Consensus Recommendations for Preventing and Managing Bleeding Complications Associated with Novel Oral Anticoagulants in Singapore

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Abstract

Introduction: Novel oral anticoagulants (NOACs) have at least equivalent efficacy compared to standard anticoagulants with similar bleeding risk. Optimal management strategies for bleeding complications associated with NOACs are currently unestablished. Materials and Methods: A working group comprising haematologists and vascular medicine specialists representing the major institutions in Singapore was convened to produce this consensus recommendation. A Medline and EMBASE search was conducted for articles related to the 3 available NOACs (dabigatran, rivaroxaban, apixaban), bleeding and its management. Additional information was obtained from the product monographs and bibliographic search of articles identified. Results: The NOACs still has substantial interactions with a number of drugs for which concomitant administration should best be avoided. As they are renally excreted, albeit to different degrees, NOACs should not be prescribed to patients with creatinine clearance of <30 mLs/min. Meticulous consideration of risk versus benefits should be exercised before starting a patient on a NOAC. In patients presenting with bleeding, risk stratification of the severity of bleeding as well as identification of the source of bleeding should be performed. In life-threatening bleeds, recombinant activated factor VIIa and prothrombin complex may be considered although their effectiveness is currently unsupported by firm clinical evidence. The NOACs have varying effect on the prothrombin time and activated partial thromboplastin time which has to be interpreted with caution. Routine monitoring of drug level is not usually required. Conclusion: NOACs are an important advancement in antithrombotic management and careful patient selection and monitoring will permit optimisation of their potential and limit bleeding events.

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Introduction

Novel oral anticoagulants (NOACs) are designed to overcome the limitations of existing anticoagulants, and have been shown in clinical trials to be viable alternatives to heparins and vitamin K antagonists.[1-9] Three NOACs are currently registered in Singapore. Rivaroxaban (Bayer Schering Pharma AG, Germany), an oral factor Xa inhibitor (anti-Xa), is approved for prophylaxis against venous thromboembolism (VTE) in orthopaedic surgery, prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) and treatment of acute deep vein thrombosis (DVT) as well as prevention of recurrent DVT and pulmonary embolism (PE). Dabigatran (Boehringer Ingelheim, Germany), an oral direct thrombin inhibitor (DTI), is indicated for orthopaedic VTE prophylaxis and prevention of stroke and systemic embolism in NVAF. A second anti-Xa, apixaban (Bristol Myers Squibb, USA), has been approved for VTE prophylaxis in orthopaedic surgery and prevention of stroke and systemic embolism in NVAF.

As with all anticoagulants, the main adverse effect of the NOACs is an increase in bleeding risk. While their safety profile has been demonstrated to be equivalent to current

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standard anticoagulants in registration trials, this does translate to a reported rate of major or any bleeding of up to 3% and 15% respectively.[1,2,4,5,8,10] In contrast to bleeding associated with heparin and warfarin, there is currently limited experience in managing NOAC-associated bleeding events and published protocols are mainly based on indirect laboratory data, case reports as well as expert consensus opinion.[11-15] These recommendations may be country-specific and are not necessarily applicable across borders.

The Chapter of Haematologists, College of Physicians Singapore, in recognising the important practical issues associated with the use of these NOACs early in their life cycle, recently convened a working group comprising haematologists and vascular medicine specialists representing the major public and private hospitals in Singapore. This group was tasked with formulating a common strategy on the prevention and management of bleeding complications associated with NOACs and recommend viable therapeutic options for our patients. This paper reports the consensus opinion of this workgroup.

Materials and Methods

Prior to the first meeting, a literature search was performed on Medline and EMBASE using the search terms "rivaroxaban", "dabigatran", "apixaban", "bleeding", "reversal", "management" and "guidelines". A similar search was performed on the internet using the search engines Google and Yahoo. The respective product monographs were reviewed for recommendations on reversal in emergency situations and interruption for invasive procedures. Pharmacological characteristics of each product were summarised. In addition, the availability of potential reversal agents in local institutions was also determined. A draft outline of this document was then circulated prior to the first meeting. The workgroup then agreed on the format of this document and debated further details and information required for each of the section. The second and subsequent final meeting permitted discussion on the content and recommendations in this document. Common consensus was sought for all contentious issues in this document with rational compromise achieved for areas without unanimous agreement. The final paper was reviewed and agreed to by all authors.

