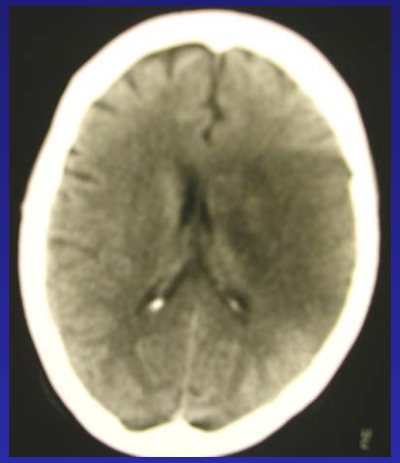
Torino 27 settembre 2013

DABIGATRAN The efficacy of anticoagulant therapy:the ischemic stroke prevention

P.Cerrato

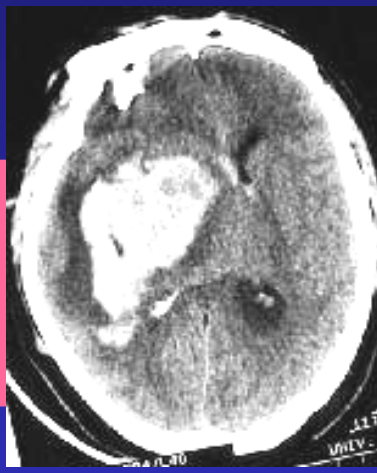
Stroke Unit
Osp Molinette

STROKE O ICTUS

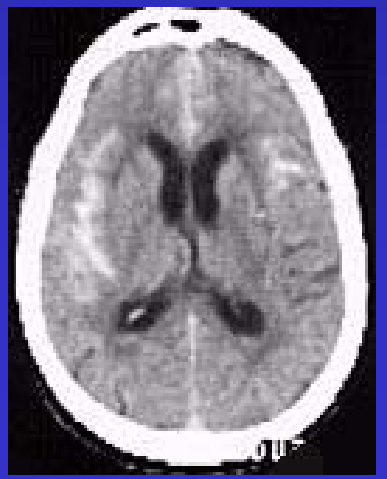


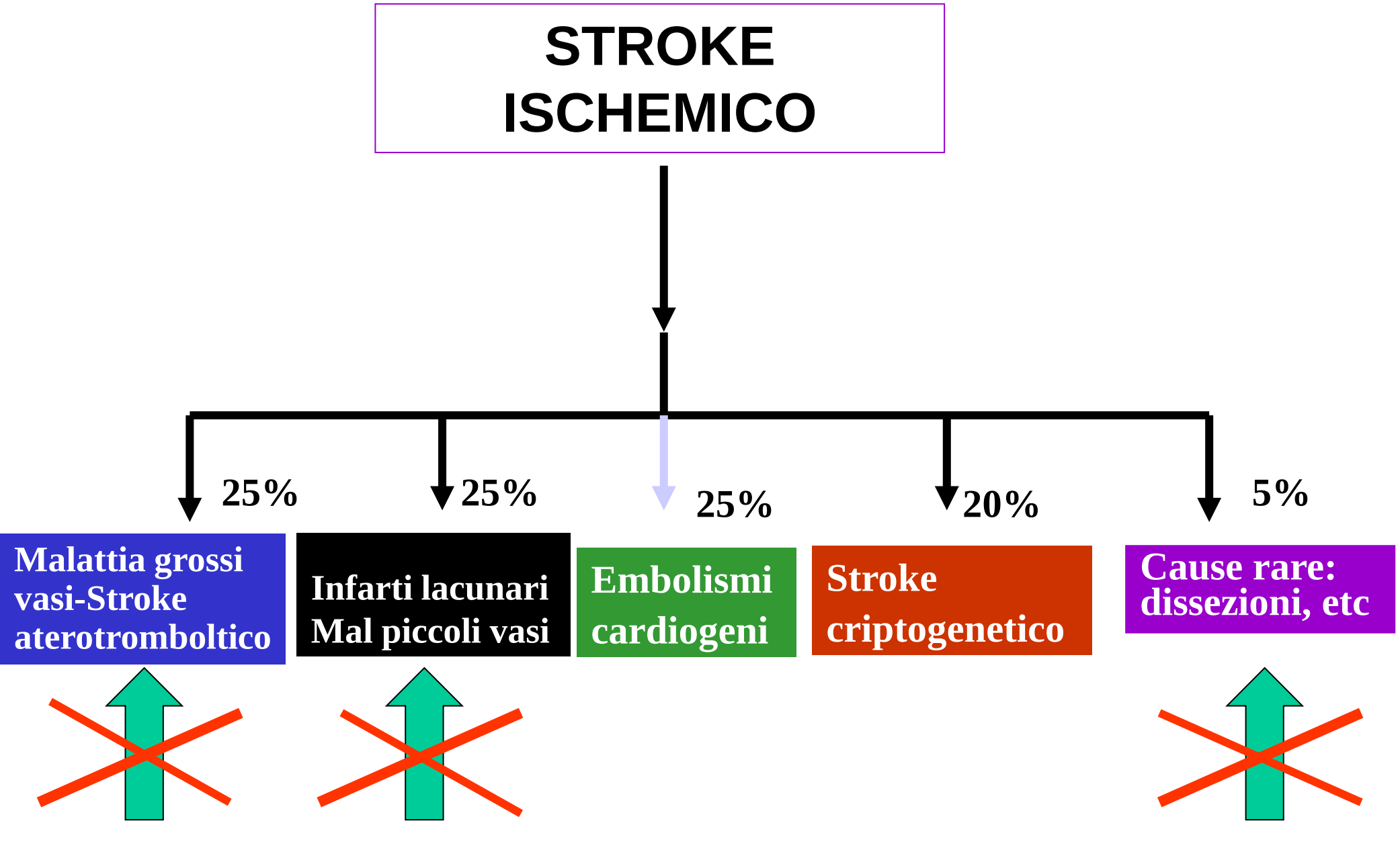
Infarto cerebrale
