

# Perioperative Management of Patients Receiving Oral Anticoagulants

## A Systematic Review

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**Background:** The safety and efficacy of various management strategies for patients receiving oral anticoagulants (OACs) who need to undergo surgery or invasive procedures are unknown.

**Methods:** We performed a systematic review and synthesis of the English-language literature examining the perioperative management and outcomes of patients receiving long-term OAC therapy.

**Results:** Thirty-one reports were identified. The quality of the identified reports was generally poor; no randomized controlled trials have been performed and duration of follow-up was typically not stated. Overall, 29 thromboembolic events occurred among 1868 patients (1.6%; 95% confidence interval, 1.0%-2.1%), including 7 strokes (0.4%; 95% confidence interval, 0%-0.7%). Thromboembolic event rates by management strategy were 0.4% (1 of 237) for continuation of OAC, 0.6% (6 of 996) for discontinuation of OAC therapy without administration of intravenous heparin, 0% (0 of 166) for discontinuation of OAC therapy with administration of

intravenous heparin, 0.6% (1 of 180) for discontinuation of OAC therapy with administration of low-molecular-weight heparin, and 8.0% (21 of 263) for unspecified or unclear strategies. Major bleeding while receiving therapeutic OAC was rare for dental procedures (0.2% [4 of 2014]), arthrocentesis (0% [0 of 32]), cataract surgery (0% [0 of 203]), and upper endoscopy or colonoscopy with or without biopsy (0% [0 of 111]).

**Conclusions:** Most patients can undergo dental procedures, arthrocentesis, cataract surgery, and diagnostic endoscopy without alteration of their regimen. For other invasive and surgical procedures, oral anticoagulation needs to be withheld, and the decision whether to pursue an aggressive strategy of perioperative administration of intravenous heparin or subcutaneous low-molecular-weight heparin should be individualized. The current literature is substantially limited in its ability to help choose an optimal strategy. Further and more rigorous studies are needed to better inform this decision.

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**O**RAL anticoagulants (OACs) are commonly prescribed for patients at risk for arterial or venous thromboembolism.

In the United States alone it has been estimated that 2.3 million patients currently have atrial fibrillation, approximately 40% of whom are receiving anticoagulants.<sup>1</sup> The perioperative management of patients receiving OACs is problematic because the medication must be discontinued to prevent excessive bleeding for many invasive and surgical procedures. Substituting intravenous heparin or subcutaneous low-molecular-weight heparin (LMWH) while oral anticoagulation is withheld can decrease the risk of thromboembolism but may increase the risk of postoperative bleeding and, in the case of intravenous heparin, increase the hospitalization requirement.

There is no consensus on the optimal management of patients receiving

OACs during the perioperative period. A rational strategy would be evidence-based and would consider the patient's risks of thromboembolism and bleeding. To better inform clinicians on the available evidence, we performed a systematic

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review and synthesis of the literature, examining studies of perioperative management of patients receiving OACs.

#### METHODS

A MEDLINE search of English-language clinical studies from January 1966 to June 2001 was performed using the MESH heading "Surgical Procedures, Operative," and the MESH heading "Anticoagulants" with subheadings "therapeutic use," "adverse effects," and "toxicity," and excluding the text terms "prophylaxis" and "prophylactic." The references of the re-

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**Table 1. Thromboembolic Event Rates by Anticoagulation Strategy**