Pharmacological Properties and Characteristics of the NOACs[16-18]

An understanding of the properties of the NOACs (Table 1)[16-18] is essential for safe and appropriate prescribing. As they have relatively short half-lives, NOACs are dosed either once or twice daily. However, their anticoagulant effect may extend across a number of half-lives as circulating drug may still be present despite discontinuing for a few days. Co-existent renal dysfunction may further prolong drug clearance. This knowledge will be relevant when deciding on the timing of stopping the NOACs while planning for interventional procedures with a high risk of bleeding.

The NOACs have rapid pharmacological effect with peak activity achieved anywhere between half to 4 hours after ingestion.[16-18] Bioavailability is significantly higher for the anti-Xas as compared to dabigatran. Both rivaroxaban and apixaban however have absorption limited by a ceiling effect which is achieved at supratherapeutic doses of 50 mg and 25 mg respectively.

Dabigatran is mainly renally excreted while rivaroxaban has alternate excretion pathway as inactive metabolites via the fecal route. Apixaban is least dependent on renal excretion. Each of the NOACs has a manufacturer recommended lower limit of creatinine clearance for which they should not be prescribed (15 mL/min for rivaroxaban and apixaban, 30 mL/min for dabigatran). These should be strictly adhered to. Additionally, given that there is limited clinical data in patients with CrCl 15 to 29, we recommend avoiding the use of antiXas altogether in patients with CrCl<30.

Table 1.Essential Pharmacologic Properties of the Novel Oral Anticoagulants Currently Available in Singapore

	Dabigatran	Rivaroxaban	Apixaban
Target	Thrombin	Factor Xa	Factor Xa
Prodrug	Yes	No	No
Bioavalability (%)	6 – 7	80	50
Time to peak (hours)	1.5	2 – 3	3 – 4
Half-life (hours)	14 – 17	7 – 11	8.3
Elimination	Primarily in the urine (85%); fecal excretion (6%).	One third unchanged in the urine, two thirds undergo metabolic degradation (half excreted in kidneys, half via hepatobiliary route).	Multiple routes. Renal clearance 27%.

The NOACs differ in their binding to protein with the anti-Xa being highly protein bound but not dabigatran. Haemodialysis is therefore an option when forced elimination of dabigatran is required but not in the case ofthe anti-Xas.

Drug Interactions[16-18]

Compared to vitamin K antagonist, the NOACs have considerably less but are not completely devoid of interactions with other drugs. Table 2 lists drugs which are known to interact with the NOACs and the consequence on its anticoagulant effect. When a significant interaction is likely to occur, concomitant use should best be avoided because of the potential for toxicity or lack of efficacy of either drug.

The prodrug form of dabigatran, dabigatranetixilate is dependent on P-glycoprotein (P-gp) for its transport across the intestinal wall. Therefore, inhibitors or inducers of the transporter P-gp will affect drug levels. P-gp inhibitors such as quinidine, verapamil and amiodarone increase the anticoagulant effect of dabigatran. Should there be an overriding need to use these drugs with dabigatran, they should be administered at least 2 hours after dabigatran. This time lag permits the absorption of dabigatran to be completed.

Rivaroxaban also interacts with drugs via P-gp as well as the microsomal enzyme CYP3A4. The simultaneous use of strong CYP3A4 and P-gp inhibitors such as azole antifungals (e.g. ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g. ritonavir) will therefore produce a clinically relevant increase in plasma concentrations of the drug and increased bleeding risk. Such drugs are contraindicated for patients on rivaroxaban.

Apixaban which is also mainly metabolised by CYP3A4 is a substrate of P-gp. It therefore has similar interactions as rivaroxaban with inhibitors and inducers of CYP3A4 and P-gp and concomitant use is contraindicated.

