THE Q & A OF ANTICOAGULATION

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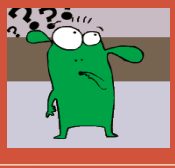


WHAT ANTICOAGULANTS ARE AVAILABLE FOR USE?

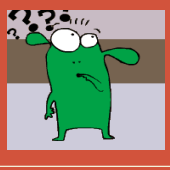
Anticoagulants in frequent use in Australia and on the PBS

oral

- Warfarin (Vitamin K antagonist)
- Apixaban (Xa antagonist)
- rivaroxaban (Xa antagonist)
- Dabigatran (Direct thrombin inhibitor)

systemic

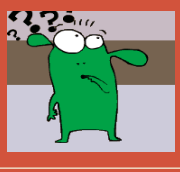
- Intravenous unfractionated heparin
- Subcutaneous enoxaparin (Xa antagonist)



WHAT IS NOT "NON-VALVULAR AF & WHEN SHOULD I USE WARFARIN?"

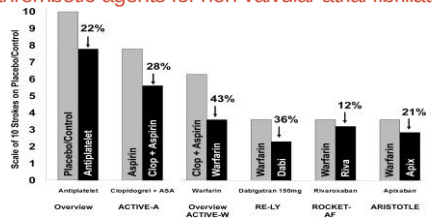
When warfarin is my friend

Mechanical heart valves	Mitral stenosis
warfarin	
Renal failure (eGFR<30)	Patient preference



REMIND ME ABOUT THE TRIALS FOR NON-VALVULAR AF?

Stroke risk reductions in randomized trials of antiplatelet & antithrombotic agents for non-valvular atrial fibrillation.

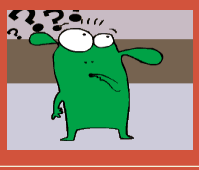


Christopher B. Granger, and Luciana V. Armaganijan
Circulation. 2012;125:159-164

Comparison of the DOAC trials

Pivotal Trial	RE-LY (Dabigatran Etexilate)		ROCKET-AF (Rivaroxaban)	ARISTOTLE (Apixaban)
Study type	Open-label, randomized		Double-blind, double-dummy, randomized	Double-blind, double-dummy, randomized
Subjects (N)	18 113		14 264	18 201
Dosages studied vs adjusted-dose warfarin	110 mg† BID	150 mg BID	20 mg/d (15 mg/d for reduced renal function)	5 mg BID (2.5 mg BID with ≥2 of: age ≥80, bw ≤60 kg, SCr ≥1.5)
Mean warfarin time in therapeutic range (%)	64		55	62
Mean $CHADS_2$ score	2.1	2.2	3.5	2.1
Mean age, y	71		73	70
Males, %	64.3	63.2	60.1	65.3
Stroke/systemic embolism vs warfarin (%/y), intention to treat	1.5 vs 1.7	1.1 vs 1.7	2.1 vs 2.4	1.3 vs 1.6
Major bleeding vs warfarin (%/y)	2.7 vs 3.4	3.1 vs 3.4	3.4 vs 3.6	2.1 vs 3.1
Intracranial hemorrhage vs warfarin (%/y)	0.2 vs 0.7	0.3 vs 0.7	0.5 vs 0.7	0.2 vs 0.5

Stroke prevention in patients with atrial fibrillation and renal dysfunction.
Kaatz S; Mahan CE. Stroke. 45(8):2497-505, 2014 Aug.



WHAT IS AVAILABLE ON SA HEALTH FORMULARY?

SA Health formulary

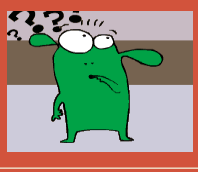
DOACs vs warfarin

Advantages of DOACS

- No monitoring of blood levels
- Less food and drug interactions
- Less intracranial haemorrhage
- Rapid onset and offset
- Reversal is only available for one agent so far

Advantages of warfarin

- Monitoring of blood levels checks on compliance
- Reversal is available



WHICH DOAC AND WHAT DOSE FOR MY PATIENT?

