Systematic Literature Review and Meta-Analysis of Venous Thromboembolism Events in Systemic Lupus Erythematosus

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SUPPLEMENTARY INFORMATION

Supplementary tables

Table S1a. Search Terms – PubMed Literature Search

Search No.	Search Terms	Hits
Population: SLE		
1	"Lupus Erythematosus, Systemic"[MeSH] or ("lupus"[All Fields] and "erythematosus"[All Fields] and "systemic"[All Fields]) or "systemic lupus erythematosus"[All Fields] or ("systemic"[All Fields] and "lupus"[All Fields] and "erythematosus"[All Fields]) or "SLE" or Lupus or "Libman-Sacks Disease"[Text Word] or ("antiphospholipid syndrome"[MeSH] or "antibodies, antiphospholipid"[MeSH] or antiphospholipid syndrome*[Text Word] or antiphospholipid antibody syndrome*[Text Word])	101,536
VTE events		
2	Venous Thrombosis[MeSH Terms] or Pulmonary Embolism[MeSH Terms] or Thromboembolism[MeSH Terms] or Thrombosis[MeSH Terms] or Pulmonary Thromboembolism[MeSH Terms] or venous thrombo*[Title/Abstract] or deep vein thrombo*[Title/Abstract] or vein thrombo*[Title/Abstract] or "pulmonary embolism"[Title/Abstract] or "pulmonary thromboembolism"[Title/Abstract]	231,948
#3	#1 and #2	6,212
Incidence, prevalence, risk, and absolute risk		
#4	prevalence[MeSH Terms] or "incidence"[MeSH Terms] or prevalence[title/abstract] or prevalent[title/abstract] or incidence[title/abstract] or incident[title/abstract] or risk factors[MeSH Terms] or risk*[title] or association[title] or associated[title] or relative risk*[title/abstract] or absolute risk*[title/abstract]	3,094,225
#5	#3 and #4	2,284
Study design: RWE		
#6	"Observational Study"[Publication Type] or "Cohort Studies"[MeSH] or "Longitudinal Studies"[MeSH] or "Follow-Up Studies"[MeSH] or ("Clinical Trials as Topic"[MeSH:NoExp] and "Follow-Up Studies"[MeSH]) or "Evaluation Study" [Publication Type] or "Cross-Sectional Studies"[MeSH] or "Retrospective Studies"[MeSH] or "Registries"[MeSH] or "Case-Control Studies"[MeSH] or cohort*[Title/Abstract] or longitudinal*[Title/Abstract] or "follow-up"[Title/Abstract] or evaluation[Title/Abstract] or "cross-sectional*"[Title/Abstract] or "non random*"[Title/Abstract] or nonrandom*[Title/Abstract] or observation*[Title/Abstract] or retrospective[Title/Abstract] or "phase iv"[Title/Abstract] or "phase four"[Title/Abstract] or "phase 4"[Title/Abstract] or "single arm"[Title/Abstract] or "one arm"[Title/Abstract] or prospective[Title/Abstract]	5,411,681
#7	#5 and #6	1,074

Search No.	Search Terms	Hits
Exclusions		
#8	"Animals"[MeSH] not "Humans"[MeSH]	4,735,550
#9	"Comment"[Publication Type] or "Editorial"[Publication Type] or "Letter"[Publication Type]	1,882,628
#10	randomized controlled trial[pt] or controlled clinical trial[pt] or randomized[title/abstract] or placebo[title/abstract] or clinical trials as topic[MeSH:noexp] or randomly[title/abstract] or trial[title]	1,322,461
#11	("Child"[MeSH] or "Infant"[MeSH] or "Adolescent"[MeSH] or child*[Text Word] or infant*[Text Word] or newborn*[Text Word] or adolescen*[Text Word] or teen*[Text Word]) not ("Adult"[MeSH] or adult*[Text Word] or elder*[Text Word] or senior citizen*[Text Word] or middle age*[Text Word])	2,234,062
All relevant studies		
#12	#7 not (#8 or #9 or #10 or #11)	**957**
#13	Publication date from 2000/01/01 to 2020/09/16	**775**

Search conducted on September 16th 2020. MeSH = Medical Subject Headings; RWE = real-world evidence; SLE = systemic lupus erythematosus; VTE = venous thromboembolism

Table S1b. Search Terms – Embase Literature Search

Search No.	Search Terms	Hits
Population: SLE		
1	'systemic lupus erythematosus'/exp or ('lupus' and 'erythematosus' and 'systemic') or 'systemic lupus erythematosus' or ('systemic' and 'lupus' and 'erythematosus') or 'sle' or lupus or 'libman-sacks disease':ti,ab,de or 'antiphospholipid syndrome'/exp or 'phospholipid antibody'/exp or 'phospholipid antibody':ti,ab,de or 'antiphospholipid syndrome*':ti,ab,de or 'antiphospholipid antibody syndrome*':ti,ab,de	165,288
VTE events		
2	'vein thrombosis'/exp or 'lung embolism'/exp or 'thromboembolism'/exp or 'thrombosis'/exp or 'deep vein thrombosis'/exp or 'venous thrombo*':ti,ab or 'deep vein thrombo*':ti,ab or 'vein thrombo*':ti,ab or 'pulmonary embolism*':ti,ab or 'pulmonary thromboembolism*':ti,ab	531,489
#3	#1 and #2	18,308
Incidence, prevalence, risk, and absolute risk		
#4	'prevalence'/exp or 'incidence'/exp or prevalence:ti,ab or prevalent:ti,ab or incidence:ti,ab or incident:ti,ab or 'risk factor'/exp or risk*:ti or association:ti or associated:ti or 'relative risk*':ti,ab or 'absolute risk*':ti,ab	4,259,944
#5	#3 and #4	6,797

