Regular Article

Venous thromboembolism prophylaxis in patients undergoing abdominal or pelvic surgery for cancer – A real-world, prospective, observational French study: PRéOBS[☆],[☆☆],[★]

Charles-Marc Samama [a],[*], Léon Boubli [b], Patrick Coloby [c], Philippe Debourdeau [d], Yves Gruel [e], Christophe Mariette [f], Dominique Mottier [g], Pascal Rischmann [h], Laurent Toubiana [i], Annick Steib [j]

[a] Service d'Anesthésie-Réanimation, CHU Cochin; Assistance-Publique - Hôpitaux de Paris; Université Paris Descartes, Paris, France
[b] Service de Gynécologie-Obstétrique, CHU Nord, Marseille, France
[c] Service d'Urologie, CH René Dubos, Pontoise, France
[d] Service d'Hématologie, HIA Desgenettes, Lyon, France
[e] Service d'Hématologie, CHU Trousseau, Chambray-les-Tours, France
[f] Service de Chirurgie Digestive, CHU Claude Huriez, Lille, France
[g] Service de Médecine Interne, CHU La Cavale Blanche, Brest, France
[h] Service d'Urologie, CHU Rangueil, Toulouse, France
[i] INSERM, EA 4067, CHU Necker, Paris, France
[j] Service d'Anesthésie-Réanimation, Hôpital civil, Strasbourg, France

ARTICLE INFO

ABSTRACT

Introduction: Data on the epidemiology and prevention of venous thromboembolism in patients undergoing abdominal or pelvic cancer surgery in real practice are limited. The primary objective of this observational study was to describe the thromboprophylactic strategy implemented in routine practice. The main secondary objective was to assess the incidence of outcomes.

Materials and Methods: Patients admitted to public or private hospitals for abdominal or pelvic cancer surgery were included between November 2009 and November 2010; endoscopic route for surgery was the only exclusion criterion. Study outcomes were recorded at hospital discharge and at routine follow-up (generally 9 ± 3 weeks).

Results: 2380 patients (mean $\pm$ SD age: 66.4 ± 11.6 years, women: 36.8%) admitted to hospital for abdominal (47.8%), urological (41%), or gynaecological (11.2%) cancer surgery were included in the analysis. Of these, 2179 had data available at study end. Perioperative antithrombotic prophylaxis, consisting mainly of low-molecular-weight heparin, was given to 99.5% of patients. At hospital discharge, thromboprophylaxis was continued in 91.7% of patients, 57.4% receiving a 4-6 week prophylaxis. This management strategy was associated with an overall venous thromboembolic event rate of 1.9%, 34.7% of events occurring after discharge. Incidences of fatal bleeding, bleeding in a critical organ and bleeding necessitating re-intervention were 0.1%, 0.3% and 1.7%, respectively. Overall mortality was 1.5%.

Conclusions: Thromboprophylaxis is routinely used in French patients undergoing major cancer surgery. For more than a third of patients, however, treatment duration did not comply with best-practice recommendations, which might explain the non-negligible rate of thromboembolic complications still observed in this patient population.

© 2013 Elsevier Ltd. All rights reserved.

Introduction

Venous thromboembolism, a serious healthcare problem resulting in significant mortality, morbidity, and resource expenditure, is a common complication of general surgery procedures, with surgery for cancer carrying a particularly high risk [1–4]. The risk of venous thromboembolism varies according to cancer type and extent, but is especially high following abdominal or pelvic cancer surgery, with a reported overall risk without prophylaxis of up to 45%, including objectively detected deep-vein thrombosis [3].

The efficacy of in-hospital heparin prophylaxis in preventing venous thromboembolic complications in patients undergoing general surgery is well documented [5,6] and its routine use in these patients is strongly recommended [1–4]. An Italian survey showed that these recommendations are implemented in routine practice, pharmacological prophylaxis being used by 93.1% of 146 surgical centres [7]. Moreover, several randomised clinical studies have demonstrated the clinical benefit of extending low-molecular-weight heparin prophylaxis for 4 weeks after surgery *versus* in-hospital prophylaxis alone (typically 1 week), in terms of reducing the incidence of thromboembolic events, without jeopardising safety [8–14], especially in patients undergoing general surgery for cancer. These findings are reflected in both current national and international guidelines [1–4] which suggest that all patients undergoing major surgical intervention for cancer should be considered for extended thromboprophylaxis after hospital discharge, for up to one month. Limited data, however, are available on whether these recommendations have led to real changes in the management of cancer surgery patients in routine clinical practice, and if so, whether these changes have modified the epidemiology of postoperative thromboembolic complications.

We therefore conducted a prospective observational study on a cohort of consecutive French patients undergoing elective abdominal or pelvic surgery for cancer. Our primary objective was to assess, in a contemporary real-world practice setting, the therapeutic strategy currently used to prevent venous thromboembolism in these patients.

Materials and Methods

The PRéOBS (PRévention des événements thrOmbo-emBoliqueS veineux dans le cadre d'une intervention chirurgicale pour un cancer abdomino-pelvien) study was a national, multicentre, observational, prospective study of a cohort of consecutive patients undergoing abdominal or pelvic cancer surgery in France.

Patients

All consecutive patients at least 18 years old admitted to public or private hospitals for major cancer surgery, i.e. abdominal, urological or gynaecological surgery, were considered for inclusion in the study. Use of the endoscopic route for cancer surgery was the only exclusion criterion.

