

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

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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

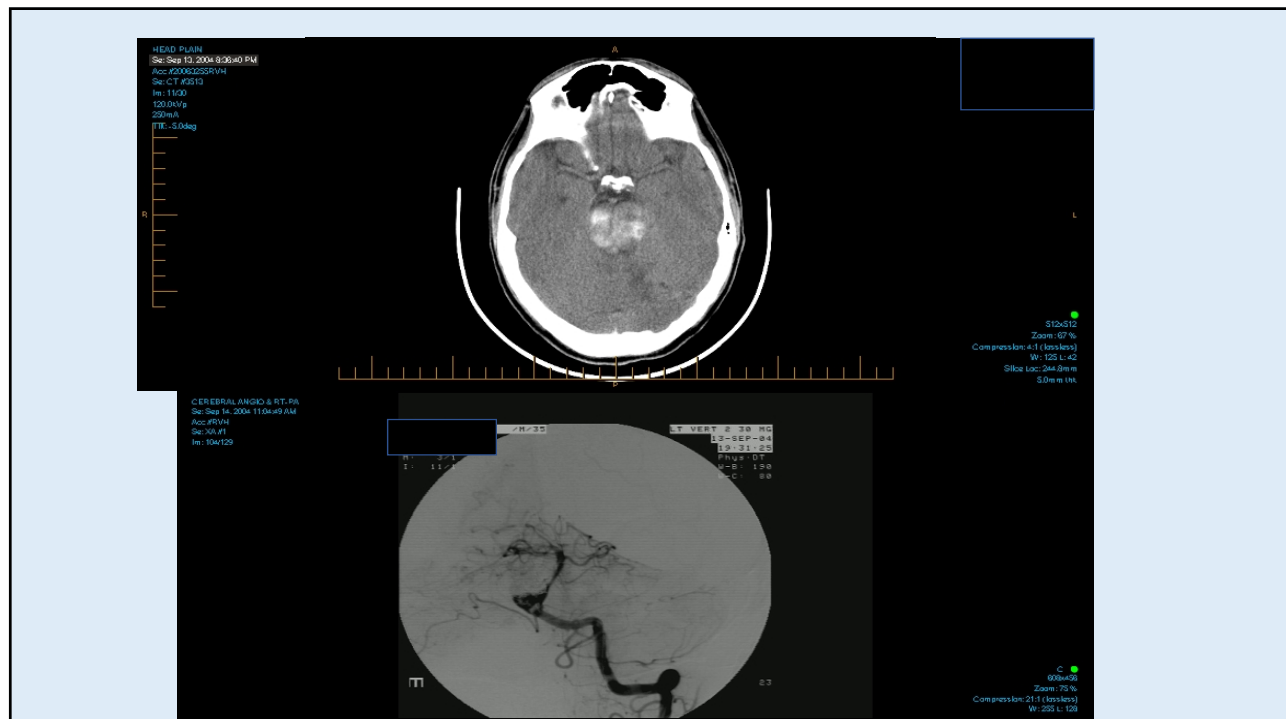


Case #1 con't

- 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 on set of left hemiplegia
- Brought to JGH ED, large right MCA stroke-NIHSS =22
- Had IV tpa and transferred to MNH for thrombectomy

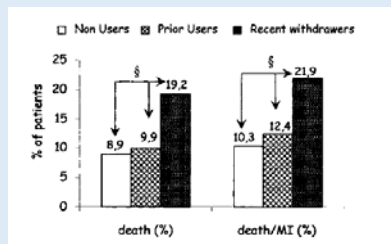
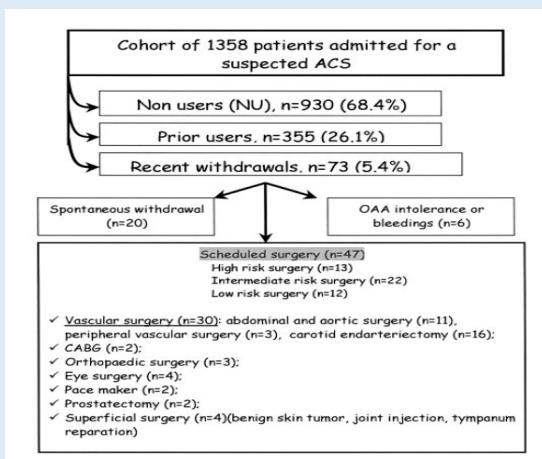


