

# Peri-procedural management of patients taking oral anticoagulants

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## ABSTRACT

The use of oral anticoagulants is becoming increasingly common. For many years warfarin was the main oral anticoagulant available, but therapeutic options have expanded with the introduction of oral direct thrombin (dabigatran) and factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban). Management of patients taking any oral anticoagulant in the peri-procedural period poses a challenge to medical and surgical providers because of the competing risks of thrombosis and hemorrhage. Bridging therapy has been used to minimize time without anticoagulation when warfarin is interrupted for invasive procedures, but validated strategies based on high quality data are lacking. Existing data suggest that the use of bridging therapy may increase the risk of bleeding for some patients without reducing the risk of thrombosis. Clinical trials are currently under way to answer these questions. Because the half lives and time to anticoagulant activity of newer oral anticoagulants are shorter than for warfarin, bridging therapy is not thought to be necessary with these agents. Peri-procedural management of patients taking these agents is complicated by the lack of demonstrated reversal agents in emergency situations, although specific antidotes are being developed and tested. Existing guidelines for peri-procedural management of patients on oral anticoagulants highlight the importance of individualized patient decision making and suggest strategies to minimize complications. From a patient's perspective, given the uncertainties surrounding optimal management, explicit discussions regarding risks and benefits of treatment options and demonstration of effective communication among medical and surgical providers are essential.

## Introduction

Oral anticoagulants are used for the treatment and prevention of thromboembolism in many patients, including those with atrial fibrillation, venous thromboembolism, and mechanical heart valves. Thus, millions of people worldwide are taking these agents, and the number is projected to grow over the next few decades.<sup>1-5</sup> Although vitamin K antagonists (VKAs) have been the primary class of oral anticoagulants for decades, new ones—such as dabigatran, rivaroxaban, apixaban, and edoxaban—are now approved for use. Although warfarin is still the most commonly prescribed oral anticoagulant, these other agents have entered clinical practice, so physicians and surgeons are likely to encounter patients taking one of these drugs who need peri-procedural management.<sup>6-7</sup>

When a patient taking an oral anticoagulant has an invasive procedure, the drug may need to be stopped temporarily to mitigate bleeding. While treatment is interrupted, the patient is at risk of thrombosis, mostly because of the underlying condition for which the drug was prescribed. Conversely, when the anticoagulant is restarted, the risk of bleeding may be increased during the post-procedure period.

This review summarizes the pharmacology of oral anticoagulants relevant to the peri-procedural period, reported outcomes of peri-procedural management of oral anticoagulants used for therapeutic purposes, and selected guidelines. It also reviews the management of oral anticoagulation in emergency situations.

## Sources and selection criteria

Figure 1 illustrates the primary search strategy used for this review. The aim was to identify literature related to management of anticoagulants in the peri-procedural period. Once this search was conducted, titles and abstracts were reviewed for relevance. Studies were selected if they described the risk assessment of patients on anticoagulants who were undergoing procedures or the outcomes of peri-procedural management. Clinical guidelines were included. Publications outlining approaches to managing complications of peri-procedural management were also included. Studies published as abstracts only, and not as a peer reviewed article, were not included. The reference lists of identified articles were also reviewed to find additional relevant literature.

- PRIMARY SEARCH STRATEGY FOR PERI-PROCEDURAL MANAGEMENT OF ORAL ANTICOAGULANTS**  
 The following strategy was used to search Embase (1988 to 2014, Week 45) and Ovid MEDLINE(R) (1946 to 2004, Week 32):
- 1 Anticoagulants/or 4hydroxycoumarins/or acenocoumarol/or coumarins/or dalteparin/or dicumarol/or enoxaparin/or heparin/or heparin, low-molecular-weight/or heparinoids/or nadroparin/or warfarin/
  - 2 Anticoagulant agent/or antivitamin k/or coumarin anticoagulant/or heparin derivative/
  - 3 (Anticoagula\* or "4-hydroxycoumarin\*" or acenocoumarol or coumarin\* or dalteparin or dicumarol or enoxaparin or heparin\* or heparinoid\* or nadroparin or warfarin or eliquis or xarelto or pradaxa or apixaban or rivaroxaban or dabigatran or edoxaban or coumadin).mp.
  - 4 1 or 2 or 3
  - 5 (Periprocedur\* or "peri-procedur\*").mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]
  - 6 Exp Perioperative period/
  - 7 (Perioperativ\* or "peri-operativ\*").mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]
  - 8 5 or 6 or 7
  - 9 4 and 8
  - 10 Limit 9 to English language

Fig 1 | Primary search strategy for peri-procedural management of oral anticoagulants

**Normal coagulation and clinical pharmacology of oral anticoagulants**

The coagulation cascade is a multi-step process that leads to the production of the primary clot stabilizing molecule, fibrin; understanding this pathway has facilitated the development of anticoagulants. Figure 2 summarizes the coagulation pathway and shows which step(s) in the pathway each drug affects. The table provides selected pharmacologic information on current oral anticoagulants. This review is limited to management of patients taking therapeutic, not postoperative thromboprophylactic, doses of oral anticoagulants.

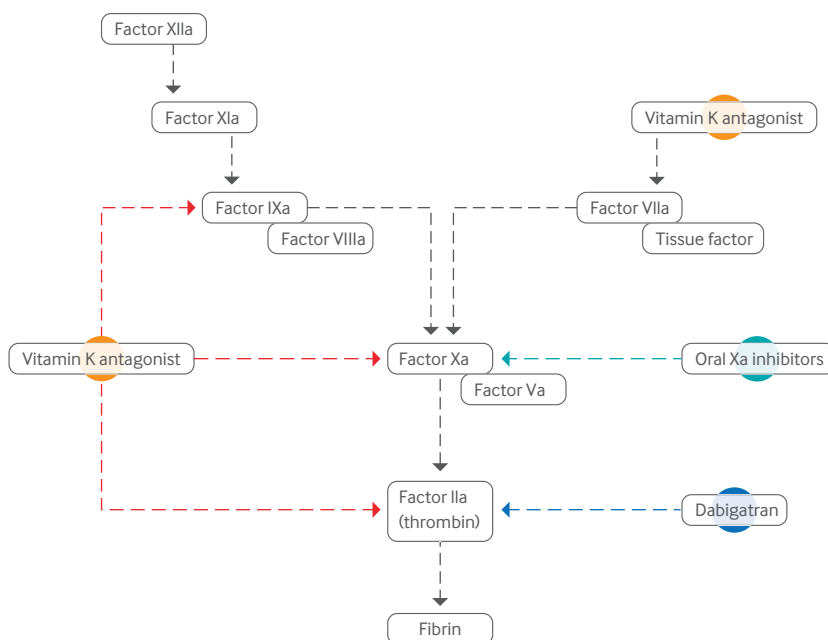


Fig 2 | Simplified coagulation cascade and sites of activity of oral anticoagulants

**Vitamin K antagonists**

VKAs act by depleting the active (reduced) form of vitamin K, which is needed for normal coagulation. Reduced vitamin K is involved in the  $\gamma$ -carboxylation of clotting factors II (prothrombin), VII, IX, and X.<sup>42</sup> After being oxidized in this reaction, vitamin K must be reduced to participate in the carboxylation reaction again, and VKAs inhibit vitamin K epoxide reductase, which catalyses this reduction.<sup>43</sup> The anticoagulant effect of VKAs is therefore the result of a decrease in the carboxylated forms of factors II, VII, IX, and X.<sup>44</sup> Management of patients taking these drugs is also complicated by variable dietary vitamin K content and drug-drug interactions.<sup>45</sup> Fluctuations in effects of VKAs expose patients to the risks of bleeding and thrombosis. Although inconvenient for patients, monitoring of the international normalized ratio (INR) allows VKAs to be titrated to the target level of effect.<sup>46 47</sup> All of the VKAs reviewed have been used in patients with atrial fibrillation, venous thromboembolism, and mechanical heart valves.

**Warfarin**

Warfarin is a highly bioavailable VKA that is readily absorbed from the gastrointestinal tract and oxidatively metabolized primarily through the CYP2C9 enzyme in the cytochrome P450 system.<sup>13 48-50</sup> Warfarin has a half life of 36-42 hours, so it usually takes several days for its anticoagulant effect to develop when it is started and to abate when it is stopped.<sup>21</sup>

**Phenprocoumon**

Phenprocoumon is another VKA that is highly bioavailable and metabolized through the CYP2C9 enzyme.<sup>14</sup> Phenprocoumon differs from other VKAs in that its elimination half life is long—estimated to be 100-150 hours.<sup>14 21 22</sup> As a result, this drug needs to be interrupted for longer when patients undergo invasive procedures.

