XXVIII GIORNATE CARDIOLOGICHE TORINESI

ADVANCES IN CARDIAC ARRHYTHMIAS and GREAT INNOVATIONS IN CARDIOLOGY

Città della Salute e della Scienza di Torino

UNIVERSITÀ DEGLI STUDI DI TORINO

GVM Maria Pia Hospital

From Caliper to Catheter

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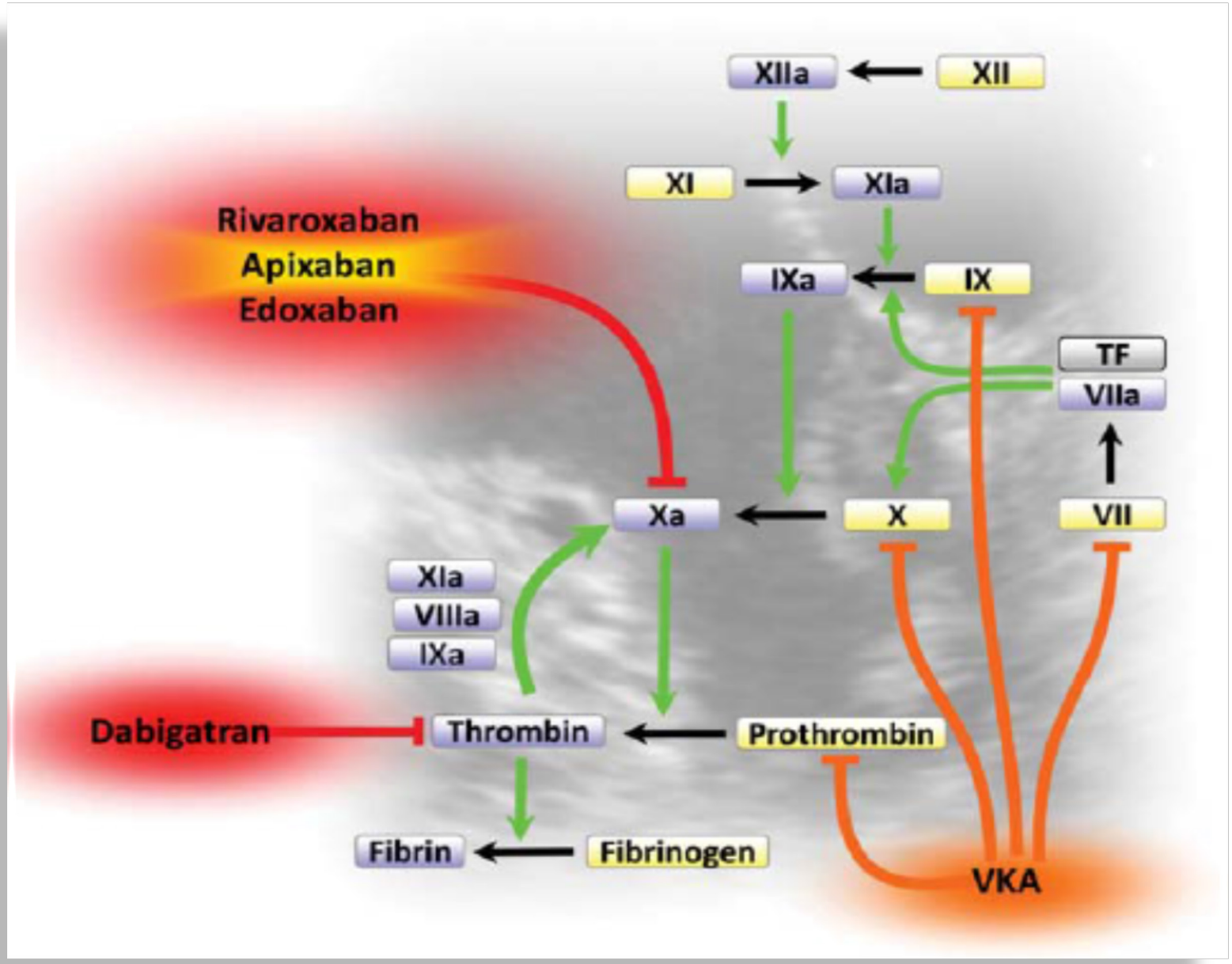
Are all non-vitamine-K antagonist created equal?

15.40 Apixaban \ *M. Bo*

GERIATRIA –CITTA' DELLA SALUTE E DELLA SCIENZA-MOLINETTE-TORINO

Turin
October 13-15, 2016
Centro Congressi
Unione Industriale di Torino


XIIa
XII
XI
XIa
Rivaroxaban
Apixaban
Edoxaban
IXa
IX
TF
VIIa
Xa
X
VII
XIa
VIIIa
IXa
Dabigatran
Thrombin
Prothrombin
Fibrin
Fibrinogen
VKA

European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

Table 4 Absorption and metabolism of the different NOACs

	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Bio-availability	3–7%	50%	62%[17]	66% without food Almost 100% with food
Prodrug	Yes	No	No	No
Clearance non-renal/renal of absorbed dose (if normal renal function; see also Section 8)	20%/80%	73%/27%[18]	50%/50%[9]	65%/35%
Liver metabolism: CYP3A4 involved	No	Yes (elimination; minor CYP3A4 contribution)[19]	Minimal (<4% of elimination)	Yes (elimination)
Absorption with food	No effect	No effect	6–22% more[20]	+39% more[21]
Intake with food recommended?	No	No	No official recommendation yet	Mandatory
Absorption with H2B/PPI	−12–30%[22–24]	No effect	No effect	No effect[21,25]
Asian ethnicity	+25%[24]	No effect	No effect[20]	No effect
GI tolerability	Dyspepsia 5–10%	No problem	No problem	No problem
Elimination half-life	12–17 h[23]	12 h	9–11 h[9]	5–9 h (young) 11–13 h (elderly)

[a]No EMA approval yet. Needs update after finalization of SmPC.
H2B, H2-blocker; PPI, proton-pump inhibitor; GI, gastro-intestinal.

Europace (2013) **15**, 625–651
doi:10.1093/europace/eut083

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 SEPTEMBER 15, 2011 VOL. 365 NO. 11

Apixaban versus Warfarin in Patients with Atrial Fibrillation

and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

R-DBT **APIXABAN 5 mg** bid (**2.5 mg** bid if 2/3 of age >=80, weight<60 kg, creatinine level>=1.5 mg/dl) vs WARFARIN in 18201 patients with AF and 1+ RF for stroke ; **primary outcome**: ischemic or hemorrhagic stroke or SE; median duration 1.8 years

Età mediana:70 anni (17%>80 anni); femmine 36%; FAP vs FAC: 85/15; CHADS2 medio 2.1

Outcome	Apixaban Group (N=9120)		Warfarin Group (N=9081)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	*%/yr*	*no.*	*%/yr*		
Primary outcome: stroke or systemic embolism	212	1.27	265	1.60	0.79 (0.66–0.95)	0.01
Stroke	199	1.19	250	1.51	0.79 (0.65–0.95)	0.01
Ischemic or uncertain type of stroke	162	0.97	175	1.05	0.92 (0.74–1.13)	0.42
Hemorrhagic stroke	40	0.24	78	0.47	0.51 (0.35–0.75)	<0.001
Systemic embolism	15	0.09	17	0.10	0.87 (0.44–1.75)	0.70
Key secondary efficacy outcome: death from any cause	603	3.52	669	3.94	0.89 (0.80–0.998)	0.047
Other secondary outcomes						
Stroke, systemic embolism, or death from any cause	752	4.49	837	5.04	0.89 (0.81–0.98)	0.02
Myocardial infarction	90	0.53	102	0.61	0.88 (0.66–1.17)	0.37
Stroke, systemic embolism, myocardial infarction, or death from any cause	810	4.85	906	5.49	0.88 (0.80–0.97)	0.01
Pulmonary embolism or deep-vein thrombosis	7	0.04	9	0.05	0.78 (0.29–2.10)	0.63

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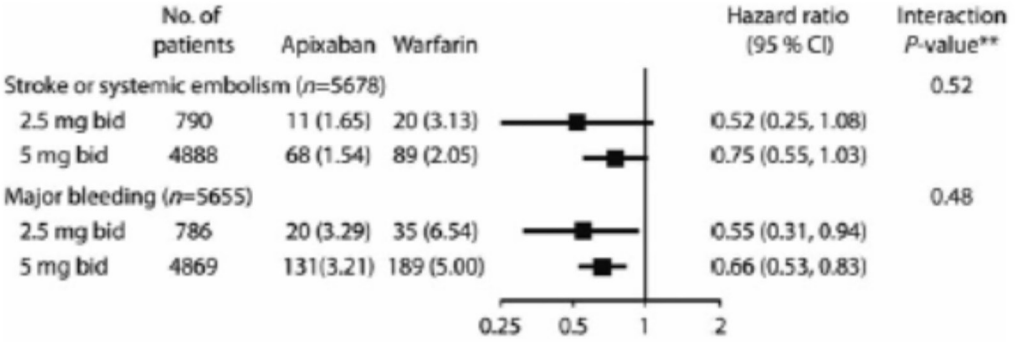
Table 3. Bleeding Outcomes and Net Clinical Outcomes.*

