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TITLE

Identification of outcomes in clinical studies of interventions for venous thromboembolism in non-pregnant adults: A scoping review

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SHORT TITLE

Outcomes in VTE treatment studies

ESSENTIALS

- We aimed to generate a list of unique outcomes reported in venous thromboembolism (VTE) studies
- We performed a scoping review of prospective studies reporting on interventions for VTE
- A total of 205 unique outcomes were identified that were grouped into 48 outcome domains
- Few VTE studies reported outcomes that align with aspects of life impact or resource use

ABSTRACT

Introduction: The development of a core outcome set (COS), defined as an agreed minimum set of outcome domains that should be measured and reported in all trials of a specific disease, aims to increase the relevance of study findings to stakeholder groups and improve standardization.

Objectives: As the first step in developing a COS for venous thromboembolism (VTE) treatment studies, we aimed to generate an inclusive list of unique outcomes reported in previous VTE treatment studies and classify them into domains and core areas.

Methods: MEDLINE, Embase and CENTRAL were searched for prospective studies reporting on interventions for VTE in non-pregnant adults. Study selection and data extraction were performed in blocks based on publication date, starting with 2015-2020 and subsequent 1-year periods, until no new outcome was identified. Outcomes were classified into domains, which are groups of closely related outcomes, and domains into four core areas including death, pathophysiological manifestations/abnormalities, life impact, and resource use.

Results: Of 7100 records identified, we included 240 publications, representing 165 distinct studies. We identified 205 unique outcomes that were grouped into 48 domains. A total of 30 (13%) studies covered ≥3 core areas; death was included in 102 (43%), pathophysiological manifestations/abnormalities in 218 (91%), life impact in 41 (17%), and resource use in 25 (10%) studies.

Conclusion: Most VTE treatment studies evaluated pathophysiological features of VTE, but few studies reported outcomes that measured life impact or resource use. Our findings will inform next steps in the development of a COS for VTE treatment studies.

KEY WORDS

Core outcome set, Outcome assessment, Scoping review, OMERACT, Venous thromboembolism.

INTRODUCTION

Venous thromboembolism (VTE) is a common condition comprised of deep vein thrombosis (DVT) and/or pulmonary embolism (PE). The clinical manifestation of VTE ranges from mild and asymptomatic to severe and life-threatening. Untreated PE carries a significant, though variable, risk of mortality [1,2], but timely and appropriate treatment with anticoagulation reduces recurrent fatal events to less than 1% [3]. VTE treatment studies commonly report recurrent VTE and major bleeding as primary efficacy and safety outcomes. However, other outcomes characterizing the burden of VTE at both the patient and health systems level such as post-thrombotic syndrome, quality of life, symptom resolution, and psychological effects are rarely measured in VTE studies [4,5]. No study to date has assessed which VTE study outcomes are most important to patients and caregivers.

Although efforts have been made [6-9], valid and standardized definitions and measures of outcomes in VTE treatment studies are often lacking, resulting in discrepancies in how these outcomes are reported and utilized in clinical studies. This inconsistency creates challenges in comparing and synthesizing the results of trials and can compromise the ability to demonstrate clinically meaningful effects [10]. The development of a core outcome set (COS), defined as an agreed minimum set of domains that should be measured and reported in all trials of a specific condition, addresses this lack of standardization. Domains are defined as an aspect of health or a health condition (e.g., major bleeding), and outcomes define how to measure domains (e.g., International Society on Thrombosis and Haemostasis [ISTH] major bleeding). The Core Outcome Measures in Effectiveness Trials (COMET) and Outcome Measures in Rheumatology (OMERACT) initiatives aim to stimulate the development and application

of COS, adopting best practices and robust methodology that are based on evidence [11,12]. The development of a COS begins with a scoping or systematic review of the literature to identify outcome domains that have been used previously. The results of this scoping review, in combination with findings from a concurrent review and synthesis of qualitative work investigating the impact of VTE from patients' perspectives, will provide an initial foundation to base future interviews and priority settings with multiple stakeholders to create a COS for clinical studies of interventions for VTE. We therefore have conducted a scoping review to generate an inclusive list of unique outcomes that have been reported in previous VTE treatment studies, and classified them in terms of domains, which are groups of closely related outcome measures.

