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Periprocedural Bridging in Patients with Venous Thromboembolism: A Systematic Review

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Periprocedural Bridging in Patients with Venous Thromboembolism: A Systematic Review

Clinical Significance

Word count: 60

- Periprocedural bridging is widely used in patients with previous venous thromboembolism who require interruption of vitamin K antagonists due to an invasive procedure
- This systematic review found that periprocedural bridging in patients with previous venous thromboembolism increases the risk of bleeding without reducing the risk of periprocedural venous thromboembolism
- Most patients with venous thromboembolism do not benefit from periprocedural bridging

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 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.

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 study¹⁸ 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 one²⁰ 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 study⁷ 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.

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Disclosures

None.

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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.

Critical revision of the manuscript for important intellectual content: Baumgartner, de Kouchkovsky, Whitaker, Fang.

Statistical analyses: Baumgartner.

Study supervision: Fang.

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Figure

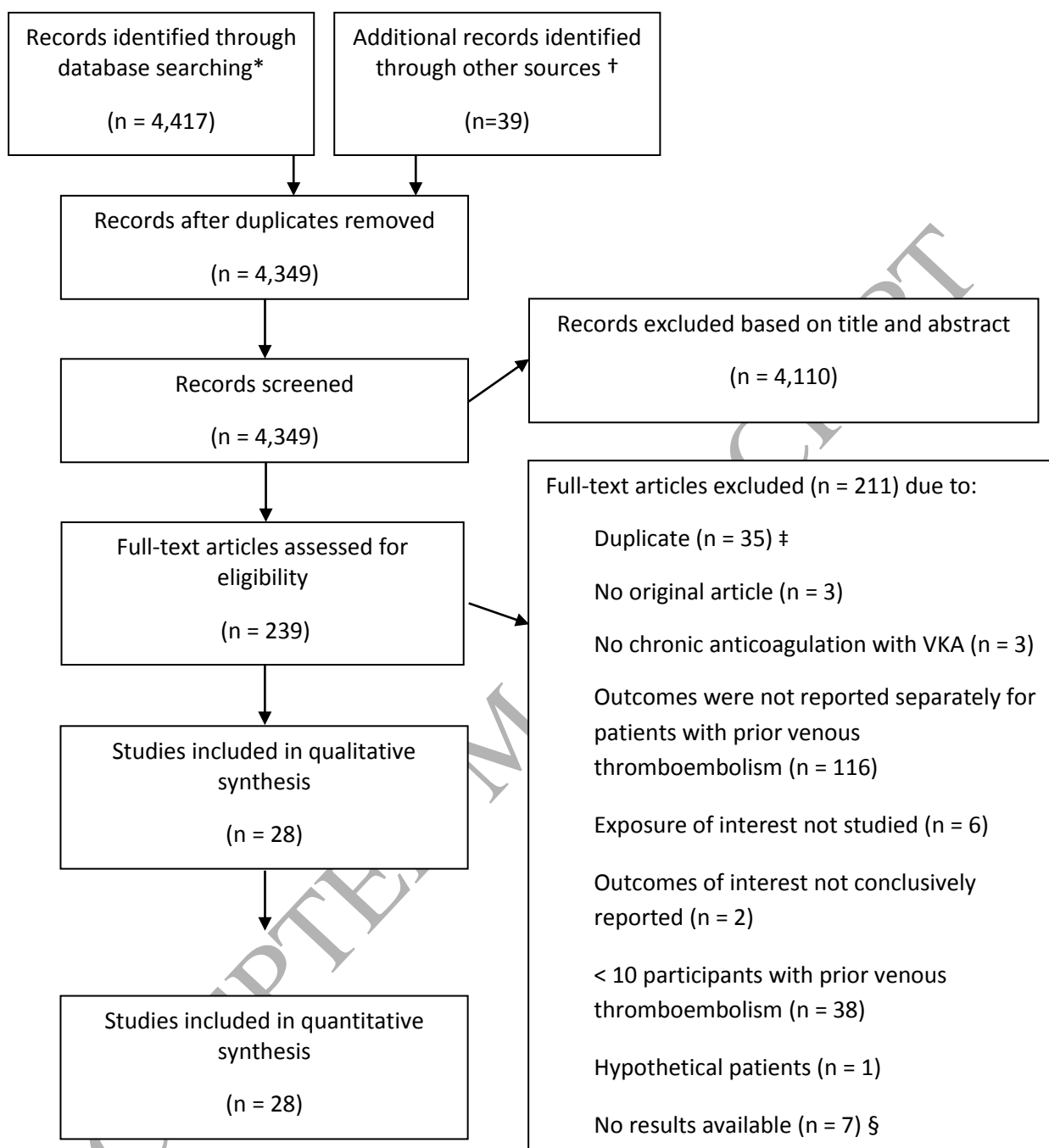


Figure Legend. Study flow diagram. Studies evaluated for inclusion, adapted from PRISMA

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

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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
	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)
	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

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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			Venous thromboembolism/ 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)
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)
Clark, 2015 ⁷	30d	0/555 (0)	12/555 (2.2)	15/555 (2.7)	3/1257 (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)
Garcia, 2008 ²⁹	30d	0/22 (0)	not clear	not clear	2/179 (1.1)
