AVC périopératoire et la gestion des antithrombotiques périprocedurale
Perioperative stroke and the management of periprocedural antithrombotics

Jeffrey Minuk MD, MSc, FRCPC
Professeur Agrégé
Université McGill
Chef Département de Neuroscience
Hôpital général juif
Montréal, Québec

Conflits d’intérêts (deux dernières années)

- Membre du conseil consultatif « advisory board »
  - AstraZeneca
  - BMS-Canada

- Participation dans une étude multi-centres
  - Boehringer-Ingelheim (RESPECT-ESUS)
Plan

• Introduction to the topic with case presentations
• Evidence supporting risk of harm with antithrombotic (antiplatelet) cessation
• Surgery and risk of bleeding and stroke
• “bridging therapy” for anticoagulants
• Recommendations for antithrombotic management for surgery and procedures

Objectifs scientifique

• After this presentation, you should be more comfortable:
  • Discussing the risks of recurrent stroke associated with antiplatelet cessation
  • Discussing the risks of bleeding and stroke in the setting of surgery
  • Discussing the notion of bridging and related controversies
  • Recommending pre-operative management strategies for stroke patients taking antiplatelet agents, warfarin or NOAC’s
Case #1

• 32 year old man presented with a 6 month history of intermittent brief episodes of right facial tingling

• CTA/MRI/MRA showed a large saccular aneurysm at the junction of the right vertebral artery and basilar artery

• Patient underwent stent assisted coiling of the aneurysm

Case #1 con’t

• Procedure complicated stent basilar artery occlusion-partial recanalization with IA tpa

• Patient awoke with severe dysarthria and bilateral hemipareses

• CT head showed bilateral basis pontine strokes-placed on ASA and clopidogrel

• ASA/clopidogrel held 6 weeks later for PEG

• 4 days later-became locked in
Case #1 con’t

- Swallowing deemed inadequate and PEG requested
- GI insisted on antithrombotic cessation prior to procedure
- At time, had completed a full 6 weeks of dual antiplatelet therapy
- ASA and clopidogrel held on a Thursday in anticipation of the PEG being inserted Monday, DVT prophylaxis continued
- Early Monday morning, patient became increasingly obtunded-locked in plus
- Transferred to MNH-occlusion of basilar artery-IA thrombolysis-good reperfusion
- Remained locked-in plus and died several months later
Case #2

- 79 year old woman brought to LGH after a syncopal episode
- Rapid atrial fibrillation diagnosed
- Pacemaker inserted, discharged on apixaban 5mg BID
- Had been scheduled for cataract surgery
- Told to stop apixaban 5 days prior to cataract surgery and did so
- Morning of the proposed surgery, abrupt onset of left hemiplegia
- Brought to JGH ED, large right MCA stroke-NIHSS =22
- Had IV tpa and transferred to MNH for thrombectomy
Antiplatelet cessation and the risk of recurrent stroke

Temporary antiplatelet cessation

• Frequent issue prior to minor and major surgical interventions
• Temporary cessation for 7-10 days frequently recommended prior to dental, dermatological, cataract surgery and major surgeries
• Recall that for many revascularization procedures, antiplatelets are not discontinued; e.g. carotid endarterectomy
• Over many years, case reports anecdotally associated antiplatelet cessation with late stent stenosis, limb ischemia, ACS, stroke
• Case series have documented ASA withdrawal in 2-4% of ACS presentations
Coronary risk and antiplatelet cessation

5% of all patients admitted with an ACS had stopped antiplatelets within previous 3 weeks

(Circulation. 2004;110:2361-2367.)

