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REVIEW

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

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ABSTRACT

The objective of this work was to conduct a systematic literature review (SLR) and meta-analysis (MA) to evaluate the relative risk (RR) of venous thromboembolism (VTE) events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients with systemic lupus erythematosus (SLE) compared with patients without SLE, as well as the absolute risk (AR) (measured by incidence proportion) and incidence rate (IR) of VTE events in patients with SLE. The SLR was conducted using Embase, MEDLINE, and MEDLINE In-Process to identify observational studies evaluating the risk of VTE, DVT, and PE events in adult patients with SLE compared with the general population, published January 2000 to September 2020. Random-effects models were used as the primary approach in the MA. Heterogeneity was assessed on the basis of the I^2 value. Sensitivity analyses were performed to assess the robustness of results to various conditions, and subgroup analysis was performed for the AR of VTE by antiphospholipid status (aPLs) and antiphospholipid syndrome (APS). Of the 50 publications included for data extraction, 44 contained data for consideration in the MA of any one of the measures of interest (RR, AR, or IR) for VTE, DVT, or PE. The pooled RR indicates statistically significantly higher risk of VTE (RR 4.38, 95% confidence interval 2.63–7.29) in patients with SLE compared with the general population. Considerable heterogeneity was present in nearly all MA (I^2 = 75–100%). Moreover, a higher pooled AR of VTE was estimated in patients with SLE with aPLs (n/N = 0.13) and APS (n/N = 0.63) compared with patients with SLE without aPLs/APS (n/N = 0.07). Overall, there was evidence of an increased risk of VTE, DVT, and PE in patients with SLE compared with the general population.

Keywords: Meta-analysis; Systematic literature review; Systemic lupus erythematosus; Venous thromboembolism

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Key Summary Points

Patients with systemic lupus erythematosus (SLE) have an increased risk of cardiovascular complications, including venous thromboembolism (VTE) events.

Despite substantial heterogeneity across studies, this meta-analysis showed evidence of an increased risk of VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients with SLE compared with the general population.

A considerably higher incidence of VTE events was also observed in the SLE population than the general population and patients with concomitant antiphospholipid syndrome.

The absolute risk and incidence rate of VTE events were also found to be higher in younger (< 40 years) patients with SLE versus those aged 41–64 years.

Future research is needed to inform on the impact of traditional and SLE-specific risk factors for VTE to further identify patients with SLE at highest risk, allowing for improved prevention and treatment strategies.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an acquired [1], chronic, heterogeneous autoimmune inflammatory disease [2, 3]. Patients with immune-mediated diseases, such as SLE, have an increased risk of cardiovascular complications, including venous thromboembolism (VTE) events [4]. Like other autoimmune diseases, hypercoagulability and inflammation are general features of SLE, and both factors are responsible for inciting VTEs [5]. Mortality risk in SLE is two to three times greater than the general population [6] with a threefold increase in risk [7] of cardiovascular death compared with the general population. In a large cohort of European patients followed during a 10-year period, it was shown that 25% of deaths were secondary to active disease or to thrombotic events [1].

The presence of antiphospholipid antibodies (aPLs) has been described in about 50% of patients with SLE [8, 9], and has been widely shown to be a significant and independent risk factor for thrombotic events [1]. Independent of aPLs, increased incidence of traditional cardiovascular and lupus-related thrombosis risk factors significantly increases the risk of premature atherosclerosis and/or thrombosis in patients with SLE [10].

While current evidence suggests that patients with SLE have an increased risk of VTE [4, 11], meta-analyses (MAs) that integrate evidence across studies to estimate the pooled relative risk (RR) and absolute risk (AR) have not been performed. The primary objective of this work was to evaluate the RRs of VTE events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients with SLE compared with patients without SLE (and no other specific disease state), the general population, or suitable proxies for general population controls, as well as the AR (as measured by incidence proportion) and incidence rate (IR) of VTE events including DVT and PE in patients with SLE. An additional systematic literature review and meta-analysis was the focus of another study, which explores aspects of cardiovascular events in patients with SLE, including acute coronary syndrome, relative to the general population.

METHODS

Search Strategy and Eligibility Criteria

This systematic literature review (SLR) and MA was performed according to the Cochrane Handbook for Systematic Reviews of Interventions [12], and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [13]. Embase (using Elsevier Platform), MEDLINE, and MEDLINE In-Process

(using PubMed Platform including Daily Update) were searched to identify all relevant, English-only, full-text publications of observational studies (cohort, cross-sectional, and case–control studies and analysis of hospital records/database) that evaluated the RR, AR, or IR of VTE, PE, or DVT in patients with SLE. SLE diagnoses were established according to the International Classification of Diseases (ICD-7, ICD-8, ICD-9, or ICD-10) codes or American College of Rheumatology criteria. The search was limited to published manuscripts dated between 1 January 2000 and 16 September 2020. Abstracts of unpublished studies were excluded. Detailed lists of the search terms are available in Supplementary Material (Tables S1a and S1b). Reference lists of included articles were also searched by hand for further studies of interest.

Supplementary Material Tables S2a and S2b list all the criteria used during the initial (screen 1) and full-text (screen 2) review process. In short, studies were eligible for inclusion if they were observational, included a cohort of adult patients with SLE, and reported either an RR, AR, or IR for the outcomes of interest (VTE, DVT, or PE).

Data Extraction and Quality Assessment

Double screening was conducted (two reviewers independently performed two-stage screening) and achieved consensus. Data extraction and quality assessment were quality checked by a second researcher. Data extraction was verified against the source document by a researcher not involved with the extraction. Studies that met eligibility criteria and reported original data were included in the review. Data on study characteristics and measures for outcomes of interest (VTE, DVT, PE events) in patients with SLE were extracted. Data on aPL status/antiphospholipid syndrome (APS) presence were also extracted as available and included as a qualitative description in this review.

The Critical Appraisal Skills Programme (CASP) [14] was used to assess the quality of each observational study. Studies were classified as low, unclear, medium, or high quality. Several studies met the majority of CASP standards for high quality, although none uniformly met all criteria. Studies included in the MA and their endpoint availability are presented in Supplementary Material Table S3.

STATISTICAL METHODS

MA for RR, AR (as measured by incidence proportion), and IR were conducted for outcomes of interest for which there were at least three high-quality studies reporting usable data. Details for each of these risk measures are described below, including the sensitivity analyses. Heterogeneity for all MAs was assessed using the Higgins' [12] I^2 to estimate the percentage of variance and the P value of the chi-squared test. All analyses were conducted in R using the metafor package.

Meta-analysis Methods for Relative Effects

Comparative measures of risk for VTE, DVT, or PE in patients with SLE versus patients without SLE/the general population included hazard ratios (HRs), IR ratios, or standardized IRs (SIRs). These measures are henceforth referred to broadly as RR and were pooled in the primary MA owing to the paucity of studies available. A leave-one-out sensitivity analysis was conducted to assess the robustness of primary results to any one study. Studies were included in the RR analysis regardless of the length of follow-up under the assumption of proportional hazards over time. The restricted maximum likelihood (REML) random-effects (RE) model was used to calculate the pooled RR and 95% confidence intervals (CIs) for all outcomes. Fixed effects (FE) models were also fit for completeness. Owing to differences in factors adjusted for across the studies, unadjusted measures were used in preference to adjusted measures where both were available.

Meta-analysis Methods for Proportions

The AR of VTE, DVT, or PE events within the SLE population was measured by an incidence

proportion and reported as a percentage [i.e., the number of VTE, DVT, or PE events within the SLE population (*n*/*N*)]. The double-arcsine transformation was used for the MA of AR. Studies reporting AR of VTE, DVT, or PE events were pooled via MA for the respective outcome via the REML RE model. The exact binomial approach was used for the reporting of CI of the proportions. FE models were also fit for completeness. Scatter plots that were created considered the AR against the length of follow-up. As no apparent effect of the AR by length of follow-up was observed, sensitivity analyses were not performed according to length of follow-up. Two sensitivity analyses were performed: (1) limiting analysis to only studies of high quality and (2) grouping studies by definition of VTE, i.e., studies defining VTE as only DVT or PE, those defining VTE more broadly, and those that did not report VTE definition. Finally, subgroup analyses looking at the AR of VTE, DVT, and PE events in patients with SLE by APS presence or aPLs were performed.

Meta-analysis Methods for Incidence Rates

IRs reported within individual studies were shifted to be in consistent form of per 1000 patient years (PY). Where PY data were not reported directly, estimates were calculated using the mean length of follow-up. The Freeman–Tukey double-arcsine transformation was used to calculate the overall IR. Random-effects models were fit using the REML option, and FE estimates were used for completeness. Sensitivity analyses were conducted limiting to only high-quality studies.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Study Selection Process

The initial search returned 1556 references. After screening titles and abstracts, 187 publications were progressed to a full-text review. Following the second round of screening, 50 articles met the predefined inclusion criteria and were included in the SLR and MA (Fig. 1). Of the 50 publications selected for data extraction in the SLR, 44 contained data for one or more endpoints for consideration in the MA. Six of the 50 studies were excluded for a variety of reasons, including populations that were dissimilar from the general population of patients with SLE, population/endpoint combination not of interest for MA of priority endpoints, and some endpoint data reported in a format not suitable for MA. A list of excluded studies and the reason for exclusion is outlined in Supplementary Material Table S3. The MA was conducted on the endpoints presented in Supplementary Material Table S4 after conducting a feasibility assessment of the data extracted as part of the SLR.

