ACC Middle East Conference 2018

In partnership with:

جمعية القلب السعودية
Saudi Heart Association

Anticoagulation Management

Therapeutic Selection and Dosing

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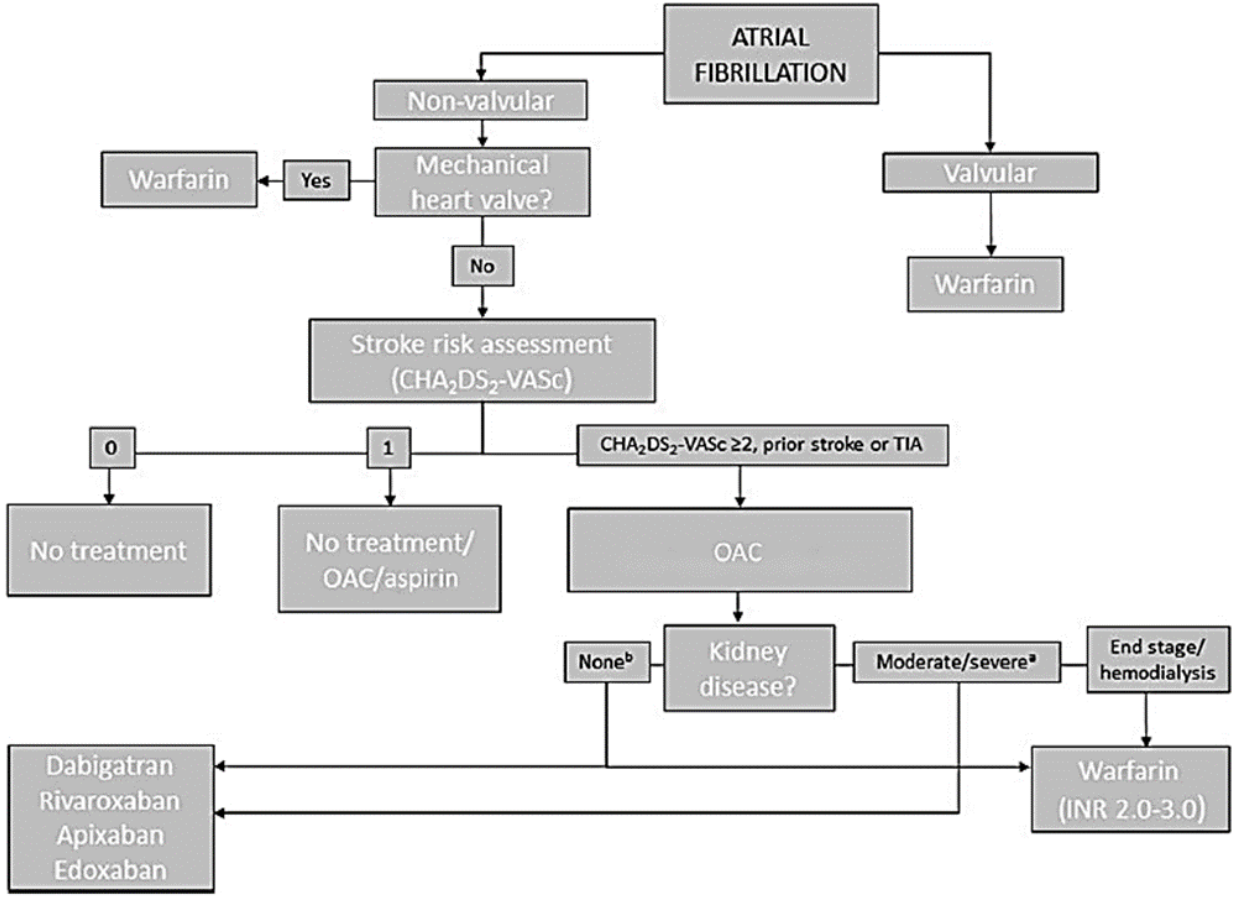
Approach to Anticoagulation in AF Patients



1. **Confirm presence of AF**
   - Valvular vs. Non Valvular AF

2. Determine **Stroke risk** (CHA2DS2-Vasc)

   Determine the **Bleeding risk** (HAS-BLED, ATRIA…)

3. Match the anticoagulation regimen to the individual patient
   - **Warfarin vs. NOACs** (contraindications)
     - Renal disease, liver disease, other medications etc..
   - **Which NOAC**? does it matter?

Saliba W. Am J Cardiovasc Drugs (2015) 15:323–335

Stroke and Bleeding Risk Scores in NVAF

$CHADS_2$-VASc	Score
CHF	1
HT	1
Age > 75 years	1
Diabetes	1
Stroke	2
Vascular Disease	1
Age 65-74 years	1
Sex **c**ategory	1

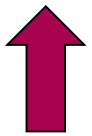
Annual Risk of Stroke (%)

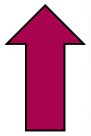
CHA_2DS_2-VASc* Score	Annual % Stroke Risk
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7

HAS-BLED	
HT	1
Abnormal renal or liver function	1
Stroke	1
Bleeding	1
Labile INR	1
Elderly (> 65 years)	1
Drug or alcohol use	1

Annual Risk of Bleed (%)

HAS-BLED** Score	Annual % Bleed Risk
0	0.9
1	3.4
2	4.1
3	5.8
4	8.9
5	9.1





Apostolakis S et al. *J Am Coll Cardiol.* 2012;60:861.

