New Oral Anticoagulants

Are they better than what we have?

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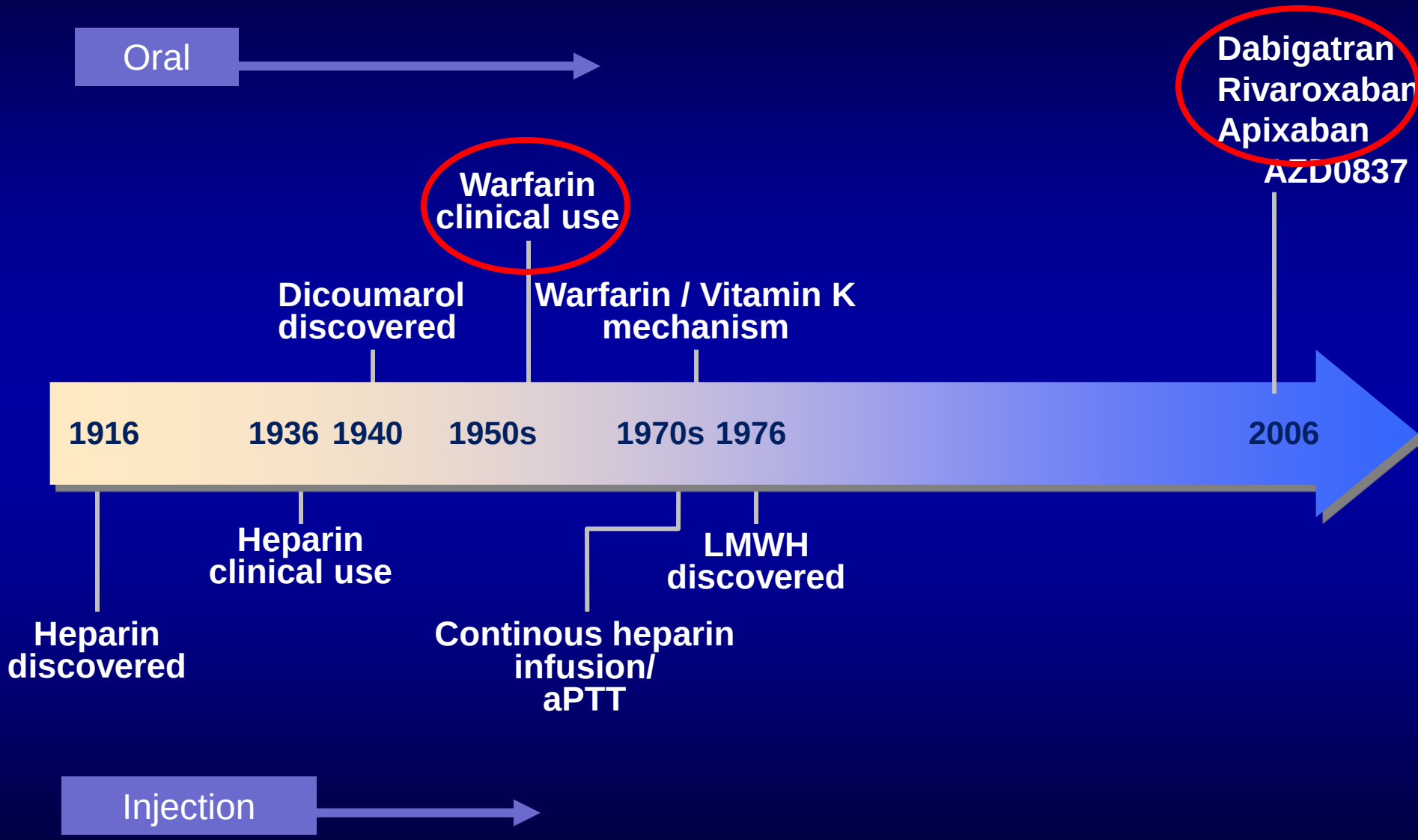
Anticoagulants – historical development



