Periprocedural Bridging of Antithrombotic Therapy

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Interests: Dr. Reimold is a noninvasive cardiologist focusing on patient care and cardiac imaging. Interests include pregnancy and heart disease, valvular heart disease, geriatric cardiology, and atrial dysrhythmias.

Purpose: The purpose of this presentation is to understand the magnitude of the patient risk from vitamin K antagonist interruption, the influence of the surgical procedures on this risk and the associated bleeding risks associated with perioperative bridging.

Educational Objectives: The objectives are to

1) Understand the CHADS2 criteria for stroke risk in atrial fibrillation
2) Review the concept of bleeding risk in patients treated with anticoagulants for atrial fibrillation
3) Learn about the concept of net clinical benefit
4) Understand the current state of bridging therapy as it applies to patients on vitamin K antagonists and are undergoing procedures or operations.

Approximately 2.5 million Americans are anticoagulated with vitamin K antagonists (VKA) therapy annually in the United States (1). The most common reasons for chronic systemic anticoagulation are mechanical heart valves, atrial fibrillation (AF), and deep venous thrombosis. The primary VKA therapy in this country is warfarin. Newer antithrombotic agents including dabigatran, rivaroxaban, and apixaban are increasing in use for the prevention of thromboembolic events in nonvalvular atrial fibrillation. Although patients take these medications on a daily basis, up to 10% percent of patients interrupt this therapy annually at the time of an operation or invasive procedure (1,2). In these patients there is concern about the risk of thromboembolic events while they are off of VKA or antithrombotic therapy. This has led to the concept of "bridging" therapy, replacement of VKA therapy with shorter acting unfractionated heparin and low molecular weight heparins around the time of a procedure in an attempt to reduce the risk of adverse thromboembolic events.

While the concept of bridging therapy has been used for many years, there are no major randomized trials comparing bridging to nonbridging strategies. Thus, the clinician is forced to make treatment decisions based on nonrandomized trials and personal experience. The purpose of this presentation is to understand the magnitude of the patient risk from VKA interruption, the influence of the surgical procedure on this risk and the associated bleeding risks associated with perioperative bridging.

Atrial fibrillation

Stratification of patient risk for thromboembolism

The most frequent indication for chronic anticoagulation is atrial fibrillation. Multiple studies from the early 1990's nicely demonstrated the reduction in stroke risk in patients with atrial fibrillation who were treated with VKA as opposed to aspirin or no therapy. The absolute risk reduction varied between these trials, and the absolute reduction in thromboembolic risk varied from 1-3%.

Early studies focused on the total population with atrial fibrillation and did not account for variation in individual patient risk for embolic events. Subsequently there have been several risk stratification schemes developed. The most widely used scheme is known as the CHADS2 score (3). In this scoring system the risk factors for thromboembolism are congestive heart failure, hypertension, age > 75 years old, diabetes, and stroke/transient ischemia attack (TIA). Prior stroke/TIA is weighted more heavily and given a score of 2 if present. Validated in the National Registry of AF, the annual risk of thromboembolism increases with CHADS2 score (Table 1 (3)). This scoring system has been validated in several cohorts and has been used extensively in deciding whether to recommend warfarin or aspirin therapy to protect against thromboembolism (4,5). In several recent studies, the apparent annual stroke risk rate in patients with a CHADS2 score of is 2% per year, somewhat less than the 2.8% rate noted in the initial CHADS2 cohort (4). As result of a decrease in the embolic risk over the last 2 decades, there is a

revised CHADS2 qualitative estimate of risk. In the original cohort (3), CHADS2 of 0 = low risk, 1 or 2 = moderate risk, and > 2 = high risk. In the more recent cohorts, this has been altered; CHADS2 0 = low risk, 1 = moderate risk, and $\geq$ 2 = high risk (5).

CHADS Score	No. of Patients (n=1733)	No. of Strokes (n=94)	NRAF Crude Stroke Rate Per 100 Patient Years	NRAF Adjusted Stroke Rate, (95% CI)
0	120	2	1.2	1.9 (1.2-3.0)
1	463	17	2.8	2.8 (2.0-3.8)
2	523	23	3.6	4.0 (3.1-5.1)
3	337	25	6.4	5.9 (4.6-7.3)
4	220	19	8.0	8.5 (6.3-11.1)
5	65	6	7.7	12.5 (8.2-17.5)
6	5	2	44.0	18.2 (10.5-27.4)

Table 1. Data from the National Registry of Atrial Fibrillation (NRAF), validating the CHADS 2 score

Of the risk factors in this stratification, heart failure appears to be the weakest and may fall out in multivariable analyses. Inclusion of an assessment of left ventricular function may provide more useful information, but this is not currently incorporated into clinical management (4). Because heart failure is associated with altered myocardial and atrial mechanics, it is logical that this should be predictive of atrial fibrillation and abnormal flow patterns in the left atrium. In the original CHADS2 scheme, a clinical presentation of heart failure was used as the criteria without documented evidence of left ventricular dysfunction.

The importance of increasing age as a risk for thromboembolism has been recognized (6). There is a progressive increase in the risk of thromboembolism in AF by age looking at those patients less than 65, 65-75, 75-85, and greater than 85 years old. In addition, women are at higher risk of thromboembolic events than men and the presence of other vascular problems can

lead to increased risk of embolic risk. Recognition of these risk factors led to the development of the Birmingham 2009 schema otherwise known as the CHA2DS2-VASC score. This risk scheme classifies fewer patients in the intermediate and low risk groups compared to other groups. In the CHA2DS2-VASC scheme, low risk patients had no embolic events as compared to 1.4% risk of events in the conventional CHADS2 scheme (6). In this scheme 0 = low risk, 1 = intermediate risk, and $\geq$ 2 = high risk (Table 2). With this scheme, 9.2% were classified as low risk and 15.1% were classified as moderate risk. The importance of the small intermediate group was that the risk of thromboembolic events also remained low at 0.7%. It should be noted that all existing stratification schemes have only moderate predictive valve in predicting stroke and thromboembolic events.

