Practical & Appropriate Oral Anticoagulant Use Initiative

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Foreword

Based on distinctive demographics, geographical considerations and care delivery models employed throughout our region for patients with atrial fibrillation (AF), the Atlantic Cardiovascular Society (ACS) embarked on an initiative to provide Atlantic clinicians with practical and appropriate use recommendations when managing this patient population. It should be noted that these recommendations specifically focus on the management of patients with non-valvular AF. The Panel did not consider patients with mechanical valves as the DOAC class (Direct Oral Anticoagulants) do not possess an indication for use in this population.

The intent of the ACS was not to create a regional guideline, rather to identify and support best guideline practices for Atlantic clinicians who manage patients with AF. In addition to the published clinical evidence, the panel also considered guideline recommendations from the Canadian Cardiovascular Society, the American Heart Association/American College of Cardiology, the European Society of Cardiology and the Heart & Stroke Foundation (Canadian Stroke Best Practice Recommendations).

By generating practical and appropriate use recommendations the ACS will collaborate with the appropriate clinical and regulatory bodies within each Province in an effort to standardize care for patients with AF throughout the Atlantic region. The recommendations below represent the first step toward that goal.

A detailed and transparent account of the process used to generate these recommendations can be found in the Appendix. Each primary panelist declared all potential conflicts of interest associated with this initiative and these documents are available for review on the ACS website. Industry partners provided unrestricted and untied funding in support of this project but did not participate in or influence the process in anyway.

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THE GRADE RECOMMENDATION SYSTEM

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group developed this tool in 2000 as a common, sensible and transparent approach to grading the quality of recommendation evidence and strength. Based on the tool's utility and international popularity the Primary Panel decided to utilize the GRADE system.

Systematic reviews of the effects of healthcare provide essential, but not sufficient information for making well informed decisions. Reviewers and people who use reviews draw conclusions about the quality of the evidence, either implicitly or explicitly. Such judgments often guide subsequent decisions. For example, clinical actions are likely to differ depending on whether one concludes that the evidence for prescribing warfarin to reduce the risk of stroke in patients with AF is convincing (high quality) or unconvincing (low quality).

Similarly, individuals who use practice guidelines draw conclusions about the strength of recommendations, either implicitly or explicitly. Using the example above, a guideline that recommends patients with AF be treated may suggest that all patients should definitely be treated or that patients should probably be treated, implying that treatment may not be warranted in all patients.

A systematic and explicit approach to making judgments can help prevent errors, facilitate critical appraisal and ultimately improve communication. Unfortunately organizations use different systems to grade evidence and recommendations, which confuses and often impedes effective communication. The GRADE Working Group has attempted to reduce unnecessary confusion arising from multiple systems and offers the criteria below. Further details surrounding the GRADE recommendation system can be reviewed at: www.gradeworkinggroup.org.

Grade of Recommendation	Clarity of risk/benefit	Implications
Strong recommendation. High quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Strong recommendation, can apply to most patients in most circumstances without reservation
Strong recommendation. Moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Strong recommendation, likely to apply to most patients
Strong recommendation. Low quality evidence	Benefits appear to outweigh risk and burdens, or vice versa	Relatively strong recommendation; might change when higher quality evidence becomes available
Weak recommendation. High quality evidence	Benefits closely balanced with risks and burdens	Weak recommendation, best action may differ depending on circumstance or patients or societal values
Weak recommendation. Moderate quality evidence	Benefits closely balanced with risks and burdens, some uncertainty in the estimates of benefits, risks and burdens	Weak recommendation, alternative approaches likely to be better for some patients under some circumstances
Weak recommendation. Low quality evidence	Uncertainty in the estimates of benefits, risks and burdens; benefits may be closely balanced with risks and burdens	Very weak recommendation; other alternatives may be equally reasonable

ABREVIATIONS AND ACRONYMS

ACS	Acute coronary syndrome
PCC	Prothrombin complex concentrate
ASA	Acetylsalicylic acid
CCS	Canadian Cardiovascular Society
CrCl	Creatinine clearance
DOAC	Direct Oral Anticoagulant
ECT	Ecarin clotting time
ESC	European Society of Cardiology
ICH	Intracranial hemorrhage
LMWH	Low molecular weight heparin
MRI	Magnetic resonance imaging
PCC	Prothrombin complex concentrate
PT	Prothrombin time
TIA	Transient ischemic attack
VKA	Vitamin K antagonist
AF	Atrial fibrillation
aPTT	Activated partial thromboplastin time
CAD	Coronary artery disease
CKD	Chronic kidney disease
CT	Computed tomography
ECG	Electrocardiogram
ER	Emergency room
FFP	Fresh frozen plasma
INR	International normalized ratio
MI	Myocardial infarction
OAC	Oral anticoagulant
PCI	Percutaneous coronary intervention
RCT	Randomized control trial
US	Ultrasound

SCREENING FOR ATRIAL FIBRILLATION

GRADE Rating

We recommend that Atlantic clinicians proactively screen all patients aged ≥ 65 years for AF via pulse palpation and/or cardiac auscultation; clinicians should then explore positive pulse diagnoses by ECG. (Hobbs 2005, Fitzmaurice 2007) Screening for the co-morbidities of hypertension, hyperthyroidism (via serum TSH) and diabetes is also recommended for patients exhibiting a positive pulse diagnosis.

Strong Recommendation; Moderate Quality Evidence

PRACTICAL TIP:

① Atlantic ER physicians and institutions can positively influence the quality of care for AF patients by implementing communication processes and/or tools that rapidly inform primary care physicians of any diagnosis or tests ordered within the Emergency Room.

STROKE RISK STRATIFICATION — GRADE Rating

We recommend the use of the new "CCS Algorithm" (Appendix) as an efficient and easy means through which a physician can determine a patient's eligibility for OAC. (Verma 2014). If physicians wish to communicate the estimated percentage annual risk of stroke to patients with AF based on their clinical profiles then we recommend that the CHA_2DS_2-VASc risk stratification tool should be preferentially used for this purpose (Table 1A & 1B). (Gage 2001, Connelly 2009a, Karthikeyan 2010, Lip 2010, Boirani 2011, Keogh 2011, Olesen 2011a, Camm 2012, Olesen 2012a).