Patient Selection on the Basis of Bleeding Risks

The selection of patients for initiation of anticoagulation therapy should entail careful consideration of its benefits and risks with detailed discussion and involvement of the patient and family in the decision making. The NOACs do not make this process redundant. Assessment tools for stratifying the likelihood of bleeding, such as the HASBled score, are available to assist clinicians.[19-21] While they have mainly been validated for atrial fibrillation patients receiving vitamin K antagonists, they are possibly still useful tools for estimating the risk of bleeding for patients on the NOACs.

Table 2. Interactions Between NOACs and Some Commonly Used Drugs

Interacting drug	Class	Anticoagulant effects		
		Dabigatran	Rivaroxaban	Apixaban
Ketoconazole	Anti-fungal	↑↑	↑↑	↑↑
Itraconazole	Anti-fungal	ND	↑↑	↑↑
Voriconazole	Anti-fungal	ND	↑↑	↑↑
Posaconazole	Anti-fungal	ND	↑↑	↑↑
Fluconazole	Anti-fungal	ND	↑	↑
Clarithromycin	Antibiotic	↑	↑	↑
Erythromycin	Antibiotic	ND	↑	↑
Ritonavir	Anti-HIV	ND	↑↑	↑↑
Verapamil	Anti-arrhythmic	↑	↑	↑
Amiodarone	Anti-arrhythmic	↑	↑	↑
Diltiazem	Anti-arrhythmic	ND	↑	↑
Quinidine	Anti-arrhythmic	↑	↑	ND
Rifampicin	Anti-tuberculosis	↓	↓	↓
Phenytoin	Anti-convulsant	ND	↓	↓
Carbamazepine	Anti-convulsant	↓	↓	↓
St John'sWort	Herbal	↓	↓	↓

ND: No data; HIV: human immunodeficiency virus

↑↑: anticoagulant effect likely to be increased; ↑: anticoagulant effect may be increased; ↓: anticoagulant effect may be decreased

A significant proportion of patients who qualify for anticoagulation therapy may also be receiving antiplatelet agents. The combined use of vitamin K antagonists with antiplatelet agents has been demonstrated in clinical studies and meta-analysis to be associated with a significant increase in the risk of bleeding.[22,23] Clinical studies involving the NOACs up till now have mostly permitted concomitant use of aspirin up to 100 mg orclopidogrel 75 mg.[1,2] As with vitamin K antagonists, the concomitant use of NOACs and antiplatelet agents will invariably increase the risk of bleeding.[24] Co-administration should only be considered when the benefits significantly outweigh the risk. The use of dual anti-platelet agents with NOACs should probably be best avoided.

Drawing from the experience of colleagues in other countries, additional precautions should be given to patients with significant renal impairment or the potential for rapid deterioration of renal function. This will include elderly patients with multiple comorbidities and borderline renal function who have limited renal reserves.[25] In our opinion, the NOACs should be avoided in patients with a creatinine clearance of less than 30mL/min rather than 15 mL/min as recommended by the manufacturers of rivaroxaban and apixaban.[16-18] In patients with borderline renal impairment, serum creatinine should be measured as frequently as once every 3 months with creatinine clearance estimated using the Cockcroft-Gault method. Additionally, renal function has to be assessed during any inter-current illnesses to detect deterioration in renal function and discontinue the NOACs if appropriate.

A touted benefit of the NOACs is the reduction in the number of intra-cranial events.[26] While this may be an important consideration in choosing anticoagulants or switching from vitamin K antagonists to NOACs, it is essential to consider other risk factors that influence the overall bleeding risk. The NOACs have conversely been associated with an increase in incidence of gastrointestinal bleeding from as yet uncertain mechanisms.[27] They should therefore be used with caution in patients with previous history or recent gastrointestinal bleeding. Table

Table 3. Concerns and Recommendations for Using Novel Oral Anticoagulants (NOACs) in Special Populations