Risk Factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age $\geq$ 75 years	2
Diabetes	1
Stroke/TIA/Thromboembolism	2
Vascular disease	1
Age 65-74 years	1
Sex category (female gender)	1

Table 2. List of parameters included in the CHA2DS2-VASc Scoring system (6)

Recent studies of the clinical utility of VKA in practice suggest a lower risk of embolic events than seen in the original studies. The ATRIA study (AnTicoagulation and Risk Factors in Atrial Fibrillation) study cohort included 13,559 adults with nonvalvular AF who received care from Kaiser Permanente (7). Baseline demographics, warfarin exposure, and outcome data were

obtained in a rigorous fashion. Therapy was not randomized. INR values were in the therapeutic range approximately 65% of the time. These patients were followed for a median of 6 years. During the followup period there were 1092 thromboembolic events in the cohort (407 on warfarin and 685 not on warfarin) and 299 intracranial hemorrhages (193 on warfarin). The unadjusted annual rate of ischemic stroke/embolism was 2.1% (1.96%, 2.28%) in patients not on warfarin and 1.27% (1.19%, 1.44%) on patients taking warfarin. The annual rate of intracranial hemorrhage was 0.32% (0.27%, 0.39%) in patients not on warfarin and 0.58% (0.51%, 0.68%) in patients on warfarin. The average annual ischemic stroke risk was only 2.1% compared to 4.5% in the initial studies evaluating warfarin in the prevention of embolic events (8).

Concept of net treatment benefit from antithrombotic therapy in AF

Just as in the business world we can estimate the net benefit (risk) from anticoagulant therapy by knowing the following variables: risk of thromboembolism on therapy, risk of thromboembolism without therapy, risk of bleeding on therapy and risk of bleeding off of therapy. In addition to these variables, the value we give to an embolic event versus a bleeding event may vary quite widely. In some instances the risk of intracranial bleeding is used for this calculation since this is the major risk factor associated with adverse outcomes.

The ATRIA study examined the concept of the net benefit of anticoagulation. This concept could obviously be used for any medical and many nonmedical therapies. The formula used for this calculation is as follows (7):

(Net effect on embolic events on VKA versus no therapy) – 1.5(Net effect on intracranial bleeding events on VKA versus no therapy).

In this study, intracranial hemorrhages were weighted at 1.5 times the impact of an embolic event. This value can depend on personal feelings as well as objective information related to the degree of disability associated with an outcome.

Based on the results above, the overall net annual benefit of warfarin in the ATRIA cohort was 0.39% unadjusted and 0.68% when adjusted for embolic and bleeding risk factors. These are annual rates of benefit in this cohort with an average followup period of 6 years.

Data were also analyzed according to patient age and CHADS2 risk score. Results demonstrated that the net benefit of anticoagulation increased with CHADS2 risk score (Figure 1). The average net clinical benefit was minimal to negative for patients with CHADS2 score of 0 or 1. Patients with a CHADS2 score of 2 had a net benefit of 0.97%. Those with a score of greater than 3 had an average benefit of approximately 2%.

The net clinical benefit also varied with age. There was no benefit in patients under the age of 75. The benefit increased to 1% in patients between the age of 75-84 and 2.34% in those over the age of 85. Practitioners are more comfortable anticoagulating patients who are younger

and shy away from anticoagulating elderly patients. Data such as these form the basis for giving therapy to older patients. In addition, some investigators have suggested that current guidelines lead to overuse of warfarin , but these new data may lead to a shift in to the point of deciding to use warfarin (9,10).

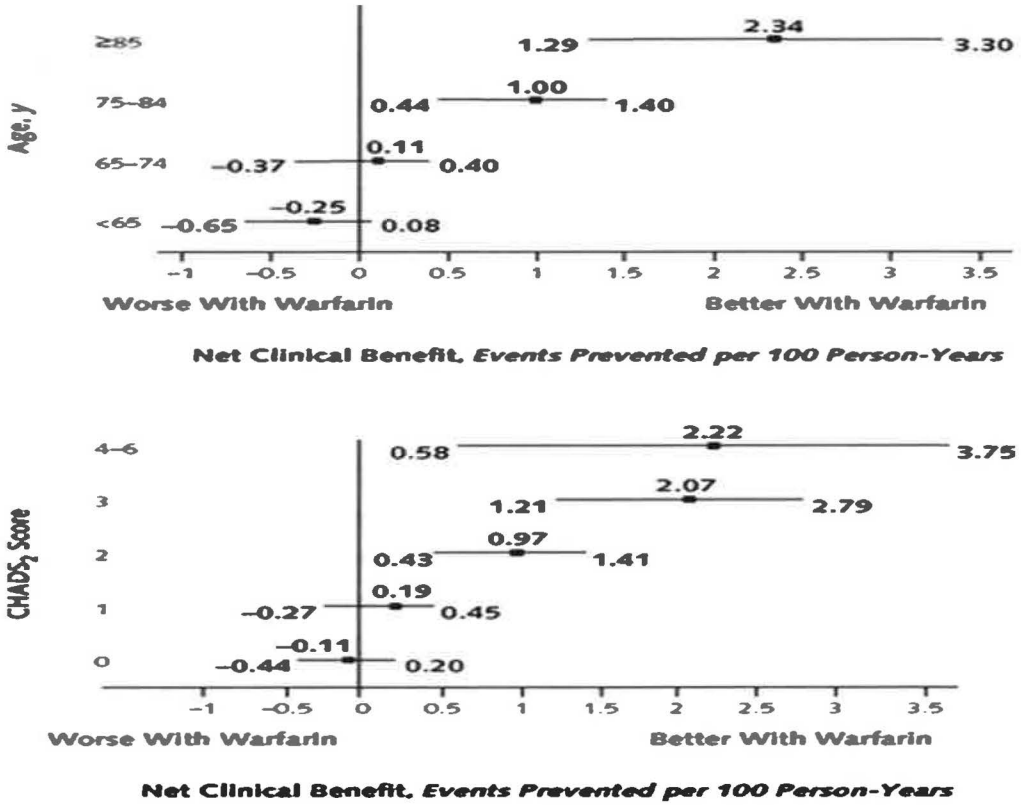

Figure 1. Net clinical benefit of warfarin stratified by age and CHADS2 score (7)

