Periprocedural Heparin Bridging in Patients Receiving Vitamin K Antagonists : Systematic Review and Meta-Analysis of Bleeding and Thromboembolic Rates

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Periprocedural Heparin Bridging in Patients Receiving Vitamin K Antagonists

Systematic Review and Meta-Analysis of Bleeding and Thromboembolic Rates

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Background—Periprocedural bridging with unfractionated heparin or low-molecular-weight heparin aims to reduce the risk of thromboembolic events in patients receiving long-term vitamin K antagonists. Optimal periprocedural anticoagulation has not been established.

Methods and Results—MEDLINE, EMBASE, and Cochrane databases (2001–2010) were searched for English-language studies including patients receiving heparin bridging during interruption of vitamin K antagonists for elective procedures. Data were independently collected by 2 investigators (κ=0.90). The final review included 34 studies with 1 randomized trial. Thromboembolic events occurred in 73 of 7118 bridged patients (pooled incidence, 0.9%; 95% confidence interval [CI], 0.0.0–3.4) and 32 of 5160 nonbridged patients (pooled incidence, 0.6%; 95% CI, 0.0–1.2). There was no difference in the risk of thromboembolic events in 8 studies comparing bridged and nonbridged groups (odds ratio, 0.80; 95% CI, 0.42–1.54). Bridging was associated with an increased risk of overall bleeding in 13 studies (odds ratio, 5.40; 95% CI, 3.00–9.74) and major bleeding in 5 studies (odds ratio, 3.60; 95% CI, 1.52–8.50) comparing bridged and nonbridged patients. There was no difference in thromboembolic events (odds ratio, 0.30; 95% CI, 0.04–2.09) but an increased risk of overall bleeding (odds ratio, 2.28; 95% CI, 1.27–4.08) with full versus prophylactic/intermediate-dose low-molecular-weight heparin bridging. Low-thromboembolic-risk and/or non–vitamin K antagonist patient groups were used for comparison. Study quality was poor with heterogeneity for some analyses.

Conclusions—Vitamin K antagonist–treated patients receiving periprocedural heparin bridging appear to be at increased risk of overall and major bleeding and at similar risk of thromboembolic events compared to nonbridged patients. Randomized trials are needed to define the role of periprocedural heparin bridging. **(*Circulation*. 2012;126:1630-1639.)**

Key Words: anticoagulants ■ bridging ■ heparin ■ periprocedural ■ thromboembolism ■ warfarin

Vitamin K antagonists (VKAs) such as warfarin are commonly used long term for the prevention of arterial thromboembolic events such as stroke and systemic embolism in patients with atrial fibrillation or mechanical heart valves and recurrent venous thromboembolic events. Approximately 10% of patients receiving long-term warfarin may require interruption of therapy for invasive procedures or surgery, and it is estimated that >250 000 patients on long-term warfarin undergo periprocedural assessment in North America each year.[1] There is concern that periprocedural interruption of warfarin may increase the risk of thromboembolic events, whereas continuation of warfarin in the periprocedural period will increase the risk of bleeding.[2] Periprocedural bridging anticoagulation with short-acting parenteral agents such as unfractionated heparin or low-molecular-weight heparin (LMWH) has been increasingly used in the past decade with the aim of minimizing thromboembolic events without incurring a clinically important increase in bleeding.[1] However, the use of periprocedural bridging anticoagulation is highly variable, with uncertainty as to when bridging should be used and which regimens are optimal. The 2012 antithrombotic practice guidelines of the

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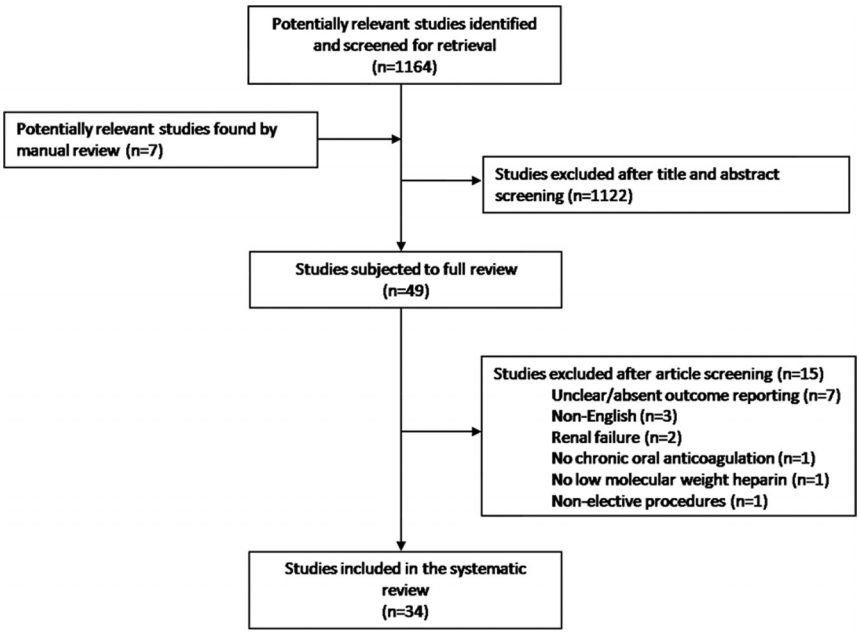

Figure 1. Identification of eligible studies.

American College of Chest Physicians (ACCP) recommend an individualized approach to determining the need for bridging anticoagulation based on the patient's estimated thromboembolic risk and periprocedural bleeding risk.[1] However, the grades of these recommendations are weak (Level 2C), reflecting the lack of high-quality evidence.

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The risks and benefits of periprocedural bridging anticoagulation were assessed in a systematic review of studies published from 1966 to 2001.[3] However, firm conclusions could not be drawn about the safety and efficacy of bridging and other management strategies mainly because of poorly described bridging regimens and a lack of reliable estimates of associated thromboembolic and bleeding risks.[3] Since this systematic review, multiple large, multicenter studies have assessed standardized periprocedural management strategies, with well-defined bridging regimens and outcomes, and objectively verified adverse events.[4]

Given the uncertainty associated with optimal periprocedural anticoagulant management and the use of bridging therapy, we performed a systematic review of studies and a meta-analysis to evaluate the safety and efficacy of periprocedural bridging anticoagulation.

Methods

Data Sources and Searches

We used the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines and searched Medline, EMBASE, and Cochrane Collaboration databases for English-language studies published from January 1, 2001, until July 31, 2010, supplemented by manual review of reference lists from the ACCP antithrombotic practice guidelines (eighth and ninth editions; R. Kunz, personal communication, June 30, 2010).[5] The search strategy was adapted from the ACCP Antithrombotic Practice Guidelines Working Group (ninth edition) and is shown in the Data Supplement (Figure I in the online-only Data Supplement; R. Kunz, personal communication).