Strong Recommendation; High Quality Evidence

Table 1A: Treatment based on CHA_2DS_2-VASc score

Score	Recommendation	Strength
0	**We recommend** that no OAC therapy be prescribed. (Skanes 2012, Camm 2012) Depending upon the clinical situation, a patient with CHA_2D_2S-VASC = 0 can receive ASA or no therapy (Skanes 2012, Lindsay 2012)	Strong Recommendation; Moderate Quality Evidence
1	**We suggest** prescribing treatment with an OAC based on the assessment of bleeding risk complications and patient preferences. (Camm 2012). **EXCEPTIONS:** – Patients at low risk of stroke (age <65 years, whether male or female) should not be considered for OAC therapy – In patients whose only risk factor is vascular disease, ASA should be considered.	Weak Recommendation; High Quality Evidence
≥ 2	**We recommend** treatment with an OAC. (Camm 2012) **We suggest** that if patients refuse OAC therapy the clinician can consider prescribing combination therapy including ASA 81mg plus clopidogrel 75mg daily* (where there is a low risk of bleeding) or ASA 75 – 325mg daily* (Recognizing that ASA alone is less efficacious). (Camm 2012, Olesen 2012, Connelly 2009) This treatment strategy should **NOT** be considered a routine alternative to OAC therapy. * If dual antiplatelet therapy is prescribed in the scenario above, consider gastric protection with a PPI to modify GI bleeding risk	Strong Recommendation; High Quality Evidence Weak Recommendation; Moderate Quality Evidence

Table 1B: CHA_2DS_2-VASc scoring for Atrial Fibrillation stroke risk

CHA_2DS_2-VASc	Score
Congestive Heart Failure / Left Ventricular Dysfunction (EF<40%)	1
Hypertension	1
Age ≥ 75 Years	2
Diabetes Mellitus	1
Prior Stroke or TIA or Systemic Embolism	2
Vascular Disease (prior MI, PAD, aortic plaque)	1
Age > 65 but < 75	1
Sex category – Female	1

CHA_2DS_2-VASc Score	Stroke Rate Per Year (%/yr.)
0	0.0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

Yip GB, *et al* Chest 2010; 137:263-72

PRACTICAL TIP:

① If patients refuse OAC therapy they should be informed that antiplatelet therapy does not prevent stroke and systemic embolism to the same extent as OAC therapy and may not result in lowering their bleeding risk versus OAC.

BLEEDING RISK STRATIFICATION — GRADE Rating

We recommend using a bleeding risk scoring system to assess bleeding risk before prescribing OAC therapy. (Fang 2006, Pisters 2010)

Strong Recommendation; High Quality Evidence

We suggest that the HAS-BLED bleeding risk assessment score (Table 2) be used preferentially due to its validation and ease of use. (Lane 2010, Pisters 2010 Olesen 2011b,)

Weak Recommendation; High Quality Evidence

Table 2: HAS-BLED Score for major bleeding risk

Risk Factor	Score
Hypertension	1
Abnormal renal/hepatic function	1 (each)
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (≥ 65 years)	1
Drugs or Alcohol use	1 (each)

HAS-BLED Score	Bleeding rate (%/year)
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
≥ 5	Insufficient data

PRACTICAL TIPS:

① Employing the ESC management process for patients with non-valvular AF places initial emphasis on stroke reduction, then bleeding risk:

A. Establish the patient's risk of stroke via CHA_2DS_2-VASc
B. Select the appropriate OAC therapy
C. Calculate a HAS-BLED risk score; define & modify the patient's bleeding risk factors

② The HAS-BLED bleeding risk assessment tool should not be used to deny required therapy.

VALUES & PREFERENCES:

In many cases bleeding is preventable; conversely, the devastating results of a stroke are permanent and as such should receive emphasis.

Major bleeding, especially ICH, is the most feared complication of anticoagulation therapy; however, HAS-BLED can be used to engage patients with AF in a conversation regarding modifiable risk factors that can potentially reduce their bleeding risk.

SELECTING OAC THERAPY FOR NON-VALVULAR AF

GRADE Rating

We suggest that one of the DOACs (dabigatran, rivaroxaban, or apixaban) should be prescribed preferentially over a VKA, based on the DOAC's ease of use and superior clinical benefit, particularly related to ICH. (Connelly 2009, Granger 2011, Patel 2011, Lindsay 2012)

Weak Recommendation; High Quality Evidence

PRACTICAL TIP:

Follow the product monograph instructions to counsel patients who miss a dose.

Dabigatran	If the prescribed dose of PRADAXA is not taken at the scheduled time, the dose should be taken as soon as possible on the same day. A forgotten PRADAXA dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose on, the missed dose should be omitted. Patients should not take a double dose to make up for missed individual doses.
Rivaroxaban	If a dose is missed, the patient should take XARELTO immediately on the same day and continue on the following day with the once daily intake as before. A double dose should not be taken to make up for a missed tablet.
Apixaban	If a dose is missed, the patient should take ELIQUIS immediately and then continue with twice daily administration as before. A double dose should not be taken to make up for a missed tablet.

VALUES & PREFERENCES:

The Panel endorses the OAC prescribing recommendations published in the CCS Atrial Fibrillation guidelines (Skanes 2012), Canadian Best Practice Recommendations for Stroke Care (Lindsay 2012) and ESC Atrial Fibrillation Guidelines (Camm 2012). In addition, the Panel agrees with the recommendation that the preference for DOACs over VKAs is less relevant for patients on VKAs who have stable INRs (greater than 65% TTR) and no bleeding complications.

The Panel's recommendation to preferentially prescribe a DOAC over warfarin when selecting pharmacotherapy for patients with AF at risk of stroke is discordant with the existing Provincial reimbursement criteria. The rationale for this difference hinges on the ease of use for the patient and superior clinical benefit afforded by the DOAC class, particularly related to ICH. Further, 45% of the Atlantic population lives in a rural environment where the care delivery model does not include access to an anticoagulation clinic. Due to regional issues, AF patients may become candidates for DOAC therapy based on limited access to INR testing. An opportunity exists to improve the identification of patients who will or will not respond to warfarin therapy as under-coagulation leaves patients vulnerable. Lastly, Panel members did not consider the cost-effectiveness of DOACs versus VKAs in formulating their suggestion; they noted that the cost-effectiveness of DOACs remains unclear.