Antiplatelet drug discontinuation is a risk factor for ischemic stroke

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age</th>
<th>Event</th>
<th>Stroke mechanism</th>
<th>NEUROLOGY 2004;62:1187-1189</th>
<th>APD previously used</th>
<th>Dosage</th>
<th>APD indication</th>
<th>Delay of disruption</th>
<th>Cause of disruption</th>
<th>Major vascular risk factors*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>65</td>
<td>TIA</td>
<td>Atherosclerosis</td>
<td>Aspirin</td>
<td>250 mg o.d.</td>
<td></td>
<td>Coronary disease</td>
<td>7</td>
<td>Cataract surgery</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>81</td>
<td>TIA</td>
<td>Atherosclerosis</td>
<td>Aspirin</td>
<td>75 mg o.d.</td>
<td></td>
<td>Lower limb</td>
<td>9</td>
<td>Bladder polyp reaction</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>81</td>
<td>TIA</td>
<td>Atherosclerosis</td>
<td>Aspirin</td>
<td>75 mg o.d.</td>
<td></td>
<td>Lower limb</td>
<td>9</td>
<td>Inguinal hernia surgery</td>
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<tr>
<td>4</td>
<td>M</td>
<td>58</td>
<td>TIA</td>
<td>Atherosclerosis</td>
<td>Aspirin</td>
<td>250 mg o.d.</td>
<td></td>
<td>Coronary disease</td>
<td>6</td>
<td>Negligence</td>
<td>2</td>
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<tr>
<td>5</td>
<td>M</td>
<td>58</td>
<td>Stroke</td>
<td>Atherosclerosis</td>
<td>Aspirin</td>
<td>250 mg o.d.</td>
<td></td>
<td>Coronary disease</td>
<td>6</td>
<td>Negligence</td>
<td>3</td>
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<td>70</td>
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<td>Atherosclerosis</td>
<td>Clopidogrel</td>
<td>75 mg o.d.</td>
<td>Stroke</td>
<td>5</td>
<td>10</td>
<td>Negligence</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>65</td>
<td>Stroke</td>
<td>Atherosclerosis</td>
<td>Aspirin</td>
<td>250 mg o.d.</td>
<td></td>
<td>Coronary disease</td>
<td>6</td>
<td>Cataract surgery</td>
<td>4</td>
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<td>8</td>
<td>M</td>
<td>51</td>
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<td>Atherosclerosis</td>
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<td>250 mg o.d.</td>
<td>Stroke</td>
<td>7</td>
<td>4</td>
<td>Negligence</td>
<td>2</td>
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<tr>
<td>9</td>
<td>M</td>
<td>69</td>
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<td>Atherosclerosis</td>
<td>Aspirin</td>
<td>100 mg o.d.</td>
<td></td>
<td>Coronary disease</td>
<td>8</td>
<td>Negligence</td>
<td>2</td>
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<tr>
<td>10</td>
<td>M</td>
<td>59</td>
<td>TIA</td>
<td>Atherosclerosis</td>
<td>Aspirin-dipyridamole</td>
<td>250/500 mg t.d.</td>
<td>Stroke</td>
<td>8</td>
<td>5</td>
<td>Radiation necrosis</td>
<td>4</td>
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<td>11</td>
<td>M</td>
<td>56</td>
<td>TIA</td>
<td>Atherosclerosis</td>
<td>Aspirin</td>
<td>250 mg o.d.</td>
<td>Stroke</td>
<td>8</td>
<td>4</td>
<td>Negligence</td>
<td>2</td>
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<td>12</td>
<td>F</td>
<td>83</td>
<td>Stroke</td>
<td>Lacunar</td>
<td>Aspirin</td>
<td>250 mg o.d.</td>
<td></td>
<td>Coronary disease</td>
<td>6</td>
<td>Cataract surgery</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>68</td>
<td>Stroke</td>
<td>Atherosclerosis</td>
<td>Aspirin</td>
<td>250 mg o.d.</td>
<td></td>
<td>Coronary disease</td>
<td>6</td>
<td>Cataract surgery</td>
<td>2</td>
</tr>
</tbody>
</table>

Survey of 320 patients admitted in Bordeaux France over 4.5 months
• Case control study looking at antiplatelet cessation in the previous 4 weeks in:
  • Cases—recent TIA/stroke admissions n=309
  • Controls—ASA users with no stroke in past 6 months n=309 (4 weeks before the interview)
• Antiplatelet cessation (usually for mundane reasons)
  • Cases—4.2%
  • Controls—1.3%
• Mean duration (SD) between cessation and event—9.5+/7 days
• Odds ratio for IS after ASA cessation within 4 weeks—3.4 (CI 1.08-10.63)