An estimate of treatment effect may be also calculated by looking at treatment or control arms alone. Extracting data from the Poli study, it was noted that higher embolic risks were associated with higher risks of bleeding on VKA (5). In this study of over 3300 patients, the embolic rate was 0.76/100 patient years while the major bleeding rate was 1.24/100 patient years. Of these bleeding events, 0.27/100 patient years were cerebral bleeds. Using the treatment group alone, the net benefit was 0.49/100 patient years if cerebral bleeds were weighted as 1 and 0.36/100 patient years if cerebral bleeds were weighted as 1.5.

These studies describe the annual risk for thromboembolism in AF. We can estimate the daily risk of being off of anticoagulants for a procedure. Multiplying this daily risk by the number of days of drug interruption should yield the overall risk of drug interruption. For atrial fibrillation, it is generally accepted that a CHADS2 score of greater than 2 places a patient in the high risk group for drug interruption. These daily risks, however, are only valid if interrupting

therapy is not associated with a change in embolic risk or if the procedure does not alter embolic risk.

Stratification of bleeding risk from VKA use in atrial fibrillation

Use of antithrombotic agents is associated with increased bleeding risk. Bleeding ranges from minor to significant gastrointestinal and intracranial bleeding. The major bleeding risk of concern is that of intracerebral hemorrhage which may lead to death in the majority of cases. Patient factors are associated with increased risk of bleeding while on these agents. The HAS-BLED study investigated bleeding events in 3978 patients enrolled in the Euro Heart Survey on AF (11). They then sought to determine predictors of bleeding. In this population, 1.5% (53) patients experienced a major bleed. Major bleeding was defined as intracranial, bleeding resulting in hospitalization or transfusion, or a decrease in hemoglobin > 2 g/L.

The derived bleeding risk score included hypertension, abnormal renal/liver function, stroke, bleeding history of predisposition, labile INR, age > 65 years old, and drugs/alcohol concomitantly (Table 3). Patients with a score of 0-1 have an annual bleeding risk of approximately 1%. A score of 2 correlated with bleeding risk of 1.88%. Scores greater than 2 were associated with a marked increase in annualized bleeding rates. A second bleeding stratification scheme is known as HEMOR2RHAGES which associates bleeding risk with hepatic or renal disease, ethanol abuse, malignancy, age > 75 years, thrombocytopenia, hypertension, anemia, genetic factors, excessive fall risk and prior stroke (11). The HAS-BLED authors recommend consideration of bleeding rates as well as embolic rates when making the decision to initiate therapy for thromboprophylaxis in atrial fibrillation. Many of these same parameters may be important in perioperative bleeding as well.

Letter	Clinical Characteristic	Points Awarded
H	Hypertension	1
A	Abnormal renal and liver function	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly	1
D	Drugs or alcohol	1 or 2

Table 3. List of clinical characteristics used in the HAS-BLED strategy (11).

Bleeding risk stratification has been examined in the Mayo Clinic Thrombophilia Center (12). They examined bleeding events in 1496 patients who received bridging therapy for venous thromboembolism (38%), atrial fibrillation (30%) and mechanical heart prostheses (27%). Major bleeding was more common in patients receiving bridging therapy (3% versus 1%). Independent risk factors for bleeding included mechanical heart valves 2.2 (1.1, 4.3), prior bleeding history 2.6 (1.5, 4.5), active cancer 1.8 (1.0, 3.1) and initiation of heparin therapy within 24 hours of the procedure/surgery 1.9 (1.1, 3.4).

Stratification of procedural risk of thromboembolism

Approximately 1/5 of procedures performed on anticoagulated patients are viewed as low risk procedures (2). These include dental, dermatologic, and ophthalmologic procedures. There are 5 cohort studies evaluating interruption of VKA prior to eye surgery. In these studies one patient suffered a periprocedural myocardial infarction. Interestingly, more patients had thromboembolic events with continuation of VKA than with interruption of therapy. Ophthalmologists vary in their acceptance of the general recommendation to continue VKA in patients undergoing cataract surgery.

Several cohort studies have assessed the impact of continuing VKA at the time of dermatologic surgery. No substantial thromboembolic events have occurred in these patients but there is a tendency for an increased clinical relevant mild bleeding.

The most common procedures performed in this population are dental. Evaluated in 3 randomized trials and 10 cohort studies, there were no embolic events with continuation of VKA therapy (2). Significant bleeding events are rare but nonmajor bleeding can be seen. This is usually managed with a variety of local prohemostatic techniques (amicar based mouthwash). As a result, it is currently recommended that VKA be continued in patients undergoing uncomplicated dental procedures.

No bridging for pacer/defibrillation placement or for ablation

Many patients undergoing electrophysiology procedures (pacer, defibrillator placement, ablation) are chronically treated with warfarin or antiplatelet agents due to their underlying associated cardiovascular problems. Previous recommendations supported the use of heparin bridging therapy for patients on VKA at the time of cardiac device implantation. There are many reports of increased bleeding in patient who receive heparin bridging in this setting with the development of many pocket hematomas with an increased overall bleeding rate (13,14).