Search No.	Search Terms	Hits
Study design: RWE		
#6	'observational study'/exp or 'cohort analysis'/exp or 'longitudinal study'/exp or 'follow-up'/exp or ('clinical trial (topic)'/de and 'follow-up'/exp) or 'evaluation study'/exp or 'cross-sectional study'/exp or 'retrospective study'/exp or 'register'/exp or 'case-control study'/exp or cohort*:ti,ab or longitudinal*:ti,ab or 'follow-up':ti,ab or evaluation:ti,ab or 'cross-sectional*':ti,ab or 'non random*':ti,ab or nonrandom*:ti,ab or observation*:ti,ab or retrospective:ti,ab or 'phase iv':ti,ab or 'phase four':ti,ab or 'phase 4':ti,ab or 'single arm':ti,ab or 'one arm':ti,ab or prospective:ti,ab	7,056,409
#7	#5 and #6	2,981
Exclusions		
#8	'animal'/exp not 'human'/exp	5,490,081
#9	comment*:ti or 'letter':it or 'editorial':it or [conference abstract]/lim or [conference paper]/lim or 'conference abstract':it or 'conference paper':it	6,494,219
#10	('crossover procedure':de or 'double-blind procedure':de or 'randomized controlled trial':de or 'single-blind procedure':de or random*:ti,ab or factorial*:ti,ab or crossover*:ti,ab or ((cross NEXT/1 over*):ti,ab) or placebo*:ti,ab or ((doubl* NEAR/1 blind*):ti,ab) or ((singl* NEAR/1 blind*):ti,ab) or assign*:ti,ab or allocat*:ti,ab or volunteer*:ti,ab)	2,459,042
#11	('child'/exp or 'infant'/exp or 'adolescent'/exp or child*:ti,ab,de or infant*:ti,ab,de or newborn*:ti,ab,de or adolescen*:ti,ab,de or teen*:ti,ab,de) not ('adult'/exp or adult*:ti,ab,de or elder*:ti,ab,de or 'senior citizen*':ti,ab,de or 'middle age*':ti,ab,de)	2,759,021
All relevant studies		
#12	#7 not (#8 or #9 or #10 or #11)	**1,396**
#13	#12 and [2000-2020]/py and [1-1-2000]/sd not [17-9-2020]/sd	**1,236**

Search conducted on September 16th 2020. RWE = real-world evidence; SLE = systemic lupus erythematosus; VTE = venous thromboembolism

Table S2a. List of Criteria for the Inclusion and Exclusion of Studies During the Initial (Level 1) Screening Process

Criteria	Included	Excluded
Population	▪ Studies that include adult patients with SLE or studies that include SLE and other populations combined but that report data separately for patients with SLE ▪ Studies that include patients with SLE and antiphospholipid syndrome	▪ Studies that focus on another population that also includes patients with SLE (e.g., studies assessing frequency of VTE events in patients with cancer that also report the risk of VTE events in patients with cancer and SLE)

Criteria	Included	Excluded
		- Studies that recruit or include only patients with a different disease or condition from SLE - Studies of only pediatric patients, i.e., those <18 years of age - Studies that include adult and pediatric patients, but do not report data separately for adult patients
Interventions and comparators	- None; not specific to a particular treatment	- None
Outcomes	- Analysis of absolute risk of VTE events (DVT, PE, VTE) in patients with SLE - Analysis of relative risk of VTE events (as noted above) in patients with SLE vs. the general population - Analysis of absolute risk of VTE events (as noted above) in subgroups[a] of patients with SLE - Analysis of relative risk of VTE events (as noted above) in subgroups[a] of patients with SLE - Incidence rate of VTE events (as noted above) in SLE population (and in the general population, if reported) - Association between VTE events and other medical conditions and traditional CV risk factors (including hypertension, obesity, smoking, diabetes, dyslipidemia, metabolic syndrome, and CKD) in SLE	- Studies that do not report the outcomes of interest in patients with SLE or within subgroups of patients with SLE
Study design	- Systematic reviews (including meta-analyses)[b] - Observational studies (prospective or retrospective), including Phase 4 trials - Cohort studies - Cross-sectional studies - Case-control studies - Registry studies - Observational phase (long-term follow-up) of controlled trial arms	- Randomized, controlled trials - Nonrandomized, controlled clinical trials - Phase 1-3 clinical trials - Non-observational studies - Studies pooling results for SLE with other patient populations - Preclinical studies - Animal studies (not in humans) - Case reports

Criteria	Included	Excluded
		• Commentaries, letters, or editorials (publication type)
		• Consensus reports
		• Nonsystematic reviews, other than pooled results (from nonsystematic reviews) where the individual study results are not available
		• Post hoc analyses of subgroup data
		• Phase 2-4 randomized, controlled, prospective, clinical trials
		• Surveys
Language	• English language	• Non-English language[c]
Date	• January 2000 to September 2020 for articles	

CKD = chronic kidney disease; CV = cardiovascular; DVT = deep vein thrombosis; PE = pulmonary embolism; SLE = systemic lupus erythematosus; SLR = systematic literature review; VTE = venous thromboembolism

Note: If it is unclear whether a study meets any criterion during the level 1 screening process, the study will be progressed to full-text screening to confirm its inclusion in the review.

[a] Age, gender, ethnicity, geographical location, disease severity, disease duration, prior treatment received, antiphospholipid syndrome. [b] Systematic reviews will be included at level 1 screening, used for identification of primary studies, and then excluded at level 2 screening. The ten most robust and relevant systematic reviews will be included at level 1 screening, used for identification of primary studies, and then excluded at level 2 screening. [c] Non-English language articles were excluded from the SLR.