Medical conditions	Concerns	Recommendations
Renal impairment (mild to moderate)	Potential for reduced excretion with enhanced or prolonged anticoagulation effect.	CrCl> 50 mL/min: No dosage adjustments. CrCl 30 – 50 mL/min: Dabigatran and rivaroxaban – reduce dose as per manufacturer recommendation. Apixaban – reduce dose in patients above 80 years of age or weight <60 kg. For all NOACs – carefully consider risk/benefits for choosing them; consider regular monitoring of renal function 3-6 monthly; check renal function during intercurrent illnesses for deterioration.
Renal impairment (severe or end-stage)	High potential for enhanced or prolonged anticoagulation effect.	Avoid NOACs when CrCl<30 mL/min. Use alternative anticoagulants that can be monitored effectively. As therapeutic plasma level for NOAC has not been established, measured levels in these patients cannot be used to guide treatment and should not be requested.
Hepatic impairment	Increased bleeding risk due to potential coagulopathy and other associated bleeding risk. Effects of NOACs on patients with pre-existing raised liver enzymes unknown because of exclusion in clinical trials.	For all NOACs: Coagulopathic – contraindicated. Potential for bleeding (Child-Pugh B and C liver cirrhosis) – avoid. Child-Pugh A liver cirrhosis– carefully consider risk versus benefits. AST/ALT > 2x upper limit of normal, total bilirubin >1.5 x ULN – consider risk versus benefits. Frequent monitoring of liver function necessary if NOACs used.
Elderly	Age-dependent increase risk of bleeding with other anticoagulants.	Dabigatran – reduce dose to 150 mg once daily in VTE prophylaxis for patients >75 years, reduce dose to 110 mg bd in stroke prevention for AF in patients >80 years. Rivaroxaban – No dose adjustment. Apixaban – Reduce dose to 2.5 mg in stroke prevention for NVAF patients above 80 years old with serum creatinine>133 umol/L. Prescribers need to be aware that serum creatinine may underestimate degree of renal impairment and should calculate CrClusing Cockcroft-Gault equation. Risk vs benefit consideration needs to take into account the likelihood of multiple comorbidities.
Paediatric patients	Absence of clinical data on efficacy and safety.	Avoid NOACs and use established anticoagulants.
Established bleeding conditions	Increased risk of bleeding.	Contraindications similar to currently established anticoagulants. NOACs have lower risk of intracranial bleeding events but higher risk of mucosal bleeding.

NOACs: Novel oral anticoagulants; CrCl: Creatinine clearance; AST: Aspartate transaminase; ALT: Alanine transaminase; ULN: Upper limit of normal; VTE: Venous thrombosis; AF: Atrial fibrillation

3 summarises some general considerations in selecting patients for anticoagulation therapy as well as specific ones pertaining to the initiation and monitoring of patients on NOACs.

Conversions Between NOACs and Other Anticoagulants

Switching from Heparin or Low Molecular Weight Heparin(LMWH) to the NOACs: Unfractionated heparin (UFH) or LMWH may have been used for initial treatment of NVAF and DVT and a conversion to the NOACs may subsequently be desired. When UFH is stopped, its effect gradually wears off in approximately 4 hours.[28] As the NOACs reach therapeutic drug level only 1 to 2 hours after oral administration, they should therefore be initiated at the time of discontinuation of UFH.[16,17] For LMWH, the NOACs should be served at the time when the next dose of LMWH is due.

Switching from Warfarin to NOACs: The international normalised ratio (INR) reading recommended by manufacturers as appropriate for converting from warfarin to the NOACs are largely based on arbitrary numbers assigned in clinical trial protocols. Dabigatran's product insert has indicated that it is appropriate to start NOACs with an INR of <2 while rivaroxaban's has indicated an INR of <3.[16,17] Local published data had previously shown that all patients with an initial stable therapeutic range INR of 2 to 3 will be sub-therapeutic by Day 3 of discontinuing warfarin.[29] In fact, 70% of patients had INRs below 1.5 by Day 3. For practical purposes, patients with INRs between 2 and 3 may be started on NOACs one day after discontinuing warfarin (day 2 of discontinuing warfarin). Those with INR <2 may have NOACs initiated on the day of consultation. When measured INR is above the therapeutic range, it should be repeated and NOACs started as above once this has declined to <3.

Special considerations should be given for patients who need assured therapeutic range anticoagulation such as acute VTE patients or those with limited liver or vitamin K reserves where the decline in INRs may be unpredictable. Such patients may require daily monitoring of INRs to attain a reading <2 prior to starting NOACs.

