Incidence of Venous Thromboembolism in Asian Populations: A Systematic Review

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Abstract

Introduction Despite a marked recent increase in the number of publications describing the incidence of venous thromboembolism (VTE) in Asia, and especially in mainland China, Hong Kong, Taiwan, Korea, Japan and Singapore, there remains a lack of consensus on the true risks, and trends over time, to inform appropriate clinical practice. The purpose of this systematic review was therefore to examine evidence about the incidence of symptomatic VTE in Asia.

Methods Databases were searched for studies from Asia, published between January 1995 and February 2016, on the incidence of symptomatic VTE, deep vein thrombosis (DVT) or pulmonary embolism. Review of eligible studies was conducted independently by two reviewers. Data were extracted on incidence, predispositions and recurrence of VTE.

Results One thousand nighty-five studies were identified, of which 73 were eligible for full text review and data extraction. Three population-wide estimates of VTE rates identified from Korea, Taiwan and Hong Kong reported annual incidences of 13.8, 15.9 and 19.9 per 100,000, respectively. Nine studies of Asian hospital registries or databases reported VTE rates ranging from 11 to 88 cases per 10,000 admissions. Population-based estimates of post-surgical DVT rates ranged from 0.15 to 1.35%. Age was a significant risk factor for VTE in all population groups.

Conclusion Population-wide incidence estimates in Asia were approximately 15 to 20% of the levels recorded in western countries but have increased over time. It is anticipated this synthesis of evidence on the incidence of VTE and its predisposing factors will increase awareness about VTE in Asian populations.

Keywords
- venous thromboembolism
- deep vein thrombosis
- pulmonary embolism
- epidemiology
- Asian population

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Introduction

Until recently, there has been a relative lack of research into the incidence of venous thromboembolism (VTE) in Asian populations,[1] perhaps partly due to early impressions that VTE was rare in Asia.[2] However, the past 15 years have seen a marked increase in the number of publications, especially from mainland China, Hong Kong, Taiwan, Korea, Japan and Singapore. Most of these studies have reported significant VTE rates in the respective Asian populations, although reported rates were generally lower than those in western populations where VTE has an estimated annual incidence of 1 per 1,000 per annum, which makes VTE a major health issue. Although VTE is ranked the third most frequent cause of cardiovascular death in Western countries,[3] there remains a lack of acknowledgement of this condition in Asian populations. This systematic review aims to encapsulate the latest findings from Asia and raise awareness of VTE as an important condition in this region.

The effective management of symptomatic deep vein thrombosis (DVT) and pulmonary embolism (PE) requires early confirmation of clinically suspected disease. In turn, early confirmation is reliant on both clinicians and the public having a high local awareness of these disorders. A recent global survey indicated that clinical awareness regarding VTE is generally low in Asian countries.[4] Since the nations that comprise Asia account for more than half the world's population, such low local awareness about VTE is likely to add considerably to the avoidable burden from this disease.

The purpose of this systematic review is to examine evidence about the incidence of symptomatic VTE, reported between January 1995 and February 2016, in publications from East Asia. The focus is on population-based and other studies of VTE incidence, temporal trends in reported VTE rates, and the contributions of age and other major predisposing conditions. The results may help increase awareness about the importance of VTE in Asian populations.

Existing Asian VTE guidelines are summarized in ►**Table 1**. The present synthesis of evidence on the incidence of VTE and predisposing factors may inform future refinements and updates of VTE-related guidelines in Asia.

Methods

For the purposes of this study only symptomatic VTE was considered and Asian populations were defined as people from the geographical regions of *East Asia* including China (including Hong Kong and Macau), Taiwan, Mongolia, Korea (North and South) and Japan, *Southeast Asia* including Vietnam, Malaysia, Thailand, Indonesia, Singapore and

Table 1 List of Asian guidelines and expert recommendations on prevention and/or management of venous thromboembolism (VTE)

Guideline title	Year	Reference	
Asian venous thromboembolism guidelines: updated recommendations for the prevention of venous thromboembolism	2017	Int Angiol 2017;36(1):1–20	[68]
Management of venous thromboembolisms: part I. The consensus for deep vein thrombosis	2016	Acta Cardiol Sin 2016;32(1):1–22	[69]
Prevention of venous thromboembolism, 2nd edition: Korean Society of Thrombosis and Hemostasis Evidence-based Clinical Practice Guidelines	2014	J Korean Med Sci 2014;29(2):164–171	[70]
Asia-Pacific Thrombosis Advisory Board consensus paper on prevention of venous thromboembolism after major orthopaedic surgery	2010	Thromb Haemost 2010;104(5):919–930	[71]
Guidelines for the diagnosis, treatment and prevention of pulmonary thromboembolism and deep vein thrombosis (JCS 2009)	2011	Circ J 2011;75(5):1258–1281	[72]
Management of venous thromboembolism	2007	J Assoc Physicians India 2007;55:49–70	[73]
Malaysian Clinical Practice Guidelines: prevention and treatment of venous thromboembolism	2013	http://www.moh.gov.my/penerbitan/CPG2017/9005.pdf	[74]
The HKSCCM Position Statement: Prevention of Venous Thromboembolism in Intensive Care Units in Hong Kong	2010	http://hksccm.org	[75]

Philippines, and *South Asia* including India, Pakistan, Afghanistan, Bangladesh and Sri Lanka.

A systematic search of the literature using the PICOT (Population, Intervention, Comparison, Outcome, Type) approach[5] and the PRISMA checklist[6] was conducted to identify English-language publications. The predetermined inclusion criteria were the following: (1) the population studied included at least 90% Asian participants or the study was conducted in one of the specified Asian countries; (2) the full publication was available in English; (3) the reported study included at least 100 subjects from the Asian population of interest; (4) the publication reported the disease burden and/or risk and demographic factors associated with symptomatic VTE; (5) the publication date was from 1995 to 2016.

Data Collection and Analysis

Selection of Studies

A wide, all-encompassing search string was developed through an iterative process and the final literature search was conducted in PubMed (MEDLINE) on 23 February 2016 (see Appendix A for search string). Two reviewers independently screened the title and abstract for each manuscript against the predefined inclusion and exclusion criteria (see ►**Fig. 1**). Full-text manuscripts were obtained for all abstracts that were deemed potentially eligible by at least one reviewer. Two reviewers then independently screened the full-text articles for eligibility using a standardised data extraction form. Any discrepancies were resolved by discussion and/or consultation with a third reviewer ($n = 42$).

Searching Other Resources

The reference lists of all papers included were hand searched to identify any additional manuscripts that may have been omitted in the initial search; the 'related article' feature in PubMed was also used to identify additional articles. Google Scholar, EMBASE and the grey literature were also searched to cross-check for additional relevant articles (see ►**Fig. 1**).

Grouping of Studies

Included studies were grouped, according to the study protocol, as belonging to one of the following categories: (1) population-based studies, defined as population-based estimates of VTE incidence or mortality in the general population, from sources such as national health system registries or health insurance databases; (2) hospital evidence, defined as single institution or multicentre estimates of VTE incidence or mortality in the general population, or reports of VTE rates in consecutive hospitalized patients, surgical patients or general oncology patients; (3) autopsy evidence, defined as studies of PE incidence in series of autopsy records or death certificates; (4) special interest studies based on large population or patient groups; (5) studies of VTE in subpopulations or patient cohorts. Only high-quality studies with a low risk of bias were reported.

For population-based studies, ICD-9 or ICD-10-CM classifications were used. This system is the ninth or tenth revision of the World Health Organization International Statistical Classification of Diseases and Related Health Problems (ICD) clinical modification (CM).