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) †
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) ‡
Skeith, 2012 ³⁷	90d	2/152 (1.3)	2/152 (1.3)	6/152 (3.9)	2/482 (0.4)
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

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Table 4. Pooled Incidence of Venous Thromboembolism and Bleeding Outcomes

Group	Any Outcome		Venous Thromboembolism			Major Bleeding		
	Studies, n	Procedures, n	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	
With bridging	27	3448	26	25 / 3427	0.7 (0.4-1.2)	13	30 / 1702	1.8 (1.2-2.5)
Without bridging	8	3459	8	15.5 / 3459	0.5 (0.3-0.8) [‡]	5	11 / 2084	0.4 (0.1-1.5)
Sensitivity analyses								
Excluding studies without specific outcome reporting for population of interest 								
With bridging	18	6648 [†]	17	40.5 / 6619		11	41 / 3557	
Without bridging	6	3406	6	15.5 / 3406	0.5 (0.3-0.8) [‡]	3	11 / 1891	0.5 (0.1-2.0)
Excluding conference abstracts								
With bridging	26	6725 [†]	25	38.5 / 6696		13	37 / 3620	
Without bridging	7	3445	7	15.5 / 3445	0.5 (0.3-0.8) [‡]	4	11 / 2070	0.4 (0.1-1.6)
Excluding Sjögren, et al. †								
With bridging	27	4245	26	25 / 4224		15	41 / 3832	
Without bridging	7	2128	7	10 / 2128	0.5 (0.2-1.2)	5	11 / 2084	0.4 (0.1-1.5)
Excluding studies with <100 procedures								
With bridging	7	6173 [†]	7	35.5 / 6165		6	39 / 3481	
Without bridging	7	2764	7	20 / 2764	0.7 (0.4-1.2)	5	28 / 1411	2.0 (1.4-2.9)
Without bridging	5	3401	5	15.5 / 3401	0.5 (0.3-0.8) [‡]	4	11 / 2070	0.4 (0.1-1.6)
Subgroup analyses								
High thromboembolic risk ††								
With bridging	9	394	9	3 / 394		NA	NA	NA
Without bridging	9	373	9	3 / 373	0.8 (0.3-2.5)	NA	NA	NA
Without bridging	1	21	1	0 / 21	NA	NA	NA	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)
Prophylactic dose	6	362	5	3 / 208	1.4 (0.5-4.4)	3	4 / 188	2.1 (0.8-5.5)

* 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

Supplemental Material**Periprocedural Bridging in Patients with Venous Thromboembolism: A Systematic Review**

Supplemental Methods 1. Data Sources and Search Strategy

Supplemental Table 1. Characteristics of Included Studies, by Individual Study

Supplemental Table 2. Periprocedural Anticoagulation Management, by Individual Study

Supplemental Table 3. Quality of Individual Studies

Supplemental Table 4. Quality of Evidence: Periprocedural Bridging in Patients with Previous VTE

