ADVANCES IN CARDIAC ARRHYTHMIAS

and

GREAT INNOVATIONS IN CARDIOLOGY

XXVII GIORNATE CARD

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

UNIVERSITÀ DEGLI STUDI DI TORINO

Daily clinical management of stroke risk in AF patients

Chairpersons: S. Marra, G. Pistis

13.20 Is there any reason for not using oral anticoagulants in older AF patients? - *M. Bo*

Directors
Fiorenzo Gaita
Sebastiano Marra

Turin
October 23-24, 2015
Centro Congressi
Unione Industriale di Torino

ee
sa
ny
sa
ce
se

ee
Monica Andriani, *Italy*
Matteo Anselmino, *Italy*
Carlo Budano, *Italy*
Davide Castagno, *Italy*

Europace Advance Access published August 24, 2012

Europace
doi:10.1093/europace/eus305

ESC GUIDELINES

2012 focused update of the ESC Guidelines for the management of atrial fibrillation

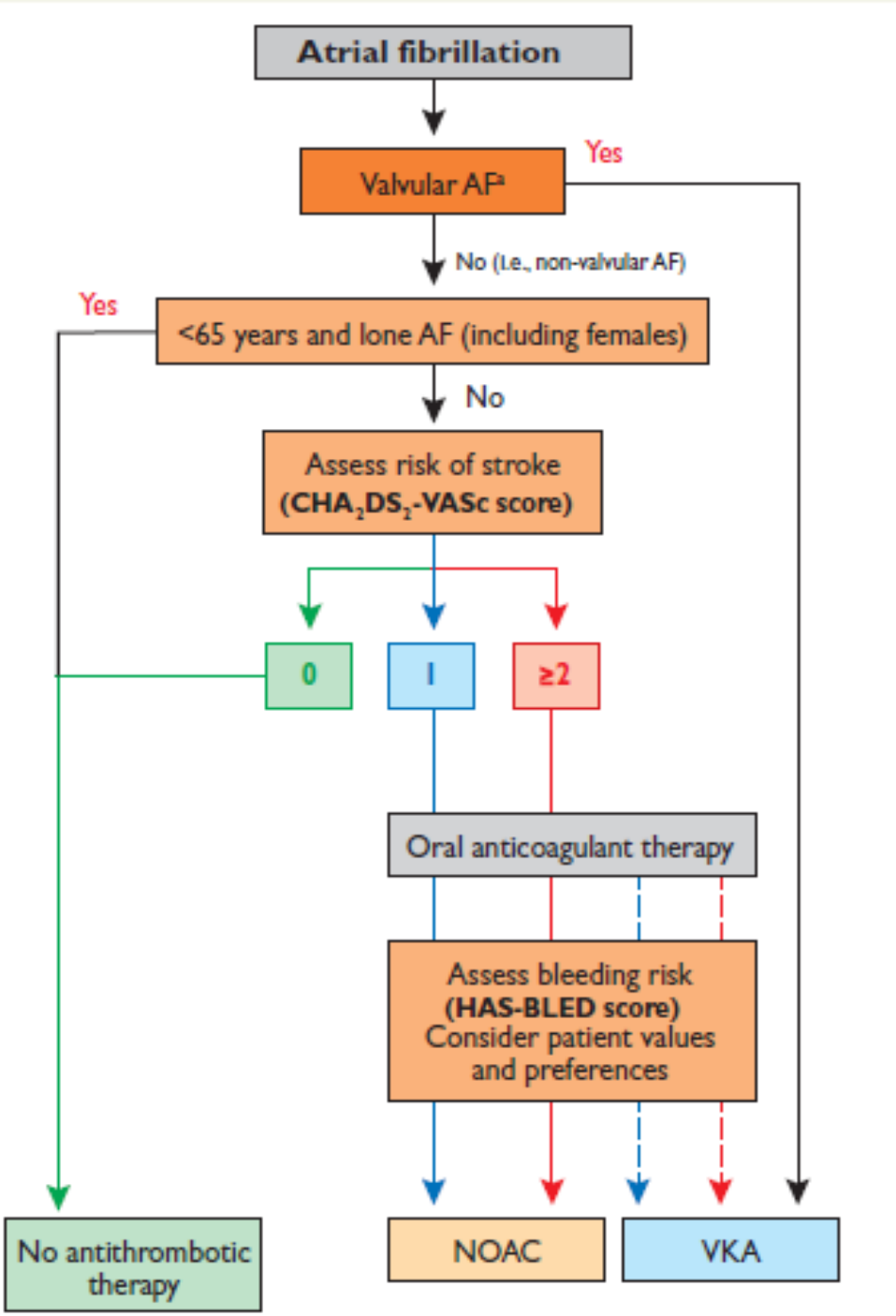
An update of the 2010 ESC Guidelines for the management of atrial fibrillation
Developed with the special contribution of the European Heart Rhythm Association

*The **evidence for effective stroke prevention with aspirin in AF is weak**, with a **potential for harm**… given the availability of NOACs, the use of antiplatelet therapy for stroke prevention in AF should be limited to the few patients who refuse any form of OAC.*

In patients with a CHA2DS2-VASc score ≥2, OAC therapy with:

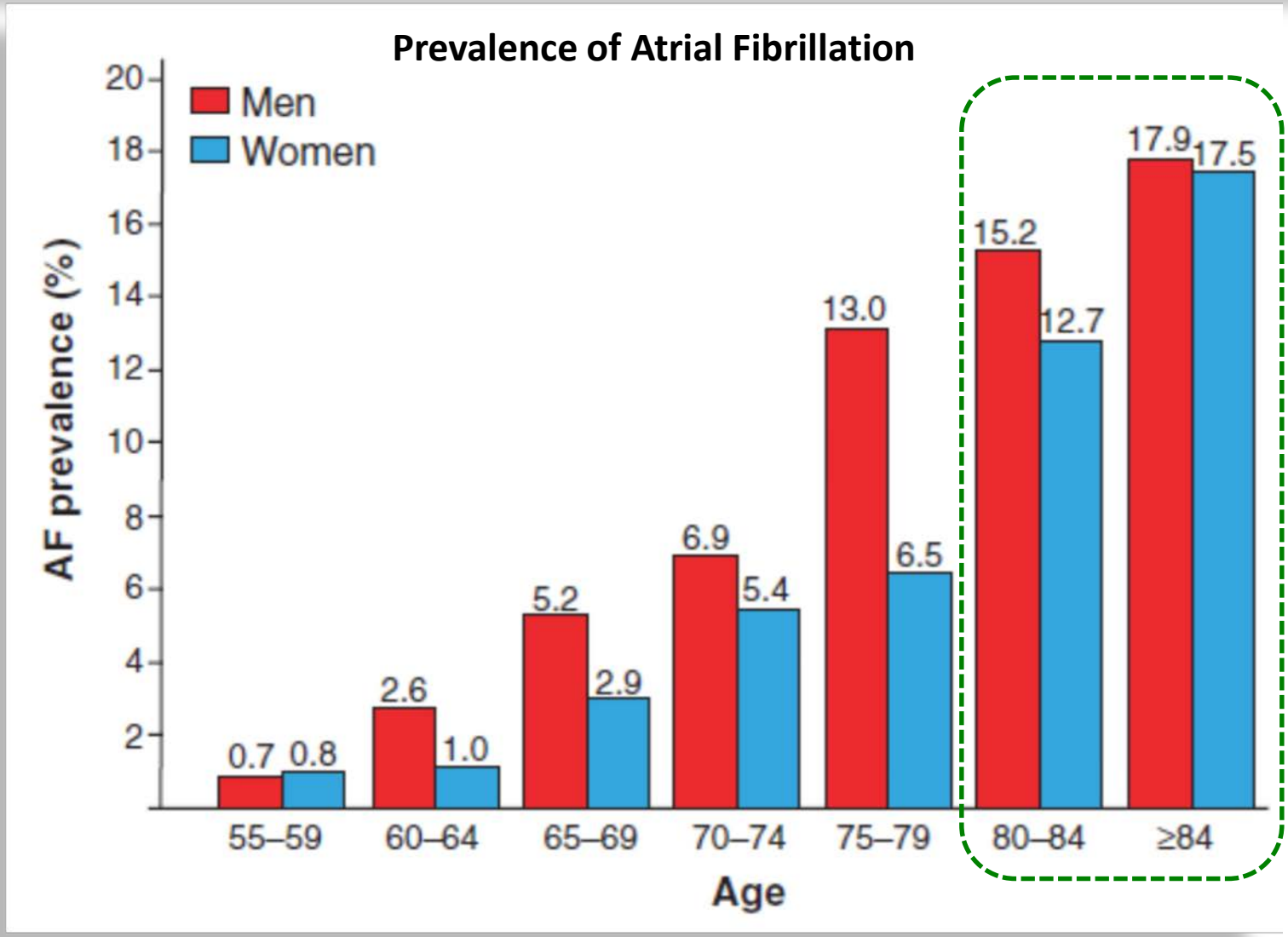
- ***adjusted dose VKA, or***
- ***a direct thrombin inhibitor (dabigatran), or***
- ***an oral factor Xa inhibitor (eg rivaroxaban, apixaban)***

is recommended, unless contraindicated (Class I, Level A)



Stroke prevention in elderly patients with atrial fibrillation: challenges for anticoagulation

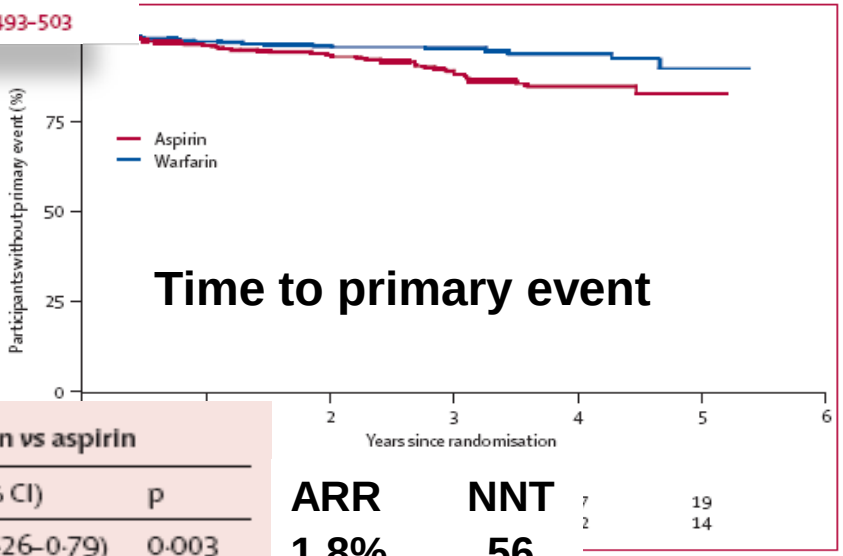
Sinnaeve PR, J Int Med 2013



Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial

Lancet 2007; 370: 493–503

973 pazienti, età media 81 anni, 60%>80 anni



Time to primary event

	Warfarin (n=488)		Aspirin (n=485)		Warfarin vs aspirin		ARR	NNT
	n	Risk per year	n	Risk per year	RR (95% CI)	p		
Stroke	21	1·6%	44	3·4%	0·46 (0·26–0·79)	0·003	1.8%	56
By severity								
Fatal	13	1·0%	21	1·6%	0·59 (0·27–1·24)	0·14		
Disabling non-fatal	8	0·6%	23	1·8%	0·33 (0·13–0·77)	0·005		
Type of stroke*								
Ischaemic	10	0·8%	32	2·5%	0·30 (0·13–0·63)	0·0004	1.7%	
Haemorrhagic	6	0·5%	5	0·4%	1·15 (0·29–4·77)	0·83		
Unknown	5	0·4%	7	0·5%	0·69 (0·17–2·51)	0·53		
Other intracranial haemorrhage†	2	0·2%	1	0·1%	1·92 (0·10–113·3)	0·65		
Systemic embolism‡	1	0·1%	3	0·2%	0·32 (0·01–3·99)	0·36		
Total number of events	24	1·8%	48	3·8%	0·48 (0·28–0·80)	0·0027	2.0%	50

RR=relative risk. *Type of stroke was determined by the endpoint committee on the basis of brain imaging or post-mortem findings. If neither of these was available, the stroke was classified as unknown. †The three other intracranial haemorrhages were subdural; two of these were fatal (one in each treatment group). ‡Two of the systemic

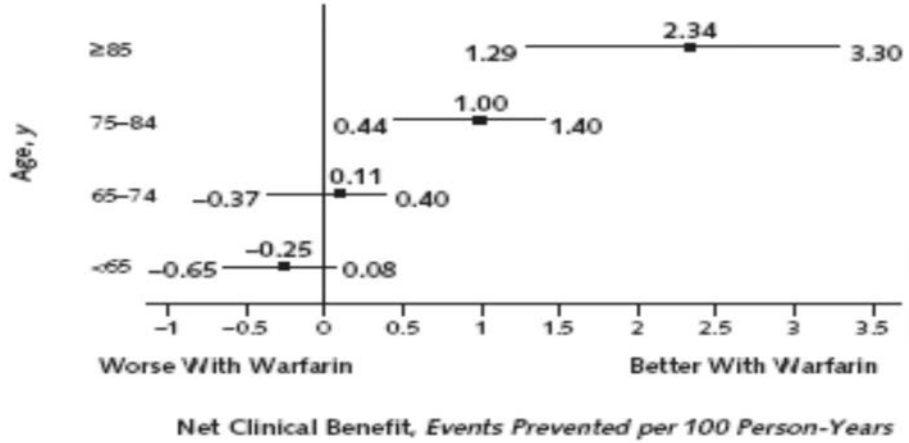
Interpretation These data support the use of anticoagulation therapy for people aged over 75 who have atrial fibrillation, unless there are contraindications or the patient decides that the benefits are not worth the inconvenience.

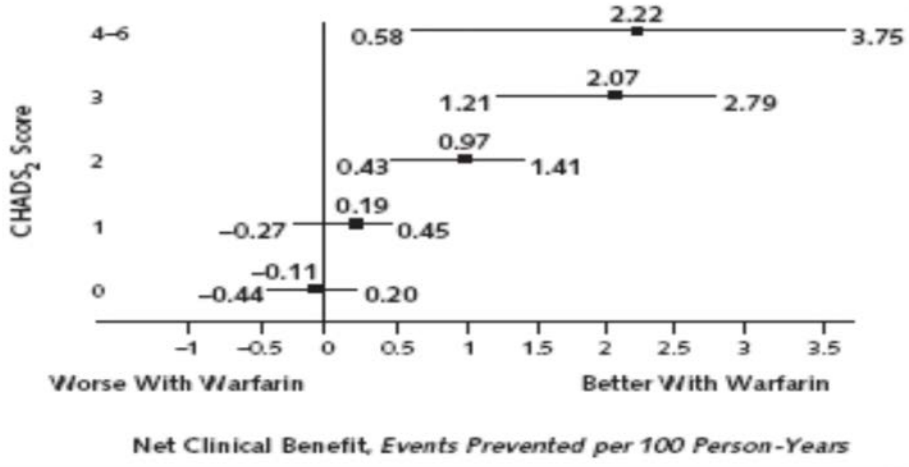
Annals of Internal Medicin Ann Intern Med. 2009;151:297-305. | ARTICLE

The Net Clinical Benefit of Warfarin Anticoagulation in Atrial Fibrillation

Daniel E. Singer, MD; Yuchiao Chang, PhD; Margaret C. Fang, MD, MPH; Leila H. Borowsky, MPH; Niela K. Pomernacki, RD; Natalia Udaltsova, PhD; and Alan S. Go, MD

Figure. **The net clinical benefit of warfarin, by age (*top*) and $CHADS_2$ score (*bottom*).**





Obiettivo: *quantificare* ***il beneficio clinico netto del warfarin*** *in 13559 pazienti con FA (****6141 età>75 anni****; 45% femmine); studio misto retrospettico e prospettico su pazienti consecutivi con FA dal 1996 al 2003*

Benefit minus harm (net treatment benefit) was highest in patients with:
-previous stroke
-age older than 84 years
-others with high stroke risk

Europace (2014) 16, 308–319
doi:10.1093/europace/eut373

CLINICAL RESEARCH
Atrial fibrillation

A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry

3119 (40.4% female; mean age 68.8 years) in- and out-patients with AF presenting to cardiologists in 9 ESC countries (Feb 2012-March 2013)

OACs were used in 80% overall, most often VKAs (71.6%), with novel OACs being used in 8.4%; no antithrombotic treatment was prescribed in 4.8% of patients.
OACs were used in 56.4% of CHA_2DS_2-VASc=0

Table 7 Independent predictors of OAC use: multivariable analysis

Variable	OR	95% CI	*P* value
Age <70 years by 10 years	1.44	1.20–1.73	0.0003
Female gender	0.65	0.51–0.83	0.0005
BMI (per increase by 5 kg/m^2)	1.22	1.05–1.42	0.01
SBP (per increase by 20 mmHg)	0.83	0.71–0.98	0.03
CHA_2DS_2-VASC: <2 vs. ≥2	0.43	0.30–0.62	<0.0001
HAS-BLED score >2 vs. ≤2	0.47	0.35–0.63	<0.0001
Hyperthyroidism	2.82	1.11–7.17	0.03
Previous ischaemic/ thrombo-embolic events	1.67	1.14–2.46	0.009
Chronic kidney disease	0.70	0.50–0.97	0.03

Adherence and Persistence in the Use of Warfarin After Hospital Discharge Among Patients With Heart Failure and Atrial Fibrillation

Patients with HF and AF >=65 years old discharged from hospitals in the Get With the Guidelines-Heart Failure registry

Among 2691 eligible patients (mean age 80 years, 43% male) 1856 (69%) were prescribed warfarin at discharge

Journal of Cardiac Failure Vol. 20 No. 1 2014

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

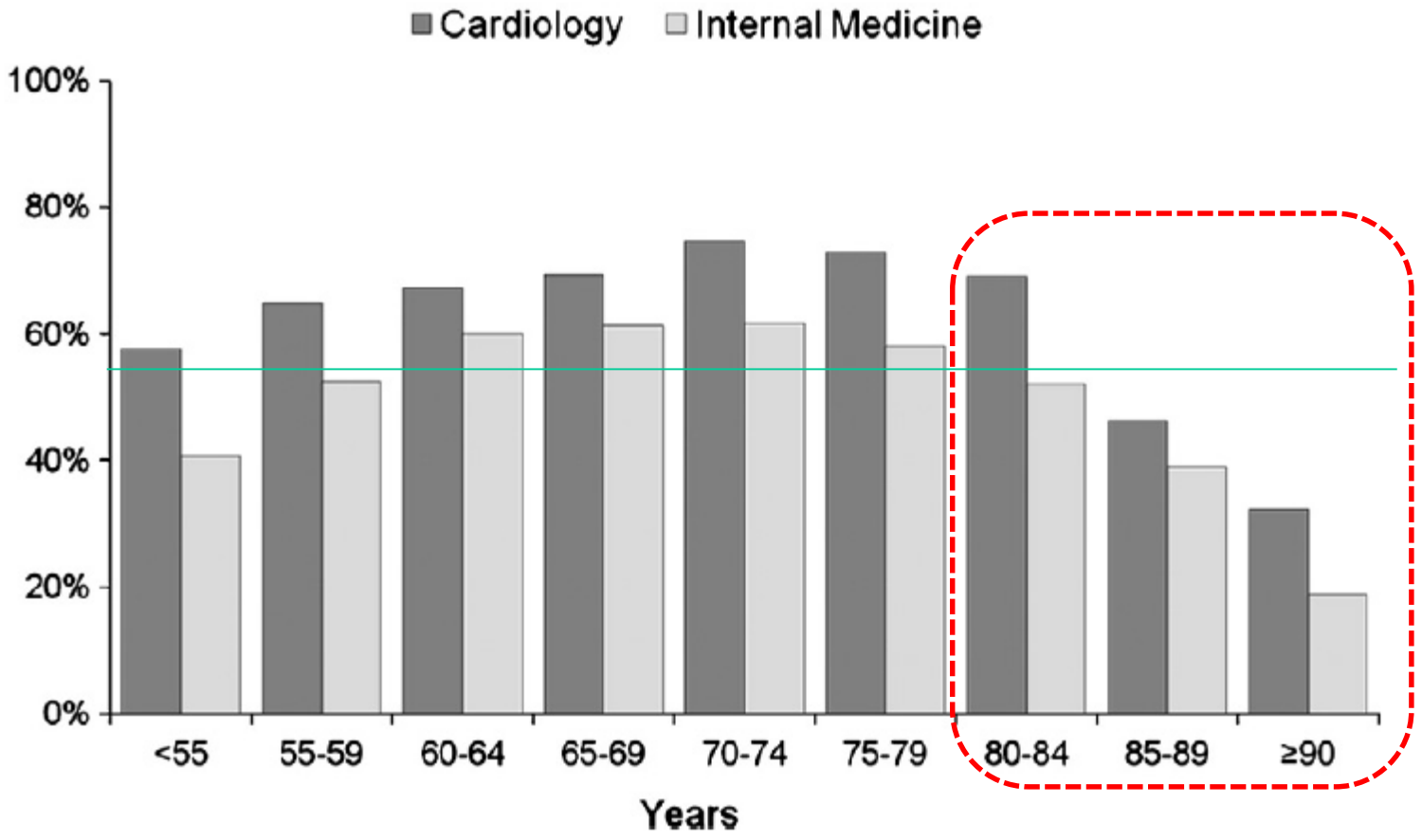


Fig. 5. OAC prescription at discharge from cardiology and internal medicine patients according to the age.

Health status, geriatric syndromes and prescription of oral anticoagulant therapy in elderly medical in-patients with atrial fibrillation: a prospective observational study

International Journal of Cardiology 187 (2015) 123–125

M. Bo [a], F. Li Puma [a], M. Badinella Martini [a], Y. Falcone [a,*], M. Iacovino [a], E. Grisoglio [a], M. Bonetto [a], G. Isaia [b], G. Ciccone [a], G.C. Isaia [a], F. Gaita [c]

Studio prospettico su 550 pazienti con FA ricoverati in area medico – geriatrica in tre grandi ospedali piemontesi (Molinette, Torino; S. Luigi, Orbassano; S Croce e Carle, Cuneo)

Age, years, m ± sd	81.7 ± 6.8
Age ≥ 75 years, n (%)	466 (84.7)
Female, n (%)	306 (55.6)
BMI, m ± sd	25.5 ± 5.3
AF known before admission, n (%)	483 (87.8)
Paroxysmal AF, n (%)	154 (28.0)
Permanent AF, n (%)	329 (59.8%)
CHARLSON, m ± sd	3.4 ± 2.2
ADL dependent, n (%)	251 (45.6)
IADL dependent, n (%)	356 (64.7)
Moderate–severe cognitive impairment, n (%)	221 (40.2)
Depression, n (%)	202 (36.7)
Frail, n (%)	426 (77.5)
At risk of malnutrition, n (%)	434 (78.9)
Dementia, n (%)	89 (16.2)
Depression, n (%)	71 (12.9)
eGFR < 60 ml/min, n (%)	157 (28.5)

At discharge 48.7% received OAT and 27.7% antiplatelet therapy

Health status, geriatric syndromes and prescription of oral anticoagulant therapy in elderly medical in-patients with atrial fibrillation: a prospective observational study

International Journal of Cardiology 187 (2015) 123–125

M. Bo [a], F. Li Puma [a], M. Badinella Martini [a], Y. Falcone [a,*], M. Iacovino [a], E. Grisoglio [a], M. Bonetto [a], G. Isaia [b], G. Ciccone [a], G.C. Isaia [a], F. Gaita [c]

	A: total sample of patients			B: without contraindications to oral anticoagulant therapy		
	OR	95% IC	P value	OR	95% IC	P value
Age, years	0.706	0.594–0.840	<.0001	0.738	0.612–0.890	0.0014
Permanent AF	1.000			1.000		
Persistent AF	0.890	0.425–1.863	0.7569	0.759	0.332–1.739	0.5148
Paroxysmal AF	0.211	0.130–0.345	<.0001	0.204	0.121–0.345	0.0010
CHA_2DS_2-VASC	1.491	1.212–1.835	0.0002	1.470	1.168–1.850	0.0010
HAS-BLED	0.642	0.493–0.837	0.0010	0.626	0.470–0.834	0.0010
CHARLSON index	0.866	0.779–0.964	0.0084	0.859	0.764–0.965	0.0108
Contraindications	0.325	0.167–0.634	0.0010			
(MNA)						
Facility vs home discharge	0.670	0.393–1.144	0.1426	0.596	0.334–1.064	0.0801

Advanced age, very short life expectancy, difficult or impossible management of therapy, perceived fear of bleeding and harm greater than benefit were the most common reasons why physicians withhold OAs.

Health status, geriatric syndromes and prescription of oral anticoagulant therapy in elderly medical in-patients with atrial fibrillation: a prospective observational study

International Journal of Cardiology 187 (2015) 123–125

M. Bo [a], F. Li Puma [a], M. Badinella Martini [a], Y. Falcone [a,*], M. Iacovino [a], E. Grisoglio [a], M. Bonetto [a], G. Isaia [b], G. Ciccone [a], G.C. Isaia [a], F. Gaita [c]

	A: total sample of patients			B: without contraindications to oral anticoagulant therapy		
	OR	95% IC	P value	OR	95% IC	P value
Age, years	0.706	0.594–0.840	<.0001	0.738	0.612–0.890	0.0014
Permanent AF	1.000			1.000		
Persistent AF	0.890	0.425–1.863	0.7569	0.759	0.332–1.739	0.5148
Paroxysmal AF	0.211	0.130–0.345	<.0001	0.204	0.121–0.345	0.0010
CHA_2DS_2-VASC	1.491	1.212–1.835	0.0002	1.470	1.168–1.850	0.0010
HAS-BLED	0.642	0.493–0.837	0.0010	0.626	0.470–0.834	0.0010
CHARLSON index	0.866	0.779–0.964	0.0084	0.859	0.764–0.965	0.0108
Contraindications	0.325	0.167–0.634	0.0010			
(MNA)						
Facility vs home discharge	0.670	0.393–1.144	0.1426	0.596	0.334–1.064	0.0801

Advanced age, very short life expectancy, difficult or impossible management of therapy, perceived fear of bleeding and harm greater than benefit were the most common reasons why physicians withhold OAs.

EFFECTS OF ORAL ANTICOAGULANT THERAPY IN OLDER MEDICAL IN-PATIENTS WITH ATRIAL FIBRILLATION: A PROSPECTIVE COHORT OBSERVATIONAL STUDY

Bo M, Li Puma F, Badinella-Martina M, Falcone Y, Iacovino M, Grisoglio E, Menditto E, Fonte G, Brunetti E, Isaia GC, D'Ascenzo F #, Gaita F #.

Mean follow-up: 300 days. Overal mortality: 33.4%

Clinical events	Overall sample (n=452)	OAT (n=225)	No OAT (n=227)	
Overall mortality, n (%)	**151 (33.4)**	**52 (23.1)**	**99 (43.6) ***	*OR 0.5367 (CI 0.41-0.83)
Fatal Ischemic stroke, n (%)	**6 (1.3)**	**0**	**6 (2.6)**	
Fatal Hemorragic stroke, n (%)	1 (0.2)	1 (0.4)	0	
Fatal Ischemic events, other sites, n (%)	11 (2.4)	5 (2.2)	6 (2.6)	
Fatal Extracranial hemorragic events, n (%)	7 (1.5)	4 (1.8)	3 (1.3)	
Fatal and non-fatal clinical events				
Ischemic stroke, n (%)	**18 (4.0)**	**4 (1.8)**	**14 (6.2) ****	** OR 0.2568 (CI 0.18-0.65)
Hemorragic stroke, n (%)	2 (0.4)	1 (0.4)	1 (0.4)	
Ischemic events, other sites, n (%)	21 (4.6)	10 (4.4)	11 (4.8)	
Major extracranial hemorragic events, n (%)	28 (6.2)	19 (8.4)	9 (4)	
Minor extracranial hemorragic events, n (%)	**35 (7.7)**	**23 (10.2)**	**12 (5.3)**	
Overall ischemic events, n (%)	**39 (8.6)**	**14 (6.2)**	**25 (11.0)**	
Overall hemorragic events, n (%)	**65 (14.4)**	**43 (19.1)**	**22 (9.7)**	
Readmissions, n (%)	**223 (49.3)**	**120 (53.3)**	**103 (45.4)**	

Results confirmed after propensity score analysis

submitted

EFFECTS OF ORAL ANTICOAGULANT THERAPY IN OLDER MEDICAL IN-PATIENTS WITH ATRIAL FIBRILLATION: A RETROSPECTIVE COHORT OBSERVATIONAL STUDY

Bo M, Li Puma F, Badinella-Martina M, Falcone Y, Iacovino M, Grisoglio E, Menditto E, Fonte G, Brunetti E, Isaia GC, Gaita F #.

Age, years, m±sd	**83.4±6.7**
Female, n (%)	593 (60.5)
Length of stay, median (25°-75°)	8(5-12)
CHA_2DS_2-VASc, m±sd	**4.8±1.4**
HASBLED, m±sd	**2.1±0.9**
AF known before admission, n (%)	**810 (82.7)**
Permanent AF, n (%)	**720 (73.5)**
CHARLSON, m±sd	**7.4±2.1**
ADL dependent, n (%)	**263 (26.8)**
IADL dependent, n (%)	**366 (37.3)**
Moderate-severe cognitive impairment, n (%)	**303 (31.0)**
Home-discharge, n (%)	792 (81.8)
Intermediate or long-term care discharge, n (%)	188 (18.2)
Number of therapeutic drugs at discharge, m±sd	8.0±2.8
Hemoglobin, g/dl, m±sd	11.9±2.0
Creatinin, mg/dl, median (25°-75°)	1.06 (0.9-1.4)
Antithrombotic therapy at discharge:	
Oral anticoagulant only, n (%)	**346 (35.3)**
Oral antiplatelet, n (%)	369 (37.7)
Double antiplatelet, n (%)	25 (2.6)
Low Molecular Weight Heparin, n (%)	88 (9.0)
Oral anticoagulant + antiplatelet, n (%)	**38 (3.8)**
None, n (%)	114 (11.6)
Antithrombotic therapy at follow-up:	
Oral anticoagulant only, n (%)	**347 (35.4)**
Oral antiplatelet, n (%)	378 (38.6)
Double antiplatelet, n (%)	17 (1.7)
Low Molecular Weight Heparin, n (%)	93 (9.5)
Oral anticoagulant + antiplatelet, n (%)	**31(3.2)**
None, n (%)	114 (11.6)

submitted

EFFECTS OF ORAL ANTICOAGULANT THERAPY IN OLDER MEDICAL IN-PATIENTS WITH ATRIAL FIBRILLATION: A RETROSPECTIVE COHORT OBSERVATIONAL STUDY

Bo M, Li Puma F, Badinella-Martina M, Falcone Y, Iacovino M, Grisoglio E, Menditto E, Fonte G, Brunetti E, Isaia GC, Gaita F #.

Mean follow-up: 571 days. Overal mortality: 51.5%

Clinical events	Overall sample	OAT	No OAT
Overall mortality, n (%)	**505 (51.5)**	**140 (36.5)**	**365 (61.2) ***
Fatal Ischemic stroke, n (%)	**40 (4.1)**	**11 (2.9)**	**29 (4.9)**
Fatal Hemorrhagic stroke, n (%)	11 (1.1)	4 (1.0)	7 (1.2)
Fatal Ischemic events, other sites, n (%)	15 (1.5)	5 (1.3)	10 (1.8)
Fatal Extracranial hemorrhagic events, n (%)	2 (0.2)	0	2 (0.3)
Non-fatal clinical events			
Ischemic stroke, n (%)	**82 (8.4)**	**22 (6.8)**	**60 (10.1)**
Hemorrhagic stroke, n (%)	13 (1.3)	6 (1.6)	7 (1.3)
Ischemic events, other sites, n (%)	43 (4.4)	15 (3.9)	28 (4.7)
Major extracranial hemorrhagic events, n (%)	43 (4.4)	18 (4.7)	25 (4.2)
Minor extracranial hemorrhagic events, n (%)	44 (4.5)	18 (4.7)	26 (4.4)
Overall ischemic events, n (%)	125 (12.8)	41 (8.4)	88 (14.8)
Overall hemorrhagic events, n (%)	100 (10.2)	41 (10.7)	59 (9.9)
All-cause hospitalization, median (25°-75°)	1 (0.0-2.0)	1 (0-2)	1 (0-1)

* OR 0.5240 (CI 0.38-0.76)

submitted

EFFECTS OF ORAL ANTICOAGULANT THERAPY IN OLDER MEDICAL IN-PATIENTS WITH ATRIAL FIBRILLATION: A RETROSPECTIVE COHORT OBSERVATIONAL STUDY

Bo M, Li Puma F, Badinella-Martina M, Falcone Y, Iacovino M, Grisoglio E, Menditto E, Fonte G, Brunetti E, Isaia GC, Gaita F #.

	Before propensity score matching			**After propensity score matching**		
Baseline clinical variables	OAT (384)	No OAT (596)	P	OAT (201)	No OAT (201)	P
Age, years, m±sd	81.8± 6.1	84.7±6.8	0,000	83.7±5.8	83.6±6.7	0,943
Female, n (%)	230 (59.9)	363 (60.9)	0,753	117 (58.2)	114 (56.7)	0,267
Length of stay, median (25°-75°)	7 (4-12)	8 (5-13)	0,162	8 (5-14)	8 (5-12)	0,128
ADL dependent, n (%)	165 (42.9.)	384 (64.4)	0,000	114 (56.7)	114 (56.7)	0,999
IADL dependent, n (%)	238 (52.0)	455 (76.4)	0,000	146 (72.6)	146 (72.6)	0,999
Moderate-severe cognitive impairment, n (%)	179 (46.6)	117 (19.6)	0,000	111 (55.2)	114 (56.7)	0,852
CHARLSON, m±sd	7.0±2.0	7.6± 2.2	0,000	7.3±2.0	7.3±2.3	0,774
CHA_2DS_2-VASc, m±sd	4.9±1.3	4.7±1.4	0,252	4.9±1.3	4.7±1.4	0,257
HASBLED, m±sd	2.0 (1-2)	2.0 (2-3)	0,000	2.0 (1-3)	2.0 (1-3)	0,306
Hemoglobin, g/dl, m±sd	12.3±1.9	11.7±2.1	0,000	12.0±1.9	12.0±2.0	0,849
Creatinin, mg/dl, median (25°-75°)	1.02 (0.88-1.41)	1.1 (0.9-1.5)	0,000	1.1 (0.87-1.42)	1.1 (0.9-1.57)	0,262
Home-discharge, n (%)	349 (90.9)	444 (74.5)	0.001	172(85.6)	169(84.1)	0,771
Permanent AF, n (%)	319 (83.1)	401 (67.3)	0.001	147(73.1)	144(71.6)	0,822
Clinical outcomes						
Overall mortality, n (%)	**140 (36.5)**	**365 (61.2)**	**0,000**	**90 (44,8)**	**120 (59.7)**	**0,008**
Ischemic stroke, n (%)	22 (6.8)	60 (10.1)	0,075	17(8.5)	19(9.5)	0,864
Hemorrhagic stroke, n (%)	6 (1.6)	7 (1.3)	0,776	3(1.5)	1(0.5)	0,625
Major extracranial hemorrhagic events, n (%)	18 (4.7)	25 (4.2)	0,861	11(5.5)	8(4.0)	0,629

submitted

Age and Ageing 2015; 44: 874–878

Impact of advanced age on management and prognosis in atrial fibrillation: insights from a population-based study in general practice

Retrospective, observational cohort study (12-month follow-up period); 2259 subjects with AF (24.8% >=85 years) from 11 GPs

Prescription of OAC in the very elderly (>=85 years) was 36% vs 57% among those aged 75-84 years (p<0.001)

Table 2. Predictors of stroke and death in patients at moderate–high risk of stroke

	Stroke		Death	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Multivariate analysis[a]				
Use of oral anticoagulation	0.53 (0.22–1.28)	0.158	0.59 (0.36–0.99)	0.047
Use of antiplatelet agents	2.45 (1.05–5.70)	0.038	0.68 (0.44–1.05)	0.081

Health status, geriatric syndromes and prescription of oral anticoagulant therapy in elderly medical in-patients with atrial fibrillation: a prospective observational study

International Journal of Cardiology 187 (2015) 123–125

M. Bo [a], F. Li Puma [a], M. Badinella Martini [a], Y. Falcone [a,*], M. Iacovino [a], E. Grisoglio [a], M. Bonetto [a], G. Isaia [b], G. Ciccone [a], G.C. Isaia [a], F. Gaita [c]

	A: total sample of patients			B: without contraindications to oral anticoagulant therapy		
	OR	95% IC	P value	OR	95% IC	P value
Age, years	0.706	0.594–0.840	<.0001	0.738	0.612–0.890	0.0014
Permanent AF	1.000			1.000		
Persistent AF	0.890	0.425–1.863	0.7569	0.759	0.332–1.739	0.5148
Paroxysmal AF	0.211	0.130–0.345	<.0001	0.204	0.121–0.345	0.0010
CHA_2DS_2-VASC	1.491	1.212–1.835	0.0002	1.470	1.168–1.850	0.0010
HAS-BLED	0.642	0.493–0.837	0.0010	0.626	0.470–0.834	0.0010
CHARLSON index	0.866	0.779–0.964	0.0084	0.859	0.764–0.965	0.0108
Contraindications	0.325	0.167–0.634	0.0010			
(MNA)						
Facility vs home discharge	0.670	0.393–1.144	0.1426	0.596	0.334–1.064	0.0801

Advanced age, very short life expectancy, difficult or impossible management of therapy, perceived fear of bleeding and harm greater than benefit were the most common reasons why physicians withhold OAs.

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2011;365:2002-12.

SPECIAL ARTICLE

Emergency Hospitalizations for Adverse Drug Events in Older Americans

- **Il 63.3% delle ospedalizzazioni correlate al warfarin sono dovute ad emorragie[1]**
  Budnitz DS et al. N Engl J Med 2011;365:2002–12
- La stima dei costi per le emorragie correlate al warfarin ammonta a centinaia di milioni di dollari ogni anno

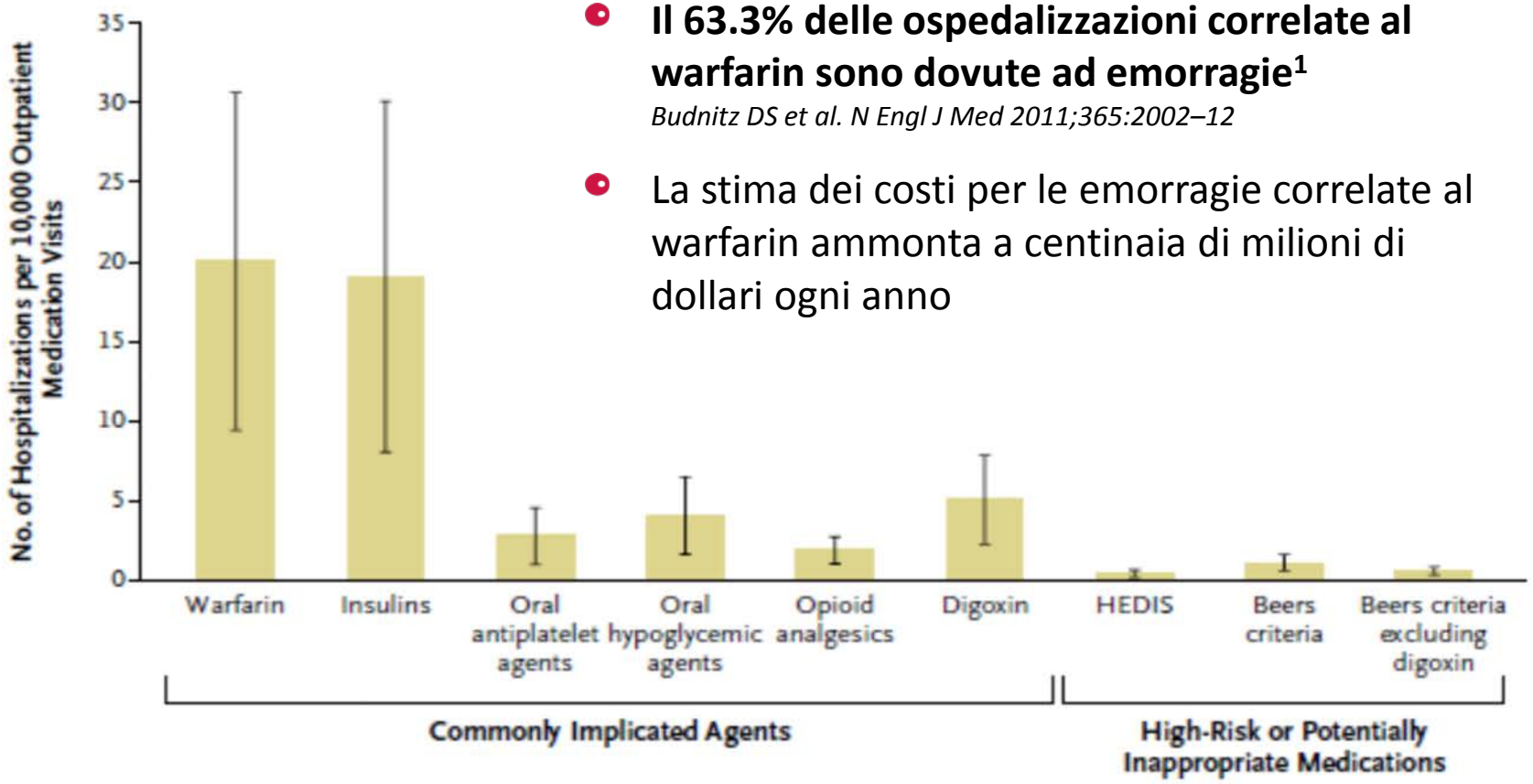


Figure 1. Estimated Rates of Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, 2007–2009.

