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Periprocedural Bridging in Patients with Venous Thromboembolism: A Systematic Review

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Abstract

Background—Vitamin K antagonists (VKA) are the most widely used anticoagulants, and bridging is commonly administered during periprocedural VKA interruption. Given the unclear benefits and risks of periprocedural bridging in patients with previous venous thromboembolism, we aimed to assess recurrent venous thromboembolism and bleeding outcomes with and without bridging in this population.

Methods—We performed a systematic review searching the PubMed and EMBASE databases from inception to December 7, 2017 for randomized and non-randomized studies that included adults with previous venous thromboembolism requiring VKA interruption to undergo an elective procedure, and that reported venous thromboembolism or bleeding outcomes. Quality of evidence was graded by consensus.

Results—We included 28 cohort studies (20 being single-arm cohorts) with overall 6915 procedures for analysis. In 27 studies reporting perioperative venous thromboembolism outcomes, the pooled incidence of recurrent venous thromboembolism with bridging was 0.7% (95% confidence interval [CI] 0.4–1.2%) and 0.5% (95% CI 0.3–0.8%) without bridging. Eighteen studies reported major and/or non-major bleeding outcomes. The pooled incidence of any bleeding was 3.9% (95% CI 2.0–7.4%) with bridging and 0.4% (95% CI 0.1–1.7%) without bridging. In bridged patients at high thromboembolic risk, the pooled incidence for venous thromboembolism

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Author Contributions

All authors participated in the research and preparation of the manuscript.
Study concept and design: Baumgartner, Fang.
Data acquisition: Baumgartner, de Kouchkovsky, Whitaker.
Data analysis and interpretation: Baumgartner, de Kouchkovsky, Fang.
Drafting the manuscript: Baumgartner, Fang.
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Statistical analyses: Baumgartner.
Study supervision: Fang.

Disclosures

None.

was 0.8% (95% CI 0.3–2.5) and 7.5% (95% CI 3.1–17.4%) for any bleeding. Quality of available evidence was very low, primarily due to a high risk of bias of included studies.

Conclusions—Periprocedural bridging increases the risk of bleeding compared to VKA interruption without bridging, without a significant difference in periprocedural venous thromboembolism rates.

Keywords

bridging; anticoagulants; periprocedural; venous thromboembolism; bleeding

Introduction

Among >6 million individuals in the US who are on chronic anticoagulation, about 250,000 patients each year need to temporarily interrupt their anticoagulants before an invasive procedure to diminish the risk of excess periprocedural bleeding.[1] Despite the rapid adoption of direct oral anticoagulants (DOACs) in recent years, vitamin K antagonists (VKAs) remain the most frequently prescribed anticoagulants in the US and worldwide.[2, 3] VKAs must be interrupted several days prior to a procedure to allow for regeneration of vitamin K dependent coagulation factors and subsequent normalization of coagulation.[1] Because of the concern of an increased risk of thromboembolism during VKA interruption, periprocedural bridging with short-acting parenteral anticoagulants has been recommended for individuals at high thromboembolic risk.[1, 4]

A previous systematic review investigated periprocedural bridging in patients on VKAs for any indication and found an increased bleeding risk in bridged compared to non-bridged patients without a difference in thromboembolic risk.[5] Similarly, a randomized trial of atrial fibrillation patients showed no difference in thromboembolic outcomes, but a significantly higher incidence of major bleeding with bridging compared with placebo.[6] However, less is known about the risks and benefits of bridging in patients anticoagulated for venous thromboembolism. A recent retrospective study found an increased bleeding risk with bridging, but no substantial risk of recurrent venous thromboembolism without bridging, irrespective of estimated thromboembolic risk,[7] suggesting that current guidelines fail to identify patients with high enough thromboembolic risk to justify bridging.

To better define risks and benefits of bridging in patients with previous venous thromboembolism requiring VKA interruption to undergo an elective invasive procedure, we performed a systematic review comparing recurrent venous thromboembolism and bleeding outcomes with and without periprocedural bridging.

Methods

We conducted this systematic review according to the protocol registered on PROSPERO (registration number CRD42017074710), and reporting conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[8]

Data Sources and Searches

We performed a systematic literature review of articles in PubMed and EMBASE, from inception to December 7, 2017, without language restrictions (Supplemental Methods 1). We also considered conference proceedings, and screened bibliographies of retrieved articles, the most recent American College of Chest Physicians (ACCP) guidelines, and two previous systematic reviews on periprocedural anticoagulation.[1, 5, 9] We searched for unpublished literature in the ClinicalTrials.gov and International Clinical Trials Registry Platform (ICTRP) databases.

