South African Family Practice 2019; 61(2):S11-S15

S Afr Fam Pract
ISSN 2078-6190 EISSN 2078-6204

NW REFRESHER COURSE

A practical approach to perioperative anticoagulation

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More than half of US citizens over 65 consume drugs impacting coagulation on a chronic basis. This excludes those using non-prescribed supplements and herbal preparations. About two thirds of agents impact platelet function. The remainder fall in the category of anticoagulants. Novel oral anticoagulants (NOACs) are also known as direct acting oral anticoagulants (DOACs) and are newer additions to our current armamentarium of heparin, LMWH, pentasaccharides and warfarin. NOACs provide more efficacious anticoagulation than current agents with a lower incidence of major and life threatening bleeding. Of the NOACs currently available in SA, rivaroxaban and apixaban are factor Xa inhibitors and dabigatran is a thrombin (Factor II) inhibitor. Although there are some differences between NOACs in this respect, the range of indications for NOACs continues to expand and includes:

1. VTE (venous thrombo-embolism) prophylaxis in orthopaedic and general surgery
2. Treatment and long term prevention of VTE – DVT or PTE – in medical and surgical patients
3. SPAF (stroke prevention in atrial fibrillation)
4. Anticoagulation for any indication in patients with current, or a history of, HIT (heparin induced thrombocytopaenia)
5. Anticoagulation in acute coronary syndromes, percutaneous coronary interventions (PCI), stents and stable coronary artery disease

Commencement of anticoagulation for postoperative prophylaxis rarely poses challenges beyond choice of an appropriate drug and dose for the patient demographic and health profile and timing of initiation, based on surgical bleeding risk. As a general rule, for effective VTE prophylaxis with acceptable bleeding risk, the t_{max} of the anticoagulant should not be achieved < 8 hours after surgery (commencement > 6 hours post-surgery) nor > 24 hours after surgery (commencement on the morning after surgery).

It is the patients on long-term anticoagulation presenting for surgery, particularly urgent or emergency surgery (whether or not related to bleeding), and those bleeding intra- and postoperatively that produce our major challenges. It is important to note that the mere presence of the drug does not imply that bleeding will occur, nor that bleeding that occurs relates to the drug. However, several factors increase the likelihood of drug related bleeding and complicate management of such bleeding:

1. The clinical duration of effect of the drug being taken (warfarin > fondaparinux > dabigatran > rivaroxaban > apixaban)
2. The dose of drug being taken and overdosage
3. Temporal proximity of the dose to the surgical procedure
4. Combinations of agents impacting coagulation
5. Organ function, particularly renal (greatest impact on dabigatran)
6. Age
7. Lean body mass
8. The nature of the surgery

WHICH DRUG IS ON BOARD?

DRUG	ACTION	HOW TO MEASURE	CLINICAL DURATION OF BLEEDING RISK
Heparin / LMWH	Anti II / Xa	aPTT; aCT; anti Xa activity	4 – 24 hours
Warfarin	Anti II / VII / IX / X	INR	3 – 7 days
Dabigatran (Pradaxa)	Anti II	aPTT etc – non-linear	24 – 48 hours
Rivaroxaban (Xarelto)	Anti Xa	INR – non-linear	18 – 36 hours
Fondaparinux (Arixtra)	Anti Xa	Anti Xa activity; INR – non-linear	1 – 3 days
Aspirin	Anti-platelet	Bleeding time; PFT	3 – 7 days
Clopidogrel / Ticagrelor	Anti-platelet	Bleeding time ; PFT	3 – 7 days

When dealing with true emergency surgery, in the absence of antidote availability (idarucizumab for dabigatran; andexant alpha for Xa inhibitors or ciraparantag for both), there is little that can be done to reverse drug effect. We need to ensure open lines of communication to the laboratory and blood bank, use point of care monitoring, have procoagulants available, defend the clotting milieu (temperature, calcium, etc.) and encourage limited and meticulous surgery.

With less emergent surgery, we can consider several factors to mitigate both the risks of thrombotic events and of major bleeding[1]:

1. The gravity of the indication for anticoagulation (active/recent VTE; high grade thrombophilia; artificial mitral valves; AF with high CHADS-VASC score) – hence the need for perioperative anticoagulant cover
2. The bleeding risk of the envisioned surgery
3. The clinical duration of effect of the drug on board
4. Safe discontinuation interval for anticoagulants
5. Age and co-morbidity
6. Bridging strategies
7. Anticoagulant reversal
8. General/non-specific prothrombotic strategies
9. Appropriate perioperative monitoring

The strength of indication for anti-coagulant in atrial fibrillation is described in terms of the CHA_2DS_2-VASc scoring system. A score of 2 or more mandates life-long anticoagulation.

