

# POCKET GUIDE



2020

V

# Different Screening Tools

## Physical Exam



## Holter (24-72 hrs)



## Personal Use Devices



# Different Screening Tools



**King of Hearts  
Express AF looping**

Transtelephonic loop event monitor,  
2-4 weeks



**Micro ER**

Transtelephonic non-looping  
post event monitor



**GEMS™ Sirona**

Continuous ECG recorder, Event and  
Holter reporting, transtelephonic,  
wireless or retrospective  
analysis, up to 30 days



**CardioSTAT**

Continuous ECG recorder, Event and  
Holter reporting, retrospective  
analysis, up to 30 days



**Reveal**

Implanted real time wireless up to  
6 months



# Is SCAF Common?

Study	Sample Size	Device	Inclusion	Rate of AF Detection
<b>ASSERT-II</b>	250	SJM Confirm	Age > 65, AND CHADS-VASc ≥ 2, or OSA, or BMI > 30; AND LA > 58mL, or NT-ProBNP > 290 pg/mL	≥ 5 min 34.4% at one year
<b>GRAF</b>	200	MDT REVEAL-XT	Age ≥ 18 CHADS-VASc ≥ 4	Pending
<b>REVEAL-AF</b>	450	MDT REVEAL-XT	Age ≥ 18 CHADS ≥ 3, or CKD/COPD/OSA/CAD	29.3% at 18 months
<b>PREDATE-AF</b>	245	REVEAL-LINQ	Age > 18, AND CHADS-VASc ≥ 2	≥ 6 min 22.4% at 451 days
<b>DANISH LOOP</b>	6,000	REVEAL-LINQ (1500)	Age > 70 One of HTN, DM, HF or stroke	Pending

ASSERT: Van Gelder IC, et al. Eur Heart J 2017; 38(17):1339-1344.



# SCAF Detection for Cryptogenic Stroke

- **Incidence of cryptogenic stroke: 25-40% of strokes**
- **Detection rates of SCAF in cryptogenic stroke: 0-25%**
- **SCAF detection strategies:**
  - In-hospital monitoring (e.g. scope, telemetry, Holter)
  - Serial ECGs
  - Outpatient Holter monitoring (24h, 48h, serial)
  - External loop recorders (eg. King of Heart)
  - Long-term outpatient monitoring (eg. CardioSTAT, Sirona)
  - Insertable cardiac monitors (ICMs) (eg. Reveal)



# 2018 Focused Update of the CCS AF Guidelines



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## RECOMMENDATIONS

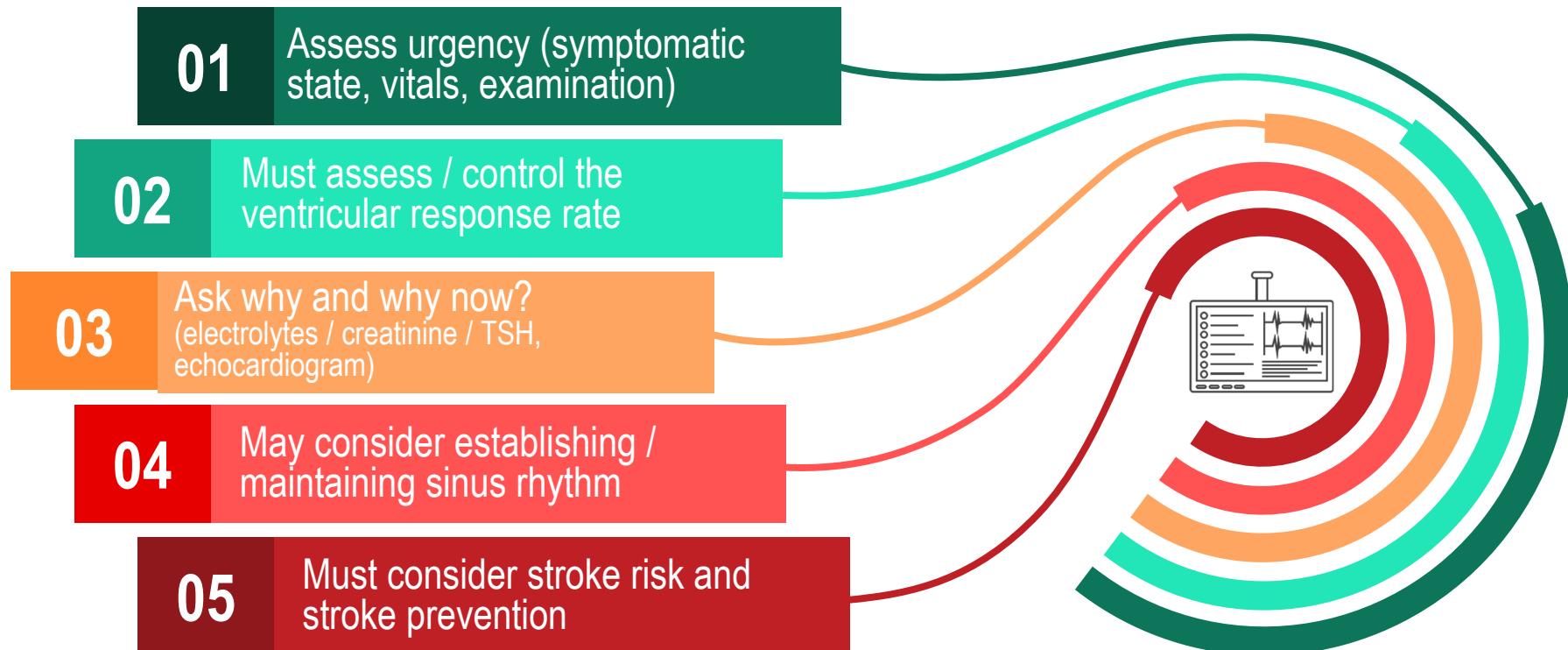
It is reasonable to prescribe OAC therapy for patients who are aged 65 years or older or with a CHADS<sub>2</sub> score of 1 (CHADS-65) who have episodes of SCAF lasting > 24 continuous hours in duration.