Management Strategy	No. of Thromboembolic Events/ No. of Patients at Risk (%) [95% CI]	Description of Thromboembolic Events (No.)	References
Continued oral anticoagulation	1/237 (0.4) [0-2.3]	Cerebrovascular accident*	4-11
Discontinued oral anticoagulation without administration of intravenous heparin or subcutaneous LMWH	6/996 (0.6) [0-1.1]	Cerebrovascular accident (2), cerebrovascular accident and peripheral arterial thrombosis (1), mitral and aortic valve thrombosis (1), popliteal artery thrombosis (1), unspecified (1)	4, 5, 7, 9, 12-16
Administered perioperative intravenous heparin	0/166 (0) [0-2.2]	None	7, 9, 15, 17-19
Administered perioperative LMWH	1/180 (0.6) [0-3.1]	Transient ischemic attack (1)	20-23
Discontinued warfarin therapy, and administered preoperative phytonadione and postoperative intravenous heparin	0/26 (0) [0-13.2]	None	12
Unspecified or unclear	21/263 (8.0) [5.0-12.0]	Cerebrovascular accident (3), transient ischemic attack (3), clotted arteriovenous graft (3), peripheral arterial embolism (12)	20, 24
Overall thromboembolic events	29/1868 (1.6) [1.0-2.1]		
Overall cerebrovascular accidents	7/1868 (0.4) [0-0.7]		

Abbreviations: CI, confidence interval; LMWH, low-molecular-weight heparin.

\*The patient experienced major bleeding postoperatively, required immediate reoperation and reversal of anticoagulation with fresh frozen plasma, and then had a stroke during the perioperative period of the second surgery.

tried articles were examined for pertinent studies. In addition, the Cochrane Collaboration database was searched, a "cited reference search" was performed to identify studies citing the retrieved studies, and the files of the authors were reviewed for relevant articles. Case reports and letters to the editor were excluded.

Event rates are reported as number of patients experiencing the event divided by number of patients at risk. Binomial and Poisson distributions were used to calculate 95% confidence intervals (CIs), as appropriate.

## RESULTS

A total of 31 reports were identified, including 2 that included patients previously reported in earlier case series<sup>2,3</sup> and 7 that reported data on bleeding complications but not thromboembolic events. Of the remaining 22 studies, 1 was a systematic review of 26 reports on the management of oral anticoagulation for patients undergoing dental procedures.

The quality of the identified reports was generally poor. There have been no randomized controlled trials that compare withholding warfarin sodium therapy and administering intravenous heparin or subcutaneous LMWH with withholding warfarin therapy without administering anticoagulation. In most reports there were small sample sizes, there was often no control group of patients not receiving long-term anticoagulation, the timing of anticoagulation administration and discontinuation were often not described, and the duration of follow-up was typically not stated. Most reports were based on the type of intervention (eg, cataract surgery) and will be described separately.

### OVERALL THROMBOEMBOLIC EVENTS

A tabulation of thromboembolic events by anticoagulation management strategy is given in **Table 1**. For studies reporting thromboembolic events, 29 thromboembolic events occurred among 1868 patients receiving long-term oral an-

ticoagulation and undergoing surgery or invasive procedures (1.6%; 95% CI, 1.0%-2.1%), including 7 strokes (0.4%; 95% CI, 0%-0.7%).

### MAJOR AND MINOR SURGICAL AND INVASIVE PROCEDURES

Katholi and colleagues<sup>4</sup> reported the results and management of 36 patients with mechanical heart valves who had undergone 44 (22 major and 22 minor) subsequent noncardiac procedures. None of the 25 patients with mechanical aortic valves who had anticoagulation withheld perioperatively had a thromboembolic event. In contrast, 2 of 10 patients with mechanical mitral valves who had anticoagulation withheld perioperatively had thromboembolic events. Of the 9 patients who had oral anticoagulation continued throughout the procedure, 4 had major bleeding. Based on these results, the same investigators developed a management protocol and performed a prospective cohort study of 39 patients undergoing 45 noncardiac procedures.<sup>12</sup> Oral anticoagulants were discontinued for all patients. For patients with isolated mechanical aortic valves, oral anticoagulation was withheld "in time to produce a normal prothrombin time," and perioperative heparin was not administered. For patients with mechanical mitral valves, warfarin therapy was withheld and parenteral phytonadione administered during the 24 hours prior to surgery, and intravenous heparin was administered postoperatively beginning 12 hours after surgery. For patients with mechanical aortic valves, no thromboembolic events or major bleeding events occurred during 10 major surgical procedures and 9 minor procedures. For patients with mechanical mitral valves, no thromboembolic events occurred, and there was 1 major bleeding event (4%) during 13 major surgical procedures and 13 minor procedures. A retrospective study performed at the Mayo Clinic, Rochester, Minn, described the management and results of 159 patients with