Figure 1 below summarises the recommendations for pre-procedural discontinuation of NOACs to ensure no residual anticoagulant effect.

In situations where the clotting risk is considered high to prohibitive but the bleeding risk of the procedure is also significant, it is considered prudent to use shorter-acting anticoagulants as **bridging** options in the perioperative period. These situations include the active phase of VTE treatment (within about 3 weeks of the acute event), mechanical mitral valves, severe thrombophilias with strong clotting history and AF with high risk scores. As a general rule, if we employ the principle that we should wait 2–3 half lives of clinical effect to ensure insignificant anticoagulation, no bridging is required with heparins, LMWH or NOACs. **The risk of a thrombotic event during drug interruption is lower than that of a bleeding event from bridging.** Bridging of NOACs must, however, be considered if there is a prohibition on oral medication intake in the postoperative period. In this instance, LMWH is recommended in a prophylactic dosing regimen (e.g., enoxaparin 40 mg s/c daily), with the first dose corresponding to the next due dose of NOAC and the final dose of LMWH 24 hours before the first postoperative dose of NOAC. No overlap is required on resumption of NOAC treatment. Warfarin therapy with its long duration of clinical effect does, however, require bridging. The recommended approach with warfarin is as follows:

- Stop warfarin 4–7 days prior to surgery
- Following day, LMWH 0.5–1 mg/kg lean body mass bid (or equivalent in IU/kg). Lower dose with maintenance anticoagulation for VTE or AF; higher dose for the obese, mechanical mitral valves and active VTE
- Last dose the night before surgery (at least 12 hours pre-op) plus measure INR – if normal:
- Proceed with surgery
- Resume LMWH > 6 but < 12 hours postoperatively

Table 1: Stroke and bleeding risk stratification with the CHA_2DS_2-VASc and HAS-BLED schemas

CHA_2DS_2-VASc	Score	HAS-BLED	Score
Congestive heart failure/LV dysfunction	1	Hypertension i.e. uncontrolled BP	1
Hypertension	1	Abnormal renal/liver function	1 or 2
Aged ≥75 years	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency or predisposition	1
Stroke/TIA/TE	2	Labile INR	1
Vascular disease [prior MI, PAD, or aortic plaque]	1	Age (e.g. >65)	1
Aged 65-74 years	1	Drugs (e.g. concomitant aspirin or NSAIDSs) or alcohol	1
Sex category [i.e. female gender]	1		
Maximum score	**9**		**9**