Use DOAC medications as described in their respective product monographs (Table 3).

Table 3: Relevant DOAC Product Monograph Information

	Dabigatran	Rivaroxaban	Apixaban
Dosage forms	110 & 150 mg Capsules	15 & 20 mg Tablets	2.5 & 5 mg Tablets
Dosing recommendations for stoke prevention	150 mg *bid*	20 mg *od*	5 mg *bid*
Dosing Adjustment Recommendations	Use the 110 mg *bid* dose for Patients ≥ 80 Years	A dose of 15 mg once daily is recommended for patients who have moderate renal impairment (30 – 49 mL/min)	In patients fulfilling at least two (2) of the following characteristics, a reduced dose of apixaban 2.5 mg twice daily is recommended: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 133 micromole/L (1.5 mg/dL). These patients have been determined to be at higher risk of bleeding.
Bioavailability	6%	80 - 100%	50%
Pro-drug	Yes	No	No
Renal Excretion	≈ 85%	≈ 35%	≈ 27%
Absorption with H_2RA/PPI	A 12 – 30% decrase in AUC (Area Under the Curve) No dosage adjustment is generally necessary	No effect	No effect
GI Tolerability	Dyspepsia 5 – 10%	No issues reported	No issues reported
Food Interactions	None	Rivaroxaban 15 mg and 20 mg tablets should be taken with food	None
C_{MAX}	≈ 2 hours	2 - 4 hours	3 – 4 hours
Elimination half life	12 - 14 hours	5 - 9 hours (Young & Healthy) 11 – 13 (Elderly)	≈ 12 hours

SWITCHING BETWEEN OAC THERAPIES — GRADE Rating

We suggest that clinicians follow the switching protocols located within the respective Canadian product monographs when considering a switch between OACs. (Table 4)

Weak Recommendation; High Quality Evidence

Table 4: Switching Between Anticoagulants

	VKA --> DOAC	DOAC --> VKA
Dabigatran* (Pradaxa)	Discontinue VKA and initiate dabigatran when INR is < 2	When converting from dabigatran to a VKA, adjust the starting time of warfarin based on creatinine clearance as follows: CrCl > 50 mL/min ----> Start VKA 3 days before stopping dabigatran CrCl 30 mL/min - 50 mL/min ----> Start VKA 2 days before stopping dabigatran
Rivaroxaban* (Xarelto)	Discontinue VKA and initiate rivaroxaban when INR is < 3	Concomitantly prescribe rivaroxaban and the VKA for 2 days. Rivaroxaban can be discontinued once the INR is > 2.0. INR should be tested just prior to the next dose of rivaroxaban (not earlier than 24 hours after the previous dose). Once rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after the last dose.
Apixaban* (Eliquis)	Discontinue VKA and initiate apixaban when INR is < 2	Concomitantly prescribe apixaban and the VKA for 2 days. Apixaban can be discontinued once the INR is > 2.0. INR testing should not occur until 12 hours after the previous apixaban dose and just prior to the next. By doing so the remaining circulatory concentrations of apixaban are too low to exert a clinically important effect on the INR.

* Canadian Product Monographs

	DOAC --> Parenternal Anticoagulant	Discontinuation of a Continuously IV Administered Parenteral Drug --> DOAC
Dabigatran* (Pradaxa)	Wait 12 hours after the last dose of dabigatran before switching to a parenteral anticoagulant	Dabigatran should be initiated 0 - 2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment.
Rivaroxaban* (Xarelto)	Discontinue rivaroxaban and give the first dose of parenteral anticoagulant at the time that the next rivaroxaban dose would be taken	Start rivaroxaban 0 - 2 hours before the next scheduled administration of the parenteral drug or at the time of discontinuation of a continuously administered parenteral drug.
Apixaban* (Eliquis)	Switching treatment from apixaban to parenteral anticoagulants can be performed at the next scheduled dose	Switching treatment from parenteral anticoagulants to apixaban can be performed at the next scheduled dose.

* Canadian Product Monographs

OAC DOSING IN CHRONIC KIDNEY DISEASE PATIENTS — GRADE Rating

We suggest that DOACs NOT be used in patients with CrCl < 30 as there are no RCT data available. (Rash 2007, Connelly 2009, Patel 2011, Heidbuchel 2013).

Weak Recommendation; High Quality Evidence

We suggest prescribing a VKA for patients with moderately severe renal insufficiency who are not on dialysis (CrCl = 15-30) and a VKA or nothing for patients with CrCl < 15 or who are on dialysis, according to physician and patient preferences. (Skanes 2012)

PRACTICAL TIPS:

① Routine anticoagulation of dialysis-dependent CKD patients with AF for primary prevention of stroke is not indicated. (Herzog 2011)

② Renal impairment increases the risk of both stroke and bleeding in patients with AF. The impact of renal function was assessed in the RELY trial comparing both dabigatran doses (110mg & 150mg) with warfarin. Results suggest that although increased bleeding was associated with decreasing renal function, no differences in bleeding rates were noted between dabigatran doses.

③ Monitor kidney function as defined in Table 5. Both CrCl and eGFR can be used to assess renal status.

VALUES & PREFERENCES:

The Panel is promoting a conservative approach when managing patients diagnosed with advanced CKD. If a patient exhibits a CrCl ≤ 30, opt for warfarin no matter which DOAC is being considered.

For patients with CrCl=15-30 who are not on dialysis we suggest clinicians use warfarin. In this group of patients there is a stronger preference for avoiding bleeding complications than preventing ischemic stroke.

