ESC European Society of Cardiology

Cardiovascular Research (2021) **117**, 576–584
doi:10.1093/cvr/cvaa044

Variations in incidence of venous thromboembolism in low-, middle-, and high-income countries

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Received 11 September 2019; revised 25 December 2019; editorial decision 8 February 2020; accepted 2 March 2020; online publish-ahead-of-print 6 March 2020

Time for primary review: 33 days

Aims To examine the rates of venous thromboembolism (VTE) in high-income, upper middle-income, and lower middle/low-income countries (World Bank Classification).

Methods and results We examined the rates of VTE in high-income, upper middle-income, and lower middle/low-income countries (World Bank Classification) in a cohort derived from four prospective international studies (PURE, HOPE-3, ORIGIN, and COMPASS). The primary outcome was a composite of pulmonary embolism, deep vein thrombosis, and thrombophlebitis. We calculated age- and sex-standardized incidence rates (per 1000 person-years) and used a Cox frailty model adjusted for covariates to examine associations between the incidence of VTE and country income level. A total of 215 307 individuals (1.5 million person-years of follow-up) from high-income ($n = 60\ 403$), upper middle-income ($n = 42\ 066$), and lower middle/low-income ($n = 112\ 838$) countries were included. The age- and sex-standardized incidence rates of VTE per 1000 person-years in high-, upper middle-, and lower middle/low-income countries were 0.87, 0.25, and 0.06, respectively. After adjusting for age, body mass index (BMI), smoking, antiplatelet therapy, anticoagulant therapy, education level, ethnicity, and incident cancer diagnosis or hospitalization, individuals from high-income and upper middle-income countries had a significantly higher risk of VTE than those from lower middle/low-income countries [hazard ratio (HR) 3.57, 95% confidence interval (CI) 2.40–5.30 and HR 2.27, 95% CI 1.59–3.23, respectively]. The effect of country income level on VTE risk was markedly stronger in people with a lower BMI, hypertension, diabetes, non-White ethnicity, and higher education.

Conclusion The rates of VTE are substantially higher in high-income than in low-income countries. The factors underlying the increased VTE risk in higher-income countries remain unknown.

Keywords Venous thromboembolism • Global • Country income status

1. Introduction

Venous thromboembolism (VTE), which includes pulmonary embolism (PE) and deep vein thrombosis (DVT), is a major cause of preventable death and disability. In contrast to ischaemic heart disease and stroke, there are few reports as to whether the burden of VTE varies in different populations.[1] Virtually all of the epidemiological data on VTE come from high-income countries.[2,3] A 2014 systematic review reported annual VTE incidence rates ranging from 0.75 to 2.69 per 1000 individuals in 12 studies from Western Europe, North America, East Asia, and Southern Latin America; all of these are high- or upper middle-income countries.[4] A modelling study based on retrospective data suggested a higher incidence of VTE in high-income compared to middle/low-income countries with estimates of hospital-associated VTE of 3.5 per 1000 population and 1.1 per 1000 population, respectively.[5] In this study, VTE was an important contributor to lost disability-adjusted life years in both

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high-income [2.3 million, 95% confidence interval (CI) 1.0–3.8] and middle/low-income countries (5.4 million, 95% CI 1.1–11.7). However, these estimates were largely based on modelling as there are very sparse actual data from low- and middle-income countries.

To further investigate the burden of VTE by country income and their variations, we combined information from four large prospective studies that we conducted on a total of 215 307 individuals from 53 countries involving 1.5 million person-years of follow-up. This included a large study of the general population and three large clinical trials which enrolled large numbers of individuals from high-, middle-, and low-income countries. In all of these studies, incident VTE and PE were prospectively documented at each follow-up visit. The objective was to explore whether the incidence of VTE varied in different populations according to country income status.

2. Methods

2.1 Study populations

Details of the design and methods of each study (PURE, ORIGIN, HOPE-3, and COMPASS) have been described previously[6–9] and are summarized in Supplementary material online, *Table S1*. PURE was an observational study of 162 678 persons (as of 19 June 2018) in 21 countries (four high-income, seven upper middle-income, five lower middle-income, and five low-income countries) who were followed for an average of 7.9 years.[6] HOPE-3 was a randomized controlled trial of 12 705 individuals in 21 countries (10 high-income, 6 upper middle-income, and 5 lower middle-income countries) with no previous cardiovascular disease and at intermediate risk of cardiovascular disease who were followed for an average of 5.6 years.[9,10] ORIGIN was a randomized controlled trial of 12 537 individuals in 40 countries (19 high-income, 14 upper middle-income, and 7 lower middle- or low-income countries) 50 years of age or older with impaired fasting glucose, impaired glucose tolerance, or early Type 2 diabetes mellitus in addition to other cardiovascular risk factors, at intermediate risk of cardiovascular disease who were followed for an average of 5.9 years.[7] COMPASS was a randomized controlled trial of 27 395 individuals from 33 countries (22 high-income, 9 upper middle-income, and 2 lower middle-income countries) with a history of stable atherosclerotic vascular disease (coronary artery disease, peripheral arterial disease, or both) followed for an average of 1.92 years.[8,11] Country income level designation was determined using the World Bank Classification at the time of study initiation.