Study Selection

We included original articles of randomized trials and observational studies that enrolled adults on long-term VKA therapy for secondary prophylaxis of venous thromboembolism who required anticoagulation interruption to undergo elective invasive procedures. Studies were eligible for inclusion if they assessed venous thromboembolism and/or bleeding outcomes in patients with or without heparin bridging; single-arm studies were also considered. Studies that did not specifically report outcomes for the population of interest or studies including <10 venous thromboembolism patients were excluded. Two physicians (C.B. and I.d.K.) independently screened titles and abstracts for eligibility, and in a second step, full-text articles of references selected in the first screening phase were screened (Figure 1). Disagreement was resolved by discussion. Non-English articles were translated by native speakers.

Data Extraction and Quality Assessment

We extracted pre-specified data on study design, population characteristics, thromboembolic risk, invasive procedures, anticoagulation management strategies, and study sponsors. In the absence of a universally accepted definition,[1] bridging was classified as receipt of prophylactic, intermediate, or therapeutic doses of any heparin in the perioperative period. Data on patients who continued VKA perioperatively were not included, because our research question related to patients who required interruption of anticoagulation. The primary outcome was recurrent venous thromboembolism including deep vein thrombosis and pulmonary embolism (as ascertained by the individual studies) within 30 days postoperatively.[10] Other follow-up periods were used if 30-day outcomes were not reported, as done previously.[11] Secondary outcomes included major bleeding (according to the definition used in the individual studies), and any major and non-major bleeding. Outcome data were extracted by two independent investigators. If outcomes were not specifically reported for the population of interest, we contacted study authors to request the information; 3 authors provided additional data.[12–14]

Two independent reviewers (C.B. and I.d.K) assessed individual study quality using criteria adapted from the ACCP Antithrombotic Therapy and Prevention of Thrombosis, 9th edition;[5, 15] this approach was chosen because it is applicable to single-arm studies. Items to assess quality of observational studies included consecutive enrollment, the existence of a study protocol prior to enrolment, the similarity of the setting and time frame of intervention and control groups, blinded outcome assessment, and loss to follow-up.[5, 15] Nonrandomized studies were considered to be at high risk of bias and were downgraded to moderate risk if

the study accounted for and reported all of the quality elements. On the other hand, they were upgraded to very high risk if they used a single-arm cohort design,[16] or if there were severe or multiple problems with these elements.[16]

Data Synthesis and Analyses

All studies were qualitatively synthesized and comprehensively presented in tables depicting study characteristics and main findings. Meta-analysis to obtain a summary relative risk estimate was not supported because of the observational design of all included studies with reporting of unadjusted results, the high number of single-arm cohorts, and the large clinical heterogeneity across studies. We calculated pooled incidence of venous thromboembolism, major bleeding, and any bleeding in procedures with and without bridging using a logistic-normal random-effects model.[17] One study used propensity score matching and weighting to compare outcomes in patients with and without bridging; this resulted in some non-integer numbers of outcome events in the non-bridging group, which were rounded to the next integer to calculate pooled incidences. In a sensitivity analysis, we rounded in the other direction. We also conducted pre-specified sensitivity analyses excluding conference abstracts or small studies (<100 procedures). Additional (not prespecified) sensitivity analyses were conducted: 1) excluding studies that did not specifically report outcomes for patients with prior venous thromboembolism, but could be included because no study patient experienced an outcome event, and 2) excluding a study[18] that used propensity score matching and weighting to equalize the number of patients in the exposure groups. Predefined subgroup analyses were conducted according to baseline thromboembolic risk and heparin dose used (therapeutic vs. prophylactic). All analyses were performed with Stata 14 (Stata, College Station, TX, USA).

Two investigators (C.B. and M.C. F.) rated the overall quality of evidence for thromboembolic and bleeding outcomes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[19]

Results

Our search yielded 4,349 records after removal of duplicates. We excluded 4,110 records based on title and abstract and then assessed 239 full texts for eligibility, of which 28 studies met our inclusion criteria (Figure 1). Included studies reported results of overall 6,915 procedures, and individual study size varied between 10 and 2670 procedures (Supplemental Table 1).

Of all included studies, 19 were prospective and 9 retrospective cohort studies, and none of them was a randomized trial comparing bridging and VKA interruption without bridging. Study characteristics are shown in Table 1 and Supplemental Table 1. Two records were conference abstracts, and 26 were published full text articles. All but 5 studies enrolled patients with different indications for anticoagulation including atrial fibrillation and mechanical heart valves, and among those we extracted only the specific data on patients with previous venous thromboembolism. Thus, specific information on demographics for this subgroup was mostly missing. Baseline thromboembolic risk was assessed in 21 studies using varying risk classifications schemes. Most studies included patients at any

thromboembolic risk (n=15), while 1 included only low risk and 5 only moderate to high risk patients. The decision to administer bridging anticoagulation was at the discretion of the provider in 11 studies and based on assessment of baseline thromboembolic risk in 6 studies; in 5 studies, all patients requiring VKA interruption received bridging. Procedure types were reported in all but 1 study.