As a result there is more interest in continuing VKA therapy periprocedurally in these patients but there are only small randomized or multicenter studies to address this question. Cheng and colleagues randomized 100 patients receiving cardiac devices to VKA interruption or

bridging based in part on thromboembolic risk (15). There were no adverse outcomes in those patients continuing VKA. Five significant adverse events occurred in patients who were bridged (2 pocket hematomas, 1 pericardial effusion, 1 transient ischemic attack, and 1 heparin induced thrombocytopenia). Given the small size, no definitive conclusions can be drawn. A meta-analysis evaluated outcomes in patients undergoing pacer or defibrillator implantation who were on antiplatelet or antithrombotic therapies (13). Strategies included no therapy, VKA held to INR < 1.5, VKA continued with INR >1.5, single antiplatelet therapy, dual antiplatelet therapy, and heparin bridging strategy with either unfractionated heparin or low molecular weight heparin. Thirteen trials enrolling 5978 patients were included in the analysis. Indications for anticoagulant therapy in the 6 trials providing data included mechanical prosthetic valves (18.9%), atrial fibrillation (71.8%), and venous thromboembolism (5.6%). Another investigator has suggested that performing cardiac devices with an INR up to 2.5 remains safe (16).

As anticipated, there was variation in the definition of significant bleeding. Overall, major bleeding was generally defined as bleeding resulting in transfusion, surgical intervention, hemothorax, hemopericardium, or bleeding that was viewed as life threatening. Unadjusted rates of bleeding were highest in patients with heparin bridging strategy and next highest for those patients on dual antiplatelet therapy (Figure 2 , 13). Adjusted odds of bleeding were 8.3 (5.5-12.9) in the heparin bridged group, 5.0(3.0-8.3) in the dual antiplatelet group, 1.7(1.0-3.1) in the VKA interruption group, 1.6(0.9-2.6) in the VKA continuation group. Only the rates in the heparin bridged group and the dual antiplatelet group were statistically significant compared to the no therapy group.

Seven of the trials reported thromboembolic events. Overall thromboembolic events were low (9/2375, 0.4%). Rates of thromboembolic events were 0.5% in the VKA held, 0.2% in the VKA continued, and 0.5% in the heparin bridging group. Heparin bridging strategy was not superior to the VKA continued/interrupted groups in any single study.

Results of this meta-analysis as well as results from individual studies have altered the management of patients on VKA who are undergoing cardiac device placement. In most cases, VKA is now continued at the time of these procedures.

Performing radiofrequency ablation while on VKA is also believed to be safe. While there is no randomized trial of patients undergoing ablation, several large studies are available enrolling 27,402 patients (17). In these studies, 6400 patients had continuation of anticoagulation periprocedurally. Continuation of therapy was associated with a decrease in thromboembolic complications OR 0.2 (0.05, 0.23) and minor bleeding complications OR 0.38 (0.21, 0.71). No significant increase in major bleeding complications was noted OR 0.67 (0.31, 1.43).

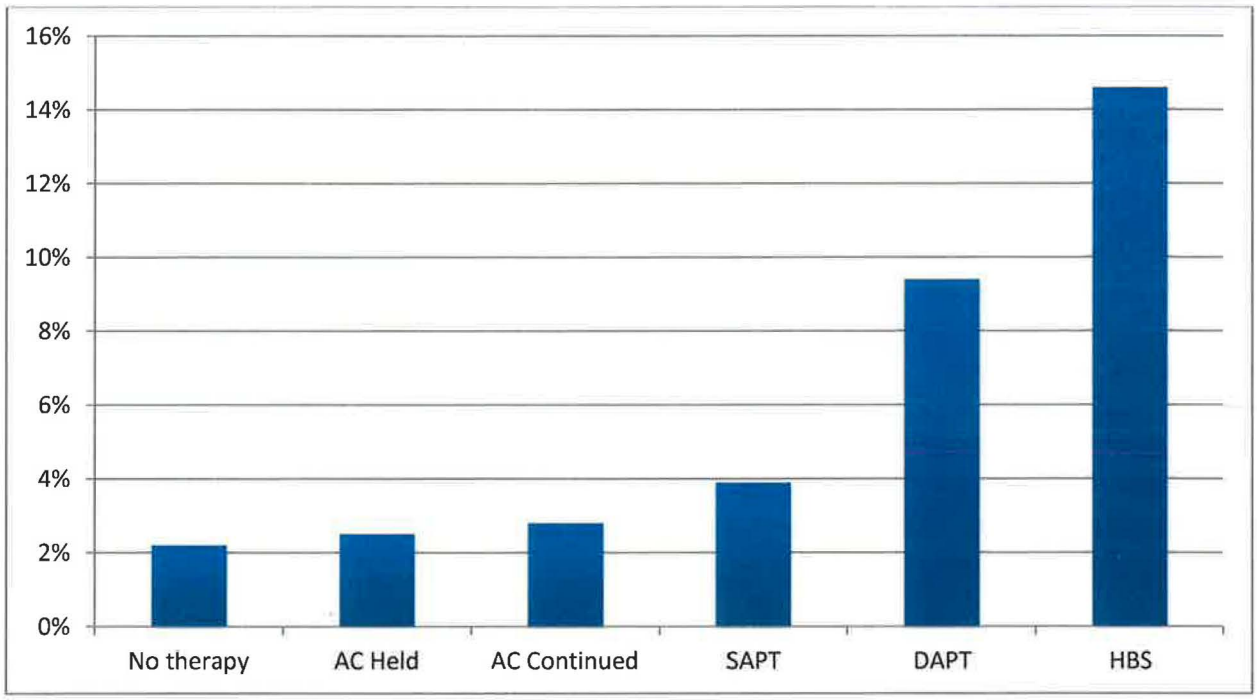

Figure 2. Unadjusted, pooled rates of bleeding complications in patients undergoing cardiac device placement. . Bleeding event rates were 33 of 1500 (2.2%) for no therapy, 26 of 1044 (2.5%) for AC held, 34 of 1200 (2.8%) for AC continued, 45 of 1165 (3.9%) for SAPT, 37 of 394 (9.4%) for DAPT and 99 of 677 (14.6%) for HBS, AC indicates anticoagulant; SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy; HBS, heparin-bridging strategy (13)

Mechanical valve prostheses

Mechanical valve prostheses are associated with an increased risk of thrombosis. Data suggest that the annualized risk of thrombosis is approximately 8.6% with older valves; few data are available for the thrombotic risk of newer bileaflet prostheses (18). The risk is higher with single tilting and caged ball valves and those valves in the mitral position (19). Because the risk of embolism is higher in patients with mechanical valves compared to those patients with atrial fibrillation, bridging therapy with heparin is frequently used perioperatively. Those patients with aortic valve prostheses who have not had an embolic event and do not have another indication for VKA are sometimes managed with simple interruption of therapy. A physician survey concurs with these general recommendations (20). Results from 5 trials using low molecular weight heparin for bridging in patients with aortic and mitral valve prostheses (1189 patients), the risk of thrombosis/embolism was 1.2% with a bleeding risk of 2.7% (1,21).