**Acenocoumarol**

The bioavailability and metabolism of acenocoumarol is similar to that of other VKAs.<sup>14</sup> However, acenocoumarol has the shortest estimated half life of the VKAs considered in this review—eight to 12 hours.<sup>21-23</sup>

**Target specific oral anticoagulants**

The limitations of VKAs have led to the development of alternative oral anticoagulants. Currently, four such drugs—dabigatran, rivaroxaban, apixaban, and edoxaban—which as a group are referred to as target specific oral anticoagulants, have been approved by the Food and Drug Administration. Importantly these drugs are given at fixed doses and coagulation does not routinely need to be monitored. They are categorized on the basis of where in the coagulation cascade they exert their inhibitory effect. The two categories currently available are direct thrombin inhibitors and factor Xa inhibitors.

**Oral direct thrombin inhibitors**

**Dabigatran**

Dabigatran is a direct thrombin inhibitor administered as the prodrug dabigatran etexilate. Once absorbed it is converted to its active form and promotes anticoagulation by directly binding to the active site of thrombin, competitively

## Selected pharmacologic properties of oral anticoagulants\*

Property	Warfarin	Phenprocoumon	Acenocoumarol	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Mechanism of action	VKA <sup>8</sup>	VKA <sup>8</sup>	VKA <sup>8</sup>	Direct thrombin inhibitor <sup>9</sup>	FXaI <sup>10</sup>	FXaI <sup>11</sup>	FXaI <sup>12</sup>
Bioavailability (%)	100 <sup>13</sup>	100 <sup>14</sup>	100 <sup>14</sup>	6.5 <sup>9</sup>	66 <sup>15</sup>	66 <sup>16</sup>	62 <sup>17</sup>
~Time to peak concentration (h)	†	†	†	1.5 <sup>18</sup>	3 <sup>15</sup>	2-4 <sup>19</sup>	1-2 <sup>20</sup>
Average half life (h)	36-42 <sup>21</sup>	100-150 <sup>14 21 22</sup>	8-12 <sup>21-23</sup>	8-14 <sup>18 24</sup>	8-15 <sup>15</sup>	7-11 <sup>19</sup>	9-10 <sup>25</sup>
Mechanism of elimination	Oxidative metabolism <sup>8</sup>	Oxidative metabolism <sup>14</sup>	Oxidative metabolism <sup>14</sup>	80% renal <sup>9</sup>	~25% renal <sup>26</sup>	33% renal <sup>19 27</sup>	35% renal <sup>28</sup>
Therapeutic indication	VTE, AF, MHV	VTE, AF, MHV	VTE, AF, MHV	VTE, AF <sup>29-31</sup>	VTE, AF <sup>32-34</sup>	VTE, AF <sup>35-37</sup>	VTE, AF <sup>38 39</sup>
Therapeutic dose (AF, normal renal function)	Variable	Variable	Variable	150 mg twice daily <sup>40</sup>	5 mg twice daily <sup>41</sup>	20 mg once daily <sup>16</sup>	60 mg once daily <sup>17</sup>

\*AF=atrial fibrillation; FXaI=FXaI inhibitor; MHV=mechanical heart valve; VKA=vitamin K antagonist (vitamin K epoxide reductase inhibitor); VTE=venous thromboembolism.

†Time to antithrombotic effect for VKA depends on time to hypoprothrombinemia.<sup>8</sup>

inhibiting the conversion of fibrinogen to fibrin.<sup>9</sup> Peak plasma concentrations are reached in about 1.5 hours and the half life ranges from about eight to 14 hours, with about 80% of the drug being eliminated through the kidneys.<sup>9 18 24</sup> Of the target specific oral anticoagulants, dabigatran has the highest degree of renal elimination. Dabigatran has been approved by the FDA for use in patients with atrial fibrillation and venous thromboembolism on the basis of clinical trials.<sup>29-31</sup> Dabigatran is the only target specific oral anticoagulant to be studied for use in patients with mechanical heart valves and was shown to increase thromboembolic and bleeding complications compared with warfarin.<sup>51</sup>

#### Oral factor Xa inhibitors

##### *Rivaroxaban*

Rivaroxaban and other oral factor Xa inhibitors target the prothrombin binding site on factor Xa, which converts prothrombin to thrombin.<sup>11</sup> Rivaroxaban reaches peak plasma concentrations in two to four hours; its half life is seven to 11 hours, and about 33% of the active drug is renally excreted.<sup>19 27</sup> The bioavailability of the 20 mg dose in the fasting state is about 66% and absorption is enhanced if it is taken with food.<sup>16</sup> Clinical trials have shown the safety and efficacy of rivaroxaban to be non-inferior to warfarin in patients with atrial fibrillation and venous thromboembolism.<sup>35-37</sup>

##### *Apixaban*

Apixaban is a direct inhibitor of factor Xa with a short time to peak plasma concentration (~3 h) and a half life of eight to 15 hours.<sup>10 15 26</sup> Only about 25% of the drug is eliminated renally, with most being eliminated through hepatic metabolism and the feces. Apixaban has been approved for use in atrial fibrillation and acute and extended treatment of VTE.<sup>32-34</sup>

##### *Edoxaban*

This direct factor Xa inhibitor has been compared with warfarin for the management of atrial fibrillation and VTE and is now approved for these indications.<sup>12 38 39</sup> Edoxaban reaches peak plasma concentration rapidly after administration (1-2 h) and its half life is similar to that of other direct Xa inhibitors (9-10 h); about 35% of the drug is renally excreted.<sup>20 25 28</sup>

#### Bridging therapy

Because the offset and onset of the effect of VKAs such as warfarin and phenprocoumon are slow, when stopped and then restarted around the time of a procedure, there

is a period during which therapeutic anticoagulation is not achieved. To minimize this time, bridging therapy is often used. Unfractionated heparin and low molecular weight heparins (LMWHs) have both been used for this purpose. Bridging therapy itself must also be interrupted during the time of the procedure, but the shorter half lives of the drugs used for bridging treatment enable the time off all anticoagulation to be minimized.

#### Elective interruption of oral anticoagulants during invasive procedures or surgery

Peri-procedural management decisions are based on assessments of competing risks—that of thrombosis when the anticoagulant is stopped and the risk of bleeding when it is restarted after a procedure. This is the basis for determining the need for bridging therapy and the timing of post-procedure anticoagulation. Communication between the providers involved is essential to developing the optimal plan for each patient; this care coordination and teamwork is highly valued by patients.

#### Assessing the risk of peri-procedural thromboembolism

A patient's risk of thrombosis when off anticoagulation depends on the condition for which the drug is prescribed. For patients with non-valvular atrial fibrillation, stroke and arterial thromboembolism are the most feared complications, and the CHADS2 score is used to estimate the risk of these events. This score adds one point for each of the following—congestive heart failure, hypertension, age 75 years or more, and diabetes mellitus—and two points for a history of stroke. The score directly correlates with a patient's annual risk of stroke in the absence of anticoagulation.<sup>52</sup>

CHA2DS2-VASc is a modified version of CHADS2 in which age 75 years or more is given two points and the presence of vascular disease (previous myocardial infarction, peripheral arterial disease, or aortic plaque), age 65-74 years, and "sex category" (female sex) are each given one point.<sup>53</sup> The CHADS2 score, but not the CHA2DS2-VASc score, has been incorporated into guideline recommendations for peri-procedural management of warfarin.<sup>21</sup> To date, no studies evaluating the use of the CHADS2 or CHA2DS2-VASc scores for predicting peri-procedural stroke have been published.