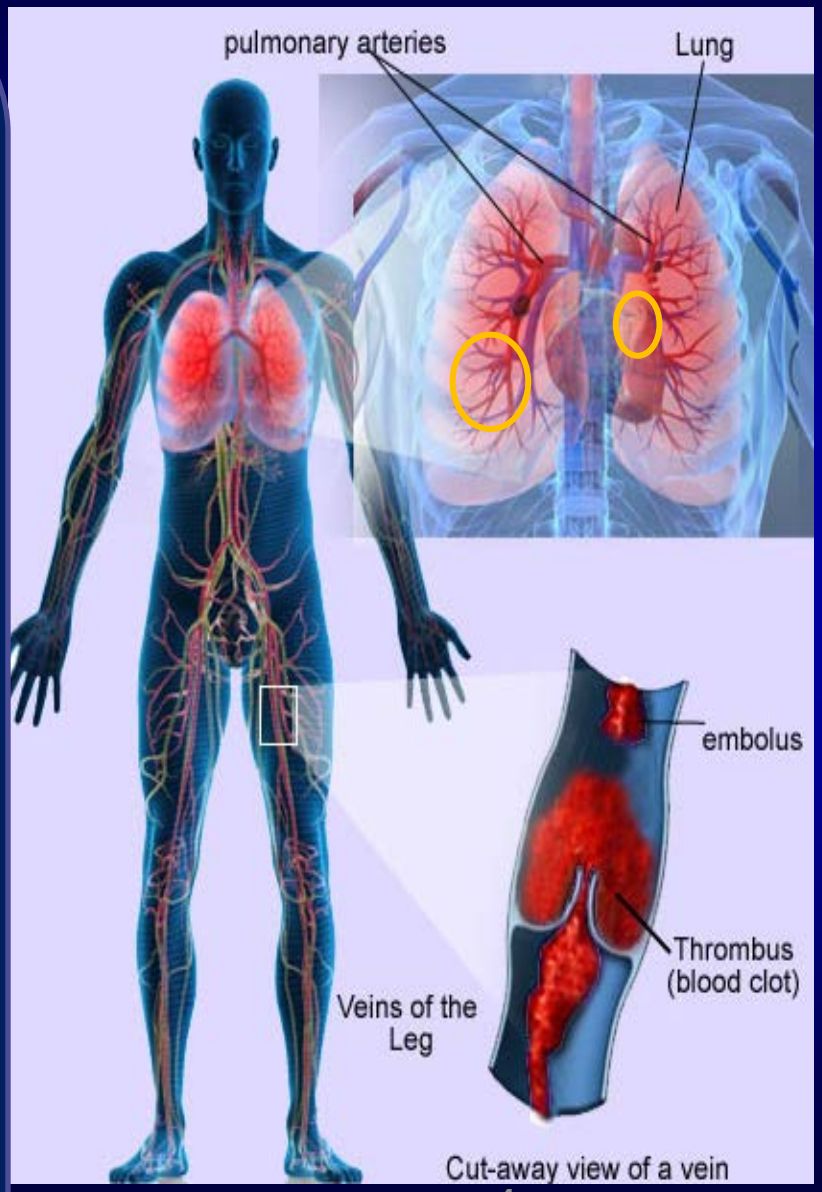
Oral anticoagulant

1) **Vitamin K Antagonists**

2) **NOACs**

Common Indications for OAC

- Any thromboembolic disease
- DVT
- PE
- Rheumatic valvular HD
- Mechanical Heart Valve
- Post surgery : hip/knee prosthesis