Results

The search strategy identified a total of 1,095 manuscripts. Initial title and abstract searches identified 227 potentially relevant studies. Hand searching of reference lists and additional searches identified a further 25 potentially relevant studies. Detailed abstract and/or full-text review identified 95 potentially relevant studies that met the criteria for data extraction. The following full-text review publications were excluded for the following reasons: small sample size (Supplementary references, 1–3); letter to the editor or literature review without new data (S4–S6); lack of denominator value, therefore no incidence reported or calculable (S7–S9); survey-based studies with poor response rates (S10–S13); duplicated data (S14); only non-symptomatic/sub-clinical disease, for example, VTE diagnosed by systematic screening with venous ultrasound imaging, or after D-dimer assay; incidence estimate extrapolated from less than 90% of the population of interest (S15); the report concerned predisposition for PE in people with a DVT(S16); or VTE was not a main study outcome of interest (S17). A total of 73 manuscripts met the eligibility criteria for data extraction (►**Fig. 1**). These were from Taiwan, Hong Kong, Singapore, China, Korea, Malaysia, Philippines, Thailand, Japan and India.

Population-Based Estimates of Incidence

Population-Wide Annual Incidences of VTE

Population-wide estimates derived from international classification of disease-coded population health data sets (ICD-9 or ICD-10-CM) were identified from Korea,[7] Taiwan[8] and Hong Kong[9] (►**Table 2**).

The Korean study utilized a data set containing all inpatient and outpatient encounters recorded from 2004 to 2008 and investigated DVT alone and PE, with or without DVT.[7] The Taiwanese study utilized data from the National Health Insurance programme, covering 99% of the population and 97% of hospitals and clinics, and recorded VTE rates from 2001 to 2002 in people older than 18 years.[8] The Hong Kong study was derived from public hospital admission and discharge statistics in 2000 and 2001, covering 95% of the population.[9]

In Korea, the age- and sex-adjusted annual VTE rates per 100,000 were 8.83 in 2004 and 13.8 in 2008. In Taiwan, the crude incidence of VTE was 15.9 per 100,000 person-years; in Hong Kong, the crude rates were 17.1 per 100,000 for DVT, 3.9 for PE and 19.9 for VTE (►**Table 2**).

A Japanese study reported death certificate data in which death was attributed to PE, as recorded in 'Vital Statistics of Japan' from 1951 to 2000, and data were adjusted to the population size in 1985. The reported rate of 'fatal PE' increased from 0.08 per 100,000 in 1956 to 0.77 per 100,000 in 1996.[10]

Population-Based VTE Rates in Patients with Specific Chronic or Acute Disorders

We identified 24 population-based retrospective cohort studies of specific disorders, injuries, toxicities or drug therapies,

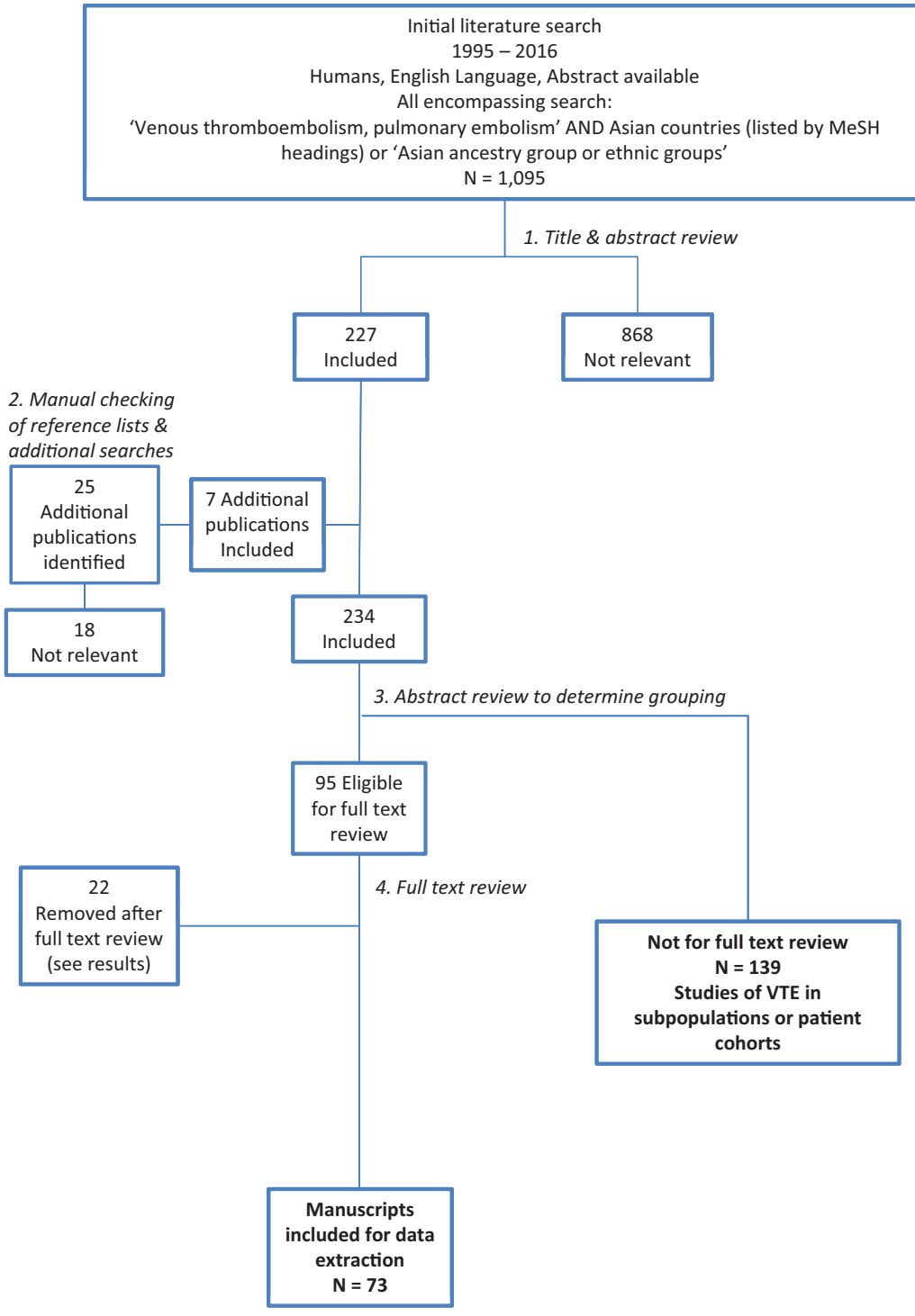

Fig. 1 Flow chart.

all derived from the Taiwan National Health Insurance databases. Each study reported absolute DVT, PE or VTE rates in cases and matched controls, together with adjusted incidence hazard ratios (HR; ►**Table 3**).

Medical Disorders, Injuries and Toxicities

The estimated incidence of PE was significantly higher in patients with chronic inflammatory disorders than in age- and sex-matched controls. The disorders included systemic lupus erythematosus (SLE; PE rate of 10.2 per 10,000 patient-years; HR: 19.7; 95% confidence interval [CI]: 11.9; 32.8),[11] systemic sclerosis (SSc) (10.8 per 10,000 patient-years),[12] chronic obstructive pulmonary disease (COPD; 12.31 per 10,000 patient-years)[13] and asthma (10.2 per 10,000 patient-years).[14] Estimated incidence rates of DVT were also significantly higher in patients with COPD,[13,15] SLE,[11] Sjogren's syndrome (SS),[16] SSc,[12] rheumatoid arthritis,[17,18] inflammatory bowel disease (IBD), pneumococcal pneumonia,[19] osteomyelitis,[20]