Antiplatelet cessation and the risk of recurrent stroke

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

Igor Sibon, MD; and Jean-Marc Orgogozo, MD

NEUROLOGY 2004;62:1187-1189

Patient no.	Sex	Age, y	Event	Stroke mechanism	APD previously used	Dosage	APD indication	Delay of disruption, d	Cause of disruption	Major vascular risk factors*
1	F	65	TIA	Atherosclerosis	Aspirin	250 mg o.d.	Coronary disease	7	Cataract surgery	3
2	M	81	TIA	Atherosclerosis	Aspirin	75 mg o.d.	Lower limb atherosclerosis	9	Bladder polyp resection	2
3	M	81	TIA	Atherosclerosis	Aspirin	75 mg o.d.	Lower limb atherosclerosis	8	Inguinal hernia surgery	2
4	M	58	TIA	Atherosclerosis	Aspirin	250 mg o.d.	Coronary disease	6	Negligence	2
5	M	58	Stroke	Atherosclerosis	Aspirin	250 mg o.d.	Coronary disease	8	Negligence	3
6	F	70	Stroke	Atherosclerosis	Clopidogrel	75 mg o.d.	Stroke	10	Negligence	3
7	M	65	Stroke	Atherosclerosis	Aspirin	250 mg o.d.	Coronary disease	6	Cataract surgery	4
8	M	51	Stroke	Atherosclerosis	Aspirin	250 mg o.d.	Stroke	7	Negligence	2
9	M	69	Stroke	Atherosclerosis	Aspirin	100 mg o.d.	Coronary disease	8	Negligence	2
10	M	59	TIA	Atherosclerosis	Aspirin-dipyridamole	25/200 mg t.d.	Stroke	8	Radicular infiltration	4
11	M	56	TIA	Atherosclerosis	Aspirin	250 mg o.d.	Stroke	8	Negligence	2
12	F	83	Stroke	Lacune	Aspirin	250 mg o.d.	Coronary disease	6	Cataract surgery	2
13	F	68	Stroke	Atherosclerosis	Aspirin	250 mg o.d.	Coronary disease	6	Cataract surgery	2

Survey of 320 patients admitted in Bordeaux France over 4.5 months

Effect of Discontinuing Aspirin Therapy on the Risk of Brain Ischemic Stroke

Alexandre Balzano Maulaz, MD; Daniel C. Bezerra, MD; Patrik Michel, MD; Julien Bogousslavsky, MD
Arch Neurol. 2005;62:1217-1220

- 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

Stroke. 2011;42:2509-2514

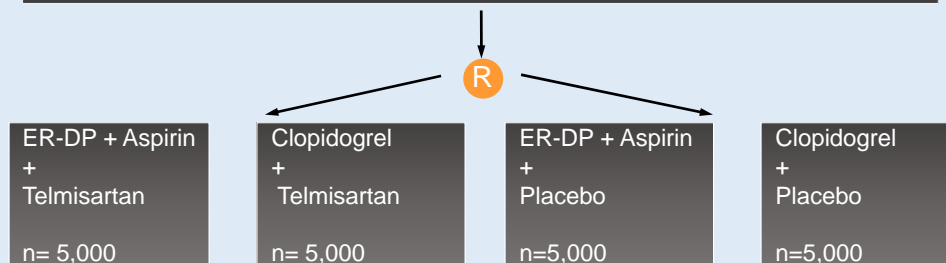
- Broderick reported results from the Greater Cincinnati/Northern Kentucky Stroke Study
- Of 2197 strokes reported in one calendar year, 114 (5.2%) occurred within 60 days of antithrombotic cessation
- Of these, ~55% occurred within 1-7 days of antithrombotic cessation

