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Incidence, clinical characteristics, and long-term prognosis of postoperative symptomatic venous thromboembolism: a retrospective cohort study

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Complete List of Authors:	Takeda, Chikashi; Kyoto University Hospital, Department of Anesthesia Yamashita, Yugo; Kyoto University Hospital Takeuchi, Masato; Kyoto University , Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health Yonekura, Hiroshi; Mie University Graduate School of Medicine Faculty of Medicine, Department of Clinical Anesthesiology Dong, Li; Kyoto University Hospital, Department of Anesthesia Hamada, Miho; Kyoto University Hospital, Department of Anesthesia Hirotsu, Akiko; Kyoto University Hospital, Department of Anesthesia Ono, Koh; Kyoto University Graduate School of Medicine, Department of Cardiovascular Medicine Kawakami, Koji; Graduate School of Medicine and Public Health, Kyoto University, Department of Pharmacoepidemiology Fukuda, Kazuhiko; Kyoto University Hospital, Department of Anesthesia Morimoto, Takeshi; Hyogo Collge of Medicine, Clinical Epidemiology Kimura, Takeshi; Kyoto University Graduate School of Medicine Faculty of Medicine, Department of Cardiovascular Medicine Mizota, Toshiyuki ; Kyoto University Hospital, Department of Anesthesia
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1	Incidence, clinical characteristics, and long-term prognosis of postoperative
2	symptomatic venous thromboembolism: a retrospective cohort study
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4	Chikashi Takeda, MD, PhD ^{1,2} ; Yugo Yamashita, MD, PhD ³ ; Masato Takeuchi, MD, PhD,
5	MPH ² ; Hiroshi Yonekura, MD ^{2,4} ; Li Dong, MD ¹ ; Miho Hamada, MD ¹ ; Akiko Hirotsu, MD,
6	PhD ¹ ; Koh Ono, MD, PhD ³ ; Koji Kawakami, MD, PhD ² ; Kazuhiko Fukuda, MD, PhD ¹ ;
7	Takeshi Morimoto, MD, PhD, MPH ⁵ ; Takeshi Kimura, MD, PhD ³ ; Toshiyuki Mizota, MD,
8	PhD ¹ *
9	
10	¹ Department of Anesthesia, Kyoto University Hospital, Kyoto, Japan
11	² Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health,
12	Kyoto University, Kyoto, Japan
13	³ Department of Cardiology, Kyoto University Hospital, Kyoto, Japan
14	⁴ Department of Clinical Anesthesiology, Mie University Hospital, Tsu, Mie, Japan
15	⁵ Department of Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya, Japan
16	
17	Corresponding Author: Toshiyuki Mizota
18	Department of Anesthesia, Kyoto University Hospital, 54 Shogoin-Kawahara-Cho, Sakyo-
19	Ku, Kyoto 606-8507, Japan

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ABSTRACT

6 7 8 9	24	Objectives: The purpose of this study was to evaluate the incidence, clinical characteristics,
10 11 12	25	and prognosis of postoperative symptomatic VTE in Japan.
13 14 15 16	26	Design: Retrospective observational study. Two datasets, COMMAND VTE Registry and
17 18 19	27	Japanese Society of Anesthesiologists (JSA) annual report, were used for current analyses.
20 21 22	28	Setting: Eighteen of 29 centres that participated in the COMMAND VTE Registry.
23 24 25	29	Participants: Acute symptomatic VTE patients who had undergone surgery 2 months prior
26 27 28 29	30	to the diagnosis at 18 centres from January 2010 to December 2013 were identified in the
30 31 32	31	COMMAND VTE Registry. From each centre's JSA annual report, the overall population
33 34 35	32	that had received anaesthetic management during this period was retrieved.
36 37 38 39	33	Interventions: None.
40 41 42	34	Primary and secondary outcome measures: The primary outcome was the incidences and
43 44 45	35	clinical characteristics of postoperative symptomatic VTE. The secondary outcomes were
46 47 48 49	36	recurrent VTE, major bleeding, and all-cause death.
50 51 52	37	Results: We identified 137 patients with postoperative symptomatic VTE, including 57
53 54 55	38	patients with pulmonary embolism. The incidences of postoperative symptomatic VTE and
56 57 58 59 60	39	pulmonary embolism were 0.067% and 0.028%, respectively, based on data from 203,943

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patients who underwent surgery, managed by anaesthesiologists, during the study period. The incidences of postoperative symptomatic VTE varied widely, depending on surgical and anaesthetic characteristics. Postoperative symptomatic VTE occurred at a median of 8 days after surgery, with 58 patients (42%) diagnosed within 7 days. The cumulative incidence, 30 days after VTE, of recurrent VTE, major bleeding, and all-cause death was 3.0%, 5.2%, and 3.7%, respectively. Conclusion: This study, combining the large real-world VTE and anaesthesiology databases in Japan revealed the incidence, clinical features, and prognosis of postoperative symptomatic VTE, providing useful insights for all healthcare providers involved in various surgeries. Trial registration: Not applicable. Key words: Venous thromboembolism; Pulmonary thromboembolism; Deep vein thrombosis; Postoperative; Prognosis

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ARTICLE SUMMARY

3 4	54	Ał	RTICLE SUMMARY
5 6 7 8 9	55	ST	TRENGTHS AND LIMITATIONS OF THIS STUDY
10 11 12 13	56	•	VTE is considered relatively rare in Asians, and the small number of cases makes
13 14 15 16	57		epidemiological studies difficult to perform.
17 18 19	58	•	This study combines data from the large real-world VTE database and anaesthetic
20 21 22	59		database in Japan for information regarding the incidence, clinical features, and prognosis
23 24 25 26	60		of postoperative symptomatic VTE.
27 28 29	61	•	Another important feature of the current study was the comparison of the incidence of
30 31 32	62		postoperative symptomatic VTE across surgical sites.
33 34 35 36	63	•	This is a retrospective cohort study with inherent limitations based on the observational
37 38 39	64		study design. Further, as a certain number of patients from ineligible centres were
40 41 42	65		excluded, the incidence of postoperative symptomatic VTE may have been influenced.
43 44 45 46	66		
40 47 48 49	67		
50 51 52	68		
53 54 55 56 57 58 59	69		
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70	INTRODUCTION
71	Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein
72	thrombosis (DVT), is a serious postoperative complication which can result in an in-hospital
73	death.[1, 2] In perioperative management, it is crucial to prevent postoperative symptomatic
74	VTE and to respond promptly, once it is recognized. Therefore, clinicians should be familiar
75	with the clinical features of postoperative symptomatic VTE to optimize their management
76	strategies.
77	Over the past 20 years, several guidelines have been recommended for the
78	prophylaxis of postoperative VTE.[3-5] Despite the use of preventive measures, the incidence
79	of postoperative VTE remains high and varies from 0.58% to 2.2%, according to reports from
80	Western countries.[6-8] However, data on postoperative VTE from a cohort/registry-based
81	study in Asian countries are scarce. A previous study reported a relatively low incidence
82	(0.031%) of postoperative VTE throughout Japan.[9] However, it was a surveillance study of
83	postoperative PE, conducted by mailing questionnaires to anaesthesiologists; therefore, the
84	possibility of underreporting of events cannot be denied. Although the incidence of VTE in
85	Asia has been considered to be lower than Western countries,[10] recent studies have

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86	suggested an underestimation of VTE in Asia.[11-13] No large-scale study has systematically
87	evaluated the incidence of postoperative symptomatic VTE in Japan.
88	Therefore, with a collaborative effort between cardiologists and anaesthesiologists,
89	we investigated the incidence, clinical characteristics, and prognosis of postoperative
90	symptomatic VTE, using a large, observational, real-world VTE database and an anaesthetic
91	database of annual reports submitted to the Japanese Society of Anesthesiologists (JSA).
92	
93	METHODS
94	Study design, setting, and population
95	In this study, two datasets were used for analyses. The first was Contemporary ManageMent
96	AND outcomes in patients with Venous ThromboEmbolism (COMMAND VTE) registry, a
97	retrospective multicentre cohort study, which provided the data on patients with
98	postoperative symptomatic VTE. The second was the JSA annual report, which provided
99	cross-sectional data of all patients, who underwent surgical operations, managed by
100	anaesthesiologists.
101	The design of the COMMAND VTE Registry has been reported in detail
102	elsewhere.[14] Briefly, this physician-initiated registry was a large cohort of consecutive

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	103	patients with acute symptomatic VTE, who were objectively confirmed by the cardiologists
	104	at 29 centres in Japan, between January 2010 and August 2014. In this registry, the hospital
0 1 2	105	databases were searched for clinical diagnoses and imaging examinations of patients with
2 3 4 5 6	106	suspected VTE, and consecutive patients who met the definition of acute symptomatic VTE
6 7 8 9	107	were enrolled. Baseline data were obtained from the hospital charts or hospital databases.
0 1	108	Follow-up data on vital status, recurrent VTE, bleeding, and status of anticoagulation
2 3 4 5 6	109	therapy, according to the prespecified definitions, were collected from the hospital charts,
6 7 8 9	110	hospital databases, or by contacting patients, relatives, and/or referring to physicians through
0 1	111	phone and/or mails.
2 3 4 5 6	112	As for the JSA annual reports, the training hospitals certified by JSA are required to
6 7 8 9	113	submit the annual reports to JSA at the end of the year, which includes the total number of
0 1	114	surgeries managed by anaesthesiologists, patient characteristics in detail, and surgical and
2 3 4 5 6	115	anaesthetic information.
7 8	116	In this study, the JSA annual reports from January 2010 to December 2013 were
9 0 1 2	117	collected from 18 centres that participated in the COMMAND VTE Registry. Furthermore,
2 3 4 5 6 7 8 9	118	additional data of patients with postoperative symptomatic VTE, namely operative date,
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	119	operative procedure, surgical sites, surgical position, and types of anaesthesia on anaesthetic
	120	charts at each centre, were obtained.
) <u>2</u>	121	In this study, the patients from the 18 centres registered in the COMMAND VTE
3 1 5	122	Registry, for which the JSA annual report had been collected between January 2010 and
5 7 3 9	123	December 2013, were enrolled (Figure 1). We could not enrol patients from the rest of the 11
) <u>2</u>	124	centres of the COMMAND VTE Registry as their JSA annual reports and/or additional data
3 1 5	125	on patients with postoperative symptomatic VTE were unavailable. We also could not
) 7 }	126	register the patients between January 2014 and August 2014, since the JSA annual report was
) <u>2</u>	127	from January to December of each year. Further, within the COMMAND VTE Registry, the
3 1 5	128	patients diagnosed with acute symptomatic VTE, who underwent surgery 2 months prior to
5 7 3 9	129	the VTE diagnosis, were identified. The overall population that had received anaesthetic
) <u>)</u>	130	management, during the study period was retrieved from each centre's JSA annual report.
3 1 5	131	Besides, additional data of patients with postoperative symptomatic VTE, namely operative
5 7 3 9	132	date, operative procedure, surgical sites, surgical position, and types of anaesthesia on
) <u>)</u>	133	anaesthetic charts at each centre, were obtained.
3 1 5	134	Ethics
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- 3 4 5 6	135	This retrospective observational study was conducted according to the 'STrengthening the
7 8 9	136	Reporting of OBservational studies in Epidemiology' (STROBE) guidelines. This study was
10 11 12	137	approved by the Ethics Committee of the Kyoto University Hospital, Kyoto, Japan (approval
13 14 15	138	number: R1822, December 18th, 2018; Chairperson Prof Shinji Kosugi). Following Ethics
16 17 18 19	139	Committee approval, additional data, including JSA annual reports, were collected from the
20 21 22	140	centres listed in the Command VTE Registry, from March 2019 to September 2019. Written
23 24 25	141	informed consent from each patient was waived, because we used clinical information
26 27 28 29	142	obtained in routine clinical practices. This method is concordant with the guidelines for
30 31 32	143	epidemiological studies issued by the Ministry of Health, Labor, and Welfare in Japan.
33 34 35	144	Patient and Public Involvement Statement
36 37 38 39	145	Patients or the public were not involved in the design, or conduct, or reporting, or
40 41 42	146	dissemination plans of our research.
43 44 45	147	Definition of postoperative symptomatic venous thromboembolism
46 47 48	148	In this study, postoperative symptomatic VTE was defined as the thromboembolic event that
49 50 51 52	149	occurred within 2 months of the postoperative period.[15] The symptoms of VTE were
53 54 55	150	defined as sudden onset dyspnoea, pleuritic and substernal chest pains, cough, fever,
56 57 58 59 60	151	haemoptysis and syncope for PE; and erythema, warmth, pain, swelling, tenderness, and pain

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152	upon dorsiflexion of the foot for DVT. Additionally, a sudden onset of abnormality in the
153	vital signs, such as a decrease in arterial oxygen saturation and hypotension were considered
154	as symptoms of PE.
155	Collection of baseline patient characteristics and clinical follow-up data
156	In the COMMAND VTE Registry, data for the patients' characteristics were collected from
157	the hospital charts or hospital databases, according to the prespecified definitions, using an
158	electronic case report form in a web-based database system. Physicians at each of the
159	institutions were responsible for data entry, and data were automatically examined for
160	missing or contradictory input and out-of-range values. Additional edits were performed at
161	the general office of the registry.
162	Patients with postoperative symptomatic VTE, identified through the COMMAND
163	VTE Registry, were further investigated at each centre using the anaesthetic charts created
164	through the collaboration of cardiologists and the anaesthesiologists at each participating
165	centre. Anaesthesia-associated data, such as surgical site, surgical position, and type of
166	anaesthesia were extracted and incorporated into the data from the COMMAND VTE
167	Registry.

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3 4 5 6	168	The outcome measures assessed in this study were recurrent VTE, major bleeding,
7 8 9	169	and all-cause death during the follow-up period, with a median of 1,507 days, in the
10 11 12 13	170	surviving patients. Recurrent VTE was defined as symptomatic PE and/or DVT accompanied
14 15 16	171	by confirmation of a new thrombus or exacerbation of the thrombus by objective imaging
17 18 19	172	examinations or autopsy. Major bleeding was defined according to the International Society
20 21 22 23	173	of Thrombosis and Haemostasis as a reduction in the haemoglobin level by at least 2 g/dL,
24 25 26	174	transfusion of at least two units of blood, or symptomatic bleeding in a critical area or an
27 28 29	175	organ.[16]
30 31 32	176	Statistical analysis
33 34 35 36	177	The incidence of postoperative symptomatic VTE was calculated using a combination of data
37 38 39	178	from the COMMAND Registry and the JSA annual reports from the 18 centres. The
40 41 42 43	179	numerator of the incidence was the number of cases of postoperative symptomatic VTE
44 45 46	180	extracted from the COMMAND Registry; the denominator was the number of surgeries in
47 48 49	181	the JSA annual report. The incidence of postoperative symptomatic VTE according to age,
50 51 52	182	sex, surgical site, surgical position, and types of anaesthesia was calculated. The baseline and
53 54 55 56	183	follow-up data were separately recorded for PE with or without DVT and DVT-only groups
57 58 59 60	184	in patients with postoperative symptomatic VTE. No imputation was performed for missing

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185	data. Categorical variables were calculated as numbers and percentages, and continuous
186	variables were calculated as the means and standard deviations or the medians and
187	interquartile ranges (IQR) based on their distributions. Additionally, the timing of the
188	postoperative symptomatic VTE occurrences after the surgery were described. The Kaplan-
189	Meier method was used to estimate the cumulative incidences of recurrent VTE, major
190	bleeding, and all-cause death. The log-rank test was used to assess the differences in the
191	cumulative incidences of the events between the PE- and DVT-only groups. Two-sided P-
192	values of less than 0.05 were considered significant. All statistical analyses were performed
193	using SAS version 9.4 for Windows (SAS Institute Inc; Cary, NC, USA) or JMP version
194	14.0.0 (SAS Institute Inc.; Cary, NC, USA).
195	
196	RESULTS
197	RESULTS
198	Figure 1 represents the flow diagram of the study. We enrolled 3,027 consecutive patients
199	with acute symptomatic VTE, after screening 19,634 consecutive patients with suspected
200	VTE for eligibility, using the chart review by the physicians at each institution. After
201	excluding 2,734 patients without a history of surgery within 2 months before VTE diagnosis,

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202	293 patients were identified with postoperative symptomatic VTE during hospitalization
203	among all 29 centres of the COMMAND VTE Registry. Furthermore, 135 patients outside
204	the eligible period and 21 patients who underwent surgery without the management by
205	anaesthesiologists, were excluded. Finally, the study population consisted of 137 patients
206	diagnosed with VTE within 2 months after surgery, from 18 centres, between January 2010
207	and December 2013. The total number of surgical cases managed by anaesthesiologists
208	during the study period in 18 centres was 203,943.
209	Incidence of postoperative symptomatic venous thromboembolism
210	The estimated incidence of postoperative symptomatic VTE was 0.067% (137/203,943) and
211	VTE with PE was 0.028% (57/203,943) (Table 1). Of the 57 PE cases, 35 patients (0.017%)
212	had hypoxic symptoms, nine patients (0.004%) presented with shock, and six patients
213	(0.003%) had cardiac arrest. As for the surgical site, the incidence of postoperative
214	symptomatic VTE was relatively high in surgeries involving the brain, hip, and upper/lower
215	limbs. In terms of the types of anaesthesia, regional anaesthesia with or without general
216	anaesthesia (0.100%) was associated with a higher incidence of VTE than general anaesthesia
217	alone (0.045%) (Table 1 and Supplemental Table 1).