Supplemental Methods 1. Data Sources and Search Strategy

The PubMed and Embase databases were searched from inception to December 7, 2017, for published articles in any language on the association between periprocedural anticoagulation management (bridging with short acting anticoagulants vs. no bridging) in adults on chronic anticoagulation treatment with vitamin K antagonists (VKA) for secondary prevention of venous thromboembolism who required interruption of VKA for an invasive elective procedure. Following search strategy was implemented in PubMed:

```
((((((((((((((temporary[tw] OR temporarily[tw]) AND (discontinue[tw] OR discontinuous[tw] OR discontinuation[tw])) OR management[tw] OR ((anticoagulation[tw] OR anticoagulant[tw] OR anticoagulants[tw] OR anticoagulate[tw] OR anti-coagulation[tw] OR anti-coagulant[tw] OR anti-coagulants[tw] OR anti-coagulate[tw]) AND (interrupt[tw] OR interrupted[tw] OR interruption[tw] OR bridge[tw] OR bridging[tw] OR wean[tw] OR weaned[tw] OR weaning[tw] OR taper[tw] OR tapers[tw] OR tapered[tw] OR tapering[tw] OR suspend[tw] OR suspended[tw] OR suspending[tw] OR suspension[tw] OR cease[tw] OR ceased[tw] OR ceasing[tw] OR cessation[tw] OR cessations[tw] OR ceasing[tw] OR stop[tw] OR stopping[tw] OR stops[tw] OR stopped[tw]) AND (operative OR operation OR operate OR operatively OR surgery[tw] OR surgeries[tw] OR surgical[tw] OR surgically[tw] OR procedure[tw] OR procedures[tw] OR procedural[tw] OR preoperative[tw] OR pre-operative[tw] OR perioperative[tw] OR peri-operative[tw])) OR Bridging[tw])))])))
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AND

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((("Surgical Procedures, Operative"[Mesh] OR "Operative Surgical Procedure" OR "Operative Surgical Procedures" OR "Operative Procedures" OR "Operative Procedure" OR invasiv* OR procedur* OR "Post-operative Procedure" OR "Postoperative Procedure" OR "Post-operative Procedures" OR "Postoperative Procedures" OR "Pre-operative Procedure" OR "Preoperative Procedure" OR "Pre-operative Procedures" OR "Preoperative Procedures" OR peri-procedural OR periprocedural OR peri-procedure OR periprocedure OR "Preoperative Care"[Mesh] OR "Preoperative Care" OR "Pre-
```

operative Care" OR "Intraoperative Care"[Mesh] OR "Intra-operative Care" OR "Intraoperative Care"
 OR "Postoperative Care"[Mesh] OR "Post-operative Care" OR "Postoperative Care" OR
 "Perioperative Care"[Mesh] OR "Peri-operative Care" OR "Perioperative Care" OR "Peroperative
 Care" OR "Per-operative Care" OR "perioperative period"[Mesh] OR peri-operative OR perioperative
 OR pre-operative OR preoperative OR post-operative OR postoperative))))

AND

((("Venous Thrombosis"[Mesh] OR DVT OR VTE OR "venous thrombosis" OR "venous thromboses"
 OR "deep vein thrombosis" OR "deep vein thromboses" OR "pulmonary embolus" OR "pulmonary
 emboli" OR "pulmonary embolism" OR "thromboembolism" OR "thromboembolic")))

AND

((("Anticoagulants/administration and dosage"[Mesh] OR "Anticoagulants/adverse effects"[Mesh]
 OR "Anticoagulants/therapeutic use"[Mesh] OR "Vitamin K/administration and dosage"[Mesh] OR
 "Vitamin K/adverse effects"[Mesh] OR "Vitamin K/agonists"[Mesh] OR "Vitamin K/antagonists and
 inhibitors"[Mesh] OR "Vitamin K/therapeutic use"[Mesh] OR "Vitamin K/therapy"[Mesh] OR
 "Warfarin/administration and dosage"[Mesh] OR "Warfarin/adverse effects"[Mesh] OR
 "Warfarin/therapeutic use"[Mesh] OR "Coumarins/administration and dosage"[Mesh] OR
 "Coumarins/adverse effects"[Mesh] OR "Coumarins/therapeutic use"[Mesh] OR "Factor Xa
 Inhibitors"[Mesh] OR "Heparin/administration and dosage"[Mesh] OR "Heparin/adverse
 effects"[Mesh] OR "Heparin/analogs and derivatives"[Mesh] OR "Heparin/therapeutic use"[Mesh]
 OR "Factor Xa Inhibitors"[Pharmacological Action] OR warfarin OR acenocoumarol OR
 phenprocoumon OR coumadin OR dicumarol OR phenindione OR "vitamin K antagonist" OR VKA OR
 dabigatran OR edoxaban OR rivaroxaban OR apixaban OR Heparin OR "Low-Molecular-Weight
 Heparin" OR "LMW heparin" OR UFH OR "unfractionated heparin" OR Dalteparin OR Enoxaparin OR
 Nadroparin OR Tinzaparin))) This search strategy was adapted for searching the Embase database.