Study Characteristics

A total of 44 studies were identified, with 3 to 21 contributing to the MA of any one endpoint (VTE, DVT, or PE) and any one risk measure (RR, AR, or IR). Study characteristics, including inclusion and exclusion criteria, are summarized in Table 1. One additional study,[1] García-Villegas et al. [15] was also included in the MA. Of the 45 studies, 21 were retrospective cohort studies and 23 were prospective cohort studies; there was 1 case–control study. Of the 45 included studies, 19 were conducted in Europe, 14[2] in North America, and 13[2] in Asia. Length of follow-up ranged from 2.5 to 15 years across included studies. Owing to the scarcity of data for the MA of any one endpoint and risk measure, the ability to carry out MA subgroup analysis was limited. Where events are reported in fewer than three comparable studies, information was not meta-analyzed but described qualitatively.

[1] This study was identified while reviewing the evidence for a related project: Meta-analysis of Cardiovascular Event Endpoints and Risk Factors in Systemic Lupus Erythematosus.

[2] Mok et al.[37] included patients from China and the USA; this has therefore been counted twice.

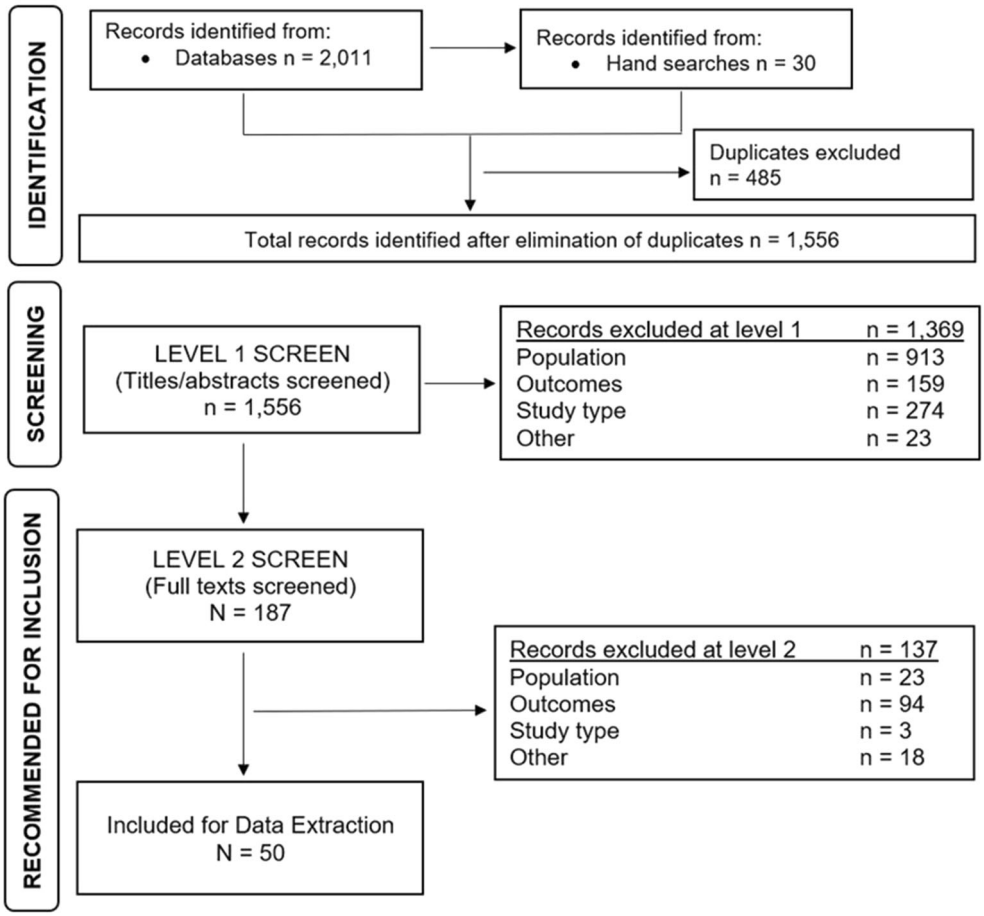


Fig. 1 Flow diagram of the systematic literature review process to evaluate the risk of VTE and risk factors in patients with SLE compared with the general population. *SLE* systemic lupus erythematosus, *VTE* venous thromboembolism

Relative Risk of VTE, DVT, and PE Events in Patients with SLE

Five studies were included in the primary analysis of the RR of VTE in patients with SLE compared with the general population (Fig. 2a). In the RE MA, the risk of VTE was 4.38 times higher in patients with SLE than that of the general population (RR 4.38, 95% CI 2.63–7.29). Substantial heterogeneity was observed in the RR estimates across the studies (I^2 = 89.32%, p = 0.00). A leave-one-out sensitivity analysis resulted in estimates ranging from 3.55 to 4.88. The study by Mok et al. [39] had a notably higher estimate than estimates observed in other studies.

When limiting the analysis to RR of DVT in patients with SLE compared with the general population, three studies were identified (Fig. 2b). The pooled risk of DVT in patients with SLE was 6.35 times higher than that of the general population, (RR 6.35, 95% CI 2.70–14.94). Substantial heterogeneity was observed in the RR estimates across the studies (I^2 = 89.75%, p = 0.00). A leave-one-out sensitivity analysis resulted in estimates ranging from 4.44 to 9.21. The study by Chung et al. [28] had a notably higher estimate than other studies.

When limiting the analysis to RR of PE in patients with SLE compared with the general population, four studies were identified (Fig. 2c). The pooled risk of PE in patients with SLE was approximately five times higher than that of the general population (RR 4.94, 95% CI 1.90–12.86). Substantial heterogeneity was observed in the RR estimates across the studies

Table 1 Summary of study characteristics included in the MA

Author (year)	Country	Study design	Inclusion criteria	Exclusion criteria	Population (s)	Reference group	Follow-up	Overall quality appraisal
Ahlehoff et al. [16]	Denmark	Retrospective cohort study	All Danish individuals ≥ 18 years from 1997 to 2011	Patients with history of CLE or SLE before the start of the study; patients treated with oral anticoagulants or with previous cardiovascular events	SLE	General population	11.36 years	High
Akimoto et al. [17]	Japan	Prospective cohort study	Patients fulfilling the 1982 ACR criteria for SLE	NR	Subgroups: § aPL+ § aPL−	NA	5 years	High
Aviña-Zubieta et al. [5]	Canada	Retrospective cohort study	Incident SLE cohort with cases diagnosed for the first time between January 1996 and December 2010 defined as follows: (a) Two ICD-9-CM 710.0 codes for SLE at least 2 months apart and within a 2-year period by a nonrheumatologist physician (b) One ICD code for SLE by a rheumatologist or from hospital (ICD-9-CM 710.0 or ICD-10 M32.1, M32.8, and M32.9) (c) Absence of a prior SLE diagnosis between January 1990 and December 1995 (to ensure incident SLE cases)	Cases that did not have an ICD code for SLE within the last 5 years prior to the end of follow-up, as long as they remained alive and residents of the province	SLE Subpopulations: § Age/sex/entry matched § CCI/age/sex/entry matched § Glucocorticoid/age/sex/entry matched § Number of medical service plan visits/age/sex/entry matched § Fully matched	Non-SLE reference population	5 years	High

Table 1 continued

Author (year)	Country	Study design	Inclusion criteria	Exclusion criteria	Population (s)	Reference group	Follow-up	Overall quality appraisal
Hansen and Jacobsen [18]	Denmark	Retrospective cohort study	Adult patients with SLE fulfilling the modified ACR 1982 or 1997 classification criteria	NR	SLE	NA	8.9 ± 7.6 years	High
Becker-Merok and Nossent [19]	Norway	Retrospective cohort study	All patients met the revised and/or updated ACR 1982 or 1997 classification criteria	NR	SLE	NA	11.9 years (mean)	High
Bizzaro et al. [20]	Italy	Prospective cohort study	At least 4 of the ACR revised criteria for the classification of SLE	NR	SLE	NA	15 years	Medium
Brouwer et al. [21]	The Netherlands	Prospective cohort study	Fulfilled at least 4 criteria for the classification of SLE, as defined by the ACR	NR	SLE Subgroups: § No aPL § LAC § aCL	NA	12.7 years	High
Burgos et al. [22]	USA	Prospective cohort study (LUMINA cohort)	Meeting ACR criteria for SLE; disease duration ≤ 5 years; ≥ 16 years of age; defined ethnicity; living in recruitment area of 3 medical centers	NR	SLE	NA	4.6 years	High
Calvo-Alén et al. [23]	USA	Prospective cohort study (LUMINA cohort)	Meeting ACR criteria for SLE; disease duration ≤ 5 years; ≥ 16 years of age; defined ethnicity; living in recruitment area of 3 medical centers	NR	SLE	NA	53 months	High
Chabbert-Buffet et al. [24]	France	Prospective cohort study	Women who fulfilled the diagnostic criteria for SLE as defined by the American Rheumatism Association	NR	All Subgroups: § CPA § CMA	NA	46 months	Medium