Before inclusion, all participating patients were informed of the study aims and procedures and provided consent. All medical and surgical procedures were performed by each centre according to its usual practice. As this prospective study had no impact on everyday clinical practice, no ethical review board approval was requested. However, the study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, as well as local regulations, in particular regarding data protection: The protocol and case report form were reviewed by the French "Commission Nationale de l'Informatique et des Libertés" before the start of the study.

Data Collection

Demographic, medical, and treatment data of patients were recorded using electronic case report forms, with data transmission by internet connection, at baseline, at hospital discharge, and at the routine follow-up visit (9 ± 3 weeks after surgery). All participating patients were instructed to contact the local investigator immediately in the event of any symptoms or signs, particularly those suggestive of venous thromboembolism or bleeding. Overall patient management, including thromboprophylaxis, was left to the investigator's discretion.

Study Objectives

The primary objective of the study was to describe the management strategy implemented to prevent venous thromboembolism in the study population, both overall and according to the type of surgery, i.e. abdominal, urological or gynaecological.

The secondary objectives were to 1) assess the incidences of venous thromboembolism (deep-vein thrombosis and/or pulmonary embolism), bleeding and death from any cause, 2) identify the proportion of patients receiving appropriate venous thromboembolism prophylaxis, according to the French recommendations in force at the time the study was conducted [3], and 3) evaluate potential predictive risk factors for venous thromboembolism.

During the hospitalisation period, deep-vein thrombosis was clinically suspected and confirmed by duplex ultrasounds or diagnosed by systematic duplex ultrasounds. Pulmonary embolism was clinically suspected and confirmed by scintigraphy, spiral computed tomography, or pulmonary angiography. After hospital discharge, deep-vein thrombosis and pulmonary embolism were clinically suspected and/or confirmed by the same techniques.

The following bleeding complications were recorded: fatal bleeding, bleeding at the surgical site leading to re-operation, bleeding in a critical organ (retroperitoneal, intraocular or intracranial, pericardial or into the adrenal glands) and bleeding leading to transfusion of at least two units of packed red blood cells or whole blood or to a haemoglobin decrease >2 g/dL compared with baseline values.

As part of the data quality control regarding the main study events, the case report forms of all patients experiencing venous thromboembolism, bleeding events or death were reviewed by an independent central committee to check for consistency. This committee could request that the investigator be contacted for data clarification.

Statistical Analysis

Assuming a 10% to 50% frequency of use of different treatment strategies, and estimating that data from approximately 10% of patients would not be analysable, it was calculated that a sample size of 3000 patients would allow description of each strategy with a precision of 1.1 to 1.9% at the national level. With 2380 patients analyzed, the precision is 0.5 to 2.0%, which in our view remains acceptable compared with what was planned initially.

Data were presented according to the usual descriptive methods. Quantitative variables were presented as the number of cases, mean (± standard deviation) and median (range) where appropriate. Qualitative variables were presented as the number of cases and percentages, with 95% confidence intervals where appropriate.

Univariate analyses for identification of risk factors for venous thromboembolic events at the end of follow-up were performed using Kaplan-Meier estimates and the Log-Rank test. Data from patients lost to follow-up were censored at the time of the last contact. A multivariate stepwise Cox's semi-parametric proportional hazards model was built to identify variables independently associated with venous thromboembolism at the end of the follow-up period. We included as variables both well-known predictors for thromboembolic complications and variables that we considered important based on previous epidemiological studies and expert clinical opinion. A p-value ≤ 0.20 in the univariate analysis was required for a variable to be considered in the multivariate model. Factors with a p value ≤ 0.05 in the multivariate analysis were considered as independent explanatory factors.

Data were processed and analysed using SAS-WINDOWS™ software version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

All French public or private centres performing abdominal, urological or gynaecological surgery, corresponding to 13,858 surgeons

or anaesthesiologists, were contacted and 524 of them agreed to participate in the study; the study was initiated in 388 centres, of which 242 included at least one patient.

Study Population

Between November 2009 and November 2010, 2519 patients were recruited in 242 centres in France. Among these, 139 patients were excluded from the analysis due to missing or inconsistent data at the hospital discharge visit. Of the remaining 2380 patients (94.5%), 20 died during hospitalisation, and for 181 no data were available at the end of follow-up, leaving 2179 patients (86.5%) for analysis at study end (Fig. 1). The mean ± SD duration of hospitalisation and follow-up were 13.0 ± 9.3 and 47.3 ± 24.4 days, respectively.

Baseline characteristics of the patients are shown in Table 1. The mean age was 66.4 years, 24.8% of patients being at least 75 years old (590/2380); there were fewer women (36.8%) than men. Almost half (47.8%) of the patients were admitted to hospital for abdominal (1138/2380), 41% for urological (976/2380) and 11.2% for gynaecological (266/2380) cancer surgery. Details of the surgical sites are provided in Appendix Table 1 available online. The majority of patients (70.1%) had a localised tumor at the time of surgery, 21.8% showed lymph node invasion and 13.3% had metastases (Table 1).

Surgical Treatment and Postoperative Management

Laparotomy was performed in 78.4% of cases (Table 2). For the majority (89.1%) of patients, operations were conducted under general anaesthesia only, with a mean ± SD surgery duration of 3.2 ± 1.5 hours.