Written informed consent was obtained by all patients participating in the included studies (PURE, ORIGIN, HOPE-3, and COMPASS). Research Ethics Board approval was obtained for the original studies which were conducted in accordance with the principles outlined in the Declaration of Helsinki. The methods and results of the included studies have been previously published.

2.2 Outcomes

The primary outcome for this analysis was VTE (PE, DVT, or thrombophlebitis). Outcome definitions used in each study are summarized in Supplementary material online, *Table S1*.[6–9] A *post hoc* sensitivity analysis was conducted with PE and DVT events alone. The following baseline covariates were recorded: age, sex, body mass index (BMI), smoking status, prior cancer diagnosis, antiplatelet therapy use, anticoagulant therapy use, education level, and ethnicity.

2.3 Statistical analysis

Categorical data are reported as counts and proportions in percentages. Continuous data are reported as means with standard deviations or medians with interquartile range. Age- and sex-standardized incidence rates (per 1000 person-years) were calculated for the overall cohort and separately by country income level (high-income, upper middle-income, and lower middle/low-income). Kaplan–Meier survival curves were used to estimate the cumulative incidence of VTE stratified by country income levels and were compared using the log-rank test. A Cox frailty model accounting for study as a random effect was used to examine the association of the incidence of VTE across country income levels. The model was adjusted for intervention effect (for randomized studies) and other covariates including age, sex, BMI, smoking status (non-smoker vs. current/former smoker), antiplatelet therapy use, anticoagulant therapy use, education level, ethnicity (White vs non-White), incident cancer diagnosis, and incident hospitalization as time-dependent covariates. To evaluate the potential effect of low event rates on event estimates, sensitivity analysis was done using Cox modelling of 1000 simulations with a dataset containing one VTE event and three randomly selected individuals without VTE to obtain average estimates. The potential effect of each covariate on the incidence of VTE by country income level was examined using tests of interaction. For all subgroup analyses, the Firth correction was used to adjust for rare outcomes without the random effect.

3. Results

3.1 Study participants

A total of 215 307 individuals with age and sex available were included in the analysis involving 1.46 million person-years of follow-up. Of these, 42 066 (19.5%) were from high-income countries, 60 403 (28.5%) were from upper middle-income countries, and 112 838 (52.0%) were from lower middle- or low-income countries. This distribution roughly reflects the global population distribution. *Table 1* shows the baseline characteristics of the study subjects by country income level. Baseline characteristics of the study subjects in individual studies are shown in Supplementary material online, *Tables S2–S5*.

3.2 Overall VTE events

A total of 410 VTE events occurred among 215 307 individuals (age- and sex-standardized incidence of 0.26 per 1000 person-years) including 190 PE events, 145 DVT events, and 90 thrombophlebitis events (*Table 2*). The age- and sex-standardized incidence rates of PE and DVT in the whole cohort were 0.12 and 0.09 per 1000 person-years, respectively. The age- and sex-standardized mortality incidence rate was 18.66 per 1000 person-years in people who experienced VTE compared to 8.37 per 1000 person-years in people without VTE ($P < 0.001$). The pattern of results was consistent within each of the four studies (*Table 2*). The cumulative incidence of VTE in the entire cohort and each study individually is shown in Supplementary material online, *Figure S1*.

3.3 Variations in VTE by country income status

There were 248 VTE events among the 42 066 individuals (0.87 per 1000 person-years) in high-income countries, 107 VTE events among the 60 403 individuals (0.25 per 1000 person-years) in upper

Table 1 Baseline characteristics of patients by country income level for the entire cohort