Study Selection

Studies were selected independently by 2 authors (D.S. and J.Y.), and discrepancies were resolved by consensus of a third author (A.C.S.). Included studies met all of the following criteria: adult patients (≥18 years of age), elective invasive procedure or surgery, long-term use of VKA preprocedurally, periprocedural bridging with LMWH in at least some patients studied, and reporting of thromboembolic and bleeding events. Studies with unclear reporting of thromboembolic or bleeding events and studies conducted explicitly in patients with severe renal failure (creatinine clearance <30 mL/min in whom LMWH bridging would be contraindicated) were excluded. Agreement between reviewers for study selection was assessed with the κ statistic.[6]

Data Extraction and Quality Assessment

Two reviewers independently collected data on study design, patient characteristics, bridging strategies (timing of interruption and resumption of oral anticoagulation, timing of heparin bridging, type and dose of heparin), and types of procedures performed. Patients were classified as bridged if they received any heparin bridging in the perioperative period. Treatment-dose LMWH was defined as follows: dalteparin 200 $IU \cdot kg^{-1} \cdot d^{-1}$ or 100 to 120 IU/kg twice daily, enoxaparin 1.5 $mg \cdot kg^{-1} \cdot d^{-1}$ or 1 mg/kg twice daily, ardeparin 100 to 130 IU/kg twice daily, and tinzaparin 175 $IU \cdot kg^{-1} \cdot d^{-1}$. All other doses were considered intermediate- or prophylactic-dose bridging regimens. High and low thromboembolic risk classification was based on definitions used in the primary studies.

Patients were classified as nonbridged if they underwent periprocedural interruption of oral anticoagulation without heparin bridging. Patients not receiving long-term oral anticoagulation but undergoing the procedure(s) under study were also classified as nonbridged. Patients who did not discontinue oral anticoagulation in the periprocedural period were classified as continued oral anticoagulation.

The primary outcomes were thromboembolic events and major bleeding events. Secondary outcomes were overall bleeding, arterial thromboembolic events (stroke, transient ischemic attack, systemic embolism, and myocardial infarction), venous thromboembolic events (deep vein thrombosis, pulmonary embolism), and death. We used the reported definitions of major bleeding provided in the primary studies. These included need for transfusion, bleeding at a critical site, decrease in hemoglobin >2 g/L, requirement for surgical hemostasis, need for rehospitalization, and fatal bleeding.

Table 1. Study Characteristics

Author	Study Design	Intervention/Comparator (When Applicable)	Participants, n	Duration of Follow-Up, d	Source of Funding	Comments
Bajkin et al,[11] 2009	Randomized	I: LMWH	I: 105	30	NR	
		C: VKA continued	C: 109			
Bombuy et al,[12] 2009	Cohort, retrospective	I: LMWH	I: 47	30	NR	
Bui et al,[13] 2009	Cohort, retrospective	I: LMWH	I: 130	60	NR	
Cheng et al,[14] 2009	Cohort, retrospective	I: LMWH	I: 42	90	NR	VKA continued and nonbridged groups were included in the study, but LMWH was used in both groups perioperatively (not considered control subjects)
Constans et al,[15] 2007	Cohort, prospective	I: LMWH	I: 98	90	Industry	
Daniels et al,[16] 2009	Cohort, retrospective	I: LMWH, UFH	I: 342	90	Nonindustry	
		C: no bridging	C: 213			
Dotan et al,[17] 2002	Cohort, prospective	I: LMWH	I: 20	90	NR	
		C: non-VKA patients	C: 20			
Douketis et al,[18] 2004	Cohort, prospective	I: LMWH	I: 650	14	No funding	High-bleed-risk patients did not receive postoperative bridging
Douketis et al,[19] 2005	Cohort, retrospective	I: LMWH	I: 73	NR	NR	
Dunn et al,[20] 2007	Cohort, prospective	I: LMWH	I: 260	28	Industry	
Ercan et al,[21] 2010	Cohort, prospective	I: LMWH	I: 44	NR	NR	
		C: non-VKA patients	C: 1421			
Garcia et al,[22] 2008	Cohort, prospective	I: LMWH, UFH	I: 108	30	Industry	
		C: no bridging	C: 1185			
Ghanbari et al,[23] 2010	Cohort, retrospective	I: LMWH, UFH	I: 29	30	NR	
		C: no bridging, VKA continued	C: 74, 20			
Halbritter et al,[24] 2005	Cohort, prospective	I: LMWH, UFH	I: 311	NR	Industry	
Jaffer et al,[25] 2005	Cohort, retrospective	I: LMWH	I: 69	30	NR	
Jaffer et al,[26] 2010	Cohort, prospective	I: LMWH, UFH	I: 229	30	Industry and nonindustry	Total perioperative events not shown; therefore, postoperative data used
		C: no bridging	I: 263			
Kovacs et al,[27] 2004	Cohort, prospective	I: LMWH	I: 224	90	NR	
Malato et al,[28] 2010	Cohort, prospective	I: LMWH	I: 328	30	NR	
Marquie et al,[29] 2006	Cohort, retrospective	I: LMWH, UFH	I: 114	30	NR	
		C: non-VKA patients	C: 114			
McBane et al,[30] 2010	Cohort, prospective	I: LMWH	I: 514	90	Nonindustry	
		C: no bridging	C: 261			
O'Donnell et al,[31] 2007	Cohort, prospective	I: LMWH	I: 93	30	Nonindustry	
Pengo et al,[32] 2009	Cohort, prospective	I: LMWH	I: 1262	30	NR	
Robinson et al,[33] 2009	Cohort, unclear	I: LMWH	I: 113	7	NR	
		C: no bridging	C: 35			
Spyropoulos et al,[34] 2004	Cohort, retrospective	I: LMWH	I: 84	60	NR	
Spyropoulos et al,[35] 2004	Cohort, retrospective	I: LMWH, UFH	I: 66	30	Nonindustry	
Spyropoulos et al,[36] 2006	Cohort, prospective	I: LMWH, UFH	I: 832	30	Industry	
Spyropoulos et al,[37] 2008	Cohort, prospective	I: LMWH, UFH	I: 233	30	Industry	
Tinmouth et al,[38] 2001	Cohort, prospective	I: LMWH	I: 24	30	NR	
Tischenko et al,[39] 2009	Cohort, prospective	I: LMWH	I: 38	30	NR	
		C: VKA continued, non-VKA patients	C: 117, 117			
Tompkins et al,[40] 2010	Cohort, retrospective	I: LMWH, UFH	I: 155	42	Industry	
		C: no bridging, VKA continued, non-VKA patients	C: 258, 45, 255			
Varkarakis et al,[41] 2005	Cohort, retrospective	I: LMWH, UFH	I: 25	NR	NR	
		C: non-VKA patients	C: 762			
Wazni et al,[42] 2007	Cohort, prospective	I: LMWH	I: 205	90	NR	
		C: VKA continued	C: 150			
Wilson et al,[43] 2001	Cohort, prospective	I: LMWH	I: 47	90	NR	
Wysokinski et al,[44] 2008	Cohort, prospective	I: LMWH, UFH	I: 204	90	Nonindustry	
		C: no bridging	C: 182			

I indicates intervention; LMWH, low-molecular-weight heparin; NR, not reported; C, comparator; VKA, vitamin K antagonist; and UFH, unfractionated heparin. No bridging refers to VKA oral anticoagulant discontinuation without heparin bridging. Non-VKA refers to patients not receiving long-term oral anticoagulation but undergoing surgical or invasive procedure under study.

