UPDATE ON CARDIAC RISK: MANAGEMENT OF THE PATIENT ON ANTICOAGULATION

Markus Kaiser MD
Department of Anesthesiology
Medical College of Wisconsin
Disclosures

• None
Objective

- Review of guidelines for the management of perioperative cardiac risk
- Update on the perioperative management of patients on antiplatelet therapy
- Update the perioperative management of patients on oral and parenteral anticoagulation therapy
2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the American College of Surgeons, American Society of Anesthesiologists, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Vascular Medicine

Endorsed by the Society of Hospital Medicine
Scope: Perioperative cardiovascular evaluation and management of the adult patient undergoing noncardiac surgery

• Stepwise preoperative risk assessment:
  • Physician role in managing risk and providing informed consent
  • Patient’s perspective in weighing risk, benefit and alternatives to cardiac testing or preventive therapies

• Cardiovascular testing
  • (When indicated) perioperative pharmacological (including anesthetic) management

• Perioperative monitoring that includes devices and biochemical markers.
Purpose: Perioperative cardiovascular evaluation and management of the adult patient undergoing noncardiac surgery

- Algorithmic approach to patient centered care
  - Determination of surgical urgency
  - Assessment of the presence or absence of a perioperative acute cardiac event
  - Assessment of perioperative risk of major adverse cardiac event (MACE)
  - Informed decision to proceed with the choice of surgery and which includes the patient’s perspective
- Determination of the need for changes in management
- Identification of cardiovascular conditions or risk factors requiring longer-term management
- Aligned with 14 clinical pathway guidelines and 6 statements of health care associations and societies
<table>
<thead>
<tr>
<th>CLASS I</th>
<th>Benefit &gt;&gt; Risk</th>
<th>Procedure/Treatment SHOULD be performed/administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class IIa</td>
<td>Benefit &gt;&gt; Risk</td>
<td>Additional studies with focused objectives needed IT IS REASONABLE to perform procedure/administer treatment</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Benefit ≥ Risk</td>
<td>Additional studies with broad objectives needed; additional registry data would be helpful Procedure/Treatment MAY BE CONSIDERED</td>
</tr>
<tr>
<td>Class III</td>
<td>No Benefit or Class III Harm</td>
<td>Procedure/Test</td>
</tr>
</tbody>
</table>

**LEVEL A**
Multiple populations evaluated*
Data derived from multiple randomized clinical trials or meta-analyses
- Recommendation that procedure or treatment is useful/effective
- Sufficient evidence from multiple randomized trials or meta-analyses

**LEVEL B**
Limited populations evaluated*
Data derived from a single randomized trial or nonrandomized studies
- Recommendation that procedure or treatment is useful/effective
- Evidence from single randomized trial or nonrandomized studies

**LEVEL C**
Very limited populations evaluated*
Only consensus opinion of experts, case studies, or standard of care
- Recommendation that procedure or treatment is useful/effective
- Only expert opinion, case studies, or standard of care

---

Fleisher et al 2014 ACC/AHA Perioperative Guideline
Stepwise approach to perioperative cardiac assessment for coronary artery disease

Fleisher et al 2014 ACC/AHA Perioperative Guideline
Stepwise approach to perioperative cardiac assessment for coronary artery disease

1. Patient scheduled for surgery with known or risk factors for CAD* (Step 1)
   - Emergency: Yes → Clinical risk stratification and proceed to surgery
   - No → ACS † (Step 2)
     - Yes → Evaluate and treat according to GDMT †
     - No → Estimated perioperative risk of MACE based on combined clinical/surgical risk (Step 3)
Stepwise approach to perioperative cardiac assessment for coronary artery disease
Case I

- 74 y/o presents with 2 large inguinal hernias with worsening symptoms for planned open repair
- Good functional capacity >> 4 METs
- During pre-operative workup PCP ordered a nuclear stress test
- Incidental finding: reversible perfusion defect
- Patient referred to an interventional cardiologist who performed a PCA and 2 DES placed…
- PCP recommends discontinuation of aspirin and clopidogrel 7 days prior to surgery
Stepwise approach to perioperative cardiac assessment for coronary artery disease

Fleisher et al 2014 ACC/AHA Perioperative Guideline
Patient With Coronary Stent

Stent implantation ≤6-8 wk

Yes

No

DES ≥30 d, but ≤365 d

Yes

No

Risk of surgical delay is greater than risk of DES thrombosis

Yes

No

Delay surgery until after optimal period (BMS: 30 d and DES: 365 d) (Class I)

Continue DAPT unless risk of bleeding is greater than risk of stent thrombosis (Class I)

Does surgery demand discontinuation of P2Y12 inhibitors?