European Journal of Internal Medicine 25 (2014) 843–846

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Understanding adverse drug reactions in older adults through drug–drug interactions

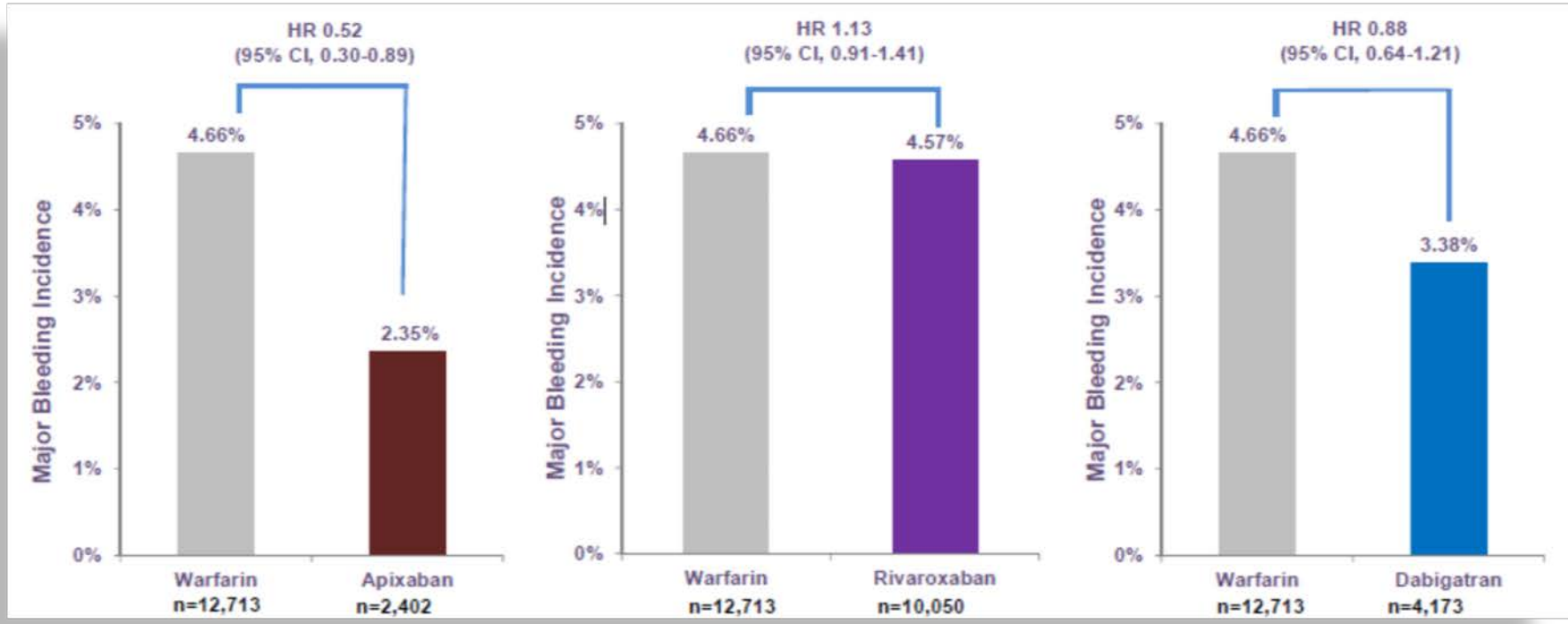
A. Marengoni [a,*], L. Pasina [b], C. Concoreggi [c], G. Martini [d], F. Brognoli [d], A. Nobili [b], G. Onder [e], D. Bettoni [f]

Valutazione di prevalenza e caratteristiche di ADRs negli anziani ricoverati in un grosso ospedale italiano durante il 2013. Le interazioni farmacologiche (DDIs) sono state valutate mediante un database dell'Istituto di Ricerche Farmacologiche Mario Negri

Di 1014 ADRs raccolte, 343 riguardavano gli anziani. Le più frequenti erano: emorragie (122, 35.5%), reazioni allergiche (56, 16.3%) e INR>6 (54,15.7%). I farmaci che contribuivano alle ADRs erano warfarin (42.5%), acenocumarolo (9%), e allopurinolo (8.5%).

Sono state osservate 912 DDIs; di queste le più frequenti erano warfarin ed eparina, warfarin e statina, warfarin e PPI. Almeno una di queste interazioni ha contribuito a 66 sanguinamenti su 122 (54%) e a 41 INR sopra range su 54 (76%)

Real World Comparison Of Major Bleeding Risk Among Non-valvular Atrial Fibrillation Patients Newly Initiated On Apixaban, Dabigatran, Rivaroxaban Or Warfarin



* Hazard ratios (HR) are adjusted HRs based on Cox proportional hazards model adjusted for: age, sex, region, embolic or primary ischemic stroke, dyspepsia or stomach discomfort, congestive heart failure, coronary artery disease, diabetes, hypertension, renal disease, myocardial infarction, history of stroke or transient ischemic attack, history of bleeding, Charlson comorbidity index, and baseline medications including angiotensin converting enzyme inhibitor, amiodarone, angiotensin receptor blocker, beta blocker, H2-receptor antagonist, proton pump inhibitor, and statins.

Lip et al. Poster presentation at ESC Aug/Sept 2015; London, UK Poster/oral poster no.P6217

Health status, geriatric syndromes and prescription of oral anticoagulant therapy in elderly medical in-patients with atrial fibrillation: a prospective observational study

International Journal of Cardiology 187 (2015) 123–125

M. Bo [a], F. Li Puma [a], M. Badinella Martini [a], Y. Falcone [a,*], M. Iacovino [a], E. Grisoglio [a], M. Bonetto [a], G. Isaia [b], G. Ciccone [a], G.C. Isaia [a], F. Gaita [c]

	A: total sample of patients			B: without contraindications to oral anticoagulant therapy		
	OR	95% IC	P value	OR	95% IC	P value
Age, years	0.706	0.594–0.840	<.0001	0.738	0.612–0.890	0.0014
Permanent AF	1.000			1.000		
Persistent AF	0.890	0.425–1.863	0.7569	0.759	0.332–1.739	0.5148
Paroxysmal AF	0.211	0.130–0.345	<.0001	0.204	0.121–0.345	0.0010
CHA_2DS_2-VASC	1.491	1.212–1.835	0.0002	1.470	1.168–1.850	0.0010
HAS-BLED	0.642	0.493–0.837	0.0010	0.626	0.470–0.834	0.0010
CHARLSON index	0.866	0.779–0.964	0.0084	0.859	0.764–0.965	0.0108
Contraindications	0.325	0.167–0.634	0.0010			
(MNA)						
Facility vs home discharge	0.670	0.393–1.144	0.1426	0.596	0.334–1.064	0.0801

Advanced age, very short life expectancy, difficult or impossible management of therapy, perceived fear of bleeding and harm greater than benefit were the most common reasons why physicians withhold OAs.

CMAJ RESEARCH

Rates of hemorrhage during warfarin therapy for atrial fibrillation

CMAJ 2013. DOI:10.1503/cmaj.121218

125195 pazienti con FA che hanno iniziato warfarin

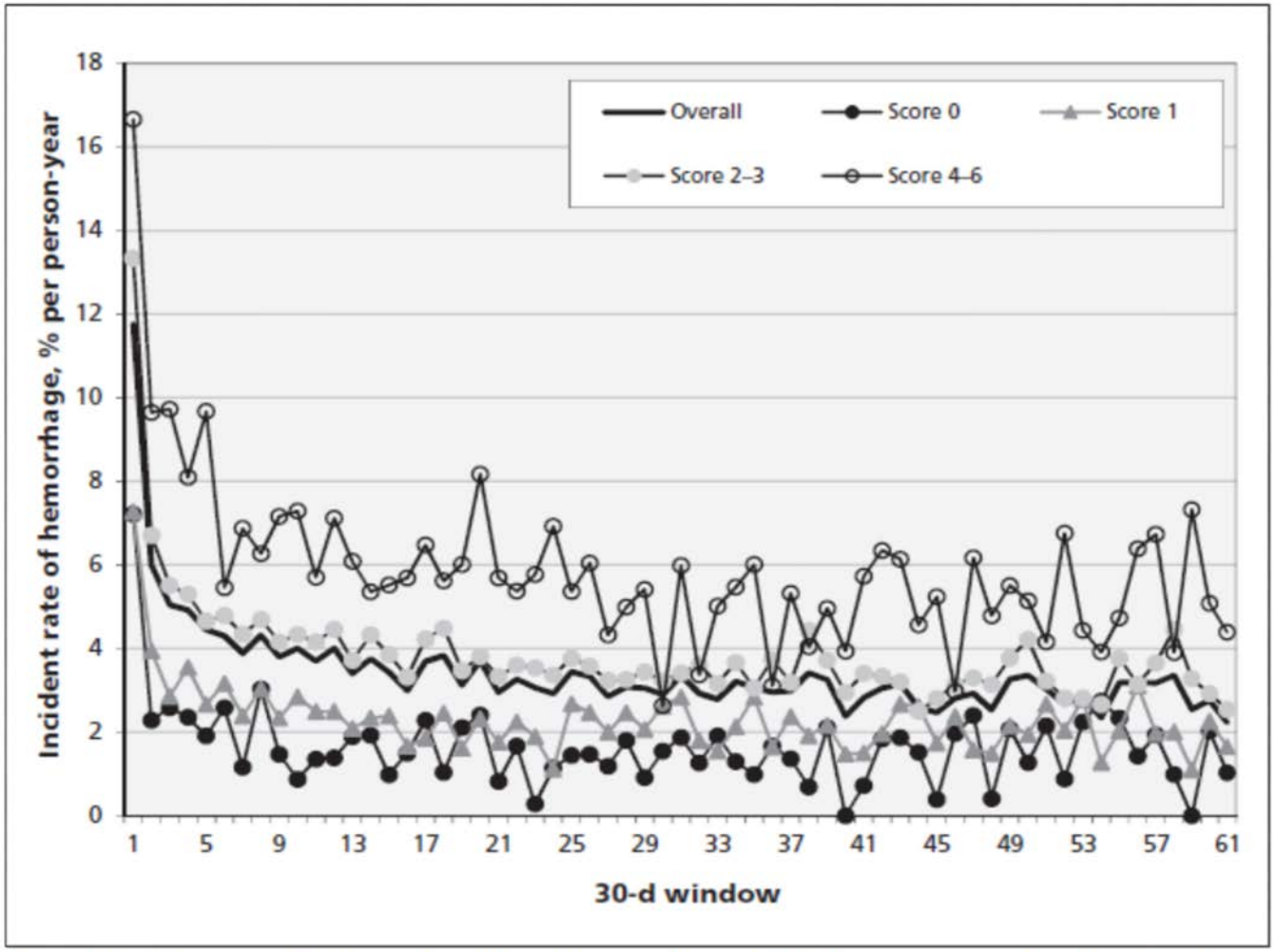


Figure 1: Incident rate of visits to hospital with hemorrhages in 30-day increments after the start of warfarin therapy among older patients (≥ 66 yr) with atrial fibrillation. Rates are stratified by $CHADS_2$ score at the start of treatment.

Clinical Investigations

Quality of Anticoagulation With Vitamin K Antagonists

Clin. Cardiol. 38, 6, 357–364 (2015)

Registro osservazionale di 948 pazienti (73.8 anni, 42.5% femmine) con FA trattati con VKA

TTR medio 63.77%±23.80%

Prevalenza di anticoagulazione non ottimale: 54%

Table 3. Multivariable Analysis, Variables Associated With TTR ≥65%

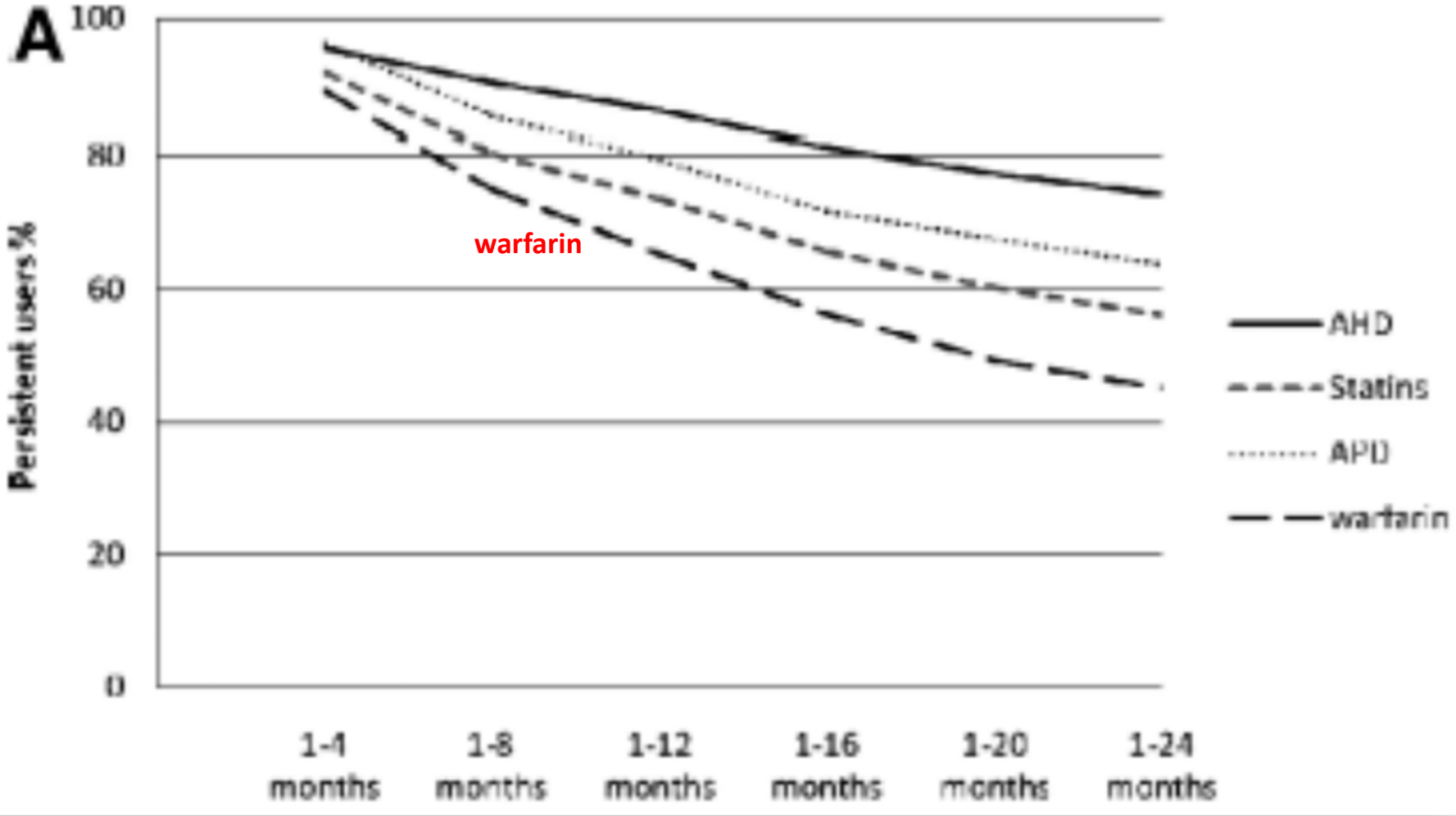
Variable	OR	95% CI	*P* Value
University studies	1.99	1.08-3.64	0.03
Chronic hepatic disease	8.15	1.57-42.24	0.01
Charlson index	0.87	0.76-0.99	0.03
No previous cardiac disease	0.64	0.41-0.98	0.04
HAS-BLED	0.81	0.69-0.95	0.01
Heart rate (bpm)	0.99	0.98-1.00	0.03

Abbreviations: CI, confidence interval; ECG, electrocardiogram; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly age, and use of drugs or alcohol; INR, international normalized ratio; OR, odds ratio; TTR, time in the therapeutic range.

Model adjusted by age, sex, kidney disease, ECG conduction disturbances, previous ablation, and diuretic treatment.

(*Stroke*. 2010;41:397-401.)

Persistent Use of Secondary Preventive Drugs Declines Rapidly During the First 2 Years After Stroke



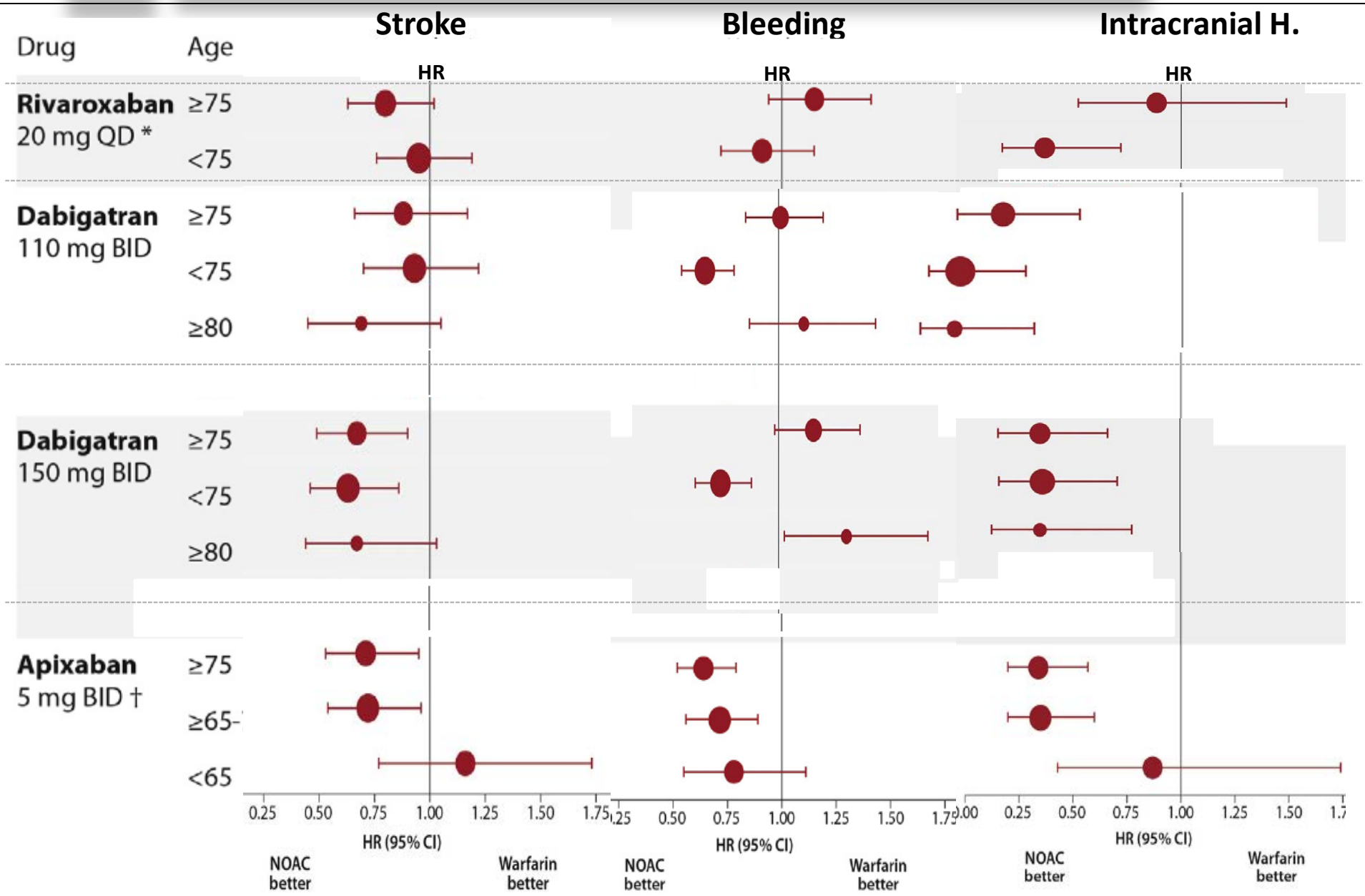
NUOVI ANTICOAGULANTI

Table 2 The 'ideal' anticoagulant

- Proven efficacy
- Low bleeding risk
- Fixed dosing
- Good oral bioavailability
- No routine monitoring
- Reversibility
- Rapid onset of action
- Little interaction with drugs or food
- Antidote available

New oral anticoagulants in elderly patients

Barco S. Best Pract Res Clin Haematol 2013

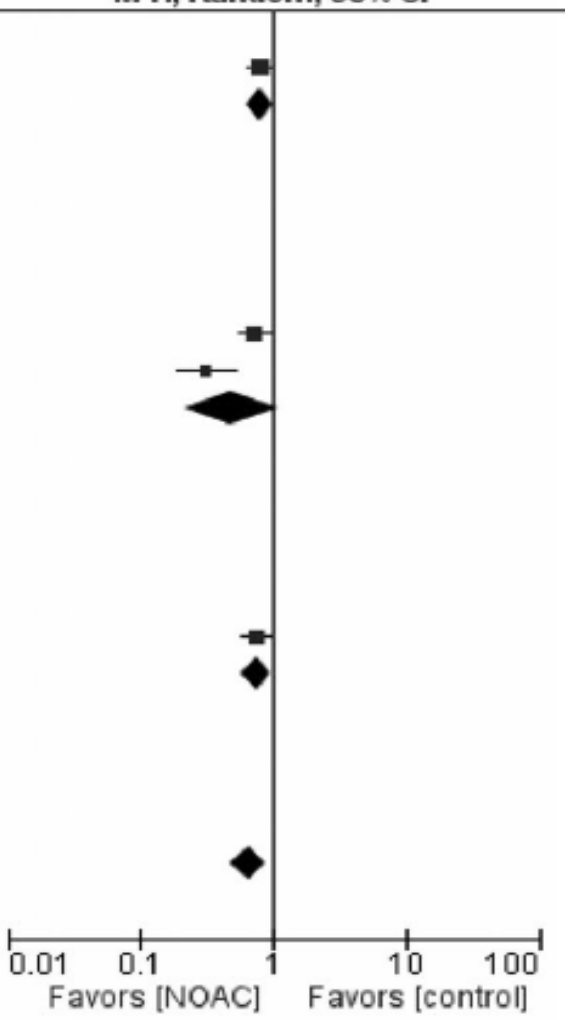


New Oral Anticoagulants in Elderly Adults: Evidence from a Meta-Analysis of Randomized Trials

J Am Geriatr Soc 62:857–864, 2014.

Patients aged more than 75 years: Stroke or systemic embolism

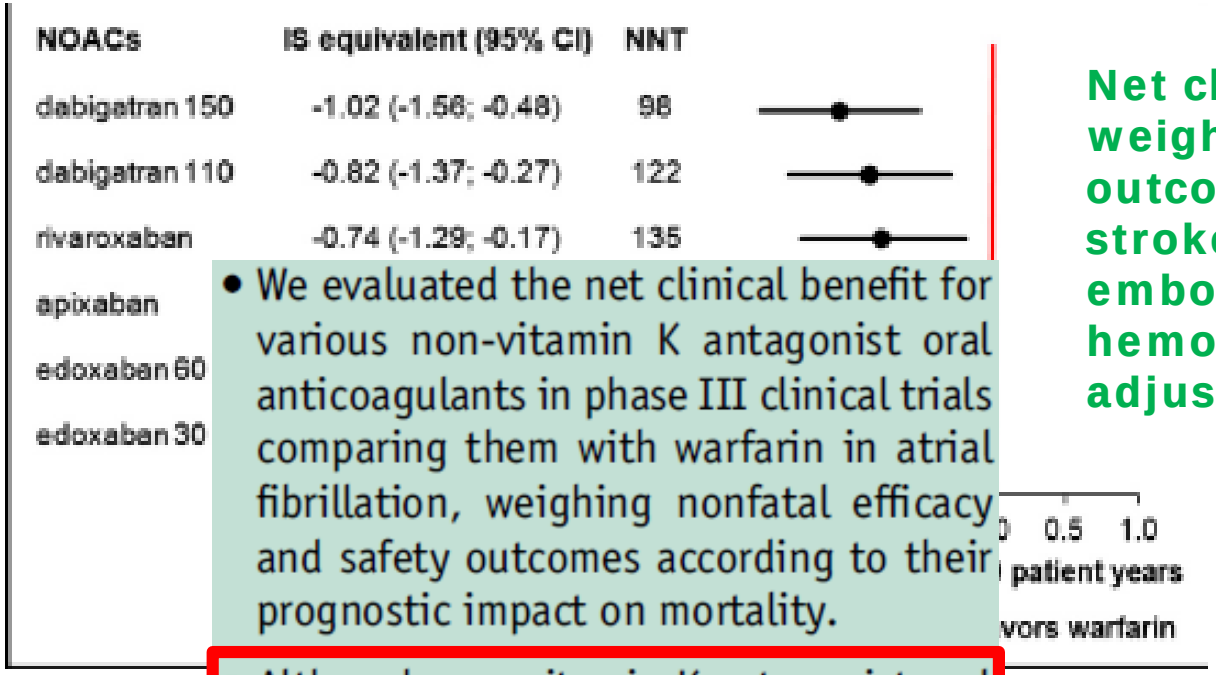
Study or Subgroup	NOAC Events	NOAC Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1 Rivaroxaban						
ROCKET-AF, 2011	125	3,082	154	3,082	28.6%	0.80 [0.63, 1.02]
Subtotal (95% CI)		**3,082**		**3,082**	**28.6%**	**0.80 [0.63, 1.02]**
Total events	125		154			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.77 (P = 0.08)						
1.2 Apixaban						
ARISTOTLE, 2011	79	2,743	109	2,752	26.2%	0.72 [0.54, 0.97]
AVERROES, 2011	20	909	66	983	17.2%	0.31 [0.19, 0.52]
Subtotal (95% CI)		**3,652**		**3,735**	**43.4%**	**0.49 [0.22, 1.10]**
Total events	99		175			
Heterogeneity: $Tau^2 = 0.30$; $Chi^2 = 7.75$, df = 1 (P = 0.005); $I^2 = 87\%$						
Test for overall effect: Z = 1.73 (P = 0.08)						
1.3 Dabigatran						
RE-LY, 2009	156	4,828	101	2,360	28.0%	0.75 [0.58, 0.96]
Subtotal (95% CI)		**4,828**		**2,360**	**28.0%**	**0.75 [0.58, 0.96]**
Total events	156		101			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.24 (P = 0.03)						
Total (95% CI)		**11,562**		**9,177**	**100.0%**	**0.65 [0.48, 0.87]**
Total events	380		430			
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 11.19$, df = 3 (P = 0.01); $I^2 = 73\%$						
Test for overall effect: Z = 2.87 (P = 0.004)						
Test for subgroup differences: $Chi^2 = 1.37$, df = 2 (P = 0.51), $I^2 = 0\%$						



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®



- We evaluated the net clinical benefit for various non-vitamin K antagonist oral anticoagulants in phase III clinical trials comparing them with warfarin in atrial fibrillation, weighing nonfatal efficacy and safety outcomes according to their prognostic impact on mortality.

- Although non-vitamin K antagonist oral anticoagulants have shown variable efficacy and safety relative to warfarin, according to this analysis all have a better and strikingly similar net clinical benefit in patients with atrial fibrillation.

Net clinical benefit for the weighed composite outcome of ischemic stroke + systemic embolism + MI + hemorrhagic stroke + adjusted major bleeding

Geropharmacology

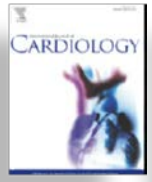
Ogbonna, J Gerontol N 2013

Moving Beyond Warfarin—Are We Ready?

A Review of the Efficacy and Safety of Novel Anticoagulant Agents Compared to Warfarin for the Management of Atrial Fibrillation in Older Adults

ENROLLMENT RATES OF OLDER ADULTS IN MAJOR ATRIAL FIBRILLATION (AF) CLINICAL TRIALS

Study	Median Age	% Age >75	% Age >80	Females %	Average weight - Kg
RE-LY	71	41	17	36	82.5
ROCKET AF	73	43	25	40	82.1
ARISTOTLE	70	31	– 13	35	82



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

Characteristics	Total (n. 7148)	Cardiology (n. 3862)	Internal medicine (n. 3286)
Age (years), median [IQR]	77 [70–83]	74 [66–80]	80 [74–86]
Females, %	47.0	43.4	51.3

Weight -Kg

mean	74± 15
male	79±14
female	64±14

Moving Beyond Warfarin—Are We Ready?

A Review of the Efficacy and Safety of Novel Anticoagulant Agents Compared to Warfarin for the Management of Atrial Fibrillation in Older Adults

Ogbonna, J Gerontol N 2013

Exclusion criteria of NOAC investigating trials

	Creatinine clearance (Cockcroft-Gault formula)			
	RE-LY	ROCKET-AF	ARISTOTLE	AVERROES
	<30 mL/min	<30 mL/min	<25 mL/min	<25 mL/min
Included with Cr Cl <50mL/min	**19%**	**20%**	**17%**	**22%**

(*Circulation*. 2015;131:157-164.

Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation

134414 new-user cohort propensity score-matched elderly patients (**57% >75 years**, 16% >85 years) enrolled in Medicare who initiated DABI or WARFA for NVAF between Oct 2010 and Dec 2012. 2715 primary outcome events during 37587 person-years of follow-up

Table 2. Outcome Event Counts, Incidence Rates, and Adjusted Hazard Ratios With 95% CIs Comparing Propensity Score–Matched New-User Cohorts of Dabigatran and Warfarin Treated for Nonvalvular Atrial Fibrillation, With Warfarin as the Reference Group

	No. of Events		Incidence Rate per 1000 Person-Years		Adjusted Hazard Ratio (95% CI)	*P* Value
	Dabigatran	Warfarin	Dabigatran	Warfarin		
Primary outcomes						
Ischemic stroke	205	270	11.3	13.9	0.80 (0.67–0.96)	0.02
Major hemorrhage	777	851	42.7	43.9	0.97 (0.88–1.07)	0.50
Gastrointestinal	623	513	34.2	26.5	1.28 (1.14–1.44)	<0.001
Intracranial	60	186	3.3	9.6	0.34 (0.26–0.46)	<0.001
Intracerebral	44	142	2.4	7.3	0.33 (0.24–0.47)	<0.001
Acute myocardial infarction	285	327	15.7	16.9	0.92 (0.78–1.08)	0.29
Secondary outcomes						
All hospitalized bleeds	1079	1139	59.3	58.8	1.00 (0.92–1.09)	0.97
Mortality*	603	744	32.6	37.8	0.86 (0.77–0.96)	0.006

Efficacy and Safety of Dabigatran Etexilate and Warfarin in "Real-World" Patients With Atrial Fibrillation

A Prospective Nationwide Cohort Study

(J Am Coll Cardiol 2013;61:2264–73)

From the Danish Registry two propensity score-matched groups of Dabigatran -treated (4978) and Warfarin -treated (8936) patients were extracted. Patients 75 years or older were 39,3% of Warfarin-treated, 18,3% of D 150 bid-treated and 52.8% of D 110 bid-treated patients

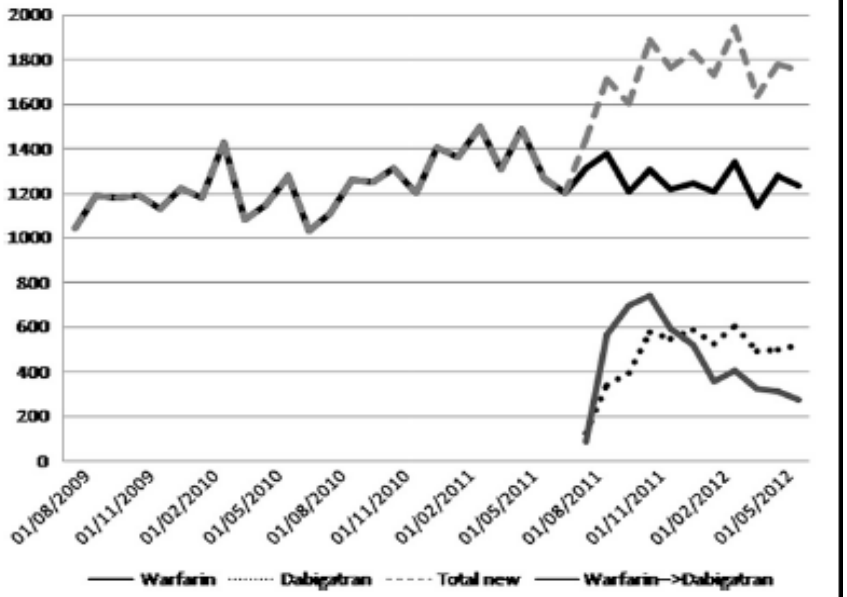
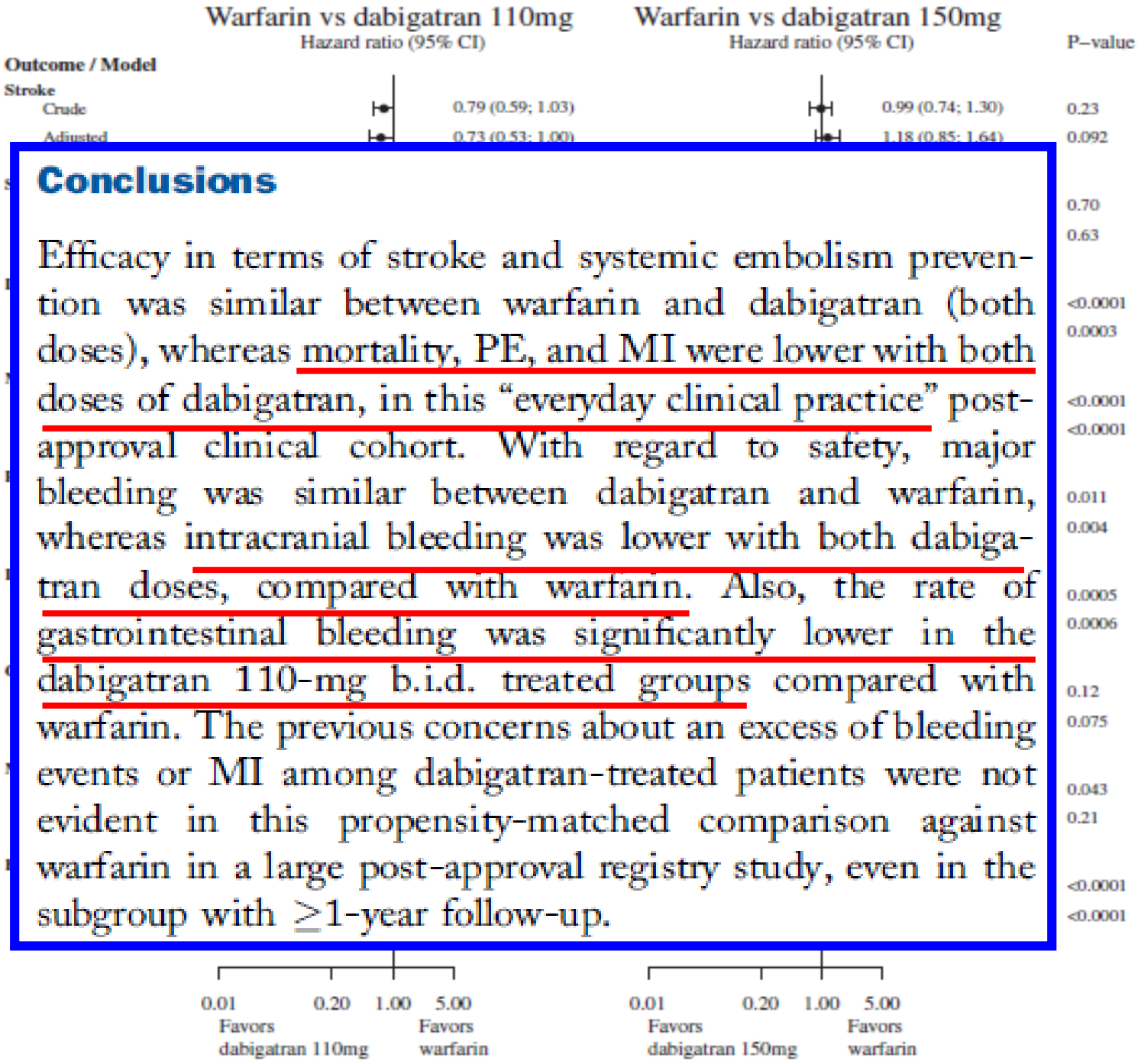


Figure 3 Monthly New Users of Warfarin and Dabigatran Etexilate for AF

Monthly new users of warfarin and dabigatran etexilate for atrial fibrillation (AF) in the period August 2009 to June 2012 in Denmark.



Conclusions

Efficacy in terms of stroke and systemic embolism prevention was similar between warfarin and dabigatran (both doses), whereas mortality, PE, and MI were lower with both doses of dabigatran, in this "everyday clinical practice" post-approval clinical cohort. With regard to safety, major bleeding was similar between dabigatran and warfarin, whereas intracranial bleeding was lower with both dabigatran doses, compared with warfarin. Also, the rate of gastrointestinal bleeding was significantly lower in the dabigatran 110-mg b.i.d. treated groups compared with warfarin. The previous concerns about an excess of bleeding events or MI among dabigatran-treated patients were not evident in this propensity-matched comparison against warfarin in a large post-approval registry study, even in the subgroup with ≥1-year follow-up.

Quali sono le ragioni per non scoagulare un paziente anziano con FA?

Quali sono le ragioni per non scoagulare un paziente anziano con FA?

CONTROINDICAZIONI ALLA TAO

1. **Patologie associate a rischio di sanguinamento**
   - **Sanguinamento maggiore*; recente evento cerebrale acuto*; recente intervento chirurgico***
   - **Cirrosi epatica; trombocitopenia grave; diatesi emorragica; ipertensione non controllata***
2. **Allergia**
3. **Non compliance / Impossibilità a eseguire controlli (limitatamente agli antiVitK)**
   - **Malattia psichiatrica; tossicodipendenza; etilismo; demenza in assenza di care-giver**

*** temporanee**

La mancanza dell’antidoto…

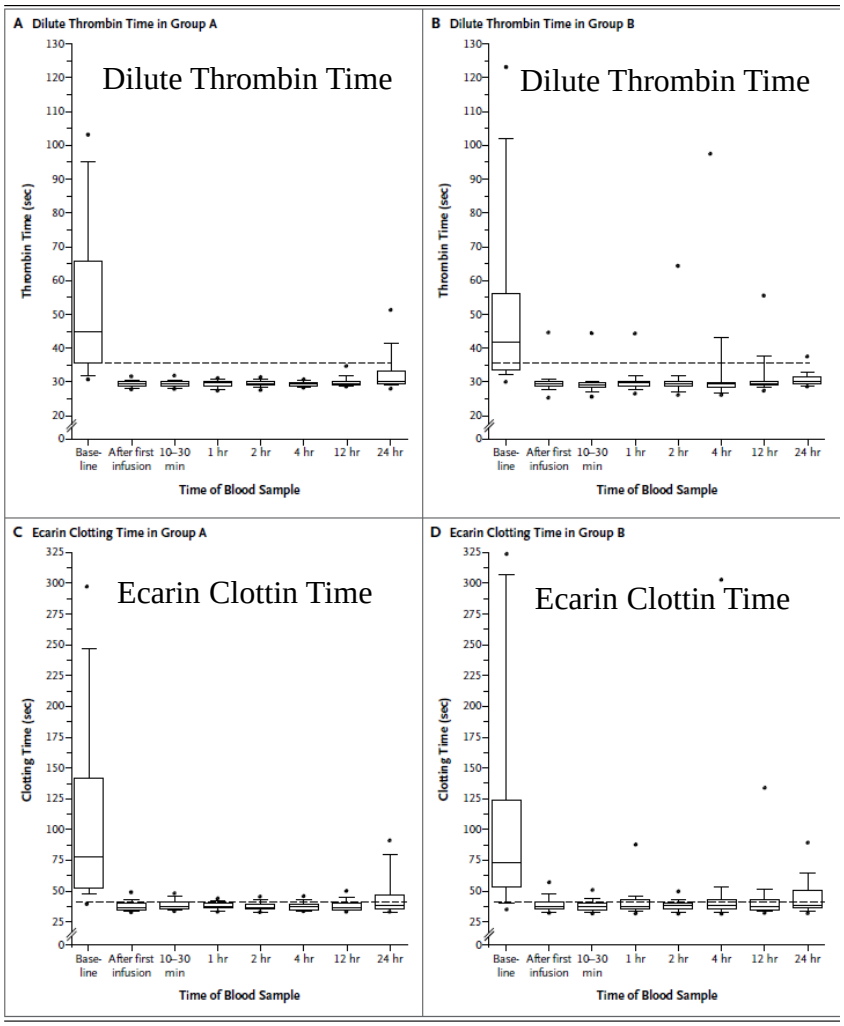
The NEW ENGLAND JOURNAL of MEDICINE

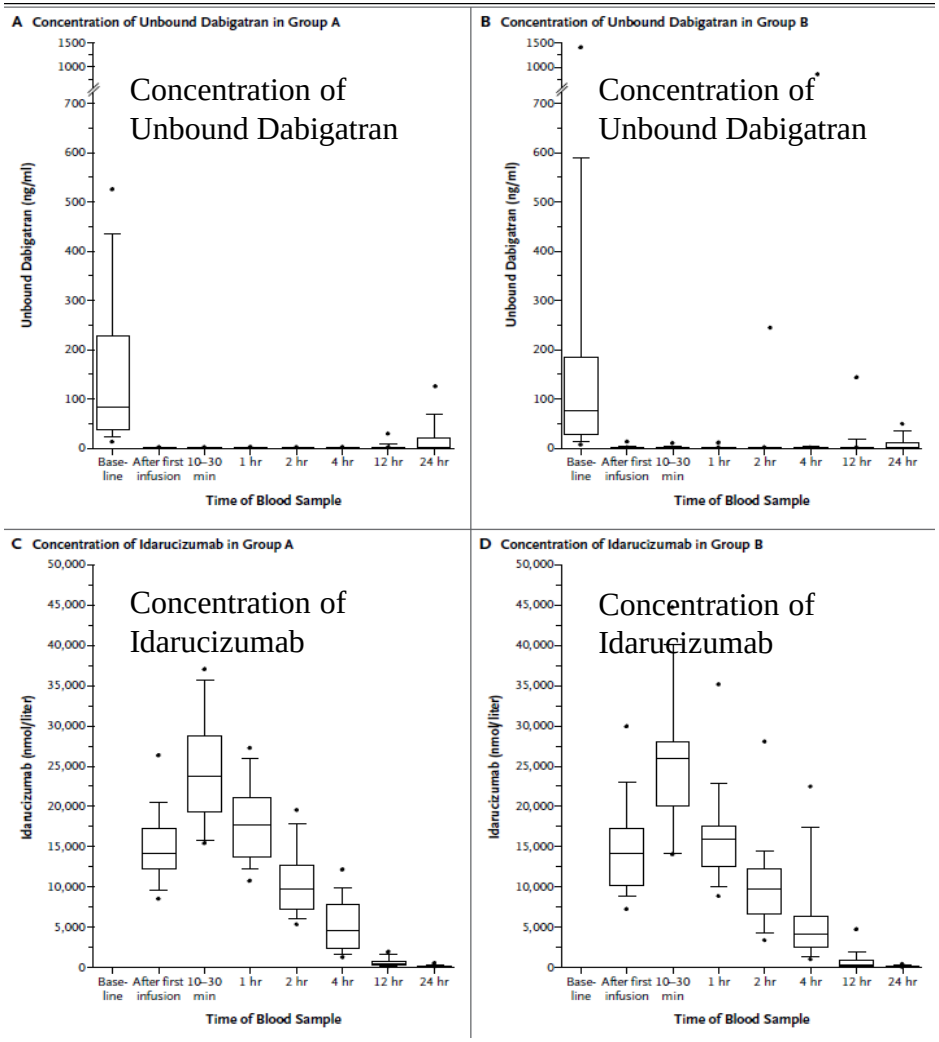
ORIGINAL ARTICLE

N Engl J Med 2015;373:511-20.