Variables	All	HIC	UMIC	LMIC-LIC
Total, *n* (%)	215 307	42 066 (20.0)	60 403 (28.1)	112 838 (52.4)
CVD, *n*	39 925	22 069	13 313	4543
No CVD, *n*	175 382	19 997	47 090	108 295
Age, mean (SD)	54.46 (11.7)	61.07 (11.5)	55.59 (11.5)	51.40 (10.8)
Men, *n* (%)	104 910 (48.7)	27 502 (65.4)	28 584 (47.3)	48 824 (43.3)
BMI, mean (SD)	26.49 (5.3)	28.43 (5.1)	28.38 (5.6)	24.77 (4.6)
Hip/waist ratio, mean (SD)	0.90 (0.1)	0.94 (0.1)	0.91 (0.1)	0.88 (0.1)
Current/former smoking, *n* (%)	83 281 (39.0)	25 086 (59.7)	25 952 (43.3)	32 243 (28.9)
Current/former smoker males, *n* (%)	63 330 (60.4)	18 775 (68.3)	17 372 (60.8)	27 183 (55.7)
Current/former smoker females, *n* (%)	19 951 (18.1)	6311 (43.3)	8580 (27.0)	5060 (7.9)
Current smoker, *n* (%)	43 109 (20.2)	6929 (16.5)	12 429 (20.7)	23 751 (21.3)
Current smoker males	33 206 (31.6)	5106 (18.6)	7842 (27.4)	20 258 (41.5)
Current smoker females	9903 (9.0)	1823 (12.5)	4587 (14.4)	3493 (5.5)
Former smoker, *n* (%)	40 172 (18.8)	18 157 (43.2)	13 523 (22.5)	8492 (7.6)
Former smoker males	30 124 (28.7)	13 669 (49.7)	9530 (33.3)	6925 (14.2)
Former smoker females	10 048 (9.1)	4488 (30.8)	3993 (12.6)	1567 (2.4)
Total cholesterol, mean (SD)	4.80 (1.2)	4.67 (1.3)	5.08 (1.2)	4.71 (1.1)
Triglycerides, mean (SD)	1.61 (1.3)	1.47 (1.6)	1.78 (1.4)	1.57 (1.2)
Prior diabetes, *n* (%)[a]	29 029 (14.3)	8050 (21.6)	9263 (16.6)	11 716 (10.7)
Hypertension, *n* (%)	97 193 (45.1)	23 396 (55.6)	31 027 (51.4)	42 770 (37.9)
Cancer, *n* (%)	4966 (2.3)	2919 (7.0)	1122 (1.9)	925 (0.8)
Antiplatelets, *n* (%)	41 510 (19.2)	22 400 (53.2)	12 381 (20.5)	6729 (6.0)
CVD	33 021 (82.7)	19 978 (90.5)	9892 (74.3)	3151 (69.4)
No CVD	8489 (4.8)	2422 (12.1)	2489 (5.3)	3578 (3.3)
Anticoagulants, *n* (%)	1332 (0.6)	684 (1.6)	386 (0.6)	262 (0.2)
CVD	966 (2.4)	501 (2.3)	285 (2.1)	180 (4.0)
No CVD	366 (0.2)	183 (0.9)	101 (0.2)	82 (0.1)
Ethnicity, *n* (%)				
South Asian	37 101 (18.8)	627 (1.5)	14 250 (23.8)	22 224 (23.1)
Other Asian	57 672 (29.1)	2828 (6.8)	2795 (4.7)	52 049 (54.2)
Black	4378 (2.2)	352 (0.8)	2746 (4.6)	1280 (1.3)
White	57 489 (29.0)	36 680 (87.5)	10 989 (18.3)	9820 (10.2)
Latin	36 414 (18.4)	1001 (2.4)	26 730 (44.6)	8683 (9.0)
Other	4865 (2.5)	429 (1.0)	2466 (4.1)	1970 (2.0)
Education, *n* (%)				
None	71 899 (33.49)	2635 (6.3)	22 746 (37.7)	46 518 (41.4)
Primary/secondary	91 114 (42.44)	16 954 (40.4)	25 933 (43.0)	48 227 (42.9)
Trade school/college/university	51 656 (24.06)	22 404 (53.4)	11 600 (19.2)	17 652 (15.7)

CVD, cardiovascular disease; HIC, high-income countries; LIC, low-income countries; LMIC, lower middle-income countries; SD, standard deviation; UMIC, upper middle-income countries.
[a]Excluding ORIGIN study.

middle-income countries, and 55 VTE events among the 112 838 individuals (0.06 per 1000 person-years) in lower middle/low-income countries (*Figure 1* and *Table 2*). As shown in *Figure 2*, there was a significant difference in cumulative incidence of VTE between high-income, upper middle-income, and lower middle/low-income countries ($P < 0.001$). This pattern was consistent within each of the studies included in the analysis.

Compared to populations from lower middle/low-income countries, those from high-income and upper middle-income countries had a higher risk of VTE [hazard ratio (HR) 3.57, 95% CI 2.40–5.30 and HR 2.27, 95% CI 1.59–3.23, respectively] despite adjusting for risk factors known to be associated with VTE. The risk factors included in the adjustments were age, BMI, smoking status, antiplatelet therapy use, anticoagulant therapy use, education level, ethnicity, incident cancer diagnosis, and incident hospitalization (*Table 3*).

The incidence of VTE was higher in high-income and upper middle-income countries compared to lower middle/low-income countries in individuals without cardiovascular disease at baseline (HR 3.89, 95% CI 2.47–6.13 and HR 2.45, 95% CI 1.66–3.62, respectively). However, this higher risk was substantially attenuated in individuals with known cardiovascular disease at baseline (HR 1.85, 95% CI 0.84–4.09 and HR 1.02, 95% CI 0.45–2.34, respectively; *P*-value of 0.01 for the interaction between income country level and baseline cardiovascular disease status).

A sensitivity analysis to explore for possible effects of low event rates on risk estimates (Cox modelling of 1000 simulations with a dataset

Table 2 Crude and age- and sex-standardized incidence of outcomes per 1000 person-years by country income level