Table 5: Monitoring Schedule for CKD Patients

A minimum of every **12** months[1]	Hemoglobin, renal and liver function
A minimum of every **6** months	If CrCl (eGFR) = 30 – 60 ml/min If prescribed dabigatran & > 75 years
A minimum of every **3** months	If CrCl = 15 – 30 ml/min
On indication	If the patient develops a medical condition which may impact renal or hepatic function

[1]CCS Grade - Strong Recommendation, Moderate Quality Evidence

PERIOPERATIVE MANAGEMENT FOR PLANNED PROCEDURES	GRADE Rating

Assessment: **We suggest** that a patient's bleeding risk (HAS-BLED) and stroke risk (CHA_2DS_2-VASc) be assessed and documented prior to a planned surgical procedure. In assessing risk, clinicians should consider kidney function, age, hypertension, history of bleeding complications, and concomitant medications. Physicians should proactively manage any modifiable risk factors. Thereafter, consider the procedural bleeding risk (Table 6) and manage OAC therapy accordingly. (Healey 2012)

Weak Recommendation; Moderate Quality Evidence

Table 6: Degree of bleeding risk by procedure

Planned Surgical Interventions & Bleeding Risk	
	Examples
Interventions not necessarily requiring the discontinuation of anticoagulation therapy	Dental Procedures Dental extractions (1 - 3 teeth) Periodontal surgery Incision of abscess Implant positioning Cataract or glaucoma intervention Endoscopy without surgery Superficial surgery (e.g. abscess incision small dermatologic excisions)
Interventions with LOW bleeding risk 2 day risk of major bleed 0% - 2%	Endoscopy with biopsy Electrophysiological study Radiofrequency catheter ablation for supraventricular tachycardia (including left-sided ablation via single transeptal puncture) Angiography Pacemaker or ICD implantation (Unless complex anatomical setting such as congenital heart disease)
Interventions with HIGH bleeding risk 2 day risk of major bleed 2% - 4%	Complex left-sided ablation (Pulmonary vein isolation; VT ablation) Spinal or epidural anesthesia; lumbar puncture Thoracic surgery Abdominal surgery Major orthopedic surgery Liver biopsy Prostate or bladder biopsy Transurethral prostate resection Kidney biopsy

Adapted from Heidbuchel et. al., Europace (2013) 15, 625–651

Management: **We suggest** that perioperative patients with AF who are on OAC therapy be managed according to the strategies defined in Figures 1 and 2 below (Product monographs, Heidbuchel 2013, Camm, 2010, Cairns 2011). DOAC therapy should reach trough concentrations (12 - 24 hours after the last dose depending upon *bid* or *OD* regimen) for planned surgical procedures that may not necessarily require drug discontinuation (Heidbuchel 2013). Consult Table 6 for a partial list of procedures that do not require DOAC discontinuation.

Weak Recommendation; High Quality Evidence

Figure 1

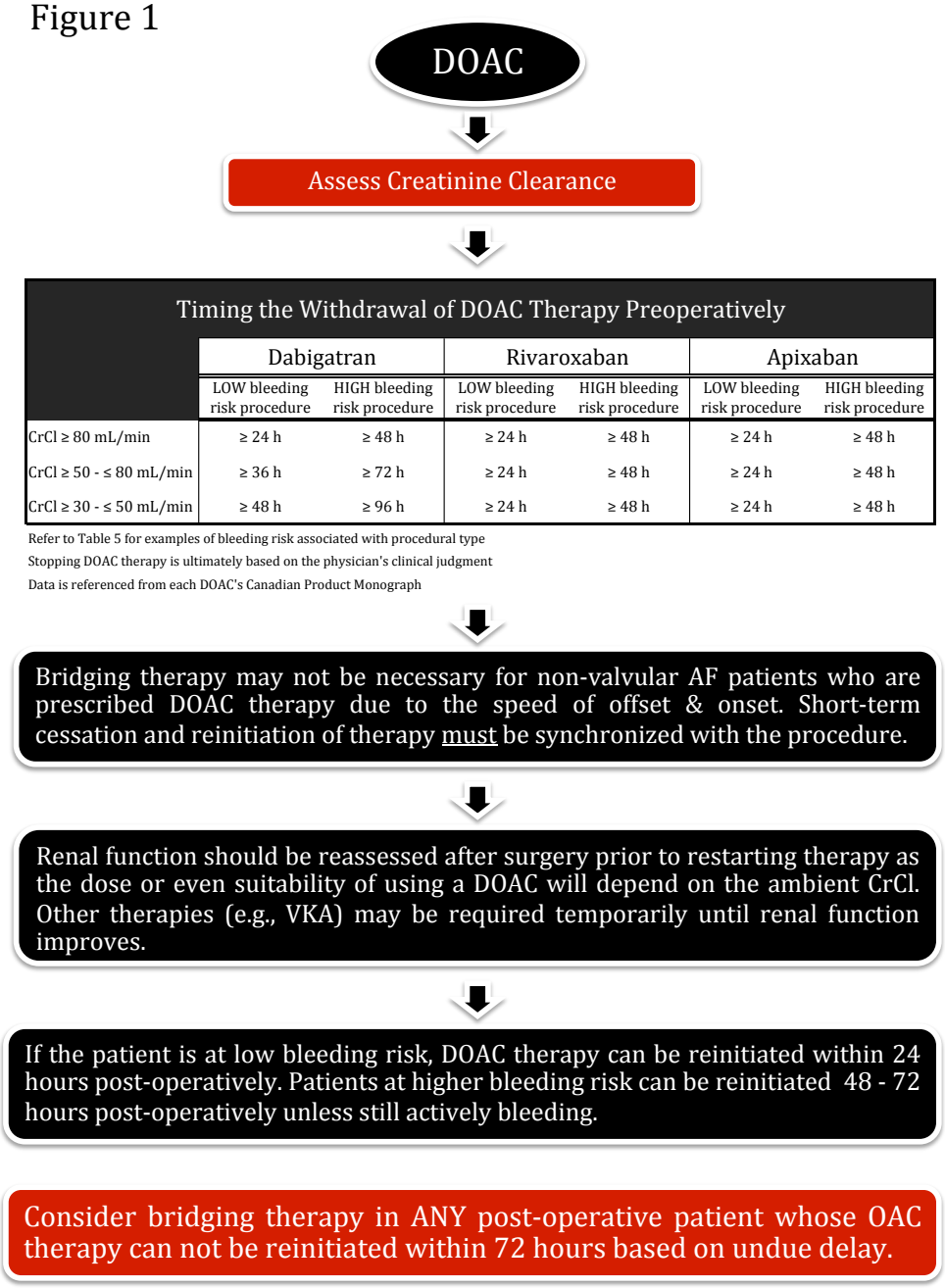
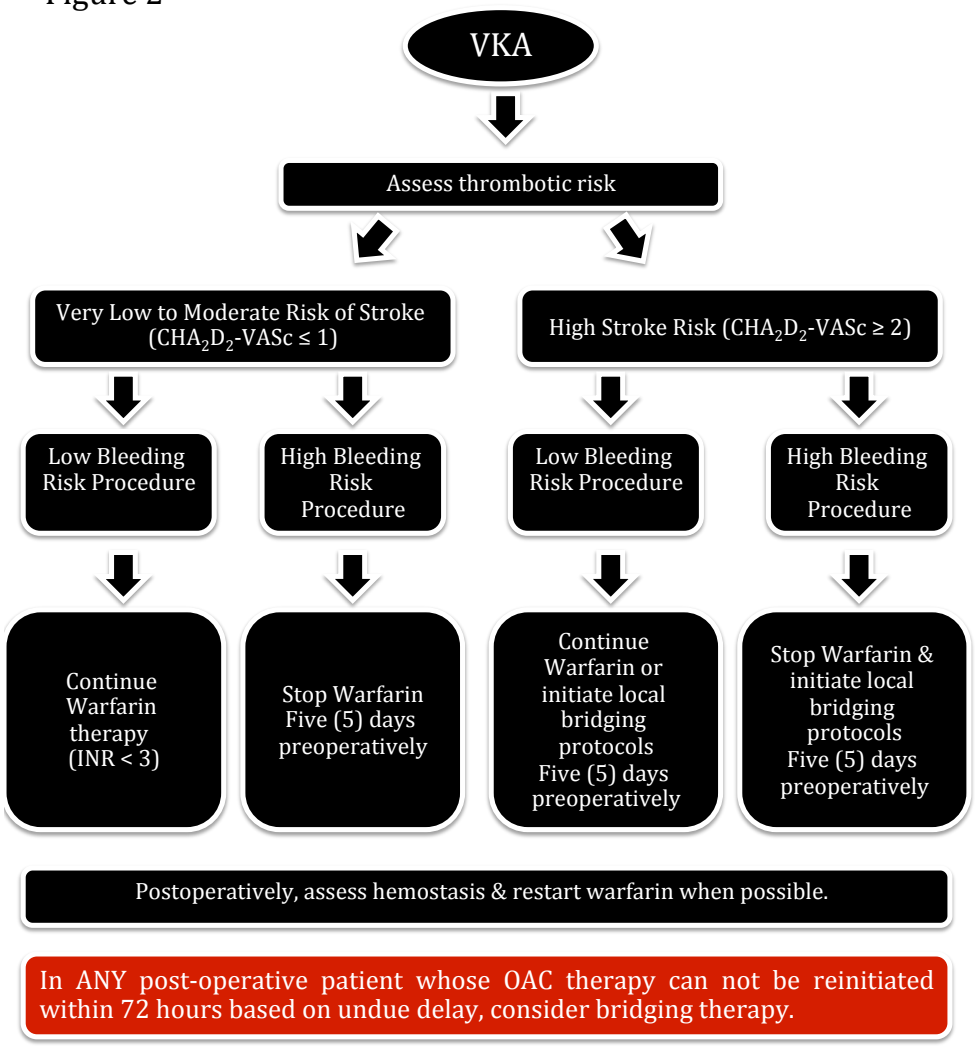