Which Oral anticoagulant?

VKA

Warfarin

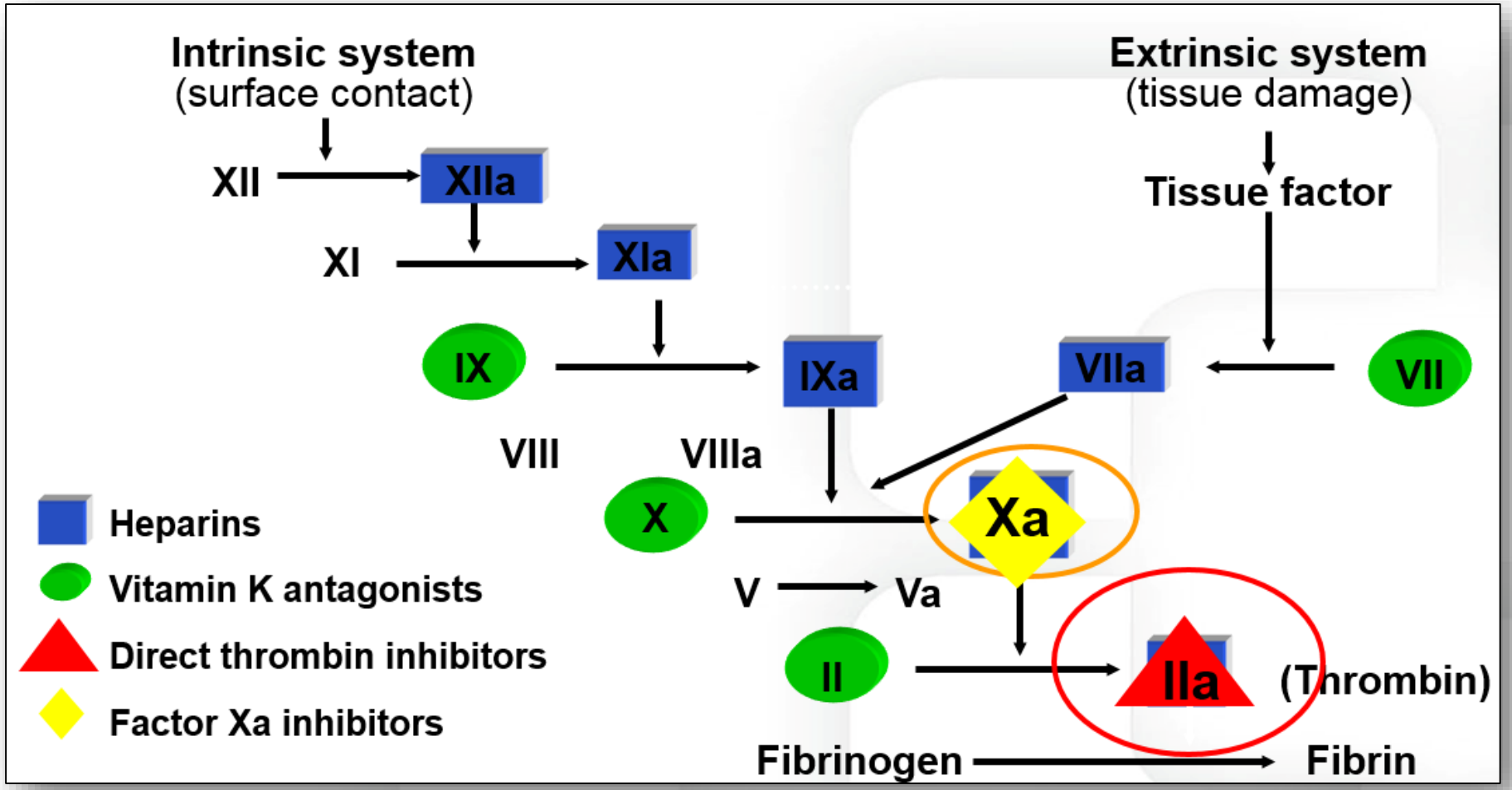
NOAC

Dabigatran

Rivaroxaban

Apixaban

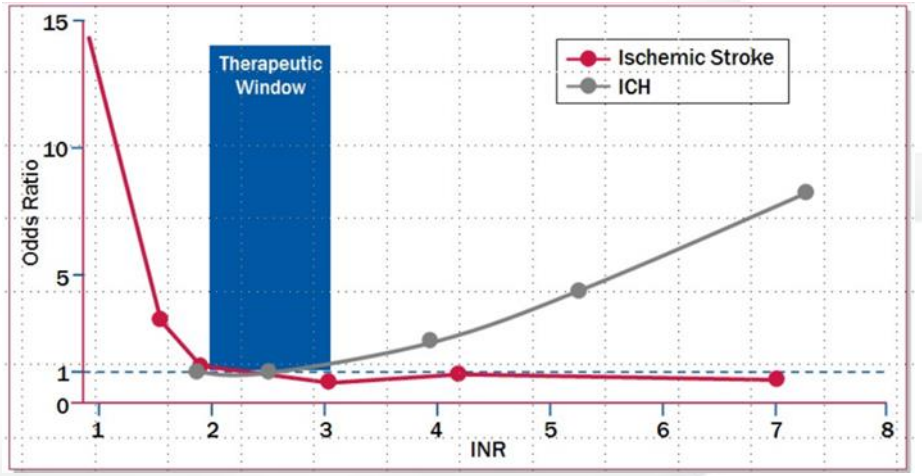
Edoxaban



Warfarin: Optimal Candidates

- Severe renal insufficiency
- Valvular Heart Disease
- Can Maintain TTR >70%
- Self-testing machines
- Cost Issues
- Concerned about “lack of reversal”

- ESC 2016 guidelines :
