CancerCare Manitoba
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Blood Disorders Day 2018 FOR Health Professionals

Don’t Skip a Beat:

A Refresher on Anticoagulation for Atrial Fibrillation in 2018

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COMMUNITY ONCOLOGY PROGRAM

Presenter Disclosure

- **Faculty / Speaker's name: Mahwash Saeed**

- **Relationships with commercial interests:**
  - **Grants/Research Support:** None
  - **Speakers Bureau/Honoraria:** Bayer
  - **Consulting Fees:** None
  - **Other:** None

Mitigating Potential Bias

- All recommendations involving clinical medicine are based on evidence from well-designed clinical trials published in peer-reviewed journals and current Canadian guidelines

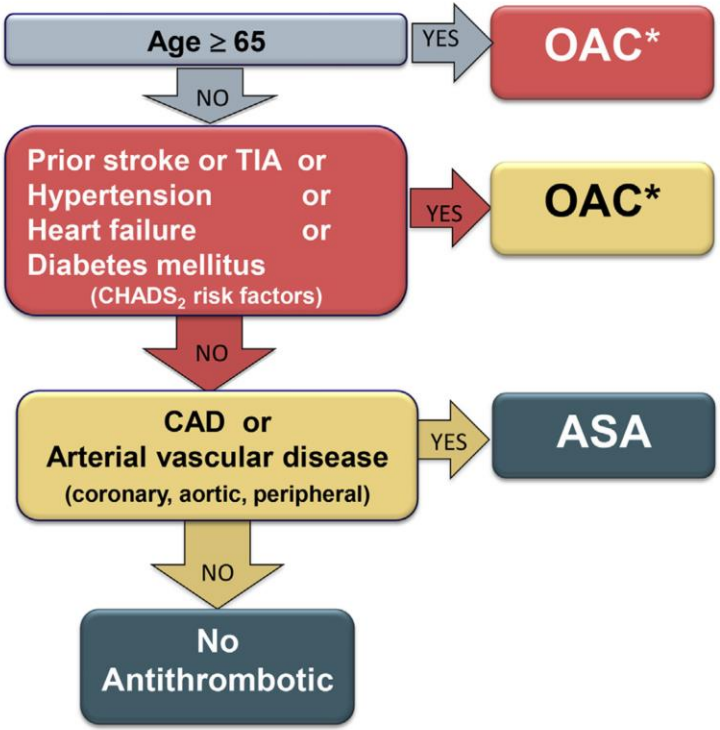
- All novel oral anticoagulants available in Canada will be discussed

Learning Objectives

1) Briefly review the mechanisms of warfarin, rivaroxaban, apixaban and dabigatran

2) Review potential anticoagulation options in common ambulatory cardiac patients with non valvular atrial fibrillation

The "CCS Algorithm" for OAC Therapy in AF



Consider and modify (if possible) all factors influencing risk of bleeding during OAC treatment (hypertension, antiplatelet drugs, NSAIDs, excessive alcohol, labile INRs) and specifically bleeding risks for NOACs (low creatinine clearance, age ≥ 75, low body weight).†

Macle et al. CJC. 2016;32:1170-85.

Anticoagulation for Atrial Fibrillation

Consider Referral to Cardiology in Patients with:

- Cardiomyopathy
- Moderate to severe valvular disease
- Symptoms (dyspnea, presyncope)
- Difficult to control ventricular rates
- Especially those over age >75 on 2 or more rate controlling agents (for possible AV node ablation/ pacemaker insertion)
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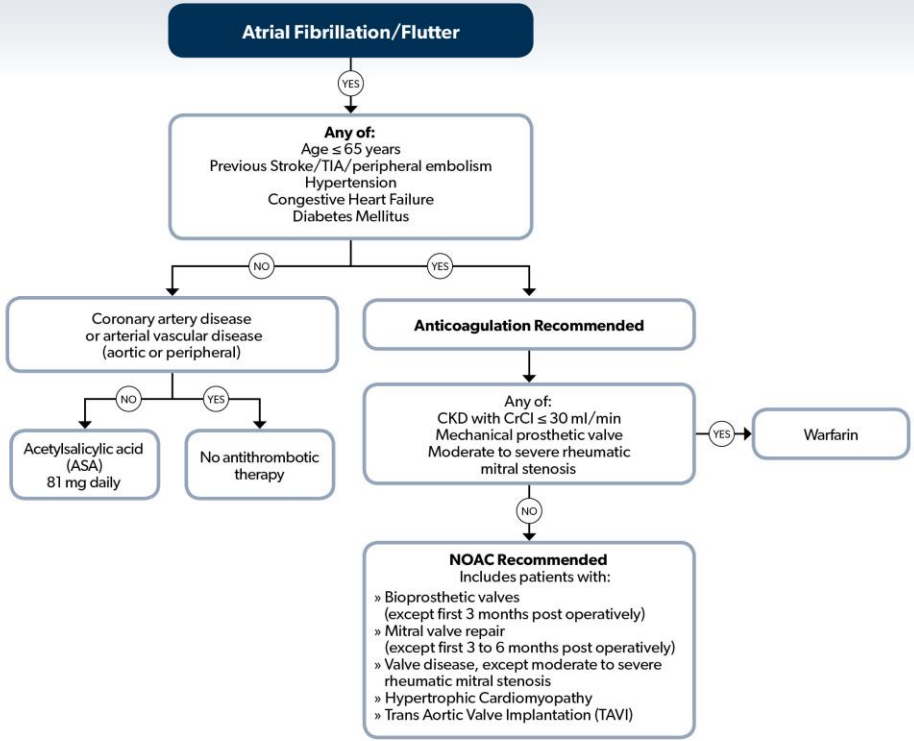
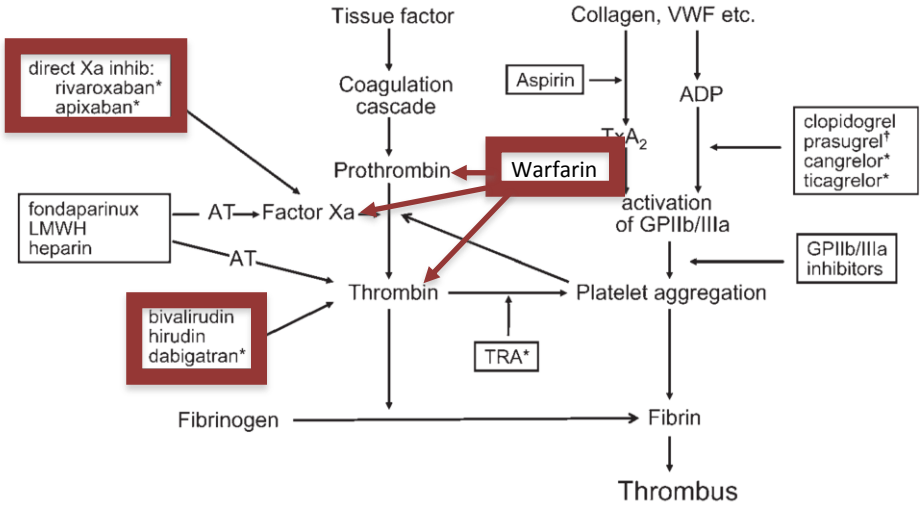


CKD = Chronic Kidney Disease
NAOC = Non vitamin K antagonist oral anticoagulants

Pathways are subject to clinical judgement and actual practice patterns may not always follow the proposed steps in this pathway.



Van de Werf F. Eur Heart J. 2009;30:1695-702

Case 1

- **89 year old gentleman, NSTEMI**
  - Receives DES x 3 to mid to distal RCA
  - New diagnosis atrial fibrillation, LVEF 30%

Meds at home:

Clopidogrel 75 mg OD
Atorvastain 80 mg OD
Candesartan 16 mg OD
HCTZ 25 mg OD
Naproxen 500 mgBID
Metformin 500 mg BID
Pregabalin 150 mg BID
Lorazepam 1 mg TID

Meds DC'd:

Candesartan
HCTZ

New Meds added:

ASA 81 mg OD
Dabigatran 110 mg OD
Ramipril 2.5 mg BID
Metoprolol 25 mg TID

Case 1

- Patient presents to GP's office 3 weeks after discharge with bruising over forearms
- Very concerned about addition of anticoagulant to his medications – he has a friend who recently fell and suffered a subdural hematoma

Polling Question

- What is your greatest concern when it comes to managing elderly patients on an oral anticoagulant?
    A. Fear of bleeding
    B. Fear of falling
    C. Concerns with renal function
    D. Adherence
    E. Other

Patient and Physician Values

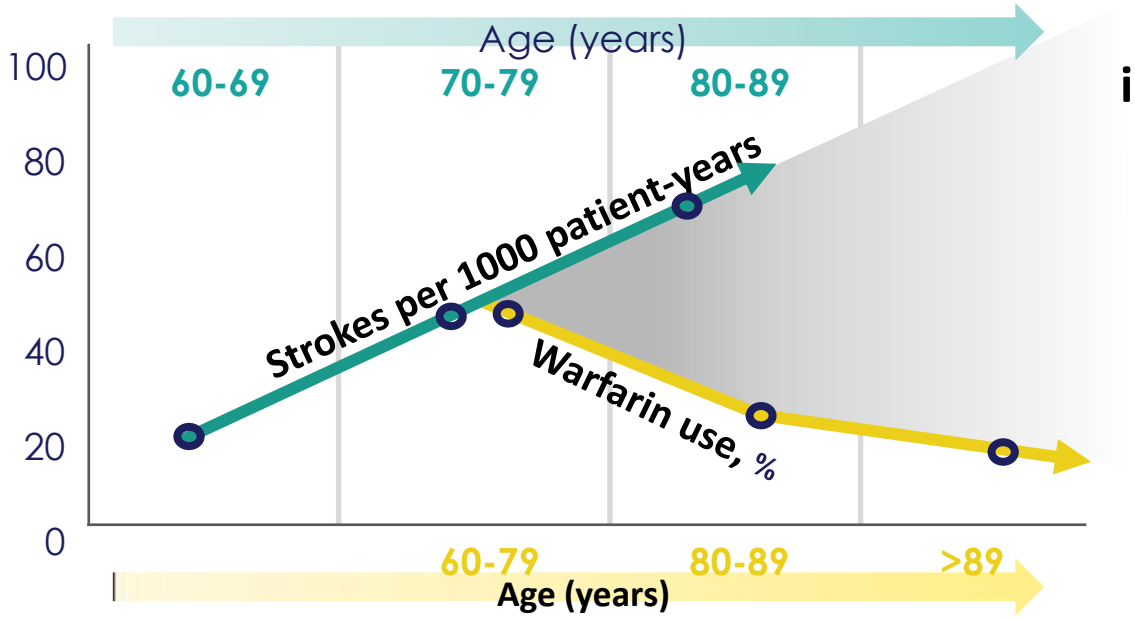
Patients	Physicians
Interactions with food/drug	Risk of major bleeding
Rapid reversal in emergency situations	Interactions with food/drug
Clinical experience	Requirement for regular blood testing
Requirement for regular blood testing	Rapid reversal in emergency situations
Risk of major bleeding	Dosing frequency
Dosing frequency	Clinical experience
Efficacy (stroke-free survival)	Efficacy (stroke-free survival)

Highest rated attribute

Lowest rated attribute

Can J Card 32(2016) 747-53

In 48% of patients, physician choice was the reason an OAC was not given to patients with a $CHADS_2$ score ≥2[3]



The risk of stroke in AF increases dramatically with age[1]

However, the use of anticoagulation decreases[2]

1. Wolf et al. Arch Intern Med. 1987;147:1561-64;
2. White et al. Am J Med. 1999;106:165-71;
3. Kakkar et al. PLoS One. 2013;8:e63479.