Comparison of DOAC pharmacokinetics

	Factor II_a (Thrombin) Inhibitor	Factor X_a Inhibitors	
	Dabigatran	Rivaroxaban	Apixaban
Bioavailability, %	6	80	50
Onset of action, min	≤30	≤30	Not stated
Duration of action, h	24–36	24	≥24
T_{max}, h	1.0–2.0	2.5–4.0	3.0
Renal excretion, %	80	36*	27
Elimination half-life (h) by degree of renal dysfunction			
Normal (CrCl >80 mL/min)	13.8	8.3	7.6
Mild (CrCl 50–79 mL/min)	16.6	8.7	7.3
Moderate (CrCl 30–49 mL/min)	18.7	9.0	17.6
Severe (CrCl <30 mL/min)	27.5	9.5	17.3

Stroke prevention in patients with atrial fibrillation and renal dysfunction.
Kaatz S; Mahan CE. Stroke. 45(8):2497-505, 2014 Aug.

Dosing algorythims

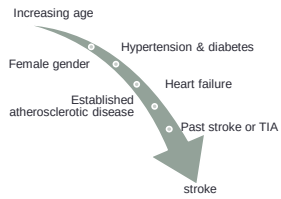
dabigatran
- Dose: 150mg twice daily
- dose reduced to 110mg bd for >75 years or CrCL 30-50 mL/min
- Contraindicated if CrCL < 30
- Reversal agent available

apixaban
- Dose: 5 mg twice daily
- Reduced dose to 2.5mg bd for ≥ 2: age >80 years; weight <60kg; Crest > 133µmol/L
- Contraindicated if CrCL < 25 mL/min

rivaroxaban
- Dose 20mg daily
- Dose reduced to15mg daily: CrCl 30-50 mL/min
- Contraindicated if CrCL < 30 mL/min

WHEN DO I START A DOAC FOR NON-VALVULAR AF?

Not all AF is equal!



PBS recommend anticoagulation if a person has AF and 1 other risk factor (not including female gender)

Current risk factor scoring systems

$CHADS_2$

- Chronic heart failure 1
- Hypertension 1
- Age > 75 years 1
- Diabetes 1
- Prior Stroke or TIA 1

US developed
The first of the scoring systems

CHA_2DS_2-VASc

- Chronic heart failure 1
- Hypertension 1
- Age ≥75 years 2
- Diabetes 1
- Prior Stroke or TIA 2
- Vascular disease 1
  - AMI or PVD or aortic plaque
- Age ≥65 years 1
- Sex category (female) 1

European developed
A refinement of the risk factors for stroke

The evidence is never straight-forward:
Stroke rates vary **widely** among worldwide registries of non-valvular AF reporting CHA_2DS_2-VASc scores

	Women's Health Initiative[37]	Stockholm Area Database[38]	Taiwan National Health Institute Database[6]	ATRIA[11]	Invite Cohort[41]	J-Rhythm, Shinkuro, Fushimi[42]	Euro Heart Survey on AF[7]	Swedish AF Study[43]	General Practice Research Database[44]	Clalit Health Services AF[45]	PLA General Hospital AF[46]	J-Rhythm[41]	AVERROES ACTIVE-A and ACTIVE-W[40]	Alberta AF Cohort[44]	Taiwan NHIRD - 1996–2011[47]	Danish National Patient Registry[9]	Queen Mary Hospital[48]
CHA_2DS_2-VASc Score																	
0	–	0.3	0.35	0.04	0	0.53	0	0.2	0.38	0.42	0	0.7	–	–	1.15	0.78	2.41
1	0.2	0.5	0.5	0.55	0.6	0.55	0.6	0.6	0.78	0.82	0.9	0.9	1.1	1.3	2.11	2.01	6.64
2	0.49		0.91	0.83	0.95	1.11	1.5	2.2	1.92	1.91	1.7	1.8	2.3	6.56	3.39	3.71	7.94
3	0.82		1.35	1.66	1.96	1.38	3.9	3.2	2.84	2.57	2.7	1.2	3.34		3.89	5.93	9.52
4	1.3		2.12	2.8	3.45	1.52	1.9	4.9	4.7	3.71	1.8	2.3			4.81	9.27	11.58
5	1.71		2.59	4.21	9.06	4.43	3.2	7.2	5.88	4.52	8.8	4.5			5.12	15.26	12.88
6	2.82		4.42‡	4.77	13.71	4.07	3.6	9.7	7.09	5.1	9	2			5.16	16.74	13.18
7				4.82		1.56	8	11.2	8.88	5.6		1.8			6.22	21.5	
8				7.82		6.95	11.1	10.8	8.01			0			7.96	22.38	
9				16.62		2.11	100	12.23	15.49			0			10.5	23.64	