Yes

No

Continue current DAPT regimen

Continue ASA and restart P2Y12 ASAP (Class I)

Fleisher et al 2014 ACC/AHA Perioperative Guideline
Summary of recommendations
Dual anti-platelet therapy after coronary stent implantation

• Importance of maintaining stent patency and minimizing the risk of perioperative stent thrombosis

• Dual antiplatelet therapy with aspirin and P2Y12 platelet inhibitor should be continued for urgent noncardiac surgery within 6 weeks of percutaneous coronary intervention regardless of stent type [bare metal stent or drug-eluting stent (DES)] (Class I, LoE C).

• Timing of elective noncardiac surgery after DES placement can be considered after 180 days (approximately 6 months) if the health risk of delaying the surgery exceeds the risks of ischemia from stent thrombosis due to cessation of antiplatelet agents (Class IIb, LoE B)
Summary of recommendations
Dual anti-platelet therapy after coronary stent implantation

• ‘Elective’ noncardiac surgery should not be performed within 30 days after bare metal stent and within 12 months after DES implantations in patients requiring discontinuation of antiplatelet therapy before surgery as the chance of harm outweighs the benefits of cessation (Class III, LoE B).

• Aspirin should be continued throughout the perioperative period if reasonable or should be restarted in the postoperative period with the P2Y12 platelet inhibitor as soon as possible after surgery in patients undergoing procedures requiring preoperative discontinuation of dual-antiplatelet therapy (Class I, LoE C).

• Discussion among clinicians caring for the patient with coronary stent implantation should address the balance between risk of perioperative coagulopathy from continuation of antiplatelet agents and the risk of stent thrombosis as a result of discontinuation (Class I, LoE C)
Summary of recommendations
Preoperative testing (EKG, laboratory markers)

• A preoperative 12-lead ECG is recommended for patients with CAD, arrhythmias, peripheral artery disease, cerebrovascular disease, and structural cardiac disease unless they are undergoing low risk surgery (Class IIa recommendation, LoE B).

• Routine preoperative ECG is not helpful in patients undergoing low-risk surgery regardless of the burden of cardiovascular disease or risk factors.

• Postoperative ECG is recommended in patients with a clinical suspicion for myocardial ischemia, infarction, and arrhythmia after non-cardiac surgery; however, routine postoperative ECGs in asymptomatic patients is not useful.

• The measurement of laboratory markers of myocardial injury (e.g., troponins) is in the high-risk patient if such measurements of injury will lead to intervention (Class IIb, LoE B).

• Evaluation of markers of injury are recommended in patients at high risk for MACE who may benefit from such an intervention and that routine management is not recommended without patient selection (Class II, LoE B).

Fleisher et al. 2014 ACC/AHA Perioperative Guideline
Summary of recommendations

**β-blockade**

- β-blockade should be continued in patients undergoing noncardiac surgery who have been prescribed these medications chronically (Class I, LoE B).
  - This recommendation recognizes that patients on chronic β-blocker therapy benefit from β-blocker administration beyond the immediate indication of heart rate control and the acute reduction in myocardial oxygen consumption.

- β-blockers should not be initiated within 1 day of noncardiac surgery.
  - Although the administration of β-blockers may prevent nonfatal myocardial infarction (MI) when initiated in the immediate preoperative period, the benefit of MI prevention is outweighed by the increased risk of may stroke, hypotension, and death (Class III, LoE B)
Summary of recommendations
ACEi and ARBs

• ACEi and angiotensin-receptor blockers (ARBs):
  • A very large retrospective study of 79 000 patients undergoing noncardiac surgery compared patients taking ACEi with patients not on ACEi. An analysis of a matched, nested cohort of the study demonstrated increased transient intraoperative hypotension among patients taking ACEi, but failed to show any difference in other outcomes*.
  • Clinical practice guidelines recommend continuing ACEi in the setting of acute heart failure treatment or hypertension.
  • Based on the available data, it is reasonable to continue ACEi or ARBs perioperatively (Class IIa, LoE B).
  • If ACEi or ARBs are held before surgery, it is recommended that they be restarted as soon as clinically feasible in the postoperative period (Class IIa, LoE C).