Variables	Overall (*N* = 215 307)			HIC (*N* = 42 066)			UMIC (*N* = 60 403)			LMIC-LIC (*N* = 112 838)		
	N	Crude rate	Std rate (95% CI)	*N*	Crude rate	Std rate (95% CI)	*N*	Crude rate	Std rate (95% CI)	*N*	Crude rate	Std rate (95% CI)
All VTE	410	0.28	0.26 (0.24–0.29)	248	1.15	0.87 (0.75–0.99)	107	0.28	0.25 (0.20–0.30)	55	0.06	0.06 (0.05–0.08)
Pulmonary embolism	190	0.13	0.12 (0.10–0.14)	131	0.60	0.47 (0.38–0.56)	35	0.09	0.08 (0.05–0.11)	24	0.03	0.03 (0.02–0.04)
Deep vein thrombosis	145	0.10	0.09 (0.08–0.11)	90	0.42	0.28 (0.22–0.34)	42	0.11	0.10 (0.07–0.13)	13	0.01	0.01 (0.01–0.02)
Thrombophlebitis	90	0.06	0.06 (0.05–0.07)	40	0.18	0.17 (0.11–0.23)	32	0.08	0.08 (0.05–0.10)	18	0.02	0.02 (0.01–0.03)
Overall mortality	13 099	8.91	8.39 (8.25–8.54)	1650	7.61	4.86 (4.60–5.12)	4217	10.98	10.11 (9.80–10.43)	7232	8.32	8.87 (8.66–9.08)
Individuals with VTE	83	32.33	18.66 (14.30–23.01)	40	27.30	15.91 (9.73–22.08)	31	44.05	26.13 (16.38–35.88)	12	30.09	28.83 (9.52–48.13)
Individuals without VTE	13 016	8.87	8.37 (8.22–8.51)	1610	7.47	4.78 (4.53–5.04)	4186	10.92	10.07 (9.75–10.39)	7220	8.31	8.86 (8.65–9.07)
Incident cancer	6816	4.68	4.48 (4.38–4.59)	2900	13.85	10.28 (9.87–10.69)	1915	5.04	4.65 (4.44–4.87)	2001	2.31	2.40 (2.30–2.51)
Individuals with VTE	71	30.05	20.05 (15.11–24.98)	57	44.54	33.20 (23.32–43.08)	13	18.89	10.91 (4.60–17.22)	1	2.53	1.24 (0.00–3.68)
Individuals without VTE	6745	4.64	4.45 (4.34–4.56)	2843	13.66	10.15 (9.74–10.55)	1902	5.02	4.63 (4.42–4.85)	2000	2.31	2.40 (2.30–2.51)
Incident hospitalization	43 318	32.51	32.21 (31.90–32.52)	15 499	90.93	74.02 (72.73–75.31)	13 674	40.37	38.96 (38.29–39.64)	14 145	17.18	17.53 (17.23–17.83)
Individuals with VTE	371	278.9	246.8 (215.8–277.9)	224	299.8	253.4 (210.1–296.7)	100	272.5	249.9 (188.3–311.4)	47	217.6	220.0 (148.0–291.9)
Individuals without VTE	42 947	32.27	31.98 (31.67–32.29)	15 275	90.01	73.31 (72.03–74.60)	13 574	40.12	38.74 (38.06–39.41)	14 098	17.13	17.48 (17.18–17.77)
PURE												
All VTE	230	0.18	0.20 (0.17–0.23)	117	0.83	0.86 (0.70–1.02)	68	0.21	0.23 (0.17–0.29)	45	0.06	0.06 (0.04–0.07)
Pulmonary embolism	108	0.08	0.10 (0.08–0.11)	70	0.50	0.52 (0.39–0.64)	18	0.06	0.06 (0.03–0.09)	20	0.02	0.03 (0.01–0.04)
Deep vein thrombosis	45	0.04	0.04 (0.03–0.05)	16	0.11	0.12 (0.06–0.17)	21	0.07	0.08 (0.04–0.11)	8	0.01	0.01 (0.00–0.02)
Thrombophlebitis	85	0.07	0.07 (0.06–0.09)	38	0.27	0.27 (0.18–0.36)	30	0.09	0.09 (0.06–0.13)	17	0.02	0.02 (0.01–0.03)
HOPE-3												
All VTE	45	0.63	0.43 (0.22–0.64)	45	0.63	0.43 (0.22–0.64)	15	0.65	0.20 (0.08–0.31)	3	0.08	0.03 (0.00–0.06)
Pulmonary embolism	14	0.20	0.14 (0.02–0.27)	14	0.20	0.14 (0.02–0.27)	4	0.17	0.05 (0.00–0.11)	1	0.03	0.01 (0.00–0.03)
Deep vein thrombosis	36	0.51	0.31 (0.14–0.47)	36	0.51	0.31 (0.14–0.47)	12	0.52	0.15 (0.05–0.25)	3	0.08	0.03 (0.00–0.06)
Thrombophlebitis	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00
ORIGIN												
All VTE	30	0.41	0.34 (0.16–0.51)	16	0.56	0.33 (0.11–0.55)	8	0.29	0.43 (0.07–0.78)	6	0.34	0.20 (0.01–0.40)
Pulmonary embolism	20	0.27	0.27 (0.10–0.43)	10	0.35	0.21 (0.02–0.39)	7	0.25	0.40 (0.05–0.75)	3	0.17	0.12 (0.00–0.29)
Deep vein thrombosis	9	0.12	0.06 (0.02–0.10)	6	0.21	0.13 (0.00–0.25)	1	0.04	0.02 (0.00–0.07)	2	0.11	0.04 (0.00–0.10)
Thrombophlebitis	2	0.03	0.02 (0.00–0.04)	1	0.03	0.01 (0.00–0.04)	0	0.00	0.00	1	0.06	0.04 (0.00–0.11)
COMPASS												
All VTE	105	2.00	0.97 (0.64–1.29)	88	2.51	1.31 (0.74–1.87)	16	1.08	0.57 (0.14–0.99)	1	0.39	0.19 (0.00–0.57)
Pulmonary embolism	48	0.91	0.37 (0.21–0.53)	42	1.20	0.57 (0.25–0.89)	6	0.40	0.12 (0.02–0.21)	0	0.00	0.00
Deep vein thrombosis	55	1.05	0.51 (0.25–0.76)	47	1.34	0.74 (0.27–1.20)	8	0.54	0.25 (0.00–0.53)	0	0.00	0.00
Thrombophlebitis	3	0.06	0.08 (0.00–0.21)	1	0.03	0.01 (0.00–0.03)	2	0.13	0.20 (0.00–0.50)	0	0.00	0.00