Wide Variation in Reported Rates of Stroke Across Cohorts of Patients With Atrial Fibrillation.
Quinn GR; Severdija ON; Chang Y; Singer DE Circulation. 135(3):208-210, 2017 Jan 17.
DOI: 10.1161/CIRCULATIONAHA.116.024057

Reported Stroke Rates Stratified by **low** CHA_2DS_2-VASc Scores of 0, 1, and 2 According to Different Cohorts

Annual stroke risk:
- <1% risk has low clinical benefit from anticoagulation
- 1-2% risk has an intermediate expected benefit from anticoagulation
- >2% risk has a high expected benefit from anticoagulation

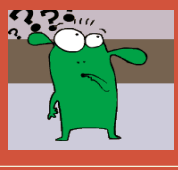
Wide Variation in Reported Rates of Stroke Across Cohorts of Patients With Atrial Fibrillation.
Quinn GR; Severdija ON; Chang Y; Singer DE

Circulation. 135(3):208-219, 2017 Jan 17.
DOI: 10.1161/CIRCULATIONAHA.116.024057

Cohort	Stroke Rates		
	CHA_2DS_2-VASc 0	CHA_2DS_2-VASc 1	CHA_2DS_2-VASc 2
Women's Health Initiative[17]	–	↓ 0.2*	↓ 0.48*
Stockholm Area Database[26]	0.3*	0.5*	–
Taiwan National Health Institute Database 1997–2008[15]	0.35*	0.5*	0.91*
ATRIA[14]	0.04*	0.55*	0.83*
Iwate Cohort[32]	↓ 0*	0.6*	0.95*
J-Rhythm, Shinken, Fushimi (Pooled)[30]	0.53*	0.55*	1.11†
Euro Heart Survey on AF[9]	0*	0.6*	1.6†
Swedish Atrial Fibrillation Study[20]	0.2*	0.6*	2.2‡
General Practice Research Database[28]	0.38*	0.78*	1.92†
Clalit Health Services AF[24]	0.42*	0.82*	1.81†
PLA General Hospital AF[25]	0*	0.9*	1.7†
J-Rhythm[29]	0.7*	0.9*	1.9†
AVERROES, ACTIVE-A, and ACTIVE-W[31]	–	1.1†	2.3‡
Alberta AF Cohort[16]	–	1.3‡	–
Danish National Patient Registry[8]	0.78*	2.01‡	3.71‡
Taiwan NHRD, 1996–2011[18]	1.15†	2.11‡	3.39‡
Queen Mary Hospital in Hong Kong[33]	↑ 2.41‡	↑ 6.64‡	↑ 7.84‡

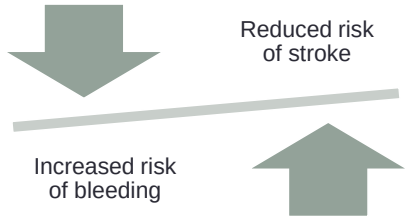
How do we interpret this ?

- The scoring systems are just a rough guide to an individuals absolute risk for stroke
- There is a need to standardise approaches to analysing administrative and clinical databases.

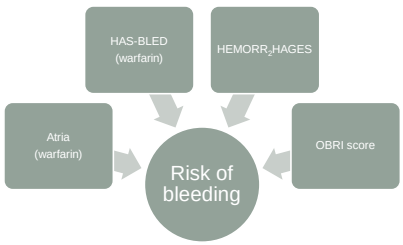


WHEN DO I STOP PRESCRIBING A DOAC FOR NON-VALVULAR AF?