Outcome	Apixaban Group (N=9088)		Warfarin Group (N=9052)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	*%/yr*	*no.*	*%/yr*		
Primary safety outcome: ISTH major bleeding†	327	2.13	462	3.09	0.69 (0.60–0.80)	<0.001
Intracranial	52	0.33	122	0.80	0.42 (0.30–0.58)	<0.001
Other location	275	1.79	340	2.27	0.79 (0.68–0.93)	0.004
Gastrointestinal	105	0.76	119	0.86	0.89 (0.70–1.15)	0.37
Major or clinically relevant nonmajor bleeding	613	4.07	877	6.01	0.68 (0.61–0.75)	<0.001
GUSTO severe bleeding	80	0.52	172	1.13	0.46 (0.35–0.60)	<0.001
GUSTO moderate or severe bleeding	199	1.29	328	2.18	0.60 (0.50–0.71)	<0.001
TIMI major bleeding	148	0.96	256	1.69	0.57 (0.46–0.70)	<0.001
TIMI major or minor bleeding	239	1.55	370	2.46	0.63 (0.54–0.75)	<0.001
Any bleeding	2356	18.1	3060	25.8	0.71 (0.68–0.75)	<0.001
Net clinical outcomes						
Stroke, systemic embolism, or major bleeding	521	3.17	666	4.11	0.77 (0.69–0.86)	<0.001
Stroke, systemic embolism, major bleeding, or death from any cause	1009	6.13	1168	7.20	0.85 (0.78–0.92)	<0.001



A reduced dose of 2.5 mg twice daily or placebo were administered to a total of 831 patients; 790 of these patients were ≥75 years.
** Interaction among treatment, age and dose based on randomized or treated population

Figure 3 The effect of apixaban vs. warfarin on stroke or systemic embolism and major bleeding in patients ≥75 years in relation to apixaban dose.

All bleeding (*n*= 0.94*
Age <65
Age 65 – <75
Age ≥75

Intracranial blee 0.20*
Age <65
Age 65 – <75
Age ≥75

Net clinical ever 0.18*
Age <65
Age 65 – <75
Age ≥75

Conclusions

This analysis of the ARISTOTLE trial shows that the benefits of apixaban vs. warfarin in reducing stroke or systemic embolism, causing less bleeding and decreasing mortality were consistent in patients with AF regardless of age, with an even greater absolute benefit with increasing age. In light of these data, apixaban was demonstrated to be very attractive for stroke prevention in AF across the spectrum of age, and particularly for the elderly.

Figure 2 The effect of apixaban vs. warfarin on major study outcomes according to age. *Interaction *P*-values are based on continuous age.

Current presentation and management of 7148 patients with atrial fibrillation in cardiology and internal medicine hospital centers: The ATA AF study☆

Di Pasquale G, Int J Cardiol 2013

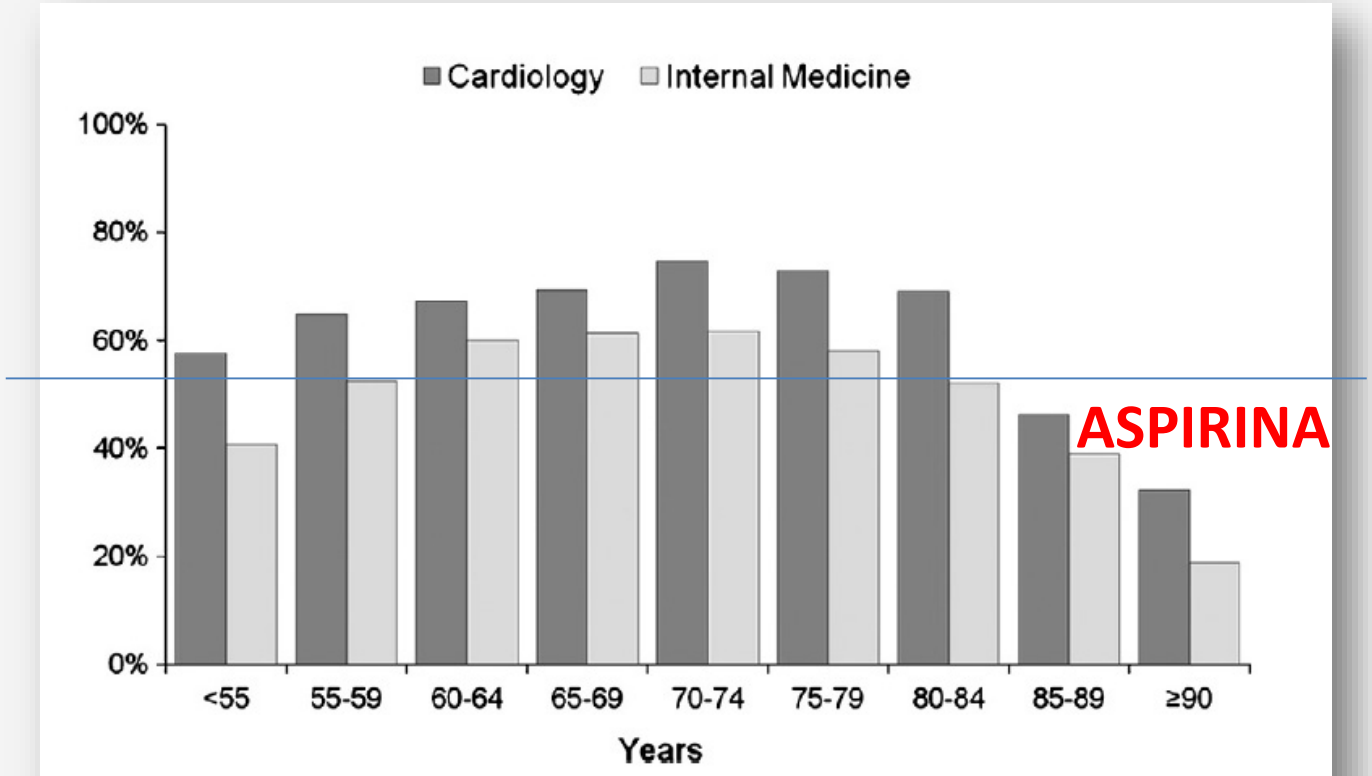


Fig. 5. OAC prescription at discharge from cardiology and internal medicine patients according to the age.

The NEW ENGLAND JOURNAL of MEDICINE

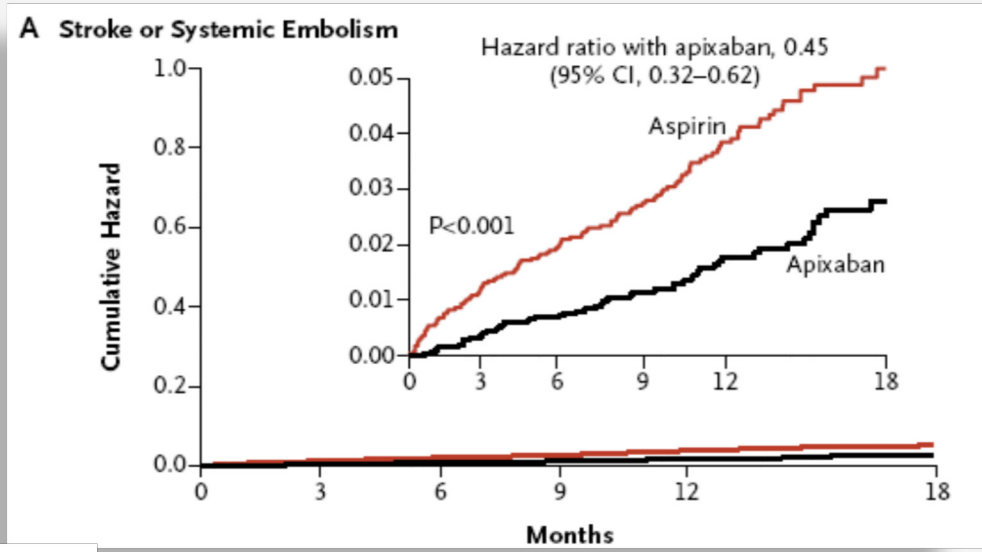
ORIGINAL ARTICLE

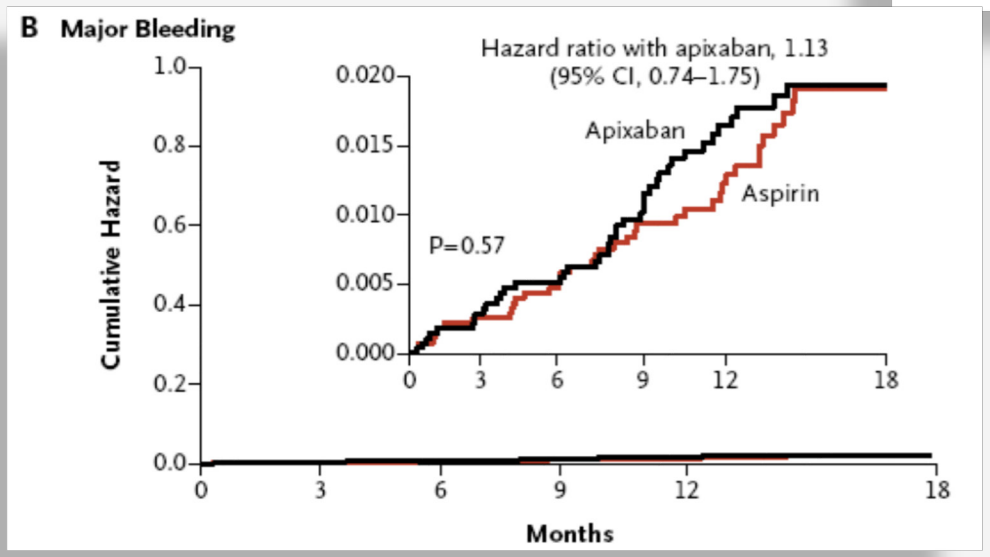
N ENGL J MED 364;9 NEJM.ORG MARCH 3, 2011