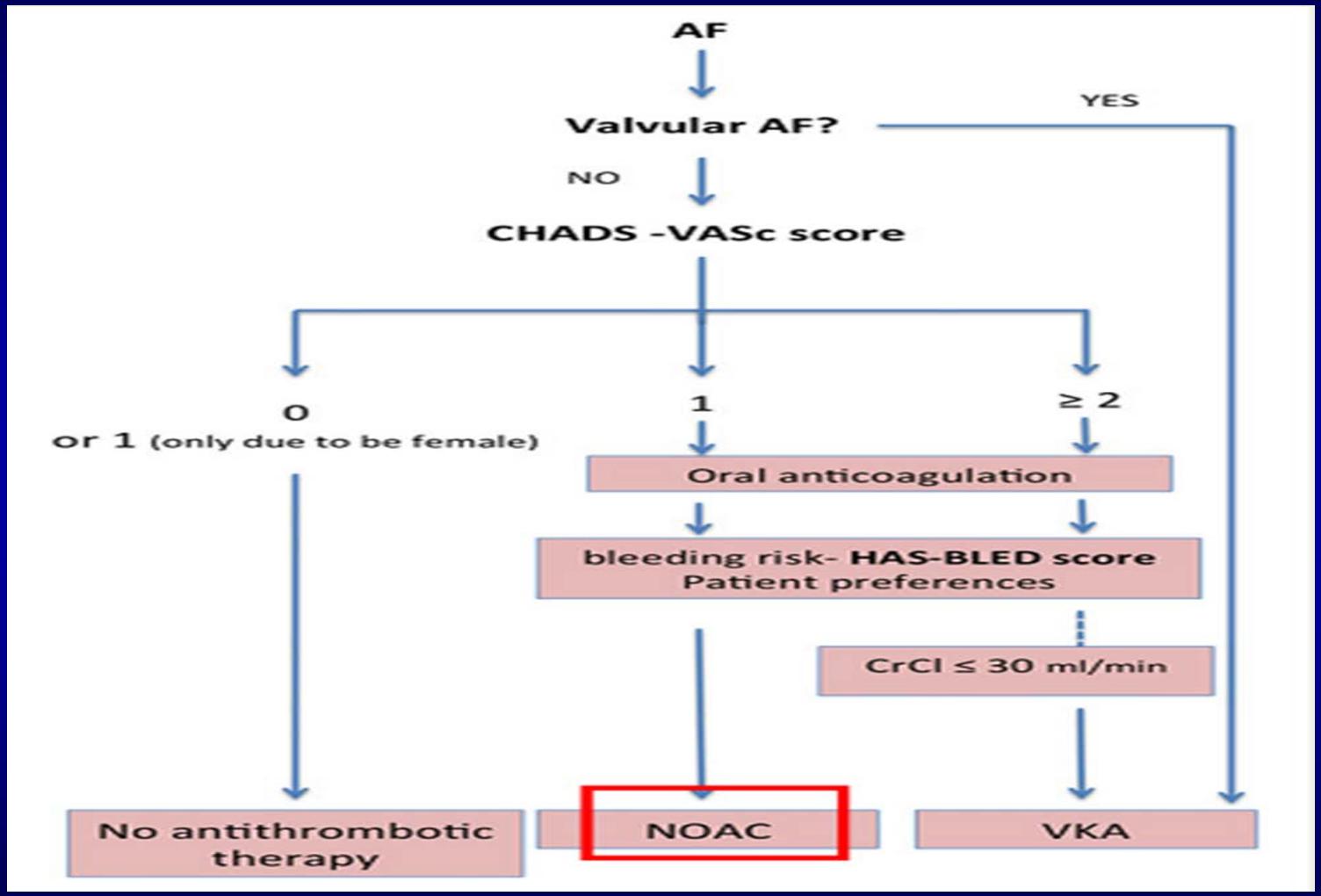
Non Valvular AF
To prevent Stroke

AF and stroke risk

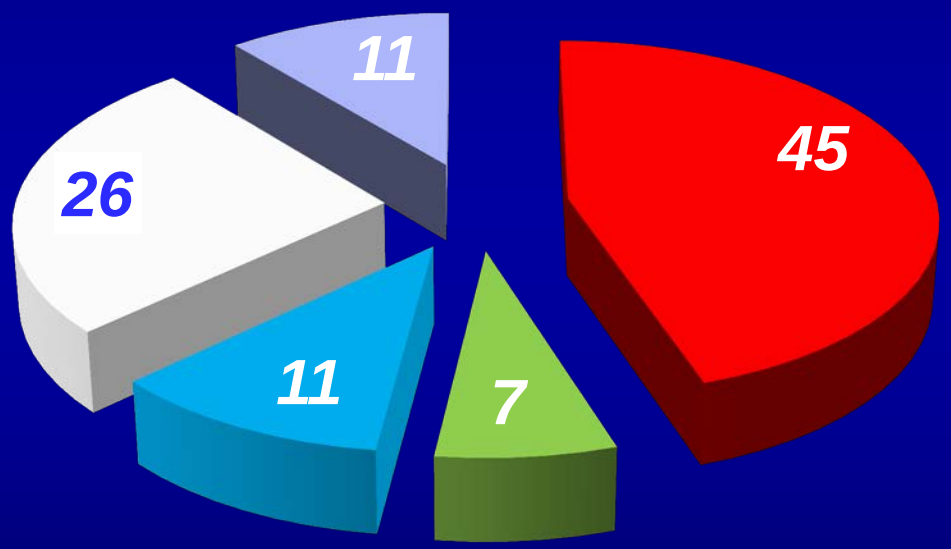
- Risk increases with ⇑ age
- **Without preventive treatment, approximately 1 in 20 patients (5%) with AF will have a stroke each year**
- AF related stroke----higher mortality and more disability

NICE AF GUIDELINE 2014

Do not offer Aspirin or Antiplatelet monotherapy for prevention of stroke in AF patients


AF
Valvular AF?
YES
NO
CHADS -VASc score
0
or 1 (only due to be female)
1
≥ 2
Oral anticoagulation
bleeding risk- HAS-BLED score
Patient preferences
CrCl ≤ 30 ml/min
No antithrombotic therapy
NOAC
VKA

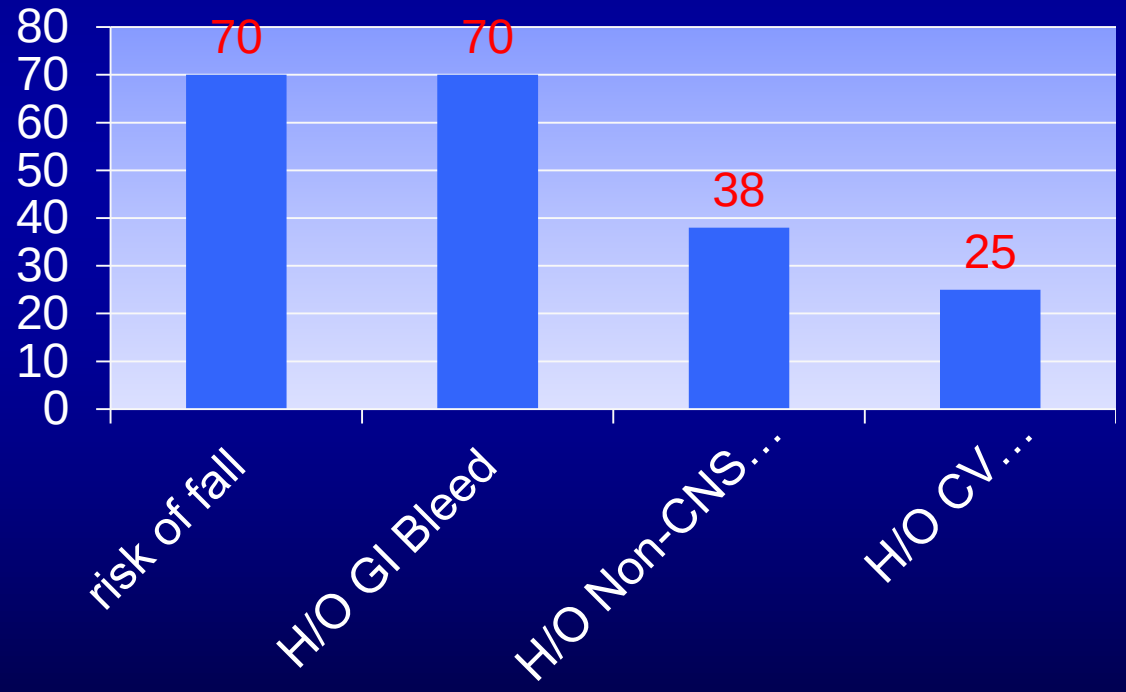
Current management of stroke prevention in AF in clinical practice in England