The dilemma of anticoagulation



There are many bleeding risk scoring systems



HEMORR$_2$HAGES score:
predicting haemorrhage in AF

Age > 75 years	1
Prior major bleed	2
Hepatic or renal disease	1
Alcohol abuse	1
Malignancy	1
Uncontrolled hypertension	1
Anaemia	1
Excessive fall risk	1
Prior stroke	1
Reduced platelet count/function	1

- Score 0 = 1.9% risk
- Score 4 = 10.4% risk
- Score 11 = 12.3% risk

Gage et al. Am Heart J 2006

Bleeding is a marker of frailty

HOW DO I REVERSE DOACS?

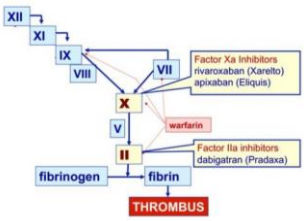
Managing elective interventions and emergencies

Elective surgery

dabigatran	• Low bleeding risk: stop for ≥ 24 hours • High bleeding risk: stop for ≥ 48 hours • Stop for longer if have renal impairment
apixaban	• Low bleeding risk: stop for ≥ 24 hours • High bleeding risk: stop for ≥ 48 hours
rivaroaban	• Stop ≥ 24 hours before procedure • Stop for longer if have renal impairment

- **No bridging anticoagulation recommended**
- **Restart at usual dose as soon as bleeding risk minimal**

The coagulation cascade and our anticoagulants



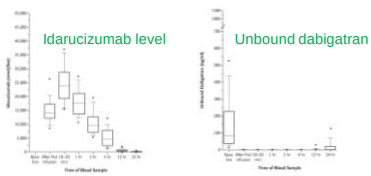
Emergency reversal of DOACs

Xa inhibitors have no specific reversal agent.

Human Prothrombin complex could be tried (no major trials)

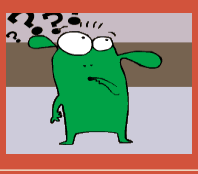
Dabigatran has a specific reversal agent: **Idarucizumab** is an antibody fragment of a human antibody specific for dabigatran

Intravenous infusion of **Idarucizumab** completely reverses the anticoagulant effect of dabigatran within minutes with no apparent toxic effects or rebound hypercoagulable state.



Available at all major hospitals in SA

Pollack CV Jr et al. N Engl J Med 2015;373:511-520



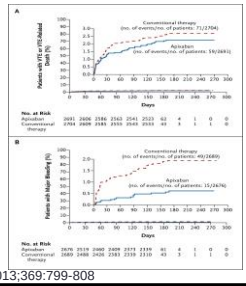
WHAT ABOUT VENOTHROMBOEMBOLISM?

DVT prophylaxis

- DOACs are well established in being non-inferior to enoxaparin to prevent DVT after orthopaedic surgery of the lower limbs
- In medically ill patients
  - Apixaban and rivaroxaban were both non-inferior to enoxaparin, but more bleeding occurred

DOACS in acute pulmonary embolism

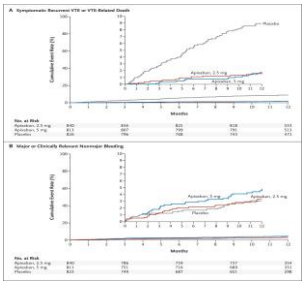
- Non-inferior to usual treatment
- Less bleeding complications
- Apixaban (shown in graphs), rivaroxaban and Dabigatran all have favourable trial results for this indication



Agnelli G et al. N Engl J Med 2013;369:799-808

DOACS for long-term prevention of recurrent venous thromboembolism

- Better than placebo (vs apixaban) or aspirin (vs rivaroxaban)
- Low and high dose were effective
- No excessive bleeding noted



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

Summary

- DOACs are here to stay and offer a better choice for anticoagulation in our patients
- Stroke prevention in AF and treatment of PE are their indications in medical patients