**Table 2. Summary of Prospective Studies Examining the Use of LMWHs for the Perioperative Management of Patients Receiving Oral Anticoagulation**

Study Feature	Johnson and Turpie <sup>21</sup>	Tinmouth et al <sup>22</sup>	Spandorfer et al <sup>23</sup>
No. of patients	112	24*	20
Excluded patients at low risk for thromboembolic events (ie, atrial fibrillation without stroke risk factors)	No	Yes	Yes
LMWH, dose and frequency	Dalteparin, 100 IU/kg every 12 h	Preoperatively, dalteparin 200 IU/kg once daily; postoperatively, 100 IU/kg twice daily when hospitalized and 200 IU/kg once daily after discharge	Enoxaparin, 1 mg/kg every 12 h
Protocol			
Time prior to procedure of discontinuation of warfarin therapy	Not stated	4 d	5-6 d
Time prior to procedure of initiation of LMWH therapy	Not stated	2 d	36 h after warfarin therapy discontinued
Time prior to procedure of last preoperative LMWH dose	12 h	1 d	12-18 h
Time after procedure of initiation of LMWH therapy	8-12 h and after "hemostasis secure"	The following morning	Once hemostasis was achieved
Outcomes, No. (%)			
Minor bleeding	5 (5)	2 (8)	2 (10)
Major bleeding	1 (1)	0	1 (5)
Thromboembolism	0	1 (5)	0

Abbreviation: LMWH, low-molecular-weight heparin.

\*Twenty-four patients underwent 26 procedures.

prosthetic heart valves undergoing 180 noncardiac operations.<sup>5</sup> Treatment with OACs was discontinued for 87% of procedures. Perioperative heparin was not administered. No perioperative thromboembolic events were noted. The authors reported that "difficulties with hemostasis" occurred during 13% of operations and that almost all bleeding complications were associated with elevated prothrombin times on the morning of surgery. A prospective cohort study of 40 patients receiving long-term anticoagulation and undergoing 50 operations reported that 5 thromboembolic events (33%) occurred after 15 operations in which warfarin therapy was withheld and that heparin was not administered perioperatively for 4 of these 5 operations.<sup>24</sup> The authors noted that bleeding occurred during 4 (13%) of 30 operations when warfarin therapy was continued and for 8 (40%) of 20 operations when warfarin was withheld and heparin administered. The timing of administration and discontinuation of warfarin and heparin therapy and the level of anticoagulation achieved for these groups were not described. Maduro and colleagues<sup>17</sup> examined the management of 21 patients receiving warfarin who required major surgery. All patients had perioperative heparin administered while warfarin therapy was withheld. There were no thromboembolic events. Seven patients (33%) experienced bleeding, all of whom required another operation. Carrel and colleagues<sup>20</sup> performed a retrospective review of the perioperative management and outcomes of 235 consecutive patients with mechanical heart valves who underwent subsequent operations. Patient treatment included continuation of oral anticoagulation, discontinuation of oral anticoagulation without administration of heparin, or discontinuation of oral anticoagulation with administration of intravenous or subcutaneous heparin or subcutaneous LMWH. Over-

all, 18 (8%) of 235 patients had hemorrhagic events and 16 (7%) of 235 had thromboembolic events. Events were not reported separately for each anticoagulation strategy. None of 22 patients treated with LMWH had a thromboembolic or bleeding event.

Three prospective cohort studies describe perioperative protocols and outcomes using LMWHs (**Table 2**).<sup>21-23</sup> All studies included patients undergoing major and minor surgery as well as invasive procedures and oral surgery. Overall, the rates of thromboembolic events and major bleeding were low; of the 156 patients studied, 1 had a transient ischemic attack and 2 experienced major bleeding.

