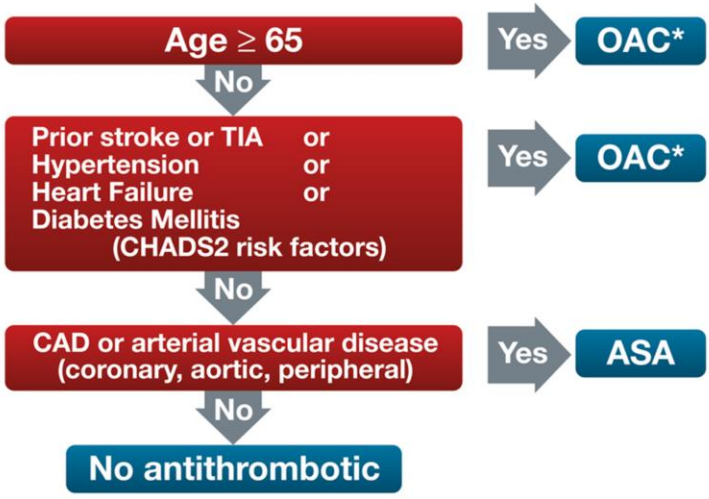
The "CCS Algorithm" for OAC Therapy in AF



Consider and modify (if possible) all factors influencing risk of bleeding with OAC (hypertension, antiplatelet drugs, NSAIDs, excessive alcohol, labile INRs) and specifically bleeding risks for DOACs (low eGFR, age ≥ 75, low body weight)**

**may require lower dosing

Verma A, et al. Can J Cardiol 2014; 30(10):1114-30.

Randomized Controlled Trials (RCTs) and Real-world Data (RWD): How Do They Differ?

- RCTs test the efficacy of a drug in ideal circumstances with strict inclusion/exclusion criteria
- RWD complements RCTs by allowing us to look at:

1. Hannan EL. JACC Cardiovasc Interv 2008; 1:211-17.
2. Sorensen HT, et al. Hepatology 2006; 1075-82.

What are the Differences and Similarities Between RWD and Data From RCTs?

Comparison	RCTs	Real-world data (RWD)
Study objectives	• Efficacy (ideal circumstances)	• Effectiveness and safety • Place in therapeutic pathway
Setting	• Protocol-driven	• Routine clinical care
Purpose	• Regulatory approval/commitments	• Drug performance in real-world settings
Interpretation	• Confirmatory association between drug and outcomes	• Exploratory association between drug and outcomes
Sample size	• Relatively small	• Larger than RCT
Comparator	• Fixed	• Broader options for comparators than RCT
Compliance	• High	• Low to high
Design	• Prospective	• Retrospective or prospective
Time to results	• Relatively slow	• Relatively fast (if retrospective)
Cost	• High	• High for prospective, mid for chart reviews, low for retrospective
Statistics	• Relatively simple	• More complex than RCTs
Internal validity	• High	• Low
External validity (general disability)	• Low to medium	• Medium to high

Real-world Data

Dabigatran

- Danish registry
- Mini-sentinel
- FDA analyses
- DOD
- GLORIA-AF
- U.S. claims/admin databases

Rivaroxaban

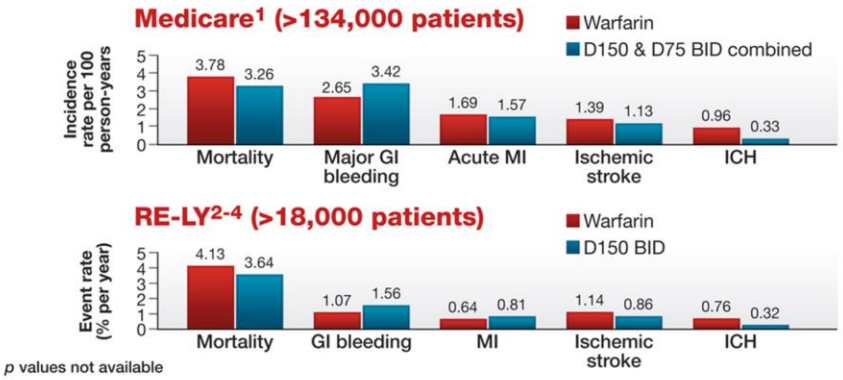
- GARFIELD AF
- GARFIELD VTE
- XAMOS
- XANTUS
- XALIA
- U.S. claims/admin databases