In patients taking oral anticoagulants for VTE, recurrence is associated with several factors, including the presence of cancer and certain molecular thrombophilias.<sup>54-57</sup> Time from last acute VTE event is also important, with the risk of recurrent VTE highest in the first six months

**Procedural bleeding risks\*****High risk (two day risk of major bleed 2-4%)**

Heart valve replacement  
 Coronary artery bypass  
 Abdominal aortic aneurysm repair  
 Neurosurgical, urologic, head and neck, abdominal, or breast cancer surgery  
 Bilateral knee replacement  
 Laminectomy  
 Transurethral prostate resection  
 Kidney biopsy  
 Polypectomy, variceal treatment, biliary sphincterotomy, pneumatic dilatation  
 Placement of a percutaneous endoscopic gastrostomy tube  
 Endoscopically guided fine needle aspiration  
 Multiple tooth extractions  
 Vascular and general surgery  
 Any major operation (duration >45 minutes)

**Low risk (two day risk of major bleed 0-2%)**

Cholecystectomy  
 Abdominal hysterectomy  
 Gastrointestinal endoscopy with or without biopsy, enteroscopy, biliary or pancreatic stent without sphincterotomy, endosonography without fine needle aspiration  
 Insertion of a pacemaker or cardiac defibrillator and electrophysiologic testing  
 Simple dental extractions  
 Carpal tunnel repair  
 Knee or hip replacement and shoulder, foot, or hand surgery  
 Arthroscopy  
 Dilatation and curettage  
 Skin cancer excision  
 Abdominal hernia repair  
 Hemorrhoidal surgery  
 Axillary node dissection  
 Hydrocele repair  
 Cataract and non-cataract eye surgery  
 Non-coronary angiography  
 Bronchoscopy with or without biopsy  
 Removal of a central venous catheter  
 Skin, bladder, prostate, thyroid, breast, and lymph node biopsies

\*Reproduced, with permission, from Spyropoulos and Douketis.<sup>68</sup>

after an event.<sup>54-58</sup> For example, in an analysis of pooled data from seven clinical trials of oral anticoagulants for patients with VTE and no cancer (2925 participants), the rate of recurrence was 12.2 events per 100 patient years in the first six months after discontinuation.<sup>59</sup>

Arterial thromboembolism and prosthetic valve thrombosis are complications in patients with mechanical heart valves, and several factors increase the risk of these events after discontinuation of anticoagulation. A mitral position or caged ball prostheses each carry a higher risk of thromboembolism compared with an aortic position and tilting disc or bileaflet valves.<sup>60</sup> Patients with mechanical heart valves and previous thromboembolism, left atrial thrombus, atrial fibrillation, left atrial enlargement, or decreased left ventricular systolic function are also at higher risk of future thromboembolic events.<sup>61</sup>

Discontinuation of warfarin can result in a temporary hypercoagulable state, known as a “rebound” effect. The clinical relevance of this is difficult to study, although small studies have shown increased concentrations of factor VII or thrombin-antithrombin complexes.<sup>62-66</sup>

**Assessing the risk of peri-procedural hemorrhage**

Bleeding complications are an important concern in patients taking any oral anticoagulant, and tools have been developed to aid decision making for patients with non-valvular atrial fibrillation. The HAS-BLED score is a widely used example. Derived from about 4000 patients with atrial fibrillation taking warfarin in the European Heart Study, this model identifies hypertension (systolic blood pressure >160 mm Hg), abnormal renal and liver function, stroke, bleeding history or predisposition to bleeding, labile INR, older age (>65 years), and drugs (use of anti-platelet agents, non-steroidal anti-inflammatory drugs, or excessive alcohol) as predictors of bleeding.<sup>67</sup>

No models are currently available to assess bleeding risk in patients who are taking oral anticoagulants for VTE or mechanical heart valves. Indeed, HAS-BLED was not specifically derived to predict peri-procedural bleeding risk.

Patients taking anticoagulants undergo many types of procedures, each with its attendant risk of bleeding. Communication among providers is essential so that the potential for procedure related bleeding is well understood. To aid decision making, experts have suggested stratifying procedures on the basis of expected rates of postoperative bleeding (box).<sup>68</sup> The potential amount of blood loss is not the only important criterion; sites where a small amount of blood loss can have serious consequences or where bleeding cannot be seen are also high risk.

**Results of elective peri-procedural management of patients taking oral anticoagulants**

Most of the data on peri-procedural management in patients taking oral anticoagulants come from observational studies of limited quality with variable outcome definitions, bridging therapy regimens, procedure types, and patient characteristics. Because of these limitations, the BRIDGE and PERIOP-2 trials—randomized prospective placebo controlled trials evaluating strategies for peri-procedural management—have been designed; results from the BRIDGE trial have been recently published.<sup>69-70</sup> Examination of all the existing literature is informative.

**Patients taking VKAs**

The trade-off between the competing risks of thromboembolism and anticoagulation related hemorrhage in patients undergoing surgery has long been recognized, and early reports indicate the potential relevance of bridging therapy.<sup>71-73</sup>

The use of LMWH as bridging therapy was first reported in 1999,<sup>74</sup> and since then the number of studies on peri-procedural management has increased. A systematic review and meta-analysis included studies of adults taking VKAs who had elective interruption for invasive procedures or surgery.<sup>75</sup> Studies were included if bridging therapy with a LMWH was given to at least some of the patients. In total, 34 studies were included, all but one of which were cohort studies.<sup>76-109</sup>

Most of the studies looked only at patients who were taking warfarin, but some included patients taking phenprocoumon or acenocoumarol.<sup>76-80 83 90 93 94 97</sup>

## STATE OF THE ART REVIEW

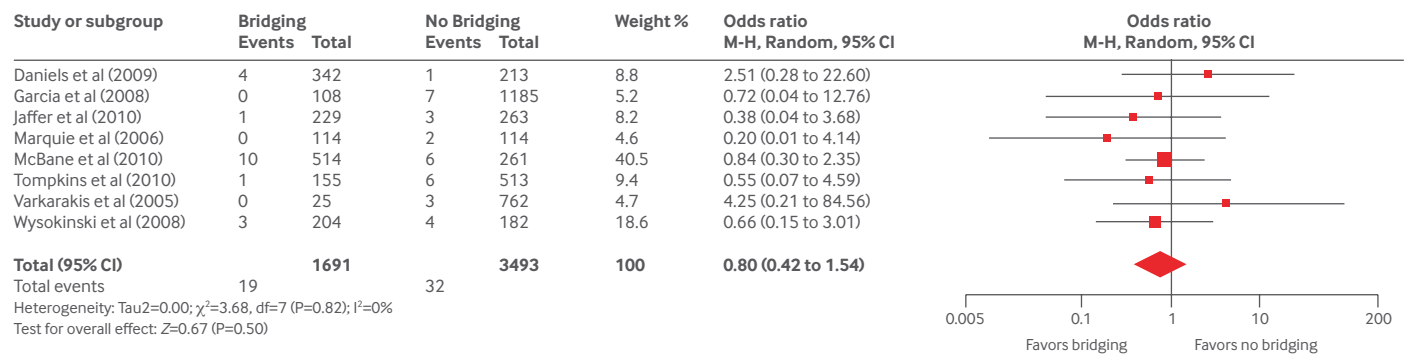


Fig 3 | Forest plot of thromboembolic events. Adapted, with permission from Siegal and colleagues<sup>75</sup>

Bridging therapy was defined as heparin given in the peri-operative period; LMWH dosing was classified as treatment, prophylactic doses, or intermediate doses. The risk of thrombosis was defined as it had been in each primary study, as were thromboembolic and bleeding events. The median duration of follow-up was 30 days after the procedure and the indications for oral anticoagulation were atrial fibrillation (44%), mechanical heart valves (24%), VTE (22%), and other (10%).

In the 16 studies that reported assessment of thrombosis risk, 53% of patients were considered to be at high risk. Procedure types varied widely and included procedures that were associated with a high and low risk of bleeding. In 20 of the studies LMWHs were used at full or therapeutic doses and in 13 studies prophylaxis or intermediate dosing was used. About half of the studies included comparison groups.

In the meta-analysis, 7118 patients received bridging therapy and 5160 did not. The rate of thromboembolism in those who received bridging therapy was 0.9% (0.0% to 3.4%) versus 0.6% (0.0% to 1.2%) in those who did not. As summarized in fig 3, the risk of thromboembolism was not significantly reduced in patients who received bridging treatment versus those who did not (odds ratio 0.80, 0.42 to 1.54). In the two studies in which patients received both options of full or low-intermediate dose bridging therapy, there was no significant difference in thromboembolic events between the groups (0.30, 0.04 to 2.09). There was no heterogeneity across the studies for thromboembolic events.

In the 24 studies that reported major bleeding complications, the reported frequency was 4.2% (0.0% to 11.3%) in patients receiving bridging therapy. In the five studies that reported major bleeding in patients not

receiving bridging therapy, the frequency of major bleeding was 0.9% (0.2% to 1.6%). In studies that compared major bleeding in patients receiving bridging treatment versus those not receiving treatment, the odds ratio was 3.60 (1.52 to 8.50) (fig 4) and an increase in overall bleeding events was seen when full dose bridging therapy was compared with low-intermediate dosing (odds ratio 2.28, 1.27 to 4.08). Heterogeneity for major bleeding was noted across the included studies.