Bleeding Risk Management

- Address reversible risk factors:
  - Falling → provide mobility aid
  - Hypertension → treat blood pressure to target
  - Alcohol → encourage abstinence
  - Labile INR → use NOACs
  - Drugs → replace NSAIDs with other analgesics, avoid ASA unless clearly indicated for secondary prevention
  - GI bleeding → use proton pump inhibitors (PPI)

Follow-up Considerations for Elderly Patients

- **Follow-up plan**
  - Patient should be seen every 3-6 months
  - Encourage adherence
  - Check concomitant/over the counter medications
  - Check for other side effects, thromboembolic or bleeding events

1. *Heidbuchel et al. Europace. 2013;15:625-51*
2. *Macle et al. Can J Cardiol. 2015;31:1207-18*

Follow-up Considerations for Elderly Patients

- Renal function should be monitored yearly, or more frequently if CKD or acute illness
- Monitor hemoglobin and liver function yearly
- Review use of NSAIDs
- Mobility aids (e.g., cane, walker and grab bars in the bathroom) can be used to help prevent falls

1. *Heidbuchel et al. Europace. 2013;15:625-51*
2. *Macle et al. Can J Cardiol. 2015;31:1207-18*

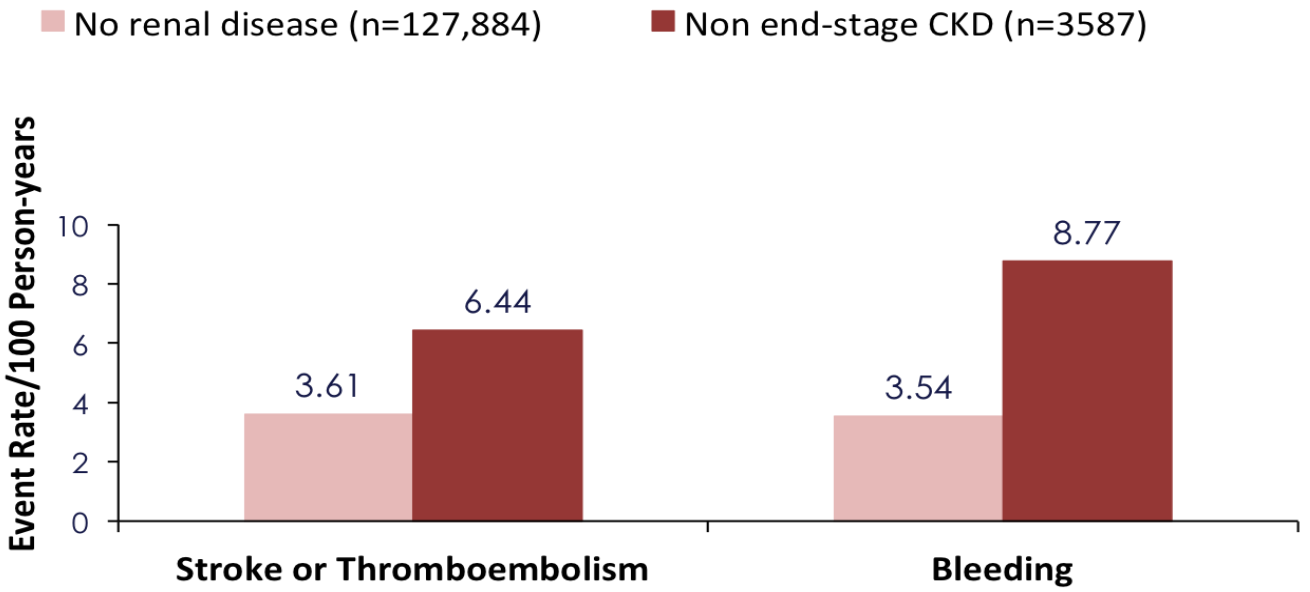
Case 2

- **75 year old lady presents with new onset palpitations and AF**
  - PmHx: DM2, HTN, CKD (CrCl 35 ml/min)
  - Was in ED last week – told to talk to GP about blood thinners
  - Very nervous – sister died of brain hemorrhage

Medications:

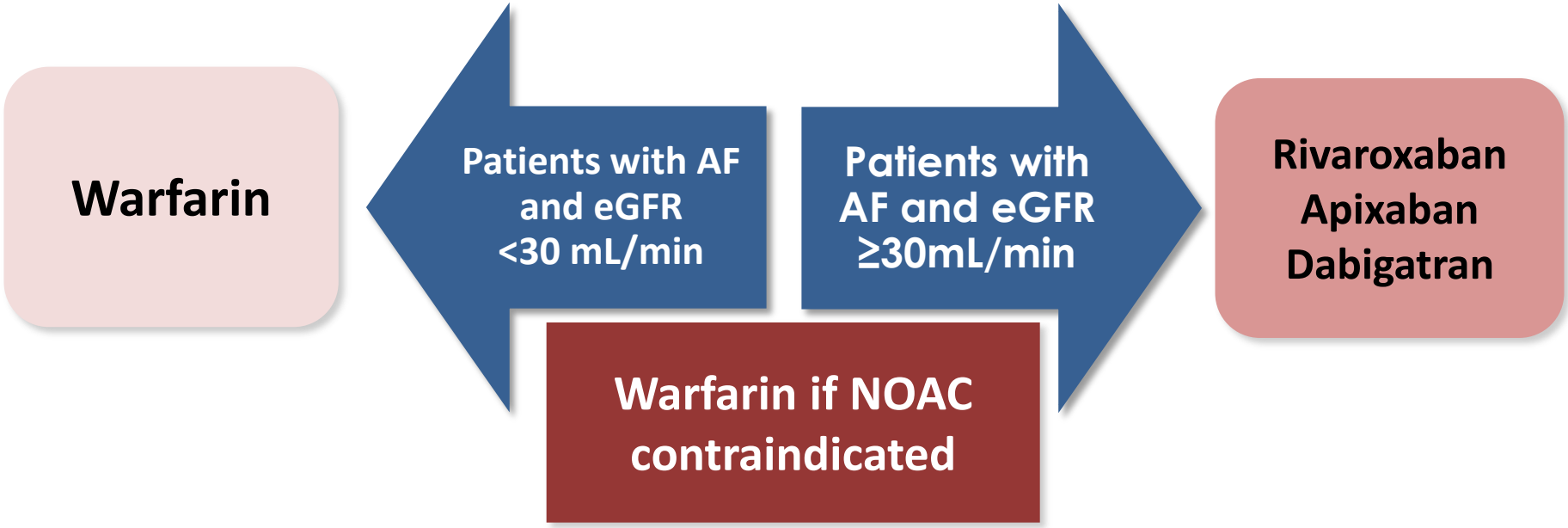
ASA 81 mg OD
Metoprolol 25 mg BID
Lasix 80 mg BID
Amlodipine 10 mg OD
Insulin varying doses
Zopiclone 3.75 mg at HS