Table S2b. Eligibility Criteria for Full-text (Screen 2) Review Process

Criteria	Included	Excluded
Population	• Studies that include adult patients with SLE or studies that include SLE and other populations combined but that report data separately for patients with SLE • Studies that include patients with SLE and antiphospholipid syndrome	• Studies that focus on another population that also includes patients with SLE (e.g., studies assessing frequency of VTE events in patients with cancer that also report the risk of VTE events in patients with cancer and SLE) • Studies that recruit or include only patients with a different disease or condition from SLE • Studies of only pediatric patients, i.e., those <18 years of age • Studies that include adult and pediatric patients, but do not report data separately for adult patients
Intervention	• None; not specific to a particular treatment	• None

Criteria	Included	Excluded
Comparator	▪ None; not specific to a particular treatment	▪ None
Outcomes	▪ Absolute risk,[a] relative risk, or prevalence of VTE events (DVT, PE, VTE) ▪ Relative risk[b] of VTE events (if reported) or number of patients with or without VTE event (as noted above) in patients with or without SLE – Overall population – By subgroups of interest[b] ▪ Absolute risk[a] of VTE events (if reported) or number of patients with SLE who develop VTE event (as noted above) – Overall population – By subgroups of interest[c] ▪ Incidence rate of VTE events (as noted above) in patients with SLE – Overall population – By subgroups of interest[c] ▪ Association between VTE events (as noted above) and other medical conditions as well as traditional CV risk factors[d] in patients with SLE	▪ Studies that do not report outcomes of interest
Study design	▪ Observational studies, including Phase 4 trials ▪ Cohort studies ▪ Cross-sectional studies ▪ Case-control studies ▪ Registry studies ▪ Observational phase (long-term follow-up) of controlled trial arms	▪ Same as 0 ▪ Systematic reviews and meta-analyses ▪ Full-text publication not available
Language	▪ English language	▪ Non-English language[c]
Date	▪ January 2000 to September 2020 for articles	

CV = cardiovascular; DVT = deep vein thrombosis; PE = pulmonary embolism; SLE = systemic lupus erythematosus; VTE = venous thromboembolism.

aThe time frame associated with the absolute risk will be captured where reported. Should absolute risk not be directly reported, but instead the number of patients developing VTE (or a VTE risk factor) in patients with SLE is reported in the study, this information will be extracted. The absolute risk relates to the number of events (in this case, patients who subsequently get VTE or who develop a VTE risk factor) in those patients with SLE. bThe relative risk measures the difference in absolute risk of VTE events in those patients with SLE compared with those without SLE. If the relative risk is directly reported, this will be extracted. If not, should the following details be available, these will be extracted: the number of patients with and without VTE events in patients with and without SLE. cSubgroups of interest are patients differentiated by age, gender, ethnicity, geographical location, disease severity, disease duration, treatment received, and antiphospholipid syndrome. dHypertension, obesity, smoking, diabetes, dyslipidemia, metabolic syndrome, chronic kidney disease.

Table S3. Studies Identified in the Systematic Literature Review and Excluded From Meta-analysis

Full citation	Reason for exclusion
Fernández M, Calvo-Alén J, Bertoli AM, Bastian HM, Fessler BJ, McGwin G Jr, et al. Systemic lupus erythematosus in a multiethnic US cohort (LUMINA L II): relationship between vascular events and the use of hormone replacement therapy in postmenopausal women. J Clin Rheumatol. 2007 Oct;13 (5):261-5.	Population is dissimilar from the general population of patients with SLE: post-menopausal women with SLE, who were either receiving or not receiving hormone-replacement therapy
Fein AW, Figgie CA, Dodds TR, Wright-Chisem J, Parks ML, Mandl LA, et al. Systemic lupus erythematosus does not increase risk of adverse events in the first 6 months after total knee arthroplasty. J Clin Rheumatol. 2016;22 (7):355-9.	Population is dissimilar from the general population of patients with SLE: patients with SLE in this study all had total knee arthroplasty
Lin JA, Liao CC, Lee YJ, Wu CH, Huang WQ, Chen TL. Adverse outcomes after major surgery in patients with systemic lupus erythematosus: a nationwide population-based study. Ann Rheum Dis. 2014 Sep;73 (9):1646-51.	Population is dissimilar from the general population of patients with SLE: patients with SLE in this study all had major surgery
Manzano-Gamero V, Pardo-Cabello AJ, Vargas-Hitos JA, Zamora-Pasadas M, Navarrete-Navarrete N, Sabio JM, et al. Effect of ethnicity on clinical presentation and risk of antiphospholipid syndrome in Roma and Caucasian patients with systemic lupus erythematosus: a multicenter cross-sectional study. Int J Rheum Dis. 2018 Nov;21 (11):2028-35.	Population/endpoint combination not of interest for MA of priority endpoints. Absolute risk of VTE available for patients with APS and SLE by ethnic group (Roma vs. Caucasian)
Roberts JE, Mandl LA, Su EP, Mayman DJ, Figgie MP, Fein AW, et al. Patients with systemic lupus erythematosus have increased risk of short-term adverse events after total hip arthroplasty. J Rheumatol. 2016 Aug;43 (8):1498-502.	Population is dissimilar from the general population of patients with SLE: patients with SLE in this study all had total hip arthroplasty
Sada PR, López-Núñez JJ, Samperiz A, Soto MJ, Pedrajas JM, Porras JA, et al. Venous thromboembolism in patients with autoimmune disorders: findings from the RIETE Registry. Angiology. 2020;71 (2):131-8.	Endpoint data (IR of VTE events) were reported in a format suitable for MA: length of follow-up was not available, and the total PYs were not clear from the study report

APS = antiphospholipid syndrome; IR = incidence rate; MA = meta-analysis; PY = person-year; SLE = systemic lupus erythematosus; VTE = venous thromboembolism.