Figure 2



Adapted from Cairns *et al. Can J Card* 2011 27:74-90

- The BRIDGE Study, published in June 2015 (Douketis, 2015), was not reviewed by the Primary Panel. This study addresses the need for bridging anticoagulation during warfarin interruption; clinicians will need to consider how to incorporate study findings into their practices.

PRACTICAL TIPS:

① If a patient on a DOAC experiences a significant decline in kidney function, a planned surgical procedure may need to be delayed until kidney function improves.

② A patient's INR must be checked immediately before and after surgery prior to restarting a VKA.

③ DOAC suitability or dose will ultimately depend on the patient's CrCl. If CrCl declines during the procedure, other treatment (e.g., a VKA) may be required until kidney function improves. (The clinical onset of DOACs is rapid versus VKAs; this has implications when reinitiating therapy).

④ Patients must be encouraged to ask all health care providers when their OAC therapy will be restarted and they must be made aware of the potentially dire implications of being off therapy.

MANAGING NON-LIFE THREATENING BLEEDING ON A DOAC — GRADE Rating

Time is the most important DOAC antidote; therefore, it is important to establish both the dosing regimen and last dose taken to determine peak and trough plasma concentrations. **We suggest** that the clinician estimate the normalization of hemostasis at 12 to 48 hours for dabigatran (depending on renal function) and 12 to 24 hours for apixaban and rivaroxaban (Table 7). (Levi 2011, Heidbuchel 2013)

Weak Recommendation; Moderate Quality Evidence

Table 7: Return to hemostasis

Normalization Estimate of Hemostasis			
Dabigatran		Rivaroxaban	Apixaban
CrCl ≥ 80 ml/min	12 - 24 hours	12 - 24 hours	12 - 24 hours
CrCl 50 - 80 ml/min	24 - 36 hours		
CrCl 30 - 50 ml/min	36 - 48 hours		

H. Heidbuchel et al. European Heart Journal, 2013

We suggest that an aPTT assay be used to qualitatively determine if dabigatran is actively circulating (van Rhyn 2010, Lindahl 2011, product monograph), a PT assay can be used for rivaroxaban (Lindhof-Last 2010, Hillarp 2011, product monograph). There is no clear method for apixaban; (Heidbuchel 2013), however, the Rotachrom anti-FXa assay may be of value. (Product monograph)

Weak Recommendation; Moderate Quality Evidence

MANAGING LIFE THREATENING BLEEDING ON A DOAC — GRADE Rating

We suggest that clinicians follow Provincial life-threatening bleeding protocols until antidotes for DOACs are available. Although clinical evidence is inadequate, CONSIDER PCC when managing life-threatening bleeding (Figure 3). (Heidbuchel 2013)