Additionally, high-risk patients (such as those with a recent embolic stroke of unknown source) with shorter-lasting episodes might also be considered for OAC therapy

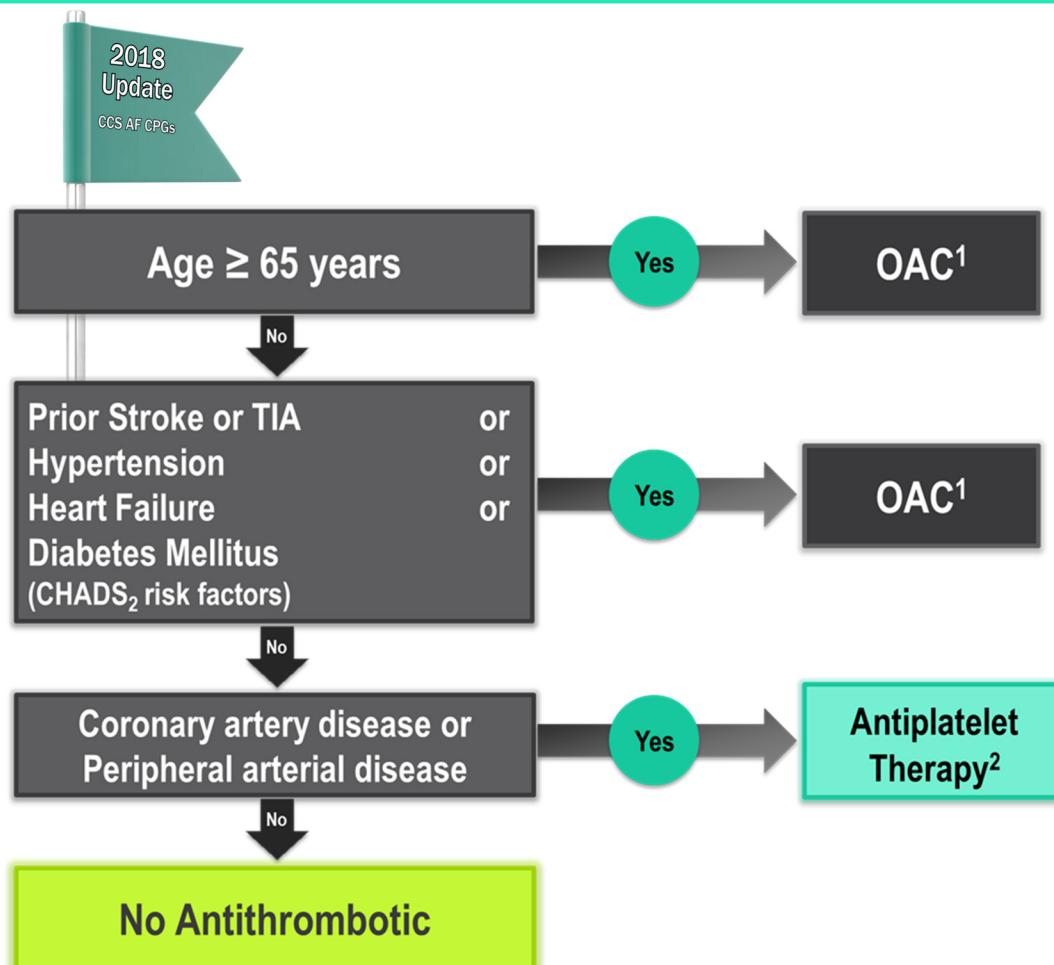
(Weak Recommendation, Low-Quality Evidence).



# An Approach to the Patient with Newly Diagnosed Atrial Fibrillation



# The “CCS Algorithm” (CHADS-65) for OAC Therapy in AF



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## Minimize Bleeding Risk:

- limit alcohol consumption
- avoid concomitant use of OAC, NSAIDs or antiplatelet drugs (unless guideline indicated) and
- consider low DOAC dosing in patients meeting dose reduction criteria

\* A DOAC is suggested in preference to warfarin for NVAF

<sup>1</sup> A DOAC is preferred over warfarin in non-valvular AF

<sup>2</sup> Therapeutic options include single antiplatelet therapy (ASA 81-100 mg daily) alone; or in combination with either a second antiplatelet agent (e.g. clopidogrel 75 mg daily or ticagrelor 60 mg BID), or an antithrombotic agent (rivaroxaban 2.5 mg BID)



# Operational Definition of Non-Valvular Atrial Fibrillation (NVAF)

**“Valvular” AF includes :**

- Mechanical heart valve
- Rheumatic moderate or severe mitral valve stenosis (MS) \*

**NVAF (“ non-valvular” AF) therefore includes :**

- Mitral regurgitation (MR)
- Aortic stenosis (AS)
- Aortic insufficiency (AI)
- Remote (3-6 months) tissue prosthetic heart valve
- Remote (3-6 months) surgical valve repair

\* It is uncertain whether patients with only mild MS or post mitral commissurotomy should be regarded as “Valvular” AF.

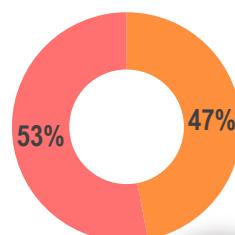
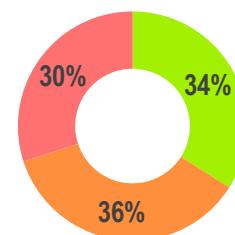
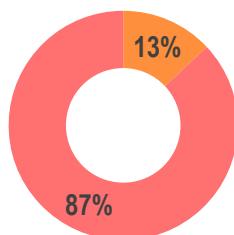
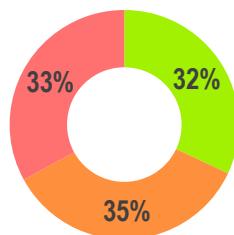
# DOACs vs Warfarin RCTs

## Baseline Characteristics

	RE-LY <sup>a</sup> (Dabigatran)	ROCKET-AF <sup>b</sup> (Rivaroxaban)	ARISTOTLE <sup>c</sup> (Apixaban)	ENGAGE AF <sup>d</sup> (Edoxaban)
Randomized, N	18,113	14,264	18,201	21,105
Age, y	72±9	73 [65-78]	70 [63-76]	72 [64-78]
Female, %	37	40	35	38
Paroxysmal AF, %	32	18	15	25
VKA naive, %	50	38	43	41
Aspirin use, %	40	36	31	29

### CHADS<sub>2</sub>

- 0-1
- 2
- 3-6



a. Connolly SJ, et al. *N Engl J Med.* 2009;361:1139-1151<sup>[3]</sup>  
b. Patel MR, et al. *N Engl J Med.* 2011;365:883-891<sup>[4]</sup>

c. Granger CB, et al. *N Engl J Med.* 2011;365:981-992<sup>[5]</sup>  
d. Giuliano RP, et al. *N Engl J Med.* 2013;369:2093-2104.<sup>[6]</sup>