This meta-analysis suggests that bridging therapy does not reduce thromboembolism in patients taking a VKA who undergo an elective invasive procedure. Instead, bridging therapy may increase the risk of bleeding complications. In addition, peri-procedural hemorrhage seems to be more common than thromboembolism. However, because of the various definitions of procedural risk and bleeding used, results should be considered suggestive and not definitive. As the authors pointed out, patients receiving bridging therapy may also have had a higher baseline risk of thromboembolism than those who did not receive bridging therapy, and bridging therapy may have reduced thromboembolic outcomes in high risk patients. These limitations underscore the importance of current clinical trials.

The BRIDGE study is a randomized, prospective, double blind, placebo controlled trial testing the safety and efficacy of bridging therapy during interruptions of warfarin for elective invasive procedures in patients with atrial fibrillation. In this trial, warfarin was stopped five days before the procedure and restarted within 24 hours of the procedure. Overall, 950 patients received no bridging therapy and 934 patients received bridging therapy with dalteparin. Dalteparin was given at a therapeutic dose (100 U/kg/12 h) from three days to 24 hours before the

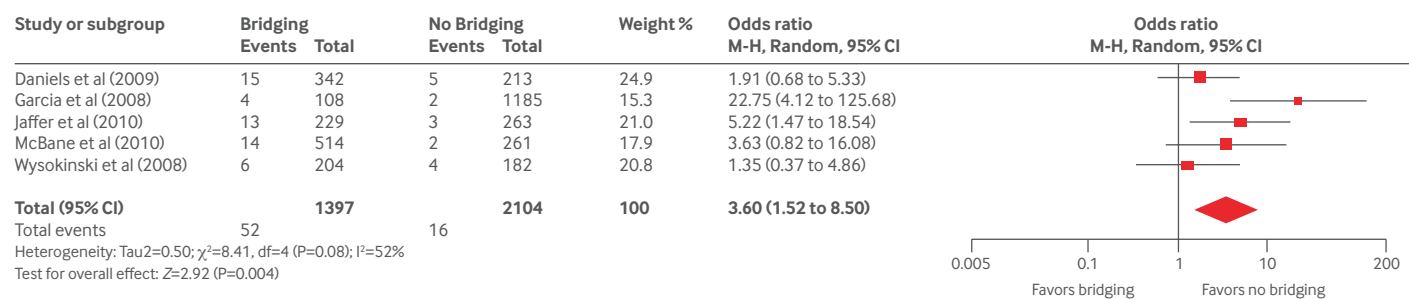


Fig 4 | Forest plot of major bleeding events. Adapted, with permission from Siegal and colleagues<sup>75</sup>

procedure until five to 10 days after the procedure. The groups did not differ significantly with respect to baseline characteristics, including the CHADS2 score; most patients (>80%) in both groups had CHADS2 scores of 1 to 3. The 30 day post-procedure rates of stroke, transient ischemic attack, or systemic embolism were 0.4% in the no bridging therapy group and 0.3% in the bridging therapy group; no bridging therapy was deemed to be non-inferior ( $P=0.01$ ). Major bleeding rates were 1.3% in the no bridging therapy group and 3.2% in the bridging therapy group, a significant difference (relative risk 0.41, 0.20 to 0.78). Thus, this clinical trial seems to confirm the findings of existing observational studies.

Other studies have tried to identify possible associations with peri-procedural hemorrhage. In an analysis of outpatients taking a VKA undergoing 1000 procedures (about half of which were cardiac catheterizations), the independent predictors of bleeding included a HAS-BLED score of 3 or more (hazard ratio 11.8, 5.6 to 24.9).<sup>110</sup> Another study assessed major bleeding events in 2182 patients undergoing 2484 procedures,<sup>111</sup> 1496 of whom received bridging therapy with a LMWH. Major bleeding occurred in 3% of those given bridging therapy and 1% of those not receiving it ( $P=0.018$ ). All major bleeds occurred in patients who received heparin within 24 hours after the procedure. In all patients, bleeding history, presence of a mitral mechanical heart valve, and active cancer were each associated with major bleeding; in those given bridging therapy a platelet count greater than 150 000 and moderate to high bleeding risk procedures were also associated with these events.

Another study evaluated the effect of active cancer on peri-procedural management of anticoagulation and reported that rates of major bleeding were significantly higher than in patients without cancer (3.4% v 1.7%;  $P=0.015$ ).<sup>112</sup> Bridging therapy increased the risk of bleeding in patients with active cancer without affecting the risk of thromboembolism.

Another systematic review and meta-analysis evaluated studies of peri-procedural management of VKAs.<sup>113</sup> Because of heterogeneity in comparison groups, the authors limited the meta-analysis to studies on patients having pacemaker or implantable cardioverter defibrillator surgery. In the pooled analysis of six studies that compared patients who continued with a VKA during the procedure with those who received bridging therapy, the risk of bleeding complications was significantly increased with bridging therapy (relative risk 3.03, 1.86 to 4.95). A subsequent multi-center, single blind, randomized clinical trial—Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial (BRUISE CONTROL)—has further defined the management of VKA in these patients.<sup>114</sup> Patients at moderate to high risk of thromboembolism ( $\geq 5\%$  annual predicted risk) were randomized to continued warfarin or warfarin interruption. Interim findings from the trial resulted in early termination of the study; the relative risk of clinically significant formation of a pocket hematoma was significantly lower without bridging therapy (0.19, 0.10 to 0.36) but with no increase in thromboembolism. This has resulted in expert recommendations that warfarin should not be interrupted

in patients with moderate-high risk of thrombosis undergoing pacemaker or cardioverter defibrillator surgery.<sup>115</sup>

Other procedures for which data support continuation of oral anticoagulation through the peri-procedural period include cataract surgery and minor dental surgery.<sup>116 117</sup> Expert review of reports of dermatologic surgery suggests that it is also reasonable to continue anticoagulation during minor skin procedures.<sup>21</sup>

### Selected guidelines for management of VKA during elective procedures

The most detailed guideline for the peri-procedural management of patients taking a VKA who have atrial fibrillation, VTE, or a mechanical heart valve comes from the American College of Chest Physicians (ACCP) and is based on expert review of the literature.<sup>21</sup>

ACCP recommendations are based on assessments of the patient's thromboembolic and bleeding risks and are designed to guide individualized decisions. The ACCP provides a scheme for thrombosis risk in which low, moderate, and high risk correspond to an estimated annual risk of thrombosis without anticoagulation of less than 5%, 5-10%, and more than 10%, respectively (fig 5). For bleeding risk assessment, the ACCP identifies the following as high risk procedures:

- Urologic surgery (transurethral resection of the prostate, bladder resection, tumor ablation, nephrectomy, kidney biopsy)
- Cardiac device procedures (implantation of a pacemaker or internal cardiac defibrillator)
- Colon polypectomy (particularly >1-2 cm in length)
- Surgery on highly vascular organs
- Bowel resection in which bleeding may occur at the anastomotic site
- Major surgery with extensive tissue injury
- Cardiac, intracranial, or spinal surgery.

The guideline suggests stopping warfarin five days before the procedure and restarting it 12-24 hours afterwards, assuming that adequate hemostasis is maintained. It does not specify the timing of such pre-procedure discontinuation for phenprocoumon or acenocoumarol. Bridging therapy is not recommended for patients with a low risk of thrombosis. For patients at moderate risk the decision should be based on patient and surgery specific factors, and for patients at high risk, bridging therapy is generally recommended.

Pre-procedure bridging therapy should start when the patient's INR is subtherapeutic. Bridging therapy with intravenous unfractionated heparin should be stopped four to six hours before the procedure, and for LMWH the last dose should be 24 hours before surgery. Figure 6 summarizes a suggested approach to elective pre-procedure management of VKAs. If bridging therapy is to be given after the procedure, it should be started 48-72 hours afterwards in patients at high risk of bleeding and 24 hours when the risk is not high. The ACCP suggests omitting bridging therapy in patients with a moderate risk of thrombosis who are undergoing major cardiac surgery or carotid endarterectomy.