Current bridging strategies recommend either low molecular weight or unfractionated heparin at therapeutic doses for patients with mitral mechanical prostheses and those with aortic valve prostheses who are at high risk. The newer antithrombotic agents dabigatran, rivaroxaban, or apixaban, are neither approved or indicated for treatment/bridging of patients with mechanical

prostheses. A recent FDA letter was released warning against the use of Pradaxa in patients with mechanical valves due to adverse results in the RE-ALIGN trial (22).

Venous thromboembolism

VKA is used to treat venous thromboembolism. The standard recommendation for most patients with venous thromboembolism or pulmonary embolism is to treat for 3 months. Patients may be treated beyond this initial phase as part of secondary prophylaxis of this disorder. This disorder, however, is recurrent with up to 30% having recurrent thromboembolism within 10 years of the initial event.

Current strategies include interruption of VKA 5 days preprocedure with reinitiation early postoperatively as well as bridging therapy with either low molecular weight heparin or unfractionated heparin. Neither of these strategies has been tested rigorously so the recommendations are based on expert opinion.

A recent manuscript explored the role of periprocedural anticoagulation in venous thromboembolism (23). Patients managed at the Thrombophilia Clinic at the Mayo Clinic from 1997-2007 were enrolled in the study. Patients were enrolled 4-7 days prior to their procedure and had an assessment of their acquired and congenital risk factors for recurrent events.

In patients at low risk for a nonminor procedure, VKA was stopped and then resumed early post procedure/operatively at their standard daily dose. In patients at a higher risk for recurrent events, warfarin was stopped 5 days before the procedure and low molecular weight heparin was started when the INR was estimated to be beneath the therapeutic range. The last dose of LMWH was given 24 hours before the procedure at 50% of the calculated daily dose. LMWH was reinitiated 24-48 hours after the procedure with an overlap with VKA for 5 days or until the INR was therapeutic.

Outcomes focused on symptomatic arterial and venous thromboembolism occurring from 5 days preprocedure to 3 months postprocedure. Major bleeding was defined as a drop in hemoglobin of $\geq$2g/dL after the procedure, need for transfusion, or intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or fatal bleeding. The study population included 775 patients (50% women with an average age of 61$\pm$15 years), 330 of whom had more than 1 prior deep venous thrombosis. Patients were more likely to receive bridging therapy if they were younger, female, had cancer, or had familial thrombophilia.

Evaluation of 3 month follow up data demonstrated 14 patients with 16 recurrent thromboembolic events (1.8% of study group). Adverse events included 10 venous thromboembolic events, 1 acute coronary syndrome and 5 cerebrovascular events. Many of these events (71%) occurred greater than 30 days after the procedure. Active cancer was associated with an increased risk of recurrent event. Two patients died from pulmonary emboli, both of whom were bridged with low molecular weight heparin.

Bleeding occurred in 37 patients, 14 of which were major bleeding. The 3 month major bleeding incidence rate was 1.8%, the same as the embolic rate. Cancer was associated with an increased risk of bleeding.

The authors concluded that the risk of embolic events was low in these patients around the time of invasive procedures. They were unable to document a benefit with this defined bridging strategy and supported the need for a randomized controlled trial to investigate this issue.

Review of studies of heparin bridging

Decisions regarding bridging come to down the concern regarding embolic risk during the interruption of VKA versus the bleeding risk associated with the use of heparin during the perioperative/procedure period. Trials investigating bridging strategies vary significantly with respect to drug use, dosing, and timing of drug administration as well as definition of the patient population. Siegal and colleagues recently published results gleaned from 34 studies published from 2001-2010 investigating the use of bridging strategies (24). A total of 7118 patients were bridged in these studies. Bridging was accomplished with dalteparin, enoxaparin, ardeparin, tinzaparin at therapeutic doses, intravenous unfractionated heparin, or subtherapeutic doses of these agents. Patients not receiving these medications were classified as unbridged. There was also a wide variety of procedures in these studies including dental, orthopedic, endoscopic, ophthalmologic, cardiac device, dermatologic and angiographic. Surgeries included urologic, general, abdominal, vascular, gynecologic, cardiothoracic, and neurologic.

Discontinuation of low molecular weight heparin occurred 12-23 hours before the procedure and greater than 24 hours in 36% patients each. Reinitiation of low molecular weight heparin occurred within 24 hours in 55% of studies and after 24 hours in 16% of studies. Full dose heparin therapy was used in 57% of studies and lower doses were used in 37% of studies.

Pooled thromboembolic events were noted in 71/7118 bridged patients (0.9% (0, 3.4)) and 32/5160 nonbridged patients (0.6% (0, 1.2)). Arterial thromboembolic events were the defined endpoint in 50 bridged and 15 nonbridged patients. Six of the studies stratified patients by thromboembolic risk and those low risk patients either received no bridging or prophylactic dose heparin had an overall thromboembolic rate of 0.6% (11/1702).

Eight studies assessed thromboembolic events in bridged and nonbridged patients; 19/1691 bridged (1.1%) and 32/3493 nonbridged (0.9%) patients had embolic events. No difference was seen between arterial or venous thromboembolic events between the bridged and nonbridged groups.