Idarucizumab for Dabigatran Reversal

Sicurezza e efficacia di IDARUCIZUMAB 5 gr ev in 90 pazienti con severo sanguinamento (51, gruppo A) o che hanno richiesto procedure invasive urgenti (39, gruppo B)





Quali sono le ragioni per non scoagulare un paziente anziano con FA?

The association between kidney function and major bleeding in older adults with atrial fibrillation starting warfarin treatment: population based observational study

Cite this as: *BMJ* 2015;350:h246

Community-based administrative data; 12403 adults aged 66 years or more, with AF, who started warfarin. Kidney function estimated using CKD-EPI equation

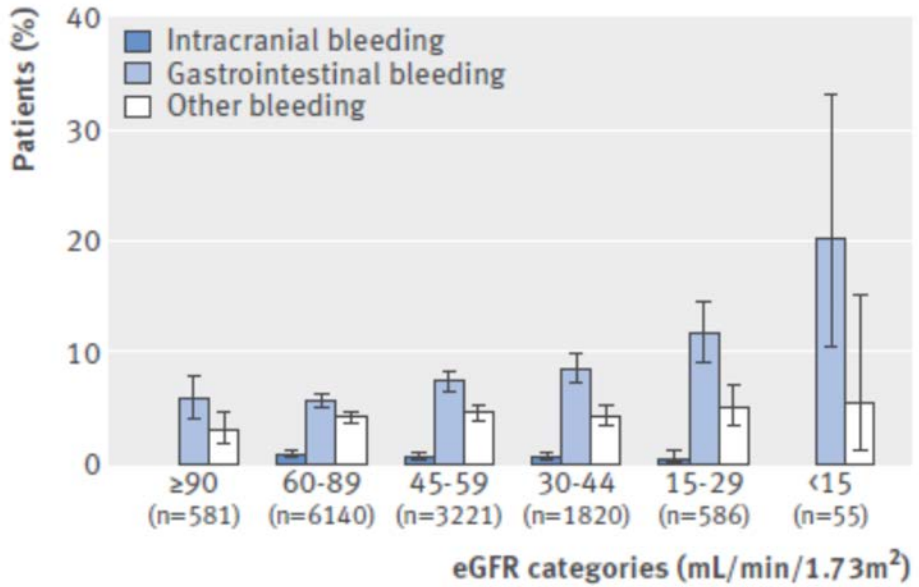


Fig 2 | Percentage of cohort experiencing a major bleeding episode, by type (intracranial bleeding, gastrointestinal bleeding, or other bleeding) and estimated glomerular filtration rate (eGFR). Results represent percentage of cohort experiencing major bleeding over the duration of study follow-up; bars represent 95% confidence intervals

During 2.1 years 1443 (11.6%) experienced a major bleeding episode. Adjusted rates of MBE increased at lower eGFR categories. Across all eGFR categories, rates of MBE were higher during the first 30 days of warfarin treatment

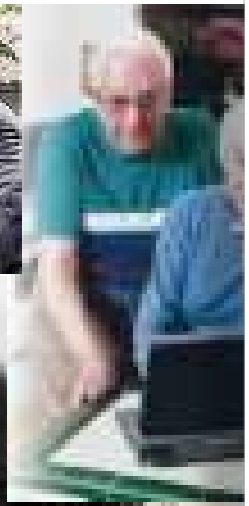
Europace
doi:10.1093/europace/euv309

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
Fraction renally excreted of absorbed dose	80%	27%[52–55]	50%[36]	35%
Bioavailability	3–7%	50%	62%[51]	66% without food Almost 100% with food
Fraction renally excreted of administered dose	4%	12–29%[52–55]	37%[36]	33%
Approved for CrCl ≥ …	≥30 mL/min	≥15 mL/min	≥15 mL/min	≥15 mL/min
Dosing recommendation	CrCl ≥ 50 mL/min: no adjustment (i.e. 150 mg BID)	Serum creatinine ≥1.5 mg/dL: no adjustment (i.e. 5 mg BID)[a]	CrCl ≥ 50 mL/min: no adjustment (i.e. 60 mg OD)[b]	CrCl ≥ 50 mL/min: no adjustment (i.e. 20 mg OD)
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	30 mg OD when CrCl 15–49 mL/min	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

Quali sono le ragioni per non scoagulare un paziente anziano con FA?










Minima spettanza di vita (<1 anno) e/o oncosi sganciata e/o severa dipendenza funzionale-allettamento e/o severo deterioramento cognitivo

A mio avviso, il mancato uso della TAO in queste condizioni non costituisce underuse o malpractice

GERIATRIA, periodo 2010-2013: **TAO** alla dimissione in pazienti con FA: **39.1%**

GERIATRIA, periodo settembre 2014-settembre 2015: **TAO** alla dimissione in pazienti con FA: **53.4%**

Sebbene la «**comodità**» di una terapia anticoagulante che non richiede un monitoraggio clinico non sia di per se stessa una ragione sufficiente per modificare le proprie attitudini cliniche, è certamente positivo vedere che, grazie ad essa, una **maggior percentuale di pazienti anziani con FA riesce attualmente ad accedere a terapie considerate lo standard** di efficacia per questa malattia. Soltanto **l'osservazione attenta e continua** di questi pazienti nel tempo potrà fornirci informazioni utili **sull'efficacia e la sicurezza** degli anticoagulanti nei pazienti con FA più anziani e clinicamente problematici. I dati preliminari del mondo clinico reale con i nuovi anticoagulanti sembrano al momento incoraggianti.

Patient outcomes using the European label for dabigatran

A post-hoc analysis from the RE-LY database

Gregory Y. H. Lip[1]; Andreas Clemens[2]; Herbert Noack[3]; Jorge Ferreira[4]; Stuart J. Connolly[5]; Salim Yusuf[5]

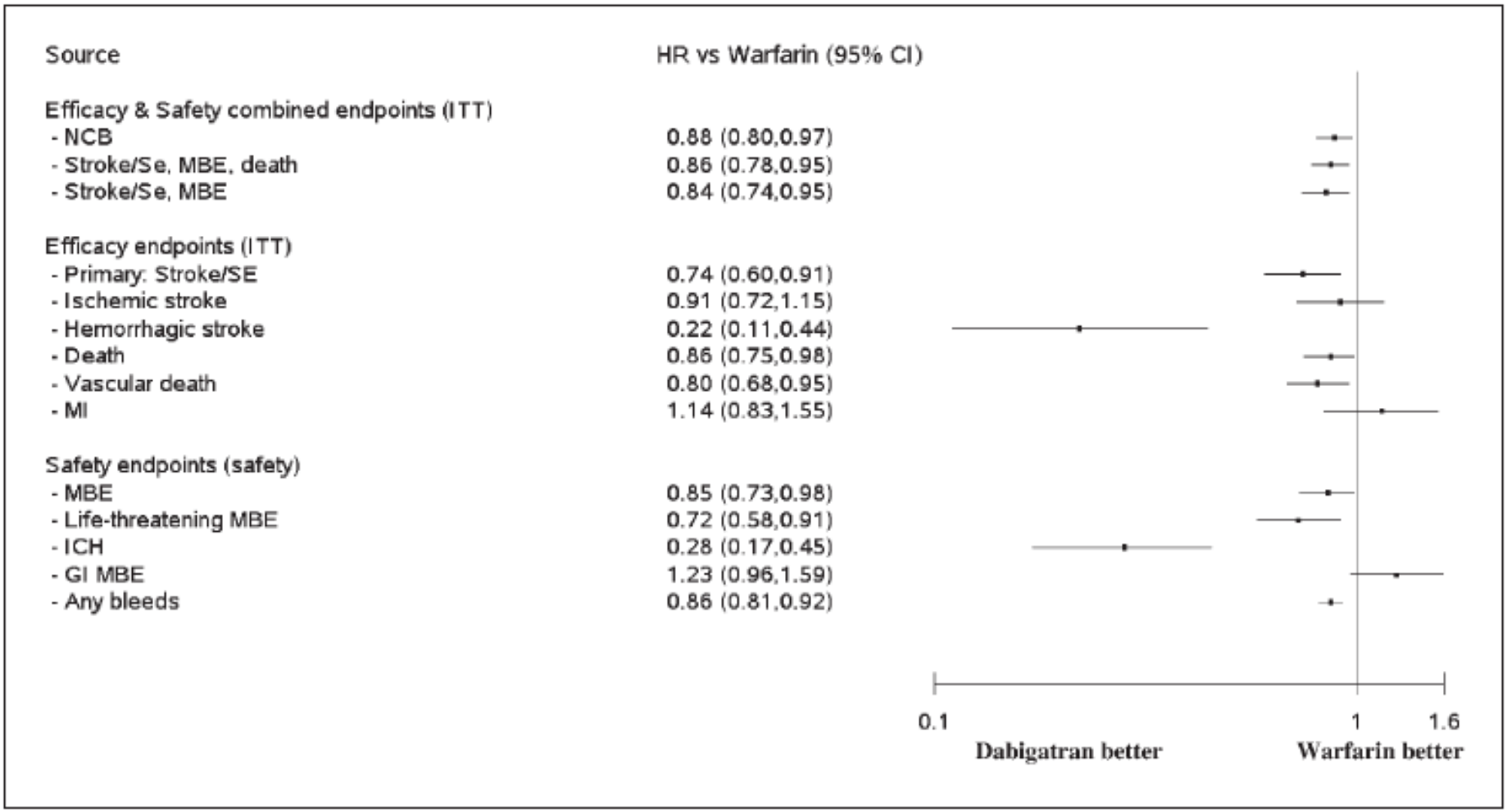


Figure 2: Summary of results for dabigatran EU label simulated dabigatran treatment group compared to warfarin. CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; ICH, intracranial haemorrhage; ITT, intention to treat analysis; MBE, major bleeding event; MI, myocardial infarction; NCB, net clinical benefit; safety, safety set analysis; SE, systemic embolism.

Thromb Haemost. 2014 May 5;111(5):933-42.

Outcomes and Safety of Antithrombotic Treatment in Patients Aged 80 Years or Older With Nonvalvular Atrial Fibrillation

(Am J Cardiol 2011;107:1489–1493)

Studio osservazionale su 269 pazienti ultraottantenni (età media 83) con FANV trattati in accordo con le raccomandazioni delle società scientifiche (61% in TAO)

Event rate

Variable	Anticoagulation		p Value
	Yes (n = 164)	No (n = 105)	
Transient ischemic attack	5 (1.08)	8 (3.32)	0.07
Nonfatal stroke	1 (0.22)	4 (1.66)	0.05
Fatal stroke	0 (0)	6 (2.49)	<0.01
Peripheral embolism	1 (0.22)	2 (0.83)	0.27
All embolic events	7 (1.52)	20 (8.30)	<0.01
Nonfatal bleeding	9 (1.95)	3 (1.25)	0.76
Fatal bleeding	5 (1.08)	0 (0)	0.17
All severe bleeding	14 (3.03)	3 (1.25)	0.14
All embolic and hemorrhagic events	21 (4.55)	23 (9.55)	<0.01
Cardiovascular death	8 (1.67)	15 (5.86)	<0.01
Other causes of death	24 (5)	13 (5.08)	0.99
All-cause death	32 (6.67)	28 (10.94)	0.04

In conclusion, OAC according to the scientific societies' recommendations is effective and safe in daily clinical practice, even in patients aged ≥80 years. (Am J Cardiol 2011;107:1489–1493)

THE AMERICAN JOURNAL of MEDICINE®

Risk of Falls and Major Bleeds in Patients on Oral Anticoagulation Therapy

The American Journal of Medicine (2012) 125, 773-778

Studio prospettico su 515 pazienti dimessi in TAO; 308 pazienti (59.8%) ad alto rischio di cadute; outcome: tempo al primo sanguinamento maggiore; follow-up: 12 mesi

Rischio di sanguinamento maggiore non significativamente aumentato nei pazienti ad alto rischio di cadute rispetto agli altri (8,0 vs 6,8/100/anno, p=.64). Il rischio di sanguinamento maggiore è risultato indipendentemente associato al sesso femminile ed alla politerapia ma non all'alto rischio di cadute. Solo 3 sanguinamenti maggiori conseguenza diretta di caduta (0.6/100/anno)

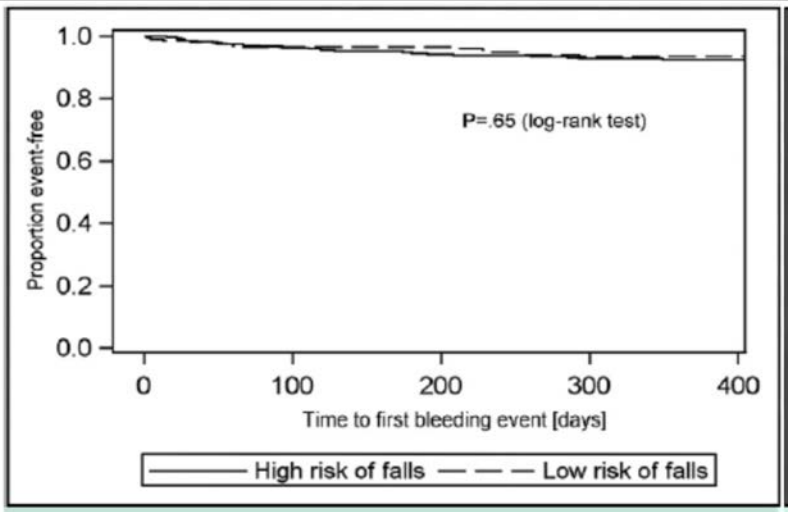


Figure Unadjusted time to first major bleeding event curves according to risk of falls (n = 515).

- The incidence rate of major bleeding in patients on oral anticoagulants is low overall, and fall-related bleeds are rare in these patients.
- A high falls risk is not statistically significantly associated with a risk of major bleeds (hazard ratio 1.09; 95% confidence interval, 0.54-2.21), suggesting that being at risk of falls is not a valid reason to avoid oral anticoagulants in medical patients.

Vascular Medicine

(*Circulation*. 2011;124:824-829.)

Bleeding Risk in Very Old Patients on Vitamin K Antagonist Treatment

Results of a Prospective Collaborative Study on Elderly Patients Followed by Italian Centres for Anticoagulation

Daniela Poli, MD; Emilia Antonucci, MD; Sophie Testa, MD; Alberto Tosetto, MD; Walter Ageno, MD; Gualtiero Palareti, MD; for the Italian Federation of Anticoagulation Clinics (FCSA)

4093 pazienti >= 80 anni (media 84) ***che hanno iniziato TAO per FA e TEP; follow-up su 9603 pazienti/anno; TTR 62%; osservati 179 sanguinamenti maggiori (1.87/100 pazienti/anno)***

Table 3. Bleeding Events

Total, n (rate per 100 patient-y)	179 (1.87)
Mean age (range), y	85 (80–94)
Time elapsed from start of VKA treatment, mo	14.2 (1–109)
Median INR (range)	2.5 (1.0–13.8)
Bleeds with INR of 2.0–3.0, n (%)	147 (82.1)
Patients <85 y, n (rate per 100 patient-y)	115 (1.71)
Patients ≥85 y, n (rate per 100 patient-y)	64 (2.22)*

EBM e MONDO CLINICO REALE

- Uso di **STATINE** post-SCA: >80%
- Uso di **BETA-BLOCCANTI** post-IMA: >80%
- Uso di **ACE-I/SARTANI** in HFrEF: >80%
- Uso di **ANTIAGGREGANTI** in prevenzione secondaria: >90%
- Uso di **ANTIPERTENSIVI** in ipertensione arteriosa: 90-100%
- Uso di **ANTICOAGULANTI** in anziani (ospedalizzati) con FA: 40-60%

(*Circulation*. 2015;132:1252-1260.

Comparison of the Short-Term Risk of Bleeding and Arterial Thromboembolic Events in Nonvalvular Atrial Fibrillation Patients Newly Treated With Dabigatran or Rivaroxaban Versus Vitamin K Antagonists

A French Nationwide Propensity-Matched Cohort Study

Background—The safety and effectiveness of non–vitamin K antagonist (VKA) oral anticoagulants, dabigatran or rivaroxaban, were compared with VKA in anticoagulant-naive patients with nonvalvular atrial fibrillation during the early phase of anticoagulant therapy.

Methods and Results—With the use of the French medico-administrative databases (SNIIRAM and PMSI), this nationwide cohort study included patients with nonvalvular atrial fibrillation who initiated dabigatran or rivaroxaban between July and November 2012 or VKA between July and November 2011. Patients presenting a contraindication to oral anticoagulants were excluded. Dabigatran and rivaroxaban new users were matched to VKA new users by the use of 1:2 matching on the propensity score. Patients were followed for up to 90 days until outcome, death, loss to follow-up, or December 31 of the inclusion year. Hazard ratios of hospitalizations for bleeding and arterial thromboembolic events were estimated in an intent-to-treat analysis using Cox regression models. The population was composed of 19713 VKA, 8443 dabigatran, and 4651 rivaroxaban new users. All dabigatran- and rivaroxaban-treated patients were matched to 16014 and 9301 VKA-treated patients, respectively. Among dabigatran-, rivaroxaban-, and their VKA-matched–treated patients, 55 and 122 and 31 and 68 bleeding events and 33 and 58 and 12 and 28 arterial thromboembolic events were observed during follow-up, respectively. After matching, no statistically significant difference in bleeding (hazard ratio, 0.88; 95% confidence interval, 0.64–1.21) or thromboembolic (hazard ratio, 1.10; 95% confidence interval, 0.72–1.69) risk was observed between dabigatran and VKA new users. Bleeding (hazard ratio, 0.98; 95% confidence interval, 0.64–1.51) and ischemic (hazard ratio, 0.93; 95% confidence interval, 0.47–1.85) risks were comparable between rivaroxaban and VKA new users.

Conclusions—In this propensity-matched cohort study, our findings suggest that physicians should exercise caution when initiating either non-VKA oral anticoagulants or VKA in patients with nonvalvular atrial fibrillation.

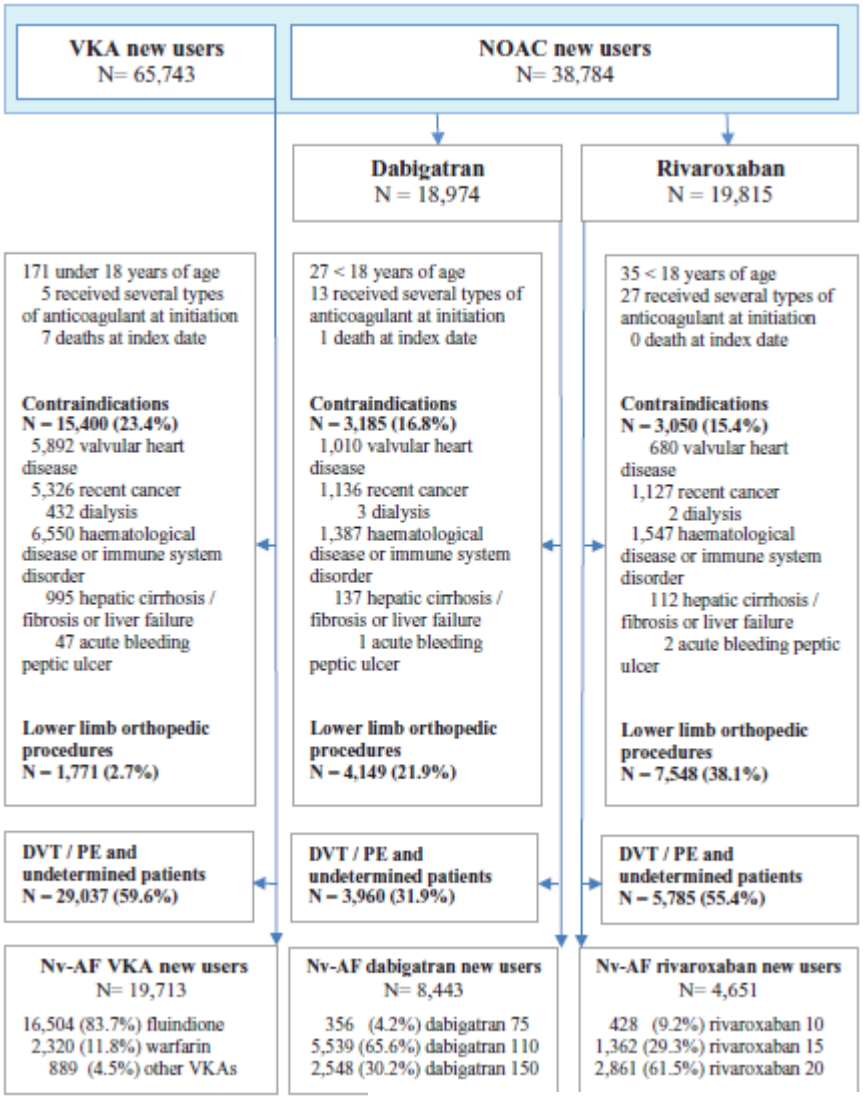


Table 1. Dabigatran- and VKA-Matched–Treated Patients: Baseline Characteristics According to Treatment Group After Propensity Score Matching

	Dabigatran All Doses n=8443	VKA D-All Doses Matched n=16014		Dabigatran 75–110 mg n=5895	VKA D75–110 Matched n=11571		Dabigatran 150 mg n=2548	VKA D150 Matched n=5096	
Characteristics	n (%)*	n (%)*	Stand Diff†	n (%)*	n (%)*	Stand Diff†	n (%)*	n (%)*	Stand Diff†
Female	3903 (46)	7430 (46)	0.011	3048 (52)	5912 (51)	0.011	855 (34)	1711 (34)	0.000
Age, mean (SD)	74.0 (11.3)	73.9 (11.2)	0.008	77.4 (10.1)	76.9 (10.0)	0.035	66.1 (10.0)	66.5 (10.3)	0.040

Table 3. Events, Person-Years at Risk, and Crude Event Rates Among NOAC New Users and Matched VKA New Users

	Dabigatran All Doses	VKA D-All Doses Matched	Dabigatran 75–110	VKA D75–110 Matched	Dabigatran 150	VKA D75–110 Matched	Rivaroxaban All Doses	VKA R-All Doses Matched	Rivaroxaban 10–15	VKA R10–15 Matched	Rivaroxaban 20	VKA R20 Matched
Bleeding events	55/1684/3.3	122/3292/3.7	43/1195/3.6	101/2368/4.3	12/489/2.5	30/1054/2.8	31/848/3.7	68/1913/3.6	16/328/4.9	36/734/4.9	15/520/2.9	40/1178/3.4
Bleeding events or death	158/1684/9.4	341/3292/10.4	137/1195/11.5	295/2368/12.5	21/489/4.3	56/1054/5.3	75/848/8.8	161/1913/8.4	43/328/13.1	89/734/12.1	32/520/6.2	80/1178/6.8
Ischemic stroke or SE	33/1687/2	58/3300/1.8	28/1198/2.3	37/2376/1.6	5/490/1	14/1056/1.3	12/851/1.4	28/1918/1.5	6/329/1.8	13/736/1.8	6/521/1.2	15/1182/1.3
Ischemic stroke or SE or death	136/1687/8.1	280/3300/8.5	121/1198/10.1	243/2376/10.2	15/490/3.1	43/1056/4.1	60/851/7.1	125/1918/6.5	37/329/11.2	66/736/9	23/521/4.4	56/1182/4.7

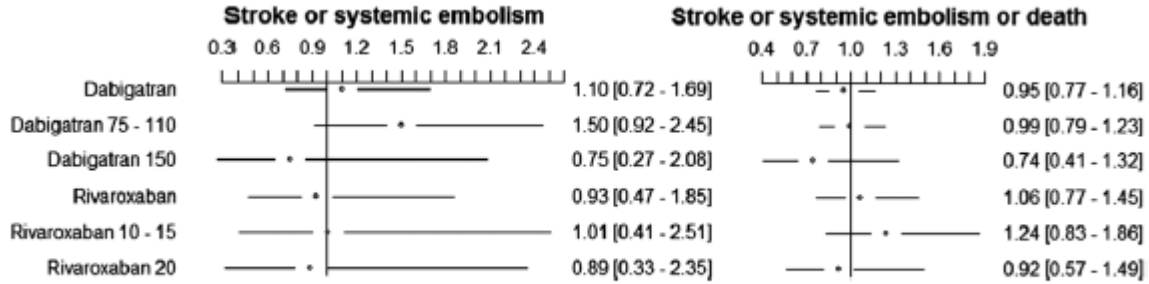


Figure 3. Hazard ratios for stroke or systemic embolism according to type and dose of NOAC. All figures are hazard ratios and their 95% confidence interval. NOAC indicates non–vitamin K antagonist oral anticoagulants.

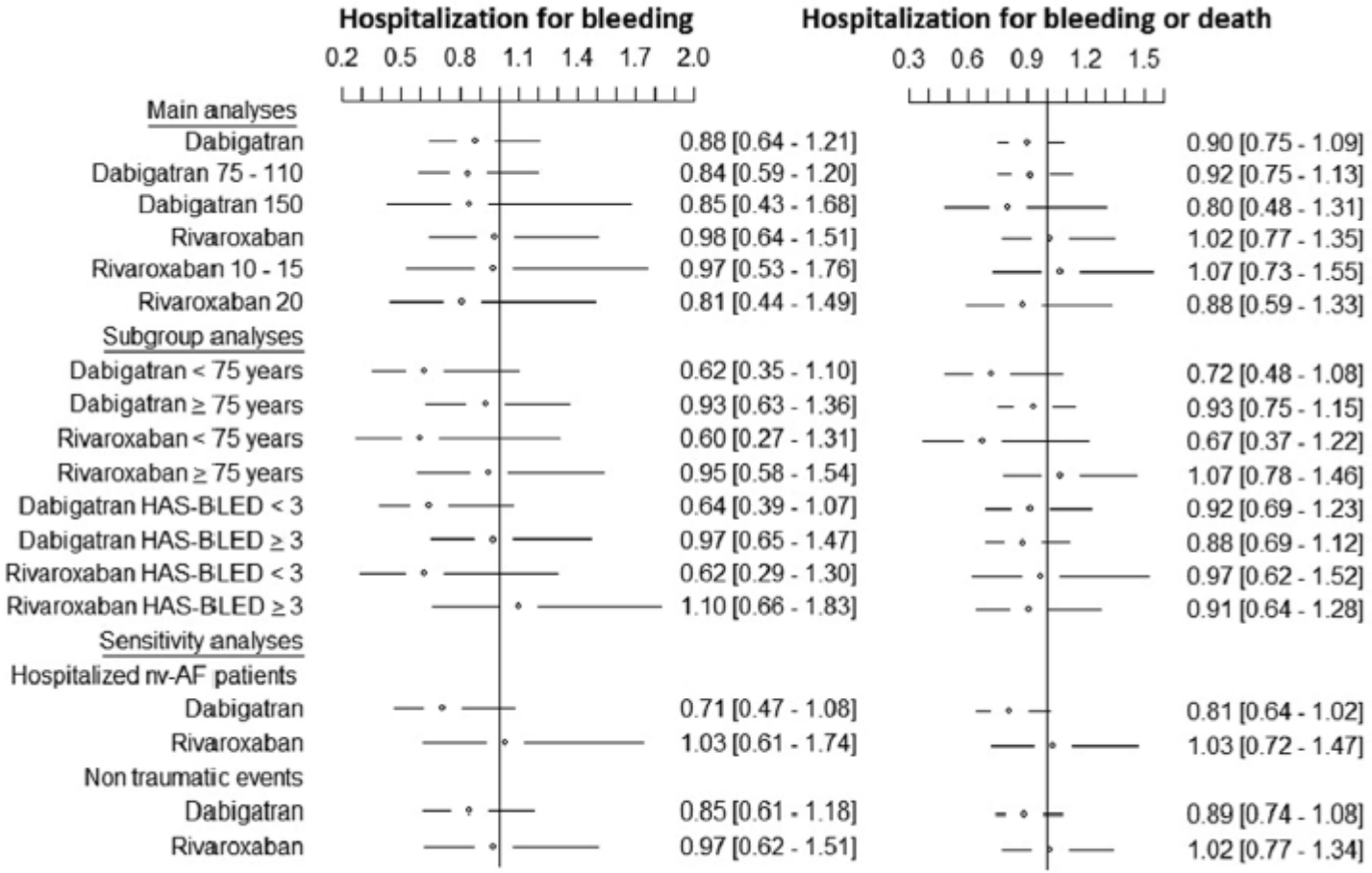


Figure 2. Hazard ratios for hospitalized bleeding events according to type and dose of NOAC. All figures are hazard ratios and their 95% confidence interval. NOAC indicates non–vitamin K antagonist oral anticoagulants; and nv-AF, nonvalvular atrial fibrillation.

In conclusion, in this study based on medico-administrative data, no statistically significant difference was observed between NOACs, dabigatran or rivaroxaban, and VKAs in terms of the risk of bleeding or arterial thromboembolic events during the early phase of anticoagulant therapy in nv-AF patients. The same level of clinical caution is therefore required when initiating either NOACs or VKAs. Similar analyses should be extended to other NOACs such as apixaban, and observational studies should now focus on NOAC head-to-head comparison in a noninferiority design.

Recommendations for prevention of thromboembolism in non-valvular AF—NOACs			
When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[a] … is recommended.	I	B	2, 28, 65, 107
Where OAC is recommended, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[a] … should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit.	IIa	A	3, 4, 70, 82
Where dabigatran is prescribed, a dose of 150 mg b.i.d. should be considered for most patients in preference to 110 mg b.i.d., with the latter dose recommended in: • elderly patients, age ≥ 80 • concomitant use of interacting drugs (e.g. verapamil) • high bleeding risk (HAS-BLED score ≥3) • moderate renal impairment (CrCl 30–49 mL/min).	IIa	B	85, 96
Where rivaroxaban is being considered, a dose of 20 mg o.d. should be considered for most patients in preference to 15 mg o.d., with the latter dose recommended in: • high bleeding risk (HAS-BLED score ≥3) • moderate renal impairment (CrCl 30–49 mL/min).	IIa	C	3, 108
Baseline and subsequent regular assessment of renal function (by CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2–3 times per year.	IIa	B	85
NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min).	III	A	3, 24, 70

(*Stroke*. 2011;42:2866-2871.)

The Unrecognized Psychosocial Factors Contributing to Bleeding Risk in Warfarin Therapy

Table 2. Multivariate Analysis of Psychosocial Risk Factors Adjusting for Demographic, Clinical, and Medication Risk Factors

	Individual Multivariate Models*			A Single Multivariate Model Including All Psychosocial Factors†		
Variables	OR	95% CI	*P*	OR	95% CI	*P*
Shortened test of Functional Health Literacy in Adults—marginal/inadequate functional health literacy (score <67)	4.8	2.9–7.8	<0.0001	3.4	2.0–5.8	<0.0001
Geriatric Depression Scale–5 Item—possible depression (score ≥2)	3.1	1.9–4.8	<0.0001	2.1	1.3–3.5	0.003
Montreal Orientation Cognition Assessment—mild cognitive impairment (score <26)	2.7	1.6–4.3	<0.0001	1.5	0.9–2.6	0.1
11-item Duke Social Support Index—self-reported social isolation (score ≤80)	2.4	1.5–4.0	<0.0001	1.3	0.8–2.3	0.3

Conclusions

We found cognition, mood, and health literacy strongly influenced the stability of INR levels in patients on warfarin. The presence of multiple psychosocial factors produced a 3.4-fold increase in bleeding risk as measured by the surrogate of an elevated INR. This is comparable to the risk conveyed by other well-established demographic, clinical, and medication-related factors.

The association between kidney function and major bleeding in older adults with atrial fibrillation starting warfarin treatment: population based observational study

Cite this as: *BMJ* 2015;350:h246

OBJECTIVE

To determine rates of major bleeding by level of kidney function for older adults with atrial fibrillation starting warfarin.

DESIGN

Retrospective cohort study.

SETTING

Community based, using province wide laboratory and administrative data in Alberta, Canada.

PARTICIPANTS

12 403 adults aged 66 years or more, with atrial fibrillation who started warfarin treatment between 1 May 2003 and 31 March 2010 and had a measure of kidney function at baseline. Kidney function was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation and participants were categorised based on estimated glomerular filtration rate (eGFR): ≥ 90, 60–89, 45–59, 30–44, 15–29, < 15 ml/min/1.73m^2. We excluded participants with end stage renal disease (dialysis or renal transplant) at baseline.

MAIN OUTCOME MEASURES

Admission to hospital or visit to an emergency department for major bleeding (intracranial, upper and lower gastrointestinal, or other).

RESULTS

Of 12 403 participants, 45% had an eGFR < 60 ml/min/1.73m^2. Overall, 1443 (11.6%) experienced a major bleeding episode over a median follow-up of 2.1 (interquartile range: 1.0–3.8) years. During the first 30 days of warfarin treatment, unadjusted and adjusted rates of major bleeding were higher at lower eGFR (P for trend < 0.001 and 0.001, respectively). Adjusted bleeding rates per 100 person years were 63.4 (95% confidence interval 24.9 to 161.6) in participants with eGFR < 15 ml/min/1.73m^2 compared with 6.1 (1.9 to 19.4) among those with eGFR > 90 ml/min/1.73m^2 (adjusted incidence rate ratio 10.3, 95% confidence interval 2.3 to 45.5). Similar associations were observed at more than 30 days after starting warfarin, although the magnitude of the increase in rates across eGFR categories was attenuated. Across all eGFR categories, adjusted rates of major bleeding were consistently higher during the first 30 days of warfarin treatment compared with the remainder of follow-up. Increases in major bleeding rates were largely due to gastrointestinal bleeding (3.5-fold greater in eGFR < 15 ml/min/1.73m^2 compared with ≥ 90 ml/min/1.73m^2). Intracranial bleeding was not increased with worsening kidney function.

Table 1 | Baseline characteristics of participants with atrial fibrillation who started warfarin treatment, by estimated glomerular filtration rate (eGFR). Values are numbers (percentages) unless stated otherwise

	eGFR (mL/min/1.73m²)					
Characteristics	≥ 90 (n = 581)	60–89 (n = 6140)	45–59 (n = 3221)	30–44 (n = 1820)	15–29 (n = 586)	< 15 (n = 55)
Women	240 (41.3)	2797 (45.5)	1689 (52.4)	1022 (56.1)	342 (58.3)	24 (43.6)
Mean (SD) age (years)	70.7 (4.5)	76.4 (6.5)	78.8 (6.7)	80.6 (6.9)	81.8 (6.8)	80.0 (7.9)
First Nations status	8 (1.3)	45 (0.7)	17 (0.5)	10 (0.5)	2 (0.3)	0 (0)
Region of residence:						
Rural	129 (22.2)	1277 (20.8)	661 (20.5)	371 (20.3)	116 (19.8)	7 (12.7)
Urban	448 (77.1)	4817 (78.4)	2531 (78.5)	1426 (78.3)	463 (79.0)	45 (81.8)
Unknown	4 (0.6)	46 (0.7)	29 (0.9)	23 (1.2)	7 (1.1)	3 (5.4)
Income fifths:						
1 (lowest)	124 (21.3)	1143 (18.6)	637 (19.7)	362 (19.8)	105 (17.9)	10 (18.1)
2	107 (18.4)	1310 (21.3)	673 (20.8)	417 (22.9)	129 (22)	10 (18.1)
3	107 (18.4)	1221 (19.8)	635 (19.7)	364 (20)	116 (19.8)	12 (21.8)
4	115 (19.7)	1080 (17.5)	582 (18)	303 (16.6)	115 (19.6)	6 (10.9)
5 (highest)	109 (18.7)	1202 (19.5)	583 (18.1)	300 (16.4)	100 (17)	14 (25.4)
Unknown	19 (3.2)	184 (3)	111 (3.4)	74 (4)	21 (3.5)	3 (5.4)
Hypertension	96 (16.5)	1025 (16.6)	495 (15.3)	218 (11.9)	47 (8.0)	6 (10.9)
Diabetes	47 (8.0)	451 (7.3)	200 (6.2)	121 (6.6)	42 (7.1)	3 (5.4)
Cancer	118 (20.3)	1100 (17.9)	550 (17.1)	305 (16.7)	116 (19.8)	9 (16.3)
Cerebrovascular disease	92 (15.8)	1150 (18.7)	713 (22.1)	387 (21.26)	143 (24.4)	12 (21.8)
Congestive heart failure	181 (31.1)	2013 (32.7)	1367 (42.4)	1026 (56.3)	380 (64.8)	35 (63.6)
Chronic obstructive pulmonary disease	238 (40.9)	1980 (32.2)	1059 (32.8)	680 (37.3)	232 (39.5)	29 (52.73)
Dementia	28 (4.8)	355 (5.7)	208 (6.4)	177 (9.7)	71 (12.1)	4 (7.2)
Metastatic solid tumour	30 (5.1)	184 (3)	69 (2.1)	49 (2.6)	19 (3.2)	2 (3.6)
Myocardial infarction	130 (22.3)	1346 (21.9)	820 (25.4)	600 (32.9)	200 (34.1)	24 (43.6)
Mild liver disease	14 (2.4)	80 (1.3)	47 (1.4)	43 (2.3)	10 (1.7)	1 (1.8)
Moderate or severe liver disease	1 (0.1)	15 (0.2)	7 (0.2)	4 (0.2)	3 (0.5)	1 (1.8)
Paralysis	18 (3.1)	198 (3.2)	89 (2.7)	50 (2.7)	11 (1.8)	1 (1.8)
Peptic ulcer disease	38 (6.5)	263 (4.2)	139 (4.3)	93 (5.1)	36 (6.1)	2 (3.6)
Peripheral vascular disease	72 (12.3)	654 (10.6)	384 (11.9)	281 (15.4)	114 (19.4)	14 (25.4)
Rheumatic disease	42 (7.2)	247 (4)	124 (3.8)	95 (5.2)	26 (4.4)	2 (3.6)
Previous admission to hospital for bleeding	31 (5.3)	237 (3.8)	164 (5.0)	107 (5.8)	43 (7.3)	7 (12.7)
CHA_2DS_2-VASc score:*						
1	110 (18.9)	728 (11.8)	183 (5.6)	63 (3.4)	11 (1.8)	2 (3.6)
≥ 2	471 (81.0)	5412 (88.1)	3038 (94.3)	1757 (96.5)	575 (98.1)	53 (96.3)
Modified HAS-BLED score:†						
1	318 (54.7)	3276 (53.3)	1539 (47.7)	697 (38.3)	120 (20.4)	4 (7.2)
2	201 (34.6)	2220 (36.1)	1196 (37.1)	730 (40.1)	282 (48.1)	29 (52.7)
3	51 (8.7)	563 (9.1)	403 (12.5)	325 (17.8)	141 (24.0)	16 (29.0)
4	11 (1.8)	74 (1.2)	78 (2.4)	57 (3.1)	39 (6.6)	4 (7.2)
5	0 (0)	7 (0.1)	5 (0.1)	11 (0.6)	4 (0.6)	2 (3.6)

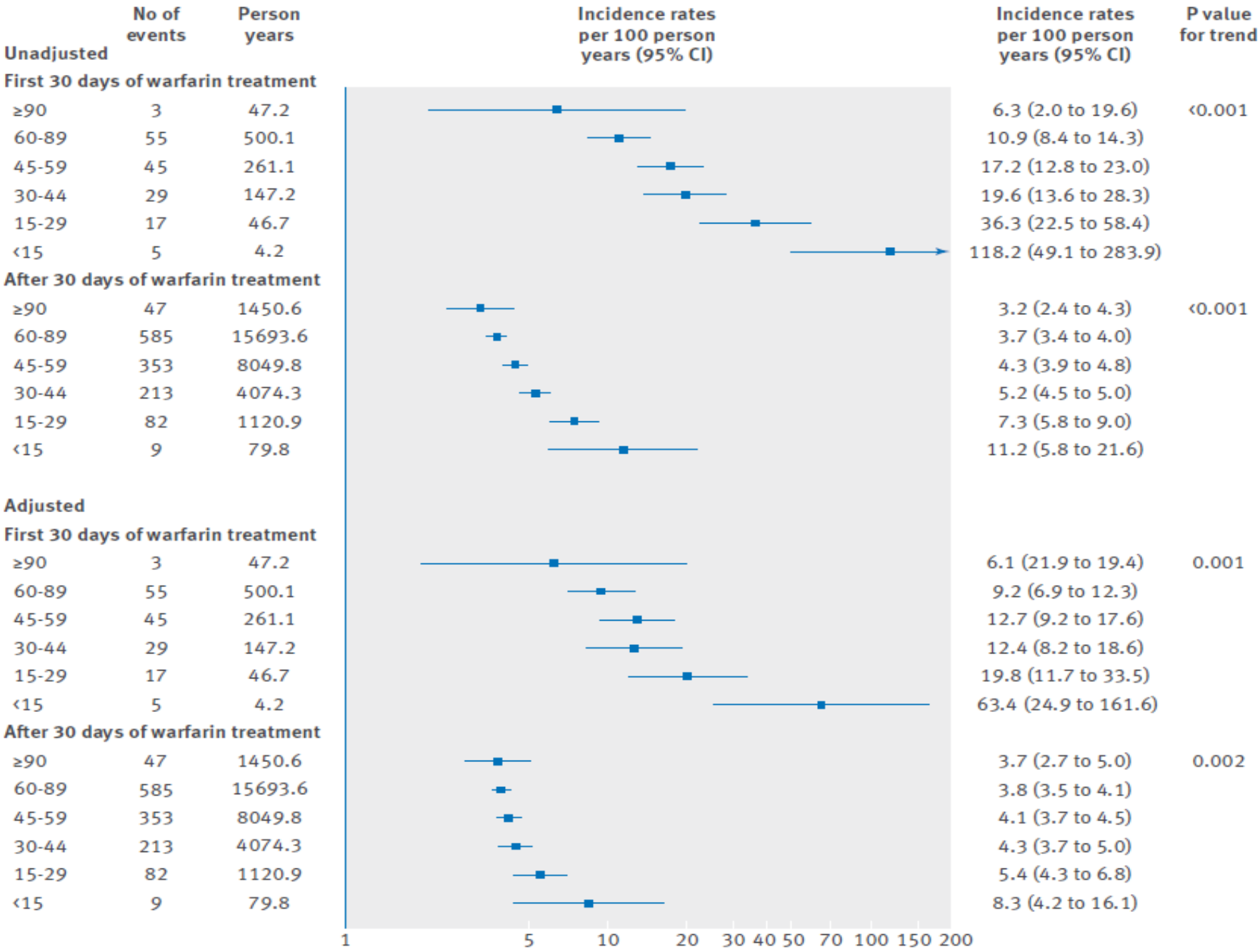


Fig 1 | Unadjusted and adjusted (see footnote to table 2 for adjustment factors) rates per 100 person years of major bleeding by estimated glomerular filtration rate (eGFR) categories

Table 2 | Incidence rate ratios of major bleeding by estimated glomerular filtration rate (eGFR) in first 30 days of warfarin treatment and after 30 days of treatment

eGFR categories by treatment duration	Incidence rate ratio* (95% CI)	P value
First 30 days of warfarin treatment		
eGFR (mL/min/1.73m²):		
≥ 90 (reference)	1.00	—
60–89	1.50 (0.46 to 4.88)	0.492
45–59	2.07 (0.63 to 6.83)	0.228
30–44	2.02 (0.59 to 6.84)	0.257
15–29	3.22 (0.90 to 11.45)	0.070
< 15	10.33 (2.34 to 45.54)	0.002
After 30 days of warfarin treatment		
eGFR (mL/min/1.73m²):		
≥ 90 (reference)	1.00	—
60–89	1.03 (0.76 to 1.39)	0.833
45–59	1.10 (0.80 to 1.50)	0.539
30–44	1.16 (0.84 to 1.62)	0.352
15–29	1.45 (1.00 to 2.11)	0.049
< 15	2.22 (1.07 to 4.59)	0.031

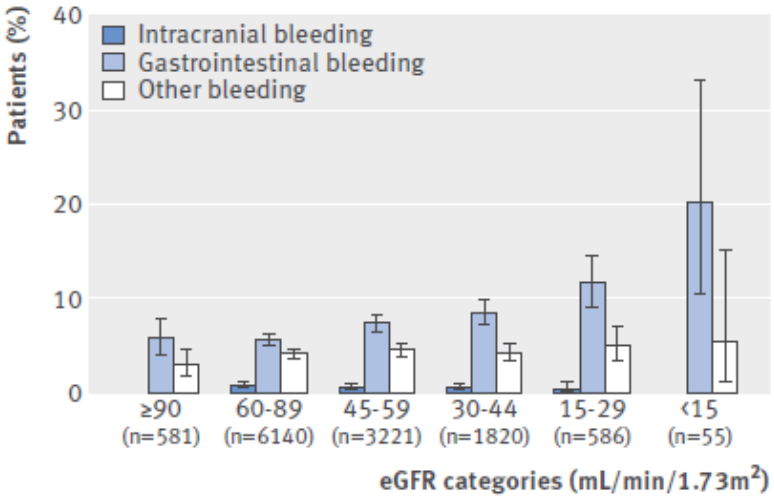


Fig 2 | Percentage of cohort experiencing a major bleeding episode, by type (intracranial bleeding, gastrointestinal bleeding, or other bleeding) and estimated glomerular filtration rate (eGFR). Results represent percentage of cohort experiencing major bleeding over the duration of study follow-up; bars represent 95% confidence intervals

CONCLUSIONS

Reduced kidney function was associated with an increased risk of major bleeding among older adults with atrial fibrillation starting warfarin; excess risks from reduced eGFR were most pronounced during the first 30 days of treatment. Our results support the need for careful consideration of the bleeding risk relative to kidney function when assessing the risk-benefit ratio of warfarin treatment in people with chronic kidney disease and atrial fibrillation, particularly in the first 30 days of treatment.