Apixaban

- U.S. claims/admin databases
- Lip G, et al
- Deitelzweig, et al
- Lin, et al
- Tepper, et al
- Benhaddi, et al (U.K.)
- Lefevre, et al (Spain)

Independent FDA Medicare Analysis (2014)

Baseline characteristics, endpoint definitions and methodology between RCT and RWD analyses show important differences; results cannot be directly compared.

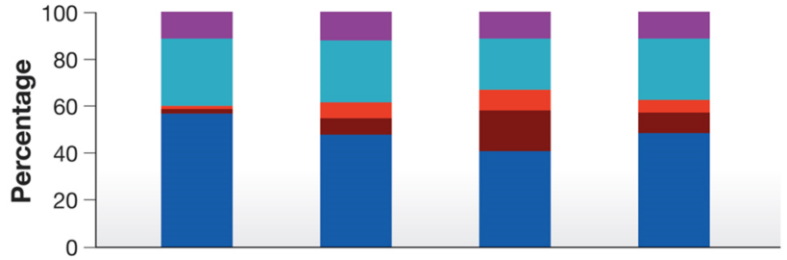


p values not available

1. Available at: *www.fda.gov/Drugs/DrugSafety/ucm396470.htm*. Accessed May 2014. 2. Connolly SJ, et al. N Engl J Med 2009; 361:1139-51.
3. Connolly SJ, et al. N Engl J Med 2010; 363:1875-6. 4. Pradaxa Product Monograph (EU), 2014.

GARFIELD: Anticoagulation Patterns

Treatment at diagnosis by cohort

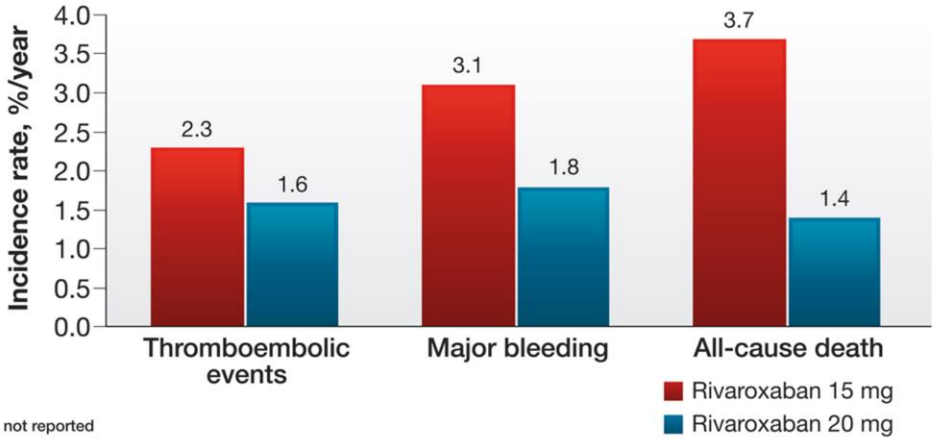


	Cohort 1 Dec 09-Oct 11 N = 10,278	Cohort 2 Oct 11-Jun 13 N = 11,557	Cohort 3 Jun 13-Jun 14 N = 9,831	Total Dec09-Jun14 N = 31,666
VKA±AP	57.5	48.5	41.1	49.1
FXa±AP	2	6.8	17.7	8.6
DTI±AP	1.1	7	8.7	5.6
AP	28.6	26.2	19.8	25
None	10.8	11.5	12.7	11.7

p values not available

Kakkar AJ. Presented at ESC 2014. Oral presentation.