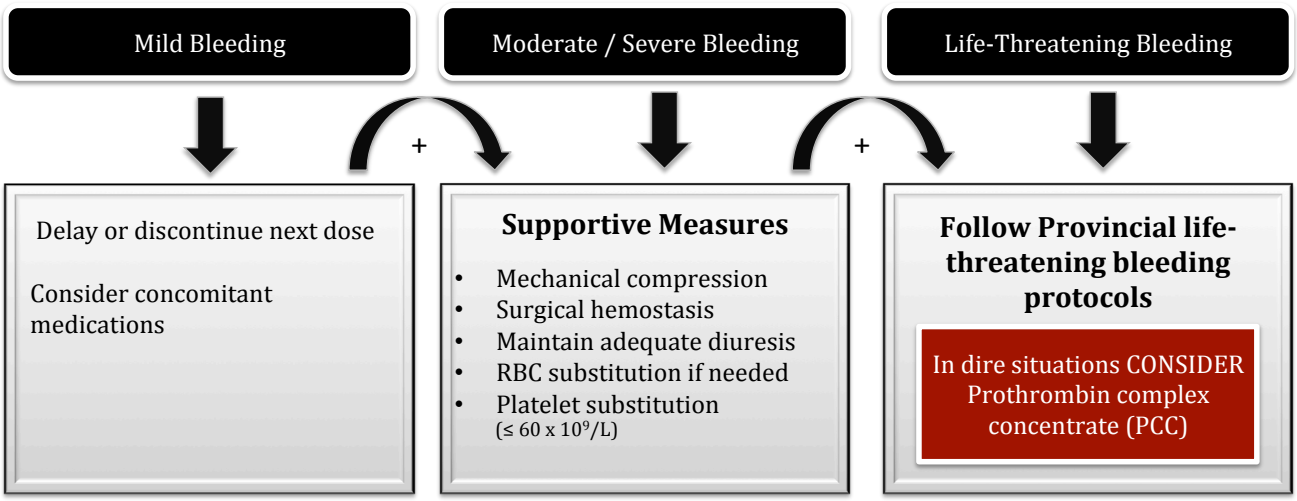
Weak Recommendation; High Quality Evidence

PRACTICAL TIPS:

① A GI bleed is not a contraindication to reinstating OAC therapy. Confirm with a local gastroenterologist regarding how soon therapy should be reinitiated.

② An opportunity exists for Atlantic tertiary & secondary hospitals to establish standardized life-threatening bleeding protocols. Doing so will elevate the consistency of patient care throughout Atlantic Canada.

Figure 3: Bleeding management strategies for AF patients prescribed a DOAC



Heidbuchel *et. al.*, EHRA Practical Guide, 2013
Kumar *et. al.* Journal of Intensive Care Medicine, 2014

ACUTE MANAGEMENT OF PATIENTS WITH NON-VALVULAR AF WHO ARE ALREADY ESTABLISHED ON OAC THERAPY AND WHO PRESENT WITH A DEFINITE ACS

GENERAL PRINCIPLES

Administration of fibrinolytic, antiplatelet and antithrombin therapy to ACS patients currently taking anticoagulant therapy should **ONLY** be considered if the ischemic-reducing benefits are felt likely to outweigh the bleeding risks.

DOAC and warfarin therapy should generally be withheld during the acute in-patient phase of ACS management while patients are receiving usual ACS antiplatelet and antithrombin therapies.

Anticoagulant therapy should generally be restarted prior to discharge; the timing and type of therapy will depend upon many factors but in particular the timing and outcome of cardiac catheterization.

ORAL ANTIPLATELET THERAPY

In the absence of allergy or active bleeding, the majority of patients with definite ACS (STEMI or NSTEACS) should receive an immediate combination of oral antiplatelet therapy with ASA (at least 162mg if ASA naïve then 81mg once daily) **and clopidogrel** (300mg oral loading dose if clopidogrel naïve then 75mg once daily). {*Clopidogrel loading dose should generally be omitted in STEMI patients >75 years receiving fibrinolytic therapy and in other patients felt to be at increased risk of intracranial hemorrhage*}

Clopidogrel is the preferred $P2Y_{12}$ receptor for acute administration to ACS patients currently receiving DOAC or VKA therapy; ticagrelor and prasugrel are generally not recommended in the acute phase management.

FIBRINOLYTIC THERAPY IN PATIENTS WITH NON-VALVULAR AF AND STEMI

STEMI patients taking **maintenance DOAC therapy** who do not have access to timely primary PCI should generally receive immediate fibrinolytic therapy and usual adjunctive antithrombin therapy.

STEMI patients taking **maintenance VKA therapy** who do not have access to timely primary PCI should have their INR checked urgently. The INR result and overall risk of bleeding should be factored into the decision whether or not to administer fibrinolytic and adjunctive antithrombin therapy. *{Excessive anticoagulation with warfarin is strongly associated with an increased risk of ICH in STEMI patients receiving fibrinolytic therapy, especially in older patients with an INR ≥ 4. (Brass, 2000)}*

Fibrinolytic therapy should *not* be administered to STEMI patients taking maintenance DOAC or VKA therapy in whom the bleeding risks are felt to be prohibitive; transfer for primary PCI should be considered even if a longer than normal treatment delay is anticipated.

PRIMARY PCI IN PATIENTS WITH NON-VALVULAR AF AND STEMI

STEMI patients taking **maintenance DOAC therapy** who have access to timely cardiac catheterization should general be referred for urgent primary PCI; radial artery access is strongly preferred. The recent administration of DOAC therapy should be taken into account when choosing appropriate adjunctive antiplatelet and antithrombin therapy.

STEMI patients taking **maintenance VKA therapy** who have access to timely cardiac catheterization should generally be referred for urgent primary PCI. The INR should be checked urgently but this should not delay PCI; radial access is strongly preferred. The INR result should be taken into account when choosing appropriate adjunctive antiplatelet and antithrombin therapy.

MANAGEMENT OF PATIENTS WITH NON-VALVULAR AF ON OAC THERAPY WHO ARE UNDERGOING PCI POST-ACS OR FOR STABLE CAD

Patients with non-valvular AF who cannot discontinue OAC after undergoing PCI following an ACS or for stable CAD will require a period of treatment with both OAC and oral antiplatelet therapy. The optimal combination and duration of treatment should be individualized and take account of the risk of stroke, bleeding and ischemia/stent thrombosis. Discussion should preferably commence before PCI and involve the Interventional Cardiologist who performs the procedure.

