Anticoagulation - Perioperative Guideline

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1. Overview

1.1 Antiplatelet Therapy

Aspirin

- Recent data shows that administration of aspirin during the perioperative period has no significant effect on the rate of a composite of death or nonfatal myocardial infarction, while the risk of major bleeding was increased. Therefore any patients on aspirin for primary prevention should have this stopped 7-10 days prior to non-cardiac surgery. Patients with a significant cardiac history e.g. MI within past 12 months, cardiac stents and/or previous CABG, should be discussed with a cardiologist.

Clopidogrel

- Some studies have shown an increased risk of major bleeding with the use of clopidogrel within five days of coronary artery bypass grafting. The decision to stop or continue clopidogrel should be individualised with respect to ischaemic complications and bleeding. For percutaneous coronary intervention, treatment with clopidogrel is recommended before and throughout the perioperative period.
- Patients with coronary stents in situ have a high thrombotic risk if antiplatelet drug therapy is interrupted. Elective non-cardiac surgery should therefore be avoided after stent placement when patients are most prone to thrombosis. This is during the first six weeks for bare metal

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stents, and the first 12 months for drug-eluting stents. *However if surgery is planned within 12 months after insertion of a drug-eluting stent, please contact a cardiologist to discuss, as this is not an absolute contraindication.*

- For patients without coronary stents who are not at high risk of cardiac events, clopidogrel can be ceased 5 days before surgery. Please consult the patient's cardiologist/stroke physician before stopping the drug. Clopidogrel should be resumed following the procedure as soon as there is adequate haemostasis, usually the morning after surgery.

Other antiplatelet agents

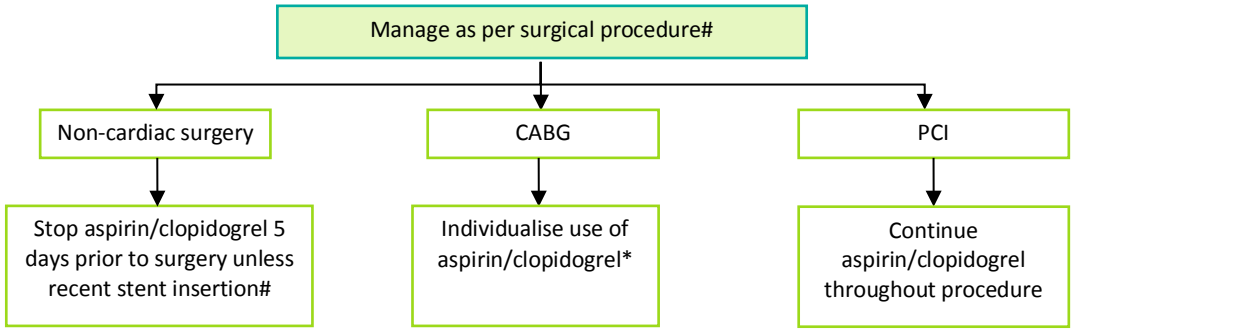
- Timing between cessation and procedure:
  - Ticagrelor: 5 days
  - Prasugrel: 7 days
  - Ticlopidine: 10–14 days
  - Dipyridamole: 7-10 days

Dual antiplatelet therapy

- Please contact the patient's primary physician to discuss.

1.2 Perioperative Management of Patients Receiving Aspirin and Clopidogrel

Fig. 1 shows a suggested perioperative management strategy.



FOOT NOTES

\# For patients with a bare metal coronary stent requiring urgent surgery within 6 weeks of insertion, or with a drug-eluting stent requiring surgery within 12 months of stent placement, it is recommended that aspirin & clopidogrel be continued in the peri-operative period. Discussion between cardiologist/ surgeon/anaesthetist is recommended for all patients with cardiac stents and/or previous CABG.