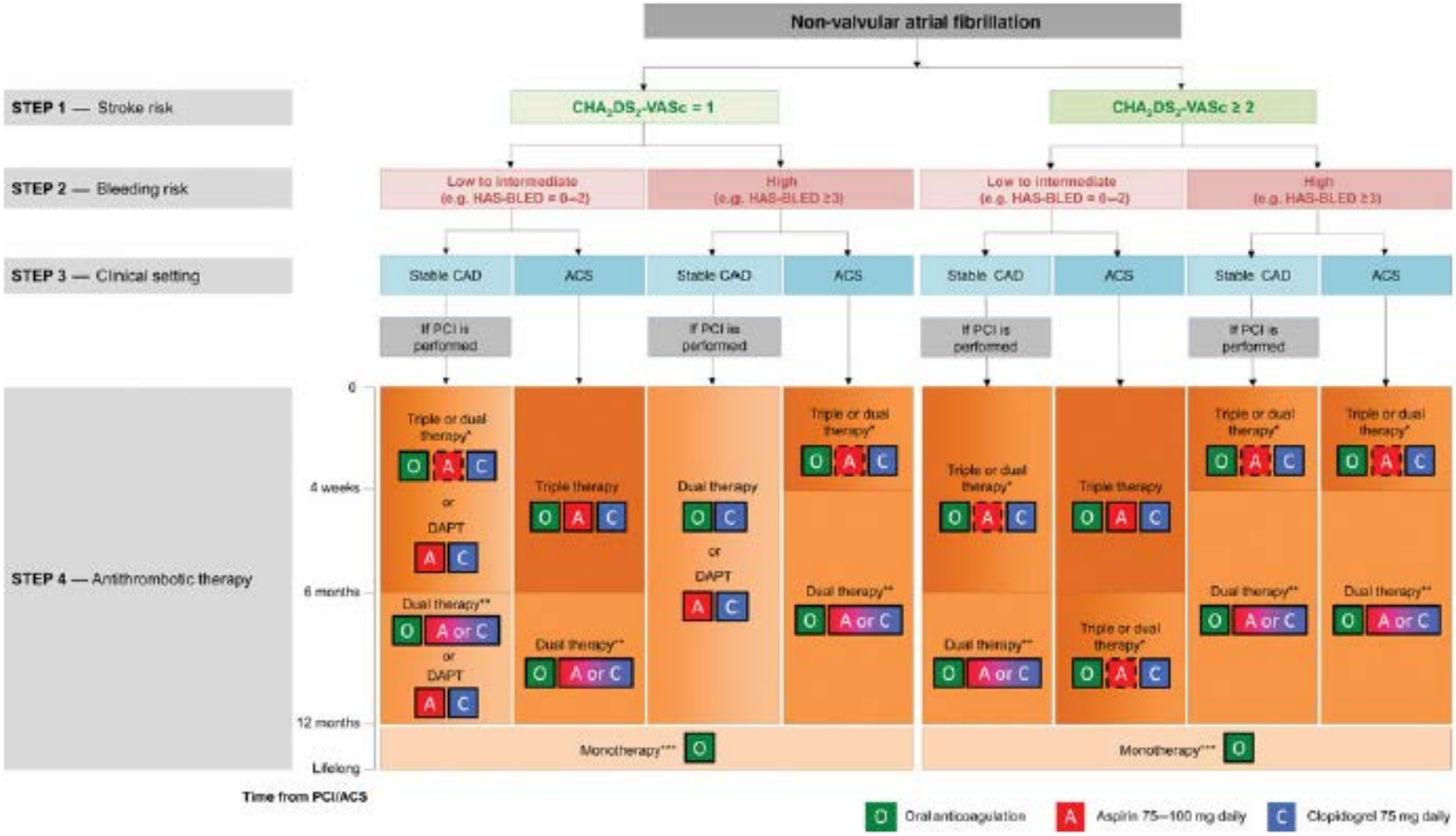
WHAT IS ALREADY KNOWN ON THIS TOPIC

Although the risk of bleeding is considerably higher among patients who require dialysis than in the general population, there are limited data about the bleeding risk associated with warfarin treatment in people with different stages of chronic kidney disease

WHAT THIS STUDY ADDS

Reduced kidney function, in patients not requiring dialysis, was associated with an increased risk of major bleeding among older adults with atrial fibrillation starting warfarin

The risk of warfarin treatment should be weighed against the potential benefits based on the presence of comorbidities and bleeding risk among patients with reduced kidney function (for example, < 60 ml/min/1.73m^2), and particularly in those with very reduced kidney function and during the first 30 days of treatment


Non-valvular atrial fibrillation
STEP 1 — Stroke risk
CHA2DS2-VASc = 1
CHA2DS2-VASc ≥ 2
STEP 2 — Bleeding risk
Low to intermediate (e.g. HAS-BLED = 0–2)
High (e.g. HAS-BLED ≥3)
Low to intermediate (e.g. HAS-BLED = 0–2)
High (e.g. HAS-BLED ≥3)
STEP 3 — Clinical setting
Stable CAD
ACS
Stable CAD
ACS
Stable CAD
ACS
Stable CAD
ACS
If PCI is performed
If PCI is performed
If PCI is performed
If PCI is performed
STEP 4 — Antithrombotic therapy
0
4 weeks
6 months
12 months
Lifelong
Time from PCI/ACS
Triple or dual therapy*
O A C
or
DAPT
A C
Dual therapy**
O A or C
or
DAPT
A C
Triple therapy
O A C
Dual therapy**
O A or C
Dual therapy
O C
or
DAPT
A C
Triple or dual therapy*
O A C
Dual therapy**
O A or C
Triple or dual therapy*
O A C
Dual therapy**
O A or C
Triple therapy
O A C
Triple or dual therapy*
O A C
Triple or dual therapy*
O A C
Dual therapy**
O A or C
Triple or dual therapy*
O A C
Dual therapy**
O A or C
Monotherapy***
O
Monotherapy***
O
O Oral anticoagulation
A Aspirin 75–100 mg daily
C Clopidogrel 75 mg daily

The NEW ENGLAND JOURNAL of MEDICINE

Dabigatran and Postmarketing Reports of Bleeding

Mary Ross Southworth, Pharm.D., Marsha E. Reichman, Ph.D., and Ellis F. Unger, M.D.

Intracranial and Gastrointestinal Bl… …m the Mini-Sentinel Distributed

Analysis	Warfarin	
	No. of Events	Incidence *no. of events/ 100,000 days at risk*
Gastrointestinal hemorrhage		
Analysis with required diagnosis of atrial fibrillation	160	3.5
Sensitivity analysis without required diagnosis of atrial fibrillation	338	3.1
Intracranial hemorrhage		
Analysis with required diagnosis of atrial fibrillation	109	2.4
Sensitivity analysis without required diagnosis of atrial fibrillation	204	1.9

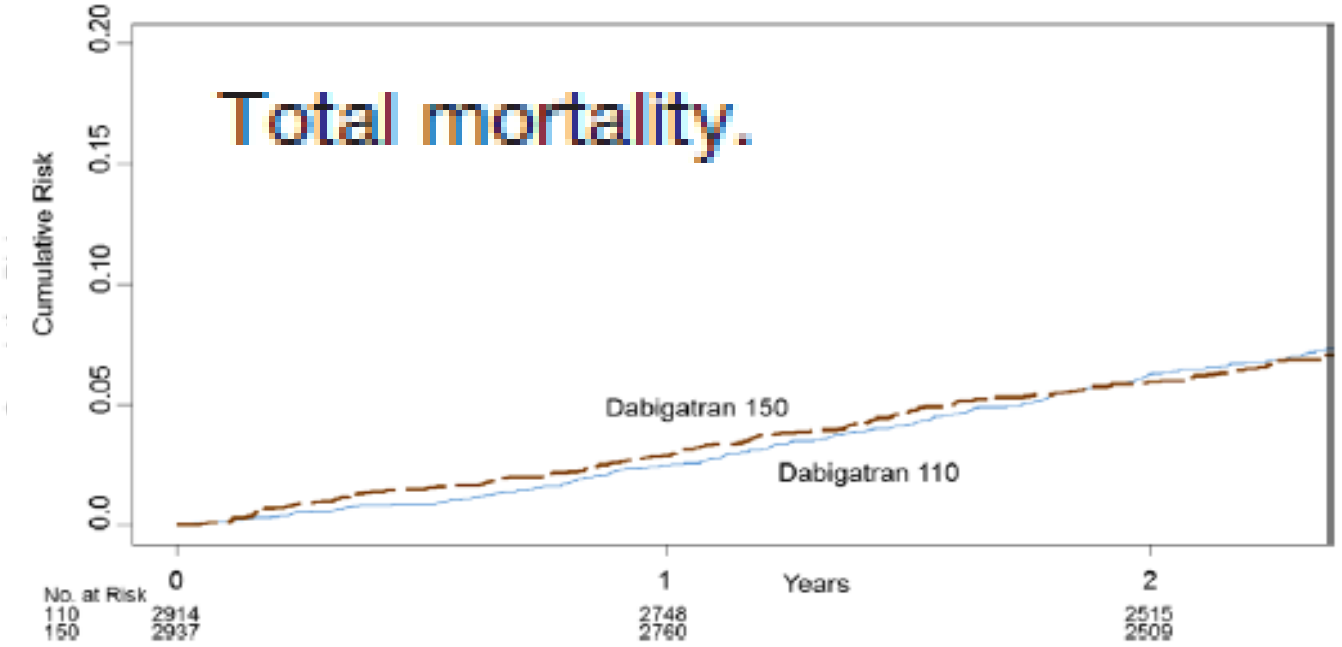
Although some have noted the lack of an available reversal agent for the anticoagulant effects of dabigatran as an important limitation of its use, data from RE-LY are reassuring with respect to bleeding. We believe that dabigatran provides an important health benefit when used as directed. Further analysis of the Mini-Sentinel and other claims databases is ongoing, as is routine postmarketing surveillance through FAERS.

Stroke

238 Circulation July 16, 2013

The Long-Term Multicenter Observational Study of Dabigatran Treatment in Patients With Atrial Fibrillation (RELY-ABLE) Study

5851 patients randomly assigned to Dabigatran in RE-LY were eligible for the Long-Term Multicenter Extension of Dabigatran Treatment in Patients with AF (RELY-ABLE); mean follow-up 28 months



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

Definition of 'non-valvular atrial fibrillation' and eligibility for non-vitamin K antagonist oral anticoagulants

Non-valvular AF refers to AF that occurs in the absence of mechanical prosthetic heart valves and in the absence of moderate to severe mitral stenosis (usually of rheumatic origin)

Atrial fibrillation in patients with biological valves or after valve repair constitute a grey area, and were included in some trials on 'non-valvular AF'. They may be suitable NOAC candidates, as will be discussed below.

Table 1 Valvular indications and contraindications for NOAC therapy in AF patients

	Eligible	Contra-indicated
Mechanical prosthetic valve		✓
Moderate to severe mitral stenosis (usually of rheumatic origin)		✓
Mild to moderate other native valvular disease	✓	
Severe aortic stenosis	✓ Limited data. Most will undergo intervention	
Bioprosthetic valve[a]	✓ (except for the first 3 months post-operatively)	
Mitral valve repair[a]	✓ (except for the first 3–6 months post-operatively)	
PTAV and TAVI	✓ (but no prospective data; may require combination with single or double antiplatelets: consider bleeding risk)	
Hypertrophic cardiomyopathy	✓ (but no prospective data)	

Table 2 Non-VKA oral anticoagulant drugs, approved for prevention of systemic embolism or stroke in patients with non-valvular AF

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Action	Direct thrombin inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor
Dose	150 mg BID 110 mg BID[a,b] (75 mg BID)[b]	5 mg BID 2.5 mg BID[a]	60 mg OD[c] 30 mg OD[a]	20 mg OD 15 mg OD[a]
Phase III clinical trial	RE-LY[25]	ARISTOTLE[26] AVERROES[27]	ENGAGE-AF[28]	ROCKET-AF[29]

Atrial Fibrillation
Oral Anticoagulation Card

for non-vitamin K antagonist anticoagulants (NOACs)

Patient name: **DOB:**

Patient address:

Oral anticoagulant, dosing, timing, with or without food:

Treatment indication and start date:

? Concomitant antiplatelet(s): type, indication, start & stop dates:

Name and address of physician, coordinating NOAC treatment:

Telephone number of coordinating physician or clinic:

EUROPEAN Heart Rhythm ASSOCIATION

EUROPEAN SOCIETY OF CARDIOLOGY®

More info:
www.NOACforAF.eu
www.noacforaf.eu

Planned or unplanned visits

Date (or date range):	Site (GP; clinic; cardiologist; pharmacist; ...):	To do / findings:

Recommended follow-up

(see EHRA at **www.NOACforAF.eu** for information & practical advice)

Check each visit: 1. Adherence (pt. should bring remaining meds)?
2. Thrombo-embolic events?
3. Bleeding events?
4. Other side effects?
5. Co-medications and over-the-counter drugs.

Blood sampling:
- **monitoring of anticoagulation level is not required!**
- **yearly:** Hb, renal and liver function
- **if >75-80 y (especially if dabigatran or edoxaban), or frail:** 6-monthly renal function
- **if CrCl ≤ 60 ml/min:** recheck interval in months = CrCl / 10
- **if intercurrent condition that may have impact:** renal and/or liver function

Date	Serum creatinine	Creatinine clearance	Hemo-globin	Liver tests

Important patient instructions

Take your drug exactly as prescribed (once or twice daily).
No drug is no protection!

Never stop your medicine without consulting your physician.

Never add any other medication without consulting your physician, not even short-term painkillers that you can get without prescription.

Alert your dentist, surgeon or other physician before an intervention.

Concomitant medication

Name:	Dose:

Emergency information

Standard tests do not quantitatively reflect level of anticoagulation!

Name & telephone of patient relative to contact:

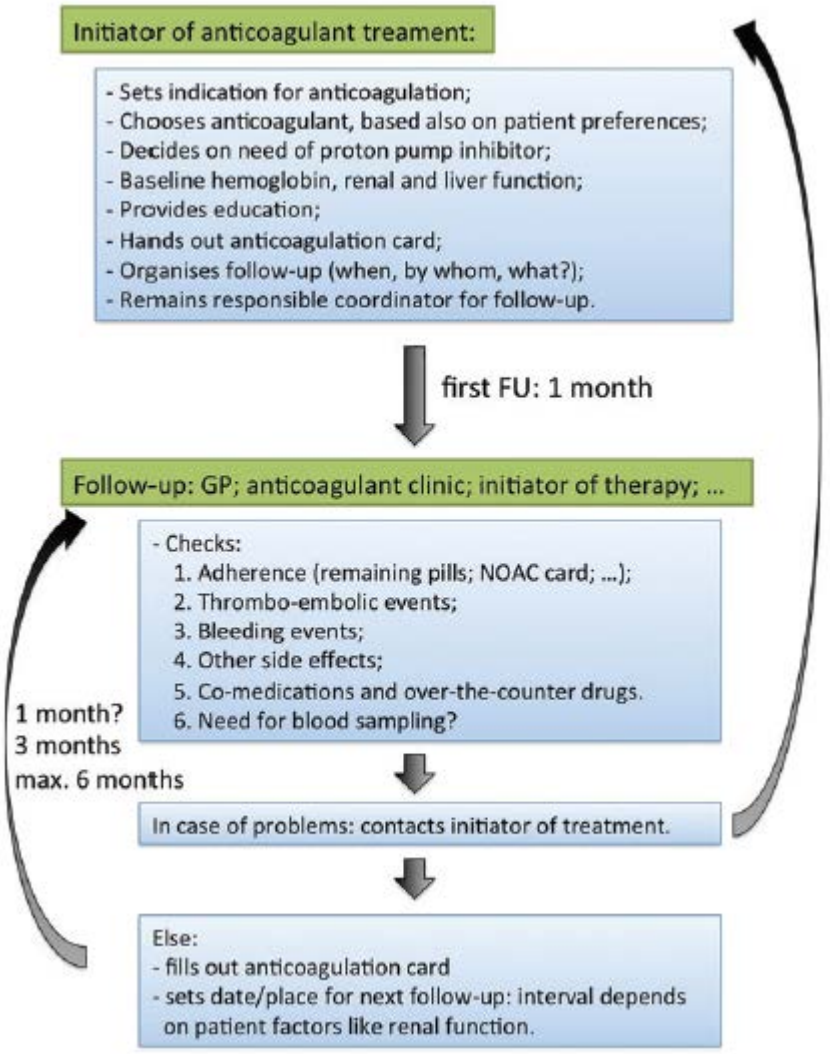


Table 3 Checklist during follow-up contacts of AF patients on anticoagulation[a]

	Interval	Comments
1. Adherence	Each visit	Instruct patient to bring NOAC card and remaining medication: make note and assess average adherence Re-educate on importance of strict intake schedule Inform about adherence aids (special boxes, smartphone applications, etc.)
2. Thromboembolism	Each visit	Systemic circulation (TIA, stroke, and peripheral) Pulmonary circulation
3. Bleeding	Each visit	'Nuisance' bleeding: preventive measures possible? (PPI, haemorrhoidectomy, etc.). Motivate patient to diligently continue anticoagulation Bleeding with impact on quality of life or with risk prevention possible? Need for revision of anticoagulation indication or dose?
4. Other side effects	Each visit	Carefully assess relation with NOAC: decide for continuation (and motivate), temporary cessation (with bridging), or change of anticoagulant drug
5. Co-medications	Each visit	Prescription drugs; over-the-counter drugs, especially aspirin and NSAID (see 'Drug–drug interactions and pharmacokinetics of non-vitamin K antagonist anticoagulants' section) Careful interval history: also temporary use can be risky!
6. Blood sampling	Yearly 6-monthly x-monthly On indication	Haemoglobin, renal and liver function ≥75–80 years (especially if on dabigatran or edoxaban), or frail[b] If renal function ≤60 mL/min: recheck interval = CrCl/10 If intercurrent condition that may impact renal or hepatic function

Table 4 **Interpretation of coagulation assays in patients treated with different NOACs and range of values at trough (P5–P95) in patients with normal function and the standard dose, as measured in clinical trials**

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Plasma peak level	2 h after ingestion	1–4 h after ingestion	1–2 h after ingestion	2–4 h after ingestion
Plasma trough level	12 h after ingestion	12 h after ingestion	24 h after ingestion[36]	24 h after ingestion
PT	Cannot be used	Can be prolonged but no known relation with bleeding risk[37]	Prolonged but variable and no known relation with bleeding risk[36,38] Range at trough: NA	Prolonged but no known relation with bleeding risk Range at trough: 12–26 s with Neoplastin Plus as reagent; local calibration required
INR	Cannot be used	Cannot be used	Cannot be used	Cannot be used
aPTT	Range (P10–P90) at trough D150: 40.3–76.4 s Range (P10–P90) at trough D110: 37.5–60.9 s At trough: >2× ULN may be associated with excess bleeding risk[39]	Cannot be used	Prolonged but no known relation with bleeding risk[36]	Cannot be used
dTT	No data from RE-LY trial on range of values At trough: >200 ng/mL ≥65 s: may be associated with excess bleeding risk[39,40]	Cannot be used	Cannot be used[41]	Cannot be used
Anti-FXa chromogenic assays	Not applicable	Quantitative; no data on threshold values for bleeding or thrombosis Range at trough: 1.4–4.8 IU/mL	Quantitative[41]; no data on threshold values for bleeding or thrombosis Range at trough: 0.05–3.57 IU/mL[a]	Quantitative; no data on threshold values for bleeding or thrombosis Range at trough: 6–239 μg/L
ECT	Range (P10–P90) at trough D150: 44.3–103 Range (P10–P90) at trough D110: 40.4–84.6 At trough: ≥3× ULN: excess bleeding risk[39]	Not affected[37]	Not affected	Not affected
ACT	Rather flat dose response. No investigation on its use. Limited utility	No data. Cannot be used	No data. Cannot be used	Minor effect. Cannot be used

Routine monitoring is not required. Assays need cautious interpretation for clinical use in special circumstances, as discussed in the text.
PT, prothrombin time; aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time; INR, international normalized ratio; ACT: activated clotting time; ULN, upper limit of normal.
[a](P2.5–P97.5) for edoxaban.

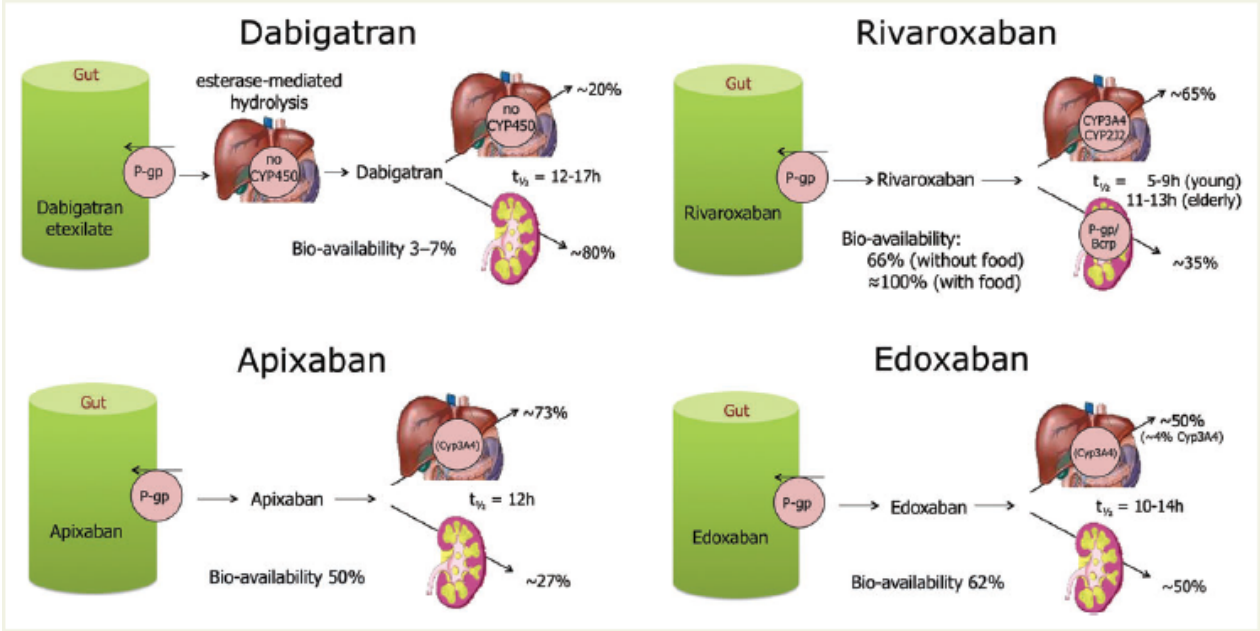


Figure 3 Absorption and metabolism of the different new anticoagulant drugs. There are interaction possibilities at the level of absorption or first transformation, and at the level of metabilization and excretion. See also *Table 5* for the size of the interactions based on these schemes.

Table 5 Absorption and metabolism of the different NOACs

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Bioavailability	3 to 7%	50%	62%[51]	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 'Patients with chronic kidney disease' section)[a]	20%/80%	73%/27%[52–55]	50%/50%[36,51,56]	65%/35%
Liver metabolism: CYP3A4 involved	No	Yes (elimination, moderate contribution)[57]	Minimal (<4% of elimination)	Yes (elimination, moderate contribution)
Absorption with food	No effect	No effect	6–22% more; minimal effect on exposure[58]	+39% more[59]
Intake with food recommended?	No	No	No	Mandatory
Absorption with H2B/PPI	−12 to 30% (not clinically relevant)[60–62]	No effect[63]	No effect	No effect[59,64]
Asian ethnicity	+25%[62]	No effect	No effect[58]	No effect
GI tolerability	Dyspepsia 5 to 10%	No problem	No problem	No problem
Elimination half-life	12 to 17 h[61]	12 h	10–14 h[51,65]	5–9 h (young) 11–13 h (elderly)

Table 6 Effect on NOAC plasma levels (AUC) from drug–drug interactions and clinical factors, and recommendations towards NOAC dose adaptation

	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Antiarrhythmic drugs:					
Amiodarone	moderate P-gp competition	+12-60%[58]	No PK data[$]	+40%[63, 64, 244]	Minor effect[$] (use with caution if CrCl <50 ml/min)
Digoxin	P-gp competition	No effect[245]	No data yet	No effect	No effect[246, 247]
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[58]	+40%[60]	No data yet	Minor effect[*] (use with caution if CrCl 15-50 ml/min)
Dronedarone	P-gp competition and CYP3A4 inhibition	+70-100% (US: 2 x 75 mg if CrCl 30-50 ml/min)	No PK or PD data: caution	+85% (Reduce NOAC dose by 50%)	Moderate effect[*] but no PK or PD data: caution and try to avoid
Quinidine	P-gp competition	+53%[248 & SMPC]	No data yet	+77%[240, 249, 250] (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12-180%[58] (reduce NOAC dose and take simultaneously)	No PK data	+53% (SR)[64, 249] (No dose reduction required by label)	Minor effect[$$] (use with caution if CrCl 15-50 ml/min)

Europace
doi:10.1093/europace/euv309

Table 6 Effect on NOAC plasma levels (AUC) from drug–drug interactions and clinical factors, and recommendations towards NOAC dose adaptation

Other cardiovascular drugs					
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%[251]	No data yet	No effect	No effect[252]
Antibiotics					
Clarithromycin; Erythromycin	moderate P-gp competition and CYP3A4 inhibition	+15-20%	No data yet	+90%[64] (reduce NOAC dose by 50%)	+30-54%[42, 247]
Rifampicin***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	**minus 66%[253]**	**minus 54%[238]**	avoid if possible: minus 35%, but with compensatory increase of active metabolites[243]	**Up to minus 50%**
Antiviral drugs					
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase[SmPC]	No data yet	Up to +153%[247]

Table 6 Effect on NOAC plasma levels (AUC) from drug–drug interactions and clinical factors, and recommendations towards NOAC dose adaptation

Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[247]
Itraconazole; Ketoconazole; Posaconazole; Voriconazole;	potent P-gp and BCRP competition; CYP3A4 inhibition	+140-150% (US: 2 x 75 mg if CrCl 30-50 ml/min)	+100%[60]	+87-95%[64] (reduce NOAC dose by 50%)	Up to +160%[247]
Immunosuppressive					
Cyclosporin; Tacrolimus	P-gp competition	Not recommended	No data yet	+73%	Extent of increase unknown
Antiphlogistics					
Naproxen	P-gp competition	No data yet	+55%[254]	No effect (but pharmacodynamically increased bleeding time)	No data yet
Antacids					
H2B; PPI; Al-Mg-hydroxide	GI absorption	Minus 12-30%[45, 53, 58]	No effect[55]	No effect	No effect[241, 242]
Others					
Carbamazepine***; Phenobarbital***; Phenytoin***; St John's wort***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	**minus 66%[253]**	**minus 54%[SmPC]**	minus 35%	**Up to minus 50%**

Table 6 Effect on NOAC plasma levels (AUC) from drug–drug interactions and clinical factors, and recommendations towards NOAC dose adaptation

Other factors:					
Age ≥ 80 years	Increased plasma level		#	%	
Age ≥75 years	Increased plasma level			%	
Weight ≤ 60 kg	Increased plasma level		#		
Renal function	Increased plasma level	See Table 8			
Other increased bleeding risk		Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history of GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3			

Table 7 Estimated drug half lives and effect on AUC NOAC plasma concentrations in different stages of CKD compared to healthy controls

	Dabigatran	**Apixaban**	**Edoxaban**	**Rivaroxaban**
CrCl >80 mL/min	12–17 h[61]	12 h	10–14 h[51,65]	5–9 h (young) 11–13 h (elderly)
CrCl 50–80 mL/min CKD Stages I and II	~17 h[122] (+50%)	~14.6 h[123] (+16%)	~8.6 h[124] (+32%)[SmPC]	~8.7 h[125] (+44%)[126]
CrCl 30–50 mL/min CKD Stage III	~19 h[122] (+320%)	~17.6 h (+29%)	~9.4 h[124] (+74%)[SmPC]	~9.0 h (+52%)[126]
CrCl 15–30 mL/min CKD Stage IV	~28 h[122] (+530%)	~17.3 h (+44%)	~16.9 h[124] (72%)[SmPC]	~9.5 h (+64%)[126]
CrCl ≤ 15 mL/min CKD Stage V; off-dialysis	No data	– (+36%)	– (+93%)[SmPC]	– (+70%)[127]

CKD, chronic kidney disease; CrCl, creatinine clearance.

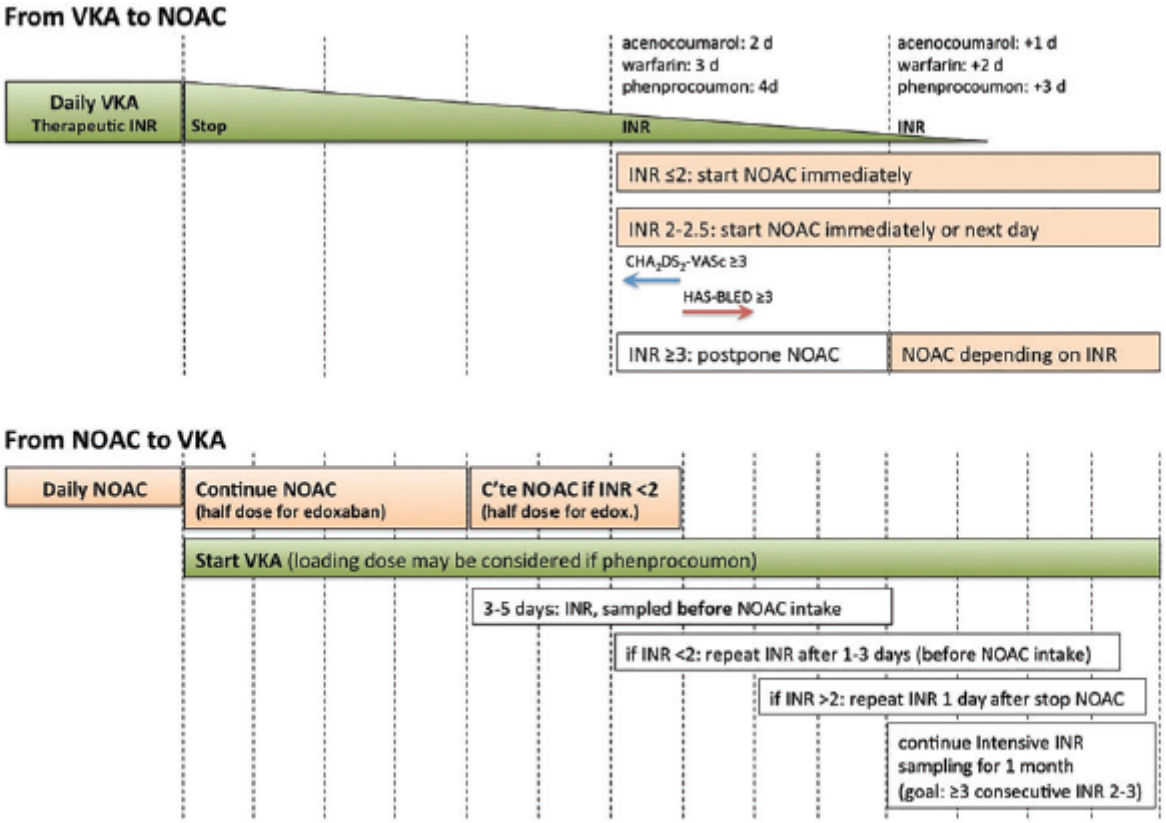


Figure 4 Switching between VKAs and non-VKA oral anticoagulants and vice versa.

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
Fraction renally excreted of absorbed dose	80%	27%[52–55]	50%[36]	35%
Bioavailability	3–7%	50%	62%[51]	66% without food Almost 100% with food
Fraction renally excreted of administered dose	4%	12–29%[52–55]	37%[36]	33%
Approved for CrCl ≥ …	≥30 mL/min	≥15 mL/min	≥15 mL/min	≥15 mL/min
Dosing recommendation	CrCl ≥ 50 mL/min: no adjustment (i.e. 150 mg BID)	Serum creatinine ≥1.5 mg/dL: no adjustment (i.e. 5 mg BID)[a]	CrCl ≥ 50 mL/min: no adjustment (i.e. 60 mg OD)[b]	CrCl ≥ 50 mL/min: no adjustment (i.e. 20 mg OD)
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	30 mg OD when CrCl 15–49 mL/min	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

Table 9 Possible measures to take in case of bleeding

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, and rivaroxaban)
None life-threatening bleeding	Inquire last intake + dosing regimen. Estimate normalization of haemostasis: Normal renal function: 12–24 h CrCl 50–80 mL/min: 24–36 h CrCl 30–50 mL/min: 36–48 h CrCl < 30 mL/min: ≥48 h Maintain diuresis. Local haemostatic measures. Fluid replacement (colloids if needed). RBC substitution if necessary. Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy). Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans. Desmopressin can be considered in special cases (coagulopathy or thrombopathy) Consider dialysis (preliminary evidence: −65% after 4 h).[122] Charcoal haemoperfusion can be considered (based on preclinical data)	Inquire last intake + dosing regimen. Normalisation of haemostasis: 12–24 h Local haemostatic measures. Fluid replacement (colloids if needed). RBC substitution if necessary. Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy). Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans. Desmopressin can be considered in special cases (coagulopathy or thrombopathy)
Life-threatening bleeding	All of the above. Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) (but no clinical ata). Activated PCC 50 U/kg; max 200 U/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available. Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence) Idarucizumab 5 g IV (approval waiting)	All of the above. Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) (healthy volunteer data) Activated PCC 50 U/kg; max 200 U/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available. Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence)

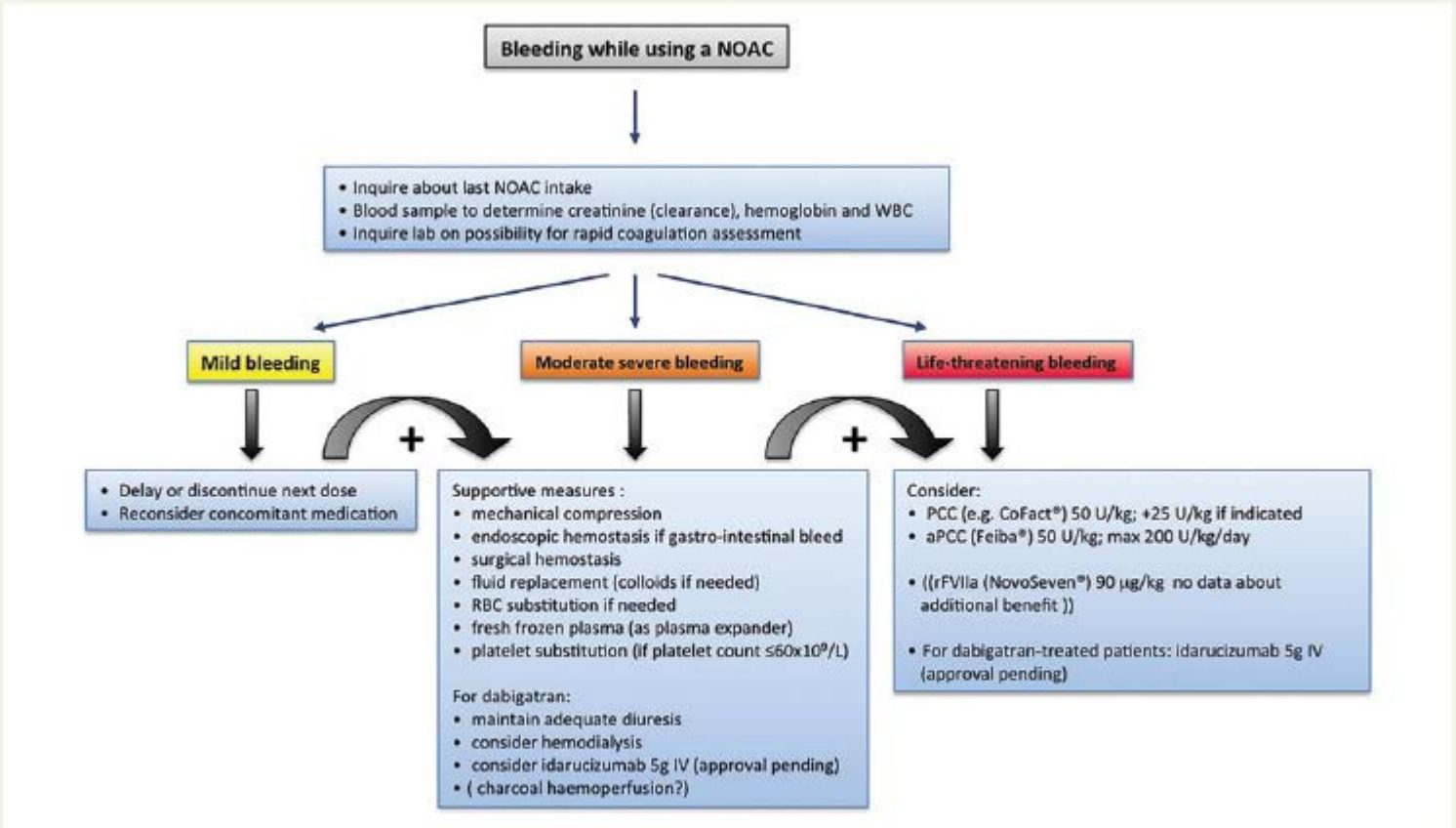
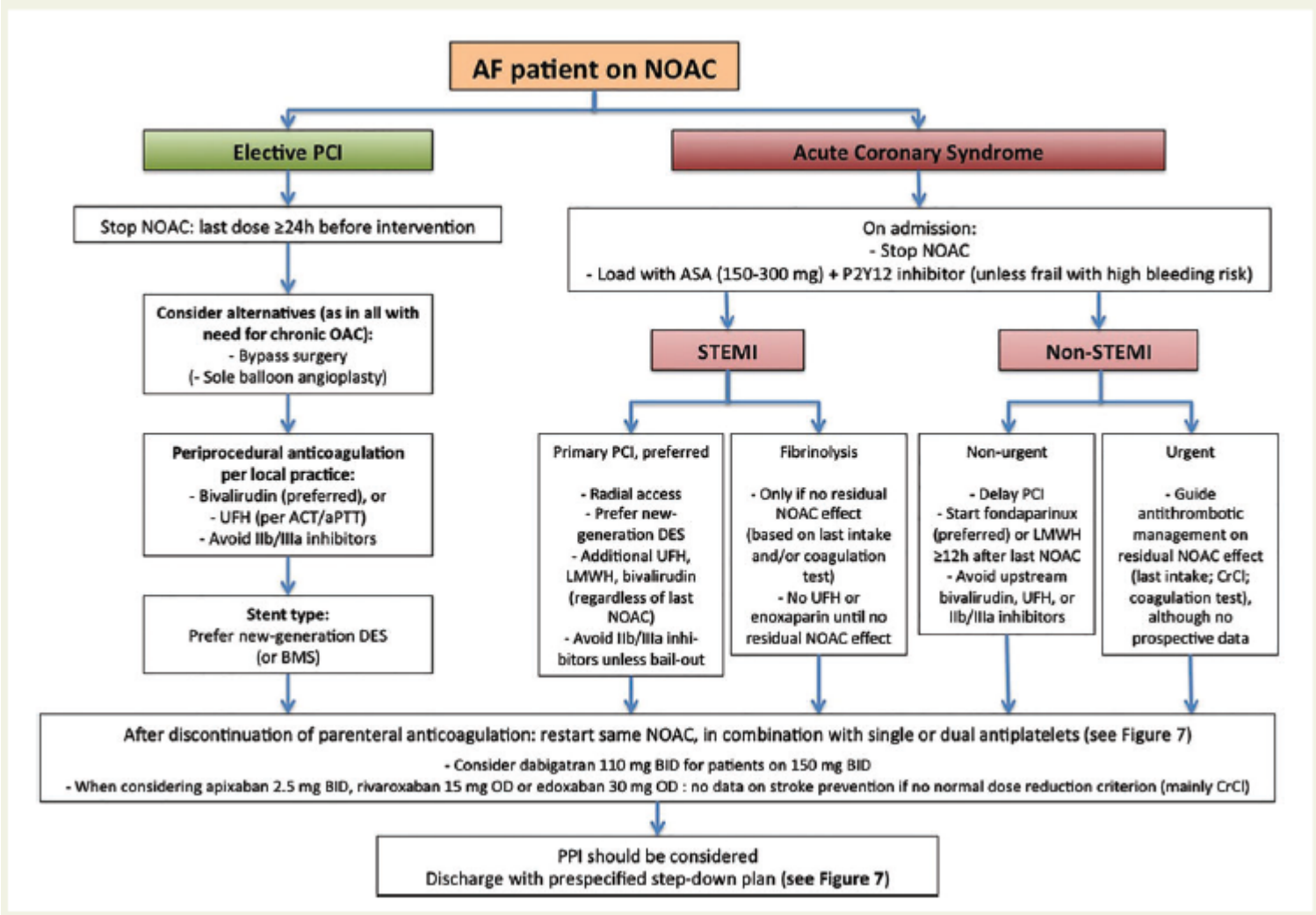