Table S4. Studies Relevant for Inclusion in Meta-analysis and Endpoint Availability

Author (year)	Absolute risk			Relative risk			Incidence rate			Absolute risk by APS presence or antibodies		
	VTE[a]	DVT	PE	VTE[a]	DVT	PE	VTE[a]	DVT	PE	VTE[a]	DVT	PE
Ahlehoff et al. (2017)				HR[b,c]			IR[d]					
Akimoto et al. (2005)			n/N (%)[e]									P
Aviña-Zubieta et al. (2015)	n/N (%)	n/N (%)	n/N (%)	HR[f]	HR[f]	HR[f]	IR[d]	IR[d]	IR[d]			
Hansen and Jacobsen (2014)	n/N (%)	n/N (%)	n/N (%)									
Becker-Merok and Nossent (2009)	n/N (%)	n/N (%)	n/N (%)				IR[g]	IR[g]	IR[g]			
Bizzaro et al. (2007)	n/N (%)	n/N (%)										
Brouwer et al. (2004)	n/N (%)[h]	n/N (%)	n/N (%)				IR[g,i]			P		
Burgos et al. (2010)		n/N (%)										
Calvo-Alén et al. (2005)	n/N (%)											
Chabbert-Buffet et al. (2011)		n/N (%)[j]	n/N (%)[j]					IR[d,j]	IR[d,j]			
Chang et al. (2006)	n/N (%)[k]	n/N (%)[k]	n/N (%)[k]				IR[g,k]					
Chen et al. (2016)	n/N (%)	n/N (%)	n/N (%)									
Choojitarom et al. (2008)		n/N (%)	n/N (%)									
Chung et al. (2014)		n/N (%)	n/N (%)		HR, IRR[l]	HR, IRR[l]	IR[m]	IR[m]				
Domingues et al. (2016)	n/N (%)						IR[g]					

Author (year)	Absolute risk			Relative risk			Incidence rate			Absolute risk by APS presence or antibodies		
	VTE[a]	DVT	PE	VTE[a]	DVT	PE	VTE[a]	DVT	PE	VTE[a]	DVT	PE
García-Villegas et al. (2015)	n/N (%)	n/N (%)	n/N (%)									
Hinojosa-Azaola et al. (2016)	n/N (%)	n/N (%)	n/N (%)				IR[d]	IR[d]	IR[d]			
Hsu et al. (2017)		n/N (%)[n]	n/N (%)[n]					IR[d,n]	IR[d,n]			
Johannesdottir et al. (2012)				IRR	IRR	IRR						
Kaiser et al. (2009)		n/N (%)	n/N (%)									
Kaiser et al. (2012)		n/N (%)	n/N (%)									
Manger et al. (2002)		% (may be feasible to estimate n/N)										
Martínez-Berriotxoa et al. (2007)	n/N (%)[h]									P		
McMahon et al. (2006)	n/N (%)											
Mok et al. (2005a)	n/N (%)	n/N (%)	n/N (%)				IR[d,o]					
Mok et al. (2010)	n/N (%)	n/N (%)	n/N (%)	SIR[l]			IR[d]					
Mok et al. (2013)		n/N (%)[e]									P	
Moroni et al. (2004)	n/N (%)											
Mok et al. (2005b)	n/N (%)	n/N (%)										

Author (year)	Absolute risk			Relative risk			Incidence rate			Absolute risk by APS presence or antibodies		
	VTE[a]	DVT	PE	VTE[a]	DVT	PE	VTE[a]	DVT	PE	VTE[a]	DVT	PE
Ramirez et al. (2020)	n/N (%)											
Reddy and Chand (2014)		n/N (%)[e]									P	
Regéczy et al. (2000)		n/N (%)[p]	n/N (%)[p]								P	P
Romero-Díaz et al. (2009)	n/N (%)						IR[d]					
Sciascia et al. (2014)	n/N (%)	n/N (%)										
Singh et al. (2013)		n/N (%)[q] by APS									P	
Somers et al. (2002)	n/N (%)						IR[d]					
Taraborelli et al. (2016)		n/N (%)[r]	n/N (%)[r]								P	P
Tarr et al. (2007)		n/N (%)[s]	n/N (%)[s]									
Tektonidou et al. (2004)		n/N (%)[t]	n/N (%)[t]									
Tektonidou et al. (2009)	n/N (%)[e]									P		
To et al. (2005)	n/N (%)[u]											
Wang and Liu (2016)	n/N (%)[e]	n/N (%)[e]	n/N (%)[e]							P	P	P
Watanabe et al. (2018)	n/N (%)[e]	n/N (%)[e]	n/N (%)[e]							P	P	P

	Absolute risk			Relative risk			Incidence rate			Absolute risk by APS presence or antibodies		
Author (year)	**VTE[a]**	**DVT**	**PE**	**VTE[a]**	**DVT**	**PE**	**VTE[a]**	**DVT**	**PE**	**VTE[a]**	**DVT**	**PE**
Yusuf et al. (2015)	n/N (%)[l]			Adj HR[l]			IR[d,l]					
Zöller et al. (2012)			n/N (%)			SIR						

aCL = anticardiolipin; Adj = adjusted; aPL = antiphospholipid antibodies; APS = antiphospholipid syndrome; APSN = antiphospholipid syndrome nephropathy; CMA = chlormadinone acetate; CPA = cyproterone acetate; DVT = deep vein thrombosis; FV = factor V; HCQ = hydroxychloroquine; HR = hazard ratio; IgG = immunoglobulin G; IgM = immunoglobulin M; IR = incidence rate; IRR = IR ratio; La = anti-La antibodies; LAC = lupus anticoagulant; OR = odds ratio; PE = pulmonary embolism; RNP = anti-RNP antibodies; Ro = anti-Ro antibodies; RR = relative risk; SIR = standardized incidence ratio; SLE = systemic lupus erythematosus; Sm = anti-SM antibodies; VTE = venous thromboembolism.

Note: The presence of RR information has been removed for Martínez-Berriotxoa et al. (2007) and Romero-Díaz et al. (2009) because the reference groups were not considered an appropriate proxy for the general population.

[a] Combined events.

[b] Reference group: general population.

[c] Adjusted HR also reported.

[d] Per 1,000 person-years.

[e] Subgroup data only: aPL+; aPL-/with APS; without APS.

[f] Reference group: patients without SLE.

[g] Per 100 person-years.

[h] Subgroup data also available: no aPL; LAC; aCL.

[i] Subgroup data only: no aPL; LAC; aCL.

[j] Subgroup data also available: CPA; CMA.

[k] Subgroup data only: 0-1 year after diagnosis; ≤30 days after diagnosis; 30 days to 1 year after diagnosis; 1-5 years after diagnosis; 5-10 years after diagnosis; 10-20 years after diagnosis; 20-30 years after diagnosis; 30-40 years after diagnosis; 40-50 years after diagnosis.

[l] Subgroup data also available: age group.