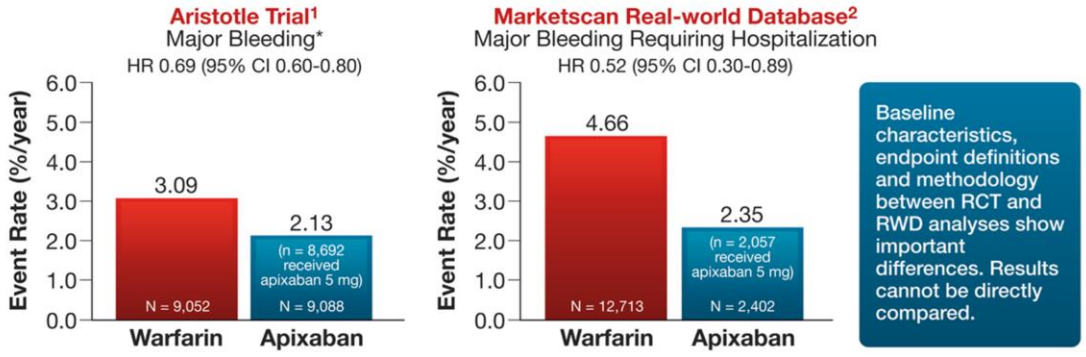
XANTUS: Outcomes According to Dose



p values not reported

Camm AJ, et al. Eur Heart J 2015; doi: 10.1093/eurheartj/ehv466. [epub ahead of print]

Risk of First Major Bleed Across NVAF Patients: Apixaban vs. Warfarin



The definition of major bleeding in clinical trials was different than in the real-world data initiative.
*Clinically overt bleeding accompanied by a decrease in the hemoglobin level of at least 2 g/dL or transfusion of at least 2 units of packed red cells, occurring at a critical site, or resulting in death.
NVAF = non-valvular atrial fibrillation.
1. Granger CB, et al. N Engl J Med 2011; 365(11):981-92.
2. Lip GYH, et al. Presented at ESC 2015. Poster P6217.

Most Important Aspects of an Anticoagulant for Stroke Prevention in AF

- Efficacy in stroke risk reduction
- Reduction in all-cause mortality
- Risk of major bleeding
- Low incidence of GI bleeding
- Demonstrated safety vs. ASA
- Safe in patients with moderate-to-severe renal impairment
- Good tolerability
- Once-a-day formulation
- Appropriate for a broad range of AF patients (*e.g.,* age, risk level)

Bleeding Risks for Invasive / Surgical Procedures

High or very high risk

- Any procedure involving neuraxial anasthesia
- Neurosurgery (intracranial or spinal surgery
- Cardiac surgery (*e.g.,* CABG, heart valve replacement)
- Major vascular surgery (*e.g.,* aortic aneurysm repair, aortofemoral bypass)
- Major urological surgery (*e.g.,* prostatectomy, bladder tumor resection)
- Major lower-limb orthopedic surgery (*e.g.,* hip/knee joint replacement surgery)
- Lung resection surgery
- Intestinal anastomosis surgery
- Selected procedures (*e.g.,* kidney biopsy, prostate biopsy, cervical cone biopsy, pericardiocentesis, colonic polypectomy)

Low or standard risk

- Other intra-abdominal surgery
- Other intrathoracic surgery
- Other orthopedic surgery
- Laparoscopic cholecystectomy
- Laparoscopic inguinal hernia repair
- Dental procedures
- Dermatologic procedures
- Ophthalmologic procedures
- Coronary angiography
- Cardiac implantable electronic device† (pacemaker, implantable defibrillator)
- Gastroscopy without biopsy, colonoscopy without polypectomy
- Selected procedures (*e.g.,* bone-marrow biopsy, lymph-node biopsy, thoracentesis, paracentesis, arthrocentesis)

Very low risk*

- Tooth extraction (1 or 2 teeth) or teeth cleaning
- Skin biopsy or skin-cancer removal
- Cataract removal

† Antithrombotic therapy with ASA or warfarin (INR 2.0 - 3.0) may continue for implantation of cardiac implantable devices. In addition to the bleeding risk of a procedure, physicians should consider co-morbid conditions that might exacerbate the bleeding resk (*e.g.,* advanced age, renal or liver impairment).

* May continue warfarin at therapeutic INR 2.0 - 3.0 or other anticoagulants.