We also searched for unpublished articles by reviewing guidelines¹ and previous systematic reviews on periprocedural anticoagulation,^{2,3} screening of bibliographies of retrieved articles, and searching in the ClinicalTrials.gov and the International Clinical Trials Registry Platforms (ICTRP) databases.

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Supplemental Table 1. Characteristics of Included Studies, by Individual Study

Study	Study Design	Setting	Study Population and VTE risk; % Previous VTE in Overall Study Population	Indication for Bridging	Planned Invasive Procedure	Intervention / Control	Procedures, n	Study Sponsor
Ahmed, 2010	Cohort, retrospective	1 teaching hospital, Minnesota, USA	VTE risk NR; 8%	At the discretion of the provider	Anti-arrhythmic device surgery	I: LMWH, UFH C: no bridging	I: 12 C: 5	Non-profit
Baijkin, 2009	Cohort, prospective*	1 oral surgery clinic, Serbia	VTE risk NR; 16%	Random assignment	Simple extraction of ≥ 1 tooth	I: LMWH C: continued VKA [†]	I: 19 C: 15 [†]	NR
Birnie, 2013	Cohort, prospective*	17 centers in Canada, 1 in Brazil	moderate to high VTE risk; 5%	Random assignment	Antiarrhythmic device surgery	I: LMWH, UFH C: continued VKA [†]	I: 16 C: 21 [†]	Non-profit
Breen, 2013	Cohort, retrospective	1 tertiary care hospital, Australia	Patients who received LMWH bridging, any VTE risk; 27%	At the discretion of the provider	Various major and minor procedures	I: LMWH C: -	I: 29 C: -	NR
Burbury, 2011	Cohort, prospective	1 hospital, Australia	on warfarin >6 weeks, any VTE risk; 22%	At the discretion of the provider, based on VTE risk	Various major and minor procedures	I: LMWH C: no bridging	I: 0 C: 39	NR
Clark, 2015	Cohort, retrospective	Integrated health care system, Colorado, USA	any VTE risk; 100%	At the discretion of the provider, based on therapy plans	Various major and minor procedures	I: short-acting anticoagulant C: no bridging	I: 555 C: 1257	Non-profit
Constans, 2007	Cohort, prospective	1 tertiary care hospital, Spain	Adults requiring bridging due to endoscopy, any VTE risk; 10%	All study patients; probably all with VKA interruption	Gastroscopy or colonoscopy	I: LMWH C: -	I: 10 C: -	NR
Douketis, 2005	Cohort, prospective	1 hospital, Canada	Patients requiring bridging due to procedure, any VTE risk; 29%	All study patients; reason for bridging decision unclear	Various major and minor procedures	I: LMWH C: -	I: 21 C: -	NR
Dunn, 2007	Cohort, prospective	24 sites in North America	Outpatients for whom bridging was planned, VTE risk NR; 37%	At the discretion of the physician	Various major and minor procedures	I: LMWH C: -	I: 96 C: -	Industry
Eisele, 2012	Cohort, retrospective	Multiple hospitals and physician offices, Germany	Patients who received cetroparin bridging, VTE risk NR; 29%	At the discretion of the physician	Surgeries, endoscopy, angiography	I: LMWH C: -	I: 69 C: -	Industry
Fernandez, 2009	Cohort, prospective	NR	Any VTE risk; 44%	VTE <3 months ago and non-high bleeding risk procedure	High and low bleeding risk procedures	I: LMWH C: no bridging	I: 24 C: 14	NR
Garcia, 2008	Cohort,	101 physician	Outpatients, any VTE risk;	At the discretion of	Outpatient	I: LMWH	I: 15	Industry

