the term surgery refers here to noncancer surgery.

Study Outcomes and Measurements

The primary outcome was the diagnosis of PE in an emergency department or elsewhere in hospital. The PMSI database includes data on any hospitalization (ie, a conventional inpatient stay) and any visit to an emergency department with computed tomographic angiography or ventilation-perfusion scintigraphy (considered as a short inpatient stay) even if the visit to an emergency department is followed by treatment in an outpatient setting. Furthermore, a valid application of the case-crossover design assumes that the outcome is not serious enough to irreversibly alter the course of the patient's life.[16] We therefore used PE (all *ICD-10* codes prefixed with I26) as a marker of VTE. Furthermore, deep vein thrombosis (DVT) is routinely treated in an outpatient setting and therefore is not recorded in the PMSI database. In addition, algorithms using the *ICD-10* codes prefixed with I80 to identify inpatient stays with DVT underperform markedly (sensitivity of 58% [95% CI, 51.9%-64.1%] for DVT vs 88.9% [95% CI, 85.6%-92.2%] for PE).[17] Although unavailable in the French setting, the positive predictive value was also higher for PE as shown in a Danish registry (positive predictive value of 82.1% [95% CI, 77.2%-86.4%]).[18]

The operations were categorized using the Sweetland et al[9] classification. Inpatient stays with surgery were identified by their French national procedure-grouping code or codes (according to the Classification Commune des Actes Médicaux [CCAM]). When combined with a topographic classification (such as the Office of Population Censuses and Surveys classification of surgical operations and procedures, fourth revision used by Sweetland et al[9]), these CCAM codes enable the immediate identification of inpatient stays with surgery. Stays were therefore classified as comprising orthopedic surgery, vascular surgery, gynecological surgery, or gastrointestinal surgery. In line with Sweetland et al,[9] we divided orthopedic operations into hip or knee replacements, surgery for fractures, and other orthopedic operations. The CCAM procedure codes used to search for stays with exposure to surgery are listed in the eTable 2 in the Supplement. Each of these exposures to surgery was analyzed in a separate case-crossover analysis.

Statistical Analysis

The case-crossover analysis was performed using R software, version 3.4.2 (R Project for Statistical Computing) and the analytical tool package IT-CARES.[19] This package was designed to allow population-based analysis of large databases of electronic medical records using a self-controlled method, as recommended by the Observational Medical Outcomes Partnership (OMOP).[20] We split the case period and the control period into 6-week (42-day) intervals corresponding to the duration of postoperative prophylactic anticoagulation recommended in most countries.[7,8,10] This approach allowed us to use the second 6-week interval as an indicator of the persistence of the PE risk beyond the recommended duration of prophylaxis. A paired-matched interval approach was used as described by Mittleman et al.[21] Conditional logistic regression was used to compare the likelihood of surgery during each interval of the case period with the likelihood during the corresponding control interval. If multiple surgical procedures had been performed within a single period, we only considered the last one. An odds ratio (OR) and its 95% CI were computed for each 6-week interval. The OR reflects the risk of onset of the primary outcome relative to the baseline risk (ie, in the absence of exposure to hospitalization with surgery). In a crossover design, patients are expected to survive. We checked this assumption by calculating the proportion of patients with PE who died in hospital.

Results

Patient Population

Between January 1, 2007, and December 31, 2014, more than 2 million inpatient stays were identified in the PMSI. After application of inclusion and exclusion criteria, 60 703 eligible patients with a diagnosis of PE were included in the analysis (mean [SD] age, 56.6 [6.0] years). The male to female ratio for PE was close to 3:2 (35 766 men and 24 937 women). The study flow diagram (**Figure 2**) summarizes the patient selection process.

Early Risk of Postoperative PE

The risk of PE for each type of surgery and within each time interval is represented in **Figure 3** along with the corresponding OR (95% CI). The risk of PE was elevated during the first 6 weeks after surgery regardless of the type. The excess risk of postoperative PE ranged from OR, 5.24 (95% CI, 3.91-7.01) for vascular surgery to OR, 8.34 (95% CI, 6.07-11.45) for surgery