## SPECIFIC SURGICAL AND INVASIVE PROCEDURES

### Dental Procedures

A comprehensive review identified 26 case reports and studies examining bleeding and thromboembolism after dental procedures.<sup>13</sup> Procedures included single and multiple dental extractions, full mouth extractions, and alveolectomies. "Serious" bleeding occurred during or soon after 12 (0.6%) of 2014 dental procedures in which OACs were continued. Eight of the 12 episodes of serious bleeding were associated with a supratherapeutic international normalized ratio at the time of the procedure or the week after the procedure. Excluding 3 thromboembolic events from single case reports, 2 thromboembolic events (0.4%) were noted in 537 cases after OAC withdrawal for dental procedures. Two additional prospective studies of patients undergoing dental and oral surgery were published after the systematic review. A study of 20 patients who had warfarin therapy withheld and intravenous heparin administered and a study of 104 patients who had warfarin with-

**Table 3. Studies Examining the Perioperative Management and Incidence of Hemorrhagic Events in Patients Receiving Oral Anticoagulants Undergoing Cataract Surgery**

Source	No. of Patients/ No. of Eyes	Anticoagulation Strategy	Hemorrhagic Events, No. (%)	Comment
Hall et al <sup>6</sup>	42/49	Warfarin therapy continued	Hyphema, 3 (6)	All resolved within 14 d.
Gainey et al <sup>7</sup>	50/50	Warfarin therapy continued (n = 9); warfarin therapy withheld without administration of heparin (n = 31); warfarin therapy withheld and intravenous heparin administered (n = 10)	Hemorrhagic complications: warfarin therapy continued group, 2 (22); warfarin withheld without heparin group, 4 (13); warfarin withheld with heparin group, 0 (0)	Bleeding events for patients who had warfarin therapy continued had no effect on long-term visual acuity, though surgery was canceled for 1 patient and 1 patient required rehospitalization.
Roberts et al <sup>27</sup>	31/35	Patients receiving warfarin or antiplatelet agents who had the medication therapy continued	Retrobulbar hemorrhage, 1 (3)	Results not analyzed separately for warfarin.
Carter and Miller <sup>28</sup>	25/31	Warfarin therapy continued (n = 9); warfarin therapy withheld (n = 15); unknown (n = 7)	Subconjunctival hemorrhage, 3 (10)	All resolved without sequelae. Results not reported separately for different strategies.
Robinson and Nylander <sup>29</sup>	10/10	Warfarin therapy continued	Hyphema, 3 (30)	Two were mild and the third was associated with an international normalized ratio of 4.7.
McMahon <sup>30</sup>	22/28	Warfarin therapy continued (n = 26); warfarin withheld and intravenous heparin administered (n = 2)	Mild hyphema, 3 (12)	More minor bleeding in patients receiving anticoagulation than control patients not receiving anticoagulants. Event rates for control patients are not stated.

held for 2 days without administration of heparin reported that no patients experienced thromboembolic or bleeding events.<sup>14,18</sup>

### Cutaneous Surgery

Otley and colleagues<sup>25</sup> performed a retrospective study of 653 patients undergoing cutaneous surgery, including 127 who were being treated with warfarin. Of patients undergoing Mohs micrographic surgery, there were no moderate or severe wound complications in 14 patients who had warfarin therapy continued during the perioperative period, 2 (3%) of 61 patients who had warfarin therapy withheld during the perioperative period, and 2 (1%) of 165 control patients not receiving anticoagulants or nonsteroidal anti-inflammatory medications. Of patients undergoing excisional surgical procedures, moderate or severe wound complications were noted for 4 (33%) of 12 patients who had warfarin therapy continued during the perioperative period, 1 (2%) of 40 patients who had warfarin therapy withheld during the perioperative period, and none of 102 control patients. A prospective study of 322 patients undergoing Mohs micrographic surgery found that of 12 patients who had received warfarin within 2 days of surgery, 5 (42%) experienced "excessive" intraoperative bleeding and 1 (8%) required a procedure to be performed, compared with 4% and 0.5% of controls, respectively.<sup>26</sup>

### Cataract Surgery

A low risk of clinically important perioperative bleeding if OAC therapy is continued has been demonstrated in several studies of patients undergoing cataract surgery<sup>6,7,27-30</sup> (**Table 3**). Though continuing oral anticoagulation throughout the procedure has not been shown to affect long-term visual acuity, the available literature suggests an increase in minor bleeding events, includ-

ing mild hyphema (bleeding in the anterior chamber) and subconjunctival hemorrhage.