Table 1 continued

Author (year)	Country	Study design	Inclusion criteria	Exclusion criteria	Population (s)	Reference group	Follow-up	Overall quality appraisal
Chang et al. [25]	Canada	Prospective cohort study	Having ≥ 4 ACR criteria	NR	SLE Subgroups: § 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	NA	11.88 years	Unclear
Chen et al. [26]	China	Retrospective cohort study	Patients fulfilling the classification criteria of the ACR for SLE	NR	SLE	NA	30.01 months (range 23–48 months)	Medium

Table 1 continued

Author (year)	Country	Study design	Inclusion criteria	Exclusion criteria	Population (s)	Reference group	Follow-up	Overall quality appraisal
Choojitarom et al. [27]	Thailand	Prospective cohort study	Patients with SLE (diagnosed as SLE by the 1997 revised ACR criteria) who were regularly followed up at the outpatient department and gave consent to screen for b2GP1Ab in addition to LAC and aCL antibodies during the 1-year enrollment period Only patients who had a positive test for at least 1 type of the aPL were included in this study All included patients must have had another positive test of the same aPL at least 6 weeks apart from the first instance All enrolled patients must have had no previous evidence of vascular thrombosis	NR	SLE	NA	8.4 years	High
Chung et al. [28]	Taiwan	Retrospective cohort study	Patients newly diagnosed with SLE (ICD-9-CM: 710.0)	Patients with SLE with missing data for date of birth or sex and those with a history of DVT or PE before the index date	SLE	No SLE	NR	High
Domingues et al. [29]	USA	Prospective cohort study	Patients with SLE	< 3 measures of anticardiolipin; history of thrombosis prior to SLE diagnosis or of unknown date	All	NA	12.2 years	Medium

Table 1 continued

Author (year)	Country	Study design	Inclusion criteria	Exclusion criteria	Population (s)	Reference group	Follow-up	Overall quality appraisal
García-Villegas et al. [15]	Mexico	Prospective cohort study	Women, age ≥ 18 years, premenopausal women who qualified as SLE (≥ 4 after American Rheumatology College criteria) and who signed the FALTA	Exclusion criteria were pregnancy, nonstabilized thyroid disease, acute physical stress (< 3 months), amputation of limbs, generalized edema and/or recent liposuction (< 1 year), and having fulfilled the ACR criteria for the diagnosis of antiphospholipid syndrome	SLE	NA	NR	High
Hinojosa-Azaola et al. [30]	Mexico	Prospective cohort study	Recent onset SLE defined as ≤ 1 year since the accrual of ≥ 4 ACR revised and updated classification criteria	Patients receiving anticoagulants for severe pulmonary HTN without thrombosis, who presented with thrombosis 7 months prior to diagnosis of SLE, and patients with malignancies	SLE	NA	5.21 years	High
Hsu et al. [31]	Taiwan	Prospective cohort study	Patients with SLE (ICD-9: 710.0)	Patients diagnosed before 2001; patients whose diagnosis did not pass the catastrophic illness certification procedure; patients with acute coronary syndrome, any stroke, PE, DVT, or PAD before the diagnosis of SLE; patients with follow-up < 1 year; patients who developed vascular events in the first year; patients with HCQ use between 0 and 80%	Subgroups: § HCQ § No HCQ	NA	7.4 years	High

Table 1 continued

Author (year)	Country	Study design	Inclusion criteria	Exclusion criteria	Population (s)	Reference group	Follow-up	Overall quality appraisal
Johannesdottir et al. [32]	Denmark	Case–control study	Cases of VTE	NR	SLE	Controls	NR	High
Kaiser et al. [33]	USA	Retrospective cohort study	SLE based on ACR criteria	NR	SLE	NA	NR	High
Kaiser et al. [34]	USA	Retrospective cohort study	Patients fulfilled the ACR criteria for SLE, completed an extensive questionnaire, gave permission for medical record review, and provided a DNA sample	NR	§ Discovery cohort § Replication cohort	NA	NR	High
Manger et al. [35]	Germany	Retrospective cohort study	All patients fulfilled the 1982 and 1997 revised criteria of the ACR for the diagnosis of SLE	NR	SLE	NA	5.4 years	Medium
Martínez-Berriotxoa et al. [36]	Spain	Prospective cohort study	All patients fulfilled the 1997 ACR criteria for SLE	NR	Subgroups: § LAC § Persistent aCL § Transient aCL § aPL	NA	10 years	Medium
McMahon et al. [37]	Ireland	Retrospective cohort study	Diagnosis of SLE based on ACR criteria	NR	SLE	NA	NR	Medium
Mok et al. [38]	China, USA	Prospective cohort study	Patients who fulfilled at least 4 of the ACR criteria for SLE	NR	SLE Subgroups: § Chinese § African American § Caucasian	NA	4.95 years	High

Table 1 continued

Author (year)	Country	Study design	Inclusion criteria	Exclusion criteria	Population (s)	Reference group	Follow-up	Overall quality appraisal
Mok et al. [39]	China	Retrospective cohort study	Patients who fulfilled ≥ 4 ACR criteria for SLE	NR	SLE Subgroups: § < 30 years § 30–40 years § 40–50 years § 50–60 years	General population	9.9 years (with DVT) and 9.3 years (no DVT)	High
Mok et al. [40]	China	Prospective cohort study	Patients who were newly diagnosed as having SLE in the outpatients clinic of the hospital or during hospitalization or referred to the unit within 12 months of diagnosis of SLE	NR	Subgroups: § APS § No APS	NA	9.7 ± 7.3 years	Unclear
Mok et al. [41]	China	Retrospective cohort study	Patients who satisfied the 1982 revised ACR classification criteria for SLE	Therapeutic termination of pregnancy	SLE	NA	11 years	High
Moroni et al. [42]	Italy	Prospective cohort study	All patients met more than 4 criteria for SLE per ACR and had clinical manifestations of lupus nephritis	NR	SLE Subgroups: § aPL	NA	173 months	Medium
Ramirez et al. [43]	Italy	Prospective cohort study	All patients with SLE met the revised ACR or the 2012 SLICC classification criteria	NR	SLE	NA	1.8 years	Medium
Reddy and Chand (2014)[44]	India	Prospective cohort study	Patients who fulfilled the ACR criteria	NR	Subgroups: § With APS § Without APS	NA	< 1 year to 4 years	Low

Table 1 continued

Author (year)	Country	Study design	Inclusion criteria	Exclusion criteria	Population (s)	Reference group	Follow-up	Overall quality appraisal
Regéczy et al. [45]	Hungary	Retrospective cohort study	Patients with SLE and with or without FV Leiden mutation	NR	Subgroups: § Heterozygous FV § Normal FV § Heterozygous FV, aPL+ § Heterozygous FV, aPL− § Normal FV, aPL+ § Normal FV, aPL−	NA	11 years	High
Romero-Díaz et al. [46]	Mexico	Retrospective cohort study	All the patients with a diagnosis of SLE of recent onset, defined as less than 1 year since diagnosis	Patients with an episode of thrombosis of any kind prior to the study and those who were receiving anticoagulants for any reason	SLE	Other disease	6.1 years	High
Sciascia et al. [47]	UK	Prospective cohort study	(1) the presence of aPL (medium or high titers of aCL, defined as > 20 IgG phospholipid units and/or > 20 IgM phospholipid units and/or LAC positive) on at least 2 occasions, with an interval of 6 weeks, during the year previous to the inclusion into the study; (2) patients with SLE meeting 4 or more ACR criteria for the classification of SLE; and (3) being aged between 18 and 65 years	Positivity for aPL but without SLE, previous thrombotic events, uncontrolled hypertension, active gastric, or duodenal ulcer, severe thrombocytopenia (platelets < 50,000 mm^3), hepatic failure, severe illness (e.g., cancer), allergy to aspirin, allergy to warfarin, or being currently pregnant	SLE	NA	32.94 months	Medium

