Onorari per consulenze e relazioni scientifiche da:

- **BAYER**
- **BOEHRINGER**
- **PFIZER-BMS**

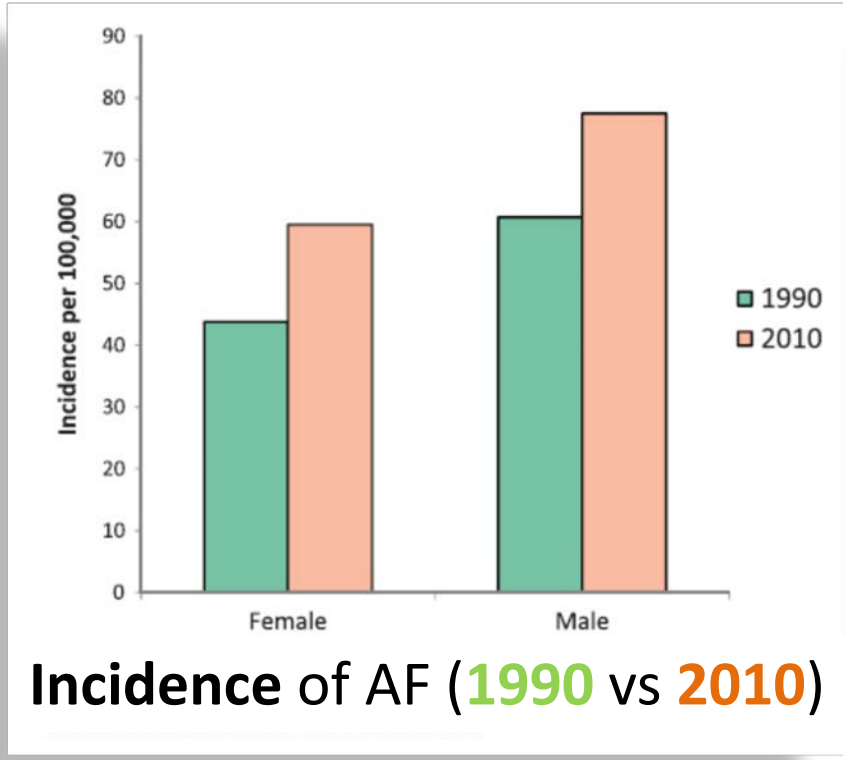
AF in complex elderly patient : is it an important issue?

Arrhythmia/Electrophysiology

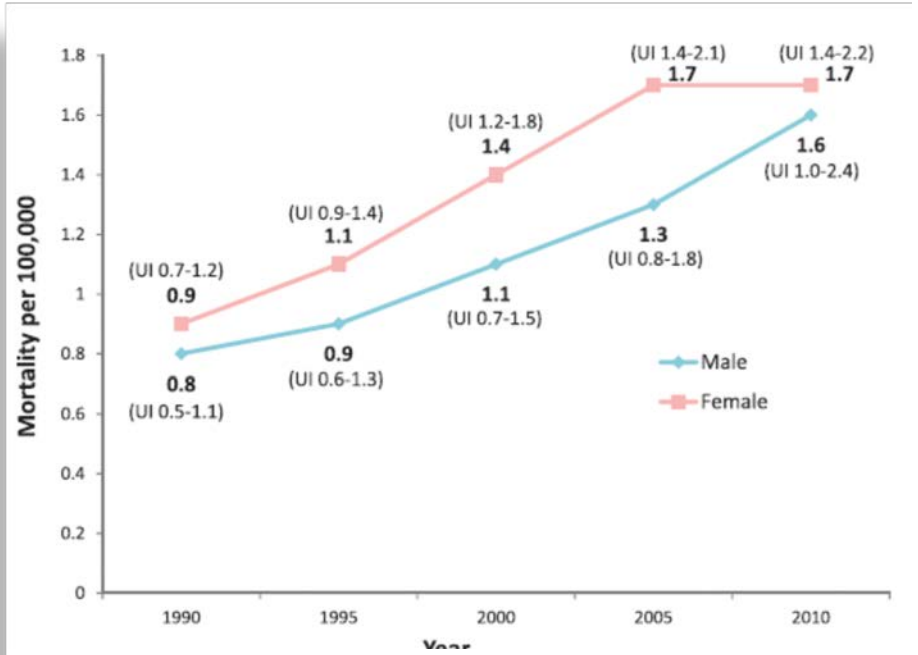
(*Circulation*. 2014;129:837-847.)

Worldwide Epidemiology of Atrial Fibrillation

A Global Burden of Disease 2010 Study



Incidence of AF (1990 vs 2010)



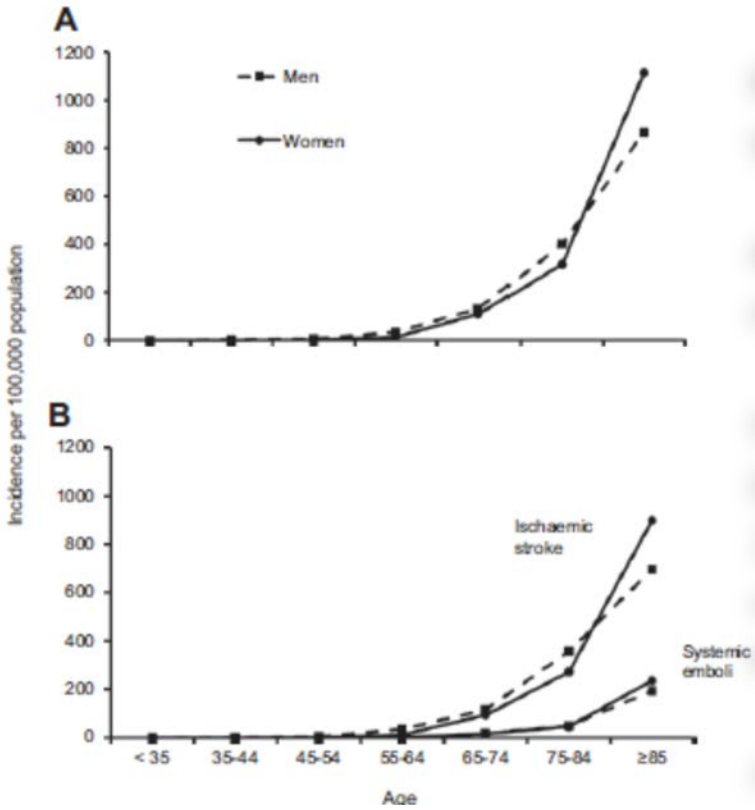
AF-associated mortality (1990 to 2010)

AF in complex elderly patient is an important issue

Age-Specific Incidence, Outcome, Cost, and Projected Future Burden of Atrial Fibrillation–Related Embolic Vascular Events

(*Circulation*. 2014;130:1236-1244.) **A Population-Based Study**

Age-specific incidence, outcome, and cost of all AF-related incident strokes (ISs) and systemic embolisms (SEs) from 2002 to 2012 in the OXVASC study.



Age and sex-specific rates (per 100.000/year) for all **incident AF-related IS and SE**

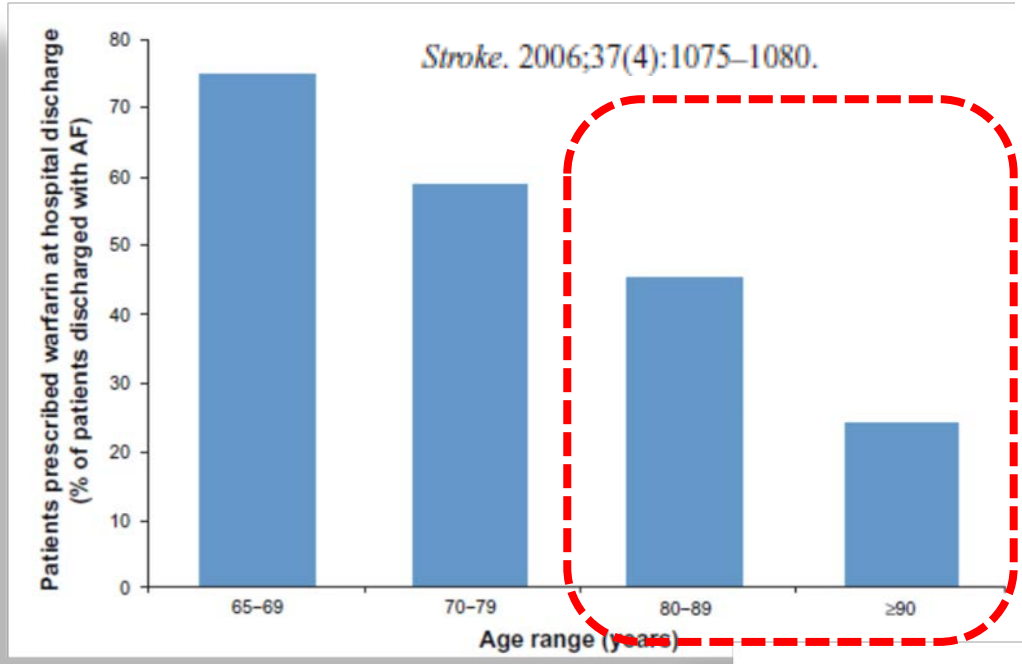
60% of incident **ISs** and SEs occurred **at 80+ years**.