### Permanent Pacemaker and Defibrillator Procedures

Goldstein and colleagues<sup>8</sup> reported their experience with outpatient pacemaker surgery for 150 patients, including 37 who were maintained on warfarin therapy perioperatively. Procedures included pacemaker implantation and revision and generator replacement. Two patients (5.4%) maintained on warfarin therapy and 2 patients (1.8%) not receiving warfarin experienced wound-related bleeding complications ( $P = .25$ ). There were no wound hematomas requiring treatment, and no patients required transfusion. A study of patients receiving OACs and undergoing implantation of a permanent pacemaker or defibrillator randomized 49 patients who had oral anticoagulation withheld preoperatively and were believed to have an "indication for intravenous anticoagulation" to initiation of intravenous heparin therapy either 6 hours or 12 hours postoperatively.<sup>15</sup> An additional 28 patients who received postoperative warfarin therapy alone and 115 patients who were not receiving OACs were followed up prospectively as controls. A pocket hematoma developed in 10 (20%) of 49 patients treated with postoperative heparin, 1 (4%) of 28 patients who received postoperative warfarin alone, and 2 (2%) of 115 patients who were not receiving anticoagulants. There was no difference in bleeding complications between patients started on intravenous heparin therapy 6 or 12 hours postoperatively.

### Cardiac Catheterization

A Swedish study examined the incidence of bleeding for 50 consecutive patients with mechanical heart valves who had oral anticoagulation continued during cardiac catheterization.<sup>31</sup> Of the 50 patients, 3 (6%) experienced hematoma formation requiring surgical intervention com-

pared with none of the 50 control patients who were not receiving anticoagulant treatment. Thromboembolic events were not reported.

### Gastrointestinal Endoscopy

A retrospective review of patients at the Palo Alto Veterans Affairs Health Care System, Palo Alto, Calif, identified 104 patients receiving warfarin who underwent 171 endoscopic procedures.<sup>9</sup> Of the procedures, 111 were classified as having a low risk for bleeding complications (eg, upper endoscopy or colonoscopy with or without biopsy) and 60 as having a high risk for bleeding complications (eg, polypectomy) based on guidelines published by the American Society for Gastrointestinal Endoscopy.<sup>32</sup> In addition, 86 patients were classified as being at low risk for thromboembolism and 18 at high risk for thromboembolism. The management strategies are given in **Table 4**. No thromboembolic or bleeding events were noted during the procedure or within 3 months of follow-up.

### Genitourinary Surgery

Several studies of patients undergoing transurethral resection of the prostate have examined contrasting management strategies. A study examining operative blood loss randomized 23 patients undergoing transurethral prostate resection to interruption of warfarin therapy with or without continuous administration of intravenous heparin throughout the perioperative period.<sup>33</sup> Mean blood loss was similar in the 2 groups. A retrospective examination of the management of 21 patients receiving warfarin for mechanical heart valves and undergoing transurethral resection of the prostate reported that all patients had warfarin therapy withheld and that phytonadione was administered to 6 patients to reverse the effect of warfarin.<sup>16</sup> No thromboembolic or bleeding events were noted. A retrospective study reported results of 12 patients undergoing transurethral resection of the prostate who had warfarin therapy withheld and intravenous heparin administered perioperatively.<sup>19</sup> The mean decrease in hemoglobin level was 1.6 g/dL compared with 1.1 g/dL in an unmatched control group of 222 patients not receiving long-term anticoagulants. Three patients in the anticoagulation group required hospitalization for bladder hemorrhage. Parr and colleagues<sup>34</sup> reported the outcomes of 14 patients receiving OACs who had anticoagulation continued throughout transurethral resection of bladder tumor or the prostate. Four patients (16%) required blood transfusion, 3 of whom had a decrease in hemoglobin level of more than 2 g/dL. A study examining the safety of continuing warfarin therapy during laser ablation of the prostate for benign prostatic hypertrophy found that 3 patients (15%) required blood transfusion.<sup>10</sup> One of these patients required reoperation in the immediate postoperative period, received fresh frozen plasma to reverse anticoagulation, and then had a stroke during the perioperative period of the second surgery.