  - Rheumatic valvular disease (predominantly MS) or mechanical heart valves
- AHA/ACC/HRS guidelines:
  - NVAF: the absence of rheumatic mitral valve disease, a prosthetic heart valve or mitral valve repair.



High Discontinuation rate ~30% at 1 year

NOAC's

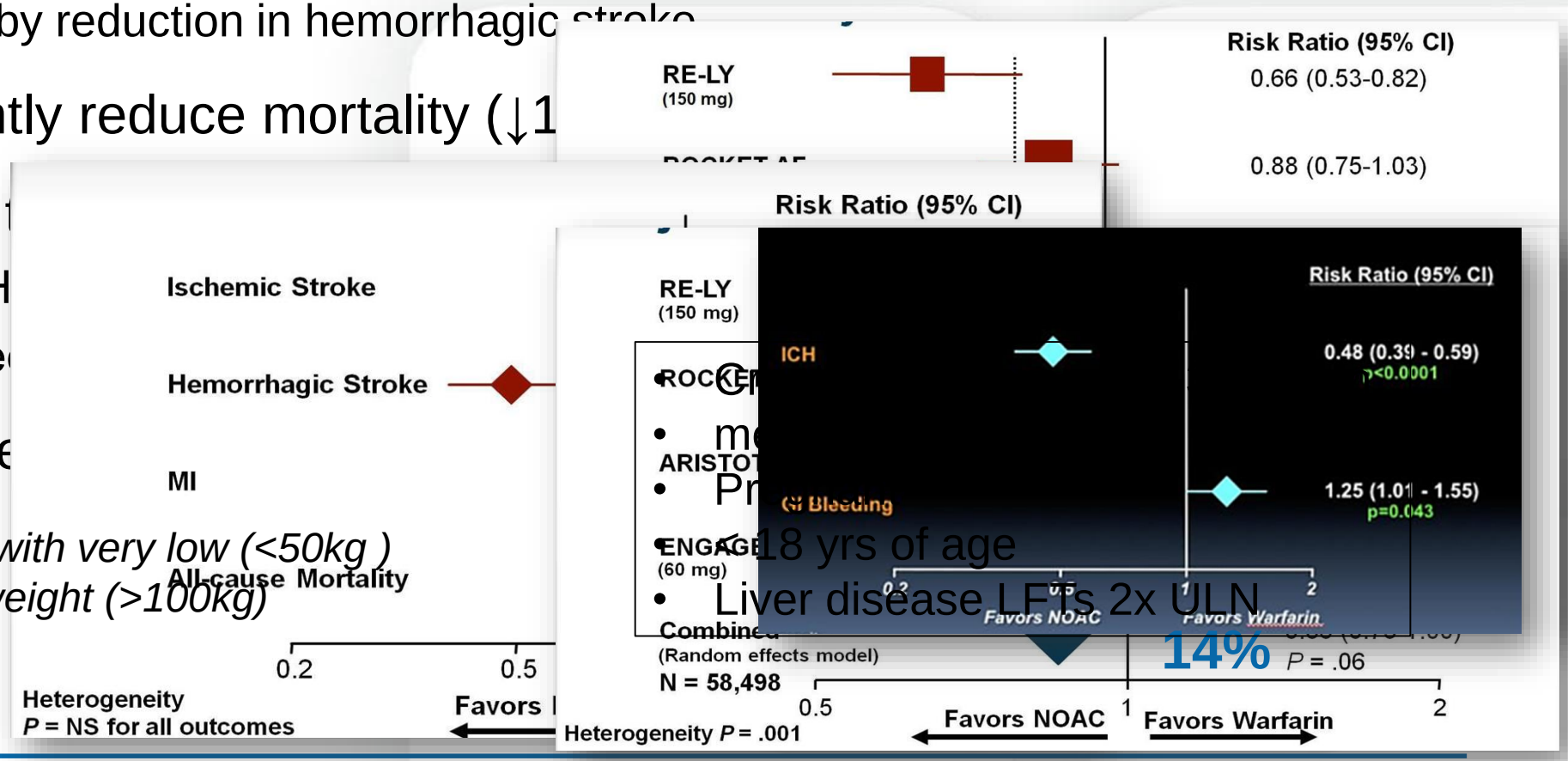
- VKA
  - Warfarin
- NOAC
  - Dabigatran (RELY Study)
  - Rivaroxaban (ROKET-AF Study)
  - Apixaban (ARISTOTLE Study)
  - Edoxaban (ENGAGE AF Study)