Table 1 continued

Author (year)	Country	Study design	Inclusion criteria	Exclusion criteria	Population (s)	Reference group	Follow-up	Overall quality appraisal
Singh et al. [48]	India	Prospective cohort study	Patients who fulfilled the ACR criteria	NR	AR of DVT and stroke by APS for those with SLE	NR	4 years	Unclear
Somers et al. [49]	USA	Prospective cohort study	All patients met the ACR classification criteria for SLE	NR	SLE	NA	< 5 years	High
Taraborelli et al. [50]	Italy	Retrospective cohort study	All the patients with a diagnosis of SLE, classified according to the 1997 ACR criteria and SLICC, who had been followed for at least 5 years and with complete aPL profiles available at the beginning of the follow-up (within ± 1 year of registry entry)	NR	All Subgroups: § Significant aPL § No significant aPL	NA	14 years	High
Tarr et al. [51]	Hungary	Prospective cohort study	All patients met 4 or more of the revised ACR classification criteria for SLE	NR	Subgroups: § aCL-IgG § aCL-IgM § aCL-IgG + IgM	NA	5 years	Low

Table 1 continued

Author (year)	Country	Study design	Inclusion criteria	Exclusion criteria	Population (s)	Reference group	Follow-up	Overall quality appraisal
Tektonidou et al. [52]	Greece	Retrospective cohort study	Patients with SLE and biopsy-proven renal involvement who were followed up on a regular basis at the Department of Pathophysiology and for whom at least 2 measurements of aPL were performed before or at the time of kidney biopsy	Patients with the appearance of thrombotic microangiopathy lesions	Subgroups: § Without APSN § With APSN	NA	7.07 years	Medium
Tektonidou et al. [53]	Greece	Retrospective cohort study	All patients with SLE fulfilled at least 4 of the ACR criteria for the classification of SLE	Previous thrombosis or pregnancy morbidity	Subgroups: § aPL + § aPL-	NA	108 months	High
To et al. [54]	USA	Prospective cohort study	Patients fulfilled the 1982 ACR revised classification criteria for SLE	Autoantibody profiles were incomplete at the time of the study	Subgroups: § Sm/RNP § DNA/Ro/La § DNA/LAC/aCL	NA	9.2 years	High
Wang and Liu [55]	China	Retrospective cohort study	Patients with SLE and APS	Pregnant women	Subgroups: § SLE + APS	NA	39.3 months	Medium
Watanabe et al. [56]	Japan	Retrospective cohort study	All patients with SLE diagnosed according to the 1997 ACR revised criteria for SLE	Patients with a history of thrombosis and those who had received any antithrombotic agent prior to or at the time of SLE diagnosis	Subgroups: § aPL+ § aPL−	NA	65 months	High

Table 1 continued

Author (year)	Country	Study design	Inclusion criteria	Exclusion criteria	Population (s)	Reference group	Follow-up	Overall quality appraisal
Yusuf et al. [57]	USA	Retrospective cohort study	All adults 18–64 years of age who were enrolled in the health insurance plans included in the MarketScan Commercial Claims databases during any time in 2007 and remained continuously enrolled for any length of time (with the cutoff for assessing continuity occurring on 31 December 2010) and who also had diagnoses of 1 or more of the 4 autoimmune diseases of interest (AIHA, ITP, RA, or SLE) during 2007	NR	All Subpopulations: § All, 18–40, 41–64 at 90 days § All, 18–40, 41–64 at 180 days § All, 18–40, 41–64 at 1 year § All, 18–40, 41–64 at 2 years § All, 18–40, 41–64 at 3 years § All, 18–40, 41–64 at 4 years Subgroups: § 18–40 years § 41–64 years	No autoimmune disease	2.6 years	High

Table 1 continued

Author (year)	Country	Study design	Inclusion criteria	Exclusion criteria	Population (s)	Reference group	Follow-up	Overall quality appraisal
Zöller et al. [58]	Sweden	Retrospective cohort study	Patients with a primary or secondary diagnosis of autoimmune disorders	Previous admission for VTE	All Subpopulations: § < 1 year of follow-up § 1–5 years of follow-up § 5–10 years of follow-up § ≥ 10 years of follow-up	No autoimmune disease	NR	High

Identification of Studies Relevant for Inclusion in Meta-analysis and Endpoint Availability can be found in the Supplementary Material (Table S3). *aCL* anticardiolipin, *ACR* American College of Rheumatology, *AIHA* autoimmune hemolytic anemia, *aPL* antiphospholipid antibodies, *APS* antiphospholipid syndrome, *APSN* antiphospholipid syndrome nephropathy, *AR* absolute risk, *b2GP1Ab* beta-2 glycoprotein 1 antibodies, *CCI* Charlson Comorbidity Index, *CLE* cutaneous lupus erythematosus, *CMA* chlormadinone acetate, *CPA* cyproterone acetate, *DVT* deep vein thrombosis, *FV* factor V, *HCQ* hydroxychloroquine, *HTN* hypertension, *ICD* International Classification of Diseases, *ICD-9* International Classification of Diseases, Ninth Revision, *ICD-9-CM* International Classification of Diseases, Ninth Revision, Clinical Modification, *IgG* immunoglobulin G, *IgM* immunoglobulin M, *ITP* immune thrombocytopenic purpura, *La* anti-La antibodies, *LAC* lupus anticoagulant, *MA* meta-analysis, *NA* not applicable, *NR* not reported, *PAD* peripheral artery disease, *PE* pulmonary embolism, *RA* rheumatoid arthritis, *RNP* anti-RNP antibodies, *Ro* anti-RO antibodies, *SLE* systemic lupus erythematosus, *SLICC* Systemic Lupus International Collaboration Clinics, *Sm* anti-SM antibodies, *VTE* venous thromboembolism

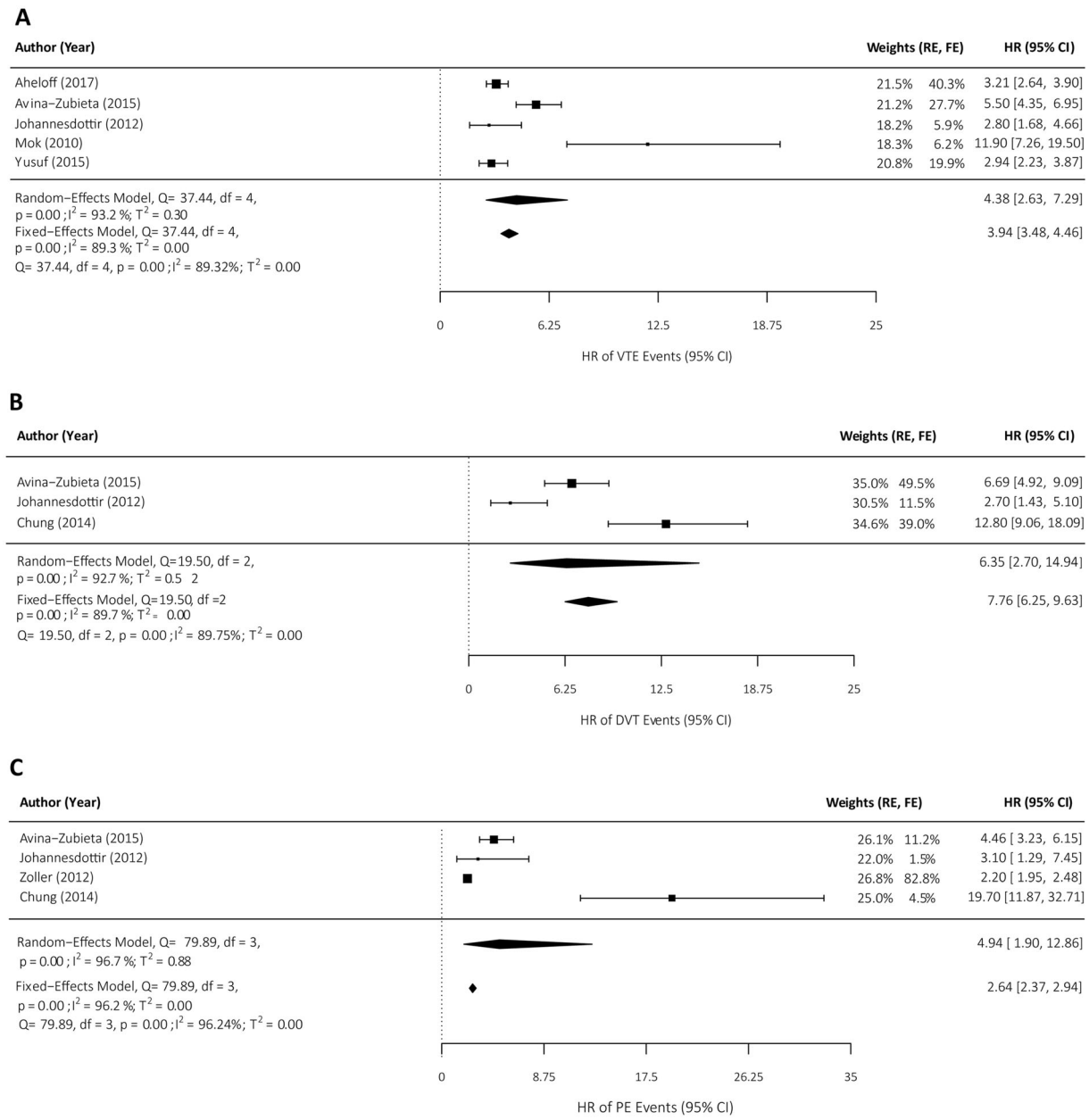


Fig. 2 Forest plots of primary analysis of RR of **a** VTE, **b** DVT, and **c** PE events in patients with SLE. Chung et al. [28] adjusted the HR for age, sex, and comorbidities. Johannesdottir et al. [32] reported both adjusted and unadjusted IRRs; adjusted IRR was chosen for this analysis owing to possible errors in the reporting and/or calculation of the unadjusted IRR. IRR adjusted for classic risk factors, comorbidities, and medication use. *CI* confidence intervals, *df* degrees of freedom, *FE* fixed effects, *HR* hazard ratio, *IRR* incidence rate ratio, *n* number of studies included in the analysis, *PE* pulmonary embolism, *RE* random effects, *RR* relative risk, *SLE* systemic lupus erythematosus, *VTE* venous thromboembolism

(I^2 = 96.24%, p = 0.00). Following the leave-one-out sensitivity analysis, estimates ranged from 3.06 to 6.65. The study by Chung et al. [28] had a notably higher estimate than other studies.