80%

EMORRAGIA
INTRAPARENCHIMALE
15%

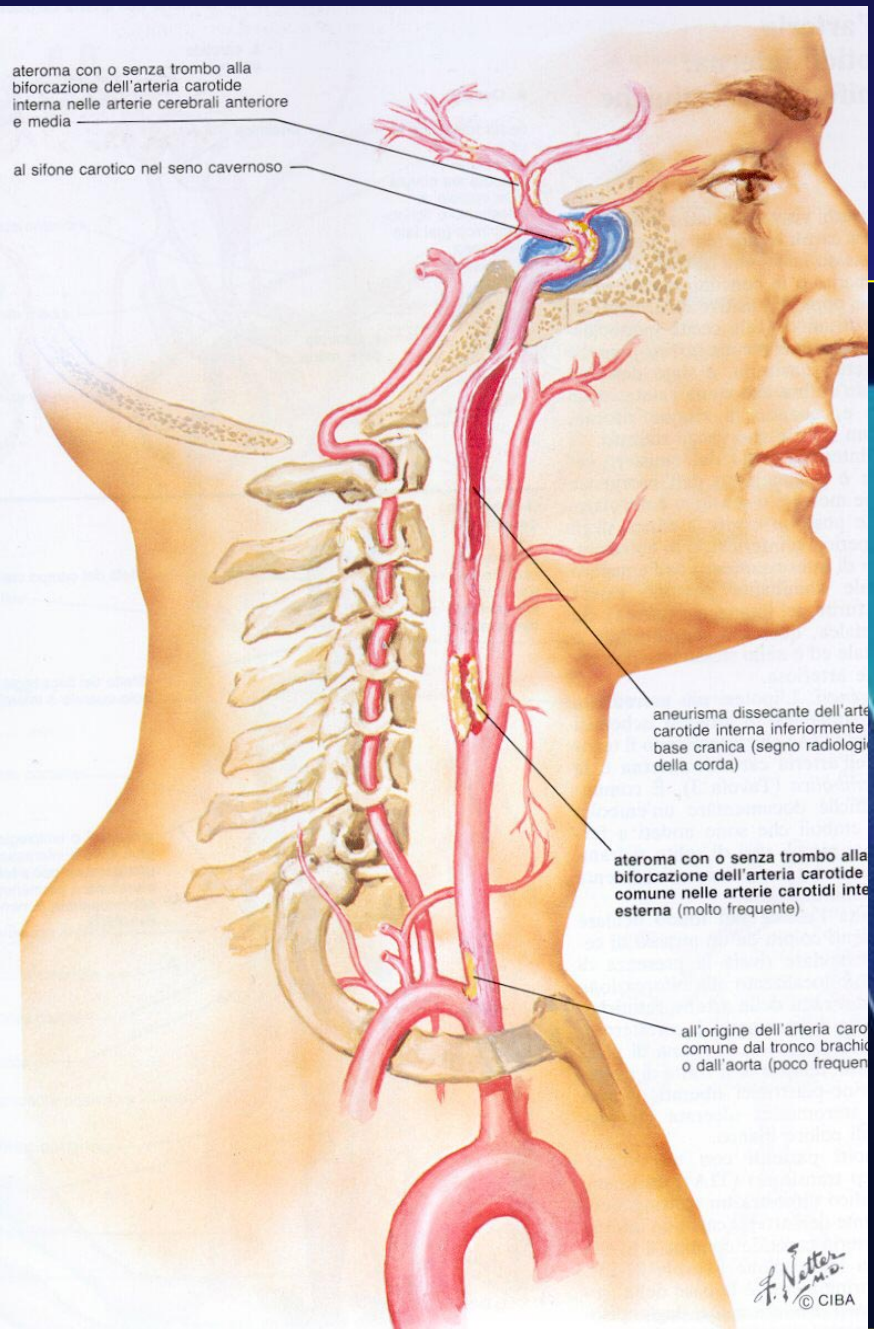


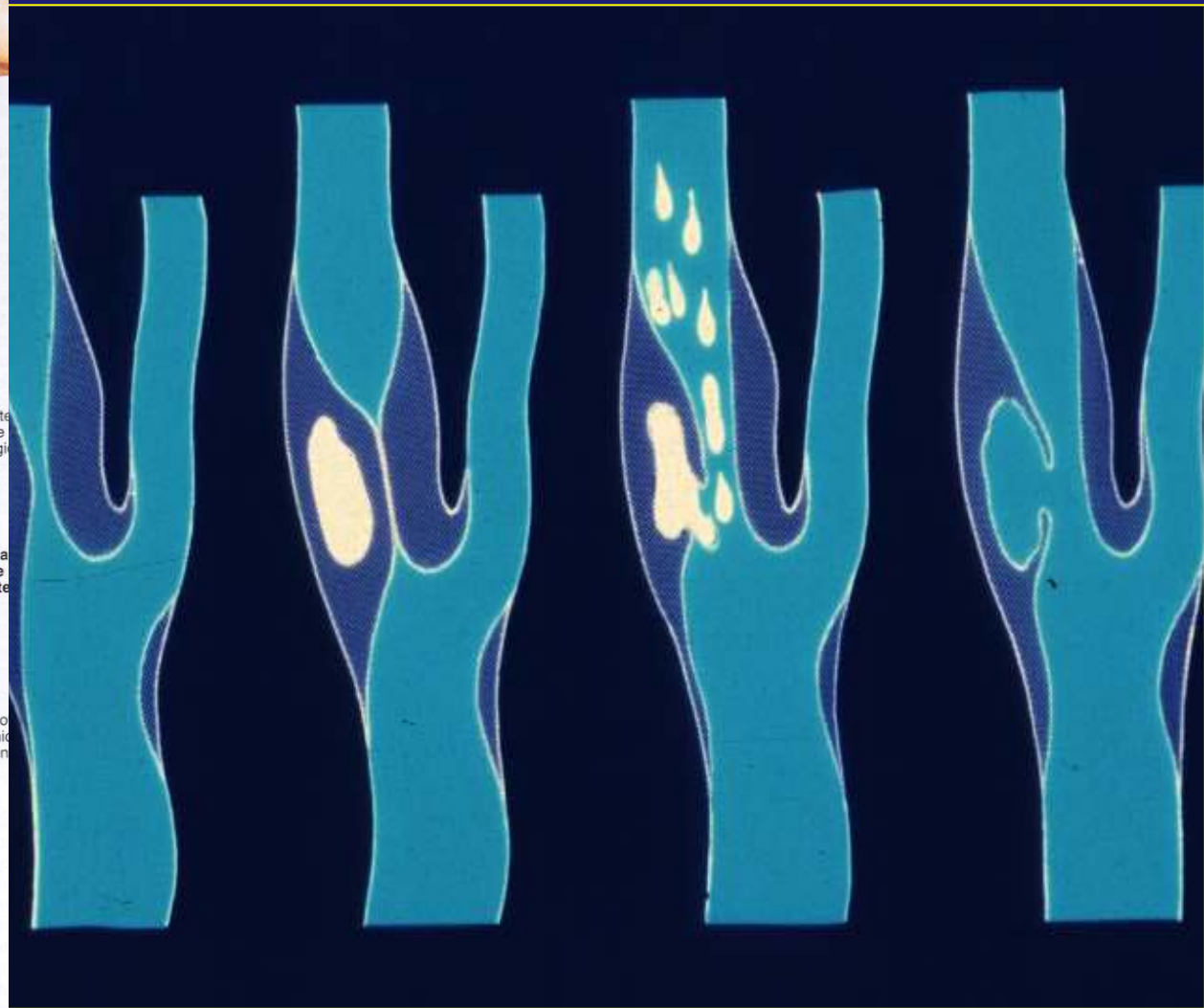
EMORRAGIA
SUBARACNOIDEA
5%




STROKE ISCHEMICO
25%
25%
25%
20%
5%
Malattia grossi vasi-Stroke aterotromboltico
Infarti lacunari Mal piccoli vasi
Embolismi cardiogeni
Stroke criptogenetico
Cause rare: dissezioni, etc