Switching from NOACs to Warfarin: In the conversion from NOACs to warfarin, the following factors will need to be considered.

1. The rate of clearance of the NOACs.
2. The time needed to titrate warfarin to therapeutic range.
3. The need for overlap therapy as determined by the indication for anticoagulation.
4. The influence of the NOACs on INR measurement.

Table 4. Recommended Number of Days of Co-administration of NOACs with Warfarin when Switching to Warfarin

Creatinine Clearance	Dabigatran (days)	Rivaroxaban/ apixaban (days)
>50 mL/min	3	4
30 – 50 mL/min	2	3
<30 mL/min	1	2

NOACs: Novel oral anticoagulants

As the NOACs are principally cleared by the kidneys, renal function of patients will need to be assessed at the point of conversion. For patients with no renal impairment, the NOACs may be overlapped with warfarin for a number of days until the therapeutic INR range is reached (Table 4).

For those with renal impairment, a shorter period of overlap as defined in Table 4 may be considered. It should be noted that this recommendation is empiric and should be individualised for each patient taking into account specific thrombotic and bleeding risk.

For monitoring of INRs during the overlap period with rivaroxaban, an INR assay should be chosen with thromboplastin that is insensitive to rivaroxaban.[30] Dabigatran is expected to have limited or no effect on the INR[31] but caution must be exercised in interpreting the INR results during the overlap period.

Switching from NOACs to LMWH/Heparin: Occasionally, NOACs may need to be switched to either LMWH or heparin. These agents should be started at the next scheduled dosing of the NOACs in patients with normal renal function. Heparin/LMWH may need to be delayed for an additional 24 to 48 hours in patients with creatinine clearance of less than 30 mL/min.

Perioperative Management of Patients on NOACs Without Bleeding

Emergency Surgical Intervention (Table 5)

The specific NOAC and timing of its last dose should be determined as accurately as possible from either the patient or caregivers. Concomitant antiplatelet therapy should be stopped. Urgent blood samples should then be drawn for the following tests: full blood count, prothrombin time, activated partial thromboplastin time, fibrinogen level, renal panel and liver panel. For patients receiving dabigatran, a thrombin time may also be requested. Further specialised tests may be useful in certain situations as discussed below.

The haemoglobin level of the patient should be maintained at a haematocrit level of close to 30% either pre- or intra-operatively if possible. A pre-existing thrombocytopenia should be addressed with pre-procedure

Table 5. Initial Checklist for Assessing the Patient on NOACs Requiring Emergency Surgery or Active Bleeding and Suggested Interventions

	Item	Rationale	Intervention
1.	Which NOAC?	• Intervention, if required, may be NOAC-specific.	• Stop NOAC.
2.	On antiplatelet?	• Increases bleeding risk.	• Stop antiplatelet. • Platelet transfusion may be necessary for uncontrolled bleed.
3.	Timing of last dose?	• Limiting gastrointestinal absorption may be possible. • Estimation of duration of effect.	• Dabigatran - <3 hours, activated charchoal. • Rivaroxaban/apixaban – no data available on value of activated charcoal. Empiric use up to 3 hours after ingestion recommended.
4.	Check full blood count	• Anaemia compromises oxygen carrying capacity. • Anaemia and thrombocytopenia reduces haemostatic capacity.	• Maintain haematocrit close to 30%. • Maintain platelet >50 x 10^9/L (100 x 10^9/L for neurosurgery/neurosurgical bleeding).
5.	Check prothrombin time (PT) and thromboplastin time (PTT)	• May provide information on presence of circulating NOACs.	• Interpret according to type of NOAC and the laboratory assay used for testing.
6.	Check fibrinogen level	• Important factor for clot formation.	• Replace with cryoprecipitate if <1 g/L. • Replacement of no value if levels are not low.
7.	Check thrombin time	• Sensitive to presence of dabigatran.	• Normal value makes it unlikely that there is significant dabigatran in plasma. • Not affected by rivaroxaban/apixaban.
8.	Liver function test normal?	• Provides indirect information on concomitant coagulopathy.	• Consider fresh frozen plasma if clotting factor deficiency suspected.
9.	Renal function	• Clearance determined by renal function	• Expect extended anticoagulation effect if renal function impaired.
10.	Is site of bleeding or nature of surgery known?	• Determines possibility of local intervention to stop bleeding.	• Refer to endoscopists or interventionist for local control measures.