Heart 2013,99
1166-1172

Why Are We Reluctant To Use Warfarin

Physicians concern about for warfarin for stroke prevention in AF



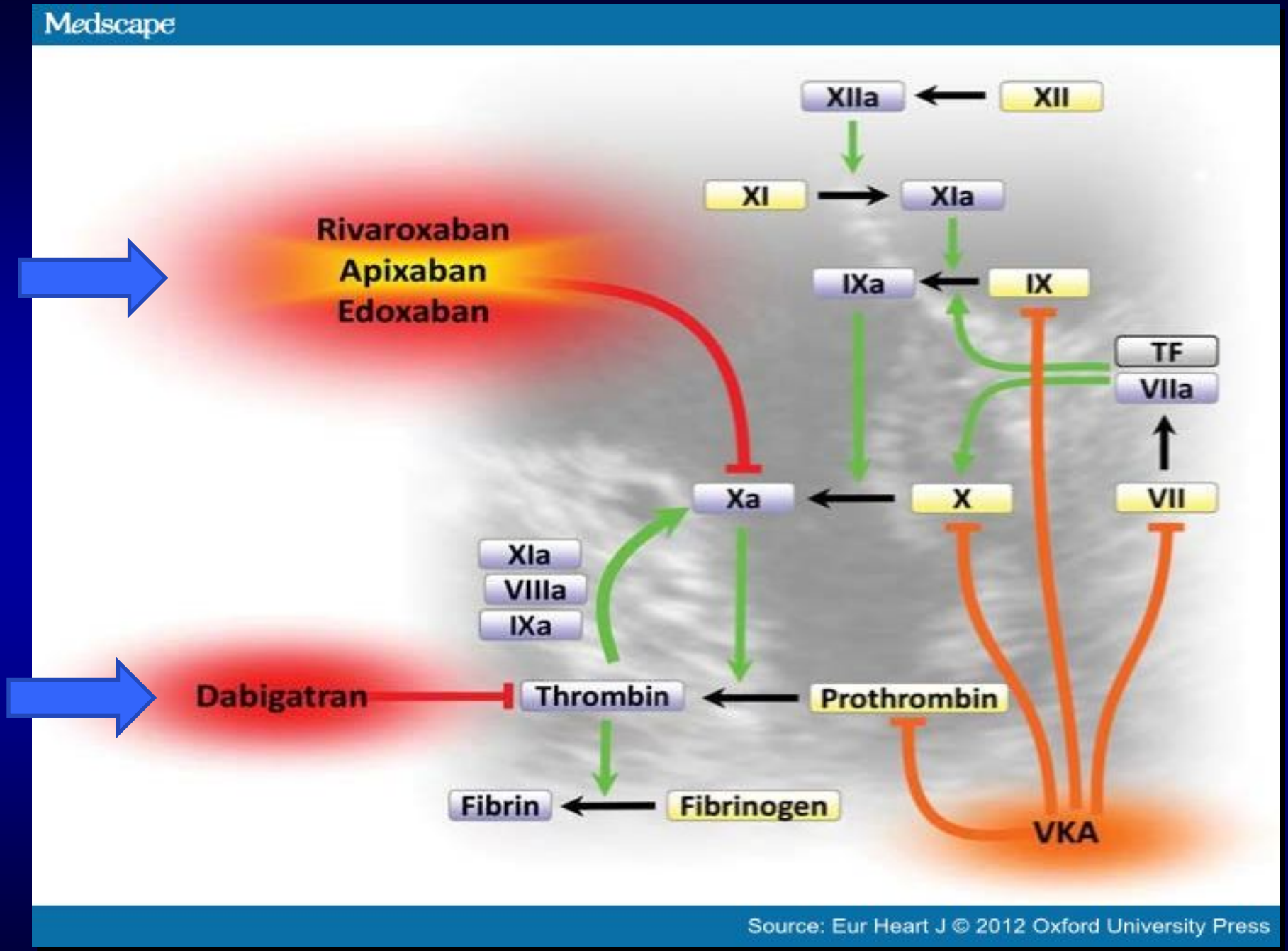
Risk vs benefit of Warfarin

- **47% benefit greatly outweigh risk**
- **34% risk slightly outweigh benefit**
- **19% risk outweigh benefit.**