Low dose heparins can be considered for bridging therapy in patients with previous VTE because this would serve as

## STATE OF THE ART REVIEW

Thrombosis risk level	Estimated annual thrombosis risk (without anticoagulation)	Indication for vitamin K antagonist therapy		
		Atrial fibrillation	Venous thromboembolism	Mechanical heart valve
HIGH	>10%	<ul style="list-style-type: none"> <li>• CHADS2 score of 5 or 6</li> <li>• Rheumatic valvular heart disease</li> <li>• Recent (within 3 months) stroke or TIA</li> </ul>	<ul style="list-style-type: none"> <li>• Recent (within 3 months) VTE event</li> <li>• Severe thrombophilia</li> </ul>	<ul style="list-style-type: none"> <li>• Any mitral valve prosthesis</li> <li>• Any caged-ball or tilting disc aortic valve prosthesis</li> <li>• Recent (within 6 months) stroke or TIA</li> </ul>
MODERATE	5-10%	CHADS2 score of 3 or 4	<ul style="list-style-type: none"> <li>• VTE within the past 3-12 months</li> <li>• Recurrent VTE</li> <li>• Non-severe thrombophilia</li> <li>• Active cancer (treated within 6 months or palliative)</li> </ul>	Bileaflet aortic valve prosthesis and 1 or more additional risk factor for stroke: <ul style="list-style-type: none"> <li>• Atrial fibrillation</li> <li>• Previous stroke or TIA</li> <li>• Hypertension</li> <li>• Diabetes mellitus</li> <li>• Congestive heart failure</li> <li>• Age over 75 years</li> </ul>
LOW	<5%	Non-valvular AF with CHADS2 score 0-2 and no previous stroke or TIA	<ul style="list-style-type: none"> <li>• VTE &gt;12 months previous and no other risk factors</li> </ul>	Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke

Fig 5 | Suggested risk stratification for perioperative thromboembolism. Adapted, with permission, from Douketis and colleagues.<sup>21</sup> Severe thrombophilia includes protein C, protein S, or antithrombin deficiency; antiphospholipid antibodies, or multiple abnormalities. Non-severe thrombophilia includes heterozygosity for factor V Leiden or prothrombin G20210A mutation. High risk patients also include those with a previous stroke or transient ischemic attack more than three months before the planned surgery and a CHADS2 score less than 5, those with previous thromboembolism during temporary interruption of vitamin K antagonists, and those undergoing certain types of surgery associated with an increased risk for stroke or other thromboembolism (such as cardiac valve replacement, carotid endarterectomy, major vascular surgery). AF=atrial fibrillation; CHADS2 score=one point for each of the following: congestive heart failure, hypertension, age 75 years or more, and diabetes mellitus, and two points for a history of stroke or transient ischemic attack; MHV=mechanical heart valve; TIA=transient ischemic attack; VTE=venous thromboembolism

VTE prophylaxis until warfarin is restarted. Figure 7 summarizes suggested post-procedure strategies for patients taking VKAs. The ACCP endorses bridging therapy for patients with a high risk of thrombosis while recognizing the potential for post-procedure bleeding when anticoagulation is used too aggressively in low or moderate risk patients.

To allow assessment and communication of competing risks, the ACCP recommends evaluating patients seven days before an intended procedure. Taking a patient centered view, the ACCP also recommends providing patients with a calendar that outlines drug management

and educating patients on the proper technique for self administration of LMWH as bridging therapy. These steps are highly valued by patients.

The American College of Cardiology and American Heart Association (ACC/AHA) guideline statements for peri-procedural management of patients taking VKA are in general agreement with those from the ACCP.<sup>119 120</sup> The ACC/AHA recommends that stopping the VKA and omitting bridging therapy is a “recognized approach” for patients with atrial fibrillation at low risk of thromboembolism, those currently in sinus rhythm, and those

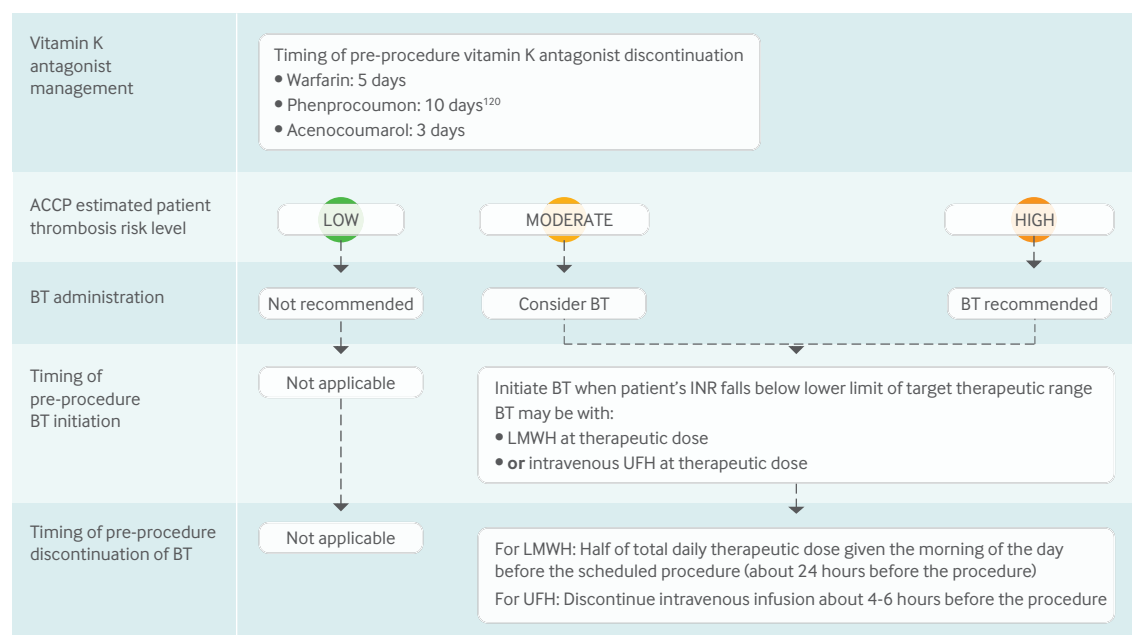


Fig 6 | Suggested approach to elective pre-procedure management of vitamin K antagonists. ACCP=American College of Chest Physicians; BT=bridging therapy; INR=international normalized ratio; LMWH=low molecular weight heparin; UFH=unfractionated heparin<sup>21 118</sup>

## STATE OF THE ART REVIEW

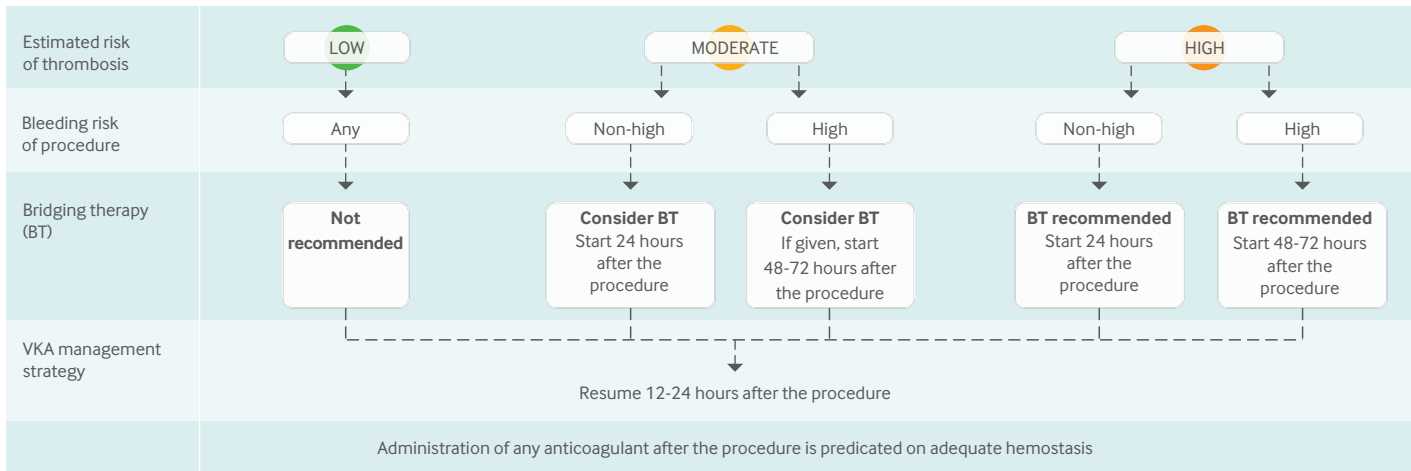


Fig 7 | American College of Chest Physicians' suggested approach to elective post-procedure management of vitamin K antagonists (VKAs)<sup>21</sup>

undergoing a procedure with a risk of bleeding. They cite the use of bridging therapy as “common practice” in patients with atrial fibrillation and a mechanical heart valve, previous stroke, or a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 or more. The ACC/AHA guideline for patients with mechanical heart valves suggests that bridging therapy is not needed in those with one bileaflet aortic mechanical valve only who have none of the following risk factors: atrial fibrillation, previous thromboembolism, “hypercoagulable condition,” older generation-type prosthesis, or left ventricular ejection fraction 30% or less. Bridging therapy is recommended in patients with a mitral, tricuspid, or aortic mechanical heart valve who have any of the risk factors listed above. If LMWH is used as bridging therapy, then twice daily dosing and last dose 12 hours before surgery is recommended. This last recommendation differs from that of the ACCP, which based its recommendation on observations of higher residual LMWH anticoagulant effect when the last pre-procedure dose is the night before surgery.<sup>84 96</sup>

