The Management of Patients on Chronic Oral Anticoagulant Therapy (VKA and DOAC) who Need Elective Surgery

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Perioperative Management - Cases

A 54 year old male with a history of chronic atrial fibrillation and s/p mechanical mitral valve replacement on chronic VKA is being evaluated for total hip replacement

A 48 year old Hispanic female on chronic VKA with antiphospholipid syndrome and recurrent thromboses is being evaluated for elective laparoscopic cholecystectomy for gallstone disease

A 75 year old male with atrial fibrillation (CHADS score of 1) on dabigatran is undergoing abdominal surgery for cancer

A 50 year old female with rheumatic heart disease, a St Jude aortic valve replacement, and a distant history of stroke on VKA will undergo pacemaker placement

A 68 year old black female on chronic rivaroxaban for recurrent deep vein thromboses will undergo a dental restoration procedure that will include local anesthetic injections

Why is periprocedural antithrombotic management relevant?

Perioperative management of patients on chronic OAC is common...

400,000-500,000 patients per year in North America alone

~1 in 6-10 patients receiving long-term warfarin are assessed for periprocedural management annually

Recommendations for standardized reporting of periprocedural anticoagulant and bridging therapy
Standardized 3-tiered low, moderate, high TE risk based on ACCP criteria

General description of type of procedure of surgery

Description of type and dose of AT therapy, including NOACs and bridging therapy

Primary outcome of arterial TE: stroke, TIA, SEE

MI and ACS secondary outcomes

ISTH surgical definitions of MB

30-day F/U period

Perioperative Management of Anticoagulation

Patient Risk Factors

(congenital and acquired)

Bleeding     Thrombosis

Risk Stratification

Surgical Risk Factors

Bleeding     Thrombosis

Risk Stratification

Thrombotic Risk with Prosthetic Heart Valves

Mitral     > Aortic Position
## CHADS Score and Risk for Postoperative Stroke in Patients with Chronic Atrial Fibrillation

<table>
<thead>
<tr>
<th>CHADS score</th>
<th>Annual Risk</th>
<th>30-day Postoperative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9 (1.2-3.0)</td>
<td>1.01</td>
</tr>
<tr>
<td>1</td>
<td>2.8 (2.0-3.8)</td>
<td>1.62</td>
</tr>
<tr>
<td>2</td>
<td>4.0 (3.1-5.1)</td>
<td>2.05</td>
</tr>
<tr>
<td>3</td>
<td>5.9 (4.6-7.3)</td>
<td>2.63</td>
</tr>
<tr>
<td>4</td>
<td>8.5 (6.3-11.1)</td>
<td>3.62</td>
</tr>
<tr>
<td>5</td>
<td>12.5 (8.2-17.5)</td>
<td>3.65</td>
</tr>
<tr>
<td>6</td>
<td>18.2 (10.5-27.4)</td>
<td>7.35</td>
</tr>
</tbody>
</table>


### Suggested Thromboembolic Risk Stratification when Discontinuing VKAs

**High**

Atrial Fibrillation

recent (<3 months) stroke/TIA
CHADS score 5-6
rheumatic heart disease

Mechanical Heart Valves
any caged-ball or tilting disc valve in mitral/aortic position
any mitral valve prosthesis
Recent (within 6 mos) stroke/TIA

Venous Thromboembolism (VTE)
VTE within past 3 months
severe thrombophilia
deficiency of protein C, protein S or antithrombin
antiphospholipid antibodies
multiple thrombophilias

Moderate
Atrial Fibrillation
CHADS score 3-4
Mechanical Heart Valves
bileaflet AVR with major risk factors
VTE
VTE within past 3-12 months
Nonsevere thrombophilia
Active cancer
Recurrent VTE
Low

Atrial Fibrillation

CHADS score 0-2

Mechanical Heart Valves

bileaflet AVR without major risk factors

VTE

VTE more than 12 months ago

Surgery/Procedure-related Bleeding Risk

High (2-day risk major bleed 2-4%)

major cardiac surgery (heart valve replacement/CABG)

major neurosurgical procedures

major cancer surgery (head and neck/abdominal/thoracic)

major orthopedic surgery (joint replacement/laminectomy)

major urologic surgery (prostate/bladder resection)

major vascular surgery

kidney biopsy

polypectomy, variceal treatment, biliary sphincterectomy, pneumatic dilatation

deroscopically-guided fine-needle aspiration

any major operation (procedure duration > 45 minutes)