Circulation. 2017;136:1183-1192

- 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)
 Double-blind. Placebo-controlled. Simultaneous randomization.
 Doses: (200 mg ER-DP + 25 mg Aspirin) 2x/day, 80 mg Telmisartan, 75 mg Clopidogrel 1x/day



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

Cerebrovascular Dis. 2007; 23/ESC 2008

Clinical trial data-PROFESS

Cerebrovasc Dis 2013;35:538–543

Characteristics	On ASA + ERDP	Discontinued ASA + ERDP	On clopidogrel	Discontinued clopidogrel
Sample size, n	7,212	2,843	7,864	2,176
Follow-up (mean \pm SD), days	915 \pm 267	915 \pm 301	917 \pm 265	905 \pm 321
Age (mean \pm SD), years	65.5 \pm 8.4	67.4 \pm 8.7*	65.8 \pm 8.4	67.5 \pm 8.9*

Daily incidence rates in the on-treatment population and patients who discontinued antiplatelet study medication

Daily incidence rate (per 1,000 patient days)	On ASA + ERDP (n = 7,212) ^a	Discontinued ASA + ERDP (n = 2,843) ^b	Incidence rate ratio	On clopidogrel (n = 7,864) ^a	Discontinued clopidogrel (n = 2,176) ^b	Incidence rate ratio
Recurrent stroke within 7 days	0.12	0.66	5.66 (p < 0.001)	0.11	0.54	4.99 (p < 0.001)
Recurrent stroke within 30 days	0.12	0.37	3.20 (p < 0.001)	0.11	0.24	2.23 (p = 0.002)
Recurrent stroke, MI or vascular death within 30 days	0.15	0.82	5.48 (p < 0.001)	0.14	0.75	5.26 (p < 0.001)

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, oph, 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

High risk bleeding (2 day rate 2-4%)

- Valve replacement, CABG
- AAA repair
- NeuroSx*/urologic*/abdominal
- Bilateral TKA, posterior ocular*
- TURP
- Renal biopsy
- Procedures >45 minutes

Low risk bleeding (2 day rate 0-2%)

- Dental/dermatologic/cataract
- Endoscopy +/- biopsy
- Pacemaker/defibrillator
- Hernia/hemorrhoids
- Bronchoscopy + biopsy
- Skin/bladder/prostate, thyroid, breast, lymph node biopsy

* 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)
[N Engl J Med 2014;370:1494-503.](#)
- >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 form 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

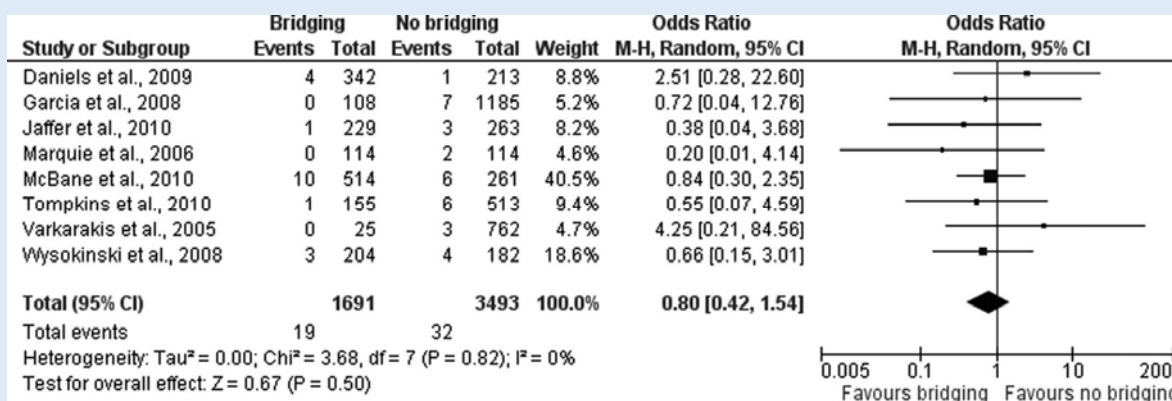
- Perioperative and periprocedural ASA (antiplatelet) administration increases bleeding frequency but the increased frequency is NOT associated with an increased severity or increased mortality from bleeding (except for intracranial surgery and TURP)
- Perioperative ASA reduces morbidity in cardiac and 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.