I Embolia artero-arteriosa

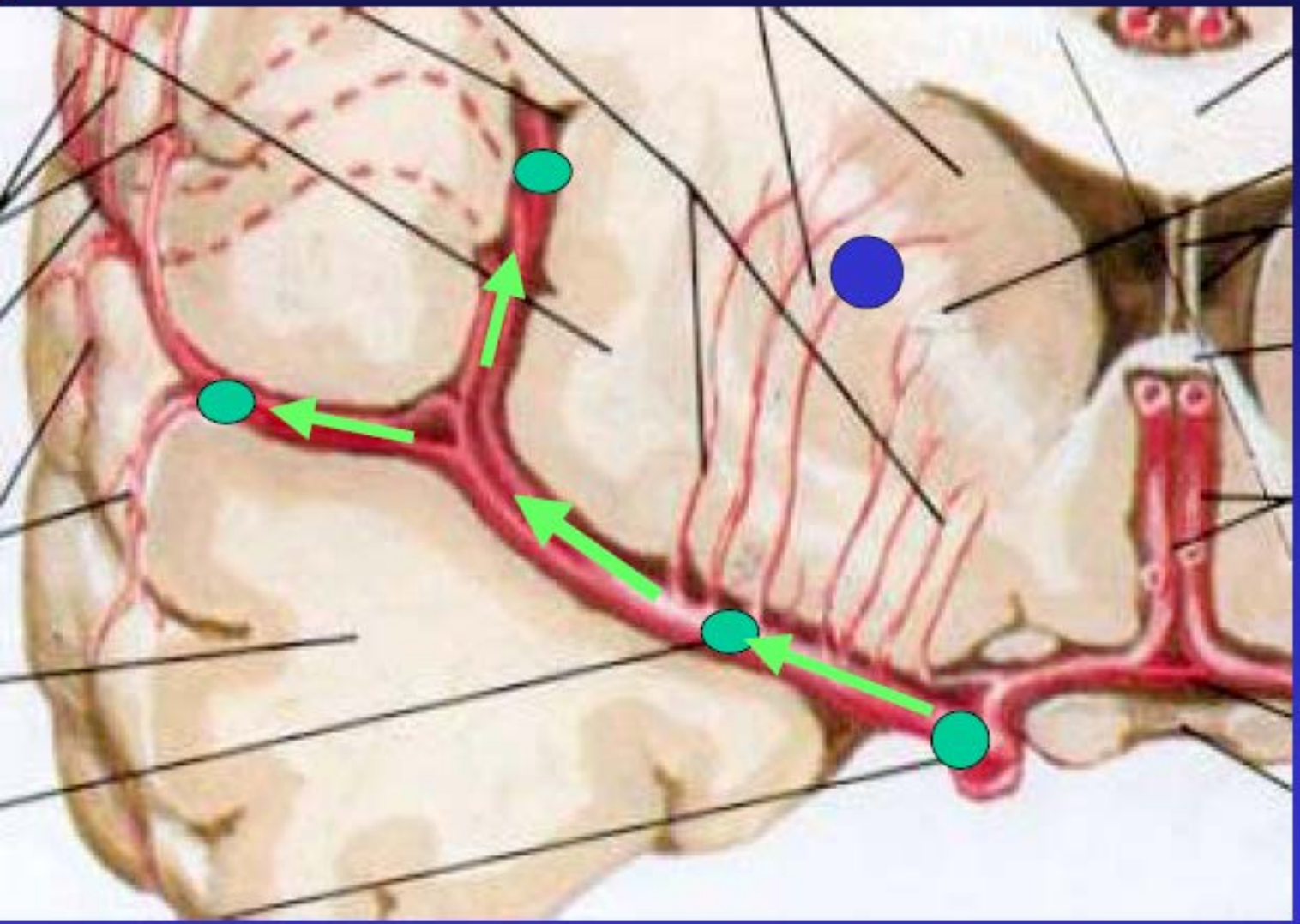


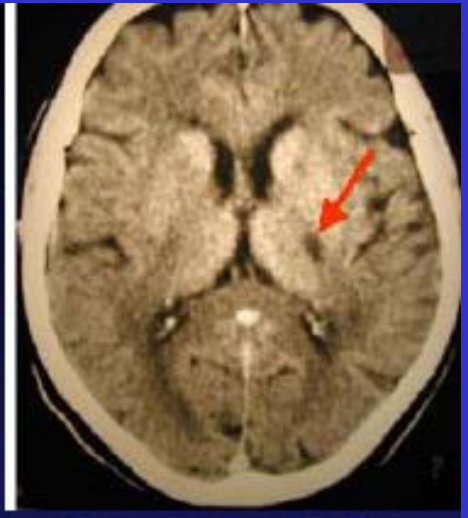


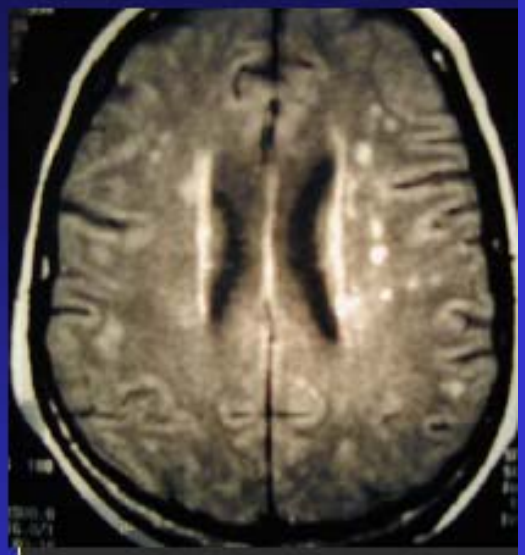
ESCLUDERE UNA MALATTIA DEI PICCOLI VASI

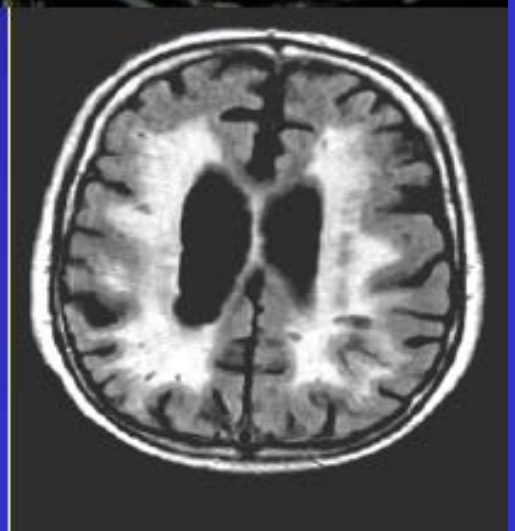
Tranne casi particolari l'infarto lacunare