43.9% of **fatal or disabling incident ISs** were **AF-related**.

Numbers of **AF-related ISs at age 80+ years increased nearly 3-fold** from 1981-1986 to 2002-2012, with potentially preventable AF-related events at age >=80 years **costing the UK 374 million per year**.

At current incident rates, number of **AF-related embolic events at age 80+ years will treble again by 2050**, with **83.5% of all events occurring in this age group**.

La TAO negli anziani con FA prima dei NAO



Di Pasquale G, Int J Cardiol 2013

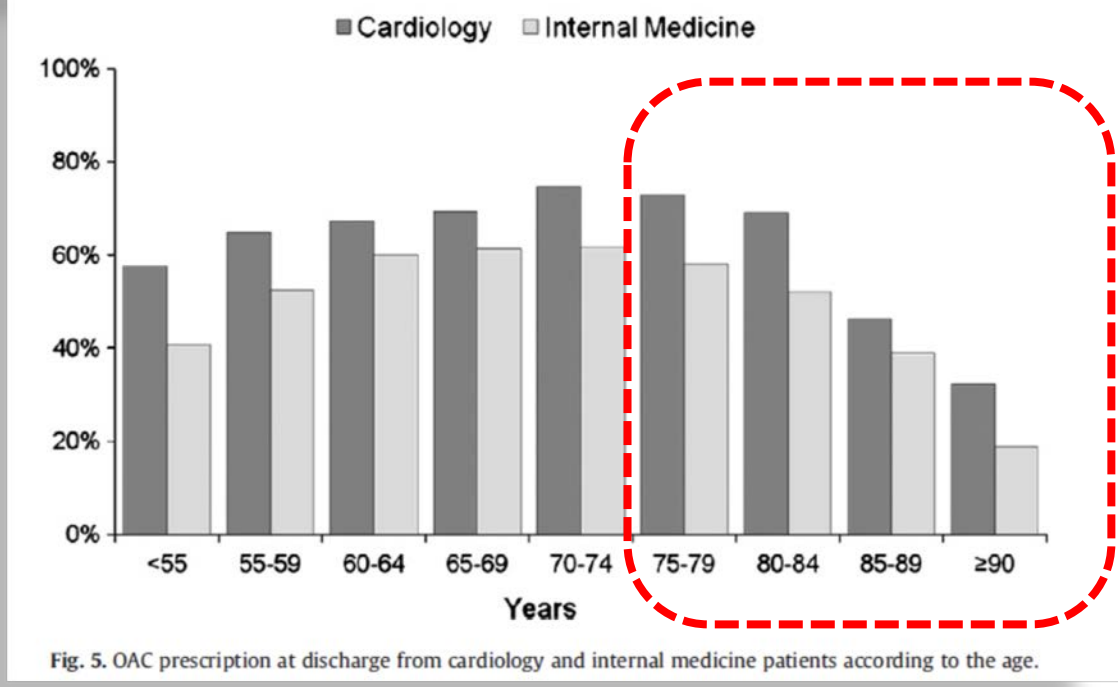


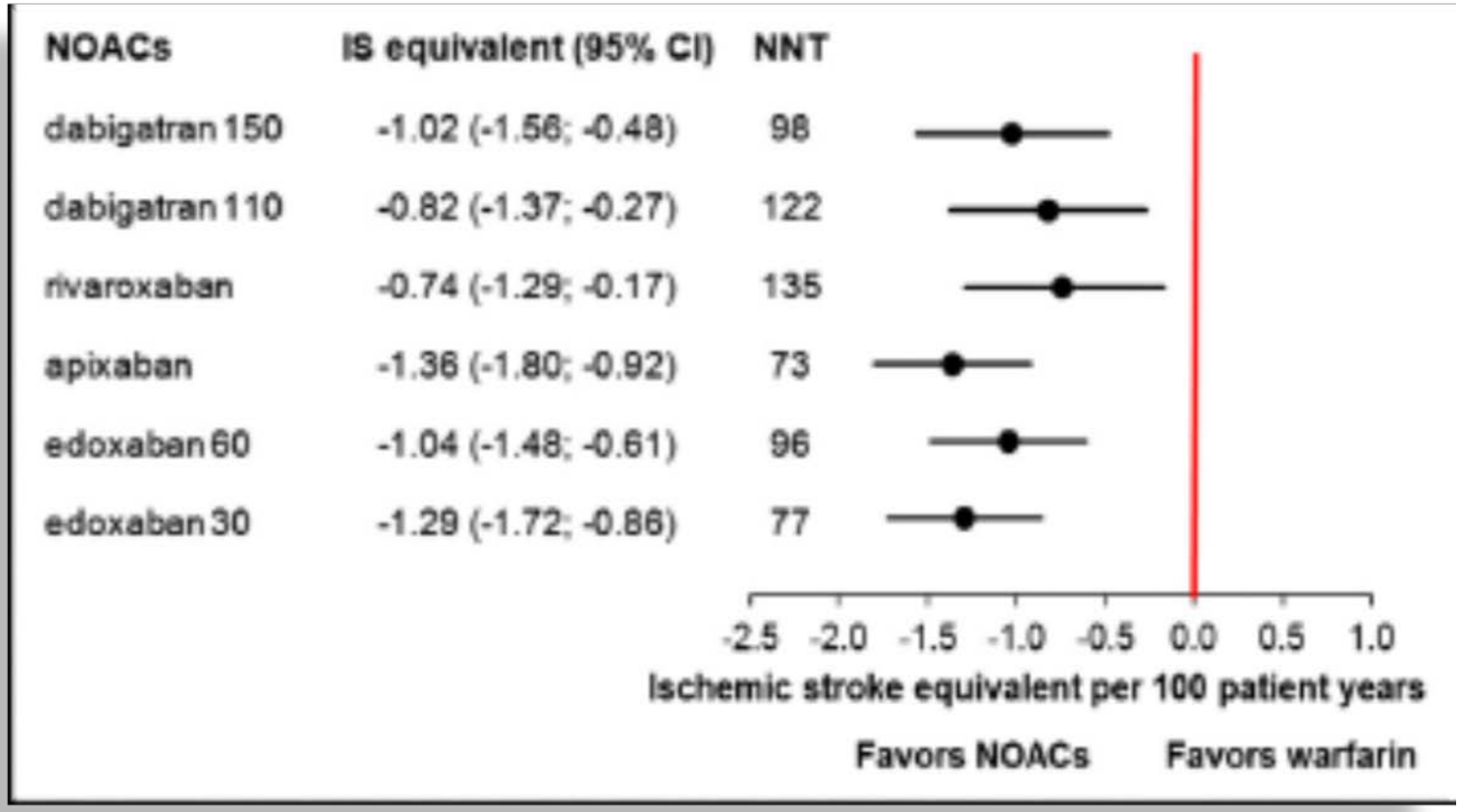
Fig. 5. OAC prescription at discharge from cardiology and internal medicine patients according to the age.

Net Clinical Benefit of Non-vitamin K Antagonist Oral Anticoagulants Versus Warfarin in Phase III Atrial Fibrillation Trials

The American Journal of Medicine (2015) 128, 1007-1014

THE AMERICAN JOURNAL of MEDICINE®

Net clinical benefit (IS+SE+MI+HS+adjusted MB) for DOACs vs VKAs



(Am J Cardiol 2017;120:786–791)

Changes in Use of Anticoagulation in Patients With Atrial Fibrillation Within a Primary Care Network Associated With the Introduction of Direct Oral Anticoagulants

Adult patients with AF cared for in an 18-practice primary network between 2010 and 2015