Figure 5 Management of bleeding in patients taking NOACs. Possible therapeutic measures in case of minor or severe bleeding in patients on NOAC therapy. Based on van Ryn et al.[39]

Table 10 Last intake of drug before elective surgical intervention

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

There is no need for bridging with LMWH/UFH


AF patient on NOAC
Elective PCI
Acute Coronary Syndrome
Stop NOAC: last dose ≥24h before intervention
Consider alternatives (as in all with need for chronic OAC):
- Bypass surgery
(- Sole balloon angioplasty)
Periprocedural anticoagulation per local practice:
- Bivalirudin (preferred), or
- UFH (per ACT/aPTT)
- Avoid IIb/IIIa inhibitors
Stent type:
Prefer new-generation DES (or BMS)
On admission:
- Stop NOAC
- Load with ASA (150-300 mg) + P2Y12 inhibitor (unless frail with high bleeding risk)
STEMI
Non-STEMI
Primary PCI, preferred
- Radial access
- Prefer new-generation DES
- Additional UFH, LMWH, bivalirudin (regardless of last NOAC)
- Avoid IIb/IIIa inhibitors unless bail-out
Fibrinolysis
- Only if no residual NOAC effect (based on last intake and/or coagulation test)
- No UFH or enoxaparin until no residual NOAC effect
Non-urgent
- Delay PCI
- Start fondaparinux (preferred) or LMWH ≥12h after last NOAC
- Avoid upstream bivalirudin, UFH, or IIb/IIIa inhibitors
Urgent
- Guide antithrombotic management on residual NOAC effect (last intake; CrCl; coagulation test), although no prospective data
After discontinuation of parenteral anticoagulation: restart same NOAC, in combination with single or dual antiplatelets (see Figure 7)
- Consider dabigatran 110 mg BID for patients on 150 mg BID
- When considering apixaban 2.5 mg BID, rivaroxaban 15 mg OD or edoxaban 30 mg OD : no data on stroke prevention if no normal dose reduction criterion (mainly CrCl)
PPI should be considered
Discharge with prespecified step-down plan (see Figure 7)

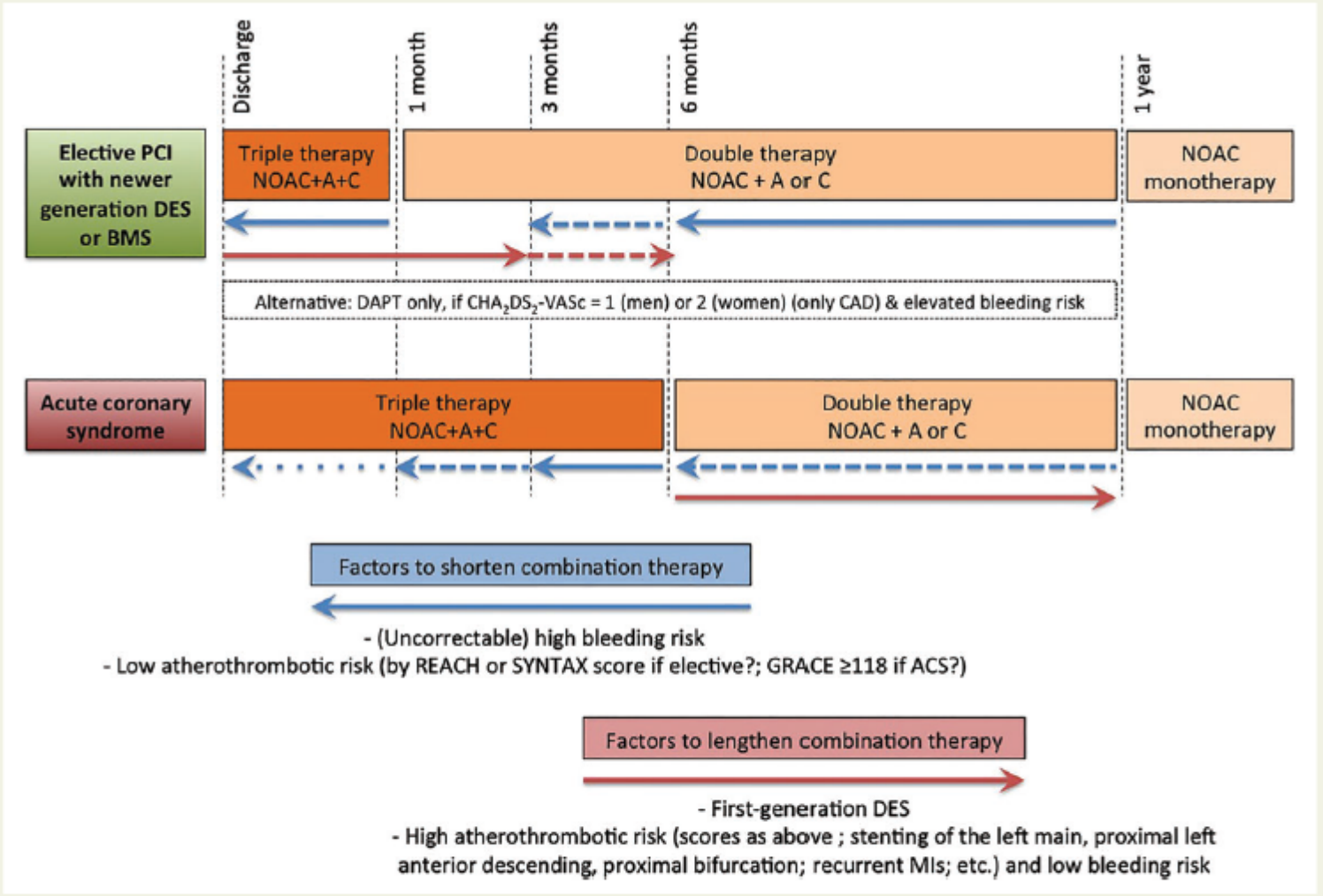


Figure 7 Default scenarios and criteria for adaptation for long-term treatment of patients on NOAC therapy after revascularization or ACS. There are innumerable possible variations on this global theme, as discussed in the text. Patient characteristics and institutional practices should be taken into account to individualize the approach. This figure wants to create a 'backbone' as guidance for such tailored approaches. A: aspirin 75–100 mg OD; C: clopidogrel 75 mg OD.

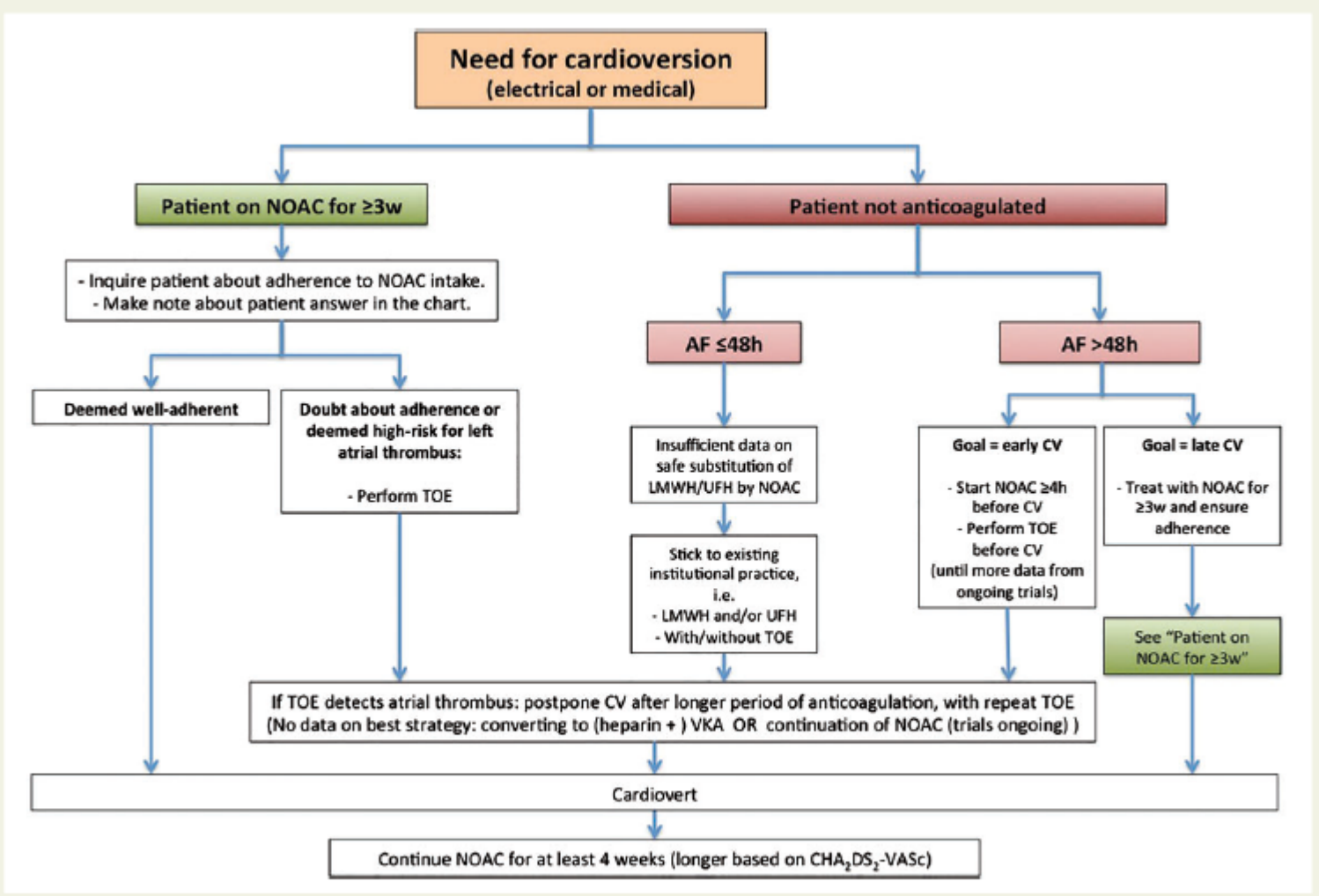


Figure 8 Cardioversion work-flow in AF patients treated with NOAC, depending on the duration of the arrhythmia and prior anticoagulation.

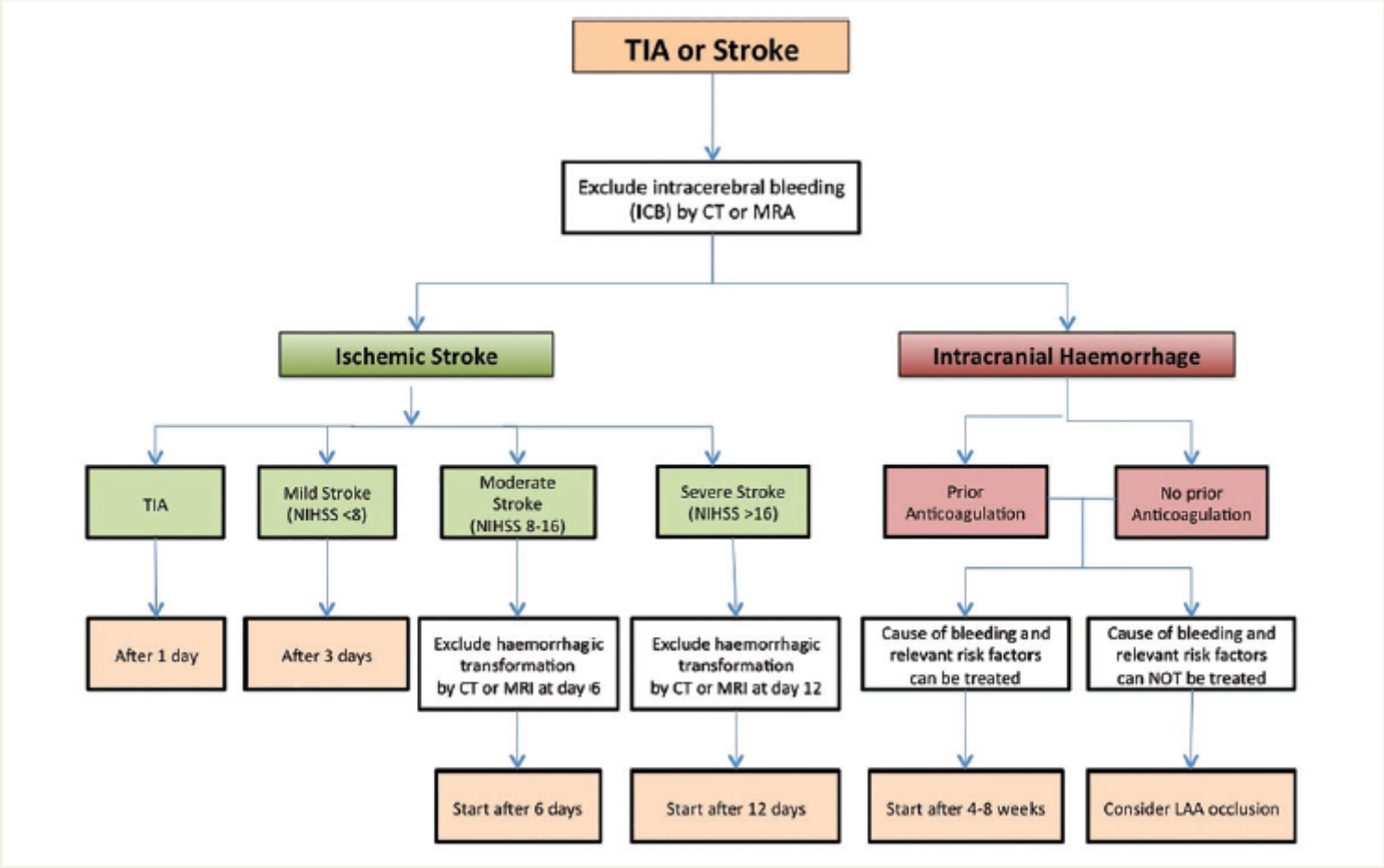


Figure 9 Flowchart for the initiation or re-initiation of anticoagulation after TIA/stroke or intracerebral haemorrhage.

Net clinical benefit of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus no treatment in a 'real world' atrial fibrillation population: A modelling analysis based on a nationwide cohort study

Summary

The concept of net clinical benefit has been used to quantify the balance between risk of ischaemic stroke (IS) and risk of intracranial haemorrhage (ICH) with the use oral anticoagulant therapy (OAC) in the setting of non-valvular atrial fibrillation (AF), and has shown that patients at highest risk of stroke and thromboembolism gain the greatest benefit from OAC with warfarin. There are no data for the new OACs, that is, dabigatran, rivaroxaban and apixaban, as yet. We calculated the net clinical benefit balancing IS against ICH using data from the Danish National Patient Registry on patients with non-valvular AF between 1997–2008, for dabigatran, rivaroxaban and apixaban on the basis of recent clinical trial outcome data for these new OACs. In patients with $CHADS_2$=0 but at high bleeding risk, apixaban and dabigatran 110 mg bid had a positive net clinical benefit. At CHA_2DS_2-VASc=1, apixaban and both doses of dabigatran (110 mg and 150 mg bid) had a positive net clinical benefit. In patients with $CHADS_2$ score≥1 or CHA_2DS_2-VASc≥2, the three new OACs (dabigatran, rivaroxaban and apixaban) appear superior to warfarin for net clinical benefit, regardless of risk of bleeding. When risk of bleeding and stroke are both high, all three new drugs appear to have a greater net clinical benefit than warfarin. In the absence of head-to-head trials for these new OACs, our analysis may help inform decision making processes when all these new OACs become available to clinicians for stroke prevention in AF. Using 'real world' data, our modelling analysis has shown that when the risk of bleeding and stroke are both high, all three new drugs appear to have a greater net clinical benefit compared to warfarin.

Keywords

Dabigatran, rivaroxaban, apixaban, atrial fibrillation, stroke prevention

Table 1: Event rates (95% confidence interval) for ischaemic stroke (IS) per 100 person years in a 'real world' cohort adjusted for effect size from dabigatran, rivaroxaban and apixaban.

	No treatment	Warfarin	NNT	Dabigatran 110 mg	NNT	Dabigatran 150 mg	NNT	Rivaroxaban (ITT)	NNT	Rivaroxaban (OTA)	NNT	Apixaban	NNT
$CHADS_2$ score													
0	0.20 (0.18,0.22)	0.10 (0.09,0.11)	1000	0.09 (0.08,0.10)	880	0.06 (0.06,0.07)	732	0.08 (0.08,0.1)	812	0.08 (0.07,0.09)	805	0.08 (0.07,0.90)	805
1	1.00 (0.92,1.09)	0.50 (0.46,0.55)	200	0.46 (0.42,0.50)	182	0.33 (0.3,0.36)	149	0.44 (0.40,0.48)	167	0.40 (0.36,0.43)	165	0.40 (0.36,0.43)	165
2–6	3.01 (2.85,3.16)	1.65 (1.56,1.74)	74	1.50 (1.42,1.58)	66	1.09 (1.03,1.15)	52	1.45 (1.37,1.53)	60	1.30 (1.23,1.37)	59	1.30 (1.23,1.37)	59
CHA_2DS_2-VASc score													
0	0.07 (0.06,0.09)	0.04 (0.03,0.05)	3333	0.04 (0.03,0.05)	2989	0.03 (0.02,0.03)	2315	0.04 (0.03,0.04)	2665	0.03 (0.03,0.04)	2637	0.03 (0.03,0.04)	2637
1	0.10 (0.09,0.12)	0.05 (0.04,0.06)	2000	0.04 (0.04,0.05)	1761	0.03 (0.03,0.04)	1464	0.04 (0.04,0.05)	1623	0.04 (0.03,0.04)	1611	0.04 (0.03,0.04)	1611
2–9	2.00 (1.91,2.10)	1.08 (1.02,1.12)	109	0.98 (0.93,1.02)	97	0.71 (0.67,0.74)	78	0.95 (0.90,0.99)	88	0.85 (0.81,0.88)	87	0.85 (0.81,0.88)	87
Overall	1.00 (0.96,1.05)	0.53 (0.51,0.56)	213	0.48 (0.46,0.51)	191	0.35 (0.34,0.37)	154	0.47 (0.45,0.49)	174	0.42 (0.40,0.44)	172	0.42 (0.40,0.44)	172

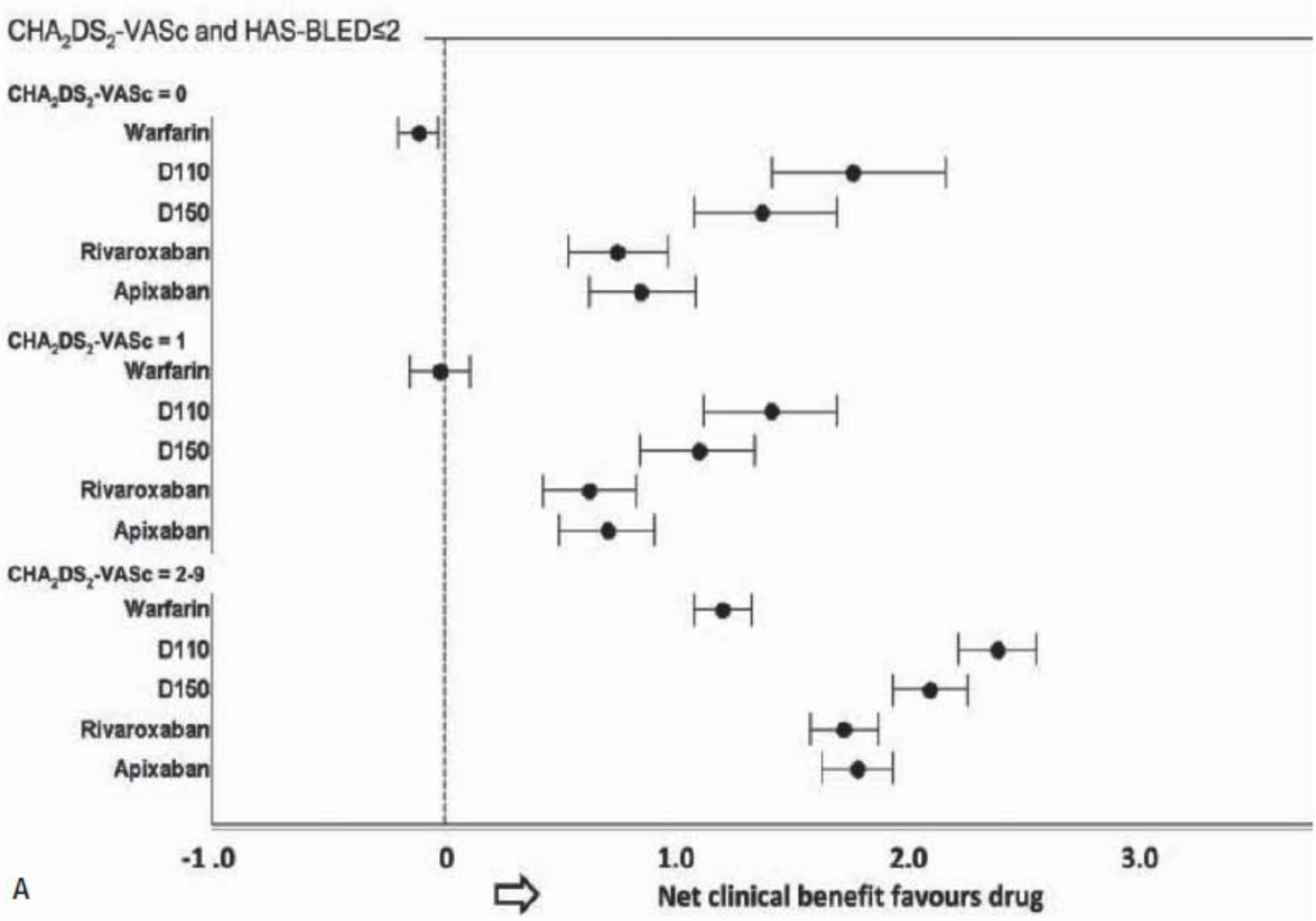
ITT: Intention-to-treat analysis; OTA: On treatment analysis. NNT: number of patients needed to treat to prevent one ischaemic stroke per year. NNT is calculated as 1/ARR, where ARR is the absolute reduction, i.e. event rate on no treatment-event rate on treatment. These data were derived from the Danish National Patient Registry, where all patients discharged with non-valvular AF in Denmark were identified (n=132,372) as described by Olesen et al. (6). Patients were followed up from index AF discharge and throughout the study period, i.e. maximum 12 years of follow-up.

Table 2: Event rates (95% confidence interval) for intracranial haemorrhage (ICH) per 100 person years in a 'real world' cohort adjusted for effect size from dabigatran, rivaroxaban and apixaban.

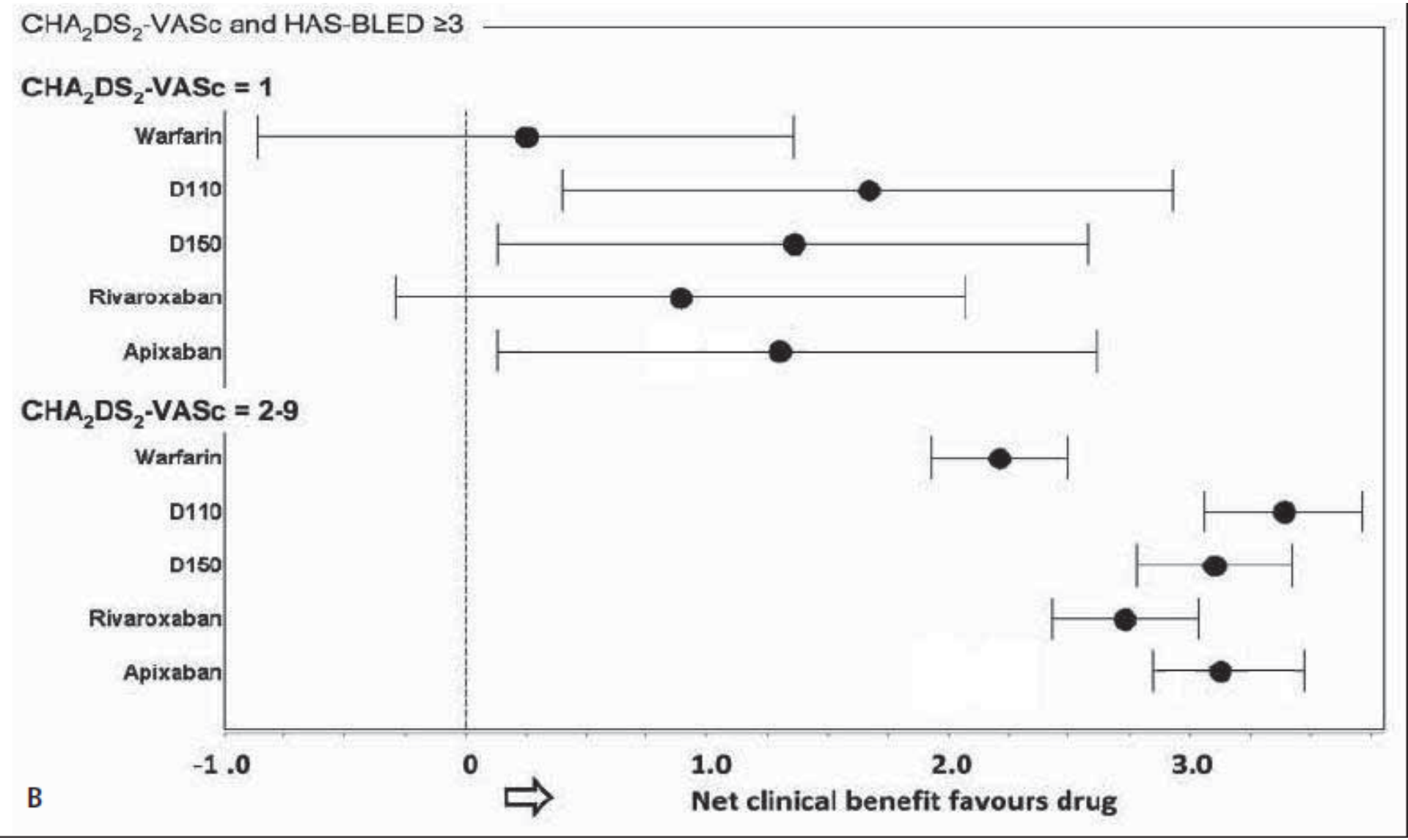
	No treatment	Warfarin	NNT	Dabigatran 110 mg	NNT	Dabigatran 150 mg	NNT	Rivaroxaban	NNT	Apixaban	NNT
$CHADS_2$ score											
0	0.10 (0.09,0.11)	0.15 (0.14,0.17)	–2000	0.05 (0.04,0.05)	2000	0.06 (0.06,0.07)	2500	0.10 (0.10,0.11)	-	0.06 (0.06,0.07)	2500
1	0.30 (0.28,0.32)	0.39 (0.37,0.42)	–1111	0.12 (0.11,0.13)	556	0.16 (0.15,0.17)	714	0.26 (0.25,0.28)	2500	0.16 (0.15,0.18)	714
2–6	0.40 (0.38,0.42)	0.44 (0.41,0.46)	–2500	0.14 (0.13,0.14)	385	0.17 (0.16,0.18)	435	0.29 (0.28,0.31)	909	0.18 (0.17,0.19)	455
CHA_2DS_2-VASc score											
0	0.05 (0.04,0.06)	0.09 (0.08,0.11)	–2500	0.03 (0.02,0.03)	5000	0.04 (0.03,0.04)	10000	0.06 (0.05,0.07)	–10000	0.04 (0.03,0.05)	10000
1	0.10 (0.09,0.11)	0.14 (0.13,0.16)	–2500	0.04 (0.04,0.05)	1667	0.06 (0.05,0.06)	2500	0.09 (0.08,0.10)	10000	0.06 (0.05,0.07)	2500
2–9	0.30 (0.29,0.31)	0.36 (0.34,0.37)	–1667	0.11 (0.11,0.11)	526	0.14 (0.14,0.15)	625	0.24 (0.23,0.25)	1667	0.15 (0.14,0.15)	667
Overall	0.30 (0.29,0.31)	0.44 (0.42,0.45)	–714	0.14 (0.13,0.14)	625	0.18 (0.17,0.18)	833	0.29 (0.28,0.30)	10000	0.18 (0.18,0.19)	833

	Net clinical benefit (95% confidence interval) of anticoagulant versus no treatment											
	Warfarin		Dabigatran 110 mg		Dabigatran 150 mg		Rivaroxaban (ITT)		Rivaroxaban (OTA)		Apixaban	
	HAS-BLED ≤2	HAS-BLED ≥3	HAS-BLED ≤2	HAS-BLED ≥3	HAS-BLED ≤2	HAS-BLED ≥3	HAS-BLED ≤2	HAS-BLED ≥3	HAS-BLED ≤2	HAS-BLED ≥3	HAS-BLED ≤2	HAS-BLED ≥3
$CHADS_2$ score												
0	−0.02 (-0.09,0.06)	0.19 (-1.39,1.77)	1.53 (1.35,1.76)	1.74 (0.05,3.47)	1.20 (1.05,1.40)	1.41 (-0.25,3.11)	0.68 (0.57,0.83)	0.89 (-0.73,2.54)	0.64 (0.53,0.78)	0.85 (-0.77,2.49)	0.77 (0.65,0.93)	1.43 (-0.24 ,3.13)
1	0.84 (0.70,0.99)	0.56 (0.16,0.95)	2.14 (1.92,2.38)	1.86 (1.38,2.34)	1.84 (1.64,2.05)	1.56 (1.10,2.01)	1.42 (1.25,1.61)	1.14 (0.71,1.57)	1.38 (1.21,1.56)	1.10 (0.67,1.52)	1.49 (1.31,1.68)	1.59 (1.12 , 2.04)
2–6	1.95 (1.70,2.20)	2.68 (2.33,3.04)	3.03 (2.72,3.34)	3.76 (3.35,4.18)	2.74 (2.45,3.04)	3.47 (3.08,3.88)	2.42 (2.15,2.70)	3.15 (2.78,3.54)	2.37 (2.10,2.65)	3.10 (2.73,3.49)	2.47 (2.19,2.75)	3.51 (3.12,3.92)
CHA_2DS_2-VASc score												
0	−0.11 (-0.20,-0.03)	-	1.75 (1.40,2.15)	-	1.36 (1.07,1.68)	-	0.74 (0.53,0.96)	-	0.68 (0.49,0.89)	-	0.84 (0.62,1.08)	-
1	−0.02 (-0.15,0.11)	0.25 (-0.86,1.36)	1.40 (1.11,1.68)	1.67 (0.40,2.93)	1.09 (0.84,1.33)	1.36 (0.13,2.58)	0.62 (0.42,0.82)	0.89 (-0.29,2.07)	0.58 (0.38,0.77)	0.85 (-0.33,2.02)	0.70 (0.49,0.90)	1.38 (0.14,2.60)
2–9	1.19 (1.07,1.32)	2.21 (1.93,2.50)	2.37 (2.20,2.54)	3.39 (3.06,3.72)	2.08 (1.92,2.24)	3.10 (2.78,3.42)	1.71 (1.57,1.86)	2.73 (2.43,3.04)	1.67 (1.53,1.81)	2.69 (2.39,2.99)	1.77 (1.62,1.92)	3.13 (2.81,3.45)

Net clinical benefit [events prevented per 100 person-years (95% confidence interval)] is calculated as annualised (thromboembolism rate off warfarin – thromboembolism rate on warfarin) – 1.5x (ICH rate on warfarin - ICH rate off warfarin), based on the study by Singer et al1. ITT: Intention-to-treat analysis; OTA: On treatment analysis.


CHA2DS2-VASc and HAS-BLED≤2
CHA2DS2-VASc = 0
Warfarin
D110
D150
Rivaroxaban
Apixaban
CHA2DS2-VASc = 1
Warfarin
D110
D150
Rivaroxaban
Apixaban
CHA2DS2-VASc = 2-9
Warfarin
D110
D150
Rivaroxaban
Apixaban
-1 .0
0
1.0
2.0
3.0
Net clinical benefit favours drug

A


CHA2DS2-VASc and HAS-BLED ≥3
CHA2DS2-VASc = 1
Warfarin
D110
D150
Rivaroxaban
Apixaban
CHA2DS2-VASc = 2-9
Warfarin
D110
D150
Rivaroxaban
Apixaban
-1 .0
0
1.0
2.0
3.0
Net clinical benefit favours drug

B

What is known about this topic?

- Several new oral anticoagulants (dabigatran, rivaroxaban and apixaban) have been the subject of recent published, randomised controlled clinical trials, showing favourable effects on both ischaemic stroke/thromboembolism and bleeding risk.
- The net clinical benefit balancing ischaemic stroke against intracranial haemorrhage is only negative with warfarin at a CHA_2DS_2-VASc score=0, reflecting the 'truly low risk' status of these patients.

What does this paper add?

- In patients with $CHADS_2$=0 but at high bleeding risk, apixaban and dabigatran 110 mg bid have a positive net clinical benefit.
- At CHA_2DS_2-VASc=1, apixaban and both doses of dabigatran (110 mg and 150 mg bid) have a positive net clinical benefit.
- In patients with $CHADS_2$ score≥1 or CHA_2DS_2-VASc≥2, the three new OACs (dabigatran, rivaroxaban and apixaban) appear superior to warfarin for net clinical benefit, regardless of risk of bleeding.
- When risk of bleeding and stroke are both high, all three new drugs appear to have a greater net clinical benefit than warfarin.

EDITORIAL COMMENT

Danger Ahead: Watch Out for Indirect Comparisons!*

So what are we to do? Should we use the indirect comparisons put forth by Lip et al. (5) since that provides the only comparative data we have? In general, the authors appear to be saying that there are more similarities between these agents than differences, as has also been previously noted by Mega (10). However, because of the statistical limitations of such comparisons, although of some interest, we feel the differences they report on some endpoints are not robust enough to be relied upon for the clinical care of patients. Instead, we would turn to direct evidence from trials and the indications put forth by the FDA to select the appropriate agent, at the dose tested, for use in the patient population studied within the trial.

COMPARISON OF TOTAL MEDICAL COST AVOIDANCE WITH THE USAGE OF NEW ORAL ANTICOAGULANTS INSTEAD OF WARFARIN AMONG ATRIAL FIBRILLATION PATIENTS, BASED ON THE ARISTOTLE, RE-LY AND ROCKET-AF TRIALS

ACC Moderated Poster Contributions
McCormick Place South, Hall A
Monday, March 26, 2012, 9:30 a.m.-10:30 a.m.

Session Title: Arrhythmias: AF/SVT: Anticoagulation for Atrial Fibrillation: Warfarin and the Newbies
Abstract Category: 16. Arrhythmias: AF/SVT
Presentation Number: 1235-92

Authors: *Steven Deitelzweig, Alpesh Amin, Yonghua Jing, Dinara Makenbaeva, Dinara Makenbaeva, Daniel Wiederkehr, Jay Lin, John Graham, Ochsner Clinic Foundation, New Orleans, LA, USA*

Background: This study compares the total medical costs with the use of the new oral anticoagulants (NOACs) apixaban, dabigatran, and rivaroxaban vs. warfarin in the US, based on the results of the ARISTOTLE, RE-LY and ROCKET-AF trials.

Methods: A cost comparison analysis was conducted from the US perspective. The rates of efficacy and safety endpoints for warfarin were estimated as the weighted averages from the ARISTOTLE, RE-LY and ROCKET-AF trials. The rates of clinical events for NOACs were calculated using the hazard ratios from the original trials. Annual incremental costs associated with clinical events from the US payer perspective were obtained from published literature and inflation adjusted to 2010 cost. Total medical cost avoidance was evaluated for each NOAC vs. warfarin.

Results: Based on data from ARISTOTLE, RE-LY and ROCKET-AF, the per patient year event rates for warfarin treatment were estimated to be 1.24% for ischemic or uncertain type of stroke (IS), 0.75% for myocardial infarction (MI), and 2.83% for major bleeding excluding hemorrhagic stroke (MB). The estimated event rates were IS: 1.14% [CI: 0.92-1.40], 0.94% [CI: 0.74-1.22] and 1.17% [CI: 0.93-1.45]; MI: 0.66% [CI: 0.50-0.88], 1.04% [CI: 0.75-1.43] and 0.61% [CI: 0.47-0.80]; MB: 2.03% [CI: 1.81-2.28], 2.92% [CI: 2.58-3.28] and 3.14% [CI: 2.78-3.51] per patient year for apixaban, dabigatran and rivaroxaban, respectively. Per patient year, the total medical cost reduction associated with NOAC use instead of warfarin was estimated to be $439, $62, and $133 for apixaban, dabigatran and rivaroxaban, respectively. For apixaban, cost avoidance was driven by the reduction in MB ($223) and hemorrhagic stroke ($110), with smaller contributions from MI ($55) and IS ($32); for dabigatran, cost avoidance came from reductions in hemorrhagic stroke ($166) and IS ($97), but with increased costs from MI ($175) and MB ($26). For rivaroxaban, cost avoidance came from hemorrhagic stroke ($92) and MI ($88), but with increased costs from MB ($87).

Conclusions: Compared to warfarin, NOACs were associated with reduction of total medical costs. The largest avoidance of medical costs was driven by decreased event rates of bleeding and stroke.

1.2 How to organize follow-up?

Regular review has to systematically document (1) therapy adherence (ideally with inspection of the prescribed medication in blister packs or bottles, in addition to appropriate questioning); (2) any event that might signal thromboembolism in either the cerebral, systemic or pulmonary circulations; (3) any adverse effects, but particularly (4) bleeding events (occult bleeding may be revealed by falling haemoglobin levels, see below); (5) co-medications, prescribed or over-the-counter; and (6) blood sampling for haemoglobin, renal (and hepatic) function.

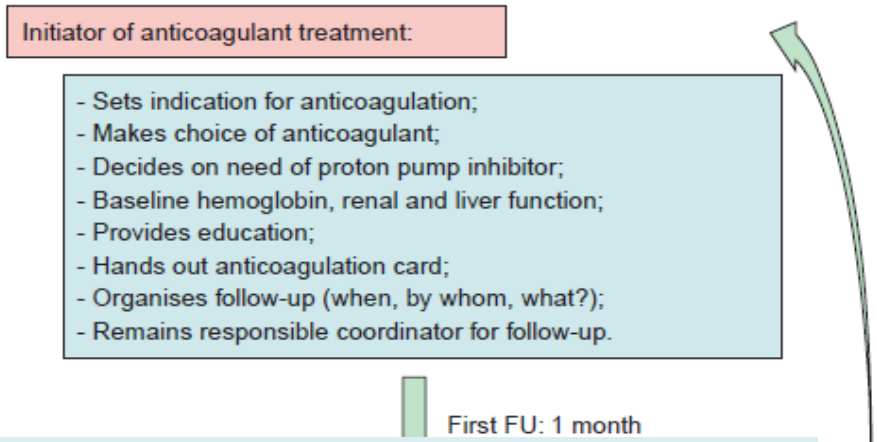


Table 2 Checklist during follow-up contacts of AF patients on anticoagulation

	Interval	Comments
1. Compliance	Each visit	• Instruct patient to bring remaining medication: note and calculate average adherence • Re-educate on importance of strict intake schedule • Inform about compliance aids (special boxes; smartphone applications; . . .)
2. Thrombo-embolism	Each visit	• Systemic circulation (TIA, stroke, peripheral) • Pulmonary circulation
3. Bleeding	Each visit	• 'Nuisance' bleeding: preventive measures possible? (PPI; haemorrhoidectomy; . . .). Motivate patient to diligently continue anticoagulation • Bleeding with impact on quality-of-life or with risk: prevention possible? Need for revision of anticoagulation indication or dose?
4. Other side effects	Each visit	• Carefully assess relation with NOAC: decide for continuation (and motivate), temporary cessation (with bridging), or change of anticoagulant drug.
5. Co-medications	Each visit	• Prescription drugs; over-the-counter drugs (see Section 4) • Careful interval history: also temporary use can be risk!
6. Blood sampling	Yearly 6 monthly 3 monthly On indication	• Haemoglobin, renal and liver function • Renal function if CrCl 30–60 ml/min, or if on dabigatran and >75 years or fragile • If CrCl 15–30 ml/min • If intercurring condition that may impact renal or hepatic function

2. How to measure the anticoagulant effect of new oral anticoagulants?

Table 3 Interpretation of coagulation assays in patients treated with different NOACs

	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Plasma peak level	2 h after ingestion	1–4 h after ingestion	1–2 h after ingestion	2–4 h after ingestion
Plasma trough level	12–24 h after ingestion	12–24 h after ingestion	12–24 h after ingestion[9]	16–24 h after ingestion
PT	Cannot be used	Cannot be used	Prolonged but no known relation with bleeding risk[5,9]	Prolonged: may indicate excess bleeding risk but local calibration required
INR	Cannot be used	Cannot be used	Cannot be used	Cannot be used
aPTT	At trough: >2x ULN suggests excess bleeding risk	Cannot be used	Prolonged but no known relation with bleeding risk[9]	Cannot be used
dTT	At trough: >200 ng/ml or >65 s: excess bleeding risk	Cannot be used	Cannot be used[10]	Cannot be used
Anti-FXa chromogenic assays	Not applicable	No data yet	Quantitative;[10] no c values for bleedi	
ECT	At trough: ≥3× ULN: excess bleeding risk	Not affected	Not affected	

[a]No EMA approval yet. Needs update after finalization of SmPC.
Routine monitoring is not required. Assays need cautious interpretation for clinical use in special circum
PT, prothrombin time; aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; INR, int

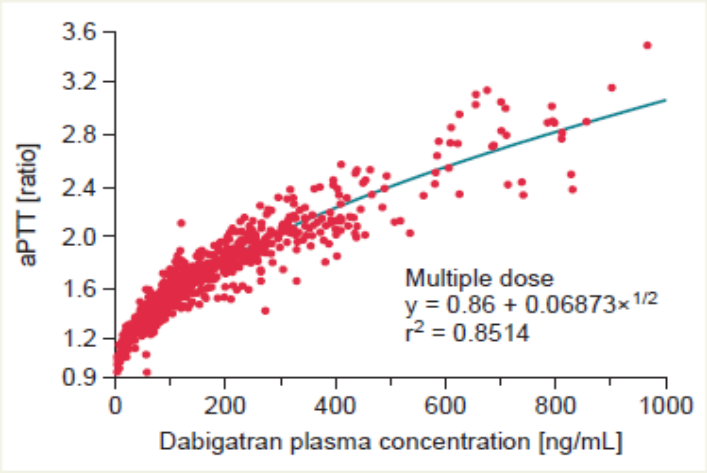


Figure 3 Curvilinear relation between aPTT and dabigatran plasma levels. From van Ryn *et al.*,[12] with permission.