Summary of recommendations

Antiplatelet therapy

- 2014 ACC/AHA guideline strongly recommends against routine aspirin therapy without previous coronary stent implantation (Class III, LoE B), (POISE-2).
- Aspirin administration, however, is recommended when risks of myocardial ischemia exceed risk of surgical bleeding (Class III, LoE C)
- The guideline therefore recommends strong consideration be given to the administration of aspirin for elective noncardiac surgery without history of percutaneous coronary intervention and stenting when the risk of myocardial ischemia exceeds the risk of surgical bleeding (Class IIb, LoE B)

Fleisher et al 2014 ACC/AHA Perioperative Guideline
Perioperative Management of Patients on Oral Anticoagulation

• Risk
  • Interruption of anticoagulation may increase thromboembolic risk
  • Continuing anticoagulation may increase risk of bleeding
  • Both may lead to increase in morbidity and mortality

• Timing of interruption
  • Elective vs. urgent/emergent procedure

• Bridging
  • Increase in bleeding risk vs. reducing the rate of thromboembolic events
  • High risk patients (mechanical heart valves, recent strokes)
Oral Vitamin K antagonists

- Indications:
  - S/p venous or arterial thromboembolic events (PE, DVT, HIT II)
  - Hypercoagulation disorders
  - Mechanical heart valves
  - Ventricular assist devices (HeartMate II, HeartWare, Total Artificial Heart)
  - Atrial Fibrillation

- Products:
  - Warfarin
  - Acenocoumarol
  - Phenprocoumon
  - Fluindione
Coagulation cascade - simplified

- Tissue injury
  - FIX → FIXa
  - FII (Prothrombin) → FIIa (Thrombin)
  - FVIIa (Cofaktor) → FXa
- FIIa (Thrombin) → FVa
- Fibrinogen → Fibrin
- FXa
- FX
- FVIIIa
- FVII
- Tissue factor + phospholipids
Warfarin Therapy

- Inhibits vitamin K dependent synthesis of clotting factors II, VII, IX and X as well as protein C and protein S
- Biological half life 40 (20-60) hrs
- For routine surgery warfarin should be stopped five days before elective surgery, PT/INR checked on the day before/of surgery
New oral anticoagulants

• 4 new oral anticoagulants approved in most countries
• Mechanism of these agents is to selectively inhibit
  • Thrombin (Factor IIa) or
  • Factor Xa
• Direct oral anticoagulants have several pharmacologic advantages over vitamin K antagonists
  • Wider therapeutic window,
  • A rapid onset of action
  • Shorter half-lives (7 - 14 hrs) in healthy persons
New oral anticoagulants

• Direct factor Xa inhibitors
  • Rivaroxaban (Xarelto®)
  • Edoxaban (Savaysa®) – FDA approval 01/2015
  • Apixaban (Eliquis®)

• Direct thrombin inhibitor
  • Dabigatran (Pradaxa®)
Coagulation cascade - simplified

- **Tissue injury**
  - FIX → FIXa
  - FX → FXa
  - FII (Prothrombin) → FIIa (Thrombin)
  - FVa
  - Fibrinogen

- **FVIIIa (Cofaktor)**
  - FX → FVa

- **FXIIa (Thrombin)**
  - Fibrin
  - FXIIIa

**Polymerized Fibrin**

**Tissue factor + phospholipids**

**FIXa**

**FVIIa**
Coagulation cascade - simplified

Tissue injury

- FIX
  - FIXa
  - FVIIa (Cofaktor)

- FX
  - FII (Prothrombin)
  - FVa

- Fibrinogen

FXa

- FIIa (Thrombin)

- FVIII

- FVa

Fibrin

polymerized Fibrin

Rivaroxaban
Edoxaban
Apixaban

Dabigatran

Tissue factor + phospholipids

FXIIIa
The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systematic review and meta-analysis