# DOACs as Compared to Warfarin

## Indirect Comparisons from the Clinical Trials

	APIXABAN <sup>1</sup>	DABIGATRAN 110 <sup>2</sup>	DABIGATRAN 150 <sup>2</sup>	EDOXABAN 60	RIVAROXABAN <sup>3</sup>
Stroke/SE					
Major Bleed					
Intracranial Bleed					
GI Bleed					
All Cause Death					

To date there are no head-to-head trials between apixaban, dabigatran, edoxaban and rivaroxaban, therefore comparative efficacy and safety have not been established



Significant Increase



Significant Reduction



Non-Significant Difference

1. Granger et al., NEJM 2011; 365: 981-992
2. Connolly et al., NEJM 2009; 361: 1139-1151

3. Patel et al., NEJM 2011; 365: 883-891
4. Giuliano RP et al NEJM 2013; 369:2091



# Stroke Prevention in AF: Clinical Pharmacology and Dosing of DOACs

	APIXABAN	DABIGATRAN	EDOXABAN	RIVAROXABAN
<b>Mechanism of action</b>	Direct Factor Xa inhibitor	Direct thrombin inhibitor	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor
<b>Oral bioavailability</b>	~50%	~6.5%	62%	80-100%
<b>Pro-drug</b>	No	Yes	No	No
<b>Food effect</b>	No	No	No	Yes (needs to be taken with food)
<b>Renal clearance</b>	~27%	85%	50%	36% *
<b>Mean half-life (<math>t_{1/2}</math>)</b>	~12 h	11-17h	10-14h	5-13 h
<b>T<sub>max</sub></b>	3-4 h	0.5-2 h	1-2h	2-4 h
<b>Recommended daily dose</b>	5 mg BID	150 mg BID	60 mg QD	20 mg QD

Pfizer Canada Inc./BMS Canada. Eliquis (apixaban) Product Monograph, June 16, 2016.  
Boehringer Ingelheim Canada Ltd. Pradaxa (dabigatran) Product Monograph. August 11, 2016.  
Bayer Inc. Xarelto (rivaroxaban) Product Monograph. July 20, 2015.  
Daiichi Sankyp Inc. Lixiana (edoxaban) Product Monograph. November 2, 2016.

\* Rivaroxaban is 66% renally cleared and its active metabolite is 36% renally cleared



# Considerations for Dosing of DOACs

DOAC	USUAL STARTING DOSE	DOSING ADJUSTMENT CRITERIA
<b>APIXABAN (ELIQUIS)</b>	5 mg BID	<b>2.5 mg BID if any 2 of the following criteria:</b> <ul style="list-style-type: none"><li>- Age ≥80 years</li><li>- Body weight ≤60 kg</li><li>- Creatinine ≥133 µmol/L</li></ul>
<b>DABIGATRAN (PRADAXA)</b>	150 mg BID	<b>110 mg BID if</b> <ul style="list-style-type: none"><li>- Age &gt;80 <b>or</b></li><li>- &gt; 75 + ≥ one hemorrhagic risk factors <b>or</b></li><li>- CrCl 30-50 ml/min</li></ul>
<b>EDOXABAN (LIXIANA)</b>	60 mg OD	<b>30 mg OD if</b> <ul style="list-style-type: none"><li>- If CrCl 30-50 ml/min <b>or</b></li><li>- body weight ≤60 kg <b>or</b></li><li>- concomitant use of P-gp inhibitors (ex: quinidine, dronedarone) except amiodarone and verapamil</li></ul>
<b>RIVAROXABAN (XARELTO)</b>	20 mg OD taken with food	<b>15 mg OD taken with food if</b> <ul style="list-style-type: none"><li>- CrCl 15-49 mL/min</li></ul>

Pfizer Canada Inc./BMS Canada. Eliquis (apixaban) Product Monograph, 2018.

Boehringer Ingelheim Canada Ltd. Pradaxa (dabigatran) Product Monograph. August 11, 2016.

Bayer Inc. Xarelto (rivaroxaban) Product Monograph. 2018.

Daiichi Sankyo Inc. Lixiana (edoxaban) Product Monograph. 2017.



# DOAC Dosing Recommendations for Stroke Prevention in AF in Patients with Renal Impairment According to the Canadian Product Monographs

OAC THERAPY	Renal Clearance	KD GRADE				
		Mild RI [CrCl :50-79 mL/min]	Moderate RI [CrCl :30-49 mL/min]	Severe RI [CrCl :25-29 mL/min] / [CrCl :15-24mL/min]		Kidney Failure [CrCl :<15 mL/min]
APIXABAN <sup>1</sup>	27%	Yes 5 mg BID  Dose adjustment only if ≥2 of ABC* criteria			Yes No dosing recommendation can be made	Not Recommended
RIVAROXABAN <sup>2</sup>	36%	Yes 20 mg QD with food	Yes 15 mg QD with food	Yes 15mg QD with food Use with caution	Yes 15mg QD with food Use with caution Due to limited clinical data	Not Recommended
DABIGATRAN <sup>3</sup>	85%	Yes 150 mg BID  Dose reduction if ≥ 80 yrs or at higher risk for bleeding		Contraindicated		
EDOXABAN <sup>4</sup>	50%	Yes 60 mg QD	Yes 30 mg QD	Not Recommended		
WARFARIN <sup>5</sup>	0%	No dosage adjustment is necessary for patients with renal failure				