OAC THERAPY & THROMBOLYSIS FOR ACUTE ISCHEMIC STROKE

GRADE Rating

MANAGING OAC THERAPY AND THROMBOLYSIS

A.	**We suggest** that AF patients on a VKA and diagnosed with an acute ischemic stroke NOT be thrombolyzed if INR > 1.7. (Lindsay 2012)	Weak Recommendation; Moderate Quality Evidence
B.	**We recommend** that until such time as there is a commercially available and validated assessment tool for DOAC levels, and until such time it is reliably known what these levels mean clinically, tPA should not routinely be administered to patients on DOACs presenting with acute ischemic stroke. (Lindsay 2012)	Strong Recommendation; Low Quality Evidence

REINITIATING OAC THERAPY

A.	**We recommend** that patients with TIA and AF should begin oral anticoagulation (dabigatran, or rivaroxiban, or apixaban, or warfarin) immediately after brain imaging has excluded ICH or large infarct. (Lindsay 2012)	Weak Recommendation; Low Quality Evidence
B.	For patients with acute ischemic stroke, **we suggest** that the optimal timing to reinitiate OAC therapy is unclear; common practice is to wait 2 to 14 days and repeat brain imaging (CT or MRI) to rule out asymptomatic ICH before reinitiating OAC therapy. Infarct size and other clinical circumstances will factor in when anticoagulation is reinitiaited. (Lindsay 2012)	Weak Recommendation; Low Quality Evidence

SWITCHING OAC THERAPY AFTER AN ACUTE STROKE

A.	**We recommend** switching to a DOAC if a patient's INR remains outside of the acceptable TTR. (Lindsay 2012)	Strong Recommendation; Moderate Quality Evidence
B.	If a stroke or TIA is diagnosed while the patient is on a VKA and their INR is consistently documented within therapeutic levels in the previous months, **we suggest** switching therapy from the VKA to a DOAC. (Lindsay 2012)	Weak Recommendation; Low Quality Evidence
C.	If a patient is diagnosed with a cardioembolic stroke while prescribed a DOAC, **we suggest** that medication adherence be assessed; relevant risk factors explored (e.g., hypertension, diabetes, dyslipidemia, smoking, obesity, sleep apnea) and non-cardioembolic mechanisms excluded before considering a switch to a VKA. (Lindsay 2012)	Weak Recommendation; Low Quality Evidence

OAC THERAPY & CARDIOVERSION	GRADE Rating
For patients with AF of duration ≥ 48 hours (or unknown), **we recommend**, OAC therapy for ≥ 3 weeks prior to and ≥ 4 weeks after cardioversion, regardless of cardioversion method (electrical or oral / IV pharmacological). (Camm 2012)	Strong Recommendation; Moderate Quality Evidence
• Based on pharmacodynamic parameters, a DOAC could be preferentially considered for OAC naïve patients who require elective cardioversion. (Cappato, 2014)	
For patients with risk factors for stroke or AF recurrence, **we recommend** that OAC therapy (dose-adjusted VKA at INR 2 - 3 or a DOAC) be continued lifelong irrespective of the apparent maintenance of sinus rhythm following cardioversion. (Camm 2012)	Strong Recommendation; Moderate Quality Evidence

PRACTICAL TIP:

① For this patient group, education, adherence and reinforcement are essential.

DOAC USE IN CHILDREN	GRADE Rating
The safety and efficacy of DOACs have not been established in children (≤18 years) and no indication currently exists. **We recommended** that DOACs should NOT be used.	Strong Recommendation; Low Quality Evidence

DOAC USE DURING PREGNANCY	GRADE Rating
Thrombolytic and anticoagulant agents can induce teratogenic effects, placental hemorrhage, prematurity and potential fetal loss. **We recommended** that DOACs NOT be prescribed during pregnancy.	Strong Recommendation; Low Quality Evidence

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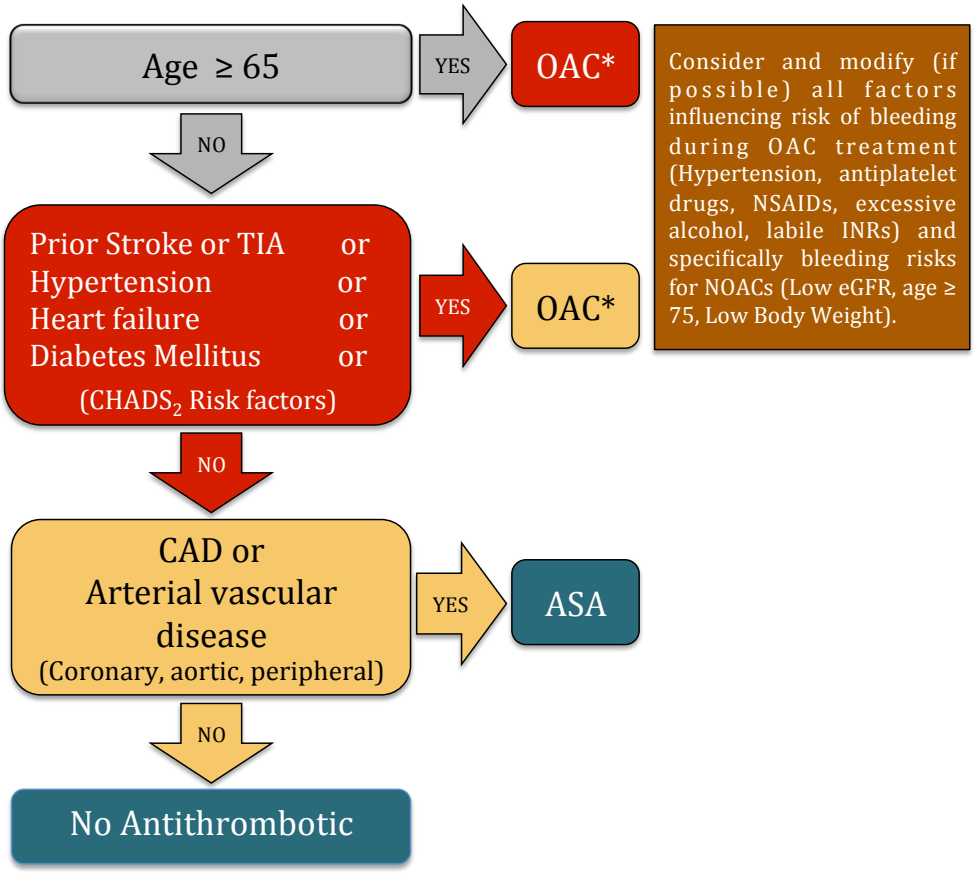
APPENDIX

① CCS Algorithm for OAC Therapy in Atrial Fibrillation



Verma et. al., 2014 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation, Canadian Journal of Cardiology, Volume 30, Issue 10, October 2014.