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				E	3MJ Ot	ben		6/bmjopen-202 1 by copyright,	PE with shock		Page
218	Table 1. Incidence of postoperative	• •	tic VT	E VTE		DE	DE	nt, including with hypoxet with hypoxet	DE with shealy	ы	F with annot
	Overall	Total cases 203943	137	(0.067%)	57	PE (0.028%)	35	<u>(0.017%) المعامة</u> (0.017%) المعاد		6	E with arrest (0.003%)
	Overan	203743	157	(0.00770)	57	(0.02070)	55	(0.01770)ses r rebr	(0.00+70)	0	(0.00570)
	Surgical Site							February 2022. Erasmush (0.011%) te			
	Brain	9299	15	(0.161%)	8	(0.086%)	1	(0.011%) ⁶ mush (0.011%)) (0.000%)	0	(0.000%)
	Thorax	11100	4	(0.036%)	3	(0.027%)	2	(0.018%) بي 20 الإيراني (0.018)	(0.009%)	1	(0.009%)
	Cardiovascular	13637	6	(0.044%)	1	(0.007%)	1	(0.007%)data (0.007%)data	(0.007%)	1	(0.007%)
	Thorax and abdomen	1656	2	(0.121%)	0	(0.000%)	0	ta o de (0.000%)∃ · a	(0.000%)	0	(0.000%)
	Upper abdomen	27035	17	(0.063%)	11	(0.041%)	8	(0.000%)m ⁱⁿ in (0.030%)m ⁱⁿ in (0.030%)m ⁱⁿ in (0.030%)m ⁱⁿ in	(0.004%)	0	(0.000%)
	Lower abdomen	42875	31	(0.072%)	16	(0.037%)	11	(0.026%) ≥	(0.007%)	1	(0.002%)
	Caesarean section	5056	0	(0.000%)	0	(0.000%)	0	(0.026%)≱ ∰ (0.000%)jning (0.006%) a) (0.000%)	0	(0.000%)
	Head, pharynx, larynx	35414	4	(0.011%)	2	(0.006%)	2	(0.006%) a) (0.000%)	0	(0.000%)
	Chest, abdominal wall, perineum	22633	3	(0.013%)	2	(0.009%)	2	(0.009%)) (0.000%)	0	(0.000%)
	Spine	7040	7	(0.099%)	3	(0.043%)	2	(0.009%) ^{ind} ind (0.028%) ⁱⁿⁱ ar 001	(0.014%)	1	(0.014%)
	Hip, upper/lower limbs	25160	48	(0.191%)	11	(0.044%)	6	(0.024%) g 92	2 (0.008%)	2	(0.008%)
	Other	2038	0	(0.000%)	0	(0.000%)	0) (0.000%)	0	(0.000%)
219	All data were described as number a	and percentage	e.					ogii			
220	Abbreviations: PE, pulmonary emb	olism; VTE, v	enous	thromboemb	olism			25			
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221	Baseline characteristics and timing of venou	ıs thrombo	embolism	diagnosis	à			
222	Table 2 shows the demographic and clinical ch	naracteristic	es of patient	ts with po	stoperative			
223	symptomatic VTE. Figure 2 presents the duration	ion from th	e surgery to	the diag	nosis of			
224	postoperative symptomatic VTE. The median i	inter-quarti	le duration	was 8 day	vs (4–15 da	ays);	т	
225	and 58 patients (42%) were diagnosed within 7	7 days of su	ırgery, whil	e 79 patie	ents (58%)	were	rotected	
226	diagnosed 7 days after the surgery. The greates	st number c	of patients w	vere diagr	nosed with	VTE	by copyri	
227	on postoperative day 8.						ght, inclu	
228	Table 2. Baseline patients' characteristics						ding for	
		Total VTE PE with or without DVT					vere VTE DVT only eat	
							<u> </u>	
		N	=137	(N	(=57)	(N=80) 5	
	Baseline characteristics	N	=137	(N	[=57)	(N=80) to text	
	Baseline characteristics Age (years)	2	= 137 ±15.5	(N 67.7	,	65.1	±17.2	
		66.2		X	,		o text a	
	Age (years)	66.2 55	±15.5	67.7 22	±12.6	65.1 33	±17.2 dd (41.3%) ±12.3 m	
	Age (years) Men	66.2 55 56.3	±15.5 (40.1%)	67.7 22 57.8	±12.6 (38.6%)	65.1 33	±17.2 dd (41.3%) ±12.3 m	
	Age (years) Men Body weight (kg)	66.2 55 56.3	±15.5 (40.1%) ±11.8	67.7 22 57.8	±12.6 (38.6%) ±11.1	65.1 33 55.3	±17.2 dd (41.3%) ±12.3 m	
	Age (years) Men Body weight (kg) Body mass index (kg/m ²)	66.2 55 56.3	±15.5 (40.1%) ±11.8	67.7 22 57.8	±12.6 (38.6%) ±11.1	65.1 33 55.3	±17.2 dd (41.3%) ±12.3 m	
	Age (years) Men Body weight (kg) Body mass index (kg/m ²) Surgical and anaesthesia characteristics	66.2 55 56.3 23.2	±15.5 (40.1%) ±11.8	67.7 22 57.8	±12.6 (38.6%) ±11.1	65.1 33 55.3	±17.2 dd (41.3%) ±12.3 m	
	Age (years) Men Body weight (kg) Body mass index (kg/m ²) Surgical and anaesthesia characteristics ASA PS	66.2 55 56.3 23.2	±15.5 (40.1%) ±11.8 ±4.3	67.7 22 57.8 23.6	±12.6 (38.6%) ±11.1 ±3.7	65.1 33 55.3 22.9	±17.2 dda (41.3%)	
	Age (years) Men Body weight (kg) Body mass index (kg/m ²) Surgical and anaesthesia characteristics ASA PS ASA PS 1	66.2 55 56.3 23.2 19	±15.5 (40.1%) ±11.8 ±4.3 (13.9%)	67.7 22 57.8 23.6 10 42	± 12.6 (38.6%) ± 11.1 ± 3.7 (17.5%)	65.1 33 55.3 22.9 9	±17.2 dda (41.3%) mining, ±12.3 ning, Al training, ±4.7 Al training, (11.3%) dd	
	Age (years) Men Body weight (kg) Body mass index (kg/m ²) Surgical and anaesthesia characteristics ASA PS ASA PS 1 ASA PS 2	66.2 55 56.3 23.2 19 91	±15.5 (40.1%) ±11.8 ±4.3 (13.9%) (66.4%)	67.7 22 57.8 23.6 10 42	± 12.6 (38.6%) ± 11.1 ± 3.7 (17.5%) (73.7%)	65.1 33 55.3 22.9 9 49	±17.2 dag mining, ±12.3 ning, Al training, ±4.7 Al training, (11.3% and signila (61.3% and signila (22.5% are	
	Age (years) Men Body weight (kg) Body mass index (kg/m ²) Surgical and anaesthesia characteristics ASA PS ASA PS 1 ASA PS 2 ASA PS 3	66.2 55 56.3 23.2 19 91 22	±15.5 (40.1%) ±11.8 ±4.3 (13.9%) (66.4%) (16.1%)	67.7 22 57.8 23.6 10 42 4	± 12.6 (38.6%) ± 11.1 ± 3.7 (17.5%) (73.7%) (7.0%)	65.1 33 55.3 22.9 9 49 18	±17.2 data mining, ±17.2 data mining, ±12.3 ning, Al training, ±4.7 Al training, (11.3% at signila (61.3% at signila (22.5% acching) (22.5% acching) (5.0%) no	
	Age (years) Men Body weight (kg) Body mass index (kg/m ²) Surgical and anaesthesia characteristics ASA PS ASA PS 1 ASA PS 2 ASA PS 3 ASA PS 4	66.2 55 56.3 23.2 19 91 22 5	±15.5 (40.1%) ±11.8 ±4.3 (13.9%) (66.4%) (16.1%) (3.6%)	67.7 22 57.8 23.6 10 42 4 1	± 12.6 (38.6%) ± 11.1 ± 3.7 (17.5%) (73.7%) (73.7%) (7.0%) (1.8%)	65.1 33 55.3 22.9 9 49 18 4	±17.2 dag mining, ±12.3 ning, Al training, ±4.7 Al training, (11.3% and signila (61.3% and signila (22.5% are	
	Age (years) Men Body weight (kg) Body mass index (kg/m ²) Surgical and anaesthesia characteristics ASA PS ASA PS 1 ASA PS 2 ASA PS 3 ASA PS 4 Emergent surgery	66.2 55 56.3 23.2 19 91 22 5	±15.5 (40.1%) ±11.8 ±4.3 (13.9%) (66.4%) (16.1%) (3.6%)	67.7 22 57.8 23.6 10 42 4 1	± 12.6 (38.6%) ± 11.1 ± 3.7 (17.5%) (73.7%) (73.7%) (7.0%) (1.8%)	65.1 33 55.3 22.9 9 49 18 4	±17.2 data mining, ±17.2 data mining, ±12.3 ning, Al training, ±4.7 Al training, (11.3% at signila (61.3% at signila (22.5% acching) (22.5% acching) (5.0%) no	
	Age (years)MenBody weight (kg)Body mass index (kg/m²)Surgical and anaesthesia characteristicsASA PSASA PS 1ASA PS 2ASA PS 3ASA PS 4Emergent surgerySurgical site	66.2 55 56.3 23.2 19 91 22 5 18	± 15.5 (40.1%) ± 11.8 ± 4.3 (13.9%) (66.4%) (16.1%) (3.6%) (13.1%)	67.7 22 57.8 23.6 10 42 4 1 11	± 12.6 (38.6%) ± 11.1 ± 3.7 (17.5%) (73.7%) (73.7%) (7.0%) (1.8%) (19.3%)	65.1 33 55.3 22.9 9 49 18 4 7	±17.2 dda mining, and standard training, and	

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1 2 3 4 5 6 7 8 9 10 11 12 13	
14 15 16 17 18 20 21 22 23 24 25 26 27 28	
29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44	
45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	

Cardiovascular	6	(4.4%)	1	(1.8%)	5	(6.3%)
Thorax and abdomen	2	(1.5%)	0	(0.0%)	2	(2.5%)
Upper abdomen	17	(12.4%)	11	(19.3%)	6	(7.5%)
Lower abdomen	31	(22.6%)	16	(28.1%)	15	(18.8%)
Head and neck	4	(2.9%)	2	(3.5%)	2	(2.5%)
Chest abdominal wall and perineum	3	(2.2%)	2	(3.5%)	1	(1.3%)
Spine	7	(5.1%)	3	(5.3%)	4	(5.0%)
Гуре of Anaesthesia						(43.8%
General anaesthesia	61	(44.5%)	26	(45.6%)	35	(43.8%
General anaesthesia with regional anaesthesia	56	(40.9%)	24	(42.1%)	32	(40.0%)
Local anaesthesia	20	(14.6%)	7	(12.3%)	13	(16.3%
Surgical position						ght,
Supine position	100	(73.0%)	39	(68.4%)	61	(16.3%) (16.3%) (76.3%) (76.3%)
Prone position	6	(4.4%)	2	(3.5%)	4	(5.0%) <mark>ā</mark>
Lateral position	18	(13.1%)	7	(12.3%)	11	(13.8% த
Lithotomy position	11	(8.0%)	8	(14.0%)	3	(3.8%) s
Other position	2	(1.5%)	1	(1.8%)	1	(1.3%) e
Comorbidities						(1.3%)ated to
Aypertension 🦉	43	(31.4%)	22	(38.6%)	21	(1.3 %)ated to tsinusnog (26.3%)t a
Diabetes mellitus	15	(10.9%)	7	(12.3%)	8	(10.0%)
Chronic kidney disease	24	(17.5%)	8	(14.0%)	16	(20.0%)
Dialysis	2	(1.5%)	0	(0.0%)	2	(2.5%) <u>a</u> .
History of chronic lung disease	13	(9.5%)	3	(5.3%)	10	(12.5%)
History of heart failure	6	(4.4%)	3	(5.3%)	3	(3.8%)
History of myocardial infarction	4	(2.9%)	0	(0.0%)	4	(5.0%) (5.0%)
History of stroke	9	(6.6%)	5	(8.8%)	4	(5.0%)
Atrial fibrillation	8	(5.8%)	7	(12.3%)	1	(1.3%)
Liver cirrhosis	3	(2.2%)	2	(3.5%)	1	(1.3%) ^{ila} r
Connective tissue disease	5	(3.6%)	1	(1.8%)	4	(5.0%)
History of VTE	1	(0.7%)	1	(1.8%)	0	(0.0%) <u>8</u>
History of major bleeding	17	(12.4%)	7	(12.3%)	10	(12.5%)
Active cancer	41	(29.9%)	24	(42.1%)	17	(21.3%)
Varicose vein	8	(5.8%)	3	(5.3%)	5	(6.3%)
Drogontation						

1 2								
- 3 4		PE with hypoxemia	-	-	35	(61.4%)	-	-
5		PE with Shock	-	-	9	(15.8%)	-	-
6 7		PE with cardiac arrest/collapse	-	-	6	(10.5%)	-	
8 9		Proximal DVT	64	(46.7%)	21	(36.8%)	43	(53.8%)
10		Laboratory tests at diagnosis						-
11 12		Anaemia	109	(82.6%)	45	(83.3%)	64	(82.1%)
13 14		Thrombocytopenia	6	(4.4%)	5	(8.8%)	1	(1.3%)
15 16		$CEP (mI/min/m^2)$	70.2	(59.0-	707	(51.2-	<u>00</u> 4	(62.4- te
17		eGFR (mL/min/m ²)	78.3	91.8)	72.7	87.7)	80.4	(62.4- dected) 93.6) de
18 19		eGFR <60mL/min/m ²	36	(26.3%)	17	(29.8%)	19	(23.8%)
20 21		D-dimer (µg/mL, n=122)	16.5	(8.6-	16.8	(8.6-	16.4	ම් (7.9-2 සි 3)
22		D-dimer ($\mu g/mL$, $m-122$)	10.5	31.5)	10.8	39.3)	10.4	(7.9-2 6 3)
23 24		Thrombophilia	4	(2.9%)	3	(5.3%)	1	(1.3%) ²
25 26		Initial anticoagulation therapy	115	(83.9%)	53	(93.0%)	62	(77.5%) 2015
27		Heparin	107	(78.1%)	52	(91.2%)	55	(68.8%)
28 29		Fondaparinux	11	(8.0%)	2	(3.5%)	9	(11.3%)
30 31		Thrombolysis	8	(5.8%)	5	(8.8%)	3	(3.8%) en Era
32		Inferior vena cava filter use	26	(19.0%)	13	(22.8%)	13	(16.3%) Sing
33 34		Ventilator support	6	(4.4%)	6	(10.5%)	0	(0.0%) though
35 36		Percutaneous cardiopulmonary support	2	(1.5%)	2	(3.5%)	0	(0.0%)d d
37 38 39	229	Categorical variables are presented as numbers	and percer	ntages, and o	continuo	us variables	s are	hool . data minin
40 41 42	230	presented as the mean and standard deviation of	or the media	an and interc	quartile r	ange based	on	ig, Al traii
43 44 45 46	231	their distributions.						, ing, and
47 48 49	232	Chronic kidney disease was diagnosed if there	was persis	tent proteinu	iria or if	eGFR was	<60	, similar te
50 51 52	233	mL/min/1.73 m^2 for more than 3 months. The	values of e	GFR were ca	alculated	based on t	he	a mining, Al training, and similar technologies
53 54 55	234	equation reported by Japan Association of Chro	onic Kidne	y Disease In	itiative [man:		es.
56 57 58 59 60	235	194*Scr-1.094*age-0.287, woman: 194*Scr-1	1.094*age-	0.287*0.739]. Anaer	nia was		-

3		
4 5 6	236	diagnosed if the value of haemoglobin was <13 g/dL for men and <12 g/dL for women.
7 8 9	237	Thrombophilia included protein C deficiency, protein S deficiency, antithrombin deficiency,
10 11 12 13	238	and antiphospholipid syndrome.
14 15 16	239	Abbreviations: ASA PS, American society anaesthesiologists performance status; DVT, deep
17 18 19	240	venous thrombosis; eGFR, estimated glomerular filtration rate; PE, pulmonary embolism;
20 21 22 23	241	VTE, venous thromboembolism
24 25 26	242	
27 28	243	Clinical outcomes after postoperative symptomatic venous thromboembolism
29	215	Chinear outcomes arter postoperative symptomatic venous thromotemoonsm
30 31 32	244	The cumulative incidence of recurrent VTE was 3.0% at 30-day follow-up, 5.3% at 90-day
33 34 35 36	245	follow-up, and 5.3% at the 5-year follow-up after postoperative symptomatic VTE (Figure
37 38 39	246	3a). The cumulative incidence of major bleeding was 5.2% at 30-day follow-up, 6.7% at 90-
40 41 42 43	247	day follow-up, and 12.6% at 5-year follow-up (Figure 3b). The cumulative incidence of all-
44 45 46	248	cause death was 3.7% at 30-day follow-up, 5.1% at 90-day follow-up, and 27.4% at 5-year
47 48 49	249	follow-up (Figure 3c). The details of clinical events within 90 days are given in Supplemental
50 51 52	250	Table 2. VTE recurrence occurred in seven patients (4 patients were treated with
53 54 55 56	251	anticoagulant therapy), all of which were early recurrences within 60 days of diagnosis.
57 58 59 60	252	Difference in the cumulative incidence of recurrent VTE, major bleeding, and all-cause death

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2 3		
4 5 6	253	was not significant between the PE- and DVT-only groups, although 30-day incidence of
7 8 9	254	major bleeding and all-cause death was higher in the PE group than the DVT-only group
10 11 12 13	255	(11.1% versus 1.3%, and 8.8% versus 0.0%, respectively) (Figure 4).
13 14 15 16	256	
17 18 19	257	DISCUSSION
20 21 22 23	258	The main findings of this study are as follows: 1) the incidence of postoperative symptomatic
23 24 25 26	259	VTE within 2 months after surgery was 0.067% and VTE with PE was 0.028%, representing
27 28 29	260	203,943 patients from 18 centres in Japan; 2) the incidences of postoperative symptomatic
30 31 32	261	VTE varied widely, according to surgical and anaesthetic characteristics; and 3) nearly half
33 34 35 36	262	of the patients were diagnosed within 7 days of the surgery, while the rest were diagnosed 7
37 38 39	263	days after surgery, with the highest number of patients diagnosed on postoperative day 8.
40 41 42	264	VTE is considered relatively rare in Asians and the small number of cases makes
43 44 45 46	265	epidemiological studies difficult to perform.[10] Previously, two major studies from Japan
47 48 49	266	had evaluated the incidence of the postoperative complication of VTE. The first study was
50 51 52	267	based on the JSA initiated questionnaire annual survey, where the incidence of PE was
53 54 55 56	268	0.031% (3,667/11,786,489.[9] The second study used the diagnosis-procedure combination
57 58 59 60	269	(DPC) database, and the VTE and PE incidences were 0.24% (2,485/1,016,496) and 0.05%
00		

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270	(538/1,016,496), respectively.[17] The incidence of postoperative symptomatic VTE in the
271	current study was lower than that in the DPC study. In the DPC study, VTE was identified
272	based on the International Classification of Diseases, 10th version (ICD-10) codes; and
273	therefore, may have been misclassified and overrated. The incidences of postoperative VTE
274	were reported to be 0.58%-2.2%, based on the clinical databases in the USA. Therefore,
275	postoperative VTE incidence was suggested to be lower in Japan than in the United States
276	and Europe. These differences could be explained by ethnic variations.[10] Western
277	guidelines, [4, 5] due to racial disparities, are more likely to lead to over-triage in the Japanese
278	population.
279	Another important feature of the current study was the comparison of the incidence of
280	postoperative symptomatic VTE across surgical sites. As with the JSA initiated questionnaire
281	study,[9] neurosurgeries and orthopaedic surgeries (hip, upper, and lower extremity) were
282	associated with a higher incidence of postoperative symptomatic VTE. According to the
283	Japanese guidelines, there is a high risk of postoperative symptomatic VTE in patients over
284	40 years of age undergoing major cancer surgery; however, in the present study, abdominal
285	surgery was not identified with high risk. Therefore, risks should be stratified according to

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2 3 4 5	286	the surgical sites and procedures, and the additional risks in each patient should be considered
6 7 8 9	287	in the preventive strategies.
10 11 12	288	Additionally, in this study, the timing of the onset of postoperative symptomatic VTE
13 14 15 16	289	was bimodal in nature. These results may suggest that postoperative symptomatic VTE
17 18 19	290	occurs, not only in the very acute postoperative period, which is directly affected by surgical
20 21 22 22	291	immobilization, but also approximately 10 days after surgery; the information can guide the
23 24 25 26	292	healthcare providers involved in surgery, regarding the risk perception and diagnosis of
27 28 29	293	postoperative symptomatic VTE.
30 31 32 33	294	The duration of anticoagulant therapy is generally divided into an initial treatment
34 35 36	295	phase (up to 7 days), a maintenance treatment phase (~3 months after the initial treatment),
37 38 39	296	and a prolonged treatment phase (beyond 3 months).[18] Surgery is a transient risk factor of
40 41 42 43	297	VTE; prolonged treatment is usually not performed, as the possibility of recurrence is
44 45 46	298	considered relatively low. In this study, VTE recurrence had occurred in all the affected
47 48 49 50	299	seven patients within 3 months of the onset, and no recurrence was observed after 3 months,
50 51 52 53	300	suggesting the importance of relatively early recurrence.
54 55 56	301	PE was apparently associated with a higher mortality, especially in the early phase of
57 58 59 60	302	postoperative symptomatic VTE, although the difference between the PE- and DVT-only

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> groups was not significant. The difference may be explained by insufficient sample size. Notably, the initial mortality rate and recurrence rate was higher for acute PE than for DVT.[19, 20] Therefore, in comparison to DVT, postoperative PE should be more closely monitored and aggressively treated.[3] **Study limitations** First, two different databases were combined to estimate the incidence of postoperative symptomatic VTE. Although the COMMAND Registry included real consecutive patients with acute symptomatic VTE,[9, 17] for determining VTE incidence, we included only the cases in which intraoperative management was performed by an anaesthesiologist. Second, patients outside the eligible period in the COMMAND VTE Registry were also excluded, which may have influenced the results of this study. As a certain number of patients were excluded due to ineligible centres, the incidences of postoperative symptomatic VTE could have been greatly influenced, especially as the analysis targeted the low event rates. Third, this is a retrospective cohort study with inherent limitations based on the observational study design. In particular, the prophylactic and therapeutic management for postoperative symptomatic VTE were based on the discretion of the attending physicians, which may have influenced clinical outcomes. However, in the COMMAND Registry, the definitions of VTE