Table 2 Population-wide incidence estimates

Country	Reference	Study years	Population based or extrapolated	Data source	*N* per 100,000		
					DVT	PE	VTE
Japan[10]	Sakuma M, et al. Circ J 2002; 66:1144	1951–2000	Population based	Annual reports from 'Vital Statistics of Japan'		Attributed death rates: 0.08 (1956); 0.77 (1996); 0.8 (2000)	
Korea[7]	Jang MJ, et al. J Thromb Haemost 2011; 9:85	2004–2008	Population based	National Health Insurance database; ICD-0-coded data for PE and/or DVT (includes intra-abdominal and site not specified)	3.91 (2004); 5.31 (2008)	3.74 (2004); 7.01 (2008)	8.83 (2004); 13.8 (2008)
Taiwan[8]	Lee CH, et al. J Thromb Haemost 2010; 8:1515	2001–2002	Population based	National Health Insurance claims database; ICD-9-CM-coded data for inpatient or outpatient VTE			15.9
Hong Kong[9]	Cheuk BL, et al. Br J Surg 2004;91:424	2000–2001	Population based	Hong Kong Hospital Authority Clinical Data Analysis and Report System (95% of secondary and tertiary inpatient services); ICD-9-CM codes	17.1	3.9	19.9

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

tuberculosis[21] and hepatitis C virus infection[22] compared with controls (►**Table 3**). Two studies only recorded VTE incidence, and both showed significantly higher rates in patients with dermatomyositis (HR: 11.1; 95% CI: 5.2, 23.6) and liver cirrhosis (HR: 7.7; 95% CI: 5.2, 11.4)[23] compared with controls.

Other conditions with higher estimated incidence rates of DVT or VTE, compared with controls, included spinal cord injury,[24] organophosphate toxicity,[25] carbon monoxide poisoning,[26] schizophrenia,[27] sleep disorders,[28] hormone replacement therapy[29] and type 2 diabetes mellitus.[30] Metformin use in type 2 diabetes was associated with a reduced risk of DVT with 0.22% of cases compared with 0.56% of controls affected (HR: 0.43; 95% CI: 0.24, 0.56;[31] ►**Table 3**).

Post-surgical VTE Rates

Seven population-based studies reported the rates of VTE recorded within 4 to 5 weeks, or within 3 months, of surgery[32–38] (►**Table 4**). Five studies were of patients who had major joint surgery (Taiwan $n = 3$; Korea $n = 2$), another (Korea) examined VTE rates after major surgery (including joint surgery) and a study from Japan investigated rates after spinal surgery. The estimated incidences of symptomatic VTE following total hip arthroplasty (THA) were 0.15,[37] 0.27,[32] 0.40,[34] 0.98[36] and 1.35%[39] in five separate studies. After total knee arthroplasty (TKA), the reported incidence ranged from 0.22 to 1.2%. Hip fracture surgery (1.60%) and cancer surgery (0.67%) were associated with high VTE incidence rates in Korea[36] (►**Table 4**).

Pregnancy-Related VTE Rates

Only one large-scale population study investigating pregnancy-related VTE rates was identified, and reported the annual rate increased from 2006 to 2010 in South Korea (the overall incidence was 0.82 per 10,000 deliveries during the 5-year period).[40]

VTE as a Hospital Discharge Diagnosis

Prevalence of VTE among All Hospital Inpatients

Nine studies[9,41–48] reported the number of patients with a discharge diagnosis of DVT, PE or VTE per 10,000 hospital inpatients, as recorded in hospital or registry databases in mainland China, Hong Kong, India, Japan, Korea and Singapore. These ranged widely from 11 to 65 per 10,000 for DVT, 2.5 to 23 per 10,000 for PE and 11 to 88 per 10,000 for VTE. In Singapore, the prevalence of DVT among inpatients increased from 16 cases per 10,000 admissions in 1996/1997 to 65 cases per 10,000 admissions in 2006 (►**Table 5**).

Prevalence of VTE in Medical Inpatients

Three studies of symptomatic VTE among medical or 'high-risk' medical inpatients in Thailand and Singapore[49] and one study of VTE after an ischaemic or haemorrhagic stroke in Taiwan are shown in ►**Table 6**. The reported VTE prevalence was 0.2 to 0.9% of inpatients (1.6% in patients with chronic liver disease).

Prevalence of VTE among Surgical Inpatients

The rates of symptomatic post-surgical VTE in 10 single hospital studies or multicentre registries from East Asia,

Table 3 Population-based estimated incidence in medical subgroups

Predisposition	Reference	Study period	Cases	Controls	Mean age (y)	Cases: VTE/10,000 patient-years adjusted HR (95% CI)			Controls: VTE/10,000 patient-years		
						DVT	PE	VTE	DVT	PE	VTE
Inflammatory disorders											
Systemic lupus erythematosus (SLE)[11]	Chung WS, et al. J Thromb Haemost 2014;12:452	Index 1998–2008; median 7-y follow-up to 2010	13,084	matched 4:1	35.5	15.1 HR 12.8 (9.06, 32.8)	10.2 HR 19.7 (11.9, 32.8)		1.13	0.47	
Sjogren's syndrome (SS)[16]	Chung, WS, et al. J Rheumatol 2014;41:909	Index 1998–2008; median 5.1-y follow-up to 2010	8,920	matched 4:1	53.5	5.81 HR 1.83 (1.16, 2.89)	6.43 HR 3.29 (2.03, 5.31)		3.11	1.97	
Rheumatoid arthritis[17]	Chung, WS, et al. Ann Rheum Dis 2014;73:1774	Index 1998–2008; follow-up to 2010	29,238	matched 4:1	52	10.7 HR 3.36 (2.79, 4.03)	3.6 HR 2.07 (1.55, 2.76)		3.22	1.75	
Rheumatoid arthritis[18]	Kang JH et al, J Vasc Surg 2012;56:1642	Index 2001–2009	5,193 first DVT	matched 4:1		OR 1.96 (1.45, 2.64)					
Systemic sclerosis (SSc)[12]	Chung WS, et al, Rheumatology 2014;53:1639	Index 1998–2008; follow-up to 2010	1,895	matched 4:1	50	10.9 HR 10.5 (3.64, 30.3)	10.8 HR 7.00 (2.64, 18.5)		1.08	1.51	
Inflammatory bowel disease (IBD)[76]	Chung WS, et al, Thromb Res 2015;135:492	Index 2000–2010; follow-up to 2011	11,445	matched 4:1	53	9.81 HR 1.98 (1.45,2.7)	3.98 HR 1.80 (1.11, 2.90)		4.5	2.15	
Chronic obstructive pulmonary disease (COPD)[13]	Chen WJ, et al, COPD 2014;11:438	2000–2008; follow-up to 2009	355,878	matched 1:1	71		12.31 HR 3.45 (3.10, 3.83)			3.16	
Asthma[14]	Chung WS et al, Eur Respir J;43(3):801–807	2002–2008; follow-up to 2010	31,356	matched 4:1	39		10.2 HR 3.24 (1.74, 6.01)			3.09	
Dermatomyositis/ polymyositis[77]	Chung WS et al, Thromb Res 2014;134:622	Index 2000–2010	2,031	matched 4:1	47.5			25.0 HR 11.1 (5.2, 23.6)			2.08
Pulmonary Tuberculosis (TB)[21]	Chung WS et al, Thromb Haemost 2014;112:1325	Index 2000–2010	9,985	matched 4:1	59		2.10 HR 2.46 (1.10, 5.51)			0.72	
Chronic Obstructive Pulmonary Disease (COPD)[13]	Chen CY and KM Liao 2015; Medicine (Balt.) 94:e1741	Index 1998–2008; followed to Dec 2009	8,810 age >40 years	matched 2:1	72	18.78 HR 1.38 (1.06, 1.80)			13.26		
Pneumococcal pneumonia[19]	Chen YG et al Respirology 2015;20:799	1998–2010	18,928	matched 4:1	66	12.4 HR 1.78 (1.39,2.28)	7.8 HR 1.97 (1.43,2.72)		6.4		3.5
Osteomyelitis[20]	Lin TY, et al. Thromb Haemost 2014;112:573	1998–2008; follow-up to end 2010	24,335	matched 1:1	55.4	12.7crude HR 2.49 (1.76, 3.52)	4.11crude HR 1.77 (0.97, 3.20)		6.71	3.58	
Hepatitis C virus infection[22]	Wang CC et al. Medicine 2015;94:e1585	1998–2011; mean 5.14 year follow-up	3,686	matched 4:1	51.9	7.92 HR 1.96 (1.03,3.73)	4.22 HR 2.10 (0.88, 5.06)		3.51	1.93	