Stroke after antithrombotic withdrawal: data from stroke registries

• Broderick reported results from the Greater Cincinnati/Northern Kentucky Stroke Study
• Of 2197 strokes reported in one calendar year, 114 (5.2%) occurred within 60 days of antithrombotic cessation
• Of these, ~55% occurred within 1-7 days of antithrombotic cessation

• In >600,000 Swedish low dose ASA users, cessation was associated with an increased rate of stroke MI or VD (HR 1.37 or 37% increased risk)
• Corresponds to one additional event per year for every 74 patients who stopped ASA
**PRoFESS Trial: Study Design**

20,332 patients ≥ 50 years with at least ischemic stroke* (see inclusion criteria)
Doses: (200 mg ER-DP + 25 mg Aspirin) 2x/day, 80 mg Telmisartan, 75 mg Clopidogrel 1x/day

- **ER-DP + Aspirin + Telmisartan**
  - n = 5,000
- **Clopidogrel + Telmisartan**
  - n = 5,000
- **ER-DP + Aspirin + Placebo**
  - n = 5,000
- **Clopidogrel + Placebo**
  - n = 5,000

2.5 yrs. mean follow-up

- Primary Endpoint: rate of first recurrent stroke
- Secondary Endpoints: stroke, MI, vascular death, rate of new diabetes mellitus
- Tertiary Endpoints: major hemorrhagic event, all deaths, new or worsening congestive heart failure

*Clinical trial data-PROFESS*

Most recurrent strokes occurred within 7 days of cessation
Summary: antiplatelet cessation and risk of stroke

• About 5% of ischemic strokes occur in those who have recently discontinued antiplatelet therapy

• Antiplatelet cessation in those with previous stroke or mi is associated with a 3-5 fold increase in risk of a cardiac event or ischemic stroke within 2-11 days of cessation

Surgery: stroke, bleeding, risk and benefits of antiplatelet agents
Risk of stroke in the perioperative

- Surgery within 30 days has been shown to be an independent risk factor for ischemic stroke
- Reported stroke risk:
  - Non-high risk 0.08-0.4% (derm, opth, GI)
  - High risk 2.2-5.2% (major GI, NSx, ENT)
- Emergency surgery risk > elective surgery risk
- Risk higher with GA than with neuraxis blockade
- Mortality of perioperative stroke is high ~ 26%

Factors increasing risk of periprocedural stroke

- AF with CHADS or CHADS-Vasc >5
- Any mechanical mitral valve or old mechanical valve
- Stroke/TIA in the previous 3-6 months
- Presence of asymptomatic carotid stenosis
- Presence of intracranial stenosis
- History of a previous periprocedural ischemic event
- Surgeries with inherently increased stroke risk (CABG, CEA, ENT, neurosurgical, ?orthopedic)
- Increased age and multiple co-morbidities

Based on: Circulation. 2012;125:e496-e498
The other side of the coin: the inherent risk of bleeding with surgery

<table>
<thead>
<tr>
<th>High risk bleeding (2 day rate 2-4%)</th>
<th>Low risk bleeding (2 day rate 0-2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Valve replacement, CABG</td>
<td>• Dental/dermatologic/cataract</td>
</tr>
<tr>
<td>• AAA repair</td>
<td>• Endoscopy +/- biopsy</td>
</tr>
<tr>
<td>• NeuroSx*/urologic*/abdominal</td>
<td>• Pacemaker/defibrillator</td>
</tr>
<tr>
<td>• Bilateral TKA, posterior ocular*</td>
<td>• Hernia/hemorrhoids</td>
</tr>
<tr>
<td>• TURP</td>
<td>• Bronchoscopy + biopsy</td>
</tr>
<tr>
<td>• Renal biopsy</td>
<td>• Skin/bladder/prostate, thyroid,</td>
</tr>
<tr>
<td>• Procedures &gt;45 minutes</td>
<td>breast, lymph node biopsy</td>
</tr>
</tbody>
</table>

* Bleeding may be associated with transfusion requirements and/or increased morbidity

What about surgical bleeding if antiplatelet agents are maintained?