Hammerstingl, 2009	prospective Cohort, prospective	practices, USA Unclear, probably 1 hospital, Germany	14% Patients receiving bridging with therapeutic enoxaparin, VTE risk NR; 14%	the physician Not clear	procedures Minor surgery and invasive procedures	C: no bridging I: LMWH C: -	C: 179 I: 10 C: -	NR
Hwang, 2017	Cohort, retrospective	1 tertiary care center, South Korea	Referred to clinic for bridging, VTE risk NR; 70%	At the discretion of the provider	Various major and minor procedures	I: LMWH C: -	I: 34 C: -	Non-profit
Jaffer, 2005	Cohort, retrospective	1 anticoagulation clinic, Ohio, USA	High enough VTE risk to justify bridging; 26%	Sufficiently high VTE risk	Various major and minor procedures	I: LMWH C: -	I: 18 C: -	NR
Klamroth, 2010	Cohort, prospective	Unclear, probably 1 hospital, Germany	Any VTE risk; 32%	All patients without contraindication to LMWH	Major (75%) and minor surgeries	I: LMWH C: -	I: 63 C: -	NR
Majluf-Cruz, 2011	Cohort, prospective	NR	Patients with recurrent VTE, high VTE risk, 100%	All study patients (recurrent VTE)	Various major and minor procedures	I: LMWH C: rivaroxaban †	I: 152 C: 158 †	NR
Malato, 2010	Cohort, prospective	1 tertiary care center, Italy	Outpatients, any VTE risk; 14%	All patients without contraindication to LMWH	Various major and minor procedures	I: LMWH C: -	I: 45 C: -	NR
McBane, 2010	Cohort, prospective	1 tertiary care clinic, USA	Referred for VKA management, any VTE risk; 100%	Moderate to high VTE risk patients	Various major and minor procedures	I: LMWH C: no bridging	I: 342 ‡ C: 152 ‡	Non-profit
Pengo, 2009	Cohort, prospective	22 anticoagulation centers, Italy	Any VTE risk; 17%	All requiring periprocedural VKA interruption	Various high and low bleeding risk procedures	I: LMWH C: -	I: 210 C: -	Non-profit
Sacullo, 2012	Cohort, prospective	1 tertiary care center, Italy	Cancer patients on long-term VKA for whom bridging was planned, any VTE risk; 33%	Indication unclear	Major and minor surgery, chemotherapy induced thrombocytopenia	I: LMWH C: -	I: 52 C: -	NR
Santamaria, 2013	Cohort, prospective*	10 hospitals, Spain	Outpatients, any VTE risk; 6%	All patients requiring VKA interruption for outpatient surgery	Outpatient surgical or invasive procedures	I: LMWH or UFH C: -	I: 10 C: -	Industry
Sjögren, 2017	Cohort, retrospective	Multiple health care centers, Sweden	VTE risk NR; 41%	At the discretion of the provider	Indication for VKA interruption unclear	I: LMWH C: no bridging	I: 1331 C: 1331 §	Non-profit
Skeith, 2012	Cohort, retrospective	1 medical center, Canada	Patients with VTE events >3 months ago; 100%	Patients requiring postinterventional inpatient treatment	Various major and minor procedures	I: LMWH C: no bridging	I: 152 C: 482	NR

Spyropoulos, 2004	Cohort, retrospective	Integrated health care system, USA	Patients receiving bridging, any VTE risk; 36%	At the discretion of the provider	Various major and minor procedures	I: LMWH C: -	I: 45 C: -	NR
Spyropoulos, 2006	Cohort, prospective	14 centers, USA and Canada	On VKA for ≥ 3 months, on perioperative heparin for ≥ 2 d, any VTE risk; 12%	At the discretion of the provider	Various major and minor procedures	I: LMWH or UFH C: -	I: 22 C: -	Industry
Wilson, 2001	Cohort, prospective	1 anticoagulation clinic, Canada	Referred to clinic, high VTE risk; 55%	High VTE risk	Various major and minor procedures	I: LMWH C: -	I: 26 C: -	NR
Wisniewsky, 2011	Cohort, prospective	1 clinic, Poland	Thrombophilia or APS, high to very high VTE risk; 100%	High and very high VTE risk	Various major and minor procedures	I: LMWH C: -	I: 63 C: -	NR