Table 3 (*Continued*)

Predisposition	Reference	Study period	Cases	Controls	Mean age (y)	Cases: VTE/10,000 patient-years adjusted HR (95% CI)			Controls: VTE/10,000 patient-years		
						DVT	PE	VTE	DVT	PE	VTE
Miscellaneous											
Spinal cord Injury[24]	Chung WS et al, Thromb Res 2014; 133(4):579–84	Index 1998–2008; follow-up to 2010	47,916	matched 4:1	50	8.99 HR 2.46 (2.11, 2.87)	3.24 HR 1.57 (1.23, 1.99)		3.52	1.9	
Organophosphate toxicity[25]	Lim YP et al, Medicine 2015;94:1	Index 2000–2011	9,223	matched 4:1	54	6.35 HR 1.55 (1.03, 2.34)	3.27 HR 1.44 (0.83, 2.52)		3.67	2.15	
Liver cirrhosis[23]	Ng KJ et al, J Thromb Haemost 2015;13:206	2005–2010; mean 3.2 year follow-up	2,779	755,161	59 (LC) 44 (no LC)			HR 7.7 (5.2, 11.4)			
Type 2 diabetes[30]	Chung WS et al. Thromb Haemost 2015;114:812	2000–2011; follow-up to 2011	56,158	168,474	57.1 (T2DM) 56.4 (no T2DM)	8.96 HR 1.43 (1.23, 1.65)	3.92 HR 1.52 (1.22, 1.90)	12.0 HR 1.44 (1.27, 1.63)	5.61	2.33	7.51
Metformin use in type 2 diabetes[31]	Lu D et al. BMC Cardio Dis 2014;14:187	1997–2003; mean 3.74 year follow-up	7,154	7,778	57.70	0.22% HR 0.43 (0.24, 0.76)			0.56%		
Carbon monoxide poisoning[26]	Chung WS et al J Epi Comm Health 2015;69 (5):557	Index 2000–2011	8,316	matched 4:1	39.6	5.67 HR 3.85 (2.17,6.83)	1.97 HR 1.66 (0.70,3.92)		1.47	1.02	
Pregnancy[40]	Jang MJ et al J Thromb Haemost 2011;9 (12):2519	2006–2010	147	1,795,064 deliveries				0.82 (per 10,000 deliveries)			
Sleep disorders[28]	Chung WS, et al. Sleep Med 2015;16:168	Index 1998–2001	46,371	Matched 2:1	52.2			6.05 HR 1.79 (1.49, 2.16)			3.7
Schizophrenia[27]	Hsu WY, et al. Schizophr Res 2015;162:248	Index 2000–2011, 6.4-y follow-up	60,264	matched 1:1	38.8	4.17 HR 2.02 (1.52, 2.70)	1.43 HR 1.99 (1.21, 3.27)		2.02	0.69	
Hormone replacement therapy (HRT)[29]	Lee CH, et al. Circ J 2015;79:1107	1998–2008 2-y follow-up	499,594	424,963	60.7			4.4 HR 1.796 (1.27, 2.54)			2.6
Atrial fibrillation[78]	Wang CC et al. Thromb Haemost 2015;113:185	2000–2010	11,458	matched 4:1	71.6	2.69 HR 1.74 (1.36, 2.24)	1.55 HR 2.18 (1.51, 3.15)		1.12	0.46	

Abbreviations: DVT, deep vein thrombosis; HR, hazard ratio; OR, odds ratio; PE, pulmonary embolism; VTE, venous thromboembolism.

Table 4 Population-wide estimates of post-surgical VTE rates

Procedures	Country	Reference	Study Years	Study Design	Procedure	Incidence (%)		
						DVT	PE	VTE
THA and TKA[32]	Taiwan	Wu PK et al, Thromb Res 2014;133:719	2002–2006	Population based: National Health Insurance Research Database (VTE within 28 days).	61,460 THA	0.22%	0.04%	0.27%
					52,556 TKA	0.57%	0.07%	0.64%
THA and TKA (primary or revision)[34]	Taiwan	Lee CH et al, J Thromb Haemost 2013;11:1930	1998–2007	Population based: National Health Insurance Research Database; age $\geq$ 45 y	107,679 THA			0.40%
					113,844 TKA			0.46%
TKA[33]	Taiwan	Lee CH et al, J Thromb Haemost 2012;10:56	1998–2007	Population based: National Health Insurance Research Database (VTE within 3 mo)	113,844 TKA			0.46%
Major joint surgery, Surgery for Cancer, Prostate, Benign Gynecology[36]	Korea	Yhim HY et al, J Thromb Haemost 2014;12:1035	2007–2011	Population based: Health Insurance Review and Assessment Service database; ICD-10 coding (VTE within 5 wk)	993,459 (All)	0.44% (DVT alone)	0.27% (PE $\pm$ DVT)	0.71%
					349,696 Joint			1.24%
					190,341 TKA	0.71%	0.37%	1.08%
					41,271 THA	0.62%	0.36%	0.98%
					118,084 HFS	0.66%	0.94%	1.60%
					384,192 cancer			0.67%
					259,571 benign			0.05%
Spinal Surgery[35]	Japan	Masuda K et al, Spine J 2012;12:1029	2007 and 2008 (July–Dec)	Extrapolated: DRG-like database: 855 hospitals in 2008; including 42.7% of acute admissions in Japan; in-hospital deaths from PE	49,867 (47,743 eligible)		4 deaths from PE	
Major orthopaedic surgery[37]	Korea	Lee SY et al, Yonsei Med J 2015;56:139	2007–2011 (2008–2011 for TKA)	Population based: Health Insurance Review and Assessment Service database; ICD-10 coding (VTE within 4 wk)	THA 89,710 TKA 180,611 HFS 75,328 (not known if prophylaxis)	0.15% 0.22% 0.16%		
THA and TKA[39]	Korea	Lee S et al, J Korean Med Sci 2016;31:80	2010 (Jan to Dec).	Population based: Health Insurance Review and Assessment Service database; ICD-10 coding (VTE within 90 days)	THA 13,868/22,127 TKA 27,305/52,882 (without/with chemoprophylaxis)	1.35% 1.2%	0.9% 0.4%	2.0% 1.5%

Abbreviations: DRG, diagnosis-related group; DVT, deep vein thrombosis; HFS, hip fracture surgery; PE, pulmonary embolism; THA, hip arthroplasty; TKA, knee arthroplasty; VTE, venous thromboembolism.