Chatree Chai-Adisaksoph,1,2 Mark Crowther,1 Tetsuya Isayama,3 and Wendy Lim1

1Department of Medicine, McMaster University, Hamilton, ON, Canada; 2Department of Medicine, Chiang Mai University, Chiang Mai, Thailand; and
3Sunnybrook Health Sciences Center, University of Toronto, Toronto, ON, Canada

- How safe are target specific oral anticoagulants (TSOACs) compared to vitamin K antagonists (VKAs)?
- Review and meta-analysis of phase III RTCs to compare TSOACs and VKAs in patients with venous thromboembolism or atrial fibrillation
- 12 RTCs involving 102,607 patients
- TSOAC significantly reduced the risk of overall major bleeding (RR 0.72, p < .01), fatal bleeding (RR 0.53, p < .01), clinically relevant, nonmajor bleeding (RR 0.78, p < .01) and total bleeding (RR 0.76, p < .01)
- No difference in major GI bleeding (RR 0.94, p = 0.62)
Major bleeding events comparing target specific oral anticoagulants with VKAs

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>TSOACs</th>
<th>VKAs</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>EINSTEIN-DVT, 2010</td>
<td>14</td>
<td>1718</td>
<td>20</td>
<td>1711</td>
</tr>
<tr>
<td>RE-MEDY, 2013</td>
<td>13</td>
<td>1430</td>
<td>25</td>
<td>1426</td>
</tr>
<tr>
<td>RE-COVER II, 2014</td>
<td>15</td>
<td>1279</td>
<td>22</td>
<td>1289</td>
</tr>
<tr>
<td>RE-COVER, 2009</td>
<td>20</td>
<td>1274</td>
<td>24</td>
<td>1265</td>
</tr>
<tr>
<td>AMPLIFY, 2013</td>
<td>15</td>
<td>2676</td>
<td>49</td>
<td>2689</td>
</tr>
<tr>
<td>J-ROCKET AF, 2012</td>
<td>26</td>
<td>639</td>
<td>30</td>
<td>639</td>
</tr>
<tr>
<td>EINSTEIN-Pe, 2012</td>
<td>26</td>
<td>2412</td>
<td>52</td>
<td>2405</td>
</tr>
<tr>
<td>HOKUSAI-VTE, 2013</td>
<td>56</td>
<td>4118</td>
<td>66</td>
<td>4122</td>
</tr>
<tr>
<td>ARISTOTLE, 2011</td>
<td>327</td>
<td>9088</td>
<td>462</td>
<td>9052</td>
</tr>
<tr>
<td>ROCKET AF, 2011</td>
<td>395</td>
<td>7111</td>
<td>386</td>
<td>7125</td>
</tr>
<tr>
<td>RE-LY, 2009</td>
<td>741</td>
<td>12091</td>
<td>421</td>
<td>6022</td>
</tr>
<tr>
<td>ENGAGE-AF-TIMI-48, 2013</td>
<td>672</td>
<td>14014</td>
<td>524</td>
<td>7012</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>57850</td>
<td>44757</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Total events            2320  2081
Heterogeneity: Tau² = 0.04; Chi² = 48.96, df = 11 (P < 0.00001); I² = 78%
Test for overall effect: Z = 3.98 (P < 0.0001)
Test for subgroup differences: Not applicable