3. Drug–drug interactions and pharmacokinetics of new oral anticoagulants

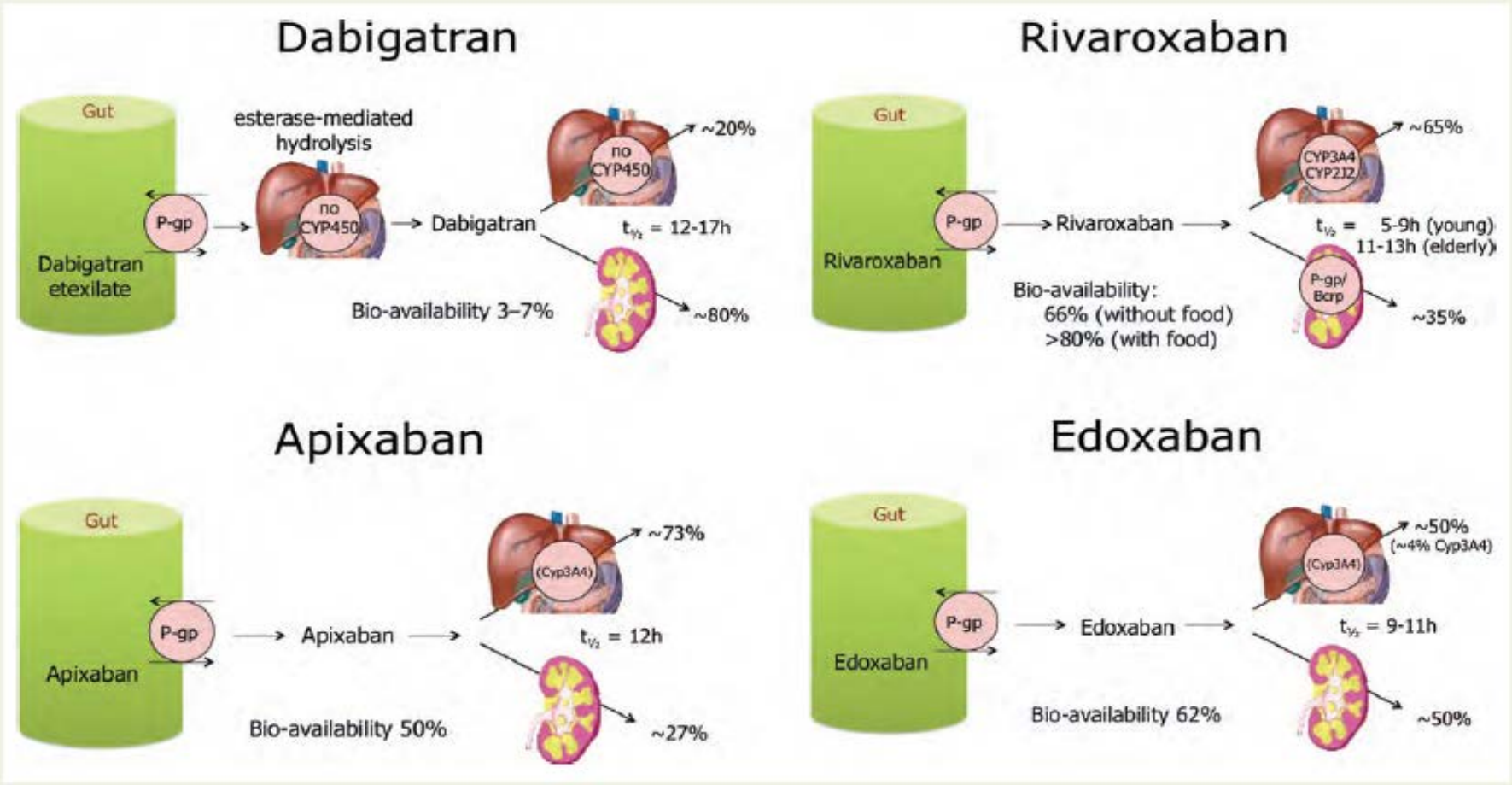


Figure 5 Absorption and metabolism of the different new anticoagulant drugs. There are interaction possibilities at the level of absorption or first transformation, and at the level of metabolisation and excretion. The brackets around (Cyp3A4) in the apixaban graph indicate a minor contribution of this pathway to hepatic clearance, the majority of the drug being excreted as unchanged parent. See also *Table 4* for the size of the interactions based on these schemes.

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.

Many drugs used in AF patients are P-gp substrates (e.g. verapamil, dronedarone, amiodarone, quinidine). CYP3A4 type cytochrome P450-dependent elimination is involved in rivaroxaban and apixaban hepatic clearance.[27] Strong CYP3A4 inhibition or induction may affect rivaroxaban plasma concentrations and effect, and should be evaluated in context (see below). Most of the hepatic clearance of apixaban is as unchanged molecule, with only a minority being metabolized (in part via CYP3A4), which makes CYP3A4 interactions of less importance for this drug.[19]

There is good rationale for reducing the dose of NOACs in patients with a high bleeding risk and/or when a higher plasma level of the drug can be anticipated.[1,4,28] We have chosen an approach with three levels of alert for drug–drug interactions or other clinical factors that may affect NOAC plasma levels or effects (*Table 5*): (1) 'red' interactions, precluding the use of a given NOAC in combination (i.e. 'contraindication' or 'discouragement' for use); (2) 'orange' interactions, with the recommendation to adapt the NOAC dose, since they result in changes of the plasma levels or effect of NOACs that could potentially have a clinical impact; and (3) 'yellow' interactions, with the recommendation to keep the original dose, unless two or more concomitant 'yellow' interactions are present. Two or more 'yellow' interactions need expert evaluation, and may lead to the decision of not prescribing the drug ('red') or of adapting its dose ('orange'). Unfortunately,

Table 5 Effect on NOAC plasma levels ('area under the curve, AUC') from drug–drug interactions and clinical factors and recommendations towards NOAC dosing

	Via	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%[29]	No data yet	No effect[30]	No effect[27,31]
Digoxin	P-gp competition	No effect[32]	No data yet	No effect[30]	No effect[27,33]
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12–180%[24] (reduce dose and take simultaneously)	No data yet	+53% (SR)[30] (reduce dose by 50%)[a]	Minor effect (use with caution if CrCl 15–50 ml/min)
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[24]	+40%[SmPC]	No data yet	Minor effect (use with caution if CrCl 15–50 ml/min)
Quinidine	P-gp competition	+50%	No data yet	+80%[30] (reduce dose by 50%)[b]	+50%
Amiodarone	P-gp competition	+12–60%[24]	No data yet	No effect[30]	Minor effect (use with caution if CrCl 15–50 ml/min)
Dronedarone	P-gp and CYP3A4 inhibitor	+70–100% (US: 2 × 75 mg)	No data yet	+85% (reduce dose by 50%)[a]	No data yet
Ketoconazole; itraconazole; voriconazole; posaconazole	P-gp and BCRP competition; CYP3A4 inhibition	+140–150% (US: 2 × 75 mg)	+100%[SmPC]	No data yet	Up to +160%[27]
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[27]
Cyclosporin; tacrolimus	P-gp competition	No data yet	No data yet	No data yet	+50%
Clarithromycin; erythromycin	P-gp competition and CYP3A4 inhibition	+15–20%	No data yet	No data yet	+30–54%[26,27]
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase[SmPC]	No data yet	Up to +153%[27]
Rifampicin; St John's wort; carbamazepine; phenytoin; phenobarbital	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	−66%[24]	−54%[SmPC]	−35%	Up to −50%
Antacids (H2B; PPI; Al-Mg-hydroxide)	GI absorption	−12–30%[22–24]	No data yet	No effect	No effect[21,25]
Other factors					
Age ≥80 years	Increased plasma level			No data yet	
Age ≥75 years	Increased plasma level			No data yet	
Weight ≤60 kg	Increased plasma level				
Renal function	Increased plasma level	See Table 7			
Other increased bleeding risk		Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history or active GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3			

7. Patients with chronic kidney disease

In the context of NOAC treatment, CrCl is best assessed by the Cockroft method, as this was used in most NOAC trials.

Table 6 Estimated drug half-lives and effect on area under the curve NOAC plasma concentrations in different stages of chronic kidney disease compared to healthy controls

	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
CrCl ≥60 ml/min CKD Stage I and II	~14 h[48]	No data	~8.6 h[49]	~8.5 h[50] (+44%)
CrCl 30–60 ml/min CKD Stage III	~18 h[48]	No data	~9.4 h[49]	~9 h (+52%)
CrCl 15–30 ml/min CKD Stage IV	~28 h[48]	No data	~16.9 h[49]	~9.5 h (+64%)
CrCl ≤15 ml/min CKD Stage V	No data	No data	No data	No data

Practical suggestions

In patients on NOACs, renal function needs to be monitored carefully, at least yearly, to detect changes in renal function and adapt the dose accordingly. If renal function is impaired (≤60 ml/min), 6 monthly checks are required. Renal function monitoring is especially relevant for dabigatran, which is predominantly cleared renally: in elderly patients (>75 years) or otherwise frail patients on dabigatran, renal function should be evaluated at least once every 6 months (see also *Table 2* and *Figure 2*). Acute illness often transiently affects renal function (infections, acute heart failure, . . .), and therefore should trigger re-evaluation.

Renal function can deteriorate within a few months, and the nature of the kidney disease as well as concomitant conditions that could change the time course of CKD should be considered when deciding on a monitoring scheme.

(i) Monitor every year for CKD stage I–II (CrCl ≥ 60 ml/min)
(ii) Monitor every 6 months for CKD stage III (CrCl 30–60 ml/min)
(iii) Monitor every 3 months for CKD stage IV (CrCl ≤30 ml/min)

Table 7 NOACs in renal dysfunction: Approved European labels and dosing in chronic kidney disease

	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Fraction renally excreted of absorbed dose	80%	27%	50%[9]	35%
Bio-availability	3–7%	50%	62%[17]	66% without food Almost 100% with food
Fraction renally excreted of administered dose	4%	14%	37%[9]	33%
Approved for CrCl ≥ ...	≥30 ml/min	≥15 ml/min	Not available	≥15 ml/min
Dosing recommendation	CrCl ≥50 ml/min: no adjustment (i.e. 150 mg bid)	Serum creatinine ≥1.5 mg/dl: no adjustment (i.e. 5 mg bid)	Not available	CrCl ≥50 ml/min: no adjustment (i.e. 20 mg qd)
Dosing if CKD	When CrCl 30–49 ml/min, 150 mg bid is possible (SmPC) but 110 mg bid if 'high risk of bleeding' (SmPC) or 'recommended' (GL update)[2] Note: 75 mg bid approved in US only:[b] • if CrCl 15–30 ml/min • if CrCl 30–49 ml/min and other orange factor Table 5 (e.g. verapamil)	CrCl 15–29 ml/min: 2.5 mg bid Serum creatinine ≥1.5 mg/dl in combination with age ≥80 years or weight ≤60 kg,[SmPC] or with other 'yellow' factor (Table 5): 2.5 mg bid	Not available	15 mg qd when CrCl 15–49 ml/min
Not recommended if	CrCl <30 ml/min	CrCl <15 ml/min	Not available	CrCl <15 ml/min

9. Management of bleeding complications

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
Non life-threatening bleeding	Inquire last intake + dosing regimen Estimate normalization of haemostasis: Normal renal function: 12–24 h CrCl 50–80 ml/min: 24–36 h CrCl 30–50 ml/min: 36–48 h CrCl <30 ml/min: ≥48 h Maintain diuresis Local haemostatic measures Fluid replacement (colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans Desmopressin can be considered in special cases (coagulopathy or thrombopathy) Consider dialysis (preliminary evidence: -65% after 4 h)[48] Charcoal haemoperfusion not recommended (no data)	Inquire last intake + dosing regimen Normalization of haemostasis: 12–24 h Local haemostatic measures Fluid replacement (colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans Desmopressin can be considered in special cases (coagulopathy or thrombopathy)
Life-threatening bleeding	All of the above Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence) Activated PCC 50 IE/kg; max 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available Activated factor VII (rFVIIa; 90 µg/kg) no data about additional benefit + expensive (only animal evidence)	All of the above Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence) Activated PCC 50 IE/kg; max. 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available Activated factor VII (rFVIIa; 90 µg/kg) no data about additional benefit + expensive (only animal evidence)

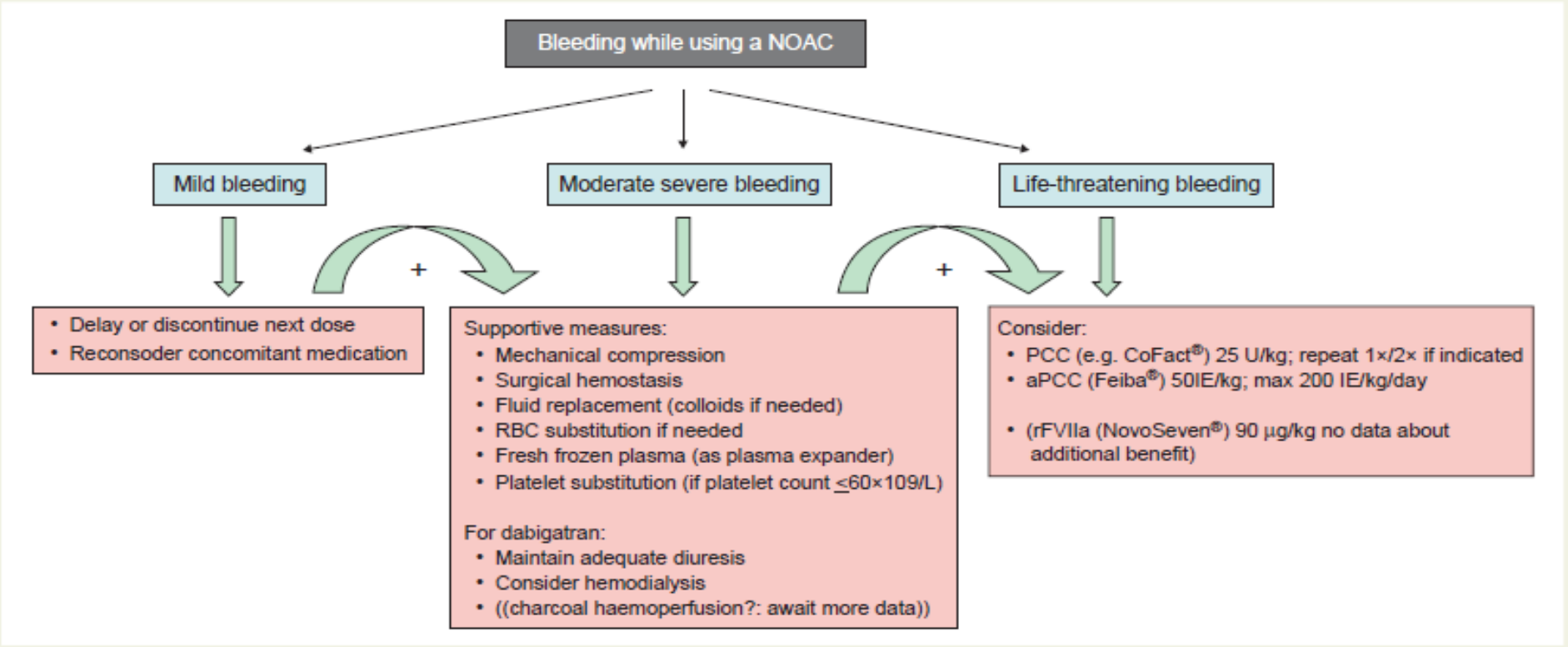


Figure 6 Management of bleeding in patients taking NOACs. Possible therapeutic measures in case of minor or severe bleeding in patients on NOAC therapy. Based on van Ryn *et al.*[12]

Review

Journal of INTERNAL MEDICINE

doi: 10.1111/joim.12360

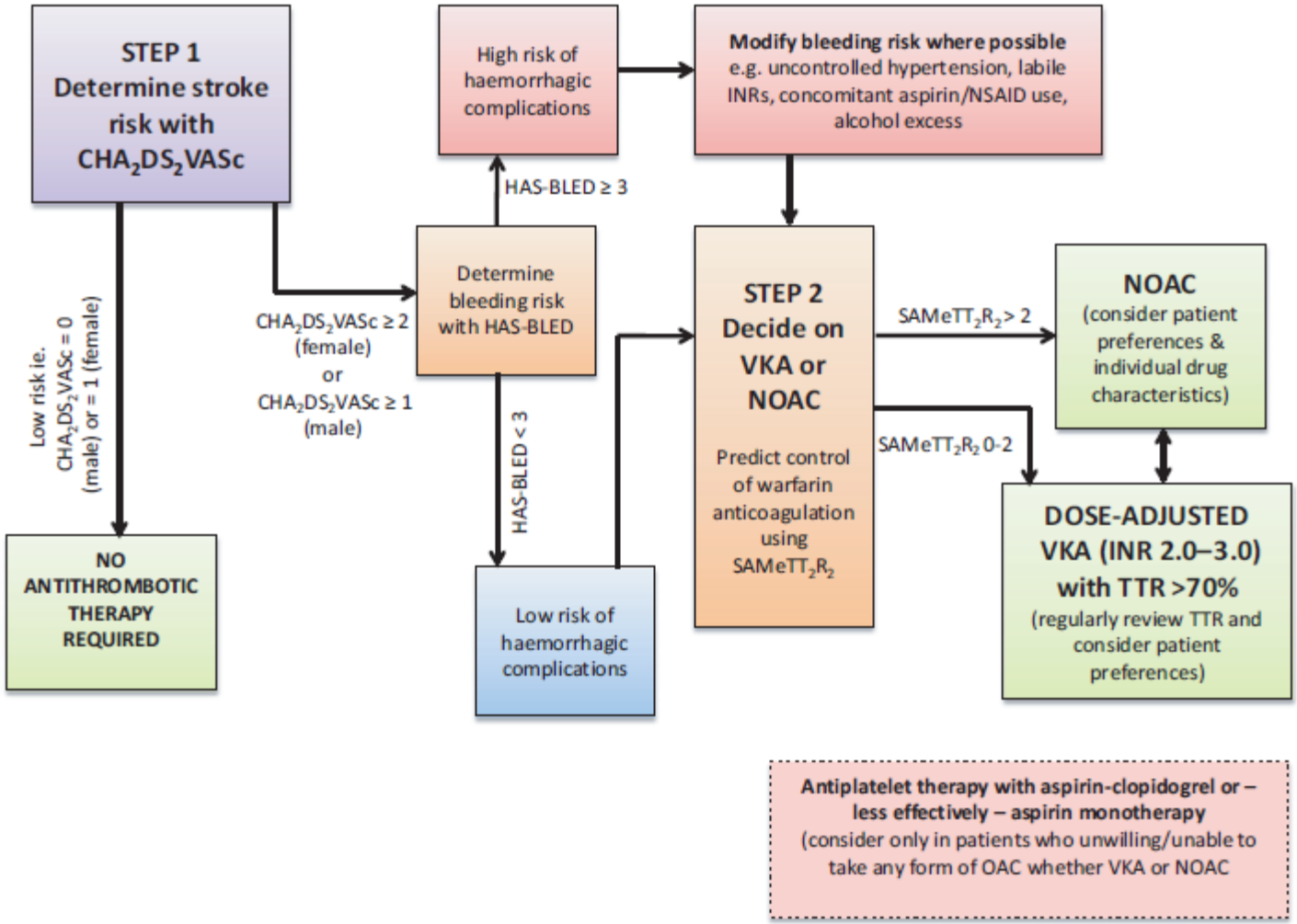
Choosing the right drug to fit the patient when selecting oral anticoagulation for stroke prevention in atrial fibrillation

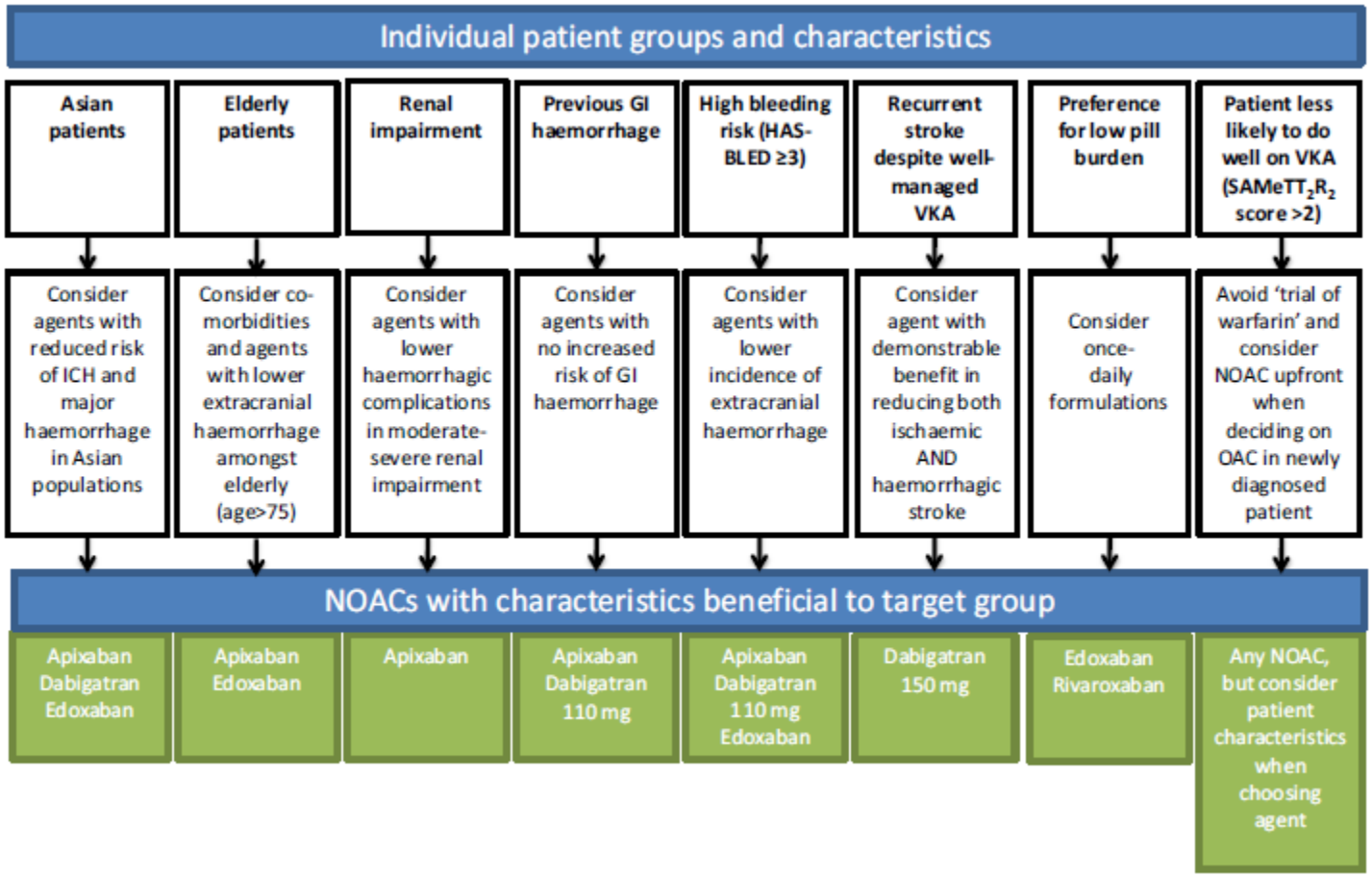
A. M. Shields[1] & G. Y. H. Lip[2,3]

J Intern Med 2015; **278**: 1–18.

Table 2 *The pharmacokinetic and pharmacodynamic properties of warfarin and the nonwarfarin oral anticoagulants*

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Molecular target	Vitamin K dependent clotting factors	Thrombin	Factor Xa	Factor Xa	Factor Xa
Dosing in AF	Once daily	Twice daily	Once daily	Twice daily	Once daily
Time to peak plasma concentration (mins)	240.00	85–150	30–180	30–120	30–60
Time to peak effect (h)	96–120	2	2–3	1–2	1–2
Half life (h)	40.00	14–17	5–9 (increased to 11–13 in elderly)	8–15	9–11
Renal clearance	<1%	≈80%	≈30%	≈27%	0.35
Food and drug interactions	Foods rich in vitamin K, Substrates of CYP2C9, CYP3A4 and CYP1A2	Strong P-gp inhibitors and inducers	Strong CYP3A4 inducers, strong inhibitors of both CYP3A4 and P-gp	Strong inhibitors and inducers of CYP3A4 and P-gp	Strong P-gp inhibitors
Creatine clearance below which drug is contraindicated	n/a	<30 mL min^{-1}	<15 mL min^{-1}	<15 mL min^{-1}	<30 mL min^{-1} (Japan)


STEP 1
Determine stroke risk with CHA_2DS_2VASc
Low risk ie. $CHA_2DS_2VASc = 0$ (male) or = 1 (female)
NO ANTITHROMBOTIC THERAPY REQUIRED
$CHA_2DS_2VASc \geq 2$ (female) or $CHA_2DS_2VASc \geq 1$ (male)
Determine bleeding risk with HAS-BLED
HAS-BLED ≥ 3
High risk of haemorrhagic complications
Modify bleeding risk where possible e.g. uncontrolled hypertension, labile INRs, concomitant aspirin/NSAID use, alcohol excess
HAS-BLED < 3
Low risk of haemorrhagic complications
STEP 2
Decide on VKA or NOAC
Predict control of warfarin anticoagulation using $SAMeTT_2R_2$
$SAMeTT_2R_2 > 2$
$SAMeTT_2R_2$ 0-2
NOAC
(consider patient preferences & individual drug characteristics)
DOSE-ADJUSTED VKA (INR 2.0–3.0) with TTR >70%
(regularly review TTR and consider patient preferences)
Antiplatelet therapy with aspirin-clopidogrel or – less effectively – aspirin monotherapy
(consider only in patients who unwilling/unable to take any form of OAC whether VKA or NOAC


Individual patient groups and characteristics
Asian patients
Elderly patients
Renal impairment
Previous GI haemorrhage
High bleeding risk (HAS-BLED ≥3)
Recurrent stroke despite well-managed VKA
Preference for low pill burden
Patient less likely to do well on VKA (SAMeTT2R2 score >2)
Consider agents with reduced risk of ICH and major haemorrhage in Asian populations
Consider co-morbidities and agents with lower extracranial haemorrhage amongst elderly (age>75)
Consider agents with lower haemorrhagic complications in moderate-severe renal impairment
Consider agents with no increased risk of GI haemorrhage
Consider agents with lower incidence of extracranial haemorrhage
Consider agent with demonstrable benefit in reducing both ischaemic AND haemorrhagic stroke
Consider once-daily formulations
Avoid 'trial of warfarin' and consider NOAC upfront when deciding on OAC in newly diagnosed patient
NOACs with characteristics beneficial to target group
Apixaban Dabigatran Edoxaban
Apixaban Edoxaban
Apixaban
Apixaban Dabigatran 110 mg
Apixaban Dabigatran 110 mg Edoxaban
Dabigatran 150 mg
Edoxaban Rivaroxaban
Any NOAC, but consider patient characteristics when choosing agent

Stroke Prevention in Atrial Fibrillation
A Systematic Review

JAMA. 2015;313(19):1950-1962.

Table 2. Summary of Guideline Recommendations[a]

Stroke Risk Stratification	Treatment Recommendation	Comments
ACCP,[29] 2012		
$CHADS_2$ score		
≥2	OAC	Warfarin or dabigatran
1	OAC	Warfarin or dabigatran
0 plus additional non-$CHADS_2$ risk factors (eg, age 65-74 y, woman, and vascular disease)	OAC	Warfarin or dabigatran
No risk factors	No antithrombotic therapy	
ESC,[4] 2012		
Initial step: identify 'low risk' patients (CHA_2DS_2-VASc 0 in males, 1 in females)	No antithrombotic therapy	
Subsequent step: for patients with ≥1 additional stroke risk factors	OAC is recommended for CHA_2DS_2-VASc score ≥2 or should be considered for CHA_2DS_2-VASc score of 1 in men	OAC refers to a VKA (eg, warfarin) with TTR>70%, or a NOAC (preferred); antiplatelet therapy with aspirin-clopidogrel combination therapy or—less effectively—aspirin monotherapy is recommended only when patients refuse any form of OAC
CCS,[30] 2014		
Algorithm: identify those aged ≥65 y and $CHADS_2$ score risk factors	OAC	Warfarin or a NOAC, preferred
Algorithm: vascular disease	Aspirin	
Algorithm: no risk factors, ie, age <65 y with no $CHADS_2$ risk factors nor vascular disease	No antithrombotic therapy	
AHA/ACC/HRS,[5] 2014		
CHA_2DS_2-VASc score		
≥2	OAC	OAC refers to warfarin or a NOAC as an alternative
1	Nothing, aspirin, or OAC	
0	No antithrombotic therapy	
NICE,[4] 2014		
Evaluative steps		
Initial: identify low-risk patients[b]	No antithrombotic therapy	
Subsequent: for AF patients with ≥1 additional stroke risk factors	Offer OAC (CHA_2DS_2-VASc ≥2) or consider OAC (CHA_2DS_2-VASc score of 1 in men)	OAC refers to warfarin or a NOAC as an alternative. Aspirin monotherapy should not be used for stroke prevention in AF.

Table 4. Optimal Selection of Oral Anticoagulation for Stroke Prevention in Atrial Fibrillation

	VKA, Warfarin	Direct Thrombin Inhibitors	Factor X Inhibitors			
			Rivaroxaban	Apixaban	Edoxaban	
Recurrent stroke or TIA despite treatment VKA[a]		150 mg of dabigatran, 2/d				
Moderate or severe renal impairment[b]	✓		✓	✓		
GI tract symptoms or dyspepsia[c]			✓	✓		
High risk of bleeding[d]		75 mg dabigatran, 2/d (US); 110 mg dabigatran, 2/d (rest of world)		✓	✓[e]	
Preference for 1 dose per day	✓		✓		✓	

Table 5. Definition of the SAMe-TT_2R_2 Score, Used to Aid Initial Decision Making Between Vitamin K Antagonist (With Good Quality Anticoagulation Control) and a Non-Vitamin K Antagonist Oral Anticoagulant[a]

Definitions	Points
Sex (female)	1
Age (<60 y)	1
Medical history[b]	1
Treatment (interacting drugs, eg, amiodarone for rhythm control)	1
Tobacco use (within 2 y)	2
Race (not white)	2
Maximum points	8

[a] The SAMe-TT_2R_2 score is proposed as a means to help with decision making, to identify those newly diagnosed nonanticoagulated AF patients who have a probability of doing well while taking a vitamin K antagonist (VKA) (with SAMe-TT_2R_2 score, 0-2) and achieve a time in therapeutic range (TTR) of at least 65% or 70%. In contrast, a SAMe-TT_2R_2 score of more than 2 suggests that such patients are unlikely to achieve a good TTR while taking a VKA, and a non-VKA oral anticoagulant should be used upfront, without a "trial of warfarin" period.

[b] Two of the following: hypertension, diabetes mellitus, coronary artery disease or myocardial infarctions, peripheral artery disease, congestive heart failure , previous stroke, pulmonary disease, or hepatic or renal disease.

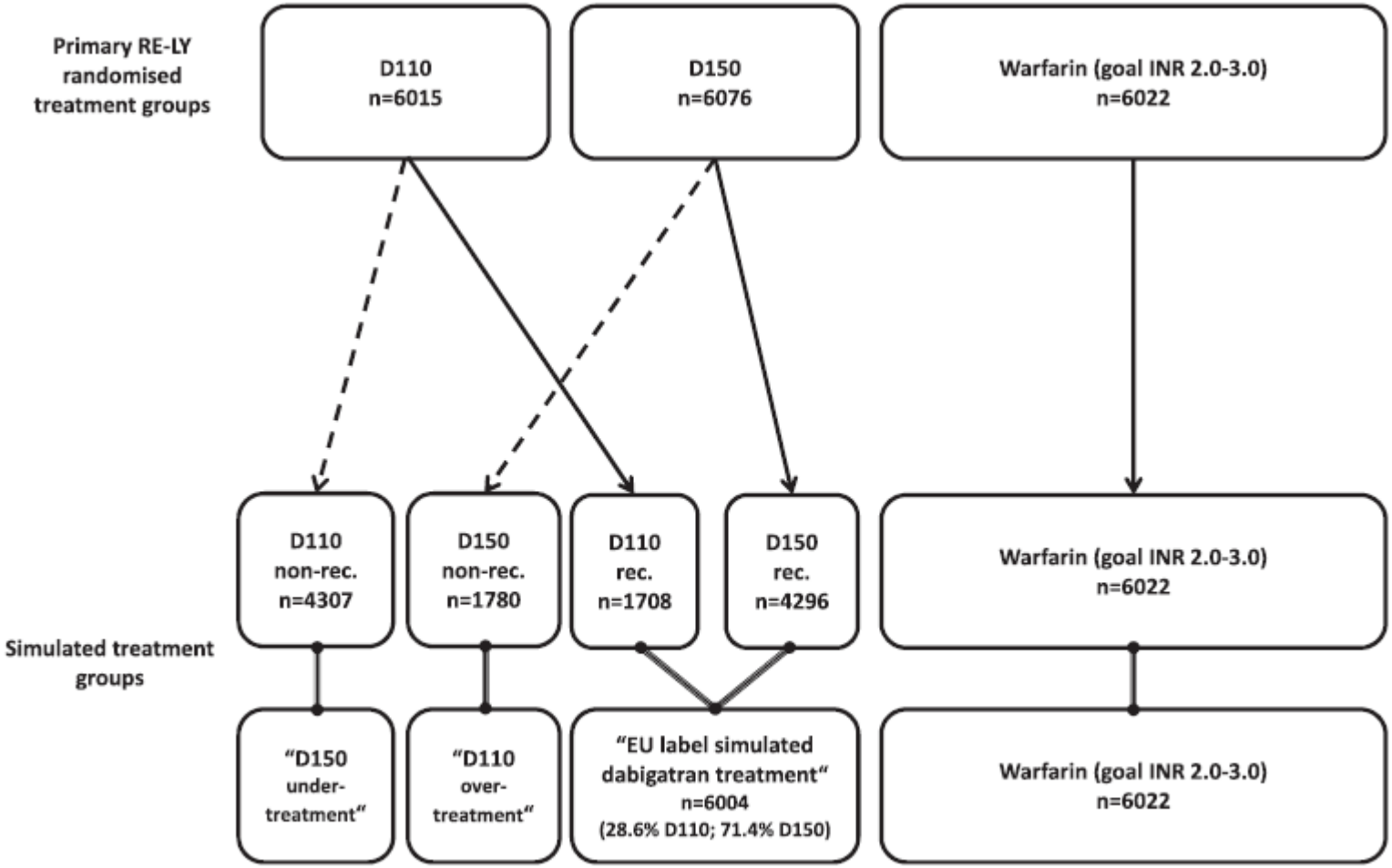
Patient outcomes using the European label for dabigatran. A post-hoc analysis from the RE-LY database.

Thromb Haemost. 2014 May 5;111(5):933-42.

Lip GY[1], Clemens A, Noack H, Ferreira J, Connolly SJ, Yusuf S

Abstract

In the RE-LY trial dabigatran 150 mg twice daily (D150) showed significantly fewer strokes, and 110 mg (D110) significantly fewer major bleeding events (MBE) compared to well-controlled warfarin in patients with atrial fibrillation (AF). The European (EU) label currently recommends the use of D150 in AF patients who are aged < 80 years without an increased risk for bleeding (e.g. HAS-BLED score <3) and not on concomitant verapamil. In other patients, D110 is recommended. In this post-hoc analysis of the RE-LY dataset, we **simulated how dabigatran (n=6,004) used according to the EU label would compare to well-controlled warfarin (n=6,022)**. "**EU label simulated dabigatran treatment**" was associated with significant reductions in stroke and systemic embolism (hazard ratio [HR] **0.74**; 95% confidence interval [CI] 0.60-0.91), haemorrhagic stroke (HR **0.22**; 95%CI 0.11-0.44), death (HR **0.86**; 95%CI 0.75-0.98), and vascular death (HR 0.80; 95%CI 0.68-0.95) compared to warfarin. Dabigatran was also associated with less major bleeding (HR **0.85**; 95%CI 0.73-0.98), life-threatening bleeding (HR **0.72**; 95%CI 0.58-0.91), intracranial haemorrhage (HR **0.28**; 95%CI 0.17-0.45), and "any bleeds" (HR 0.86; 95%CI 0.81-0.92), but not gastrointestinal major bleeding (HR 1.23; 95%CI 0.96-1.59). The net clinical benefit was significantly better for dabigatran compared to warfarin. In conclusion, this post-hoc simulation of dabigatran usage based on RE-LY trial dataset indicates that "EU label simulated dabigatran treatment" may be associated with superior efficacy and safety compared to warfarin, and are in support of the EU label and the 2012 European Society of Cardiology AF guideline recommendations. **Thus, adherence to European label/guideline use results in a clinically relevant benefit for dabigatran over warfarin, for both efficacy and safety**.



We performed an "EU label simulated dabigatran treatment" analysis, where D150 is the recommended dose for patients age < 80 years without an increased risk for bleeding (which we defined by a HAS-BLED score <3) and without concomitant treatment with verapamil. All other patients should receive the D110 dose. In the decision for one of these doses, age was the leading determining factor for the recommended dose (in 77.2% of the cases).

Table 1: Complete RE-LY population: baseline characteristics — original randomized groups and post-hoc pooled EU label simulated dabigatran treated group.

Baseline variable	RE-LY randomised groups			EU label simulated D	Warfarin (as randomised)
	D 110 mg bid	D 150 mg bid	Warfarin		
N (ITT)	6015	6076	6022	6004	6022
Age, years	71.4 ± 8.6	71.5 ± 8.8	71.6 ± 8.6	71.2 ± 8.8	71.6 ± 8.6
Weight, kg	82.9 ± 19.8	82.4 ± 19.3	82.6 ± 19.6	82.7 ± 19.6	82.7 ± 19.7
BMI, kg/m^2	28.8 ± 5.8	28.7 ± 5.7	28.8 ± 5.8	28.8 ± 5.9	28.8 ± 5.8
CrCl, ml/min	72.9 ± 27.5	72.6 ± 27.8	72.9 ± 27.0	73.2 ± 27.8	72.9 ± 27.0
Blood pressure, mmHg					
Systolic	130.8 ± 17.5	130.9 ± 17.6	131.2 ± 17.4	130.9 ± 17.4	131.2 ± 17.4
Diastolic	77.0 ± 10.6	77.0 ± 10.6	77.1 ± 10.4	77.0 ± 10.6	77.1 ± 10.4
Male sex, No. (%)	3865 (64.3)	3840 (63.2)	3809 (63.3)	3847 (64.1)	3809 (63.3)
Type of atrial fibrillation, No. (%)					
Persistent	1950 (32.4)	1909 (31.4)	1930 (32.0)	1919 (32.0)	1930 (32.0)
Paroxysmal	1929 (32.1)	1978 (32.6)	2036 (33.8)	1935 (32.2)	2036 (33.8)
Permanent	2132 (35.4)	2188 (36.0)	2055 (34.1)	2149 (35.8)	2055 (34.1)
$CHADS_2$ score	2.1 ± 1.1	2.1 ± 1.2	2.1 ± 1.1	2.1 ± 1.1	2.1 ± 1.1
0 or 1 — No. (%)	1960 (32.6)	1961 (32.2)	1862 (30.9)	1916 (31.9)	1862 (30.9)
2 — No. (%)	2088 (34.7)	2136 (35.2)	2229 (37.0)	2095 (34.9)	2229 (37.0)
3–6 — No. (%)	1966 (32.7)	1979 (32.6)	1931 (32.1)	1993 (33.2)	1931 (32.1)
Previous stroke or transient ischaemic attack, No. (%)	1195 (19.9)	1233 (20.3)	1195 (19.8)	1219 (20.3)	1195 (19.8)
Prior MI, No. (%)	1008 (16.8)	1029 (16.9)	968 (16.1)	1021 (17.0)	968 (16.1)
Heart failure, No. (%)	1937 (32.2)	1934 (31.8)	1922 (31.9)	1945 (32.4)	1922 (31.9)
Diabetes mellitus, No. (%)	1409 (23.4)	1402 (23.1)	1410 (23.4)	1404 (23.4)	1410 (23.4)
Hypertension, No. (%)	4738 (78.8)	4795 (78.9)	4750 (78.9)	4732 (78.8)	4750 (78.9)
Medications in use at baseline, No. (%)					
Aspirin	2386 (39.7)	2347 (38.6)	2438 (40.5)	2354 (39.2)	2438 (40.5)

Table 2: "D150 recommended" population comparing those receiving D150 dose, D110 dose, or warfarin (A) and the "D110 recommended" group comparing those receiving the D110 dose, D150 dose, or warfarin (B): baseline characteristics — treatment groups by randomisation.