	RELY		ROCKET-AF	ARISTOTLE	ENGAGE AF-TIMI 48	
Drug	Dabigatran		Rivaroxaban	Apixaban	Edoxaban	Edoxaban
Mechanism of action	Direct thrombin inhibition		Factor Xa inhibition	Factor Xa inhibition	Factor Xa inhibition	
Dose	110 mg twice/day	150 mg twice/day	20 mg once/day	5 mg twice/day	30 mg once/day	60 mg once/day
Study design	Randomized, open label		Randomized, double blind	Randomized, double blind	Randomized, double blind	
Patient number	18,113		14,264	18,201	21,105	
Median follow up time (years)	2.0		1.9	1.8	2.8	
Age (years)	71.5 ± 8.7 (mean ± standard deviation)		73 (65–78) median (interquartile range)	70 (63–76) median (interquartile range)	72 (64–78) median (interquartile range)	
Mean $CHADS_2$ score	2.1		3.5	2.1	2.8	
Mean warfarin TTR %	64		55	62	65	
Relative risk (95% CI) of stroke or systemic embolism *versus* warfarin	0.91 (0.74–1.11); $p < 0.001$ for non-inferiority	0.66 (0.53–0.82); $p < 0.001$ for superiority	0.88 (0.75–1.03); $p < 0.001$ for non-inferiority	0.79 (0.66–0.95); $p < 0.001$ for non-inferiority, $p = 0.01$ for superiority	1.13 (0.96–1.34) $p = 0.005$ for non-inferiority	0.87 (0.73–1.04) $p < 0.001$ for non-inferiority
Relative risk (95% CI) of ischaemic stroke *versus* warfarin	1.10 (0.89–1.40)	0.76 (0.60–0.98)	0.94 (0.75–1.17)	0.92 (0.74–1.13)	1.41 (1.19–1.67)	1.00 (0.83–1.19)
Relative risk (95% CI) of haemorrhagic stroke *versus* warfarin	0.31 (0.17–0.56)	0.26 (0.14–0.49)	0.59 (0.37–0.93)	0.51 (0.35–0.75)	0.33 (0.22–0.50)	0.54 (0.38–0.77)
Relative risk (95% CI) of intracranial bleed *versus* warfarin	0.31 (0.20–0.47)	0.40 (0.27–0.60)	0.67 (0.47–0.93)	0.42 (0.30–0.58)	0.30 (0.21–0.43)	0.47 (0.34–0.63)
Relative risk (95% CI) of major bleeding *versus* warfarin	0.80 (0.69–0.93)	0.93 (0.81–1.07)	1.04 (0.90–1.20)	0.69 (0.60–0.80)	0.47 (0.41–0.55)	0.80 (0.71–0.91)
Relative risk (95% CI) of gastrointestinal bleeding *versus* warfarin	1.10 (0.86–1.41)	1.50 (1.19–1.89)	1.61 (1.30–1.99)	0.89 (0.70–1.15)	0.67 (0.53–0.83)	1.23 (1.02–1.50)
Relative risk (95% CI) myocardial infarction *versus* warfarin	1.29 (0.96–1.75)	1.27 (0.94–1.71)	0.81 (0.63–1.06)	0.88 (0.66–1.17)	1.19 (0.95–1.49)	0.94 (0.74–1.19)
Relative risk (95% CI) of all cause death *versus* warfarin	0.91 (0.80–1.03)	0.88 (0.77–1.00)	0.85 (0.70–1.02)	0.89 (0.80–0.99)	0.87 (0.79–0.96)	0.92 (0.83–1.01)

NOAC Benefits over Warfarin
Meta Analysis summary

- NOAC significantly reduce stroke/SEE (↓19%)
  - Primarily driven by reduction in hemorrhagic stroke
- NOAC significantly reduce mortality (↓1
- There is a trend
  - Reduction in ICH
  - Increased GI Ble
- All Trials Exclude
  - Cr
  - m
  - Pr
  - <18 yrs of age
  - Liver disease LFTs 2x ULN

Few patients with very low (<50kg) or very high weight (>100kg)



Matching the NOAC to the Patient

- Age
- Renal Dysfunction
- Hepatic dysfunction
- Drugs
- ***Patient's risk of stroke/ risk of bleeding*** → Hints from the RCT
- Compliance
- GI symptoms: Dyspepsia
- Preference
- Cost

