CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Secondary Prevention of Stroke

Seventh Edition, 2020

Evidence Table: *Perioperative Management of Anticoagulant and Antiplatelet Therapy*

Gladstone D, Poppe A (Writing Group Chairs)
on Behalf of the Canadian Stroke Best Practice Recommendations
Secondary Prevention of Stroke Writing Group and in collaboration with the Canadian Stroke Consortium

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Guideline	Recommendations
Mehta SR, Bainey KR, Cantor WJ, Lordkipanidzé M, Marquis-Gravel G, Robinson SD, Sibbald M, So DY, Wong GC, Abunassar JG, Ackman ML, Bell AD, Cartier R, Douketis JD, Lawler PR, McMurtry MS, Udell JA, van Diepen S, Verma S, Mancini GBJ, Cairns JA, Tanguay JF; members of the Secondary Panel. **2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Focused Update of the Guidelines for the Use of Antiplatelet Therapy.** ***Can J Cardiol.* 2018 Mar;34(3):214-233.**	8. In patients undergoing percutaneous coronary intervention (PCI) who are treated with either a bare metal stent (BMS) or drug-eluting stent (DES) and who require elective noncardiac surgery, we suggest continuing ASA perioperatively whenever possible (Weak Recommendation; Low-Quality Evidence). 9. In patients undergoing PCI who are treated with a BMS or DES and who require elective noncardiac surgery, we suggest withholding clopidogrel and ticagrelor for 5-7 days preoperatively, and prasugrel for 7-10 days preoperatively (Weak Recommendation; Low-Quality Evidence). 10. In patients undergoing PCI who are treated with a BMS or DES and who have undergone noncardiac surgery, we suggest restarting maintenance-dose DAPT after surgery, as soon as it is deemed safe by the surgeon (Weak Recommendation; Very Low-Quality Evidence).

Guideline	Recommendations
Hornor MA, Duane TM, Ehlers AP, Jensen EH, Brown PS Jr, Pohl D, da Costa PM, Ko CY, Laronga C. **American College of Surgeons' Guidelines for the Perioperative Management of Antithrombotic Medication.** ***J Am Coll Surg.* 2018 Nov;227(5):521-536.e1**	**Table 4.** Summary of Recommended Perioperative Anticoagulation Management Strategies

Category	High bleeding risk procedure	Low bleeding risk procedure
High thromboembolic risk		
Warfarin	Give last dose 6 d before operation, bridge with LMWH or UFH, resume 24 h postoperatively.	Give last dose 6 d before operation, bridge with LMWH or UFH, resume 24 h postoperatively.
DOAC	Give last dose 3 d before operation,* resume 2 to 3 d postoperatively.	Give last dose 2 d before operation,* resume 24 h postoperatively.
Intermediate thromboembolic risk		
Warfarin	Give last dose 6 d before operation, determine need for bridging by clinician judgment and current evidence, resume 24 h postoperatively.	Give last dose 6 d before operation, determine need for bridging by clinician judgment and current evidence, resume 24 h postoperatively.
DOAC	Give last dose 3 days before operation,* resume 2 to 3 d postoperatively.	Give last dose 2 d before operation,* resume 24 h postoperatively.
Low thromboembolic risk		
Warfarin	Give last dose 6 d before operation, bridging not recommended, resume 24 h postoperatively.	Give last dose 6 d before operation, bridging not recommended, resume 24 h postoperatively.
DOAC	Give last dose 3 d before operation,* resume 2 to 3 d postoperatively.	Give last dose 2 d before operation,* resume 24 h postoperatively.

*In patients with CrCl < 50 mL/min on dabigatran, the last dose should be given 3 d before the procedure for low bleeding risk surgery, and 4 to 5 d before the procedure for high bleeding risk operation.
DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