* Refer text

- CABG = coronary artery bypass grafting
- PCI = percutaneous coronary intervention

1.3 Warfarin

When considering how to manage patients on warfarin who require surgery, it is helpful to weigh up the risk of bleeding versus the risk of thromboembolism. This requires consideration of:

- indication for anticoagulation
- history of any thrombotic events

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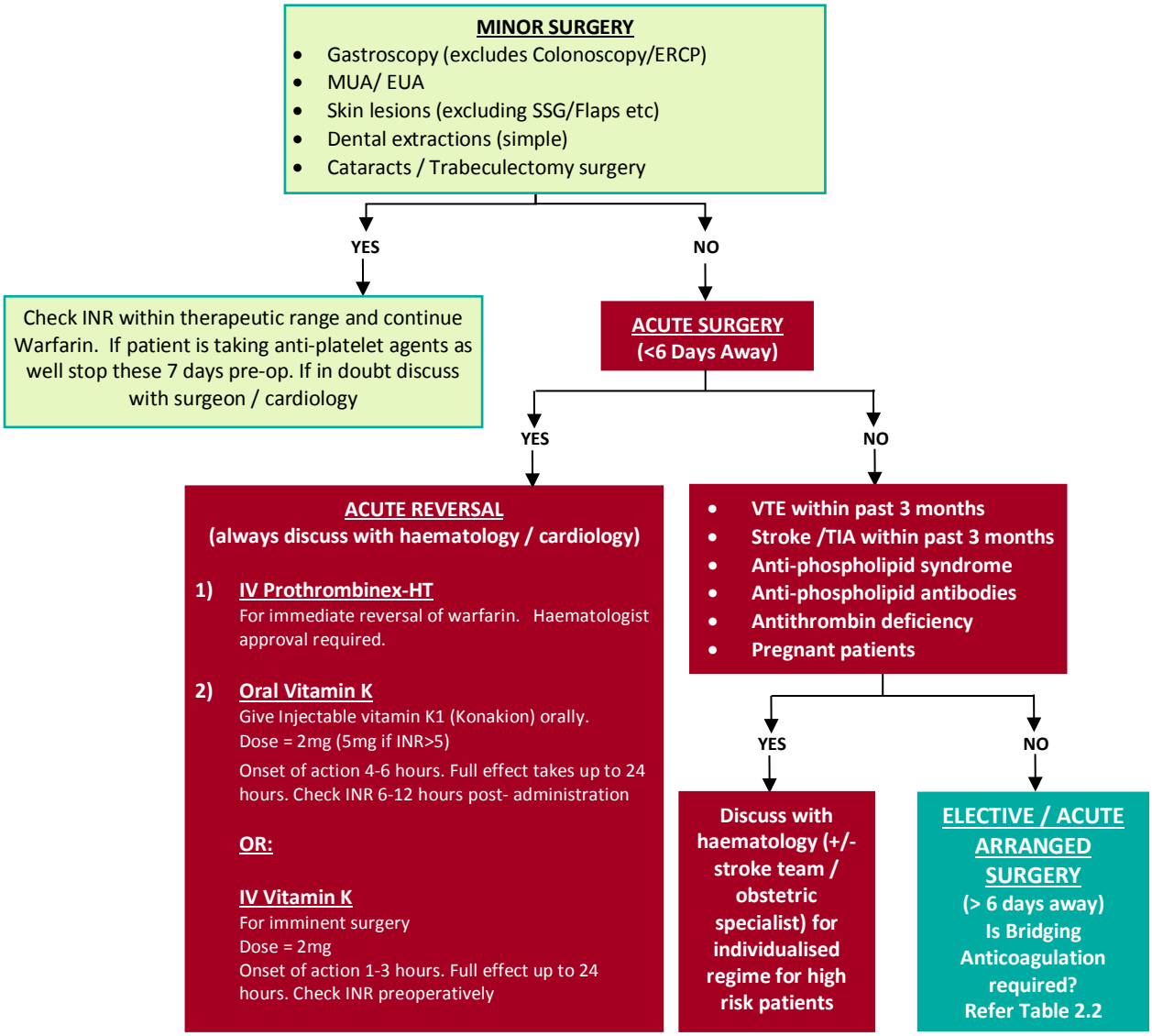
- type of surgery and its associated risks of bleeding and thromboembolism, particularly with respect to postoperative venous thromboembolism.

