Do patients on long term oral anticoagulant therapy who require short term interruption of warfarin for an elective invasive procedure benefit by receiving bridging therapy with heparin (fractionated or unfractionated)?

In order to reduce the risk of excessive bleeding associated with invasive procedures in patients on long term oral anticoagulation, discontinuation of warfarin is recommended. This peri-procedural time of warfarin discontinuation is associated with an increased risk of thromboembolic complications. In order to minimize this risk, strategies have evolved using short-acting anticoagulants, fractionated or unfractionated heparin, to decrease the duration of time for which the patient is “unprotected”. The major risk of this bridging treatment is bleeding.

The risk of peri-operative thromboembolism is related to several factors:

1. The inherent risk associated with the underlying condition for which anticoagulation was initiated. Without adequate anticoagulation the risk of recurrent venous thromboembolism after an initial event is estimated to be 50% within the first 3 months. Thereafter, in patients with a history of recurrent venous thromboembolism, inherited thrombophilia or with acquired thrombophilic conditions (cancer) the annual risk of a recurrent event is estimated to be 15%. The peri-procedural risk of arterial thromboembolism is related to the specific condition for which warfarin was instituted. In patients with mechanical heart valves the thromboembolic risk is related to valve position (mitral > aortic) and concomitant risks (atrial fibrillation, prior thromboembolic event, left ventricular dysfunction, multiple valves, hypercoagulable state). In patients with bioprosthetic or recent generation bi-leaflet mechanical aortic valves the risk of short term interruption of anticoagulation is very low. The overall risk of a systemic embolism in a patient with non-valvular atrial fibrillation is estimated to be 4-5% per year without anticoagulation. However, this is a heterogeneous population with an annual stroke rate ranging from 1 to 20% per year. This patient group can be stratified into relative risk categories; one commonly used strategy, the CHADS2 risk tool, is outlined in this table:

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>Stroke Rate, untreated (% per year)</th>
<th>NNT to prevent 1 stroke/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
<td>417</td>
</tr>
<tr>
<td>1-2</td>
<td>2.8 – 4.2</td>
<td>81 - 125</td>
</tr>
<tr>
<td>3-6</td>
<td>5.9 – 18.2</td>
<td>27 - 44</td>
</tr>
</tbody>
</table>

The CHADS2 score is calculated by giving 1 point each for CHF, HTN, age>75, Diabetes and 2 points for a prior stroke, TIA or embolic event. (Fuster, V. ACC/AHA/ESC 2006 guidelines for the management of atrial fibrillation. J Am Coll Cardiol 48:854, 2006).

Given that patients who discontinue warfarin will be inadequately anticoagulated for 4-5 days an expected stroke rate during this period in the lowest risk group can be estimated to be 0.026% and in the highest risk group 0.08 – 0.25%.
2. **Thrombophilia associated with the surgical procedure.** There is clear evidence that surgery increases the risk of venous thromboembolism due to activation of multiple thrombogenic factors. Based on observational studies, patients with prior venous thromboembolism have a 1.7% per year risk of pulmonary embolism; in this patient population this risk increases dramatically after surgery with a risk of PE of 6.4% in the first two weeks post procedure. (C. Kearon, “Management of Anticoagulation Before and After Elective Surgery”, NEJM 336: 1506-1511, 1997). In contrast, there is no evidence that the risk of arterial thromboembolism is increased by the surgical procedure itself.

3. **Possible hypercoagulable state associated with warfarin withdrawal.** While some laboratory evidence demonstrates increased thrombin activation with the abrupt withdrawal of warfarin there is no clinical evidence of this “rebound hypercoagulability” resulting in greater thromboembolic events.

Likewise, procedures can be stratified by bleeding risk:
- **High** - TURP, polypectomy, laminectomy, neurosurgical procedures, kidney biopsy, major abdominal or thoracic surgery, endoscopic sphincterotomy, procedures lasting > 1 hour.
- **Low** - Dental extraction, cataract, pacemaker insertion, D&C, arthrocentesis, herniorrhaphy, hemorrhoidectomy.

Critical to developing an anticoagulation strategy is quantifying the consequences of perioperative thromboembolism and bleeding. Recurrent episodes of venous thromboembolism are fatal in 6% and another 2% result in serious disability. Arterial thrombotic events are fatal in 20% and another 40% experience serious permanent disability. On the other hand, major postoperative bleeding results in reoperation 50% of the time and can be fatal in 3%. (C. Kearon, “Management of Anticoagulation Before and After Elective Surgery”, NEJM 336: 1506-1511, 1997)

Discontinuation of warfarin therapy results in a gradual decline in INR. White published the results of warfarin discontinuation in 22 patients on stable anticoagulation regimens, measuring INR daily (Ann. Int. Med. 122:40, 1995). INR on the day of discontinuation was 2.6; it fell to 1.6 in an average of 2.7 days and to 1.2 after 4.7 days.