During hospitalisation, pharmacological thromboprophylaxis, mainly with low-molecular-weight heparins (at the recommended doses according to their labelling in 86.3% (1969/2281) of patients), was initiated in the majority (99.5%) of patients (2367/2380), essentially at the postoperative stage (83.2%), on average 11.3 hours after surgery. During hospitalisation, two-thirds (68.3%) of the patients also received mechanical thromboprophylaxis, mainly consisting of elastic compression.

Similarly, at hospital discharge, pharmacological thromboprophylaxis, with low-molecular-weight heparins in 94.7% of cases (at the recommended doses according to their labelling in 88.2% (1767/2003)of patients), was prescribed for the majority (91.7%) of patients (2165/2360) (Table 3). The duration of treatment was between 4 and 6 weeks for 57.4% of patients. Mechanical thromboprophylaxis, essentially elastic compression stockings (99.3%), was prescribed for approximately a third (35.9%) of the patients. The percentage of patients considered by the investigator to have been compliant with the planned duration of thromboprophylaxis at hospital discharge was high (97.8% overall, i.e. 1897 of the 1940 patients for whom the information is available), regardless of the type of surgery (data not shown).
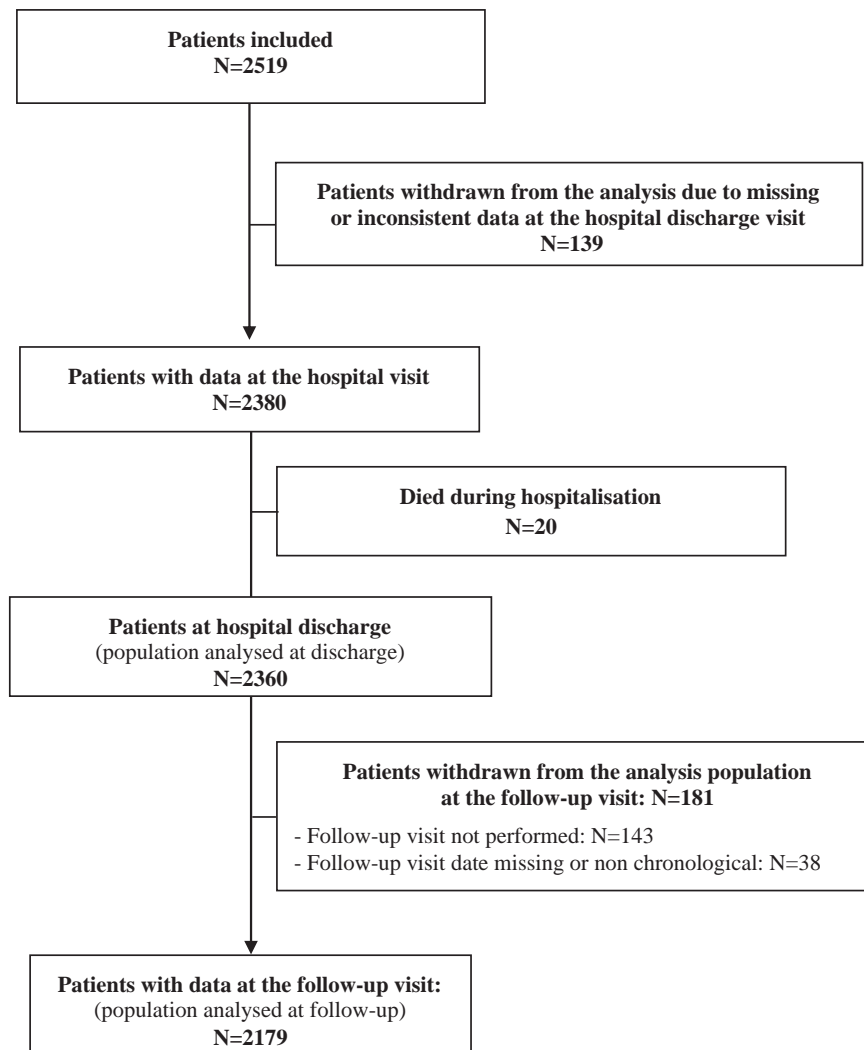

Fig. 1. Study flow diagram.

Table 1
Baseline characteristics of study patients*.