### Fatal bleeding events comparing TSOAC with VKAs

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>TSOACs Events</th>
<th>Total</th>
<th>VKAs Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-MEDY, 2013</td>
<td>0</td>
<td>1430</td>
<td>1</td>
<td>1426</td>
<td>0.4%</td>
<td>0.33 [0.01, 8.15]</td>
</tr>
<tr>
<td>RE-COVER II, 2014</td>
<td>0</td>
<td>1279</td>
<td>1</td>
<td>1289</td>
<td>0.4%</td>
<td>0.34 [0.01, 8.24]</td>
</tr>
<tr>
<td>RE-COVER, 2009</td>
<td>1</td>
<td>1274</td>
<td>1</td>
<td>1265</td>
<td>0.5%</td>
<td>0.99 [0.06, 15.86]</td>
</tr>
<tr>
<td>AMPLIFY, 2013</td>
<td>1</td>
<td>2676</td>
<td>2</td>
<td>2689</td>
<td>0.7%</td>
<td>0.50 [0.05, 5.54]</td>
</tr>
<tr>
<td>J-ROCKET AF, 2012</td>
<td>1</td>
<td>639</td>
<td>3</td>
<td>639</td>
<td>0.8%</td>
<td>0.33 [0.03, 3.20]</td>
</tr>
<tr>
<td>EINSTEIN-DVT, 2010</td>
<td>1</td>
<td>1718</td>
<td>5</td>
<td>1711</td>
<td>0.9%</td>
<td>0.20 [0.02, 1.70]</td>
</tr>
<tr>
<td>EINSTEIN-PE, 2012</td>
<td>2</td>
<td>2412</td>
<td>3</td>
<td>2405</td>
<td>1.3%</td>
<td>0.66 [0.11, 3.97]</td>
</tr>
<tr>
<td>HOKUSAI-VTE, 2013</td>
<td>2</td>
<td>4118</td>
<td>10</td>
<td>4122</td>
<td>1.7%</td>
<td>0.20 [0.04, 0.91]</td>
</tr>
<tr>
<td>ROCKET AF, 2011</td>
<td>27</td>
<td>7111</td>
<td>55</td>
<td>7125</td>
<td>19.0%</td>
<td>0.49 [0.31, 0.78]</td>
</tr>
<tr>
<td>ARISTOTLE, 2011</td>
<td>34</td>
<td>9088</td>
<td>55</td>
<td>9052</td>
<td>22.0%</td>
<td>0.62 [0.40, 0.94]</td>
</tr>
<tr>
<td>RE-LY, 2009</td>
<td>51</td>
<td>12091</td>
<td>39</td>
<td>6022</td>
<td>23.1%</td>
<td>0.65 [0.43, 0.99]</td>
</tr>
<tr>
<td>ENGAGE-AF-TIMI-48, 2013</td>
<td>53</td>
<td>14014</td>
<td>59</td>
<td>7012</td>
<td>29.3%</td>
<td>0.45 [0.31, 0.65]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>57850</td>
<td>44757</td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td>0.53 [0.43, 0.64]</td>
</tr>
</tbody>
</table>

Total events: 173

Heterogeneity: $\text{I}^2 = 0.00$; $\chi^2 = 5.25$, df = 11 ($P = 0.92$); $I^2 = 0$

Test for overall effect: $Z = 6.30$ ($P < 0.00001$)
Absorption and bioavailability of NOACs

Heidbuchel et al. Europace (2013) 15, 635-651
# New oral anticoagulants - Pharmacology

**FDA approved in January 2015**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban*++</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Direct thrombin inhibitor</td>
<td>Direct factor Xa inhibitor</td>
<td>Direct factor Xa inhibitor</td>
<td>Direct factor Xa inhibitor</td>
</tr>
<tr>
<td>Pro-drug</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bioavailability, %</td>
<td>6%</td>
<td>66% without food up to 100% with food</td>
<td>50%</td>
<td>62%</td>
</tr>
<tr>
<td>Half-life, h</td>
<td>12–17 h</td>
<td>5–9 h (young) 11–13 h (elderly)</td>
<td>12 h</td>
<td>9–11 h</td>
</tr>
<tr>
<td>Time to maximum plasma concentration</td>
<td>0.5 – 2</td>
<td>2–4 h</td>
<td>1–4 h</td>
<td>1–2 h</td>
</tr>
<tr>
<td>Renal excretion</td>
<td>80%</td>
<td>35%</td>
<td>25%</td>
<td>50%</td>
</tr>
<tr>
<td>Liver metabolism</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Minimal</td>
</tr>
<tr>
<td>Gastrointestinal tolerability</td>
<td>Dyspepsia</td>
<td>No problem</td>
<td>No problem</td>
<td>No problem</td>
</tr>
<tr>
<td>Absorption with food</td>
<td>No effect</td>
<td>+39% more</td>
<td>No effect</td>
<td>6–22% more</td>
</tr>
<tr>
<td>Intake with food?</td>
<td>No</td>
<td>Mandatory</td>
<td>No</td>
<td>No official recommendation</td>
</tr>
<tr>
<td>Dosing</td>
<td>Twice daily</td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Once daily</td>
</tr>
</tbody>
</table>

*No European Medicines Agency approved yet.