[m] Per 10,000 person-years.

[n] Subgroup data only: HCQ; no HCQ.

[o] Subgroup data also available: Chinese, African American, Caucasian.

[p] Subgroup data available: by FV and aPL.

[q] Subgroup data available: by APS.

[r] Subgroup data also available: aPL; no significant aPL.

[s] Subgroup data available: aCL-IgG, aCL-IgM, or both in patients with APS.

[t] Although ORs are provided within this publication, these are for APSN; all patients have SLE.

[u] Subgroup data only: Sm/RNP; DNA/Ro/La; DNA/LAC/aCl.

Table S5. Summary of Subgroup Analyses of AR of DVT Events in Patients With SLE by APS Presence or Antibodies

Analysis description	Outcome	Subgroup	Population 1	ES (95% CI) *P* value[a]	Heterogeneity statistics[b]
Subgroup analysis: AR of DVT events	AR of DVT events in patients with SLE by APS presence or antibodies, measured as cumulative incidence proportion	aPL Status	Patients with SLE and aPL (n = 6)	**RE Model:** ▪ 0.11 (0.03-0.22) **FE Model:** ▪ 0.08 (0.06-0.11)	▪ I^2 = 92.6%
			Patients with SLE and no aPL (n = 3)	**RE Model:** ▪ 0.08 (0.00-0.25) **FE Model:** ▪ 0.06 (0.04-0.09)	▪ I^2 = 91.0%
Subgroup analysis: AR of DVT events		APS Status	Patients with SLE and APS (n = 6)	**RE Model:** ▪ 0.26 (0.15-0.39) **FE Model:** ▪ 0.29 (0.24-0.35)	▪ I^2 = 79.3%
			Patients with SLE and no APS (n = 3)	**RE Model:** ▪ 0.01 (0.00-0.05) **FE Model:** ▪ 0.00 (0.00-0.02)	▪ I^2 = 74.8%
Sensitivity analysis: AR of DVT events in patients with SLE by APS presence or antibodies; high-quality studies only[c]		aPL Status	Patients with SLE and aPL (n = 4)	**RE Model:** ▪ 0.18 (0.08-0.29) **FE Model:** ▪ 0.17 (0.13-0.21)	▪ I^2 = 82.2%
			Patients with SLE and no aPL (n = 3)	**RE Model:** ▪ 0.08 (0.00-0.25) **FE Model:** ▪ 0.06 (0.04-0.09)	▪ I^2 = 91.0%

aPL = antiphospholipid antibodies; APS = antiphospholipid syndrome; AR = absolute risk; CASP = Critical Appraisal Skills Programme; CI = confidence intervals; DVT = deep vein thrombosis; ES = effect size; FE = fixed effects; RE = random effects; SLE = systemic lupus erythematosus.

[a] Effect size refers to the pooled estimate of the AR of DVT in patients with SLE, measured as cumulative incidence proportion.

[b] Heterogeneity statistics correspond to the results of the FE models.

[c] Study quality assessed with CASP checklists.

Table S6. Summary of Subgroup Analyses of AR of PE Events in Patients With SLE by APS Presence or Antibodies

Analysis description	Outcomes	Subgroup	Population 1	ES (95% CI) P value[a]	Heterogeneity statistics[b]
Subgroup analysis: AR of PE events	AR of PE events in patients with SLE by APS presence or antibodies, measured as cumulative incidence proportion	aPL Status	Patients with SLE and aPL (n = 5)	**RE Model:** ▪ 0.05 (0.03-0.08) **FE Model:** ▪ 0.05 (0.03-0.08)	▪ $I^2 = 0\%$
			Patients with SLE and no aPL (n = 4)	**RE Model:** ▪ 0.01 (0.00-0.02) **FE Model:** ▪ 0.01 (0.00-0.02)	▪ $I^2 = 33.0\%$
Subgroup analysis: AR of PE events		APS Status	Patients with SLE and APS (n = 3)	**RE Model:** ▪ 0.22 (0.12-0.34) **FE Model:** ▪ 0.22 (0.16-0.29)	▪ $I^2 = 66.3\%$
			Patients with SLE and no APS (n = 1)	**RE Model:** ▪ 0.02 (0.00-0.09) **FE Model:** ▪ 0.02 (0.00-0.09)	▪ $I^2 = $ NA

aPL = antiphospholipid antibodies; APS = antiphospholipid syndrome; AR = absolute risk; CI = confidence intervals; ES = effect size; FE = fixed effects; n = number of studies included in the analysis; NA = not applicable; PE = pulmonary embolism; RE = random effects; SLE = systemic lupus erythematosus.

[a] Effect size refers to the pooled estimate of the AR of PE in patients with SLE by APS presence or antibodies, measured as cumulative incidence proportion.

[b] Heterogeneity statistics correspond to the results of the FE models.

Figure S1. Forest Plot of Sensitivity Analysis of AR of VTE Events in Patients With SLE (High-quality Studies Only; n = 14)

Study	Events	Total		Proportion	95%-CI
Yusuf (2015)	495	19427		0.03	[0.02; 0.03]
Calvo-Alen (2005)	51	570		0.09	[0.07; 0.12]
Mok (2005A)	8	258		0.03	[0.01; 0.06]
Avina-Zubieta (2015)	108	4863		0.02	[0.02; 0.03]
Somers (2002)	35	678		0.05	[0.04; 0.07]
Hinojosa-Azaola (2016)	27	219		0.12	[0.08; 0.17]
Watanabe (2018)	11	152		0.07	[0.04; 0.13]
Romero-Diaz (2009)	25	241		0.10	[0.07; 0.15]
Garcia-Villegas (2015)	7	238		0.03	[0.01; 0.06]
Tektonidou (2009)	15	288		0.05	[0.03; 0.08]
Mok (2010)	14	516		0.03	[0.01; 0.05]
Mok (2005B)	10	272		0.04	[0.02; 0.07]
Becker-Merok (2009)	8	158		0.05	[0.02; 0.10]
Brouwer (2004)	15	144		0.10	[0.06; 0.17]
Fixed effect model		**28024**		**0.03**	**[0.03; 0.03]**
Random effects model				**0.05**	**[0.04; 0.07]**

Heterogeneity: $I^2 = 92\%$, $\tau^2 = 0.0043$, $p < 0.01$

0   0.1   0.2   0.3   0.4
Proportion with VTE

Abbreviations: AR = absolute risk; CI = confidence intervals; n = number of studies included in the analysis; SLE = systemic lupus erythematosus; VTE = venous thromboembolism.