### Arthrocentesis and Joint and Soft Tissue Injections

Thumboo and Duffy<sup>11</sup> performed a prospective study of 32 joint and soft tissue aspirations and injections per-

**Table 4. Management of Oral Anticoagulation in Relation to Thromboembolic and Bleeding Risk for Patients Undergoing Gastrointestinal Endoscopy\***

Bleeding Risk	Thromboembolic Risk	
	Low	High
Low	52/93 (56): Warfarin therapy continued throughout the procedure† 20/93 (22): Warfarin therapy withheld and intravenous heparin administered 21/93 (23): Warfarin therapy withheld without heparin administration	5/18 (28): Warfarin therapy continued throughout the procedure† 13/18 (72): Warfarin therapy withheld and intravenous heparin administered
High	44/60 (73): Warfarin therapy withheld without heparin administration† 16/60 (27): Warfarin therapy withheld and intravenous heparin administered	5/5 (100): Warfarin therapy withheld and intravenous heparin administered†

\*From study by Gerson et al.<sup>9</sup> Data are number of patients/number at risk (percentage).

†Practice in agreement with American Society for Gastrointestinal Endoscopy guidelines.<sup>32</sup>

formed in 25 patients who had oral anticoagulation continued throughout the procedure. Lidocaine hydrochloride was instilled during 96% of injections. Procedure sites included the wrist, elbow, knee, ankle, greater trochanteric bursa, and subacromial bursa. None of the patients experienced joint or soft tissue hemorrhage, as determined by patient self-report 4 weeks after the procedure.

### ANALYTIC TECHNIQUES

Eckman and colleagues<sup>35</sup> performed a decision analysis and cost benefit analysis comparing an aggressive strategy of withholding warfarin therapy and administering perioperative intravenous heparin with a minimalist strategy of withholding warfarin therapy 3 days preoperatively and starting it as soon as possible postoperatively. For major and minor surgery and all valve types, the aggressive strategy produced an increase in quality-adjusted life expectancy; however, the average gain in life expectancy was generally small and associated with greatly increased health care costs. For example, prolonging hospitalization for a patient with a mechanical aortic valve for 3 days to administer intravenous heparin would produce an average gain in life expectancy of less than 1 day and cost over \$1 000 000 per additional quality-adjusted life-year. In contrast, the cost of 3 days of intravenous heparin therapy for patients who would require continued hospitalization for routine postoperative care was substantially lower (\$27 000 to \$84 000 and \$60 000 to \$202 000 per additional quality-adjusted year of life expectancy for patients with mechanical mitral and aortic valves, respectively).

Kearon and Hirsh<sup>36</sup> estimated the benefits and risks of an aggressive strategy (consisting of withholding warfarin therapy and administering intravenous heparin for

2 days prior to and 2 days after surgery) and a minimalist strategy in which warfarin therapy is withheld and intravenous heparin not administered. The authors reported that under most circumstances, administration of perioperative intravenous heparin results in a net increase in major disability or death. Several exceptions were noted: (1) patients with atrial fibrillation or mechanical valves who had a stroke or peripheral thromboembolism within the previous month benefited from intravenous heparin therapy before and after surgery, (2) patients who had had a venous thromboembolic event within the previous month benefited from intravenous heparin therapy before and after surgery, and (3) patients who had had a venous thromboembolic event 2 to 3 months prior to surgery benefited from postoperative intravenous heparin therapy.