Study quality was assessed with criteria adapted from the ninth edition of the ACCP Antithrombotic Working Group for quality assessment of single-cohort observational studies (R. Kunz, personal communication). Disagreements on study data extraction were resolved by consensus or discussion with a third reviewer.

Data Synthesis and Analysis

Descriptive statistics were reported as means and 95% confidence intervals (CIs) for continuous variables and as proportions for categorical variables. For studies with bridged and nonbridged groups, data were pooled by use of the Mantel-Haenszel method, and a random-effects model was performed with generation of odds ratios (ORs) through the use of RevMan version 5.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2011).[7] Pooled incidence rates of thromboembolic and bleeding events in all studies (including single-arm studies) were calculated with the statistical method of Laird and Mosteller[8] as previously reported.[9] The I^2 test was used to assess heterogeneity.[10] Descriptive statistics were generated with SPSS version 13.0 (SPSS Inc, Apache Software Foundation).

Results

Study Identification, Selection, and Characteristics

As shown in Figure 1, our search strategy yielded 1171 potentially eligible studies; we excluded 1122 studies after screening titles and abstracts using predefined inclusion and exclusion criteria. The remaining 49 studies were subjected to a more detailed review, and an additional 15 were excluded for the following reasons: unclear or absent outcome reporting (n=7), non-English language (n=3), renal failure (n=2), no long-term anticoagulation with VKA (n=1), no LMWH (n=1), and nonelective procedure (n=1). In total, 34 studies were included in this systematic review. The study selection process demonstrated good interobserver agreement (κ=0.90).

Study characteristics are provided in Table 1.[11–44] Median duration of patient follow-up was 30 days (range, 7–90 days). A prespecified bridging protocol was in place before enrollment in 22 studies (65%). The majority of studies (59%) did not report the source of study funding. In the remaining studies, funding was obtained from industry (21%), nonindustry (15%), or both (3%). Indications for anticoagulation of bridged patients were reported in 30 studies as atrial fibrillation (44%), mechanical heart valve (24%), previous venous thromboembolism (22%), and other (10%; Table I in the online-only Data Supplement). In 16 studies, 1593 bridged patients (53%) were classified as having a high risk of thromboembolic events as defined in individual studies. The types of invasive procedures varied among studies as follows: endoscopic (19 of 34), orthopedic (18 of 34), dental (16 of 34), ophthalmologic (15 of 34), cardiac device implantation (12 of 34), dermatologic (12 of 34), and angiographic (12 of 34). Surgical procedures included urologic (19 of 34), general (19 of 34), abdominal (14 of 34), vascular (14 of 34), gynecologic (14 of 34), cardiothoracic (13 of 34), and neurological (6 of 34). Studies may have included >1 type of invasive or surgical procedure (Table I in the online-only Data Supplement).

Periprocedural bridging strategies are shown in Table 2. The preoperative international normalized ratio was <1.5 in all 15 studies in which it was reported. Before invasive procedures or surgery, LMWH was discontinued within 12 to 23 hours in 36% of studies or beyond 24 hours in 36% of studies. Postprocedurally, LMWH was reinitiated within 24 hours in 55% of studies or beyond 24 hours in 16% of studies. Overall, 20 studies (57%) reported use of full (therapeutic)-dose LMWH and 13 studies (37%) reported use of prophylactic/intermediate-dose LMWH for bridging. Individual studies may have used >1 dose of LMWH.

Table 2. Perioperative Bridging Strategies

	Studies, n (%)
Preoperative strategy	
VKA discontinuation, d	
<3	1 (3)
≥3	28 (82)
Not specified	5 (15)
Type of heparin bridging (33 studies)*	
LMWH	33 (100)
UFH	12 (36)
LMWH discontinuation (33 studies), h	
<12	0 (0)
12–23	12 (36)
≥24	12 (36)
Not specified	9 (27)
Postoperative bridging strategy	
Reinitiation of VKA, h	
≤24	15 (44)
>24	9 (26)
Not specified	7 (21)
Unclear	2 (6)
Other	1 (3)
VKA dose	
Maintenance dose	7 (21)
Loading dose	2 (6)
Other	4 (12)
Not specified	21 (62)
Type of heparin bridging (33 studies)†	
LMWH	31 (94)
UFH	11 (33)
LMWH reinitiation (31 studies), h	
0–24	17 (55)
>24	5 (16)
Not specified	9 (29)

VKA indicates vitamin K antagonist; LMWH, low-molecular-weight heparin; and UFH, intravenous unfractionated heparin.

*One study used postoperative anticoagulation only. Individual studies may have used >1 type of bridging.

†One study used pre-operative heparin bridging only. Individual studies may have used >1 type of bridging.

Study Quality

As shown in Table 3, study quality was generally poor with potential for biased comparisons of outcomes. Only 1 study used a randomized design; the remaining 33 used an observational design. Thirteen studies reported nonbridged comparative data based on patients at low thromboembolic risk and/or those not treated long-term with oral anticoagu-