---

*European Heart Journal – Cardiovascular Pharmacotherapy (2015)*
## Interpretation of coagulation assays in patients treated with different NOACs

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma peak level</strong></td>
<td>2 h after ingestion</td>
<td>1–4 h after ingestion</td>
<td>1–2 h after ingestion</td>
<td>2–4 h after ingestion</td>
</tr>
<tr>
<td><strong>Plasma trough level</strong></td>
<td>12–24 h after ingestion</td>
<td>12–24 h after ingestion</td>
<td>12–24 h after ingestion</td>
<td>16–24 h after ingestion</td>
</tr>
<tr>
<td><strong>PT</strong></td>
<td>Cannot be used</td>
<td>Cannot be used</td>
<td>Prolonged but no known relation with bleeding risk</td>
<td>Prolonged: may indicate excess bleeding risk but local calibration required</td>
</tr>
<tr>
<td><strong>INR</strong></td>
<td>Cannot be used</td>
<td>Cannot be used</td>
<td>Cannot be used</td>
<td>Cannot be used</td>
</tr>
<tr>
<td><strong>aPTT</strong></td>
<td>At trough: &gt;2x ULN suggests excess bleeding risk</td>
<td>Cannot be used</td>
<td>Prolonged but no known relation with bleeding risk</td>
<td>Cannot be used</td>
</tr>
<tr>
<td><strong>dTT</strong></td>
<td>At trough: &gt;200 ng/ml or &gt;65 s: excess bleeding risk</td>
<td>Cannot be used</td>
<td>Cannot be used</td>
<td>Cannot be used</td>
</tr>
<tr>
<td><strong>Anti-FXa</strong> chromogenic assays</td>
<td>Not applicable</td>
<td>No data yet</td>
<td>Quantitative; no data on threshold values for bleeding or thrombosis</td>
<td>Quantitative; no data on threshold values for bleeding or thrombosis</td>
</tr>
<tr>
<td><strong>ECT</strong></td>
<td>At trough: ≥3× ULN: excess bleeding risk</td>
<td>No data</td>
<td>No data</td>
<td>Not affected</td>
</tr>
</tbody>
</table>

Heidbuchel et al. Europace (2013) 15, 635-651
<table>
<thead>
<tr>
<th>Patients characteristics</th>
<th>NOAC</th>
<th>Dose regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk of stroke (high CHADS-VASC score)</td>
<td>Dabigatran</td>
<td>150 mg BID</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>Rivaroxaban</td>
<td>20 mg QD</td>
</tr>
<tr>
<td>High risk of bleeding or previous life-threatening bleedings</td>
<td>Dabigatran</td>
<td>110 mg BID</td>
</tr>
<tr>
<td></td>
<td>Apixaban</td>
<td>5 mg BID</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Rivaroxaban</td>
<td>20 mg QD</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>Apixaban</td>
<td>5 mg BID</td>
</tr>
<tr>
<td>Medication compliance problems</td>
<td>Rivaroxaban</td>
<td>20 mg QD</td>
</tr>
<tr>
<td>Elderly (≥80 years) and impaired renal function</td>
<td>Apixaban</td>
<td>2.5 mg BID</td>
</tr>
</tbody>
</table>

European Heart Journal – Cardiovascular Pharmacotherapy (2015)
New oral anticoagulants