Apixaban in Patients with Atrial Fibrillation

and Salim Yusuf, M.B., B.S., D.Phil.,
for the AVERROES Steering Committee and Investigators*

*5599 pazienti (età media **71 anni**, 1898 pazienti>75 anni; F 40%, CHADS2 medio 2.0), **giudicati non candidabili a VKA**, trattati con Apixaban 5 mg bid vs ASA 81-324 mg*





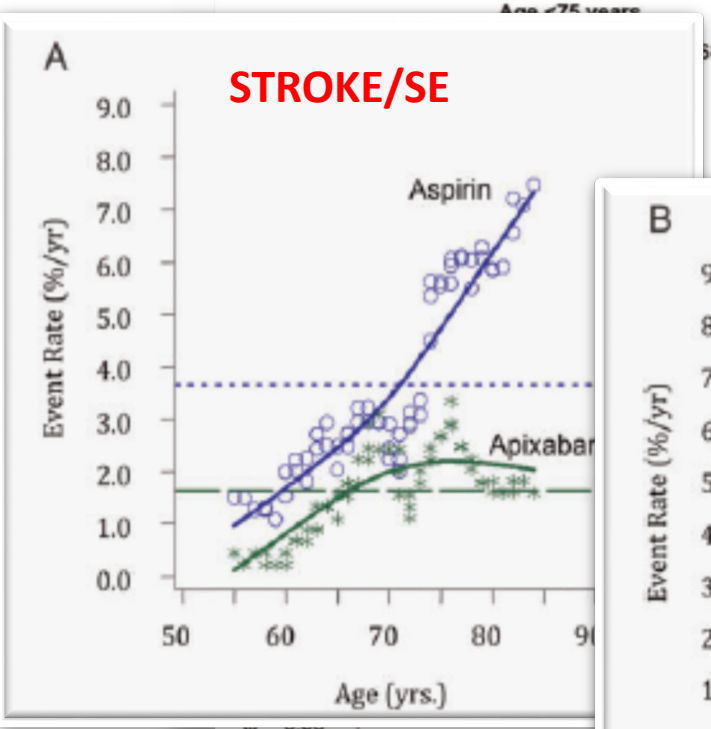
Stroke or SE: 1.6% vs 3.7%, NNT 50;
stroke, SE, death: 4.6% vs 7.2%, NNT 40
CV hospitalization: 12.6% vs 15.9%

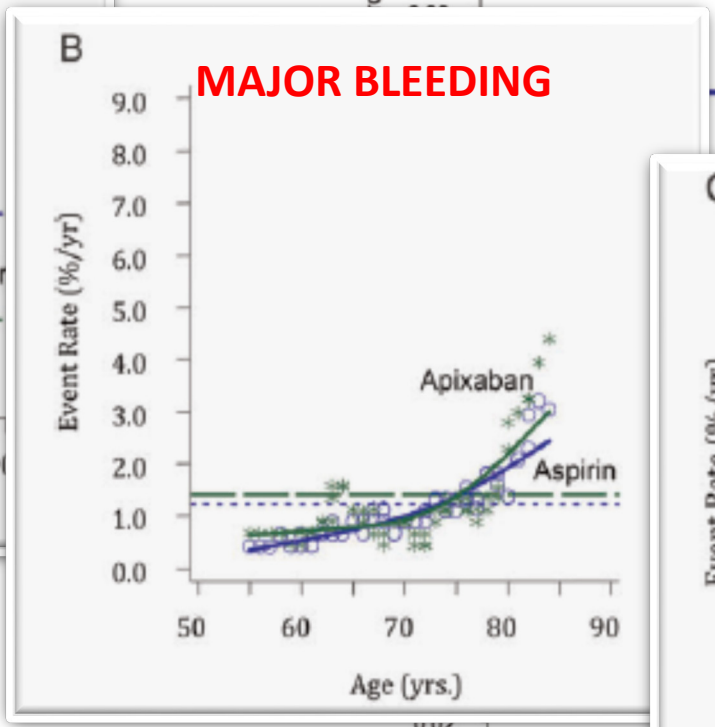
Efficacy and safety of apixaban compared with aspirin in the elderly: a subgroup analysis from the AVERROES trial

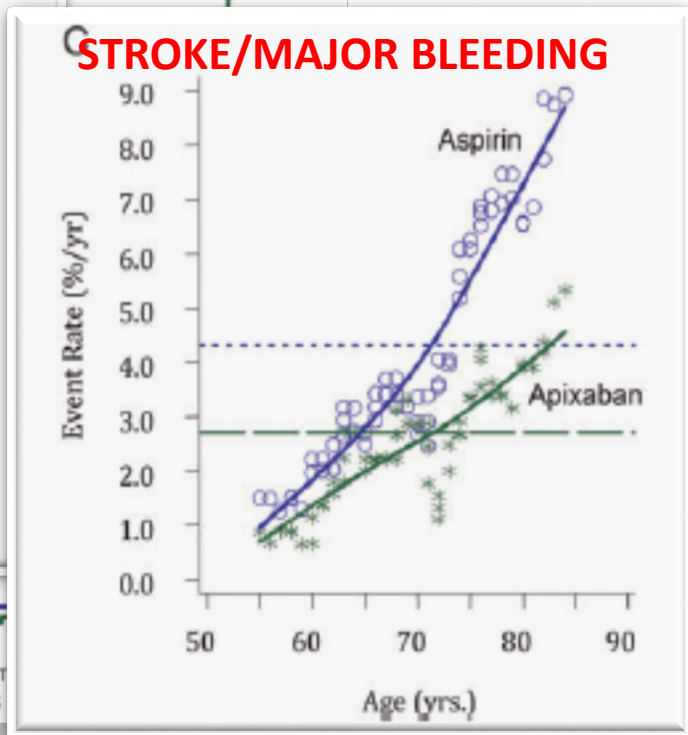
Age and Ageing 2016; **45:** 77–83

Kuan H. Ng[1], Olga Shestakovska[1], Stuart J. Connolly[1], John W. Eikelboom[1], Alvaro Avezum[2], Rafael Diaz[3], Fernando Lanas[4], Salim Yusuf[1], Robert G. Hart[1]