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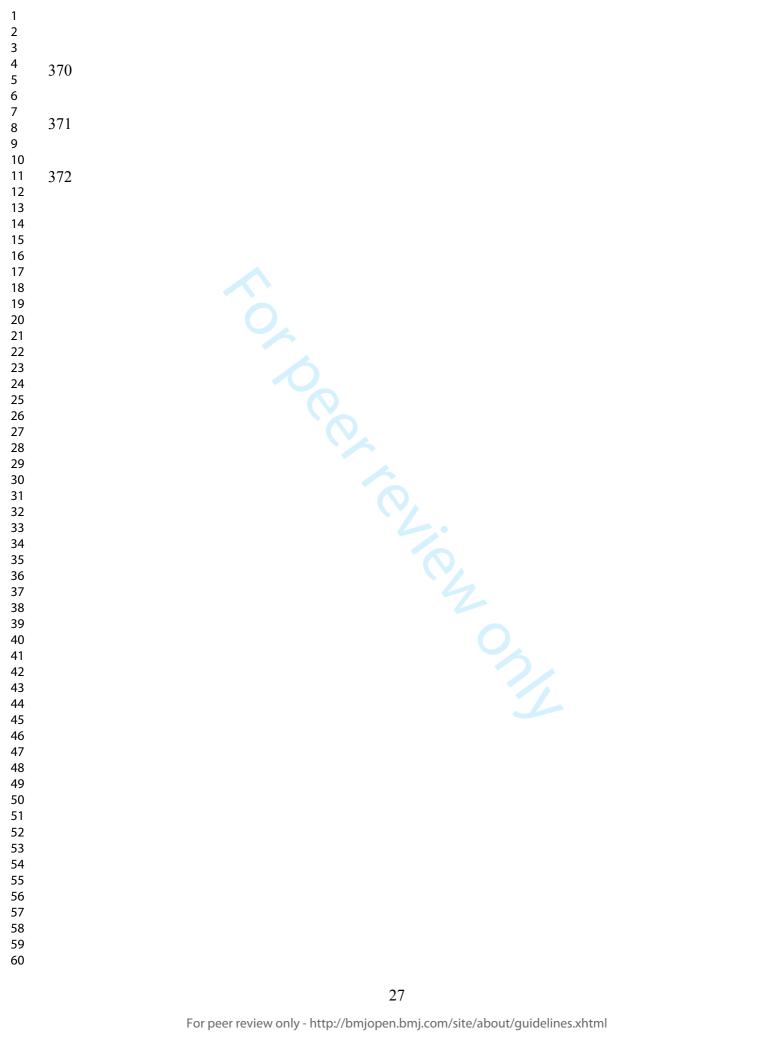
2 3		
5 4 5 6	320	were specified in advance, and the follow-up after VTE was nearly complete. Finally, we also
7 8 9	321	considered the postoperative date of onset, but the disease may have developed before the
10 11 12	322	surgery or the diagnosis. Nevertheless, we do not expect a significant gap between the onset
13 14 15	323	and diagnosis, because we included only symptomatic patients with postoperative VTE.
16 17 18 19	324	
20 21 22	325	Conclusions
23		
24 25 26	326	This study, combining the large real-world VTE database and anaesthetic database in Japan,
27 28 29	327	revealed the incidence, clinical features, and prognosis of postoperative symptomatic VTE,
30 31 32	328	providing useful information for all healthcare providers involved in various surgeries.
33 34 35	329	
36 37		
38	330	Declarations
39 40		
41 42 43	331	Acknowledgements
44		
45 46 47 48	332	We appreciate the support and collaboration of the co-investigators participating in the
40 49 50 51	333	COMMAND VTE Registry. We also thank the following doctors: Hiroshi Miyawaki,
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58 59 60	336	Yokoyama, Yoshito Shiraishi, Hiroyuki Mima, Keiji Tanimoto, Takeshi Kato, Toyohiko

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3 4 5 6	337	Ohigashi, Satoshi Takabuchi, Tetsutaro Shinomura for extracting the JSA annual report and
7 8 9	338	the additional data from each centre.
10 11 12 13 14	339	
15 16 17 18	340	Funding
19 20 21 22	341	This work was supported in part by the JSPS KAKENHI (grant number 20K09242; TM,
23 24 25	342	principal investigator). The COMMAND VTE Registry is supported by the independent
26 27 28 29	343	clinical research organization (Research Institute for Production Development, Kyoto, Japan)
30 31 32	344	and research funding from Mitsubishi Tanabe Pharma Corporation. The research funding had
33 34 35	345	no role in the design and conduct of the study; collection, management, analysis, and
36 37 38	346	interpretation of the data; and preparation, review, or approval of the manuscript.
39 40 41 42 43 44	347	
45 46 47	348	Competing interests
48 49 50 51	349	Dr. Yamashita received lecture fees from Daiichi-Sankyo, Bristol-Myers Squibb, Pfizer, and
52 53 54	350	Bayer Healthcare. Dr. Morimoto received lecture fees from Mitsubishi Tanabe Pharma and
55 56 57	351	Pfizer Japan and consultant fees from Asahi Kasei, Bristol-Myers Squibb, and Boston
58 59 60	352	Scientific. Dr. Kawakami receives consulting fees from Kaken Pharmaceutical Co., Ltd.;

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3 4 5 6	353	research funds from Sumitomo Dainippon Pharma Co., Ltd., Bayer Yakuhin Ltd., Stella
7 8 9	354	Pharma Corporation, CMIC Co., Ltd., and Pfizer Japan Inc.; honorarium from Daiichi-
10 11 12 13	355	Sankyo Co., Ltd., Mitsubishi Tanabe Pharma Corporation, AbbVie GK, Takeda
14 15 16	356	Pharmaceutical Co., Ltd., Mitsubishi Chemical Holdings Corporation, and Astra Zeneca; and
17 18 19	357	holds stocks of Real-World Data Co., Ltd. All other authors have reported that they have no
20 21 22	358	relationships relevant to the contents of this paper to disclose.
23 24 25 26	359	
27 28 29 30	360	Author Contributions
31 32 33 34	361	C.T. and Y.Y. contributed equally to this work and had full access to all the data in the study
35 36 37	362	and take responsibility for the integrity of the data and the accuracy of the data analysis. C.T.,
38 39 40 41	363	Y.Y., M.T., and T. Mizota participated in study conception. C.T. and Y.Y. performed data
42 43 44	364	analysis. C.T., Y.Y., M.T., H.Y. T. Morimoto, T.K., and T. Mizota drafted and revised the
45 46 47	365	paper. All authors approved the final draft of the manuscript for publication.
48 49 50	366	
51 52 53 54 55	367	Availability of data and materials
56 57 58	368	Data available on request from the authors. The data that support the findings of this study
59 60	369	are available from Chikashi Takeda or Yugo Yamashita, upon reasonable request.



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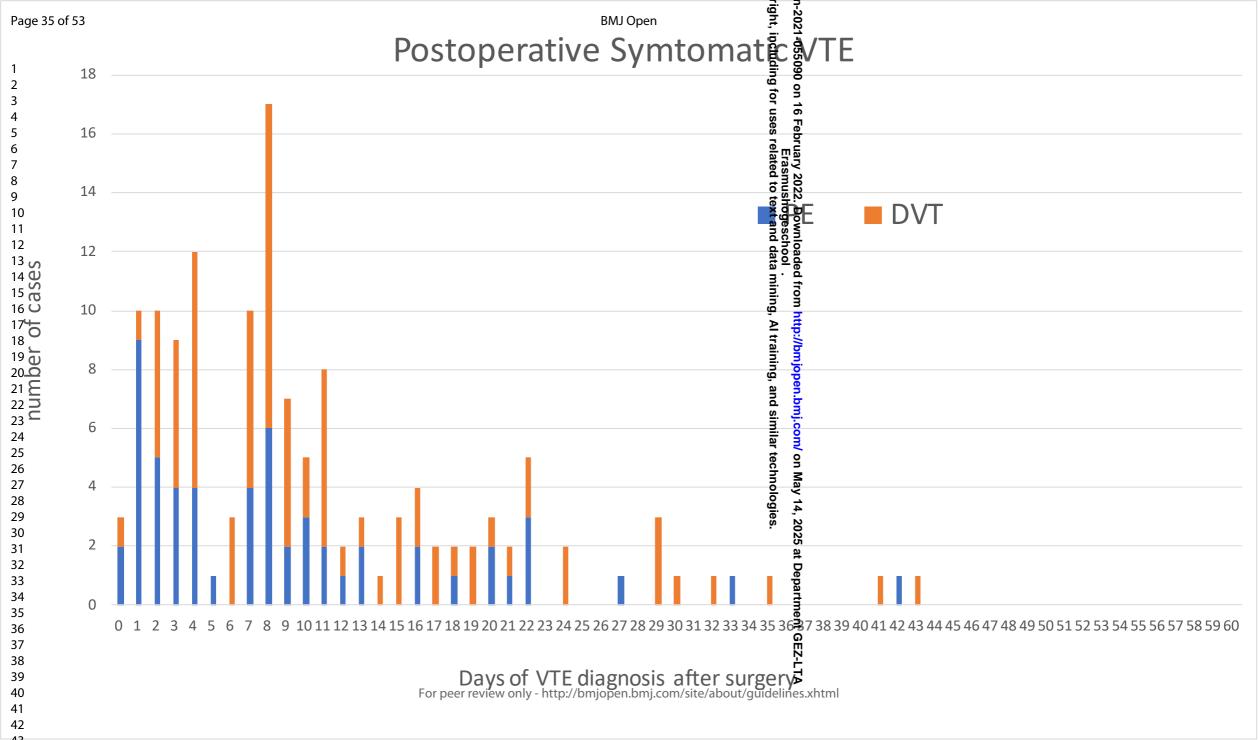
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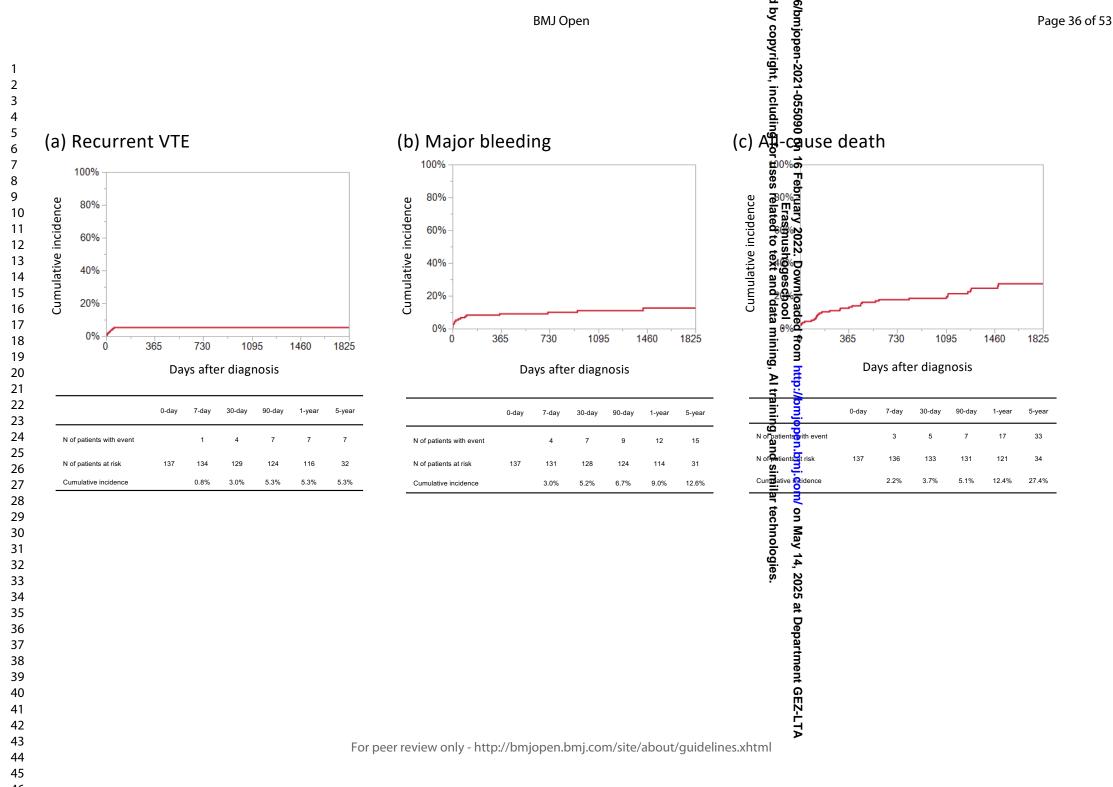
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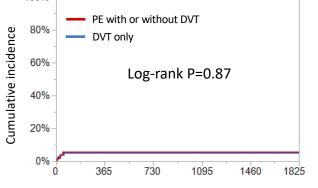
1 2		
3 4 5 6	430	Figure legends
7 8 9	431	Figure 1. Study flow diagram.
10 11 12 13	432	DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism;
14 15 16	433	JSA, Japanese Society of Anesthesiologists; COMMAND VTE, contemporary management
17 18 19	434	and outcomes in patients with venous thromboembolism.
20 21 22 23	435	
24 25 26	436	Figure 2. The distribution of days of VTE diagnosis after surgery.
27 28 29	437	DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.
30 31 32 33	438	
34 35 36	439	Figure 3. The Kaplan–Meier curves for the clinical events after VTE diagnosis.
37 38 39	440	(a) Recurrent VTE, (b) Major bleeding, and (c) All-cause death.
40 41 42 43	441	VTE, venous thromboembolism.
44 45 46	442	
47 48 49	443	Figure 4. The Kaplan–Meier curves for the clinical events after VTE diagnosis
50 51 52 53 54 55 56	444	comparing PE and DVT.
	445	(a) Recurrent VTE, (b) Major bleeding, and (c) All-cause death.
57 58 59 60	446	DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

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COMMAND VTE Registry		Annual reperts to JS/	A from each center
7 8 9 19634 patients with suspected VTE 9 10 11 12 13 14 14 15 19634 patients with suspected VTE 19634 patients with suspected VTE 19635 patients with suspected VTE 19636 patients with suspected VTE 19637 patients with suspected VTE 19636 patients with suspected VTE 19767 patients with suspected VTE 19777 patie		6 February 2022. Downloaded from http://bmjopen.bmj.com/ on May 14, Erasmushogeschool . uses related to text and data mining, Al training, and similar technologi	
12 13 14 15 16607 patients who did not meet the definition of acute symptomatic VTE	29	22. Downlu Jshogesch o text and	The training hospitals certified by JSA are obliged to submit the annual reports to JSA at the end of the year, which include total number of surgeries managed by
16 17 17 19	centres	oaded fi data mi	anesthesiologists and detailed patients' characteristics and surgical and anesthetic
 2734 patients without history of surgery within 2 months before diagnosis 		rom http: ning, Al t	information.
22 293 patients with history of surgery 23 within 2 months before diagnosis 24		/bmjope	
25 26 27 27 25 26 27 26 27		and simil	
 158 patients with history of surgery among 18 eligible centers during eligible period 		n/ on May 14, 20 ar technologies	We collected the annual reports of anesthesia from January 2010 to December
 21 patients who underwent without the management by anaesthesiologists 	18	14, 202	2013 among the 18 centers which participated in the COMMAND VTE registry.
 Study Population Study Population 137 patients who developed VTE in hospital after surgery within 2 months before diagnosis (January 2010- December 2013, 18 centers in Japan) 	centres	유 정 20 of surgery wit比the ma	93,943 cases anagement by anesthesiologists nber 2013, 18 centers in Japan)
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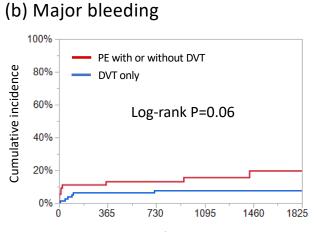


(a) Recurrent VTE



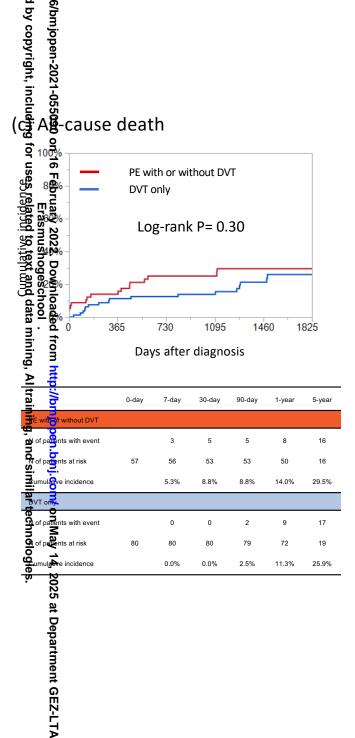
Days after diagnosis

	0-day	7-day	30-day	90-day	1-year	5-year
PE with or without DVT						
N of patients with event		0	2	3	3	3
N of patients at risk	57	56	51	50	47	16
Cumulative incidence		0.0%	3.8%	5.7%	5.7%	5.7%
DVT only						
N of patients with event		1	2	4		
N of patients at risk	80	80	79	75	70	17
Cumulative incidence		1.3%	2.5%	5.0%	5.0%	5.0%



Days after diagnosis

	0-day	7-day	30-day	90-day	1-year	5-year
PE with or without DVT						
N of patients with event		3	6	6	7	9
N of patients at risk	57	52	49	49	45	15
Cumulative incidence		5.5%	11.1%	11.1%	13.0%	19.6%
DVT only						
N of patients with event		1	1	3	5	6
N of patients at risk	80	80	80	76	70	17
Cumulative incidence		1.3%	1.3%	3.8%	6.4%	7.9%





Supplemental Table 1. Incidence	of nostoperat	tive svr	nntomatic V	/TE			6/bmjopen-2021-055090 J by copyright, including				
	Total cases	•	VTE		PE	PE	with hay poxia	PF	E with shock	Pl	E with arrest
Overall	203943	137	(0.067%)	57	(0.028%)	35	(0.0 7 %)	9	(0.004%)	6	(0.003%)
Type of anaesthesia							oruary 2(Erasm related				
Inhalation general anaesthesia	110833	49	(0.044%)	23	(0.021%)	13	(0.0 ¹ 2.00)	3	(0.003%)	1	(0.001%)
Total venous general anaesthesia	25467	12	(0.047%)	3	(0.012%)	1	Downloaded from ht hogeschood, exBand da®mining, / 0. 0.	1	(0.004%)	1	(0.004%)
Inhalation general anaesthesia							nloa scho nd da				
combined with regional	34872	46	(0.132%)	19	(0.054%)	11	(0.0 ¹ 2%)	2	(0.006%)	2	(0.006%)
anaesthesia							from http://bmjopen mining, Almaining, a (0.				
Total venous general anaesthesia							n htt				
combined with regional	12863	10	(0.078%)	5	(0.039%)	4	(0.0 🚡 1 💑	2	(0.016%)	1	(0.008%)
anaesthesia							mjoj ining				
Combined spinal and epidural anaesthesia	4078	4	(0.098%)	0	(0.000%)	0	(0.0 X 0%)	0	(0.000%)	0	(0.000%)
Epidural anaesthesia	623	0	(0.000%)	0	(0.000%)	0	sing (0.00000%)	0	(0.000%)	0	(0.000%)
Spinal anaesthesia	13522	16	(0.118%)	7	(0.052%)	6	(0.0 Å 4%)	1	(0.007%)	1	(0.007%)
Conduction anaesthesia	560	0	(0.000%)	0	(0.000%)	0	$(0.0 \overline{3} 0 \overline{3})$	0	(0.000%)	0	(0.000%)
Other	1125	0	(0.000%)	0	(0.000%)	0	(0.0%) (0.0%) 202	0	(0.000%)	0	(0.000%)
ASA classification							25 at I				
ASA PS class 1	56196	16	(0.028%)	7	(0.012%)	5	(0.009%)	1	(0.002%)	1	(0.002%)
ASA PS class 2	98410	85	(0.086%)	37	(0.038%)	22	(0.022%)	4	(0.004%)	2	(0.002%)