Bleeding events were assessed in all studies with incomplete delineation of major bleeding events in some studies. In studies where criteria were provided, need for transfusion, hospitalization, death, drop in hemoglobin of > 2g/dl, or need for surgical hemostasis were the

most common end points contributing to major bleeding. In the bridged cohort total and major bleeding were 13.1% (0, 45.2%) and 4.2% (0, 11.3%), respectively. In the nonbridged patients, total and major bleeding were 3.4% (1.1%, 5.8%) and 0.9% (0.2%, 1.6%).

This analysis demonstrated an increased risk of overall bleeding OR 5.4 (3.0, 9.74) and major bleeding risks OR 3.6 (1.52, 8.5) in bridged versus nonbridged patients. Full dose low molecular weight heparin was associated with more bleeding than lower doses of heparin OR 2.28 (1.27, 4.08). Using these data, the net clinical benefit of bridging therapy is negative (not worthwhile and is driven largely by the significant bleeding events.

Overall evaluation of these studies suggests no significant benefit of bridging in terms of reducing thromboembolic events but a significant increase in bleeding. There are many potential limitations of these data including study heterogeneity and nonuniform end points but the analysis raises the concern that bridging with anticoagulants may not be the optimal way to manage patients on VKA (25). Investigators in the field remain on both sides of the "bridge" in terms of whether these strategies are necessary (26, 27)

Use of new antithrombotic agents to prevent embolic events

Dabigatran, rivaroxaban, and apixaban have been used to prevent embolic events in atrial fibrillation. They are all associated with a comparable reduction in embolic events to VKA and a improvement in intracranial bleeding. Overall bleeding events are similar to VKA although there are concerns about gastrointestinal bleeding with dabigatran. None of these agents are easily reversible and clearance may be related to age and renal function.

In the RELY study, dabigatran was compared to warfarin for prevention of embolic events in atrial fibrillation (28). Patients undergoing procedures interrupted their dabigatran 2 days prior to the procedure and warfarin 4 days prior to the procedure. Embolic events were approximately 1.0% in all treatment arms. Bleeding rates were 3.8% in dabigatran 110 mg twice daily, 5.1% in dabigatran 150 mg twice daily, and 4.6% in warfarin. There are many limitations in interpreting these data but the data from the dabigatran groups is similar to data from the large meta-analysis discussed previously.

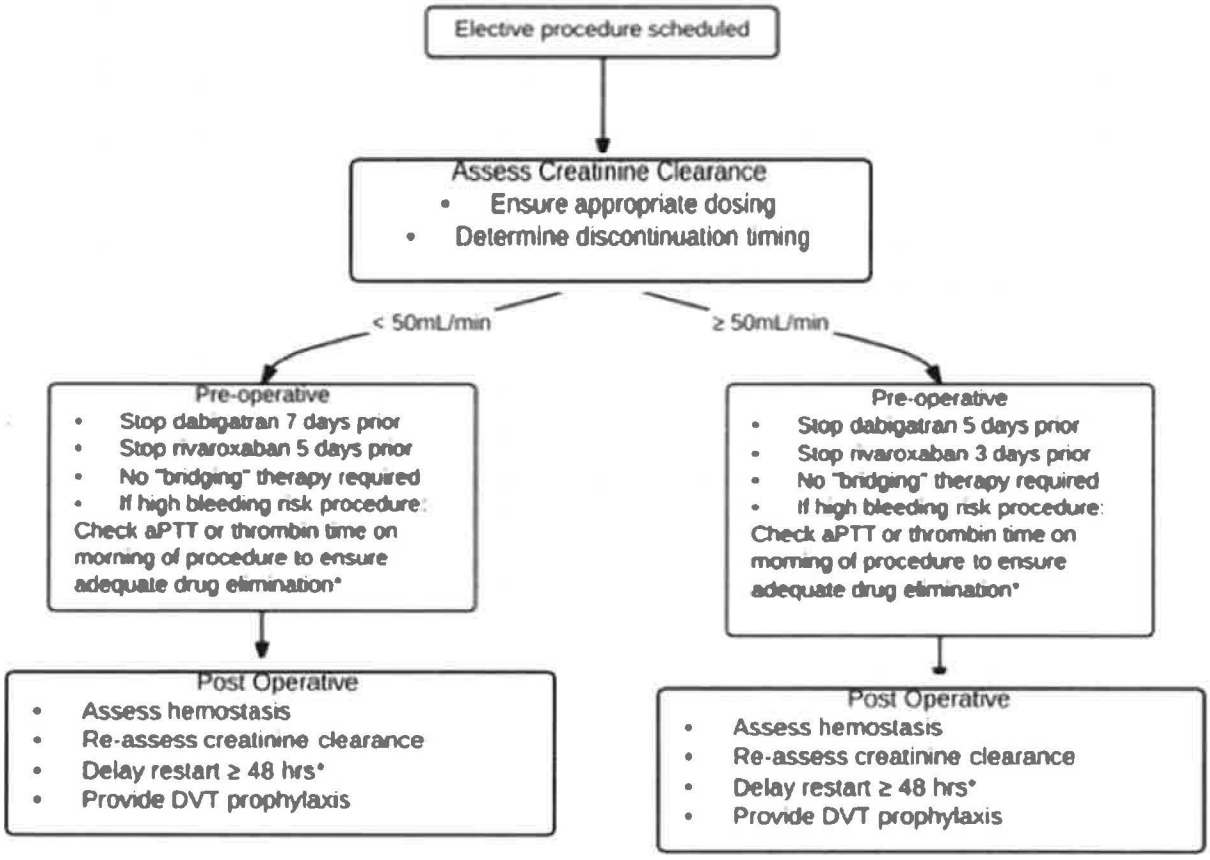

Figure 3. Algorithm for discontinuation of antithrombotic agents. Consider alternative anticoagulants during the postoperative period when risk of bleeding is high or if postoperative bleeding occurs. *Note, aPTT and thrombin time provide a sensitive measure of circulating dabigatran. Assays useful to assess complete rivaroxaban clearance are not yet validated. aPTT indicates activated partial thromboplastic time; DVT, deep vein thrombosis

There are no studies describing how to bridge these agents around the time of a procedure. Moreover, there are descriptions of thrombotic/embolic events shortly after stopping these agents suggesting a prothrombotic state. Quantitation of the likelihood of this is not available. In the absence of studies, there are suggested strategies for discontinuing these agents that incorporate choice of agent as well as renal function (Figure 3).