• In general and for a wide variety of surgical interventions, aspirin will increase bleeding complication rates about 1.5 times

• Except for bleeding associated with intracranial surgery and transurethral prostatectomy, bleeding complications are not severe

*Journal of Internal Medicine* 2005; 257: 399–414
How about this question:
Is perioperative aspirin helpful

- Reduces the risk of stroke in the setting of carotid endarterectomy
- Reduces cardiac events and mortality in CABG
  - Increased chest tube bleeding on ASA
  - No increase in reoperation rates on ASA
- No clear benefit of ASA in setting of non-cardiac surgery

Philip Devereaux et al Perioperative Ischemic Evaluation (POISE-2)
- >10,000 undergoing non cardiac surgery randomized ASA vs placebo
- Of these only 5%/4% had history of stroke/TIA
- 44% previously on ASA
- No benefit of ASA on CVA,MI or VD but major bleeding was increased

Why might antiplatelet cessation increase risk of perioperative stroke?

- Pro-coagulant effect of surgery involved in and aiding wound closure and healing
- ~20% platelet activity is required to from a clot and ~50% activity is required for surgical hemostasis
- Even in those chronically on ASA, ~ 20% of platelet function persists
- Platelet turnover is increased in those with chronic vascular disease
- Nascent platelets contribute more to hemostasis than senescent ones
- Uncertainty whether a true “rebound” thrombotic effect exists after antiplatelet agents cessation-merely return to normal function
Summary: surgery and risk of stroke and bleeding

• Perioperative and periprocedural ASA (antiplatelet) administration increases bleeding frequency but the increased frequency is NOT associated with an increased severity or increased mortality from bleeding (except for intracranial surgery and TURP)
• Perioperative ASA reduces morbidity in cardiac and carotid surgery
• Perioperative ASA use is of limited benefit and it increases bleeding in non-cardiovascular surgery in low risk populations

Anticoagulants: withdrawal and bridging
What Is Bridging Anticoagulation?