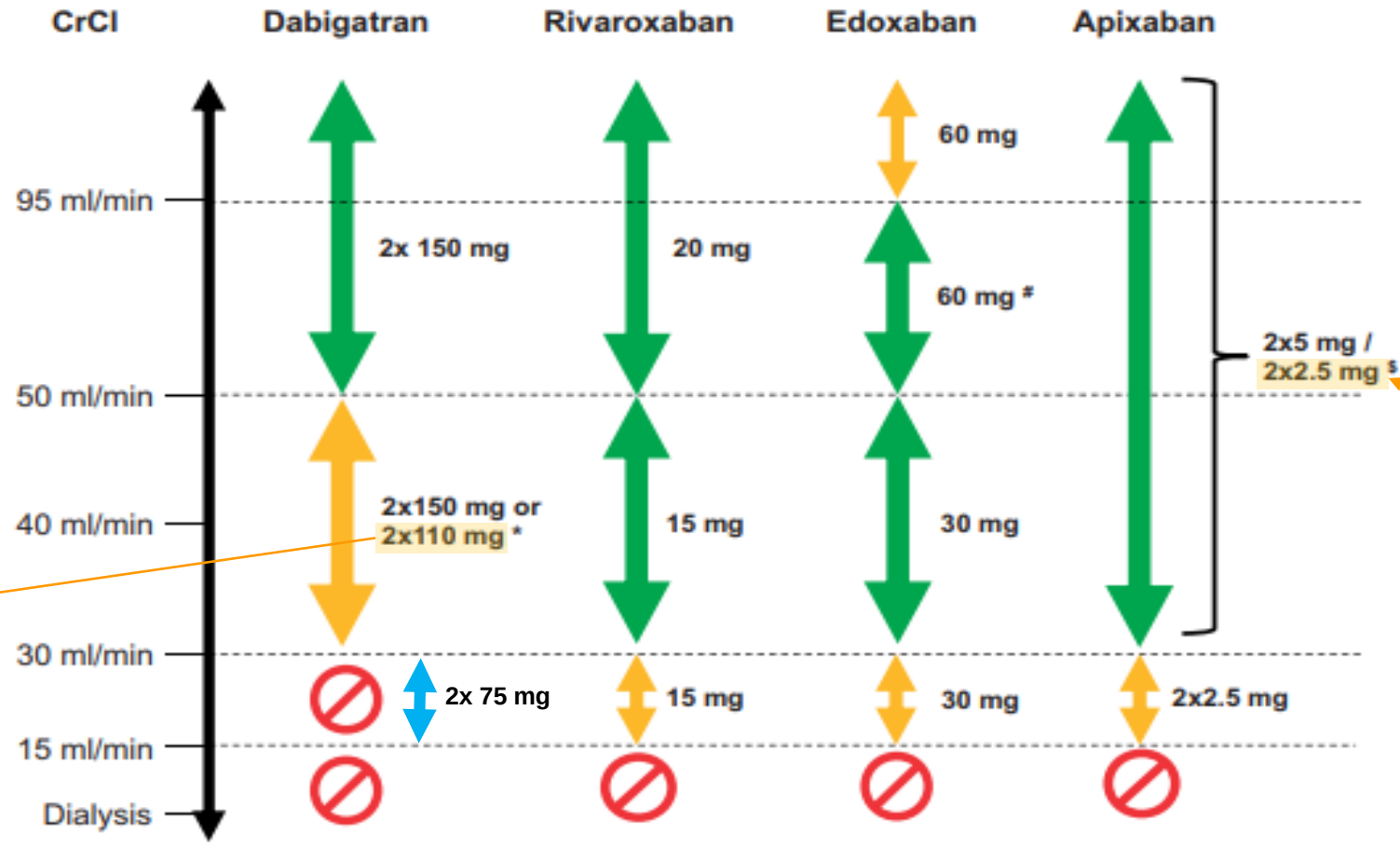
Appropriate Dosing

"Non Medical"

Comparisons New Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Time to peak (h)	1.5 -3	2-3	3-4	1-2
Oral Bioavailability	3-7%	66% without food >80% with food	50%	60%
Absorption with food	No effect	40% more	No effect	6-22% minimal effect
Half-life (h)	14-17	5-9	8-15	10-14
Renal excretion (%)	>80	66	25	50
Liver CYP3A4	No	Yes (moderate)	Yes (moderate)	Yes (minimal)
Antidote	Idarucizumab	Andexxa	Andexxa	
Regular Dosing	150 mg twice daily	20 mg once daily	5 mg twice daily	60/30 mg once daily