NOACs: Novel oral anticoagulants

platelet transfusion if it is less than 50 x 10^9/L for major surgery or less than 100 x 10^9/L for surgery involving critical areas such as neurosurgical sites. Patients receiving concomitant antiplatelet therapy should also be considered for preoperative platelet transfusion if the procedure involves critical sites. When a coagulopathy due to causes other than the use of anticoagulants is suspected e.g. disseminated intravascular coagulation, fresh frozen plasma or cryoprecipitate should be considered. Activated charcoal can be given if the NOACs are ingested within 3 hours.[16,17,32]

If the timing of ingestion is not certain, the results of the PT, PTT and thrombin time as outlined in Table 8 may be indicative of the presence of NOACs in the absence of other causes for their prolongation. For patients with significant level of NOACs going into surgery, a non-specific haemostatic agent as outline in a latter section may need to be given just prior to the procedure.

Early or Elective Interventional Procedures

NOACs and antiplatelet agents should be omitted immediately once a procedure is planned. Investigations as listed for emergency intervention should be performed and correction for pre-existing anaemia and thrombocytopenia (just prior to surgery) should be undertaken. As most current antiplatelet agents such as aspirin and clopidogrel cause irreversible inhibition of platelet function,[33] platelet transfusion may be necessary for procedures with high bleeding risk if performed within 5 days of discontinuation. Recommended duration of discontinuation of the NOACs is dependent on the risk of bleeding associated with the procedure as well as the renal function.[32] Table 6 summarises the recommended duration of discontinuation prior to elective procedures. Monitoring of residual drug level may be necessary should optimal haemostasis be desired for the intervention.

The Bleeding Patient

Evidence-based recommendations are not possible as high quality data on the optimal management of bleeding for the NOACs are lacking. Until these are available, we recommend that the clinical approach to bleeding on these new agents be based on pragmatic principles. For practical purposes, bleeding events may be classified as either minor, moderate to severe, or life-threatening. The source of any bleeding event should be identified and local control measures instituted as soon as possible. These

Table 6. Recommended Duration for Discontinuation of NOACs Prior to Surgery/Invasive Procedures

Renal Function (Creatinine clearance, mL/min)	Dabigatran		Rivaroxaban and apixaban	
	Standard Risk (hours)	High Risk (hours)	Standard Risk (hours)	High Risk (hours)
>50	24	48	24	48
30 – 50	48	96	24	48
<30	96	144	48	96

NOACs: Novel oral anticoagulants

Examples of standard risk –diagnostic endoscopy without removal of wide-based polyps, arthroscopy and arthrocentesis, oral surgery, cutaneous surgery, standard hernia repair, coronary angiography

High risk – major intra-abdominal surgery, major vascular surgery, major orthopaedic surgery, prostatectomy or bladder surgery, heart valve replacement, coronary artery bypass, major intra-thoracic surgery, major cancer surgery, pacemaker insertion/implantation, biopsy in non-compressible tissue, puncture in non-compressible artery, epidural and spinal anaesthesia, neurosurgical procedures, retinal surgery

recommendations are summarised in Table 7.

Although a number of interventions are suggested, the need for them is likely to be low given the short half-life of these new agents.[34] In addition, traditional reversal agents used for warfarin and heparin reversal including vitamin K, fresh frozen plasma (FFP) and protamine sulphate are not expected to be effective given the direct inhibitory mechanism of action of these new agents. Blood component replacement with red cells, FFP and platelets in moderate to life-threatening bleeding should be guided by clinical assessment, laboratory values and where appropriate, activation of the massive transfusion protocol.