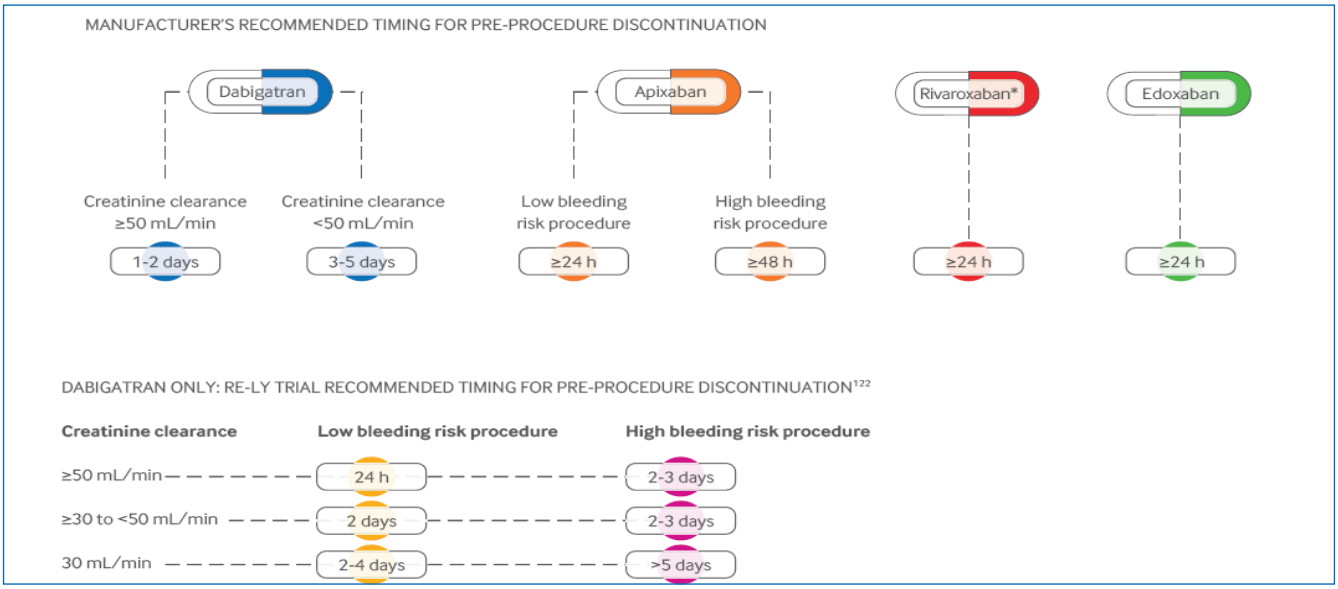


Figure 1

- Resume routine warfarin dose when feasible
- Stop warfarin, measure INR – if therapeutic:
- 2 day crossover with LMWH
- Measure INR on day 3 of warfarin therapy and, if therapeutic, suspend LMWH
- Otherwise continue LMWH and check INR daily, suspending LMWH when INR therapeutic

Reversal of anticoagulants may be necessary under the following circumstances[2]:

1. Surgery to manage a consequence of excessive anticoagulation
2. Significant intra- or postoperative bleeding as a proven consequence of anticoagulant therapy
3. Emergency surgery with a high bleeding risk, particularly in patients with a non-critical indication for anticoagulation
4. Effective reversal strategy available.

Reversal of agents except warfarin is rarely necessary or appropriate in the absence of bleeding, given that the surgery can be delayed for 2–3 drug (or drug effect) half lives. Warfarin is, however, frequently implicated in bleeding complications necessitating surgical intervention, because of its variable and fluctuating therapeutic effect, drug and food interactions, long duration of clinical effect and the relatively high concentrations of factor VII present in and required for haemostasis in the GIT and CNS. Depending on the urgency of surgery, severity of bleeding and degree of derangement of the INR, a variety of reversal options for warfarin are available. The following guidelines assist in management of warfarin-induced hypocoagulability:

- In the absence of bleeding or imminent surgery, an abnormal INR can be managed merely by omitting warfarin doses and regular INR assessment until the patient reaches the upper limit of the target INR range. Warfarin can then be resumed and a dosage titration carried out against regular INR assessments. This avoids the hypercoagulability that is inevitable with reversal.
- The presence of significant haemorrhage mandates a combination of IV vitamin K and prothrombin complex concentrate (PCC) – in SA this is marketed as Haemosolvex – or fresh frozen plasma to achieve an INR around or below 1.6. The doses of the drugs/agents are determined by the severity

Anticoagulant	Reversal agent
Heparin	Protamine sulfate
	Protamine sulfate is strongly basic and combines with acidic heparin forming a stable inactive complex
	1mg per 100 units of heparin, *not to exceed 50 mg*
	Max infusion rate - 5mg/min
	Check aPTT 5-15min after initial dose and then at 2-8 hours
Enoxaparin	Protamine sulfate
	1mg per mg of enoxaparin if last injection <8hrs 0.5mg per mg of enoxaparin if last injection >8hrs 0.5mg per mg of enoxaparin if bleeding persists after 4 hours of first dose
	Single dose not to exceed 50mg
	Max infusion rate – 5mg/min
Warfarin	4F-PCC (KCentra, Octaplex)^
	If INR 2 to <4 25 units/kg; *not to exceed 2500 units*
	If INR 4 to 6 35 units/kg; *not to exceed 3500 units*
	If INR >6 50 units/kg; *not to exceed 5000 units*
	Single dose only OR If 4F-PCC is not available Fresh Frozen Plasma: 10-20mL/kg*
	PLUS
	Vitamin K: 5-10mg IVPB (20-60 minutes) with either PCC or FFP
	Repeat INR in 30-60 minutes after administration
Fondaparinux	4F-PCC (KCentra, Octoplex)^*
	50 units/kg; *not to exceed 5000 units*
	Single dose only