Table 3. Study Quality Assessment

Randomized Controlled Trials						Observational Studies						
Author	Random Allocation	Allocation Concealment	Blinding	Unavailable for Follow-Up	Analysis	Author	Consecutive Enrollment	Protocol in Place Before Enrollment	Intervention/ Control Setting Similar (if Applicable)	Intervention/ Control Time Frame Similar (if Applicable)	Blinded Assessment of Outcome	Loss to Follow-Up Reported
Bajkin et al,[11] 2009	PN (NR)	PN (NR)	Patients, CN; caregivers, CN; data collectors, NR adjudicators, NR; data analysis, NR	NR	NR	Bombuy et al,[12] 2009	No	Yes	NA	NA	No	No
						Bui et al,[13] 2009	No	Yes	NA	NA	No	No
						Cheng et al,[14] 2009	No	No	NA	NA	No	No
						Constans et al,[15] 2007	Yes	Yes	NA	NA	No	No
						Daniels et al,[16] 2009	Yes	Yes	Yes	Yes	Yes	Yes
						Dotan et al,[17] 2002	No	Yes	Yes	Yes	No	No
						Douketis et al,[18] 2004	Yes	Yes	NA	NA	No	No
						Douketis et al,[19] 2005	Yes	No	NA	NA	No	No
						Dunn et al,[20] 2007	No	Yes	NA	NA	No	No
						Ercan et al,[21] 2010	No	Yes	Yes	Yes	No	No
						Garcia et al,[22] 2008	No	No	No	Yes	No	Yes
						Ghanbari et al,[23] 2010	Yes	Yes	Yes	Yes	No	No
						Halbritter et al,[24] 2005	Yes	No	NA	NA	No	No
						Jaffer et al,[25] 2005	Yes	Yes	NA	NA	No	No
						Jaffer et al,[26] 2010	Yes	No	Yes	Yes	No	No
						Kovacs et al,[27] 2004	Yes	Yes	NA	NA	No	Yes
						Malato et al,[28] 2010	No	Yes	NA	NA	No	Yes
						Marquie et al,[29] 2006	No	No	Yes	Yes	No	No
						McBane et al,[30] 2010	Yes	Yes	Yes	Yes	Yes	Yes
						O'Donnell et al,[31] 2007	Yes	Yes	NA	NA	Yes	Yes
						Pengo et al,[32] 2009	Yes	Yes	NA	NA	No	No
						Robinson et al,[33] 2009	Yes	No	Yes	No	No	Yes
						Spyropoulos et al,[34] 2004	No	Yes	NA	NA	No	No
						Spyropoulos et al,[35] 2004	No	Yes	NA	NA	No	No
						Spyropoulos et al,[36] 2006	Yes	No	NA	NA	Yes	No
						Spyropoulos et al,[37] 2008	Yes	No	NA	NA	Yes	No
						Tinmouth et al,[38] 2001	Yes	Yes	NA	NA	No	No
						Tischenko et al,[39] 2009	Yes	Yes	Yes	No	No	No
						Tompkins et al,[40] 2010	No	No	Yes	Yes	No	No
						Varkarakis et al,[41] 2005	No	No	Yes	No	No	No
						Wazni et al,[42] 2007	Yes	Yes	Yes	Yes	No	Yes
						Wilson et al,[43] 2001	Yes	Yes	NA	NA	No	No
						Wysokinski et al,[44] 2008	Yes	No	Yes	Yes	Yes	Yes
						Total, n (%)	33	33	14	14	33	33
						Yes	20 (61)	21 (64)	13 (93)	11 (79)	6 (18)	9 (27)
						No	13 (39)	12 (36)	1 (7)	3 (21)	27 (82)	24 (73)

PN indicates positively no; NR, not reported; CN, certainly no; and NA, not applicable.

lation. Five studies included a group who continued oral anticoagulation.

Thromboembolic Events

Thromboembolic outcome data were available for all 34 studies that included a total of 7118 patients receiving any periprocedural heparin bridging. Overall, thromboembolic events occurred in 73 of 7118 bridged patients (pooled incidence rate, 0.9%; 95% CI, 0.0–3.4) and 32 of 5160 nonbridged patients (pooled incidence rate, 0.6%; 95% CI, 0.0–1.2; Table 4). Arterial thromboembolic events represented approximately half of thromboembolic events in both bridged (n=50 of 73, 68%) and nonbridged (n=15 of 32, 47%) patients. Arterial thromboembolic and/or venous thromboembolic events were not reported in all studies, as reflected by the patients at risk in each treatment group shown in Table 4. In 6 studies that stratified patients by thromboembolic risk, patients not at high thromboembolic risk receiving prophylactic dose or no bridging had an overall thromboembolic event rate of 0.6% (11 of 1702).

In 8 studies that assessed thromboembolic events in both bridged and nonbridged patients, the outcome occurred in 19 of 1691 bridged and 32 of 3493 nonbridged patients (Figure 2). There was no reduction in the risk of thromboembolic events with the use of heparin bridging (OR, 0.80; 95% CI, 0.42–1.54; Figure 2). There was also no difference in the risk of arterial thromboembolic (OR, 0.83; 95% CI, 0.36–1.95) or venous thromboembolic (OR, 1.00; 95% CI, 0.32–3.12) events between bridged and nonbridged patients. The risk of thromboembolic events was similar in patients receiving full-dose versus intermediate- or prophylactic-dose LMWH (2 studies; OR, 0.30; 95% CI, 0.04–2.09). We found no heterogeneity for thromboembolic, arterial thromboembolic, and venous thromboembolic outcomes across studies (I^2=0%).

Table 4. Pooled Incidence Rates of Thromboembolic and Bleeding Events in Studies With and Without Bridging Comparator Groups

Group	TE Events, % (95% CI), and Events/Patients at Risk	ATE Events, % (95% CI), and Events/Patients at Risk	VTE Events, % (95% CI), and Events/Patients at Risk	Major Bleeding, % (95% CI), and Events/Patients at Risk	Overall Bleeding, % (95% CI), and Events/Patients at Risk	Mortality, % (95% CI), and Events/Patients at Risk
Total bridged cohort	0.9 (0.0–3.4)	1.0 (0.0–2.8)	0.2 (0.0–0.6)	4.2 (0.0–11.3)	13.1 (0.0–45.2)	0.3 (0.0–1.0)
	73/7118	50/6426	21/4632	211/6404	833/7188	31/6079
LMWH						
Full dose	0.4 (0.0–0.9)	1.7 (1.2–2.1)	0.4 (0.0–1.0)	3.2 (1.3–5.2)	13.6 (2.9–24.3)	0.0 (0.0–0.2)
	17/2314	17/2002	1/734	69/2126	334/2314	5/1836
Prophylactic/ intermediate dose	0.2 (0.0–0.6)	0.2 (0.0–0.6)	0.2 (0.0–0.5)	3.4 (0.0–8.7)	8.5 (2.9–14.2)	0.1 (0.0–0.3)
	14/1956	7/1824	6/1688	35/1900	133/1956	5/1800
Total nonbridged cohort	0.6 (0.0–1.2)	0.5 (0.1–0.9)	0.3 (0.0–0.7)	0.9 (0.2–1.6)	3.4 (1.1–5.8)	0.1 (0.0–0.3)
	32/5160	15/2468	11/2141	18/2104	100/5160	4/2393

TE indicates thromboembolic; CI, confidence interval; ATE, arterial thromboembolic; VTE, venous thromboembolic; and LMWH, low-molecular-weight heparin. Results shown are pooled incidence rates. The number of events in patients at risk is also shown.

In a sensitivity analysis, removal of nonanticoagulated patients resulted in a similar risk of thromboembolic events (OR, 0.82; 95% CI, 0.42–1.64).