1898 pazienti >=75 anni e 366 pazienti >= 85 anni





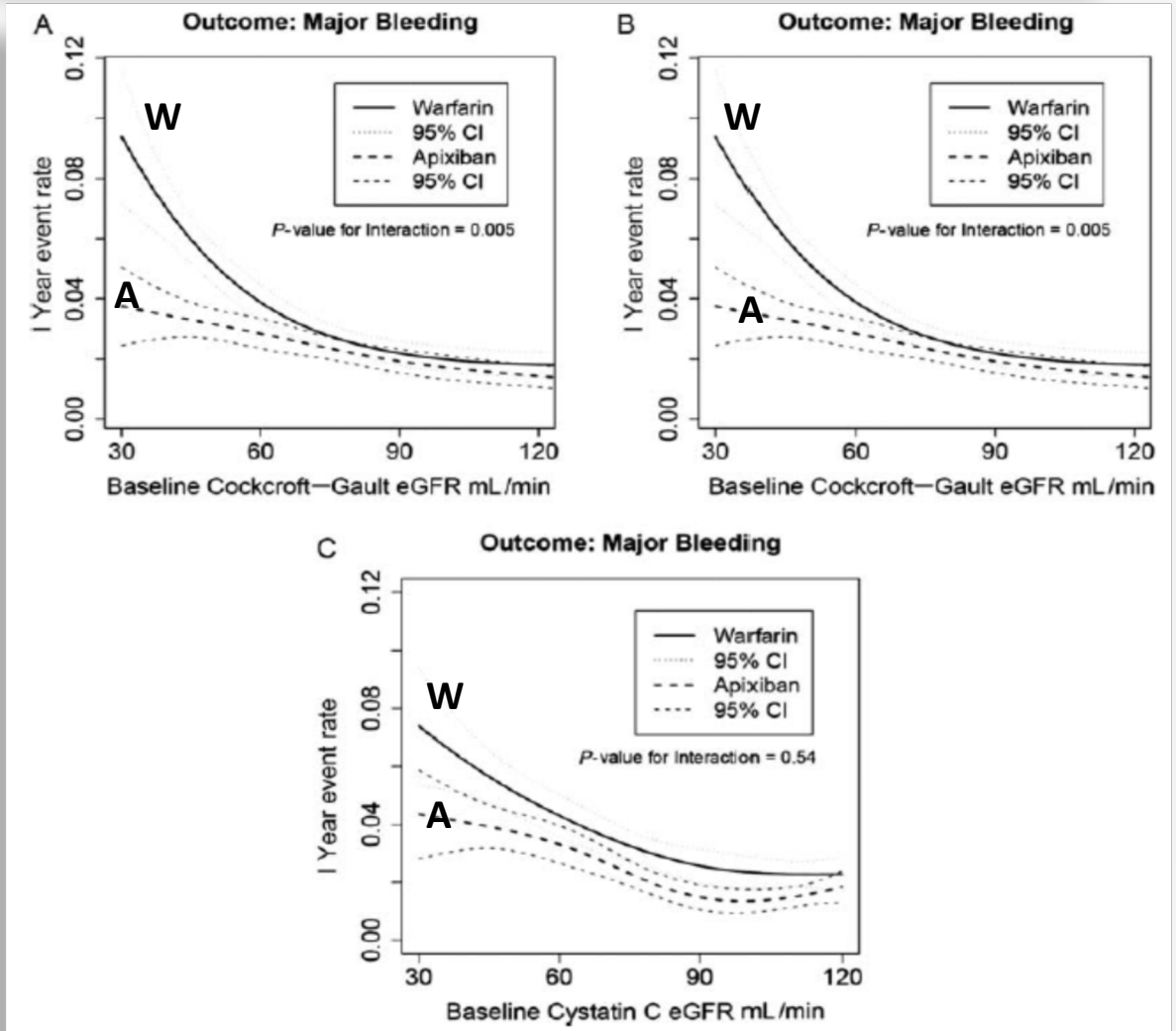


European Heart Journal (2012) 33, 2821–2830
doi:10.1093/eurheartj/ehs274

FASTTRACK
CLINICAL TRIAL & REGISTRY UPDATE

Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial

3017 patients (15%) with an eGFR <50 ml/min; mean age 77.3 years; 25.4% treated with 2.5 mg bid
(eGFR calculated according to CG, CKD-EPI, cystatin C)



Conclusions

Patients with **impaired renal function** seemed to **have tre greatest reduction in major bleeding with Apixaban**

Apixaban may be particularly suited to adddress the unmet need for a more effective and safe stroke prevention in patients with AF and renal dysfunction

Europace (2013) **15**, 625–651
doi:10.1093/europace/eut083

European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

10. Patients undergoing a planned surgical intervention or ablation

10.1 When to stop the new oral anticoagulants?

Table 9 Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban		Edoxaban[a]		Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 h or 24 h after last intake)							
	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥24 h	≥48 h	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 50–80 ml/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 30–50 ml/min[b]	**≥48 h**	**≥96 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 15–30 ml/min[b]	Not indicated	Not indicated	**≥36 h**	**≥48 h**	No data	No data	**≥36 h**	**≥48 h**
CrCl <15 ml/min	No official indication for use							

Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk.
[a]No EMA approval yet. Needs update after finalisation of SmPC.
[b]Many of these patients may be on the lower dose of dabigatran (i.e. 110 mg BID) or apixaban (i.e. 2.5 mg BID), or have to be on the lower dose of rivaroxaban (15 mg QD).
Low risk = surgery with low risk of bleeding; high risk = surgery with high risk of bleeding. See also Table 10.
CrCl, creatinine clearance.

Europace
doi:10.1093/europace/euv309

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

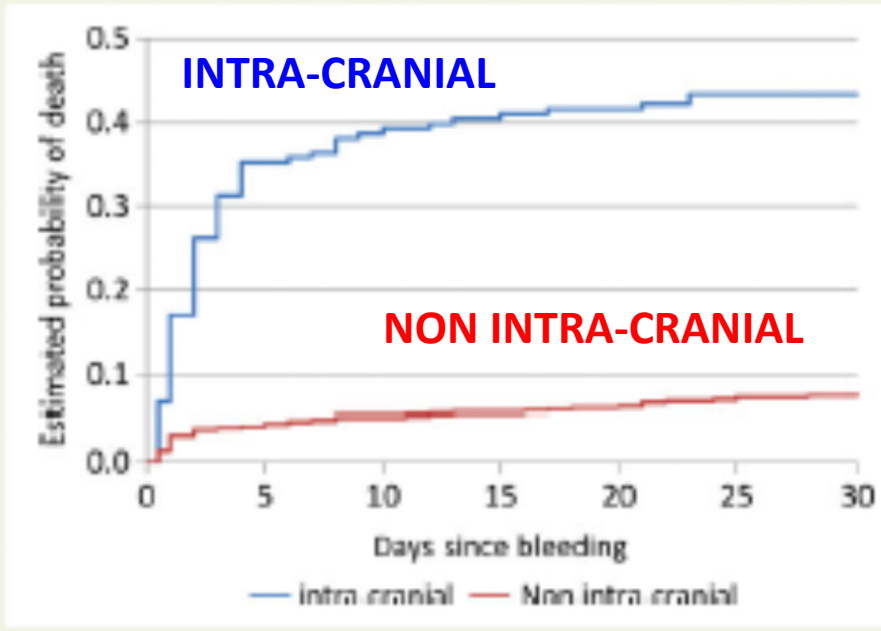
Table 8 Approved European labels for NOACs and their dosing in CKD

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Dosing if CKD	When CrCl 30–49 mL/min, 150 mg BID is possible (SmPC) but 110 mg BID should be considered (as per ESC guidelines)[5] Note: 75 mg BID approved in US only[c]: if CrCl 15–30 mL/min if CrCl 30–49 mL/min and other orange factor *Table 6* (e.g. verapamil)	CrCl 15–29 mL/min: 2.5 mg BID If two-out-of-three: serum creatinine ≥ 1.5 mg/dL, age ≥80 years, weight ≤60 kg: 2.5 mg BID	(i.e. 60 mg OD)[b] 30 mg OD when CrCl 15–49 mL/min	(i.e. 20 mg OD) 15 mg OD when CrCl 15–49 mL/min
Not recommended if	CrCl < 30 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min

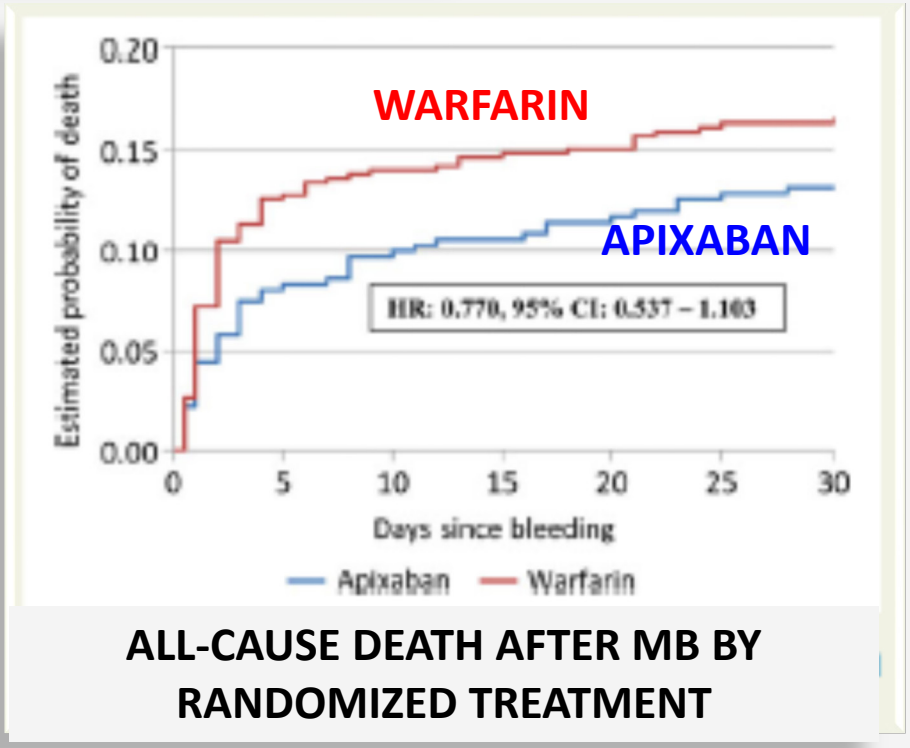
Therefore, the European guidelines recommend that the NOACs are best not used where severe renal impairment (GFR <25 to 30 ml/min) is present (75,130).

European Heart Journal (2015) 36, 1264–1272

Clinical outcomes and management associated with major bleeding in patients with atrial fibrillation treated with apixaban or warfarin: insights from the ARISTOTLE trial



ALL-CAUSE DEATH AFTER MB

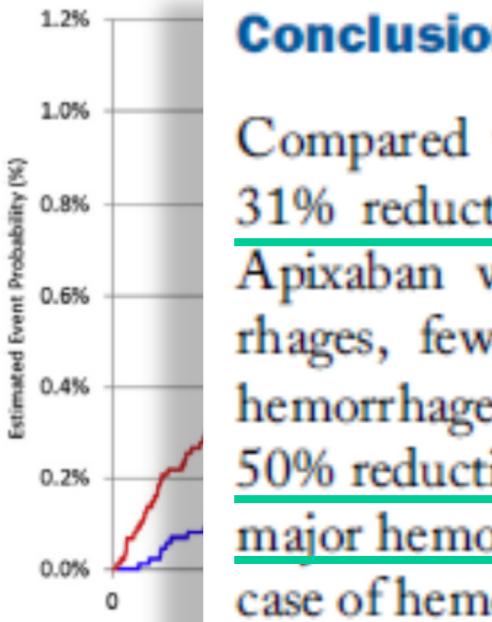


ALL-CAUSE DEATH AFTER MB BY RANDOMIZED TREATMENT

Major Bleeding in Patients With Atrial Fibrillation Receiving Apixaban or Warfarin

(J Am Coll Cardiol 2014;63:2141–7)

The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical Outcomes



Conclusions

Compared with warfarin, apixaban was associated with a 31% reduction in risk of first major ISTH hemorrhage. Apixaban was associated with fewer intracranial hemorrhages, fewer adverse consequences following extracranial hemorrhages, fewer trauma-associated hemorrhages, and a 50% reduction in fatal consequences at 30 days in case of a major hemorrhage. Therefore, concerns for complications in case of hemorrhage during anticoagulant treatment are fewer during apixaban than warfarin treatment.