NOAC: Renal Dose Adjustment

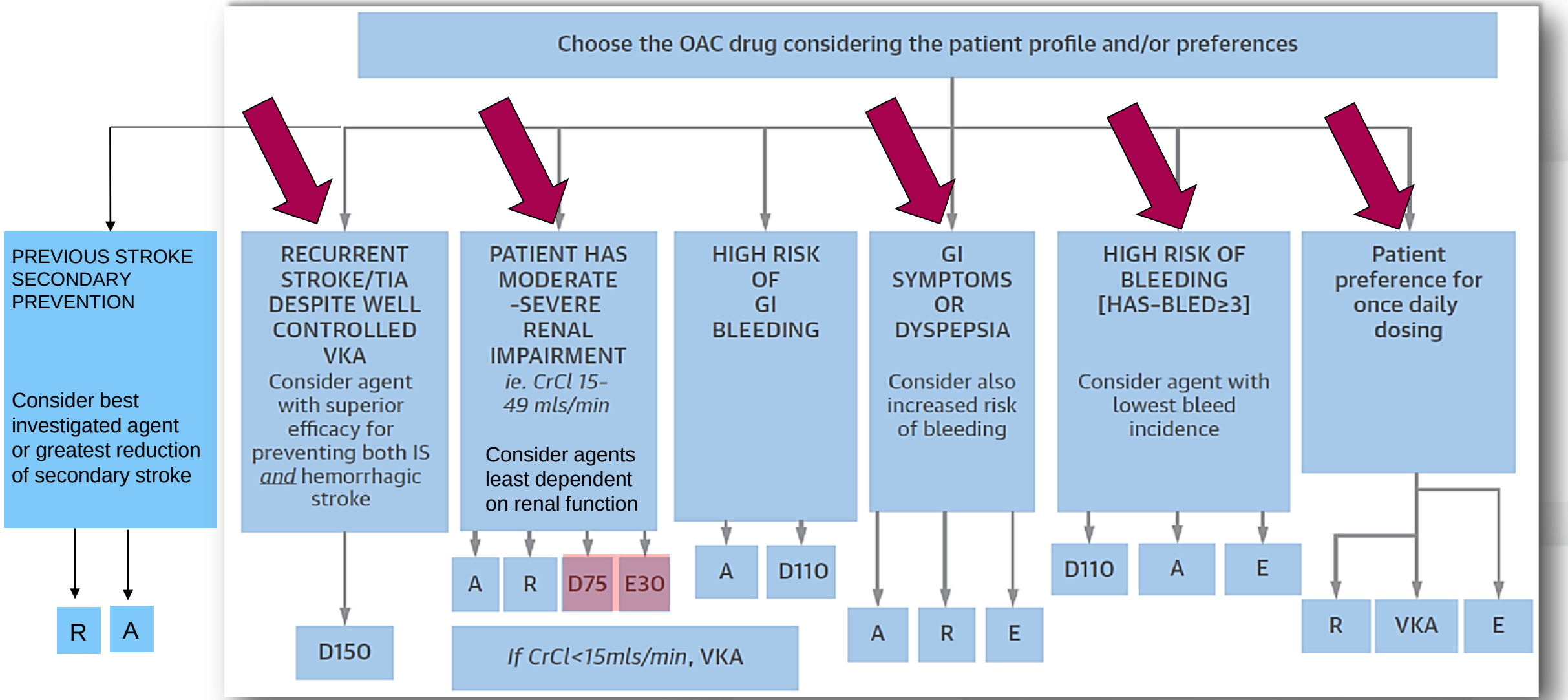


high risk of bleeding

If 2 out of 3 fulfilled:

- Age >_80
- Wt <_60 kg
- Cr >_1.5 mg/dL

Matching the NOAC to the Patient



Gregory Y.H. Lip
JACC VOL. 66, NO. 21, 2015
DECEMBER 1, 2015:2282-4

New Oral Anticoagulants: Drug Interactions

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Liver CYP3A4 involved	No	Yes (moderate)	Yes (moderate)	Yes (minimal)
Potential Drug Interaction	P-gp inhibitors in the background of renal impairment and P-gp inducers	Combined P-gp and strong CYP3A4 inhibitors and inducers	Strong dual inhibitors of CYP3A4 and P-gp increase blood levels;	Potent inhibitors of P-gp

- Apixaban: Reduce dose or avoid with strong P-gp + CYP3A4 inhibitors.
- Rivaroxaban : do not give if combined P-gp and strong inhibitors of CYP3A4.
- Dabigatran: reduce dose if moderate renal impairment (30-50) + P-gp inhibitors.

CYP 3A4*		
Inducer	**Inhibitor**	
Carbamazepine	Amiodarone	Itraconazole
Efavirenz	Aprepitant	Ketoconazole
Glucocorticoids	Cimetidine	Nefazodone
Nevirapine	Clarithromycin	Protease inhibitors
Phenobarbital	Cyclosporine	Verapamil
Phenytoin	Diltiazem	Voriconazole
Primidone	Erythromycin	Fluconazole
Rifampin	Fluoxetine	Fluvoxamine
Rifapentine		
St. John's Wort		

P-glycoprotein*		
Inducer	**Inhibitor**	
Midazolam	Amiodarone Dronaderone	Nifedipine Nicardipine
Phenobarbital	Ceftriaxone	Propranolol
Phenytoin	Clarithromycin	Quinidine
Rifampin	Diltiazem	Verapamil
St. John's Wort	Dipyridamole	
	Erythromycin	
	Hydrocortosone	
	Itraconazole	
	Ketoconazole	

Cost Implications

- **Dabigatran (Pradaxa®)**
  - 150 mg twice daily
    - $286/month
  - 75 mg twice daily
    - $252/month