Ethical and patient aspects of bridging therapy

Decisions concerning periprocedural VKA therapy should incorporate the physician/health care provider viewpoint of the relative benefit/risk of drug interruption versus bridging. Providers attach different values for embolic events versus bleeding events and many seem to be more focused on the prevention of embolic events rather than on the impact of

bridging therapies on bleeding. Rarely is there any evidence of an assessment of patient concerns/preferences in terms of the embolism/bleeding ratio. Patient values and preferences concerning thromboprophylaxis are variable and may be influenced by prior exposure or experience with the therapy as well as methods to elicit preferences (29) As we move forward in a field where there may not be a perfect answer, we should account for patient preference.

Standardized reporting in patients with indications for VKA therapy who are undergoing periprocedural antithrombotic and bridging therapy.

As seen in the multiple small studies assessing the role of bridging therapy, insufficient information is given regarding patient and surgical risk. For instance, it has been recommended that procedures be divided into a high post-procedural risk group (2 day risk of major bleeding of 2-4% without bridging therapy) which would include cardiothoracic, abdominal, and orthopedic surgeries as well as a low bleed risk group with a 2 day risk of major bleeding of 0-2%. The latter group would include same-day office procedures. These data as well as patient specific information should be included in trials to allow for effective comparison.

Recommendations for standardized reporting of periprocedural antithrombotic therapy include (30):

1) Standardized description of patient risk (type and position of valve, major stroke risk factors, CHADS2 score)
2) General description of the type of procedure/surgery
3) Description and type and dose of antithrombotic therapy including bridging protocol
4) Primary outcome should be defined as stroke, TIA, systemic embolism. Secondary endpoints may include myocardial infarction and acute coronary syndrome.
5) The ISTH surgical definitions of major bleeding should be used.
6) A 30 day followup period should be used to report outcomes.

Ongoing randomized trials

There are currently two ongoing randomized trials assessing the effectiveness and safety of bridging antithrombotic therapy at the time of procedures. As seen previously, most of the trials are nonrandomized and the active treatment group (bridging therapy) may have different risk profiles than the control group (nonbridging therapy).

The Effectiveness of Bridging Anticoagulation for Surgery (The BRIDGE Study) Study is investigating the role of dalteparin versus no bridging therapy in patients with all types of atrial fibrillation who are chronically anticoagulated for the prevention of thromboembolic events (31,32). Only patients with a CHADS2 score of at least one are included. Those individuals with a mechanical prosthetic valve and a recent history of a thromboembolic event

are excluded for participating. Patients are randomized between dalteparin administered twice daily for three days before the surgery and 6 days after the procedure versus a comparable placebo. End points include assessment of thromboembolic as well as bleeding events.

The second ongoing trial, PERIOP2 – A Safety and Effectiveness Study of LMWH Bridging Therapy Versus Placebo Bridging Therapy for Patients on Long Term Warfarin and Require Temporary Interruption of Their Warfarin is estimated to be complete early in 2013 (33). This trial is assessing major thromboembolism including ischemic stroke, myocardial infarction, peripheral embolism, valve thrombosis, venous thromboembolism and vascular death. In addition secondary measures of bleeding and overall survival will be tracked. A composite score examining the major thromboembolic events and the major bleeding events will be determined.

In PERIOP2, dalteparin is administered once daily for three days prior to the procedure, warfarin is resumed the evening of the procedure, and dalteparin is resumed the morning after the procedure. Patients deemed at high risk for bleeding will be given a prophylactic (but not therapeutic) dose of dalteparin. This trial is enrolling patients with prosthetic heart valves as well as those with atrial fibrillation. Prior to initiating this large study, a small pilot study enrolling 224 patients were performed. In this study the postoperative thromboembolic rate was 3.1% and occurred predominantly in those patients who had anticoagulation held due to bleeding.

It is likely that these two trials will give insight into the role of bridging therapy in the management of patients with atrial fibrillation, mechanical heart valves, and venous thromboembolism undergoing surgery and other procedures. Until data from these trials are available, one should make recommendations on an assessment of the patient and procedural risk of thromboembolism and bleeding.

Other investigators have suggested that protocols need to adjust dosing of low molecular weight heparin for renal dysfunction (34). In a trial of 703 patients (358 at moderate to high risk and 349 at low risk) undergoing procedures, low molecular weight heparin was used for bridging. Reduced doses were used in patients with abnormal renal function and appeared to be associated with reduced incidence of major bleeds (0.4%) of population.

Conclusion

The number of patients on VKA interrupting therapy at least once a year is substantial. Interruption of VKA therapy and performing surgery appears to be associated with an increase in the daily risk of thromboembolic events. It is unclear whether bridging therapy attenuates this risk but it is associated with an increase in the risk of bleeding. This risk may be related to patient specific details, cessation of anticoagulants, or the type of procedure performed.

The net effect of bridging therapy can be assessed as the difference between the rate of thromboembolism in bridged versus nonbridged patients compared to the rate of bleeding in these same patients. Once these data are known, physician and patients can assess their tolerance for risks versus benefits of therapy and determine appropriate management of these agents in the periprocedural period.