Absolute Risk of VTE, DVT, and PE Events in Patients with SLE

Twenty studies were included in the primary analysis of the AR of VTE in patients with SLE (Fig. 3a). The pooled estimate of the AR of VTE events (measured as cumulative incidence proportion) was 0.06 (*n*/*N*; 95% CI 0.05–0.08). Substantial heterogeneity was observed across the studies (I^2 = 95.6%, $p < 0.01$). A sensitivity analysis considering the 14 high-quality studies was comparable to the primary analysis [0.05 (*n*/*N*); 95% CI 0.04–0.07]. Sensitivity analyses looking for high-quality studies and VTE definition were conducted with heterogeneity remaining high (Fig. S1). A scatter plot of the AR of VTE, DVT, and PE was generated to inform possible heterogeneity in AR arising from between-study differences in length of follow-up. No obvious visual trend of increasing AR of VTE were observed in the studies with increasing follow-up.

When limiting the analysis to AR of DVT in patients with SLE, 21 studies were identified (Fig. 3b). The pooled AR estimate was 0.05 (*n*/*N*; 95% CI 0.03–0.07), ranging from 0.01 to 0.30 (*n*/*N*) across the studies. Substantial heterogeneity was observed (I^2 = 96.5%, $p < 0.01$). A sensitivity analysis considering the 14 high-quality studies found a pooled estimate of 0.04 (*n*/*N*; 95% CI 0.02–0.07), a comparable estimate as observed in the primary analysis, yet substantial heterogeneity remained (I^2 = 96%, $p < 0.01$) (Fig. S2). Two studies [35, 45] were clear outliers reporting a higher proportion of events than seen in the other studies identified. Visual inspection of a scatter plot of AR of DVT against the length of follow-up suggested a slight upward trend with an increasing AR of DVT events with increasing follow-up.

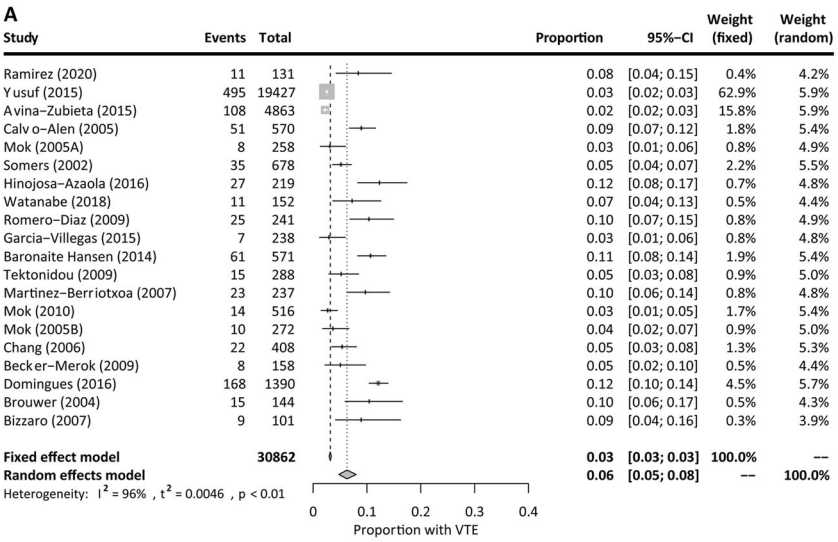
When limiting the analysis to AR of PE events in patients with SLE, 17 studies were identified (Fig. 3c). Absolute risk of PE events in patients with SLE differed across the included studies, ranging from 0.00 to 0.06 (*n*/*N*) with a pooled estimate of 0.02 (*n*/*N*; 95% CI 0.01–0.03). Substantial heterogeneity was observed in the AR estimates across the studies (I^2 = 94.1%, $p < 0.01$). A sensitivity analysis including the 13 high-quality studies did not differ from the primary analysis (AR 0.02; *n*/*N*; 95% CI 0.01–0.03), and substantial heterogeneity remained (I^2 = 95.2%, $p < 0.01$) (Fig. S3). A scatter plot of the AR of PE against the length of follow-up within the studies did not indicate an obvious trend of increasing AR with increasing follow-up time.

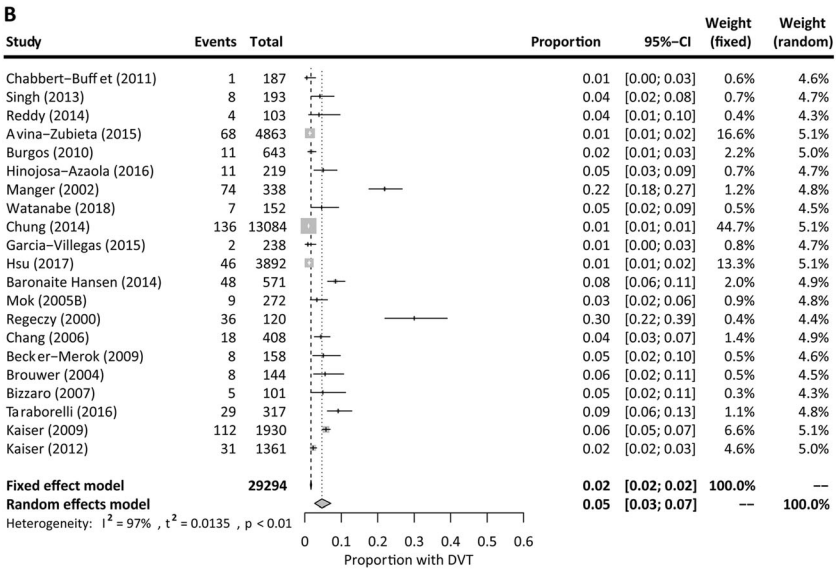
Incidence Rate of VTE, DVT, and PE Events in Patients with SLE

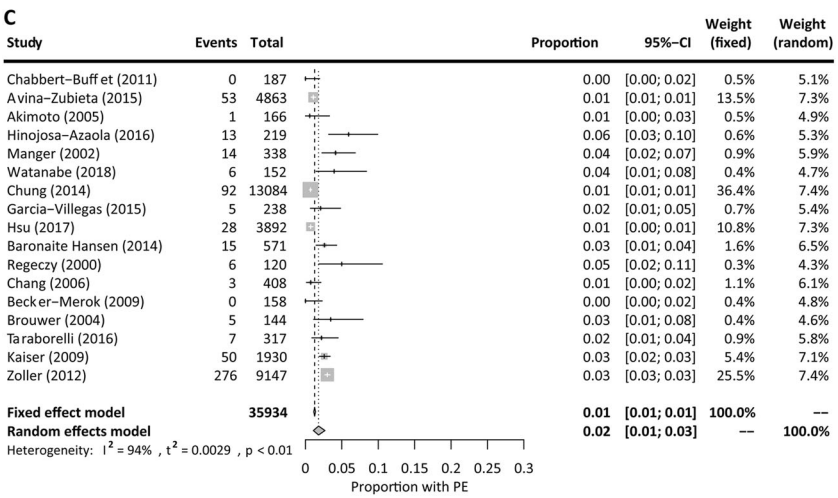
Twelve studies were included in the primary analysis of the IR of VTE events in patients with SLE (Fig. 4a). IR of VTE events differed across the included studies, ranging from 4.2 to 24 per 1000 PY. The pooled IR (RE) of VTE events in patients with SLE was 8.04 per 1000 PY (95% CI 5.48–11.08). Substantial heterogeneity was observed across the studies (I^2 = 91.9%, $p < 0.01$). A sensitivity analysis considering a subset of high-quality studies, VTE definition and studies where patients had been followed up from disease onset found a similar pooled IR of VTE events as observed in the primary analysis (8.34 per 1000 PY; 95% CI 5.23–12.15 for only the ten high-quality studies), and substantial heterogeneity remained (I^2 = 92.9%, $p < 0.01$) (Fig. S4).