Anticoagulant	Reversal/treatment options
Dabigatran	Idarucizumab (Praxbind) 50mg total dose (given as divided doses of 25mg, 15 minutes apart)
	Alternatives if idarucizumab is unavailable
	Hemodialysis
	Activated charcoal 100g po/NG if ingestion time <2 hours
	4F-aPCC (FEIBA)# 50 units/kg IV; *not to exceed 5000 units* (single dose only)
	Tranexamic acid 25mg/kg IV
	Desmopressin 0.3mcg/kg SQ or IV; limit to 2 IV doses given Increased risk of tachyphylaxis
	FFP: Not recommended rFVIIa: Not recommended
Apixaban	Activated charcoal 100g po/NG if ingestion time <6 hours
	4F-PCC (KCentra / Octaplex)#^ 50 units/kg IV; not to exceed 5000 units (single dose only)
	Tranexamic acid 25mg/kg IV
	Desmopressin 0.3mcg/kg SQ or IV; limit to 2 IV doses given Increased risk of tachyphylaxis
	Andexant alfa* 400mg IV bolus at 30mg/min followed by continous infusion at 4mcg/min for 120 minutes
	FFP: Not recommended rFVIIa: Not recommended
Rivaroxaban	Activated charcoal 100g po/NG; if ingestion time <8 hours
	4F-PCC (KCentra / Octaplex)#^ 50 units/kg IV; not to exceed 5000 units (single dose only)
	Tranexamic acid 25mg/kg IV
	Desmopressin 0.3mcg/kg SQ or IV; limit to 2 IV doses given Increased risk of tachyphylaxis
	Andexant alfa* 800mg IV bolus at 30mg/min followed by continuous infusion at 8mcg/min for 120 minutes
	FFP: Not recommended rFVIIa: Not recommended

of the derangement of INR. PCC or FFP produce a reduction in INR within 60 minutes.

- Where surgery is required for indications other than bleeding, the urgency of envisioned surgery determines the appropriate route for vitamin K administration and whether additional PCC or FFP is indicated; and the extent of INR disturbance determines the dose needed.
- Oral vitamin K produces significant reversal of warfarin toxicity in 24–48 hours and the IV route about 12 hours faster.

Reversal strategies for NOACs remain non-specific until specific antidotes and assays are available in SA. They are outlined in the following table:

It should be noted that, in correcting excessive NOAC-related anticoagulation:

- Desmopressin and tranexamic acid form part of the algorithm for reversal of excessive anticoagulation with NOACs and should be used only
  - Where urgent major/trauma surgery is envisaged and
  - The patient is bleeding clinically or
  - NOACs have been taken in the last 12 hours in therapeutic doses or
  - Renal function is significantly impaired
  - Essentially, however, they mitigate bleeding from other causes
  - PCC is recommended for more specific prophylaxis in the same situations
  - Further perioperative management of NOAC-related bleeding requires blood products guided by TEG monitoring and other specific tests (haematologist)
  - Concerns about procoagulant complications with rVIIa; FBG; PCC; products

Surgery and invasive procedures, depending on their nature and patient co-morbidity especially renal function, can be carried out safely when more than 3 half-lives of non-warfarin anticoagulants have passed or laboratory evidence reveals adequate reversal.

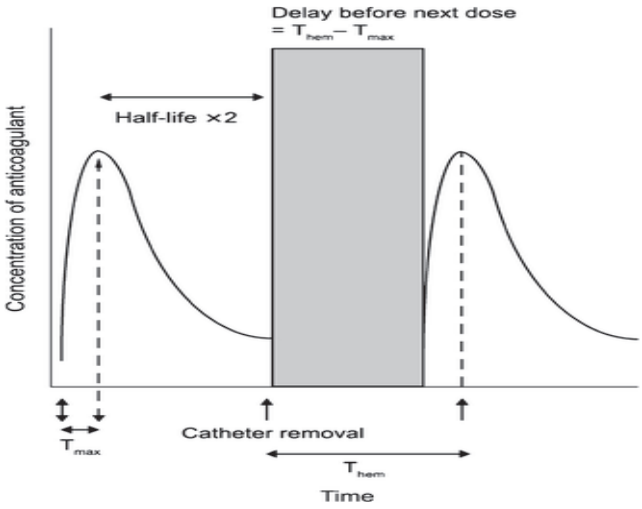
Although, in reality, seldom the domain of the anaesthesiologist, it should not be forgotten that the postoperative phase is associated with a shift in haemostatic balance towards clotting and is acknowledged to produce an incidence of VTE of 5–50% and a significant incidence in the risk and severity of adverse arterial thrombotic events compared with a non-surgical population. It is therefore absolutely mandatory, particularly in patients already at increased thrombotic risk, to resume anticoagulation and/or anti-platelet therapy as soon as safety permits and to bridge patients with short-acting. Far more patients suffer morbidity and mortality related to postoperative hypercoagulability than peri-operative bleeding. The following guidelines apply to postoperative resumption of anticoagulation:

- Stable clot is generally present 8 hours after surgery in systemically healthy patients (longer with organ dysfunction)
- Can resume the anticoagulant 1 t_{max} before this following surgery with low bleeding risk
- Higher bleeding risk surgery
  - Lower thrombotic risk patients – delay for up to 48 hours (mechanical prophylaxis)
  - Higher thrombotic risk – delay until bleeding risk is considered acceptable but bridge with LMWH, commenced > 6 hours postoperatively
- Resuming warfarin
  - If bridging indicated preoperatively, bridging also indicated postoperatively until INR is in target range

Implications for regional anaesthesia and pain therapy

The 2018 ASRA guidelines[3] have been released to expand and update guidelines and recommendations for regional anaesthesia and pain interventions in patients on all available antithrombotic and thrombolytic agents. Little has changed in terms of nature and strength of recommendations. The major highlights include:

1. Review of neuraxial haematoma reports – several case reports of provoked and unprovoked haematomas after thrombolytics; single case reports with fondaparinux and rivaroxaban. Good evidence that increased awareness of antithrombotic kinetics, guidelines and patient risk factors have dramatically reduced the incidence of haematomas since the 1999 closed claims analysis. The Rosencher model remains the reference point for calculation of safe intervals from drug to neuraxial procedure and from procedure drug resumption. Evidence (but not yet guidelines) suggests that risk decreases meaningfully from epidural catheter techniques, through single shot epidural to single shot spinal to pencil point spinal.



Rosencher model for epidural catheter removal (or neuraxial procedure in patients on chronic prophylaxis) and redosing of prophylactic anticoagulant. T_{haem} – time to formation of a stable clot – 8 hours in a normal patient

2. Inclusion of recommendations for NOACs – essentially deferring of neuraxial and deep blocks (lumbar plexus/paravertebral) and pain interventions for a minimum of 2 half-lives after prophylactic doses of oral Xa inhibitors (rivaroxaban, apixaban & edoxaban) and 3 half lives after therapeutic doses.

Anticoagulant	Recommendations to minimize risk of hematoma following regional analgesic/anesthetic procedures[a]				
	$T_{1/2}$	Anticoagulant type	AC-RA/CM	RA/CM-AC	Monitoring and precautions
Heparin (unfractionated) intravenous	1.5–2 hours	Pro-antithrombin III (anti II, X)	2–4 hours, or aPTT WNL	1–2 hours nontraumatic; 6–12 hours if traumatic	aPTT, anti-Xa/IIa, ACT
Heparin SQ BID ≤10,000 U/d	1.5–2 hours	Pro-antithrombin III (anti II, X)	None; Caution: peaks 1–4 hours postdose	No restriction	Platelets for HIT
Heparin SQ TID ≥10,000 U/d	1.5–2 hours	Pro-antithrombin III (anti II, X)	Insufficient data and caution advised, >6 hours[b]	Insufficient data (many choose nadir of effect at >6 hours[b])	Platelets for HIT
Enoxaparin (Lovenox) QD prophylaxis (0.5 mg/kg) (40 mg daily)	3–6 hours	LMWH Anti-Xa	12 hours	2 hours; 24 hours posttraumatic needle puncture	Anti-Xa–[c]
Enoxaparin (Lovenox) BID prophylaxis (0.5 mg/kg) (30 mg BID)	3–6 hours	LMWH Anti-Xa	12 hours	Not recommended with catheter. Initiate ≥2–4 hours postremoval	Anti-Xa–[c]
Enoxaparin BID therapeutic dose (≥0.5 mg/kg)	3–6 hours	LMWH Anti-Xa	24 hours	Not recommended with catheter. Initiate ≥10–12 hours postremoval	Anti-Xa–[c]
Warfarin (Coumadin)	20–60 hours	Vitamin K-dependent factor inhibition	INR ≤1.5, 4–5 days	INR <1.5	INR
Aspirin	6 hours	Antiplatelet	None	No restrictions	
Clopidogrel (Plavix)	6–8 hours	Irreversible platelet aggregation inhibitor	5–7 days; may be OK for superficial PNA SSRA without discontinuation	Not recommended with catheter. Initiate ≥2 hours postcatheter removal[b]	
Ticlopidine (Ticlid)	4–5 days	Irreversible platelet aggregation inhibitor	14 days	Not recommended with catheter. Initiate ≥2 hours postremoval[b]	
Prasugrel (Effient)	7–8 hours	Irreversible platelet aggregation inhibitor	7–10 days	6 hours	
Ticagrelor (Brilinta)	7–8.5 hours	ADP reversible receptor blocker	5–7 days	6 hours	–[d]
Abciximab (ReoPro)	0.5 hour	Glycoprotein IIb/IIIa inhibitor	48 hours	Not recommended with catheter. Initiate ≥2 hours postremoval	
Eptifibatide (Integrilin)	1–2.5 hours	Glycoprotein IIb/IIIa inhibitor	8 hours	Not recommended with catheter. Initiate ≥2 hours postremoval	
Tirofiban (Aggrastat)	2 hours	Glycoprotein IIb/IIIa inhibitor	8 hours	Not recommended with catheter. Initiate ≥2 hours postremoval	
Bivalirudin (Angiomax), lepirudin, desirudin	0.5–3 hours	Thrombin (II) inhibitor	Not recommended for neuraxial/deep-PNB Insufficient data	Not recommended for neuraxial/deep-PNB Insufficient data	aPTT
Argatroban	35–40 minutes	Thrombin (II) inhibitor	Not recommended for neuraxial/deep-PNB Insufficient data	Not recommended for neuraxial/deep-PNB Insufficient data	aPTT
Dabigatran (Pradaxa)	12–15 hours	Thrombin (II) inhibitor (oral)	4–5 days	6 hours	aPTT–[c]
Fondaparinux (Arixtra)	17–21 hours	Anti-Xa through binding to antithrombin III	3–4 days; SSRA only	Contraindicated for indwelling catheters. Initiate ≥12 hours postremoval[b]	Anti-Xa
Rivaroxaban (Xarelto)	5–9 hours	Anti-Xa	3 days	6 hours	Anti-Xa, PT–[c,d]
Apixaban (Eliquis)	10–15 hours	Anti-Xa	3–5 days	6 hours	Anti-Xa, PT–[d]