Can J Cardiol 2014;30 1114-1130. Thrombosis Canada

Thrombosis Canada Suggested Guide for PRE-OPERATIVE Management of Patients Receiving a DOAC

Drug (Dose regimen)	Renal function	Procedures with low bleeding risk* 12-25% residual anticoagulant effect at time of surgery acceptable	Procedures with high or very high bleeding risk* < 10% residual anticoagulant effect at time of surgery acceptable
Apixaban (twice daily)	Normal renal function, mild or moderate impairment (CrCl > 30 mL/min)	Give last dose 2 days before surgery/procedure* (*i.e.*, skip 2 doses)	Give last dose 3 days before surgery/procedure* (*i.e.*, skip 4 doses)
Dabigatran (twice daily)	Normal renal function or mild impairment (CrCl > 50 mL/min)	Give last dose 2 days before surgery/procedure* (*i.e.*, skip 2 doses)	Give last dose 3-4 days before surgery/procedure* (*i.e.*, skip 4-6 doses)
	Moderate renal impairment (CrCl 30-50 mL/min)	Give last dose 3 days before surgery/procedure* (*i.e.*, skip 4 doses)	Give last dose 5-7 days before surgery/procedure* (*i.e.*, skip 8-12 doses)
Rivaroxaban (once daily)	Normal renal function, mild or moderate impairment (CrCl > 30 mL/min)	Give last dose 2 days before surgery/procedure* (*i.e.*, skip 1 dose)	Give last dose 3 days before surgery/procedure* (*i.e.*, skip 2 doses)

*No anticoagulant taken on the day of surgery/procedure

†Neuraxial procedures include spinal anesthesia, epidural catheter insertion and epidural catheter removal.

NOTE: Information on this slide is based on Thrombosis Canada guidelines and might not reflect the product monographs.

Adapted from: *www.thrombosiscanada.ca*.

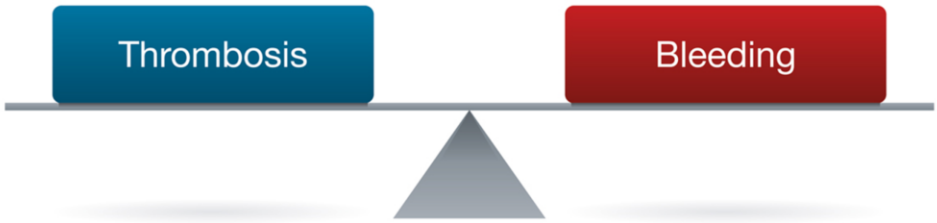
Thrombosis Canada Suggested Guide for POST-OPERTATIVE Management of Patients Receiving a DOAC

Drug	Minor surgery/procedure (low bleeding risk)	Major surgery/procedure (high bleeding risk)
Apixaban	Resume on day after surgery (~24 hours post-operative)	Resume 2 days after surgery (~48 hours post-operative)
Dabigatran	Resume on day after surgery (~24 hours post-operative)	Resume 2 days after surgery (~48 hours post-operative)
Rivaroxaban	Resume on day after surgery (~24 hours post-operative)	Resume 2 days after surgery (~48 hours post-operative)

NOTE: Information on this slide is based on Thrombosis Canada guidelines and might not reflect the product monographs.

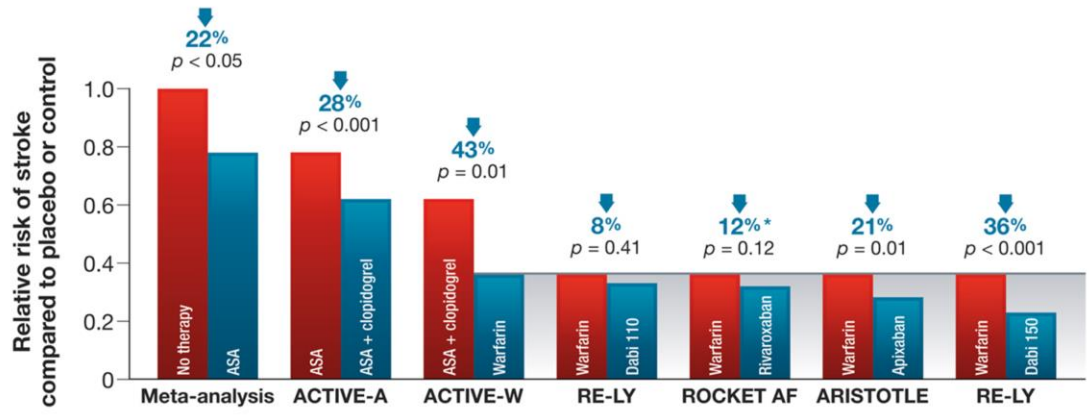
Adapted from: *www.thrombosiscanada.ca*.