Baseline variable	A) "D150 recommended" population			B) "D110 recommended" population		
	D 110 mg bid	D150 mg bid	Warfarin	D 110 mg	D 150 mg	Warfarin
N, (ITT)	4307	4296	4324	1708	1780	1698
Age, years	68.7 ± 7.5	68.5 ± 7.8	68.9 ± 7.4	78.1 ± 7.6	78.7 ± 7.0	78.4 ± 7.4
Weight, kg	85.1 ± 20.1	84.9 ± 19.8	85.1 ± 19.9	77.2 ± 17.9	76.4 ± 16.7	76.3 ± 17.5
BMI, kg/m^2	29.3 ± 5.9	29.3 ± 5.9	29.3 ± 5.9	27.5 ± 5.5	27.3 ± 5.0	27.3 ± 5.3
CrCl, ml/min	78.7 ± 27.1	79.1 ± 27.6	78.6 ± 26.3	58.2 ± 22.4	57.1 ± 21.5	58.4 ± 23.2
Blood pressure, mmHg						
Systolic	130.2 ± 17.2	130.3 ± 17.1	130.7 ± 17.0	132.5 ± 18.1	132.5 ± 18.4	132.4 ± 18.3
Diastolic	77.5 ± 10.6	77.5 ± 10.5	77.6 ± 10.3	75.8 ± 10.7	75.9 ± 10.8	75.8 ± 10.7
Male sex, No. (%)	2862 (66.4)	2844 (66.2)	2867 (66.3)	1003 (58.7)	996 (56.0)	942 (55.5)
Type of atrial fibrillation, No. (%)						
Persistent	1369 (31.8)	1338 (31.1)	1404 (32.5)	581 (34.0)	571 (32.1)	526 (31.0)
Paroxysmal	1393 (32.3)	1399 (32.6)	1459 (33.7)	536 (31.4)	579 (32.5)	577 (34.0)
Permanent	1541 (35.8)	1558 (36.3)	1460 (33.8)	591 (34.6)	630 (35.4)	595 (35.0)
$CHADS_2$ score	1.9 ± 1.0	2.0 ± 1.0	2.0 ± 1.0	2.6 ± 1.2	2.6 ± 1.3	2.6 ± 1.2
0 or 1 — No. (%)	1667 (38.7)	1623 (37.8)	1578 (36.5)	293 (17.2)	338 (19.0)	284 (16.7)
2 — No. (%)	1423 (34.7)	1500 (34.9)	1596 (36.9)	595 (34.8)	636 (35.8)	633 (37.3)
3–6 — No. (%)	1146 (26.6)	1173 (27.3)	1150 (26.6)	820 (48.0)	806 (45.3)	781 (46.0)
Previous stroke or transient ischaemic attack, No. (%)	736 (17.1)	760 (17.7)	741 (17.1)	459 (26.9)	472 (26.5)	454 (26.7)
Prior MI, No. (%)	681 (15.8)	694 (16.2)	696 (16.1)	327 (19.1)	335 (18.8)	272 (16.0)
Heart failure, No. (%)	1429 (33.2)	1437 (33.4)	1470 (34.0)	508 (29.7)	497 (27.9)	452 (26.6)
Diabetes mellitus, No. (%)	1040 (24.1)	1035 (24.1)	1073 (24.8)	369 (21.6)	367 (20.6)	337 (19.8)
Hypertension, No. (%)	3408 (79.1)	3402 (79.2)	3405 (78.7)	1330 (77.9)	1393 (78.2)	1345 (79.2)
Medications in use at baseline, No. (%)						
Aspirin	1590 (36.9)	1558 (36.3)	1663 (38.5)	796 (46.6)	789 (44.3)	775 (45.6)

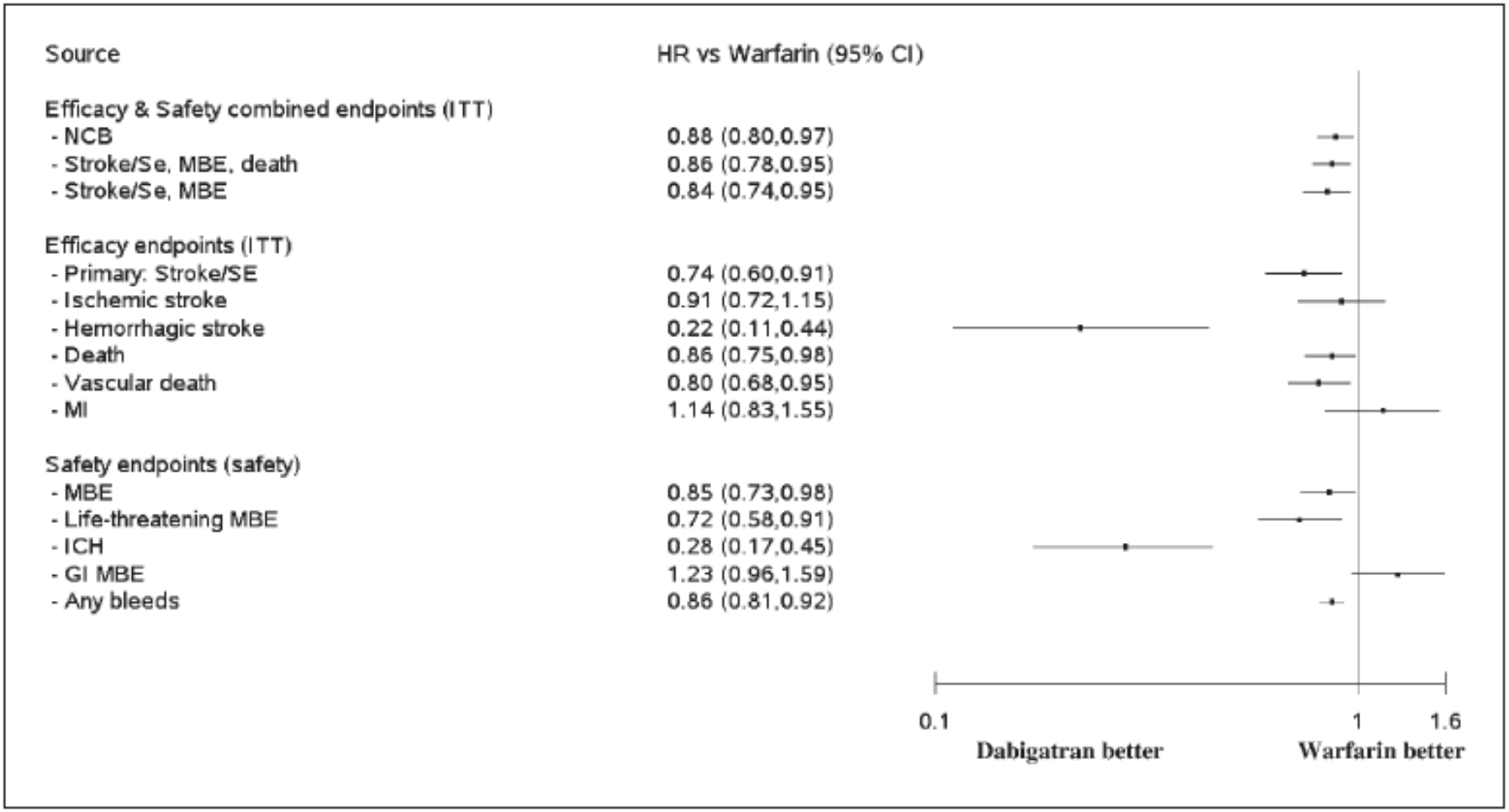


Figure 2: Summary of results for dabigatran EU label simulated dabigatran treatment group compared to warfarin. CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; ICH, intracranial haemorrhage; ITT, intention to treat analysis; MBE, major bleeding event; MI, myocardial infarction; NCB, net clinical benefit; safety, safety set analysis; SE, systemic embolism.

Table 3: Summary of results for dabigatran EU label simulated treatment group compared to warfarin.

Endpoint	Annual rate per 100 person years		Hazard ratio (95% CI)	NNTw D recom vs W
	Post-hoc EU label simulated dabigatran etexilate	Warfarin (as randomised)		
N (ITT)	6,004	6,022		
Primary: stroke/SE	1.27	1.71	0.74 (0.60, 0.91)	226 (133, 748)
Ischaemic stroke	1.10	1.21	0.91 (0.72, 1.15)	906 (260, –613)
Haemorrhagic stroke	0.08	0.38	0.22 (0.11, 0.44)	336 (232, 562)
Death	3.55	4.13	0.86 (0.75, 0.98)	173 (93, 1118)
Vascular death	2.16	2.69	0.80 (0.68, 0.95)	190 (109, 747)
MI	0.72	0.64	1.14 (0.83, 1.55)	–1142 (810, –334)
NCB	6.97	7.91	0.88 (0.80, 0.97)	107 (61, 373)
Stroke/SE, MBE, death	6.50	7.50	0.86 (0.78, 0.95)	100 (61, 285)
Stroke/SE, MBE	3.92	4.66	0.84 (0.74, 0.95)	135 (79, 441)
N (safety)	5,981	5,998		
MBE	3.02	3.55	0.85 (0.73, 0.98)	189 (99, 2180)
Life-threatening MBE	1.28	1.75	0.72 (0.58, 0.91)	210 (123, 689)
GI MBE	1.29	1.04	1.23 (0.96, 1.59)	–407 (2165, –185)
ICH	0.22	0.77	0.28 (0.17, 0.45)	181 (133, 272)
Any bleeds	17.53	19.75	0.86 (0.81, 0.92)	45 (31, 87)

CI, confidence interval; D, dabigatran etexilate; EU, European; GI, gastrointestinal; ICH, intracranial haemorrhage; ITT, intention to treat analysis; MBE, major bleeding event; MI, myocardial infarction; NCB, net clinical benefit; NNTw, number needed to treat compared with warfarin; SE, systemic embolism; W, warfarin.

Table 4A: Effects in the post-hoc defined subpopulations based on EU label (efficacy).

ITT (FAS)		Annual rate per 100 person years			Hazard ratio (95% CI)	
Endpoint	Subpopulation	D 110 mg	D 150 mg	W	D 110 mg vs. W	D 150 mg vs. W
Primary: stroke/SE	D150 bid recom	1.34	0.97	1.39	0.97 (0.75, 1.25)	0.70 (0.53, 0.92)
	D110 bid recom	2.05	1.47	2.55	0.80 (0.58, 1.10)	0.57 (0.40, 0.81)
Ischaemic stroke	D150 bid recom	1.14	0.82	1.01	1.13 (0.85, 1.51)	0.81 (0.59, 1.11)
	D110 bid recom	1.84	1.18	1.73	1.06 (0.74, 1.53)	0.68 (0.46, 1.02)
Haemorrhagic stroke	D150 bid recom	0.12	0.07	0.28	0.41 (0.20, 0.85)	0.25 (0.10, 0.60)
	D110 bid recom	0.12	0.17	0.64	0.19 (0.06, 0.55)	0.27 (0.11, 0.67)
Death	D150 bid recom	2.99	2.72	3.46	0.86 (0.73, 1.02)	0.78 (0.66, 0.93)
	D110 bid recom				.97 (0.79, 1.19)	1.01 (0.83, 1.23)
Vascular death	D150 bid recom				.88 (0.72, 1.08)	0.73 (0.59, 0.90)
	D110 bid recom				.94 (0.72, 1.22)	1.04 (0.81, 1.35)
MI	D150 bid recom				.36 (0.95, 1.95)	1.13 (0.77, 1.64)
	D110 bid recom				.16 (0.67, 2.00)	1.55 (0.93, 2.58)
NCB	D150 bid recom				.88 (0.78, 0.99)	0.81 (0.72, 0.91)
	D110 bid recom				.00 (0.86, 1.16)	1.04 (0.90, 1.21)
Stroke/SE, MBE, death	D150 bid recom				.86 (0.76, 0.97)	0.79 (0.70, 0.90)
	D110 bid recom	10.04	10.33	10.20	0.98 (0.85, 1.15)	1.03 (0.88, 1.19)
Stroke/SE, MBE	D150 bid recom	3.34	3.13	4.00	0.83 (0.71, 0.98)	0.78 (0.66, 0.91)
	D110 bid recom	5.97	6.52	6.38	0.94 (0.77, 1.14)	1.04 (0.86, 1.25)

CI, confidence interval; D, dabigatran etexilate; EU, European; MBE, major bleeding event; MI, myocardial infarction; FAS, full analysis set; ITT, intention to treat analysis; NCB, net clinical benefit; SE, systemic embolism; W, warfarin.

Conclusion

"EU label simulated dabigatran treatment" of dabigatran shows superior efficacy and safety compared to warfarin in this post-hoc analysis of the RE-LY trial. This analysis is in support of the EU label for the appropriate prescribing of dabigatran. When analysed by mainly age-related recommended treatment doses, for the endpoints that combine benefit and risk (i.e. efficacy and safety), the recommended dose provides a meaningful and clinically relevant benefit over warfarin, in support of the EU label and the recently published 2012 ESC guideline recommendations[9] for the appropriate prescribing of dabigatran.

New Oral Anticoagulants in Elderly Adults: Evidence from a Meta-Analysis of Randomized Trials

J Am Geriatr Soc 62:857–864, 2014.

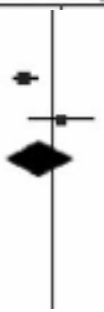
Trial (Reference)	Intervention	Control	NOAC Group According to Age, n	Control Group According to Age, n	Age, NOAC/ Conventional Therapy[a]	Male,%, NOAC/ Conventional Therapy[a]	Follow-Up
ARISTOTLE (2011)[27]	Apixaban 5 mg twice daily	Warfarin	>75 = 2,743 65–75 = 3,504	>75 = 2,752 65–75 = 3,660	70/70[d]	64.5/65	1.8 years (median)
AVERROES (2011)[28]	Apixaban 5 mg twice daily	Aspirin 81–324 mg/d	>75 = 909 65–75 = 1,090	>75 = 983 65–75 = 942	70 ± 9/ 70 ± 10[c]	59/58	1.1 years

Patients aged more than 75 years: Major or clinically relevant bleeding

Study or Subgroup	NOAC Events	NOAC Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2 Apixaban						
ARISTOTLE, 2011	151	2,542	224	2,393	15.8%	0.61 [0.49, 0.76]
AVERROES, 2011	26	909	24	983	11.5%	1.18 [0.67, 2.06]
Subtotal (95% CI)		**3,451**		**3,376**	**27.2%**	**0.80 [0.43, 1.51]**
Total events	177		248			

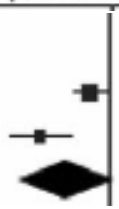
Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 4.54$, df = 1 (P = 0.03); $I^2 = 78\%$

Test for overall effect: Z = 0.68 (P = 0.50)



Patients aged more than 75 years: Stroke or systemic embolism

Study or Subgroup	NOAC Events	NOAC Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2 Apixaban						
ARISTOTLE, 2011	79	2,743	109	2,752	26.2%	0.72 [0.54, 0.97]
AVERROES, 2011	20	909	66	983	17.2%	0.31 [0.19, 0.52]
Subtotal (95% CI)		**3,652**		**3,735**	**43.4%**	**0.49 [0.22, 1.10]**



EFFECTS OF ORAL ANTICOAGULANT THERAPY IN OLDER VULNERABLE MEDICAL IN-PATIENTS WITH ATRIAL FIBRILLATION: A RETROSPECTIVE COHORT OBSERVATIONAL STUDY Bo M, Sciarrillo I, Li Puma F, Badinella-Martina M, Falcone Y, Iacovino M, Grisoglio E, Menditto E, Fonte G, Tibaldi M, Maggiani G, Isaia GC, Gaita F #.

Table 3. Variables independently associated with mortality and clinical events of interest.

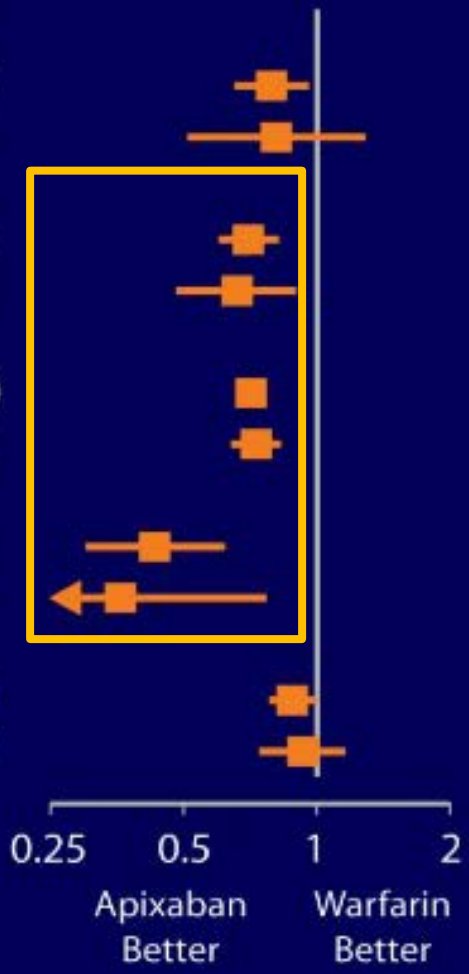
	β	SE	p	OR
Mortality				
Intermediate or long-term care facility discharge	0.8288	0.2266	.0003	2.2905
Creatinin	0.3125	0.1267	.0137	1.3668
CHARLSON index	0.1742	0.0368	.000	1.1903
Anticoagulant therapy at discharge	-0.6463	0.1516	.0000	0.5240
Functional dependence (ADL)	0.4712	0.1523	.0020	1.6018
Age	0.0673	0.0119	.0000	1.0697
Ischemic stroke				
$CHAD_2S_2VASC$	0.2374	0.0824	.0040	1.2679
Hemoglobin level	0.1842	0.0583	.0016	1.2022
Dementia	0.8874	0.2603	.0007	2.4287
Hemorrhagic stroke	-	-	-	-
Major Bleeding events				
Female gender	-0.7890	0.3285	.0163	0.4543
Known AF	-1.0905	0.3742	.0036	0.3361
Permanent AF	0.5500	0.2687	.0407	1.7333
HAS-BLED	0.2976	0.1067	.0053	1.3466
Hemoglobin level	-0.1826	0.818	.0255	0.8331
Re-hospitalizations	0.1440	0.0513	.0050	1.1549

Bo M. et al, 2015, submitted

Apixaban vs Warfarin in Patients ≥ 80 vs < 80 Years

ARISTOTLE

	Apixaban	Warfarin	HR (95% CI)	Interaction P-value
	Number of events (%/year)			
Stroke/Systemic Embolism				0.91
Age < 80	179(1.23)	225(1.55)	0.79 (0.65, 0.96)	
Age ≥ 80	33(1.53)	40(1.90)	0.81 (0.51, 1.29)	
Major Bleeding				0.74
Age < 80	260(1.93)	366(2.78)	0.70 (0.60, 0.82)	
Age ≥ 80	67(3.55)	96(5.41)	0.66 (0.48, 0.90)	
All Bleeding				0.83
Age < 80	1964(17.0)	2558(24.4)	0.71 (0.67, 0.76)	
Age ≥ 80	392(26.4)	502(37.4)	0.73 (0.64, 0.83)	
Intracranial Bleeding				0.67
Age < 80	43(0.32)	98(0.73)	0.43 (0.30, 0.62)	
Age ≥ 80	9(0.47)	24(1.32)	0.36 (0.17, 0.77)	
All-cause Mortality				0.73
Age < 80	452(3.03)	507(3.42)	0.88 (0.78, 1.00)	
Age ≥ 80	151(6.86)	162(7.44)	0.93 (0.74, 1.16)	



UCR

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®

OBJECTIVES: The evaluation of the "net clinical benefit" allows an integrated assessment of both the anti-ischemic and the prohemor anticoagulants compared with warfarin, and—in the abser decisions. We estimated the net clinical benefit of non-vita varfarin across the 4 phase III clinical trials performed in

METHODS: We considered v norrhagic events, estimating the rate ratio of all treatment g ome. Because the clinical rele-vance of the various ischen en attributed to each of them a weight, according to its im s. We evaluated a weighed net clinical benefit of each non- ed with warfarin in the 4 trials.

RESULTS: The composite o reduced by dabigatran 150 mg and apixaban. The compos ding was reduced by all non—vitamin K antagonist oral roke + systemic embolism + myocardial infarction + he d by apixaban and edoxaban at both doses. By attributing v on mortality, all non-vitamin K antagonist oral anticoagula pared with warfarin, albeit to a quantitatively different extent.

CONCLUSIONS: The choice of the proper antithrombotic treatment in patients with atrial fibrillation has to consider the net clinical benefit of each drug. However, all non-vitamin K antagonist oral anticoagulants have a better efficacy/safety profile than warfarin in patients with atrial fibrillation.

- We evaluated the net clinical benefit for various non-vitamin K antagonist oral anticoagulants in phase III clinical trials comparing them with warfarin in atrial fibrillation, weighing nonfatal efficacy and safety outcomes according to their prognostic impact on mortality.
- Although non-vitamin K antagonist oral anticoagulants have shown variable efficacy and safety relative to warfarin, according to this analysis all have a better and strikingly similar net clinical benefit in patients with atrial fibrillation.

Trial Name	Treatment Arm	Dose	No. of Patients	Median Follow-up (y)	Mean Age (y)	Male Gender (%)	Mean $CHADS_2$	Median TTR (%)
RE-LY (2)	Dose-adjusted warfarin	INR 2.0-3.0	6022	2	71.6	63.3	2.1	67
	Dabigatran 150 mg	150 mg BID	6076		71.5	63.2	2.2	NA
	Dabigatran 110 mg	110 mg BID	6015		71.4	64.3	2.1	NA
ROCKET-AF (3)	Dose-adjusted warfarin	INR 2.0-3.0	7090	1.9	71.2	60.3	3.46	58
	Rivaroxaban	20 mg (or 15 mg*) OD	7131		71.2	60.3	3.48	NA
ARISTOTLE (4)	Dose-adjusted warfarin	INR 2.0-3.0	9081	1.8	64.5	65	2.1	66
	Apixaban	5 mg (or 2.5 mg†) BID	9120		69.1	64.4	2.1	NA
ENGAGE AF-TIMI 48 (5)	Dose-adjusted warfarin	INR 2.0-3.0	7036	2.8	72	62.5	2.8	68
	Edoxaban 60 mg	60 mg (or 30 mg‡) OD	7035		72	62.1	2.8	NA
	Edoxaban 30 mg	30 mg (or 15 mg‡) OD	7034		72	61.2	2.8	NA

Table 2 Rate Ratio and Corresponding 95% Confidence Interval for Each Treatment Arm of the Various Trials Versus Warfarin for the Various Composite Outcomes Considered

Treatment	Ischemic Stroke + Hemorrhagic Stroke	Disabling Stroke + Life-threatening Bleeding	Ischemic Stroke + Hemorrhagic Stroke + Myocardial Infarction + Systemic Embolism + Adjusted Major Bleeding
Dabigatran 150 mg	0.65 (0.51-0.81)	0.8 (0.67-0.95)	0.93 (0.83-1.03)
	<.001	**.009**	.201
Dabigatran 110 mg	0.91 (0.74-1.12)	0.78 (0.66-0.93)	0.93 (0.83-1.03)
	.382	**.005**	.205
Rivaroxaban	0.83 (0.68-1.00)	0.70 (0.56-0.87)	0.92 (0.83-1.03)
	.058	**<.001**	.151
Apixaban	0.79 (0.66-0.96)	0.55 (0.44-0.68)	0.78 (0.70-0.87)
	.015	**<.001**	**<.001**
Edoxaban 60 mg	0.88 (0.75-1.02)	0.67 (0.53-0.84)	0.87 (0.79-0.95)
	.106	**<.001**	**.004**
Edoxaban 30 mg	1.12 (0.96-1.30)	0.69 (0.55-0.88)	0.85 (0.77-0.93)
	.146	**.002**	**<.001**

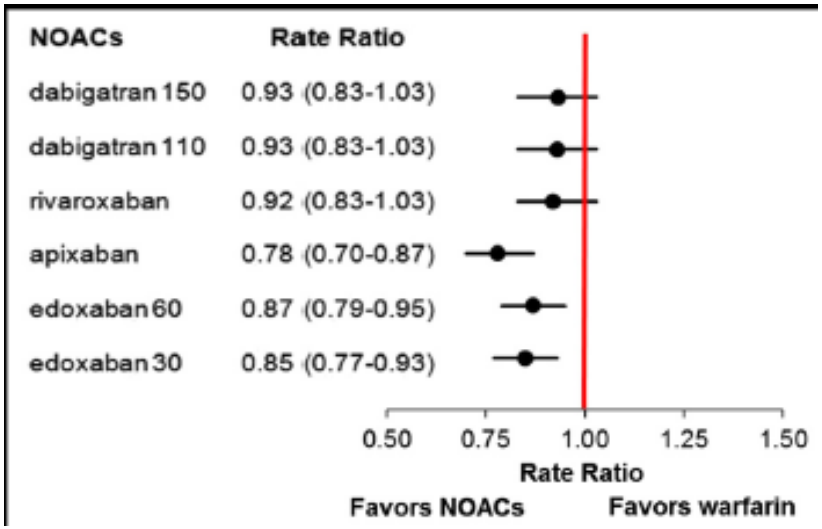


Figure 1 RR and 95% CI of all treatment arms in the phase III trials comparing a non-vitamin K antagonist oral anticoagulants with warfarin for the overall composite outcome including unweighed ischemic stroke + systemic embolism + myocardial infarction + hemorrhagic stroke + adjusted major bleeding (major bleeding minus hemorrhagic stroke). NOAC = non-vitamin K antagonist oral anticoagulant.

Table 3 Crude Incidence Rate per 100 Patient-years of Each Weighed Event for All Treatment Groups

	Ischemic Stroke	Systemic Embolism	Myocardial Infarction	Hemorrhagic Stroke	Adjusted Major Bleeding
Weight	1.00	0.61	0.89	3.23	0.63
RE-LY					
Dabigatran 150 mg	0.92	0.07	0.72	0.32	2.02
Dabigatran 110 mg	1.34	0.07	0.73	0.39	1.72
Warfarin	1.21	0.10	0.57	1.23	1.97
ROCKET-AF					
Rivaroxaban	1.40	0.02	0.81	0.84	2.10
Warfarin	1.52	0.12	1.00	1.42	1.86
ARISTOTLE					
Apixaban	0.97	0.05	0.47	0.78	1.19
Warfarin	1.05	0.06	0.54	1.52	1.65
ENGAGE AF-TIMI 48					
Edoxaban 60 mg	1.25	0.05	0.62	0.84	1.57
Edoxaban 30 mg	1.77	0.09	0.79	0.52	0.91
Warfarin	1.25	0.07	0.67	1.52	1.86

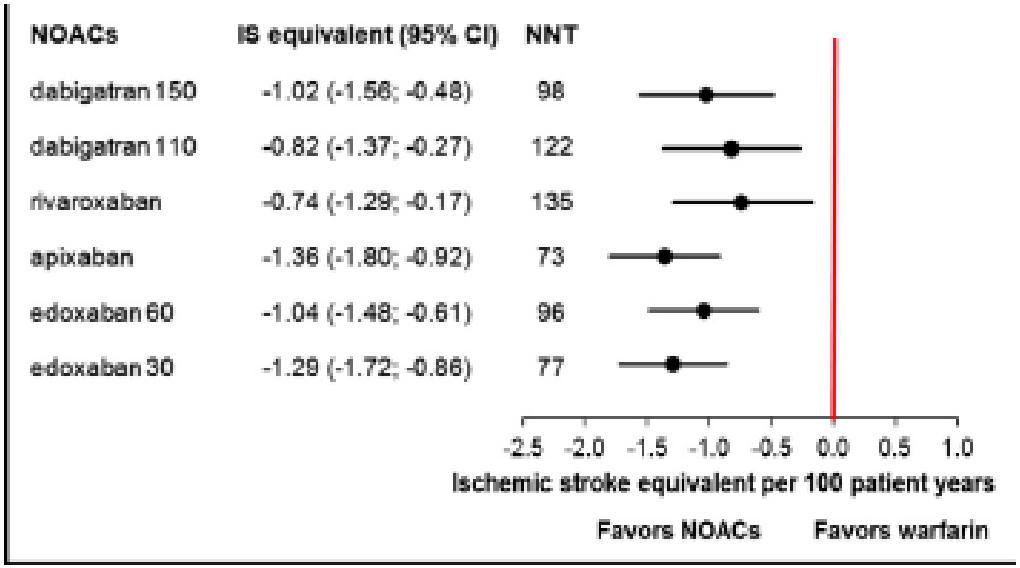


Figure 2 Net clinical benefit and 95% CI of all treatment arms of non-vitamin K antagonist oral anticoagulants versus warfarin tested in phase III clinical trials for the weighed composite outcome of ischemic stroke + systemic embolism + myocardial infarction + hemorrhagic stroke + adjusted major bleeding (major bleeding minus hemorrhagic stroke). Net clinical benefit is expressed as ischemic stroke equivalents prevented per 100 person-years using ischemic stroke as the reference event (weight = 1). CI = confidence interval; IS = ischemic stroke; NNT = number needed to treat (to prevent all grouped events included in the net clinical benefit evaluation, per year of treatment); NOAC = non-vitamin K antagonist oral anticoagulant.

(*Circulation*. 2015;131:157-164.

Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation

Background—The comparative safety of dabigatran versus warfarin for treatment of nonvalvular atrial fibrillation in general practice settings has not been established.

Methods and Results—We formed new-user cohorts of propensity score–matched elderly patients enrolled in Medicare who initiated dabigatran or warfarin for treatment of nonvalvular atrial fibrillation between October 2010 and December 2012. Among 134 414 patients with 37 587 person-years of follow-up, there were 2715 primary outcome events. The hazard ratios (95% confidence intervals) comparing dabigatran with warfarin (reference) were as follows: ischemic stroke, 0.80 (0.67–0.96); intracranial hemorrhage, 0.34 (0.26–0.46); major gastrointestinal bleeding, 1.28 (1.14–1.44); acute myocardial infarction, 0.92 (0.78–1.08); and death, 0.86 (0.77–0.96). In the subgroup treated with dabigatran 75 mg twice daily, there was no difference in risk compared with warfarin for any outcome except intracranial hemorrhage, in which case dabigatran risk was reduced. Most patients treated with dabigatran 75 mg twice daily appeared not to have severe renal impairment, the intended population for this dose. In the dabigatran 150-mg twice daily subgroup, the magnitude of effect for each outcome was greater than in the combined-dose analysis.

Conclusions—In general practice settings, dabigatran was associated with reduced risk of ischemic stroke, intracranial hemorrhage, and death and increased risk of major gastrointestinal hemorrhage compared with warfarin in elderly patients with nonvalvular atrial fibrillation. These associations were most pronounced in patients treated with dabigatran 150 mg twice daily, whereas the association of 75 mg twice daily with study outcomes was indistinguishable from warfarin except for a lower risk of intracranial hemorrhage with dabigatran. **(*Circulation*. 2015;131:157-164. DOI: 10.1161/CIRCULATIONAHA.114.012061.)**

Table 1. Sociodemographic Factors, Medical Conditions, and Medication Use at Baseline in Propensity Score–Matched Medicare Beneficiaries Initiating Dabigatran or Warfarin for Atrial Fibrillation, 2010–2012

Characteristic	Dabigatran, % (n=67 207)	Warfarin, % (n=67 207)	Standardized Mean Difference
Age group, y			
65–74	42	41	0.01
75–84	43	43	0.01
≥85	16	16	0.00
Female sex	51	52	0.01
Medical history			
General			
Diabetes mellitus	33	34	0.00
Hypercholesterolemia	74	74	0.00
Hypertension	87	87	0.00
Kidney failure			
Acute	5	5	0.00
Chronic	13	13	0.00
Obesity	11	11	0.00
Peptic ulcer disease	<1	<1	0.00
Prior bleeding event			
Hospitalized	1	1	0.00
Not hospitalized	3	3	0.01
Smoking	16	16	0.01
Cardiovascular disease			
Acute myocardial infarction			
Past 1–30 d	1	1	0.01
Past 31–183 d	1	1	0.00
Coronary revascularization	16	16	0.01
Heart failure			
Hospitalized	4	4	0.01
Outpatient	14	14	0.00
Other ischemic heart disease	48	49	0.01
Stroke			
Past 1–30 d	2	2	0.00
Past 31–183 d	1	2	0.00
Other cerebrovascular disease	13	13	0.00
Transient ischemic attack	7	7	0.00
Cardioablation	2	2	0.00
Cardioversion	9	9	0.02

Table 3. Effect of Age and Sex on Risk of Ischemic Stroke, Intracranial Hemorrhage, Major Gastrointestinal Bleeding, and Mortality in Propensity Score–Matched Cohorts Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation, With Warfarin as the Reference Group*

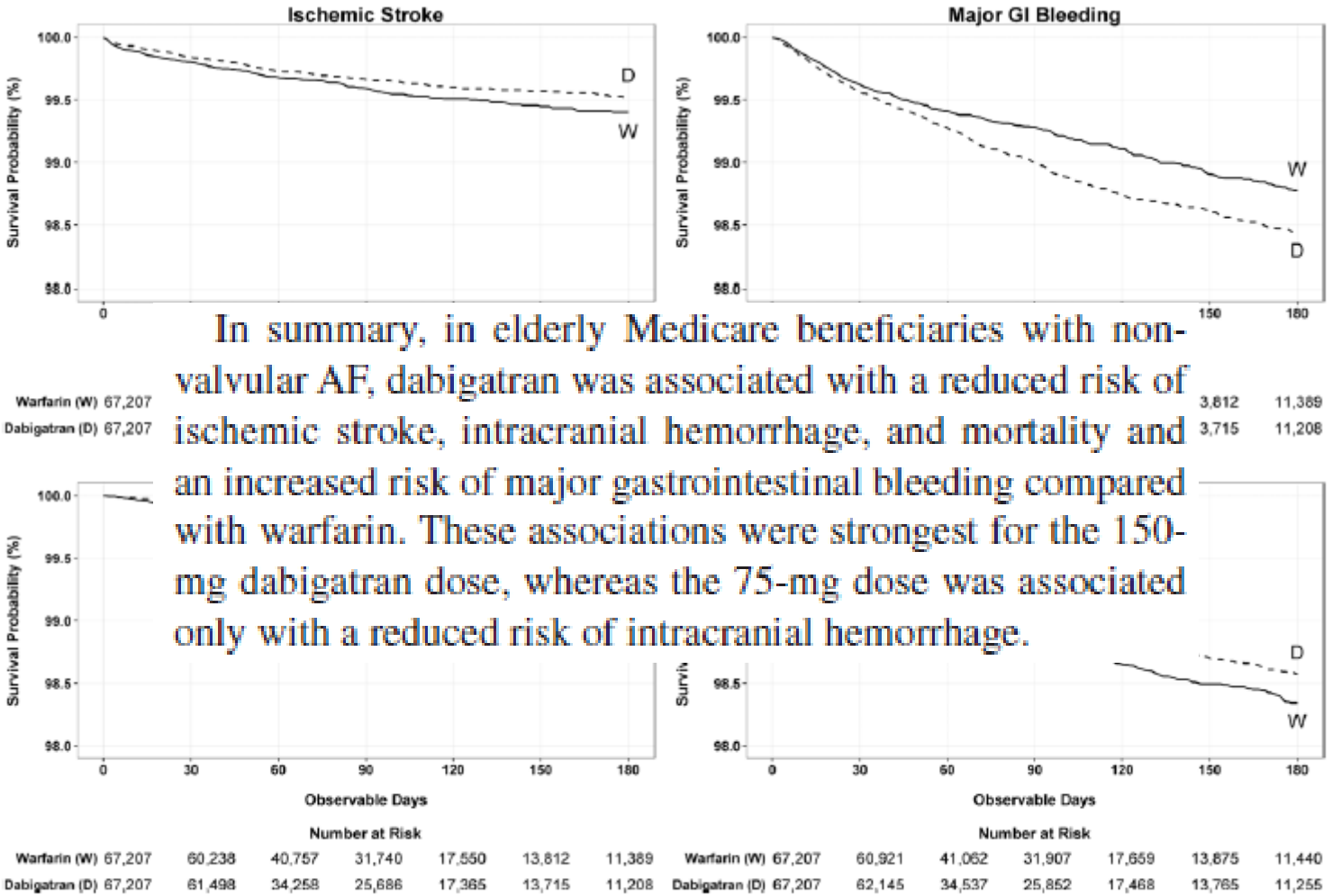
	Age Group (n)	Men, Hazard Ratio (95% CI)	Women, Hazard Ratio (95% CI)
Ischemic stroke			
	65–74 (55 761)	0.69 (0.42–1.14)	0.81 (0.51–1.31)
	75–84 (57 345)	0.98 (0.64–1.51)	0.89 (0.64–1.26)
	≥85 (21 308)	0.89 (0.41–1.90)	0.60 (0.40–0.91)
Intracranial hemorrhage			
	65–74 (55 761)	0.32 (0.15–0.68)	0.13 (0.04–0.44)
	75–84 (57 345)	0.27 (0.14–0.50)	0.59 (0.35–0.98)
	≥85 (21 308)	0.51 (0.18–1.48)	0.26 (0.12–0.56)
Major gastrointestinal bleeding			
	65–74 (55 761)	0.83 (0.60–1.14)	0.99 (0.72–1.37)
	75–84 (57 345)	1.02 (0.79–1.31)	1.50 (1.20–1.88)
	≥85 (21 308)	1.55 (1.04–2.32)	2.18 (1.61–2.97)
Mortality			
	65–74 (55 761)	0.81 (0.62–1.05)	0.72 (0.52–0.99)
	75–84 (57 345)	0.73 (0.58–0.92)	0.82 (0.65–1.03)
	≥85 (21 308)	0.92 (0.64–1.33)	1.24 (0.96–1.60)

Table 2. Outcome Event Counts, Incidence Rates, and Adjusted Hazard Ratios With 95% CIs Comparing Propensity Score–Matched New-User Cohorts of Dabigatran and Warfarin Treated for Nonvalvular Atrial Fibrillation, With Warfarin as the Reference Group

	No. of Events		Incidence Rate per 1000 Person-Years		Adjusted Hazard Ratio	
	Dabigatran	Warfarin	Dabigatran	Warfarin	(95% CI)	*P* Value
Primary outcomes						
Ischemic stroke	205	270	11.3	13.9	0.80 (0.67–0.96)	0.02
Major hemorrhage	777	851	42.7	43.9	0.97 (0.88–1.07)	0.50
Gastrointestinal	623	513	34.2	26.5	1.28 (1.14–1.44)	<0.001
Intracranial	60	186	3.3	9.6	0.34 (0.26–0.46)	<0.001
Intracerebral	44	142	2.4	7.3	0.33 (0.24–0.47)	<0.001
Acute myocardial infarction	285	327	15.7	16.9	0.92 (0.78–1.08)	0.29
Secondary outcomes						
All hospitalized bleeds	1079	1139	59.3	58.8	1.00 (0.92–1.09)	0.97
Mortality*	603	744	32.6	37.8	0.86 (0.77–0.96)	0.006

Table 4. Effect of Daily Dose of Dabigatran on Risk of Ischemic Stroke, Major Gastrointestinal Bleeding, Intracranial Hemorrhage, and Mortality Compared With Treatment With Warfarin for Nonvalvular Atrial Fibrillation*

	Ischemic Stroke, Hazard Ratio (95% CI)	Major Gastrointestinal Bleed, Hazard Ratio (95% CI)	Intracranial Hemorrhage, Hazard Ratio (95% CI)	Mortality, Hazard Ratio (95% CI)
75 mg twice daily (n=10 522)	0.88 (0.60–1.27)	1.01 (0.78–1.31)	0.46 (0.26–0.81)	0.95 (0.78–1.16)
150 mg twice daily (n=56 576)	0.70 (0.57–0.85)	1.51 (1.32–1.73)	0.30 (0.21–0.42)	0.76 (0.67–0.86)



In summary, in elderly Medicare beneficiaries with nonvalvular AF, dabigatran was associated with a reduced risk of ischemic stroke, intracranial hemorrhage, and mortality and an increased risk of major gastrointestinal bleeding compared with warfarin. These associations were strongest for the 150-mg dabigatran dose, whereas the 75-mg dose was associated only with a reduced risk of intracranial hemorrhage.

Figure. Kaplan–Meier plots showing risk of ischemic stroke, major gastrointestinal (GI) bleeding, intracranial hemorrhage, and mortality in propensity score–matched cohorts treated with dabigatran (D; dotted line) or warfarin (W; solid line) for nonvalvular atrial fibrillation.

Efficacy and Safety of Dabigatran Etexilate and Warfarin in "Real-World" Patients With Atrial Fibrillation

A Prospective Nationwide Cohort Study

(J Am Coll Cardiol 2013;61:2264–73)

From the Danish Registry of Medicinal Product Statistics, we identified a dabigatran-treated group and a 1:2 propensity-matched warfarin-treated group of 4,978 and 8,936, respectively. Comparisons on efficacy and safety outcomes were made on the basis of Cox-proportional hazards models stratified on propensity-matched groups.