Figure S2. Forest Plot of Sensitivity Analysis of AR of DVT Events in Patients With SLE (High-quality Studies Only; n = 14)

Study	Events	Total		Proportion	95%-CI
Burgos (2010)	11	643		0.02	[0.01; 0.03]
Avina-Zubieta (2015)	68	4863		0.01	[0.01; 0.02]
Hinojosa-Azaola (2016)	11	219		0.05	[0.03; 0.09]
Watanabe (2018)	7	152		0.05	[0.02; 0.09]
Chung (2014)	136	13084		0.01	[0.01; 0.01]
Garcia-Villegas (2015)	2	238		0.01	[0.00; 0.03]
Hsu (2017)	46	3892		0.01	[0.01; 0.02]
Mok (2005B)	9	272		0.03	[0.02; 0.06]
Regeczy (2000)	36	120		0.30	[0.22; 0.39]
Becker-Merok (2009)	8	158		0.05	[0.02; 0.10]
Brouwer (2004)	8	144		0.06	[0.02; 0.11]
Taraborelli (2016)	29	317		0.09	[0.06; 0.13]
Kaiser (2009)	112	1930		0.06	[0.05; 0.07]
Kaiser (2012)	31	1361		0.02	[0.02; 0.03]
Fixed effect model		27393		**0.01**	**[0.01; 0.02]**
Random effects model				**0.04**	**[0.02; 0.07]**

Heterogeneity: $I^2 = 96\%$, $\tau^2 = 0.0134$, $p < 0.01$

Proportion with DVT (0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6)

Abbreviations: AR = absolute risk; CI = confidence intervals; DVT = deep vein thrombosis; n = number of studies included in the analysis; SLE = systemic lupus erythematosus.

Figure S3. Forest Plot of Sensitivity Analysis of AR of PE Events in Patients With SLE (High-quality Studies Only; n = 13)

Study	Events	Total		Proportion	95%-CI
Akimoto (2005)	1	166		0.01	[0.00; 0.03]
Avina-Zubieta (2015)	53	4863		0.01	[0.01; 0.01]
Hinojosa-Azaola (2016)	13	219		0.06	[0.03; 0.10]
Watanabe (2018)	6	152		0.04	[0.01; 0.08]
Chung (2014)	92	13084		0.01	[0.01; 0.01]
Garcia-Villegas (2015)	5	238		0.02	[0.01; 0.05]
Hsu (2017)	28	3892		0.01	[0.00; 0.01]
Regeczy (2000)	6	120		0.05	[0.02; 0.11]
Becker-Merok (2009)	0	158		0.00	[0.00; 0.02]
Brouwer (2004)	5	144		0.03	[0.01; 0.08]
Taraborelli (2016)	7	317		0.02	[0.01; 0.04]
Kaiser (2009)	50	1930		0.03	[0.02; 0.03]
Zoller (2012)	276	9147		0.03	[0.03; 0.03]
Fixed effect model		34430		**0.01**	**[0.01; 0.01]**
Random effects model				**0.02**	**[0.01; 0.03]**

Heterogeneity: $I^2 = 95\%$, $\tau^2 = 0.0028$, $p < 0.01$

0   0.05 0.1 0.15 0.2 0.25 0.3
Proportion with PE

Abbreviations: AR = absolute risk; CI = confidence intervals; n = number of studies included in the analysis; PE = pulmonary embolism; SLE = systemic lupus erythematosus.
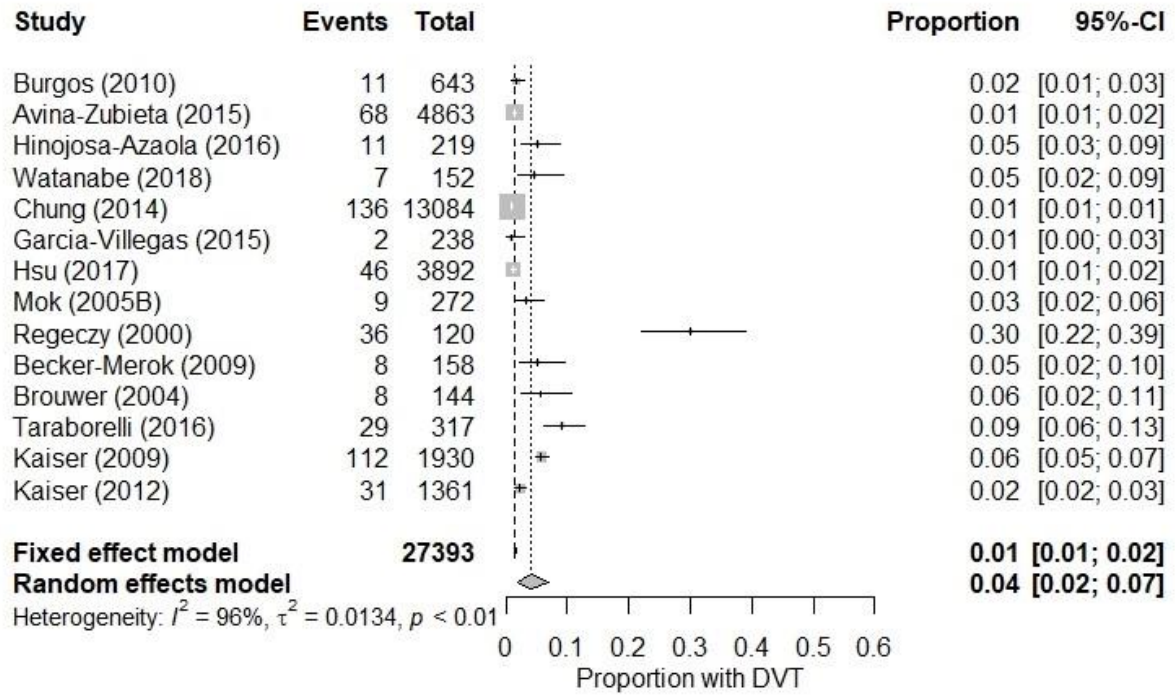
Figure S4. Forest Plot of Sensitivity Analysis of IR of VTE Events in Patients With SLE (High-quality Studies Only; n = 10)