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4 5	ASA PS class 3		25563	17	(0.067%)	2	(0.008%)	2	(0.058%)	1	(0.004%)	1	(0.004%)
6	ASA PS class 4		549	1	(0.182%)	0	(0.000%)	0		0	(0.000%)	0	(0.000%)
7 8	ASA PS class 5		11	0	(0.000%)	0	(0.000%)	0	(0.0.0000000000000000000000000000000000	0	(0.000%)	0	(0.000%)
9	ASA PS class 6		1	0	(0.000%)	0	(0.000%)	0		0	(0.000%)	0	(0.000%)
10 11	ASA PS class 1E		5300	3	(0.057%)	3	(0.057%)	0		0	(0.000%)	0	(0.000%)
12	ASA PS class 2E		9575	6	(0.063%)	5	(0.052%)	4		2	(0.021%)	1	(0.010%)
13 14	ASA PS class 3E		6514	5	(0.077%)	2	(0.031%)	1		0	(0.000%)	0	(0.000%)
15	ASA PS class 4E		1446	4	(0.277%)	1	(0.069%)	1	(0.0 6 2 3)	1	(0.069%)	1	(0.069%)
16 17	ASA PS class 5E		109	0	(0.000%)	0	(0.000%)	0	(0.06)	0	(0.000%)	0	(0.000%)
18	ASA PS class 6E		1	0	(0.000%)	0	(0.000%)	0		0	(0.000%)	0	(0.000%)
19 20	Classification error		268	-	-	-	_	-	ng n	-	_	-	-
21									http://bmj j¦ Al trainii				
22 23	Surgical position								– –				
24	Supine position		147838	100	(0.068%)	39	(0.026%)	22	(0.0 5%)	5	(0.003%)	3	(0.002%)
25 26	Prone position		10106	6	(0.059%)	2	(0.020%)	2	(0.0 20)	1	(0.010%)	1	(0.010%)
27	Lateral position		20642	18	(0.087%)	7	(0.034%)	4		2	(0.010%)	2	(0.010%)
28 29	Lithotomy position		22882	11	(0.048%)	8	(0.035%)	6	(0.026%)	1	(0.004%)	0	(0.000%)
30	Sitting position		1069	0	(0.000%)	0	(0.000%)	0	(0.000 T	0	(0.000%)	0	(0.000%)
31 32	Other		1406	2	(0.142%)	1	(0.071%)	1		0	(0.000%)	0	(0.000%)
33									, 202 es.				
34 35	Age (years old)								5 at				
36	0-5		9518	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
37 38	6-18		10255	2	(0.020%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
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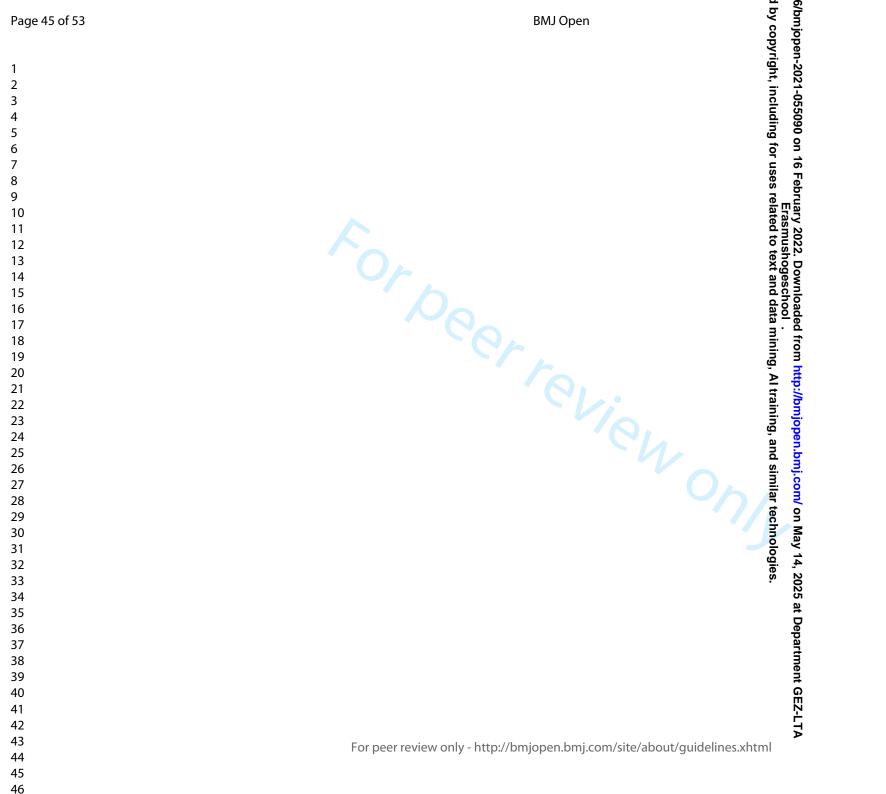
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19-65	99283	47	(0.047%)	19	(0.019%)	11	(0.0 4 1%8)	4	(0.004%)	3	(0.003%)
66-85	79796	82	(0.103%)	36	(0.045%)	22	(0.0 2 8% <u>)</u>)	4	(0.005%)	2	(0.003%)
86-	5081	6	(0.118%)	2	(0.039%)	2	(0.0	1	(0.020%)	1	(0.020%)
Classification error	10	-	-	-	-	-	bruai Er réla	-	-	-	-
Sex	4						oruary 2022. Erasmush rélated to te				
Men	99712	45	(0.045%)	16	(0.016%)	10		2	(0.002%)	1	(0.001%)
Women	104223	92	(0.088%)	41	(0.039%)	25	(0.02 data	7	(0.007%)	5	(0.005%)
Classification error	8	P_	-	-	-	-	ata r	-	-	-	-
All data were described as Abbreviations: ASA PS, A thromboembolism	number and percentage merican society anesth	e. nesiolog	gists perform			ulmona	₽ 🗧	; VTE	, venous		
Abbreviations: ASA PS, A	number and percentag	e. nesioloş	gists perform		status; PE, pr	ulmon	from <mark>Sttp://bmjopen.bmj.com/</mark> on May 14, 2025 at Department GEZ-LTA nining Al training, and similar technologies. ary	, VTE	, venous		

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	Cases of 1	recurr	ent VTE		(days)		(days)		ASA classification	y y y 2022. Dowi asmushoges ted to text an			bleedin
	1	73	Woman	24.8	9	PE with DVT	5		2	adea (I) adea fro	Spinal position		
	2	69	Woman	26.5	48	PE	Q 4	Upper abdomen	2	m Grosson (I) with R R mjoped.bmj.com (I) Al training, and similar technologi	Spinal position	AC	
	3	75	Man	21.3	27	PE with DVT	21	Lower abdomen	2	njoped.bmj.com	Lithotomy position	HT, DM, CKD, AC	
	4	53	Man	21.6	7	DVT	11	Brain	2	incont (I)	Spinal position	HT, CKD	
	5	40	Woman	14.3	59	DVT	7	Lower abdomen	2	technologies.	Spinal position	CKD, AC	
	6	60	Woman	25.8	38	DVT	6	Lower abdomen	1	C1	Spinal position	CKD	
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7	75	Woman	17.7	17	DVT	4	Lower abdomen	2	6/bmjopen-2021-055090Gn 16 Fe	Spinal position	CKD (Dialysis), AC	Major bleeding
Cases of m	ajor	bleeding		~					bruary 20 Erasm related			
1	73	Woman	24.8	25	PE with DVT	5	Brain	2	to text and data mi	Spinal position		
5	40	Woman	14.3	44	DVT	7	Lower abdomen	2	add Ga (I) with mining m	Spinal position	CKD, AC	
7	75	Woman	17.7	62	DVT	04	Lower abdomen	2	mining, Al training, and similar technologies.	Spinal position	CKD (Dialysis), AC	Major bleeding
8	62	Woman	22.3	3	PE	10	Brain	O^2	and similar	Spinal position	AC	VTE, Major bleeding
9	49	Man	22.5	4	PE	1	Brain	2		Spinal position	HT, Af, AC	
10	59	Woman	22.4	16	PE with DVT	20	Brain	3E	GÅ (I)	Spinal position	HT, CKD,	Major bleeding
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5 6 7 8 9	11	50	Man	23.5		14	PE with DVT	7	Head, pharynx, larynx Hip,	2E	990 orA(I) Ing for uses re	Spinal position	AC	
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hy copyright, including for for 6/bmjopen-2021-055090 on STROBE Statement-checklist of items that should be included in reports of observational studies Item Page **Relevant text from manuscript** No. Recommendation No. (a) Indicate the study's design with a commonly used term in the title or the abstract 1.3 "Incidence, clinical characteristics, and long-term Title and abstract 1 prognosis of postoperative symptomatic venous theomboembolism: a retrospective cohort study" Design: Retrospective observational study. Two Batasets, COMMAND VTE Registry and **B**aganese Society of Anesthesiologists (JSA) .ve and balanc. Initial report, were used for current analyses." **E** dentified 137 patients with postoperative (b) Provide in the abstract an informative and balanced summary of what was done 3-4 gy inptomatic VTE, including 57 patients with and what was found monary embolism. The incidences of Sectoperative symptomatic VTE and pulmonary **a** 'enholism were 0.067% and 0.028%, respectively, **b** based on data from 203,943 patients who Вu underwent surgery, managed by \blacktriangleright are sthesiologists, during the study period. The r incidences of postoperative symptomatic VTE valied widely, depending on surgical and anaesthetic characteristics. Postoperative symptomatic VTE occurred at a median of 8 days after surgery, with 58 patients (42%) diagnosed within 7 days. The cumulative incidence, 30 days <u>s</u> after VTE, of recurrent VTE, major bleeding, and alEcause death was 3.0%, 5.2%, and 3.7%, fe respectively." "Venous thromboembolism (VTE), including hno Introduction Explain the scientific background and rationale for the investigation being reported Background/rationale 2 6-7 <u>lo</u>g pulmonary embolism (PE) and deep vein ē the mbosis (DVT), is a serious postoperative complication which can result in an in-hospital death.[1, 2] In perioperative management, it is cracial to prevent postoperative symptomatic VE and to respond promptly, once it is reeognized. Therefore, clinicians should be faziliar with the clinical features of postoperative

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symptomatic VTE to optimize their management

strategies.

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1	3 State specific objectives, including any prespecified hypotheses 7	 including the past 20 years, several guidelines have been recommended for the prophylaxis of proventive measures, the incidence of proventive measures, the incidence of proventive measures, the incidence of proventive vTE remains high and varies from 0.5% to 2.2%, according to reports from Western countries.[6-8] However, data on postoperative VTE from a cohort/registry-based study in Asian countries are scarce. A previous attractive y reported a relatively low incidence attractive y reported a relatively low incidence attractive PE, conducted by mailing attractive PE, conducted by mailing attractive of toperative PE, conducted by mailing attractive of toperative PE, conducted by mailing attractive study of toperative of underreporting of events cannot be attractive.[10] recent studies have suggested an underestimation of VTE in Asia.[11-13] No large-scale study has systematically evaluated the incidence of postoperative symptomatic VTE in Jaaan." If therefore, with a collaborative effort between cadiologists and anaesthesiologists, we intrestigated the incidence, clinical characteristics, and prognosis of postoperative symptomatic VYEE in Jaaan." If the database and an anaesthetic database of angual reports submitted to the Japanese Society of anesthesiologists (JSA)."
32 Methods 33 Study design 34 35 36 37 38 39 40 41	m 4 Present key elements of study design early in the paper 7	 The first was Contemporary The first was Contemporary MageMent AND outcomes in patients with Venous ThromboEmbolism (COMMAND VTE) realistry, a retrospective multicentre cohort study, which provided the data on patients with postoperative symptomatic VTE. The second was the JSA annual report, which provided cross-sectional data of all patients, who underwent
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			- ,	L. subgical operations, managed by and are sthesiologists."
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-9	"Is this study, the JSA annual reports from Jaguary 2010 to December 2013 were collected from 18 centres that participated in the COMMAND VTE Registry. Furthermore, activitional data of patients with postoperative manptomatic VTE, namely operative date, perative procedure, surgical sites, surgical witton, and types of anaesthesia on anaesthet bitton, and types of anaesthesia on anaesthet that at each centre, were obtained. The bit study, the patients from the 18 centres sistered in the COMMAND VTE Registry, f the bit of the JSA annual report had been collected to be been been collected by the patient of the 11 centres of the COMMA VIE Registry as their JSA annual reports and/of activitional data on patients with postoperative symptomatic VTE were unavailable."
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	9	symptomatic VTE were unavailable." "If this study, the patients from the 18 centres registered in the COMMAND VTE Registry, f which the JSA annual report had been collecter between January 2010 and December 2013, we encolled (Figure 1). We could not enrol patient from the rest of the 11 centres of the COMMA VE Registry as their JSA annual reports and/ additional data on patients with postoperative symptomatic VTE were unavailable. We also could not register the patients between January 2014 and August 2014, since the JSA annual report was from January to December of each your. Further, within the COMMAND VTE Registry, the patients diagnosed with acute symptomatic VTE, who underwent surgery 2 months prior to the VTE diagnosis, were identified. The overall population that had repeived anaesthetic management, during the study period was retrieved from each centre's JSM annual report. Besides, additional data of
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Page 49 of 53	BMJ Open	6/bmjopen-20 4 by copyrigh
1 2 3 4 5 6		provide the symptomatic VTE, provide the symptomatic VTE, nationally operative date, operative procedure, subject of subject of an esthesia on an aesthetic charts at each centre, of were obtained."
7 8 9 10	(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	us of the second
11 Variables 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41	 Clearly define all outcomes, exposures, predictors, potential confounders, and effect 11-12 modifiers. Give diagnostic criteria, if applicable 	 2 The COMMAND VTE Registry, data for the text of pital charts or hospital databases, according to prespecified definitions, using an electronic text of prespecified definitions were elements with postoperative symptomatic VTE, identified through the COMMAND VTE Registry. Pa prespecified definition of cardiologists and the anaesthesiologists at each participating centre. Anaesthesia-associated data, such as surgical site, suggical position, and type of anaesthesia were exacted and incorporated into the data from the COMMAND VTE Registry. U outcome measures assessed in this study were recurrent VTE, major bleeding, and all-case death during the follow-up period, with a madian of 1,507 days, in the surviving patients. Refurrent VTE was defined as symptomatic PE angl/or DVT accompanied by confirmation of a new thrombus or exacerbation of the thrombus by objective imaging examinations or autopsy. Major bleeding was defined according to
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				t, includ	H le	Semostasis as a reduction in the haemoglobin by at least 2 g/dL, transfusion of at least two so of blood, or symptomatic bleeding in a cal area or an organ.[16]"
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		g for use	N	B relevant text
Bias	9	Describe any efforts to address potential sources of bias		s rela		Erelevant text
Study size	10	Explain how the study size was arrived at		ted to	asmus	Grelevant text verelevant text verelevant text verelevant text verelevant text verelevant text
				tex	5	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		ō	Ϋ́,	
Statistical methods	12	(<i>a</i>) Describe all statistical methods, including those used to control for confounding(<i>b</i>) Describe any methods used to examine subgroups and interactions	12	a mining, Al training,	with ref inc po th th	he incidence of postoperative symptomatic VTE s calculated using a combination of data from COMMAND Registry and the JSA annual orts from the 18 centres. The numerator of the adence was the number of cases of toperative symptomatic VTE extracted from COMMAND Registry; the denominator was number of surgeries in the JSA annual report." he incidence of postoperative symptomatic VTE
		СV (20	d similar te	po Th rec on sy	Fording to age, sex, surgical site, surgical sition, and types of anaesthesia was calculated. The baseline and follow-up data were separately orded for PE with or without DVT and DVT- by groups in patients with postoperative inptomatic VTE."
		(c) Explain how missing data were addressed	12	no		to imputation was performed for missing data."
		 (d) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses 		ogies.	, 1010 at D	Arelevant text
		(c) Describe any sensitivity analyses			11	
Results						<u></u>
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13-14		W	gure 1 represents the flow diagram of the study consecutive patients with acute ptomatic VTE, after screening 19,634
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2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18			(b) Give reasons for non-participation at each stage	 consecutive patients with suspected VTE for elbibility, using the chart review by the plasticians at each institution. After excluding 2,604 patients without a history of surgery within 2 months before VTE diagnosis, 293 patients were identified with postoperative symptomatic VTE during hospitalization among all 29 centres of the COMMAND VTE Registry. Furthermore, 135 The main of the eligible period and 21 patients without the management of the study population consisted of 137 patients The main of the consistent of 137 patients The management of the study population consisted of 137 patients The management of the study population consisted of 137 patients The management of the study population consisted of 137 patients The management of the study population consisted of 137 patients The management of the study population consisted of 137 patients The management of the study population consisted of 137 patients The management of the study population consisted of 137 patients The management of the study population consisted of 137 patients The management of the study population consisted of 137 patients The management of the study population consisted of 137 patients The management of the study population consisted of 137 patients The management of the study population consisted of 137 patients The population of the study population consistent of the study population consistent of surgical patients at the study population consistent of the study population consiste
19 20				G eath stage.
20 21 22 23 24	Descriptive data	14*	 (c) Consider use of a flow diagram (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders 	Figure 1 ≥ "The study flow diagram is shown in Figure 1" Table1 Table1 Table2 Table3
25 26			(b) Indicate number of participants with missing data for each variable of interest	A Norelevant text
27			(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	No relevant text
28 29 30 31 32 33 34 35 36 37 38 39 40 41	Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	14,16 The estimated incidence of postoperative symptomatic VTE was 0.067% (137/203,943) and VE with PE was 0.028% (57/203,943) (Table 1). Of the 57 PE cases, 35 patients (0.017%) had hypoxic symptoms, nine patients (0.004%) presented with shock, and six patients (0.003%) had cardiac arrest. As for the surgical site, the incidence of postoperative symptomatic VTE was reputively high in surgeries involving the brain, high, and upper/lower limbs. In terms of the types of naesthesia, regional anaesthesia with or whout general anaesthesia (0.100%) was associated with a higher incidence of VTE than general anaesthesia alone (0.045%) (Table 1 and
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	Supplemental Ta "Table 2 shows t claracteristics of symptomatic VT from the surgery symptomatic VT duration was 8 di (42%) were diag multicle 79 patients of a symptomatic v duration was 8 di (42%) were diag a symptomatic v duration was 8 di (42%) were diag (42%) were diag (42%) were diag (42%) were diag (42%) were diag (43%) were diag (44%) were diag (43%) were diag (43%) were diag (43%) were diag (43%) were diag (43%) were diag (43%) were diag (43%) were diag (43%) were diag (ble 1)." he demographic and clinical patients with postoperative E. Figure 2 presents the duration to the diagnosis of postoperative E. The median inter-quartile ays (4–15 days); and 58 patients nosed within 7 days of surgery, 6 (58%) were diagnosed 7 days The greatest number of patients with VTE on postoperative day
	Case-control study—Report numbers in each exposure category, or summary The second study - Report numbers of outcome events or summary measures Cross-sectional study—Report numbers of outcome events or summary measures The second study - Report numbers of outcome events or summary measures	
Main results	 16 (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included 14 a Under the estimated in the symptomatic VT adjusted for and why they were included 14 b Under the estimated in the symptomatic VT adjusted for and why they were included 14 b Under the estimate in the symptomatic VT adjusted for and why they were included 14 b Under the estimate in the symptomatic VT adjusted for and why they were included 14 b Under the estimate in the symptomatic VT adjusted for and why they were included 14 b Under the estimate in the symptomatic VT adjusted for and why they were included 14 b Under the estimate in the symptomatic VT adjusted for and why they were included 14 b Under the estimate in the symptomatic VT adjusted for and why they were included 14 b Under the estimate in the symptomatic VT adjusted for and why they were included 14 b Under the estimate in the symptomatic VT adjusted for and why they were included 14 b Under the estimate in the symptomatic VT adjusted for and why they were included 14 b Under the estimate in the symptomatic VT adjusted for adjusted for and why they were included 14 b Under the symptomatic VT adjusted for adjuste	ncidence of postoperative E was 0.067% (137/203,943) and s 0.028% (57/203,943) (Table 1). es, 35 patients (0.017%) had ns, nine patients (0.004%) nock, and six patients (0.003%) t."
	(b) Report category boundaries when continuous variables were categorizedG© If relevant, consider translating estimates of relative risk into absolute risk for agmeaningful time periodg	••
Other analyses	17 Report other analyses done—eg analyses of subgroups and interactions, and sensitivity Si 17 Report other analyses done—eg analyses of subgroups and interactions, and sensitivity Si	
Discussion	chno Ma	
Key results	18 Summarise key results with reference to study objectives 20 G 4 The main findir 20 C 4 Th	ngs of this study are as follows: 1) postoperative symptomatic VTE s after surgery was 0.067% and as 0.028%, representing 203,943 18 centres in Japan; 2) the postoperative symptomatic VTE according to surgical and acteristics; and 3) nearly half of e diagnosed within 7 days of the the rest were diagnosed 7 days th the highest number of patients
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3 of 53	BMJ Open	6/bmjopen-20 1 by copyrigh
		L. diagnosed on postoperative day 8."
Limitations	19 Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	23-24 Construction 23-24 Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construction Construc
Interpretation	20 Give a cautious overall interpretation of results considering objectives, limitations,	 because we included only symptomatic patients with postoperative VTE." 24 "This study, combining the large real-world VT
incipictution	multiplicity of analyses, results from similar studies, and other relevant evidence	database and anaesthetic database in Japan, recealed the incidence, clinical features, and prognosis of postoperative symptomatic VTE, providing useful information for all healthcare providers involved in various surgeries."
Generalizability	21 Discuss the generalizability (external validity) of the study results	21 "Igrst, two different databases were combined to estimate the incidence of postoperative