non riconosce un meccanismo embolico







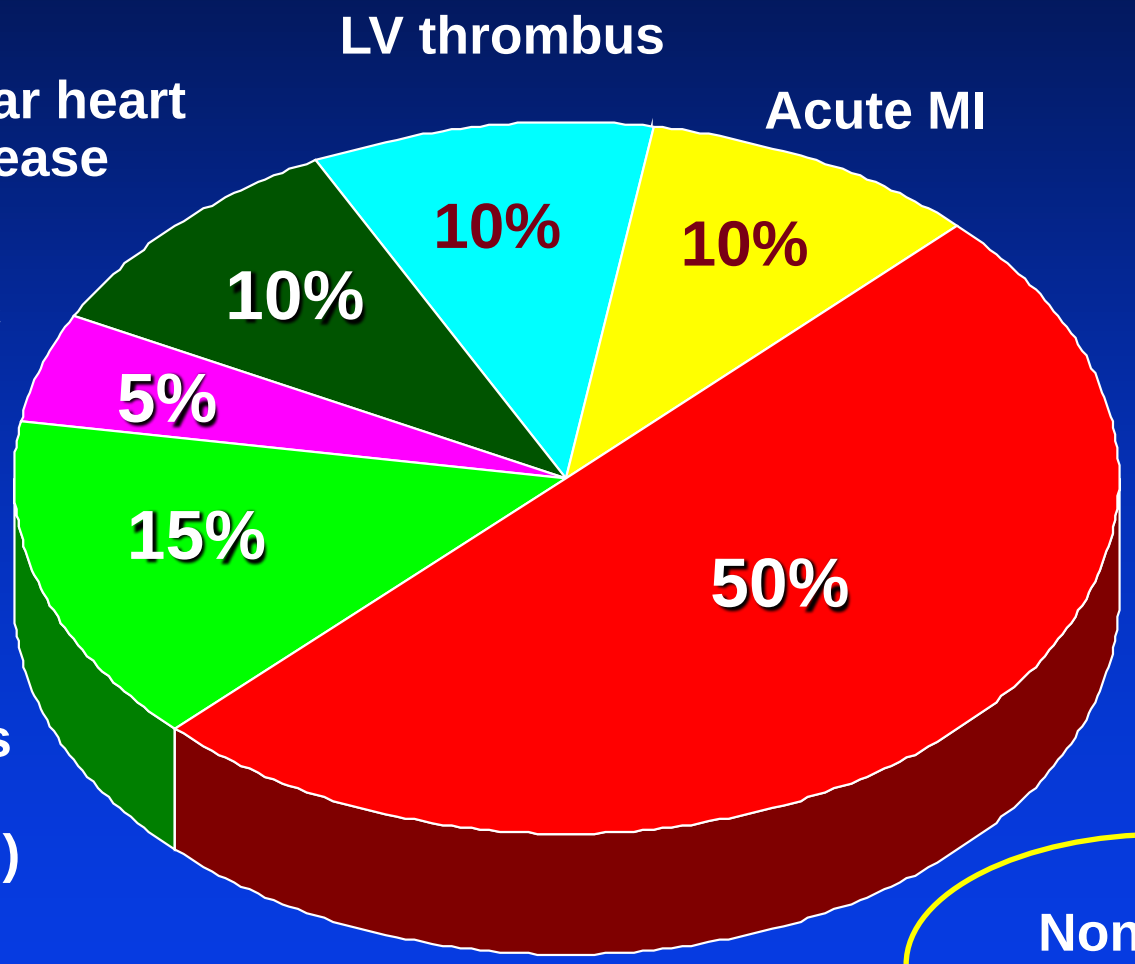


STROKE CARDIOEMBOLICO
Presenza di cardiopatia

Cardiopatie ad alto rischio *(Hart: Lancet 1992)*

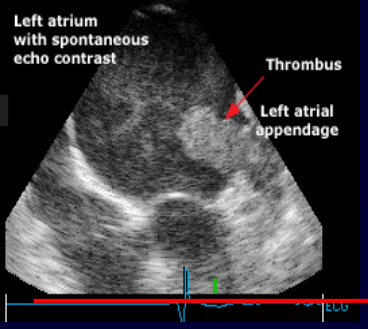
- **fibrillatione atriale**
- **stenosi mitralica**
- **protesi valvolari**
- **IMA recente**
- **trombosi ventricolare sinistra**
- **mixoma atriale**
- **endocardite infettiva**
- **cardiomiopatia dilatativa (ischemica e non)**
- **endocardite trombotica abatterica**