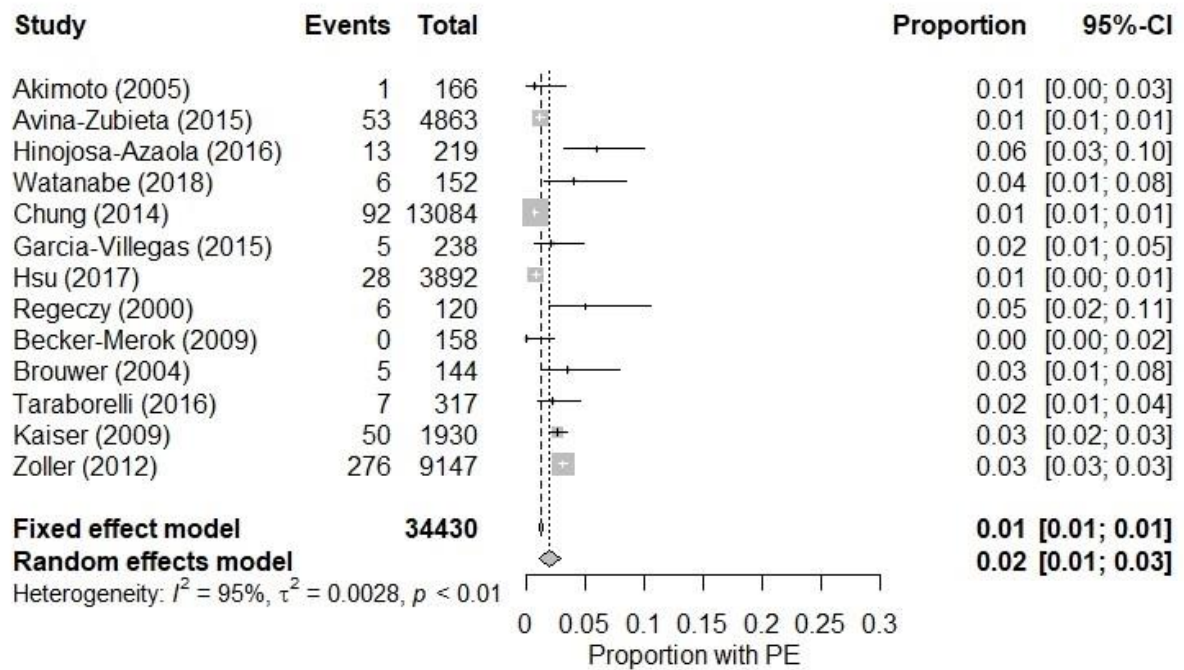| Author (Year)	Person Years	IR/1000 PY	IR/1000 PY	95% CI	Weight (FE)	Weight (RE)
Aheloff (2017)	21944.00		5.24	[4.32; 6.24]	19.6%	11.0%
Avina-Zubieta (2015)	20300.75		5.32	[4.36; 6.37]	18.1%	10.9%
Becker-Merok (2009)	1880.58		4.30	[1.76; 7.86]	1.7%	9.6%
Brouwer (2004)	1030.00		5.80	[1.91; 11.57]	0.9%	8.6%
Mok (2010)	4285.71		4.20	[2.46; 6.39]	3.8%	10.4%
Mok (2005A)	3094.00		13.00	[9.27; 17.35]	2.8%	10.1%
Romero-Diaz (2009)	1349.00		18.50	[11.88; 26.54]	1.2%	9.1%
Somers (2002)	6862.75		5.10	[3.54; 6.94]	6.1%	10.6%
Yusuf (2015)	50073.00		9.89	[9.04; 10.78]	44.7%	11.0%
Hinojosa-Azaola (2016)	1139.00		24.00	[15.77; 33.92]	1.0%	8.8%
Fixed effect model			**7.40**	**[6.90; 7.92]**	**100.0%**	--
Random effects model			**8.34**	**[5.23; 12.15]**	--	**100.0%**

Heterogeneity: $I^2 = 93\%$, $\tau^2 = 0.0008$, $p < 0.01$

Incidence Rate per 1000 PY
0 5 10 15 20 25 30 35

Abbreviations: CI = confidence intervals; FE = fixed effects; IR = incidence rate; n = number of studies included in the analysis; PY = person-years; RE = random effects; SLE = systemic lupus erythematosus; VTE = venous thromboembolism.