Mean follow-up 6.92 years.
HIC, high-income countries; LIC, low-income countries; LMIC, lower middle-income countries; UMIC, upper middle-income countries; VTE, venous thromboembolism.

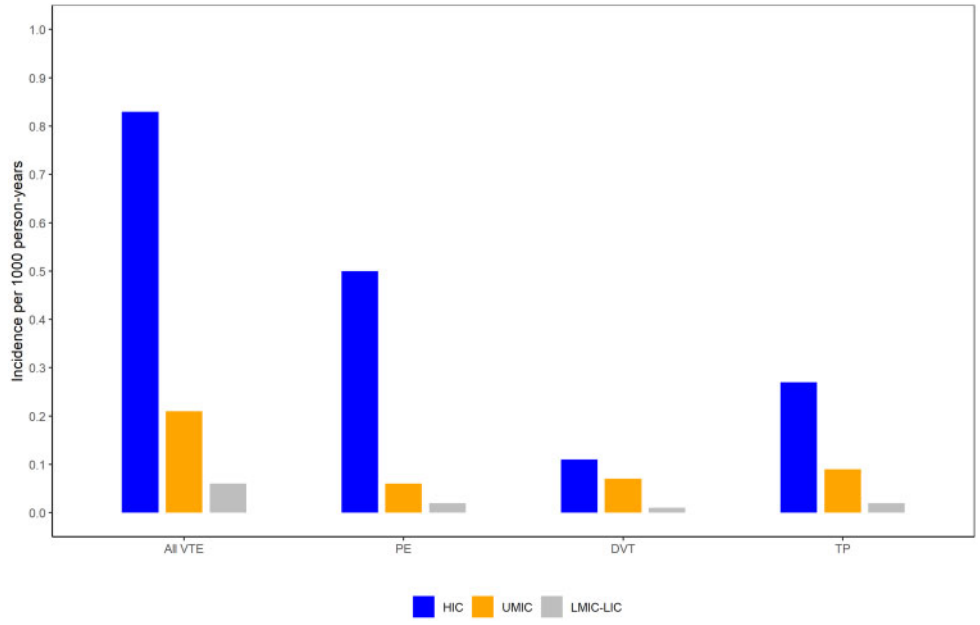

Figure 1 Age- and sex-standardized incidence of VTE events per 1000 person-years according to country income level.

containing one VTE event and three randomly selected individuals without VTE to obtain average estimates) showed an increased risk of VTE in those from high-income countries (HR 2.52, 95% CI 2.00–3.10) and upper middle-income (HR 2.11, 95% CI 1.76–2.49) compared to lower middle/low-income countries.

3.4 The effect of country income level on VTE risk

We tested whether the magnitude of the effect of country income level varied by baseline differences in sex, BMI, smoking, hypertension, diabetes, ethnicity, education level, incident myocardial infarction, and incident stroke (*Figure 3* and *Table 4*). The effect of country income level on VTE risk was markedly stronger in people with a lower BMI compared to those with higher BMI ($P < 0.001$), in those without hypertension compared to those with hypertension ($P = 0.003$), in those without diabetes compared to those with diabetes ($P = 0.003$), non-White compared to White ethnicity ($P < 0.001$), and higher education compared to lower education ($P = 0.037$). There was no variations in the rates of VTE by sex, smoking status, cancer diagnosis at baseline, incident hospitalization, incident myocardial infarction, or incident stroke.