Bleeding Events

Overall bleeding was included as an outcome in all 34 studies, whereas major bleeding was reported in 24 studies. The criteria for major bleeding were provided in 21 studies: need for transfusion (n=19), bleeding at a critical site (n=17), >2-g/L decrease in hemoglobin (n=16), surgical hemostasis required (n=11), fatal bleeding (n=9), and need for hospitalization (n=7). Pooled incidence rates of overall and major bleeding in the total bridged cohort were 13.1% (34 studies; 95% CI, 0.0–45.2) and 4.2% (24 studies; 95% CI, 0.0–11.3), respectively (Table 4). In the nonbridged cohort, pooled incidence rates of overall and major bleeding were 3.4% (13 studies; 95% CI, 1.1–5.8) and 0.9% (5 studies; 95% CI, 0.2–1.6), respectively. Three studies assessed bleeding complications stratified by procedural bleed risk, with bleeding complication (including major bleeding) rates of 7.8%, 1.85%, and 20%, respectively, in mostly bridged patients undergoing major surgery or high-bleed-risk procedures compared with bleed rates of 6.0%, 0.74%, and 0.5% in patients undergoing non–high-bleed-risk/invasive procedures or minor surgery.

There was an increased risk of overall bleeding (13 studies; OR, 5.40; 95% CI, 3.00–9.74) and major bleeding (5 studies; OR, 3.60; 95% CI, 1.52–8.50) in bridged versus nonbridged patients (Figures 3 and 4). There was also an increased risk of overall bleeding in patients receiving full versus prophylactic- or intermediate-dose LMWH (OR, 2.28; 95% CI, 1.27–4.08). We found significant heterogeneity for overall bleeding (I^2=77%) and major bleeding (I^2=52%) outcomes across studies.

In a sensitivity analysis, removal of nonanticoagulated patients resulted in a similar risk of overall bleeding (OR, 3.79; 95% CI, 1.98–7.23). The risk of major bleeding was unchanged.

Discussion

We reviewed 34 studies that assessed perioperative thromboembolic and bleeding events in >12 000 patients undergoing elective surgical invasive or invasive procedures. Of these, 7118 patients on long-term VKA received periprocedural heparin bridging with LMWH during VKA interruption. The principal finding from this study is that patients who receive heparin bridging appear to have an increased risk of overall and major bleeding events in the periprocedural period but a similar risk of thromboembolic events compared with patients who receive no periprocedural bridging. Thus, heparin bridging conferred a >5-fold (OR, 5.40) increased risk for overall bleeding and a >3-fold (OR, 3.60) increased risk for major bleeding, whereas the risk of thromboembolic events was not significantly different in bridged and nonbridged patients (OR, 0.80). Use of therapeutic-dose LMWH bridging was also associated with an increased risk of bleeding

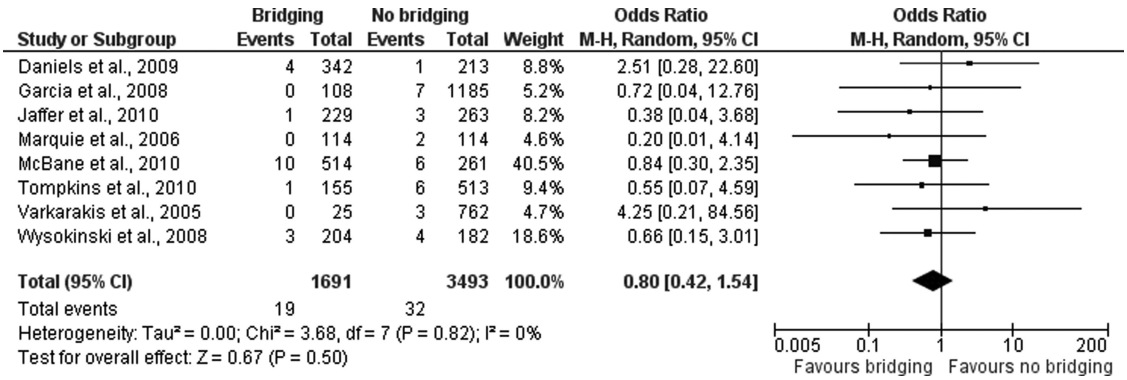

Figure 2. Forest plot of thromboembolic events. M-H indicates Mantel-Haenszel; CI, confidence interval.

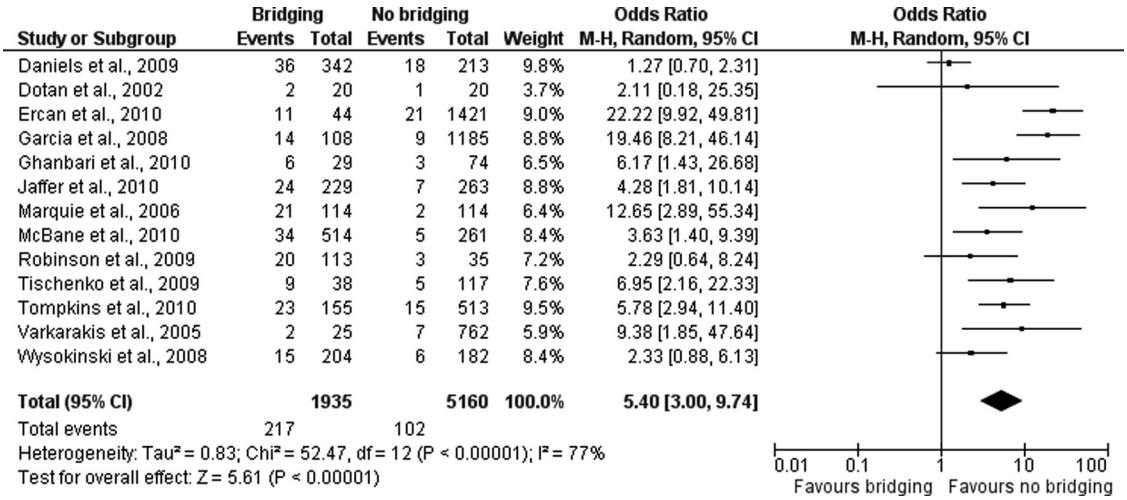

Figure 3. Forest plot of overall bleeding events. M-H indicates Mantel-Haenszel; CI, confidence interval.

compared with prophylactic- or intermediate-dose LMWH (OR, 2.28), although thromboembolic event rates did not significantly differ.

The main strength of our study is that it represents, to the best of our knowledge, the largest systematic review and meta-analysis of the efficacy and safety of periprocedural bridging anticoagulation. Our study contributes data from 34 additional studies and >7000 patients since the systematic review by Dunn and colleagues[3] in 2003. We provide a characterization of contemporary bridging practice, demonstrating that bridging is accomplished predominantly with LMWH that is discontinued ≥12 hours before and restarted within 24 hours after procedures. Our observed overall pooled thromboembolic event rate of 0.9% in bridged patients is similar to the 1.6% reported in the above-mentioned review.[3] However, in that study, bleeding event data were difficult to interpret, thereby precluding specific conclusions on periprocedural bleeding complications. All studies in our review included bleeding outcome data and provided more reliable estimates of overall (13.1%) and major (4.2%) bleeding rates associated with bridging anticoagulation.