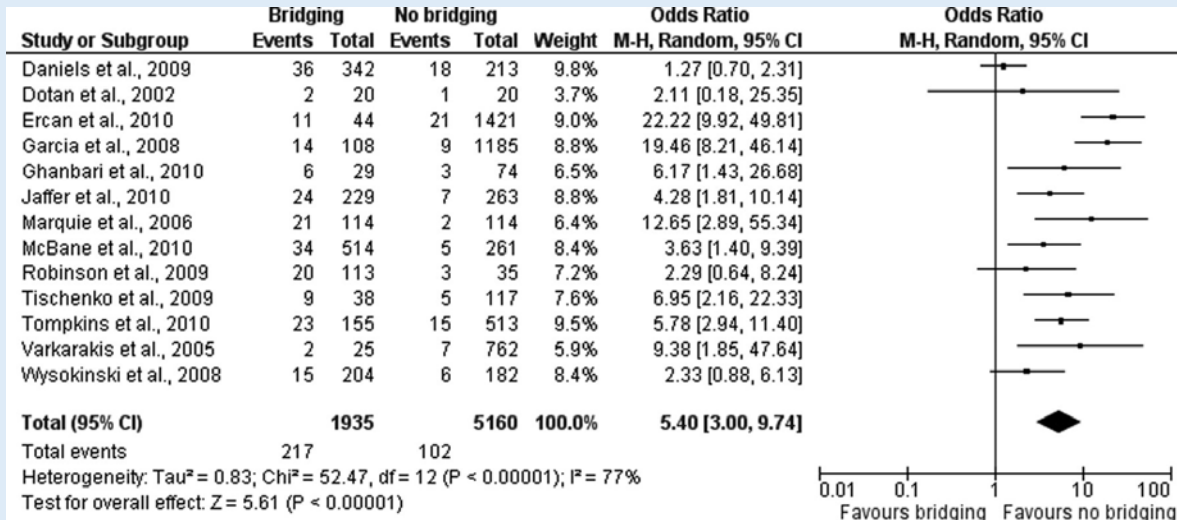
Ischemic events in bridged vs. non-bridged



Circulation. 2012; 126: 1630-1639

Circulation. 2012; 126: 1630-1639

Bleeding complications: bridged vs. non-bridged



Circulation. 2012; 126: 1630-1639

Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

N Engl J Med 2015;373:823-33.

- 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%)

Table 3. Study Outcomes.

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

Low event rates

mainly non-stroke

BRIDGE trial: conclusion

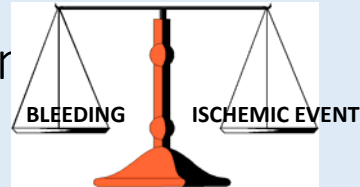
In conclusion, in the BRIDGE trial, we found that for patients with atrial fibrillation who require temporary interruption of warfarin treatment for an elective operation or other elective invasive procedure, a strategy of forgoing bridging anticoagulation was noninferior to perioperative bridging with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

mainly
non-stroke

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)