- ICH
- Variable dose response
- Narrow therapeutic window
- Need for frequent monitoring
- Long half-life

New oral anticiagulants

Direct thrombin inhibitirors	Oral direct Factor Xa inhibitors
Dabigatrans	Rivaroxaban
	Apixaban
	Edoxaban


Medscape
XIIa
XII
XI
XIa
Rivaroxaban
Apixaban
Edoxaban
IXa
IX
TF
VIIa
Xa
X
VII
XIa
VIIIa
IXa
Dabigatran
Thrombin
Prothrombin
Fibrin
Fibrinogen
VKA
Source: Eur Heart J © 2012 Oxford University Press

Pharmacologic Characteristics

	Dabigatran	*Rivaroxaban*	*Apixaban*
Target	**IIa**	**Xa**	**Xa**
Bioavailability	**7%**	**60%-80%**	**80%**
Onset of action	**0.5-1 hr**	**2-4 hr**	**1-4 hr**
Half-Life	**12-17 hrs**	**7-11 hrs**	**12 hrs**
Clearance	**80% renal**	**60% renal** **33% biliary**	**25% renal** **75% biliary**
Metabolism	**Conjugation to active glucuronides**	**CYP3A4** **CYP2J2**	**CYP3A4**

Novel Oral Anticoagulants
Pivotal Clinical Trials

RE-LY	Dabigatran 110 mg BID or 150 mg BID vs adjusted-dose warfarin
ROCKET AF	Rivaroxaban 20 mg QD vs adjusted-dose warfarin
ARISTOTLE	Apixaban 5 mg BID vs adjusted-dose warfarin

Connolly SJ, et al. *N Engl J Med.* 2009;361:1139-1151.
Patel MR, et al. *N Engl J Med.* 2011;365:883-891.
Granger CB, et al. *N Engl J Med.* 2011;365:981-992.

Trials of novel oral anticoagulants for stroke prevention

Direct thrombin inhibitor

Factor Xa inhibitors

RE-LY

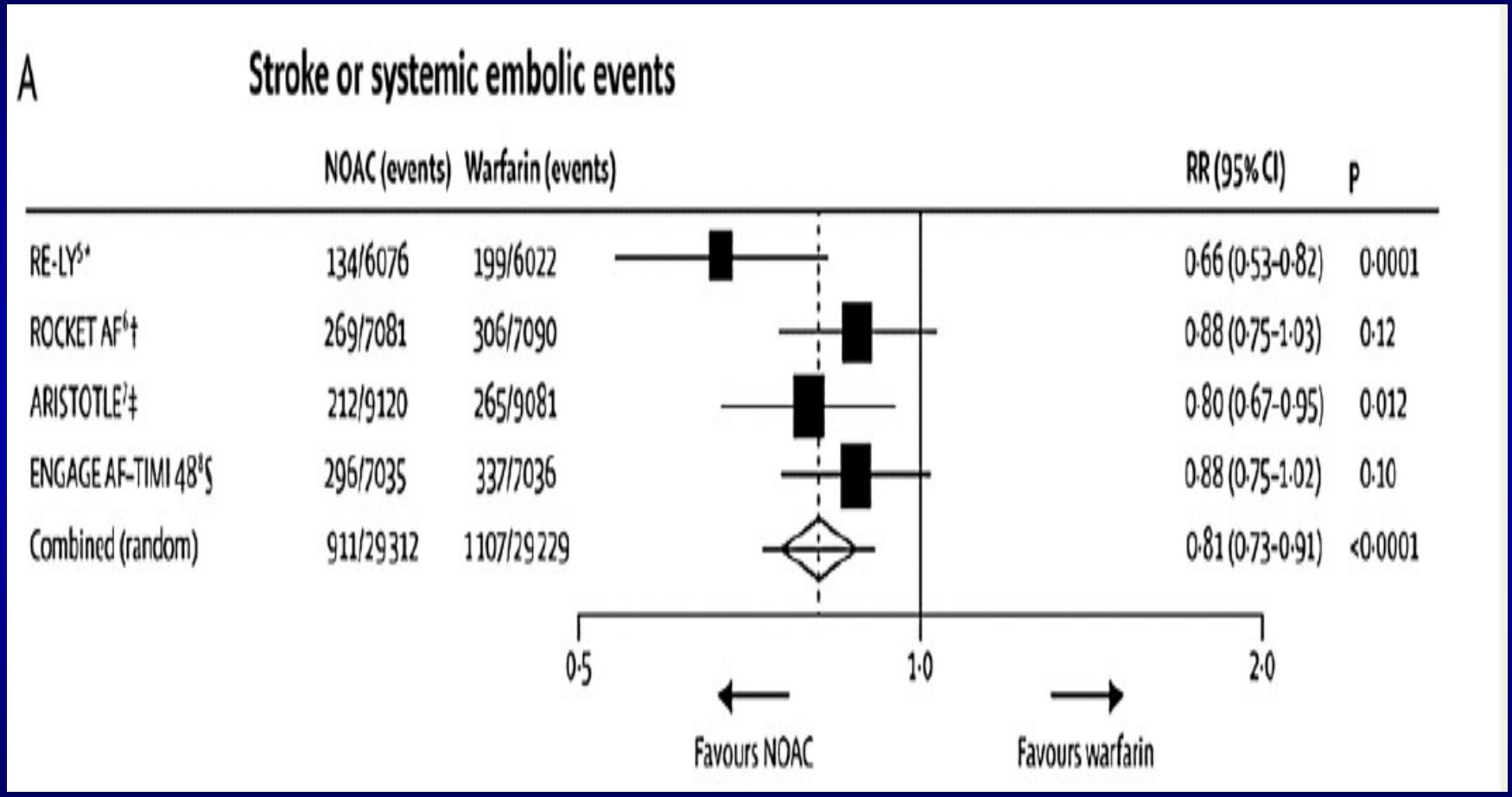
- Dabigatran
- ~18 000 pts
- PROBE design
- Mean $CHADS_2$ 2.1
- Stroke or systemic embolism
- Major bleeding