Figure 1 Major Bleeding Following by Death Within 30 Days

CI = confidence interval; HR = hazard ratio.

ORIGINAL ARTICLE

N ENGL J MED 375;12 NEJM.ORG SEPTEMBER 22, 2016

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

67 patients (77 years) with acute MB treated with ANDEXANET (bolus 400 mg + 480 mg 2-hour infusion if last dose > 7 hours or bolus 800 mg and 960 mg 2-hour infusion if last dose < 7 hours)

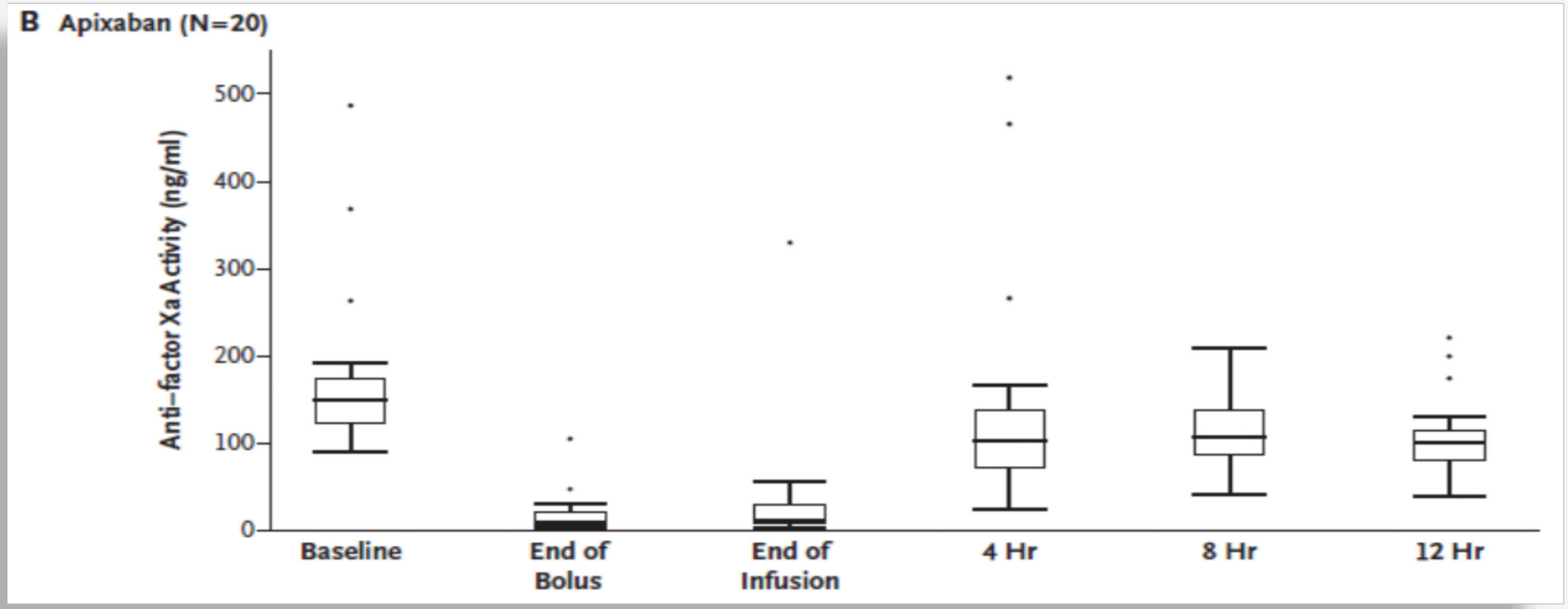
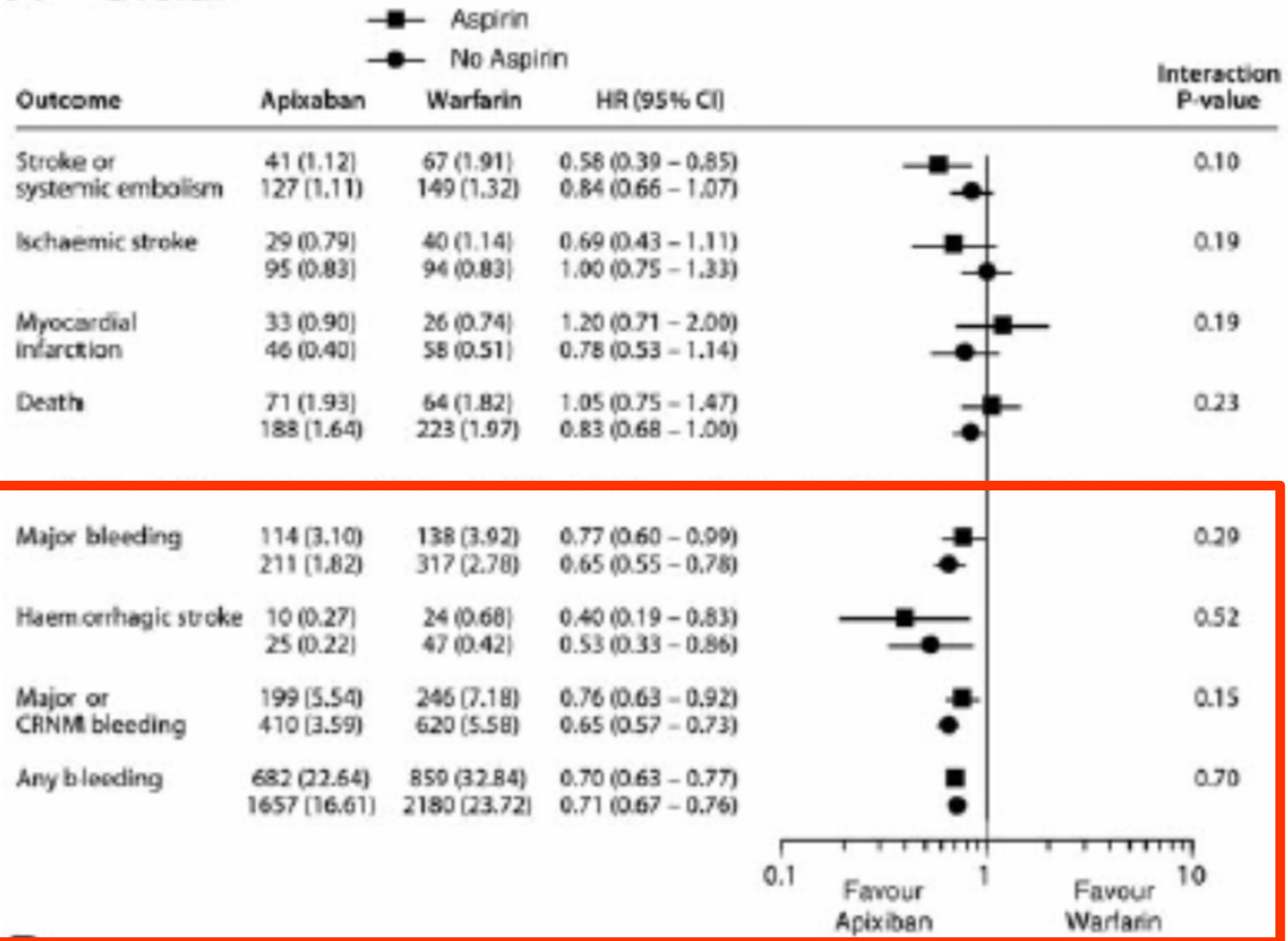


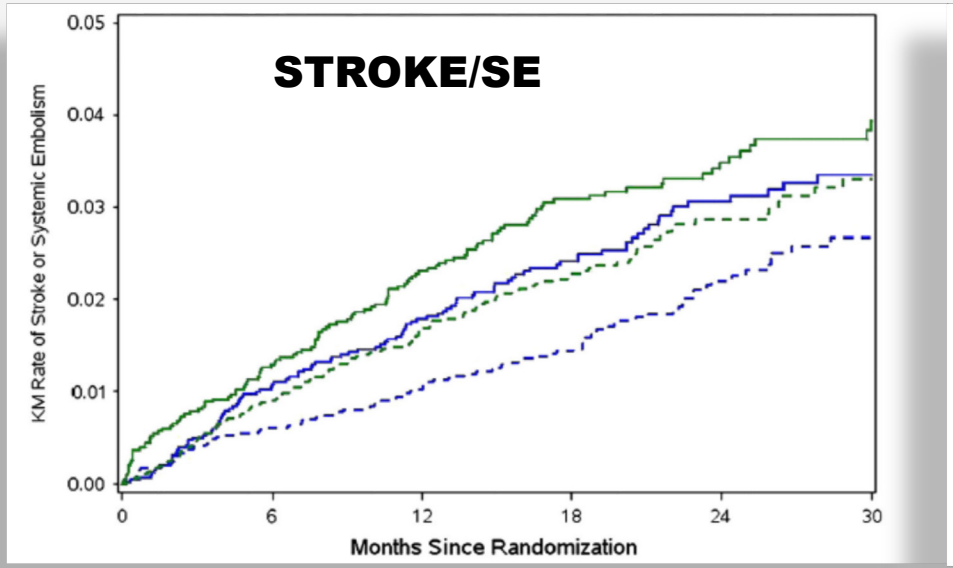
Figure 1. Anti–Factor Xa Activity and Percent Change from Baseline in Patients Receiving Rivaroxaban and Apixaban (Efficacy Population).