4. Discussion

In this analysis of 215 307 individuals involving nearly 1.5 million person-years of follow-up from four prospective studies involving 53 countries, the age- and sex-standardized incidence of VTE was substantially higher in high-income countries (0.87 per 1000 person-years), compared to upper middle-income countries (0.25 per 1000 person-years), and lower middle/low-income countries (0.06 per 1000 person-years). This pattern of results was consistent within the individual studies. To our knowledge, this is the first prospective study documenting differences in the incidence of VTE between populations from countries at different economic

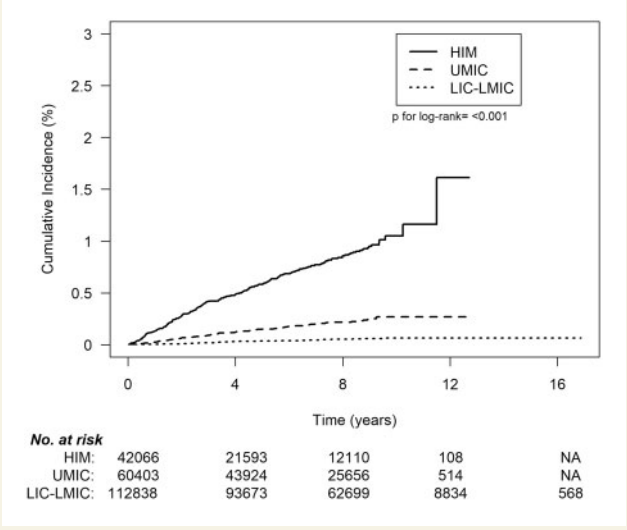

Figure 2 Kaplan–Meier curves of VTE events according to country income level. There were 248 VTE events among the 42 066 individuals (0.87 per 1000 person-years) in HIC, 107 VTE events among the 60 403 individuals (0.25 per 1000 person-years) in UMIC, and 55 VTE events among the 112 838 individuals (0.06 per 1000 person-years) in LMIC-LIC. HIC, high-income countries; LMIC-LIC, lower middle/low-income countries; UMIC, upper middle-income countries.

levels. The risk of VTE was 3.6-fold higher in high-income countries and 2.3-fold higher in upper middle-income countries compared to lower middle/low-income countries. After adjusting for clinical risk factors, these differences persisted indicating that unknown factors are chiefly responsible for these variations. However, our results are limited by a lack

Table 3 Association of country income level with VTE events

Model	Events/*N*	Incidence rate per 1000 person-years	Hazard ratio of association vs. LIC-LMIC (95% CI)			
			HIC vs. LIC-LMIC	*P*-value	UMIC vs. LIC-LMIC	*P*-value
Adjusted for age and sex	410/215 307	0.28	11.70 (8.57–15.95)	<0.001	3.69 (2.66–5.13)	<0.001
Adjusted for intervention and covariates[a]	400/187 252	0.33	3.57 (2.40–5.30)	<0.001	2.27 (1.59–3.23)	<0.001
Adjusted for intervention and covariates (DVT and PE only)[a]	309/187 252	0.25	4.86 (3.00–7.89)	<0.001	2.43 (1.56–3.77)	<0.001
Subgroup of individuals with cardiovascular disease at baseline (ORIGIN and COMPASS)[a]	135/39 885	1.07	1.85 (0.84–4.09)	0.127	1.02 (0.45–2.34)	0.959
Subgroup of individuals without cardiovascular disease at baseline (PURE and HOPE-3)[a]	265/147 367	0.24	3.89 (2.47–6.13)	<0.001	2.45 (1.66–3.62)	<0.001

CI, confidence interval; HIC, high-income countries; HR, hazard ratio; LIC, low-income countries; LMIC, lower middle-income countries; UMIC, upper middle-income countries.
[a]Adjusted for intervention and covariates age, sex, body mass index, current smoker, antiplatelets, anticoagulants, education levels and ethnicity (White vs. non-White), incident cancer diagnosis, and hospitalization within 30 days of VTE event.