METHODS

The protocol for this scoping review was developed following guidance from the COMET and OMERACT handbooks and the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) statement [11-13], registered with the University of Ottawa's digital repository of research (available at http://hdl.handle.net/10393/40459) and published [14]. Deviations from the protocol are described in Appendix Table 1. The VTE-COS project is registered with the COMET database (http://www.comet-initiative.org) and endorsed by the Scientific and Standardization Committee (SSC) on Predictive and Diagnostic Variables in Thrombotic Disease of the ISTH, the Canadian Venous Thromboembolism Research Network (CanVECTOR), and the International Network of VENous Thromboembolism Clinical Research Networks (INVENT). Reporting of this scoping review adheres to the PRISMA extension for Scoping Reviews (PRISMA-ScR) [15].

Eligibility criteria

Eligible papers were either randomized controlled trials (RCTs) or prospective cohort studies that enrolled non-pregnant adults diagnosed with DVT, PE, or both. The studies had to report on one of the following interventions for the treatment of VTE: 1. anticoagulation; 2. aspirin and other nonsteroidal anti-inflammatory drugs; 3. compression stockings; 4. pharmacomechanical catheter-directed thrombolysis; 5. systemic thrombolysis; 6. statins; 7. surgery; 8. venous angioplasty and stenting; or 9. venous filters. Studies evaluating other therapies for VTE were excluded. Studies that enrolled pregnant women (including antepartum, peripartum, and postpartum periods) were excluded since there is already a completed systematic review assessing reported outcome domains in this specific population [16].

Information sources and search strategy

To identify potentially relevant publications, MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were systematically searched without language restrictions using a strategy (Appendix Table 2) developed by an experienced information specialist and reviewed by a second independent information specialist according to the Peer Review of Electronic Search Strategies (PRESS) guideline statement [17]. The search for studies that were published between 2015 and 2020 (see "study selection and data extraction") was performed on March 17, 2020. Grey literature was not searched.

Study selection and data extraction

Screening of titles/abstracts (Level 1 screening) and full texts (Level 2 screening) was performed in Covidence (www.covidence.org), an online software management program for the performance of systematic reviews. All studies were independently reviewed by two team members and disagreement was resolved by discussion or by involving a third reviewer, if needed.

To maximize efficiency of the study selection process, records for Level 1 screening were sorted in reverse chronologic order and screened in blocks based upon date of publication. We first screened records published between 2015 and 2020. Following Level 1 and 2 screening, complete data extraction was performed on eligible studies to establish a list of all outcomes measured within that period. This process was repeated in subsequent one-year intervals (i.e., 2014, 2013, 2012, etc.) until saturation of unique outcomes was reached. Saturation was defined to have occurred when, over a one-year period of the search results, no new outcome measures were identified from the set of included studies. This approach was adapted from the COMET and OMERACT guidance, and results in a robust source of information for the review while offering efficiencies in both study selection and data extraction [11,12]. Because studies assessing different categories of interventions may be variably represented over time, saturation was assessed for each of the 9 above-defined intervention categories. If a certain category was not represented by at least 1 study within one of the assessment periods (i.e., 2015-2020 and subsequent 1-year periods), selection of additional studies was not halted for that category.

Using a standardized data abstraction form (Microsoft Excel), data were extracted in duplicate from the source publications of included studies by two study team

members. This included study characteristics of setting, sample size, design, intervention, VTE location, and publication year. All primary and secondary outcomes, including composite outcomes, were extracted verbatim, along with outcome descriptions, and timing of outcome measurement. Discrepancies for study selection and data extraction were resolved by consensus or by involving a third reviewer if needed.

Outcomes and prioritization

The primary outcome of this scoping review was a list of unique outcomes reported in the included studies. Unique outcomes, defined as those with original meaning and context, were selected as per the proposed methods of Young and colleagues [18]. First, duplicate verbatim outcomes were removed after homogenizing spelling (e.g., bleeding and bleed, rates and rate, etc.). Second, outcomes meaning the same were re-written to develop non-verbatim outcomes and changes documented. Finally, the outcomes remaining after removal of duplicate non-verbatim outcomes defined the list of unique outcomes. Outcomes differing only in timing of the outcome assessment (e.g., 10-day versus 30-day all-cause mortality) were not considered unique.