The Efficacy and Safety Dilemma of Oral Anticoagulants for Stroke Prevention



Is this the correct metaphor?

Antithrombotic Therapy in Perspective

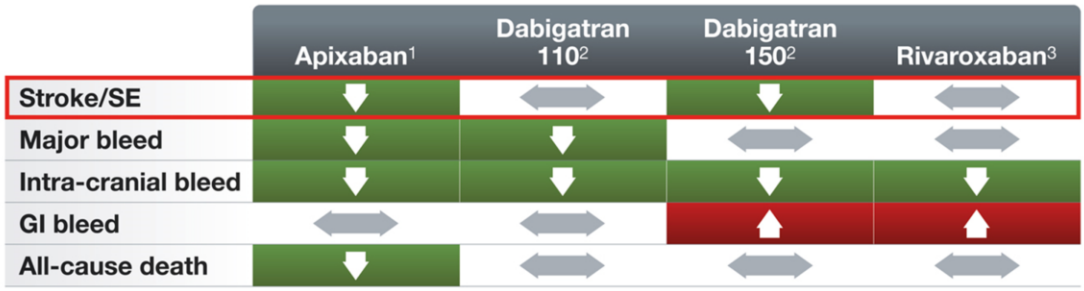


*Data for ROCKET AF is for RR stroke + SE

1. Verma A, et al. Can J Cardiol 2014; 30:1114-30. 2. Granger C, et al. N Eng J Med 2011; 365:981-92.
3. Connolly SJ, et al. N Engl J Med 2009; 361:1139-51. 4. Patel MR, et al. N Engl J Med 2011; 365:883-91.
5. Eur Heart J 2012; 33:2163-71.

Direct Oral Anticoagulants Compared to Warfarin

Indirect Comparisons from the Clinical Trials



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

▲ Significant increase ▼ Significant reduction ⟷ Non-significant difference

1. Granger C, et al. N Engl J Med 2011; 365:981-92.
2. Connolly SJ, et al. N Engl J Med 2009; 361:1139-51.
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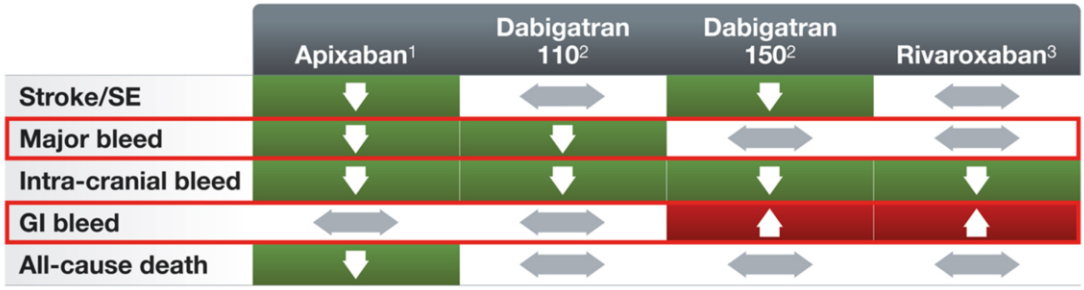