Cardioembolic Sources



Nonvalvular Atrial Fibrillation

Cerebral Embolism Task Force, Arch. Neurol 1986; 43: 71-84

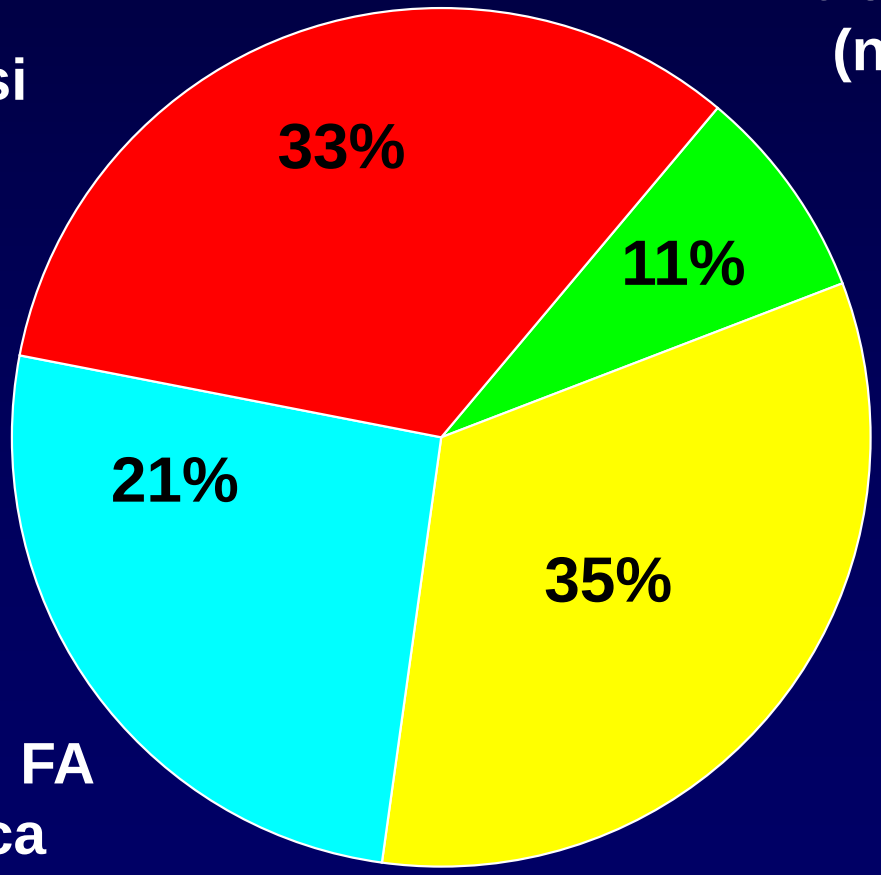


Fibrillazione Atriale e Stroke

Stroke Unit Ospedale Maggiore, Bologna

Casistica 2004-2008

STROKE CARDIOEMBOLICO (n=466)



FA di nuova diagnosi
n=156

Altre cause
(n=50)

FA persistente
n=164

Anamnesi di FA
parossistica
n=96

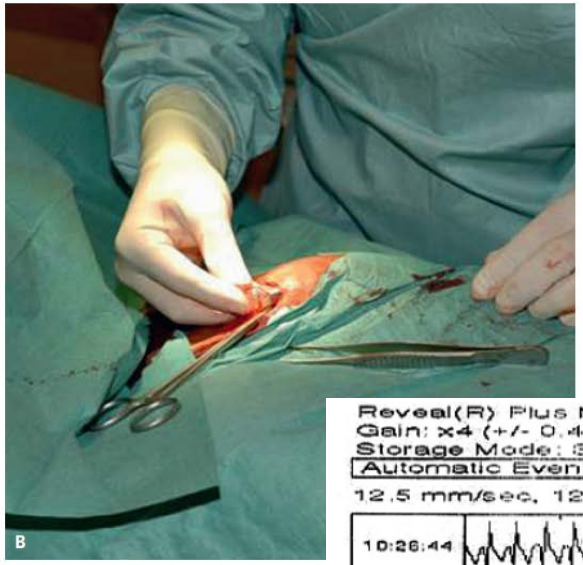
The implantable loop recorder: a critical review

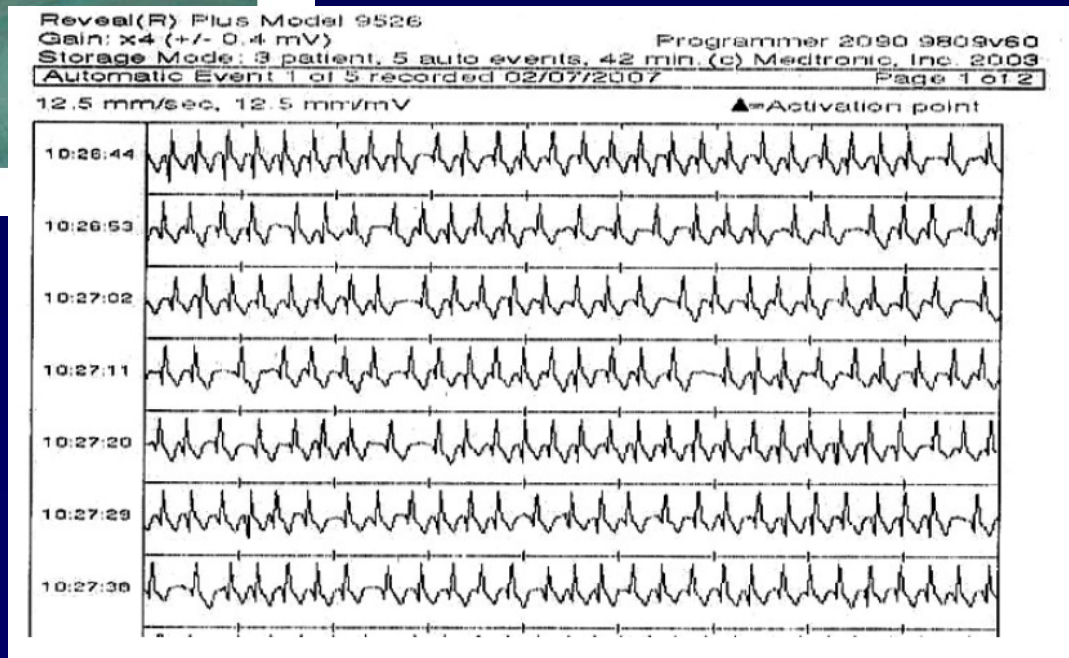
Juan F. Iglesias, Denis Graf, Patrizio Pascale, Etienne Pruvot

Unité des Troubles du Rythme, Service de Cardiologie, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Figure 1

A shows on the left hand side an ILR (Reveal XT®, Medtronic Inc., USA) and its hand-held activator on the right hand side.
B shows the implantation of an ILR. After local anesthesia, a 2-cm wide incision is performed in the left subclavian region.
A 6-cm long pocket is created for insertion of the ILR.





Scene di vita quotidiana

TERAPIA ANTICOAGULANTE NELL'ICTUS ISCHEMICO

OBIETTIVO:

PREVENZIONE RECIDIVE: rischio embolico della FA

RISCHIO: emorragia cerebrale: diversi fattori

Quantificazione rischio embolico della FA

Table 3 Risk factors for ischaemic stroke/TIA/systemic embolism in patients with AF: the Swedish Cohort Atrial Fibrillation study (adapted from Friberg *et al.*[25])

	Multivariate hazard ratios (95% CI)
Age (years)	
<65	1.0 (Reference)
65–74	2.97 (2.54–3.48)
≥75	5.28 (4.57–6.09)
Female sex	1.17 (1.11–1.22)
Previous ischaemic stroke	2.81 (2.68–2.95)
Intracranial bleeding	1.49 (1.33–1.67)
Vascular disease (any)	1.14 (1.06–1.23)
• Myocardial infarction	1.09 (1.03–1.15)
• Previous CABG	1.19 (1.06–1.33)
• Peripheral artery disease	1.22 (1.12–1.32)
Hypertension	1.17 (1.11–1.22)
Heart failure (history)	0.98 (0.93–1.03)
Diabetes mellitus	1.19 (1.13–1.26)
Thyroid disease	1.00 (0.92–1.09)
Thyrotoxicosis	1.03 (0.83–1.28)