Several study limitations may affect the validity of our findings. First, we acknowledge that only a proportion of included studies contributed to the random effects model, and caution is required in the interpretation of our results. The internal validity of our data is supported by a lack of heterogeneity in analyses of thromboembolic events, both arterial and venous, when assessed in patients who received bridging or no bridging and in full-dose versus prophylactic- or intermediate-dose LMWH patient cohorts. However, there was significant heterogeneity for analyses of bleeding events in bridged versus nonbridged patients, which was likely related to variability in procedural bleeding risk and nonstandard definitions of bleeding events across studies. This is particularly relevant to the major bleeding data that were derived from 24 studies with a wide range of definitions and surgical procedures. Only a few studies systematically reported bleeding risk according to the type of procedure. Second, the large majority of studies were observational; most were cohort studies lacking control groups. When control groups were included, they consisted of low-thromboembolic-risk and/or non-VKA patient groups for comparative analysis, especially in assessments of baseline procedure-related bleeding rates. Therefore, the treatment and comparison groups may have had different thromboembolic risks at baseline, and because we were unable to perform regression analyses to account for potential differences in baseline risks, there is a risk of systemic bias in regard to which patients were bridged and not bridged. It is possible that with a majority of bridged patients considered high risk for thromboembolic events (57% in 19 studies), such high-thromboembolic-risk patients may have preferentially received bridging therapy whereas low-thromboembolic-risk patients did not. Thus, bridging may have reduced a very high thromboembolic rate in the high-risk, bridged group to that of the lower-thromboembolic-risk, nonbridged patients.

Our findings are relevant to VKA-treated patients who require temporary discontinuation of oral anticoagulation for

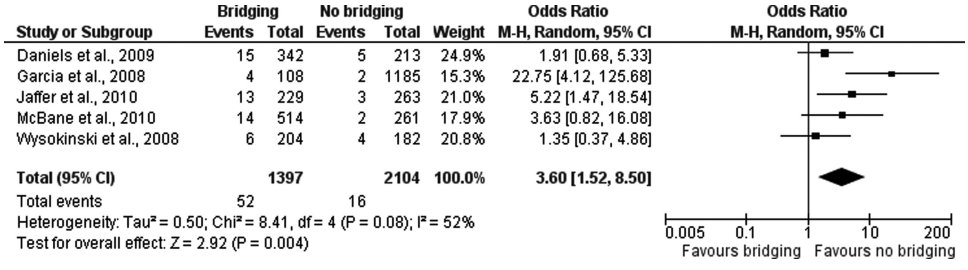

Figure 4. Forest plot of major bleeding events. M-H indicates Mantel-Haenszel; CI, confidence interval.

elective surgical or invasive procedures and address first how to administer bridging anticoagulation—its timing and dose regimen used—and second which patients should receive bridging. In regard to the first point, our findings suggest for the first time that bridging therapy, especially with therapeutic-dose regimens, may be associated with increased postprocedural bleeding complications and should be used cautiously, especially after the procedure. Although the present analysis did not allow us to precisely differentiate bleed risk according to the procedure type, this finding should be more applicable to high-bleed-risk procedures such as major surgery, which had the highest bleeding rates with bridging therapy. Approaches that have been proposed to mitigate this risk but have not been studied in prospective clinical studies include delaying the administration of postprocedural therapeutic-dose bridging at least 24 hours after the procedure (assuming hemostasis is secured) and for 48 to 72 hours in high-bleed-risk cases.[1] Alternatively, prophylactic- or intermediate-dose LMWH bridging regimens, which may be associated with a decreased risk of bleeding events, can be considered. In regard to the second point, our findings raise important questions about the overall premise of heparin bridging, regardless of the dose regimen, to minimize the risk for periprocedural thromboembolic events during temporary interruption of oral anticoagulant therapy. Our findings indicate that bridging therapy should be avoided in patients not at high thromboembolic risk, given the low thromboembolic rates in the absence of bridging therapy. However, a major potential confounder in these studies is that bridged patients may have been at higher risk for thromboembolic events than nonbridged patients. Overall, what is unclear is whether the higher rate of periprocedural bleeding associated with heparin bridging is an acceptable tradeoff for a presumed (but unproven) decreased risk for thromboembolism, especially in the high-thromboembolic-risk patients. An attempt to quantify the relative clinical impact of death and disability in atrial fibrillation patients suggests that compared with ischemic strokes, major extracranial bleeding, hemorrhagic stroke, and subdural hemorrhage have relative weights of 0.75, 1.60, and 0.43 respectively.[45]

Our study also should be considered within the context of emerging novel oral anticoagulants such as dabigatran, rivaroxaban, and apixaban, which have the potential to displace warfarin and, because of their more rapid offset and onset of action compared with warfarin, may obviate the need for perioperative bridging. However, bridging therapy may also be applicable to patients on these novel agents. For example, selected patients receiving dabigatran (with a half-life of 12–17 hours) may require 3 to 5 days of periprocedural interruption, and recent data from the large Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial in atrial fibrillation revealed that ≈16% of patients in the dabigatran groups underwent heparin bridging therapy.[46,47]

Finally, our study emphasizes the need for standard definitions of procedural bleeding risk and bleeding outcomes, including major bleeding. To this end, the International Society on Thrombosis and Hemostasis Control of Anticoagulation Subcommittee has recently endorsed recommendations to standardize reporting of patient/procedural thromboembolic and bleed risk and outcomes, including major bleeding, and thereby to enable outcome pooling and across-study comparisons.[48]

Conclusions

We found that VKA-treated patients who require an elective surgical or invasive procedure and receive periprocedural bridging anticoagulation with LMWH appear to be at increased risk of overall and major bleeding and at similar risk of thromboembolic events compared with nonbridged patients. The ACCP and other antithrombotic guidelines advocate that bridging anticoagulation should be undertaken with consideration of individual patient thromboembolic risk and procedural bleeding risk by balancing expected benefits and harms.[1] The present analysis suggests that bridging anticoagulation, especially in therapeutic-dose regimens and in patients not at high thromboembolic risk undergoing high-bleed-risk procedures, should be avoided in the periprocedural setting. The methodological limitations of our analyses, however, preclude definitive conclusions about the relative efficacy and safety of bridging. Given the large number of patients who require periprocedural anticoagulation management, coupled with the paucity of high-quality studies, randomized trials are urgently needed to determine the role, if any, of bridging anticoagulation and to better inform practices concerning the dose and timing of periprocedural anticoagulation if bridging is used. To address these aims, 2 large randomized, placebo-controlled trials (Effectiveness of Bridging Anticoagulation for Surgery [BRIDGE] and A Safety and Effectiveness Study of LMWH Bridging Therapy Versus Placebo Bridging Therapy for Patients on Long Term Warfarin and Require Temporary Interruption of Their Warfarin [PERIOP-2]) assessing bridging with therapeutic-dose LMWH are ongoing.[49,50]

