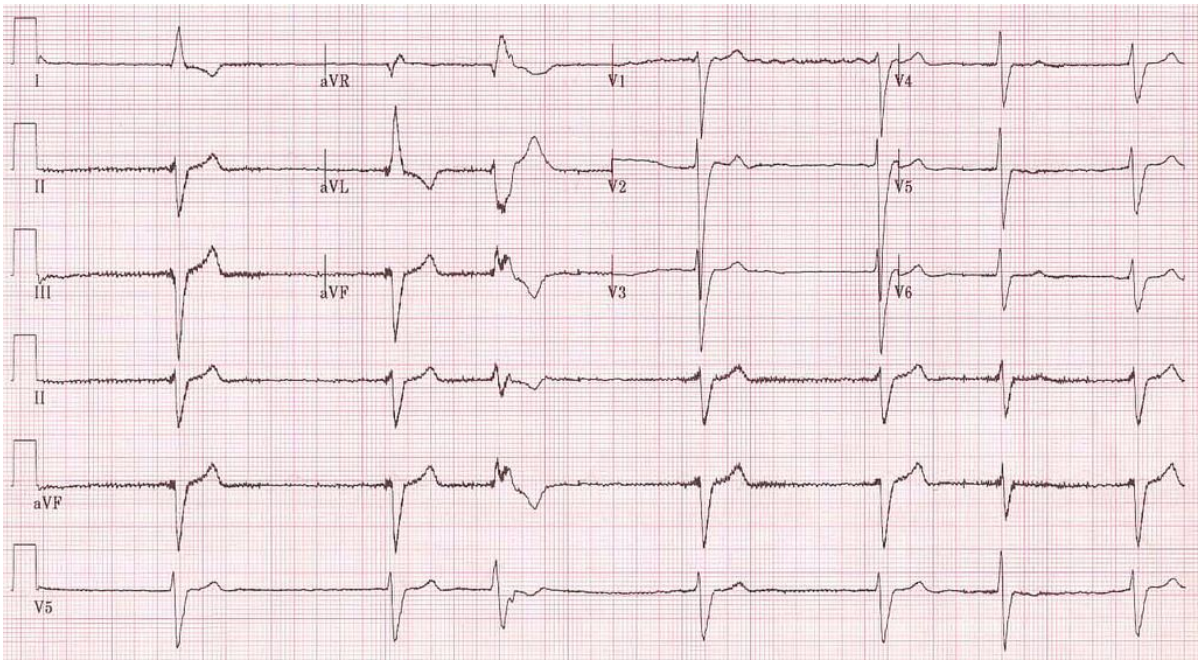
Oral Anticoagulants in



Atrial Fibrillation

Academic Detailing Service

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Table of Contents

Tables, Figures and Appendices

Definitions and Abbreviations

ACCP	American College of Chest Physicians
ACS	Atlantic Cardiovascular Society
AE	Adverse event
AF	Atrial fibrillation
AHA	American Heart Association
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
CADTH	Canadian Agency for Drugs and Technologies in Health
CCS	Canadian Cardiovascular Society
$CHADS_2$	**C**ongestive heart failure, **H**ypertension, **A**ge > 75, **D**iabetes Mellitus, and Prior **S**troke or Transient Ischemic Attack
CHA_2DS_2-VASc	**C**ongestive heart failure, **H**ypertension, **A**ge > 75, **D**iabetes Mellitus, and Prior **S**troke or Transient Ischemic Attack, Vascular disease, Age 65-74, Sex
CrCl	Creatinine clearance
DOAC	Direct oral anticoagulant
eGFR	Estimated glomerular filtration rate
FP	Frozen plasma
ICH	Intracranial hemorrhage
INR	International normalized ratio
MI	Myocardial infarction
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNT/NNH	Number needed to treat/ Number needed to harm
OAC	Oral anticoagulant
PCC	Prothrombin complex concentrate
RCT	Randomized controlled trial
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
ROCKET-AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in AF
SrCr	Serum Creatinine
TTR	Time in therapeutic range
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

Summary

Who needs anticoagulation? (Page 9)

- People with atrial fibrillation are at increased risk of ischemic stroke**.** Guidelines recommend that all patients with AF or atrial flutter (paroxysmal or persistent) should be stratified using a predictive index for risk of
  - Stroke (CHA_2DS_2VASc)
  - Bleeding (HAS-BLED)
- Patients with a CHA_2DS_2VASc **score of ≥ 2** have sufficient stroke risk to justify use of an OAC.
- Most patients with a CHA_2DS_2VASc score of 1 have sufficient risk to **consider** use of an OAC.
  - However, a single CHA_2DS_2VASc point based on **vascular disease or female gender** implies a stroke risk of < 1.5% per year and anticoagulants would not be indicated.
    - The 2014 CCS update suggests aspirin for AF patients who are less than 65 and have vascular disease, but no other stroke risk factors.

Effectiveness of warfarin (Page 13)

- Warfarin reduces the risk of stroke in patients with AF by more than 60% compared with no treatment, and by 30% to 40% when compared with low-dose aspirin.
- Compared to **no treatment**, various meta-analyses give warfarin treatment
  - An NNT of 25 to 37 per year to prevent stroke in primary prevention and
  - An NNT of approximately 12 per year in secondary prevention.
- Patients on warfarin should have their INRs in the therapeutic range (2 to 3) at least 65% of the time. This requires regular monitoring with a systematic approach.
- Disadvantages of warfarin include need for frequent INR monitoring, as well as numerous food and drug interactions.
  - With INR monitoring, there is the ability to detect the presence and magnitude of drug interactions.

DOACs: advantages and disadvantages compared with warfarin and recommendations

- Compared with warfarin, the DOACs provide **(Page 19-32)**
  - Overall in meta-analysis,
    - Approximately 20% reduction in the primary outcome of systemic embolism and stroke. The absolute risk reduction is 0.6%, NNT 167 over approximately 2 years.
    - No statistically significant benefit in ischemic stroke and major bleeding.
    - Approximately 56% relative reduction in intracranial bleeding. The absolute risk reduction is 0.7%, NNT 143 over approximately 2 years.

- In individual studies
  - Only dabigatran 150 mg and apixaban showed statistically significant benefit in the primary outcome of stroke and systemic embolism.
  - Only dabigatran 150 mg showed statistically significant benefit in reducing ischemic strokes (RRR 24%: NNT 188 [95% CI 96-4764] for approximately 2 years). All other DOACs provide equivalent protection against ischemic stroke.
  - Only dabigatran 110 mg and apixaban showed statistically significant benefit in reducing major bleeds.
  - All DOACs showed statistically significant benefit in reducing intracranial hemorrhage.

- There is no current requirement for routine monitoring of the anticoagulation effects of DOACs. However, renal function should be monitored at least annually or when there is a change in health status; patients should be monitored for adherence and signs of bleeding. **(Page 25)**
- DOACs require lower doses in renal impairment. **(Page 29)**
- DOACs are new drugs and there is limited data on their long-term safety and effectiveness.
- Guidelines and reviews differ in their approach to DOACs. Some recommend DOACs in preference to warfarin while others consider either to be options. CADTH considers warfarin as first line. **(Page 33)**
- Patients ≥ 75 years old who are healthy appear to have the same benefits from DOACs as younger patients. However, there is little evidence in those ≥ 80 years. **(Page 38)**

Introduction

- Atrial fibrillation (AF) is the most common abnormal heart rhythm and currently affects approximately 350,000 Canadians. Its incidence increases with age, so the number of patients affected is likely to increase as our population continues to age.[1]
  - It affects approximately 1% of the general population and up to 10% of people > 80 years old.[2]
- AF can lead to serious complications. Patients with AF have a 3 to 5 times greater risk of an ischemic stroke. In addition, an estimated 20% of all strokes are caused by AF.[1]
- Strokes due to AF are generally more severe than those occurring in patients in sinus rhythm and are associated with higher case-fatality, longer hospitalization, and increased disability.[3]
- Antithrombotic drugs, including anticoagulants and antiplatelets are used to help prevent ischemic stroke in patients with non-valvular AF. They also increase the risk of serious bleeding.
- Warfarin, a vitamin K antagonist, has been the mainstay of therapy for many years. It is effective in preventing ischemic strokes in patients with AF. Its use comes with some challenges: drug and food interactions, the need for regular international normalized ratio (INR) monitoring, and sometimes frequent dosing changes.[1]
- Three new direct oral anticoagulants (DOACs) have been approved for use in Canada: dabigatran, rivaroxaban and apixaban. Another oral anticoagulant, edoxaban is not available in Canada.
  - Dabigatran is a direct thrombin inhibitor while rivaroxaban, apixaban and edoxaban are direct factor Xa inhibitors.
  - The DOACs are approved for use in patients with **non-valvular** AF.
    - The efficacy and safety of rivaroxaban and apixaban have not been studied in patients with prosthetic heart valves, with or without AF, or those with hemodynamically significant rheumatic heart disease, especially mitral stenosis.[4]
    - Dabigatran has been compared with warfarin therapy in patients **with mechanical heart valves**.[5]
      - The use of dabigatran was associated with **increased** rates of thromboembolic and bleeding complications compared with warfarin.
      - The trial was stopped and the manufacturer has updated the worldwide labeling to **contraindicate** the use of dabigatran in patients with prosthetic heart valves requiring anticoagulant treatment due to their valvular status.
- The DOACs have emerged as **alternatives** to warfarin in patients with **non-valvular** AF. Physicians and patients now have a choice for oral anticoagulation.
  - Some guidelines recommend that the DOACs are preferable to warfarin; others suggest they are on par with warfarin. See question 5 for details.

- The DOACs offer **convenience** for the patient as routine monitoring of anticoagulant effect is currently not required. However, monitoring of renal function and adherence is essential.
- A summary of the evidence comparing the DOACs to warfarin (see Question 3 and Appendix 2) indicates that for many efficacy outcomes, including ischemic stroke, the benefit is the same.
- RCTs have consistently shown a reduction in **intracranial hemorrhage** associated with the use of DOACs **compared with warfarin**. The DOACs provide a relative risk reduction of about 56% while the absolute risk reduction is about 0.7% leading to a NNT of 143 (95% CI 100-200) for approximately 2 years.

- In developing this topic we have reviewed
  - Reports from the Canadian Agency for Drugs and Technologies in Health (CADTH)
  - Cochrane and other reviews
  - Original publications
  - National and international guidelines
  - Official product monographs
- **We will address six questions**
  1. Who needs anticoagulation?
  2. How effective is warfarin?
  3. What are the advantages of the DOACs compared with warfarin?
  4. What are the disadvantages of the DOACs compared with warfarin?
  5. What are the current recommendations?
  6. What are the special considerations for the elderly (≥ 75)?

Notes

1. This document deals with NON-VALVULAR atrial fibrillation, patients without significant aortic or mitral valve disease.

2. In this document OACs refers to ALL oral anticoagulants which include warfarin and the direct oral anticoagulants. Antithrombotic therapy refers to antiplatelet and/or anticoagulant therapy.

3. NOAC has been misinterpreted as "no anticoagulant". Therefore, a new term is appearing in the literature, direct oral anticoagulant or "DOAC".

Question 1. Who needs anticoagulation?