ROCKET-AF

- Rivaroxaban
- ~14 000 pts
- Double blind
- Mean $CHADS_2$ 3.5
- Stroke or systemic embolism
- Major and non-major clinically relevant bleeding

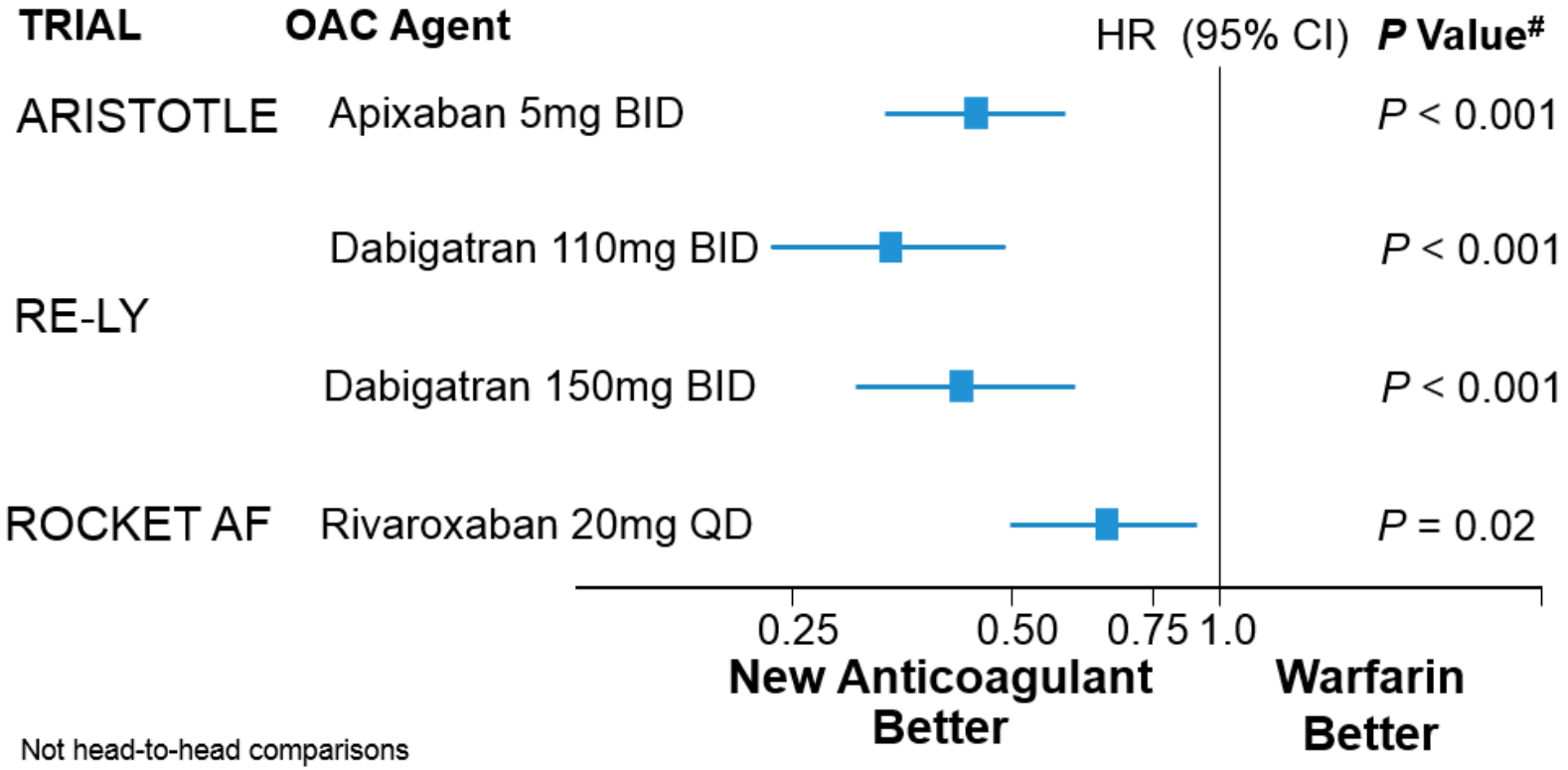
ARISTOTLE

- Apixaban
- ~18 000 pts
- Double blind
- Mean $CHADS_2$ 2.1
- Stroke or systemic embolism
- Major bleeding