2. Patient Risk Stratification for Perioperative Arterial or Venous Thromboembolism

2.1 Peri-Operative Management of Patients on Warfarin Protocol



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2.2 If Any of the Following Conditions Apply then Patient Needs Bridging Therapy (Refer Table 2.3)

Mechanical Heart Valves and Valvular Heart Disease • Always discuss this group with the patient's cardiologist • Need to establish patient's target INR in order to bridge when sub-therapeutic	• Mitral Valve Replacement - any type • More than one mechanical valve • "Non bi-leaflet" Aortic Valve Replacement (AVR) • Bi-leaflet Aortic Valve Replacement AND any of following complications: – previous stroke /TIA – intra-cardiac thrombus – cardio-embolic event – LVEF<35% – Severe LA dilation (diameter >50mm) • Rheumatic mitral valve disease +/ - Atrial fibrillation
Venous thromboembolism (VTE)	• Recurrent VTE (includes proximal DVT) • VTE AND severe thrombophilia – Protein C or Protein S deficiency – Homozygous Prothrombin C20210A – Homozygous Factor V Leiden • VTE and current cancer
Atrial fibrillation	AF AND: • Previous stroke or TIA • Rheumatic mitral valve disease • CHA_2DS_2-VASc score ≥ 5 *This score can be calculated and saved in Concerto by logging on and using the patient's NHI*

If none of the above conditions apply then the patient does not need bridging therapy. Follow warfarin cessation protocol, Table 2.4

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2.3 Patient Needs Bridging Therapy

Day	eGRF > 30ml/min	eGFR < 30ml/min
Pre-Op Day 6	Last dose of warfarin. Check INR.	Last dose of warfarin. Check INR.
Pre-Op Day 5	No anticoagulation ±	No anticoagulation ±
Pre-Op Day 4	No anticoagulation ±	No anticoagulation ±
Pre-Op Day 3	Check INR. Once sub-therapeutic start Enoxaparin 1mg/kg*subcut twice daily at 0800h/2000h	Check INR. Once sub-therapeutic start Enoxaparin 1mg/kg* subcut once daily at 0800h
Pre-Op Day 2	Enoxaparin 1mg/kg* subcut twice daily at 0800h/2000h	Enoxaparin 1mg/kg* subcut once daily at 0800h
Pre-Op Day 1	Enoxaparin 1mg/kg* subcut once daily (last dose at 0800h)	Enoxaparin 1mg/kg* subcut once daily (last dose at 0800h)
Day of surgery	Check INR at 0700h to ensure <1.5	Check INR at 0700h to ensure <1.5
Post Op Days 1-3	• Surgical team to discuss with anaesthesia +/- haematology/cardiology re: post-op management: • Aim to restart heparin 12-24 hours post op (as per surgical preference) - Enoxaparin 1mg/kg* subcut twice daily (1mg/kg* subcut once daily if eGFR<30ml/min) or Unfractionated heparin IV infusion • Refer also to "Guideline for anticoagulant administration before and after epidural catheter manipulation or removal" • Start patients usual warfarin dose (no loading) at 1800h on day 0 or day 1 after surgery (as per surgical preference) + daily INR once restarted (If epidural in situ delay warfarin until after epidural catheter removed) • Stop daily INR and enoxaparin/IV heparin when INR within target range for 2 consecutive days AND when minimum of five days of enoxaparin/unfractionated heparin have been given	

* Enoxaparin doses should be based on actual body weight, rounded down to nearest 10mg. Maximum of 150mg Enoxaparin as a single dose.