Abbreviations: APS, antiphospholipid antibody syndrome; LMWH, low molecular weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

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

† patients with continued anticoagulation during surgery or received periprocedural bridging with direct oral anticoagulants did not meet the inclusion criteria for our systematic review and were therefore not further considered for our analyses

‡ personal communication by the investigator

§ comparison group was propensity score matched and weighted; actual overall number of patients with previous VTE was 2670 in the bridging and non-bridging group combined.

|| Outcomes for patients with previous VTE were only available for patients in the group of patients who received UFH (rather than LMWH)

Supplemental Table 2. Perioperative Anticoagulation Management, by Individual Study

Study	Peri-procedural Bridging	Type of Bridging Anticoagulant	Preoperative Management			Postoperative Management			
			VKA Interruption, d	Dosing of Bridging Anticoagulant	Last Dose of LMWH, h	Restart of LMWH, h	Restart of VKA	Initial Dosing of VKA	Stop of Bridging
Ahmed, 2010	Pre/post	LMWH, UFH	3-5	therapeutic	12-18	24	Evening of procedure	NR	When INR therapeutic
Baijkin, 2009	Pre/post	LMWH	3-4	Prophylactic or subtherapeutic	≥ 12	Evening of procedure	Evening of procedure	NR	When INR therapeutic
Birnie, 2013	Pre/post	LMWH, UFH	5	therapeutic	>24	24	Evening or morning after procedure	At investigator's discretion	When INR therapeutic
Breen, 2013	Pre/post	LMWH	5	Low or therapeutic	Day prior	At provider's discretion	At provider's discretion	NR	NR
Burbury, 2011	Post only	LMWH	1 *	Prophylactic or therapeutic	NA	12-24	12-24h	maintenance	When INR therapeutic
Clark, 2015	Not specified	LMWH, UFH	NR	Prophylactic or therapeutic	NR	NR	NR	NR	NR
Constans, 2007	Pre/post	LMWH	Aceno-coumarol: 3 Warfarin: 5	prophylactic	≥ 12	<24	1 day after procedure	maintenance	On day 3-4 postoperatively
Douketis, 2005	Pre/post	LMWH	5-6	Prophylactic or therapeutic	≥ 12	24	Evening or day after procedure	NR	NR
Dunn, 2007	Pre/post	LMWH	5	therapeutic	Morning prior	12-24	Evening of procedure or day after	maintenance	When INR therapeutic
Eisele, 2012	Pre/post	LMWH	Mean 6.4	Prophylactic, sub- or therapeutic	Mean 16.2	Mean 12.2	Mean 3.6d	NR	Overall duration mean 7d
Fernandez, 2009	Pre/post, post only	LMWH	4-5	Therapeutic	24	12-48	Evening of procedure or day after	NR	NR
Garcia, 2008	Not specified	Almost exclusively LMWH	>7 (6.3%) ≤ 5 (87.4%)	NR	NR	NR	NR	NR	NR
Hammerstingl, 2009	Pre/post	LMWH	5-6	therapeutic	Evening prior	NR	NR	NR	When INR therapeutic