Figure S5. Forest Plot of Sensitivity Analysis of IR of DVT Events in Patients With SLE (High-quality Studies Only; n = 5)
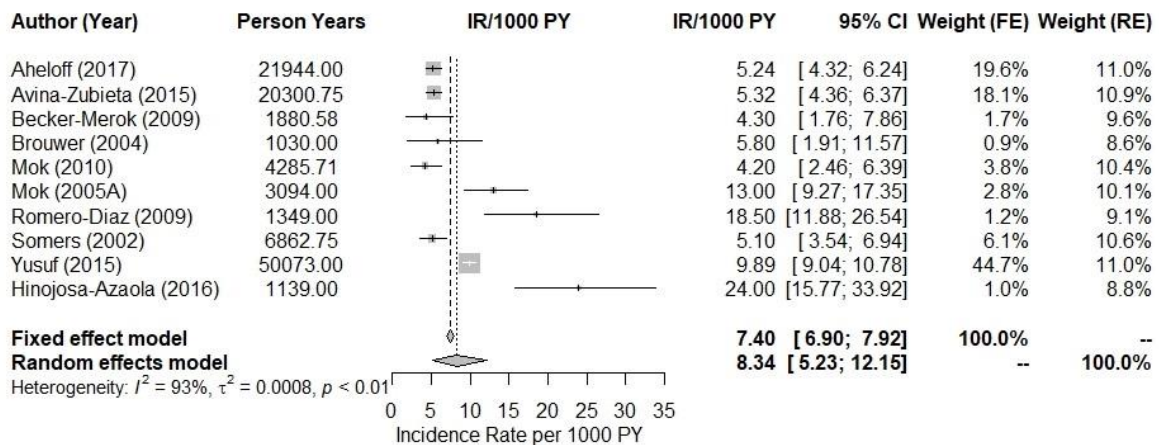
Author (Year)	Person Years	IR/1000 PY	IR/1000 PY	95% CI	Weight (FE)	Weight (RE)
Avina-Zubieta (2015)	20420.42		3.33	[2.58; 4.17]	15.9%	22.6%
Becker-Merok (2009)	1880.58		4.30	[1.76; 7.86]	1.5%	17.3%
Hsu (2017)	14500.00		2.00	[1.33; 2.80]	11.3%	22.3%
Hinojosa-Azaola (2016)	1139.00		9.66	[4.67; 16.33]	0.9%	14.8%
Chung (2014)	90237.00		1.51	[1.27; 1.77]	70.4%	23.1%
Fixed effect model			**1.75**	**[1.52; 2.00]**	**100.0%**	**--**
Random effects model			**3.28**	**[1.46; 5.79]**	**--**	**100.0%**

Heterogeneity: $I^2 = 91\%$, $\tau^2 = 0.0004$, $p < 0.01$

Incidence Rate per 1000 PY (0 5 10 15 20)

Abbreviations: CI = confidence interval; DVT=deep vein thrombosis; FE = fixed effects; IR = incidence rate; n = number of studies included in the analysis; PY = person-years; RE = random effects; SLE = systemic lupus erythematosus.

Figure S6. Forest Plot of Sensitivity Analysis of IR of PE Events in Patients With SLE (High-quality Studies Only; n = 5)
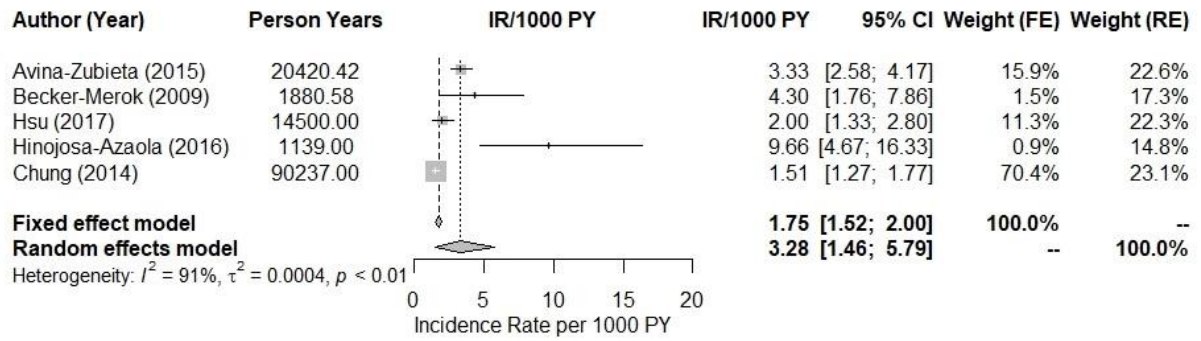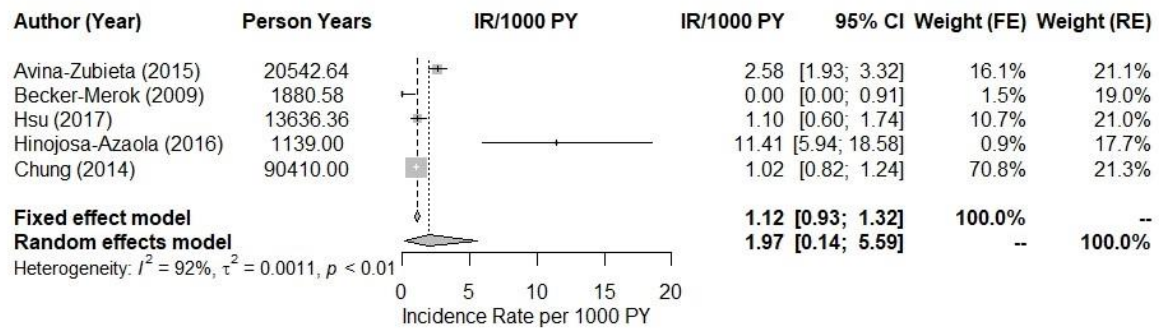
Author (Year)	Person Years	IR/1000 PY		IR/1000 PY	95% CI	Weight (FE)	Weight (RE)
Avina-Zubieta (2015)	20542.64			2.58	[1.93; 3.32]	16.1%	21.1%
Becker-Merok (2009)	1880.58			0.00	[0.00; 0.91]	1.5%	19.0%
Hsu (2017)	13636.36			1.10	[0.60; 1.74]	10.7%	21.0%
Hinojosa-Azaola (2016)	1139.00			11.41	[5.94; 18.58]	0.9%	17.7%
Chung (2014)	90410.00			1.02	[0.82; 1.24]	70.8%	21.3%
Fixed effect model				**1.12**	**[0.93; 1.32]**	**100.0%**	**--**
Random effects model				**1.97**	**[0.14; 5.59]**	**--**	**100.0%**

Heterogeneity: $I^2 = 92\%$, $\tau^2 = 0.0011$, $p < 0.01$

0   5   10   15   20
Incidence Rate per 1000 PY

Abbreviations: CI = confidence intervals; FE = fixed effects; IR = incidence rate; n = number of studies included in the analysis; PE = pulmonary embolism; PY = person-years; RE = random effects; SLE = systemic lupus erythematosus.