Acknowledgments

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Disclosures

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CLINICAL PERSPECTIVE

Periprocedural heparin bridging with low-molecular-weight heparin (LMWH) in patients on long-term warfarin aims to reduce the risk of thromboembolic events in the immediate periprocedural period. However, although periprocedural anticoagulation remains a common clinical problem, optimal methods have not been established. Recently published international guidelines on antithrombotic therapy recommend an individualized approach to determining the need for bridging anticoagulation based on a patient's estimated thromboembolic risk and periprocedural bleed risk. Using established methods, we conducted a systematic review and meta-analysis of 34 studies (including 1 randomized trial) that used low-molecular-weight heparin as periprocedural bridging therapy. We used low-thromboembolic-risk groups who did not receive bridging therapy or patients who were not on warfarin for comparators to assess baseline periprocedural thromboembolic and bleed risks. We found a >5-fold increased risk of overall bleeding and >3-fold increased risk of major bleeding associated with the use of bridging therapy, with a similar risk of thromboembolism (including arterial thromboembolism) in bridged and nonbridged patients. There was also an increased risk of overall bleeding when full and prophylactic or intermediate doses of low-molecular-weight heparin bridging were compared. In studies that stratified procedural bleed risk, bleed rates were highest in mostly bridged patients undergoing high-bleed-risk procedures. We concluded that patients on long-term warfarin should avoid routine periprocedural bridging with low-molecular-weight heparin, especially patients not at high thromboembolic risk using therapeutic doses of bridging therapy and undergoing high-bleed-risk procedures. Randomized trials are urgently needed to define the role of periprocedural heparin bridging.

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Supplemental Material

1.exp Preoperative Care/
2. exp Perioperative Care/
3. exp Intraoperative Care/
4. exp Postoperative Care/
5. exp Surgical Procedures, Operative/
6. exp Anticoagulants/ad, tu, ae [Administration & Dosage, Therapeutic Use, Adverse Effects]
7. exp Vitamin K/tu, ai, ad, ag, th, ae [Therapeutic Use, Antagonists & Inhibitors, Administration & Dosage, Agonists, Therapy, Adverse Effects]
8. exp Warfarin/ad, tu, ae [Administration & Dosage, Therapeutic Use, Adverse Effects]
9. exp Coumarins/ad, tu, ae [Administration & Dosage, Therapeutic Use, Adverse Effects]
10. Factor Xa/ai [Antagonists & Inhibitors]
11. exp Heparin/aa, ad, tu, ae [Analogs & Derivatives, Administration & Dosage, Therapeutic Use, Adverse Effects]
12. (temporar$ or discontinu$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
13. management.mp.
14. ((anticoagul$ or anti-coagul$) adj5 (interrupt$ or bridg$ or wean$ or taper$ or suspend$ or suspension or cease$ or cessat$ or ceasing or stop or stopping or stops or stopped) adj10 (operat$ or surger$ or surgic$ or procedur$ or preop$ or pre-op$ or periop$ or peri-op$)).mp.
15. Bridging.mp.
16. 4 or 1 or 3 or 2 or 5
17. 11 or 7 or 6 or 9 or 8 or 10
18. 12 or 13 or 14 or 15
19. 16 and 17
20. 18 and 19
21. limit 20 to (humans and yr="2001-Current")
22. limit 21 ("adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")
23. limit 21 to (case reports or clinical conference or comment or congresses or editorial or in vitro or letter)
24. 22 not 23

Supplemental Table 1. Indications for anticoagulation and type of surgical or invasive procedures

Author, year	Indications for anticoagulation	Invasive procedure or surgery
Bajkin, 2009 [1]	Atrial fibrillation	Dental procedures
	Mechanical heart valve	
	Venous thromboembolism	
	Ischemic heart disease	
	Stroke	
Bombuy, 2009 [2]	Atrial fibrillation	General surgery
	Mechanical heart valve	
	Stroke	
	Other	
Bui, 2009 [3]	Atrial fibrillation	Abdominal surgery
	Mechanical heart valve	Cardiothoracic surgery
		Dermatologic procedures
		Endoscopy
		General surgery
		Gynecologic surgery
		Head and neck surgery
		Orthopedic surgery
		Neurological procedures
		Urologic surgery
		Vascular surgery
Cheng, 2009 [4]	Not specified	Cardiac device implantation
Constans, 2007 [5]	Atrial fibrillation	Endoscopy
	Mechanical heart valve	
	Venous thromboembolism	
	Myocardial infarction	
	Thrombophilia	
	Systemic embolism	
Daniels, 2009 [6]	Not specified	Angiography
		Biopsies
		Cardiac procedures

		Cardiothoracic surgery
		Dental procedures
		Endoscopy
		General surgery
		Gynecologic surgery
		Head and neck surgery
		Miscellaneous procedures (thoracentesis)
		Neurological procedures
		Neurosurgery
		Ophthalmological surgery
		Orthopedic surgery
		Urologic surgery
		Vascular surgery
Dotan, 2002 [7]	Atrial fibrillation	Urologic surgery
	Mechanical heart valve	
	Venous thromboembolism	
	Congestive heart failure	
	Hypercoagulable state	
	Stroke	
Douketis, 2004 [8]	Atrial fibrillation	Abdominal surgery
	Mechanical heart valve	Angiography
	Stroke/TIA	Biopsy
		Cardiac device implantation
		Cardiothoracic surgery
		Dental procedures
		Dermatological procedures
		Endoscopy
		General surgery
		Gynecologic surgery
		Head and neck surgery
		Neurosurgery
		Ophthalmological surgery
		Orthopedic surgery
		Urologic surgery

		Vascular surgery
Douketis, 2005 [9]	Atrial fibrillation	Not specified
	Mechanical heart valve	
	Venous thromboembolism	
Dunn, 2007 [10]	Atrial fibrillation	Abdominal surgery
	Venous thromboembolism	Angiography
		Cardiac device implantation
		Cardiac procedures
		Cardiothoracic surgery
		Dental procedures
		Dermatological procedures
		Endoscopy
		General surgery
		Gynecologic surgery
		Head and neck surgery
		Ophthalmological surgery
		Orthopedic surgery
		Urologic surgery
Ercan, 2010 [11]	Atrial fibrillation	Abdominal surgery
	Mechanical heart valve	
	Mitral stenosis	
	Aortic stenosis	
	Peripheral vascular disease	
Garcia, 2008 [12]	Atrial fibrillation	Biopsy
	Mechanical heart valve	Dental procedures
	Stroke	Dermatological procedures
	Left ventricular dysfunction	Endoscopy
	Other (not specified)	Neurological procedures
		Ophthalmological surgery
		Urologic surgery
Ghanbari, 2010 [13]	Atrial fibrillation	Cardiac device implantation
	Mechanical heart valve	
Halbritter, 2005 [14]	Atrial fibrillation	Angiography
	Mechnical heart valve	Cardiac device implantation
	Venous thromboembolism	Endoscopy