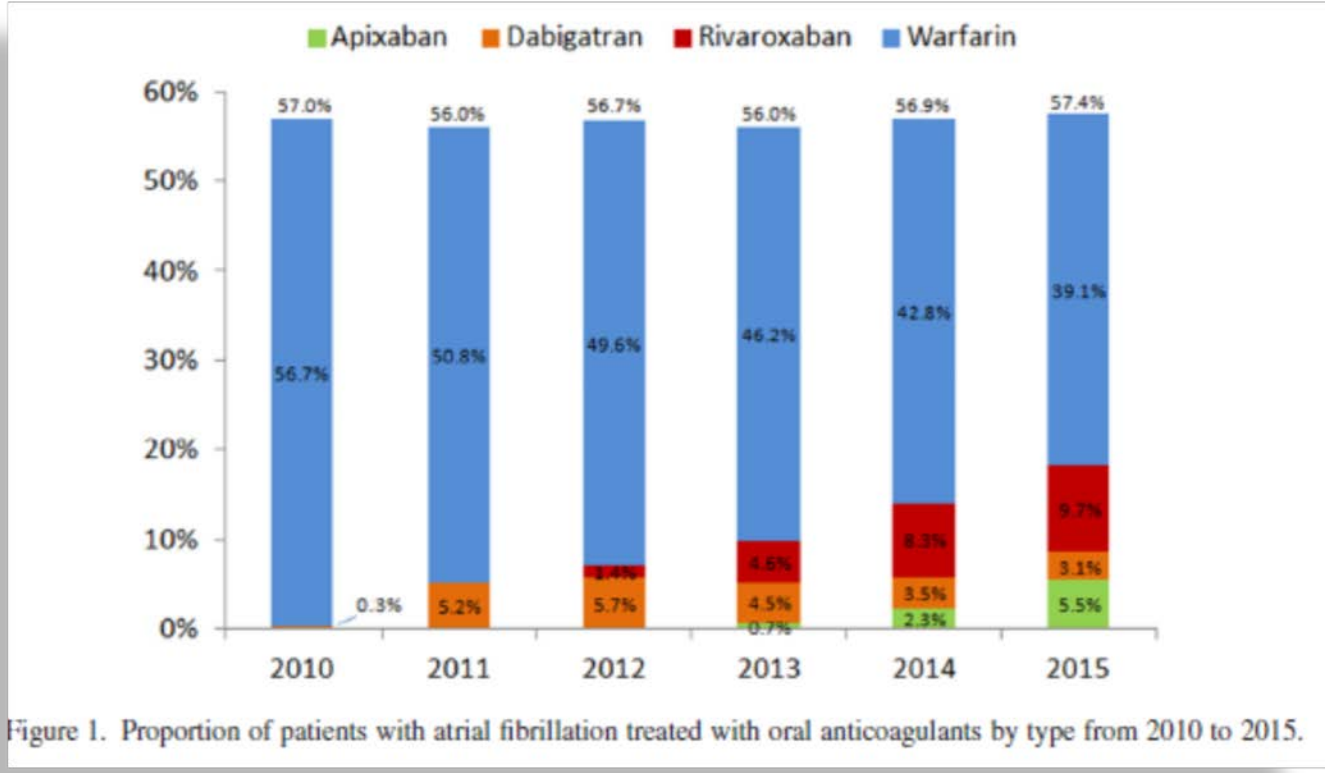


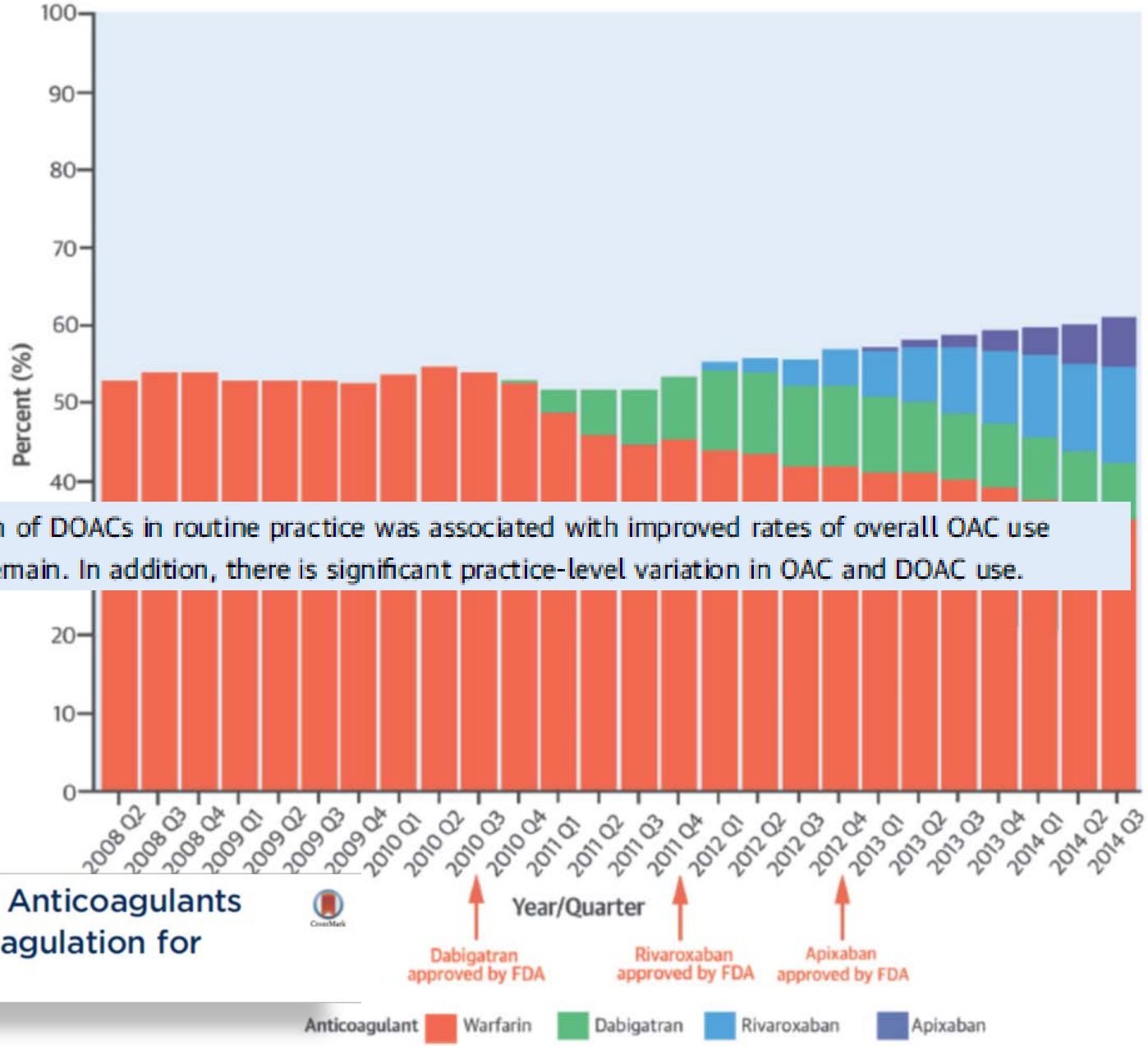
Figure 1. Proportion of patients with atrial fibrillation treated with oral anticoagulants by type from 2010 to 2015.

…The use of DOACs increased over time; however, the proportion of patients treated with OAC did not increase over time…

Patients prescribed DOACs were younger, with lower risk of stroke.

655000 patients with NVAF and CHADS2VASC2>1 enrolled in the **PINNACLE registry** between april 1, 2008 and september 30, 2014

CENTRAL ILLUSTRATION Introduction of Direct Oral Anticoagulants Is Associated With Increase in Overall Rates of Oral Anticoagulation for Atrial Fibrillation



CONCLUSIONS Introduction of DOACs in routine practice was associated with improved rates of overall OAC use for AF, but significant gaps remain. In addition, there is significant practice-level variation in OAC and DOAC use.

Influence of Direct Oral Anticoagulants on Rates of Oral Anticoagulation for Atrial Fibrillation

Marzec, L.N. et al. J Am Coll Cardiol. 2017;69(20):2475-84.

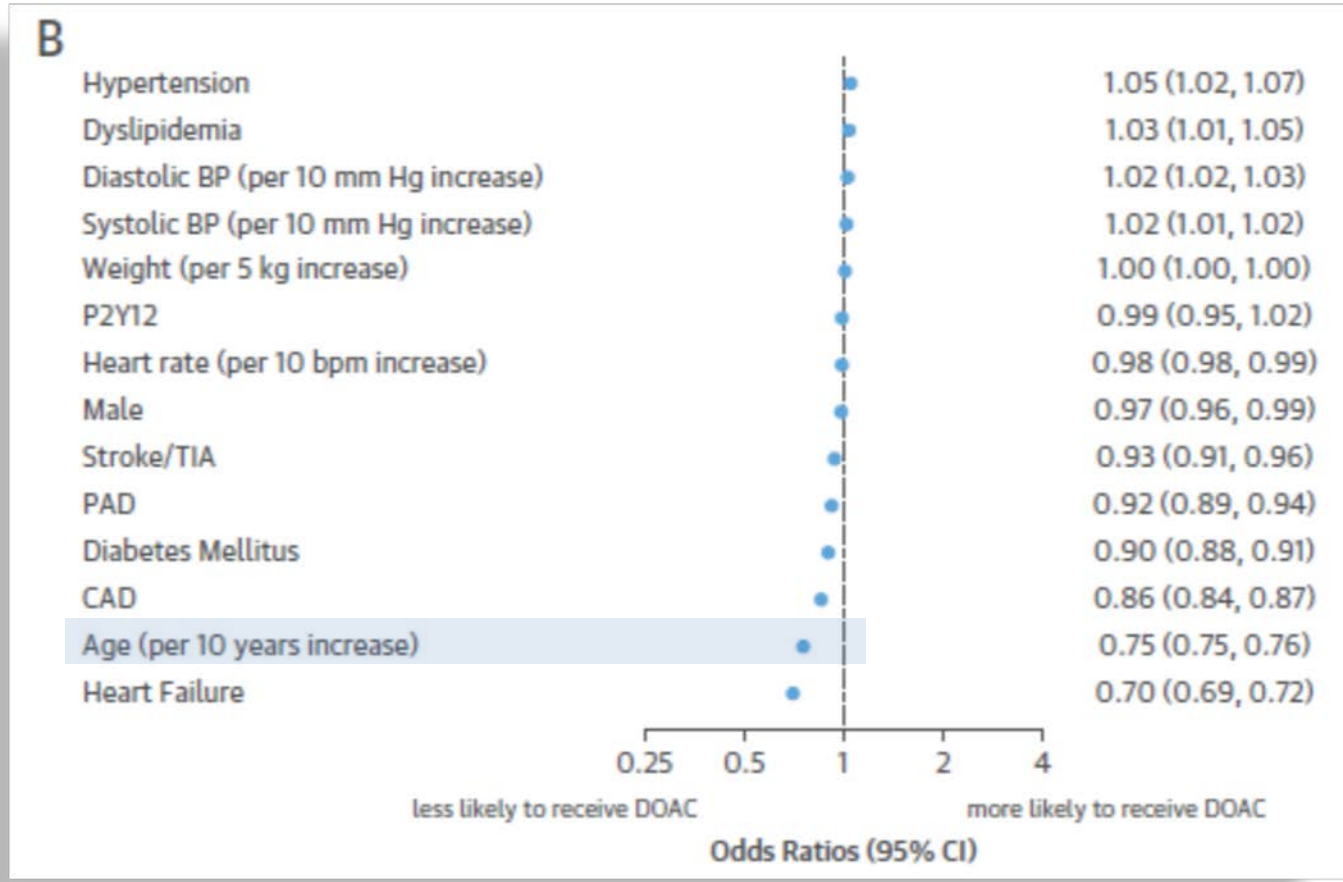
Influence of Direct Oral Anticoagulants on Rates of Oral Anticoagulation for Atrial Fibrillation