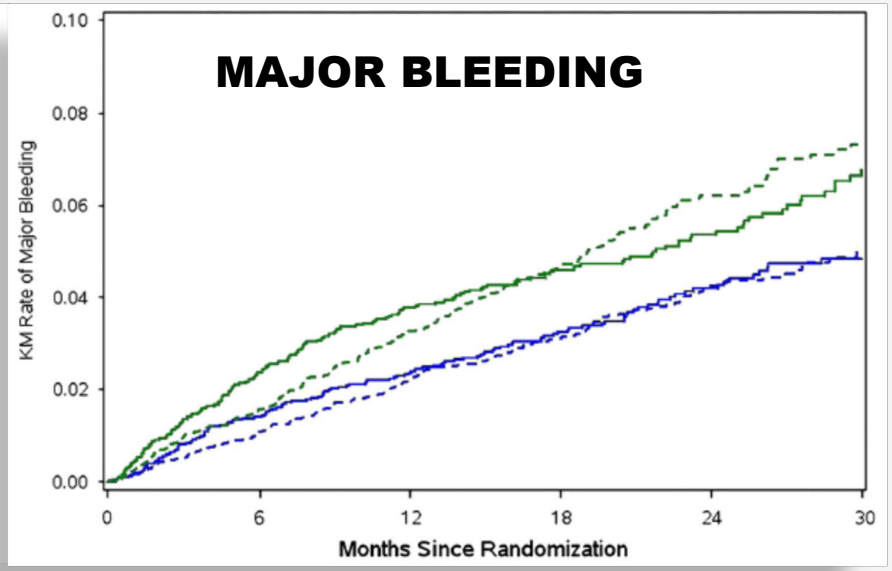
European Heart Journal (2014) **35**, 224–232
doi:10.1093/eurheartj/eht445

A Overall



Apixaban versus warfarin in patients with atrial fibrillation according to prior warfarin use: Results from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial





Conclusion The treatment effects of apixaban (vs warfarin) were not modified by VKA naivety. The rates of stroke/systemic embolism and major bleeding were numerically lower among the patients assigned to apixaban, irrespective of prior VKA use. (Am Heart J 2013;166:549-58.)

(Am Heart J 2013;166:549-58.)

Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial

Lancet Neurol 2012; 11: 503–11

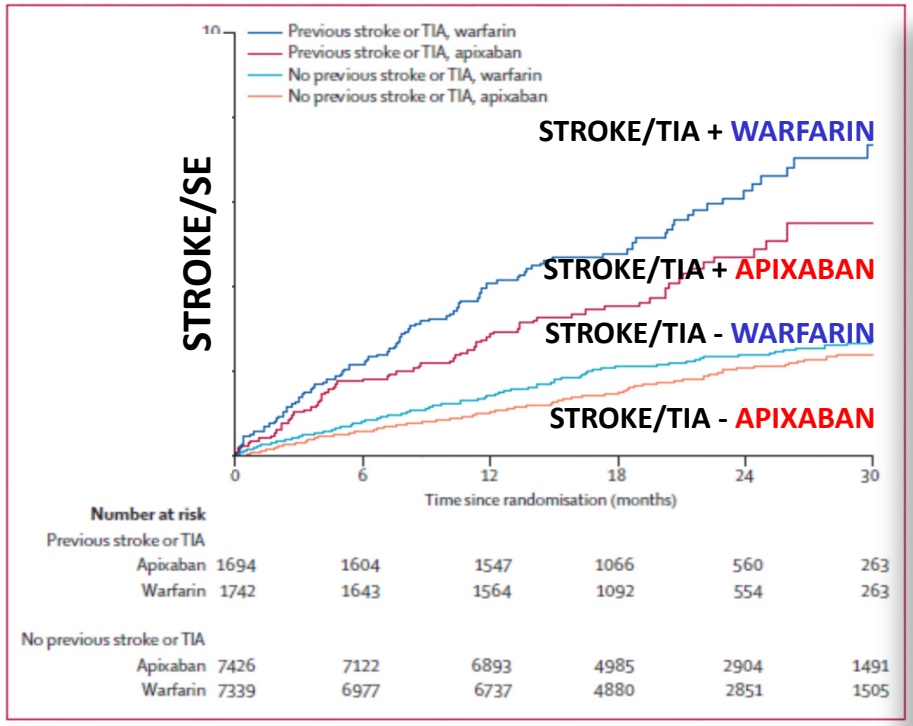


Figure 2: **Time to stroke or systemic embolism in patients with and without previous stroke or TIA**
TIA=transient ischaemic attack. Plot shows the Kaplan-Meier estimated probability of an event.

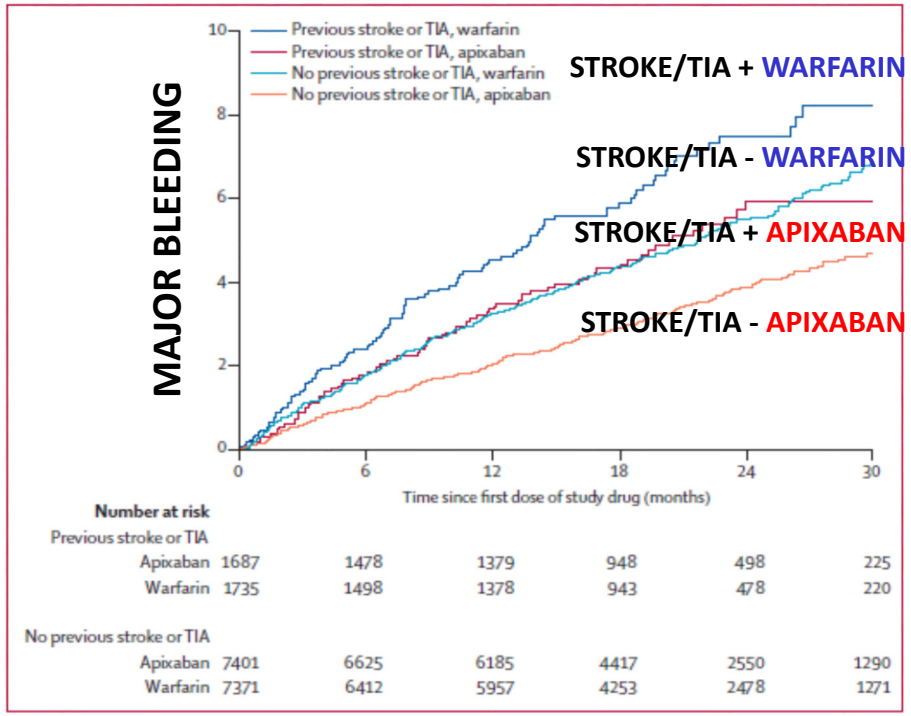
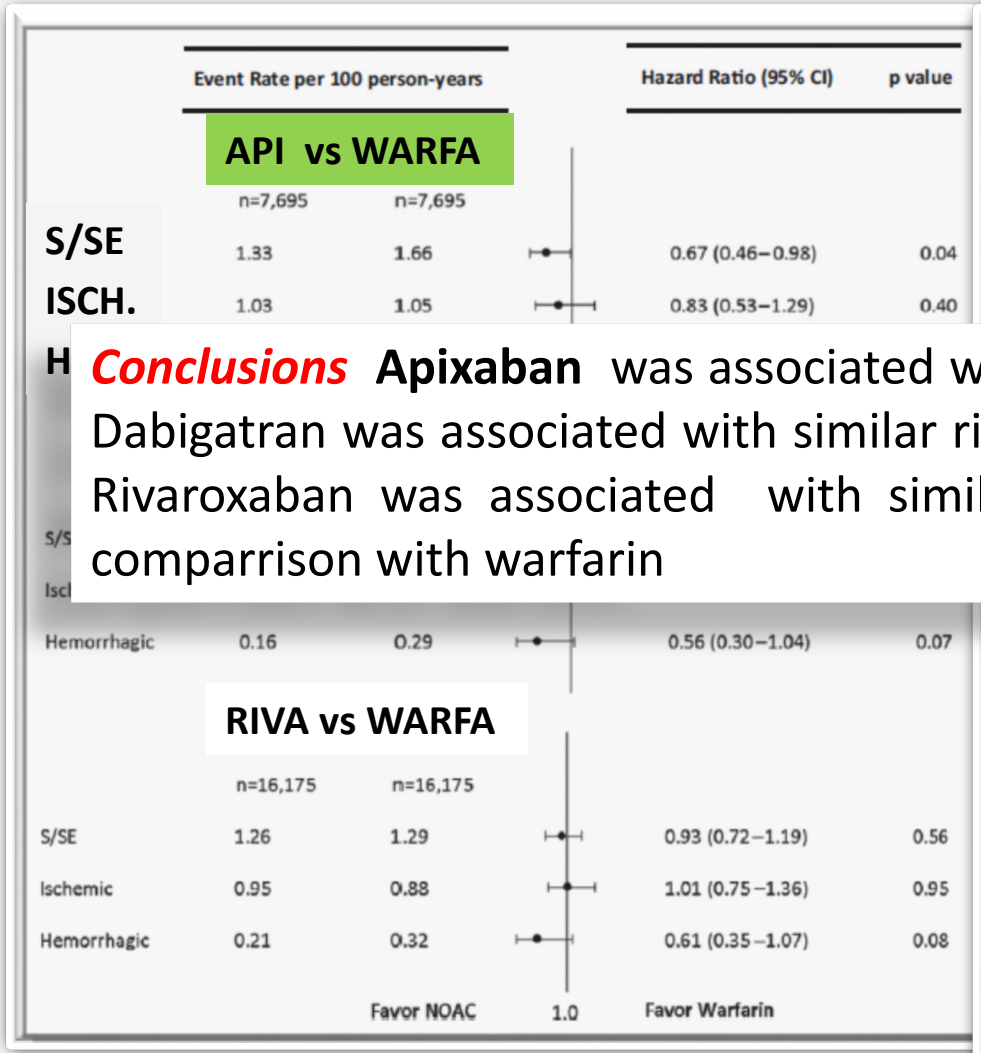