- **Apixaban (Eliquis®)**
  - Atrial Fibrillation
    - 2.5 and 5 mg twice daily
      - $291/month

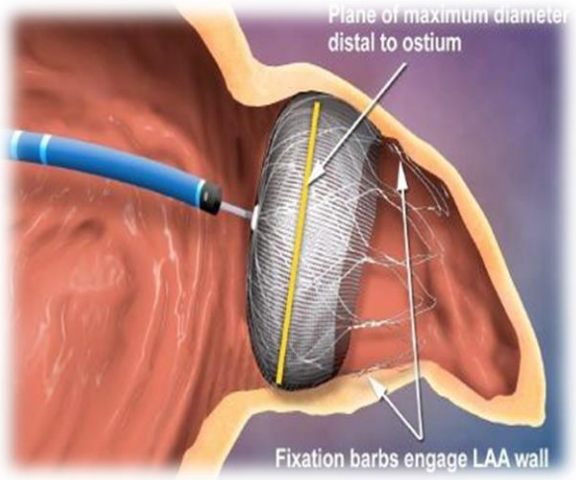
- **Rivaroxaban (Xarelto®)**
  - Atrial fibrillation
    - 15 mg daily
      - $281/month
    - 20 mg daily
      - $281/month

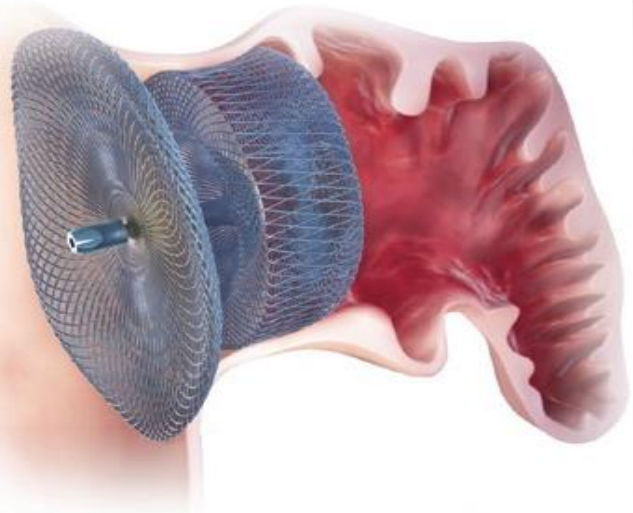
Prices are obtain from WalMart

LAA Occlusion / Exclusion

OAC issues →

Bleeding
Side effects
Cost
Discontinuation rate
Compliance
Preference





Case 1

Case 1

- 66 year old engineer
- HTN, CAD (PCI to LAD 3 years ago) COPD and sleep apnea
- Recurrent paroxysmal AF and Prior history of stroke, no residual deficit
- Meds:
  - Atorvastatin, ASA, Lisinopril, Metoprolol, Dabigatram (150 bid)
- Now presenting with increasing palpitations and associated dyspnea over past 2 months.
  - EKG: NSR and unchanged
  - LVEF 60%
  - Stress test: No ischemia at 85% THR
  - Monitoring showed increased Afib burden up to 20% now compared to < 1% (3 years ago)
  - Blood tests: Normal (Hgb, Cr, TSH, LFT's)
- Decision to proceed with a trial of AA drug: Dronedarone 400 mg bid added.

Case 1 (cont'd)

- He is coming now for a second opinion
- I do not want to have another stroke.

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)[131]
Antiarrhythmic drugs					
Amiodarone	moderate P-gp competition	+12 to 60%[SmPC]	No PK data[a]	+40%[132–134]	Minor effect[a]
Digoxin	P-gp competition	No effect[SmPC]	No effect[135]	No effect	No effect[SmPC]
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[SmPC]	+40%[136]	No data yet	No effect
Dronedarone	P-gp competition and CYP3A4 inhibition	+70 to 100% (US: 2 × 75 mg if CrCl 30–50 mL/min)	No PK or PD data: caution	+85%[b]	Moderate effect, should be avoided
Quinidine	P-gp competition	+53%[SMPC]	No data yet	+77%[137] (no dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12 to 180%[SmPC] (if taken simultaneously)	No PK data	+53% (SR)[137,142] (no dose reduction required by label)	No effect

Next step:

1. Continue same medical regimen
2. Switch NOAC (eg. Rivoroxaban highest CHADS in clinical trial)
3. Stop Dronedarone and Add Verapamil for better rate control
4. Consider AF ablation in 4 months if no response to Dronedarone
5. Anything else…?