Critical appraisal of individual sources of evidence

Risk of bias assessment of included studies was not applicable to this scoping review as the purpose of this review was to describe an inclusive set of outcomes. This is consistent with recommendations in the PRISMA-ScR [15,19].

Data synthesis

Similar unique outcomes were grouped into domains based on discussions among the review team members including investigators, clinicians, and patient partners. A domain was defined as a component or concept of "an aspect of health or health condition that needs to be measured to appropriately assess the effects of a health intervention" [12]. Within the identified domains, outcomes were checked for internal homogeneity (i.e., coherence of outcomes within each domain) and external heterogeneity (i.e., distinction to outcomes in other domains) [20]. As per the OMERACT Filter 2.1 conceptual framework, the domains were categorized into four core areas including manifestations/abnormalities, life impact, death/lifespan, and resource use [21]. Definitions for each domain were decided by the team by consensus, taking into consideration any standardized or common definitions found in the published studies.

Descriptive statistics were used to report the number of unique outcomes overall and per study, and the number of domains and core areas covered in each individual study. Subgroup analyses were performed for study design, location of initial VTE and type of intervention.

Patient involvement

Two patient partners from CanVECTOR with lived VTE experience are core members of the VTE-COS project team and sit on the Steering Committee. They contributed to the conception and protocol of this scoping review and reviewed the outcome domains and the final manuscript.

RESULTS

Of the 7,100 records identified from the literature search, we included 240 full-text articles (Figure 1, Appendix Table 3, Appendix Table 4), representing 165 (69%) distinct studies. Of those, 185 articles were published between 2015 and 2020, and 52 articles between 2012 and 2014. The latter set of articles was used to evaluate saturation of unique outcome, which was reached in the year 2012. Since we did not identify any eligible studies evaluating statins or surgery to assess saturation in the years 2012-2014, we performed a search from inception up to 2011 for these two interventions. For this 64-year period, a total of 3 studies evaluating surgery and no study evaluating statins were included.

A total of 139 (58%) studies were RCTs and 101 (42%) prospective cohort studies. Sample size ranged from 8 to 8292 participants (median, 257; interquartile range [IQR], 8-870; Table 1). In 101 (42%) studies, participants with DVT and or PE were eligible; totals of 71 (30%) and 68 (28%) studies restricted inclusion to participants with DVT (±PE) and PE (±DVT), respectively. Most studies were multicontinental or conducted in Europe, North America, or Asia (Table 1). Anticoagulation was the most frequent intervention (Table 1).

Outcomes

After re-writing from verbatim outcomes to homogenized non-verbatim outcomes (Appendix Table 5), a total of 205 unique outcomes (Appendix Table 6) were identified. The number of unique outcomes measured in individual studies ranged from 1 to 19 (median, 4; IQR, 2-6). Primary outcomes were specifically defined in the text of 187 (78%) studies of which 76 (41%) used a composite primary outcome. The median

number of unique outcomes per study was 4 (IQR, 3-7) in RCTs and 4 (IQR, 2-5) in prospective cohort studies. Corresponding median numbers of unique outcomes of 4 (IQR, 2-6), 4 (IQR, 3-6) and 5 (IQR, 2-7) were identified in studies including patients with either PE and or DVT, patients that must have DVT and patients that must have PE, respectively. The median number of unique outcomes per study by type of intervention are displayed in Table 2.

Domains and core areas

The 205 unique clinical outcomes were grouped into 48 outcome domains and categorized within the four pre-specified core areas (Table 3). The most frequently reported domains were limb DVT or PE (61% of studies), major bleeding (53%), and death (43%). The median number of domains covered per study was 3 (IQR, 2-5; range, 1-10) (Table 2). The median number of domains per study was 4 (IQR, 3-5) in RCTs and 3 (IQR, 2-5) in prospective cohort studies, and 3 (IQR, 2-4), 4 (IQR, 3-5) and 4 (IQR, 2-6) in studies including patients with either PE and or DVT, patients that must have DVT and patients that must have PE, respectively. Domains per study by intervention are displayed in Appendix Table 7. Most studies measured outcome domains at multiple time points or over the entire follow-up duration (Appendix Table 8).