CKD is a Risk Factor for Thrombotic and Bleeding Events

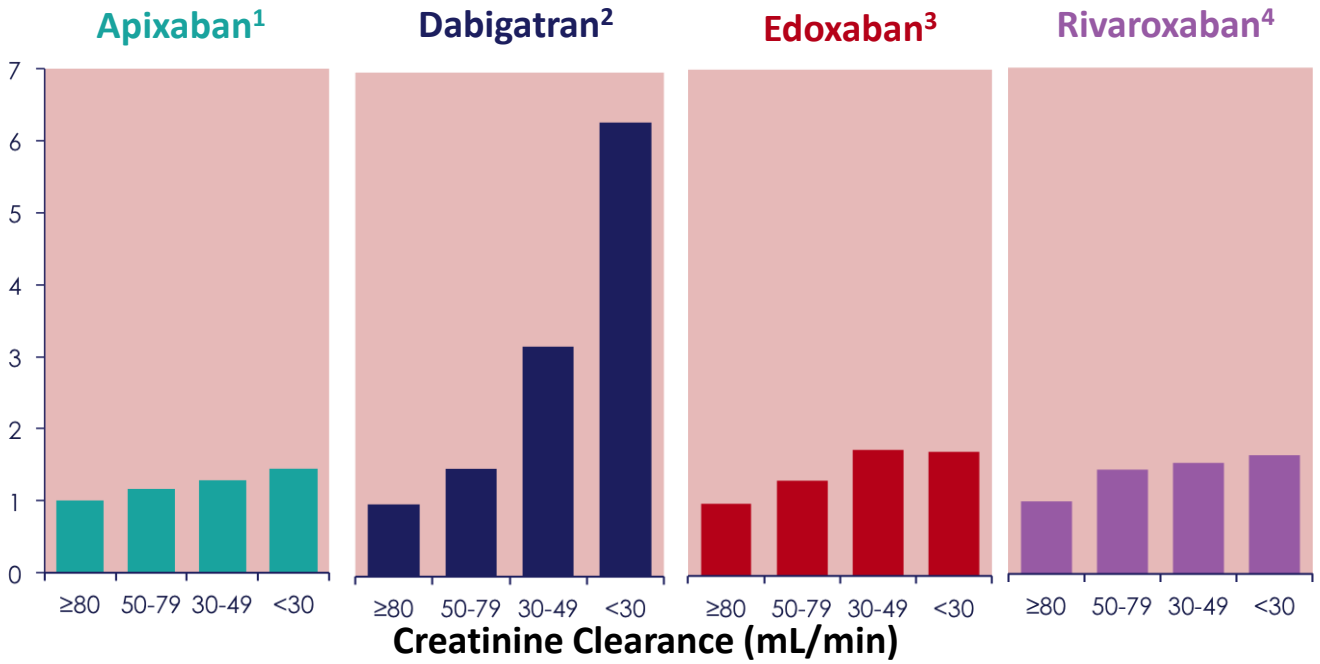


1. *Olesen et al. N Engl J Med. 2012;367:625–35*
2. *Capodanno et al. Circulation. 2012;125:2649–61*

CCS Guidelines Recommend NOACs for Eligible AF Patients with eGFR ≥30 mL/min



Verma et al. Can J Cardiol. 2014:30;1114-30



1. *Apixaban (Eliquis) Product Monograph. Bristol-Meyers Squibb Canada*
2. *Dabigatran (Pradaxa) Product Monograph. Boehringer Ingelheim Canada Ltd*
3. *Edoxaban (Lixiana) Product Monograph. Progress Therapeutics*
4. *Rivaroxaban (Xarelto) Product Monograph. Bayer Inc*

Drug	Mechanism of Action	Excretion
Warfarin	Vitamin K Antagonist Inhibits synthesis of Factors II, VII, IX, X	Hepatic
Dabigatran	Direct Thrombin Inhibitor	Renal
Rivaroxaban	Direct Factor Xa Inhibitor	Renal and Hepatic
Apixiban	Direct Factor Xa Inhibitor	Renal and Hepatic
Edoxaban	Direct Factor Xa Inhibitor	Renal and Biliary

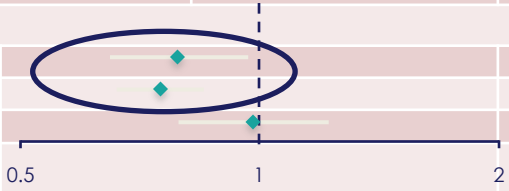
Braunwald's 10th edition

NOACs remain safe and effective in patients with moderate renal impairment

Increased Rates of SSE and Major Bleeding in Warfarin Arm with Declining Renal Function

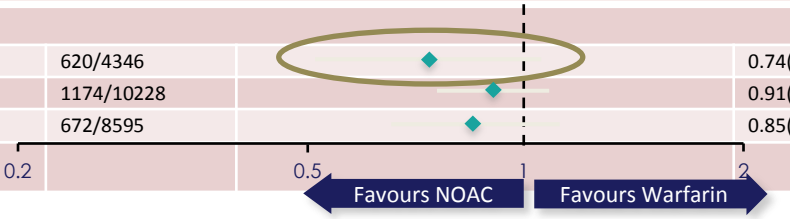
Stroke or Systemic Embolism

	Pooled NOAC (events)	Pooled warfarin (events)	RR (95% CI)	p interaction
Creatinine clearance (mL/min)				
<50	249/5539	311/5503	0.79(0.65-0.96)	
50-80	405/13055	546/13155	0.75(0.66-0.85)	0.12
>80	256/10626	255/10533	0.98(0.79-1.22)	



Major Bleeding

Creatinine clearance (mL/min)				
<50	514/4376	620/4346	0.74(0.52-1.05)	
50-80	1104/10139	1174/10228	0.91(0.76-1.08)	0.57
>80	625/8681	672/8595	0.85(0.66-1.10)	



Ruff et al. Lancet. 2014;383:955-62.