CHADS2 e CHA2DS2VASc

CHADS2 Risk	Score
CHF	1
Hypertension	1
Age > 75	1
Diabetes	1
Stroke or TIA	2

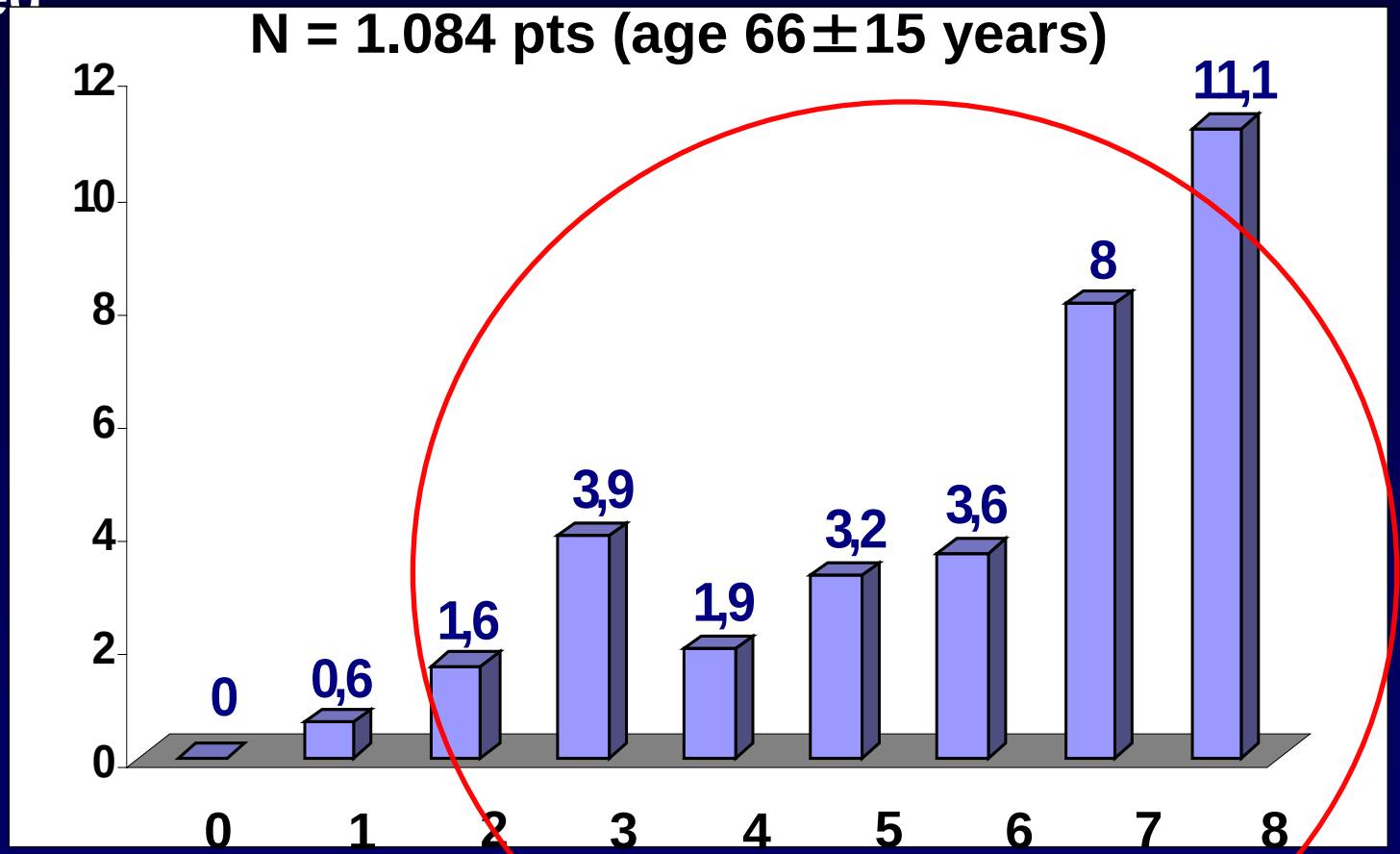
CHA2DS2-VASc Risk	Score
CHF or LVEF ≤ 40%	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke/TIA/ Thromboembolism	2
Vascular Disease	1
Age 65 - 74	1
Female	1