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Other information	nloa da
Funding 22 Give the source of funding and the role of the funders for the present study and, if 2: applicable, for the original study on which the present article is based 2: 2:	 A manual state of the study; collection, management, analysis, and interpretation of the manuscript."
*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed grou	te o
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and publish checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosm http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at	edicing org/, Annals of Internal Medicine at
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Incidence, clinical characteristics, and long-term prognosis of postoperative symptomatic venous thromboembolism: a retrospective cohort study

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1	Incidence, clinical characteristics, and long-term prognosis of postoperative
2	symptomatic venous thromboembolism: a retrospective cohort study
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4	Chikashi Takeda, MD, PhD ^{1,2} ; Yugo Yamashita, MD, PhD ³ ; Masato Takeuchi, MD, PhD,
5	MPH ² ; Hiroshi Yonekura, MD ^{2,4} ; Li Dong, MD ¹ ; Miho Hamada, MD ¹ ; Akiko Hirotsu, MD,
6	PhD ¹ ; Koh Ono, MD, PhD ³ ; Koji Kawakami, MD, PhD ² ; Kazuhiko Fukuda, MD, PhD ¹ ;
7	Takeshi Morimoto, MD, PhD, MPH ⁵ ; Takeshi Kimura, MD, PhD ³ ; Toshiyuki Mizota, MD,
8	PhD ¹ *
9	
10	¹ Department of Anesthesia, Kyoto University Hospital, Kyoto, Japan
11	² Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health,
12	Kyoto University, Kyoto, Japan
13	³ Department of Cardiology, Kyoto University Hospital, Kyoto, Japan
14	⁴ Department of Clinical Anesthesiology, Mie University Hospital, Tsu, Mie, Japan
15	⁵ Department of Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya, Japan
16	
17	Corresponding Author: Toshiyuki Mizota
18	Department of Anesthesia, Kyoto University Hospital, 54 Shogoin-Kawahara-Cho, Sakyo-
19	Ku, Kyoto 606-8507, Japan

1 2		
3 4 5	20	E-mail: mizota@kuhp.kyoto-u.ac.jp
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ABSTRACT

6 7 8 9	24	Objectives: The purpose of this study was to evaluate the incidence, clinical characteristics,
10 11 12	25	and prognosis of postoperative symptomatic VTE in Japan.
13 14 15 16	26	Design: Retrospective observational study. Two datasets, COMMAND VTE Registry and
17 18 19	27	Japanese Society of Anesthesiologists (JSA) annual report, were used for current analyses.
20 21 22	28	Setting: Eighteen of 29 centres that participated in the COMMAND VTE Registry.
23 24 25 26	29	Participants: Acute symptomatic VTE patients who had undergone surgery 2 months prior
27 28 29	30	to the diagnosis at 18 centres from January 2010 to December 2013 were identified in the
30 31 32	31	COMMAND VTE Registry. From each centre's JSA annual report, the overall population
33 34 35	32	that had received anaesthetic management during this period was retrieved.
36 37 38 39	33	Interventions: None.
40 41 42	34	Primary and secondary outcome measures: The primary outcome was the incidences and
43 44 45	35	clinical characteristics of postoperative symptomatic VTE. The secondary outcomes were
46 47 48 49	36	recurrent VTE, major bleeding, and all-cause death.
50 51 52	37	Results: We identified 137 patients with postoperative symptomatic VTE, including 57
53 54 55	38	patients with pulmonary embolism. The incidences of postoperative symptomatic VTE and
56 57 58 59 60	39	pulmonary embolism were 0.067% and 0.028%, respectively, based on data from 203,943

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patients who underwent surgery, managed by anaesthesiologists, during the study period. The incidences of postoperative symptomatic VTE varied widely, depending on surgical and anaesthetic characteristics. Postoperative symptomatic VTE occurred at a median of 8 days after surgery, with 58 patients (42%) diagnosed within 7 days. The cumulative incidence, 30 days after VTE, of recurrent VTE, major bleeding, and all-cause death was 3.0%, 5.2%, and 3.7%, respectively. Conclusion: This study, combining the large real-world VTE and anaesthesiology databases in Japan revealed the incidence, clinical features, and prognosis of postoperative symptomatic VTE, providing useful insights for all healthcare providers involved in various surgeries. Trial registration: Not applicable. Key words: Venous thromboembolism; Pulmonary thromboembolism; Deep vein thrombosis; Postoperative; Prognosis

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ARTICLE SUMMARY

5	STRENGTHS	AND LIMIT	ATIONS OF	THIS STUDY
-				

- VTE is considered relatively rare in Asian people, and the small number of cases makes
- 7 epidemiological studies difficult to perform.
- This study combines data from the large real-world VTE database and anaesthetic
- 59 database in Japan to provide information about the incidence, clinical features, and
- 60 prognosis of postoperative symptomatic VTE.
 - Another important feature of the current study was the comparison of the incidence of
 - 62 postoperative symptomatic VTE across surgical sites.
 - This was a retrospective cohort study with inherent limitations based on its observational
 - nature. Furthermore, as a certain number of patients from ineligible centres were
- 65 excluded, the incidence of postoperative symptomatic VTE may have been influenced.

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66	INTRODUCTION
67	Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein
68	thrombosis (DVT), is a serious postoperative complication which can result in an in-hospital
69	death. [1, 2] In perioperative management, it is crucial to prevent postoperative symptomatic
70	VTE and to respond promptly, once it is recognized. Therefore, clinicians should be familiar
71	with the clinical features of postoperative symptomatic VTE to optimise their management
72	strategies.
73	Over the past 20 years, several guidelines have been recommended for the
74	prophylaxis of postoperative VTE.[3-5] Despite the use of preventive measures, the incidence
75	of postoperative VTE remains high and varies from 0.58% to 2.2%, according to reports from
76	Western countries.[6-8] Furthermore, the incidence rate of symptomatic VTE in patients after
77	spinal surgery for metastases in the spine has been reported to be substantially higher
78	(11%).[9] However, data on postoperative VTE from a cohort/registry-based study in Asian
79	countries are scarce. A previous study reported a relatively low incidence (0.031%) of
80	postoperative VTE throughout Japan.[10] However, it was a surveillance study of
81	postoperative PE, conducted by mailing questionnaires to anaesthesiologists; therefore, the
82	possibility of underreporting of events cannot be denied. Although the incidence of VTE in

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40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57	

83	Asia has been considered to be lower than Western countries,[11] recent studies have
84	suggested an underestimation of VTE in Asia.[12-14] No large-scale study has systematically
85	evaluated the incidence of postoperative symptomatic VTE in Japan.
86	Therefore, with a collaborative effort between cardiologists and anaesthesiologists,
87	we investigated the incidence, clinical characteristics, and prognosis of postoperative
88	symptomatic VTE, using a large, observational, real-world VTE database and an anaesthetic
89	database of annual reports submitted to the Japanese Society of Anesthesiologists (JSA).
90	
91	METHODS
92	Study design, setting, and population
93	In this study, two datasets were used for analyses. The first was Contemporary ManageMent
94	AND outcomes in patients with Venous ThromboEmbolism (COMMAND VTE) registry, a
95	retrospective multicentre cohort study, which provided the data on patients with
96	postoperative symptomatic VTE. The second was the JSA annual report, which provided
97	cross-sectional data of all patients, who underwent surgical operations, managed by
98	anaesthesiologists.

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<u> </u>		
3 1 5 5	99	The design of the COMMAND VTE Registry has been reported in detail
7 3 9	100	elsewhere.[15] Briefly, this physician-initiated registry was a large cohort of consecutive
0 1 2	101	patients with acute symptomatic VTE, who were objectively confirmed by the cardiologists
3 4 5 6	102	at 29 centres in Japan, between January 2010 and August 2014. In this registry, the hospital
7 8 9	103	databases were searched for clinical diagnoses and imaging examinations of patients with
20 21 22	104	suspected VTE, and consecutive patients who met the definition of acute symptomatic VTE
21 22 23 24 25 26 27 28	105	were enrolled. Baseline data were obtained from the hospital charts or hospital databases.
27 28 29	106	Follow-up data on vital status, recurrent VTE, bleeding, and status of anticoagulation
30 31 32 33 34 35	107	therapy, according to the prespecified definitions, were collected from the hospital charts,
83 84 85 86	108	hospital databases, or by contacting patients, relatives, and/or referring to physicians through
80 87 88 89	109	phone and/or mail.
10 11 12	110	As for the JSA annual reports, the training hospitals certified by the JSA are required
13 14 15 16	111	to submit the annual reports to the JSA at the end of the year, which includes the total number
17 18 19	112	of surgeries managed by anaesthesiologists, patient characteristics in detail, and surgical and
50	113	anaesthetic information.
51 52 53 54 55	114	In this study, the JSA annual reports from January 2010 to December 2013 were
56 57 58 59 50	115	collected from 18 centres that participated in the COMMAND VTE Registry. Furthermore,

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4 5 6	116	additional data of patients with postoperative symptomatic VTE, namely operative date,
7 8 9	117	operative procedure, surgical sites, surgical position, and types of anaesthesia on anaesthetic
10 11 12	118	charts at each centre, were obtained.
13 14 15 16	119	In this study, patients from the 18 centres registered in the COMMAND VTE
17 18 19	120	Registry, for which the JSA annual report was collected between January 2010 and
20 21 22	121	December 2013, were enrolled (Figure 1). We could not enrol patients from the remaining 11
23 24 25 26	122	centres of the COMMAND VTE Registry as their JSA annual reports and/or additional data
27 28 29	123	on patients with postoperative symptomatic VTE were unavailable. We also could not
30 31 32	124	register the patients between January 2014 and August 2014, since the JSA annual report was
33 34 35 36	125	from January to December of each year. Furthermore, within the COMMAND VTE Registry,
37 38 39	126	cases of symptomatic postoperative VTE within 2 months [16] were identified. The overall
40 41 42	127	population that had received anaesthetic management, during the study period was retrieved
43 44 45 46	128	from each centre's JSA annual report. Besides, additional data of patients with postoperative
47 48 49	129	symptomatic VTE, namely surgery date, surgical procedure, surgical site, surgical position,
50 51 52	130	and type of anaesthesia on anaesthetic charts at each centre, were obtained.
53 54 55 56 57 58 59	131	Ethics
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	132	This retrospective observational study was conducted according to the STrengthening the
	133	Reporting of OBservational studies in Epidemiology (STROBE) guidelines. This study was
) <u>!</u>	134	approved by the Ethics Committee of the Kyoto University Hospital, Kyoto, Japan (approval
; ; ;	135	number: R1822, December 18th, 2018; Chairperson Prof Shinji Kosugi). Following Ethics
, , ,	136	Committee approval, additional data, including the JSA annual reports, were collected from
) !	137	the centres listed in the Command VTE Registry, from March 2019 to September 2019.
; ; ;	138	Written informed consent from each patient was waived, because we used clinical
) 7 }	139	information obtained in routine clinical practice. This method is concordant with the
) <u>!</u>	140	guidelines for epidemiological studies issued by the Ministry of Health, Labor, and Welfare
; ; ;	141	in Japan.
) , }	142	Patient and Public Involvement Statement
)	143	Patients or the public were not involved in the design, conduct, reporting, or dissemination
; ;	144	plans of our research.
; ; ;	145	Definition of postoperative symptomatic venous thromboembolism
,)	146	In this study, postoperative symptomatic VTE was defined as a thromboembolic event that
; ;	147	occurred within 2 months of the postoperative period.[16] The symptoms of VTE were
; ; ;	148	defined as sudden onset dyspnoea, pleuritic and substernal chest pain, cough, fever,
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149	haemoptysis and syncope for PE; and erythema, warmth, pain, swelling, tenderness, and pain
150	upon dorsiflexion of the foot for DVT. Additionally, a sudden onset of abnormality in the
151	vital signs, such as a decrease in arterial oxygen saturation and hypotension were considered
152	as symptoms of PE.
153	Collection of baseline patient characteristics and clinical follow-up data
154	In the COMMAND VTE Registry, data for the patients' characteristics were collected from
155	the hospital charts or hospital databases, according to the prespecified definitions, using an
156	electronic case report form in a web-based database system. Physicians at each of the
157	institutions were responsible for data entry, and data were automatically examined for
158	missing or contradictory input and out-of-range values. Additional edits were performed at
159	the general office of the registry.
160	Patients with postoperative symptomatic VTE, identified through the COMMAND
161	VTE Registry, were further investigated at each centre using the anaesthetic charts created
162	through the collaboration of cardiologists and anaesthesiologists at each participating centre.
163	Anaesthesia-associated data, such as surgical site, surgical position, and type of anaesthesia
164	were extracted and incorporated into the data from the COMMAND VTE Registry.

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3 4 5 5	165	The outcome measures assessed in this study were recurrent VTE, major bleeding,
7 3 9	166	and all-cause death during the follow-up period, with a median of 1,507 days, in the
10 11 12	167	surviving patients. Recurrent VTE was defined as symptomatic PE and/or DVT accompanied
13 14 15 16	168	by confirmation of a new thrombus or exacerbation of the thrombus by objective imaging
17 18 19	169	examinations or autopsy. Major bleeding was defined according to the International Society
20 21 22	170	of Thrombosis and Hemostasis as a reduction in the haemoglobin level by at least 2 g/dL,
21 22 23 24 25 26 27 28	171	transfusion of at least two units of blood, or symptomatic bleeding in a critical area or an
27 28 29	172	organ.[17]
30 31 32	173	Statistical analysis
30 31 32 33 34 35 36 37	174	The incidence of postoperative symptomatic VTE was calculated using a combination of data
37 38 39	175	from the COMMAND Registry and the JSA annual reports from the 18 centres. The
40 41 42	176	numerator of the incidence was the number of cases of postoperative symptomatic VTE
43 44 45	177	extracted from the COMMAND Registry; the denominator was the number of surgeries in
46 47 48 49	178	the JSA annual report. The incidence of postoperative symptomatic VTE according to age,
50 51	179	sex, surgical site, surgical position, and type of anaesthesia was calculated. The baseline and
52 53 54 55 56	180	follow-up data were separately recorded for PE with or without DVT and DVT-only groups
56 57 58 59	181	in patients with postoperative symptomatic VTE. No imputation was performed for missing
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182	data. Categorical variables were calculated as numbers and percentages, and continuous
183	variables were calculated as the means and standard deviations or the medians and
184	interquartile ranges (IQR) based on their distributions. Additionally, the timing of the
185	postoperative symptomatic VTE occurrence after the surgery was described. The Kaplan-
186	Meier method was used to estimate the cumulative incidences of recurrent VTE, major
187	bleeding, and all-cause death. The log-rank test was used to assess the differences in the
188	cumulative incidences of the events between the PE- and DVT-only groups. In addition, we
189	conducted an exploratory analysis to compare patients with and without active cancer. Two-
190	sided P-values of less than 0.05 were considered significant. All statistical analyses were
191	performed using SAS version 9.4 for Windows (SAS Institute Inc.; Cary, NC, USA) or JMP
192	version 14.0.0 (SAS Institute Inc.; Cary, NC, USA).
193	
194	
195	RESULTS
196	Figure 1 represents the flow diagram of the study. We enrolled 3,027 consecutive patients
197	with acute symptomatic VTE, after screening 19,634 consecutive patients with suspected
198	VTE for eligibility, using the chart review by the physicians at each institution. After

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	199	excluding 2,734 patients without a history of surgery within 2 months before VTE diagnosis,
	200	293 patients were identified with postoperative symptomatic VTE during hospitalisation
0 1 2 3 4 5 6	201	among all 29 centres of the COMMAND VTE Registry. Furthermore, 135 patients outside
	202	the eligible period and 21 patients who underwent surgery without the management by
6 7 8 9	203	anaesthesiologists, were excluded. Finally, the study population consisted of 137 patients
0 1 2 3	204	diagnosed with VTE within 2 months after surgery, from 18 centres, between January 2010
3 4 5 6	205	and December 2013. The total number of surgical cases managed by anaesthesiologists
6 7 8 9	206	during the study period in 18 centres was 203,943.
9 0 1 2 3	207	Incidence of postoperative symptomatic venous thromboembolism
4 5	208	The estimated incidence of postoperative symptomatic VTE was 0.067% (137/203,943) and
6 7 8 9	209	VTE with PE was 0.028% (57/203,943) (Table 1). Of the 57 PE cases, 35 patients (61.4%)
0 1	210	had hypoxic symptoms, 9 patients (15.8%) presented with shock, and 6 patients (10.5%) had
2 3 4 5 6 7 8	211	cardiac arrest. As for the surgical site, the incidence of postoperative symptomatic VTE was
6 7 8	212	relatively high in surgeries involving the brain, hip, and upper/lower limbs. In terms of the
9 0 1 2	213	types of anaesthesia, regional anaesthesia with or without general anaesthesia (0.100%) was
1 2 3 4 5 6 7	214	associated with a higher incidence of VTE than general anaesthesia alone (0.045%) (Table 1
6 7 8 9	215	and Supplemental Table 1).