- DOAC are administered at fixed doses to adults without laboratory monitoring
- vs. warfarin with its requirement for monitoring of the INR and periodic dose adjustments
- Good anticoagulation management (RTCs showed INR generally in the desired therapeutic range of 2 to 3 for >60% of the time)
- DOAC were noninferior, and in some cases superior, to dose-adjusted warfarin for the prevention and treatment of thrombosis.
- As compared with warfarin, direct oral anticoagulants reduced the rate of major bleeding by 28% and the rates of intracranial and fatal hemorrhage by 50%.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Mechanism of action</th>
<th>Dosage</th>
<th>Stopping medication before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Vitamin K antagonist</td>
<td>Varies across individuals</td>
<td>Withheld for approximately 5 days</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Direct thrombin inhibitors</td>
<td>150 mg twice daily for most patients 110 mg BD for patients aged &gt;75 years or with ClCr 30-49 ml/min</td>
<td>24 hours: low bleeding risk and normal renal function 96 hours high-bleeding-risk individual and impaired renal function(^{11})</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Factor Xa inhibitor</td>
<td>20 mg daily for most patients 15 mg daily if ClCr 30-49 ml/min Avoid if ClCr &lt;30 ml/min</td>
<td>24–48 hours(^{11})</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Factor Xa inhibitor</td>
<td>5 mg twice daily for most patients 2.5 mg twice daily for age &gt;80 years, weight &lt;60 kg S creat &gt;133 microM/L</td>
<td>24–48 hours</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Inhibits thromboxane A2 synthesis by irreversibly acetylating cyclooxygenase-1 in platelets and megakaryocyte</td>
<td>75–325 mg once daily</td>
<td>Most often can be continued May need to be stopped 5–7 days before surgery</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Metabolised in the liver to active compounds that bind covalently to ADP receptors on platelets and reduce platelet activation</td>
<td>75 mg daily</td>
<td>5–7 days prior to surgery</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>An ADP receptor antagonist</td>
<td>10 mg once daily for adults &gt;60 kg 5 mg once daily for patients &lt;60 kg</td>
<td>5–7 days prior to surgery</td>
</tr>
</tbody>
</table>

\(^{11}\) Refer to medical guidelines for specific instructions.
To bridge or not to bridge…?

• BRIDGE trial
Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation


- 1884 Patients with atrial fibrillation enrolled
- Randomized, double-blind, placebo-controlled trial
- Perioperative interruption of warfarin therapy,
  - Bridging anticoagulation therapy with low-molecular-weight heparin (100 IU of dalteparin per kilogram of body weight) or matching placebo
  - from 3 days before the procedure until 24 hours before the procedure and then for 5 to 10 days after the procedure
Table 3. Study Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No Bridging (N = 918)</th>
<th>Bridging (N = 895)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of patients (percent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial thromboembolism</td>
<td>4 (0.4)</td>
<td>3 (0.3)</td>
<td>0.01*, 0.73†</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (0.2)</td>
<td>3 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>2 (0.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>12 (1.3)</td>
<td>29 (3.2)</td>
<td>0.005†</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>5 (0.5)</td>
<td>4 (0.4)</td>
<td>0.88†</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7 (0.8)</td>
<td>14 (1.6)</td>
<td>0.10†</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0.25†</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0.25†</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>110 (12.0)</td>
<td>187 (20.9)</td>
<td>&lt;0.001†</td>
</tr>
</tbody>
</table>

* P value for noninferiority.
† P value for superiority.
To bridge or not to bridge…?

• “In conclusion, in the BRIDGE trial, we found that for patients with atrial fibrillation who require temporary interruption of warfarin treatment for an elective operation or other elective invasive procedure, a strategy of forgoing bridging anticoagulation was noninferior to perioperative bridging with low-molecular-weight heparin for the prevention of arterial thromboembolism. The strategy of forgoing bridging treatment also decreased the risk of major bleeding.”

N Engl J Med 2015;373:823-33
Emergency reversal of oral anticoagulants

• Warfarin
  • Withholding the vitamin K antagonist
  • Administration of oral or intravenous vitamin K
  • Replacement of the deficient factors using PCC or FFP
  • By-passing the coagulation cascade with recombinant activated factor VII (rFVIIa)

• New Oral Anticoagulants
  • Discontinuation of therapy
  • ????
## Available Treatments for Reversal of VKA-Associated Coagulopathy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vitamin K</th>
<th>Fresh Frozen Plasma</th>
<th>3-Factor PCC</th>
<th>4-Factor PCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constituents</td>
<td>Vitamin K</td>
<td>All vitamin K–dependent clotting factors</td>
<td>Factor II, IX, X, proteins C and S*</td>
<td>Factor II, VII, IX, X, proteins C and S*</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Oral or intravenous</td>
<td>Intravenous</td>
<td>Intravenous</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Dose</td>
<td>5–10 mg</td>
<td>10–15 mL/kg</td>
<td>25–50 IU of factor IX/kg</td>
<td>25–50 IU of factor IX/kg</td>
</tr>
<tr>
<td>Onset of effect</td>
<td>6–8 h</td>
<td>Duration of infusion†</td>
<td>15–30 min†</td>
<td>15–30 min†</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Rare anaphylaxis</td>
<td>Fluid overload; febrile and</td>
<td>Possible increase in thromboembolic</td>
<td>Possible increase in thromboembolic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>allergic reactions; viral</td>
<td>complications</td>
<td>complications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>transmission; transfusion-related</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>acute lung injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>Minimal</td>
<td>Moderate</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Other</td>
<td>Intravenous administration</td>
<td>Requires coadministration of vitamin K to sustain reversal</td>
<td>Requires coadministration of vitamin K to sustain reversal; may require coadministration of plasma or recombinant factor Vila as a source of factor VII</td>
<td>Requires coadministration of vitamin K to sustain reversal</td>
</tr>
</tbody>
</table>