Bridging strategies implemented in the different studies varied substantially (Table 2 and Supplemental Table 2). Most of the studies (n=22) defined bridging as administration of short-acting anticoagulants in both the pre- and postprocedural periods, while 2 studies also considered bridging that was administered in the preprocedural and 4 in the postprocedural periods only.

Overall quality of included studies was low (Supplemental Table 3). Only 8 studies compared outcomes in bridging and non-bridging groups, while the remaining were single-arm studies. All studies reported results that were unadjusted for potential confounding except for Sjögren et al.,[18] where propensity score matching was used.

Risk of Venous Thromboembolism

All but one[20] study reported venous thromboembolism outcomes in overall 6886 procedures. Over a follow-up duration that varied from the time of postprocedural INR normalization to 180 days in the different studies, incidence of perioperative venous thromboembolism ranged from 0% to 4.4% with bridging (pooled incidence 0.7%, 95% confidence interval [CI] 0.4–1.2%) and from 0% to 2% without bridging (pooled incidence 0.5%, 95% CI 0.3–0.8%; Tables 3 and 4).

The pooled incidence of venous thromboembolism in bridging and non-bridging groups remained similar in sensitivity analyses (Table 4). Among patients with high thromboembolic risk, we found a similar pooled incidence of perioperative venous thromboembolism events with bridging (pooled incidence 0.8%, 95% CI 0.3–2.5%). Only 1 study[7] reported venous thromboembolism outcomes in high risk patients without bridging, and found 0 events in 21 procedures (Table 4). Incidence of venous thromboembolism was similar with therapeutic LMWH doses compared to prophylactic doses (pooled incidence 0.9% [95% CI 0.4–2.1%] and 1.4% [95% CI 0.5–4.4%], respectively), but the number of studies included in this subgroup analysis was limited (Table 4).

Risk of Bleeding

Data on major bleeding or any bleeding were available in 15 and 18 studies, respectively (Tables 3 and 4). Incidence of major bleeding as reported in included studies varied between 0% and 5.6% for patients with bridging (pooled incidence 1.8%, 95% CI 1.2–2.5%), while it was generally lower in patients without bridging, ranging from 0% to 1.6% (pooled incidence 0.4%, 95% CI 0.1–1.5%; Tables 3 and 4). Results were similar in sensitivity analyses (Table 4). Therapeutic LMWH doses resulted in a similar pooled incidence of major bleeding compared to prophylactic doses (2.6% [95% CI 1.4–4.7%] and 2.1% [95% CI 0.8–5.5%]), but the number of studies was low.

Incidence of any major and non-major bleeding differed even more considerably between the bridging and non-bridging groups, with a pooled incidence of 3.9% (95% CI 2.0–7.4%) and 0.4% (95% CI 0.1–1.7%), respectively (Table 3 and 4).

Quality of Overall Evidence

The quality of the overall body of evidence for the association of periprocedural bridging with venous thromboembolism, major bleeding and any bleeding was very low (Supplemental Table 4). All included studies had an observational design with a very high risk of bias. Also, we assumed publication bias to be substantial for all outcomes, because some studies that did not separately report outcomes for our specific population of interest could not be included in our systematic review (Figure 1), and a search in clinical trial registries yielded two studies without published results that potentially met inclusion criteria.

Discussion

This systematic review showed that periprocedural bridging in patients with previous venous thromboembolism considerably increases bleeding risk compared to VKA interruption without bridging, without resulting in differences of venous thromboembolic outcomes. Our results suggest that most venous thromboembolism patients will not benefit from bridging. However, the quality of the available evidence on the risks and benefits of periprocedural bridging in this population is low.

Our results show substantial differences in the definition and management of periprocedural bridging across studies. However, no specific bridging strategy or dosing regimen has proven to be superior.[4] To date, no randomized study has shown a clear benefit of periprocedural bridging for patients on long-term anticoagulants, while the bulk of available data suggests an increased bleeding risk with bridging. A recent randomized trial found that foregoing bridging was not associated with an increased risk of arterial thromboembolic events but conferred a significant reduction in major bleeding in patients with atrial fibrillation requiring periprocedural warfarin interruption.[6] Another trial comparing bridging with continued anticoagulation in patients undergoing cardiac device surgery similarly found a 3- to 4-fold higher bleeding risk with bridging.[23] A systematic review that assessed periprocedural bridging in patients with any indication for anticoagulation concluded that overall and major bleeding was increased in patients with bridging compared to those without, while the risk of thromboembolism did not differ.[5] However, the low quality of included studies precluded firm conclusions about risks and benefits of bridging particularly for high risk patients, similar to our study. No previous or ongoing trial investigated bridging in patients with previous venous thromboembolism.