Table 5 Prevalence of VTE as a proportion of hospital admissions, from hospital and registry databases

Country	Reference	Study period	Data source	Admissions or procedures	Subjects	Clinical VTE (*N* per 10,000 admissions or *N* per 100 procedures)			Case-fatality rate
						DVT	PE	VTE	
China[41]	Yang Y et al, PLoS ONE 2011;6:e26861	1997–2008	PE registry; 60 level 3 hospitals. All imaging independently reviewed	16,972,182	18,206 first or recurrent PE	N/R	10.7	N/R	25.1% (in 1997); 8.6% (in 2008)
China[79]	Zhou HX et al, Thromb Res 2012;130:735	2010–2011	Retro/prospective search. Hospital VTE registry and discharge coding (ICD-10)	~66,000	347 VTE: 92 PE, 82 PE + DVT, 173 DVT	N/R	N/R	26	
Hong Kong[9]	Cheuk BL et al, Br J Surg 2004;91:424	2000–2001	Hong Kong Hospital Authority database (ICD-9)	2,082,045 admissions	2,304 DVT and 526 PE (150 with DVT)	11.1	2.5	N/R	7.3% for DVT; 23.8% for PE
India[43]	Lee AD et al, Eur J Endovasc Surg 2009;37:482	1996–2005	Hospital database (ICD codes)	438,667	722 VTE	N/R	N/R	17.46	All VTE: 13% suspected; PE: 50% confirmed; PE: 14%
Japan[44]	Kishimoto M et al, Thromb Haemost 2005;93:876	1987–1999	Hospital database (ICD-9-CM)	131,060	141 VTE	N/R	N/R	11	N/R
Korea[45]	Choi WI et al, Clin Appl Thromb Haem 2011;17:297	2005–2007	Hospital database (ICD-9-CM)	61,542	247 VTE (51 PE, 37 PE + DVT, 159 DVT alone)	31.9 (±PE)	14.3 (±DVT)	40.1	N/R
Singapore[46]	Lee LH et al, Ann Acad Med Singapore 2002;31:761	1996–1997	Hospital vascular laboratory database for confirmed DVT	202,869	388 DVT	15.8	N/R	N/R	N/R
Singapore[47]	Ng HJ, Lee LH. Thromb Haemost 2009;101:1095	2002–2003	Hospital vascular laboratory database and inpatient records search (ICD-9-CM)	109,217	495 DVT	45.3	N/R	N/R	12.3% (61 patients); deaths from PE: 6
Singapore[48]	Molina JA, et al. Ann Acad Med Singapore 2009;38:470	2006	Hospital database (ICD-9-CM)	98,121	860 VTE (636 DVT, 224 PE)	65	23	88(73[a])	N/R

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.
[a]Age adjusted.

Table 6 Prevalence of VTE as a proportion of non-surgical and surgical subgroup admissions to hospital (from hospital or registry databases)

Predisposition or procedure	Country	Reference	Study period	Procedures	Outcomes	VTE rate per 100 procedures or predispositions			Case-fatality rate
Non-surgical						**DVT**	**PE**	**VTE**	
Adult medical, ICU and stroke unit admissions	Thailand[80]	Aniwan S, Rojnuckarin P. Blood Coag Fibrinol 2010;21:334	2007–2008	7,126	42 VTE (23 PE; 20 confirmed + 3 possible fatal PE (32 per 100); 4 DVT and PE	32	32	59	50%: 21/42 deaths, 9 attributed to PE
High-risk medical admissions	Thailand[81]	Rojnuckarin P et al. Thromb Haemost 2011;106:1103	2009	1,290	20 VTE (13 DVT, 7 PE) in hospital and 7 VTE (5 DVT, 2 PE) after discharge); total 18 DVT and 9 PE	14	7	21	
All medically managed patients (chronic liver disease the subgroup of interest)	Singapore[49]	Yang Y et al. Thromb Res 2015;136:548	2004–2011	199,904 (all); 193,532 (not CLD); 6,372 (CLD, with or without cirrhosis)	1,744 (0.9%) VTE; 1,541 (0.8%) VTE; 102 (1.6%) VTE (non-cirrhosis 1.5%, cirrhosis 2.0%)	N/R; 0.7%; 1.15%;	N/R; 0.3%; 0.6%	0.9%; 0.8%; 1.6%	2567 (1.3%) total, number attributable to VTE not stated
Ischaemic or haemorrhagic stroke	Taiwan[82]	Chen CC et al. Top Stroke Rehabil 2012;19:361	2002–2009	Ischaemic: 21,129	45 DVT and 14 PE	0.21%	0.07%	N/R	5/15 (35.7%)
				Haemorrhagic: 5,662	15 DVT and 1 PE	0.27%	0.02%	N/R	
Surgical						DVT	PE	VTE	
Major trauma	Singapore[83]	Wong TH et al. Eur J Trauma Emerg Surg 2013;39:495	1998–2007	8,615 patients	34 VTE; 13 PE (7 with DVT); 21 DVT alone	0.24%	0.15%	0.39%	3/34 (8.8%)
General surgery with G-E and major joint surgery subgroups	Japan[50]	Kunisawa S et al. World J Surg 2012;36:280	2008–2010	All: 1,016,496	2,485 VTE (1,947 DVT; 538 PE ± DVT)	0.24%	0.05%	0.24%	67/1947 (3.44%) DVT; 123/538 (22.86%) PE
				G-E: 86,181	200 VTE (118 DVT, 82 PE)	0.14%	0.10%	0.23%	2/118 (1.69%) DVT; 19/82 (23.17%) PE
				Joint: 50,226	931 VTE (817 DVT, 114 PE)	1.63%	0.23%	1.85%	4/817 (0.49%) DVT; 15/114 (13.16%) PE
Elective TKA or THA	Korea[84]	Won MH et al. J Arthroplasty 2011;26:1106	1996–2009	1,608	32 VTE (32 DVT, 4 PE)	1.99%	0.24%	1.99%	N/R
TKA	Taiwan[85]	Wu PK et al. J Chinese Med Ass 2014;77:155	2007–2010	1,768	4 PE		0.23%		0/4 PE
Major joint surgery (TKA, THA, Hip)	Multinational[86]	Leizorovicz A et al. J Thromb Haemost 2005;3:28	2001–2002	All: 2,420	22 DVT, 6 PE, 24 VTE	0.91%	0.25%	1.0%	
				TKA: 944	13 DVT, 3 PE, 13 VTE	1.38%	0.32%	1.38%	
				THA: 408	4 DVT and 0 PE, 4 VTE	0.98%	0%	0.98%	
				Hip #: 1,068	5 DVT, 3 PE and 7 VTE	0.47%	0.28%	0.66%	
TKA	Korea[87]	Park YG et al. J Arthroplasty 2016;31:1072	2002–2011	TKA: patients 1,933 (2,891 operations)	26/2891 TKA (0.90%) VTE	10 (0.35%) DVT alone	16 (0.55%) PE (5 with DVT)	26/2891 TKA (0.90%); 0.86% primary TKA; 1.98% revision TKA	0/16 (0%)
Haemi-arthroplasty (for femoral neck fracture)	Japan[88]	Tsuda Y Orthop Sci 2014;19:991	2007–2010	22,776 total # NOF; 17,984 receiving mechanical but not chemical prophylaxis	160/17,984 PE (non-chemical prophylaxis group)		0.89%		21/160 (13.1%)
Gynaecological surgery	Hong Kong[89]	Chan LY et al. Acta Obstet Gynecol Scand 2002;81:343	1998–2000	6,077	31 VTE (29 DVT, 2 PE); 27/29 DVT limited to calf veins	0.48%	0.03%	0.51% (overall); 0.17% (1998) 0.76% (1999); 0.69% (2000)	N/R
Gynaecological surgery	China[90]	Qu H et al. Medicine (Baltimore) 2015;94(39):e1653	2008–2013	739	16 symptomatic DVT; 6 symptomatic PE	2.17%	0.81%		0/739
Colorectal surgery	Korea[91]	Yang SS et al. World J Surg 2011;35:881	2006–2008	3,645	31 VTE: 23 DVT (8 with PE), 16 PE (8 with DVT)	0.63%	0.44%	0.85%	2/16 PE

Abbreviations: CLD, chronic liver disease; DVT, deep vein thrombosis; G-E, gastroenterological; ICU, intensive care unit; N/R, not recorded; PE, pulmonary embolism; THA, hip arthroplasty; TKA, knee arthroplasty; VTE, venous thromboembolism.
Note that rates of DVT and of PE may add up to more than the VTE rate, because some patients had both DVT and PE.

with various times of clinical follow-up, are presented in ►**Table 6**. The reported rates were 0.39% (major trauma), 0.23 to 0.24% (general and gastric and bowel surgery), 0.85% (colorectal surgery), 0.51% (gynaecological surgery in Hong Kong [0.17% in 1998, rising to 0.76% and 0.69% in 1999 and 2000]; higher in mainland China), 0.66% after hip fracture and 1.0 to 1.85% after major joint arthroplasties.