Evidence Tables

Perioperative Management

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Douketis et al. 2019 **Canada** **Prospective cohort**	NA	3,007 participants recruited from 23 centres from 2014-2018 who were included in the PAUSE study. Inclusion criteria were: AF, ≥18 years who were long-term users of DOACs (apixaban [48%], dabigatran [22%], and rivaroxaban [36%]) and were scheduled for an elective surgery or procedure. Mean age was 72.5 years, 66.1% were men.	The DOAC regimens were omitted for 1 day before a low–bleeding-risk procedure and 2 days before a high–bleeding-risk procedure. The DOAC regimens were resumed 1 day after a low–bleeding-risk procedure and 2 to 3 days after a high–bleeding-risk procedure.	**Primary outcomes:** Major bleeding and arterial thromboembolism (ischemic stroke/TIA and systemic embolism) at 30 days after the procedure	Frequency of arterial thromboembolism was 0.16% (95% CI, 0%-0.48%) in the apixaban cohort, 0.60% (95% CI, 0%-1.33%) in the dabigatran cohort, and 0.37% (95% CI, 0%-0.82%) in the rivaroxaban cohort. The 30-day postoperative frequency of major bleeding was 1.35% (95% CI, 0%-2.00%) in the apixaban cohort, 0.90% (95% CI, 0%-1.73%) in the dabigatran cohort, and 1.85% (95% CI, 0%-2.65%) in the rivaroxaban cohort. Among the 1,007 patients (33%) who were deemed to be at high risk of bleeding, the frequency of 30-day postoperative major bleeding was 2.96% (95% CI, 0%-4.68%) in the apixaban cohort, 2.95% (95% CI, 0%-4.76%) in the rivaroxaban cohort and 0.88% (95% CI 0%-2.62%) in the dabigatran cohort.
Kovacs et al. 2018 **USA** **RCT (abstract)**	CA: ☒ Blinding patient: ☑ assessor: ☑ ITT: ☒	1,471 patients with AF (n=1167) or a mechanical heart valve (n=304) who required interruption of warfarin for a planned procedure. Mean age was 69.7 years, 64.3% were men.	All patients received pre-procedure bridging therapy with dalteparin in the morning day-3 and day-2, and 24 hours pre-procedure. Warfarin was resumed in the evening of the procedure at twice the usual dose for the first two days and then titrated according to INR. After the procedure (same day or next day), patients were randomized to receive dalteparin (n=821) or placebo (n=650) for at least 4 days and until the	**Primary outcome:** Major thromboembolism (stroke, proximal DVT, PE, MI, peripheral embolism) over 90 days **Secondary outcomes:** Major bleeding, all-cause mortality and a composite outcome of major thromboembolism and major bleeding.	The primary outcome occurred in 6/820 (0.73%) dalteparin patients and 7/650 (1.08%) placebo patients (p=0.48). Major post-procedure bleeding occurred in 12 (1.46%) dalteparin patients and 16 (2.46%) placebo patients (p=0.16). There were 6 deaths (9.2%) in the no bridging group and 6 deaths (0.73%) in the bridging group (p=0.69). There were 23 cases of the secondary composite outcome (3.54%) in the no bridging group and 18 (2.2%) in the bridging group (p=0.16). Findings were similar in subgroups of patients with AF alone and in patients with mechanical