Evaluation of patient- and procedure-related risk factors for thromboembolism and bleeding as well as estimation of clinical consequences of these potential adverse events is needed to determine the optimal perioperative anticoagulation management in patients on chronic VKA therapy.[43] An increasing evidence base suggests that VKAs can be safely continued in a number of procedures with low bleeding risk.[6, 22, 23, 44] More uncertainty exists about periprocedural management strategies in non-minimal bleeding risk procedures, where anticoagulation interruption is needed. While arterial thromboembolic events in patients

with mechanical heart valves or atrial fibrillation are related to a substantial 15–70% risk of disability and death which outweighs mortality risks of major bleeding events 2 to 10-fold,[43, 45, 46] the case-fatality of recurrent venous thromboembolism (5–13%) and major bleeding events (8–10%) are more similar.[43, 47] Therefore, the number of major bleeding events that would theoretically be acceptable to prevent one thromboembolic event is substantially lower for patients with previous venous thromboembolism compared to patients anticoagulated for prevention of arterial thromboembolic events, so the threshold to provide treatments that increase the risk of major bleeding should be higher for venous thromboembolism patients. Our results suggest that bridging exposes these patients to a markedly higher bleeding risk and should therefore not be used if thromboembolic risk is low or moderate. Based on the available evidence, admittedly of low quality, a potential benefit of bridging has not been established even in patients at high thromboembolic risk.

Periprocedural bridging continues to be overused in patients with previous venous thromboembolism, mainly because of overestimation of thromboembolic risk,[7, 48] reflecting the uncertainty about the role of bridging and the assessment of baseline thromboembolic risk. Efforts to standardize anticoagulation management in the periprocedural setting and high quality studies to further clarify the efficacy and safety of bridging in patients at high risk of venous thromboembolism are needed to optimize their care. Although VKAs continue to be the most frequently prescribed oral anticoagulants,[2] the role of bridging, if any, will further diminish with the increased use of DOACs.[4, 49] The shorter half-life of DOACs, which limits the duration of preprocedural anticoagulation interruption, and their rapid time-to-onset obviate the need of periprocedural bridging.[4, 43, 49] Only few observational studies and substudies of randomized trials investigated periprocedural management strategies in patients on DOACs, and did not find a benefit of bridging in this population.[50, 51]

To our knowledge, this is the first study systematically assessing available literature on the risks and benefits of periprocedural bridging in the specific population of patients with previous venous thromboembolism. Another strength of this study includes the rigorous search for available data, without language restriction and with consideration of unpublished articles.

The results of our systematic review need to be interpreted in the context of several limitations. First, overall quality of included studies was low: all included studies were non-randomized and many of them lacked a comparison group. Second, most studies included a heterogeneous population of patients at high and low thromboembolic risk and procedures at varying degrees of bleeding risk, yielding difficult to interpret results that are likely affected by confounding by indication, as patients at high thromboembolic risk might be more likely to receive bridging compared to non-high risk patients. Third, some studies did not specifically report outcomes for patients with previous venous thromboembolism and could thus not be included in our systematic review (Figure 1), potentially resulting in publication bias. Fourth, follow-up duration differed between studies, and although we calculated pooled incidences of perioperative outcome events, these incidences might differ if follow-up duration in included studies were more homogeneous. Finally, the definition of major

bleeding and ascertainment of thromboembolic events was not uniform across studies, which may have limited the reliable estimation of pooled outcome incidences.

In conclusion, our systematic review showed that patients at low and moderate thromboembolic risk do not benefit from periprocedural bridging because of a considerably increased risk of bleeding associated with bridging compared to VKA interruption without bridging, while the risk of periprocedural thromboembolic events was similar with or without bridging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Role of the Sponsor

The sponsor had no role in in the design and conduct of the study, in the collection, management, analysis, or interpretation of the data, or the preparation, review, or approval of the manuscript.