# Bleeding Risks for Invasive / Surgical Procedures

LOW RISK	MODERATE RISK	HIGH RISK
<ul style="list-style-type: none"><li>Dental extractions (1 or 2 teeth), endodontic (root canal) procedure,</li><li>Subgingival scaling or other cleaning</li><li>Cataract surgery</li><li>Dermatologic procedures (e.g. biopsy)</li><li>Gastroscopy or colonoscopy without biopsies</li><li>Coronary angiography</li><li>Permanent pacemaker insertion or internal defibrillator placement (if bridging anticoagulation is not used)</li><li>Selected procedures (e.g. thoracentesis, paracentesis, arthrocentesis)</li></ul>	<ul style="list-style-type: none"><li>Other intra-abdominal surgery (e.g. laparoscopic cholecystectomy, hernia repair, colon resection)</li><li>Other general surgery (e.g. breast)</li><li>Other intrathoracic surgery</li><li>Other orthopedic surgery</li><li>Other vascular surgery</li><li>Non-cataract ophthalmologic surgery</li><li>Gastroscopy or colonoscopy with biopsies</li><li>Selected procedures (e.g. bone marrow biopsy, lymph node biopsy)</li><li>Complex dental procedure (e.g. multiple tooth extractions)</li></ul>	<ul style="list-style-type: none"><li>Any surgery or procedure with neuraxial (spinal or epidural) anesthesia</li><li>Neurosurgery (intracranial or spinal)</li><li>Cardiac surgery (e.g. CABG, heart valve replacement)</li><li>Major intra-abdominal surgery (e.g. intestinal anastomosis)</li><li>Major vascular surgery (e.g. aortic aneurysm repair, aortofemoral bypass)</li><li>Major orthopedic surgery (e.g. hip or knee replacement)</li><li>Lung resection surgery</li><li>Urological surgery (e.g. prostatectomy, bladder tumor resection)</li><li>Extensive cancer surgery (e.g. pancreas, liver)</li><li>Reconstructive plastic surgery</li><li>Selected procedures (e.g. kidney biopsy, prostate biopsy, cervical cone biopsy, pericardiocentesis, colonic polypectomy)</li></ul>

<sup>t</sup> Antithrombotic therapy with ASA, warfarin (INR between 2.0 and 3.0) or a NOAC may continue for implantation of cardiac devices.



# Peri-Operative Guide

DRUG (DOSE REGIMEN)	RENAL FUNCTION	MODERATE BLEED RISK SURGERY/PROCEDURE*	HIGH BLEED RISK SURGERY/PROCEDURE* (INCLUDES ANY USE OF NEURAXIAL ANESTHESIA†)
<b>Dabigatran (twice daily)</b>	Normal renal function or mild impairment (CrCl >50 mL/min) $t_{1/2}$ 7-17 hours	Give last dose 2 days before surgery/procedure <b>(i.e. skip 2 doses)</b>	Give last dose 3 days before surgery/procedure <b>(i.e. skip 4 doses)</b>
	Moderate renal impairment (CrCl 30-49 mL/min) $t_{1/2}$ 17-20 hours	Give last dose 3 days before surgery/ procedure <b>(i.e. skip 4 doses)</b>	Give last dose 5 days before surgery/procedure <b>(i.e. skip 8 doses)</b>
<b>Rivaroxaban (once daily)</b>	Normal renal function, mild or moderate impairment (CrCl >30 mL/min) $t_{1/2}$ 7-11 hours	Give last dose 2 days before surgery/procedure <b>(i.e. skip 1 dose)</b>	Give last dose 3 days before surgery/procedure <b>(i.e. skip 2 doses)</b>
<b>Apixaban (twice daily)</b>	Normal renal function, mild or moderate impairment (CrCl >30 mL/min) $t_{1/2}$ 8-12 hours	Give last dose 2 days before surgery/procedure <b>(i.e. skip 2 doses)</b>	Give last dose 3 days before surgery/procedure <b>(i.e. skip 4 doses)</b>
<b>Edoxaban (once daily)</b>	Normal renal function, or mild impairment (CrCl >50 mL/min) $t_{1/2}$ 10-14 hours	Give last dose 2 days before surgery/procedure <b>(i.e. skip 1 dose)</b>	Give last dose 3 days before surgery/procedure <b>(i.e. skip 2 doses)</b>



# Post-Operative Guide

DRUG	MODERATE BLEED RISK SURGERY/PROCEDURE	HIGH BLEED RISK SURGERY/PROCEDURE
<b>Dabigatran (twice daily)</b>	Resume on day after surgery (~24 hours post-operative)	Resume therapeutic doses 2-3 days after surgery (~48-72 hours post-operative); prophylactic dose anticoagulants can be considered in the interim
<b>Rivaroxaban (once daily)</b>	Resume on day after surgery (~24 hours post-operative)	Resume therapeutic doses 2-3 days after surgery (~48-72 hours post-operative); prophylactic dose anticoagulants can be considered in the interim
<b>Apixaban (twice daily)</b>	Resume on day after surgery (~24 hours post-operative)	Resume therapeutic doses 2-3 days after surgery (~48-72 hours post-operative); prophylactic dose anticoagulants can be considered in the interim
<b>Edoxaban (once daily)</b>	Resume on day after surgery (~24 hours post-operative)	Resume therapeutic doses 2-3 days after surgery (~48-72 hours post-operative); prophylactic dose anticoagulants can be considered in the interim



# Estimating Renal Function

May be estimated with:

- Modification of Diet in Renal Disease (MDRD) equation (eGFR)
- Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (eGFR)
- Cockcroft-Gault (C-G) equation, which estimates creatinine clearance (CrCl)

Cockcroft-Gault using actual body weight, used in all phase 3 direct oral DOAC trials



# Kidney Function Calculations

## Backgrounder

- Multiple formulae have been developed to provide an accurate estimate of renal function.
- The most commonly applied formulae estimate creatinine clearance (CrCl) or filtration of creatinine by the glomerulus (estimated glomerular filtration rate [GFR] or eGFR).
- While the eGFR equations (Modification of Diet in Renal Disease (MDRD) formula or the Chronic Kidney Disease (CKD) Epidemiology Collaboration (CKD- EPI) formula) are more accurate estimates of renal function, **drug manufacturers have used the CrCl (Cockcroft-Gault formula) when recommending medication dosage adjustments for patients with renal dysfunction.**



# Estimating Renal Function

**Renal function cutoffs varied between trials**

- Calculated CrCl  $\leq$  30 mL/min for dabigatran
- Calculated CrCl  $<30$  mL/min for edoxaban and rivaroxaban,
- Serum creatinine  $>2.5$  mg/dL (221  $\mu$ mol/L) or a calculated CrCl of  $<25$  mL/min for apixaban

**Use of equations other than Cockcroft-Gault may result in incorrect DOAC dosing**

**Large database study showed renal function estimations other than Cockcroft-Gault would result in failure to reduce rivaroxaban or edoxaban doses in 28% of patients, and 18%-21% of doses among dabigatran patients.**



# How Often Should We Measure Renal Function?

For patients with renal dysfunction, kidney function should be measured:

- eGFR of **15-30** ml/min/1.73 m<sup>2</sup>: every **3 months**
- eGFR of **30-60** ml/min/1.73 m<sup>2</sup> : every **6 months**
- eGFR of **> 60** ml/min/1.73 m<sup>2</sup> : every **12 months**