655000 patients with NVAF and CHADS2VASC2>1 enrolled in the **PINNACLE registry** between april 1, 2008 and september 30, 2014

Age and **OAC prescription**:

Warfarin	76.2 (10.2)
Dabigatran	72.8 (10.5)
Rivaroxaban	72.9 (10.4)
Apixaban	74.2 (10.2)
None	73.2 (13.3)

P<0.001



Adjusted Patient Factors Associated With Overall OAC Use and DOAC Use in the Primary Analysis Cohort

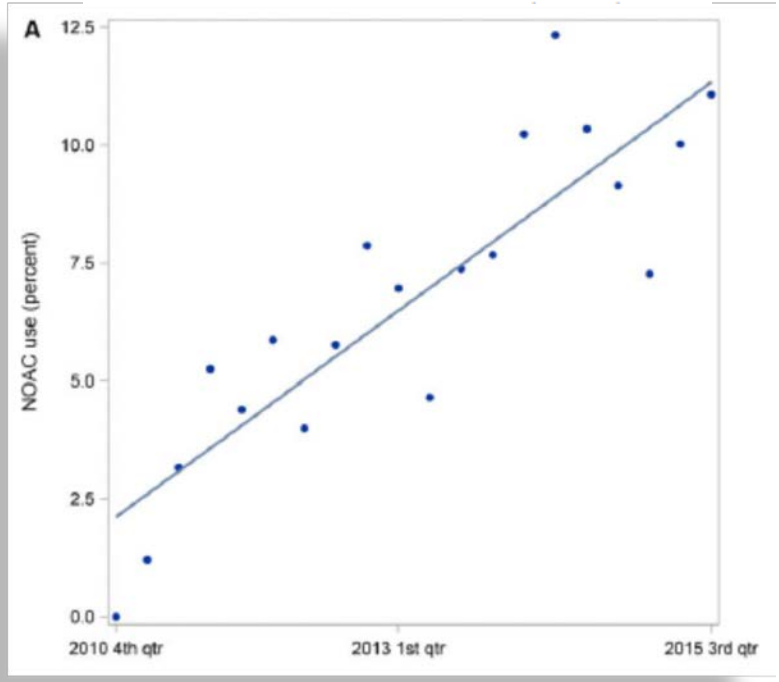
Effect of New Oral Anticoagulants on Prescribing Practices for Atrial Fibrillation in Older Adults

J Am Geriatr Soc 2017.

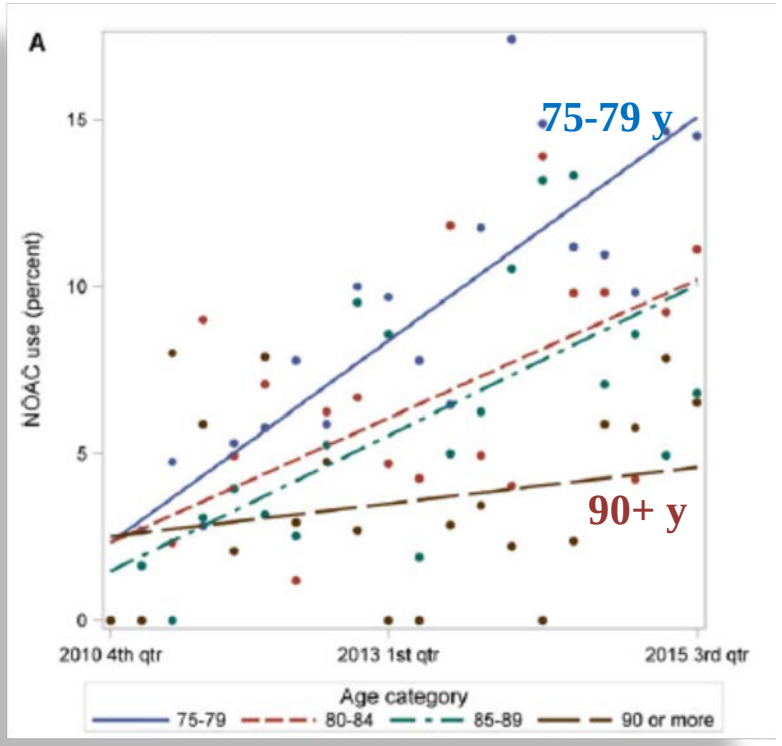
Raymond B. Fohtung, MD, Eric Novak, MS, and Michael W. Rich, MD

Retrospective study; 6568 patients aged 75+ years with AF admitted to hospital from Oct 2010 to Sept 2015

(A) Quarterly trend in novel oral anticoagulant use



(A) Quarterly trends in novel oral anticoagulant use according to age group:



CONCLUSION …Nonetheless, despite high risk of stroke, fewer than 45% of participants were discharged on an anticoagulant

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

	DABI 150	DABI 110	RIVA	API	EDO 60	EDO30
STROKE/SSE	**0.65 (0.52-0.81) <.001 SUP**	0.89 (0.73-1.09) <.001 NON INF	0.88 (0.75-1.03) .001 NON INF	**0.79 (0.66-0.95) .01 SUP**	0.87 (0.73-1.04) .001 NON INF	1.13 (0.96-1.34) .005 NON INF
ISCHEMIC STROKE	**0.76 (0.59-0.97) .03**	1.10 (0.88-1.37)	0.94 (0.75-1.17)	0.92 (0.74-1.13)	1.00 (0.83-1.19)	**1.41 (1.19-1.67) .001**
HEMORR. STROKE	**0.26 (0.14-0.49) <.001**	**0.31 (0.17-0.56) <.001**	**0.59 (0.35-0.75) <.001**	**0.51 (0.35-0.75) <.001**	**0.54 (0.38-0.77) <.001**	**0.33 (0.22-0.50) <.001**
MAJOR BLEEDING	0.94 (0.82-1.08)	**0.80 (0.70-0.93) .003**	1.04 (0.90-2.30)	**0.69 (0.60-0.80) <.001**	**0.80 (0.71-0.91) <.001**	**0.47 (0.41-0.55) <.001**
INTRACRAN. BLEEDING	**0.42 (0.29-0.61) <.001**	**0.29 (0.19-0.45) <.001**	**0.67 (0.47-0.93) .02**	**0.42 (0.30-0.58) <.001**	**0.39 (0.34-0.63) <.001**	**0.30 (0.21-0.43) <.001**
GI MAJOR BLEEDING	**1.48 (1.19-1.86) <.001**	1.04 (0.82-1.33)	**1.61 (1.30-1.99) <.001**	0.89 (0.70-1.15)	**1.23 (1.02-1.50) .03**	**0.67 (0.53-0.83) <.01**
MI	1.27 (0.94-1.71)	1.29 (0.96.1.75)	0.81 (0.63-1.06)	0.88 (0.66-1.17)	0.94 (0.74-1.19)	1.19 (0.95-1.49)
DEATH	0.88 (0.77-1.00)	0.91 (0.80-1.03)	0.85 (0.70-1.02)	**0.89 (0.80-0.99) <.05**	0.92 (0.83-1.01)	**0.87 (0.79-0.96) .006**
CHADS	2.1	2.1	3.5	2.1	2.8	2.8

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European Journal of Internal Medicine