	Surgery			Total N = 2380
	Abdominal N = 1138	Urological N = 976	Gynaecological N = 266	
Age – yr	69.2 ± 12.3	64.2 ± 9.5	62.4 ± 12.5	66.4 ± 11.6
<**60**, no. (%)	232 (20.4)	256 (26.2)	100 (37.6)	588 (24.7)
[60-75[, no. (%)	473 (41.6)	610 (62.5)	119 (44.7)	1202 (50.5)
≥**75**, no. (%)	433 (38.0)	110 (11.3)	47 (17.7)	590 (24.8)
Female, no. (%)	483 (42.4)	127 (13.0)	266 (100.0)	876 (36.8)
Body weight – kg	72.5 ± 14.9	76.9 ± 12.4	69.0 ± 14.9	73.9 ± 14.2
Body mass index – kg/m^2†	25.8 ± 4.7	26.0 ± 3.8	26.0 ± 5.8	25.9 ± 4.5
≥30 kg/m^2, no. (%)	185 (16.3)	123 (12.6)	52 (19.5)	360 (15.1)
Creatinine clearance – mL/min‡				
≥60, no. (%)	762 (73.2)	735 (83.0)	142 (81.6)	1639 (78.0)
[30-60], no. (%)	255 (24.5)	138 (15.6)	30 (17.2)	423 (20.1)
<**30**, no. (%)	24 (2.3)	13 (1.5)	2 (1.1)	39 (1.9)
Thromboembolic risk factors, no. (%)				
History of venous thromboembolism	86 (7.6)	50 (5.1)	27 (10.2)	163 (6.8)
Reduced mobility/Bed rest	304 (26.7)	266 (27.3)	48 (18.0)	618 (26.0)
Smoking	148 (13.0)	226 (23.2)	34 (12.8)	408 (17.1)
Varicose veins	90 (7.9)	100 (10.2)	67 (25.2)	257 (10.8)
Central venous catheter	178 (15.6)	50 (5.1)	20 (7.5)	248 (10.4)
Heart failure	116 (10.2)	41 (4.2)	14 (5.3)	171 (7.2)
Respiratory failure	81 (7.1)	53 (5.4)	7 (2.6)	141 (5.9)
Cancer – other than abdominal or pelvic	80 (7.0)	45 (4.6)	14 (5.3)	139 (5.8)
ASA category ≥ 3, no. (%)§	321 (28.2)	116 (11.9)	26 (9.8)	463 (19.5)
Interval between cancer diagnosis and surgery,days	82.8 ± 242.2	84.0 ± 212.5	96.3 ± 275.3	84.8 ± 234.5
Cancer extension at surgery, no. (%)				
Lymph node invasion	345 (30.3)	80 (8.2)	95 (35.7)	520 (21.8)
Metastases	230 (20.2)	25 (2.6)	62 (23.3)	317 (13.3)
No extension	648 (56.9)	884 (90.6)	137 (51.5)	1669 (70.1)

* Plus-minus values are mean ± SD. †Missing data: urological surgery: n = 1.‡Creatinine clearance was calculated in 2101 patients at inclusion. §ASA: American Society of Anesthesiologists Physical Status scale.

Outcomes

Overall, 46 (1.9%) patients experienced at least one venous thromboembolic event during the study: 32 (1.3%) during hospitalisation and 17 (0.8%) during the follow-up period, with 3 patients presenting with a venous thromboembolic event both at hospitalisation and after hospital discharge (Table 4). The rate of venous thromboembolism was higher among patients undergoing gynaecological surgery than among patients undergoing abdominal or urological surgery. The overall incidence of pulmonary embolism was similar irrespective of the type of surgery.

In addition, 35 (1.5%) patients died during the study: 20 (0.8%) during hospitalisation and 15 (0.7%) during the follow-up period. The overall mortality rate was higher among patients undergoing abdominal surgery than among those undergoing urological or gynaecological surgery.

Finally, 47 (2.0%) of patients experienced a bleeding episode that was either fatal, in a critical organ, or that necessitated re-intervention. Details of the bleeding complications are provided in Table 4.

Risk Factors for Venous Thromboembolism

Appendix Table 2, available online, shows the results of the univariate analysis. On multivariate analysis (Fig. 2), the only significant (p < 0.05) predictors of venous thromboembolism were: a duration of antithrombotic treatment of <4 weeks (p < 0.0001), the presence of varicose veins (p = 0.0006) and the presence of bone metastases (p = 0.017), which increased the risk of venous thromboembolism by a factor of 7.9, 3.6 and 3.3, respectively.

Discussion

The main finding of this French prospective observational study evaluating the contemporary management strategy and epidemiology of venous thromboembolism in a large population of high-risk patients undergoing abdominal or pelvic surgery for cancer in a real-world practice setting, is that routine extended thromboprophylaxis with low-molecular-weight-heparin for up to 4-6 weeks was used in only 57.4% of patients, often in combination with mechanical thromboprophylaxis. This management strategy was associated with a 1.9% overall rate of venous thromboembolism, with 34.7% (17/46) of events occurring after hospital discharge.

The 1.3% (32/2380) rate of postoperative venous thromboembolism observed during hospitalisation in our study is in the higher range of the rates previously reported in patients undergoing abdominal surgery and receiving in-hospital low-molecular-weight heparin prophylaxis (0.2-1.4%) [15–19], confirming that patients undergoing abdominal or pelvic surgery for cancer are among those at highest risk of developing venous thromboembolism. This rate was higher than that observed in the ENOXACAN trial (0.7%) including similar patients [20], reflecting the fact that our study was a real-life study, with only one exclusion criterion, and was thus likely to include a population more fragile than that enrolled in randomised clinical trials. The 1.9% rate of venous thromboembolism observed in our study overall, i.e. during hospitalisation and the follow-up period, is consistent with the 2.1% rate of clinically overt venous thromboembolic events reported in @RISTOS [21], the only previous prospective observational study including a population similar to that of PRéOBS.

In agreement with previous cohort studies highlighting the persistence of the risk of venous thromboembolism long after general surgery [22–24], 34.7% of the thromboembolic events observed in our study occurred after hospital discharge, even though 57.4% of patients received prolonged pharmacological thromboprophylaxis, as recommended. This finding was in accordance with current guidelines recommending prolonged out-of-hospital prophylaxis for all patients undergoing major cancer surgery [1,2]. The high rate of late-occurring venous thromboembolic events still observed in our study might be explained by the failure to prescribe such extended prophylaxis in 38.4% of patients, rather than failure to use the appropriate dose, as the vast majority of our study population received the

Table 2
Surgery and treatments during hospitalisation.