Low (2-day risk major bleed 0-2%)

cholecystectomy

abdominal hernia repair

abdominal hysterectomy
coronary angiography /PCI/electrophysiologic testing
pacemaker/cardiac defibrillator insertion*
gastrointestinal endoscopy ± biopsy, enteroscopy, biliary/pancreatic stent without sphincterotomy, endonosonography without aspiration
minor plastic surgery (carpal tunnel repair)
minor orthopedic surgery/arthroscopy
minor gynecologic surgery (D & C)
minor dental procedures (extractions)
minor skin procedures (cancer excision)
minor eye procedures (cataract)
*delayed initiation of bridging to minimize
risk for pocket hematoma
Consequences of Thromboembolism and Major Bleeding
arterial thromboembolism
15% case-fatality for heart valve thrombosis
70% rate of death or disability in stroke
venous thromboembolism
6% rate of death or permanent disability for DVT; 25% rate for PE
major bleeding
8-9% case-fatality

Hypercoagulability Associated with Surgery: Newer Concepts

Surgery increases risk of arterial thromboembolism

[Wahl 1998]
Perioperative arterial thromboembolic and stroke rates (1.6% and 0.6%) 10-fold higher than modelling suggests (~0.1-0.2% for 8d)

[Dunn A et al Arch Intern Med 2003; White RH, JTH, 2007]

Three Key Questions Regarding Perioperative Management of Patients on Chronic OACs?

Should oral anticoagulant therapy be discontinued?

When VKA is discontinued, should the patient have perioperative “bridging” therapy with heparin (UFH or LMWH)?

What is the optimal periprocedural management of patients on DOACs needing interruption?

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BRUISE Control Study for Pacemaker or Defibrillator Surgery

N = 6811

Minimal Bleed Risk Procedures
Minor dermatologic, cutaneous, dental, ophthalmologic procedures (cataract surgery), pacemaker/cardioverter-defibrillator device implantation

Do not interrupt OAC*

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Bridging Therapy: Key Questions

The perceived need for bridging therapy is driven by TE risk

In high TE risk patients, the need to prevent TE will dominate management irrespective of bleed risk and thus an aggressive strategy (such as bridging) is justified
In moderate TE patients, a single strategy is not dominant and management will depend on individual RFs for bleeding/thrombosis

In low TE risk patients, the need to prevent TE is less dominant thus strategies to avoid bleeding are justified

Adverse Events Caused or Prevented by Pre- and Post-operative Use of IV Heparin According to the Indication for Anticoagulation

Indication for Heparin

**Acute venous thromboembolism***

<table>
<thead>
<tr>
<th>Month</th>
<th>TE</th>
<th>Major Bleeding</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 1</td>
<td>-7162†</td>
<td>+300</td>
<td>-559</td>
</tr>
<tr>
<td>Months 2 and 3</td>
<td>-1328†</td>
<td>+300</td>
<td>-93</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>-332†</td>
<td>+300</td>
<td>-13</td>
</tr>
<tr>
<td>NVAF</td>
<td>-2</td>
<td>+300</td>
<td>+12</td>
</tr>
<tr>
<td>NVAF and previous embolism</td>
<td>-4</td>
<td>+300</td>
<td>+11</td>
</tr>
<tr>
<td>Mechanical heart valve</td>
<td>-3</td>
<td>+300</td>
<td>+12</td>
</tr>
<tr>
<td>Arterial embolism</td>
<td>Month 1</td>
<td>TE</td>
<td>Major Bleeding</td>
</tr>
</tbody>
</table>

No. of Events per 10,000 patients
Recent Prospective Cohort Studies Assessing Bridging Therapy after VKA Interruption

Meta-Analysis and Systematic Review of Bridging vs No-Bridging: Thromboembolic Events

Meta-Analysis and Systematic Review of Bridging vs No-Bridging: Major Bleeding

Periprocedural Bridging vs No-Bridging Studies

Hypotheses

We hypothesized that in patients with AF on chronic VKA with at least one stroke risk factor undergoing temporary interruption of VKA for an elective procedure:

Forgoing bridging anticoagulation would be non-inferior to bridging with low-molecular-weight heparin (LMWH) for the prevention of perioperative arterial thromboembolism (ATE)

- and –

Forgoing bridging anticoagulation would be superior to bridging with respect to major bleeding

BRIDGE - Trial Design

Primary Outcomes

Secondary Outcomes

Limitations

Few patients had a high CHADS2 score (e.g., 5–6)
Most patients underwent low-risk procedures, such as colonoscopy or ambulatory surgery

Overall rate of ATE was lower than expected

Findings should not be applied to patients with mechanical heart valves or venous thromboembolism

Findings are not applicable to patients with AF treated with a direct oral anticoagulant

Conclusions:
The BRIDGE Study

For patients with AF who require temporary interruption of warfarin treatment for an elective operation or invasive procedure