Bridging anticoagulation refers to administering low-molecular-weight heparin during the peri-operative period, when warfarin is interrupted and its anticoagulant effect is outside a therapeutic range. Bridging anticoagulation aims to reduce patients' risk for stroke or other major ischemic events, but may also increase patients' risk for developing potentially serious bleeding complications after surgery.
**Bleeding complications: bridged vs. non-bridged**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Bridging Events</th>
<th>No bridging Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daniels et al., 2009</td>
<td>36</td>
<td>34</td>
<td>18</td>
<td>213</td>
<td>9.8%</td>
<td>1.27 [0.70, 2.31]</td>
</tr>
<tr>
<td>Dotan et al., 2002</td>
<td>2</td>
<td>20</td>
<td>1</td>
<td>20</td>
<td>3.7%</td>
<td>2.11 [0.19, 25.36]</td>
</tr>
<tr>
<td>Erkan et al., 2010</td>
<td>11</td>
<td>44</td>
<td>21</td>
<td>1421</td>
<td>9.0%</td>
<td>22.22 [9.92, 49.81]</td>
</tr>
<tr>
<td>Garcia et al., 2008</td>
<td>14</td>
<td>108</td>
<td>9</td>
<td>1185</td>
<td>8.8%</td>
<td>19.46 [8.21, 46.14]</td>
</tr>
<tr>
<td>Ghanbari et al., 2010</td>
<td>6</td>
<td>29</td>
<td>3</td>
<td>74</td>
<td>6.5%</td>
<td>6.17 [1.43, 26.68]</td>
</tr>
<tr>
<td>Jaffer et al., 2010</td>
<td>24</td>
<td>229</td>
<td>7</td>
<td>263</td>
<td>8.8%</td>
<td>4.28 [1.81, 10.14]</td>
</tr>
<tr>
<td>Marquie et al., 2006</td>
<td>21</td>
<td>114</td>
<td>2</td>
<td>114</td>
<td>6.4%</td>
<td>12.65 [2.89, 55.34]</td>
</tr>
<tr>
<td>McBane et al., 2010</td>
<td>34</td>
<td>514</td>
<td>5</td>
<td>261</td>
<td>0.4%</td>
<td>3.63 [1.40, 9.39]</td>
</tr>
<tr>
<td>Robinson et al., 2009</td>
<td>20</td>
<td>113</td>
<td>3</td>
<td>35</td>
<td>7.2%</td>
<td>2.29 [0.64, 0.24]</td>
</tr>
<tr>
<td>Tschenko et al., 2009</td>
<td>9</td>
<td>38</td>
<td>5</td>
<td>117</td>
<td>7.8%</td>
<td>6.95 [2.18, 22.33]</td>
</tr>
<tr>
<td>Tompkins et al., 2010</td>
<td>23</td>
<td>155</td>
<td>15</td>
<td>513</td>
<td>9.5%</td>
<td>5.78 [2.94, 11.40]</td>
</tr>
<tr>
<td>Varkarakis et al., 2005</td>
<td>2</td>
<td>25</td>
<td>7</td>
<td>762</td>
<td>5.9%</td>
<td>9.38 [1.85, 47.64]</td>
</tr>
<tr>
<td>Wysokinski et al., 2008</td>
<td>15</td>
<td>204</td>
<td>6</td>
<td>182</td>
<td>8.4%</td>
<td>2.33 [0.88, 6.13]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1935</td>
<td>5160</td>
<td>100.0%</td>
<td>5.40 [3.00, 9.74]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>217</td>
<td>102</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.83; Chi² = 52.47, df = 12 (P < 0.00001); I² = 77%

Test for overall effect: Z = 5.61 (P < 0.00001)

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**Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation**

- 1884 atrial fibrillation patients undergoing surgery had warfarin stopped 5 days prior to surgery and were randomized to bridging with dalteparin or placebo beginning -3 days prior to surgery
- 9% had previous stroke and 8% previous TIA
- 87% had CHADS2 score of 3 or less
  - no difference in occurrence of arterial embolism (~0.4%)
  - Risk of major bleeding higher in those bridged with dalteparin (3.2% vs 1.3%)
Low event rates

BRIDGE trial: conclusion

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.
So many factors to consider-how do I decide?

• Is it safe to temporarily stop antithrombotics after a TIA/stroke?
• What is the risk associated with continuing an antiplatelet agent for a surgical procedure?
• If we recommend temporary cessation:
  • For how long should the agent be stopped?
  • How long after an ischemic should we wait before recommending cessation?
  • Is any form of bridging therapy required?
  • Should a neurologist or internist/hematologist be consulted?
• Does or should temporary cessation depend upon the reasons for cessation, the type of surgery or anesthesia?
• For antiplatelet agents, are they interchangeable?

How to manage perioperative and periprocedural antithrombotics

• Assess the bleeding risk of the procedure
• Assess the risk the procedures poses for a recurrent ischemic stroke
• For antiplatelets
  • If on ASA-decide if can be held
  • If on clopidogrel-decide if switch to ASA indicated
  • If on DAPT-decide whether one can be held
• For anticoagulants
  • Decide if can be held and if bridging is indicated (warfarin only)
### Factors increasing risk of periprocedural stroke

- AF with CHADS or CHADS-Vasc >5
- Any mechanical mitral valve or old mechanical valve
- Stroke/TIA in the previous 3-6 months
- Presence of asymptomatic carotid stenosis
- Presence of intracranial stenosis
- History of a previous periprocedural ischemic event
- Surgeries with inherently increased stroke risk (CABG, CEA, ENT, neurosurgical, ?orthopedic)
- Increased age and multiple co-morbidities

*Based on: Circulation. 2012;125:e496-e498*
CCS 2014 Clinical Practice Recommendations

• When a decision to interrupt aspirin or clopidogrel therapy for an invasive procedure has been made for a patient with AF/AFL, we suggest that interruption begin 5-7 days before the procedure, except for procedures with a very high risk of bleeding, in which case we suggest interruption 7-10 days before the procedure (Conditional Recommendation, Low-Quality Evidence).