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6 T	Table 1. Incidence of pos	" SUUDEI ALI T.	A symnt/	omatic VTE				clu			
		Total cases		VTE		PE	PE wi		PE with shock	P	E with arrest
=	Overall	203943	137	(0.067%)	57	(0.028%)	35	(0.017%) Erasmushogest P<0.001 (0.011%) and (0.011%) Erasmushogest to text and (0.011%)	9 (0.004%)	6	(0.003%)
_	Surgical Site		P<	<0.001	Р	P<0.001	P	ed to te 2<0.001	P<0.001		P<0.001
-	Brain	9299	15	(0.161%)	8	(0.086%)	1) (0.000%)	0	(0.000%)
	Thorax	11100	4	(0.036%)	3	(0.027%)	2		(0.009%)	1	(0.009%)
	Cardiovascular	13637	6	(0.044%)	-1	(0.007%)	1	(0.007%) ⁵ - قر	(0.007%)	1	(0.007%)
,	Thorax and abdomen	1656	2	(0.121%)	0	(0.000%)	0	(0.018%) aded from (0.007%) mining (0.000%) mining (0.000%) mining) (0.000%)	0	(0.000%)
	Upper abdomen	27035	17	(0.063%)	11	(0.041%)	8	(0.030%) È	(0.004%)	0	(0.000%)
	Lower abdomen	42875	31	(0.072%)	16	(0.037%)	11	(0.026%)	3 (0.007%)	1	(0.002%)
	Caesarean section	5056	0	(0.000%)	0	(0.000%)	0	(0.030%) training (0.026%) ining (0.000%) a) (0.000%)	0	(0.000%)
	Head, pharynx, larynx	35414	4	(0.011%)	2	(0.006%)	2			0	(0.000%)
	Chest, abdominal wall, perineum	22633	3	(0.013%)	2	(0.009%)	2	(0.006%) ^{similar} (0.009%) ^r tech (0.009%) ^r tech) (0.000%)	0	(0.000%)
	Spine	7040	7	(0.099%)	3	(0.043%)	2	(0.028%) <u>o</u> Maj	(0.014%)	1	(0.014%)
	Hip, upper/lower limbs	25160	48	(0.191%)	11	(0.044%)	6	(0.024%)jes 14,2	2 (0.008%)	2	(0.008%)
	Other	2038	0	. , ,	0	(0	(0.024%) (0.000%) (0.000%)) (0.000%)	0	(0.000%)
	All data are described as n		nd percer					a			× ,
	Abbreviations: PE, pulmo							- - -		-	

219	Baseline characteristics and timing of venous th	rombo	embolism dia	agnosis	5			
220	Table 2 shows the demographic and clinical charac	cteristic	s of patients w	with po	stoperative			
221	symptomatic VTE. Figure 2 presents the duration from the surgery to the diagnosis of							
222	postoperative symptomatic VTE. The median inter	-quartil	le duration wa	ıs 8 day	ys (4–15 da	ys);	-	P
223	and 58 patients (42%) were diagnosed within 7 day	ys of su	rgery, while 7	9 patie	ents (58%)	were	T only	rotected k
224	diagnosed 7 days after the surgery. The greatest nu	imber o	of patients were	e diagr	nosed with	VTE	יז כטרין. פווינקסט ני	y copyric
225	on postoperative day 8.						y,	aht. inclu
226	Table 2. Baseline patients' characteristics							ding for u
	Total VTE		PE with or without DVT		DV	T only	E Ises rela	
		N=137						tra,
		N=	=137		[=57)		N=80) a	rasmus ated to
	Baseline characteristics	N	=137			(1	N=80) 8	smushou
	Baseline characteristics Age (years)		= 137 ±15.5		I=57)	(1	N=80) 8	smushou
		66.2		(N 67.7	I=57)	(1	5	smushou
	Age (years)	66.2 55	±15.5	(N 67.7 22	±12.6	(1 65.1 33	N=80) ±17.2 (41.3%	smushogeschool . ed to text and data n
	Age (years) Men	66.2 55 56.3	±15.5 (40.1%)	(N 67.7 22 57.8	±12.6 (38.6%)	(1 65.1 33	N=80) ±17.2 (41.3%	smushogeschool . ed to text and data n
	Age (years) Men Body weight (kg)	66.2 55 56.3	±15.5 (40.1%) ±11.8	(N 67.7 22 57.8	±12.6 (38.6%) ±11.1	(1 65.1 33 55.3	N=80) ±17.2 (41.3%	smushogeschool .
	Age (years) Men Body weight (kg) Body mass index (kg/m ²)	66.2 55 56.3	±15.5 (40.1%) ±11.8	(N 67.7 22 57.8	±12.6 (38.6%) ±11.1	(1 65.1 33 55.3	N=80) ±17.2 (41.3%	smushogeschool .
	Age (years) Men Body weight (kg) Body mass index (kg/m ²) Surgical and anaesthesia characteristics	66.2 55 56.3	±15.5 (40.1%) ±11.8	(N 67.7 22 57.8 23.6	±12.6 (38.6%) ±11.1	(1 65.1 33 55.3	N=80) ±17.2 (41.3%	smushogeschool .
	Age (years) Men Body weight (kg) Body mass index (kg/m ²) Surgical and anaesthesia characteristics ASA PS	66.2 55 56.3 23.2	±15.5 (40.1%) ±11.8 ±4.3	(N 67.7 22 57.8 23.6	±12.6 (38.6%) ±11.1 ±3.7	(1 65.1 33 55.3 22.9	N=80) ±17.2 (41.3% ±12.3	smushogeschool.
	Age (years) Men Body weight (kg) Body mass index (kg/m ²) Surgical and anaesthesia characteristics ASA PS ASA PS 1	66.2 55 56.3 23.2 19	±15.5 (40.1%) ±11.8 ±4.3 (13.9%)	(N 67.7 22 57.8 23.6 10 42	± 12.6 (38.6%) ± 11.1 ± 3.7 (17.5%)	(1 65.1 33 55.3 22.9 9	N=80) ± 17.2 $(41.3)^{6}$ ± 12.3 ± 4.7 $(11.3)^{6}$ $(61.3)^{6}$ $(22.5)^{6}$	smushogeschool. ed to text and data mining. Al training. and statilarte
	Age (years) Men Body weight (kg) Body mass index (kg/m ²) Surgical and anaesthesia characteristics ASA PS ASA PS 1 ASA PS 2	66.2 55 56.3 23.2 19 91	± 15.5 (40.1%) ± 11.8 ± 4.3 (13.9%) (66.4%)	(N 67.7 22 57.8 23.6 10 42 4	$\begin{array}{l} \pm 12.6 \\ (38.6\%) \\ \pm 11.1 \\ \pm 3.7 \end{array}$ (17.5%) (73.7%)	(1 65.1 33 55.3 22.9 9 49	N=80) ± 17.2 $(41.3)^{6}$ ± 12.3 ± 4.7 $(11.3)^{6}$ $(61.3)^{6}$ $(22.5)^{6}$	smushogeschool. ed to text and data mining. Al training. and statilarte
	Age (years) Men Body weight (kg) Body mass index (kg/m ²) Surgical and anaesthesia characteristics ASA PS ASA PS 1 ASA PS 2 ASA PS 3	66.2 55 56.3 23.2 19 91 22	± 15.5 (40.1%) ± 11.8 ± 4.3 (13.9%) (66.4%) (16.1%)	(N 67.7 22 57.8 23.6 10 42 4 1	$\begin{array}{l} \pm 12.6 \\ (38.6\%) \\ \pm 11.1 \\ \pm 3.7 \end{array}$ $(17.5\%) \\ (73.7\%) \\ (7.0\%) \\ (7.0\%) \end{array}$	(1 65.1 33 55.3 22.9 9 49 18	N=80) ± 17.2 $(41.3)^{6}$ ± 12.3 ± 4.7 $(11.3)^{6}$ $(61.3)^{6}$ $(22.5)^{6}$	smushogeschool. ed to text and data mining. Al training. and statilarte
	Age (years) Men Body weight (kg) Body mass index (kg/m ²) Surgical and anaesthesia characteristics ASA PS ASA PS 1 ASA PS 2 ASA PS 3 ASA PS 4	66.2 55 56.3 23.2 19 91 22 5	± 15.5 (40.1%) ± 11.8 ± 4.3 (13.9%) (66.4%) (16.1%) (3.6%)	(N 67.7 22 57.8 23.6 10 42 4 1	$\begin{array}{l} \pm 12.6 \\ (38.6\%) \\ \pm 11.1 \\ \pm 3.7 \end{array}$ $\begin{array}{l} (17.5\%) \\ (73.7\%) \\ (7.0\%) \\ (1.8\%) \end{array}$	(1 65.1 33 55.3 22.9 9 49 18 4	N=80) ± 17.2 (41.3%) ± 12.3 ± 4.7 (11.3%) (61.3%)	smushogeschool. ed to text and data mining. Al training. and statilarte
	Age (years) Men Body weight (kg) Body mass index (kg/m ²) Surgical and anaesthesia characteristics ASA PS ASA PS 1 ASA PS 2 ASA PS 3 ASA PS 4 Emergent surgery	66.2 55 56.3 23.2 19 91 22 5	± 15.5 (40.1%) ± 11.8 ± 4.3 (13.9%) (66.4%) (16.1%) (3.6%)	 (N 67.7 22 57.8 23.6 10 42 4 1 11 	$\begin{array}{l} \pm 12.6 \\ (38.6\%) \\ \pm 11.1 \\ \pm 3.7 \end{array}$ $\begin{array}{l} (17.5\%) \\ (73.7\%) \\ (7.0\%) \\ (1.8\%) \end{array}$	(1 65.1 33 55.3 22.9 9 49 18 4	N=80) ± 17.2 (41.3%) ± 12.3 ± 4.7 (11.3%) (61.3%) (22.5%) (5.0%) (8.8%)	smushogeschool ad to text and data mining. Al training, and similaritechnologies.
	Age (years) Men Body weight (kg) Body mass index (kg/m ²) Surgical and anaesthesia characteristics ASA PS ASA PS 1 ASA PS 2 ASA PS 3 ASA PS 4 Emergent surgery Surgical site	66.2 55 56.3 23.2 19 91 22 5 18	± 15.5 (40.1%) ± 11.8 ± 4.3 (13.9%) (66.4%) (16.1%) (3.6%) (13.1%)	 (N 67.7 22 57.8 23.6 10 42 4 1 11 	$\begin{array}{l} \pm 12.6 \\ (38.6\%) \\ \pm 11.1 \\ \pm 3.7 \\ (17.5\%) \\ (73.7\%) \\ (7.0\%) \\ (1.8\%) \\ (19.3\%) \end{array}$	(1 65.1 33 55.3 22.9 9 49 18 4 7	N=80) ± 17.2 (41.3%) ± 12.3 ± 4.7 (11.3%) (61.3%) (22.5%) (5.0%) (8.8%)	smushogeschool.

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2 3	Condicuscoulor	C	(4,40/)	1	(1.00/)	F	(6.20/)
4 5	Cardiovascular Thorax and abdomen	6	(4.4%)	1	(1.8%)	5	(6.3%) (2.5%)
6		2	(1.5%)	0	(0.0%)	2	
7 8	Upper abdomen	17	(12.4%)	11	(19.3%)	6 15	(7.5%)
9 10	Lower abdomen	31	(22.6%)	16	(28.1%)	15	(18.8%)
11	Head and neck	4	(2.9%)	2	(3.5%)	2	(2.5%) -
12 13	Chest abdominal wall and perineum	3	(2.2%)	2	(3.5%)	1	(1.3%)
14 15	Spine	/	(5.1%)	3	(5.3%)	4	(5.0%)
16	Type of Anaesthesia	(1	(1150 / 1)	20	(15, 0)	25	(43.8%)
17 18	General anaesthesia	61	(44.5%)	26 24	(45.6%)	35	(43.8% g)
19 20	General anaesthesia with regional anaesthesia	56	(40.9%)	24	(42.1%)	32	(40.0%)
21	Local anaesthesia	20	(14.6%)	1	(12.3%)	13	(40.0%) (16.3%) ight,
22 23	Surgical position	100		20	((0.40/)	(1	nt, in
24 25	Supine position	100	(73.0%)	39	(68.4%)	61	(76.3% Qud
26	Prone position	6	(4.4%)	2	(3.5%)	4	(5.0%)g
27 28	Lateral position	18	(13.1%)	7	(12.3%)	11	
29	Lithotomy position	11	(8.0%)	8	(14.0%)	3	(3.8%)§
30 31	Other position	2	(1.5%)	1	(1.8%)	1	(1.3%)ated
32 33	Comorbidities						ed to test (26.3%)
34	Hypertension	43	(31.4%)	22	(38.6%)	21	(26.3%) a
35 36	Diabetes mellitus	15	(10.9%)	7	(12.3%)	8	(10.0%) d
37 38	Chronic kidney disease	24	(17.5%)	8	(14.0%)	16	
39	Dialysis	2	(1.5%)	0	(0.0%)	2	(2.5%) ⁿ ii
40 41	History of chronic lung disease	13	(9.5%)	3	(5.3%)	10	(12.5%)
42 43	History of heart failure	6	(4.4%)	3	(5.3%)	3	(3.8%) fa ir
44	History of myocardial infarction	4	(2.9%)	0	(0.0%)	4	(5.0%) j
45 46	History of stroke	9	(6.6%)	5	(8.8%)	4	(5.0%) ^a
47	Atrial fibrillation	8	(5.8%)	7	(12.3%)	1	(1.3%) <u>s</u>
48 49	Liver cirrhosis	3	(2.2%)	2	(3.5%)	1	(1.3%) ^a
50 51	Connective tissue disease	5	(3.6%)	1	(1.8%)	4	(5.0%) <mark>Š</mark>
52	History of VTE	1	(0.7%)	1	(1.8%)	0	(0.0%) <u>8</u>
53 54	History of major bleeding	17	(12.4%)	7	(12.3%)	10	(12.5%)
55 56	Active cancer	41	(29.9%)	24	(42.1%)	17	(21.3%)
57	Varicose vein	8	(5.8%)	3	(5.3%)	5	(6.3%)
58 59	Anticoagulants at VTE diagnosis	14	(10.2%)	6	(10.5%)	8	(10.0%)
<u> </u>							

<u>2</u>								
3 4		Heparin	6	(4.4%)	3	(5.3%)	3	(3.8%)
5		Warfarin	3	(2.2%)	2	(3.5%)	1	(1.3%)
7		Direct oral anticoagulant	5	(3.6%)	1	(1.8%)	4	(5.0%)
3		Presentation						
10 11		PE with hypoxemia	-	-	35	(61.4%)	-	-
12		PE with Shock	-	-	9	(15.8%)	-	-
13 14		PE with cardiac arrest/collapse	-	-	6	(10.5%)	-	
15 16		Proximal DVT	64	(46.7%)	21	(36.8%)	43	(53.8%
17		Laboratory tests at diagnosis						(53.8%) ected
18 19		Anaemia	109	(82.6%)	45	(83.3%)	64	(82.1%)
20 21		Thrombocytopenia	6	(4.4%)	5	(8.8%)	1	(1.3%) (62.4-,i,t
22		- CED (mit /min/m ²)	70.2	(59.0-	707	(51.2-	<u>00</u> 1	(62.4- <u></u> ,
23 24		eGFR (mL/min/m ²)	78.3	91.8)	72.7	87.7)	80.4	93.6) inclu
25 26		eGFR <60mL/min/m ²	36	(26.3%)	17	(29.8%)	19	93.6) includi
27		$D = \frac{1}{2} m \cos\left(\frac{1}{2} m - 122\right)$	16.5	(8.6-	160	(8.6-	1 <i>C A</i>	for
.8 .9		D-dimer (µg/mL, n=122)	10.5	31.5)	16.8	39.3)	16.4	(7.9-2753)
80 81		Thrombophilia	4	(2.9%)	3	(5.3%)	1	(1.3%)ar
2		Initial anticoagulation therapy	115	(83.9%)	53	(93.0%)	62	(77.5%)
3 4		Heparin	107	(78.1%)	52	(91.2%)	55	(68.8%)
5 6		Fondaparinux	11	(8.0%)	2	(3.5%)	9	(11.3%)
7		Thrombolysis	8	(5.8%)	5	(8.8%)	3	(3.8%)
8 9		Inferior vena cava filter use	26	(19.0%)	13	(22.8%)	13	(16.3%)
0 1		Ventilator support	6	(4.4%)	6	(10.5%)	0	(0.0%) ng
2		Percutaneous cardiopulmonary support	2	(1.5%)	2	(3.5%)	0	
³ 227	7	Categorical variables are presented as numbers and	l perce	ntages, and con	ntinuo	us variables a	are	ning,
5 228	8	presented as the means and standard deviations or	the me	dians and inter	quarti	le ranges bas	ed	(0.0%) training, and similar technologies.
7 229	9	on their distributions. Chronic kidney disease was	diagno	sed if there wa	s persi	istent		simi
³ 230	0	proteinuria or if eGFR was <60 mL/min/1.73 m ² fo	or more	e than 3 month	s. The	values of		lar te
23	1	eGFR were calculated based on the equation report	ted by	the Japan Asso	ociation	n of Chronic		€chn
1 2 232	2	Kidney Disease Initiative [man: 194*Scr-1.094*ag	ge-0.28	87, woman: 194	4*Scr-	-1.094*age-		ologi
³ 233	3	0.287*0.739]. Anaemia was diagnosed if the value	of hae	moglobin was	<13 g	/dL for men		es.
5 234	4	and <12 g/dL for women. Thrombophilia includes	proteir	n C deficiency,	protei	n S deficiend	cy,	
6 7 235	5	antithrombin deficiency, and antiphospholipid synd	drome.					
i8 i9								

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3 4	236	Abbreviations: ASA PS, American society anesthesiologists Performance Status; DVT, deep
5	237	venous thrombosis; eGFR, estimated glomerular filtration rate; PE, pulmonary embolism;
6 7 8	238	VTE, venous thromboembolism
9 10 11	239	
12 13 14	240	Clinical outcomes after postoperative symptomatic venous thromboembolism
15 16 17 18	241	The cumulative incidence of recurrent VTE was 3.0% at the 30-day follow-up, 5.3% at the
19 20 21	242	90-day follow-up, and 5.3% at the 5-year follow-up after postoperative symptomatic VTE
22 23 24	243	(Figure 3a). The cumulative incidence of major bleeding was 5.2% at 30-day follow-up, 6.7%
25 26 27 28	244	at the 90-day follow-up, and 12.6% at the 5-year follow-up (Figure 3b). The cumulative
29 30 31	245	incidence of all-cause death was 3.7% at the 30-day follow-up, 5.1% at the 90-day follow-up,
32 33 34	246	and 27.4% at the 5-year follow-up (Figure 3c). The details of clinical events within 90 days
35 36 37 38	247	are given in Supplemental Table 2. VTE recurrence occurred in seven patients (4 patients
39 40 41	248	were treated with anticoagulant therapy), all of which were early recurrences within 60 days
42 43 44	249	of diagnosis. The difference in the cumulative incidence of recurrent VTE, major bleeding,
45 46 47 48	250	and all-cause death was not significant between the PE- and DVT-only groups, although the
49 50 51	251	30-day incidence of major bleeding and all-cause death was higher in the PE group than in
52 53 54	252	the DVT-only group (11.1% versus 1.3%, and 8.8% versus 0.0%, respectively) (Figure 4).
55 56 57	253	The cumulative 5-year incidence of recurrent VTE was not significantly different between
58 59 60	254	patients with and without active cancer (9.9% versus 3.3%, Log-rank P=0.13) (Figure 5). In

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	255	contrast, the cumulative 5-year incidences of major bleeding and all-cause death were
	256	significantly higher in patients with active cancer than in those without active cancer (major
0 1 2 3	257	bleeding: 21.3% versus 8.8%, Log-rank P=0.046, all-cause death: 45.5% versus 19.8%, Log-
3 4 5 5	258	rank P=0.001) (Figure5).
5 7 8 9	259	
9 0 1 2 3	260	DISCUSSION
3 4 5 5	261	The main findings of this study are as follows: 1) the incidence of postoperative symptomatic
5 7 8 9	262	VTE within 2 months after surgery was 0.067% and VTE with PE was 0.028%, representing
0 1 2 3	263	203,943 patients from 18 centres in Japan; 2) the incidence of postoperative symptomatic
3 4 5 5	264	VTE varied widely, according to surgical and anaesthetic characteristics; and 3) nearly half
7 8 9	265	of the patients were diagnosed within 7 days of the surgery, while the rest were diagnosed 7
0 1 2 3	266	days after surgery, with the highest number of patients diagnosed on postoperative day 8.
3 4 5 6 7	267	The strength of the present study is that the diagnosis of symptomatic VTE was
5 7 8 9	268	accurately diagnosed by cardiologists (specialists for VTE in Japan), and the detailed
0 1 2 3	269	information about this post-operative complication and its long-term prognosis could be
3 4 5	270	evaluated, in contrast to previous studies on the subject.
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271	VTE is considered relatively rare in Asian people and the small number of cases
272	makes epidemiological studies difficult to perform.[11] Previously, three major studies from
273	Japan had evaluated the incidence of the postoperative complication of VTE.[10,18,19] The
274	first study was based on the JSA initiated questionnaire annual survey, where the incidence of
275	PE was 0.031% (3,667/11,786,489).[10] The second study used the diagnosis-procedure
276	combination (DPC) database, and the incidence of VTE and PE was 0.24% (2,485/1,016,496)
277	and 0.05% (538/1,016,496), respectively.[18] The third study used the National Clinical
278	Database (NCD), a nationwide project linked to the surgical board certification system. The
279	incidence of DVT and PE was 0.26% (984/382,124) and 0.14% (553/382,124),
280	respectively.[19] The incidence of postoperative symptomatic VTE in the current study was
281	lower than that in the DPC study. In the DPC study, VTE was identified based on the
282	International Classification of Diseases, 10th version (ICD-10) codes; and therefore, it may
283	have been misclassified and overrated. In this study, we used data on symptomatic VTE
284	confirmed by cardiologists. This may explain the lower incidence compared with the NCD
285	study, which included asymptomatic VTE. The incidence of postoperative VTE was reported
286	to be 0.58%–2.2%, based on the clinical databases in the USA. Therefore, postoperative VTE
287	incidence was suggested to be lower in Japan than in the United States and Europe. These

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4 5 6	288	differences could be explained by ethnic variations.[11] Western guidelines, [4, 5] due to
7 8 9	289	racial disparities, are more likely to lead to over-triage in the Japanese population.
10 11 12	290	Another important feature of the current study was the comparison of the incidence of
13 14 15 16	291	postoperative symptomatic VTE across surgical sites. Similar to the JSA initiated
17 18 19	292	questionnaire study,[10] neurosurgeries and orthopaedic surgeries (hip, upper, and lower
20 21 22	293	extremity) were associated with a higher incidence of postoperative symptomatic VTE.
23 24 25	294	According to the Japanese guidelines, there is a high risk of postoperative symptomatic VTE
26 27 28 29	295	in patients over 40 years of age undergoing major cancer surgery; however, in the present
30 31 32	296	study, abdominal surgery was not identified with high risk. Therefore, risks should be
33 34 35	297	stratified according to the surgical sites and procedures, and the additional risks in each
36 37 38 39	298	patient should be considered in the preventive strategies.
40 41 42	299	Additionally, in this study, the timing of the onset of postoperative symptomatic VTE
43 44 45	300	was bimodal. These results may suggest that postoperative symptomatic VTE occurs, not
46 47 48	301	only in the very acute postoperative period, which is directly affected by surgical
49 50 51 52	302	immobilisation, but also approximately 10 days after surgery; the information can guide the
53 54 55	303	healthcare providers involved in surgery, regarding the risk perception and diagnosis of
56 57 58 59 60	304	postoperative symptomatic VTE.