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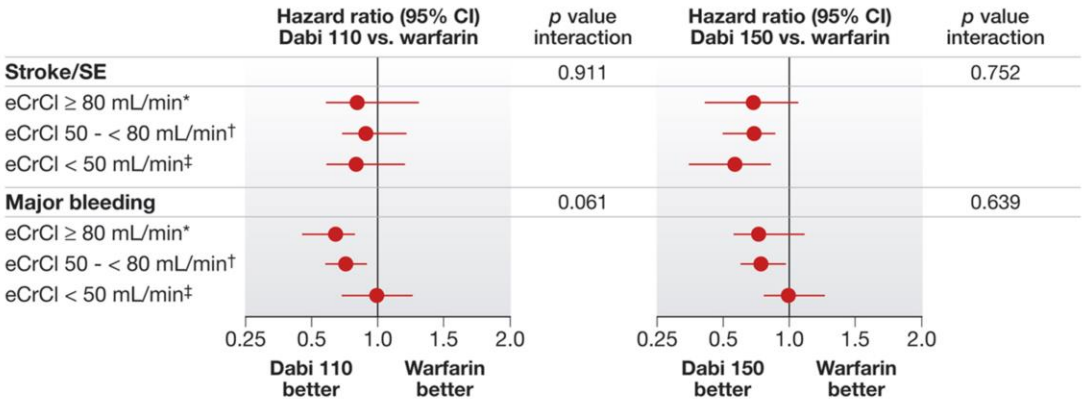
3. Patel MR, et al. N Engl J Med 2011; 365:883-91.

Efficacy and Safety of Dabigatran According to Creatinine Clearance (Cockcroft-Gault)

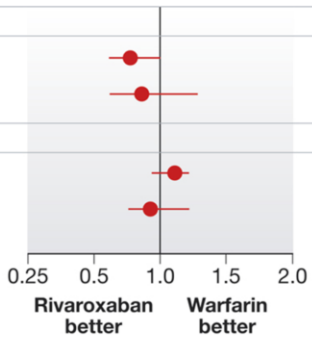


*n = 5,844 (32.6%); †n = 8,553 (47.6%); ‡n = 3,554 (19.8%). Results were consistent regardless of methods for GFR estimation.

Hijazi Z, et al. Circulation 2014; 129:961-70.

Efficacy and Safety of Rivaroxaban According to Creatinine Clearance (Cockcroft-Gault)

	Rivaroxaban	Warfarin	Hazard ratio (95% CI)	*p* value interaction
Stroke/SE	Number of events per 100 pt-yrs			0.76
eCrCl ≥50 mL/min*	1.57	2.00		
eCrCl 30-49 mL/min†	2.32	2.77		
Major bleeding				0.48
eCrCl ≥50 mL/min*	3.39	3.17		
eCrCl 30-49 mL/min†	4.49	4.70		

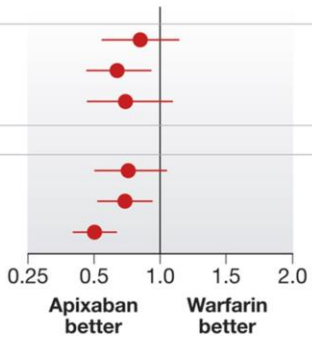


*rivaroxaban 20 mg (n = 5,637; 79%); †rivaroxaban 15 mg (n = 1,474; 21%); per protocol population.

Fox KAA, et al. Eur Heart J 2011; 32:2387-94.

Efficacy and Safety of Apixaban According to Creatinine Clearance (Cockcroft-Gault)

	Apixaban	Warfarin	Hazard ratio (95% CI)	*p* value interaction
Stroke/SE	Number of events (%/yr)			0.705
eCrCl >80 mL/min*	0.99% (70)	1.12% (79)		
eCrCl >50-80 mL/min†	1.24% (87)	1.69% (116)		
eCrCl ≤50 mL/min‡	2.11% (54)	2.67% (69)		
Major bleeding				0.03
eCrCl >80 mL/min*	1.46% (96)	1.84% (119)		
eCrCl >50-80 mL/min†	2.45% (157)	3.21% (199)		
eCrCl ≤50 mL/min‡	3.21% (73)	6.44% (142)		



*n = 7,518 (41%); †n = 7,587 (42%); ‡n = 3,017 (17%). Results were consistent regardless of methods for GFR estimation.

Hohnloser SH, et al. Eur Heart J 2012; 22:2821-30.

Frequency of Measurements

For preserved renal function

- Annual renal function, hemoglobin, and hepatic function

For patients with renal dysfucntion

- If eGFR 30-60 mL/min: renal function every six months
- If eGFR 15-30 mL/min: renal function every three months

CCS AF Guidelines. Available at: www.ccs.ca.