The use of low molecular weight heparin (LMWH) has largely replaced unfractionated heparin (UFH) for the treatment and prevention of thromboembolic disorders. There are no controlled trials comparing LMWH and UFH in the setting of periprocedural bridging anticoagulation. However Montalescot (Circ. 101:1083, 2000) compared LMWH with UFH in patients after mechanical valve replacement (very high risk group). Patients on LMWH achieved effective anticoagulation more quickly, as measured by anti-factor Xa activity and experienced at least equal efficacy in the short term prevention of thromboembolism. However, until more data is available on the use of LMWH in patients with high risk mechanical heart valves the American College of Cardiology recommends the use of UFH. The altered metabolism of LMWH in pregnant patients makes its use more complicated and requires careful monitoring of anti-factor Xa levels to insure adequate protection.
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Three prospective observational or cohort studies have investigated the use of LMWH in perioperative bridging strategies demonstrating similar therapeutic benefit to UFH:

1. Kovacs, MJ, Circ 110:1658, 2004. In a multi-center cohort study 224 patients, 50% with mechanical heart valves, 50% with high risk atrial fibrillation (AF) were treated with dalteparin. A thromboembolic event occurred in 3.6% (3/4 of these had their warfarin held postoperatively due to concerns about possible bleeding) and 6.7% had a major bleed.

2. Dunn, AS, Blood 104:488, 2004. A multicenter cohort study of 260 patients (68% with high risk AF, 31% DVT) treated with Enoxaparin resulted in 1.5% rate of thromboembolism and 3.5% rate of major bleeding. Of this patient population 15% had a major operation and 8 of the 9 major bleeds were in this subgroup.

3. Douketis, JD, Arch IM 164:1319, 2004. A single center registry of 650 patients, 33% with mechanical heart valves, and 53% high risk AF treated with dalteparin. Of these 650 patients 83% had a non-high bleeding risk procedure, were bridged pre and post operatively and had a thromboembolic risk was 0.4% and major bleed risk 0.7%. The remaining 17% had high bleeding risk procedures and thus did not receive postoperative anticoagulation. Of this group there was a 1.8% death rate (presumably thromboembolic) and 1.8% bleeding risk.

Attached is an algorithm for management of patients on oral anticoagulation who require interruption in therapy for an elective surgery/procedure. While this is meant to provide a rational approach based on the available evidence, the lack of clinical trials in large populations measuring patient-oriented outcomes necessitates the evaluation of individual patient circumstances when developing the optimum strategy. (Strength of Recommendation C).
Is patient having any of the following procedures?
1. Dental extraction (1)
2. Cataract extraction/IOL (2,3)
3. Upper GI endoscopy (4)
4. Carpal Tunnel Release
5. Needle breast biopsy
6. Cutaneous Procedures
   - Mohs, excisions
   
   **CONTINUE WARFARIN with NO DOSE ADJUSTMENT**

   **LOW THROMBOEMBOLIC RISK**

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Is it in the tricuspid or mitral position (8) OR is it in the aortic position with any of these associated conditions:
- Atrial Fibrillation?
- LV dysfunction (EF <30%)?
- Prior thromboembolism?
- More than one mechanical valve?
- Hypercoagulable state?
- Older generation aortic valves?

**HIGH THROMBOEMBOLIC RISK REGIMEN - Mechanical Heart Valve**

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Does the patient have:
1. Mechanical Heart Valve (5)

   **YES**

   **HIGH THROMBOEMBOLIC RISK REGIMEN - Mechanical Heart Valve**

   **NO**

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Does the patient have:
- Hypercoagulable state?
- Recurrent venous thromboembolism?
- Venous thromboembolism (VTE) within the past three months?

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Does patient have Atrial Fibrillation WITH a combination of risks (7)?
- a. prior CVA or embolism
- b. age over 75
- c. poorly controlled HTN
- d. CHF/LV dysfunction
- e. Diabetes mellitus

**INTERMEDIATE THROMBOEMBOLIC RISK**

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**HIGH THROMBOEMBOLIC RISK REGIMEN - VTE**

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**CONTINUE WARFARIN with NO DOSE ADJUSTMENT**
Clinical Practice Committee
Anticoagulation Bridging Document

Bridging Regimens

HIGH THROMBOEMBOLIC RISK- VTE
1. 4 days prior to procedure - discontinue warfarin
2. 2 days prior – start Full Dose Enoxaparin (1mg/KG BID)
3. 12 hours prior – discontinue Enoxaparin
4. Day of procedure – check INR, should be <1.5
5. Evening of the day of procedure – restart warfarin
6. Approximately 12 hours post procedure – restart Full Dose Enoxaparin
7. 3-5 days post – begin regularly monitoring INR, stop Enoxaparin when INR > 2.