	Surgery			Total N = 2380
	Abdominal N = 1138	Urological N = 976	Gynaecological N = 266	
Treatments before surgery, no. (%)				
Chemotherapy	189 (16.6)	18 (1.8)	59 (22.2)	266 (11.2)
Antiplatelet agents	192 (16.9)	135 (13.8)	22 (8.3)	349 (14.7)
Preoperative stop	136 (12.0)	111 (11.4)	17 (6.4)	264 (11.1)
Vitamin K antagonist	88 (7.7)	41 (4.2)	15 (5.6)	144 (6.1)
Preoperative stop	88 (7.7)	41 (4.2)	15 (5.6)	144 (6.1)
Type of anaesthesia, no. (%)				
General only	982 (86.3)	902 (92.4)	237 (89.1)	2121 (89.1)
Regional only	4 (0.4)	9 (0.9)	6 (2.3)	19 (0.8)
Both	152 (13.4)	65 (6.7)	23 (8.6)	240 (10.1)
Laparotomy, no. (%)	969 (85.1)	672 (68.9)	226 (85.0)	1867 (78.4)
Duration of surgery, h (mean ± SD)	3.2 ± 1.6	3.1 ± 1.3	3.0 ± 1.5	3.2 ± 1.5
Nonsteroidal antiinflammatory drugs after surgery, no. (%)	169 (14.9)	181 (18.5)	115 (43.2)	465 (19.5)
Duration of hospital stay, days*	15.7 ± 10.1	10.4 ± 7.1	10.9 ± 9.7	13.0 ± 9.3
Pharmacological thromboprophylaxis received				
during hospitalisation, no. (%)	1136 (99.8)	968 (99.2)	263 (98.9)	2367 (99.5)
Initiated postoperatively, no. (%)	906 (79.6)	830 (85.0)	233 (87.6)	1969 (83.2)
Time after intervention, mean ± SD†	11.8 ± 7.2	10.9 ± 6.6	11.1 ± 6.7	11.3 ± 6.9
Low-molecular-weight heparin, no. (%)	1066 (93.7)	940 (96.3)	259 (97.4)	2265 (95.2)
Unfractionated heparin, no. (%)	56 (4.9)	22 (2.3)	2 (0.8)	80 (3.4)
Fondaparinux, no. (%)	13 (1.1)	6 (0.6)	2 (0.8)	21 (0.9)
Vitamin K antagonist, no. (%)	0 (0)	0 (0)	0 (0)	0 (0)
Mechanical thromboprophylaxis received during hospitalisation, no. (%)	617 (54.2)	796 (81.6)	212 (79.7)	1625 (68.3)
Intermittent pneumatic compression, no. (%)	30 (2.6)	16 (1.6)	6 (2.3)	52 (2.2)
Elastic compression, no. (%)	600 (52.7)	783 (80.2)	207 (77.8)	1590 (66.8)

*Missing data: abdominal surgery: n = 18, urological surgery: n = 2, corresponding to patients who died during hospitalisation. †Missing data - abdominal surgery: n = 2.

dose of low-molecular-weight heparin recommended for high-risk situations according to each product's labelling. Similarly, in the @RISTOS study [21], in which only 23% of patients received an anti-thrombotic prophylaxis extending beyond 3 weeks after surgery, 40% of venous thromboembolic events were observed later than postoperative day 21. The importance of continuing prophylaxis for an appropriate duration is further emphasised by the results of our multivariate analysis, which identified a treatment duration of <4 weeks as being the main factor predictive of venous thromboembolism. The failure to meet best-practice recommendations for extended prophylaxis highlighted in PRéObS, and other real-world studies [21,25], may reflect insufficient assertiveness of the guidelines at the time these studies were performed [3,4]. The high rate of patients who were compliant with the prescribed extended prophylaxis observed in PRéOBS (97.8% overall) underscores the feasibility of prolonged prophylaxis in routine practice. Furthermore, a recent economic analysis has suggested that besides the clinical benefit, post-discharge prophylaxis is also cost-effective for cancer surgery patients [26].

One of the main fears of using extended routine prophylaxis in patients undergoing major surgery for cancer is the increased risk of bleeding complications, since malignancy and complex surgery are already in themselves risk factors for bleeding [27]. In our study, however, few cases of fatal bleeding, bleeding in a critical organ or bleeding necessitating re-intervention were observed overall. Notably, only a very limited number of bleeding events occurred after hospital discharge, confirming the findings of randomised clinical studies [8–11]. This low bleeding rate was observed despite the fragility of the population studied, as indicated by an overall death rate of 1.5%, comparable to the mortality rate of 1.7% observed in @RISTOS [21].

The predictive factors for the occurrence of a thromboembolic event identified by the multivariate analysis in this study were:

Table 3
Thromboprophylactic treatment prescribed at hospital discharge.