#### COMMENT

It is not possible to draw firm conclusions on the relative efficacy and safety of different management strategies using the available literature owing to variations in patient populations, procedures, anticoagulation regimens, definitions of events, and durations of follow-up. Randomized controlled trials or large rigorous cohort studies are needed to provide reasonable estimates of the perioperative risks of thromboembolism and bleeding for patients managed with an aggressive strategy of perioperative intravenous heparin therapy or subcutaneous LMWH therapy and a minimalist strategy of withholding warfarin therapy without administration of heparin.

The available literature provides insight on the risk of major postoperative bleeding for patients who have OAC therapy continued perioperatively and indicates that OAC therapy can be continued without increasing the risk of major bleeding for single and multiple dental extractions, joint and soft tissue injections and arthrocentesis, cataract surgery, and upper endoscopy or colonoscopy with or without biopsy. If OAC therapy is continued, the international normalized ratio should be within the therapeutic range at the time of the procedure.

For procedures and surgery requiring discontinuation of oral anticoagulation, the decision needs to be individualized based on the available literature, though substantially limited, and the patient's preference. Our analysis found arterial thromboembolism and stroke rates of 1.6% (95% CI, 1.0%-2.1%) and 0.4% (95% CI, 0%-0.7%) for all patients and 0.6% (95% CI, 0%-1.1%) and 0.3% (95% CI, 0%-0.7%) for patients who had warfarin therapy withheld without administration of intravenous heparin or subcutaneous LMWH (Table 1). These observed thromboembolism and stroke rates are greater than would be expected for nonanticoagulated patients with atrial fibrillation or mechanical heart valves, based on a mathematical model of thromboembolism rates derived from studies of patients in nonsurgical settings. For example, a patient with a mechanical aortic valve who does not receive anticoagulation has an annual risk of stroke of approximately 4%,<sup>37,38</sup> and an aggressive strategy of hospital admission for intravenous heparin therapy for 2 days prior to and 2 days after surgery provides approximately 4 more days of anticoagulation than a minimalist strategy of withholding warfarin

therapy 4 days prior to surgery and restarting it the night of surgery. The calculated risk of stroke over these 4 days without anticoagulation is approximately 0.04%. This expected rate contrasts sharply with the observed overall stroke rate of 0.4% (95% CI, 0%-0.7%), which includes patients who did not receive perioperative anticoagulation as well as patients who received perioperative intravenous heparin and subcutaneous LMWH.

Anticoagulation decreases the risk of stroke for patients with mechanical heart valves by approximately 75%.<sup>38</sup> Therefore, based on a calculated expected perioperative stroke rate of 0.04%, anticoagulating the patient for 4 days produces an absolute reduction in risk of stroke of 0.03% (equivalent to prevention of 1 stroke for every 3333 patients treated); the observed overall stroke rate of 0.4% produces an absolute reduction in risk of stroke of 0.3% (equivalent to prevention of 1 stroke for every 333 patients treated). Thus, the difference in the calculated and observed stroke rates has important clinical implications.

Potential explanations for the difference in the expected and observed thromboembolic rates are the unclear duration of follow-up from most of the reports, hypercoagulability due to discontinuation of warfarin therapy, a prothrombic state induced by the surgical milieu, or chance. The lack of a standard or explicit duration of follow-up for most of the reports is a crucial limitation because the number of days patients were monitored for thromboembolic events would be expected to have a great impact on the number of events reported. A theoretical risk of rebound hypercoagulability after discontinuation of OAC therapy has been described based on studies demonstrating increases in markers of thrombin generation, including prothrombin fragment 1 and 2, thrombin-antithrombin complexes, fibrinopeptide A, and D-dimers, and increased levels of factor VIII.<sup>39-42</sup> Whether these laboratory findings translate into an increased risk of thromboembolic events is controversial. Similarly, the surgical milieu has been found to induce a hypercoagulable state, including increased levels of plasminogen activator inhibitor 1.<sup>43,44</sup> While these findings are implicated in the increased risk of venous thromboembolic events in the perioperative period, their impact on the risk of arterial events is uncertain.