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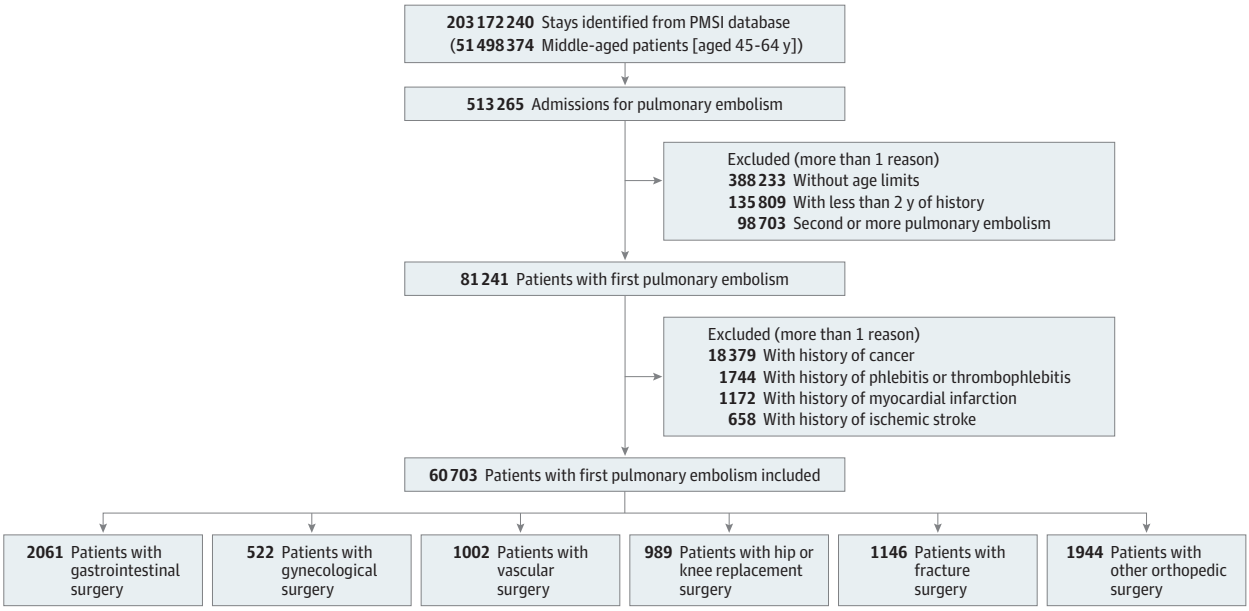
Figure 2. Patient Selection Flow Diagram



PMSI indicates Programme de Médicalisation des Systèmes d'Information.

for fractures. The second-highest risk of early postoperative PE was observed after gynecological surgery, with an estimated OR of 8.17 (95% CI, 5.19-12.86). The most frequent procedures recorded during exposure stays leading to postoperative PE in the case-crossover analysis are hysterectomy or trachelectomy (n = 163 cases; n = 91 controls, gynecology), gastrointestinal tract biopsy (n = 399 cases; n = 205 controls, gastroenterology), saphenous vein stripping (n = 160 cases; n = 87 controls, vascular surgery), lower leg osteosynthesis (n = 199 cases; n = 90 controls, surgery for fractures), and shoulder joint, arthroscopic surgery (n = 166 cases; n = 91 controls, other orthopedic operations) (eTable 3 in the Supplement).

Late Risk of Postoperative PE

The excess risk of postoperative PE remained elevated beyond the first 6 weeks for all types of surgery. The highest risk of late postoperative PE was observed for surgery for fractures, with an OR of 4.23 (95% CI, 3.01-5.92) between postoperative weeks 7 and 12 and an OR of 2.39 (95% CI, 1.65-3.46) between postoperative weeks 13 to 18. The risks of late postoperative PE were lower after orthopedic surgery not related to fractures: between postoperative weeks 7 to 12, the OR was 3.64 (95% CI, 2.66-4.99) after hip or knee replacement and 2.82 (95% CI, 2.20-3.61) after other orthopedic operations. The lowest risks of late postoperative PE between postoperative weeks 7 to 12 were observed after gastrointestinal (OR, 2.26; 95% CI, 1.81-2.82) and gynecological operations (OR, 2.29; 95% CI, 1.39-3.75). The very late excess risk of PE corresponded to an OR>2 up until 18 weeks postsurgery for fractures (OR, 2.39; 95% CI, 1.65-3.46), hip or knee replacement (OR, 2.26; 95% CI, 1.53-3.35), and vascular surgery (OR, 2.64; 95% CI, 1.80-3.89). The risk of postoperative PE was not clinically significant beyond 18 weeks postsurgery for all types of procedures. Last, as required by the crossover design, the proportion of patients with PE who died in hospital was low (4.7%).

Discussion

Using a French national medical and administrative database, we assessed the duration and magnitude of the late postoperative risk of PE among cancer-free middle-aged patients as a function of the type of surgery. The early postoperative risk of PE (from postoperative weeks 1 to 6) was elevated for all types of surgery; the highest risks were observed for gynecological surgery and surgery for fractures. The excess risk of postoperative PE remained significantly elevated between 6 and 12 weeks after surgery.