- People with atrial fibrillation are at increased risk of stroke.
- Guidelines recommend that all patients with AF or atrial flutter (whether paroxysmal or persistent) should be stratified using a predictive index for risk of
  - Stroke (CHA_2DS_2VASc)
  - Bleeding (HAS-BLED)

Estimating risk of stroke

- The 2012 Canadian Guidelines referred to the use of the **$CHADS_2$** index and encouraged the use of the factors used in the **CHA_2DS_2VASc** index to assist in risk prediction in patients at lower risk.[6]
- The updated 2014 Canadian Cardiovascular Society (CCS) Guidelines refer to the use of a new CCS algorithm based on the **$CHADS_2$** index.
  - The new CCS algorithm differs from the 2012 algorithm in only one respect: women with vascular disease no longer qualify for OAC therapy unless they are age ≥ 65 or have an additional $CHADS_2$ risk factor.[7]
- Guideline updates from the American College of Cardiology, American Heart Association, Heart Rhythm Society[8] and the European Society of Cardiology[9] now recommend the use of the **CHA_2DS_2VASc** index to estimate risk of stroke.
- For simplicity, we suggest going directly to the **CHA_2DS_2VASc** index. The **C**ongestive heart failure, **H**ypertension, **A**ge > 75, **D**iabetes Mellitus, and Prior **S**troke or Transient Ischemic Attack or systemic embolism, **V**ascular disease, **A**ge 65-74, **S**ex (**CHA_2DS_2VASc**) index scoring system is presented in Table 1.[12]
  - Patients with a CHA_2DS_2VASc **score of ≥ 2** have sufficient stroke risk to justify use of an OAC.
  - Most patients with a CHA_2DS_2VASc score of 1 have sufficient risk to consider the use of OACs.
    - However, a single CHA_2DS_2VASc point based on **vascular disease or female gender** implies a stroke risk of < 1.5% per year and anticoagulants would **not** be indicated.[6]
      - The 2014 CCS update[7] suggests aspirin for AF patients who are less than 65 and have vascular disease, but no other stroke risk factors.
- Canadian Cardiovascular Society Guidelines suggest that patients with an annual stroke risk of **>2%** require oral anticoagulants regardless of the stroke risk index used.[6]
- Patients with transient ischemic attack or ischemic stroke and **atrial fibrillation** should be considered for oral anticoagulation as they automatically have an annual stroke risk of >2%.[10]

Estimating risk of hemorrhage

- **HAS-BLED** (**H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile INR, **E**lderly, **D**rugs/Alcohol Concomitantly) is recommended to predict risk of hemorrhage.[6]
  - See Table 1 for assigning points and Table 2 for associated bleeding risk.
  - A **score of ≥ 3** indicates a **high risk** of having a bleeding event requiring some caution and regular evaluation of antithrombotic treatment.[13,14]
  - Many of the factors that determine stroke risk are also bleeding risk predictors.
  - Some elements comprising the HAS-BLED score can be modified and improved (hypertension, alcohol use, drug use) thereby lowering the score.
  - Studies looking at physician's clinical practice in Canada have consistently demonstrated a tendency to **over-estimate** bleeding risk, and to **under-estimate** stroke risk.[15] In other words, we see the bleeds we cause, but we never see the strokes we prevent.
  - Approximately 70% of strokes with AF are either fatal or leave severe residual deficits. However, major bleeding related to anticoagulant use is less often fatal and is less likely to leave significant residual effects, unless the bleeding is intracranial, in which case a fatal or devastating outcome is also highly likely.
  - Patients receiving antithrombotic therapy who are at increased risk of major bleeding should be counselled to report episodes of bleeding.
  - Only when the stroke risk is **low** and the bleeding risk particularly **high** does the benefit/risk ratio favor no antithrombotic therapy. Discussing the benefits and risks with the patient is of great importance.[6]

Table 1: CHA_2DS_2VASc Index[11,12] and HAS-BLED Risk Criteria[14]

	CHA_2DS_2VASc Risk Criteria	Score			HAS-BLED Risk Criteria	Score
C	Congestive heart failure, left ventricular dysfunction	1		**H**	Hypertension SBP > 160mmHg	1
H	Hypertension	1		**A**	Abnormal renal function (dialysis, transplant or SrCr > 200 µmol/L) **OR** Abnormal liver function (cirrhosis or bilirubin > 2 X upper limit of normal with AST/ALK/Alk Phos > 3 X upper limit of normal) 1 point each	1 or 2
A	Age ≥ 75	2		**S**	History of stroke	1
D	Diabetes mellitus	1		**B**	Bleeding (history or predisposition e.g. anemia)	1
S	History of stroke or TIA	2		**L**	Labile INR	1
V	Vascular disease	1		**E**	Age > 65	1
A	Age 65 to 74 years	1		**D**	Drugs (concomitant antiplatelet agents, NSAIDS), Alcoholism 1 point each	1 or 2
S	Female gender	1				

Table 2: Risk of stroke and risk of bleeding [11,12,14]

CHA_2DS_2VASc Score	Stroke risk per year		HAS-BLED Score	Bleeding risk per year*
0	0		0	1.13%
1	1.3%		1	1.02%
2	2.2%		2	1.88%
3	3.2%		3	3.74%
4	4.0%		4	8.70%
5	6.7%		5	12.50%
6	9.8%			
7	9.6%			
8	6.7%			
9	15.2%			

***Intracranial bleeding, hospitalization, Hg decrease >20g/L, ± transfusion
Validated with warfarin only (N=7329)

Absolute and relative contraindications of ALL oral anticoagulants

- The following list of contraindications for oral anticoagulants is adapted from an NHS document.[16]

Absolute contraindications

- Known large esophageal varices.
- Significant thrombocytopenia (platelet count < 50 x 10^9/L). Refer to a hematologist.
- Within 72 hours of major surgery with risk of severe bleeding – defer anticoagulation reassess risk postoperatively. It is advised to have a discussion with the surgeon about when they feel the risk of major bleeding related to starting or restarting an OAC is diminished. The time to initiate an OAC will also depend on the time needed to achieve a therapeutic drug level (shorter time with DOACs, longer with warfarin).
- Previously documented hypersensitivity to the drug.
- Decompensated liver disease or deranged baseline clotting screen (INR>1.5) – refer to gastroenterology /hepatology.
- Pregnancy or within 48 hours post partum – seek urgent hematological / obstetrical advice.

Relative contraindications

- Acute clinically significant bleed – re-assess stroke versus bleeding risk. Some sources of bleeding can be managed so as to prevent further bleeding (e.g., GI bleed or nosebleed with a treatable cause).
- Previous history of intracranial hemorrhage – as some AF patients, especially those considered at higher stroke risk (i.e. CHA_2DS_2VASc score ≥4), may benefit from anti-thrombotic therapy, seek the opinion of a stroke specialist.
- Recent major extracranial bleed within the last 6 months where the cause has not been identified or treated – decision for oral anti-thrombotic therapy should be deferred.
- Recent documented peptic ulcer within last 3 months – decision for oral anti-thrombotic therapy should be based on a careful benefit/risk assessment. Patients with a recent history of a peptic ulcer should be considered for a proton pump inhibitor while on anti-thrombotic therapy.
- Poor compliance with medications, or no access to caregiver support in patients who need supervision when taking medication e.g., cognitive impairment.
- Chronic alcohol abuse – especially if associated with binge drinking.
- Recent history of recurrent falls in patient at higher bleeding risk (HAS-BLED ≥ 3)

  Note: A risk of falls is not a contraindication to initiating oral anticoagulation. (e.g. a patient with an annual stroke risk of 5% would need to fall 295 times for fall risk to outweigh stroke reduction benefit of warfarin).[17]

Question 2. How effective is warfarin?

Background

- Warfarin is a vitamin K antagonist (VKA) that has been in use for more than 70 years for the treatment of venous thromboembolism (VTE).
- In the 1980's standardization of an INR and therapeutic windows for many diseases were established. Warfarin demonstrated efficacy and safety in preventing stroke in patients with non-valvular atrial fibrillation and has been the mainstay for treating this condition.

Evidence for benefit

- Vitamin K antagonists reduce the risk of stroke in patients with AF by more than 60% when compared with no treatment, and by 30% to 40% when compared with low-dose aspirin.[18,19]
- In AF, compared to **no treatment**, various meta-analyses give warfarin treatment
  - An NNT of 25 to 37 per year to prevent stroke in primary prevention and
  - An NNT of approximately 12 per year in secondary prevention.[20,21]

Limitations of warfarin

- In Canada, as in other countries, only about 50% of those with atrial fibrillation who should be anticoagulated for stroke prevention actually receive medications.[22] Some of the reasons for this care gap may be due to the limitations described below:
  - Warfarin has a slow onset of action, taking several days to reach therapeutic levels.
  - Warfarin has a narrow therapeutic window: insufficient anticoagulation may result in stroke, whereas over-anticoagulation increases the risk of bleeding.
  - Warfarin therefore requires regular monitoring of blood levels (INR).
  - The pharmacokinetics and pharmacodynamics of warfarin are affected by genetic factors, drug-drug interactions and consumption of foods containing vitamin K.
    - Many acute medications such as antibiotics have significant interactions with warfarin meaning doses may have to be changed and monitored during and around acute events.
    - It is important to eat a consistent healthy diet. Apart from moderation in quantity, dietary restrictions are not recommended because they may affect quality of life. However, INR should be monitored if there are sudden changes in the quantity of foods containing vitamin K (e.g., spinach, broccoli, liver).

Monitoring

- Ongoing monitoring of INR must occur when patients are on warfarin. While it is ideal that a patient's INR should be in the therapeutic range (time in therapeutic range =TTR) 100% of the time, this is not usually possible. It is suggested that a patient's INR should be in the therapeutic range at least 65% of the time,[23] but this does not ensure that a patient is protected from stroke (INR is too low), or adverse bleeding events (INR is too high).
- To help ensure TTR of ≥ 65%, health-care providers should have a systematic and coordinated approach to managing oral anticoagulation therapy.[1] This should include patient education, systematic INR testing, tracking, follow-up, and good patient communication of results and dosing decisions.[1]
- Specialized anticoagulation services do not consistently reduce hemorrhages, thromboembolism, or the need for additional medical care.[1] Specialized anticoagulation services improve TTR compared with usual care (for example by a family physician) by a modest amount though the evidence comparing different specialized models of care or service components is limited in both quantity and quality.[1]
- Patient self-directed care with point of care testing appears to offer improved clinical outcomes.[1] It is not an option for many but does work well and is reliable for those who have the interest and education to self-manage. Roche Coaguchek for home INR testing costs about $500 in Canada; 50 strips cost $200. http://bit.ly/Coaguchek
- Patients with Nova Scotia Pharmacare Coverage who, despite their best efforts, are not able to maintain an INR in the therapeutic range more than 65% of the time (with appropriate documentation) are eligible to be treated with a DOAC through the Exception Drug Status Program. See page 32 for Nova Scotia Pharmacare's DOAC exception status criteria.

Adverse Events – primarily bleeding events

- Warfarin reversal agents are available for use in clinically significant bleeding. The choice and dose of reversal agent is dependent on the clinical problem, i.e. minor bleeding vs. major bleeding, and the need for future warfarin therapy.[24,25]
- Bridging anticoagulation refers to giving a short-acting anticoagulant (usually LMWH) when an oral anticoagulant, usually warfarin, is interrupted and its anticoagulant effect is outside a therapeutic range.[26]
  - There are currently no completed studies clearly defining who should be bridged, but two studies are ongoing, BRIDGE and PERIOP-2.
  - Until these studies are published and incorporated into practice, please refer to the 2014 CCS Guidelines for suggestions.[7]
- Reversal agents include
  - Vitamin K (vitamin K1)
    - May be given orally or IV (For doses, see box page 17)
    - Competes with the anticoagulant effect of warfarin but the effects on clinical outcomes are variable (see pages 18 and 31).
    - Major bleeding
      - IV is recommended as it gives faster reversal than oral administration
    - Minor bleeding
      - INR reductions are approximately equal with either route 24 hours after administration. Therefore, the oral route is recommended for minor bleeding.
    - After oral administration it will take up to 24 hours to normalize the INR.
    - After IV administration, the INR will start to drop within 2 hours and will become normal within 12 to 16 hours. Note that IV administration of vitamin K has a risk of anaphylaxis.
    - A residual resistance to antithrombotic effect may remain after administration of vitamin K. This may set up warfarin resistance making it difficult to re-anticoagulate quickly and thus expose the patient to longer than desired **thrombotic risks**. Use of high vitamin K doses (≥ 10mg) may cause warfarin resistance for ≥ 1 week.[25]
  - Prothrombin complex concentrate (PCC) *(Recommended method for the reversal of VKA effect from the Nova Scotia Provincial Blood Coordinating Program. Available at* http://novascotia.ca/dhw/nspbcp/clinical-practice-guidelines.asp).[27]
    - PCC is a lyophilized blood product and may carry the same risks associated with a blood component such as infections, allergic reactions, fever, and acute lung injury. PCCs do not require crossmatching.
    - PCCs are easily and quickly reconstituted providing a significant advantage in time to administration compared to frozen plasma.