In life-threatening bleeding, therapeutic intervention and/or administration of non-specific haemostatic agents may proceed before laboratory tests are completed. Haemodialysis or haemoperfusion are options for dabigatran removal, especially if renal failure is present.[32] Dialysis however does not remove rivaroxabanor apixaban as they are highly protein bound. Hemoperfusion using activated charcoal is theoretically possible for NOACs but only in vitro

Table 7. Recommendations for Management of Bleeding Patients

Bleeding Severity	Suggested management options
Mild*	• No intervention if bleeding is isolated and spontaneously stops. • Delay or omit next dose if bleeding is persistent or recurrent. • Restart NOACs once bleeding has stopped • Check FBC, renal function, aPTT and PT if bleeding is recurrent or persistent despite discontinuation.
Moderate to Severe†	• Ascertain time of the last drug dose and discontinue drug • Oral activated charcoal can be given for NOACs if drug intake was within 3 hours of presentation. It has a low side-effect profile. (Dose: Liquid charcoal with sorbitol 50 g PO x 1 dose). • Check FBC, renal function, APTT and PT. Coagulation testing with an appropriate drug-sensitive assay should be requested to determine the presence of residual drug to guide management. • Supportive measures including fluid resuscitation, maintenance of good urine output to protect renal function and appropriate blood component replacement. • Local hemostatic measures including mechanical compression, surgical, endoscopic and/or radiological intervention should be used where appropriate. • Anti-fibrinolytic agent (tranexamic acid) may be considered in the absence of frank haematuria. • Consider consultation with a Haematology service.
Life-threatening‡	• Measures taken to manage moderate to severe bleeding. • Dabigatran: haemodialysis or hemofiltration especially if renal failure is present . • Consider any of the following: o Recombinant factor VIIa 90 mcg/kg IV (Novoseven). o 3-factor prothrombin complex concentrate(Profilnine) 50 – 100 @iu/kg. o Activated prothrombin complex concentrate (FEIBA) 50 – 100 @iu/kg.

*Examples of mild bleeding – nose bleeds, small bruises, bleeding after minor trauma such as shaving.

†Moderate to severe bleeding – frank haematuria, spontaneous large bruises, any bleeding that requires transfusion but does not lead to haemodynamic instability.

‡Life-threatening – bleeding into critical sites (e.g. intra-cranial, retroperitoneal), haemodynamic instability .

NOACs: Novel oral anticoagulants; FBC: Full blood count; APTT: Activated partial thromboplastin time; PT: Prothrombintime

@ Dosage chosen will need to be individualised according to the severity of the bleeding and concerns about thrombotic complications. When in doubt, start with the lower dose.

evidence is available for dabigatran.[32] The use of additional haemostatic agents can be considered after an individual risk-benefit assessment. The safety, efficacy, optimal dose and frequency of these agents are not established in this population.

Non-specific Haemostatic Agents

There is currently no antidote for any of the NOACs. While a number of animal studies have been published on the use of potential reversal agents, the relevance of these animal studies to the in-vivo patient situation has been questioned.[12,35] The non-specific haemostatic agents that have been studied include recombinant factor VIIa (rVIIa), 4-factor prothrombin complex concentrate (4-factor PCC) and activated prothrombin complex concentrate (APCC, FEIBA). Human data is presently limited to one clinical trial in healthy male volunteers.[13] There are no studies comparing different procoagulant and/or looking at bleeding outcomes in patients who develop bleeding on dabigatran or rivaroxaban. Although specific antidotes have been identified, these are still under development for human use.[36]

In summary, the only clinical study in healthy human volunteers showed that 4-factor PCC normalised prothrombin time in healthy human volunteers receiving rivaroxaban but not APTT, thrombin time (TT) nor ecarin clotting time (ECT) in those receiving dabigatran.[13] It is difficult to conclude from the results of animal studies due to heterogeneous models, different dosing regimens for dabigatran and/or rivaroxaban and procoagulant agents and different clinical and laboratory outcome measures used.

Currently, only recombinant factor VIIa (NovoSeven®, Novo Nordisk), activated prothrombin complex (FEIBA®, Baxter Healthcare) and 3-factor prothrombin complex (Profilnine®, Grifols) is available in Singapore. The often-cited 4 factor prothrombin complex is not available in Singapore and many other countries.