A total of 30 (13%) studies covered 3 or more core areas; death was included in 102 (43%), pathophysiological manifestation in 218 (91%), life impact in 41 (17%), and resource use in 25 (10%) studies.

DISCUSSION

In this comprehensive scoping review including 240 publications reporting on 165 distinct studies that evaluated 9 categories of current pharmacological and non-pharmacological treatments for VTE, we identified 205 unique outcomes that were grouped into 48 outcome domains. As anticipated, (recurrent) VTE, major bleeding, and death were the most frequently reported outcomes. Life impacts on individuals with VTE or impacts on society in terms of resource use and costs of VTE treatment were less often studied.

Our scoping review is the initial step in the development of a COS that is intended to be relevant to users of VTE treatment studies. Using OMERACT's conceptual framework, 36 (75%) of the 48 identified domains aligned with pathophysiological manifestations of VTE and treatment response. A total of 218 (91%) studies measured these domains, while only 41 (17%) and 25 (10%) studies measured domains aligning with aspects of VTE on life impact or resource use, respectively. Accordingly, only 30 (13%) studies covered 3 or more OMERACT core areas. To gain insights into patient experiences and outcomes that are important to patients, this review of RCTs and cohort studies was accompanied by a scoping review of qualitative studies, and will be followed by individual interviews with patients and representatives of several stakeholder groups. Combined results from all three studies will provide a comprehensive list of domains that will be considered in a Delphi survey of key stakeholders aiming to prioritize domains prior to defining the final COS in a consensus meeting. Further steps will be to determine which tools and definitions should be used to measure outcome domains, and align with ISTH standardization efforts and the common data element project [6-9].

Our review included studies with 9 different categories of interventions. They can be broadly grouped as pharmacological therapy, a one-time procedure or surgery, an implanted device, or compression stockings. It is not surprising that there is heterogeneity in the types of outcomes measured with these varied interventions (Appendix Table 7). This has important implications for the development of a COS because it may be unrealistic to expect that a single set of domains will be applicable to all studies. Rather, it will be important to establish domains that are relevant in specific circumstances, which could relate to the characteristics of the patient population or the treatment. The OMERACT process involves several steps including selecting and voting on the final COS. These domains are then categorized as mandatory in all trials of a condition and those that are mandatory in specific circumstances. Additional domains may be identified as "important but optional", or as "research agenda domains" when additional evaluation is required before including it. For example, when there is consensus that a domain is important but valid measurement tools do not yet exist.

Our scoping review has potential limitations. First, new treatments and discoveries over time impacted the number of studies per intervention published in each period. For example, we did not identify any studies before 2015 that evaluated statins for VTE treatment and only few studies on surgery for VTE. For other interventions, we halted study selection once outcome saturation was reached. Since the number of studies per intervention other than anticoagulation or pharmacomechanical catheter-directed thrombolysis was low, we may have missed unique outcomes that were reported before 2011 for less frequently evaluated interventions. Similarly, we may have missed unique outcomes for less frequently reported core areas (i.e., life impact or resource use) that were used in studies before 2011, because the number of unique outcomes per core

area was not considered for the assessment of outcome saturation. Second, of the 240 publications, 75 did not represent a distinct study which led to overrepresentation of certain outcomes and domains that were reported in different publications from the same study cohort. However, because the primary aim of the scoping review was to generate an inclusive list of any reported outcome in previous VTE treatment studies, we have decided to include secondary publications since they may report additional outcomes that were not included in the primary study publication. Finally, the searches of VTE were limited to medical subject headings, titles, and keywords because of the large number of VTE studies. However, we do not expect that potentially missed studies would have significantly influenced our results, because saturation of unique outcome was achieved for all interventions except statins and surgery.