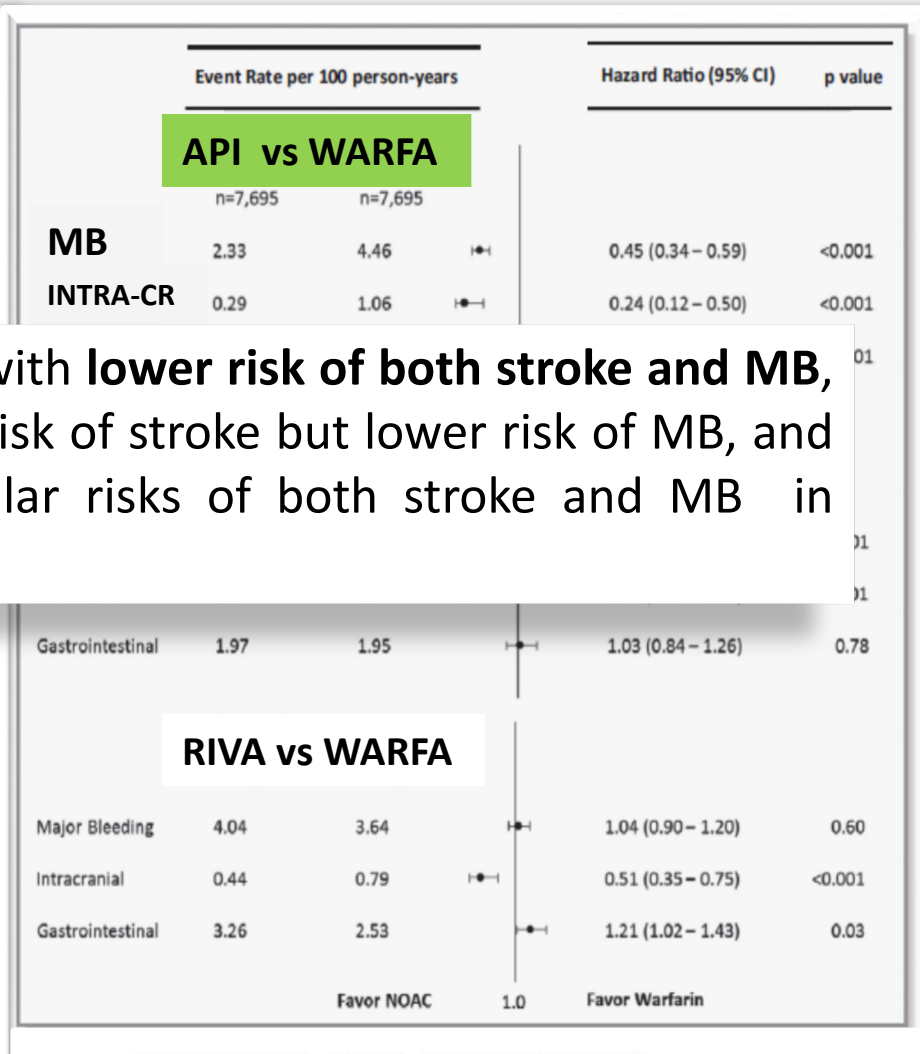
Figure 3: **Time to major bleeding in patients with and without previous stroke or TIA**
TIA=transient ischaemic attack. Plot shows the Kaplan-Meier estimated probability of an event.

Interpretation The effects of apixaban versus warfarin were consistent in patients with AF with and without previous stroke or TIA. Owing to the higher risk of these outcomes in patients with previous stroke or TIA, the absolute benefits of apixaban might be greater in this population.

Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation

Methods US Insurance database users of OAs between Oct 2010 and June 2015; **propensity-score matched analysis** 1:1 **API vs WARFA (15390),** DABI vs WARFA (28614) and RIVA vs WARFA (32350)





Conclusions **Apixaban** was associated with **lower risk of both stroke and MB**, Dabigatran was associated with similar risk of stroke but lower risk of MB, and Rivaroxaban was associated with similar risks of both stroke and MB in comparrison with warfarin

(*J Am Heart Assoc.* 2016;5:e003725

Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin

A propensity score matched analysis

Thrombosis and Haemostasis 116.5/2016

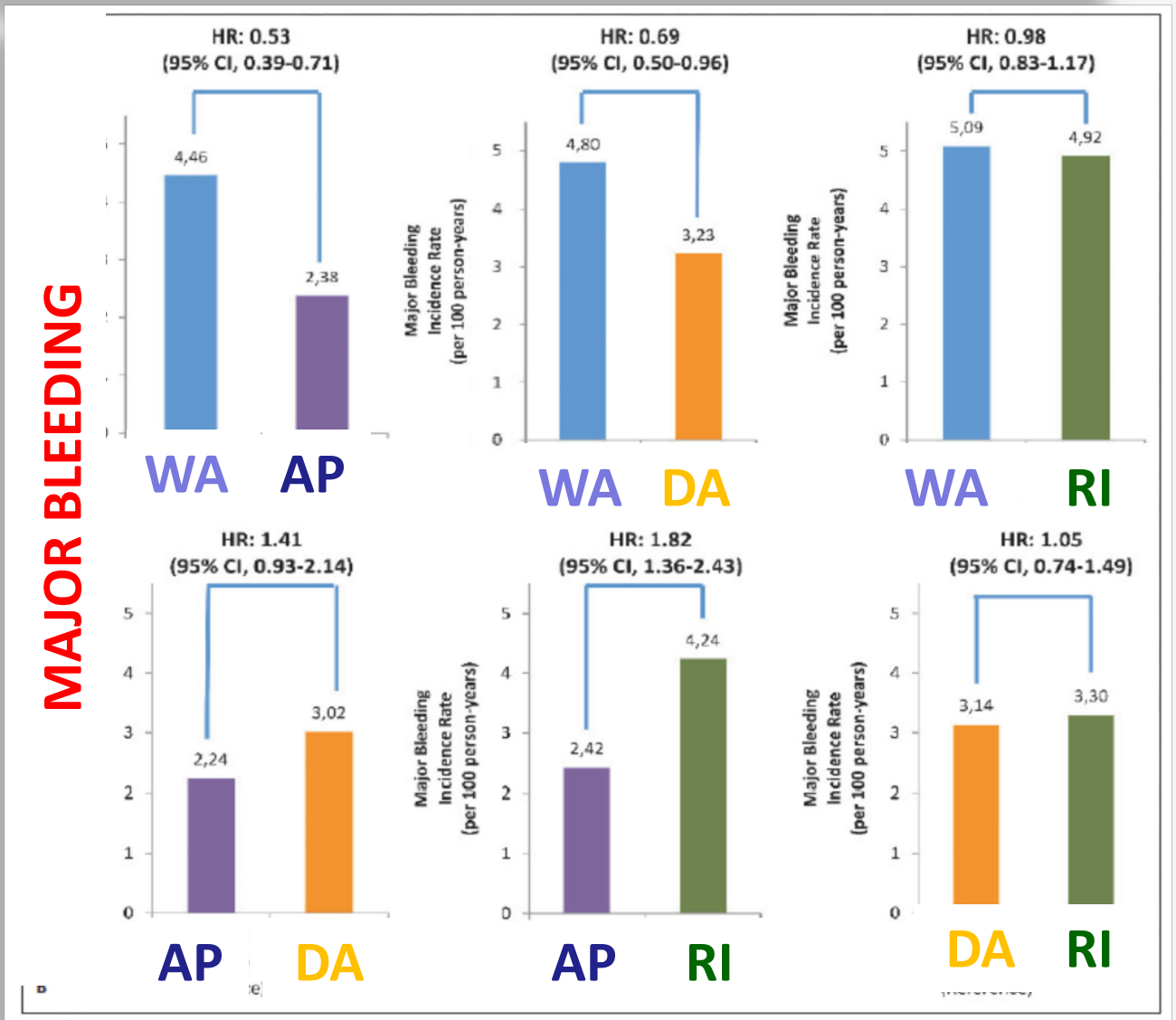


Figure 3: Major bleeding incidence rates and hazard ratios in warfarin-NOAC propensity score matched cohorts (A) and in NOAC-NOAC propensity score matched cohorts (B). CI: confidence interval; HR: hazard ratio.