± Unless INR subtherapeutic

2.4 Patient Does Not Need Bridging Therapy

Day Pre-Op	eGFR > 30ml/min or eGFR <30ml/min
Pre-Op Day 6	Last dose of warfarin
Pre-Op Day 5	No anticoagulation
Pre-Op Day 4	No anticoagulation
Pre-Op Day 3	No anticoagulation
Pre-Op Day 2	No anticoagulation
Pre-Op Day 1	No anticoagulation
Day of surgery	Check INR at 0700h to ensure <1.5
Post Op Days 1-3	• Consider prophylactic dose enoxaparin / TEDS for DVT prevention. Refer also to "Guideline for anticoagulant administration before and after epidural catheter manipulation or removal" • Start patients usual warfarin dose (no loading) at 1800h on day 0 or day 1 post -op (as per surgical preference) + check INR daily once restarted. (If epidural in situ delay warfarin until after epidural catheter removed) • Stop daily INR and enoxaparin when INR within target range for 2 consecutive days AND when minimum of five days of enoxaparin/unfractionated heparin have been given • If warfarin not restarted by Day 2 post-op discuss with cardiology/haematology for advice re need for interim anticoagulation

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3. Heparin (Unfractionated and Low Molecular Weight)

3.1 Stopping Preoperatively

For patients who receive bridging anticoagulation with therapeutic doses of enoxaparin, the last dose should be administered in the morning, at least 24 hours before the procedure. There is evidence suggesting that there will be a residual anticoagulant effect if enoxaparin is given too close to the time of the procedure. For unfractionated heparin, it is recommended that the IV infusion be stopped 4-6 hours before the procedure.

3.2 Resuming Postoperatively

The factors that affect the risk of postoperative bleeding include the timing of the anticoagulant dose after surgery, the dose of anticoagulant and the type of surgery along with its associated bleeding risk. The following recommendations take all of these factors into consideration:

- Low molecular weight heparin or unfractionated heparin can be resumed 12-24 hours following the procedure for minor surgery. For major surgery, for most patients the first dose should be 12-24 hours post-surgery, but if the bleeding risk is perceived to be very high then this should be delayed until 48-72 hours post-surgery (refer table 2 below for periprocedural bleeding risks).** The initial dose will vary from the prophylactic dose (for example, enoxaparin 40 mg once daily) to the therapeutic dose (for example, enoxaparin 1 mg/kg twice daily) depending on the risk of thrombosis, and the risk of bleeding. This needs to be individualised for each patient. Daily review of VTE prophylaxis/dosing is vital.

** Please also consult "Guideline for anticoagulant administration before and after epidural catheter manipulation or removal"

Table 2: Procedural Bleeding Risks

High (2-day risk of major bleed 2%-4%)
Heart valve replacement
Coronary artery bypass
Abdominal aortic aneurysm repair
Neurosurgical/urologic/head and neck/abdominal/ breast cancer surgery
Bilateral knee replacement
Laminectomy
Transurethral prostate resection
Kidney biopsy
Polypectomy, variceal treatment, biliary sphincterectomy, pneumatic dilatation
PEG placement
Endoscopically guided fine-needle aspiration
Multiple tooth extraction
Vascular and general surgery
Knee/hip joint replacement
Any major operation (procedure duration > 45 minutes)

Low (2-day risk of major bleed 0%-2%)
Gastrointestinal endoscope ± biopsy, enteroscopy, biliary/pancreatic stent without sphincterotomy, endonosonography without fine-needle aspiration
Pacemaker and cardiac defibrillation insertion and electrophysiologic testing
Simple dental extractions
Carpal tunnel repair
Shoulder/foot/hand surgery and arthroscopy
Dilatation and curettage
Skin cancer excision
Abdominal hernia repair
Haemorrhoidal surgery
Axillary node dissection
Hydrocele repair
Cataract and noncataract eye surgery
Noncoronary angiography
Bronchoscopy ± biopsy
Central venous catheter removal
Cutaneous and bladder/prostate/thyroid/breast/ lymph node biopsies

(*Adapted from Spyropoulos & Douketis, Blood 2012*)

If in doubt regarding bleeding risk, please discuss with surgeon.