Study	Peri-procedural Bridging	Type of Bridging Anticoagulant	Preoperative Management			Postoperative Management			
			VKA Interruption, d	Dosing of Bridging Anticoagulant	Last Dose of LMWH, h	Restart of LMWH, h	Restart of VKA	Initial Dosing of VKA	Stop of Bridging
Hwang, 2017	Pre/post	LMWH	5	therapeutic	Morning prior	48-72 after major, 12-24 after minor surgery	With LMWH or day after	loading	When INR therapeutic on 2d
Jaffer, 2005	Pre/post	LMWH	5-6 depending on INR	therapeutic	24	24	Day of procedure or day after	maintenance	When INR therapeutic on 2d
Klamroth, 2010	Pre/post	LMWH	7	Half-therapeutic	≥ 12	8-12	At provider's discretion (mean 5d)	NR	When INR therapeutic
Majluf-Cruz, 2011	Not specified	LMWH, rivaroxaban†	10	prophylactic	NR	NR	NR	NR	NR
Malato, 2010	Pre/post	LMWH	5	Subtherapeutic or prophylactic	Evening prior	12	Day after procedure	maintenance	When INR therapeutic
McBane, 2010	Pre/post, pre only, post only	LMWH	5	therapeutic	24 (only ½ dose)	24-48	Mean 3.9d	maintenance	When INR therapeutic on 2d
Pengo, 2009	Pre/post	LMWH	5	Subtherapeutic or prophylactic	≥ 12	≥ 12	Day after procedure	loading	When INR therapeutic, ≥6d
Sacullo, 2012	Pre/post	LMWH	5	Prophylactic or subtherapeutic	Evening prior	12	Day after procedure	maintenance	When INR therapeutic
Santamaria, 2013	Pre/post	LMWH, UFH	Acenocoumarol: 3 Warfarin: 5	prophylactic	≥ 12	Evening of procedure	Day after procedure	NR	5-6d after procedure
Sjögren, 2017	Not specified	LMWH	NR	Prophylactic, sub- or therapeutic	NR	NR	NR	NR	NR
Skeith, 2012	Post only	LMWH	5	Prophylactic or therapeutic	NA	Morning after procedure	Day of surgery	NR	At discharge or when INR >1.9
Spyropoulos, 2004	Pre/post	LMWH, UFH	≥ 4	Prophylactic or therapeutic	Morning prior, or evening prior at ½ dose if procedure after 10am	Evening of procedure	Evening of procedure	maintenance	When INR therapeutic on 2d

Study	Peri-procedural Bridging	Type of Bridging Anticoagulant	Preoperative Management			Postoperative Management			
			VKA Interruption, d	Dosing of Bridging Anticoagulant	Last Dose of LMWH, h	Restart of LMWH, h	Restart of VKA	Initial Dosing of VKA	Stop of Bridging
Spyropoulos, 2006	Pre/post, pre only, post only	LMWH‡, UFH	NR	Therapeutic and non-therapeutic	NR	NR	<24h after procedure in 38.3%	NR	Overall duration mean 6.8d
Wilson, 2001	Pre/post	LMWH	5	Prophylactic or therapeutic	NR	12	Evening of procedure	maintenance	When INR therapeutic
Wiszniewsky, 2011	Pre/post	LMWH	2	Half-therapeutic	2-12h at ¼ therapeutic dose	6-12	d 4 after surgery	loading	When INR therapeutic on 2d

Abbreviations: d, day; h, hours; INR, international normalized ratio; LMWH, low molecular weight heparin; NA, not applicable; NR, not reported;

UFH, unfractionated heparin; VKA, vitamin K antagonist.

*and administration of 3mg intravenous Vitamin K

† this treatment arm was not included in our study, as it did not meet the inclusion criteria

‡ this treatment arm was not included in our analysis, because outcomes were not specifically reported for patients with prior venous thromboembolism