Take Home message:
Check list for AF patients on NOAC

- Adherence and compliance
- Thromboembolism
- Bleeding
- Other side effects
- **Medications (new/change)**
- Blood sampling (Hb,LFT,Cr)

Case 2

- 76 year old female patient
- HTN, DM, HFpEF (LVEF 65%)
- Permanent atrial Fibrillation on Warfarin
- Prior history of falling (tripped) with trauma to head: CT negative
- h/o TIA while sub-therapeutic on Warfarin (INR 1.5)
- Lives alone. Her son brings her meals every other day. (variable left over)
- Meds: Verapamil, Losartan, Metformin
- Exam:
  - Thin with small body habitus (Wt: 58 kg)
  - BP: 140/80 HR: 85bpm
  - Blood tests: Cr: 1.2, A1C: 7%

- Because of labile INR→ wants to switch to NOAC
- You suggest
  1. Dabigatram 150 mg bid
  2. Dabigatram 75 mg bid
  3. Rivaroxaban 20 mg OD
  4. Apixaban 2.5 mg bid
  5. Apixaban 5 mg bid
  6. Edoxaban 60 mg OD

Misconception about NOAC Dosing

- Underutilization:
  - 30-50% of high risk patients are not anticoagulated
- Underdosing / “nontherapeutic dose”
  - Fear of bleeding
  - 40% increased risk of stroke with no reduction in bleeding risk

FANTASIA Registry

NOAC's are **Underused or Underdosed**

- 32% of patients suboptimal dosing
- Factors:
  - Female
  - Older age
  - Antiplatelet drugs
  - Frail
  - Low BMI
  - Apixaban / Rivaroxaban use

Higher CHADSVasc score than those who actually received appropriate dose.

Ortiz et al. Europace 2018

Take Home Messages

- Anticoagulation is safe for the treatment of AF patients
  - **—Even the frail, the elderly, the obese, the concerned …**
- The differences between NOAC's are far smaller than the difference between VKA and NOACs
- The biggest difference is between no Anticoagulation and Anticoagulation
- Appropriate dosing based on renal clearance and concomitant medications is Important

Thank You

Hepatic Dysfunction

Parameters	1 point	2 points	3 points
Encephalopathy	No	Grade 1–2 (suppressed with medication)	Grade 3–4 (refractory/chronic)
Ascites	No	Mild (diuretic-responsive)	Moderate–severe (diuretic-refractory)
Bilirubin	<2 mg/dL	2–3 mg/dL	>3 mg/dL
	<34 µmol/L	34–50 µmol/L	>50 µmol/L
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
	>35 g/L	28–35 g/L	<28 g/dL
INR	<1.7	1.71–2.30	>2.30

Child–Pugh category	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
A (5–6 points)	No dose reduction	No dose reduction	No dose reduction	No dose reduction
B (7–9 points)	Use with caution	Use cautiously	Use cautiously	Do not use
C (10–15 points)	Do not use	Do not use	Do not use	Do not use

Mils hepatic dysfunction:
No dose reduction needed.

Severe hepatic dysfunction:
All NOACs are contraindicated.

	Stroke or systemic embolism		Ischemic stroke[b]		Primary safety outcome[c]		GI bleeding		Intracranial bleeding	
	Rate[a]	HR *p* value			Rate[a]	HR *p* value	Rate[a]	HR *p* value	Rate[a]	HR *p* value
RE-LY										
Dabigatran	1.53	0.91 (0.74–1.11)	1.34	1.11 (0.89–1.40)	2.71	0.80 (0.69–0.93)	1.12	1.10 (0.86–1.41)	0.23	0.31 (0.20–0.47)
110 mg bid		<0.001		0.35		0.003		0.43		<0.001
Dabigatran	1.11	0.66 (0.53–0.82)	0.92	0.76 (0.60–0.98)	3.11	0.93 (0.81–1.07)	1.51	1.50 (1.19–1.89)	0.30	0.40 (0.27–0.60)
150 mg bid		<0.001		0.03		0.31		<0.001		<0.001
Warfarin	1.69		1.20		3.36		1.02		0.74	
ROCKET AF										
Rivaroxaban	1.70	1.7 (0.66–0.96)	1.34	0.94 (0.75–1.17)	14.90	1.03 (0.96–1.11)	3.20	NR	0.50	0.67 (0.47–0.93)
20 mg od[d]		<0.001		0.581		0.44		<0.001		0.02
Warfarin	2.20		1.42		14.50		2.20		0.70	
ARISTOTLE										
Apixaban	1.27	0.79 (0.66–0.95)	0.97	0.92 (0.74–1.13)	2.13	0.69 (0.60–0.80)	0.76	0.89 (0.70–1.15)	0.33	0.42 (0.30–0.58)
5 mg bid[e]		<0.01[g]		0.42		<0.001		0.37		<0.001
Warfarin	1.60		1.05		3.09		0.86		0.80	
ENGAGE AF										
Edoxaban	1.18	0.79 (0.63–0.99)	1.25	1.00 (0.83–1.19)	2.75	0.80 (0.71–0.91)	1.51	1.23 (1.02–1.50)	0.39	0.47 (0.34–0.63)
60 mg od[f]		<0.001		0.97		<0.001		0.03		<0.001
Edoxaban	1.61	1.07 (0.87–1.31)	1.77	1.41 (1.19–1.67)	1.61	0.47 (0.41–0.55)	0.82	0.67 (0.53–0.83)	0.26	0.30 (0.21–0.43)
30 mg od[f]		0.005		<0.001		<0.001		<0.001		<0.001
Warfarin	1.50		1.25		3.43		1.23		0.85	