When limiting the analysis to IR of DVT events in patients with SLE, seven studies were identified (Fig. 4b). IR of DVT events differed across the included studies, ranging from 1.39 to 9.66 per 1000 PY with a pooled IR (RE) of 3.11 per 1000 PY (95% CI 1.73–4.86). Substantial heterogeneity was observed (I^2 = 88.4%, $p < 0.01$). A sensitivity analysis considering high-quality studies and studies where patients had been followed up from disease onset found a comparable pooled IR (RE) as to the primary analysis (3.28 per 1000 PY; 95% CI 1.46–5.79), and substantial heterogeneity remained (I^2 = 90.9%, $p < 0.01$) (Fig. S5).

When limiting the analysis to PE events in patients with SLE, seven studies were identified (Fig. 4c). Incidence rate of PE events in patients with SLE differed across the included studies, ranging from 0 to 11.41 per 1000 PY with a pooled IR (RE) of 1.40 per 1000 PY (95% CI 0.15–3.60). Substantial heterogeneity was observed (I^2 = 89.0%, $p < 0.01$). A sensitivity analysis considering high-quality studies and studies where patients had been followed up


A
Study Events Total Proportion 95%–CI Weight (fixed) Weight (random)
Ramirez (2020) 11 131 0.08 [0.04; 0.15] 0.4% 4.2%
Yusuf (2015) 495 19427 0.03 [0.02; 0.03] 62.9% 5.9%
Avina−Zubieta (2015) 108 4863 0.02 [0.02; 0.03] 15.8% 5.9%
Calvo−Alen (2005) 51 570 0.09 [0.07; 0.12] 1.8% 5.4%
Mok (2005A) 8 258 0.03 [0.01; 0.06] 0.8% 4.9%
Somers (2002) 35 678 0.05 [0.04; 0.07] 2.2% 5.5%
Hinojosa−Azaola (2016) 27 219 0.12 [0.08; 0.17] 0.7% 4.8%
Watanabe (2018) 11 152 0.07 [0.04; 0.13] 0.5% 4.4%
Romero−Diaz (2009) 25 241 0.10 [0.07; 0.15] 0.8% 4.9%
Garcia−Villegas (2015) 7 238 0.03 [0.01; 0.06] 0.8% 4.8%
Baronaite Hansen (2014) 61 571 0.11 [0.08; 0.14] 1.9% 5.4%
Tektonidou (2009) 15 288 0.05 [0.03; 0.08] 0.9% 5.0%
Martinez−Berriotxoa (2007) 23 237 0.10 [0.06; 0.14] 0.8% 4.8%
Mok (2010) 14 516 0.03 [0.01; 0.05] 1.7% 5.4%
Mok (2005B) 10 272 0.04 [0.02; 0.07] 0.9% 5.0%
Chang (2006) 22 408 0.05 [0.03; 0.08] 1.3% 5.3%
Becker−Merok (2009) 8 158 0.05 [0.02; 0.10] 0.5% 4.4%
Domingues (2016) 168 1390 0.12 [0.10; 0.14] 4.5% 5.7%
Brouwer (2004) 15 144 0.10 [0.06; 0.17] 0.5% 4.3%
Bizzaro (2007) 9 101 0.09 [0.04; 0.16] 0.3% 3.9%
Fixed effect model 30862 0.03 [0.03; 0.03] 100.0% −−
Random effects model 0.06 [0.05; 0.08] −− 100.0%
Heterogeneity: I^2 = 96% , t^2 = 0.0046 , p < 0.01
0 0.1 0.2 0.3 0.4
Proportion with VTE


B
Study Events Total Proportion 95%–CI Weight (fixed) Weight (random)
Chabbert−Buffet (2011) 1 187 0.01 [0.00; 0.03] 0.6% 4.6%
Singh (2013) 8 193 0.04 [0.02; 0.08] 0.7% 4.7%
Reddy (2014) 4 103 0.04 [0.01; 0.10] 0.4% 4.3%
Avina−Zubieta (2015) 68 4863 0.01 [0.01; 0.02] 16.6% 5.1%
Burgos (2010) 11 643 0.02 [0.01; 0.03] 2.2% 5.0%
Hinojosa−Azaola (2016) 11 219 0.05 [0.03; 0.09] 0.7% 4.7%
Manger (2002) 74 338 0.22 [0.18; 0.27] 1.2% 4.8%
Watanabe (2018) 7 152 0.05 [0.02; 0.09] 0.5% 4.5%
Chung (2014) 136 13084 0.01 [0.01; 0.01] 44.7% 5.1%
Garcia−Villegas (2015) 2 238 0.01 [0.00; 0.03] 0.8% 4.7%
Hsu (2017) 46 3892 0.01 [0.01; 0.02] 13.3% 5.1%
Baronaite Hansen (2014) 48 571 0.08 [0.06; 0.11] 2.0% 4.9%
Mok (2005B) 9 272 0.03 [0.02; 0.06] 0.9% 4.8%
Regeczy (2000) 36 120 0.30 [0.22; 0.39] 0.4% 4.4%
Chang (2006) 18 408 0.04 [0.03; 0.07] 1.4% 4.9%
Becker−Merok (2009) 8 158 0.05 [0.02; 0.10] 0.5% 4.6%
Brouwer (2004) 8 144 0.06 [0.02; 0.11] 0.5% 4.5%
Bizzaro (2007) 5 101 0.05 [0.02; 0.11] 0.3% 4.3%
Taraborelli (2016) 29 317 0.09 [0.06; 0.13] 1.1% 4.8%
Kaiser (2009) 112 1930 0.06 [0.05; 0.07] 6.6% 5.1%
Kaiser (2012) 31 1361 0.02 [0.02; 0.03] 4.6% 5.0%
Fixed effect model 29294 0.02 [0.02; 0.02] 100.0% −−
Random effects model 0.05 [0.03; 0.07] −− 100.0%
Heterogeneity: I^2 = 97% , t^2 = 0.0135 , p < 0.01
0 0.1 0.2 0.3 0.4 0.5 0.6
Proportion with DVT


C
Study Events Total Proportion 95%–CI Weight (fixed) Weight (random)
Chabbert−Buffet (2011) 0 187 0.00 [0.00; 0.02] 0.5% 5.1%
Avina−Zubieta (2015) 53 4863 0.01 [0.01; 0.01] 13.5% 7.3%
Akimoto (2005) 1 166 0.01 [0.00; 0.03] 0.5% 4.9%
Hinojosa−Azaola (2016) 13 219 0.06 [0.03; 0.10] 0.6% 5.3%
Manger (2002) 14 338 0.04 [0.02; 0.07] 0.9% 5.9%
Watanabe (2018) 6 152 0.04 [0.01; 0.08] 0.4% 4.7%
Chung (2014) 92 13084 0.01 [0.01; 0.01] 36.4% 7.4%
Garcia−Villegas (2015) 5 238 0.02 [0.01; 0.05] 0.7% 5.4%
Hsu (2017) 28 3892 0.01 [0.00; 0.01] 10.8% 7.3%
Baronaite Hansen (2014) 15 571 0.03 [0.01; 0.04] 1.6% 6.5%
Regeczy (2000) 6 120 0.05 [0.02; 0.11] 0.3% 4.3%
Chang (2006) 3 408 0.01 [0.00; 0.02] 1.1% 6.1%
Becker−Merok (2009) 0 158 0.00 [0.00; 0.02] 0.4% 4.8%
Brouwer (2004) 5 144 0.03 [0.01; 0.08] 0.4% 4.6%
Taraborelli (2016) 7 317 0.02 [0.01; 0.04] 0.9% 5.8%
Kaiser (2009) 50 1930 0.03 [0.02; 0.03] 5.4% 7.1%
Zoller (2012) 276 9147 0.03 [0.03; 0.03] 25.5% 7.4%
Fixed effect model 35934 0.01 [0.01; 0.01] 100.0% −−
Random effects model 0.02 [0.01; 0.03] −− 100.0%
Heterogeneity: I^2 = 94% , t^2 = 0.0029 , p < 0.01
0 0.05 0.1 0.15 0.2 0.25 0.3
Proportion with PE

◀**Fig. 3** Forest plot of primary analysis of AR of **a** VTE, **b** DVT, and **c** PE events in patients with SLE. Both Somers et al. [49] and Domingues et al. [29] used patient data from the Hopkins Lupus Cohort; an assessment of the dates considered by each study indicates that there is no overlap between them. Mok et al. [38] included patients from centers in Hong Kong and a cohort of patients from the Hopkins Lupus Cohort study. Only Chinese patients from Mok et al. [38] have been included, with results for the African American or white patients not included in the data of the meta-analysis by Mok et al. [38]. This is to minimize the possibility of including results from patients within Mok et al. [38] who are already included within the patients included for Domingues et al. [29], which also used data from the Hopkins Lupus Cohort. *AR* absolute risk, *CI* confidence intervals, *DVT* deep vein thrombosis, *n* number of studies included in the analysis, *PE* pulmonary embolism, *SLE* systemic lupus erythematosus, *VTE* venous thromboembolism

from disease onset found a comparable pooled IR as the primary analysis (1.97 per 1000 PY; 95% CI 0.14–5.59), and substantial heterogeneity remained (I^2 = 92.5%, $p < 0.01$) (Fig. S6).