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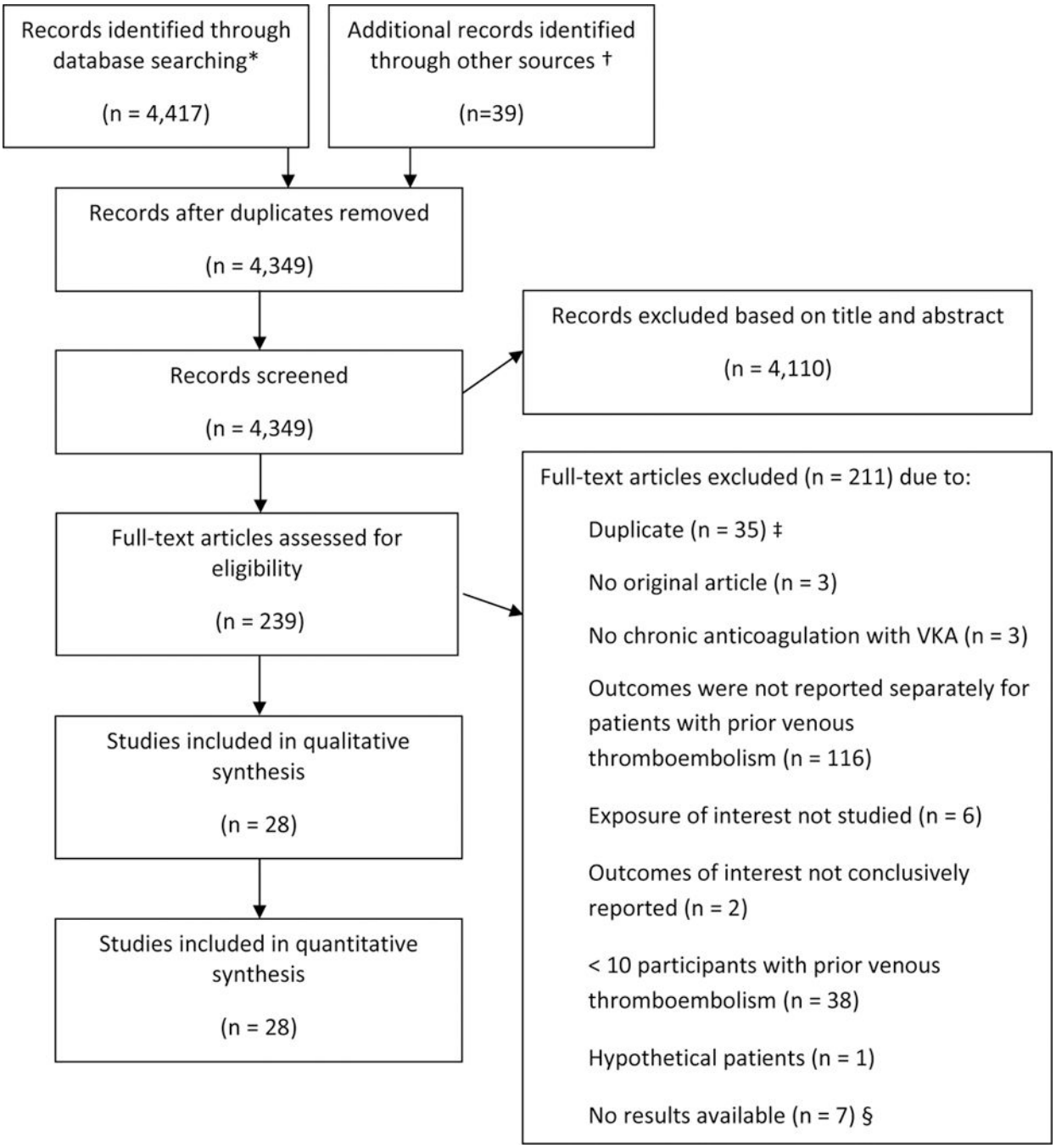

Figure 1.

Study flow diagram. Studies evaluated for inclusion, adapted from PRISMA Statement Flow Diagram.[8] Abbreviations: VKA, vitamin K antagonist.

* Until December 7, 2017

† identified through searching of bibliographies and clinical trial databases

‡ refers to duplicate publication (e.g. conference abstract) or studying the same population as another publication

§ because abstract/publication was not available and results could not be obtained from authors, or study was still ongoing

Table 1.

Characteristics of Included Studies

Characteristic		Studies, n (%)
Design and Setting		
Study design	Randomized controlled trial	0 *
	Cohort, prospective	19 (68)
	Cohort, retrospective	9 (32)
	Single-arm studies	20 (71) †
Year of Publication	Before 2010	12 (43)
	2010 and later	16 (57)
Publication Type	Full text article	26 (93)
	Conference abstract	2 (7)
Study sponsors	Industry	5 (18)
	Non-profit	7 (25)
	Not reported	16 (57)
Geographical region	North America	11 (39)
	South America	1 (4)
	Europe	11 (39)
	Asia	1 (4)
	Australia	2 (7)
	Not reported	2 (7)
Number of study sites	Single center	14 (50)
	Multicenter	10 (36)
	Not reported	4 (14)
Treatment setting	Outpatients only	4 (14)
Population		
% of patients with previous venous thromboembolism	0–19%	10 (36)
	20–99%	13 (46)
	100%	5 (18)
Thromboembolic risk of included patients	Any risk	15 (54)
	Only low risk	1 (4)
	Only moderate to high risk	5 (18)
	No risk stratification performed	7 (25)
Reason for VKA interruption	Antiarrhythmic device surgery	2 (7)
	Dental procedures	1 (4)
	Only minor surgeries or procedures	4 (14)
	Minor and major surgeries/procedures	20 (71)
	Unclear	1 (4)
Indication for bridging	At the discretion of the provider	11 (39)
	Strictly based on thromboembolic risk	6 (21)