DOAC Dosing for Patients with AF According to Renal Function†

DOAC	CrCl (mL/min)	Drug dose	Comment
Dabigatran	> 50	110 or 150 mg twice daily	Consider 110 mg dose in patients at increased risk for bleeding or in the elderly (*e.g.*, age ≥ 80 years). Measure CrCl every 12 months.
	30-50	110 or 150 mg twice daily	Consider 110 mg dose in patients at increased risk for bleeding or in the elderly (*e.g.*, age ≥ 80 years). Measure CrCl every 12 months **and** with acute illness. Consider avoiding if deteriorating renal function.
	< 30	Avoid dabigatran	Consider warfarin as alternative anticoagulant.
Rivaroxaban	> 50	20 mg once daily	Measure CrCl every 12 months.
	30-50	15 mg once daily	Measure CrCl every 12 months **and** with acute illness. Consider avoiding if deteriorating renal function.
	< 30	Avoid rivaroxaban	Consider warfarin as alternative anticoagulant.
Apixaban	> 50	5 mg twice daily	Measure CrCl every 12 months.
	25-50	5 mg twice daily	2.5 mg twice daily in patients with creatinine ≥133 µmol/L who are also ≥ 80 years or ≤ 60 kg. Measure CrCl every 12 months **and** with acute illness.
	< 25	Avoid apixaban	Consider warfarin as alternative anticoagulant.

†It is advised to consult with a specialist if there is uncertainty about the appropriate DOAC and dose regimen and if warfarin provides a better oral anticoagulation option for individual patients.

NOTE: Information on this slide is based on Thrombosis Canada guidelines and might not reflect the product monographs.

Thrombosis Canada. Stroke Prevention in Atrial Fibrillation. Available at: www.thrombosiscanada.ca. Accessed January 2016.

Baseline Factors Independently Associated With Increased Risk of Major Hemorrhage

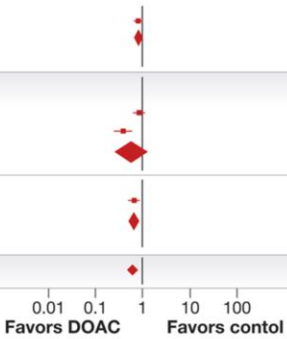
- Older age
- Poor renal function (CrCl < 85 mL/min/1.73 m^2)
- History of bleeding
- Low hematocrit (< 45%)
- ASA or NSAIDs at randomization
- Prior stroke/TIA/SE or diabetes
- Male

Hylek et al. J Am Coll Cardiol 2014; pii:S0735-1097(14)01386-2.

DOACs in Elderly Adults: Evidence From a Meta-analysis of Randomized Trials

Stroke or systemic embolism: Patients aged ≥ 75 years

DOAC/study	Odds ratio vs. control* (95% CI)
Rivaroxaban	
ROCKET-AF†	0.80 (0.6-1.0)
Subtotal (n = 3,082)	**0.80 (0.6-1.0)**
Apixaban‡	
ARISTOTLE†	0.72 (0.5-0.9)
AVERROES†	0.31 (0.2-0.5)
Subtotal (n = 3,652)	**0.49 (0.2-1.1)**
Dabigatran	
RE-LY†	0.75 (0.6-0.9)
Subtotal (n = 4,828)	**0.75 (0.6-0.9)**
Total (n = 11,562)	**0.65 (0.5-0.9)**



†AF patients
‡For apixaban, comparisons vs. warfarin or ASA; others are vs. heparin or warfarin.