SUBGROUP ANALYSES

Absolute Risk of VTE, DVT, and PE in Patients with SLE by aPL Status or APS Presence

Subgroup analyses were conducted focusing on patients with SLE by aPL status and APS presence. The pooled AR of VTE events in patients with SLE (measured as cumulative incidence proportion) and aPLs was 0.13 (*n*/*N*; 95% CI 0.07–0.21), and in patients with SLE and no aPLs was 0.07 (*n*/*N*; 95% CI 0.04–0.10) (Fig. 5a). The pooled AR (RE) of VTE events in patients with SLE and APS was 0.63 (*n*/*N*; 95% CI 0.00–1.00) (Fig. 5b). Considerable heterogeneity was observed for patients with SLE and aPLs (I^2 = 90.8%, $p < 0.01$), and for patients with SLE and APS (I^2 = 98.5%, $p < 0.01$).

Subgroup analyses of the AR of DVT events (Supplementary Material Table S5) and the AR of PE events (Supplementary Material Table S6) in patients with SLE by APS presence or aPLs were conducted. The pooled estimate of the AR of DVT events in patients with SLE and aPL was 0.11 (*n*/*N*; 95% CI 0.03–0.22), and in patients with SLE and no aPL was 0.08 (*n*/*N*; 95% CI 0.00–0.25). Substantial heterogeneity was observed for both groups (I^2 = 92.6%, $p < 0.01$ and I^2 = 91.0%, $p < 0.01$, respectively). The pooled estimate of AR of DVT events in patients with SLE and APS (measured as cumulative incidence proportion) was 0.26 (*n*/*N*; 95% CI 0.15–0.39), and in patients with SLE and no APS was 0.01 (*n*/*N*; 95% CI 0.00–0.05). Similarly, considerable heterogeneity was observed for both groups (I^2 = 79.3%, $p < 0.01$ and I^2 = 74.8%, p = 0.02, respectively). The pooled AR of PE events in patients with SLE and aPL was 0.05 (*n*/*N*; 95% CI 0.03–0.08), and in patients with SLE and no aPL was 0.01 (*n*/*N*; 95% CI 0.00–0.02). No to minimal heterogeneity was observed (I^2 = 0%, p = 0.75 and I^2 = 33%, p = 0.21, respectively). The pooled estimate of the AR of PE events in patients with SLE and APS was 0.22 (*n*/*N*; 95% CI 0.12–0.34), with moderate heterogeneity (I^2 = 66%, p = 0.05).

Descriptive Analyses—Subgroup Evaluation of Age

Owing to the limited number of comparable studies reporting relevant endpoint data by age, only narrative descriptions of the studies were conducted. The study by Mok et al. [39] calculated the SIR of VTE events in patients with SLE, compared with the general population, stratified by age group: < 30 years, ≥ 30 to 40 years, ≥ 40 to 50 years, and ≥ 50 to 60 years. The highest RR of VTE events was observed in those aged < 30 years (SIR 65.8; 95% CI 29.3–147.9) with the lowest risk observed in the ≥ 50 to 60 years (SIR 4.3; 95% CI 0.6–31.2). The RR in the remaining age groups declined with age. The study by Yusuf et al. [57] found a similar trend in the adjusted HR of VTE in patients with SLE, compared with the general population with higher risk observed in patients aged 18–40 years (adjusted HR 7.18; 95% CI 3.64–14.14) versus patients aged 41–64 years

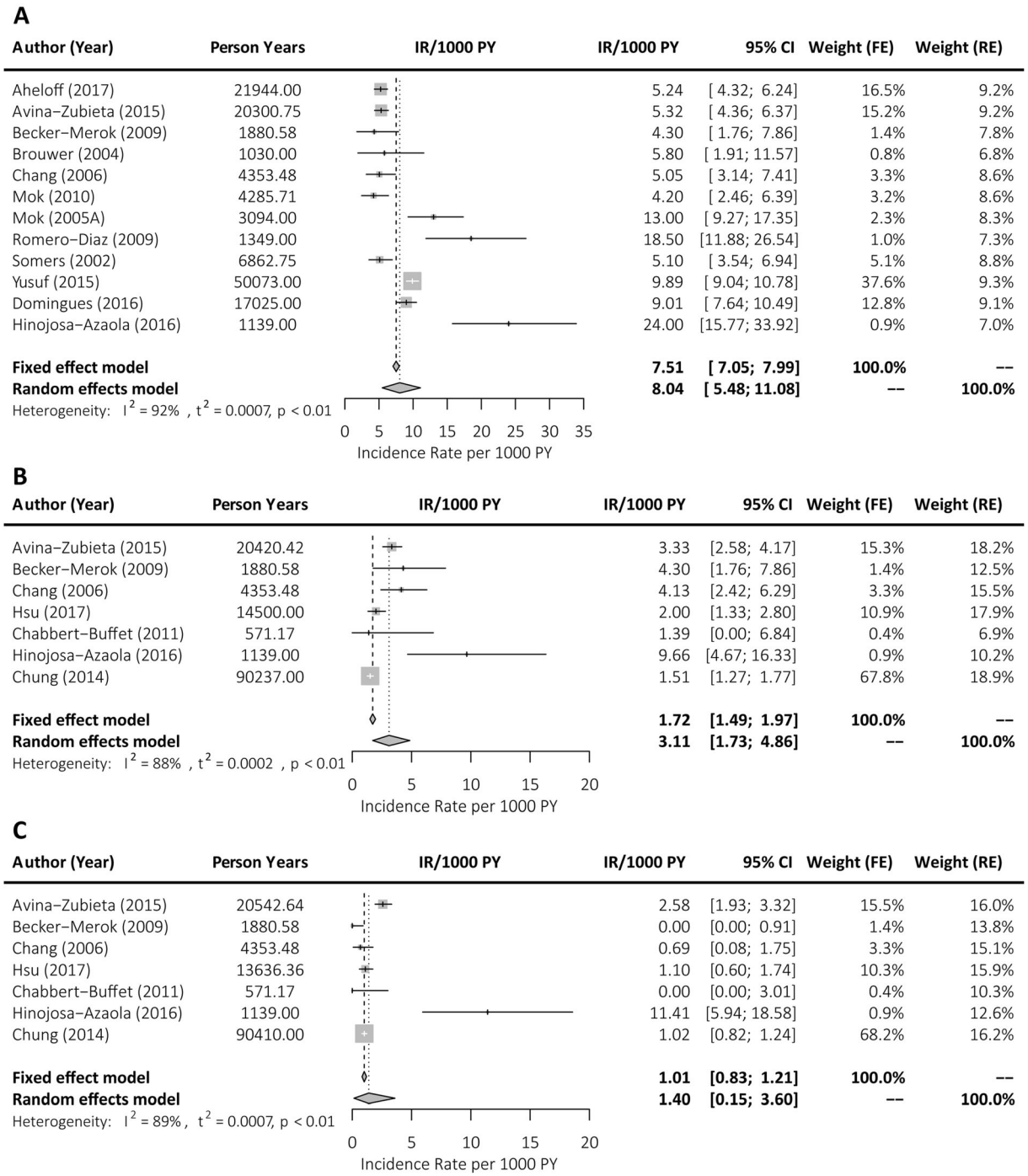


Fig. 4 Forest plot of primary analysis of IR of **a** VTE, **b** DVT, and **c** PE events in patients with SLE. *CI* confidence intervals, *DVT* deep vein thrombosis, *FE* fixed effects, *IR* incidence rate, *n* number of studies included in the analysis, *PE* pulmonary embolism, *PY* person-years, *RE* random effects, *SLE* systemic lupus erythematosus, *VTE* venous thromboembolism