A strategy of forgoing bridging anticoagulation was non-inferior to perioperative bridging with LMWH for prevention of arterial thromboembolism

Forgoing bridging treatment also decreased the risk of major bleeding compared to perioperative bridging with LMWH

“Experimental” arm with excellent clinical outcomes: ATE 0.4% and MB 1.3%

The PERIOP 2 Study - Design

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Discontinuation of dabigatran and renal function:
AC Activity within 24 to 48 hours

Activated partial thromboplastin time (aPTT) can be used to estimate the time to get to a particular level of recovery, even when the time since the last dose of dabigatran is not precisely known

*Simulations based on PK data from a study in subjects with renal impairment and PK/aPTT relationships derived from the RELY study; aPTT prolongation in RE-LY was measured centrally in citrate plasma using PTT Reagent Diagnostics GmbH, Mannheim, Germany. There may be quantitative differences between established methods for aPTT assessment.1

In RELY, CrCl was calculated using the Cockroft-Gault equation.2


Periprocedural DOAC Outcomes in SPAF Trials

Peri-interventional Management of DOACs:
Dresden NOAC Registry

595 patients on NOACs undergoing 863 procedures (90% minimally invasive or minor procedures)

Results:
30 ± 5 day outcomes:
CV events 1.0% (95% CI, 0.5 – 2.0%)
MB 1.2% (95% CI, 0.6 – 2.1%)

Major procedures independent RF for CV events and MB (OR 7.3 and 16.8)
Perioperative Management of Dabigatran: The Periop Dabigatran Study

541 cases using a pre-specified dabigatran protocol

Timing of last dose based on CrCl and procedure-related bleed risk

Last dose 24hr before low bleed risk Sx; 48hr before high bleed risk Sx

For CrCl 30-50ml/min, add 1d for low bleed risk and 2d for high bleed risk

Resumption based on complexity of surgery and consequences of a bleeding complication

24hr post-op low bleed risk; 48-72hr high bleed risk

Results:

60% of procedures with standard bleed risk; 46% of cases with last dose 24hrs before surgery; bridging used in 1.7% of cases post-op

30-day outcomes:

0.2% TE (95% CI, 0 – 0.5%)

1.8% MB (95% CI, 0.7 – 3.0%)

Residual Anticoagulant Effects at the Time of a Procedure using a Standardized Dabigatran Protocol

In patients with high bleeding risk procedures, the proportions with normal PT, APTT, TT, dTT levels were 93.7%, 85.7%, 57.1%, and 87.3%, respectively

Aim for >95% normal coagulation test results for high bleed risk procedures

Add 12 – 24 hrs of dabigatran interruption for high bleed risk procedures

Clinical Outcomes: Bridged vs. Non-Bridged in RELY Trial:

Periprocedural heparin bridging:
Warfarin 28.5%; Dabigatran 110 mg 15.3%; Dabigatran 150 mg 17%

General principles of pre-procedure DOAC discontinuation
General principles of post-procedure
DOAC resumption

Perioperative Anticoagulant Use for Surgery Trial (PAUSE)

Study population:
AF on a DOAC that require an elective procedure

Primary aim:
Standardized protocol for DOAC (including dabigatran, rivaroxaban, apixaban) is safe with low rates of major bleeding (1.0%, UL 2.0%) and ATE (0.5%, UL 1.5%)

Secondary aim:
The effect of the pre-operative DOAC interruption protocol on the level of residual anticoagulation

Routine coagulation tests (i.e. aPTT)
DOAC-specific tests (i.e. TT, dTT [e.g. HemoclotTM], anti FXa)

N = 3,300; ~15 centers in Canada; July 2014 – July 2017

ClinicalTrials.gov Identifier: NCT022228798

The Management of Patients on Chronic OAC who Need Elective Surgery

Is interruption of OACs indicated?

COMPARE, BRUISE Control, ARISTOTLE

No - PM/defibrillator/catheter ablation and DOACs. Proof of concept studies for strategy of OAC continuation in minimal/low bleed risk procedures

Is heparin bridging necessary?

Large meta-analysis and large observational/sub-study data

Over 3-4 fold increased risk of major bleeding and no advantages in TE reduction

BRIDGE – landmark Pb controlled RCT in AF patients
“Proof-of-concept” study of no efficacy and harm of heparin bridging
Likely can be extended to high risk populations incl MHV (PERIOP-2)
Optimal periprocedural management of DOACs
Large Phase 3 SPAF substudy, outcome study, and registry data
Excellent outcomes from simple discontinuation/re-initiation based on PK properties, procedural bleed risk, and patient renal fxn (dabi)
Heparin bridging causes harm (>3-fold increase MB risk)
PAUSE Trial