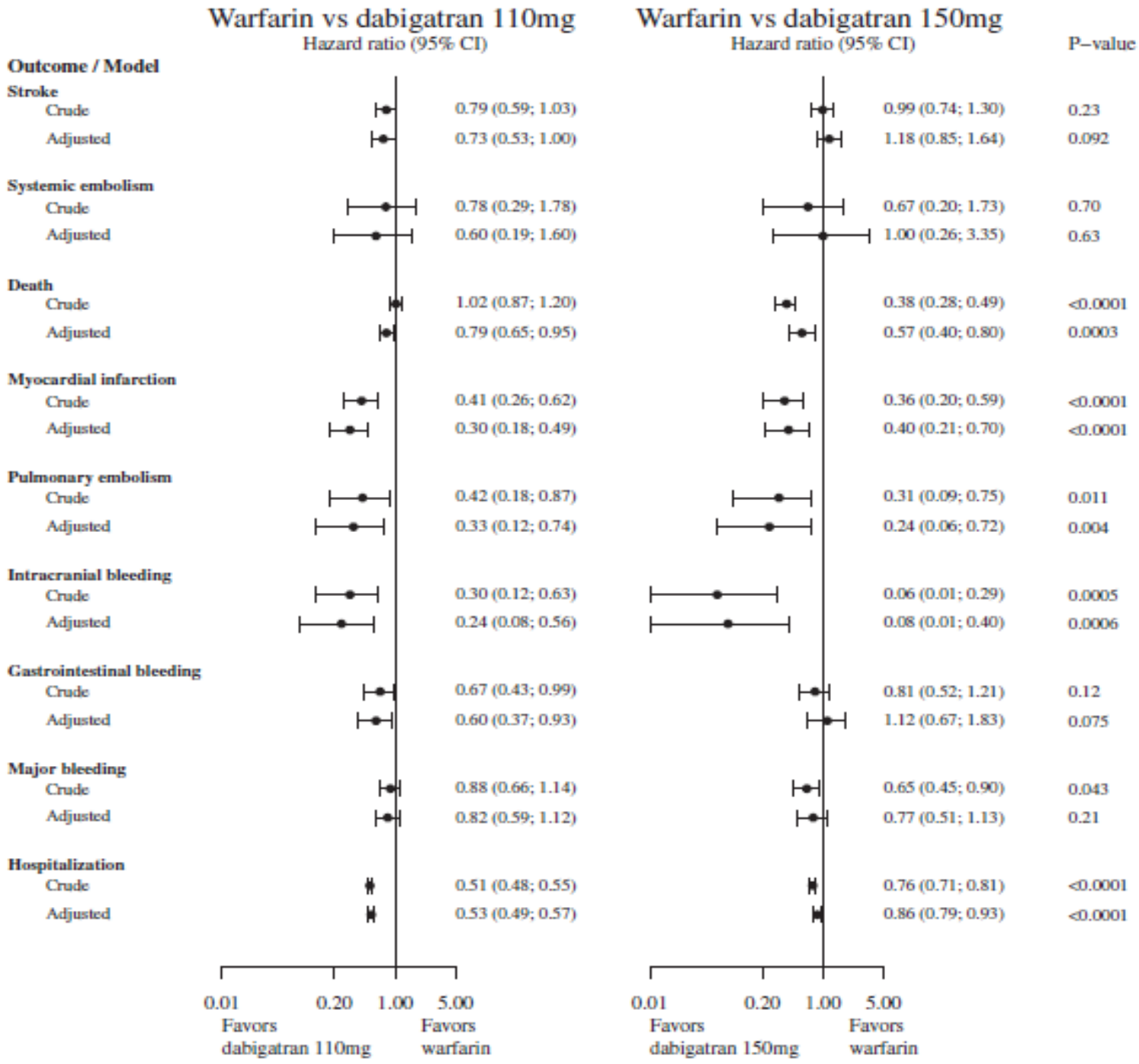
Stroke and systemic embolism were not significantly different between warfarin- and dabigatran-treated patients. Adjusted mortality was significantly lower with both dabigatran doses (110 mg b.i.d., propensity-match group stratified hazard ratio [aHR]: 0.79, 95% confidence interval [CI]: 0.65 to 0.95; 150 mg b.i.d., aHR: 0.57, 95% CI: 0.40 to 0.80), when compared with warfarin. Pulmonary embolism was lower compared with warfarin for both doses of dabigatran. Less intracranial bleeding was seen with both dabigatran doses (110 mg b.i.d., aHR: 0.24, 95% CI: 0.08 to 0.56; 150 mg b.i.d., aHR: 0.08, 95% CI: 0.01 to 0.40). The incidence of MI was lower with both dabigatran doses (110 mg b.i.d., aHR: 0.30, 95% CI: 0.18 to 0.49; 150 mg b.i.d., aHR: 0.40, 95% CI: 0.21 to 0.70). Gastrointestinal bleeding was lower with dabigatran 110 mg b.i.d. (aHR: 0.60, 95% CI: 0.37 to 0.93) compared with warfarin but not dabigatran 150 mg b.i.d. The main findings were broadly consistent in a subgroup analysis of dabigatran users with ≥1-year follow-up (median follow-up 13.9 months [interquartile range: 12.6 to 15.3 months]).

In this "everyday clinical practice" post-approval nationwide clinical cohort, there were similar stroke/systemic embolism and major bleeding rates with dabigatran (both doses) compared with warfarin. Mortality, intracranial bleeding, pulmonary embolism, and MI were lower with dabigatran, compared with warfarin. We found no evidence of an excess of bleeding events or MI among dabigatran-treated patients in this propensity-matched comparison against warfarin, even in the subgroup with ≥1-year follow-up. (J Am Coll Cardiol 2013;61:2264–73)

	2009–2010*	2011–2012†				
	Warfarin (n = 8,936)	Warfarin and Dabigatran All (n = 14,267)	Dabigatran, 150 mg (n = 2,239)	Dabigatran, 110 mg (n = 2,739)	Warfarin (n = 9,289)	RE-LY Trial All (n = 18,113)
Age, yrs	69.7 ± 12.5	70.8 ± 12.1	67.4 ± 8.5	74.7 ± 11.8	70.4 ± 12.6	71.8 ± 8.7
≥65	70.0 (6,242)	73.8 (10,524)	68.6 (1,536)	80.5 (2,206)	73.0 (6,782)	N/A
≥75	37.0 (3,295)	38.6 (5,508)	18.3 (410)	52.8 (1,445)	39.3 (3,653)	N/A
≥80	20.1 (1,797)	23.0 (3,275)	2.4 (54)	40.9 (1,121)	22.6 (2,100)	N/A
≥85	7.6 (670)	10.1 (1,437)	0.8 (19)	19.7 (540)	9.5 (878)	N/A
Female	40.2 (3,595)	43.5 (6,203)	38.5 (861)	53.1 (1,455)	41.9 (3,887)	36.4 (6,599)
$CHADS_2$‡	1.17 ± 1.18	1.16 ± 1.18	0.96 ± 1.07	1.27 ± 1.27	1.18 ± 1.17	2.13 ± 1.13
$CHADS_2$ 3–6	14.2 (1,271)	14.3 (2,047)	9.5 (212)	18.9 (518)	14.2 (1,317)	32.5 (5,882)
Prior stroke, transient ischemic attack, or systemic embolism	17.3 (1,542)	16.1 (2,297)	17.1 (383)	17.5 (478)	15.5 (1,436)	20.0 (3,623)
Heart failure	8.5 (764)	8.3 (1,179)	5.2 (116)	6.9 (188)	9.4 (875)	32.0 (5,793)
Myocardial infarction	9.6 (861)	9.5 (1,362)	6.1 (136)	8.0 (218)	10.9 (1,008)	16.6 (3,005)
Diabetes mellitus	12.3 (1,099)	12.0 (1,713)	12.1 (270)	10.8 (295)	12.4 (1,148)	23.3 (4,221)
Hypertension	19.3 (1,721)	20.9 (2,977)	22.7 (509)	18.0 (493)	21.2 (1,975)	78.3 (14,183)
Moderate/severe renal disease	4.0 (354)	3.9 (552)	1.2 (27)	2.0 (55)	5.1 (470)	N/A
Moderate/severe hepatic disease	0.3 (29)	0.2 (34)	0.0 (0)	0.2 (6)	0.3 (28)	N/A

Table 2 Efficacy and Safety for New Atrial Fibrillation Patients Treated With Dabigatran

	Warfarin D150 Matched* (n = 3996)	Dabigatran 150 mg (n = 2239)	Warfarin D110 Matched (n = 4940)	Dabigatran 110 mg (n = 2739)
Primary endpoints				
Stroke	109/3,626/3.0	60/1,722/3.5	157/4,333/3.6	62/2,299/2.7
Systemic embolism	8/3,684/0.2	4/1,758/0.2	18/4,402/0.4	6/2,322/0.3
Intracranial bleeding	27/3,680/0.7	1/1,760/0.1	42/4,398/1.0	6/2,323/0.3
Secondary endpoints				
Death from any cause	172/3,689/4.7	52/1,760/3.0	453/4,411/10.3	185/2,326/8.0
Gastrointestinal bleeding	53/3,661/1.5	26/1,749/1.5	90/4,369/2.1	28/2,311/1.2
Traumatic intracranial bleeding	11/3,684/0.3	0/1,760/0	10/4,408/0.2	4/2,324/0.2
Major bleeding	104/3,630/2.9	37/1,744/2.2	151/4,329/ 3.5	65/2,296/2.8
Other endpoints				
Myocardial infarction	70/3,650/1.9	15/1,752/0.9	111/4,342/2.6	22/2,316/1.0
Pulmonary embolism	20/3,675/0.5	4/1,760/0.2	36/4,397/0.8	7/2,324/0.3
Hospital stay	2,438/2,082/117.1	1,003/1,129/88.8	2,981/2,534/117.6	970/1,726/56.2


Warfarin vs dabigatran 110mg
Hazard ratio (95% CI)
Warfarin vs dabigatran 150mg
Hazard ratio (95% CI)
P–value
Outcome / Model
Stroke
Crude
0.79 (0.59; 1.03)
0.99 (0.74; 1.30)
0.23
Adjusted
0.73 (0.53; 1.00)
1.18 (0.85; 1.64)
0.092
Systemic embolism
Crude
0.78 (0.29; 1.78)
0.67 (0.20; 1.73)
0.70
Adjusted
0.60 (0.19; 1.60)
1.00 (0.26; 3.35)
0.63
Death
Crude
1.02 (0.87; 1.20)
0.38 (0.28; 0.49)
<0.0001
Adjusted
0.79 (0.65; 0.95)
0.57 (0.40; 0.80)
0.0003
Myocardial infarction
Crude
0.41 (0.26; 0.62)
0.36 (0.20; 0.59)
<0.0001
Adjusted
0.30 (0.18; 0.49)
0.40 (0.21; 0.70)
<0.0001
Pulmonary embolism
Crude
0.42 (0.18; 0.87)
0.31 (0.09; 0.75)
0.011
Adjusted
0.33 (0.12; 0.74)
0.24 (0.06; 0.72)
0.004
Intracranial bleeding
Crude
0.30 (0.12; 0.63)
0.06 (0.01; 0.29)
0.0005
Adjusted
0.24 (0.08; 0.56)
0.08 (0.01; 0.40)
0.0006
Gastrointestinal bleeding
Crude
0.67 (0.43; 0.99)
0.81 (0.52; 1.21)
0.12
Adjusted
0.60 (0.37; 0.93)
1.12 (0.67; 1.83)
0.075
Major bleeding
Crude
0.88 (0.66; 1.14)
0.65 (0.45; 0.90)
0.043
Adjusted
0.82 (0.59; 1.12)
0.77 (0.51; 1.13)
0.21
Hospitalization
Crude
0.51 (0.48; 0.55)
0.76 (0.71; 0.81)
<0.0001
Adjusted
0.53 (0.49; 0.57)
0.86 (0.79; 0.93)
<0.0001
0.01
0.20
1.00
5.00
Favors dabigatran 110mg
Favors warfarin
0.01
0.20
1.00
5.00
Favors dabigatran 150mg
Favors warfarin

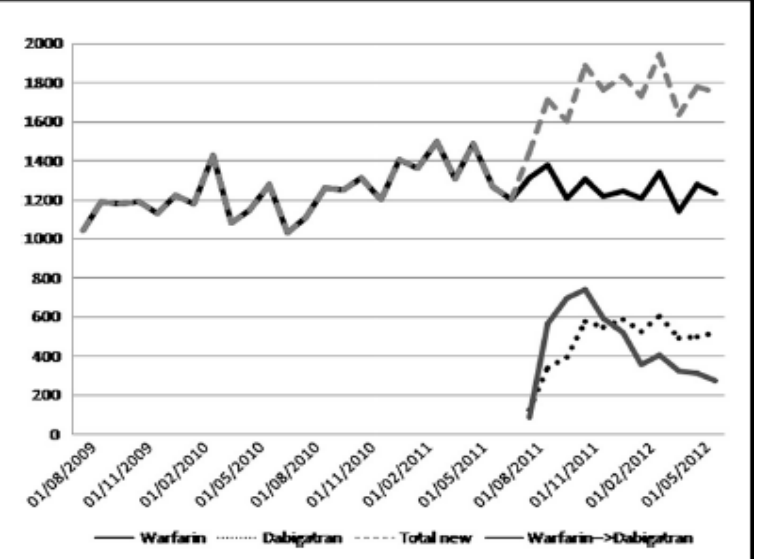


Figure 3 Monthly New Users of Warfarin and Dabigatran Etexilate for AF

Monthly new users of warfarin and dabigatran etexilate for atrial fibrillation (AF) in the period August 2009 to June 2012 in Denmark.

Table 3 Subgroup Analysis on Dabigatran Users With More Than 1-Year Follow-Up

Outcome	Warfarin vs. Dabigatran 110 mg b.i.d. HR	95% CI	Warfarin vs. Dabigatran 150 mg b.i.d. HR	95% CI	p Value*
Stroke					
Crude	0.95	(0.62–1.41)	1.58	(1.06–2.30)	0.05
Adjusted	0.84	(0.53–1.31)	1.53	(0.96–2.43)	0.15
Death					
Crude	0.93	(0.72–1.18)	0.39	(0.25–0.59)	<0.0001
Adjusted	0.82	(0.62–1.06)	0.58	(0.35–0.92)	0.03
Myocardial infarction					
Crude	0.60	(0.33–1.02)	0.62	(0.30–1.14)	0.10
Adjusted	0.50	(0.26–0.89)	0.74	(0.34–1.48)	0.06
Major bleeding					
Crude	0.77	(0.51–1.14)	0.63	(0.36–1.02)	0.12
Adjusted	0.74	(0.47–1.14)	0.66	(0.36–1.14)	0.15
Gastrointestinal bleeding					
Crude	0.58	(0.30–1.02)	0.70	(0.34–1.29)	0.15
Adjusted	0.61	(0.30–1.13)	0.78	(0.35–1.59)	0.26

Table 4 Contraindicated or Potential Hazardous Co-Medication for Dabigatran Group

	Baseline*	Follow-Up
Contraindicated drugs		
Systemic ketoconazole	<0.1 (1)	0 (0)
Cyclosporine	0 (0)	0 (0)
Itraconazole	<0.1 (1)	0.1 (6)
Tacrolimus	0 (0)	0 (0)
Potential hazardous co-medication		
Amiodarone	0.3 (13)	3.1 (155)
Dronedarone	0.1 (5)	0.4 (18)
Verapamil	2.1 (105)	4.3 (216)
Quinidine†	0 (0)	0 (0)
Clarithromycin	0.1 (4)	0.9 (42)
Coumarins	<0.1 (2)	4.8 (239)
Concomitant drug use that can increase bleeding risk		
Aspirin	32.8 (1,630)	16.3 (811)
Thienopyridines (clopidogrel, ticagrelor, prasugrel)	5.3 (262)	2.9 (141)
Low molecular weight heparins	0.3 (13)	0.3 (14)
Fondaparinux	0 (0)	0 (0)
GP IIb/IIIa antagonists (eptifibatide)	0 (0)	0 (0)
Sulfinpyrazone	1.3 (66)	2.3 (114)
NSAIDs	11.7 (585)	21.3 (1,059)

Conclusions

Efficacy in terms of stroke and systemic embolism prevention was similar between warfarin and dabigatran (both doses), whereas mortality, PE, and MI were lower with both doses of dabigatran, in this "everyday clinical practice" post-approval clinical cohort. With regard to safety, major bleeding was similar between dabigatran and warfarin, whereas intracranial bleeding was lower with both dabigatran doses, compared with warfarin. Also, the rate of gastrointestinal bleeding was significantly lower in the dabigatran 110-mg b.i.d. treated groups compared with warfarin. The previous concerns about an excess of bleeding events or MI among dabigatran-treated patients were not evident in this propensity-matched comparison against warfarin in a large post-approval registry study, even in the subgroup with ≥1-year follow-up.

Effect of *Dabigatran* on Referrals to and Switching From *Warfarin* in Two Academic Anticoagulation Management Services

(Am J Cardiol 2013;112:387–389)

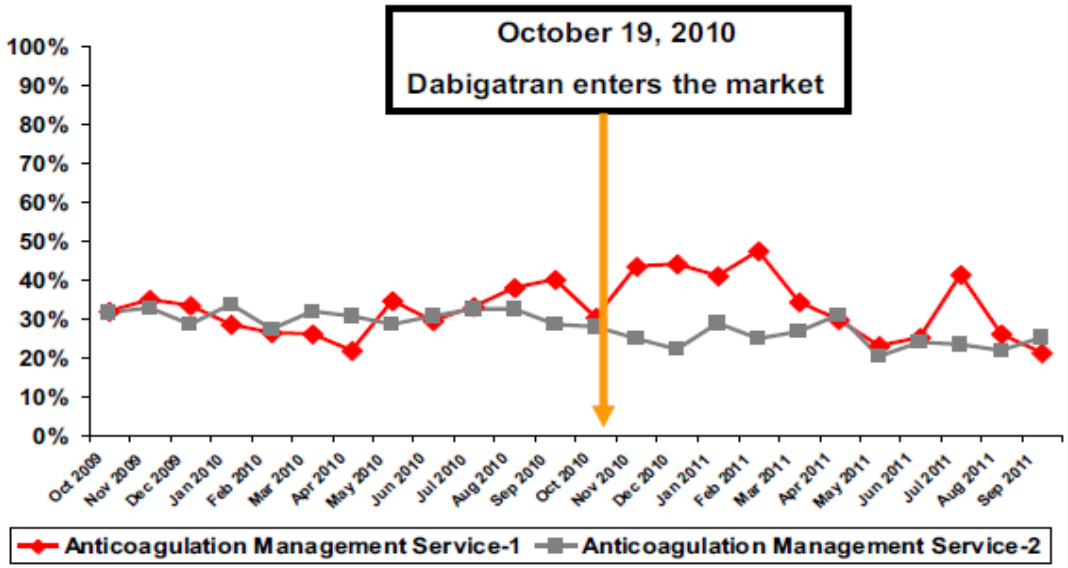


Figure 1. Percent of Anticoagulation Management Service referrals for stroke prevention in nonvalvular AF.

Eighty-one patients (6.6%) from Anticoagulation Management Service 1 and 44 (3.9%) from Anticoagulation Management Service 2 have switched from warfarin to dabigatran. The frequency of initial prescription of dabigatran for stroke prevention in AF and the frequency of transition from warfarin to dabigatran have been less than expected.

238 Circulation July 16, 2013

The Long-Term Multicenter Observational Study of Dabigatran Treatment in Patients With Atrial Fibrillation (RELY-ABLE) Study

Background—During follow-up of between 1 and 3 years in the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial, 2 doses of dabigatran etexilate were shown to be effective and safe for the prevention of stroke or systemic embolism in patients with atrial fibrillation. There is a need for longer-term follow-up of patients on dabigatran and for further data comparing the 2 dabigatran doses.

Methods and Results—Patients randomly assigned to dabigatran in RE-LY were eligible for the Long-term Multicenter Extension of Dabigatran Treatment in Patients with Atrial Fibrillation (RELY-ABLE) trial if they had not permanently discontinued study medication at the time of their final RE-LY study visit. Enrolled patients continued to receive the double-blind dabigatran dose received in RE-LY, for up to 28 months of follow up after RE-LY (median follow-up, 2.3 years). There were 5851 patients enrolled, representing 48% of patients originally randomly assigned to receive dabigatran in RE-LY and 86% of RELY-ABLE–eligible patients. Rates of stroke or systemic embolism were 1.46% and 1.60%/y on dabigatran 150 and 110 mg twice daily, respectively (hazard ratio, 0.91; 95% confidence interval, 0.69–1.20). Rates of major hemorrhage were 3.74% and 2.99%/y on dabigatran 150 and 110 mg (hazard ratio, 1.26; 95% confidence interval, 1.04–1.53). Rates of death were 3.02% and 3.10%/y (hazard ratio, 0.97; 95% confidence interval, 0.80–1.19). Rates of hemorrhagic stroke were 0.13% and 0.14%/y.

Conclusions—During 2.3 years of continued treatment with dabigatran after RE-LY, there was a higher rate of major bleeding with dabigatran 150 mg twice daily in comparison with 110 mg, and similar rates of stroke and death.

Table 1. Patient Disposition in RE-LY and RELY-ABLE

	Dabigatran 150 mg	Dabigatran 110 mg
Randomized to dabigatran in RE-LY	6076	6015
Completed RE-LY alive and still receiving study dabigatran	4519	4492
Patient followed at site participating in RELY-ABLE	3397	3395
Patient enrolled in RELY-ABLE *	2937	2914
Completed RELY-ABLE still receiving study medication†	2508	2511
Continued in RELY-ABLE beyond the 28-month visit‡	1102	1086

Table 3. Stroke, Ischemic Outcomes, and Hospitalizations

	150 mg n (%/y)	110 mg n (%/y)	HR (150 mg vs 110 mg)	95% CI
Stroke or systemic embolism	93 (1.46)	102 (1.60)	0.91	0.69–1.20
All stroke	79 (1.24)	88 (1.38)	0.89	0.66–1.21
Ischemic or type uncertain	73 (1.15)	79 (1.24)	0.92	0.67–1.27
Hemorrhagic	8 (0.13)	9 (0.14)	0.89	0.34–2.30
Nondisabling (modified Rankin score 0–2)	36 (0.57)	49 (0.77)	0.73	0.48–1.13
Disabling (modified Rankin score 3–5) or fatal	40 (0.63)	39 (0.61)	1.03	0.66–1.59
Myocardial infarction	44 (0.69)	46 (0.72)	0.96	0.63–1.45
Pulmonary embolism	8 (0.13)	7 (0.11)	1.14	0.41–3.15
Cardiovascular hospitalization	634 (9.96)	619 (9.74)	1.03	0.92–1.15
Any hospitalization	1204 (18.9)	1170 (18.4)	1.04	0.96–1.12

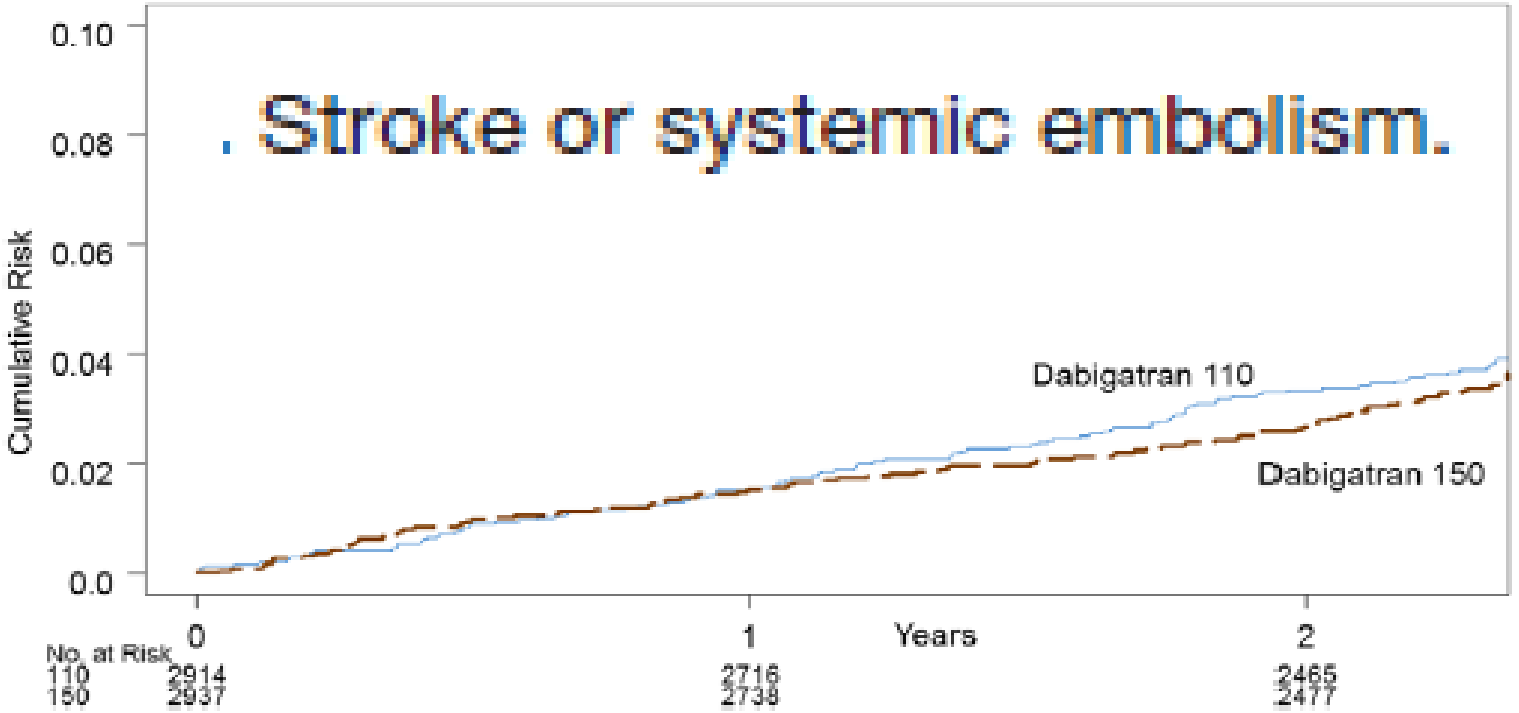
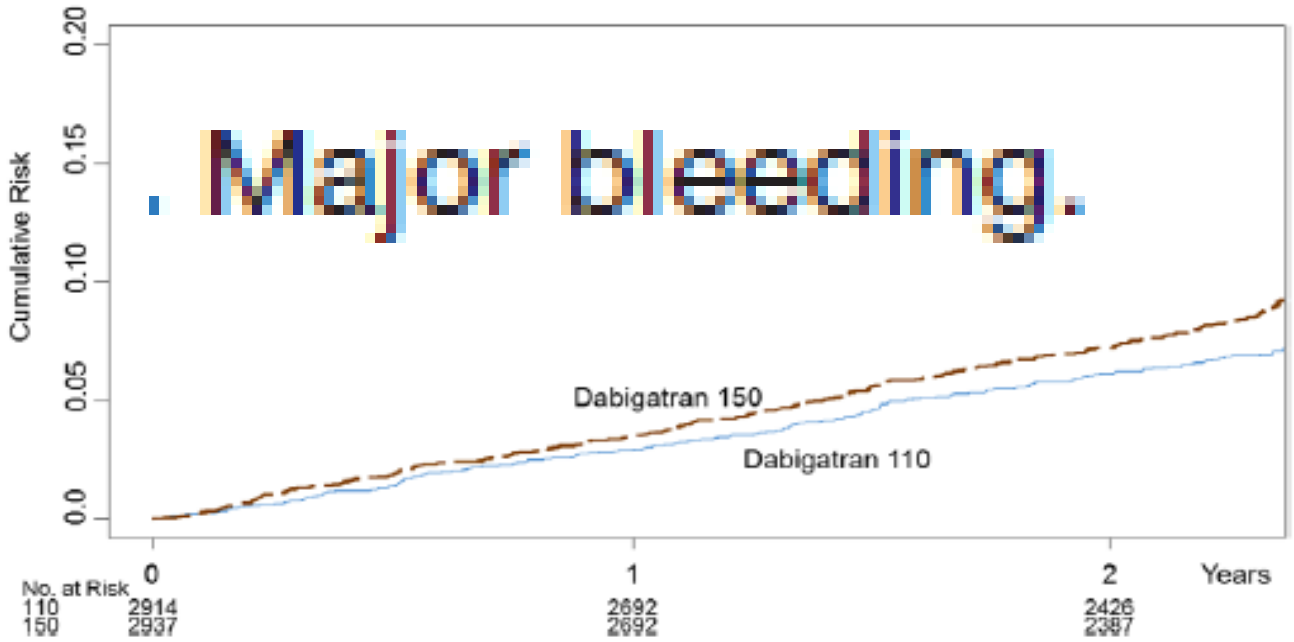
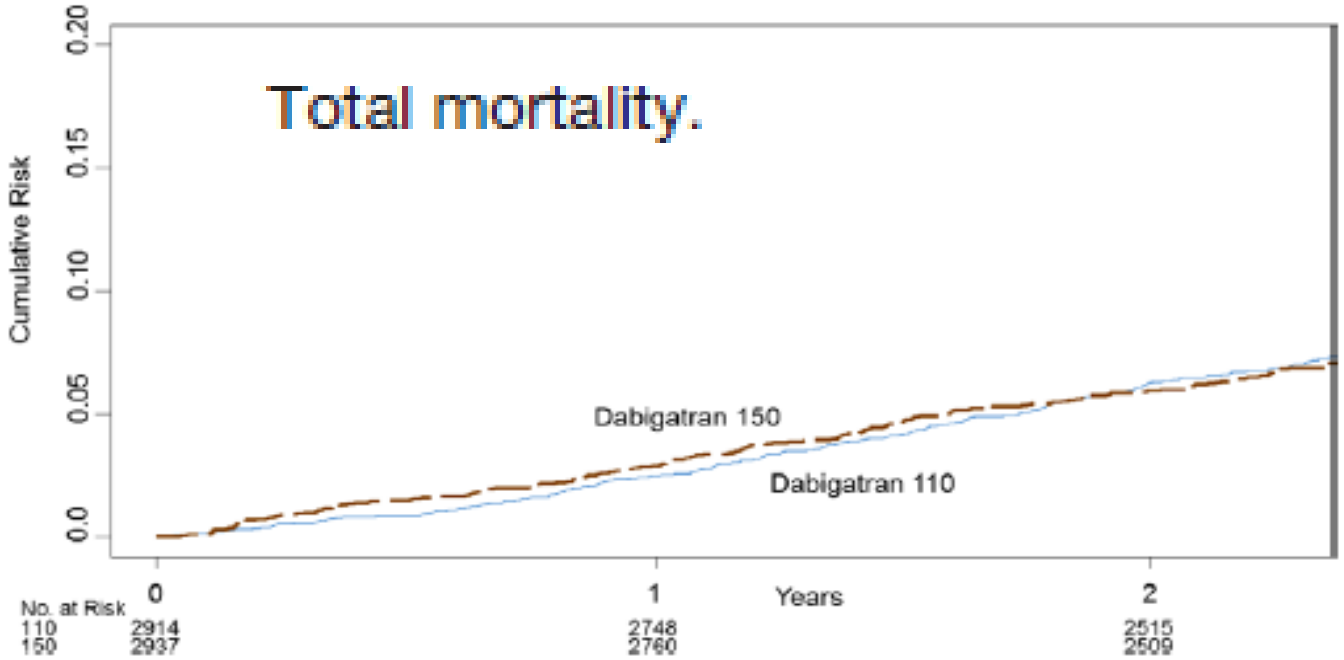


Table 4. Bleeding and Net Benefit Outcomes

	150 mg n (%/y)	110 mg n (%/y)	HR (150 mg vs 110 mg)	95% CI
Major bleeding	238 (3.74)	190 (2.99)	1.26	1.04–1.53
Life-threatening	114 (1.79)	100 (1.57)	1.14	0.87–1.49
Gastrointestinal	98 (1.54)	99 (1.56)	0.99	0.75–1.31
Intracranial	21 (0.33)	16 (0.25)	1.31	0.68–2.51
Extracranial	218 (3.43)	179 (2.82)	1.23	1.01–1.49
Fatal	15 (0.24)	16 (0.25)	0.94	0.46–1.89
Minor bleeding	617 (9.70)	521 (8.19)	1.21	1.07–1.36
Net clinical benefit outcomes				
Total mortality	192 (3.02)	197 (3.10)	0.97	0.80–1.19
Vascular mortality	106 (1.67)	103 (1.62)	1.03	0.78–1.35
Disabling stroke, life-threatening bleed, or death	288 (4.53)	283 (4.45)	1.02	0.86–1.20
Stroke, systemic embolism, myocardial infarction, pulmonary embolism, major bleed, or death	468 (7.36)	438 (6.89)	1.07	0.94–1.22





In summary, the RELY-ABLE study provides additional safety information for a large cohort of patients continuing the same dose of dabigatran as assigned in the RE-LY trial during 2.3 years of additional treatment (total mean follow-up, 4.3 years). During the additional 2.3 years of treatment, the rates of major events were not inconsistent with those seen in RE-LY. In the comparison of the 2 dabigatran doses in RELY-ABLE, there was no significant difference in stroke or mortality, but there was a higher rate of major bleeding with the higher dabigatran dose. There was no difference between the doses in net clinical benefit as estimated by the composite of stroke, bleeding, and death.

Geriatria, Molinette, 2010-2013: 1078/4072 (29.5%) pazienti con FA

Età media 83.4±6.6 anni, 60,3% femmine
27,3% dipendente alle ADL
30,9% con **det. cognitivo** moderato-severo
24,9% con **controindicazioni maggiori** di cui:
30,5% recenti sanguinamenti severi
26,8% neoplasie avanzate
23,0% scarsa compliance del paziente

Medicina e Geriatria, Molinette, gennaio-aprile 2014: 550 FA

Età media 81.7±6.8 anni, 56% femmine
Fragili: 77,5%
ADL dipendenti: 45.6%
deterioramento cognitivo: 40.2%
controindicazioni maggiori alla TAO: 22%

	A: total sample of patients			B: without contraindications to OAC		
	OR	95% IC	P value	OR	95% IC	P value
Age, years	0,707	0,594-0,841	**<.0001**	0,733	0,591-0,910	**0,0049**
Permanent AF	1,000			1,000		
Persistent AF	0,876	0,420-1,825	0,724	0,634	0,250-1,611	0,3381
Paroxysmal AF	0,210	0,129-0,344	**<.0001**	0,170	0,093-0,310	**<.0001**
CHA_2DS_2VASC	1,502	1,222-1,845	**0,0001**	1,391	1,071-1,806	**0,0132**
HASBLED	0,629	0,485-0,816	**0,0005**	0,651	0,467-0,909	**0,0116**
CHARLSON Index	0,885	0,796-0,983	**0,0228**	0,999	0,865-1,153	0,9875
Contraindications	0,437	0,272-0,702	**0,0006**			
Dependent (ADL)	0,684	0,403-1,159	0,1582	0,493	0,251-0,969	**0,0403**
Cognitive impairment (SPMSQ)	0,862	0,506-1,468	0,5854	0,852	0,429-1,690	0,6460
Depression (GDS)	1,391	0,859-2,253	0,1790	1,677	0,921-3,053	0,0906
Frailty (Groningen)	0,820	0,440-1,528	0,5323	0,746	0,360-1,544	0,4297
No malnutrition (MNA)	1,482	0,808-2,718	0,2039	1,435	0,690-2,983	0,3337
Facility vs Home discharge	0,630	0,367-1,082	0,0938	0,721	0,371-1,400	0,3344

Bo M et al, 2014, submitted

Interventional hypertension: a new hope or a new hype? The need to redefine resistant hypertension

Journal of Hypertension 2013, 31:2118–2122

IS IT TIME TO CHANGE THE DEFINITION OF RESISTANT HYPERTENSION?

1. Uncontrolled hypertension has been documented with 24-h ABPM. In a large cohort of 68 045 treated hypertensive patients from the Spanish Ambulatory Blood Pressure Monitoring Registry, 8295 (12.2%) had resistant hypertension (office BP $\geq$140 and/or 90 mmHg while being treated with at least three antihypertensive drugs, one of them being a diuretic). After ABPM, 62.5% of patients were classified as true resistant hypertensive patients, the remaining 37.5% as having white-coat resistance. This study emphasized that ABPM must be encouraged for a correct diagnosis and management of all patients with resistant hypertension, particularly if interventional procedures are planned.
2. Nonadherence to medications has been adequately documented by determining discordance between medications prescribed and medications actually taken [33].
3. Intolerance to drugs has been ascertained after several attempts with different combinations.
4. A patient has been given chlortalidone, in substitution of hydrochlorothiazide. This has been adequately reviewed in the AHA recommendations [2].
5. A patient has received a trial of spironolactone or eplerenone. In the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm, patients with resistant hypertension who received spironolactone mainly as a fourth-line antihypertensive agent manifested a decrease in BP from 156.9/85.3 by 21.9/9.5 mmHg [34,35].
6. A patient has been given a trial of clonidine (preferably the patch) or labetalol.
7. A patient has been given a trial of minoxidil [36].
8. Potentially correctable secondary forms of hypertension have been adequately excluded (renovascular hypertension; primary aldosteronism; pheochomocytoma; hypothyroidism and hyperthyroidism; hyperparathyroidism; and so on).

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

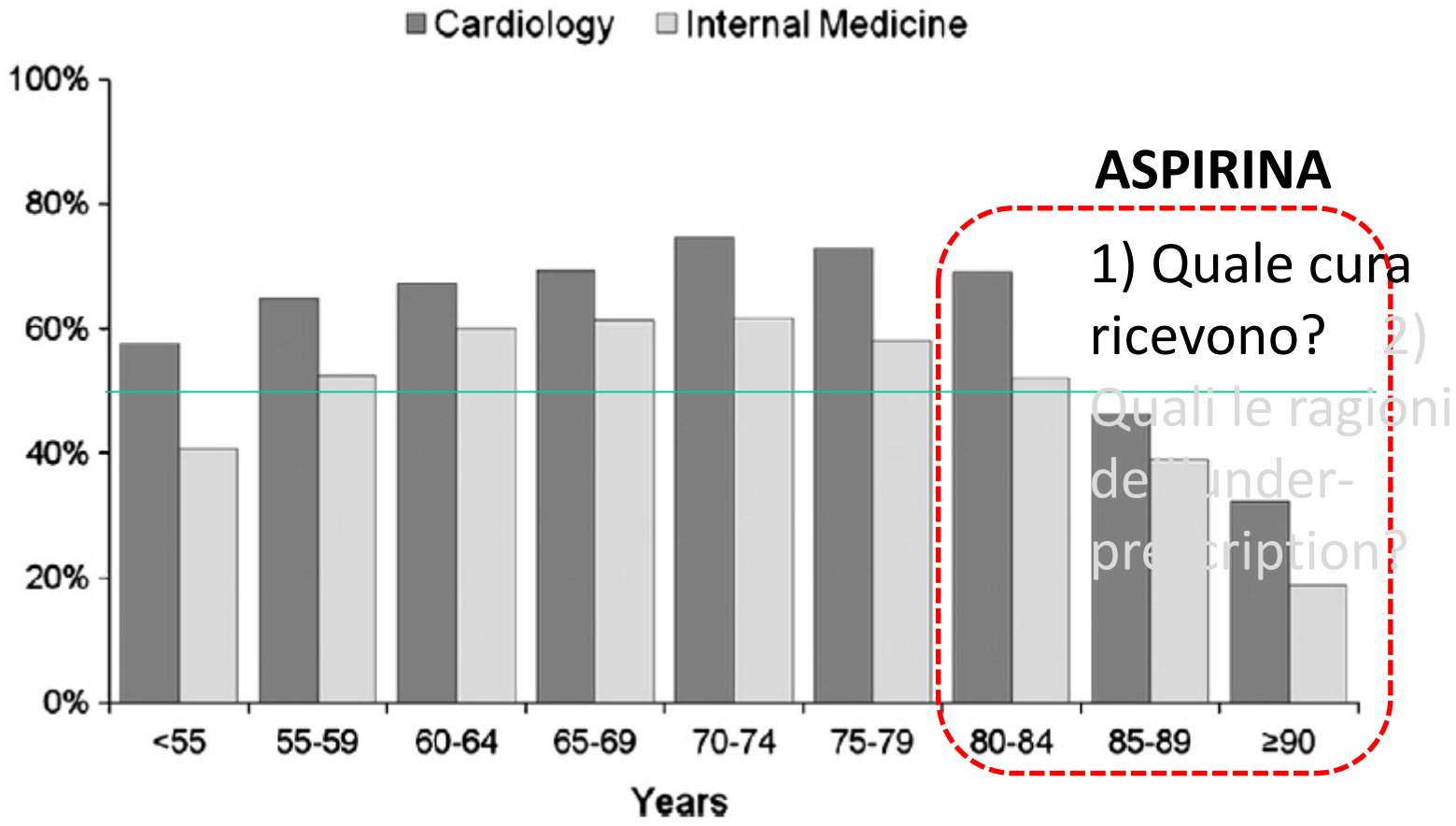
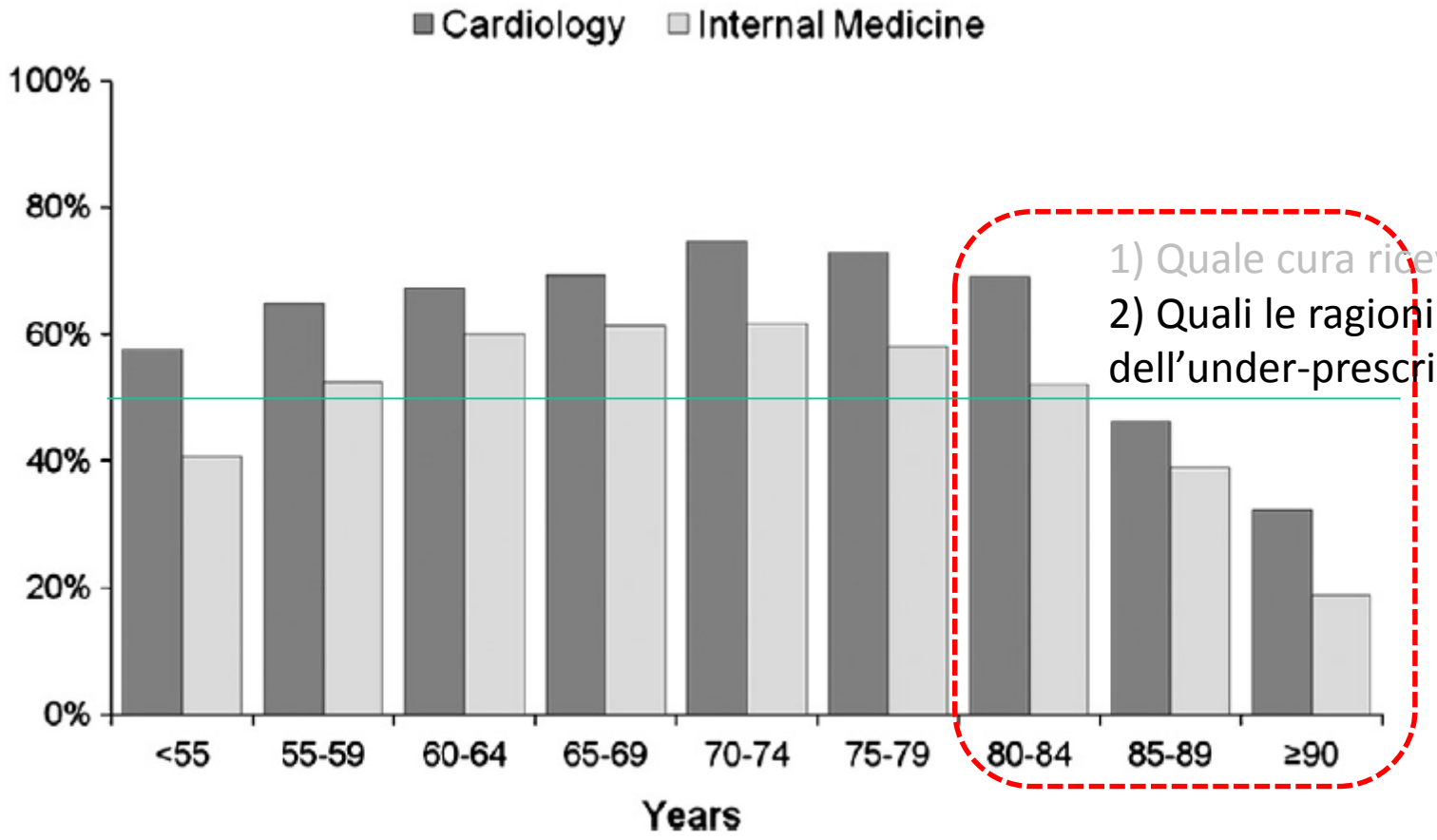


Fig. 5. OAC prescription at discharge from cardiology and internal medicine patients according to the age.

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



1) Quale cura ricevono?

2) Quali le ragioni dell'under-prescription?

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