CrCl (mL/min)	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
>50	5 mg BID	150 mg BID	60 mg daily	20 mg daily	Dose adjusted for INR 2.0-3.0
30-49	5 mg BID (consider 2.5 BID)	150 mg BID	30 mg daily	15 mg daily	
15-29	Limited data	No RCT data	Limited data	No RCT data	No RCT data
<15 or dialysis	No RCT data	No RCT data	No RCT data	No RCT data	No RCT data

1. Apixaban (Eliquis) Product Monograph. Bristol-Myers Squibb Canada;
2. Dabigatran (Pradaxa) Product Monograph. Boehringer Ingelheim Canada Ltd.; 3. Edoxaban (Lixiana) Product Monograph. Progress Therapeutics; 4. Rivaroxaban (Xarelto) Product Monograph. Bayer Inc; 5. Warfarin (Coumadin) Product Monograph. Bristol-Myers Squibb Canada.

Summary – Renal Dysfunction

- Renal impairment is associated with an increased risk of stroke and bleeding
- NOACs are safe and effective in patients with moderate renal impairment and worsening renal function
- Dosing recommendations for patients with renal impairment differ among NOACs
- Warfarin is preferred over NOACs for patients with severe renal impairment (eGFR 15-30 mL/min/1.73 m^2)

Case 3

67 year old gentleman, AF on NOAC

- Scheduled for hernia surgery
- Normal renal function

- **When should we hold his NOAC?**
  - A. 1 day before surgery?
  - B. 2 days before surgery?
  - C. 3 days before surgery?
  - D. 5 days before surgery?
  - E. I would not stop his NOAC.

Perioperative Considerations for NOACs

- Reliable laboratory tests to assess anticoagulant effect of NOACs are not widely available
- Half-lives vary and increase with worsening renal function
- NOACs have a rapid onset of action, with peak anticoagulant effect occurring 1-2 hours after oral intake

Thrombosis Canada. New/Novel Oral Anticoagulants (NOACs): Peri-operative Management

Low Risk of Bleeding		Intermediate to High Risk of Bleeding	
1 Day Before	**3 Days Before**	**2 Days Before**	**5 Days Before**
Apixiban CrCl >30 ml/min Skip 2 doses	Dabigatran CrCl 30 to 50ml/min Skip 6 doses	Apixiban CrCl >30 ml/min Skip 4 doses	Dabigatran CrCl 30 to 50ml/min Skip 10 doses
Dabigatran CrCl > 50 ml/min Skip 2 doses		Dabigatran CrCl > 50 ml/min Skip 4 doses	
Edoxaban CrCl > 30 ml/min Skip 1 dose		Edoxaban CrCl > 30 ml/min Skip 2 doses	
Rivaroxaban CrCl > 30 ml/min Skip 1 dose		Rivaroxaban CrCl > 30 ml/min Skip 2 doses	

1. Thrombosis Canada. New/Novel Oral Anticoagulants (NOACs): Peri-operative Management. Available from: http://thrombosiscanada.ca/wp-content/uploads/2016/07/21_NOACs-Peri-Operative-Management_2016July13-FINAL.pdf ; 2. Edoxaban (Lixiana) Product Monograph. Progress Therapeutics; 3. Consensus recommendations of the Planning Committee.

Bridging?