Dabigatran package insert specifically contra-indicates the use of neuraxial anaesthesia after dabigatran use. No specific recommendations are made regarding deep blocks.

3. Emphasis on the risk factors for reduced anticoagulant clearance and prolongation of half life – renal function; advanced age and low lean body mass – particularly relevant for the highly renally cleared dabigatran.
4. Emphasis that, barring those with artificial mitral valves and active thrombo-embolic disease, bridging is more harmful than beneficial and has largely been abandoned.
5. There is a shift in focus from early postoperative chemical prophylaxis to mechanical means or early mobilization in moderate to low risk procedures and patients, enhancing RA safety.

The Table on the next page summarises the delays between last anticoagulant dose and RA/neuraxial block. There are substantial differences between recommendations of various societies.

Rules of thumb include:

1. Decide on the need for/nature of the RA based on the merits of the case.
2. If the risk of not doing RA – either physiologically or in terms of pain relief – is substantial, plan to do the most superficial/peripheral possible RA.
3. If a neuraxial/deep block is essential, follow the timing guidelines/specific exclusions rigorously.
4. If the RA/deep block must be performed within an "unsafe" time period, preferentially opt for a single shot spinal anaesthetic with a small bore pencil point needle over a deep block, a deep block over a single shot epidural and a single shot epidural over an epidural catheter technique.
5. Monitoring for the development of a neuraxial haematoma (or a major deep compartment bleed) should continue for 48–72 hours after the last intervention in the neuraxis or deep compartment (irrespective of whether timing rules were followed or not). Continuous epidural analgesic techniques should be with solutions sufficiently dilute to allow monitoring of motor function.
6. Aspirin is thought not to confer added risk.
7. Informed consent regarding bleeding and possible neural compression complications of deep and neuraxial blocks should be obtained before embarking on these procedures, despite the relative rarity of these adverse events.
8. It is of the utmost importance to resume anticoagulation as soon as safe after your RA (as per Rosencher model) and, in the case of epidural infusions and very high thrombotic risk situations, to bridge with LMWH.

For a practical way of planning your RA in patients on anticoagulants, download the ASRA Coags 2.0 App

Major references

1. Kearon C, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149(2):315-52.
2. Christos S, Naples R. Anticoagulation Reversal and Treatment Strategies in Major bleeding: Update 2016. West J Emerg Med. 2016 May;17(3):263-70.
3. Horlocker TT, et al. Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (4th ed). RAPM. 2018 Apr 43(3):263-301.