- PCCs contain factors II, IX, and X, with variable amounts of factor VII. Variation in factor VII concentrations in PCC has led to their classification as either 3- or 4- factor. Only 4-factor PCCs are available in Canada.
- In Nova Scotia, Octaplex® and Beriplex® P/N are indicated for the rapid reversal of the warfarin VKA effect when an anticoagulated patient presents with an INR greater than or equal to 1.7 and is bleeding or requires an urgent invasive procedure or surgery. The following provides the dosing for patients meeting the above indications:
  - INR 1.7 to 5.0 – give 40 mL PCC
  - INR greater than 5.1 *OR* major bleeding with an unknown INR *OR* intracranial hemorrhage – give 80 mL

  Repeat the INR 15 – 20 minutes after PCC administration. If the INR remains above 1.7, an additional dose of 20 mL may be administered with the INR checked again in 15 – 20 minutes. The maximum dosing for Octaplex® is 120 mL and Beriplex® P/N is 200 mL.[27]
- **PCCs restore INR to normal within minutes.** However, because the PCC effect is approximately 6 hours, **IV vitamin K must also be administered** to ensure continued reversal of the VKA.
- Expensive
- PCCs are available in most facilities in Nova Scotia where emergency care and surgeries are performed.
- A Preprinted Physician Order (PPO) Form has been developed by the Nova Scotia Provincial Blood Coordinating Program (NSPBCP). Facilities within Nova Scotia either employ the form in Appendix 5 or have formatted this PPO for their specific facility.
- The NSPBCP collects utilization data from the various Blood Transfusion Services in Nova Scotia whereby the appropriateness of use can be monitored.
- Current recommendations in Nova Scotia indicate DOACs are not reversed by the administration of PCCs (see page 31).

o Frozen plasma (FP)[27]

- FP is a blood component and may carry the risks associated with blood components such as infections, allergic reactions, fever, and acute lung injury.
- FP must be crossmatched which may prolong the time to initiate administration.
- FP should only be administered for the reversal of VKA if PCCs are not available. Large volumes of FP are required to reverse the VKA effect by replenishing clotting factors, which can lead to volume overload.
- FP is **not recommended** for the reversal of DOACs (see page 31).

- The box below provides the warfarin reversal regimens recommended by American College of Chest Physicians.[28]

Reversal of Warfarin Effects[28]

Omit 1-2 doses or hold warfarin; monitor INR and consider treatment as below

INR	Bleeding	Treatment
4.5-10	No bleeding	No routine use of vitamin K1
>10	No bleeding	Vitamin K1 2.5-5.0 mg PO once Monitor INR over 24-48 hour and repeat dose if necessary
Any elevated	Minor	Consider vitamin K1 2.5-5.0 mg PO once Repeat if necessary after 24 hours
Any elevated	Major	PCC complex Vitamin K1 5-10 mg IV (dilute in 50 mL IV fluid and infuse over 20 min)

NOTE: High vitamin K1 doses (10 mg or more) may cause warfarin resistance for a week or more; consider using heparin, low molecular weight heparin (LMWH), or direct thrombin inhibitors to provide adequate thrombosis prophylaxis in conditions requiring chronic anticoagulation therapy (e.g., AF).

- **Spontaneous intracerebral hemorrhage**
  - This is a **rare** but potentially life-threatening consequence of anticoagulants.
  - Some risk factors for intracerebral hemorrhage during anticoagulation have been firmly established.[29]
    - Advancing age (especially older than 75 years)
    - Hypertension (especially systolic blood pressure >160 mm Hg)
    - History of cerebrovascular disease
    - Intensity of anticoagulation
  - Other possible risk factors include[29]
    - Concomitant use of aspirin
    - Cerebral amyloid angiopathy
    - Asian or Mexican-American ethnicity
    - Tobacco smoking
    - Heavy alcohol consumption
  - **Several of these risk factors are components of the HAS-BLED score: it is important to address the modifiable risk factors for intracerebral hemorrhage, especially hypertension, to decrease the risk.**

- Studies done before the availability of DOACs indicate the mortality rate after ICH is doubled in patients who are anticoagulated with warfarin compared to those who are not anticoagulated.[30] We could not find comparable data for the DOACs.
- There is limited RCT evidence comparing the benefit of the different anticoagulant reversal strategies for patients on warfarin who experience an ICH.
- Protocols for warfarin-associated ICH emphasize immediate
  - Discontinuation of warfarin
  - Immediate administration of PCC or FP (FP should only be used if PCCs are not available).
    - PCC is preferred over FP due to rapid normalization of the INR, quicker administration time and fewer complications from fluid overload.
  - Administration of IV vitamin K[28,31]
- 4-factor PCCs restore INR to normal within minutes and attenuate hematoma expansion in patients with ICH, but data regarding safety and outcome after treatment are scant and non-definitive.[32]
- Two studies, one in Canada[33] and a multinational study,[34] **showed no evidence** that treatment with a 4-factor PCC improved survival after warfarin-associated ICH.
- Warfarin may be restarted after a spontaneous intracranial hemorrhage, depending on what the underlying cause of the bleeding was felt to be.[63] It is important to discuss the risk of recurrent bleeding versus the benefit of reducing the ongoing risk of thromboembolism with a stroke specialist.

➢ **Gastrointestinal Bleeding**

- GI bleeding can be
  - Major and sufficient to stop the OAC or
  - Minor and the OAC can be continued.
- The decision to restart an OAC after a GI bleed depends on the risk of thrombosis versus the risk of bleeding in the context of short- and long-term treatment goals.
- Recent evidence from 2 retrospective cohort studies[35,36] suggests that resuming warfarin therapy after an episode of GI bleeding is associated with a lower risk for thrombosis and death. The optimal duration of warfarin interruption after a GI bleed requires further study.
  - Qureshi et al[35] found that restarting warfarin between 7 and 30 days of the GI bleed was associated with a decreased risk of thromboembolism and mortality without a significant increased risk of recurrent GI bleed when compared with restarting warfarin after 30 days.
  - Witt et al[36] found that restarting warfarin between 2 and 9 days of the GI bleed was associated with a numerical but not statistically significant increase in recurrent GI bleed as well as a decreased risk of both thrombosis and death from any cause compared with those who did not restart warfarin within the first 90 days.

- Among the 260 patients who resumed warfarin, there was one thrombotic event, 26 episodes of recurrent GI bleeding (10%), and 15 deaths (5.8%) in the 90 days following the initial GI bleeding event.
- Among the 182 patients who did **not** resume warfarin, there were 10 thrombotic events (5.5%), 10 episodes of recurrent GI bleeding (5.5%), and 37 deaths (20%).

- Clear evidence identifying an optimal reversal strategy for GI bleeds associated with warfarin overdose is not yet available.

Question 3. What are the advantages of DOACs compared with warfarin?

- When considering the evidence for the DOACs it is important to define the outcomes of interest. Important outcomes to consider include:
  A. Clinical outcomes (thromboembolic events such as ischemic stroke; adverse effects such as major bleeding; and mortality)
  B. Convenience
  C. Interactions with drugs

A. Clinical outcomes

- There are 3 main studies that assessed the efficacy of the DOACs available in Canada with respect to preventing strokes in people with non-valvular AF. Each of these RCTs compared a DOAC to warfarin therapy:
  - Dabigatran: Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY)[37]
  - Rivaroxaban: Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF)[38]
  - Apixaban: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)[39]
- The studies were similar in several ways:
  - The outcomes reflected the balance between preventing thromboembolic events and causing or preventing major bleeds.
  - The primary efficacy outcome was a combination of stroke and systemic embolism.
  - Bleeding outcomes included major bleeding, major GI bleeding and intracranial bleeding.
  - **Hemorrhagic stroke** was included as an efficacy outcome and a safety outcome in all three trials.

- The studies did an analysis to determine if the study drugs were non-inferior to (as effective as) warfarin. If non-inferiority was demonstrated, a further analysis was done to determine if the study drugs were superior to (better than) warfarin.
- Patients with a high risk of bleeding were excluded. None of the studies reported the HAS-BLED scores of the study subjects.
- They lasted approximately 2 years.
- They were multi-site, international studies.

- The studies[37,38,39] had some important differences:
  - ROCKET AF enrolled patients at higher stroke risk ($CHADS_2 \geq 2$, mean $CHADS_2$ score = 3.5) than RE-LY or ARISTOTLE ($CHADS_2 \geq 1$, mean $CHADS_2$ score in both = 2.1).
  - ROCKET AF and ARISTOTLE were blinded whereas RE-LY was open label.
  - ARISTOTLE included patients with atrial flutter as well as atrial fibrillation whereas RE-LY and ROCKET AF included only patients with atrial fibrillation.
  - RE-LY tested two doses of study drug (dabigatran 110 and 150 mg) against warfarin whereas ROCKET AF and ARISTOTLE tested only one dose of study drug.
  - The study characteristics are summarized in Appendix 2.
- We reviewed a 2013 Cochrane meta-analysis and other meta-analyses which included various DOACs:[40,41,42]
  - The Cochrane review included Factor Xa inhibitors though most of the data was from studies of rivaroxaban and apixaban. Smaller studies and not just the large major studies were included.[40]
    - Data in this review have been questioned and it is currently being redone but is not published to date.
  - Ruff[41] focused on the major studies of dabigatran, rivaroxaban, apixaban, and edoxaban (RE-LY[37], ROCKET AF[38], ARISTOTLE[39], and ENGAGE AF-TIMI 48[43]). RE-LY and ENGAGE included low and regular doses of dabigatran (110 mg and 150 mg) and edoxaban (30 mg and 60 mg). The primary analysis of the meta-analysis included the regular doses, but a separate analysis included only the low doses.[41]
  - Gomez-Outes[42] included just the 3 major studies of dabigatran, rivaroxaban, and apixaban (RE-LY, ROCKET AF, ARISTOTLE) and combined the high and low doses of dabigatran in the analysis. The authors also conducted some sub-group analyses to determine the effect of the DOACs in different populations.[42]
- Despite these differences in the meta-analyses, the overall effect of the DOACs on various clinical outcomes was **consistent**.
- In order to calculate numbers needed to treat (NNTs), we took data from the meta-analyses and also conducted our own meta-analysis using a program called Comprehensive Meta-analysis v2.2.064 to arrive at the results summarized in Table 3 which includes data from the three major studies of the DOACs (RE-LY[37], ROCKET-AF[38], and ARISTOTLE[39].)