From ESC AF Guidelines

http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-afib-FT.pdf

CHA_2DS_2 - VAsc Score: Validation for Predicting Stroke

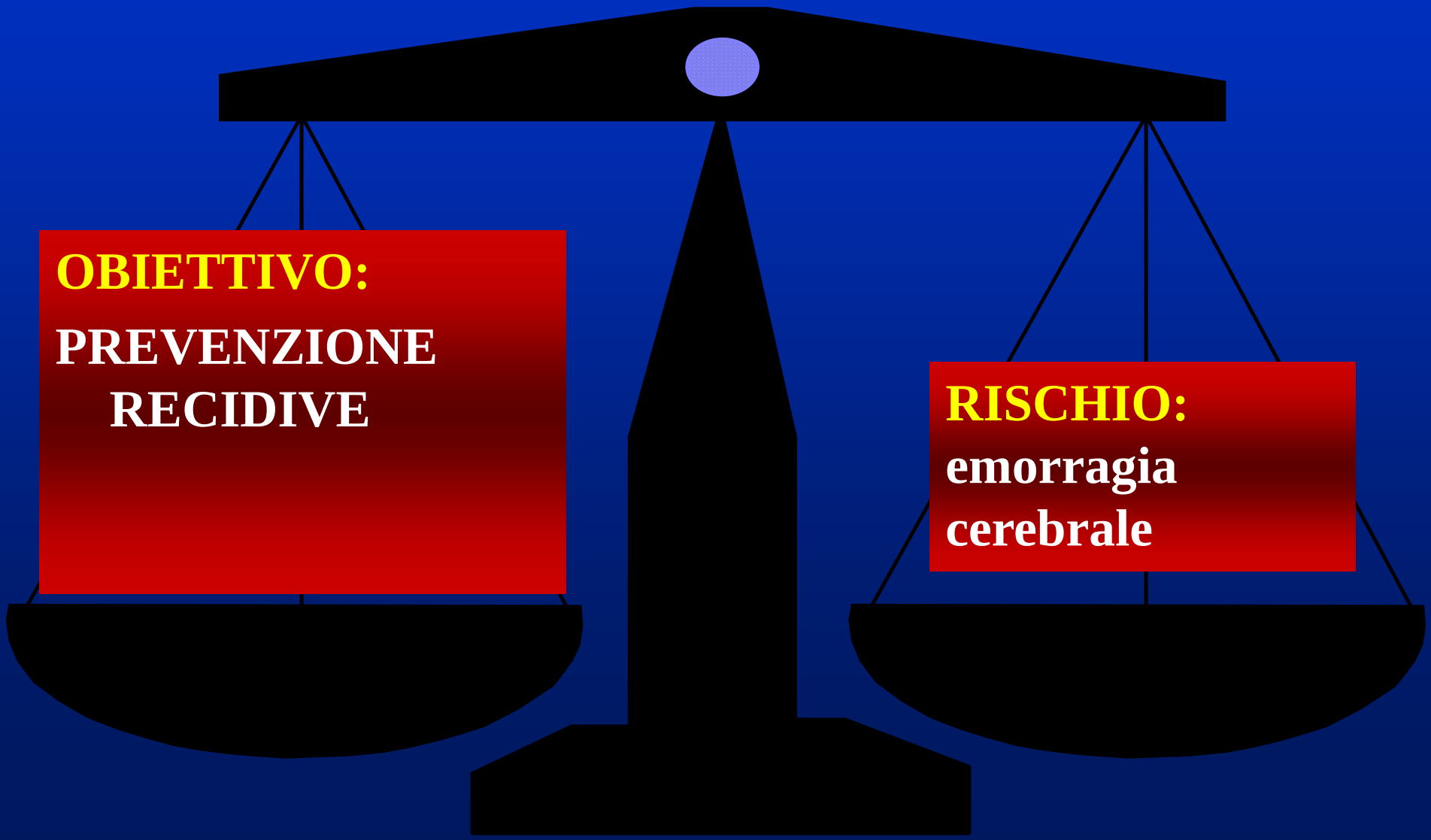
The Euro Heart Survey on AF



- 1 point: CHF/LV dysfunction, Hypertension, Diabetes mellitus, Vascular disease,
  Age 65-74 y, Sex category
- 2 points: Age ≥ 75 y, Stroke/TIA/TE

Lip et al. Chest 2010;137(2): 26

TERAPIA ANTICOAGULANTE NELL'ICTUS ISCHEMICO



FA: Rischio di sanguinamento

Table 10 Clinical characteristics comprising the HAS-BLED bleeding risk score

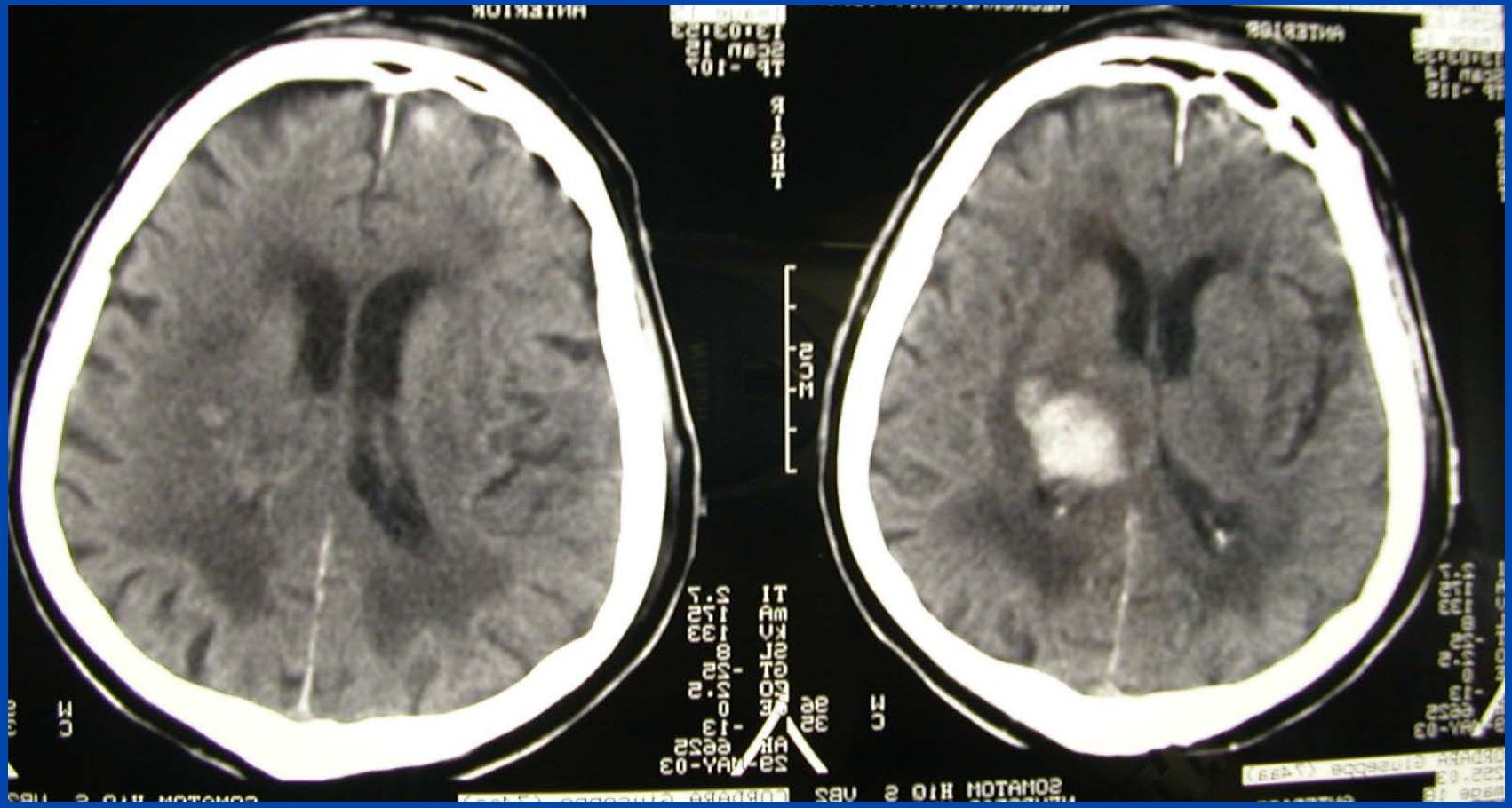
Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1 ←
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1 ←
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1 ←
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

CHA_2DS_2-VASc: 9 ⟶ Rischio di stroke 15.2%/anno (European Society of Cardiology's guidelines)