Characteristic		Studies, n (%)
	All patients requiring VKA interruption	5 (18)
	Random assignment	2 (7) ‡
	Only inpatients	1 (4)
	unclear	3 (11)

Abbreviations: INR, international normalized ratio; VKA, vitamin K antagonist.

* three studies were designed as randomized controlled trials comparing bridging to continued VKA or comparing two different bridging strategies. We considered these studies as prospective cohorts for our study because none of these trials compared bridging and VKA interruption without bridging.

† among all prospective and retrospective cohort studies

‡ patients were randomly assigned to bridging or continuation of VKA in two studies, but none used random assignment to bridging vs. VKA interruption without bridging

§ Some studies implemented multiple strategies

Table 2.

Periprocedural Anticoagulation Management

Management Strategy*		Studies, n (%)
Periprocedural Bridging	Pre- and postprocedural	22 (79)
	Only preprocedural	2 (7)
	Only postprocedural	4 (14)
	Not specified	4 (14)
Type of bridging anticoagulant	LMWH	28 (100)
	Unfractionated heparin	6 (21)
Dosing of bridging anticoagulant	Therapeutic	18 (64)
	Sub-therapeutic	9 (32)
	Prophylactic	16 (57)
	Not reported	1 (4)
Preprocedural Management		
VKA interruption, days	≥6	7 (25)
	5	19 (68)
	≤4	9 (32)
	not reported	3 (11)
Last dose of LMWH, hours	< 12	1 (4)
	12–23	13 (46)
	≥24	7 (25)
	NA (only postop bridging)	2 (7)
	Not reported	6 (21)
Postprocedural Management		
Restart of LMWH, hours	0–23	16 (57)
	≥24	7 (25)
	Not specifically reported	7 (25)
Restart of VKA, hours	Evening of procedure	10 (36)
	Day after procedure	18 (64)
	2 or more days after procedure	4 (14)
	Not reported	6 (21)
Initial dosing of VKA	Maintenance dose	9 (32)
	Loading dose	3 (11)
	Not reported	16 (57)
Duration of bridging	Prespecified no. of days	2 (7)
	Until INR therapeutic	12 (43)
	Until INR therapeutic on 2 consecutive days	5 (18)
	Not reported	9 (32)

Abbreviations: INR, international normalized ratio; LMWH, low molecular weight heparin; VKA, vitamin K antagonist.

*Some studies implemented multiple strategies

Table 3.

Venous Thromboembolism and Bleeding Outcomes

Study	Follow-up Duration	Bridging			No Bridging		
		Venous thromboembolism/ Procedures, n (%)	Major Bleeding/ Procedures, n (%)	Any Bleeding ‖/ Procedures, n (%)	Venous thromboembolism/ Procedures, n (%)	Major Bleeding/ Procedures, n (%)	Any Bleeding ‖/ Procedures, n (%)
Ahmed, 2010[21]	8 weeks	0/12 (0)	NA	1/12 (8.3)	0/5 (0)	NA	0/5 (0)
Bajkin, 2009[22] *	30d	0/19 (0)	NA	not clear	-	-	-
Birnie, 2013[23] *	not clear	0/16 (0)	NA	not clear	-	-	-
Breen, 2016[24]	30d	0/29 (0)	not clear	6/29 (20.7)	-	-	-
Burbury, 2011[25] *	6 weeks	-	-	-	0/39 (0)	not clear	not clear
Clark, 2015[7]	30d	0/555 (0)	12/555 (2.2)	15/555 (2.7)	3/1257 (0.2)	2/1257 (0.2)	2/1257 (0.2)
Constans, 2007[42] *	90d	0/10 (0)	not clear	not clear	-	-	-
Douketis, 2005[20]	until INR 2–3	NA	0/21 (0)	0/21 (0)	-	-	-
Dunn, 2007[26]	28d	1/96 (1.0)	not clear	not clear	-	-	-
Eisele, 2012[27] *	not clear	0/69 (0)	NA	not clear	-	-	-
Fernandez, 2009[28] *	30d	0/24 (0)	not clear	not clear	0/14 (0)	0/14 (0)	0/14 (0)
Garcia, 2008[29]	30d	0/22 (0)	not clear	not clear	2/179 (1.1)	0/179 (0)	0/179 (0)
Hammerstingl, 2009[30] *	not clear	0/10 (0)	0/10 (0)	0/10 (0)	-	-	-
Hwang, 2017[31] *	30d	0/34 (0)	not clear	not clear	-	-	-
Jaffer, 2005[32]	30d	0/18 (0)	1/18 (5.6)	1/18 (5.6)	-	-	-
Klamroth, 2010[12]	28d	0/63 (0)	0/63 (0) †	0/63 (0) †	-	-	-
Majluf-Cruz, 2011[33]	not clear	2/152 (1.3)	4/152 (2.6)	26/152 (17.1)	-	-	-
Malato, 2010[34]	30d	2/45 (4.4)	1/45 (2.2)	1/45 (2.2)	-	-	-
McBane, 2010[13]	90d	4/342 (1.2) †	9/342 (2.6) †	24/342 (7.0) †	3/152 (2.0) †	1/152 (0.7) †	3/152 (2.0) †
Pengo, 2009[14]	30d	2/210 (1.0)	1/210 (0.5) †	9/210 (4.3) †	-	-	-
Saccullo, 2012[35]	30d	2/52 (3.8)	not clear	not clear	-	-	-
Santamaria, 2013[36] *	90d	0/10 (0)	not clear	not clear	-	-	-
Sjögren, 2017[18]	30d	10/1331 (0.8)	NA	10/1331 (0.8)	5.5/1331 (0.4) ‡	NA	2.1/1331 (0.2) ‡