In conclusion, we identified 205 unique outcomes that were reported in 240 publications of prospective VTE treatment studies. These outcomes were grouped into 48 domains which were classified into the four core areas according to OMERACT's conceptual framework. Most studies evaluated pathophysiological aspects of VTE and its treatment and about half assessed mortality, but few studies reported domains from the core areas of life impact or resource use. The results of this study will inform next steps in the development of COS for VTE treatment studies, which is relevant to different key stakeholders.

AUTHOR CONTRIBUTIONS

Study concept and design: Tobias Tritschler, Nicole Langlois, Brian Hutton, Beverley J. Shea, Risa Shorr, Sara Ng, Suzanne Dubois, Carol West, Peter Tugwell, and Grégoire Le Gal. Study selection and data extraction: Tobias Tritschler, Ellen Cusano, Marie-Eve Mathieu, Nicole Langlois, and Sara Ng. Data analysis: Tobias Tritschler. Definition of outcome domains: Tobias Tritschler, Ellen Cusano, Nicole Langlois, Beverley J. Shea, Leslie Skeith, Lisa Duffett, Lindsay Cowley, Suzanne Dubois, Carol West, and Grégoire Le Gal. Drafting of the manuscript: Tobias Tritschler, Ellen Cusano, Nicole Langlois and Grégoire Le Gal. Critical revision of the manuscript for important intellectual content: All authors. Final approval of the manuscript: All authors.

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COMPETING INTERESTS

The authors state that they have no competing interests.

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Table 1. Characteristics of included studies by type of intervention.

Characteristic	Overall (N=240), n (%)	Anticoagulation (n=158), n (%)	Aspirin and other nonsteroidal anti-inflammatory drugs (n=3), n (%)	Compression stockings (n=8), n (%)	Pharmaco-mechanical catheter-directed thrombolysis (n=37), n (%)	Statins (n=3), n (%)	Surgery (n=4), n (%)	Systemic thrombolysis (n=16), n (%)	Venous angioplasty and stenting (n=4), n (%)	Venous filters (n=7), n (%)
Number of participants										
1-50	20 (8.3)	6 (3.8)	1 (33)	0	7 (19)	0	2 (50)	2 (12)	2 (50)	0
51-100	41 (17)	19 (12)	0	1 (12)	9 (24)	0	1 (25)	8 (50)	2 (50)	1 (14)
101-500	89 (37)	56 (35)	1 (33)	1 (12)	17 (46)	3 (100)	1 (25)	4 (25)	0	6 (86)
501-1000	41 (17)	30 (19)	1 (33)	6 (75)	4 (11)	0	0	0	0	0
>1000	49 (20)	47 (30)	0	0	0	0	0	2 (12)	0	0
Setting										
Africa	1 (0.4)	0	0	0	0	0	0	1 (6.2)	0	0
Asia	33 (14)	17 (11)	0	0	4 (11)	0	0	7 (44)	4 (100)	1 (14)
Australia/New Zealand	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0
Europe	92 (38)	60 (38)	2 (67)	4 (50)	16 (43)	3 (100)	4 (100)	2 (12)	0	1 (14)
Multicontinental	67 (28)	63 (40)	1 (33)	0	2 (5.4)	0	0	1 (6.2)	0	0
North America	36 (15)	12 (7.6)	0	4 (50)	12 (32)	0	0	3 (19)	0	5 (71)
South America	2 (0.8)	2 (1.3)	0	0	0	0	0	0	0	0
Turkey	8 (3.3)	3 (1.9)	0	0	3 (8.1)	0	0	2 (12)	0	0
Design										
Prospective cohort study	101 (42)	72 (46)	0	0	19 (51)	0	1 (25)	4 (25)	3 (75)	2 (29)
RCT	139 (58)	86 (54)	3 (100)	8 (100)	18 (49)	3 (100)	3 (75)	12 (75)	1 (25)	5 (71)
Location of VTE										
DVT and or PE	101 (42)	93 (59)	2 (67)	0	1 (2.7)	2 (67)	0	0	0	3 (43)
DVT ±PE	71 (30)	28 (18)	0	8 (100)	23 (62)	1 (33)	3 (75)	0	4 (100)	4 (57)