Venous thromboembolism accounts for more than 100 000 deaths per year in the United States.[22] The current guidelines recommend mechanical prophylaxis, early mobilization, and hydration after all types of surgical procedures.[7,8,10] According to these guidelines, the optimal duration of postoperative prophylactic anticoagulation ranges from 1 to 2 weeks depending on the type of surgery. The extension of prophylaxis for up to 5 weeks is recommended after a major orthopedic procedure[23-25] and after major abdominal or pelvic surgery.[26,27] To our knowledge, the persistence of excess risk (especially in the late postoperative period) has not been extensively investigated for most types of surgery. The persistence of excess risk occurs mainly because randomized clinical trials may be considered too short.[11] However, the availability of substantial amounts of medical data over long periods and the use of appropriate pharmacoepidemiologic analysis methods offer opportunities for investigating long-term risks or events.

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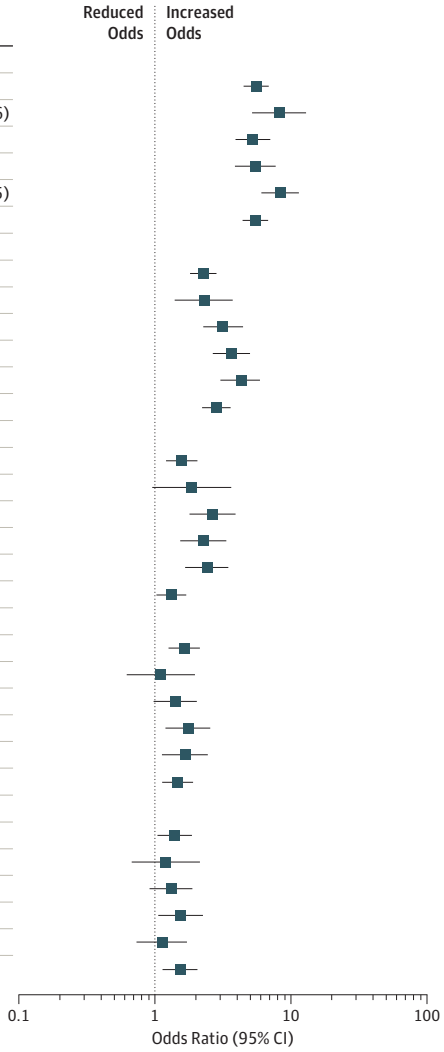
Figure 3. Risk of Pulmonary Embolism as a Function of the Time Since Surgery

Surgical Category	Cases, No.	Odds Ratio (95% CI)
Weeks 1-6		
Gastrointestinal	535	5.51 (4.45-6.82)
Gynecological	169	8.17 (5.19-12.86)
Vascular	275	5.24 (3.91-7.01)
Hip or knee replacement	207	5.44 (3.86-7.66)
Fracture	353	8.34 (6.07-11.45)
Other orthopedic	522	5.46 (4.40-6.78)
Weeks 7-12		
Gastrointestinal	254	2.26 (1.81-2.82)
Gynecological	51	2.29 (1.39-3.75)
Vascular	136	3.15 (2.25-4.41)
Hip or knee replacement	176	3.64 (2.66-4.99)
Fracture	173	4.23 (3.01-5.92)
Other orthopedic	235	2.82 (2.20-3.61)
Weeks 13-18		
Gastrointestinal	137	1.57 (1.20-2.04)
Gynecological	24	1.86 (0.96-3.61)
Vascular	91	2.64 (1.80-3.89)
Hip or knee replacement	81	2.26 (1.53-3.35)
Fracture	94	2.39 (1.65-3.46)
Other orthopedic	139	1.31 (1.02-1.69)
Weeks 19-25		
Gastrointestinal	142	1.63 (1.25-2.13)
Gynecological	24	1.10 (0.62-1.96)
Vascular	67	1.41 (0.97-2.03)
Hip or knee replacement	72	1.75 (1.20-2.55)
Fracture	66	1.66 (1.12-2.45)
Other orthopedic	138	1.47 (1.13-1.91)
Weeks 26-32		
Gastrointestinal	109	1.39 (1.04-1.86)
Gynecological	25	1.20 (0.67-2.14)
Vascular	67	1.31 (0.91-1.89)
Hip or knee replacement	67	1.54 (1.05-2.25)
Fracture	45	1.12 (0.73-1.72)
Other orthopedic	111	1.52 (1.14-2.04)



The population-based study by Sweetland et al[9] of middle-aged women in the United Kingdom found that the risk of VTE was highest in the 6 weeks following surgery, with a relative risk of 69.1 (95% CI, 63.1-75.6) and a peak at postoperative week 3.[9] The researchers observed large differences in the postoperative thromboembolic risk between types of surgery, and the risks reported were higher than in the present study. In a UK prospective cohort study (including all newly diagnosed cases of VTE in the General Practice Research Database), Huerta et al[28] also reported an elevated risk of VTE during the first 6 months after surgery (OR, 9.39; 95% CI, 8.02-10.99). In a population-based study focusing on total hip and total knee replacements in a Danish nationwide cohort of adult patients, Lalmohamed et al[12] reported that the risk of VTE remained substantially elevated for at least 4 months; the reported ORs were consistent with ours, which raises the question of whether it would be beneficial to extend prophylactic measures beyond the currently recommended time limit.