Current recommendations for bridging therapy are provided in the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (35). These guidelines recommend the following:

1) In patients who require temporary interruption of a VKA before surgery, we recommend stopping VKAs approximately 5 days before surgery instead of stopping VKAs a shorter time before surgery.
2) In patients who require temporary interruption of VKA before surgery, recommend resuming VKAs approximately 12-24 hours after surgery and when there is adequate hemostasis
3) In patients with a mechanical heart valve, atrial fibrillation, or venous thromboembolism at high risk for thromboembolism, we suggest bridging anticoagulation instead of no bridging during interruption of VKA therapy.
4) In patients with a mechanical heart valve, atrial fibrillation, or venous thromboembolism at low risk for thromboembolism, we suggest no bridging during interruption of VKA therapy.
5) In patients who require a minor dental procedure, we suggest continuing VKAs with coadministration of an oral prohemostatic agent instead of stopping VKAs 2-3 days before the procedure. In patients who require minor dermatologic procedures and are receiving VKA therapy, we suggest continuing VKAs around the time of the procedure and optimizing local hemostasis. In patient who require cataract surgery and are receiving VKA therapy, we suggest continuing VKA around the time of the surgery.
6) In patients who are receiving bridging anticoagulation with therapeutic-dose IV UFH, we suggest stopping UFH 4-6 hours before surgery
7) In patients who are receiving bridging anticoagulation with therapeutic dose subcutaneous LMWH, we suggest administering the last preoperative dose of LMWH approximately 24 hours before surgery (and likely should be administered at 50% of the therapeutic dose.)
8) In patients who are receiving bridging anticoagulation with therapeutic dose LMWH and are undergoing high-bleeding risk surgery, we suggest resuming therapeutic-dose LMWH 48-72 hours after surgery.

An algorithm for perioperative bridging is shown below (Figure 4):

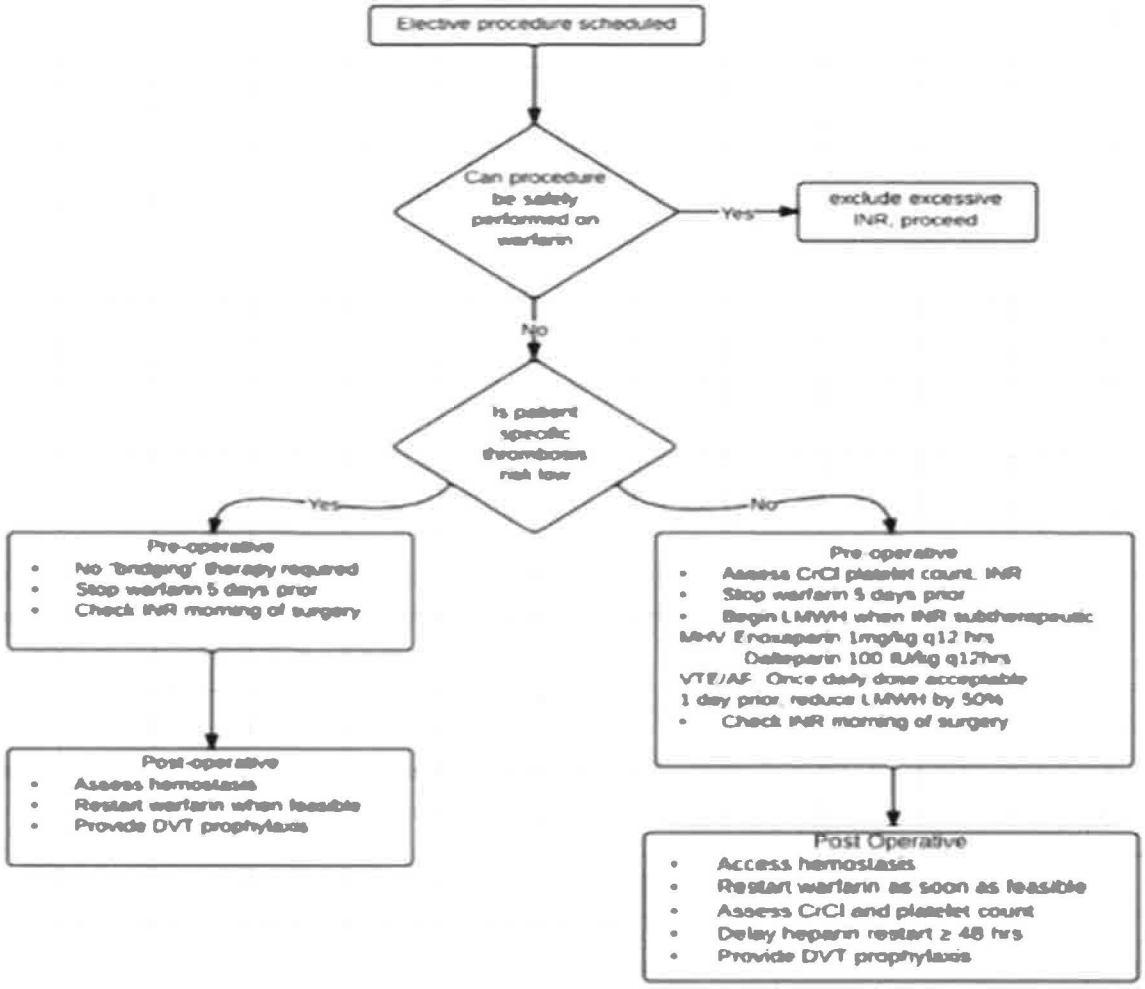

Figure 4. Bridging algorithm for warfarin. Patients with low thrombosis risk include those with aortic bileaflet valve in sinus rhythm and no previous thromboembolism; AF without previous thromboembolism, intracardiac thrombus, and CHADS2 score ≤ 2; VTE ≥3 month previously without active cancer; INR indicates international normalized ratio; CrCl creatinine clearance; LMWH, low molecular weight heparin; MHV, mechanical heart valve; VTE, venous thromboembolism; AF, atrial fibrillation; and DVT, deep vein thrombosis.

Data from ongoing clinical trials may help answer the question of the effectiveness of periprocedural bridging therapy for antithrombotic agents. Moreover, we must look at the balance between effectiveness and safety if we are to make solid and informed clinical decisions.

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