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4. Other Anticoagulant Drugs

4.1 Rivaroxaban, Apixaban, Dabigatran

- Rivaroxaban and apixaban are direct Xa inhibitors, with half-lives of 7-11 hours and 8-14 hours, respectively, in those with normal renal function. Dabigatran is a direct thrombin inhibitor and has a half-life of 14-17 hours in those with normal renal function. These drugs do not have antidotes outside of clinical trials; therefore careful planning is required for perioperative management.
- Dabigatran is primarily renally excreted. Renal function should be checked at the pre-admission assessment and the patient should be given clear written instructions about when to stop the dabigatran treatment. The tables below provide guidance on discontinuation and resumption for each of these. It is generally safe to proceed if the thrombin clotting time (TCT) is normal in patients who have been on dabigatran; if in doubt a dabigatran serum level can be requested (available at North Shore Hospital).
- Rivaroxaban is 33% excreted unchanged, and apixaban 25% unchanged. INR/APTT are not a reliable measure of anticoagulant effect, in particular for apixaban, and depending on the reagent, a patient can still have significant residual Xa inhibitor present with a normal INR and APTT. Anti-Xa levels calibrated for rivaroxaban and apixaban are available through the Auckland Hospital laboratory.
- If high risk patient e.g. $CHA_2DS_2Vasc \geq 5$ and on a direct oral anticoagulant, please discuss with cardiologist re need for bridging.
- If a patient needs an urgent procedure and is taking a direct oral anticoagulant, please ask for a coagulation screen including thrombin clotting time, and discuss with the haematologist on call.

4.2 Table 3: Perioperative Interruption and Resumption of Rivaroxaban, Apixaban and Dabigatran

Interruption of Anticoagulation (Spyropoulos & Douketis, Blood 2012)

Drug (dose)*	Patient renal function	Low bleeding risk surgery† (2 or 3 drug half-lives between last dose and surgery)	High bleeding risk surgery± (4 or 5 drug half-lives between last dose and surgery)
Dabigatran (110-150 mg twice daily)			
$t_{½}$ = 14-17 h	Normal or mild impairment (CrCl > 50 mL/min)	Last dose: 48 h before surgery	Last dose: 72 h before surgery
$t_{½}$ = 16-18 h	Moderate impairment (CrCl 30-50 mL/min)	Last dose: 72 h before surgery	Last dose: 96-120 h before surgery
Rivaroxaban (15-20 mg once daily)			
$t_{½}$ = 8-9 h	Normal or mild impairment (CrCl > 50 mL/min)	Last dose: 48 h before surgery	Last dose: 72 h before surgery
$t_{½}$ = 9 h	Moderate impairment (CrCl 30-50 mL/min)	Last dose: 48 h before surgery	Last dose: 72 h before surgery
$t_{½}$ = 9-10 h	Severe impairment (CrCl 15-29.9 mL/min)	Last dose: 72 h before surgery	Last dose: 96 h before surgery
Apixaban (2.5- 5 mg twice daily)			
$t_{½}$ = 7-8 h	Normal or mild impairment (CrCl > 50 mL/min)	Last dose: 48 h before surgery	Last dose: 72 h before surgery
$t_{½}$ = 17-18 h	Moderate impairment (CrCl 30-50 mL/min)	Last dose: 72 h before surgery	Last dose: 96 h before surgery

*Estimated $t_{1/2}$ based on renal clearance

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† Aiming for mild to moderate residual anticoagulant effect at surgery (<12-25%)
± Aiming for no or minimal residual anticoagulant effect at surgery (<3-6%)

Resumption of Anticoagulation

Drug	Low Bleeding Risk Surgery	High Bleeding risk surgery
Dabigatran	Resume on day after surgery (24 h postoperative), 150 mg twice daily or 110 mg BD	Resume 2-3 days after surgery (48-72 h postoperative), 150 mg twice daily or 110 mg BD
Rivaroxaban	Resume on day after surgery (24 h postoperative), 15-20 mg once daily	Resume 2-3 days after surgery (48-72 h postoperative), 5 mg twice daily†
Apixaban	Resume on day after surgery (24 h postoperative), 2.5-5 mg twice daily	Resume 2-3 days after surgery (48-72 h postoperative), 5 mg twice daily

- Alternatively, consider Enoxaparin 20-40mg subcut once daily or unfractionated heparin 5000 units subcut twice daily or three times daily during the period of high bleeding risk.