A
Stroke or systemic embolic events
NOAC (events)
Warfarin (events)
RR (95% CI)
P
RE-LY[5]*
134/6076
199/6022
0·66 (0·53-0·82)
0·0001
ROCKET AF[6]†
269/7081
306/7090
0·88 (0·75-1·03)
0·12
ARISTOTLE[7]‡
212/9120
265/9081
0·80 (0·67-0·95)
0·012
ENGAGE AF-TIMI 48[8]§
296/7035
337/7036
0·88 (0·75-1·02)
0·10
Combined (random)
911/29312
1107/29229
0·81 (0·73-0·91)
<0·0001
0·5
1·0
2·0
Favours NOAC
Favours warfarin

NOACs Trials-Intracranial Hemorrhage

NOACs are consistently associated with a lower risk of intracranial hemorrhage



Not head-to-head comparisons

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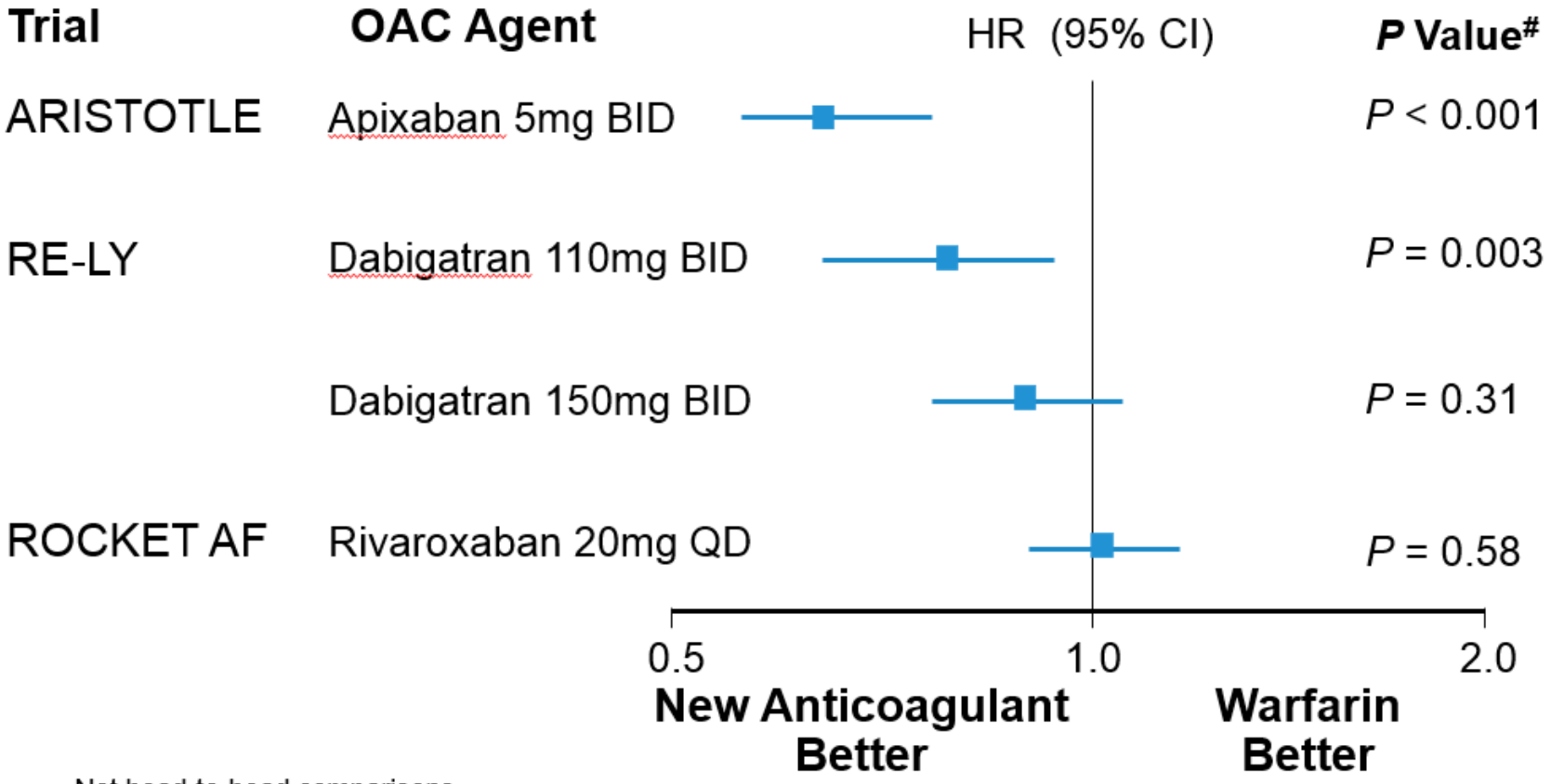
Patel MR, et al. *N Engl J Med.* 2011; 365:883–91.
Granger CB, et al. *N Engl J Med.* 2011; 365:981–92.