	Surgery			Total N = 2360
	Abdominal N = 1120	Urological N = 974	Gynaecological N = 266	
Pharmacological thromboprophylaxis, no. (%)	1021 (91.2)	919 (94.4)	225 (84.6)	2165 (91.7)
Low-molecular-weight heparin	946 (84.5)	886 (91.0)	219 (82.3)	2051 (86.9)
Unfractionated heparin	33 (2.9)	14 (1.4)	3 (1.1)	50 (2.1)
Fondaparinux	18 (1.6)	11 (1.1)	1 (0.4)	30 (1.3)
Vitamin K antagonist	20 (1.8)	7 (0.7)	2 (0.8)	29/2165 (1.3)
Planned duration of thromboprophylaxis, %*				
<4 weeks	353 (31.5)	428 (43.9)	126 (47.4)	907 (38.4)
[4–6] weeks	695 (62.1)	535 (54.9)	123 (46.2)	1353 (57.4)
> 6 weeks	71 (6.3)	11 (1.1)	17 (6.4)	99 (4.2)
Mechanical thromboprophylaxis, no. (%)	262 (23.4)	437 (44.9)	149 (56.0)	848 (35.9)
Intermittent pneumatic compression, no. (%)	1 (0.1)	2 (0.2)	3 (1.1)	6 (0.3)
Elastic compression stockings, no. (%)	261 (23.3)	435 (44.7)	146 (54.9)	842 (35.7)
Duration of follow-up, days (meanSD)†	42.8 ± 20.3	51.9 ± 25.9	49.5 ± 30.6	47.3 ± 24.4

* Planned duration of thromboprophylaxis: duration of thromboprophylaxis during hospitalisation plus duration of thromboprophylaxis prescribed at hospital discharge; missing data in the abdominal surgery group: n = 1.
† (Follow-up visit – discharge visit) +1.

Table 4
Clinical outcomes during the study.

	Surgery			Total
	Abdominal N = 1138	Urological N = 976	Gynaecological N = 266	N = 2380
Venous thromboembolism, no. (%)*	**26 (2.3)**	**12 (1.2)**	**8 (3.0)**	**46 (1.9)**
During hospitalisation	19	8	5	32
After hospital discharge	10	4	3	17
Deep-vein thrombosis, no. (%)	**19 (1.7)**	**7 (0.7)**	**8 (3.0)**	**34 (1.4)**
During hospitalisation†	12	5	5	22
Proximal DVT	*7*	*1*	*1*	*9*
Distal DVT	*7*	*4*	*4*	*15*
After hospital discharge	7	2	3	12
Proximal DVT	*3*	*1*	*3*	*7*
Distal DVT	*4*	*1*	*0*	*5*
Pulmonary embolism, no. (%)‡	**12 (1.1)**	**8 (0.8)**	**3 (1.1)**	**23 (1.0)**
During hospitalisation	11	5	3	19
After hospital discharge	3	3	0	6
Death, no. (%)	**29 (2.5)**	**5 (0.5)**	**1 (0.4)**	**35 (1.5)**
During hospitalisation	18	2	0	20
After hospital discharge	11	3	1	15
Fatal bleeding, no. (%)	**3 (0.3)**	**0 (0.0)**	**0 (0.0)**	**3 (0.1)**
During hospitalisation	2	0	0	2
After hospital discharge	1	0	0	1
Bleeding in a critical organ, no. (%)	**4 (0.4)**	**2 (0.2)**	**1 (0.4)**	**7 (0.3)**
During hospitalisation	4	1	1	6
After hospital discharge	0	1	0	1
Bleeding at surgical site, necessitating re-intervention, no. (%)	**16 (1.4)**	**19 (1.9)**	**5 (1.9)**	**40 (1.7)**
During hospitalisation	12	13	4	29
After hospital discharge	4	6	1	11
Bleeding leading to transfusion of ≥2 units of packed red blood cells or whole blood(%)	**61 (5.4)**	**69 (7.1)**	**30 (11.3)**	**160 (6.7)**
During surgery	24	34	20	78
During hospitalisation, postoperative§	36	33	11	80
After hospital discharge	4	5	0	9
Bleeding leading to a haemoglobin decrease >2 g/dL(%)	**84 (7.4)**	**152 (15.6)**	**43 (16.2)**	**279 (11.7)**
During surgery	30	97	29	156
During hospitalisation, postoperative¶	48	48	14	110
After hospital discharge	8	14	3	25

*Three patients experienced a venous thromboembolic event both during hospitalisation and after hospital discharge. †in 4 cases during hospitalisation (3 among patients undergoing abdominal surgery and 1 among patients undergoing urological surgery), deep-vein thrombosis was detected by systematic duplex ultrasonography. ‡None was fatal. Two patients presented with pulmonary embolism both during hospitalisation and after hospital discharge. §Six patients experienced bleeding which led to transfusion of ≥2 units of packed red blood cells or whole blood that started during surgery, three, two and one in the abdominal, urological and gynaecological surgery groups, respectively. ¶Six patients experienced bleeding which led to a haemoglobin decrease of >2 g/dL that started during surgery, one, three and two in the abdominal, urological and gynaecological surgery groups, respectively. A patient could experience more than one type of bleeding.