Study	Follow-up Duration	Bridging			No Bridging		
		Venous thromboembolism/ Procedures, n (%)	Major Bleeding/ Procedures, n (%)	Any Bleeding ‖/ Procedures, n (%)	Venous thromboembolism/ Procedures, n (%)	Major Bleeding/ Procedures, n (%)	Any Bleeding ‖/ Procedures, n (%)
Skeith, 2012[37]	90d	2/152 (1.3)	2/152 (1.3)	6/152 (3.9)	2/482 (0.4)	8/482 (1.6)	16/482 (3.3)
Spyropoulos, 2004[38]	60d	0/45 (0)	0/45 (0)	2/45 (4.4)	-	-	-
Spyropoulos, 2006[39]*	30d	0/22 (0) §	not clear	not clear	-	-	-
Wilson, 2001[40]	90d	0/26 (0)	0/26 (0)	0/26 (0)	-	-	-
Wiszniewsky, 2011[41]	180d	0/63 (0)	0/63 (0)	13/63 (20.6)	-	-	-

Abbreviations: NR, not available because outcome was not assessed in study.

*these studies did not specifically report venous thromboembolism outcomes by indication for anticoagulation (i.e. patients with previous venous thromboembolism), but were included because the number of outcome events was 0 for all indications

†personal communication by the authors

‡patients not receiving bridging anticoagulation were propensity score matched and weighted to equal the number of patients who received bridging

§the number of venous thromboembolic events in subgroup of patients with a previous venous thromboembolism could only be identified in the 22 patients who received unfractionated heparin

‖includes major bleeding and any other bleeding outcome that was specifically reported for patients with previous venous thromboembolism

Table 4.