European Journal of Internal Medicine 41 (2017) 18–27

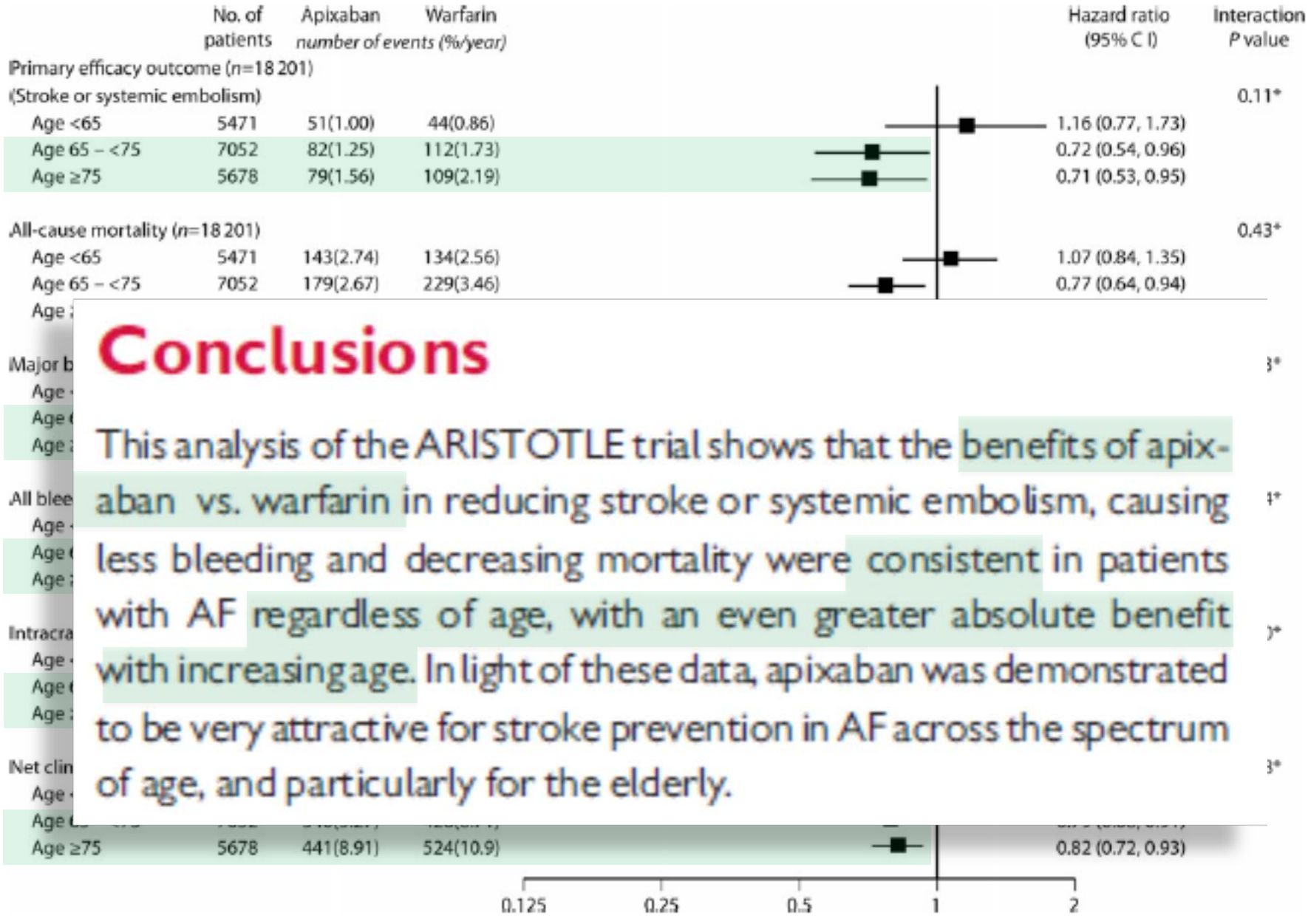
Oral anticoagulant therapy for older patients with atrial fibrillation: a review of current evidence

Mario Bo [a], Enrica Grisoglio [a], Enrico Brunetti [a,*], Yolanda Falcone [a], Niccolò Marchionni [b]

Efficacy and safety outcomes in patients >=75 years

Efficacy and safety outcomes in patients ≥ 75 years from sub-analysis of Phase III RCTs on DOACs.
Abbreviations: y = years; n = number; TTR = time in therapeutic range; N.A. = not available; SD = standard deviation; IQR = interquartile range; SE = systemic embolism; HR = hazard ratio; CI = confidence interval; IC = intracranial; GI = gastrointestinal.

	RE-LY [74]		ROCKET AF [75]	ARISTOTLE [76]	AVERROES [77]	ENGAGE AF-TIMI 48 [78]	
Patients ≥ 75 y/total (%)	7258/18,113 (40.1%)		6229/14,264 (43.7%)	5678/18,201 (31.2%)	1898/5599 (33.9%)	8474/21,105 (40.2%)	
TTR in patients ≥ 75 y control arm	TTR according to age group N.A.		TTR higher in patients ≥ 75 y 56.9 ± 21.6% (mean ± SD)	TTR higher in patients ≥75 y Median: 67.2% (IQR: 53.7%–77.4%)	N.A.	TTR higher in patients ≥ 75 y Median: 69.6% (IQR: 57.1%–78.3%)	
Dose	**Dabigatran 150 mg**	**Dabigatran 110 mg**	**Rivaroxaban**	**Apixaban**	**Apixaban**	**Edoxaban High dose**	**Edoxaban Low dose**
STROKE/SE	0.67 (0.49–0.90)	0.88 (0.66–1.17)	0.80 (0.63–1.02)	0.71 (0.53–0.95)	0.33 (0.19–0.54)	0.83 (0.67–1.04)	1.12 (0.91–1.40)
MAJOR BLEEDING	1.18 (0.98–1.42)	1.01 (0.83–1.23)	1.11 (0.92–1.34)	0.64 (0.52–0.79)	1.21 (0.69–2.12)	0.83 (0.70–0.99)	0.47 (0.38–0.58)
IC BLEEDING	0.42 (0.25–0.70)	0.37 (0.21–0.64)	0.80 (0.50–1.28)	0.34 (0.20–0.57)	0.81 (0.28–2.35)	0.40 (0.26–0.62)	0.31 (0.19–0.49)
GI BLEEDING	1.79 (1.35–2.37)	1.39 (1.03–1.98)	N.A.	N.A.	N.A.	1.32 (1.01–1.72)	0.72 (0.53–0.98)

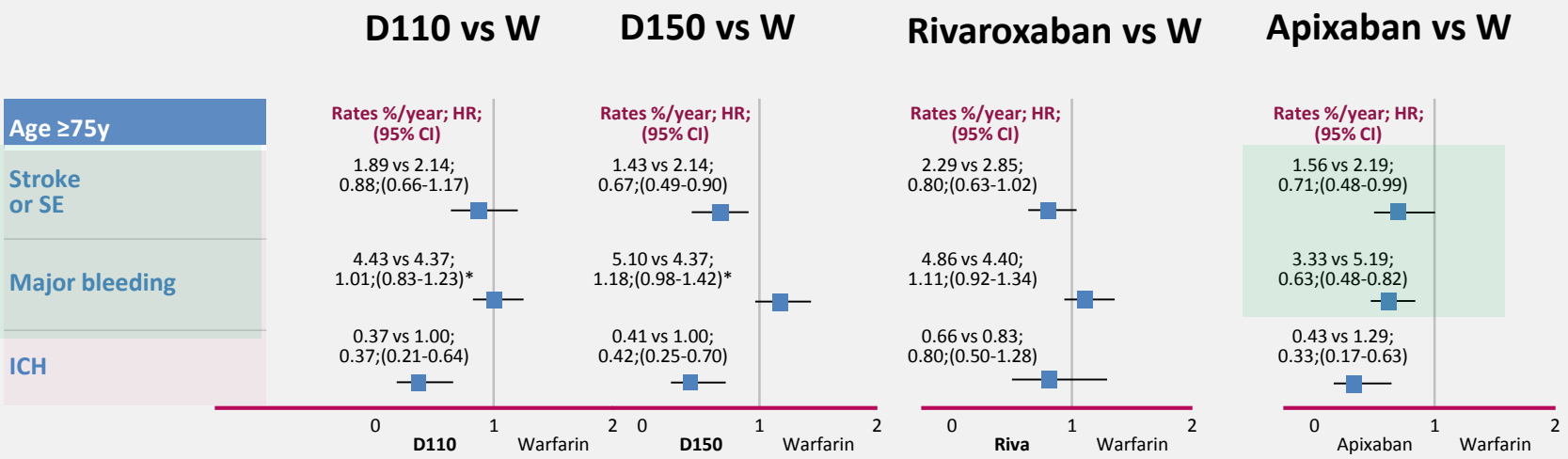


Conclusions

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.