Table 3: Results of random effects meta-analysis[a] of RE-LY[37], ROCKET[38], and ARISTOTLE[39]

Efficacy outcomes	Event Rate		RRR	ARR	NNT for ~2 yrs	
	Warfarin N~28215	DOAC N~28292			NNT	95% CI
Primary outcome – systemic embolism and stroke	3.4%	2.8%	18%	0.6%	167	100-333
Mortality	6.7%	6.0%	11%	0.7%	143	91-333
Ischemic stroke	2.2%	2.1%	7%	0.1%	NS	
Hemorrhagic stroke	0.8%	0.3%	58%	0.4%	250	167-333
Safety outcomes	**Warfarin**	**DOAC**	**RRR**	**ARR**	**NNT**	**95% CI**
Major bleeding	5.8%	5.0%	12%	0.8%	NS	
Intracranial hemorrhage	1.3%	0.6%	56%	0.7%	143	100-200
			RRI	**ARI**		
GI bleeding	1.8%	2.3%	22%	0.5%	NS	

ARR, absolute risk reduction; ARI, absolute risk increase; RRR, relative risk reduction; RRI, relative risk increase; NNT, number needed to treat; NNH, number needed to harm; CI, confidence intervals; NS not stastically significant.

a – meta-analysis done by Academic Detailing Service using Comprehensive Meta-analysis v2.2.064

- Overall, in meta-analysis, compared with warfarin the DOACs showed
  - a statistically significant benefit in reducing strokes and systemic embolism;
  - no statistically significant benefit in reducing ischemic strokes;
  - no statistically significant benefit in reducing major bleeds or GI bleeds;
  - a statistically significant benefit in reducing ICH.
- For the clinical outcomes of stroke and systemic embolism, mortality, and intracranial bleeding, the DOACs provide **relative** benefit but the **absolute** benefit is small when compared with warfarin. (See Table 3)
  - The small absolute benefit is also illustrated in Figure 1.

Effects of hemorrhagic stroke and intracranial hemorrhage on interpreting trials of DOACs vs warfarin

- The reason to put patients with AF on an OAC is to prevent an **ischemic** stroke.
  - It is correct to consider ischemic stroke as an **efficacy** outcome.
- A **hemorrhagic stroke or intracranial** hemorrhage is an **adverse** effect of anticoagulation.
  - Hemorrhagic stroke and intracranial hemorrhage should be considered **safety** outcomes.
- The primary **efficacy** outcome reported in the DOAC trials is a combination of stroke and systemic embolism. However the stroke component includes hemorrhagic stroke, which should be considered a **safety** outcome. This potentially biases results in favour of the DOACs.[44]

- In the individual trials, dabigatran 150 mg and apixaban were the only two DOACs to show statistically significant benefit in the primary outcome of stroke and systemic embolism compared with warfarin. However only dabigatran 150 mg showed benefit in decreasing **ischemic** stroke. (Note that RE-LY was an open label study which increases the risk of bias.) See Table 4.

Table 4: Results of DOAC studies: primary outcome and ischemic stroke

	Relative risk (95% confidence interval)		Number needed to treat (95% confidence interval)[a]	
	Primary Outcome	Ischemic Stroke	Primary Outcome	Ischemic Stroke
Dabigatran 110	0.91 (0.74 - 1.11)	1.11 (0.89 - 1.40)	NS	NS
Dabigatran 150	0.66 (0.53 - 0.82)	0.76 (0.60 - 0.98)	91 (59 - 194)	188 (96 - 4764)
Rivaroxaban	0.88 (0.75 - 1.03)	0.94 (0.75 - 1.17)	NS	NS
Apixaban	0.79 (0.66 - 0.95)	0.92 (0.74 - 1.13)	168 (95 - 773)	NS

a number needed to treat for length of studies (1.8 to 2 years).
NS Not statistically significant (Number needed to treat is given only for statistically significant results)

- Much of the benefit from DOACs compared with warfarin is due to reduction in intracranial hemorrhage.[42]
  - While ICH is a devastating outcome, it is uncommon.
  - In the DOAC studies ICH occurred in 1.3% of the warfarin group over approximately 2 years.
    - The relative risk reduction of ICH from DOACs was **large** (56%).
    - However the **absolute** benefit of treating with a DOAC instead of warfarin is **small**
    - The absolute risk reduction is 0.7%
    - The number needed to treat is 143 (95% CI 100-200). (If you treat 143 patients with a DOAC instead of warfarin for approximately 2 years, 142 would not benefit by avoiding an ICH.)
- Another consideration is that the rate of intracranial bleeding may be higher in the studies than in Canadian practice. In the studies, the rate of intracranial bleeding was approximately 0.7% per year in the warfarin group.
  - However an observational study of Ontario patients found the rate of intracranial bleeding in patients on warfarin was approximately 0.2% per year.[45]
  - Applying the relative risk reduction found in our meta-analysis to this 0.2% baseline yields an NNT of 894 (95% CI 736-1221) for 1 year. (If you treat 894 patients with a DOAC instead of warfarin for 1 year, 893 would not benefit by avoiding an ICH.)

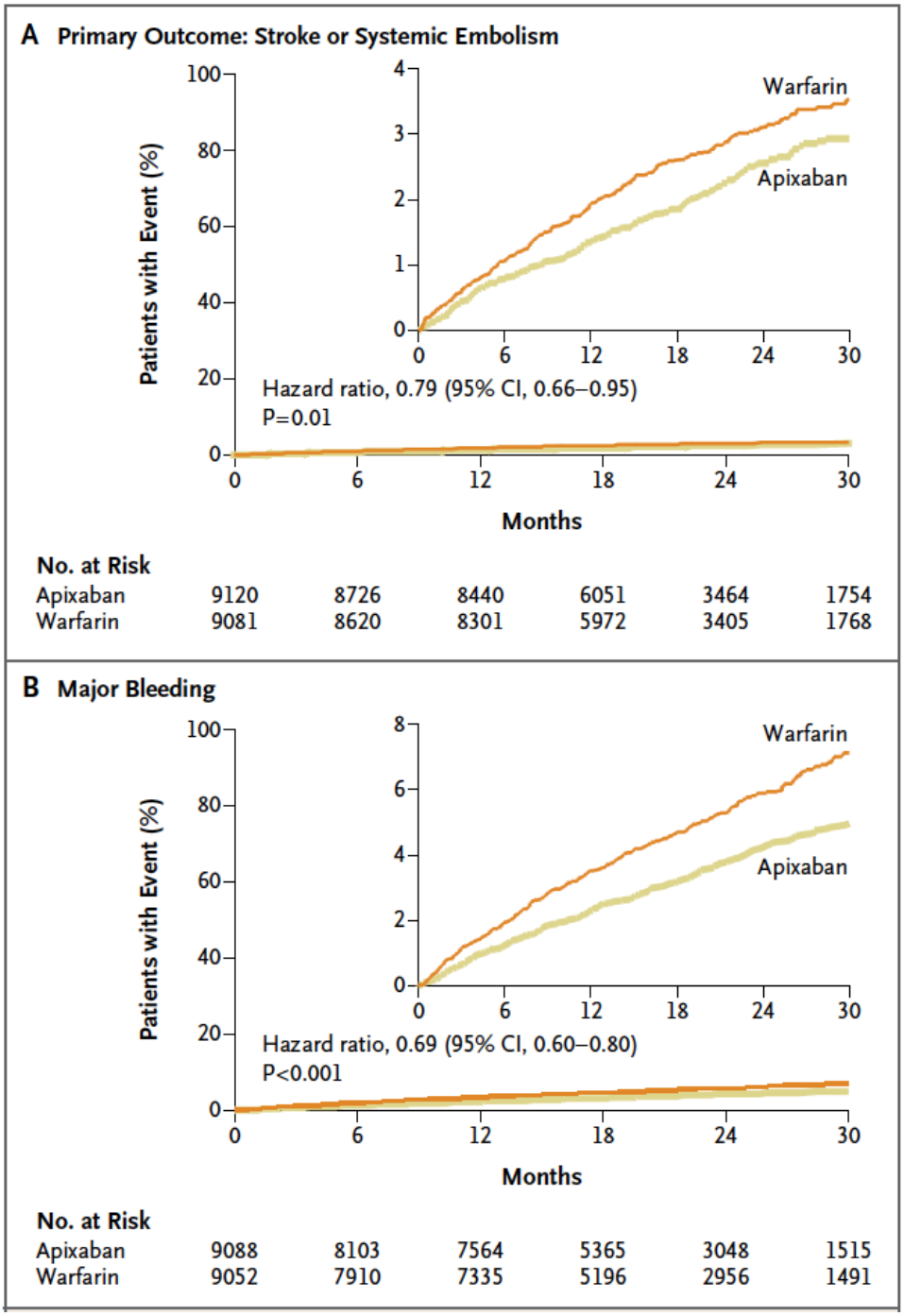

Figure 1 Primary efficacy and major bleeding outcomes of apixaban vs warfarin in ARISTOTLE. The inset shows the same data on an enlarged segment of the y-axis.

- The almost overlapping lines on the 100% scale show the small absolute benefit of apixaban versus warfarin. Similar images exist for RE-LY[37] (dabigatran) and ROCKET-AF[38] (rivaroxaban) trials.

From Apixaban versus Warfarin in Patients with Atrial Fibrillation, Granger CB, Alexander JH, McMurray JJV, et al. The New England Journal of Medicine 2011;365:981-92. Copyright © 2011 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

Major Bleeding

- While there was some variation in the definition of major bleeding among the DOAC studies, common features were:
  - Reduction of Hgb by at least 20 g/L
  - Transfusion of at least 2 units of packed red blood cells
  - Occurring at a critical site, (intracranial, intra-spinal, intra-ocular, pericardial, intra-articular, intra-muscular with compartment syndrome, retroperitoneal)
  - Causing permanent disability or death
- Overall, in meta-analysis, the DOACs do not provide statistically significant benefit in reduction of **major bleeds**.
- However, in the individual studies
  - Dabigatran 110 mg and apixaban resulted in fewer major bleeds.
  - Dabigatran 110 mg and apixaban did not significantly increase major GI bleeds; dabigatran 150 mg and rivaroxaban did significantly increase major GI bleeds.

Mortality

- Overall, in meta-analysis, there was a decrease in mortality with an 11% relative risk reduction (absolute risk reduction 0.7%, number need to treat 143 (95% CI 91 to 333) for 2 years.
  - While the point estimates of all the DOAC studies indicated a benefit in mortality, only apixaban achieved statistical significance (relative risk reduction 10.3%; absolute risk reduction 0.8%; number needed to treat 132, 95% CI 67 to 6951).

Effect of time in therapeutic range (TTR) of warfarin on clinical outcomes

- While it is ideal that a patient's INR should be in the therapeutic range 100% of the time, this is not usually possible. It is suggested that a patient's INR should be in the therapeutic range (INR 2-3) at least 65% of the time.[23]
- In North America and Europe in RE-LY and ROCKET AF the TTR of patients on warfarin was 63% to 70% while in Asian and Latin American countries it was below 50%.[46]
- Some benefits of the DOACs compared with warfarin depended on percentage of time which patients on warfarin spent within the therapeutic range.[41,42]
  - However, these results should be **treated with caution** because patients were not randomized to different levels of TTR. It is possible that patients with higher TTR received better overall care, were more adherent to care recommendations, or were at lower risk than those with lower TTRs.

B. Convenience

- The DOACs have a rapid onset of action, with anticoagulant levels of drug achieved within several hours of ingestion.
  - This can be helpful in circumstances where a DOAC is indicated (such as with a new diagnosis of AF in a high risk patient in the Emergency Department), and when it may take several days for the patient to be seen in follow up with their primary health care provider.
  - Rapid onset of the DOACs eliminates the need for parenteral bridging therapy when anticoagulation is needed quickly.
- The DOACs do not currently require regular anticoagulation monitoring thus relieving the patient from the burden of going for blood tests and the physician from the burden of following them. However since the DOACs are partially excreted renally, it is important to monitor renal function and adjust the dosage accordingly.[47] See page 29 for more information on adjusting doses for renal insufficiency.
- Rivaroxaban is given once daily in AF patients while dabigatran and apixaban are given twice daily, a consideration for convenience, but also for patient adherence.
- Guidelines from the European Heart Rhythm Association point out that prescribing the DOACs requires vigilance because this is a new class of drugs with potentially serious complications and the patients taking them may be fragile.[48] The guideline suggests patients be reviewed regularly, preferably every 3 months with consideration of:
  - Therapy adherence; (ideally with inspection of the prescribed medication in blister packs or bottles), in addition to appropriate questioning;
    - Dabigatran requires an acidic environment for absorption and has an acidic coating leading to a high incidence of dyspepsia and drop-out[37]
    - Dabigatran SHOULD NOT be removed from its packaging until it is to be taken. Dabigatran CANNOT be combined with other medications in blister packs.
  - Events that might signal thromboembolism in the cerebral, systemic, or pulmonary circulations;
  - Adverse effects, particularly bleeding events (occult bleeding may be revealed by falling hemoglobin levels);
  - Co-medications, prescribed or over-the-counter; and
  - Blood sampling for hemoglobin, and renal and hepatic function should be done annually or more frequently if indicated. For example
    - 6 monthly if CrCl 30–60 ml/min, or if on dabigatran and >75 years or frail.