Pooled Incidence of Venous Thromboembolism and Bleeding Outcomes

	Any Outcome		Venous Thromboembolism			Major Bleeding			All Bleeding*		
Group	**Studies, n**	**Procedures, n**	**Studies, n**	**Events/ Procedures, n**	**Pooled incidence, % (95% CI)**	**Studies, n**	**Events/ Procedures, n**	**Pooled incidence, % (95% CI)**	**Studies, n**	**Events/ Procedures, n**	**Pooled incidence, % (95% CI)**
Main Analysis											
All studies	28	6915†	27	40.5 / 6886		15	41 / 3786		18	137.1/ 6494	
With bridging	27	3448	26	25 / 3427	0.7 (0.4–1.2)	13	30 / 1702	1.8 (1.2–2.5)	16	114 / 3074	3.9 (2.0–7.4)
Without bridging	8	3459	8	15.5 / 3459	0.5 (0.3–0.8)‡	5	11 / 2084	0.4 (0.1–1.5)	7	23.1 / 3420	0.4 (0.1–1.7)§
Sensitivity analyses											
Excluding studies without specific outcome reporting for population of interest //	18	6648†	17	40.5 / 6619		11	41 / 3557		14	137.1/ 6265	
With bridging	18	3234	17	25 / 3213	0.8 (0.5–1.3)	11	30 / 1666	1.8 (1.3–2.6)	14	114 / 3038	4.4 (2.3–8.2)
Without bridging	6	3406	6	15.5 / 3406	0.5 (0.3–0.8)‡	3	11 / 1891	0.5 (0.1–2.0)	5	23.1 / 3227	0.6 (0.1–2.4)¶
Excluding conference abstracts	26	6725†	25	38.5 / 6696		13	37 / 3620		16	111.1/ 6328	
With bridging	25	3272	24	23 / 3251	0.7 (0.4–1.2)	12	26 / 1550	1.6 (0.8–3.2)	15	88 / 2922	3.4 (1.8–6.6)
Without bridging	7	3445	7	15.5 / 3445	0.5 (0.3–0.8)‡	4	11 / 2070	0.4 (0.1–1.6)	6	23.1 / 3406	0.4 (0.1–1.8) **
Excluding Sjögren, et al. †	27	4245	26	25 / 4224		15	41 / 3832		17	125 / 3878	
With bridging	26	2117	25	15 / 2096	0.6 (0.3–1.3)	13	30 / 1702	1.8 (1.2–2.5)	15	104 / 1743	4.9 (2.7–8.7)
Without bridging	7	2128	7	10 / 2128	0.5 (0.2–1.2)	5	11 / 2084	0.4 (0.1–1.5)	6	21 / 2089	0.6 (0.1–2.8)
Excluding studies with <100 procedures	7	6173†	7	35.5 / 6165		6	39 / 3481		7	113.1/ 6143	
With bridging	7	2764	7	20 / 2764	0.7 (0.4–1.2)	5	28 / 1411	2.0 (1.4–2.9)	6	90 / 2742	4.0 (1.8–8.7)
Without bridging	5	3401	5	15.5 / 3401	0.5 (0.3–0.8)‡	4	11 / 2070	0.4 (0.1–1.6)	5	23.1 / 3401	0.5 (0.1–1.9)
Subgroup analyses											
High thromboembolic risk ††	9	394	9	3 / 394					7	45 / 361	
With bridging	9	373	9	3 / 373	0.8 (0.3–2.5)	NA	NA	NA	7	44 / 340	7.5 (3.1–17.4)

Group	Any Outcome		Venous Thromboembolism			Major Bleeding			All Bleeding*		
	Studies, n	Procedures, n	Studies, n	Events/ Procedures, n	Pooled incidence, % (95% CI)	Studies, n	Events/ Procedures, n	Pooled incidence, % (95% CI)	Studies, n	Events/ Procedures, n	Pooled incidence, % (95% CI)
Without bridging	1	21	1	0 / 21	NA	NA	NA	NA	1	1 / 21	NA
LMWH dose ††											
Therapeutic dose	11	981	10	5 / 580	0.9 (0.4–2.1)	4	10 / 387	2.6 (1.4–4.7)	6	35 / 800	3.9 (2.0–7.5)
Prophylactic dose	6	362	5	3 / 208	1.4 (0.5–4.4)	3	4 / 188	2.1 (0.8–5.5)	4	32 / 342	4.4 (0.9–18.3)

*includes major bleeding and any other bleeding outcomes that were specifically reported for patients with previous venous thromboembolism

†in the study by Sjögren et al,[18] procedures in the non-bridging group were propensity score matched and weighted to equal the number of procedures in the bridging group; therefore, the number of procedures with bridging and without bridging does not add up to the exact number of overall procedures

‡the non-integer number of outcome events (5.5 venous thromboembolic events) in the study by Sjögren et al was rounded to the next integer for this analysis. When rounding down to the next lower integer, the results were similar (pooled incidence 0.4%, 95%CI 0.3–0.7%)

§the non-integer number of outcome events (2.1 events of any bleeding) in the study by Sjögren et al was rounded to the next integer for this analysis. When rounding up to the next higher integer, the results were similar (pooled incidence 0.5%, 95%CI 0.1–1.8%)

‖some studies did not report results separately for patients with prior venous thromboembolism and could only be included because there were no venous thromboembolism [22, 23, 25, 27, 28, 30, 31, 36, 39, 42] or bleeding[28–30, 40] outcomes in the overall population. As this might bias our study sample to studies with a low number of outcome events, we excluded these studies for this subgroup analysis.

¶the non-integer number of outcome events (2.1 events of any bleeding) in the study by Sjögren et al was rounded to the next integer for this analysis. When rounding up to the next higher integer, the results were similar (pooled incidence 0.7%, 95%CI 0.2–2.4%)

**the non-integer number of outcome events (2.1 events of any bleeding) in the study by Sjögren et al was rounded to the next integer for this analysis. When rounding up to the next higher integer, the results were similar (pooled incidence 0.5%, 95%CI 0.1–1.9%)

††for these analyses, we included only studies that reported outcomes separately for the specific subgroup of interest