Old Age, Gender and Other Potentially Contributing Conditions

Old Age

Four population-based studies (►**Table 2**) describe strong associations of VTE risk with advancing age. In Korea, relative to the 30- to 39-year age group, there was a sixfold increase in risk by age 60 to 69 years, and a 15-fold increase by age greater than 80 years when the absolute annual rate was just over 1/1,000 people.[7] The absolute annual VTE rate of 0.02 per 1,000 women and 0.03 per 1,000 men aged less than 30 years, increased to 1.2 and 0.8 per 1,000 among women and men aged greater than 80 years.[8] Observations were similar in Hong Kong and Japan.[9,10]

Gender

Three population-wide studies reported on gender and VTE risks. In one study, women were less likely to have a diagnosis of VTE (relative risk [RR]: 0.96) or DVT alone (RR: 0.87) but more likely to have a diagnosis of PE (RR: 1.11).[7] In a second study, 54% of patients with VTE were female,[8] while the third study reported no significant difference.[9] Women slightly outnumbered men in seven of nine hospital or registry-based cohorts of patients with VTE (a tendency most pronounced in two of the three studies from Japan; ►**Table 7**).[44,50]

Other Comorbidities and Potential Predispositions

In Taiwan, a population-based analysis of VTE rates and associated risk factors, or predispositions, showed that 16% of cases had previous VTE, and most VTE was associated with predisposing conditions (22% malignancy, 17% serious neurological disease, 8% major trauma 8% and 38% major surgery during the preceding 3 months), although 27% had no recorded predisposition.[8] Similar potentially contributing conditions were recorded among hospital inpatients with VTE (►**Table 8**): age older than 70, 75 or 80 years (15–42% of patients); cancer (13–52% of patients); previous VTE (1–16% of patients); immobility (up to 74% of patients), acute or chronic heart or lung conditions (up to 36% of patients); stroke or paresis; various inflammatory disorders; and a body mass index (BMI) $\geq$ 25 kg/m^2.

Cancer-Related Venous Thromboembolism

►**Table 8** shows the incidences of symptomatic VTE in patients with various cancers, reported from East Asia. One population-based cohort study from Taiwan searched all hospital admissions for any form of newly diagnosed cancer;[51] another searched a randomly selected 15% subset of all admissions.[52] The studies estimated that 1.85 and 3.4 patients per 1,000 patient-years of follow-up developed VTE (using somewhat different identifying algorithms). VTE was more likely if there was previous VTE,[51] or cancer of the pancreas, lung or liver, a sarcoma or multiple myeloma,[52] and VTE was associated with reduced survival. In a large cohort of Korean patients with non–small cell lung cancer (NSCLC), 6.4% developed VTE during 2 years of observation, and this was associated with reduced survival if patients had limited stage disease.[53] In a study from China, 1.3% of patients with any form of lung cancer developed VTE (all VTE patients had NSCLC).[54] Patients with a gynaecological malignancy had VTE rates of 3.3% during 5 years of follow-up in a population-based study from Taiwan,[55] and 1.3% in a hospital cohort from Thailand (where most VTE was associated with ovarian cancer).[56] The 2-year incidence of VTE was 4.9% after inoperable gastric cancer (metastatic or recurrent) in a cohort from Korea.[57] VTE rates were 1.4% during 4 months after starting thalidomide for relapsed or refractory multiple myeloma in Japan,[58] and less than 1% in Korean patients with acute myeloid leukaemia.[59]

Other Observations: Recurrence Rates and Case Fatality Rates

A population-wide study of over 5,000 Taiwanese adults discharged from hospital after an admission with VTE in 2001 or 2002 found that annual crude recurrence rates were 5.1% in men and 5.2% in women, during up to 4 years (average 2.26 years) of follow-up.[8] A recurrence was most likely during the first 12 months after VTE (with cumulative rates of 4.6, 6.7 and 9.4%, after 3, 6 and 12 months, respectively, which reached 14.4% at 4 years), and was three to four times more likely in patients with a previous VTE or cancer than if the predisposition was transient or the index VTE was apparently unprovoked.[8]

This and another population-based report found high case fatality rates. In Taiwan, 4.3% of patients with VTE died in hospital, 7.5% died within 1 month and 14.9% died within 6 months; mortality was higher after PE than DVT.[8] In Hong Kong, 7.3% of admissions with a DVT and 23.8% of those with PE died in hospital, and VTE-associated mortality was greatest in the elderly.[9] High 30-day or in-hospital mortalities were also reported in a questionnaire-based survey from Japan (7% after DVT, 13% after PE),[60] a PE registry from China (9% in 2008)[41] and hospital cohorts in Singapore (12%)[47] and India (13%).[43]

Temporal Trends

The reported incidence of VTE has increased during recent decades, in population-wide studies from Korea and Japan (see above) in registries, and in hospital databases. There was an almost fivefold increase in the annual number of patients recorded between 1997 and 2008 in a very large Chinese PE registry,[41] and a fivefold rise in admissions with acute DVT at a Singaporean hospital between 1990 and 1997.[46,47] In China, the start of a nationwide project to improve diagnosis and management of VTE coincided with a sharp upturn in the number of patients registered as having PE.[41]

Discussion

This systematic literature review of evidence regarding the population-based incidence of symptomatic VTE in East Asian populations confirms the frequency and importance of this

Table 7 Predisposing conditions in hospital cohorts

Country	Reference	Study period	VTE (*N*)	Male (%)	Age ≥70, 75 or 80 y	BMI ≥ 25	Open surgery	Acute or chronic lung	Heart	Acute infection	Not mobile	Stroke paresis	Cancer	Inflammatory bowel or joint	Auto-imm	Pregnt	Prior VTE	Fam history	None
All admissions					%	%	%	%	%	%	%	%	%	%	%	%	%	%	%
China[79]	Zhou HX et al. Thromb Res 2012;130:735	2010–2011	347	55	15 (≥75)	27	12	36	6	1	11	–	13	1	–	1	5	1	–
Hong Kong[92]	Liu HS et al. Hong Kong Med J 2002;8:400	1997–2000	376	46	42 (>70) from Fig	–	21	–	–	–	–	–	16.5	–	–	5	3	–	42
India[43]	Lee AD, et al. Eur J Endovasc Surg 2009;37:482	1996–2005	722	48	–	–	30	–	–	–	–	–	31	–	–	–	–	–	–
Japan[44]	Kishimoto M, et al. Thromb Haemostas 2005;93:876	1987–1999	141	30	40 (≥70)	40	21	–	10	–	53	18	16	–	–	–	8.5	–	–
Korea[45]	Choi WI, et al. Clin Appl hromb Haem 2011;17:297	2005–2007	88	–	42 (≥70)	22	–	22	16	–	45	19	27	–	–	–	–	–	–
Singapore[46]	Lee LH, et al. Ann Acad Med Singapore 2002;31:761	1996–1997	388	–	7 (≥80)	–	30	–	–	–	67	–	33	–	–	–	9	1	–
Singapore[48]	Molina JA et al. Ann Acad Med Singapore 2009;38:470	2006	860	45	31 (≥75)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Singapore[47]	Ng HJ, Lee LH. Thromb Haemost 2009;101:1095	2002–2003	495	40	12 (≥80)	–	32	–	–	–	–	–	23	–	–	–	8	–	–
Taiwan[8]	Lee CH et al, J Thromb Haemost 2010;8:1515	2001–2002	5,347	54	13 (≥80)	–	46	30	18	–	–	14	22	–	–	–	16	–	27
Medical																			
Hong Kong[93]	Cheng G et al, Thrombosis 2011	2005–2008	687	–	–	–	–	16	14	24	–	7	45	–	–	–	–	–	–
Japan[94]	Nakamura M et al. J Thromb Thrombolysis 2006;21:131	1994–2003	133	46	30 (≥70)	17 (≥26.4)	–	10	16	3	62	28	24	–	3	–	–	–	–
Thailand[80]	Aniwan S, Rojnuckarin P. Blood Coag Fibrinol 2010;21:334	2007–2008	42	–	–	12	–	12	2	–	74	–	52	5	7	–	–	–	–
Thailand[81]	Rojnuckarin P et al. Thromb Haemost 2011;106:1103	2009	27	–	–	–	–	–	–	41	–	7	48	–	22	–	–	–	–
Surgical																			
Japan[50]	Kunisawa S et al, World J Surg 2012;36:280	2008–2010	2,485	33	44 (≥ 75)	–	–	–	–	–	–	–	62 G-E surg	–	–	–	–	–	–