PE ±DVT	68 (28)	37 (23)	1 (33)	0	13 (35)	0	1 (25)	16 (100)	0	0
Follow-up duration										
≤14 days	5 (2.1)	1 (0.6)	0	0	1 (2.7)	0	0	3 (19)	0	0
15-30 days	15 (6.2)	4 (2.5)	1 (33)	0	4 (11)	2 (67)	0	4 (25)	0	0
31-90 days	25 (10)	15 (9.5)	0	0	4 (11)	1 (33)	0	4 (25)	0	1 (14)
91-180 days	39 (16)	34 (22)	0	0	2 (5.4)	0	1 (25)	0	0	2 (29)
181-360 days	59 (25)	55 (35)	0	0	3 (8.1)	0	0	0	1 (25)	0
>360 days	91 (38)	48 (30)	2 (67)	8 (100)	21 (57)	0	3 (75)	3 (19)	3 (75)	3 (43)
Not reported	6 (2.5)	1 (0.6)	0	0	2 (5.4)	0	0	2 (12)	0	1 (14)
Year of publication										
2015-2020	185 (77)	135 (85)	1 (33)	4 (50)	26 (70)	3 (100)	1 (25)	9 (56)	3 (75)	3 (43)
2014	24 (10)	12 (7.6)	0	3 (38)	4 (11)	0	0	5 (31)	0	0
2013	16 (6.7)	9 (5.7)	0	0	4 (11)	0	0	2 (12)	1 (25)	0
2012	12 (5.0)	2 (1.3)	2 (67)	1 (12)	3 (8.1)	0	0	0	0	4 (57)
up to 2011	3 (1.2)	NA	NA	NA	NA	0	3 (75)	NA	NA	NA

Abbreviations: DVT, deep vein thrombosis; NA, not applicable; PE, pulmonary embolism; RCT, randomized controlled trial; VTE, venous thromboembolism.

Table 2. Unique outcomes, outcome domains, and core areas by type of intervention.

Intervention	**Unique outcomes per study,** median (IQR) or single data values	**Outcome domains per study,** median (IQR) or single data values	**≥3 OMERACT core areas covered,** n (%)
Anticoagulation (n=158)	4 (2-5)	3 (2-5)	17 (11)
Aspirin and other nonsteroidal anti-inflammatory drugs (n=3)	2, 8, 11	2, 4, 5	0
Compression stockings (n=8)	3 (2-4)	3 (1-4)	2 (25)
Pharmacomechanical catheter-directed thrombolysis (n=37)	6 (3-7)	5 (3-6)	7 (19)
Statins (n=3)	1, 5, 10	1, 1, 10	1 (33)
Surgery (n=4)	1, 3, 4, 4	1, 3, 4, 4	0
Systemic thrombolysis (n=16)	6 (3-7)	5 (2-6)	2 (13)
Venous angioplasty and stenting (n=4)	1, 3, 6, 10	1, 3, 5, 7	0
Venous filters (n=7)	5 (2-9)	3 (2-5)	1 (14)
Total (N=240)	4 (2-6)	3 (2-5)	30 (13)

Abbreviations: IQR, interquartile range; OMERACT, Outcome Measures in Rheumatology.

Table 3. Outcome domains.