NOACs – RCTs in SPAF: efficacy and safety in patients ≥ 75 y



*p<0.001 for interaction between age and treatment

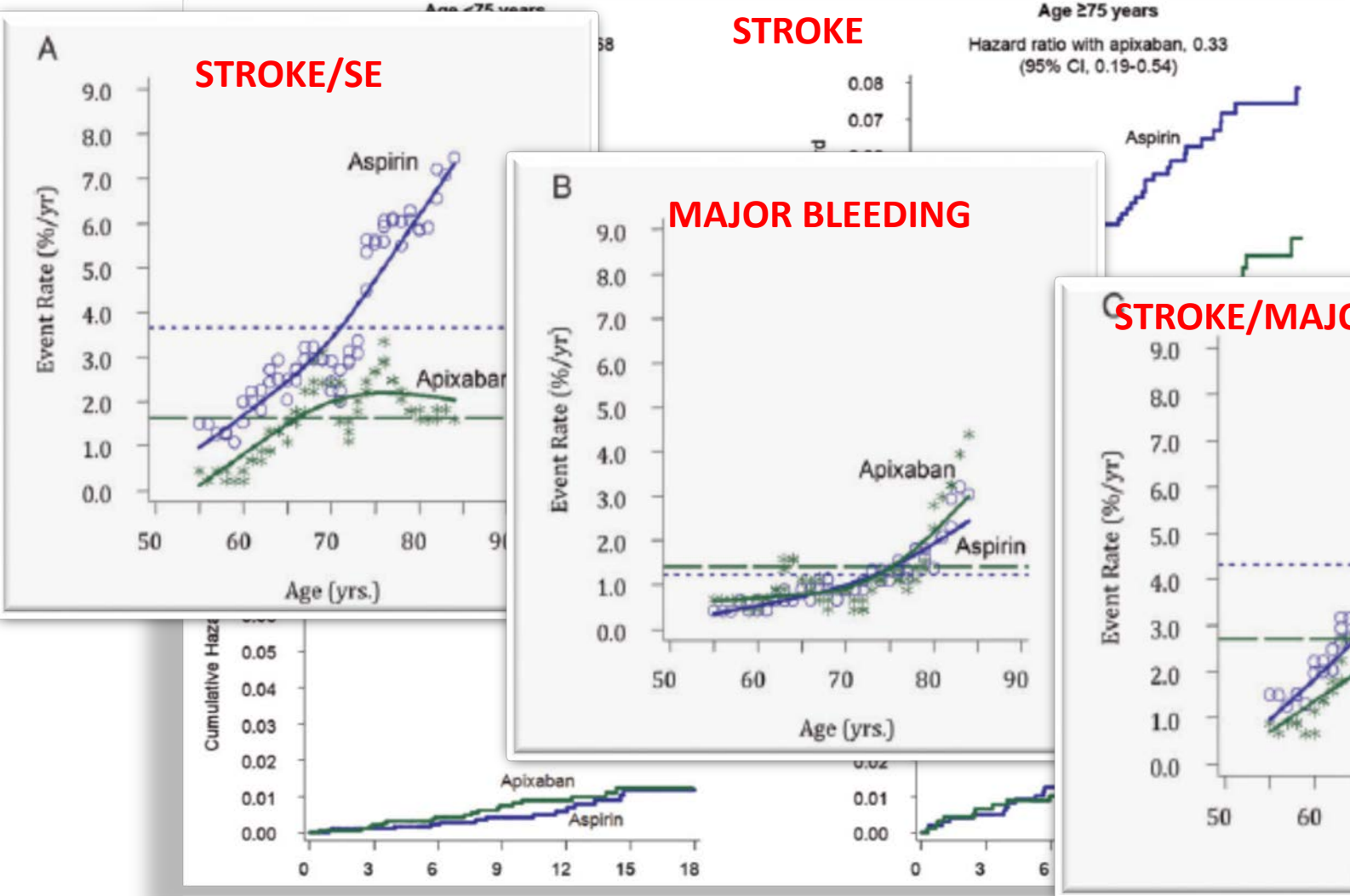
Estratto da Capranzano P et al. Expert Rev Cardiovasc Ther 2013;11:959-73; Granger et al. N Engl J Med 2011;365:981-92; Connolly et al. N Engl J Med 2009;361:1139-51; and Patel et al. N Engl J Med 2011;365:883-91

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



Geriatric Care 2016; volume 2:6120

Antiplatelet therapy is not a safer alternative to oral anticoagulants, even in older hospital-discharged patients with atrial fibrillation

Mario Bo,[1] Yolanda Falcone,[1] Enrica Grisoglio,[1] Margherita Marchetti,[1] Federica Li Puma,[1] Marina Iacovino,[1] Enrico Brunetti,[1] Gianfranco Fonte[2]

(n=962).

Baseline clinical variables	After propensity score matching OAT (n=236)	APT (n=236)	P
Overall mortality, n (%)	77 (33.0%)	118 (50.0%)	0.0004
Total ischemic stroke, n (%)	16 (6.8%)	23 (9.7%)	0.3239
Fatal ischemic stroke, n (%)	6 (2.5%)	13 (5.5%)	0.1687
Ischemic events, other sites, n (%)	12 (5.1%)	13 (5.5%)	1.0000
Hemorrhagic stroke/intracranial bleeding, n (%)	5 (2.1%)	1 (0.4%)	0.2188
Major extra-cranial bleeding, n (%)	13 (5.5%)	9 (3.8%)	0.4807
Major bleeding, total, n (%)	18 (7.6%)	10 (4.2%)	0.1338
Fatal bleeding, n (%)	4 (1.7%)	3 (1.3%)	1.0000
Minor bleeding, n (%)	15 (6.4%)	12 (5.1%)	0.7003
eGFR (CKD-EPI) <60 mL/min, n (%)		587 (61.0%)	
ADL dependent, n (%)		466 (48.4%)	
IADL dependent, n (%)		639 (66.4%)	
Cognitive impairment, n (%)		478 (49.7%)	
Number of drugs at discharge, median (25°-75°)		8 (6-10)	

Clinical events	Total sample (n=962)	OAT (n=520)	APT (n=442)	Chi square	P
Overall mortality, n (%)	384 (39.9%)	155 (29.8%)	229 (51.8%)	48.225	0.00000
Total ischemic stroke, n (%)	66 (6.9%)	26 (5.0%)	40 (9.0%)	6.132	0.01327
Fatal ischemic stroke, n (%)	28 (2.9%)	10 (1.9%)	18 (4.1%)	4.115	0.0425
Ischemic events, other sites, n (%)	50 (5.2%)	25 (4.8%)	25 (5.7%)	0.349	0.55467
Hemorrhagic stroke/intracranial bleeding, n (%)	9 (0.9%)	6 (1.15%)	3 (0.68%)	0.581	0.44556
Major extra-cranial bleeding, n (%)	40 (4.1%)	25 (4.8%)	15 (3.4%)	1.198	0.27357
Major bleeding, total, n (%)	49 (5.1%)	31 (6.0%)	18 (4.1%)	1.763	0.18414
Fatal bleeding, n (%)	11 (1.1%)	6 (1.1%)	5 (1.1%)	0.001	0.9738
Minor bleeding, n (%)	56 (5.8%)	37 (7.1%)	19 (4.3%)	3.457	0.06296

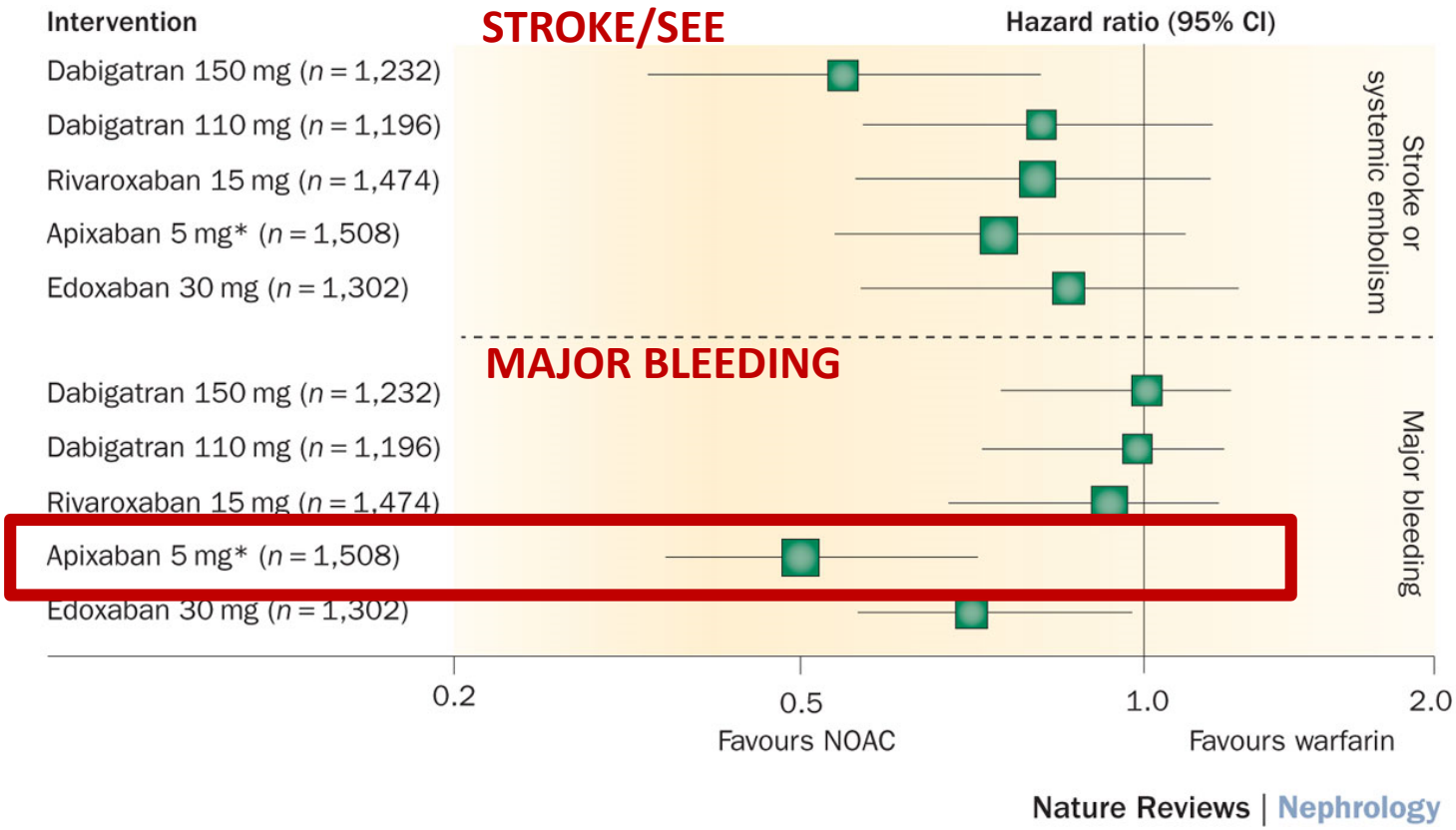
European Heart Journal Advance Access published February 4, 2016