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			INR was greater than 1.9. For patients at high risk for post-procedure major bleeding, dalteparin or placebo was administered at a fixed daily dose of 5000 IU. For patients at low risk for post-procedure major bleeding, dalteparin or placebo was administered at a daily dose of 200 IU per kilogram (max 18,000 IU).		heart valves (with or without AF).
Myles et al. 2016 **Australia** **RCT**	CA: ☑ Blinding patient: ☑ assessor: ☑ ITT: ☑	2,100 patients who were scheduled to undergo coronary artery surgery and were at increased risk for complications. Mean age was 66 years, 82% were men.	Patients were randomized 1:1 to receive 100 mg aspirin or placebo, preoperatively (1-2 hours prior to surgery).	**Primary outcome:** Composite of death and thrombotic complications (nonfatal MI, stroke, pulmonary embolism, renal failure, or bowel infarction) within 30 days after surgery. **Secondary outcomes:** Death, nonfatal MI, major hemorrhage, cardiac tamponade, and a requirement for transfusion.	The primary outcome occurred in 202 patients (19.3%) in the aspirin group and in 215 patients (20.4%) in the placebo group (RR=0.94, 95% CI 0.80 to 1.12; p = 0.55). There were 19 major hemorrhages (1.8%) in the aspirin group and 22 in the placebo group (2.1). RR=0.87, 95% CI 0.47–1.60, p=0.75. There were no significant differences between groups for any of the other secondary outcomes. Death: 1.3% (aspirin) vs. 0.9% (placebo) MI: 13.8% (aspirin) vs. 15.8% (placebo) Stroke: 1.3% (aspirin) vs. 1.1% (placebo) Cardiac tamponade: 1.1% (aspirin) vs. 0.4% (placebo) The percentage of patients with postoperative adverse events was similar between groups (7.1% [aspirin] and 6.7% [placebo]). For the primary outcome, there were no interactions based on age, sex, previous MI, diabetes, unstable angina, EUROscore, surgical type, or cross-clamp duration.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Douketis et al. 2015 **USA** **RCT** ***BRIDGE trial***	CA: ☑ Blinding patient: ☑ assessor: ☑ ITT: ☒	1,884 patients ≥18 years with AF, had received warfarin therapy for ≥3 months, were undergoing an elective operation or other elective invasive procedure that required interruption of warfarin therapy; and had ≥1 of the following $CHADS_2$ stroke risk factors: congestive heart failure or left ventricular dysfunction, hypertension, ≥ 75 years, diabetes or previous ischemic stroke, systemic embolism, or TIA. M mean age was 71.7 years, 73.4% were men.	Patients were randomized 1:1 to receive bridging anticoagulation therapy with low-molecular-weight heparin (100 IU of dalteparin per kilogram of body weight) or matching placebo administered subcutaneously twice daily, from 3 days before the procedure until 24 hours before the procedure and then for 5 to 10 days after the procedure. Warfarin treatment was stopped 5 days before the procedure and was resumed within 24 hours after the procedure.	**Primary outcomes:** Arterial thromboembolism (stroke/TIA or systemic embolism) and major bleeding within 30 days **Secondary outcomes:** Acute MI, DVT, PE, minor bleeding and death	Arterial thromboembolism occurred in 4 (0.4%) of patients in the no bridging group and 3 (0.3%) in the bridging group (p= 0.01 for non-inferiority, p=0.73 for superiority). Major bleeding occurred significantly more in the bridging group (3.2% vs. 1.3%, p<0.005 for superiority). There were 5 deaths (0.5%) in the no bridging group and 4 (0.4%) in the bridging group (p=0.88) There were 7 MIs (0.8%) in the no bridging group and 14 (1.6%) in the bridging group (p=0.10). There were no DVTs or PEs in the no bridging group and 1 of each in the bridging group. Minor bleeding occurred significantly more in the bridging group (12% vs. 20.9%, p<0.001 for superiority).
Devereaux et al. 2014 **Canada** **RCT** ***POISE-2 trial***	CA: ☑ Blinding patient: ☑ assessor: ☑ ITT: ☒	10,010 patients ≥45 years, scheduled for noncardiac surgery with ≥1 of the following: a history of CAD, PVD, stroke, were to undergo major vascular surgery, or had any 3 of 9 criteria to undergo major surgery, history of CHF, TIA, diabetes, ≥70 years, hypertension, serum creatinine > 175 µmol/L, smoking within previous 2 years or need for urgent surgery. Mean age was 68.6 years, 52.8% were men. 5.4% had a previous stroke.	Patients were stratified according to whether they had not been taking aspirin before the study (initiation stratum, n=5,628 patients) or if they were already on an aspirin regimen (continuation stratum, n=4,382 patients). Patients were randomized to start taking 200 mg aspirin (n=4,998) or placebo (n=5,012) just before surgery and continued it daily (100 mg) for 30 days in the initiation	**Primary outcome:** Composite of death or nonfatal MI at 30 days **Secondary outcomes:** 1) Death, nonfatal MI or nonfatal stroke; 2) death, nonfatal MI, cardiac revascularization, nonfatal PE or nonfatal DVTs **Safety outcomes:** Stroke, CHF, life-threatening bleeding, and major bleeding at 30 days	The primary outcome occurred in 7.0% of patients in the aspirin group and 7.1% in the placebo group (HR=0.99; 95% CI 0.86 to 1.15; p=0.92). The first secondary outcome occurred in 7.2% of patients in the aspirin group and 7.4% in the placebo group (HR=0.98; 95% CI 0.85 to 1.13; p=0.92). The second secondary outcome occurred in 8.0% of patients in the aspirin group and 8.1% in the placebo group (HR=0.98; 95% CI 0.86 to 1.14; p=0.90). Life-threatening bleeding occurred in 1.7% of patients in the aspirin group and 1.5% in the placebo group (HR=1.19; 95% CI 0.88 to 1.63; p=0.26).

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			stratum and for 7 days in the continuation stratum, after which patients resumed their regular aspirin regimen.		Major bleeding occurred significantly more in the aspirin group (4.6% vs. 3.8%; HR=1.23, 95% CI 1.01–1.49, p=0.04). Stroke occurred in 0.03% of patients in the aspirin group and 0.4% in the placebo group (HR=0.84; 95% CI 0.43 to 1.64; p=0.62). In subgroup analysis, there were no significant interactions based on aspirin strata, type of surgery, revised cardiac index or vascular disease.

Abbreviations

AF: atrial fibrillation	CA: concealed allocation	CHF: congestive heart failure
CI: confidence interval	DOAC: direct oral anticoagulant	DVT: deep vein thrombosis
HR: hazard ratio	ITT: intention-to-treat	PE: pulmonary embolus
TIA: transient ischemic attack		

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Kovacs MJ, Rodger M, Wells PS, et al. Double-blind randomized control trial of postoperative low molecular weight heparin bridging therapy for patients who are at high risk for arterial thromboembolism (PERIOP 2). *Blood.* 2018;132(Supplement 1):424-424.

Myles PS, Smith JA, Forbes A, et al. Stopping vs. continuing aspirin before coronary artery surgery. *The New England journal of medicine* 2016;374(8):728-37.