Abbreviations: BMI, body mass index (kg/m^2); G-E, gastroenterological; VTE, venous thromboembolism.

Table 8 Population, registry and hospital-based VTE rates in patients with cancer

Reference	Index cases	Study design	Patients	*n* (%) VTE (*n*/patient-years)			Comments
				DVT	PE	VTE	
Yu YB et al. Thromb Haemost 2012;108:225[51]	1997–2005	All admissions newly diagnosed cancer (National Health Insurance Database, NHID, Taiwan). Median follow-up: 21 (0–120) mo to end 2006	497,180	0.94% ($163/10^5$ pt y)	0.16% ($28/10^5$ pt y)	1.07% ($185/10^5$ pt y)	28.5% VTE at cancer presentation; median 5.8 mo to VTE after diagnosis; lower survival if DVT or PE ($p < 0.001$)
Chew TW et al. BMC Cancer 2015;15:298[52]	2001–2008	Admissions newly diagnosed cancer, from random 15% subset of NHID, Taiwan. Two algorithms to identify VTE:[1] if coded as having VTE;[2] if coded and treated as VTE. Up to 10 y follow-up	43,855			Algorithm 1: 3.2% ($9.9/10^3$ pt y); algorithm 2: 1.1% ($3.4/10^3$ pt y)	Algorithm 2 includes fewer intra-abdominal DVT (19 vs. 53% with algorithm 1). Highest VTE risks if cancer of pancreas, lung, liver, multiple myeloma or sarcoma
Lee YG et al. Thromb Haemost 2014;111:1112[53]	2006–2010	Retrospective cohort all non–small cell lung cancer (NSCLC) at Seoul National University Hospital, Korea. Median 3.8-y follow-up. Search electronic medical records for VTE	1,998			6.6% (cumulative 4.2% after 6 mo, 6.4% after 2 y)	2-y cumulative incidence: 2.5% (localized), 5.5% (locally advanced) and 14.1% (metastatic) disease. Reduced survival if VTE and localized NSCLC
Wang Z et al. Support Care Cancer 2015;23:635[54]	2004–2013	Retrospective 10-y cohort all primary lung cancer; Guangdong General Hospital, Guangzhou, China	4,726	45 DVT alone (0.95%)	16 (0.3%); (11 with DVT)	61 (1.3%)	All patients with VTE had NSCLC (no VTE if SCLC). 2 PE subclinical, at staging CT.
Tsai SJ et al. BMC Res Notes 2012;5:316[55]	2003–2008	Retrospective cohort newly diagnosed cancer cervix. NHID (Taiwan); Median 5-y follow-up	1,013			3.3% (5-y cumulative)	VTE associated with reduced survival. 5-y VTE risk = 0.3% in age- and sex-matched appendectomy patients
Oranratanaphan S et al. Asian Pac J Cancer Prev 2015;16:6705[56]	2004–2013	Retrospective cohort gynaecologic oncology at King Chulalongkorn Memorial Hospital, Bangkok, Thailand	2,316	11 alone (0.5%)	19 (0.8%), 14 with DVT	30 (1.3%)	9 VTE before (up to 13 mo before); 6 VTE at the time of and 15 VTE after cancer diagnosis. 18/30 VTE in 5.9% of cases with ovarian cancer
Kang MJ et al. Eur J Cancer 2012;48:492[57]	2000–2008	9-y retrospective cohort inoperable advanced gastric cancer (metastatic or recurrent after initial resection); Oncology Dept., Asan Medical Centre, Seoul, Korea	3,095	N/R	N/R	103 (3.3%); cumulative = 3.5% after 1 y and 4.9% after 2 y (1.88/100 pt y)	Median time from cancer diagnosis to VTE = 4.6 (0–41) mo
Kato A et al. Thromb Res 2013;131:140[58]	2009–2010	Japanese post-marketing data on registered refractory or relapsed myeloma treated with thalidomide for median of 31 d; median follow-up of 112 d	1,035	14 (1.4%)	3 (0.3%)	14 (1.4%)	12 leg DVT, 1 superficial VT, 1 thrombosis 'unknown vein of lower extremity'
Lee YG et al. Thromb Haemost 2015;113:201[59]	2007–2011	Retrospective cohort all acute myeloid leukaemia (AML); two referral hospitals, Seoul, Korea	811	4 (0.5%)	2 (0.25%)		26 vein thromboses (13 catheter related, 2 cerebral vein, 2 splanchnic, 3 'others', 4 leg DVT, 2 PE)

Abbreviations: CT, computed tomography; DVT, deep vein thrombosis; N/R, no result; NSCLC, non–small cell lung cancer; PE, pulmonary embolism; pt y, patient-years; VTE, venous thromboembolism.

disease is increasing, especially among the aged. Our search for evidence was focused on symptomatic VTE, because it is symptomatic DVT or PE that determines the clinical burden from VTE.

VTE Incidence in Asia Compared with the West

Recently published population-wide estimates of annual symptomatic VTE rates in Korea, Taiwan and Hong Kong are approximately 15 to 20% of the level recorded in Western countries (~100 per 100,000 people).[61] However, the reported annual incidence in East Asian populations increases to approximately 1 per 1,000 people aged ≥80 years,[7–9] as compared with 3 per 1,000 in some Caucasian populations.[57] In addition, the National Health Insurance data from Korea, Japanese vital statistics of deaths attributed to PE, data from PE registries and hospital admission statistics all indicate a rise in reported VTE rates over time across East Asia.[7,8,46]

Hospital data from large registries and databases corroborate the findings in population-health studies and potentially provide more accurate and robust estimates of VTE rates in certain patient groups (►**Table 5**). Across nine studies, the prevalence of VTE and the increasing temporal trend across three studies from Singapore echoed that of population-based studies. Rates of symptomatic, post-operative VTE (►**Table 6**) are difficult to compare with Western values due to differing methodologies. In a South Korean population-based study,[40] the incidence of pregnancy-related VTE was 0.82 per 10,000 deliveries, much lower than the Western rates of between 10 and 20 per 10,000 deliveries.