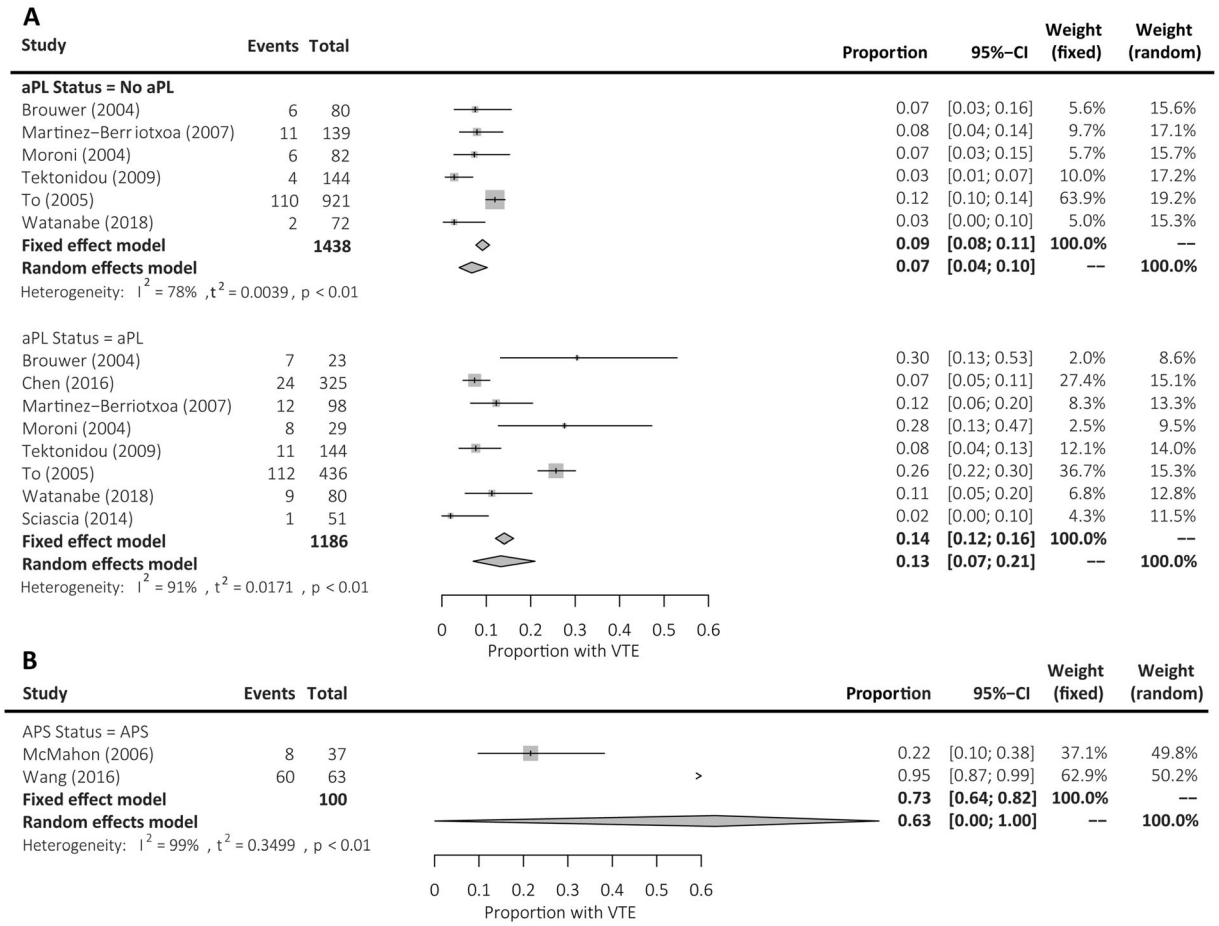


Fig. 5 Forest plot of subgroup analysis of AR of VTE events in patients with SLE by **a** aPL status and **b** APS status. *aPL* antiphospholipid antibodies, *APS* antiphospholipid syndrome, *AR* absolute risk, *CI* confidence interval, *n* number of studies included in the analysis, *SLE* systemic lupus erythematosus, *VTE* venous thromboembolism

(adjusted HR 2.58; 95% CI 1.88–3.54). The study by Chung et al. [28] also observed a similar trend for PE in patients ≤ 35 years (adjusted HR 52.8; 95% CI 23.0–121.3) and in patients ≥ 65 years (adjusted HR 2.97; 95% CI 1.23–7.20), and the RR of PE events was highest in patients ≤ 35 years (adjusted HR 71.5; 95% CI 22.3–228.9) and lowest in patients ≥ 65 years (adjusted HR 3.81; 95% CI 1.15–12.7). The risk of VTE events after 4 years of follow-up was found to be greater for patients aged 18–40 years than for patients aged 41–64 years.

DISCUSSION

VTEs are well-recognized complications in patients with SLE; in this MA, patients with SLE had a statistically significantly increased risk of VTE (RR 4.38). This is in line with previously published analyses [59, 60], one of which found that the risk of VTE was over three- to sixfold higher in patients with SLE compared with the general population [59]. Descriptive analyses suggest that the RR of VTE in younger patients with SLE is greater relative to younger patients in the general population, supporting findings of the studies by Mok et al. [39] and Yusuf et al.

[57] for VTE, and Chung et al. [28] for DVT and PE. Additionally, this MA found a considerably higher incidence of VTE events in the SLE population (AR 0.06; *n*/*N* and IR = 8.04/1000 PY) than observed in the general population [5, 59, 60], and in patients with other autoimmune diseases [46]. Furthermore, a higher AR of VTE was estimated in patients with SLE with aPLs (*n*/*N* = 0.13) and APS (*n*/*N* = 0.63) versus patients with SLE without aPLs/APS (*n*/*N* = 0.07). The AR and IR of VTE events were also found to be higher in younger (< 40 years) patients with SLE (*n*/*N* = 0.03 and 11.28/1000 PY, respectively) versus those aged 41–64 years (*n*/*N* = 0.02 and 9.29/1000 PY, respectively) [57]. Similarly, the risk of DVT (RR 6.35) and PE (RR 4.94) in patients with SLE was found to be statistically significantly greater than in the general population. The pooled estimated AR and IR of DVT (AR 0.05, IR 3.11/1000 PY) and PE (AR 0.02, IR 1.4/1000 PY) in patients with SLE is considerably higher than the IR of DVT and PE events in the general population (0.57 [5] and 0.67 [5]/1000 PY, respectively). Overall, the findings of this analysis suggest that patients with SLE have a higher incidence of VTE, DVT, and PE compared with other groups.

The differences between the results across the studies are likely due to a complex mix of different factors, such as definitions of VTE, study design, patient inclusion criteria, medical practice for screening of VTE, and additional factors such as duration or severity of SLE disease. Our study is strengthened by a rigorous methodological approach based on international guidelines for conduct and reporting of systematic reviews and MAs. Findings aligned with expectations and with results reported in previous publications; however, evidence gaps were identified in a range of outcomes of interest relating to both VTE events and the association between VTE and cardiovascular risk factors. Furthermore, data for subgroups of interest were very limited and, when available, inconsistently defined. It would be beneficial for these gaps in the literature to be addressed with future research.

Limitations

Substantial heterogeneity was observed for most of the endpoints. A potential limitation of the included studies is that several were conducted in the same countries with some studies using the same cohort of patients. This heterogeneity is not explained by the methodological quality of the included studies as substantial heterogeneity was still present in sensitivity analyses in which only high-quality studies were considered. Nonetheless, the studies included in this MA consisted of a mix of cohort and database studies from medical records or registries. These databases differ in terms of data completeness, accuracy, and coverage of the population, hence being a potential source of variation across studies. Additional sources of heterogeneity may also be due to differences in the patients included in the studies; in relation to the pooled estimates of the RR of VTE events in patients with SLE, some studies [5, 16, 57] included incident cases of SLE, whereas another study [39] included a mix of incident and prevalent cases. Differences were also seen in the mean age of patient groups, disease duration, percentage of patients with baseline comorbidities, treatment regimens, and aPL positivity. Similar variation was observed across the studies reporting the RR of DVT and PE events in patients with SLE, compared with the general population or a suitable proxy. In relation to pooled AR estimates for VTE and PE, the length of follow-up does not appear to be responsible for this heterogeneity; however, similar to the RR analyses, additional sources of heterogeneity may have resulted from between-study differences of AR and IR of VTE, DVT, and PE events. Definitions of VTE were also considered as a source of heterogeneity; definitions varied in their comprehensiveness, with some studies defining VTE events as comprising DVT of the limbs and PE only, and other studies expanding their definitions to include other anatomical sites or organs. However, sensitivity analysis by definition did not lead to a reduction in heterogeneity.

CONCLUSION

Despite substantial heterogeneity across studies, there is evidence of an increased risk of VTE, DVT, and PE in patients with SLE compared with the general population. Moreover, subgroup analyses suggest that the AR of VTE, DVT, and PE events is higher in patients with APS or with aPL. Despite differences across the studies and the observed heterogeneity in the pooled estimates, the sensitivity analysis found comparable results to the primary analysis, adding confidence to the estimates of risk. Elevated risks of VTEs and the associated risk factors among patients with immune-mediated disorders should be carefully considered when optimizing treatment to appropriately balance risks and benefits of the chosen therapy. Future research is needed to inform on the impact of traditional and SLE-specific risk factors for VTE to further identify patients with SLE at highest risk, allowing for improved prevention and treatment strategies. Additionally, a harmonization of subgroup definitions and other variables (e.g., age groups, steroid dosing categories) is needed to allow for better cross-trial comparisons and to assist future MA-type analyses.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. This study is an SLR and MA and no novel data were generated. All data relevant to the study are either included in the article or uploaded as supplementary material.

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