NOTE: In pregnant patients continuous unfractionated heparin should be used unless anti-factor Xa activity is measured and the dose of Enoxaparin appropriately adjusted.

HIGH THROMBOEMBOLIC RISK- MECHANICAL HEART VALVE(MHV)
Unfractionated heparin has been the standard bridging anticoagulant for patients with mechanical heart valves. Early studies with Low Molecular Weight Heparin (LMWH) bridging revealed an increased thromboembolic risk in pregnant women with MHV’s. It is now known that LMWH doses require adjustment in pregnancy to account for altered metabolism of the drug (based on measurements of anti-Xa activity). However, because of inadequate comparative trials the American College of Cardiology/American Heart Association gives its highest recommendation (Ia) to the use of UFH as outlined below with a IIb recommendation for the LMWH regimen outlined above for VTE.
1. 4 days prior to procedure - discontinue warfarin
2. 2 days prior (or when INR<2.0) start continuous UFH maintaining aPTT 55-70
3. 6 hours prior discontinue heparin
4. Day of procedure – check INR, should be <1.5
5. Evening of the day of procedure – restart warfarin
6. Approximately 12 hours post procedure – restart UFH, continuing until INR>2.0

INTERMEDIATE THROMBOEMBOLIC RISK
This is a heterogeneous group with a relatively low, however broad range of thromboembolic risk during this brief period of inadequate anticoagulation. The vast majority of these patients do not achieve a significant clinical benefit from bridging and can thus be managed using the Low Thromboembolic Risk strategy. The Department of Cardiology at Dean does not bridge this group of patients unless they have had a recent embolic event (i.e. stroke).

LOW THROMBOEMBOLIC RISK
1. 4 days prior - discontinue warfarin
2. Day of procedure – check INR, should be <1.5
3. Day of procedure – restart warfarin

The Department of Cardiology at Dean is available for discussion of individual patient concerns; especially in the management of the intermediate-high risk patient groups such as patients with prosthetic valves, atrial fibrillation with multiple other risk factors and pregnant patients.
Specific circumstances, such as emergency surgery may necessitate alternative strategies including warfarin reversal and the use of vena cava filters which are not covered in this algorithm which specifically addresses elective procedures.

Enoxaparin is largely cleared by the kidney. Because of this the manufacturer has recommended against its use in patients with “significant” renal insufficiency. The only study available directly comparing unfractionated with low molecular weight heparin in patients with renal insufficiency revealed an increased risk of bleeding with both agents. In patients with a creatinine clearance below 10 ml/min Enoxaparin was associated with an increased risk of minor bleeding (Thorevska, N. Chest 125(3), March 2004). Pharmacokinetic studies have demonstrated a prolonged half life of Enoxaparin in patients with severe renal insufficiency (average creatinine clearance of 11.4). (Nagge, J. Arch. IM, 162(22), Dec. 2002) Therefore in patients with severe renal insufficiency (creatinine clearance below 10-15 ml/min.) and a high risk of thromboembolism the use of unfractionated heparin should be considered.

REFERENCES

   Extensive review of published literature including studies and case reports including single and multiple extractions, full mouth extractions and alveolectomies. 12 of 2014 cases had postoperative bleeding problems, all of which were controlled by local measures. 5 of these 12 had INR above the recommended therapeutic range. In 5 of 542 procedures where anticoagulation was specifically discontinued for the dental procedure a thromboembolic event was reported with 4 resulting in death.


   33 patients on warfarin undergoing cataract extraction with no bleeding complications.

4. Gerson, L.B. “Effect and outcomes of the periendoscopic management of patients who take anticoagulants. Am. J. Gastroenter. 95:1717-24, 2000. Retrospective review of 104 patients undergoing 171 endoscopic procedures. There were no bleeding complications in 93 procedures considered of low risk when patients continued warfarin therapy. Low risk procedures were upper endoscopy and colonoscopy without polypectomy.

5. Katholi, R.E. “Living with prosthetic heart valves. Subsequent noncardiac operations and the risk of thromboembolism or hemorrhage. Am. Heart. J. 92:162-7, 1976. 44 patients had a noncardiac operation and discontinued warfarin. Of these, 25 were aortic valve only and no thromboembolic events occurred. The remaining mitral and combined valve prostheses experienced 2 fatal thromboembolic events.

   Comprehensive review of studies available up to 1996 evaluating thromboembolic risk. The risk of recurrent venous thrombosis within the first 3 months of the initial event is 50% and this is reduced to 10% with the use of warfarin.

The Seventh ACCP conference reviewed all of the published evidence for antithrombotic therapy in patients with atrial fibrillation. The overall risk of thromboembolic stroke was 4.5% per year without anticoagulation and this rate dropped by 80% with warfarin for a number needed to treat of 32 to prevent 1 stroke in 1 year. The relative risk of stroke based on coexisting features were prior CVA-2.5, age>75-3.7, systolic BP>160-2.2, diabetes-1.6.