Note: A dabigatran App is available for Smart Phones to aid with management; type "Managing Dabigatran" into App Store

5. Procedures

5.1 Epidural or Spinal Anaesthesia

Epidural Catheter Insertion

In patients receiving bridging anticoagulation, the last dose of subcut enoxaparin should be given 24 hours before, and intravenous unfractionated heparin should be stopped 4-6 hours before the insertion or removal of the epidural or spinal needle. The procedure should be performed by an experienced anaesthetist. It is preferable to avoid therapeutic doses of enoxaparin with an epidural catheter in situ. Rivaroxaban and dabigatran should be stopped preoperatively as per table 3 above.

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5.2 Table 4: Guideline for timing of anti-coagulant administration before and after removal or manipulation epidural catheter

	Minimum time to wait **BEFORE** removal or manipulation of epidural catheter	Time to next anti-coagulation dose **AFTER** removal or manipulation of epidural catheter
Prophylactic low-dose unfractionated subcutaneous heparin, *e.g. 5000units of* ***heparin*** *subcut twice daily* *NB: Safety of >10,000u/day or 8-hourly subcut heparin with indwelling epidural catheters not established. Discuss with anaesthetist before administering q8h heparin.*	6 hours + Check platelets if received unfractionated heparin for 5 days or more	1 hour
Therapeutic unfractionated heparin, *e.g.* ***Heparin*** *IV bolus and infusion targeting APTT 60-100 seconds*	4 hours + Check APTT (below 38 seconds)	1 hour
Prophylactic Low Molecular Weight Heparin (LMWH), *e.g.* ***Enoxaparin*** *(Clexane®) 40mg subcut once daily OR 20mg subcut daily if TBW < 45kg or eGFR <30ml/min, e.g.* ***Enoxaparin*** *(Clexane®) 40mg subcut twice daily for obesity BMI>40* ** Avoid giving other anti-coagulant or antiplatelet medication while giving LMWH.* ** NSAIDs may increase bleeding risk – benefits and risks of concomitant administration should be carefully considered.*	12 hours If once daily dosing 24 hours If twice daily dosing (i.e. withhold morning dose)	2 hours
Therapeutic Low Molecular Weight Heparin (LMWH), *e.g.* ***Enoxaparin*** *(Clexane®) 1mg/kg subcut 12 hrly or 1.5mg/kg subcut daily*	24 hours	2 hours
Oral vitamin-K dependant factor anticoagulant **Warfarin** (Marevan®, Coumadin®)	*Should not be administered unless on the advice of an Anaesthetist or the Acute Pain Service*	If Warfarin treatment commences with epidural in situ, epidural must be removed while INR <1.5 within first 48 hours
Oral direct factor Xa inhibitor, *e.g.* ***Rivaroxaban*** *(Xarelto®)*	*Should not be administered to a patient with an epidural catheter in situ. If Rivaroxaban is administered with an epidural catheter in situ, wait at least 22-26 hours before removing epidural catheter*	6 hours
Dabigatran (Pradaxa ®) **Clopidogrel** (Arrow-Clopid®, Apo-Clopidogrel®) **Ticagrelor** (Brilinta®) **Dipyridamole** (Persantin®, Pytazen SR®) **Prasugrel** (Effient®)	*Should not be administered to a patient with an epidural catheter in situ.*	

- While patients with an epidural are receiving anti-coagulation for DVT prophylaxis, avoid the co-administration of other anticoagulant or antiplatelet medication (e.g. clopidogrel, dipyridamole, ticagrelor, prasugrel).