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	305	The duration of anticoagulant therapy is generally divided into an initial treatment
	306	phase (up to 7 days), a maintenance treatment phase (~3 months after the initial treatment),
) <u>2</u>	307	and prolonged treatment phase (beyond 3 months).[20] Surgery is a transient risk factor for
3 4 5	308	VTE; prolonged treatment is usually not performed, as the possibility of recurrence is
5 7 3 9	309	considered relatively low. In this study, VTE recurrence had occurred in all seven affected
) <u>2</u>	310	patients within 3 months of the onset, and no recurrence was observed after 3 months,
3 1 5	311	suggesting the importance of relatively early recurrence.
5 7 3 9	312	PE was apparently associated with a higher mortality, especially in the early phase of
) <u>)</u>	313	postoperative symptomatic VTE, although the difference between the PE- and DVT-only
3 1 5	314	groups was not significant. This difference may be explained by the insufficient sample size.
5 7 3 9	315	Notably, the initial mortality rate and recurrence rate was higher for acute PE than for
) <u>)</u>	316	DVT.[21, 22] Therefore, in comparison to DVT, postoperative PE should be more closely
3 1 5	317	monitored and aggressively treated.[3]
5 7 3	318	Study limitations
) 2	319	First, two different databases were combined to estimate the incidence of postoperative
3 1 5	320	symptomatic VTE. Although the COMMAND Registry included real consecutive patients
5 7 3	321	with acute symptomatic VTE,[10, 18] for determining VTE incidence, we included only the

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	322	cases in which intraoperative management was performed by an anaesthesiologist. Second,
	323	patients outside the eligible period in the COMMAND VTE Registry were also excluded,
0 1 2	324	which may have influenced the results of this study. As a certain number of patients were
2 3 4 5 6 7	325	excluded due to ineligible centres, the incidence of postoperative symptomatic VTE could
5 7 8 9	326	have been greatly influenced, especially as the analysis targeted low event rates. Third, this
) 1	327	was a retrospective cohort study with inherent limitations based on the observational study
2 3 4 5 6 7	328	design. In particular, the prophylactic and therapeutic management for postoperative
5 7 8 9	329	symptomatic VTE were based on the discretion of the attending physicians, which may have
) 1	330	influenced the clinical outcomes. However, in the COMMAND Registry, the definitions of
2 3 4 5 5 7	331	VTE were specified in advance, and the follow-up after VTE was nearly complete. Fourth,
5 7 8	332	the incidence of postoperative symptomatic VTE may depend on the status of VTE
9 0 1 2	333	prophylaxis. However, the JSA annual report does not include data on prophylaxis status, and
2 3 4 5 5 7	334	we could not determine this status for the entire study population. Fifth, the JSA annual
В	335	report does not include data on the status of malignancy either, and we could not determine it
9 0 1	336	for the entire study population. Finally, we also considered the postoperative date of onset,
2 3 4 5	337	but the disease may have developed before the surgery or the diagnosis. Nevertheless, we do
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9 0		

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2 3		
4 5 6	338	not expect a significant gap between the onset and diagnosis, because we included only
7 8 9	339	symptomatic patients with postoperative VTE.
10 11 12	340	
13 14 15 16	341	Conclusions
17 18 19	342	This study, combining the large real-world VTE database and anaesthetic database in Japan,
20 21 22 23	343	revealed the incidence, clinical features, and prognosis of postoperative symptomatic VTE,
23 24 25 26	344	providing useful information for all healthcare providers involved in various surgeries.
27 28 29	345	
30 31 32 33	346	Declarations
34 35 36 37	347	Declarations Acknowledgements
38 39 40 41	348	We appreciate the support and collaboration of the co-investigators participating in the
42 43 44	349	COMMAND VTE Registry. We also thank the following doctors: Hiroshi Miyawaki,
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58 59 60	354	the additional data from each centre.

2 3 4 5	355	
5 6 7		
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16 17 18	358	principal investigator). The COMMAND VTE Registry is supported by an independent
19 20 21	359	clinical research organisation (Research Institute for Production Development, Kyoto, Japan)
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29 30 31	362	interpretation of the data; and preparation, review, or approval of the manuscript.
32 33 34 35 36	363	
37 38 39 40	364	Competing interests
41 42 43	365	Dr. Yamashita received lecture fees from Daiichi-Sankyo, Bristol-Myers Squibb, Pfizer, and
44 45 46 47	366	Bayer Healthcare. Dr. Morimoto received lecture fees from Mitsubishi Tanabe Pharma and
47 48 49 50 51 52 53	367	Pfizer Japan and consultant fees from Asahi Kasei, Bristol-Myers Squibb, and Boston
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57 58 59 60	370	Pharma Corporation, CMIC Co., Ltd., and Pfizer Japan Inc.; honorarium from Daiichi-

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2 3		
4 5 7 8 9 10 11 12 13	371	Sankyo Co., Ltd., Mitsubishi Tanabe Pharma Corporation, AbbVie GK, Takeda
	372	Pharmaceutical Co., Ltd., Mitsubishi Chemical Holdings Corporation, and Astra Zeneca; and
	373	holds stocks of Real-World Data Co., Ltd. All other authors have reported that they have no
14 15 16	374	relationships relevant to the contents of this paper to disclose.
17 18 19	375	
20 21 22 23	376	Author Contributions
23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54	377	Chikashi Takeda, MD, PhD: This author had full access to all the data in the study and take
	378	responsibility for the integrity of the data and the accuracy of the data analysis. This author
	379	helped design and conduct the study, analyse the data, and write and revise the manuscript.
	380	Yugo Yamashita, MD, PhD: This author also had full access to all the data in the study and
	381	take responsibility for the integrity of the data and the accuracy of the data analysis. This
	382	author helped design and conduct the study, analyse the data, and write and revise the
	383	manuscript.
	384	Masato Takeuchi, MD, PhD, MPH: This author helped analyse the data and write and revise
	385	the manuscript.
55 56 57	386	Hiroshi Yonekura, MD MPH: This author helped analyse the data and write and revise the
58 59 60	387	manuscript.

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2 3		
4 5 6	388	Li Dong, MD: This author helped analyse the data and write the manuscript.
7 8 9	389	Miho Hamada, MD: This author helped analyse the data and write and revise the manuscript.
10 11 12	390	Akiko Hirotsu, MD, PhD: This author helped analyse the data and write and revise the
13 14 15 16	391	manuscript.
17 18 19	392	Koh Ono, MD, PhD: This author helped analyse the data and write and revise the manuscript.
20 21 22	393	Koji Kawakami, MD, PhD: This author helped analyse the data and write and revise the
23 24 25 26	394	manuscript.
20 27 28 29	395	Kazuhiko Fukuda, MD, PhD: This author helped design and conduct the study and write the
30 31 32	396	manuscript.
33 34 35 36	397	Takeshi Morimoto, MD, PhD, MPH: This author helped design and conduct the study,
37 38 39	398	analyse the data, and write and revise the manuscript.
40 41 42	399	Takeshi Kimura, MD, PhD: This author helped conduct the study, analyse the data, and write
43 44 45 46	400	and revise the manuscript.
40 47 48 49	401	Toshiyuki Mizota, MD, PhD: This author helped design and conduct the study, analyse the
50 51 52	402	data, and write and revise the manuscript.
53 54 55	403	
56 57 58 59 60	404	Availability of data and materials

1 2 3		
5 4 5 6	405	Data available on request from the authors. The data that support the findings of this study
7 8 9	406	are available from Chikashi Takeda or Yugo Yamashita, upon reasonable request.
10 11 12 13	407	
14 15 16	408	
$\begin{array}{c} 17\\ 18\\ 19\\ 20\\ 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 45\\ 46\\ 47\\ 48\\ 49\\ 50\\ 51\\ 52\\ 53\\ 54\\ 55\end{array}$	409	
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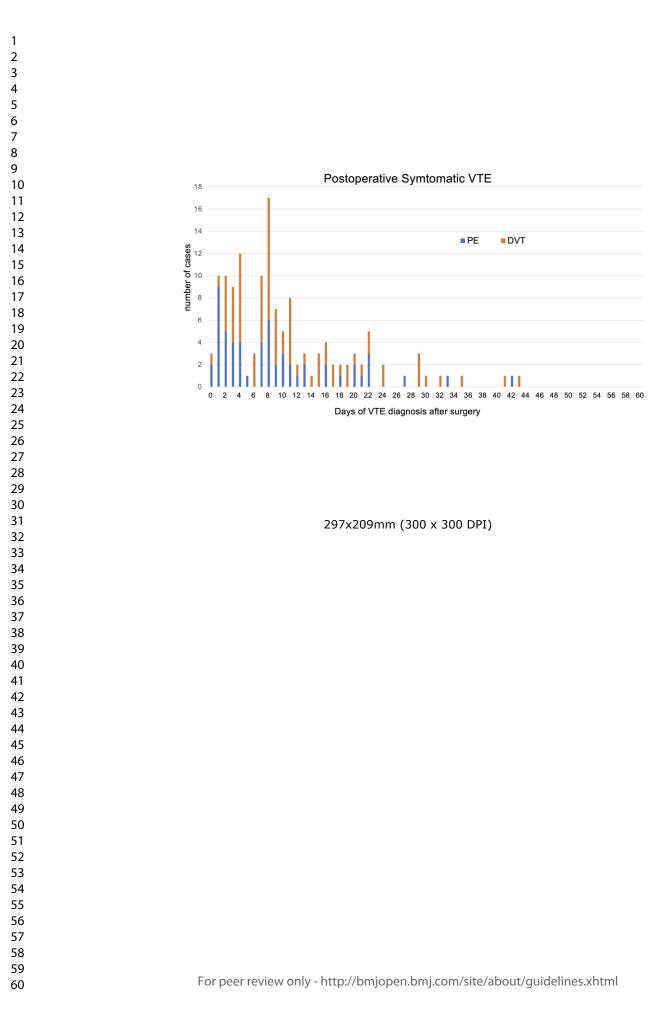
1 2		
3 4 5 6	473	Figure legends
7 8 9	474	Figure 1. Study flow diagram.
10 11 12 13	475	DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism;
14 15 16	476	JSA, Japanese Society of Anesthesiologists; COMMAND VTE, Contemporary management
17 18 19	477	and outcomes in patients with venous thromboembolism.
20 21 22 23	478	
24 25 26	479	Figure 2. The distribution of days of VTE diagnosis after surgery.
27 28 29	480	DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.
30 31 32 33	481	
34 35 36	482	Figure 3. The Kaplan–Meier curves for the clinical events after VTE diagnosis.
37 38 39	483	(a) Recurrent VTE, (b) Major bleeding, and (c) All-cause death.
40 41 42 43	484	VTE, venous thromboembolism.
44 45 46	485	
47 48 49	486	Figure 4. The Kaplan–Meier curves for the clinical events after VTE diagnosis
50 51 52	487	comparing PE and DVT.
53 54 55 56	488	(a) Recurrent VTE, (b) Major bleeding, and (c) All-cause death.
57 58 59 60	489	DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

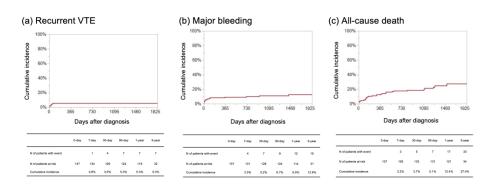
Figure 5. The Kaplan-Meier curves for clinical events after VTE diagnosis with and without active cancer. (a) Recurrent VTE, (b) Major bleeding, and (c) All-cause death. DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism to beet teries only

COMMAND VTE Registry		Annual reports to JSA from each centre
19,634 patients with suspected VTE screened for eligibility (January 2010-August 2014, 29 centres in Japan) 16,607 patients who did not meet the definition of acute symptomatic VTE 3,027 patients with acute symptomatic VTE 2,734 patients without history of surgery within 2 months before diagnosis 293 patients with history of surgery within 2 months before diagnosis	29 centres	The training hospitals certified by JSA are obliged to submit the annual reports to JSA at the end of the year, which include total number of surgeries managed by anaesthesiologists and detailed patients' characteristics and surgical and anaesthetic information.
135 patients out of 18 eligible centres and out of eligible period		
158 patients with history of surgery among 18 eligible centres during eligible period 21 patients who underwent without the management by anaesthesiologists	18	We collected the annual reports of anaesthesia from January 2010 to December 2013 among the 18 centres which participated in the COMMAND VTE registry.
Study Population 137 patients who developed VTE in hospital after surgery within 2 months before diagnosis (January 2010- December 2013, 18 centres in Japan)	centres	203,943 cases of surgery with the management by anaesthesiologists (January 2010- December 2013, 18 centres in Japan)

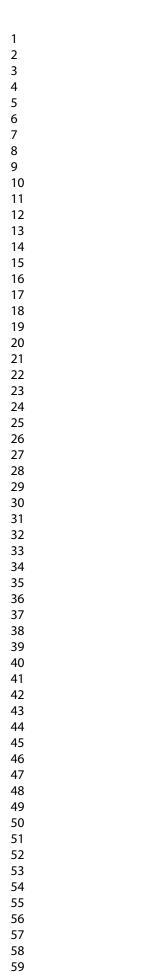
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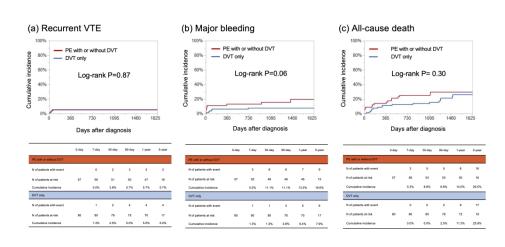
BMJ Open: first published as 10.1136/bmjopen-2021-055090 on 16 February 2022. Downloaded from http://bmjopen.bmj.com/ on May 14, 2025 at Department GEZ-LTA Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.





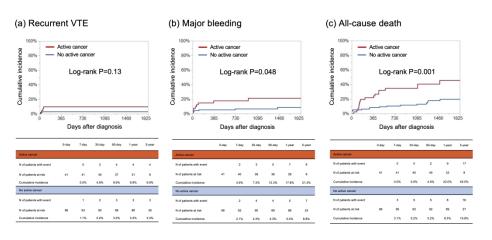
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Supplemental Table 1. Incidence	e of postopera	tive syr	nptomatic V	VTE			6/bmjopen-2021-055090 . 4 by copyright, including				
	Total cases	•	VTE	_	PE	PE	with he poxia	P	E with shock	PJ	E with arrest
Overall	203943	137	(0.067%)	57	(0.028%)	35	(0.0% 7%)	9	(0.004%)	6	(0.003%)
Type of anaesthesia							ruary 20 Erasm related 1				
Inhalation general anaesthesia	110833	49	(0.044%)	23	(0.021%)	13	(0.0 2 2 k)	3	(0.003%)	1	(0.001%)
Total venous general anaesthesia	25467	12	(0.047%)	3	(0.012%)	1	0.000 (0.000 (0.000 (0.000 (0.000 (0.000 (0.000 (0.0000)	1	(0.004%)	1	(0.004%)
Inhalation general anaesthesia							nloa scho 1d d:				
combined with regional	34872	46	(0.132%)	19	(0.054%)	11	(0.0 ¹ / <u>8</u> 2 ¹ / <u>8</u>)	2	(0.006%)	2	(0.006%)
anaesthesia							l from h nining,				
Total venous general anaesthesia							י http ig, A				
combined with regional	12863	10	(0.078%)	5	(0.039%)	4	(0.03112)	2	(0.016%)	1	(0.008%)
anaesthesia							mjop				
Combined spinal and epidural anaesthesia	4078	4	(0.098%)	0	(0.000%)	0	d from http://bmjopen.emj. mining, All@aining, aee sir (0.	0	(0.000%)	0	(0.000%)
Epidural anaesthesia	623	0	(0.000%)	0	(0.000%)	0	(0.000)	0	(0.000%)	0	(0.000%)
Spinal anaesthesia	13522	16	(0.118%)	7	(0.052%)	6	(0.0 គ្គ 4%)	1	(0.007%)	1	(0.007%)
Conduction anaesthesia	560	0	(0.000%)	0	(0.000%)	0		0	(0.000%)	0	(0.000%)
Other	1125	0	(0.000%)	0	(0.000%)	0	(0.000) (0.00) (0.000)	0	(0.000%)	0	(0.000%)
ASA classification)25 at I				
ASA PS class 1	56196	16	(0.028%)	7	(0.012%)	5	(0.009%)	1	(0.002%)	1	(0.002%)
ASA PS class 2	98410	85	(0.086%)	37	(0.038%)	22	(0.022%)	4	(0.004%)	2	(0.002%)

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Page 43 of 57					ВМЈ Ор	ben			6/bmjo d by co				
1 2 3									6/bmjopen-2021-0550) o 1 by copyright, includ) 0.0.000000000000000000000000000000000				
4 5	ASA PS class 3		25563	17	(0.067%)	2	(0.008%)	2	(0.0 5)8%	1	(0.004%)	1	(0.004%)
6	ASA PS class 4		549	1	(0.182%)	0	(0.000%)	0		0	(0.000%)	0	(0.000%)
7 8	ASA PS class 5		11	0	(0.000%)	0	(0.000%)	0	(0.0.0000000000000000000000000000000000	0	(0.000%)	0	(0.000%)
8 9	ASA PS class 6		1	0	(0.000%)	0	(0.000%)	0		0	(0.000%)	0	(0.000%)
10	ASA PS class 1E		5300	3	(0.057%)	3	(0.057%)	0		0	(0.000%)	0	(0.000%)
11 12	ASA PS class 2E		9575	6	(0.063%)	5	(0.052%)	4		2	(0.021%)	1	(0.010%)
13 14	ASA PS class 3E		6514	5	(0.077%)	2	(0.031%)	1		0	(0.000%)	0	(0.000%)
15	ASA PS class 4E		1446	4	(0.277%)	1	(0.069%)	1	م an es (0.00 کو کو کو کو کو	1	(0.069%)	1	(0.069%)
16 17	ASA PS class 5E		109	0	(0.000%)	0	(0.000%)	0	(0.06)	0	(0.000%)	0	(0.000%)
18	ASA PS class 6E		1	0	(0.000%)	0	(0.000%)	0		0	(0.000%)	0	(0.000%)
19 20	Classification error		268	_		-	-	-	ng n	-	-	-	-
20									http://bmj j¦ Al trainii				
22 23	Surgical position								ainir				
24	Supine position		147838	100	(0.068%)	39	(0.026%)	22	(0.0 5%)	5	(0.003%)	3	(0.002%)
25 26	Prone position		10106	6	(0.059%)	2	(0.020%)	2		1	(0.010%)	1	(0.010%)
27	Lateral position		20642	18	(0.087%)	7	(0.034%)	4		2	(0.010%)	2	(0.010%)
28 29	Lithotomy position		22882	11	(0.048%)	8	(0.035%)	6	(0.0 ² / ₂ 6%)	1	(0.004%)	0	(0.000%)
30	Sitting position		1069	0	(0.000%)	0	(0.000%)	0	(0.00) (0.00)	0	(0.000%)	0	(0.000%)
31 32	Other		1406	2	(0.142%)	1	(0.071%)	1		0	(0.000%)	0	(0.000%)
33									, 202 es.				
34 35	Age (years old)								15 at				
36	0-5		9518	0	(0.000%)	0	(0.000%)	0	(0.000° 2)	0	(0.000%)	0	(0.000%)
37 38	6-18		10255	2	(0.020%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
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66-85 79796 82 $(0.103%)$ 36 $(0.045%)$ 22 $(0.028%)$ 4 $(0.005%)$ 2 $(0.003%)$ $86 5081$ 6 $(0.118%)$ 2 $(0.039%)$ 2 $(0.020%)$ 1 $(0.001%)$ 1 0				ВМЈ Ор	en			6/bmjopen-2021-0550阕 o y by copyright, includ近g (().				Pag
66-85 79796 82 (0.103%) 36 (0.045%) 22 (0.028%) 4 (0.005%) 2 (0.003%) 86- 5081 6 (0.118%) 2 (0.039%) 2 (0.028%) 1 (0.020%) 1 (0.020%) 1 (0.020%) 1 (0.020%) 1 (0.020%) 1 (0.020%) 1 (0.020%) 1 (0.020%) 1 (0.020%) 1 (0.020%) 1 (0.020%) 1 (0.020%) 1 (0.020%) 1 (0.001%) Sex -	19-65	99283	47	(0.047%)	19	(0.019%)	11	ندة (0.000 1%) (0.000 1%)	4	(0.004%)	3	(0.003%)
Sex Image: Classification error 10 Image: Classification error 45 (0.045%) 16 (0.016%) 10 (0.02%) 1 (0.001%) Women 104223 92 (0.088%) 41 (0.039%) 25 (0.002%) 7 (0.007%) 5 (0.005%) Classification error 8 -	66-85	79796	82	(0.103%)	36	(0.045%)	22	(0.0 2 8% <u>t</u>)	4	(0.005%)	2	(0.003%)
Sex Image: Classification error 10 - <	86-	5081	6	(0.118%)	2	(0.039%)	2	(0.0 kg 9%)	1	(0.020%)	1	(0.020%)
Men9971245(0.045%)16(0.016%)10(0.074000)2(0.002%)1(0.001%)Women10422392(0.088%)41(0.039%)25(0.0076000)7(0.007%)5(0.005%)Classification error8All data were described as number and percentage.Abbreviations: ASA PS, American society anesthesiologists performance status; PE, pulmonary embolism; VTE, venousVTE, venousthromboembolism	Classification error	10	-	-	-	-	-	bruar Er rela	-	-	-	-
Women 104223 92 (0.088%) 41 (0.039%) 25 (0.009%) 7 (0.007%) 5 (0.005% Classification error 8	Sex	4										
Women 104223 92 (0.088%) 41 (0.039%) 25 (0.009%) 7 (0.007%) 5 (0.005%) Classification error 8 -	Men	99712	45	(0.045%)	16	(0.016%)	10	(0.0 to the second seco	2	(0.002%)	1	(0.001%)
All data were described as number and percentage. Abbreviations: ASA PS, American society anesthesiologists performance status; PE, pulmonary enfolding, and similar technologies. thromboembolism	Women	104223	92	(0.088%)	41	(0.039%)	25		7	(0.007%)	5	(0.005%)
thromboembolism	Classification error	8	Q	-	-	-	-	ideo ata -	-	-	-	-
Department GEZ-LTA		number and percentage merican society anesth	e. esiolog	gists perform			ulmona	≤ 3	; VTE	, venous		