In addition to the potential benefit from perioperative anticoagulation, the increased risk of postoperative major bleeding must be considered. Interpretation of the bleeding rates from the available reports is difficult because bleeding rates for invasive procedures and minor and major surgery are often not analyzed separately and different definitions of major bleeding are used. Based on the available data, the increase in major bleeding over 2 days in the postoperative period is likely to be approximately 2% to 4% for major surgery and 0% to 2% for invasive procedures.<sup>6,9,11-13,45-52</sup>

The substantial difference in the consequences of major bleeding and thromboembolism must also be considered. Permanent disability or death is common after arterial thromboembolism (approximately 70%-75%) and infrequent after venous thromboembolism (approximately 4%-10%) or postoperative major bleeding (approximately 1%-6%).<sup>20,49,53-56</sup>

**Table 5. Guideline for the Perioperative Management of Anticoagulation for Procedures Requiring Discontinuation of Oral Anticoagulant Therapy**

Indication for Anticoagulation	Examples	Recommendation
Indication with low annual risk of thromboembolic stroke (<4%) without anticoagulation	Atrial fibrillation without history of thromboembolic stroke; cardiomyopathy without atrial fibrillation	Withhold oral anticoagulation.
Indication with moderate annual risk of thromboembolic stroke (4%-7%) without anticoagulation	Mechanical aortic valve	Withhold oral anticoagulation. Optional administration of either treatment-dose intravenous heparin or subcutaneous LMWH while INR subtherapeutic.
Indication with high annual risk of thromboembolic stroke (>7%) without anticoagulation	Mechanical mitral valve; atrial fibrillation with history of thromboembolic stroke	Withhold oral anticoagulation and administer either treatment-dose intravenous heparin or subcutaneous LMWH while INR subtherapeutic.

Abbreviations: INR, international normalized ratio; LMWH, low-molecular-weight heparin.

Low-molecular-weight heparins may cause less bleeding than unfractionated heparin by causing less of a decrease in platelet aggregation and less of an increase in vascular permeability than unfractionated heparin.<sup>57-60</sup> Though clinical trials have not consistently found a decreased bleeding rate for LMWHs, meta-analyses of trials of deep vein thrombosis treatment have found a 40% relative risk reduction in major bleeding.<sup>61,62</sup> In addition, LMWHs can be given subcutaneously and without laboratory monitoring<sup>63-65</sup> and thus afford an opportunity to provide perioperative anticoagulation at home while oral anticoagulation is withheld preoperatively or reinitiated postoperatively. The lack of a readily available laboratory test for monitoring may also be a disadvantage, since clinicians cannot be certain of the amount of anticoagulant effect present at the time of surgery. In addition, LMWHs are only partially reversible by protamine sulfate.<sup>66</sup> Further studies are needed to determine whether outpatient perioperative LMWH therapy is a safe and efficacious alternative to hospitalization for intravenous heparin.

### CONCLUSIONS

Most patients undergoing dental procedures, joint and soft tissue injections and arthrocentesis, cataract surgery, and upper endoscopy or colonoscopy with or without biopsy can undergo the procedure without alteration of their OAC regimen. For other invasive and surgical procedures, oral anticoagulation needs to be withheld, and the decision whether to pursue an aggressive strategy of perioperative administration of intravenous heparin or subcutaneous LMWH should be individualized based on an estimation of the patient's risks of thromboembolism and bleeding and the patient's preference. Though the literature is limited, a guideline to assist clinicians based on the available evidence is presented in **Table 5**.

The current literature suggests that the perioperative stroke rate for patients who have anticoagulation withheld may be substantially greater than would be predicted based on the annual thromboembolic rates of patients with atrial fibrillation or mechanical heart valves determined in nonsurgical settings. Whether this is due to the lack of rigorous methodology of most of the reports of perioperative management or to a hypercoagulable state induced by the withdrawal of warfarin or the sur-

gical milieu is unclear. More rigorous studies are needed to better inform physicians and patients on the risks and benefits of the available management strategies.

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