C. Food and Drug Interactions

- Unlike warfarin, the DOACs do not have any known food interactions.
- At present, the information about DOAC drug interactions is limited and likely to change.

- Like warfarin, some drugs affect the anticoagulant activity of the DOACs.
  - Some relevant drug interactions are those with antifungal agents, verapamil, amiodarone, macrolides, and NSAIDs.[47,48,49] Please consult a pharmacist for up to date information.
- Unlike warfarin, there is currently no method to evaluate the impact of drug interactions on the anticoagulant effect of the DOACs.[49]

Summary of Question 3

- The DOACs are similar to warfarin in most clinical outcomes.
- The DOACS do show a statistically significant reduced risk of causing an intracranial hemorrhage compared with warfarin but the absolute reduction is small.
- An advantage of the DOACs is that there is no current requirement for routine monitoring of their anticoagulation effects.

Question 4. What are the disadvantages of DOACs compared with warfarin?

- Much of the potential risk associated with the DOACs arises from the limited clinical experience with these drugs.
- The medications will be given for many years, as long as the patient has AF; however the randomized controlled studies of the drugs approved in Canada only lasted approximately 2 years.

Specific areas of uncertainty are:

- Patients aged > 80 years: The median age in the three major studies was approximately 72 years. About 20% of patients in the DOAC studies were 80 or over but this age group was not reported separately. Many patients with AF are in their 80s and more likely to have comorbidities.
- Impaired hepatic function: Patients with active liver disease were excluded from all three major DOAC trials.
  - Like warfarin, patients with elevated serum transaminases exceeding twice the upper limits of normal should not generally be started on DOACs especially in the presence of laboratory signs of hepatic coagulopathy.
  - Patients with slightly elevated transaminases and/or bilirubin can take DOACs, however they require monitoring of abnormal liver transaminases, beginning within 3 months of anticoagulation initiation.
  - DOACs can cause transient elevation of hepatic transaminases in about 2% of patients which requires drug withdrawal. Liver enzymes usually return to normal within 2 weeks. In this case, switch to another class of OAC.[50]

- Thrombocytopenia: Generally, patients with platelet counts less than 100,000/µl were excluded from the studies. A platelet count between 50,000/µl and 100,000/µl is not a contraindication for oral anticoagulants but careful monitoring is recommended. Patients with a persistent platelet count of 50,000/µl or less **should not take any OAC (DOAC or warfarin)**.
- Concomitant antiplatelet therapies:

  The combination of warfarin and antiplatelet therapy is occasionally used in patients with AF and coronary artery disease. The following summarizes the data available on DOACs with antiplatelet drugs.

  - *Aspirin*
    - Low-dose aspirin was allowed in the DOAC studies; 30-40% of patients were on aspirin.
    - Like warfarin, DOAC plus aspirin therapy increases the risk of bleeding by about 60% compared with DOAC alone.[48]
  - *Clopidogrel, prasugrel, or ticagrelor*
    - Little is known about combining DOACs with clopidogrel, prasugrel or ticagrelor. Such therapy should be avoided, where possible, due to the likely increased risk of bleeding.[51] DOAC product monographs comment that prasugrel and ticagrelor have not been studied with DOACs and are not recommended as concomitant therapy.
- *Triple antithrombotic therapy (DOAC plus two antiplatelet agents)*
  - Few patients were on triple therapy in the major studies. The 2012 Canadian Best Practice Recommendations for stroke care make the following statement:[10]
    - Concomitant antiplatelet therapy with oral anticoagulation is **not recommended** in patients with AF unless there is a specific medical indication such as a coronary stent.
- Patients with previous bleeds on OACs: Generally the major studies excluded patients with any previous intracranial or intra-ocular bleeding as well as GI bleeding occurring up to one year before study entry. None of the 3 major DOAC trials reported the HAS-BLED scores of study subjects. Therefore little is known about the use of DOACs in this setting.
- Patients with valvular defects: Patients with hemodynamically significant valve disease were **excluded** from RE-LY[37], ARISTOTLE[39], and ROCKET-AF[38].
  - Most experts agree that either warfarin or DOACs can be used in patients with AF and concomitant **inconsequential** valvular disease. Clinically, if no heart murmur or heart failure is present, warfarin or DOACs can be started while waiting for ECHO results to definitively exclude mitral stenosis.

- Patients with prosthetic valves:
  - There are two main types of prosthetic heart valve design: *mechanical* and *bioprosthetic*.
  - A study comparing dabigatran and warfarin in patients with mechanical heart valves was stopped early because of more thrombotic events in the dabigatran group.[5]
  - Rivaroxaban and apixaban have not been studied in patients with prosthetic heart valves (mechanical or bioprosthetic).
  - Manufacturers **do not recommend** DOACs be used in patients with prosthetic valves.
- Patients with recent stroke:
  - All three major studies excluded patients with recent stroke, the definition of which varied from disabling stroke within 6 months (RE-LY[37]) to any stroke within 7 days (ARISTOTLE[39]).
  - In some patients, stroke is their first indication of AF. The optimal timing of OAC initiation after acute stroke, for the prevention of subsequent stroke, is not clearly defined. Such patients should be reviewed with a stroke specialist.
  - The 2012 Canadian Best Practice Recommendations for stroke care make the following statements:
    - "It is common practice to wait two to fourteen days and repeat brain imaging (CT or MRI) to rule out asymptomatic intracranial hemorrhage before starting warfarin.
    - Physicians will often use the size of the infarct and other clinical circumstances to help judge timing to initiate anticoagulation. For example, in patients with very small strokes on imaging, anticoagulation may be initiated immediately; in patients with large strokes, initiation of anticoagulation may be deferred for several weeks."[10]
- Patients with less recent stroke:
  - All three major trials included patients with previous stroke, TIA, or systemic embolism. There was no difference in efficacy or safety in patients who did or did not have a previous stroke, TIA, or systemic embolism.[39,42,52]
- Patients with stroke while on anticoagulant therapy
  - Stroke can occur even in well-anticoagulated patients as no treatment decreases risk by 100%. In such an event, it is important to check the INR if the patient is on warfarin or patient adherence if on a DOAC.
    - If despite skillful management of the warfarin dose, INR cannot be maintained within therapeutic range, the patient may benefit from treatment with a DOAC.
    - If INR is therapeutic or the patient is adherent to DOAC therapy, search for other causes of stroke. It may be helpful to consult with a stroke specialist.

        - Some specialists suggest switching to another OAC if no reasonable cause is found for the stroke although there is no evidence to support or refute this approach.
    - Clinical study data regarding the timing and method of re-institution of OAC after stroke are lacking. Referral to a stroke specialist is recommended.

- Other disadvantages of the DOACs compared with warfarin include
    - Need to change dose for impaired renal function: Patients with CrCl <30mL/min were excluded from both ROCKET-AF[38] and RE-LY[37]. ARISTOTLE[39] excluded those with a CrCl <25 ml/min. The following are recommendations for each DOAC.
        - Dabigatran[4]
            - Should not be used in patients with CrCl <30 ml/min
            - Decrease dose to 110 mg bid for those age ≥ 80 OR for age ≥ 75 with a risk factor for bleeding (CrCl = 30-50 mL/min, concomitant treatment with P-glycoprotein inhibitors, antiplatelets or a previous GI bleed).
        - Rivaroxaban[4]
            - Should not be used in patients with CrCl <30 ml/min
            - Dose should be decreased to 15 mg/day with CrCl 30-49 ml/min
        - Apixaban[4]
            - Has a lower rate of renal excretion and based on kinetics may be a better choice in people with impaired renal function.
            - Should not be used in patients with CrCl <15 ml/min
            - In patients with CrCl 15-24 ml/min, no dosing recommendations can be made
            - For CrCl 25-30 ml/min no dose adjustment is necessary but
                - Reduce dose to 2.5 mg twice daily if the patient has any 2 of the following:
                    - Serum creatinine ≥ 133 µmol/L or
                    - ≥ 80 years, or
                    - ≤ 60 kg

    - Rapid dissipation of antithrombotic effect in case of bleeding / decreased antithrombotic effect if poor adherence
        - Based on half-lives, it is predicted that the antithrombotic effect of the DOACs fades rapidly **12 to 24 hours** after the last dose.[48]
        - Thus their effect will rapidly dissipate if there is a need to decrease their anticoagulation effect. This is not desirable in routine care, but may be an advantage when preparing for surgical procedures where the surgeon wishes to stop the drug in advance, as no bridging is needed.[53]
        - Patients must be strongly advised to take DOACs regularly so they are not at risk of a thrombotic event. There are no data yet on the actual compliance rates of patients on DOACs outside of trial conditions.

- Lack of requirement for regular blood tests for anticoagulation effect also means a lack of ability to monitor level of anticoagulation
  - There is currently no readily available way to monitor the blood levels or associated effectiveness of the DOACs in routine clinical practice. Work is underway to develop DOAC assays; these will likely be commercially available within the next several years.
  - While it is convenient for the majority of patients not to need regular blood tests for monitoring the anticoagulation effectiveness of DOACs, there are times when it would be helpful to have the ability to assess the effect of the drugs:
    - If major bleeding occurs to determine if the cause is high drug levels or another etiology.
    - Before some surgical procedures.
    - Identification of sub or supra-therapeutic levels in some patients
      - Taking drugs known to interact
      - At extremes of body weight
      - With uncertain absorption (i.e. gastric-bypass, lap band surgery for obesity or resection of large portions of the small bowel)
      - Deteriorating renal function
    - Assessing adherence in patients suffering thrombotic events while on treatment.[32]
  - The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in AF patients in the RE-LY trial has been analyzed.[54]
    - The investigators concluded that ischemic stroke and bleeding outcomes were correlated with dabigatran plasma concentrations. Age was the most important covariate and individual benefit-risk might be improved by tailoring dabigatran dose after considering selected patient characteristics.
    - This publication has received attention in the media as the published article was revised from the original paper because of concerns within the manufacturing company that the original paper might jeopardize sales. The original paper stated
      - Patients with extremely low levels of dabigatran, e.g., below 35 ng/ml were at higher risk of stroke while levels above 250 to 300 ng/mL were associated with a higher risk of major bleeding.
      - Up to 20% of patients treated with 110 and 150 mg doses in RE-LY may fall outside this range.
      - Monitoring of plasma dabigatran concentrations or antithrombotic activity e.g. aPTT would be required to identify these patients and that a dose adjustment could improve the benefit/risk ratio.

- A New York Times article, with the original paper and company emails are at http://bit.ly/nytimes_pradaxa
- A recent BMJ feature article provides important details about the lack of transparency in publications regarding the monitoring of dabigatran, including the publication mentioned above.[55]
- Other authors have noted the wide variability of dabigatran plasma concentrations and have expressed the need to be able to monitor the effects of DOACs.[49,56,57]
- Currently, plasma levels are not readily available and are not standardized between labs. The Hemoclot test is a dilute thrombin time test that measures the activity of dabigatran and is standardized, but it is not available in Nova Scotia. (It is available in Europe.)