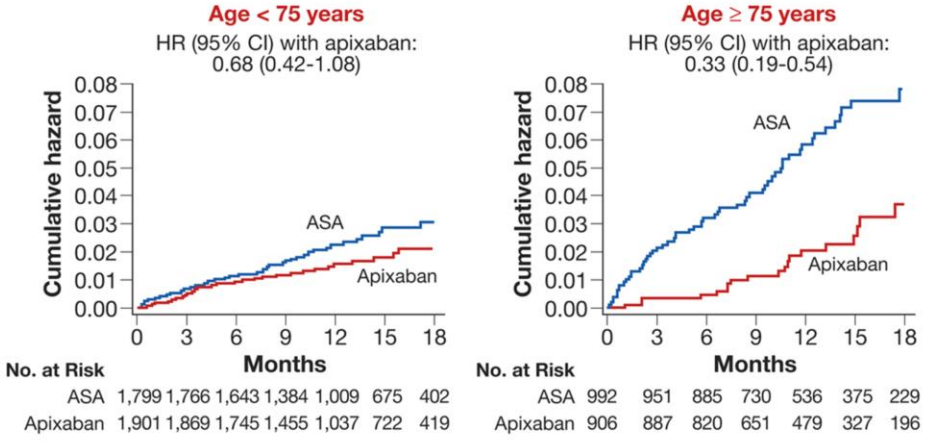
Sardar P, et al. J Am Geriatr Soc 2014; 62(5):857-64.

DOACs vs. Control Therapy in Patients ≥ 75 Years

Trial/DOAC	No. of participants ≥ 75 years	HR for stroke risk (95% CI)	HR for major hemorrhage (95% CI)
RE-LY vs. warfarin			
Dabigatran 110 mg bid	7,258	0.88 (0.7-1.2)	1.01 (0.8-1.2)
Dabigatran 150 mg bid		0.67 (0.5-0.9)	1.18 (0.9-1.4)
ROCKET-AF vs. warfarin Rivaroxaban 20 mg bid	6,229	0.88 (0.8-1.0)	1.04 (0.9-1.2)
ARISTOTLE vs. warfarin Apixaban 5 mg bid	5,678	0.79 (0.6-0.9)‖	0.69 (0.6-0.8)
AVERROES vs. ASA Apixaban 5 mg bid	1,897	0.46 (0.3-0.6)‖	1.13 (0.7-1.8)

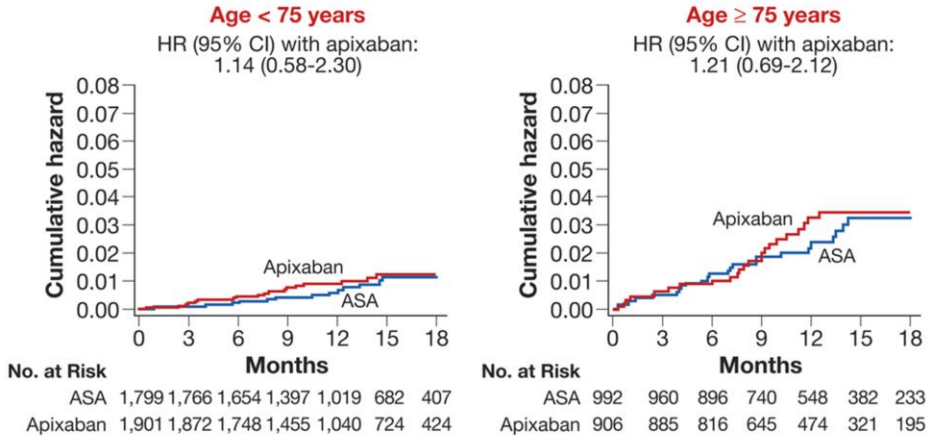
Ng KH, et al. Cardiol Ther 2013; 2:135-49

Cumulative hazard rates of stroke with ASA vs. apixaban in patients aged < 75 years or ≥ 75 years



Ng KH, et al. Age Ageing 2016; 45(1):77-83.

Cumulative hazard rates of major bleeding with ASA vs. apixaban in patients aged < 75 years or ≥ 75 years



Ng KH, et al. Age Ageing 2016; 45(1):77-83.

Bleeding Reversal for Patients Taking a DOAC

Activated charcoal can be considered if the offending DOAC was taken within 2 hours.

Reversal agents:

Agent	Dabigatran	Rivaroxaban or Apixaban
PCC	Possibly beneficial	Probably beneficial
Activated PCC	Probably beneficial	Probably beneficial
rFVIIa	Possibly beneficial	Possibly beneficial

Dialysis may be beneficial for diabigatran.

Fawole A, et al. Cleve Clin J Med 2013; 80(7):443-51.