The European Society of Cardiology (ESC) and the British Committee for Standards in Hematology (BCSH) have both published recommendations on peri-procedure management of VKAs.<sup>118 121</sup> The ESC recommends interrupting warfarin five days before invasive procedures and phenprocoumon 10 days before. It also recommends considering bridging therapy in patients with a mechanical heart valve or atrial fibrillation who are at high risk of thromboembolism. The BCSH recognizes the potential harm of postoperative bridging therapy and states that for procedures with a high risk of bleeding, bridging therapy should be given only 48 hours or more after the procedure. For patients who have had a VTE more than three months earlier the BCSH recommends prophylactic doses of LMWH rather than therapeutic dose bridging therapy. It also states that bridging therapy is not needed for patients with atrial fibrillation and no history of stroke or a transient ischemic attack or for patients with a bileaflet aortic mechanical valve and “no other risk factors.” It does recommend bridging therapy for patients with atrial fibrillation with any of the following risk factors: previous stroke or transient ischemic attack, a mitral mechanical valve, or VTE in the preceding three months.

### Patients taking target specific oral anticoagulants

Reports of the management of peri-procedural target specific oral anticoagulants are emerging. Figure 8 summarizes outcomes of peri-procedural management during clinical trials of target specific oral anticoagulants and warfarin. Investigators from the RE-LY trial have reported outcomes within 30 days after temporary interruption of dabigatran.<sup>122</sup> RE-LY compared two dosing regimens of dabigatran (110 mg and 150 mg twice daily) with warfarin in patients with atrial fibrillation.




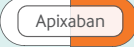
Data were collected on whether oral anticoagulation was interrupted for procedures, the urgency of the procedure (urgent or elective), and the duration of the procedure. Early in the study, investigators were recommended to stop dabigatran 24 hours before the procedure when needed. Later, dabigatran was stopped 24 hours before procedures with a low risk of bleeding but from two to five days beforehand for high risk procedures, depending on the patient’s renal function. Anticoagulation was interrupted at least once in 4591 subjects—about 25% in each study arm.

The most common procedures were the insertion of a pacemaker or cardiac device, dental surgery, and colonoscopy. Bridging therapy was used most often in people taking warfarin (28.5%). The incidence of major bleeding did not differ significantly across the three study groups (3.8%, 5.1%, and 4.6% in dabigatran 110 mg, dabigatran 150 mg, and warfarin groups, respectively), and the peri-procedural risk of ischemic stroke or systemic embolism was about 0.5% in each group and also not significantly different.

For urgent procedures, the risk of major bleeding and ischemic stroke or systemic embolism increased five-fold to sixfold and fourfold, respectively, regardless of treatment arm. Major surgery (>1 hour duration) was also associated with higher rates of major bleeding. For patients receiving dabigatran, there was no significant difference in major bleeding complications before or after the changes in recommended pre-procedure stopping time.

When all cases in which anticoagulant was stopped less than 48 hours before the procedure were examined, both dabigatran groups had lower rates of bleeding than



STUDY	RE-LY <sup>122</sup>	ROCKET AF <sup>123</sup>	ARISTOTLE <sup>124</sup>	
<b>Comparison groups</b>	 (110 mg twice daily) v warfarin	 (150 mg twice daily) v warfarin	 v warfarin	 v warfarin
<b>Patients (n)</b>	1487 v 1558	1546 v 1558	968 v 1162	2701 v 2738
<b>Management</b>	Interruption of study drug for invasive procedure	Interruption of study drug for invasive procedure	Interruption of study drug for invasive procedure	Interruption and non-interruption of study drug for invasive procedure
<b>Stroke or systemic embolism<sup>†</sup></b>	Relative risk (95% CI) 1.05 (0.55 to 2.01)	Relative risk (95% CI) 1.01 (0.35 to 2.87)	Hazard ratio (95% CI) 0.65 (0.20 to 2.13)	Odds ratio (95% CI) 0.60 (0.32 to 1.12)
<b>Major bleeding<sup>†</sup></b>	Relative risk (95% CI) 0.83 (0.59 to 1.17)	Relative risk (95% CI) 1.09 (0.80 to 1.49)	Hazard ratio (95% CI) 1.02 (0.50 to 2.06)	Odds ratio (95% CI) 0.846 (0.61 to 1.17)

<sup>†</sup>Events per patient used in RE-LY analysis; events per procedure used in ROCKET AF and ARISTOTLE analyses.

**Fig 8 | Comparison of 30 day post-procedure outcomes of peri-procedural management of target specific oral anticoagulants and warfarin in the RE-LY, ROCKET AF, and ARISTOTLE trials**

the corresponding warfarin group; however, the warfarin subgroup was more likely to have undergone an urgent procedure.

Investigators from the ROCKET AF trial assessed temporary interruption of rivaroxaban and warfarin.<sup>123</sup> This report included patients whose anticoagulant was stopped for three or more days and resumed within 30 days for an invasive procedure. Investigators could use bridging therapy at their discretion.

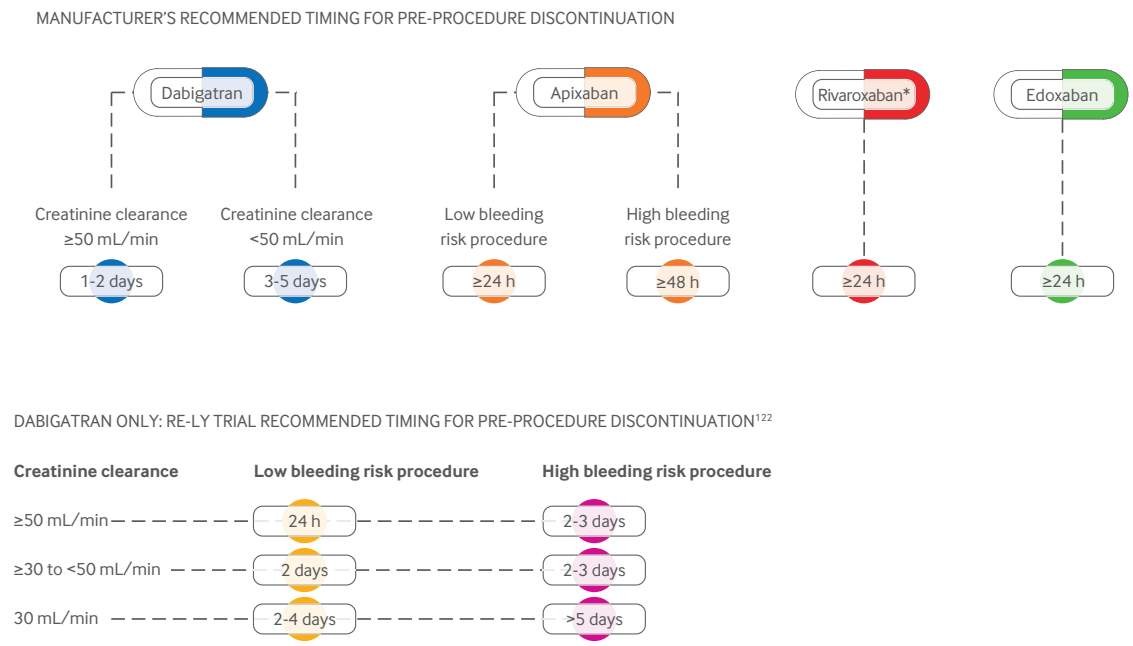
Of the 14 236 patients in this trial, 4692 experienced at least one temporary interruption of anticoagulant treatment. The most common reason for interruption was a surgical or invasive procedure. There were 1309 interruptions for surgery or invasive procedures in the rivaroxaban group and 1688 in the warfarin group. The most common procedures were colonoscopy, gastrointestinal endoscopy, and dental procedures. Oral anticoagulation was stopped three or more days before the procedure in 90% of cases, and the median duration of interruption did not differ between groups. Bridging therapy, typically with LMWH, was used in 431 patients; those given bridging therapy were older and had higher mean CHADS2 scores (3.52 v 3.40; P=0.009) than those not given bridging therapy. There was no significant difference in the rates of stroke or thromboembolism in those taking rivaroxaban and those taking warfarin (0.27% v 0.42%), or in major bleeding complications (0.99% v 0.97%) within 30 days of the procedure. There were also no significant differences in the rates of major bleeding or thromboembolic complications in patients who received bridging therapy and those who did not.