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	Supple Case Number	ement: Age	al Table 2 Sex	<mark>. Details</mark> BMI	5 of clinical ev Time from index VTE to events	vents within Types of index VTE	1 90 days after Time from surgery to index VTE		<mark>tive symptoma</mark> ASA classificatior	⇒ ¥		Preexisting Medical Conditions	History VTE c major
	Cases of 1	ecurr	ent VTE		(days)	VIL	(days)		ASA classification	s ry 2022. Dowr rasmushoges ited to text an			bleedir
	1	73	Woman	24.8	9	PE with DVT	5		2	adea (I) adea fro	Spinal position		
	2	69	Woman	26.5	48	РЕ	04	Upper abdomen	2	ng Al training, and similar technologi	Spinal position	AC	
	3	75	Man	21.3	27	PE with DVT	21	Lower abdomen	2	ing, and similar	Lithotomy position	HT, DM, CKD, AC	
	4	53	Man	21.6	7	DVT	11	Brain	2	.con (I) milar GA (I)	Spinal position	HT, CKD	
	5	40	Woman	14.3	59	DVT	7	Lower abdomen	2	es. KA . 02	Spinal position	CKD, AC	
	6	60	Woman	25.8	38	DVT	6	Lower abdomen	1	C1	Spinal position	CKD	
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7	75	Woman	17.7	17	DVT	4	Lower abdomen	2	6/bmjopen-2021-0550906n 16 Fe	Spinal position	CKD (Dialysis), AC	Major bleeding
Cases of m	ajor	bleeding		~					bruary 20 Erasm related			
1	73	Woman	24.8	25	PE with DVT	5	Brain	2	to ushogeschoo text and data mi	Spinal position		
5	40	Woman	14.3	44	DVT	7	Lower abdomen	2	action of the second se	Spinal position	CKD, AC	
7	75	Woman	17.7	62	DVT	04	Lower abdomen	2	mining, Al training, and similar technolog	Spinal position	CKD (Dialysis), AC	Major bleeding
8	62	Woman	22.3	3	PE	10	Brain	O^2	Al training, and similar technologies.	Spinal position	AC	VTE, Major bleeding
9	49	Man	22.5	4	PE	1	Brain	2		Spinal position	HT, Af, AC	
10	59	Woman	22.4	16	PE with DVT	20	Brain	3E	GÅ(I)	Spinal position	HT, CKD,	Major bleeding
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1 2 3 4									II.a.d		א-2021-0550g ight, includi			
5 6 7 8 9	11	50	Man	23.5		14	PE with DVT	7	Head, pharynx, larynx Hip,	2E	ng for uses re	Spinal position	AC	
10 11 12 13 14	12	93	Woman	15.5		1	PE	0	upper / lower limbs	2	ary 26/22. Dov Erasmushoge lated to text a	Lateral position	HT, CKD	
15 16 17 18 19 20	13	55	Woman	20.2		6	DVT	2	Hip, upper / lower limbs	3	ل) 6/bmjopen-2021-055090 of 16 February 2022. Downloadeed from ht BrasRushogeschool ທ 4 by copyright, including for uses related to text and data mining, <i>y</i>	Spinal position	MI, CTD	
21 22 23 24	Cases of al	ll-cau	se death					61	10.		tp://bmjop Al training			
25 26 27 28	7	75	Woman	17.7	8	85	DVT	4	Lower abdomen	O ²	, and similar technologies.	Spinal position	CKD (Dialysis), AC	Major bleeding
29 30 31 32	10	59	Woman	22.4		17	PE with DVT	20	Brain	3E	on May 14, ; echnologie	Spinal position	HT, CKD,	Major bleeding
33 34 35 36 37 38	12	93	Woman	15.5		10	PE	0	Hip, upper / lower limbs	2	14, 2025 at Department S	Lateral position	HT, CKD	
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hy copyright, including for for 6/bmjopen-2021-055090 on STROBE Statement-checklist of items that should be included in reports of observational studies Item Page **Relevant text from manuscript** No. Recommendation No. (a) Indicate the study's design with a commonly used term in the title or the abstract 1.3 "Incidence, clinical characteristics, and long-term Title and abstract 1 prognosis of postoperative symptomatic venous theomboembolism: a retrospective cohort study" Design: Retrospective observational study. Two Batasets, COMMAND VTE Registry and **Bag**anese Society of Anesthesiologists (JSA) .ve and balance Initial report, were used for current analyses." **E** dentified 137 patients with postoperative (b) Provide in the abstract an informative and balanced summary of what was done 3-4 gy inptomatic VTE, including 57 patients with and what was found monary embolism. The incidences of Sectoperative symptomatic VTE and pulmonary **a** 'enholism were 0.067% and 0.028%, respectively, **b** based on data from 203,943 patients who Вu underwent surgery, managed by \blacktriangleright are sthesiologists, during the study period. The r incidences of postoperative symptomatic VTE valied widely, depending on surgical and anaesthetic characteristics. Postoperative symptomatic VTE occurred at a median of 8 days after surgery, with 58 patients (42%) diagnosed within 7 days. The cumulative incidence, 30 days <u>s</u> after VTE, of recurrent VTE, major bleeding, and alEcause death was 3.0%, 5.2%, and 3.7%, fe respectively." "Venous thromboembolism (VTE), including hno Introduction Explain the scientific background and rationale for the investigation being reported Background/rationale 2 6-7 <u>l</u> Bo pulmonary embolism (PE) and deep vein ē the mbosis (DVT), is a serious postoperative complication which can result in an in-hospital death.[1, 2] In perioperative management, it is cracial to prevent postoperative symptomatic VE and to respond promptly, once it is reeognized. Therefore, clinicians should be faziliar with the clinical features of postoperative symptomatic VTE to optimize their management strategies.

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1	3 State specific objectives, including any prespecified hypotheses	 9 Solution of the past 20 years, several guidelines have been recommended for the prophylaxis of proventive measures, the incidence of protoperative VTE (3-5) Despite the use of proventive measures, the incidence of protoperative VTE remains high and varies from 0.50% to 2.2%, according to reports from Wastern countries.[6-8] However, data on protoperative VTE from a cohort/registry-based study in Asian countries are scarce. A previous and the protoperative VTE throughout text and protoperative PE, conducted by mailing to toperative PE, conducted by mailing for uses study of underreporting of events cannot be detected. Although the incidence of VTE in Asia has been considered to be lower than Western contries.[10] recent studies have suggested an underestimation of VTE in Asia.[11-13] No large-scale study has systematically evaluated the incidence of postoperative symptomatic VTE in Jaaan." 7 min difference, with a collaborative effort between cardiologists and anaesthesiologists, we investigated the incidence, clinical characteristics, and prognosis of postoperative symptomatic VTE in and prognosis of postoperative symptomatic version of an anaesthesiologists, we investigated the incidence, clinical characteristics, and prognosis of postoperative symptomatic VTE in and prognosis of postoperative symptomatic version of an anaesthesiologists (JSA)."
32 Methods		ogie
33 Study design 34 35 36 37 38 39 40 41	4 Present key elements of study design early in the paper	 "Is this study, two datasets were used for analyses. The first was Contemporary ManageMent AND outcomes in patients with Vanous ThromboEmbolism (COMMAND VTE) reastry, a retrospective multicentre cohort study, which provided the data on patients with postoperative symptomatic VTE. The second was the JSA annual report, which provided cross- sectional data of all patients, who underwent
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				Subject Subject Image: stress of the stres
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-9	"Is this study, the JSA annual reports from Jaguary 2010 to December 2013 were collected from 18 centres that participated in the COMMAND VTE Registry. Furthermore, activitional data of patients with postoperative activitional data of patients with postoperative manptomatic VTE, namely operative date, activition, and types of anaesthesia on anaesthetic to the procedure, surgical sites, surgical dition, and types of anaesthesia on anaesthetic to the procedure, were obtained. The provident of the study, the patients from the 18 centres and the common the COMMAND VTE Registry, for the procedure of the COMMAND VTE Registry, for the procedure of the 11 centres of the COMMAN VBE Registry as their JSA annual reports and/or activitional data on patients with postoperative
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	9	 symptomatic VTE were unavailable." "If this study, the patients from the 18 centres registered in the COMMAND VTE Registry, for which the JSA annual report had been collected between January 2010 and December 2013, were encoded (Figure 1). We could not enrol patients from the rest of the 11 centres of the COMMAN VE Registry as their JSA annual reports and/or additional data on patients with postoperative symptomatic VTE were unavailable. We also could not register the patients between January 2014, since the JSA annual report was from January to December of each your. Further, within the COMMAND VTE Registry, the patients diagnosed with acute symptomatic VTE, who underwent surgery 2 months prior to the VTE diagnosis, were identified. The overall population that had regeived anaesthetic management, during the study period was retrieved from each centre's JSM annual report. Besides, additional data of
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Page 53 of 57	BMJ Open	6/bmjopen-20 4 by copyrigh
2 3 4 5 6		 patients with postoperative symptomatic VTE, namely operative date, operative procedure, subject sites, surgical position, and types of and esthesia on anaesthetic charts at each centre, were obtained."
7 8 9 10	(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	es Nærelevant text Felavant text Felavant text Felavant text
11 Variables 7 12 Variables 7 13 14 15 16 17 18 19 20 21 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41		The Normalized States and the system of the system of the system of the system of the registry. The outcome measures assessed in this study were subjected at a symptomatic PE and of the system of the analysis of the system of the system of the registry. The outcome measures assessed in this study were subjected at the system of the analysis of th
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				t, includ	Ha leg	The mostasis as a reduction in the haemoglobin when the by at least 2 g/dL, transfusion of at least two has of blood, or symptomatic bleeding in a hacal area or an organ.[16]"
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		g for use	N	relevant text
Bias	9	Describe any efforts to address potential sources of bias		s rela	Në Er	relevant text
Study size	10	Explain how the study size was arrived at		ted to t	asmus	relevant text
				lex	2 5	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		ā	Ϋ́Ξ	
Statistical methods	12	(<i>a</i>) Describe all statistical methods, including those used to control for confounding	12	a mining, Al t	we the real of the the	he incidence of postoperative symptomatic VTE calculated using a combination of data from COMMAND Registry and the JSA annual orts from the 18 centres. The numerator of the idence was the number of cases of toperative symptomatic VTE extracted from COMMAND Registry; the denominator was number of surgeries in the JSA annual report."
		(b) Describe any methods used to examine subgroups and interactions	12	d similar te	accept por The reconstruction	the incidence of postoperative symptomatic VTE cording to age, sex, surgical site, surgical sition, and types of anaesthesia was calculated. the baseline and follow-up data were separately orded for PE with or without DVT and DVT- by groups in patients with postoperative aptomatic VTE."
		(c) Explain how missing data were addressed	12	out		b imputation was performed for missing data."
		 (d) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses 		logies.	N04, 2023 at D	relevant text
		(c) Describe any sensitivity analyses			1 10	
Results					3	<u> </u>
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13-14		W	gure 1 represents the flow diagram of the study. enrolled 3,027 consecutive patients with acute potomatic VTE, after screening 19,634
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Page 55 of	f 57		BMJ Open	6/bmjopen-20 1 by copyrigh
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18			(b) Give reasons for non-participation at each stage	 consecutive patients with suspected VTE for elbibility, using the chart review by the plasicians at each institution. After excluding 2,64 patients without a history of surgery within 2 months before VTE diagnosis, 293 patients were identified with postoperative symptomatic VTE during hospitalization among all 29 centres of the COMMAND VTE Registry. Furthermore, 135 Fasients outside the eligible period and 21 patients in underwent surgery without the management of study population consisted of 137 patients Figure 1 m. Figure 1 gives reasons for non-participation at
19 20				eath stage.
21 22 23 24	Descriptive data	14*	 (c) Consider use of a flow diagram (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders 	Figure 1 ≥ "The study flow diagram is shown in Figure 1" Table1 Table1 Shows the baseline patient characteristics Supplement of oth groups." tal Table1 G
25 26			(b) Indicate number of participants with missing data for each variable of interest	No relevant text
27			(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	No relevant text
28 29 30 31 32 33 34 35 36 37 38 39 40 41	Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	14,16 The estimated incidence of postoperative symptomatic VTE was 0.067% (137/203,943) and VE with PE was 0.028% (57/203,943) (Table 1). Of the 57 PE cases, 35 patients (0.017%) had hypoxic symptoms, nine patients (0.004%) presented with shock, and six patients (0.003%) had cardiac arrest. As for the surgical site, the indidence of postoperative symptomatic VTE was relatively high in surgeries involving the brain, hig, and upper/lower limbs. In terms of the types of inaesthesia, regional anaesthesia with or without general anaesthesia (0.100%) was associated with a higher incidence of VTE than general anaesthesia alone (0.045%) (Table 1 and
42 43 44 45 46			6 For peer review only - http://bmjopen.bmj.com/site/about/gu	idelines.xhtml

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		 Supplemental Table 1)." Supplemental Table 1)." "Gable 2 shows the demographic and clinical characteristics of patients with postoperative symptomatic VTE. Figure 2 presents the duration from the surgery to the diagnosis of postoperative duration was 8 days (4–15 days); and 58 patier (49%) were diagnosed within 7 days of surgery for the surgery. The greatest number of patient of patient of patients (58%) were diagnosed 7 days of a patient of patients (58%) were diagnosed 7 days of a patient of patient of patients (58%) were diagnosed 7 days of a patient of patient of patients (58%) were diagnosed 7 days of a patient of patient of patients (58%) were diagnosed 7 days of a patient of patients (58%) were diagnosed 7 days of a patient of patient of
	Case-control study—Report numbers in each exposure category, or summary measures of exposure Cross-sectional study—Report numbers of outcome events or summary measures	22. Downloa shogeschoo text and da
Main results	16 (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included 14	 a a b a b a b a b a b a b a b a b a b a
	(b) Report category boundaries when continuous variables were categorized © If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	ng, and
Other analyses	17 Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	s. <u></u> <u></u> ar Ne relevant text fo or
Discussion		c n hn Ma
Key results	18 Summarise key results with reference to study objectives 20	 "The main findings of this study are as follows," "The main findings of this study are as follows, the incidence of postoperative symptomatic W within 2 months after surgery was 0.067% V E with PE was 0.028%, representing 203, patients from 18 centres in Japan; 2) incidences of postoperative symptomatic W wither a study, according to surgical amesthetic characteristics; and 3) nearly hal the patients were diagnosed within 7 days of surgery, while the rest were diagnosed 7 cather surgery, with the highest number of patients
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Discuss limitations of the study, taking into account sources of potential bias or nprecision. Discuss both direction and magnitude of any potential bias	23-24	by copyright diagnosed on postoperative day 8." "Torst, two different databases were combined to esomate the incidence of postoperative symptomatic VTE. Although the COMMAND Registry included real consecutive patients with actite symptomatic VTE,[9, 17] for determining VTE incidence, we included only the cases in which intraoperative management was performe the eligible period in the COMMAND VTE eligible period in the COMMAND VTE sittly were also excluded, which may have sittly uenced the results of this study. As a certain on bar of patients were excluded due to incomplicible centres, the incidences of postoperative on protomatic VTE could have been greatly the uenced, especially as the analysis targeted the the uenced, especially as the analysis targeted the
nprecision. Discuss both direction and magnitude of any potential bias		 "Brst, two different databases were combined to estimate the incidence of postoperative symptomatic VTE. Although the COMMAND Registry included real consecutive patients with a te symptomatic VTE,[9, 17] for determining
		 low event rates. Third, this is a retrospective conort study with inherent limitations based on the observational study design. In particular, the prophylactic and therapeutic management for postoperative symptomatic VTE were based on the discretion of the attending physicians, which
		in may have influenced clinical outcomes. However inche COMMAND Registry, the definitions of VEE were specified in advance, and the follow- and the router was nearly complete. Finally, we also considered the postoperative date of onset, but the disease may have developed before the surgery the diagnosis. Nevertheless, we do not expect a similar the diagnosis because we included only symptomatic patients with postoperative VTE."
		"By is study, combining the large real-world VT database and anaesthetic database in Japan, receled the incidence, clinical features, and prognosis of postoperative symptomatic VTE, providing useful information for all healthcare providers involved in various surgeries."
iscuss the generalizability (external validity) of the study results	21	"Igrst, two different databases were combined to estimate the incidence of postoperative symptomatic VTE. Although the COMMAND
1	Give a cautious overall interpretation of results considering objectives, limitations nultiplicity of analyses, results from similar studies, and other relevant evidence Discuss the generalizability (external validity) of the study results	Give a cautious overall interpretation of results considering objectives, limitations, 24 nultiplicity of analyses, results from similar studies, and other relevant evidence

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	К _о	Registry included real consecutive patients with actie symptomatic VTE,[9, 17] for determining VEE incidence, we included only the cases in which intraoperative management was performed by an anaesthesiologist. Second, patients outside the eligible period in the COMMAND VTE Registry were also excluded, which may have influenced the results of this study. As a certain much of patients were excluded due to influenced the results of this study. As a certain the eligible centres, the incidences of postoperative to prove the period in the analysis targeted the second patients."
Other information		and dia and di
Funding22Give the source	of funding and the role of the funders for the present study and, if he original study on which the present article is based	 25 25 25 25 25 26 25 26 27 28 29 20 20 21 21 25 25 25 25 26 27 28 29 20 21 21 21 22 23 24 25 25 26 27 27 28 29 20 <
*Give information separately for cases and c	ontrols in case-control studies and, if applicable, for exposed and unexposed	i o
checklist is best used in conjunction with thi	e discusses each checklist item and gives methodological background and pu s article (freely available on the Web sites of PLoS Medicine at http://www.p t http://www.epidem.com/). Information on the STROBE Initiative is availab	blosmedicing org/, Annals of Internal Medicine at
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