Bleeding Risks for Various Invasive / Surgical Procedures

HIGH OR VERY HIGH RISK	LOW OR STANDARD RISK	VERY LOW RISK*
<ul style="list-style-type: none"> Any procedure involving neuraxial anesthesia Neurosurgery (intracranial or spinal surgery) Cardiac surgery (e.g. CABG, heart valve replacement) Major vascular surgery (e.g. aortic aneurysm repair, aortofemoral bypass) Major urological surgery (e.g. prostatectomy, bladder tumour resection) Major lower limb orthopedic surgery (e.g. hip/knee joint replacement surgery) Lung resection surgery Intestinal anastomosis surgery <p>Selected procedures (e.g. kidney biopsy, prostate biopsy, cervical cone biopsy, pericardiocentesis, colonic polypectomy)</p> <p>Selected procedures (e.g. kidney biopsy, prostate biopsy, cervical cone biopsy, pericardiocentesis, colonic polypectomy)</p>	<p>Other intra-abdominal surgery</p> <ul style="list-style-type: none"> Other intrathoracic surgery Other orthopedic surgery Other vascular surgery Laparoscopic cholecystectomy Laparoscopic inguinal hernia repair Dental procedures Dermatologic procedures Ophthalmologic procedures Coronary angiography Cardiac implantable electronic device† (pacemaker, implantable defibrillator) Gastroscopy without biopsy, colonoscopy without polypectomy Selected procedures (e.g. bone marrow biopsy, lymph node biopsy, thoracentesis, paracentesis, arthrocentesis) 	<p>Tooth extraction (1 or 2 teeth) or teeth cleaning</p> <ul style="list-style-type: none"> Skin biopsy or skin cancer removal Cataract removal <p>† Antithrombotic therapy with ASA or warfarin (INR 2.0 – 3.0) may continue for implantation of cardiac implantable devices. In addition to the bleeding risk of a procedure, physicians should consider co-morbid conditions that might exacerbate the bleeding risk (e.g. advanced age, renal or liver impairment).</p> <p>*MAY CONTINUE WARFARIN AT THERAPEUTIC INR 2.0 – 3.0 OR OTHER ANTICOAGULANTS)</p>

Can J Cardiol 2014;30:1114-1130
Thrombosis Canada

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 (pace-maker 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

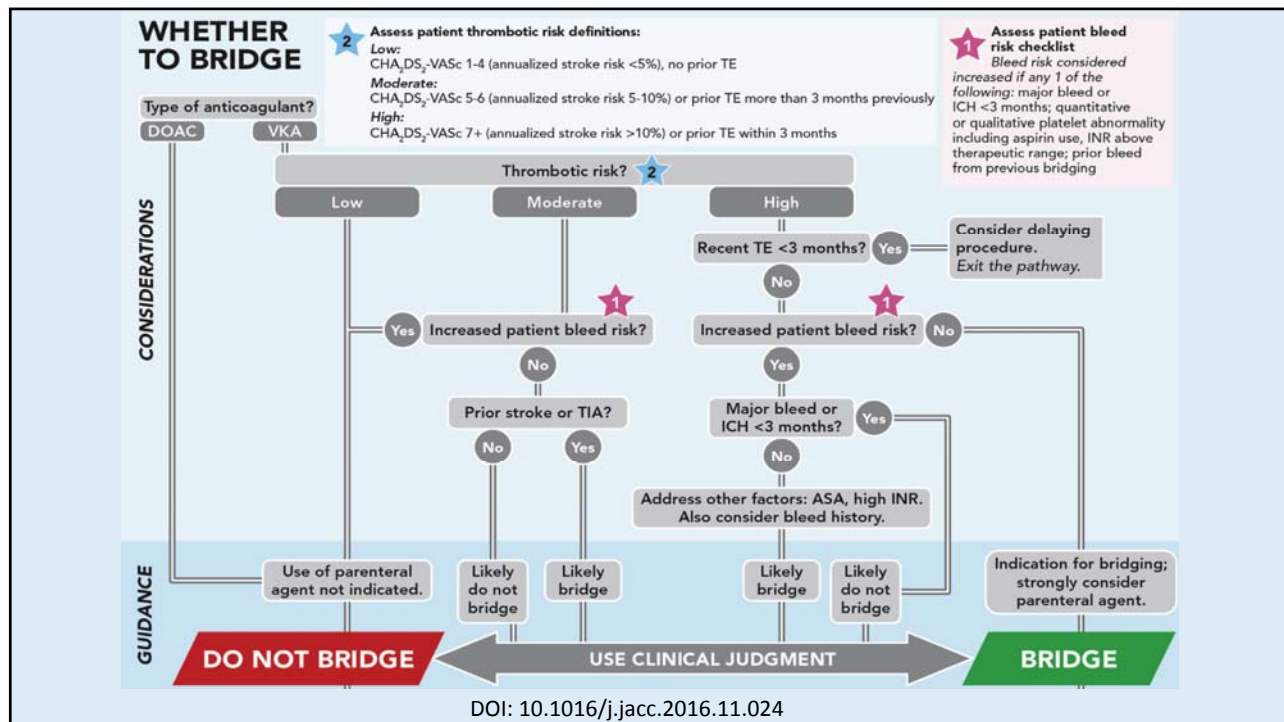
- We recommend that interruption of anticoagulant therapy in a patient with AF or AFL will be necessary for most procedures with an intermediate or high risk of major bleeding (Strong Recommendation, Low-Quality Evidence).