Investigators from the ARISTOTLE trial reported the outcomes of peri-procedural management of patients taking apixaban and warfarin.<sup>124</sup> Of the 18 201 patients enrolled in this trial, 5439 underwent 9260 invasive procedures for which anticoagulation might be interrupted. Data were collected on whether (and if so, for how long) oral anticoagulation was interrupted, whether bridging therapy was used, and whether the procedure was major (general anesthesia used) or emergent. Outcome variables included stroke and systemic embolism, death, and bleeding events within 30 days of the procedure. Local

investigators were provided with suggested strategies, but management decisions including use of bridging therapy were at the discretion of the local investigators. Most procedures (89.8%) were non-major and only 2.9% were emergent. The proportion of procedures for which anticoagulation was interrupted was similar in the apixaban and warfarin groups—62.1% and 63.0% respectively; bridging therapy was given to 11.7% of patients in each group. The timing of discontinuation was also similar between the two groups. In people taking apixaban in whom anticoagulation was interrupted, the drug was stopped two to five days before the procedure in most cases.

For all procedures, whether the study drug was interrupted or not, there was no significant difference in the risk of stroke or systemic embolism and major bleeding between patients taking apixaban and those taking warfarin. Stroke or systemic embolism was seen after 0.35% and 0.57% of procedures in patients taking apixaban and warfarin, respectively (odds ratio 0.601, 0.322 to 1.120). Major bleeding occurred in 1.62% of procedures in patients taking apixaban and 1.93% of procedures in those taking warfarin (0.846, 0.614 to 1.166). For procedures in which anticoagulation was interrupted, the rates of stroke or systemic embolism per procedure were 0.31% and 0.35% in apixaban and warfarin recipients, respectively. Rates of major bleeding were 1.65% in apixaban recipients and 1.26% in those taking warfarin (odds ratios for comparisons not reported). In patients taking apixaban, the risk of thromboembolism and major bleeding was not significantly different between those in whom the drug was interrupted and those with no interruption. Similarly, in those taking warfarin, the risk of stroke or systemic embolism was not significantly different, but the risk of major bleeding seemed to be lower in those whose warfarin was interrupted (adjusted odds ratio 0.223, 0.133 to 0.374). The authors do not report the effect of bridging therapy on complication rates.

The Dresden NOAC registry records data on procedural interruption of target specific oral anticoagulants.<sup>125</sup> This registry comprises more than 2000 patients taking a target specific oral anticoagulant, with rivaroxaban



\*Rivaroxaban only: most subjects in ROCKET AF had rivaroxaban stopped ≥3 days before the procedure

**Fig 9 | Manufacturers suggested approach to discontinuation of target specific oral anticoagulants before elective procedures<sup>16 17 40 41</sup> and recommendations from the RE-LY trial<sup>122</sup>**

being the most common (76%), followed by dabigatran (23.5%), and apixaban (0.5%). In this cohort, 595 patients have undergone 863 procedures (74.3% classified as “minor”). Major cardiovascular events occurred in 1% of all patients undergoing procedures, with major and non-major clinically relevant bleeding rates of 1.2% and 3.4%, respectively. Each of these complications was significantly more common in patients undergoing major procedures (odds ratio for major bleeding with a major procedure 16.8, 3.8 to 78.9). Patients had their anticoagulant continued throughout the procedure (21.7%), had it interrupted with no bridging (48.6%), had bridging with prophylactic dosing (7.3%), or had therapeutic dose bridging (22.5%). Bridging therapy was more likely to be given to patients undergoing major procedures. There was no difference in cardiovascular events when bridging therapy was compared with no bridging therapy. However, the odds ratio for major bleeding was 5.0 (1.2 to 20.4) when patients receiving bridging were compared with those who did not.

A multicentre prospective cohort study has evaluated rates of thromboembolism and bleeding in patients undergoing elective procedural interruption of dabigatran.<sup>126</sup> This study used a dabigatran management strategy that was a slightly modified protocol from that recommended in the latter part of the RE-LY trial. Most (97%) of the 541 patients in this study were taking anticoagulants for atrial fibrillation, and 60% of the procedures performed had a standard bleeding risk and 40% had a high bleeding risk. In 89% of cases the pre-procedure timing of dabigatran cessation followed the protocol and 77% of cases met the recommended post-procedure timing of re-initiation. Only 1.7% of patients received post-procedure LMWH or unfractionated heparin, other-

wise no bridging therapy was used. Major bleeding was noted within 30 days of the procedure in 1.8% (0.7 to 3.0%) of study patients and thromboembolism in 0.2% (0 to 0.5%). Of the 10 patients with major bleeding, eight underwent a high bleeding risk procedure.

Overall, the incidence of peri-procedural thromboembolic and bleeding complications among patients taking target specific oral anticoagulants seems to be low, although many of the procedures in published reports do not carry a high risk of bleeding. These initial reports of outcomes from interruption of target specific oral anticoagulants also seem to support a no bridging therapy approach to peri-procedural management, which is consistent with the known pharmacokinetics of these agents. Additional evaluation of approaches to peri-procedural management target specific oral anticoagulants is under way.<sup>127</sup>

**Recommendations and guidelines for elective interruption of target specific oral anticoagulants**

Figure 9 summarizes manufacturers’ recommendations and the schedule used in the RE-LY trial for the timing of pre-procedure discontinuation of target specific oral anticoagulants.<sup>16 17 40 41 122</sup> The manufacturer of rivaroxaban recommends discontinuation at least 24 hours before surgery or a procedure, whereas the manufacturer of apixaban recommends discontinuation at least 24 hours before an elective procedure with low bleeding risk and at least 48 hours before one with a moderate to high bleeding risk. The recommendations state that pre-procedure bridging therapy is generally not needed.

The manufacturer of dabigatran presents more detailed pre-procedure instructions related to the patient’s renal function, owing to the high renal elimination of this drug. For patients with estimated creatinine

clearance 50 mL/min or more, the manufacturer recommends stopping dabigatran one to two days before the procedure, and for creatinine clearance less than 50 mL/min the recommendation is three to five days before. For edoxaban, the manufacturer recommends discontinuing the drug at least 24 hours before invasive or surgical procedures. The manufacturers of rivaroxaban, apixaban, and edoxaban suggest restarting the drug when adequate hemostasis has been established. There is no explicit instruction for dabigatran but the principle should be the same. Because the time to peak concentration with all target specific oral anticoagulants is rapid, adequate hemostasis is vital to prevent bleeding complications.

The European Heart Rhythm Association (EHRA) has published guidelines for the management of target specific oral anticoagulants during elective procedures.<sup>128</sup> EHRA recommendations incorporate procedure related bleeding risk and patient's renal function. The association recommends discontinuing rivaroxaban and apixaban at least 24 hours and 48 hours before low and high bleeding risk procedures, respectively. The same recommendations apply to dabigatran if creatinine clearance is greater than 80 mL/min. For patients taking dabigatran who have creatinine clearance 50-80 mL/min, the association recommends interrupting anticoagulation at least 36 hours and 72 hours before low and high bleeding risk procedures, respectively. Finally, for creatinine clearance 30-50 mL/min, discontinuation is recommended at least 48 hours and 96 hours before low and high risk procedures. For patients taking rivaroxaban or apixaban with creatinine clearance 15-30 mL/min, the association recommends that the drug be stopped at least 36 hours before low bleeding risk procedures.

The EHRA does not provide any pre-procedure recommendations for edoxaban. The association recommends that a target specific oral anticoagulant may be restarted six to eight hours after a procedure if there is immediate and complete hemostasis, but it notes that resumption of therapeutic dose anticoagulation in the first 48-72 hours after a procedure may increase the risk of bleeding. For patients who are immobile after a procedure, the association recommends considering prophylactic LMWH until the target specific oral anticoagulant is restarted.