Supplemental Table 3. Quality of Individual Studies

Cohort Studies	Consecutive Enrollment	Existence of Protocol before Enrollment	Intervention / Control		Blinded Outcome Assessment	Loss to Follow-up <5%	Risk of Bias
			Setting Similar	Time Frame Similar			
Ahmed, 2010	yes	no	yes	yes	no	NR	high
Baijkin, 2009*	NA*	yes	NA	NA	no	NR	very high*
Birnie, 2013*	NA*	yes	NA	NA	yes	yes	very high*
Breen, 2013	PY	no	NA	NA	no	NR	very high
Burbury, 2011	PN	yes	NA	NA	no	yes	very high
Clark, 2015	yes	no	yes	yes	no	NR	high
Constans, 2007	yes	yes	NA	NA	no	NR	very high
Douketis, 2005	yes	no	NA	NA	no	NR	very high
Dunn, 2007	no	yes	NA	NA	no	NR	very high
Eisele, 2012	no	no	NA	NA	no	no	very high
Fernandez, 2009 †	PN	PN	PY	yes	PN	NR	very high
Garcia, 2008	no	yes	yes	yes	no	yes	high
Hammerstingl, 2009	yes	yes	NA	NA	no	NR	very high
Hwang, 2017	no	no	NA	NA	no	NR	very high
Jaffer, 2005	yes	PN	NA	NA	no	NR	very high
Klamroth, 2010	yes	PY	NA	NA	no	NR	very high
Majluf-Cruz, 2011 †	PN	PY	NA	NA	no	NR	very high
Malato, 2010	yes	yes	NA	NA	no	yes	very high
McBane, 2010	yes	yes	yes	yes	PY	yes	moderate
Pengo, 2009	yes	yes	NA	NA	no	NR	very high
Sacullo, 2012	yes	yes	NA	NA	no	yes	very high
Santamaria, 2013*	NA*	yes	NA	NA	no	no	very high*
Sjögren, 2017	no	no	NR	NR	no	NR	very high
Skeith, 2012	no	PN	yes	yes	no	yes	high
Spyropoulos, 2004	no	PN	NA	NA	no	NR	very high
Spyropoulos, 2006	yes	PN	NA	NA	yes	NR	very high
Wilson, 2001	yes	yes	NA	NA	no	NR	very high
Wiszniewsky, 2011	no	yes	NA	NA	no	NR	very high

Abbreviations: NA, not applicable; NR, not reported; PN, probably no; PY, probably yes. Quality of observational studies was assessed using criteria adapted from the American College of Chest Physicians working group for the 9th guidelines on antithrombotic therapy and prevention of

thrombosis, which included guidance to for quality assessment of cohort studies without internal controls.⁴ Observational or nonrandomized interventional 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 reported quality elements. On the other hand, they were upgraded to very high risk if they used a single-arm cohort design without an internal comparison group, or there are severe or multiple problems with these elements.⁵

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

† conference abstract, no corresponding full text published

Supplemental Table 4. Quality of Evidence: Periprocedural Bridging in Patients with Previous VTE

Quality assessment							Summary				
Outcome	No. of studies (design)	Risk of Bias*	Inconsistency†	Indirectness‡	Imprecision§	Publication Bias	No Bridging		Bridging		Quality
							No. of procedures	Pooled incidence, % (95% CI)	No. of procedures	Pooled incidence, % (95% CI)	
Perioperative VTE	27 (cohort studies)	very high	consistent	direct	imprecise	substantial	3459	0.5 (0.3-0.8)	3427	0.7 (0.4-1.2)	very low
Major bleeding	15 (cohort studies)	very high	inconsistent	direct	imprecise	substantial	2084	0.4 (0.1-1.5)	1702	1.8 (1.2-2.5)	very low
Any bleeding	18 (cohort studies)	very high	inconsistent	direct	precise	substantial	3420	0.4 (0.1-1.7)	3420	3.9 (2.0-7.4)	very low

Abbreviations: CI, confidence interval; VTE, venous thromboembolism. Quality of evidence was assessed using the GRADE (grading of

recommendations assessment, development, and evaluation) framework.⁶ Observational studies were considered low quality of evidence, and were downgraded to very low quality depending on risk of bias, inconsistency, indirectness, imprecision, and publication bias. One of four possible scores (high, moderate, low, or very low) for the quality of the overall body of evidence was assigned for each outcome.

*based on following criteria: failure to develop appropriate eligibility criteria, lack of internal control group (single-arm cohorts), flawed measurement of exposure and/or outcome, inadequacy of control for confounding, incomplete follow-up.

† based on differences in effect sizes of studies comparing outcomes in both exposure groups, their overlap in 95% confidence intervals, and statistical heterogeneity

‡ evidence was considered indirect if the population, the intervention, or the outcomes that were measured in the included studies differed from those of interest in our systematic review, or if there were no head-to-head comparisons available

§ based on optimal information size criterion and 95% confidence interval

|| The potential for publication bias was determined by searching for unpublished literature and conducting a sensitivity analysis excluding conference abstracts. A quantitative assessment of publication bias was not supported by the data (mostly single-arm studies).

ACCEPTED MANUSCRIPT

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