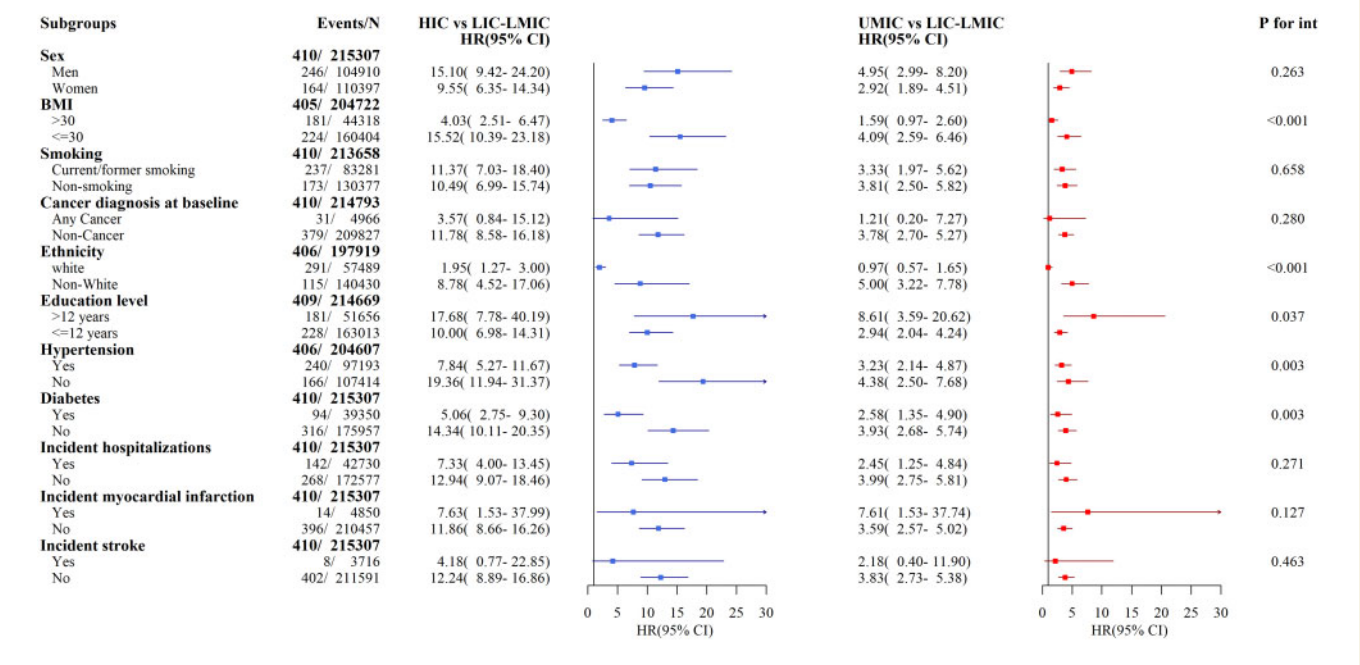

Figure 3 Age- and sex-adjusted HR for VTE according to country income level by key subgroups.

of information about additional traditional VTE risk factors such as exogenous oestrogen use, pregnancy, and immobility, comorbidities associated with VTE such as atrial fibrillation and chronic kidney disease, and factors such as diet or physical activity which are likely to differ across country income levels.

The incidence of VTE in high-income countries of 0.87 per 1000 person-years in our study is similar to prior population studies, which have reported incidence rates of 0.75–2.69 VTE cases per 1000 person-years.[4] Although the estimates obtained for upper middle-income countries (0.25 per 1000 person-years) and lower middle/low-income

Table 4 Age- and sex-adjusted HR for VTE according to country income level by subgroups.

	Events/*N*	Incidence rate per 1000 person-years	HIC vs LIC-LMIC, HR (95% CI)	UMIC vs LIC-LMIC, HR (95% CI)	*P*-int
Sex	410/215 307				
Men	246/104 910	0.37	15.10 (9.42–24.20)	4.95 (2.99–8.20)	0.263
Women	164/110 397	0.20	9.55 (6.35–14.34)	2.92 (1.89–4.51)	
BMI	405/204 722				
>30	181/44 318	0.67	4.03 (2.51–6.47)	1.59 (0.97–2.60)	<0.001
≤30	224/160 404	0.20	15.52 (10.39–23.18)	4.09 (2.59–6.46)	
Smoking	410/213 658				
Current/former smoking	237/83 281	0.46	11.37 (7.03–18.40)	3.33 (1.97–5.62)	0.658
Non-smoking	173/130 377	0.18	10.49 (6.99–15.74)	3.81 (2.50–5.82)	
Cancer diagnosis at baseline	410/214 793				
History of cancer	31/4966	1.14	3.57 (0.84–15.12)	1.21 (0.20–7.27)	0.280
No history of cancer	379/209 827	0.26	11.78 (8.58–16.18)	3.78 (2.70–5.27)	
Ethnicity	406/197 919				
White	291/57 489	0.89	1.95 (1.27–3.00)	0.97 (0.57–1.65)	<0.001
Non-White	115/140 430	0.12	8.78 (4.52–17.06)	5.00 (3.22–7.78)	
Education level	409/214 669				
>12 years	181/51 656	0.58	17.68 (7.78–40.19)	8.61 (3.59–20.62)	0.037
≤12 years	228/163 013	0.20	10.00 (6.98–14.31)	2.94 (2.04–4.24)	
Hypertension	406/204 607				
Yes	240/97 193	0.40	7.84 (5.27–11.67)	3.23 (2.14–4.87)	0.003
No	166/107 414	0.21	19.36 (11.94–31.37)	4.38 (2.50–7.68)	
Diabetes	410/215 307				
Yes	94/39 350	0.43	5.06 (2.75–9.30)	2.58 (1.35–4.90)	0.003
No	316/175 957	0.25	14.34 (10.11–20.35)	3.93 (2.68–5.74)	
Incident hospitalizations	410/215 307				
Yes	142/42 730	0.49	7.33 (4.00–13.45)	2.45 (1.25–4.84)	0.271
No	268/172 577	0.23	12.94 (9.07–18.46)	3.99 (2.75–5.81)	
Incident myocardial infarction	410/215 307				
Yes	14/4850	0.45	7.63 (1.53–37.99)	7.61 (1.53–37.74)	0.127
No	396/210 457	0.27	11.86 (8.66–16.26)	3.59 (2.57–5.02)	
Incident stroke	410/215 307				
Yes	8/3716	0.27	4.18 (0.77–22.85)	2.18 (0.40–11.90)	0.463
No	402/211 591	0.28	12.24 (8.89–16.86)	3.83 (2.73–5.38)	

P-int value for interaction between income country levels and the given variables incident hospitalization, stroke, and MI were analysed as time-dependent covariates.
BMI, body mass index; CI, confidence interval; HIC, high-income countries; HR, hazard ratio; LIC, low-income countries; LMIC, lower middle-income countries; MI, myocardial infarction; UMIC, upper middle-income countries.