an antithrombotic treatment of <4 weeks, as discussed previously, the presence of varicose veins and the presence of bone metastases, which increased the risk of venous thromboembolism by a factor of 8, 3.6 and 3.3, respectively. In @RISTOS [21], where a similar multivariate analysis was used to identify venous thromboembolic risk factors, age >60 years, previous thromboembolism, advanced
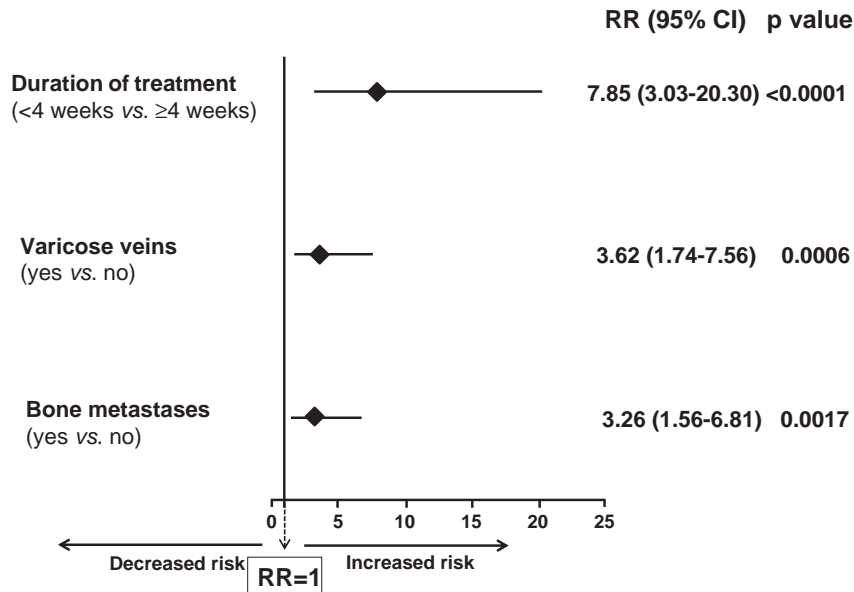

Fig. 2. Multivariate analysis of significant risk factors for venous thromboembolism.

cancer, anaesthesia lasting >2 hours and bed rest for >3 days were identified.

Our study presents certain limitations inherent to observational studies, such as lack of controls, non-standardised treatments, and patients lost to follow-up. On the other hand, it has several strengths that, we believe, render our results valid, i.e. consecutive patients were included, there was only one exclusion criterion, and all suspected thromboembolic events and major complications were validated by an independent adjudication committee. Moreover, this study was conducted in a real-world setting.

In conclusion, our study shows that, in contemporary real-life French practice, more than a third of patients undergoing major abdominal or pelvic surgery for cancer did not receive the extended thromboprophylaxis recommended by current national and international guidelines. The non-negligible occurrence of thromboembolic events still observed in this high-risk patient population might thus be reduced if best-practice recommendations for prophylaxis were better respected in routine clinical practice. Further efforts should therefore be made to improve adherence to guidelines.

Disclosure of Conflicts of Interest

CMS has received research grants, consulting fees as a member of advisory boards, and speaker and/or investigator fees from Abbott, AstraZeneca, Baxter, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb (BMS), CSL Behring, Daichii, Fresenius-Kabi, GlaxoSmithKline, Haemonetics, Laboratoire français du Fractionnement et des Biotechnologies (LFB), Lilly, NovoNordisk, Pfizer, Rovi and Sanofi-aventis.

LB received fees from Sanofi-aventis for participation in this study as a steering committee member, regional scientific committee member and investigator.

PC has received research grants, consulting fees as a member of advisory boards, and speaker and/or investigator fees from AMS, Astellas, Astra Zeneca, Bouchara-Recordati, Ferring, Ipsen, Lilly, Novartis, Pierre Fabre, Sanofi-aventis and Takeda.

PD has no conflict of interest to declare.

YG has received consulting fees as a member of advisory boards, and speaker and/or investigator fees from Bayer, Boehringer-Ingelheim, LFB, Lilly, Octapharma, Pfizer, Sanofi-aventis and Stago.

CM has received fees from Sanofi-aventis for participation in this study as a steering committee member, regional scientific committee member and investigator.

DM has received research grants, consulting fees as a member of advisory boards, and speaker and/or investigator fees from Bayer, Boehringer-Ingelheim and Sanofi-aventis.

PR has received research grants, consulting fees as a member of advisory boards, and speaker and/or investigator fees from Amgen, AstraZeneca, GlaxoSmithKline, Lilly, Ipsen, Janssen, Novartis, Pierre Fabre, Schering, Takeda and Sanofi-aventis.

LT has received research grants, consulting fees as a member of advisory boards, and investigator fees from Sanofi.

AS has received research grants, consulting fees as a member of advisory boards, and speaker and/or investigator fees from Boehringer-Ingelheim, Bayer, BMS-Pfizer, CSL Behring, Covidien, LFB and Sanofi.

Acknowledgements

Appendix A. Supplementary Data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.thromres.2013.10.038.

References

[1] Samama CM, Gafsou B, Jeandel T, Laporte S, Steib A, Marret E, et al. Prévention de la maladie thromboembolique veineuse postopératoire. Actualisation 2011. Texte court. Ann Fr Anesth Reanim 2011;30:947–51.

[2] Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in Nonorthopedic Surgical Patients: Antithrombotic Therapy and Prevention of Thrombosis. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition). Chest 2012;141:e227S–77S.

[3] Société Française d'Anesthésie et de Réanimation. Prévention de la maladie thromboembolique veineuse péri-opératoire et obstétricale. Recommandations pour la pratique clinique. Texte court, 2005. http://www.sfar.org/article/209/prevention-de-la-maladie-thromboembolique-veineuse-perioperatoire-et-obstetricale-rpc-2005.

[4] Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of Venous Thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:381S–453S.