• JM considers briefer interruption; 3-5 days

Canadian Journal of Cardiology 30 (2014) 1114–1130

CCS 2016 Clinical Practice Recommendations

• We suggest that interruption of anticoagulant therapy, particularly for VKAs, in a patient with AF/AFL is not necessary for most procedures with a low risk of bleeding, such as cardiac device implantation (pacemaker or implantable defibrillator), and most dental procedures (Conditional Recommendation, Moderate-Quality Evidence).

http://dx.doi.org/10.1016/j.cjca.2016.07.591
CCS 2014 Clinical Practice Recommendations

• We recommend that interruption of anticoagulant therapy in a patient with AF or AFL will be necessary for most procedures with an intermediate or high risk of major bleeding (Strong Recommendation, Low-Quality Evidence).

CCS 2016 Clinical Practice Recommendations

• When a decision to interrupt warfarin therapy for an invasive procedure has been made for a patient with AF/AFL, we suggest that bridging therapy with LMWH or UFH be instituted when the INR is below therapeutic level only in patients at high risk of thromboembolic events (CHADS2, score =>4, mechanical heart valve, stroke/transient ischemic attack within 3 months, rheumatic heart disease) (Conditional Recommendation, Low-Quality Evidence).

http://dx.doi.org/10.1016/j.cjca.2016.07.591
CCS 2014 and 2016 Clinical Practice Recommendations

• When a decision to interrupt NOAC therapy for an invasive procedure has been made for a patient with AF/AFL, we suggest that interruption begin 1-2 days before a procedure with low risk of major bleeding and 2-3 days before a procedure with an intermediate or high risk of major bleeding (Conditional Recommendation, Low-Quality Evidence).

• Renal function may impact interruption time

• Due to short half life and data from clinical trials and registries, bridging not required

Canadian Journal of Cardiology 30 (2014) 1114–1130
http://dx.doi.org/10.1016/j.cjca.2016.07.591
Summary recommendations for perioperative antiplatelet management

• For any cataract, dental or dermatologic procedures in any patient with or without a previous stroke or TIA, do not stop antithrombotic therapy
• For those with a history of stroke or TIA, maintain ASA for most procedures (consider interruption for urological, neurosurgical and some posterior ocular)
• If on clopidogrel, consider temporary switch to ASA
• If on DAPT, consider holding clopidogrel and maintaining ASA
• Avoid all elective surgeries for at least 6-9 months after a recent stroke or TIA

Summary recommendations for perioperative anticoagulation management

• All those on anticoagulation with warfarin and a history of TIA or stroke in the setting of NVAF are at high risk for stroke recurrence during cessation and should be considered for bridging
• for those patients on a NOAC, the period of interruption is necessarily shorter and most patients can successfully be managed off anticoagulation (usually 1-4 days) if brief interruption is indicated-(see CCS 2014, 2016 guidelines)
• You can help decide if bridging is indicated but get help for the bridging procedures
JM’s advice

When asked regarding antithrombotic cessation in a stroke patient:

- Avoid knee jerk responses like:
  - “No problem-OK to stop ASA for 10 days”
  - “Absolutely not”
  - “BRIDGE trial says no one needs bridging”
  - “why are you calling me?”

- Always consider:
  - Type of agent (ASA, clopidogrel, DAPT, warfarin NOAC)
  - Indication for therapy (primary prevention, stroke, stroke in setting of a fib, etc.)
  - Recentness of stroke
  - Stroke recurrence risk
  - Type of surgery, risk of surgical bleeding, clinical impact of bleeding, risk of periop stroke

- Always involve the patient/family in decision making and fully document your discussions
Merci

Questions?