- Bridging (LMWH or UFH) is not required for non valvular a fib patients on a NOAC undergoing elective surgery or invasive procedures requiring interruption of anticoagulation

- Bridging in warfarin patients is required in:
  - Patients with mechanical mitral valves or older aortic valves
  - Patients with INR below therapeutic level in patients at high risk of thromboembolic events ($CHADS_2$ ≥4)

- **NOACs and warfarin should be restarted once adequate hemostasis has been established**

1. Macle et al. CJC. 2016;32:1170-85; 2. Thrombosis Canada. New/Novel Oral Anticoagulants (NOACs): Peri-operative Management. 2.Douketis et al. N Engl J Med. 2015;373:823-33; 2. Macle et al. CJC. 2016;32:1170-85

Summary – Perioperative Management

- **Prolonged discontinuation of a NOAC perioperatively is unnecessary**
- Perioperative management of NOACs must take into consideration:
  - Renal function
  - Half-life
  - Bleeding risk of the procedure

Summary – Perioperative Management

- Determine timing of temporary discontinuation as per recommendations
- Bridging therapy is generally not required unless procedure will be delayed longer than 72 hours
- **Ensure anticoagulant is restarted following procedure**

Take home messages

- Elderly patients are at high risk of stroke and should be considered for anticoagulation in the right clinical setting
  - Care must be taken to reduce risk of serious bleeding

Take home messages

- NOACs are safe and effective in patients with moderate renal impairment and worsening renal function
  - Care must be taken to dose adjust NOACs in the setting of renal dysfunction
  - Warfarin is preferred at an eGFR of less than 30 ml/min

Take home messages

- Perioperative management of NOACs must take into consideration renal function, half life and bleeding risk of the procedure
- Always ensure anticoagulant is restarted post procedure!

Anticoagulation for Atrial Fibrillation

Consider Referral to Cardiology in Patients with:

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- Moderate to severe valvular disease
- Symptoms (dyspnea, presyncope)
- Difficult to control ventricular rates
- Especially those over age >75 on 2 or more rate controlling agents (for possible AV node ablation/ pacemaker insertion)
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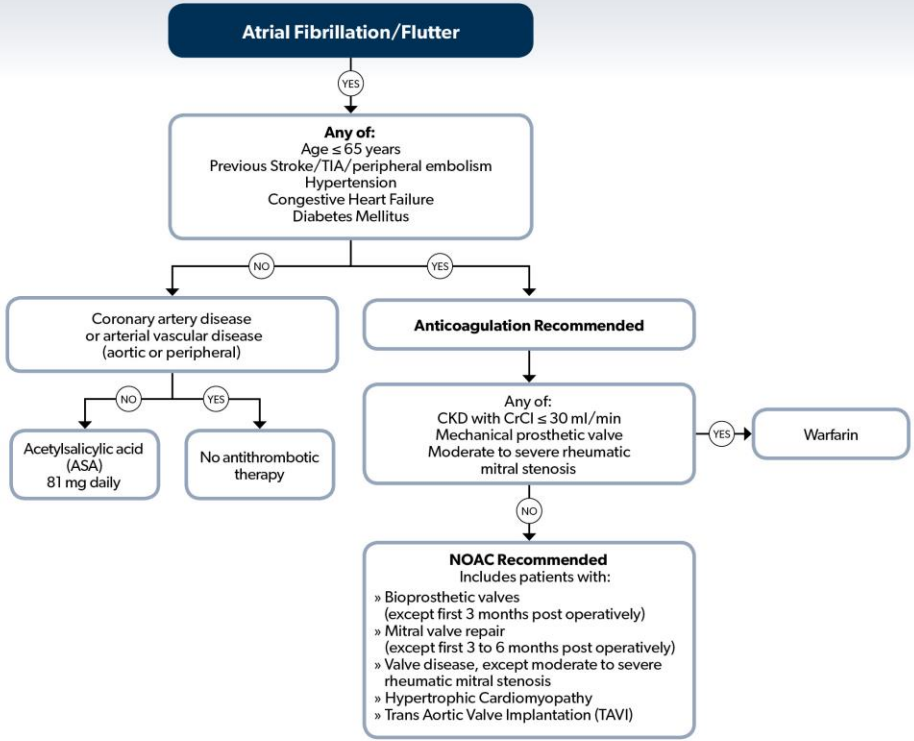

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Thank you

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