Core area	Outcome domain	Help text	No. studies (N=240), n (%)
Death	Death	Death, regardless of the cause.	102 (43)
Pathophysiological manifestations/ abnormalities	Limb DVT or PE	New or recurrent non-fatal or fatal blood clot in limb vein or lung artery.	146 (61)
	Non-limb DVT	New or recurrent blood clot in non-limb deep vein (unusual site thrombosis).	7 (2.9)
	Superficial vein thrombosis	New or recurrent blood clot in superficial vein.	1 (0.4)
	Miscellaneous (thrombosis)	Miscellaneous outcomes related to manifestation of blood clots.	3 (1.3)
	Major bleeding	Bleeding that is life-threatening or fatal, leads to a substantial blood loss or transfusion, or occurs in a critical organ (e.g., brain, eye, etc.).	128 (53)
	Clinically relevant non-major bleeding	Bleeding that does not meet criteria for major bleeding but requires a medical intervention, in-person evaluation or increase in level of care.	67 (28)
	Minor or nuisance bleeding	Any bleeding that does not meet criteria for more severe bleeding but is unusual for the patient.	47 (20)
	Clinical course of bleeding	Measures and interventions to treat a bleed and the outcome of the bleed	4 (1.7)
	Miscellaneous (bleeding)	Miscellaneous outcomes related to manifestation of bleeding.	6 (2.5)
	Thrombus burden	Quantitative assessment of blood clot burden.	15 (6.3)
	Residual thrombosis	Quantitative assessment of remaining blood clot after treatment/intervention.	44 (18)
	Arterial thrombosis or thromboembolism	New or recurrent blood clot in arteries other than lung arteries, e.g., myocardial infarction, stroke, or limb ischemia.	22 (9.2)
	Post-thrombotic syndrome	Presence of post-thrombotic syndrome which is a chronic disease and can occur following DVT and consists of ≥1 of the following signs or symptoms: limb discomfort, swelling, skin discoloration, or ulcers.	43 (18)
	Chronic venous insufficiency	Presence of chronic venous insufficiency which occurs when veins are not working effectively and leads to pooling of blood in legs or arms and limb discomfort, swelling, skin discoloration, or ulcers.	17 (7.1)
	Chronic thromboembolic pulmonary hypertension	High blood pressure in lung arteries after PE.	5 (2.1)
	Post-PE Impairment	Impairment following PE, assessed by lung tests or symptoms, e.g., shortness of breath, exercise limitation etc.	2 (0.8)
	Heart failure	Clinical, laboratory and imaging signs of heart failure.	1 (0.4)

	Functional exercise capacity	Quantitative assessment of exercise capacity.	1 (0.4)
	Pain intensity	Intensity of pain.	6 (2.5)
	Dyspnea intensity	Severity of shortness of breath.	3 (1.3)
	Swelling	Swelling of leg or arm.	5 (2.1)
	Overall symptom burden	Perception of overall symptoms on a quantitative scale.	2 (0.8)
	Anticoagulation quality	Laboratory measurement of anticoagulation.	9 (3.8)
	Inflammation	Blood tests for markers of inflammation.	1 (0.4)
	Markers of thrombosis	Blood tests for markers of blood clotting.	8 (3.3)
	Renal function	Kidney function.	1 (0.4)
	Liver function	Liver function.	2 (0.8)
	Cardiopulmonary function	Measurement of heart and lung function by laboratory or imaging tests.	24 (10)
	Adverse event	Any negative response to treatment.	27 (11)
	Procedure-related complication	Complications directly related to a procedure to treat VTE.	15 (6.3)
	Hemodynamic deterioration	Development of low/unstable blood pressure which can lead to organ failure.	11 (4.6)
	Additional intervention	Requirement of a new procedure to treat VTE after starting VTE treatment.	4 (1.7)
	Treatment success	Overall assessment of treatment success.	7 (2.9)
	Treatment adherence	Following the prescribed VTE treatment.	8 (3.3)
	Treatment duration	Duration of VTE treatment.	1 (0.4)
	Adherence to treatment guidelines	Following published VTE treatment guidelines.	2 (0.8)
Life impact	Generic quality of life	Overall quality of life.	24 (10)
	Disease-specific quality of life	Quality of life related specifically to VTE effects or treatments.	19 (7.9)
	Ability to return to previous work, activities, or life plans	Ability to return to previous work, activities, or life plans.	1 (0.4)
	Dyspnea impact on daily activities	The impact of shortness of breath on the abilities to perform daily activities and roles other than work.	1 (0.4)
	Fatigue impact on daily activities	The impact of fatigue on the abilities to perform daily activities and roles other than work.	1 (0.4)
	Overall symptom burden impact on daily activities	The impact of any VTE symptoms on the abilities to perform daily activities and roles other than work.	1 (0.4)
	Patient-reported treatment satisfaction	Patient-reported satisfaction with VTE treatment.	8 (3.3)
	Patient-reported treatment preference	Patient-reported preferences related to VTE treatment.	1 (0.4)