Management of Overdosing

There is currently limited clinical information on the implications and management of an overdose of NOACs. An increased and prolonged risk of bleeding can be expected and recommendations on management of such patients are based on manufacturers' recommendations.[16-18] Dissolution-limited absorption ceiling of the anti-Xa may limit the maximum plasma concentration of the ingested product. General measures such as the maintenance of adequate diuresis to promote excretion and monitoring for active bleeding should be instituted. Activated charcoal may be given if overdosing is discovered within 3 hours.

Table 8. Effects of NOACs on Common Coagulation Assays

	Dabigatran	Rivaroxaban	Apixaban
Prothrombin time	↑ or N	↑ or N (assay dependent)	↑ or N (assay dependent)
Activated partial thromboplastin time	↑↑	↑	↑
Thrombin time	↑↑	N	N

N: normal, NOACs: Novel Oral Anticoagulants

Effects of NOACs on Common Coagulation Tests

The effects of the NOACs on three commonly available coagulation assays, namely prothrombin time (PT), activated partial thromboplastin time (aPTT) and thrombin time (TT) is summarised in Table 8.[31,37,38] These tests have no place in the management of stable, compliant patients. However, because of their ready availability and quick turnaround times, they may be useful in bleeding patients or those requiring urgent surgical procedures. Clinicians must however be aware of the important caveats in interpreting these tests.

1. These tests, if abnormal, provide a qualitative measure of the presence of NOACs but do not correlate well with their plasma levels especially at high concentration.
2. The effect of the anti-Xas on PT are highly dependent on the sensitivity of thromboplastin used in the coagulation laboratory.[30,39] The type of thromboplastin used in the various institutions and their sensitivity to the anti-Xas is summarised in Table 9. Insensitive PT assays therefore do not exclude the presence of anti-Xa. Sensitive PT assays conversely cannot be used to titrate warfarin in patients being switched from anti-Xas.
3. The thrombin time is highly sensitive to dabigatran.[31] A normal TT essentially excludes the presence of dabigatran in patients.

Table 9. Commonly Used Thromboplastin for Prothrombin/INR Measurement in Singapore and Their Sensitivity to Rivaroxaban and Apixaban

Thromboplastin	Sensitivity	Institutions Using Thromboplastin*
Neoplastin	Sensitive, PT/INR prolonged	Tan Tock Seng Hospital, National University Hospital, Alexandra Hospital, Kandang Kerbau Women and Children's Hospital
Innovin	Insensitive, minimal effect on PT/INRresult	Singapore General Hospital, Changi General Hospital, Khoo Teck Puat General Hospital, Raffles Hospital, Parkway Group Hospitals, Thomson Medical Centre

*Information correct as at 1 April 2013.

Monitoring of NOACs levels

Routine monitoring of drug levels for patients receiving the NOACs is not necessary. In patients whom routine monitoring is thought to be necessary, switching to traditional anticoagulants is probably the best option for preventing unwanted side effects attributable to the NOACs. Monitoring of NOAC level may however be indicated in the following instances:

1. Prior to surgical intervention where residual NOAC effect is not desired.
2. Bleeding patients where NOAC effect needs to be excluded.
3. In patients with overdose of NOACs where consideration may be given for alternate methods of clearance if levels remains high.
4. In patients developing a thrombotic event when compliance is doubted.

Anti-Xa level of rivaroxaban can be measured through a commercial assay which has been specifically calibrated for rivaroxaban.[39] Dabigatran level may be measured via the Haemoclot assay.[40] Both tests are currently available from the Haematology Laboratory of Tan Tock Seng Hospital. Ranges for patients on usual doses of both agents have been determined. These are however not therapeutic ranges as there is currently no available reference. The result of NOAC level for any particular patient therefore indicates the presence or absence of NOACs in the circulation and its level in relation to a group of patients who have been routinely given the drug. At the time of writing, monitoring of apixaban level is not available in Singapore.

Conclusion

The NOACs are a significant advancement and timely addition to the therapeutic armament against thrombotic disorders but carry the same adversity of haemorrhagic complication. This document will hopefully provide the needed guidance to local clinicians as we assimilate the NOACs into our practice. As with all novel products, uncertainties breeds caution which can only improve our understanding of the product and subsequently permit optimisation of their potential.

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