PCC indicates prothrombin complex concentrate.

*Some preparations also contain antithrombin and small amounts of heparin.

†Onset can also be affected by the dose administered.

Quinlan et al. Circulation, 2013
Prothrombin complex (PCC)

- Highly purified virus inactivated human plasma derived products
- Contain 3 or 4 Vitamin K dependent clotting factors (F II, F VII, F IX and F X and antithrombotic proteins C and S)
- 4 factor containing PCC available in the US since April 2013 (Kcentra®)
- Indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, such as warfarin) therapy in adult patients with:
  - Acute major bleeding
  - Need for urgent surgery or other invasive procedure
Efficacy and Safety of a 4-Factor Prothrombin Complex Concentrate in Patients on Vitamin K Antagonists Presenting With Major Bleeding
A Randomized, Plasma-Controlled, Phase IIIb Study

Ravi Sarode, MD; Truman J. Milling Jr, MD; Majed A. Refaai, MD; Antoinette Mangione, MD, PharmD; Astrid Schneider, PhD; Billie L. Durn, BS; Joshua N. Goldstein, MD, PhD

- Effective hemostasis was achieved in 72.4% of patients receiving 4F-PCC versus 65.4% receiving plasma, demonstrating noninferiority
- Rapid international normalized ratio reduction was achieved in 62.2% of patients receiving 4F-PCC versus 9.6% receiving plasma, demonstrating 4F-PCC superiority
- The safety profile (adverse events, serious adverse events, thromboembolic events, and deaths) was similar between groups; 66 of 103 (4F-PCC group) and 71 of 109 (plasma group) patients experienced ≥ 1 adverse event
ACCP guidelines

- For patients with VKA-associated major bleeding, we suggest rapid reversal of anticoagulation with four-factor prothrombin complex concentrate rather than with plasma. (Grade 2C).

- We suggest the additional use of vitamin K 5 to 10 mg administered by slow IV injection rather than reversal with coagulation factors alone (Grade 2C).
“Both the consultants and ASA members strongly agree that for urgent reversal of warfarin, administer PCCs in consultation with the appropriate specialist, or administer FFP”

“The ASA members agree and the consultants strongly agree regarding the administration of vitamin K for the non-urgent reversal of warfarin, except when rapid restoration of anticoagulation after surgery is required. ”

Plasma products (e.g., FFP, PF24, or Thawed Plasma)‡

- FFP is indicated:
  - …”For urgent reversal of warfarin therapy when PCCs are not available”
Case II

- 79 y/o male presents to ER at outside hospital with hypotension and severe back pain
- Transferred with acute Type A aortic dissection
- Patient was started by his PCP on Dabigatran (Prodaxa®) 3 months prior for paroxysmal atrial fibrillation per the patient’s request
Management protocol for hemorrhage in patients taking dabigatran, rivaroxaban, or apixaban

Reversal of novel oral anticoagulation agents

- Currently no direct antagonists FDA approved
- Dabigatran (direct thrombin inhibitor):
  - Activated charcoal
  - Hemodialysis
  - rFVIIa
  - FEIBA
  - PCC,
  - Desmopressin?

- Rivaroxaban and Apixiban (anti factor Xa):
  - PCCs
  - rFVIIa
  - Desmopressin?

“additional clinical studies are still needed to determine the best method for NOACs reversal when bleeding occurs”

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

- Phase III trial.
- Specific reversal agents for non–vitamin K antagonist oral anticoagulants are lacking.
- Idarucizumab, an antibody fragment, was developed to reverse the anticoagulant effects of dabigatran.
- Opportunity for complete reversal of dabigatran within minutes

N Engl J Med 2015;373:511-20
THANK YOU