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2

Non-vitamin K oral anticoagulants and age

First choice	In patients older than 75 years, we suggest apixaban 5 mg twice daily [2.5 mg if ≥2 of the following: age ≥80 years, body weight ≤60 kg, or creatinine ≥1.5 mg/dL (133 μmol/L)]
Second choice	Dabigatran 110 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily

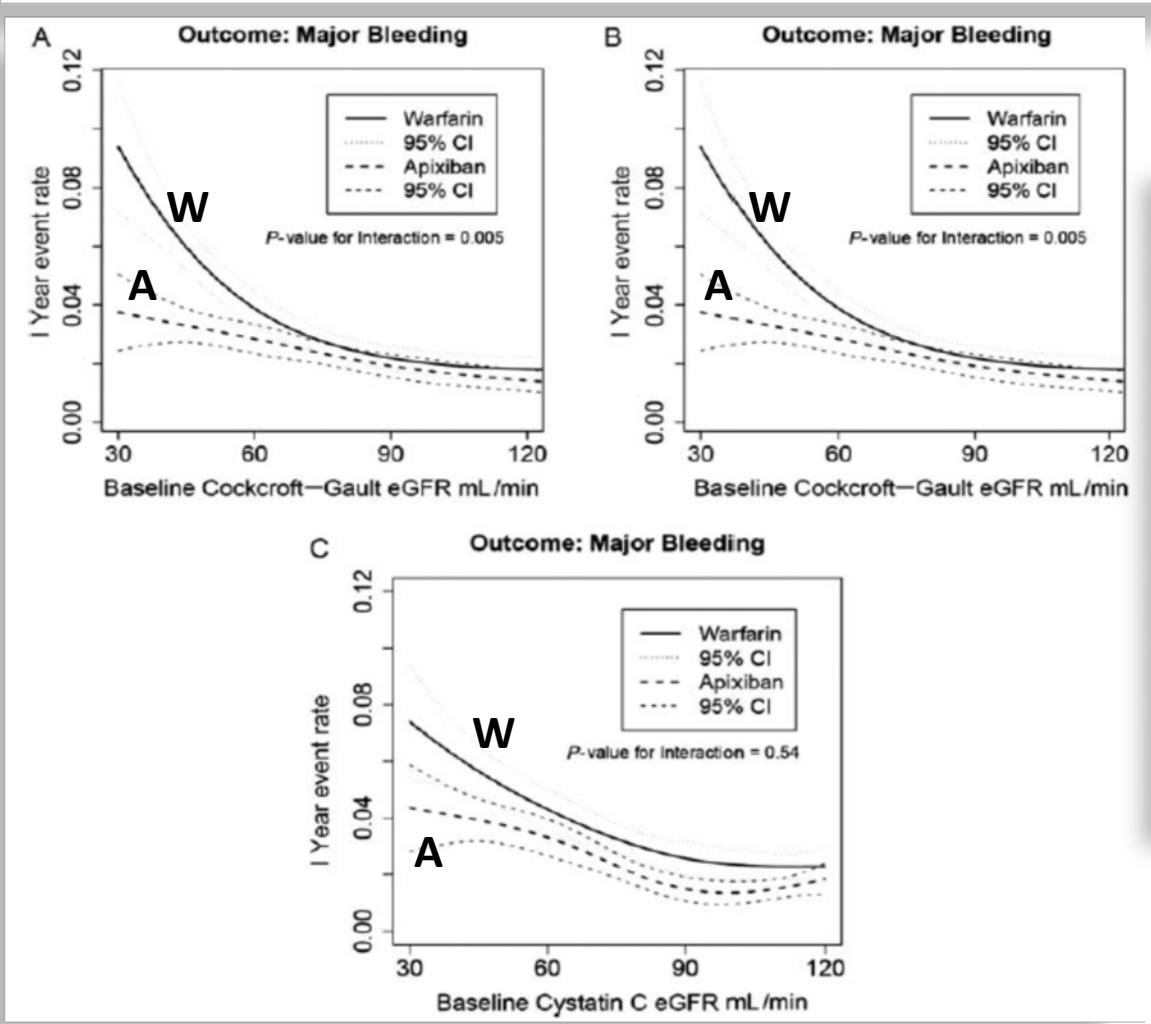
Efficacy and safety of NOACs versus warfarin in patients with moderate CKD



Qamar, A. & Bhatt, D. L. (2015) Balancing the risks of stroke and bleeding in CKD
Nat. Rev. Nephrol. doi:10.1038/nrneph.2015.14

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

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



Conclusions …compared with Warfarin, **Apixaban** treatment **reduced the rate of stroke, death, and major bleeding**, regardless of renal function. **Patients with impaired renal function seemed to have the greatest reduction in major bleeding with Apixaban**

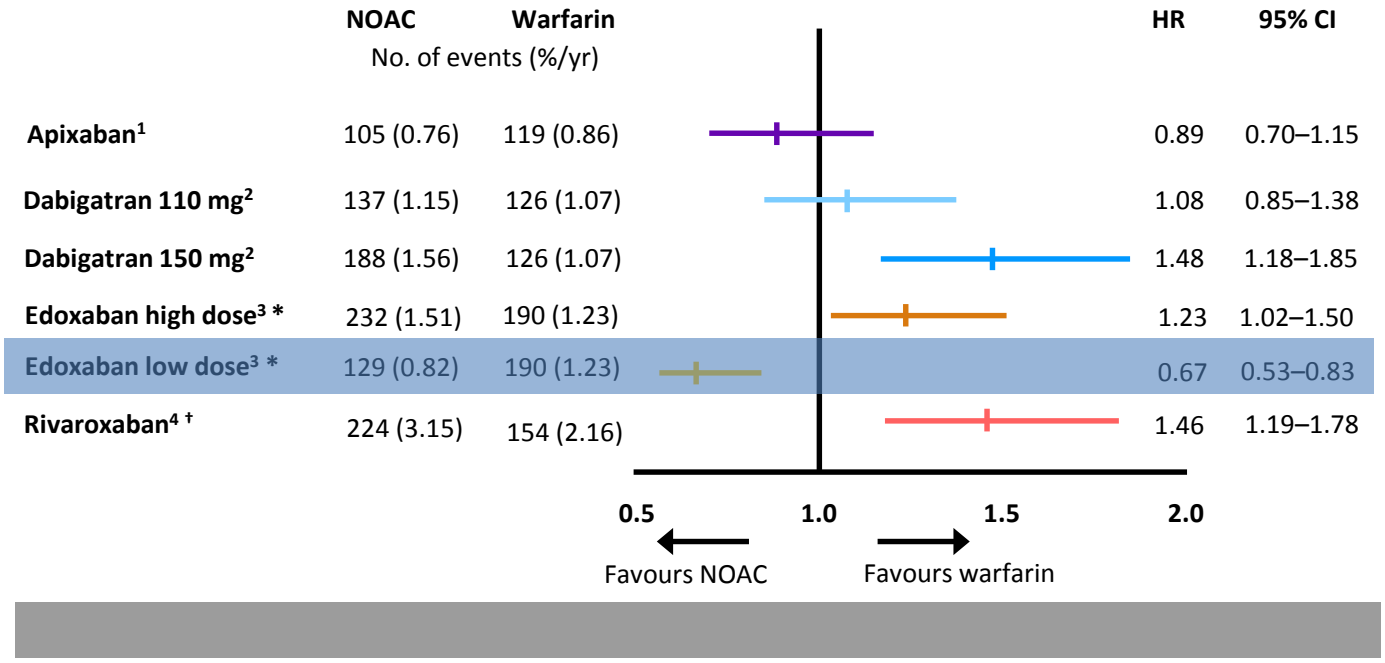
European Heart Journal Advance Access published February 4, 2016

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2

Patients with renal impairment and on dialysis

First choice	Patients with AF and stage III CKD (creatinine clearance 30–49 mL/min) may be treated with apixaban 5 mg twice daily (apixaban 2.5 mg twice a day if ≥1 additional criteria: age ≥80 years, body weight ≤60 kg, serum creatinine ≥ 1.5 mg/dL (133 μmol/L are present), rivaroxaban 15 mg daily, or edoxaban 30 mg once daily
Second choice	Dabigatran 110 mg twice daily
Not recommended	Dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily

NOACs vs. warfarin: major gastrointestinal bleeding



Created from: 1. Granger *et al. N Engl J Med* 2011;365:981-92; 2. Connolly *et al. N Engl J Med* 2010;363:1875-6, suppl app; 3. Giugliano *et al. N Engl J Med* 2013;369:2093-104; 4. Patel *et al. N Engl J Med* 2011;365:883-91, suppl app.