[5] Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med 1988;318:1162–73.

[6] Mismetti P, Laporte S, Darmon JY, Buchmüller A, Decousus H. Meta-analysis of low-molecular-weight heparin in the prevention of venous thromboembolism in general surgery. Br J Surg 2001;88:913–30.

[7] de Franciscis S, Agus GB, Bisacci R, Botta G, Gasbarro V, Domanin M, et al. Guidelines for venous thromboembolism and clinical practice in Italy: a nationwide survey. Ann Vasc Surg 2008;22:319–27.

[8] Bergqvist D, Agnelli G, Cohen AT, Eldor A, Nilsson PE, Le Moigne-Amrani A, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med 2002;346:975–80.

[9] Rasmussen MS, Jorgensen LN, Wille-Jørgensen P, Nielsen JD, Horn A, Mohn AC, et al. Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicenter randomized open-label study. J Thromb Haemost 2006;4:2384–90.

[10] Kakkar VV, Balibrea JL, Martinez-Gonzalez J, Prandoni P, on behalf of the CANBESURE study group. Extended prophylaxis with bemiparin for the prevention of venous thromboembolism after abdominal or pelvic surgery for cancer: the CANBESURE randomized study. J Thromb Haemost 2010;8:1223–9.

[11] Lausen I, Jensen R, Jorgensen LN, Rasmussen MS, Lyng KM, Andersen M, et al. Incidence and prevention of deep venous thrombosis occurring late after general surgery: Randomised controlled study of prolonged thromboprophylaxis. Eur J Surg 1998;164:657–63.

[12] Bottaro FJ, Elizondo MC, Doti C, Bruetman JE, Perez Moreno PD, Bullorsky EO, et al. Efficacy of extended thrombo-prophylaxis in major abdominal surgery: What does the evidence show? A meta-analysis. Thromb Haemost 2008;99:1104–11.

[13] Akl EA, Terrenato I, Barba M, Sperati F, Muti P, Schünemann HJ. Extended perioperative thromboprophylaxis in patients with cancer. Thromb Haemost 2008;100:1176–80.

[14] Rasmussen MS, Jørgensen LN, Wille-Jørgensen P. Prolonged thromboprophylaxis with Low-molecular-weight heparin for abdominal or pelvic surgery. Cochrane Database Syst Rev 2009;1:CD004318.

[15] The European Fraxiparin Study (EFS) group. Comparison of a low-molecular-weight heparin and unfractionated heparin for the prevention of deep vein thrombosis in patients undergoing abdominal surgery. Br J Surg 1988;75:1058–63.

[16] Agnelli G, Bergqvist D, Cohen AT, Gallus AS, Gent M, on behalf of the PEGASUS investigators. Randomized clinical trial of postoperative fondaparinux *versus* perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. Br J Surg 2005;92:1212–20.

[17] Kakkar VV, Cohen AT, Edmonson RA, Phillips MJ, Cooper DJ, Das SK, et al. Low-molecular-weight versus standard heparin for prevention of venous thromboembolism after major abdominal surgery. The Thromboprophylaxis Collaborative Group. Lancet 1993;341:259–65.

[18] McLeod RS, Geerts WH, Sniderman KW, Greenwood C, Gregoire RC, Taylor BM, et al. Subcutaneous heparin versus low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery. Ann Surg 2001;233:438–44.

[19] Simonneau G, Laporte S, Mismetti P, Derlon A, Samii K, Samama CM, et al. A randomized study comparing the efficacy and safety of nadroparin 2850 IU (0.3 ml) vs. enoxaparin 4000 IU (40 mg) in the prevention of venous thromboembolism after colorectal surgery for cancer. J Thromb Haemost 2006;4:1693–700.

[20] ENOXACAN study group. Efficacy and safety of enoxaparin *versus* unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a

double-blind randomized multicentre trial with venographic assessment. Br J Surg 1997;84:1099–103.

[21] Agnelli G, Bolis G, Capussotti L, Scarpa RM, Tonelli F, Bonizzoni E, et al. A clinical outcome-based prospective study on venous thromboembolism after cancer surgery. The @RISTOS project. Ann Surg 2006;243:89–95.

[22] Huber O, Bounameaux H, Borst F, Rohner A. Postoperative pulmonary embolism after hospital discharge. An underestimated risk. Arch Surg 1992;127:310–3.

[23] Scurr JH, Coleridge-Smith PD, Hasty JH. Deep venous thrombosis: a continuing problem. BMJ 1988;297:28.

[24] White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. Thromb Haemost 2003;90:446–55.

[25] Kalka C, Spirk D, Siebenrock K-A, Metzger U, Tuor P, Sterzing D, et al. Lack of extended venous thromboembolism prophylaxis in high-risk patients undergoing major orthopaedic or major cancer surgery - Electronic assessment of VTE prophylaxis in high-risk surgical patients at discharge from Swiss hospitals (ESSENTIAL). Thromb Haemost 2009;102:56–61.

[26] National Clinical Guideline Centre – Acute and chronic conditions. Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. NICE Clinical guideline No. 92: 1-517. Available at: http://www.nice.org.uk/nicemedia/live/12695/47920/47920.pdf . [Accessed 5 March 2013].

[27] Cohen AT, Wagner MB, Mohamed MS. Risk factors for bleeding in major abdominal surgery using heparin thromboprophylaxis. Am J Surg 1997;174:1–5.