- **Lack of antidote**
  - There are currently no specific antidotes to reverse the anticoagulant effects of dabigatran, rivaroxaban, or apixaban. However some are in clinical development and may be commercially available within the next 18-24 months.
  - A lack of antidote is often perceived as a limitation of the DOACs compared with warfarin since warfarin has effective reversal agents available. However the clinical relevance of this perceived limitation is dependent on the presenting clinical problem.
    - For **minor** bleeds and **elective** surgery there is **no definitive clinical superiority** of vitamin K as a reversal agent for warfarin compared to the rapid dissipation of the DOACs antithrombotic effect.
      - After discontinuing DOACs, their short half-lives lead to a rapid decrease of anticoagulant effect so they typically wear off in the time that it takes Vitamin K to reverse the effects of warfarin.
      - The only exception may be in patients with decreased renal function taking dabigatran. Dissipation of antithrombotic effect may take up to 72 hours.
    - For **major** bleeds (not ICH) and **urgent** surgery there **is potential clinical superiority** of 4-factor PCC as a reversal agent for warfarin compared to the rapid dissipation of the DOACs.
    - In patients with ICH on warfarin, 4-factor PCCs restore INR to normal within minutes and attenuate hematoma expansion, but the limited data to date indicate clinical outcomes are poor.[33,34]
    - **The take home message is that ICH should be prevented**. This is best accomplished by treating underlying risk factors for ICH, the most important being hypertension. See page 17 for risk factors for ICH.
    - See page 15 for further details on warfarin reversal agents.

- Until the availability of an approved antidote, the Nova Scotia Provincial Blood Coordinating Program has developed an algorithm for managing patients on DOACs who experience bleeding. (Appendix 4)

Cost

- The DOACs are considerably more expensive than warfarin. This may be an important consideration for patients who do not have a drug plan that will cover the cost of the DOAC.
- For Nova Scotians covered by Senior's Pharmacare (and in some instances, for persons receiving Family Pharmacare), there are circumstances where the DOACs can be covered under an "exceptional" circumstance (See box.)

Criteria for Nova Scotia Pharmacare coverage of DOACs

Inclusion Criteria:

At-risk[1] patients with non-valvular AF who require a DOAC for the prevention of stroke and systemic embolism AND in whom:

- Anticoagulation is inadequate[2] following a reasonable trial[3] on warfarin; OR
- Anticoagulation with warfarin is contraindicated or not possible due to inability to regularly monitor via INR testing (i.e. no access to INR testing services at a laboratory, clinic, pharmacy, and at home)

Exclusion Criteria:

- Patients with impaired renal function[4] (creatinine clearance < 30mL/min for dabigatran and rivaroxaban; < 25 ml/min for apixaban) OR
- ≥ 75 years of age and without documented stable renal function[5] OR
- Hemodynamically significant rheumatic valvular heart disease[6], especially mitral stenosis; OR
- Prosthetic heart valves.

*Please Note: Patients starting a DOAC should have ready access to appropriate medical services to manage a major bleeding event.

1. *At risk patients with non-valvular atrial fibrillation are defined as those with a $CHADS_2$ score of ≥ 1.*
2. *Inadequate anticoagulation is defined as INR testing results that are outside the desired INR range for at least 35% of the tests during the monitoring period (i.e. adequate anticoagulation is defined as INR test results that are within the desired INR range for at least 65% of the tests during the monitoring period).*
3. *A reasonable trial on warfarin is defined as at least two months of therapy.*
4. *Since renal impairment can increase bleeding risk, renal function should be regularly monitored. Other factors that increase bleeding risk should also be assessed and monitored (see DOAC Product Monographs).*
5. *Documented stable renal function is defined as creatinine clearance or estimated glomerular filtration rate that is maintained for at least three months.*
6. *There is currently no data to support that dabigatran provides adequate anticoagulation in patients with rheumatic valvular disease or those with prosthetic heart valves, so dabigatran is not recommended in these populations.*

The exception status form can be found at: http://bit.ly/DOAC-request

Question 5. What are the current recommendations?

Guidelines

- A number of guidelines on the management of AF have been published that include detailed discussions on the management of OAC therapy. See Table 5 for summary of recommendations.

Table 5: Comparison of guideline recommendations for stroke prophylaxis

AAN[58]	ACC, AHA and HRS[8]	ESC[9]	CBP[10]	CHEST-ACCP[59]	CCS[7]
Recommend risk assessment but not specific tools. Decisions to treat based on preferences and values not absolute thresholds on risk assessment tools. OAC not recommended in lone AF (Level C) OAC recommended in patients with hx of TIA or stroke (Level B) Options include warfarin, dabigatran, rivaroxaban, apixaban (Level B) When warfarin not an option, apixaban is recommended over dabigatran and rivaroxaban (Level B) DOAC recommended when patient at higher risk of ICH (Level B)	$CHADS_2$ not used CHA_2DS_2VASc recommended (1B) CHA_2DS_2VASc **≥ 2** - OAC recommended (1A) CHA_2DS_2VASc **=** 1 - Consider no therapy, an OAC or ASA (2b C) CHA_2DS_2VASc **=** 0 - No therapy (2a B) Options include warfarin (1A), dabigatran, rivaroxaban, apixaban (1B)	$CHADS_2$ not used CHA_2DS_2VASc recommended (1A) CHA_2DS_2VASc **≥ 2** - OAC recommended (1A) CHA_2DS_2VASc **≥1** — OAC should be considered (2aA) CHA_2DS_2VASc = **0** — no therapy (1B) Dabigatran, rivaroxaban & apixaban should be considered over warfarin (Level 2aA) If OAC refused, ASA + clopidogrel or less effectively, ASA monotherapy (2aB)	$CHADS_2 \geq 2$ - OAC recommended Options include warfarin (1A), dabigatran, rivaroxaban, or apixaban (1A); $CHADS_2$ =1 - OAC recommended in most. Options include warfarin (1A), dabigatran, rivaroxaban, or apixaban (1B); ASA alternative in some lower risk (1A) $CHADS_2$ = 0 – ASA (Level A) As part of the risk stratification, patients should be assessed for additional risk factors for stroke, including age 65-74yr, female sex, and presence of vascular disease.	$CHADS_2$ **≥ 1 -** OAC recommended (1A) $CHADS_2$ = **0** – No therapy [ASA if therapy requested (2B)] Dabigatran recommended over warfarin (Grade 2B) If OAC unsuitable, ASA + clopidogrel recommended	An updated (2014) "CCS algorithm" based on the $CHADS_2$ model is recommended for risk assessment which includes some, but not all, of the CHA_2DS_2VASc criteria (Strong Recommendation High - Quality Evidence) **$CHADS_2$≥ 1** - OAC recommended for most (Strong Recommendations, Moderate- Quality Evidence) $CHADS_2$ = **0 - If ≥ 65 years old** - OAC recommended for most (Strong Recommendations, Moderate- Quality Evidence) If <65 years old with arterial disease - ASA recommended (Conditional[a] Recommendation, Moderate-Quality Evidence). If <65 years old & no arterial disease - no treatment (Conditional[a] Recommendation, Low-Quality Evidence). When OAC recommended dabigatran, rivaroxaban & apixaban recommended over warfarin. (Strong Recommendation, High-Quality Evidence).

OAC - oral anticoagulant; ICH – intracranial hemorrhage; AAN – American Academy of Neurology; ACC, AHA and HRS - American College of Cardiology, American Heart Association, Heart Rhythm Society; CCS - Canadian Cardiovascular Society; ESC - European Society of Cardiology; CBP – Canadian Best Practice recommendations for stroke care; CHEST ACCP- American College of Chest Physicians

[a] A conditional recommendation is a weak recommendation

Note about table 5

- The 2014 ACC, AHA and HRS guidelines[8] take a cautionary individualized approach and suggest that the approved DOACs are **on par** with warfarin rather than preferable to warfarin because of concerns about their use in renal failure, safety in the absence of antidotes, and cost that could affect affordability and patient compliance.
- The 2012 Canadian Best Practice recommendations for stroke care[10] and the 2014 AAN[58] guidelines also recommend **either** the DOACs or warfarin. They state the choice of OAC should be based on patient factors including age, renal function, additional health factors, likelihood of compliance, and patient preferences.
- In contrast, the DOACs are broadly recommended as **preferable to** warfarin in the 2014 CCS,[7] the 2012 ECS,[9] and the 2012 Chest ACCP guidelines.[59]

Canadian Agency for Drugs and Technologies in Health (CADTH)

- **CADTH** reviewed clinical and economic evidence for the use of warfarin and the DOACs for stroke prevention in patients with non-valvular AF (Preventing Stroke in Patients with Atrial Fibrillation www.cadth.ca/clots).
- They make the following conclusions:
  - Warfarin is the recommended first-line therapy for preventing stroke in patients with AF.
  - DOACs are a **second line** option for some patients with non-valvular AF not doing well on warfarin.
    - Compared with warfarin, the benefits of the DOACs are small.
    - Bleeding risks for patients treated with the DOACs compared with warfarin were similar overall, with a modest decrease in intracranial bleeding and small increase in GI bleeding. There is no reversal agent or proven management strategy if bleeding occurs with the DOACs.
    - DOACs are more expensive than warfarin and little is known about their long-term safety.

National Institute of Clinical Excellence (NICE)

- NICE recently (2014) updated clinical guideline 36 (2006)[64], titled "Atrial Fibrillation: The management of atrial fibrillation". http://bit.ly/NICE-AF
- They make the following recommendations:
  - Use CHA_2DS_2VASc to assess stroke risk.
  - Offer an OAC to people with a CHA_2DS_2VASc score ≥ 2 taking bleeding risk into account.
  - Consider an OAC for men with a CHA_2DS_2VASc score = 1, taking bleeding risk into account.
  - Apixaban, dabigatran, and rivaroxaban are recommended as **options** to warfarin.
  - Do **not** offer ASA monotherapy solely for stroke prevention in people with atrial fibrillation.

Management of DOACs in patients undergoing interventions

- The 2014 focused update from the Canadian Cardiovascular Society[7] provides recommendations for periprocedural anticoagulation management. The document is available at http://dx.doi.org/10.1016/j.cjca.2014.08.001
  - The risk of a thromboembolic event while the antithrombotic is reduced or stopped must be weighed against the risk of bleeding during or after the procedure.
  - Major patient factors that suggest a greater risk of a thromboembolic event are recognized by a higher CHA_2DS_2VASc score, recent (< 3 months) stroke or TIA, mechanical prosthetic heart valve, or rheumatic heart disease.
  - Major patient factors that suggest a higher risk of bleeding are reflected in a higher HAS-BLED score.
  - Major procedural factors that suggest a higher risk of bleeding are when periprocedural hemostasis might be difficult to achieve and/or when a patient would be put at significant risk should bleeding occur.
  - Ideally, interventions with clinically important bleeding should involve a discussion with the surgeon.
- Thrombosis Canada, available at http://bit.ly/ThrombCan_Warf_Periop has categorized population risk for major bleeding as very low, low, intermediate and high risk.
  - Procedures with a very low or low probability of major bleeding can usually be safely performed without interruption of antithrombotic therapy (provided, in the case of warfarin that the INR is not supratherapeutic).
    - Very low risk procedures include
      - Dental extractions (1 or 2 teeth) or teeth cleaning
      - Skin biopsy or skin cancer removal
      - Cataract removal
    - For other procedures at increased risk, please refer to the CCS guidelines.