Canadian Journal of Cardiology 30 (2014) 1114–1130

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.cica.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

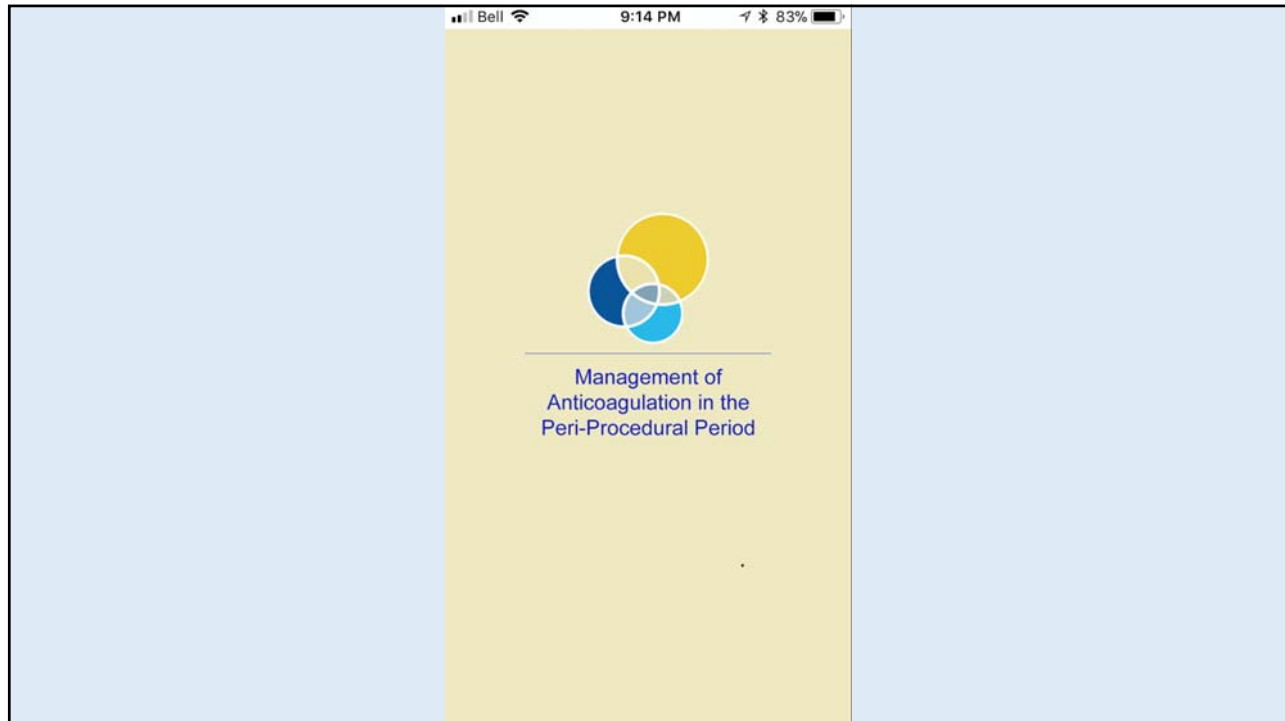
Summary recommendations for perioperative anticoagulation management

- 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?