countries (0.06 per 1000 person-years) obtained in our study are lower than those previously reported (1.1 per 1000 population in low/middle-income countries combined), our data support an association between country income level and risk of VTE.[5,12,13] Importantly, the majority of previously published data regarding VTE in middle/low-income countries are based on modelling of retrospective data collected as part of World Health Organization commissioned reports on adverse events during hospitalization and not from free-living people. The differences in estimates of incidence may reflect differences in the populations studied (hospitalized in previous studies vs. community-dwelling individuals in our study) and methods (statistical modelling in previous studies vs. individual-level prospective data collection with standardized event recording in the studies included in this analysis). Data from middle-income and low middle/low-income countries were not reported separately in previous reports.[5]

In our analysis, adjustment for clinical risk factors such as cancer diagnosis, hospitalization, obesity, and age, which are known to be associated with VTE, did not explain the differences in VTE risk across country income levels. It is possible that the detection of VTE events may have been affected by reduced access to hospital and diagnostic facilities in lower-income countries. However, study participants were systematically monitored at specific time intervals within each study as part of structured prospective follow-up. Although outcome events were ascertained prospectively by direct questioning of all participants in each of the studies, VTE events were also recorded and defined using Medical Dictionary for Regulatory Activity (MedDRA) codes based on hospital and/or emergency department visits. These could lead to some underestimation of the true incidence of VTE if events did not lead to hospitalization or death, or if there are differences in access to medical care between different countries. Importantly, the difference in

hospitalization rates between high-income and lower middle/low-income countries was less marked (five-fold) than the difference in the rate of VTE (20-fold) suggesting that access to care is unlikely to entirely explain the effect of country income level on VTE risk. Our results are based on data from the general population (e.g. the PURE study which constitutes the largest proportion of participants in this analysis), those enrolled in a primary prevention trial (e.g. HOPE-3), those with diabetes (e.g. ORIGIN) and a secondary prevention trial (e.g. COMPASS). The consistency of the pattern of the differences across country income levels within the individual studies indicates that our findings are robust and independent of the populations included.

The association observed between income country level and rate of VTE is similar to the marked variations in the prevalence of atrial fibrillation in the PURE study (Joseph *et al.*, unpublished data). In contrast, major cardiovascular events (death from cardiovascular causes, myocardial infarction, stroke, or heart failure) are higher in low-income compared to middle- and high-income countries.[6] The association of country income level with risk of VTE appeared to be attenuated in patients with established cardiovascular disease which might reflect the use of secondary prevention therapies (e.g. statins and aspirin) or promotion of activity or healthier diets that may also reduce the risk of VTE. This is supported by a stronger effect of country income level on VTE risk in individuals not receiving antiplatelet and anticoagulant therapies and those without cardiovascular risk factors such as hypertension and diabetes.

In conclusion, our large prospective analysis of VTE events from four studies showed that the incidence of VTE is higher in richer than in poorer countries despite adjusting for differences in VTE risk factors. The factors underlying the markedly increased VTE risk in higher-income countries remain unknown and future studies should explore whether these findings can be explained by differences in genetic or other markers, or whether they are due to differences in access to health care.

Supplementary material

Supplementary material is available at *Cardiovascular Research* online.

Authors' contributions

D.M.S. designed the study, interpreted the data and wrote the manuscript. J.W.E. and S.Y. designed the study, interpreted the data and revised the manuscript. S.F.L. acquired the data, conducted the analyses and revised the manuscript. S.R. acquired the data and revised the manuscript. J.B. and J.Z. acquired data and revised the manuscript. All authors approved the final version of the manuscript and are accountable for all aspects of the work.

Conflict of interest: D.M.S. reports receiving honoraria from Bayer, BMS-Pfizer, Servier Canada, Leo Pharma, Aspen Pharmaceuticals, and Novartis. J.W.E. reports receiving grant support and honoraria from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, Janssen, AstraZeneca, Eli Lilly, GlaxoSmithKline, and Sanofi-Aventis. J.Z. reports receiving lecture fees from Bayer, Boehringer Ingelheim, and Sanofi. S.Y. reports receiving grant support and honoraria from Bayer, Boehringer Ingelheim, Astra-Zeneca, Bristol-Myers Squibb, and Cadila Pharmaceuticals. All other authors have no conflict of interest to disclose.

Funding

COMPASS and ORIGIN were sponsored by Bayer and Sanofi, respectively. PURE and HOPE-3 were funded by multiple peer-reviewed and industry sources. Sponsors were not involved in study design, analysis, interpretation, or manuscript preparation. D.M.S. had full access to all the data and final responsibility for the decision to submit for publication. D.M.S. is supported by a Research Early Career Award from the Hamilton Health Sciences Foundation.

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Translational perspective

We investigated the burden of venous thromboembolism (VTE) by country income by combining information from four large prospective studies (215 307 individuals from 53 countries). This is the largest study on the global incidence of VTE published to date. We observed a higher incidence of VTE in richer compared to poorer countries. We also demonstrated that differences in rates of VTE are not explained by risk factors commonly associated with VTE. Further study is needed to understand whether these findings can be explained by differences in genetic or other markers, or whether they are due to differences in access to health care.