- The absence of a proven antidote for the DOACs along with interindividual variability in their elimination half-lives suggest a conservative approach for recommendations regarding the use of these drugs around the time of procedures during which any bleeding could confer serious adverse outcomes. Therefore, the DOACs **should not be used** in the perioperative period when neuraxial anaesthesia or lumbar puncture is planned.[7]
- The 2014 CCS[7] comments that reported experience with the DOACs in the periprocedural period is limited and so recommendations regarding their use are necessarily empirical.
- When the decision is made to interrupt DOAC therapy, the CCS suggests

  Stopping DOACs

  - Apixaban and rivaroxaban should be **stopped** 24-48 hours prior to a procedure with low risk of major bleeding and 48-72 hours prior to procedures associated with intermediate or high risk of major bleeding.
  - Dabigatran's pre-intervention termination depends on renal function. (Table 6)

Table 6: Recommendations for last intake of dabigatran before intervention

CrCl	Low risk of major bleed	Higher risk of major bleed
CrCl ≥ 80 ml/min	≥ 24 hours	≥ 48 hours
CrCl 50-80 ml/min	≥ 48 hours	≥ 72 hours
CrCl 30-50 ml/min	≥ 72 hours	≥ 96 hours

  Restarting DOACs

  - After invasive procedures **restarting** DOACs is often deferred 48 hours after a procedure with low risk of bleeding and 72 hours for a procedure with an intermediate or high risk of bleeding.[7]
  - Maximal anticoagulation effect of the DOACs is achieved within 2 hours of ingestion.[48]
  - Based on kinetics, bridging is not necessary in DOAC treated patients since the predictable waning of effect allows properly timed short term stopping and restarting of therapy before and after surgery.[60]

- **Urgent Interventions**
  - The DOAC should be discontinued if an emergency intervention is required. If possible, the intervention should be deferred for at least 12 hours and ideally 24 hours after the last dose of DOAC.[48]

How to manage DOAC dosing errors

- **Missed dose**
  - A missed dose should be taken only if remembered within a certain time frame.
    - Dabigatran or apixaban up until 6 hours after the scheduled intake;
    - Rivaroxaban up until 12 hours after the scheduled intake.
  - Beyond that time the dose should be skipped and the next scheduled dose taken.[48]
- **Double dose**
  - If two doses of[48]
    - Dabigatran or apixaban are taken at once, there are two options:
      1. Take the next scheduled dose at the usual time
      2. Miss the next scheduled dose 12 hours later and resume regular dosing 24 hours after the double dose ingestion.

         For example option 1 might apply to a patient with normal body weight and renal function.

         Option 2 might apply to a patient with low body weight and poor renal function.
    - Rivaroxaban are taken at once, the patient should continue the normal dosing regimen.
- **Overdose**
  - Action depends on the amount of the suspected overdose. Hospitalization for monitoring and urgent measures should be advised if the patient is currently bleeding or excessive intake is suspected. See appendix 4 for management of bleeding in patients taking DOACs.
  - In case of a suspected overdose without bleeding, a wait-and-see management can be recommended in many cases given the short half-life of the DOACs.[48]

Switching between warfarin and DOACs

- Switching from warfarin to a DOAC
  - After stopping warfarin, you should wait until the INR is ≤2.0 before starting a DOAC. Maximal anticoagulation effect of the DOACs is achieved within 2 hours of ingestion. If INR testing is not readily available, it is reasonable to wait 2-3 days after the last dose of warfarin before starting a DOAC. http://bit.ly/ThrombCan_DOAC_Warf
- Switching from a DOAC to warfarin[4]
  - The DOAC and warfarin should be given together until the INR is in a range that is considered appropriate. Dabigatran, which is primarily excreted by the kidneys, is cleared more slowly in patients with diminished renal clearance. As a result the duration of overlap with dabigatran and warfarin is dependent on CrCl. The better the CrCl, the longer the overlap;

- For rivaroxaban and apixaban, start warfarin and discontinue the DOAC when INR ≥ 2.
- For dabigatran and a CrCl > 50 ml/min, start warfarin 3 days before discontinuation of dabigatran.
- For dabigatran and a CrCl 31-50 ml/min, start warfarin 2 days before discontinuation of dabigatran.

- If switching from DOAC to warfarin, the DOAC (especially the Factor Xa Inhibitors) may affect the INR measurement while on combined treatment during the overlap phase.
  - INR should be measured just before the next dose of the DOAC during concomitant administration and be re-tested 24 hours after the last dose of DOAC (on sole warfarin therapy).[48]

Question 6: What are the special considerations for the elderly (≥ 75 years)?

Background

- Atrial fibrillation affects up to 10% of those aged 80 years and older. AF is associated with a four to five-fold increase in the risk of ischemic stroke and this risk increases with age.
  - The Framingham Heart Study found that up to 36% of strokes were attributable to AF in patients aged 80 years, compared with 21% in those aged 70–79 years and 8% in those aged 60–69 years.[2]
- Age alone is included as a risk factor in stroke and bleed risk-stratification schemes. Age 75 and older contributes 2 points toward a maximum score of 9 in the CHA_2DS_2VASc score and 1 point toward a maximum risk score of 6 in the $CHADS_2$ score. Age 65 and older contributes 1 point in the HAS-BLED risk score.
- Elderly adults are also more likely to possess other risk factors included in the stroke and bleed risk-stratification schemes, such as hypertension, prior stroke, diabetes mellitus, and heart failure.
- Age and impaired renal function, significant risk factors in both stroke and bleed risk, increase the risk of frailty. Bleed risk may be particularly high in the frail elderly due to the presence of other bleed risk contributors such as low body weight. All patients require careful evaluation of the risks and benefits of treatment before starting OACs, especially those 80 years of age or older with impaired renal function.
- A risk of falls and subsequent subdural or intracranial hemorrhage may unnecessarily discourage elderly patients from being put on warfarin.
  - For instance, an extensive analysis of patients ≥ 65 years old with atrial fibrillation found that a patient with an annual stroke risk of 5% would need to fall 295 times for fall risk to outweigh stroke reduction benefit of warfarin.[17]

Evidence

- The BAFTA trial[19] randomized 973 patients ≥ 75 years old with atrial fibrillation to treatment with warfarin (INR 2 – 3) or aspirin 75 mg once daily. The warfarin group had fewer strokes than the aspirin group (1.6% per year vs 3.4% per year; ARR 1.8%; NNT 56). There was no difference in major bleeding (1.9% per year vs 2.0% per year).
- In the DOAC trials approximately 40% of patients were over 75 years old.
- About 20% of patients in the DOAC studies were 80 or over but this age group was not reported separately. Many patients with AF are in their 80s and more likely to have comorbidities.
- A meta-analysis of DOACs versus warfarin specifically looking at the elderly population (≥ 75 years old) was performed on the recent trials of AF and VTE applications.[61]
  - The meta-analysis included studies comparing DOACs to warfarin, aspirin, placebo, and enoxaparin.
  - We extracted data from the trials comparing DOACs to warfarin (RE-LY, ROCKET AF, and ARISTOTLE) and performed a meta-analysis for the outcomes of stroke/systemic embolism and major bleeding.
  - Overall results were similar in the elderly and in the general population. While this is reassuring, it is important to note that patients in the studies were healthier with less comorbidity, better physical and cognitive function, and less polypharmacy than the typical elderly adult population in practice.[61] It is therefore uncertain if the results apply to the frail elderly and those with increased risk of bleeding.
- In a study relating various factors to plasma levels of dabigatran, age was found to be a major determinant of plasma level which was approximately 67% higher in patients >75 years old compared with those <65 years old. Plasma levels in turn are related to the risk of bleeding. Concomitant aspirin use was also related to increased risk of bleeding.[54]

Implications for Practice

- The benefit of antithrombotic therapy is well established in elderly adults, including those who are at high risk of falling or bleeding. The current studies suggest that DOACs are similar in effect to conventional anticoagulants in elderly adults. Old age per se should not be a criterion for withholding anticoagulation with DOACs.
- Our content expert suggests warfarin may be a familiar medication to physicians who deal with the elderly and LTC facilities, who have an established understanding of warfarin's nuances and monitoring. When there are issues with medication compliance, as may be the case for patients with dementia who may intermittently refuse medications or skip a day in a blister pack, warfarin has a more forgiving dosing schedule.
- Assessing **renal function** is essential when using the DOACs in patients, and it is suggested that for those over age 75 it should be done every 6 months.[48,61] It is important to use a validated formula to assess renal function and not just consider serum creatinine.

- The Cockcroft-Gault equation has been validated for adjusting drug doses in renal impairment whereas the eGFR has not.
- When using the Cockcroft-Gault equation the patient should be weighed to provide accurate information on body weight.
- Consideration should be given to withdrawing DOACs in situations with acute deterioration of renal function.

- It is important to make sure patients are not taking aspirin concomitantly with warfarin or a DOAC except in cases of acute coronary syndrome or post-stent placement.
- The consequences of stroke may often have important clinical implications in functioning.
  - In a fit elderly person, stroke versus bleeding benefit is easy to assess.
  - Even a minor stroke in a person with frailty may impact ADL/IADL functioning to the point that they may require a move to a nursing home.

Dosing

- The following summarize recommendations from product monographs for dosing the DOACs in the elderly:
  - Dabigatran – 110 mg bid for those age ≥ 80 OR for age ≥ 75 with a risk factor for bleeding (CrCl = 30-50 mL/min, concomitant treatment with P-glycoprotein inhibitors, antiplatelets or a previous GI bleed).
  - Rivaroxaban – No dose change for age but decreased dose to 15 mg once daily with CrCl 30-49 mL/min/1.73 m^2
  - Apixaban – Has a lower rate of renal excretion and based on kinetics may be a better choice in people with impaired renal function.
    - Should not be used in patients with CrCl <15 ml/min
    - In patients with CrCl 15-24 ml/min, no dosing recommendations can be made
    - For CrCl 25-30 ml/min no dose adjustment is necessary but
      - Reduce dose to 2.5 mg twice daily if the patient has any 2 of the following:
        - Serum creatinine ≥ 133 µmol/L or
        - Age ≥ 80 years, or
        - Body weight ≤ 60 kg

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APPENDIX 1

Estimating Stroke Risk using $CHADS_2$

- **$CHADS_2$** The **C**ongestive heart failure, **H**ypertension, **A**ge > 75, **D**iabetes Mellitus, and Prior **S**troke or Transient Ischemic Attack ($CHADS_{2)}$ index assigns points as indicated in the table below.
  - It has been well validated with an annual stroke rate increasing by approximately 2.0% for each 1-point increase in $CHADS_2$ score.[62]

$CHADS_2$ Index

	$CHADS_2$ Risk Criteria	**Score**
C	Congestive heart failure	1
H	Hypertension	1
A	Age ≥ 75	1
D	Diabetes mellitus	1
S_2	History of stroke or TIA	2

Risk of stroke stratified by $CHADS_2$ Score

$CHADS_2$ Score	**Incidence of stroke (95% CI)**
0	1.9 % (1.2-3.0)
1	2.8 % (2.0-3.8)
2	4.0 % (3.1-5.1)
3	5.9 % (4.6-7.3)
4	8.5 % (6.3-11.1)
5	12.5 % (8.2-17.5)
6	18.2 % (10.5-27.4)