② Important Pharmacokinetic Drug-Drug Interactions with the Direct Oral Anticoagulant (DOAC) Class

Drug-drug & Drug-herb interactions described in the tables do NOT represent a comprehensive list, other documented or potential interactions are possible. Please consult additional established sources prior to combining pharmacotherapies. Drugs shaded in RED should not be used concomitantly or are overtly contraindicated in the respective DOAC product monograph. Caution should be used with those drugs shaded in YELLOW.

The concomitant use of DOAC's with drugs affecting hemostasis increases the risk of bleeding. Care should be taken if patients are treated concomitantly with drugs such as non-steroidal anti-inflammatories (NSAIDS), acetylsalicylic acid or platelet aggregation inhibitors.

Dabigatran (Pradaxa®)	
Amiodarone	Can increase dabigatran concentrations; no dosage recommendation recommended for treatment of Atrial Fibrillation at the present time
Antacids	Administration of dabigatran should occur at least 2 hours prior to ingesting an antacid. An increased pH may decrease the absorption of dabigatran
Carbamazepine	Co-administration is not recommended; dabigatran concentrations may be decreased
Dronedarone	Should not be used with dabigatran
Ketoconazole	Use is contraindicated
Itraconazole	Use with caution; dabigatran concentrations may be increased
Posaconazole	Use with caution; dabigatran concentrations may be increased
Quinidine	Quinidine may increase the concentrations of dabigatran, it is suggested that dabigatran be administered 2 hours before quinidine in order to minimize the interaction
Rifampin	Combination should be avoided as inadequate anticoagulation can result
Verapamil (PO)	Dabigatran should be administered 2 hours prior to verapamil if possible
Saint John's Wort	Concomitant use may lead to a decreased dabigatran plasma concentration resulting in inadequate anticoagulation.

Dabigatran Product Monograph (Update June 2014)

Rivaroxaban (Xarelto®)	
Carbamazepine	Combination should be avoided as inadequate anticoagulation can result
Phenobarbital	Combination should be avoided as inadequate anticoagulation can result
Phenytoin	Combination should be avoided as inadequate anticoagulation can result
Ketoconazole	Use is contraindicated
Itraconazole	Use is contraindicated
Posaconazole	Use is contraindicated
Clarithromycin	Combination should be used with caution as the risk of bleeding may increase
Ritonavir	Use is contraindicated
Rifampin	Combination should be avoided as inadequate anticoagulation can result
Saint John's Wort	Concomitant use may lead to a decreased rivaroxaban plasma concentration resulting in inadequate anticoagulation.

Rivaroxaban Product Monograph (Updated July 2014)

Apixaban (Eliquis®)	
Carbamazepine	Combination should be avoided as inadequate anticoagulation can result
Phenobarbital	Combination should be avoided as inadequate anticoagulation can result
Phenytoin	Combination should be avoided as inadequate anticoagulation can result
Ketoconazole	Use is contraindicated
Itraconazole	Use is contraindicated
Posaconazole	Use is contraindicated
Voriconazole	Use is contraindicated
Ritonavir	Use is contraindicated
Rifampin	Use should be avoided as efficacy of apixaban may be decreased
Saint John's Wort	Concomitant use may lead to a decreased apixaban plasma concentration resulting in inadequate anticoagulation.

Apixaban Product Monograph (Updated August 2014)

③ Incidence of ICH in significant DOAC Clinical trials

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., , and the RE-LY Steering Committee and Investigators. N Engl J Med 2009; 361:1139-1151September 17, 2009.

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D. and the ROCKET AF Steering Committee for the ROCKET AF Investigators. N Engl J Med 2011; 365:883-891 September 8, 2011.

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D. and Lars Wallentin, M.D., Ph.D. for the ARISTOTLE Committees and Investigators. N Engl J Med 2011; 365:981-992 September 15, 2011.

Study	Event Rate		RRR	ARR	NNT for ~1.8 yrs.	
	Warfarin	DOAC			NNT	95% CI
RE-LY 110 mg	1.4%	0.4%	69%	1.0%	100	75-154
RE-LY 150 mg	1.4%	0.6%	59%	0.9%	117	83-202
ROCKET AF	1.2%	0.8%	34%	0.4%	247	137-1211
ARISTOTLE	1.3%	0.6%	58%	0.8%	129	94-203

④ Process used to generate Panel recommendations & the final document

Initiative co-chairs explored the community need and potential scope of the practical and appropriate use recommendations

Unrestricted and untied initiative funding was secured from several industry partners. Thereafter, Industry had absolutely no involvement in any aspect of the process.

The initiative co-chairs recruited a 15 member Primary Panel representing several therapeutic disciplines and all four Atlantic Provinces. Panelists signed a confidentiality agreement and declared all potential *conflicts of Interest (COI)* related to this initiative. Primary Panel participants and their potential COI statements can be reviewed on the Atlantic Cardiovascular Society website.

An extensive review of oral anticoagulant literature and professional society guidelines were distributed to all panelists prior to participating in the face-to-face meeting. This literature formed the foundation on which Panel recommendations for Atlantic Canada were based.

Panelists participated in a face-to-face meeting in order to debate and generate recommendations. Voting consensus was achieved when 75% of participants supported the recommendation; all recommendations were required to meet the consensus threshold in order to be included in the final document.

Interventional Cardiology did not participate on the Primary Panel, however, that group's recommendations addressing the acute management of AF patients who experience an ACS was sought. A consensus threshold of 75% agreement in support of their recommendations was required and surpassed by the 20 Atlantic Interventional cardiologists.

Panel recommendations were circulated to a Secondary Panel of reviewers. The secondary Panel included both clinicians and organizations from throughout Atlantic Canada. The Primary Panel considered the feedback and appropriate adjustments were made.

The manuscript of recommendations was circulated to the Primary Panel for final review. Once ratified, the completed manuscript was posted on the Atlantic Cardiovascular Society website for public consumption.