# Transitioning from DOACs to Warfarin

Transitioning To → From ↓	Warfarin
<b>Apixaban</b>	<ul style="list-style-type: none"><li>When converting from apixaban to warfarin, continue apixaban for at least 2 days after starting warfarin therapy.<ul style="list-style-type: none"><li>After 2 days of co-administration, obtain an INR prior to the next scheduled dose of apixaban.</li><li>Continue co-administration until the INR is 2 or more</li></ul></li></ul>
<b>Dabigatran</b>	<ul style="list-style-type: none"><li>When converting from dabigatran to warfarin, adjust the starting time of warfarin based on creatinine clearance as follows:<ul style="list-style-type: none"><li>CrCl &gt;50 mL/min, start warfarin 3 days before discontinuing dabigatran.</li><li>CrCl 31-50 mL/min, start warfarin 2 days before discontinuing dabigatran.</li><li>CrCl 15-30 mL/min, start warfarin 1 day before discontinuing dabigatran</li></ul></li></ul>
<b>Edoxaban</b>	<ul style="list-style-type: none"><li>When converting from edoxaban to warfarin, continue edoxaban until the INR is <math>\geq 2.0</math>.<ul style="list-style-type: none"><li>A loading dose of warfarin is not recommended.</li><li>For patients currently on a 60 mg dose, administer edoxaban at a dose of 30 mg once daily together with an appropriate VKA dose.</li><li>For patients currently on a 30 mg dose, administer edoxaban at a dose of 15 mg once daily together with an appropriate VKA dose.</li><li>During the first 14 days of concomitant therapy measure the INR at least 3 times, just prior to the daily dose of edoxaban.</li><li>Edoxaban can contribute to an elevated INR.</li></ul></li></ul>
<b>Rivaroxaban</b>	<ul style="list-style-type: none"><li>When converting from rivaroxaban to warfarin, rivaroxaban should be continued until the INR is <math>\geq 2.0</math>.<ul style="list-style-type: none"><li>For the first two days of the conversion period, standard initial dosing of warfarin should be used followed by warfarin dosing guided by INR testing.</li><li>While patients are on both rivaroxaban and warfarin, the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of rivaroxaban.</li><li>Once rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after the last dose</li></ul></li></ul>

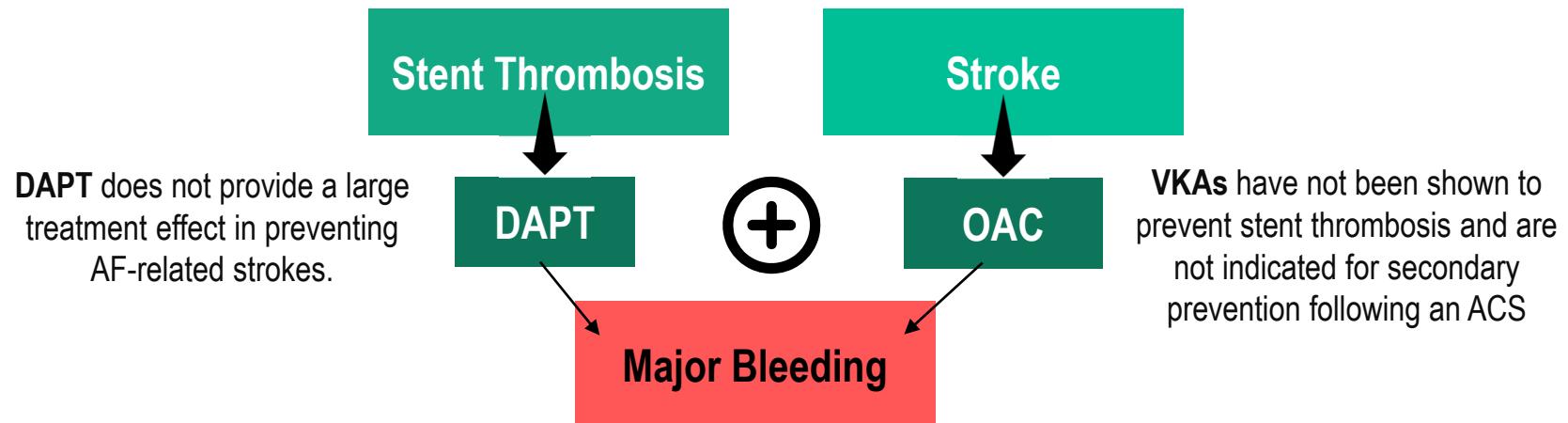


# Background

- Atrial fibrillation (AF) is the most common cardiac arrhythmia, with increasing prevalence among the elderly.
- Approximately 20 to 30% of patients with AF also have concomitant coronary artery disease (CAD) and 5 to 10% of patients who undergo percutaneous coronary intervention (PCI) have AF.



A clinical conundrum arises when patients with AF on oral anticoagulation (OAC) develop an acute coronary syndrome (ACS) and/or require PCI.



**Triple therapy significantly increases the risk of bleeding**

1. Lopes RD et al. *Am Heart J.* June 2018; 200:17-23 doi:10.1016/j.ahj.2018.03.001

2. Adapted from Lopes RD et al. Oral presentation at ACC Apr 2016; Chicago, IL, USA. Abstract number 695-15

3. Dewilde WJ et al. *Lancet* 2013;381:1107-1115

ACS, acute coronary syndrome; AF, atrial fibrillation; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; VKA, vitamin K antagonist.



# Background

## Factors That Increase Risk Of Bleeding

### ■ Patient Factors

- Age (>65 years)
- Low body weight (<60 kg)
- Hypertension
- History of bleeding (esp. within 1y)
- Prior stroke or intracranial bleed
- Combined OAC and antiplatelet use
- Concomitant NSAID or prednisone use
- Excess alcohol consumption
- Abnormal liver function
- CKD (eGFR <60 mL/min)
- Anemia (hemoglobin <110 g/L)
- Labile INR (TTR <60%)

## Factors That Increase Risk Of Ischemic Coronary Events

### ■ Patient Factors

- Diabetes mellitus treated with OHG or insulin
- Current smoker
- CKD (eGFR <60 mL/min)
- Prior ACS
- Prior stent thrombosis

### ■ Clinical Presentation

- ACS (STEMI, NSTEMI, UA)

### ■ Angiographic Factors

- Multi vessel disease
- Multiple ( $\geq 3$ ) stents implanted
- Stenting of a bifurcation lesion
- Total stent length >60 mm
- Left main or proximal LAD stenting
- Chronic occlusion intervention
- Bioabsorbable vascular scaffold



# 2018 Focused Update of the CCS AF Guidelines



**Canadian Cardiovascular Society**  
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## RECOMMENDATION

**When an OAC is indicated in the presence of coronary or arterial vascular disease, we suggest a DOAC in preference to warfarin**

**(Weak Recommendation, Moderate-Quality Evidence)**



# 2018 Focused Update of the CCS AF Guidelines



**Canadian Cardiovascular Society**

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## RECOMMENDATIONS

For patients with NVAF/AFL aged < 65 years with no CHADS<sub>2</sub> risk factors, we suggest no antithrombotic therapy for stroke prevention (Weak Recommendation, Moderate-Quality Evidence), with management of their coronary or arterial vascular disease as directed by the 2018 CCS/CAIC focused update of the guidelines for the use of antiplatelet therapy.