APPENDIX 2: DOAC trial characteristics

	RE-LY[37] (Median 2 yrs)			ROCKET-AF[38] (Median 1.9 yrs)		ARISTOTLE[39] (Median 1.8 yrs)	
DOAC	dabigatran (Pradaxa)			rivaroxaban (Xarelto)		apixaban (Eliquis)	
Trial design	Open label versus warfarin, 2 doses			Double blind		Double blind	
# enrolled	18,113			14,264		18,201	
Age	Mean: 71			Median: 73		Mean: 70	
Mean $CHADS_2$	2.1			3.5		2.1	
Prior stroke / TIA	20%[a]			55%		19%[a]	
Mean TTR, warfarin arm	64%			55%		62%	
DOAC vs warfarin	**110mg bid n=6015**	**150mg bid n=6076**	**W n=6022**	**20mg od[b] n=7,061**	**W n=7,082**	**5mg bid[c] n=9,120**	**W n=9,081**
STROKE OR SEE[d]							
Event rate/yr %	1.5	1.1	1.7	2.1	2.4	1.3	1.6
ARR% (NNT/yr)	-	0.6 (167)		-		0.33 (303)	
Hazard ratio (95%CI)	NS	0.65 (0.52-0.81)		NS		0.79 (0.66-0.95)	
Clinical significance	**Same**	**Same in 166 of 167 treated**		**Same**		**Same in 302 of 303 treated**	
ALL CAUSE MORTALITY[d]							
Event rate/yr %	3.7	3.6	4.1	1.9	2.2	3.5	3.9
ARR% (NNT/yr)	-	-		-		0.5 (238)	
Hazard ratio (95%CI)	NS	NS		NS		0.89 (0.8-0.998)	
Clinical significance	**Same**	**Same**		**Same**		**Same in 237 of 238 treated**	
MAJOR BLEED[d]							
Event rate/yr%	2.9	3.3	3.6	3.6	3.4	2.1	3.1
ARR% (NNT/yr)	0.7 (143)	-		-		0.96 (104)	
Hazard ratio (95%CI)	0.80 (0.70-0.93)	NS		NS		0.69 (0.60-0.80)	
Clinical Significance	**Same in 142 of 143**	**Same**		**Same**		**Same in 103 of 104 treated**	
INTRACRANIAL BLEED[d]							
Event rate/yr%	0.23	0.32	0.76	0.5	0.7	0.33	0.8
ARR% (NNT/yr)	0.53 (189)	0.44 (227)		0.2 (500)		0.47 (213)	
Hazard ratio (95%CI)	0.30 (0.19-0.45)	0.41 (0.28-0.60)		0.67 (0.47-0.93)		0.42 (0.3-0.58)	
Clinical Significance	**Same in 188 of 189**	**Same in 226 of 227 treated**		**Same in 499 of 500 treated**		**Same in 212 of 213 treated**	
GI BLEED							
Event rate/yr%	1.15	1.56	1.07	2.0	1.37	0.76	0.86
ARR% (NNH/yr)	-	0.49 (204)		0.63 (160)		-	
Significance	NS	P<0.05		P<0.05		NS	
Clinical significance	**Same**	**Same in 203 of 204 treated**		**Same in 159 of 160 treated**		**Same**	

TTR- time in therapeutic range; NS- Not significant; [a] Prior stroke, transient ischemic attack or systemic embolism; [b] 15mg daily in patients with CrCl 30-49ml/min; [c] 2.5 mg twice daily in patients with 2 or more of the following criteria: age≥80 years, body weight ≤60kg, or SrCr ≥133 umol/l; [d] **includes hemorrhagic stroke**

Same = no statistically significant difference between DOAC and warfarin
DOAC superior to warfarin (**NNT** - e.g. For every 500 patients treated with rivaroxaban instead of warfarin for one year, there would be one **less** intracranial hemorrhage)
Warfarin superior to DOAC (**NNH** - e.g. For every 204 patients treated with dabigatran instead of warfarin for one year, there would be one **more** GI bleed)

The above table shows that for important measures like stroke, mortality and bleeding, warfarin and the DOACs perform similarly (at least in patients similar to those enrolled in the DOAC trials).

It is unknown whether the safety profile of the DOACs in clinical practice will reflect event rates reported in the clinical trials. It is also unclear if outcomes between agents may be different once bleeding occurs.

APPENDIX 3: Selected features of the OACs

	WARFARIN[4]	DABIGATRAN[4]	RIVAROXABAN[4]	APIXABAN[4]
Mechanism of action	Vitamin K antagonist Inhibits synthesis II, VII, IX, X	Direct IIa (thrombin) inhibitor	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor
Recommended Dosing (Dosing may differ in indications other than non-valvular AF)	**Once** daily (INR- adjusted) Most start at 5mg daily, unless ↑ bleed risk, use < 5mg	150mg **BID** 110mg BID in: • Age ≥ 80 • Age ≥ 75 + bleeding risk factor[a]	20mg **once** daily with food 15mg once daily with food if CrCl 30-49 ml/min	5mg **BID** 2.5 mg BID if any 2 of the following: • SrCr≥133 umol/L • Age ≥ 80 years, or • Weight ≤ 60kg
Coagulation Monitoring	INR	Routine coagulation monitoring not available		
T1/2 in normal renal function	36-42 hours	12-14 hours	5-9 hours	8-13 hours
		Loss of effect within 12 to 24 hours after last dose Adherence is essential		
Reversing agents	Vitamin K – PO/IV FP 4 F PCC (Octaplex or Beriplex)	None currently available		
Elimination	Hepatically metabolized	80% renal	67% renal (1/2 is in-active drug), 33% fecal	27% renal, 73% fecal
		CrCl <30ml/min: contraindicated	CrCl <30ml/min: contraindicated	CrCl <25ml/min: excluded from RCT
Drug interaction mechanism	CYP 2C9, 3A4 and 1A2	Potent P-gp inhibitors & P-gp inducers	Strong dual CYP 3A4 & P-gp inhibitors /inducers	Strong dual CYP 3A4 & P-gp inhibitors /inducers
Drug interactions	↑'d bleeding risk Examples include NSAIDs, antiplatelets, anticoagulants	↑'d bleeding risk Examples include NSAIDs, antiplatelets (i.e. asa, clopidogrel; prasugrel, ticagrelor specifically not recommended) Anticoagulants contraindicated		
	See below[b]	Interaction knowledge limited & likely to change; refer to reputable drug interaction resources for the most up to date recommendations		
Estimated annual cost (drug cost + tests)	$433[c] ($81 + $352)	$1,249[d] ($1214 + $35)	$1,118[d] ($1,083 + $35)	$1,249[d] ($1214 + $35)

a CrCl = 30-50 mL/min, concomitant treatment with P-glycoprotein inhibitors, antiplatelets or a previous GI bleed.
b http://cph.sagepub.com/content/144/1/21/T1.expansion.html
c drug cost & dispensing fees based on 5 mg daily, $81; INR tests & telephone consultations, $352 (assuming 16 INR tests per year)
d Includes drug cost & dispensing fees based on usual dose ($1,083 to $1,214) and two serum creatinine tests per year ($35) based on estimates in 2013.
Cost based on wholesale costs from McKesson Pharmalik online as of October 2014
FP – Frozen plasma; PCC- Prothrombin Complex Concentrates

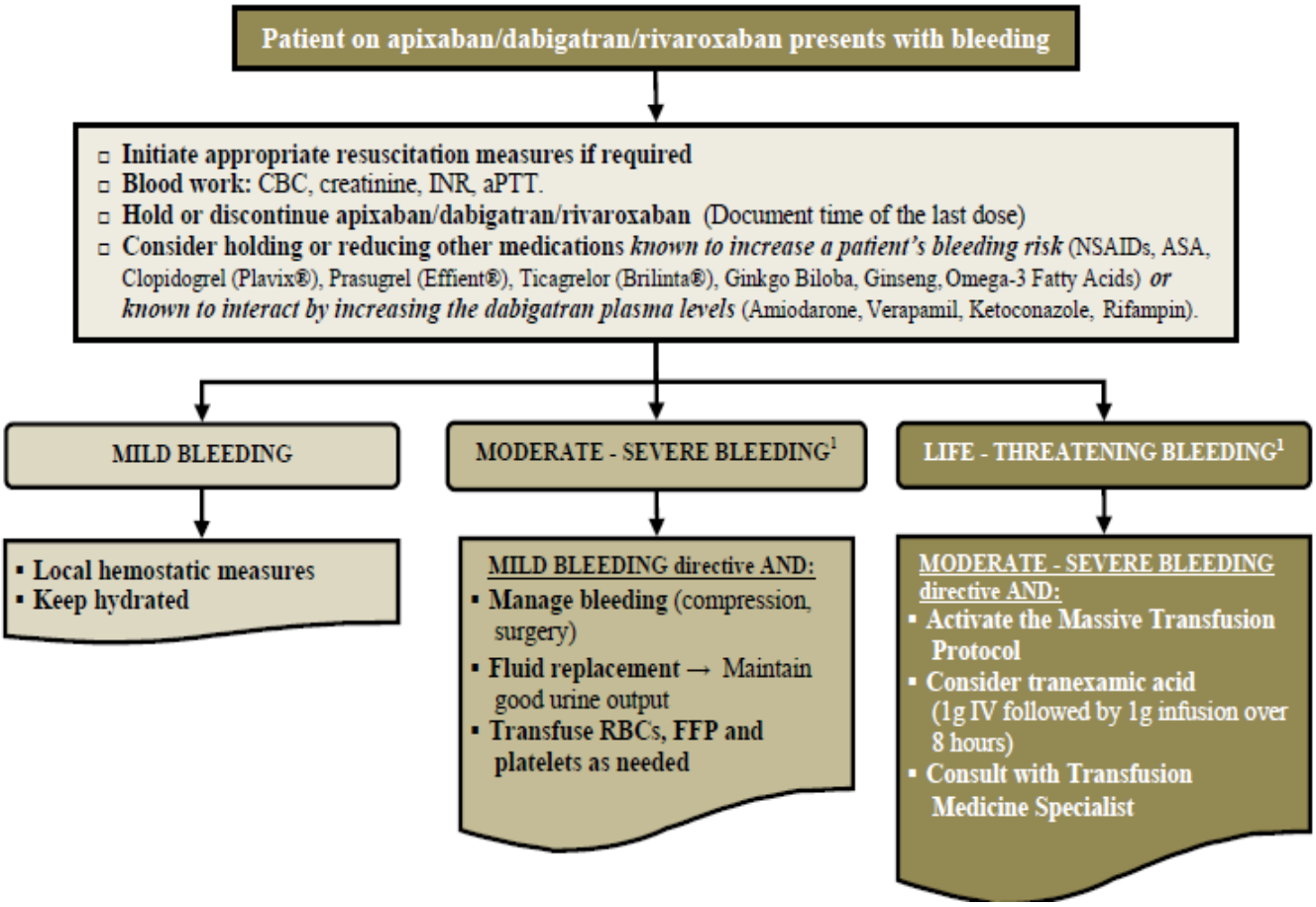
APPENDIX 4: NS Blood Coordinating Program; Managing patients on OACs who experience bleeding

The NSBCP

The Nova Scotia Blood Coordinating Program developed the Atlantic Collaborative recommendation for the management of bleeding with DOACs. The NS Blood Coordinating Program was created in January 2003 to provide the leadership to collaborate with health care providers across Nova Scotia and Canadian Blood Services to maximize the safe and appropriate management of blood and related products. http://bit.ly/NSPBCP-CPG

Atlantic Collaborative Recommendations for Managing the Bleeding Patient on Apixaban, Dabigatran or Rivaroxaban

There is limited clinical data related to reversal of apixaban, dabigatran and rivaroxaban. With no proven antidote available at the current time, the recommendations below may change as new evidence becomes available.



The anticoagulant effect of apixaban, dabigatran or rivaroxaban will not be reversed by the administration of vitamin K or plasma infusion.[1] DO NOT TRANSFUSE PLASMA to reverse an elevated aPTT or INR.

There is insufficient evidence to recommend the use of Prothrombin Complex Concentrates (Octaplex® or Beriplex®P/N), FEIBA or rFVIIa (NiaStase®) for the reversal of these medications.[4]

In overdose situations without bleeding, activated charcoal may be considered for apixaban, dabigatran and rivaroxaban. Hemodialysis may be considered for patients with renal failure while taking dabigatran however apixaban and rivaroxaban are not expected to be dialyzable.[5,7,8]

Moderate to severe bleeding – a reduction in Hgb ≥ 20g/L, symptomatic bleeding in an organ or critical area, e.g. intraocular, intracranial, intramuscular, retroperitoneal, intra-articular or pericardial bleeding.[1]
Life-threatening bleeding – a reduction in Hgb ≥ 50g/L, symptomatic intracranial bleed, hypotension requiring inotropic agents, e.g. dopamine, bleeding requiring surgery.[1]

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