The benefits of prophylaxis must always be balanced against the associated risk of bleeding. Comparative studies of major bleeding events and clinically relevant nonmajor bleeding events have not found differences between treatment regimens after major orthopedic surgery.[29] However, the bleeding risk observed in randomized clinical trials (absolute numbers of bleeding events and thromboses) is clinically significant.[30] Most of the clinically relevant bleedings were not life threatening; the fact that bleeding was not life threatening contrasts with the potentially fatal outcome of PE. These results highlight the need to evaluate the risk-benefit ratio of extending the duration of pharmacological prophylaxis in high-risk patients.

The Crossover Design

The OMOP evaluation of study designs for analyses of medical administrative databases showed that a crossover design provides the highest level of evidence for our kind of study.[20] This design's good level of performance can be attributable to good control of time-constant confounding factors, which is a major challenge for many observational methods. Using a case as his or her own control also avoids complex case-control matching. Use of the

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case-crossover design involves considering a patient twice (ie, during the case period and during the control period); we therefore decided to include only middle-aged patients and thus limit the risk of death among the study participants. Nevertheless, our choice of design led us to exclude patients with a history of cancer. Cancer is a well-known risk factor that alone may justify thromboprophylaxis.[31,32] After cancer surgery, the risk remains elevated for up to 12 months, which prevents one from comparing case and control periods.[9,33] The persistence of the risk is true for major abdominal or pelvic surgery and especially for cancer, when extended-duration thromboprophylaxis is recommended.[33,34] The relatively low late risk observed for gastrointestinal surgery in our study might be owing to this limitation.

Limitations

The present study has limitations. First, we studied a broad range of surgical procedures, which limited the precision of our conclusions because major surgery was mixed with minor procedures (such as biopsies). However, PE is infrequent in patients having undergone low-risk surgical procedures. Furthermore, and despite the large size of our database, the use of broad categories may be required to achieve sufficient statistical power. Second, the risks computed during the first 6-week interval were modified by the systematic administration of postoperative prophylactic anticoagulation in accordance with the current guidelines.[7,8,10] Thus, our analysis reflects the real-life risks (relative to the baseline) and accounts for cases of PE prevented by postoperative prophylactic anticoagulation. Conversely, associations computed for the second and subsequent 6-week intervals are less likely to be limited in this way. Third, the analysis of the PMSI administrative database raises issues similar to those detailed by Stulberg and Haut[35] for the US Agency for Healthcare Research and Quality Nationwide Inpatient Sample data. One of these issues is the quality of the data. Casez et al[17] reported that diagnostic codes for PE displayed high metrological quality. Moreover, patients with massive PE who died before reaching the emergency department were not detected and thus not included in our study. We might also miss low-risk patients for whom computed tomographic angiography or ventilation-perfusion scintigraphy have been performed before a visit to the emergency department and who are then treated in an outpatient setting; however, the management procedure for PE in France means that this scenario was very unlikely during the study period. Fourth, our study database did not specify the drugs administered during the stay. Even though we estimated the population-based risk of PE, we cannot distinguish between the risk associated with the surgery per se and the risk associated with other components of current practice (the drugs administered and other risk exposure during the stay). Last, our analysis used PE as a proxy for VTE, raising the question as to whether our findings can be generalized (eg, to DVT). The literature data on whether DVT and PE are significantly associated are contradictory.[36]

Conclusions

In this case-crossover study, the postoperative risk of PE was found to be elevated for at least 12 weeks after all types of surgery. Although the risk (relative to baseline) between postoperative weeks 6 and 12 is markedly lower than that in the immediate postoperative period (from 1 to 6 weeks), it is still nonnegligible, with the highest risk for orthopedic and vascular surgery. The present study appears to generate important new knowledge about the very late excess risk of PE, which to our knowledge had not been well documented previously. Although prophylactic anticoagulation is prescribed for up to 5 weeks after surgery in routine clinical practice, physicians typically ask patients about any history of surgery in the 3 months preceding the thrombotic event. Our findings raise the question as to whether the duration of prophylactic anticoagulation could be extended. Further randomized clinical trials may thus be recommended to evaluate the benefit-to-risk ratio of this strategy and define the optimal duration of treatment with regard to both the thrombotic and bleeding risks.

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Concept and design: Caron, Chazard, Ficheur.
Acquisition, analysis, or interpretation of data: Caron, Depas, Yelnik, Jeanpierre, Paris, Beuscart, Ficheur.
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