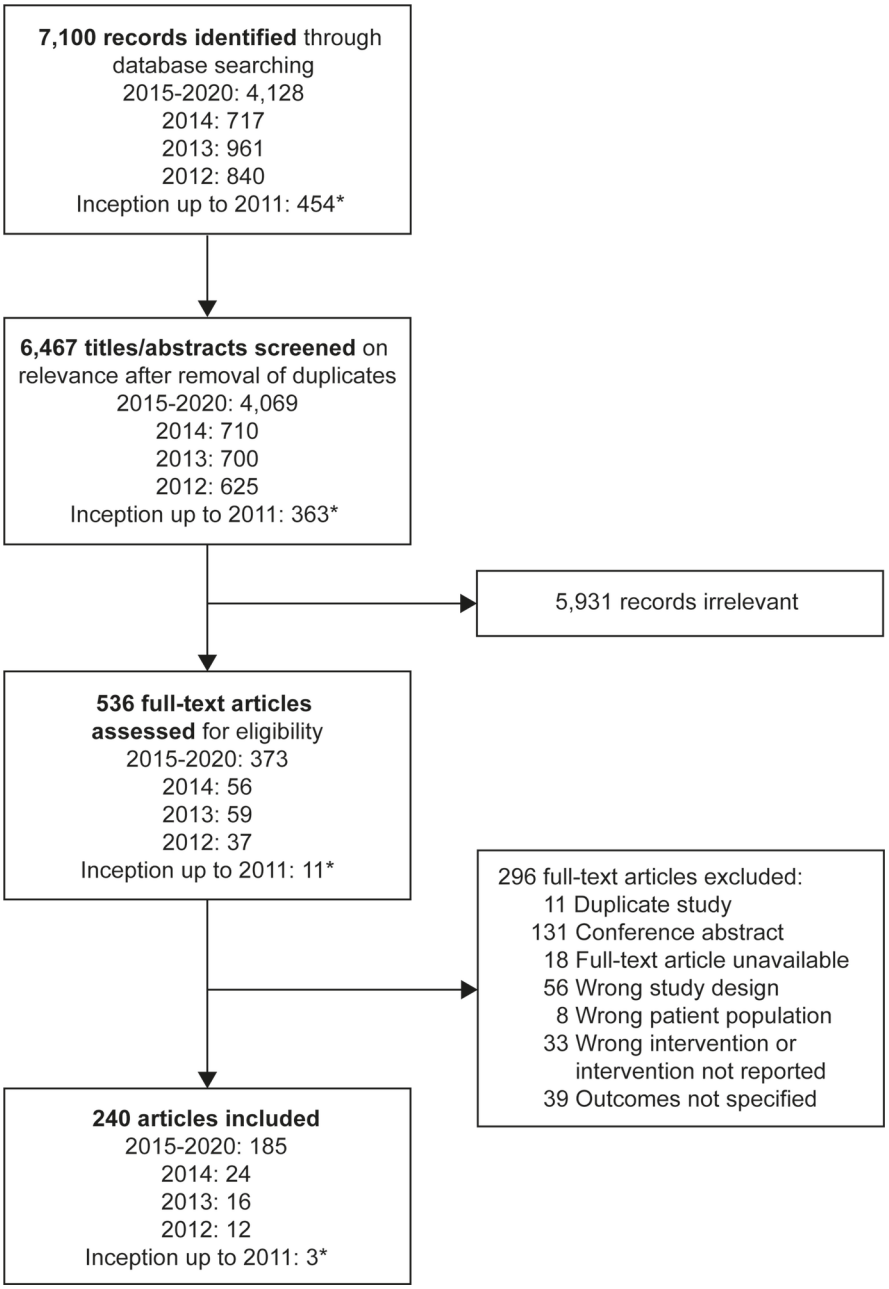
Resource use	Societal resource	Societal resource, e.g., indirect costs caused by inability to work, care provided by relatives, etc.	2 (0.8)
	Costs	Direct medical costs related to VTE care.	5 (2.1)
	Healthcare utilization	Use of the healthcare system, e.g., healthcare visits, hospitalization, or rehabilitation.	21 (8.8)

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

FIGURE LEGEND

Figure 1. Evidence search and study selection.

Legend: *Search for surgery or statins only.
Reasons for exclusion of full-text articles are ordered hierarchically.



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