For patients with AF aged ≥ 65 years or with a CHADS<sub>2</sub> score ≥ 1 and coronary or arterial vascular disease (peripheral vascular disease or aortic plaque), we recommend long-term therapy with an OAC alone (Strong Recommendation, High-Quality Evidence).

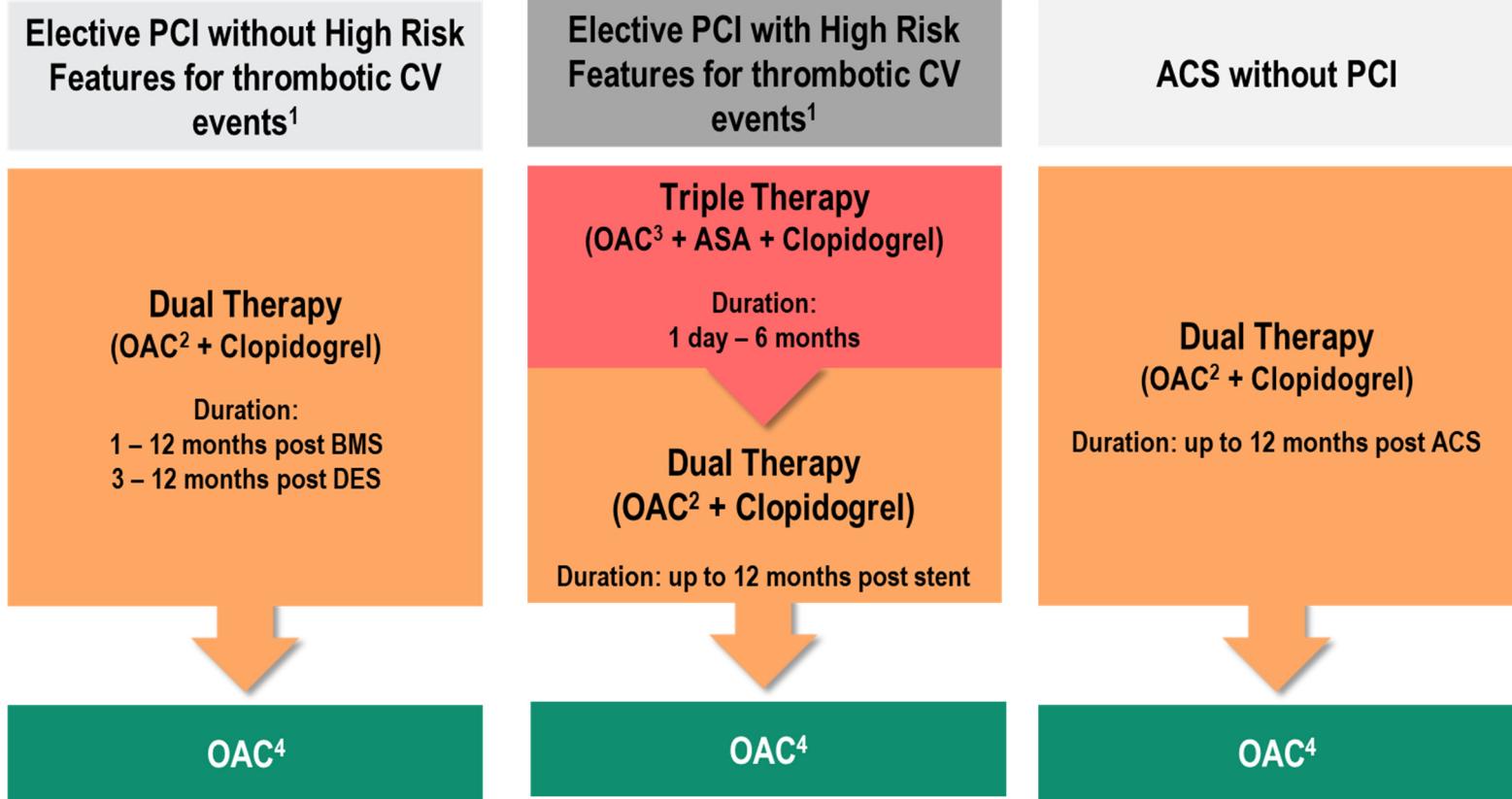
**ASA alone** is appropriate in AF patients at low risk of embolic stroke (< 1.5%/yr)

**DOAC alone** is appropriate in AF patients with stable CAD when anticoagulation is indicated (risk of embolic stroke ≥ 1.5 %/yr)



# AF Patients with Coronary or Peripheral Arterial Disease and an Indication for OAC\*

## 2018 Focused Update of the CCS AF Guidelines



# The FORTA (Fit for the Aged) List

- Classifies medications frequently prescribed to older patients
- Structured literature search identified evidence for experts
- Delphi process – individual ranking by experts into Class A, B, C, D
- Considers age-dependent tolerance, compliance, polypharmacy, multi-morbidity, frequency of relative contraindications
- Updated list at <http://www.umm.uni-heidelberg.de/ag/forta/>
- Utility demonstrated in prospective randomized trials



# The FORTA (Fit for the Aged) List

<b>Class A (absolutely)</b>	Indispensable drug, clear-cut benefit in terms of efficacy/safety ratio proven in elderly patients for a given indication
<b>Class B (beneficial)</b>	Drugs with proven or obvious efficacy in the elderly, but limited extent of effect or safety concerns
<b>Class C (careful)</b>	Drugs with questionable efficacy/safety profiles in the elderly, to be avoided or omitted in the presence of too many drugs, lack of benefits or emerging side effects; review/find alternatives
<b>Class D (don't)</b>	Avoid in the elderly, omit first, review/find alternatives