Among **45361** newly anti-coagulated NVAF patients 15461 (34.1%) initiated Warfa, 7438 (16.4%) initiated Apixaban, 17801 (39.2%) initiated Rivaroxaban and 4661 (10.3%) initiated Dabigatran

Review

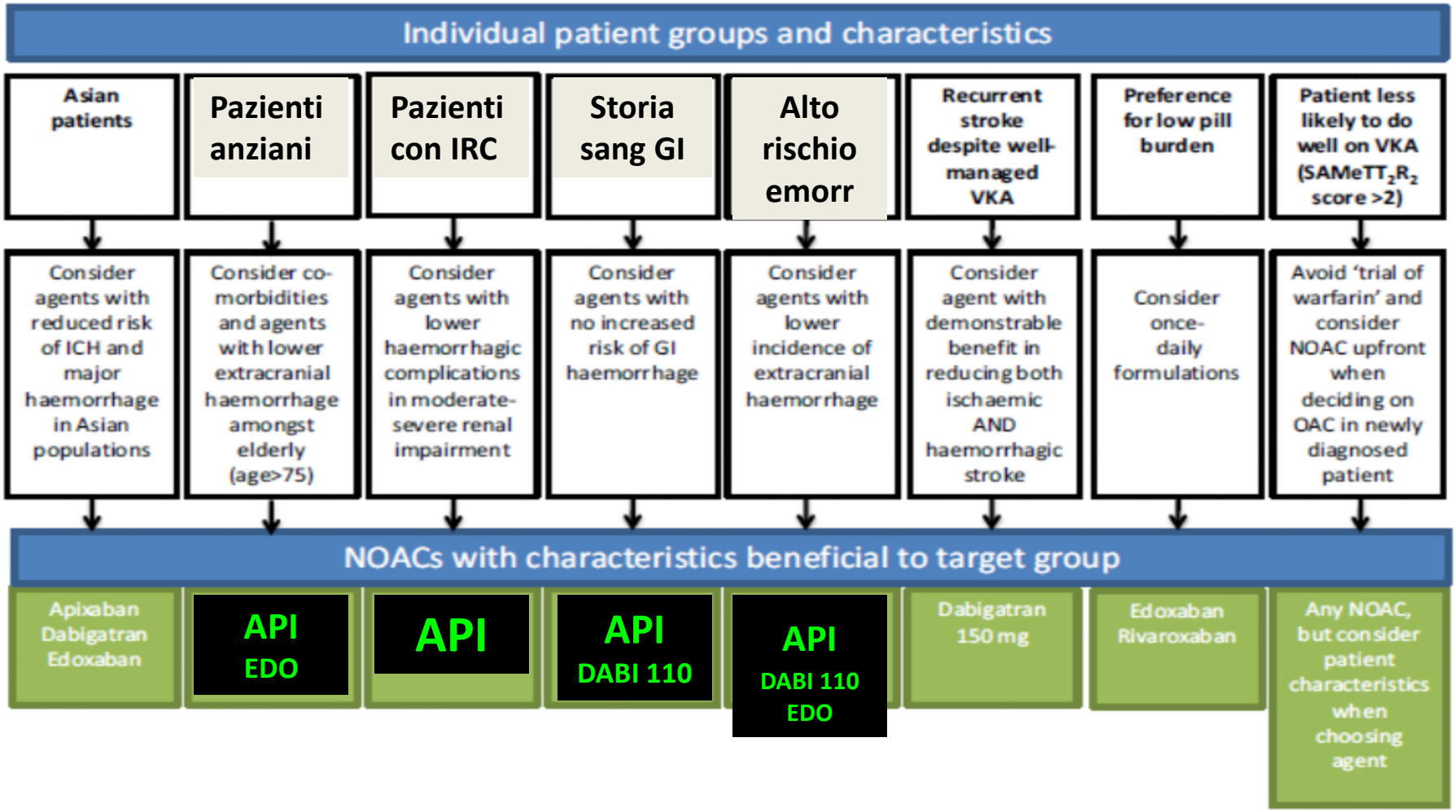
Journal of INTERNAL MEDICINE

doi: 10.1111/joim.12360

Choosing the right drug to fit the patient when selecting oral anticoagulation for stroke prevention in atrial fibrillation

A. M. Shields[1] & G. Y. H. Lip[2,3]

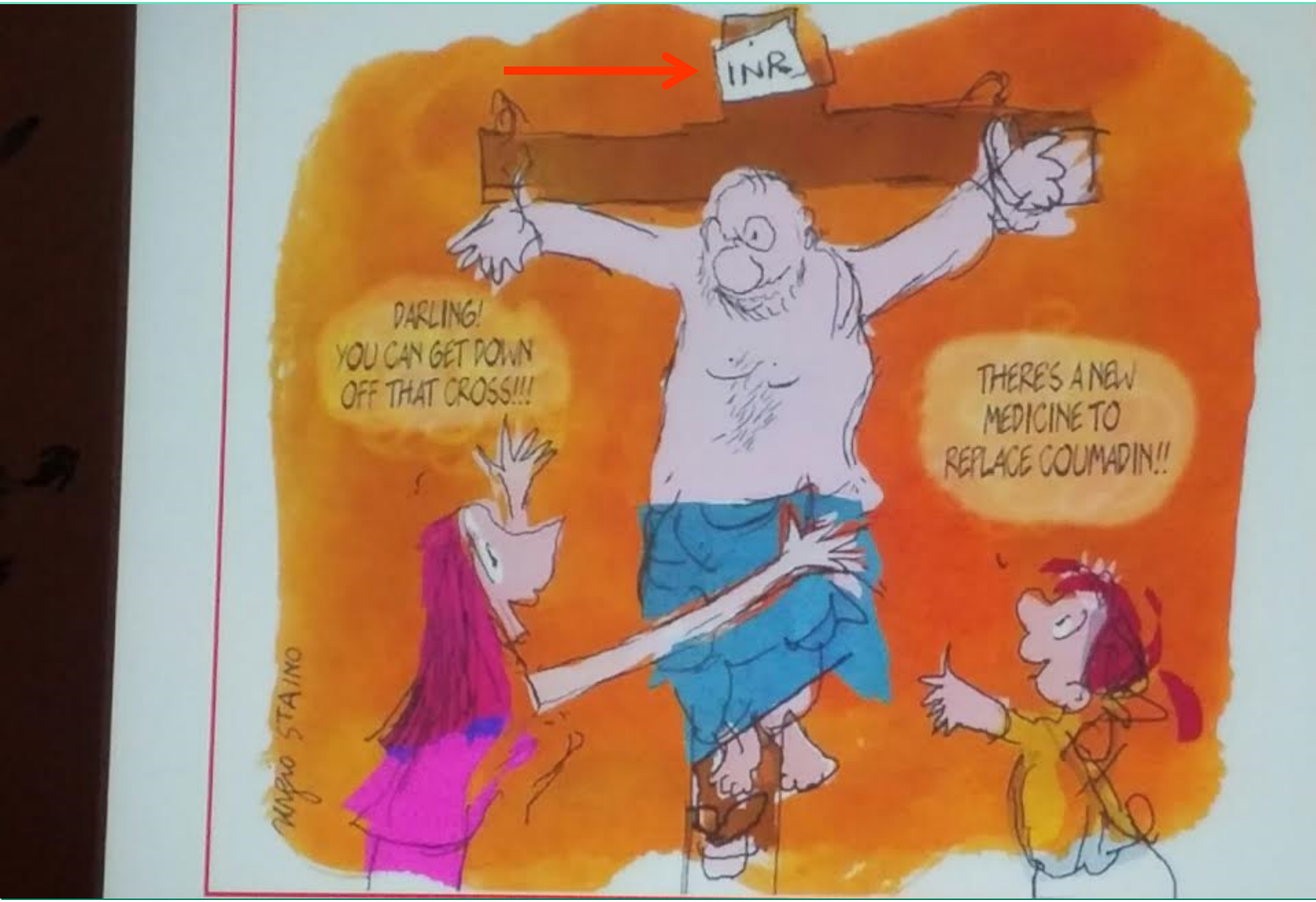
Intern Med 2015; **278**: 1–18.



CONCLUSIONI

APIXABAN presenta complessivamente eccellenti caratteristiche di efficacia e sicurezza in tutti i pazienti con FA

Nei pazienti con FA, APIXABAN si candida come farmaco di scelta nei soggetti anziani, in quelli con insufficienza renale, in quelli ad alto rischio emorragico ed in quelli con storia di sanguinamento gastrico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DARLING!
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OFF THAT CROSS!!!
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MEDICINE TO
REPLACE COUMADIN!!
ANGELO STAINO