Gastrointestinal Safety of Direct Oral Anticoagulants: A Large Population-Based Study

Gastroenterology 2017;152:1014–1022

Table 4. Stratified Analysis in Propensity Score Matched Rivaroxaban vs Dabigatran Users

	Rivaroxaban (n = 15,787)		Dabigatran (n = 15,787)		Rivaroxaban vs dabigatran (n = 31,574)	
Variable	Events, n	IR	Events, n	IR	HR (95% CI)	*P* for interaction
Overall	222	2.74	215	2.02	1.20 (1.00–1.45)	
Age						
18–64 y	26	1.05	14	0.46	2.03* (1.06–3.90)	.10
65–74 y	66	2.54	54	1.56	1.44* (1.00–2.06)	
≥75 y	130	4.29	147	3.54	1.06 (0.84–1.34)	

Table 5. Stratified Analysis in Propensity Score Matched Apixaban vs Dabigatran Users

	Apixaban (n = 6542)		Dabigatran (n = 6542)		Apixaban vs dabigatran (n = 13,084)	
Variable	Events, n	IR	Events, n	IR	HR (95% CI)	*P* for interaction
Overall	33	1.38	121	2.73	0.39*** (0.27–0.58)	
Age						
18–64 y	2	0.34	7	0.73	0.38 (0.08–1.84)	.54
65–74 y	5	0.69	29	2.12	0.25** (0.10–0.65)	
≥75 y	26	2.43	85	4.06	0.45*** (0.29–0.71)	

Table 6. Stratified Analysis in Propensity Score–Matched Apixaban vs Rivaroxaban Users

	Apixaban (n = 6565)		Rivaroxaban (n = 6565)		Apixaban vs rivaroxaban (n = 13,130)	
Variable	Events, n	IR	Events, n	IR	HR (95% CI)	*P* for interaction
Overall	32	1.34	116	3.54	0.33*** (0.22–0.49)	
Age						
18–64 y	2	0.34	6	0.81	0.38 (0.08–1.89)	.36
65–74 y	5	0.69	32	3.24	0.18*** (0.07–0.47)	
≥75 y	25	2.32	78	5.05	0.39*** (0.25–0.61)	

European Heart Journal Advance Access published February 4, 2016

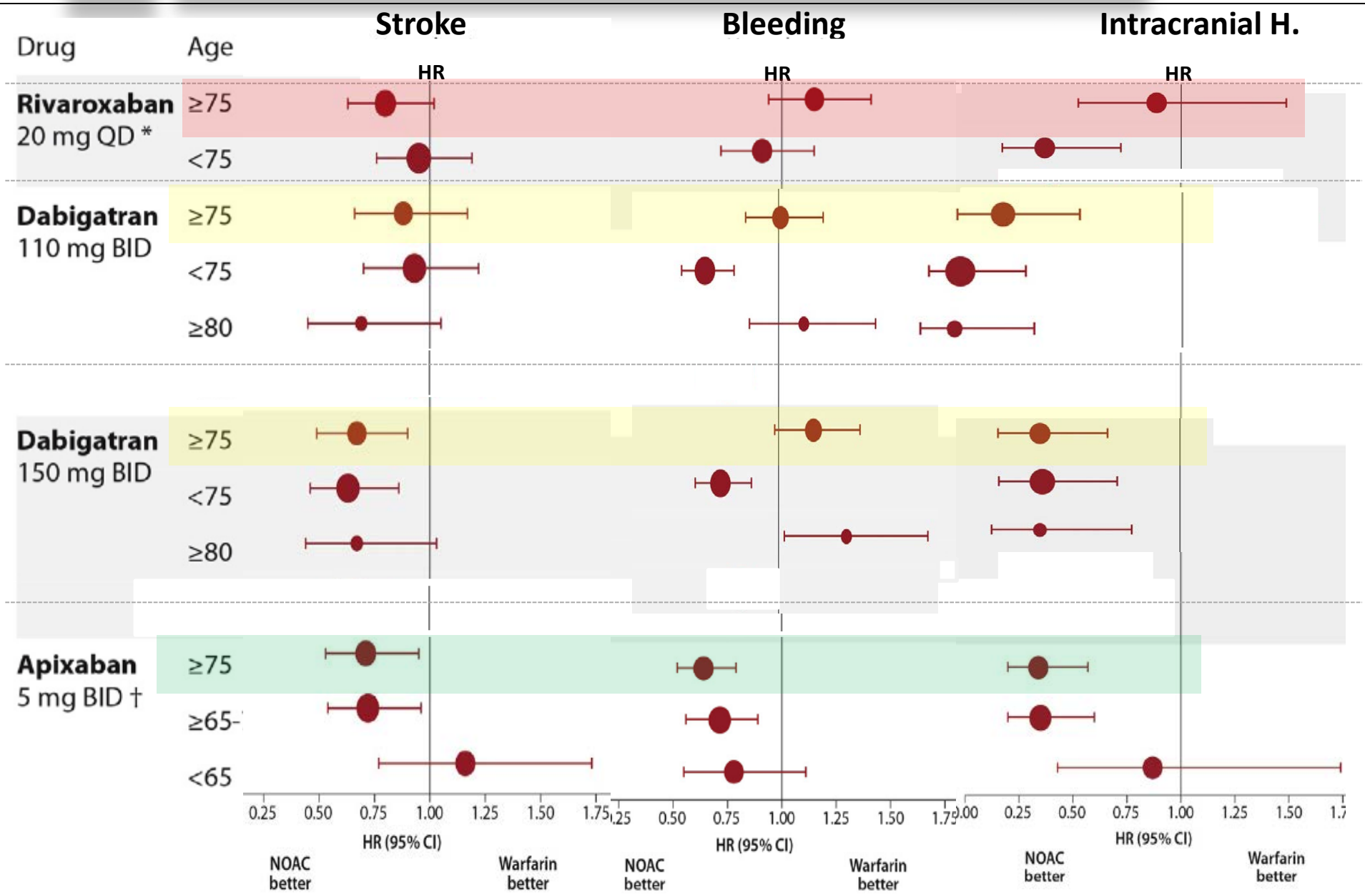
Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 1

Patients with a high risk of gastrointestinal bleeding

First choice	For patients with a high risk of gastrointestinal bleeding, apixaban 5 mg twice daily or dabigatran 110 mg twice daily may be used
Second choice	Dabigatran 150 mg twice daily, edoxaban 60 mg once daily, or rivaroxaban 20 mg once daily
Comments	Gastrointestinal bleeding, even in the setting of anticoagulation, does usually not cause death or permanent major disability. Thus, the choice of OAC should be driven mainly by stroke prevention considerations. The label 'high risk of gastrointestinal bleeding' is imprecise. For example, patients with *H. pylori*-related ulcer haemorrhage may no longer be at high risk of bleeding once the infection has been eradicated. The gastrointestinal bleeding risk associated with any anticoagulant is increased by concurrent use of antiplatelet agents, including aspirin.[41]

New oral anticoagulants in elderly patients

Barco S. Best Pract Res Clin Haematol 2013



Original Investigation

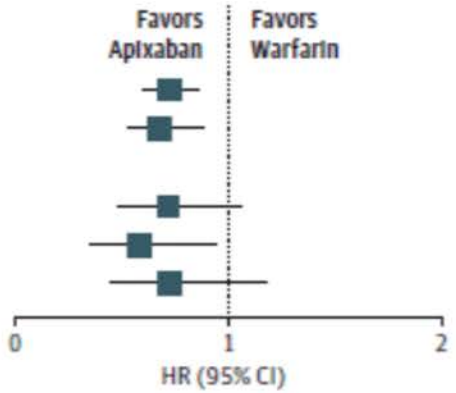
Apixaban 5 mg Twice Daily and Clinical Outcomes in Patients With Atrial Fibrillation and Advanced Age, Low Body Weight, or High Creatinine

A Secondary Analysis of a Randomized Clinical Trial

To evaluate the **effects of the 5 mg twice daily dose** of Apixaban on **stroke** or SE and **bleeding** among **patients with 1** or no **dose reduction criteria**

Figure 1. Rates of Major Bleeding and the Effect of Apixaban Compared With Warfarin

Subgroup	No. of Events (Annual %) Apixaban Treatment	Warfarin Treatment	HR (95% CI)
No dose-reduction criteria	204 (1.8)	279 (2.5)	0.7 (0.6-0.9)
1 Dose-reduction criterion	102 (3.2)	145 (4.8)	0.7 (0.5-0.9)
Criteria			
Age ≥80 y	46 (3.5)	61 (4.9)	0.7 (0.5-1.1)
Weight ≤60 kg	26 (2.3)	44 (4.0)	0.6 (0.4-0.9)
Creatinine level ≥1.5 mg/dL	30 (4.2)	40 (5.8)	0.7 (0.5-1.2)



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APIXABAN: Safety and efficacy in complex elderly patients

La prescrizione della **TAO** nei pazienti con FA rimane **subottimale**, soprattutto negli **anziani**, anche dopo l'introduzione dei DOACs.

Vi è una considerevole **eterogeneità** in termini di **safety** tra i vari **DOAC**, soprattutto nei pazienti **anziani e polipatologici**.

APIXABAN presenta **eccellenti caratteristiche di efficacia e sicurezza nei pazienti con FA**, e 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, o ad alto rischio, di **sanguinamento gastro-intestinale**. In base ai dati di sicurezza del farmaco è consigliabile una stretta **aderenza alle posologie raccomandate** in rapporto ad età, massa corporea e funzionalità renale.