# The FORTA (Fit for the Aged) List

<b>Class A (absolutely)</b>	ACE-I for HT, calcium antagonists for HT, statins for cardiovascular protection, ACE-I for CHF, diuretics for CHF
<b>Class B (beneficial)</b>	diuretic for HT, beta-blocker for HT, bisphosphonates for osteoporosis
<b>Class C (careful)</b>	spironolactone for HT, ezetimibe for cholesterol lowering, amiodarone for atrial fibrillation
<b>Class D (don't)</b>	benzodiazepines, promethazine, pentazocine



# The FORTA (Fit for the Aged) List

## Anticoagulants for Atrial Fibrillation

### **Class A (absolutely)**

Indispensable drug, clear-cut benefit in terms of efficacy/ safety ratio proven in elderly patients for a given indication

- **apixaban**

### **Class B (beneficial)**

Drugs with proven or obvious efficacy in the elderly, but limited extent of effect or safety concerns

- **rivaroxaban**
- **edoxaban (high)**
- **dabigatran (high and low)**
- **warfarin**

### **Class C (careful)**

Drugs with questionable efficacy/safety profiles in the elderly, to be avoided or omitted in the presence of too many drugs, lack of benefits or emerging side effects; review/find alternatives

- **acenocoumarol**
- **fluindione**
- **phenprocoumon**

### **Class D (don't)**

Avoid in the elderly, omit first, review/find alternatives



# Pretest Diagnosis

## Two Level Wells Score for DVT Diagnosis



CLINICAL FINDINGS	Point	Stella
Paralysis, paresis or recent cast lower extremity	1	0
Bedridden > 3 days or major surgery within 4 weeks	1	0
Tenderness of the deep veins	1	1
Swelling of entire leg	1	0
Calf Swelling 3 cm > greater than other leg	1	1
Pitting edema greater in the symptomatic leg	1	0
Non –varicose collateral superficial veins	1	0
Active cancer or cancer treated within 6 months	1	0
Previously documented DVT	1	0
Alternative diagnosis at least as likely as DVT (Baker's cyst, cellulitis, muscle damage, superficial vein thrombosis, post-thrombotic syndrome, inguinal lymphadenopathy, extrinsic venous compression)	-2	0
<b>Total Score</b>	<b>-2 to +9</b>	<b>2</b>



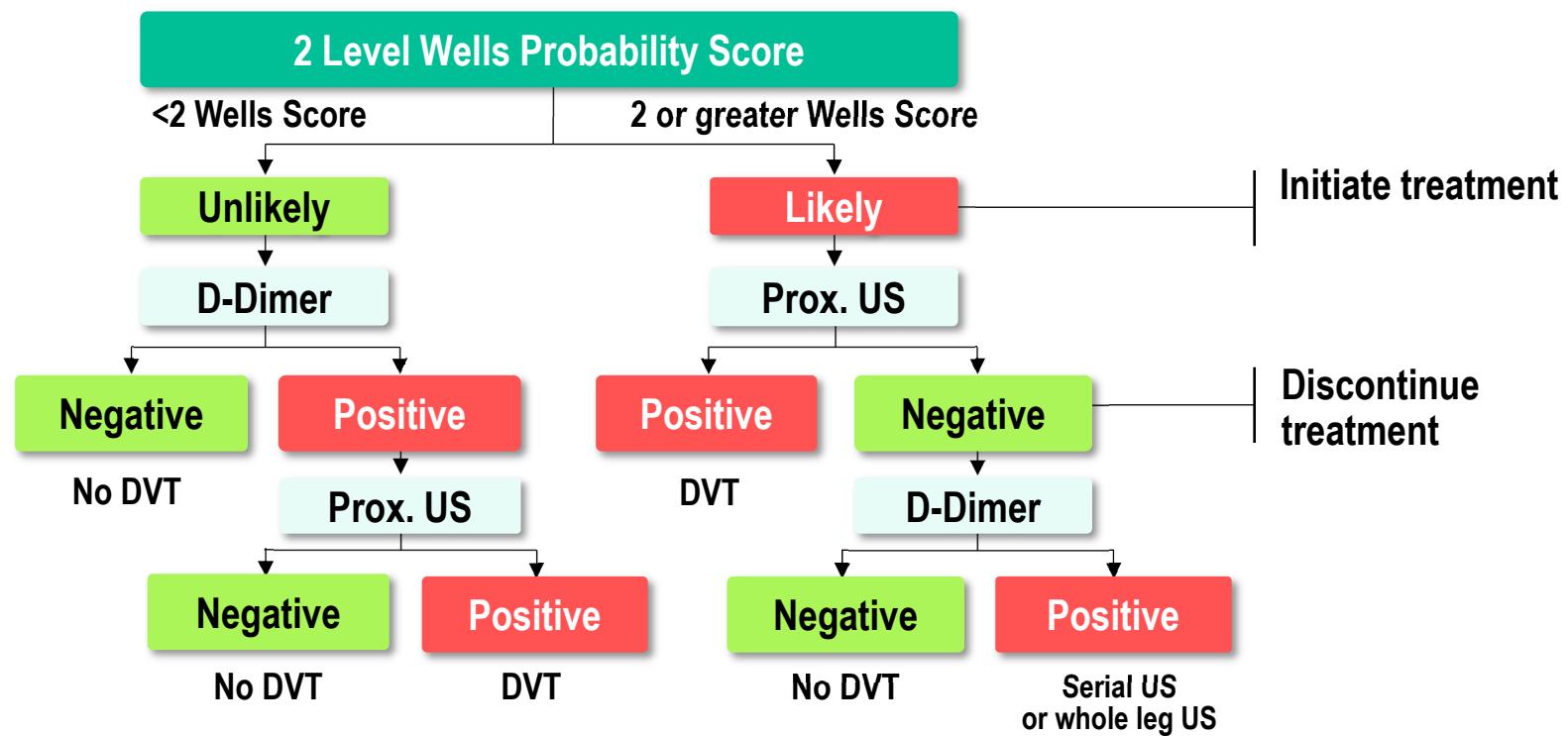
# Two-Level Pretest Probability for DVT Diagnosis

Wells Score	Probability of DVT	Likelihood
< 2	6%	Unlikely
≥ 2	28%	Likely



# DVT Diagnostic & Treatment Algorithm

Assuming initial U/S was a full leg U/S



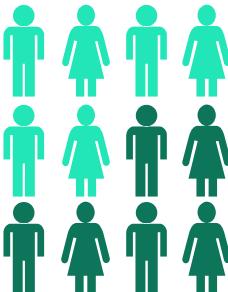
\*DVT, deep vein thrombosis; US, ultrasound

Adapted from: Thrombosis Canada. Deep Vein Thrombosis: Diagnosis. Available at: [http://thrombosiscanada.ca/?page\\_id=18#](http://thrombosiscanada.ca/?page_id=18#).