### Special considerations

#### Oral anticoagulants and neuraxial anesthesia and epidural catheters

A detailed discussion of this subject is beyond the scope of this review. Placement and removal of catheters for anesthesia in the presence of anticoagulation can result in spinal hematoma and paralysis. For target specific oral anticoagulants, package inserts contain black box warnings that outline suggested uses of these drugs in these circumstances. The American Society of Regional Anesthesia provides detailed guidelines for the management of anticoagulants in these situations.<sup>129</sup>

#### Urgent and emergent peri-procedural management of oral anticoagulants

When a patient taking a VKA or a target specific oral anticoagulant needs an urgent or emergent procedure or has

developed bleeding after resumption of anticoagulation, the approach differs from that in the elective setting.

Discontinuation of the anticoagulant and supportive care for those who are actively bleeding is the first management step. With VKAs, INR testing will indicate the degree of anticoagulation and provide information on how to proceed. It is also important to know when the last dose of a target specific oral anticoagulant was taken because this could identify patients for whom the current level of anticoagulation is minimal. The degree of urgency for a necessary procedure should also be assessed. If a procedure can be safely delayed for 24-48 hours to allow normalization of coagulation, no further intervention for reversal is needed in patients taking a target specific oral anticoagulant. For patients taking these drugs, it is also important to know about current kidney function because drug clearance may be partially or substantially renal, which will have an effect on the drug's half life. For instance, if a patient has acute kidney injury, drug clearance may be prolonged and the anticoagulant effect may persist longer than otherwise anticipated.

#### Prothrombin complex concentrates

For patients taking a VKA who need emergency surgery or who have serious bleeding complications, phytonadione is administered to provide reduced form vitamin K, which is necessary for factor activation, and coagulation factors are supplemented with prothrombin complex concentrates.

These concentrates were developed to treat patients with hemophilia B and contain either three (factors II, IX, and X) or four (factors II, VII, IX, and X) inactive-form coagulation factors. They provide higher than normal concentrations of these factors and can be associated with a risk of thromboembolism.<sup>130</sup> A meta-analysis of 27 studies evaluated complications from concentrates used to reverse VKA anticoagulation. The rate of thromboembolism complications across these studies was 1.4-1.8% in patients treated with four factors and 0.7% in those treated with three factors. The thromboembolism rate was 1.9% and 0.8% in patients given the concentrate for bleeding or before an urgent procedure, respectively.

To mitigate the risk of thrombosis, most concentrates also contain protein C, protein S, antithrombin, or heparin. Concentrates have several advantages over fresh frozen plasma, the traditional form of factor supplementation.<sup>131 132</sup> Concentrates are stored in a lyophilized form and can be prepared and administered more rapidly than fresh frozen plasma, which must be thawed before administration. Compared with fresh frozen plasma, concentrates do not require ABO matching, carry a lower risk of infection risk and transfusion related acute lung injury, and are administered in smaller volumes.

Currently, the only prothrombin complex concentrate approved by the FDA for patients on warfarin who have serious bleeding or are in need of urgent surgery is Kcentra—a four factor concentrate. Approval was based on a trial that showed superiority in the rapid attainment of INR reduction and non-inferior rates of effective hemostasis when Kcentra plus 5-10 mg of intravenous vitamin K was compared with fresh frozen plasma plus vitamin

**HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE**

I consulted with a patient taking warfarin who has experienced interruptions of anticoagulation for procedures. She endorsed the importance of explicit discussions of the risks of thromboembolism and bleeding in these situations. She identified the importance of communication between medical and procedural providers so that these risks can be managed. I have incorporated these concerns into this article by including sections on risk assessment and mentioning the importance of communication between providers. She also reviewed the manuscript before submission.

K.<sup>133</sup> The ACCP 2012 guideline for management of serious bleeding in patients taking a VKA recommends co-administration of a four factor concentrate and slow infusion of 5-10 mg of intravenous vitamin K.<sup>134</sup>

**Monitoring**

Although it is not necessary to monitor the anticoagulant effect of target specific oral anticoagulants in their longitudinal use, in emergency situations an assessment of effect is desirable. However, commonly used tests of coagulation, such as prothrombin time and activated partial thromboplastin time (aPTT), have proved problematic. For example, prothrombin time is relatively insensitive to dabigatran, whereas aPTT may be too sensitive.<sup>135 136</sup> Sharp increases in the aPTT response to increasing dabigatran concentrations mean that even low levels of the drug may be associated with a prolonged aPTT.<sup>137 138</sup> Although linear associations between dabigatran concentrations and both the dilute thrombin time and ecarine clotting time make these assays potentially useful in estimating drug levels, limited availability may hinder their applicability.<sup>137 138</sup>

Studies of coagulation testing for factor Xa inhibitors have also shown mixed results. Prothrombin time seems to be more sensitive than aPTT for rivaroxaban, whereas prothrombin time is insensitive for apixaban.<sup>138-140</sup> Instead, chromogenic anti-factor Xa testing shows a linear association with drug concentration for both rivaroxaban and apixaban and offers a reasonable test for estimating drug levels. However, the availability of this type of assay may be limited and results problematic if the laboratory has not calibrated the assay to the specific Xa inhibitor. In emergency situations, the commonly available coagulation tests may not be helpful for many patients on target specific oral anticoagulants.

**Reversal of target specific oral anticoagulants**

Human clinical studies of factor concentrates to reverse target specific oral anticoagulants are lacking. Rather, prothrombin complex concentrates, activated prothrombin complex concentrates, and recombinant factor VIIa have been evaluated in multiple animal studies and in vitro human studies, and these studies have been the subject of detailed reviews.<sup>141 142</sup>

Recombinant factor VIIa and activated prothrombin complex concentrates were developed for use in hemophilia related bleeding in patients with factor inhibitors. Activated prothrombin complex concentrate contains

**QUESTIONS FOR FUTURE RESEARCH**

What is the optimal time to stop each target specific oral anticoagulant before an invasive procedure to minimize peri-procedural thromboembolic and hemorrhagic complications?

Does administration of prothrombin complex concentrates to patients taking a target specific anticoagulant in need of emergency surgery affect the incidence of peri-procedural thromboembolism or bleeding?

In patients at high risk of thromboembolism, does the use of bridging therapy during interruptions of treatment with a vitamin K antagonist for invasive procedures result in a lower incidence of thromboembolic and hemorrhagic complications?

Does omission of bridging therapy for patients at low risk of thromboembolism result in a decreased incidence of peri-procedural bleeding complications?

In patients given bridging therapy, are intermediate or prophylactic doses of heparin as safe and efficacious as therapeutic doses?

factors II, VII, IX, and X in activated forms, produced during the manufacturing process. Studies of these agents have shown mixed results depending on animal bleeding model, dose of factor concentrate, and laboratory assays used.

In addition, the applicability of animal models and in vitro data to clinical situations involving target specific oral anticoagulants is unclear. However, on the basis of preclinical data, some experts have suggested that prothrombin complex concentrates may be considered for severe or life threatening bleeding in patients taking a target specific oral anticoagulant.<sup>143</sup> These would be off-label uses for these factor concentrates but not unreasonable in dire circumstances. For less than severe bleeding and for patients who are not bleeding but who need surgery, the thrombotic risk of administering these products must be considered. For patients taking dabigatran, hemodialysis is another possibility—four hours of hemodialysis removes about 50% of the dabigatran present.<sup>144 145</sup>

Antidotes to target specific oral anticoagulants for use in emergency situations are in development. Andexanet (PRT 064445), a modified recombinant form of factor Xa that binds directly to the factor Xa inhibitors rivaroxaban and apixaban, has shown promising results in animal and in vitro testing.<sup>146</sup> Similarly, idarucizumab (BI 655075) directly binds to dabigatran and is being evaluated for its ability to reverse the effects of this drug.<sup>147 148</sup> Finally, aripazine (PER977, ciraparantag) is a small molecule in development which binds both dabigatran and the oral factor Xa inhibitors.<sup>149</sup>

**Conclusion**

Many oral anticoagulant options are now available. Despite the long experience with VKA, the optimal approach to peri-procedural management, specifically the role of bridging therapy, is still uncertain. To reduce bleeding and costs, bridging therapy should be avoided in patients at low risk of thrombosis while clinical trials aim to clarify strategies for managing patients at higher risk. Elective peri-procedural management of target specific

oral anticoagulants is also evolving; the pharmacology of these drugs should result in shorter times off anticoagulation without bridging therapy, but optimal strategies need to be validated. For patients on oral anticoagulants who need emergency surgery or who have postoperative bleeding, the management of those taking warfarin is relatively clear, and for patients taking a target specific oral anticoagulant, approaches are being defined. For these patients the advent of target specific oral anticoagulant antidotes offers promise. As approaches are validated by clinical trials, the remaining challenge will be to develop and implement guidelines in an area where individualized care is vital.

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