Accuracy of Population-Based Datasets

Estimates of population-wide VTE rates, based on population-wide databases, not only require these to include both inpatient and outpatient encounters, but also rely on accurate reporting using International Classification of Diseases (ICD) or local disease classification, evidence of anticoagulant therapy and the assumption that every patient at discharge or at censure had confirmatory tests or a post-mortem to identify VTE. Therefore, any attempt to estimate population-wide VTE rates has limitations and inherent biases. There is a risk of under-reporting, because VTE must be identified in the medical record to ensure a correct discharge diagnosis, and clinically significant PE or DVT is often misdiagnosed or unrecognized.[62] It is also important to note that the algorithms used to define DVT, VTE and PE based on ICD-9 or ICD-10 codes can vary from study to study and result in inaccurate estimation. For example, in some studies, the category DVT also included inferior vena cava (IVC) thrombosis, renal vein thrombosis and/or thrombophlebitis.[7–9]

A systematic review of studies done to validate the identification of VTE using administrative and claims data showed that reliability varies considerably and positive predictive values (PPVs) are highest when multiple codes are combined.[63] The range of PPVs reported using combined ICD-9 codes for DVT, PE or VTE was 65 to 95%. Ng et al[23] also validated their Taiwanese database by medical chart review of a random sample and found a PPV of 94.0% for VTE.

The strengths of population-based data include large sample size and ability to capture the entire population.

Risk Factors and Recurrence

It is of interest that the comorbidities and likely predispositions for VTE are similar in East Asia and in the West, most notably old age, cancer, previous VTE, immobility, trauma and surgery, and inflammation. Of particular note are the population-based cohorts with case-control comparisons, from Taiwan, which show high HR for VTE in many acute or chronic autoimmune and other inflammatory disorders (e.g. systemic lupus, SS and rheumatoid arthritis) compared with controls. There is a noteworthy finding that DVT rates were less in type 2 diabetes patients prescribed metformin;[31] recent laboratory studies have shown that metformin inhibits platelet activation and release of mitochondrial DNA (deoxyribonucleic acid).[64]

Apart from the South Korean population study in pregnancy-related VTE,[40] it is important to acknowledge the lack of published evidence from large VTE studies in Asian populations for the predispositions of pregnancy, the perinatal and post-partum period, and gynaecological laparoscopic surgery.

The overall recurrence rate of 10% during the first year after presenting with VTE, recorded in a population-based study from Taiwan, is similar to 1-year recurrence rates reported in the West of 5.6 to 12.9%.[65] Surprisingly, the risks of a recurrence after a transiently provoked or supposedly unprovoked VTE were similar (~5% during 1 year), which suggests that Western guidance on treatment duration should be validated in Asia.

Lower Asian Venous Thromboembolism Rates

There has been much speculation about why the reported VTE rates might be lower in Asia than the West.[61,66] Explanations have included under-diagnosis, low clinician awareness and the near absence in Asia of thrombophilias commonly found in Caucasian populations, such as factor V Leiden and prothrombin gene mutations. Yet this review has confirmed a clear trend of increasing VTE rates over time, across multiple population- and hospital-based studies. It is likely that in part under-diagnosis and under-reporting in early studies, followed by improved diagnosis in later years with greater awareness and perception that VTE is an issue in Asian populations, have contributed to this trend. In Singapore[47] and Hong Kong,[67] it was shown that reported VTE rates have increased as Doppler ultrasound scans were used more often and the institutions established a lower threshold for performing diagnostic tests. Similarly, PE rates in China surged following a nationwide programme to improve awareness and management of this condition.

Nevertheless, it seems likely that there has also been a genuine increase in VTE prevalence in Asian populations, perhaps because of increasing population age, increasing cancer rates and an increasing number of surgeries. The rates reported in elderly people from Asian countries suggest that the gap between VTE rates in Asia and the West will diminish further still.

Improving Awareness of VTE in Asia

A recent survey found variable public awareness of VTE worldwide and very low awareness in Asia.[66] Low and

inadequate clinician awareness as well as low public awareness of VTE in Asia[61] is likely to result in a general trend towards under-diagnosis. This is exemplified by the Chinese PE registry, where a sharp upturn in the number of reported patients with PE coincided with a nationwide programme to improve awareness and management of this condition.[9] The increase in reported VTE rates over time recorded by several studies identified in this systematic review suggests initial under-diagnosis and rising diagnostic awareness. Most of the population-based studies reviewed here were based on data collected more than 10 years ago (2000–2008), and the current VTE rates may be considerably higher.

Implications for Guidelines and Other Asian Countries

Our estimates of population burden from VTE in East Asia come from Hong Kong, Korea, Taiwan and (with less methodological confidence) Singapore. It is important to stress that these estimates should not be directly extrapolated to places with different health care systems and less extensive databases, so that similar statistics from other countries in the region such as India, Malaysia, the Philippines and Indonesia are much needed. Data on the population disease burden of VTE across Asia will also allow racial and ethnic differences in VTE to be better studied.

►**Table 1** lists guidelines and expert recommendations from Asia about VTE risk assessment, prevention and management. Several of these include summaries of the literature on VTE rates and VTE prevention trials in Asia. Most base their recommendations for anticoagulant prophylaxis, explicitly or implicitly, on international guidelines derived from Western data for Western populations, where the balance of absolute benefit and absolute risk may not be the same as in Asia. This and other recent surveys of evidence[68] find an increasing incidence of VTE in Asian populations. This emphasizes the need to validate Western VTE management guidelines in populations from Asia.

Conclusion

Together, Asian countries account for more than half the world's population and their contribution to the global VTE-related burden of disease is considerable, albeit at lower levels than Western countries. This systematic review reinforces and extends conclusions from previous reviews that VTE rates in Asia are significant and rising, both community-wide and among medical and surgical inpatients. Although the published data have methodological limitations, the evidence is consistent and persuasive regarding the incidence and predispositions for VTE in East Asia.

There is a need for greater awareness of VTE and its diagnosis and management in old age, cancer, inflammatory disorders and after surgery. Advice on anticoagulant or other VTE prophylaxis after surgery in Asia requires more extensive studies of both incidence and potential bleeding risks. Without more local evidence, the local guidelines on VTE prevention and management, which are tailored to needs of the Asia-Pacific region, must rely heavily on North American or European guidance. Doubts about their local applicability may contribute to poor guideline adherence.

What is known on this topic?

- There tends to be a lack of awareness of venous thromboembolism (VTE) as a problem in Asian populations.
- Although a large number of studies have investigated the incidence of VTE in Asia, there remains a lack of agreement regarding the true present risks of VTE in Asian populations.

What this paper adds?

- This systematic literature review brings together and summarizes published evidence on VTE from several Asian countries.
- The review examines literature published since 1995 on the incidence of symptomatic VTE (DVT or PE) in Asian populations and includes data from 73 studies.
- Population-wide estimates of annual VTE rates in Korea, Taiwan and Hong Kong (13.8, 15.9 and 19.9 per 100,000 people, respectively) are approximately 15 to 20% of the level recorded in Western countries (~100 per 100,000 people).
- The reported incidence of VTE in Asia has increased over time.
- These findings highlight the need for awareness that VTE is an important disorder in Asian populations.

Authors' Contributions
All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication.
Study conception and design: L.H.L., A.G., R.J., C.W., and C.C.W.
Acquisition of data: L.H.L. and A.G.
Analysis and interpretation of data: L.H.L., A.G., R.J., C.W., and C.C.W.

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Appendix A

Search string: ((“Venous Thromboembolism”[All Fields] OR “Venous Thrombosis”[All Fields]) OR “Pulmonary Embolism”[All Fields]) AND ((“asian continental ancestry group”[MeSH Terms] OR (“asian”[All Fields] AND “continental”[All Fields] AND “ancestry”[All Fields] AND “group”[All Fields]) OR “asian continental ancestry group”[All Fields] OR “asian”[All Fields]) OR “Taiwan”[Mesh] OR “Hong Kong”[Mesh] OR “Singapore”[Mesh] OR “China”[Mesh] OR “Korea”[Mesh] OR “Malaysia”[Mesh] OR “Philippines”[Mesh] OR “Thailand”[Mesh] OR “Japan”[Mesh] OR “India”[Mesh] OR “Indonesia”[Mesh] OR “Ethnic groups”[Mesh]) AND ((“1995/01/29”[PDAT]: “2016/02/23”[PDAT]) AND English[lang]).