# Risks of Untreated DVT

~50% ➡



of people with proximal lower extremity DVT will develop PE if not treated

The mortality rate for PE without treatment is approximately



30% ➡

compared to 1–8% with adequate therapy



# Starting Anticoagulation in Patients with a likely Pretest Probability of DVT/PE



Anticoagulation should be started immediately\* in patients with a likely Pretest Probability of DVT/PE

- In patients with a high clinical suspicion of acute DVT, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C).
- In patients with an intermediate clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C)
- In patients with a low clinical suspicion of acute VTE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C)



# Starting Anticoagulation in Patients with a likely Pretest Probability of DVT/PE



**\*2. In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy (all Grade 2B).**

**Remarks:** Initial parenteral anticoagulation is given before dabigatran and edoxaban, is not given before rivaroxaban and apixaban, and is overlapped with VKA therapy.



# Antithrombotic Dosing in VTE

Drug	Initial Treatment	Long Term (additional 3 months)	Extended >6 months if indicated
Apixaban	10 mg bid x 7 days	5 mg bid	2.5 mg bid
ASA	Not indicated	Not indicated	81-100 mg daily if OAC not possible
Dabigatran	LMWH for 5-10 days	150 mg bid *	150 mg bid *
Edoxaban	LMWH for 5-10 days	60 mg daily	60 mg daily
Rivaroxaban	15 mg bid x 21 days	20 mg daily	20 mg daily
Warfarin	LMWH for 5 days min & INR $\geq$ 2 for 2 days	Variable (INR 2-3)	Variable (INR 2-3)

\*(110 mg bid if age  $\geq$  80, or age  $\geq$  75 + higher risk of bleeding, including CrCl 30-50 mL/min)



# Overview: Indirect Comparisons of DOAC Trials for Acute VTE Treatment

	APIXABAN <sup>1</sup>	DABIGATRAN <sup>4,5</sup>	EDOXABAN <sup>7</sup>	RIVAROXABAN <sup>*2,3,6</sup>
Trial design: double-blind	Yes (n= 5395)	Yes (n=5132)	Yes (n=8292)	No (n=8281)
Single agent (i.e., no LMWH and/or UFH lead-in )	Yes	No	No	Yes
Duration of treatment	6 months	6 months	3 to 12 months	3, 6 or 12 months
Non-inferior efficacy vs. comparator* (recurrent or fatal VTE)	Yes	Yes	Yes	Yes
Major bleeding vs. comparator*		NS	NS	
Major or CRNM bleeding vs. comparator*				NS
Dosing	BID	BID	QD	BID then QD



Significant Reduction p<0.05

NS = no significant difference

\*Pooled analysis

To date there are no head-to-head trials between DOACs, therefore comparative efficacy and safety have not been established

\*Comparator was LMWH or UFH followed by either a VKA (warfarin or acenocoumarol) in the rivaroxaban trials or warfarin in the other NOAC trials.  
Agnelli G, et al. N Engl J Med 2013; 369:799-808. 2. The EINSTEIN Investigators. New Engl J Med 2010; 363:2499-510.

3. The EINSTEIN-PE Investigators. New Engl J Med 2012; 366:1287-97. 4. Schulman S, et al. N Engl J Med 2009; 361:2342-52.

5. Schulman S, et al. Blood (ASH Annual Meeting Abstracts) 2011; 118: Abstract 205. 6. Prins et al. Thrombosis Journal 2013, 11:21 <http://www.thrombosisjournal.com/content/11/1>. 7. The HOKUSAI-VTE Investigators. N Engl J Med. 2013; 369:1406-15.



# Indirect Comparisons Overview: DOAC Trials for Extended VTE Treatment $\geq$ 6 months

	Apixaban <sup>1</sup>	Dabigatran <sup>3</sup>	Rivaroxaban <sup>2</sup>	Rivaroxaban <sup>4</sup>
Trial design: double-blind	Yes N=2482	Yes N=1353	Yes N= 1196	Yes
Comparator	Placebo	Placebo	Placebo	ASA
Duration of treatment	12 months	6 months	6 or 12 months	12 months
Dosing	BID	BID	QD	QD
Dose/s of DOAC studied/approved	2.5mg & 5mg	150mg or 110mg*	20mg	10mg/20mg
Superior efficacy (recurrent or fatal VTE) vs comparator	Yes	Yes	Yes	Yes
Major bleeding vs comparator	NS	NS	NS	NS
Major or clinically-relevant non-major bleeding vs comparator	NS	↑	↑	NS

NS = no significant difference



Significant increase p<0.05

*To date there are no head-to-head trials between DOACs, therefore comparative efficacy and safety have not been established*

1. Agnelli G et al. N Engl J Med 2013; 368: 699-708

2. The EINSTEIN Investigators. N Engl J Med. 2010;363:2499-2510

3. Schulman S et al. N Engl J Med. 2013; 368:709-718

4 Weitz JL et all, N. Engl. J. Med. 2017.



# Duration of Anticoagulant Therapy for DVT

CATEGORIES OF VTE	DURATION OF TREATMENT
Provoked by a transient risk factor*	3 months
First unprovoked VTE†	Minimum of 3 months and then reassess
Proximal DVT or PE with no or only minor risk factors for bleeding	Indefinite therapy with annual review, depending on patient preference
Isolated distal DVT	3 months
Second unprovoked VTE	Minimum of 3 months, then reassess. For patients with no or only minor risk factors for bleeding, indefinite therapy with annual review‡
Cancer-associated VTE	Minimum 3 months, then reassess and continue if active cancer (overt evidence of cancer) or continuing to receive anticancer therapy

\* eg. surgery, hospitalization or plaster cast immobilization, all within 3 months; estrogen therapy, pregnancy, leg injuries or immobilizations more recently (e.g. within 6 weeks).

† Absence of a transient risk factor or active cancer

‡ Indefinite therapy is suggested if there is a low or moderate risk of bleeding, and 3 months is suggested if there is a very high risk of bleeding; both of these decisions are sensitive to patient preference.





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