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5.3 Dental, Dermatological or Ophthalmological Procedures

- It is usually safe to continue aspirin around the time of the procedure. However, clopidogrel should be stopped 5 days before the procedure unless the patient has had a recent stent insertion.
- Warfarin can usually be continued in patients having minor dental procedures (single or multiple tooth extraction and root canal procedures), minor dermatological procedures (including excisions of skin lesions) and minor ophthalmological procedures (including cataract extraction). Dentists can consider co-administration of an antifibrinolytic drug such as tranexamic mouth wash.

5.4 Endoscopy

- For patients having elective gastroscopy, the recommendations as for dental, dermatologic and opthalmological procedures can apply. However if the patient requires a biopsy or intervention (e.g. ERCP), then follow the recommendations for patients undergoing general surgery.

6. References

1	Management of Antithrombotic Therapy in Patients Undergoing Invasive Procedures. Baron T, Kamath P, McBane R. NEJM 2013; 368:2113-24.
2	Aspirin in Patients Undergoing Noncardiac Surgery. Devereaux PJ, Mrkobrada M, Sessler DI, Leslie K, Alonso-Coello P et al. N Engl J Med 2014;370(16):1494-503.
3	Merritt JC, Bhatt DL. The efficacy and safety of perioperative antiplatelet therapy. J Thromb Thrombolysis 2004;17:21-7.
4	Mangano DT. Aspirin and mortality from coronary bypass surgery. N Engl J Med 2002;347:1309-17.
5	Yende S, Wunderink RG. Effect of clopidogrel on bleeding after coronary artery bypass surgery. Crit Care Med 2001;29:2271-5.
6	Fitchett D, Eikelboom J, Fremes S, Mazer D, Singh S, Bittira B, et al. Dual antiplatelet therapy in patients requiring urgent coronary artery bypass grafting surgery: a position statement of the Canadian Cardiovascular Society. Can J Cardiol 2009;25:683-9.
7	Douketis JD, Berger PB, Dunn AS, Jaffer AK, Spyropoulos AC, Becker RC, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133(6 Suppl):299S-339S.
8	O'Donnell MJ, Kearon C, Johnson J, Robinson M, Zondag M, Turpie I, et al. Brief communication: Preoperative anticoagulant activity after bridging low-molecular-weight heparin for temporary interruption of warfarin. Ann Intern Med 2007;146:184-7.
9	Spyropoulos AC, Turpie AG, Dunn AS, Spandorfer J, Douketis J, Jacobson A, et al. Clinical outcomes with unfractionated heparin or low-molecular-weight heparin as bridging therapy in patients on long-term oral anticoagulants: the REGIMEN registry. J Thromb Haemost 2006;4:1246-52.
10	Dunn AS, Spyropoulos AC, Turpie AG. Bridging therapy in patients on long-term oral anticoagulants who require surgery: the Prospective Peri-operative Enoxaparin Cohort Trial (PROSPECT). J Thromb Haemost 2007;5:2211-8.
11	Sacco R, Sacco M, Carpenedo M, Moia M. Oral surgery in patients on oral anticoagulant therapy: a randomized comparison of different INR targets. J Thromb Haemost 2006;4:688-9.
12	Al-Mubarak S, Rass MA, Alsuwyed A, Alabdulaaly A, Ciancio S. Thromboembolic risk and bleeding in patients maintaining or stopping oral anticoagulant therapy during dental extraction. J Thromb Haemost 2006;4:689-91.
13	Weitz JI. New oral anticoagulants in development. Thromb Haemost 2010;103:62-70.
14	Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864-70.
15	van Ryn et al. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost 2010; 103: 1116–1127.
16	Spyropoulos A, Douketis J. How I treat anticoagulated patients undergoing an elective procedure or surgery. Blood 2012; 120: 2954-2962.