	Left ventricular dysfunction	General surgery
	Other (not specified)	Orthopedic surgery
		Vascular surgery
Jaffer, 2005 [15]	Atrial fibrillation	Abdominal surgery
	Mechanical heart valve	Angiography
	Venous thromboembolism	Biopsy
	Thrombophilia	Cardiac device implantation
	Stroke	Cardiothoracic surgery
	Atrial tachycardia	Dental procedures
		Dermatological procedures
		Endoscopy
		General surgery
		Gynecologic surgery
		Ophthalmological surgery
		Orthopedic surgery
		Procedures (thoracentesis)
		Urologic surgery
Jaffer, 2010 [16]	Atrial fibrillation	Abdominal surgery
	Mechanical heart valve	Angiography
	Venous thromboembolism	Cardiothoracic surgery
	Stroke with patent foramen ovale	Dental procedures
	Cryptogenic stroke	Dermatological procedures
	Antiphospholipid antibody with thrombosis	Endoscopy
		Geneal surgery
	Dilated cardiomyopathy	Head and neck surgery
	Multiple indications (not specified)	Ophthalmological surgery
		Orthopedic surgery
		Vascular surgery
Kovacs, 2004 [17]	Atrial fibrillation	Abdominal surgery
	Mechanical heart valve	Angiography
		Biopsy
		Cardiothoracic surgery
		Dental procedures
		Endoscopy
		General surgery

		Ophthalmological surgery
		Orthopedic surgery
		Urologic surgery
Malato, 2010 [18]	Atrial fibrillation	Abdominal surgery
	Mechanical heart valve	Biopsy
	Venous thromboembolism	Dermatological procedures
	Arterial hypertension	Endoscopy
	Dilated cardiomyopathy	General surgery
	Valvulopathy	Gynecologic surgery
	Myocardial infarction	Neurosurgery
	Coronary artery bypass graft	Orthopedic surgery
		Urologic surgery
Marquie, 2006 [19]	Atrial fibrillation	Cardiac device implantation
	Mechanical heart valve	
McBane, 2010 [20]	Venous thromboembolism	Abdominal surgery
		Cardiothoracic surgery
		Dental procedures
		General surgery
		Gynecologic surgery
		Head and neck surgery
		Interventional radiology
		Neurosurgery
		Ophthalmological surgery
		Orthopedic surgery
		Plastic surgery
		Urologic surgery
		Vascular surgery
O'Donnell, 2007 [21]	Atrial fibrillation	Angiography
	Mechanical heart valve	Cardiac device implantation
	Venous thromboembolism	Dental procedures
	Coronary artery disease	Dermatological procedures
	Valvular heart disease	Orthopedic surgery
	Other (not specified)	Vascular surgery
Pengo, 2009 [22]	Atrial fibrillation	Abdominal surgery
	Mechanical heart valve	Angiography

	Venous thromboembolism	Biopsies
		Cardiac device implantation
		Dermatological procedures
		Endoscopy
		General surgery
		Gynecologic surgery
		Head and neck surgery
		Neurosurgery
		Ophthalmological surgery
		Orthopedic surgery
		Urologic surgery
		Vascular surgery
Robinson, 2009 [23]	Not specified	Cardiac device implantation
Spyropoulos, 2004a [24]	Atrial fibrillation	Abdominal surgery
	Mechanical heart valve	Angiography
		Biopsies
		Cardiac device implantation
		Cardiothoracic surgery
		Dental procedures
		Endoscopy
		General surgery
		Head and neck surgery
		Neurological procedures
		Orthopedic surgery
		Urologic surgery
		Vascular surgery
Spyropoulos, 2004b[25]	Mechanical heart valve	Cardiothoracic surgery
	Venous thromboembolism	Endoscopy
	Other arterial/cardiac disease	General surgery
		Gynecologic surgery
		Interventional radiology
		Ophthalmological surgery
		Urologic surgery
Spyropoulos, 2006 [26]	Atrial fibrillation	Cardiothoracic surgery
	Mechanical heart valve	Dental procedures

	Venous thromboembolism	Dermatological procedures
	Other (not specified)	Endoscopy
		General surgery
		Gynecologic surgery
		Head and neck surgery
		Interventional radiology
		Ophthalmological surgery
		Orthopedic surgery
		Urologic surgery
		Vascular surgery
Spyropoulos, 2008 [27]	Mechanical heart valve	Cardiothoracic surgery
		Dental procedures
		Dermatological procedures
		Endoscopy
		General surgery
		Gynecologic surgery
		Head and neck surgery
		Interventional radiology
		Ophthalmological surgery
		Orthopedic surgery
		Urologic surgery
		Vascular surgery
Tinmouth, 2001 [28]	Atrial fibrillation with bioprosthetic valve	Abdominal surgery
	Atrial fibrillation with valve disease	Angiography
	Mechanical heart valve	Biopsies
	Venous thromboembolism	Dental procedures
		Dermatological procedures
		Endoscopy
		General surgery
		Gynecologic surgery
		Ophthalmological surgery
		Orthopedic surgery
		Urologic surgery
		Vascular surgery
Tischenko, 2009 [29]	Atrial fibrillation	Cardiac device implantation

	Prosthetic heart valve	
	Venous thromboembolism	
	Stroke/transient ischemic attack	
Tompkins, 2010 [30]	Not specified	Cardiac device implantation
Varkarakis, 2005 [31]	Atrial fibrillation	Abdominal surgery
	Mechanical heart valve	
	Venous thromboembolism	
	Other (not specified)	
Wazni, 2007 [32]	Atrial fibrillation	Cardiac procedure
Wilson, 2001 [33]	Atrial fibrillation	Abdominal surgery
	Mechanical heart valve	Angiography
	Venous thromboembolism	Dental procedures
	Congestive heart failure	Endoscopy
		General surgery
		Gynecologic surgery
		Ophthalmological surgery
		Orthopedic surgery
		Urologic surgery
		Vascular surgery
Wysokinski, 2008 [34]	Atrial fibrillation	Abdominal surgery
		Cardiothoracic surgery
		Dental procedures
		General surgery
		Gynecologic surgery
		Neurosurgery
		Ophthalmological surgery
		Orthopedic surgery
		Other (not specified)
		Urologic surgery
		Vascular surgery

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Figure Legend

Supplemental Figure 1. Search Strategy