NOAC trials - Major bleeding

New OACs are associated with a lower or similar risk of major bleeding



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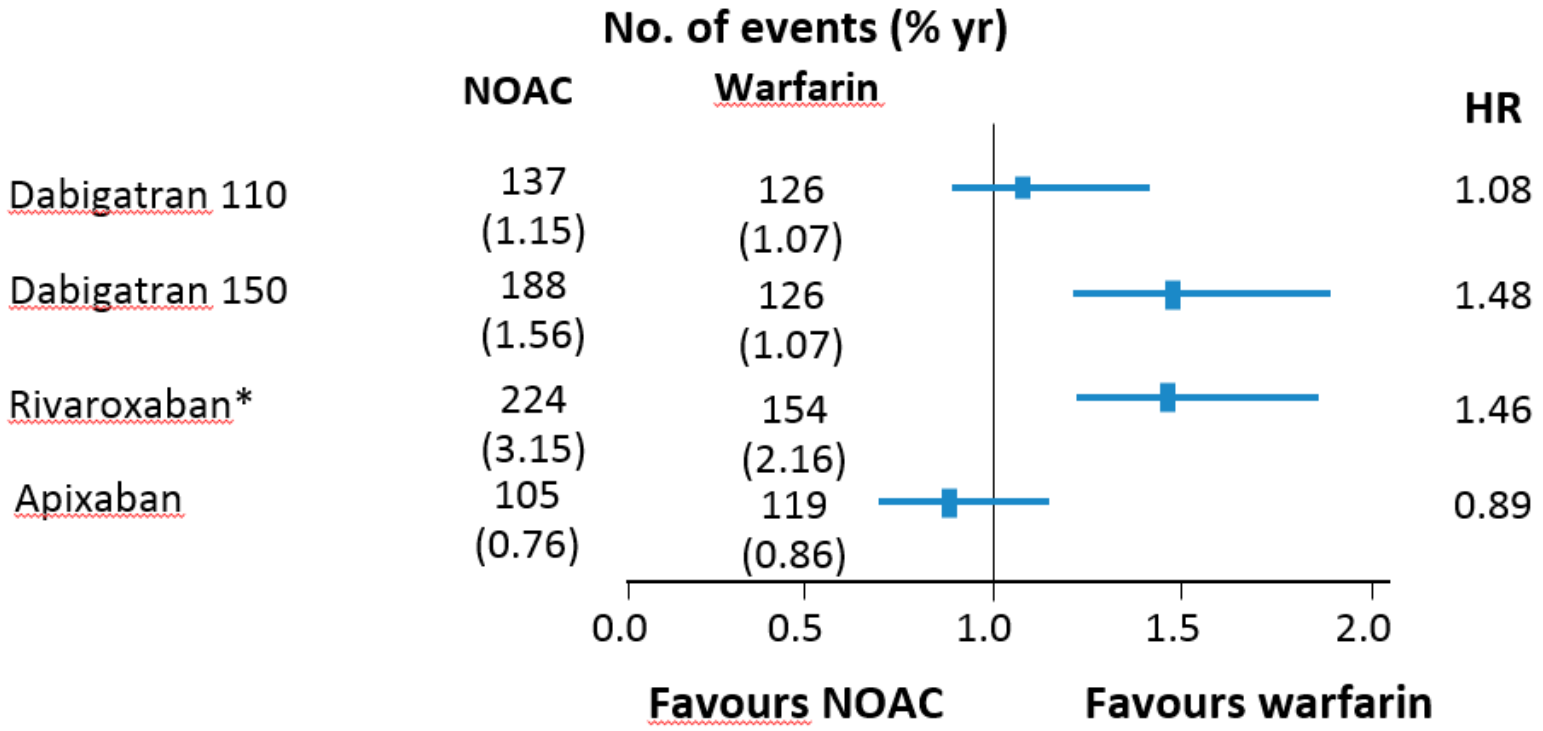
NOAC vs Warfarin: Major GI Bleeding

New OACs are associated with a similar or higher risk of GI bleeding



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**Rivaroxaban: *% and not %/yr are reported; RR, not reported, was calculated: http://www.spc.univ-lyon1.fr/mfcalc*

So why we choose NOAC over warfarin

Advantages of NOACs to warfarin

- Do not require monitoring
- Predictable anticoagulant effect
- No or limited interaction with other drugs/food
- Effective in stroke prevention with less ICM
- No heparin bridging
- Short half life and rapid elimination

Should NOACs Replace Warfarin

- Mechanical heart valve
- Renal failure and Liver failure
- Pregnant or baby.
- Lack of Antidote.
- Cost

Summary

- NOACs are one step ahead in safety and monitoring
- Short half and rapid onset of action –other important aspect
- But still warfarin is better option in mechanical prosthetic heart valve and renal impairment.
- Its too early to decide which one is better and both drug effective and provide protection

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