HAS-BLED: 5 ⟶ Rischio 12.5%/anno

Patologia dei piccoli vasi

TC cranio: estesa sofferenza della sostanza bianca + emorragia talamica



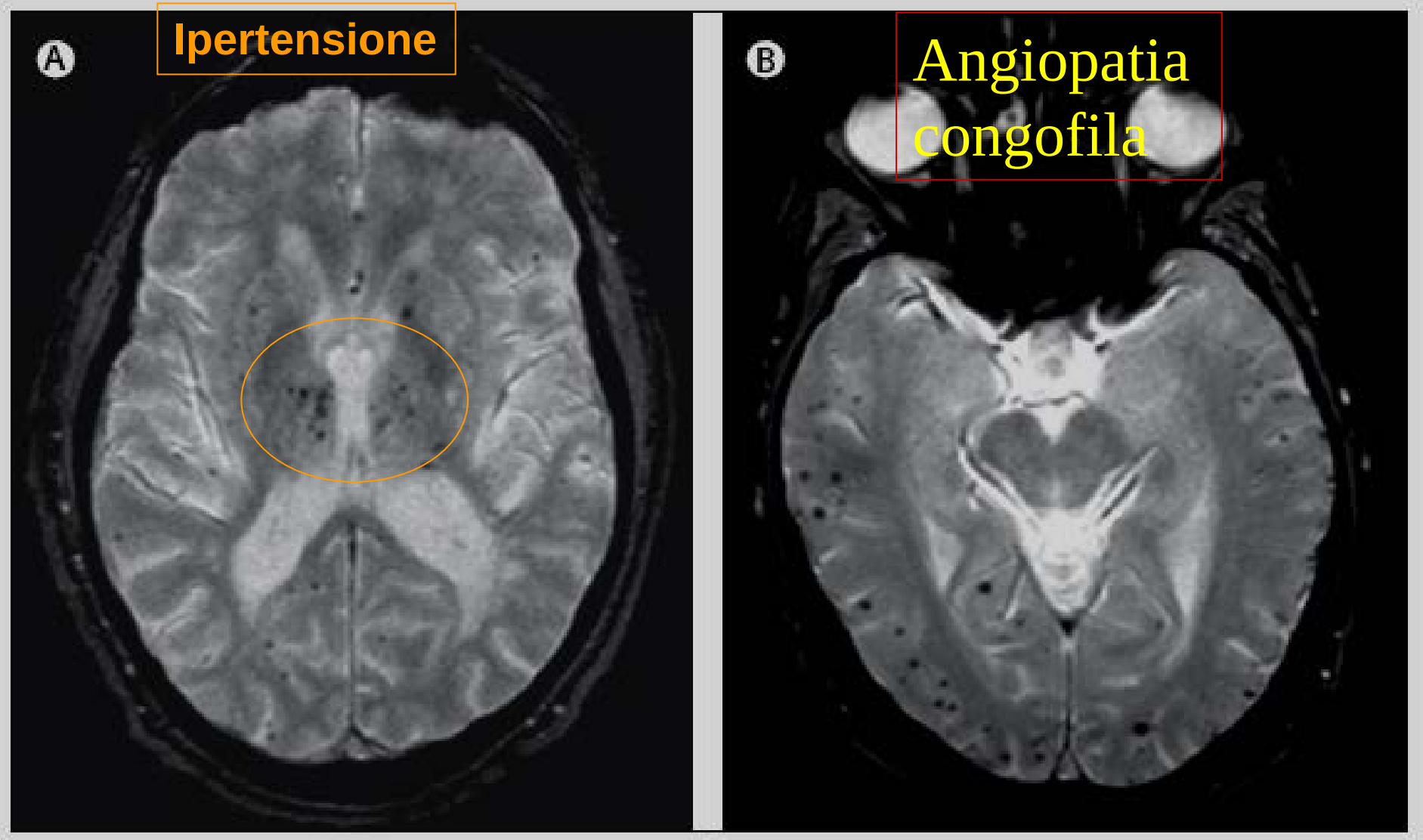


Figure 3: **Deep hemispheric and isolated lobar patterns of CMB distribution**
(A) A T2*-weighted MRI scan from an 84-year-old woman with long-standing hypertension. CMBs are present predominantly in the bilateral thalamus, putamen, caudate, and cerebellum, with only a small number in lobar brain regions (not shown in this image). (B) A T2*-weighted MRI scan from a 77-year-old woman without hypertension. CMBs are present only in lobar brain regions, meeting criteria for probable cerebral amyloid angiopathy.[37] CMB=cerebral microbleed.

Intracranial Hemorrhages in RE-LY

n = 154

Intracerebral	Subdural	Subarachnoid
46%	45%	8%

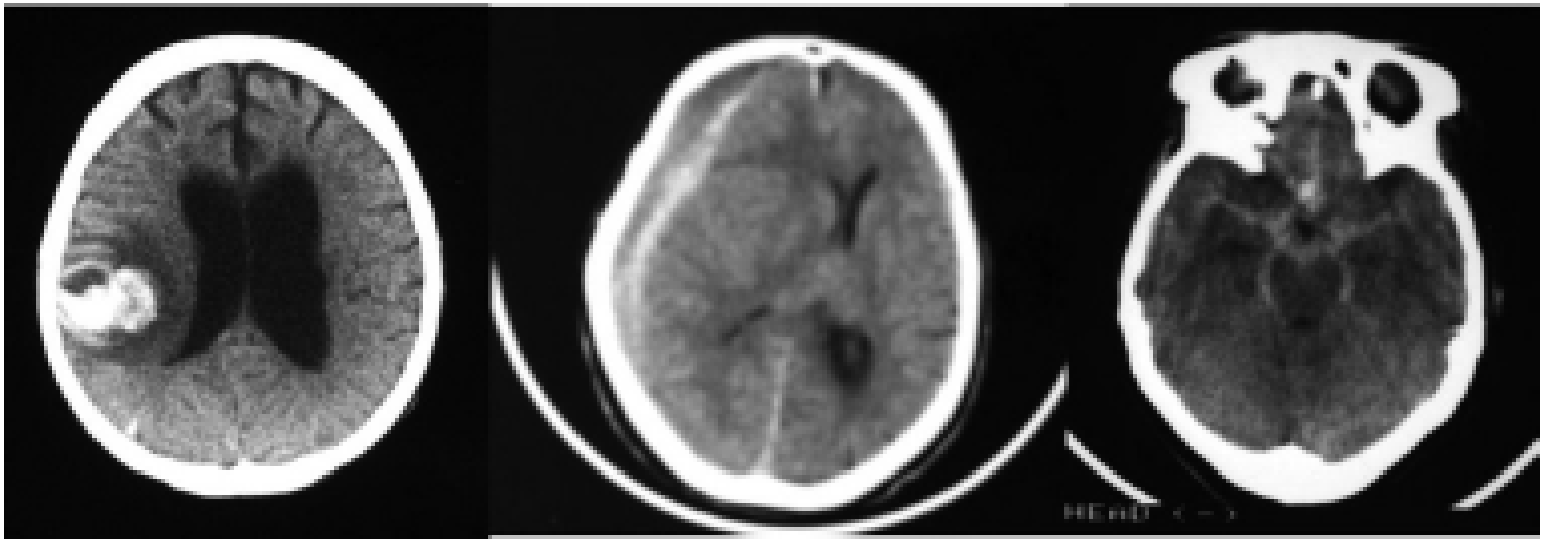
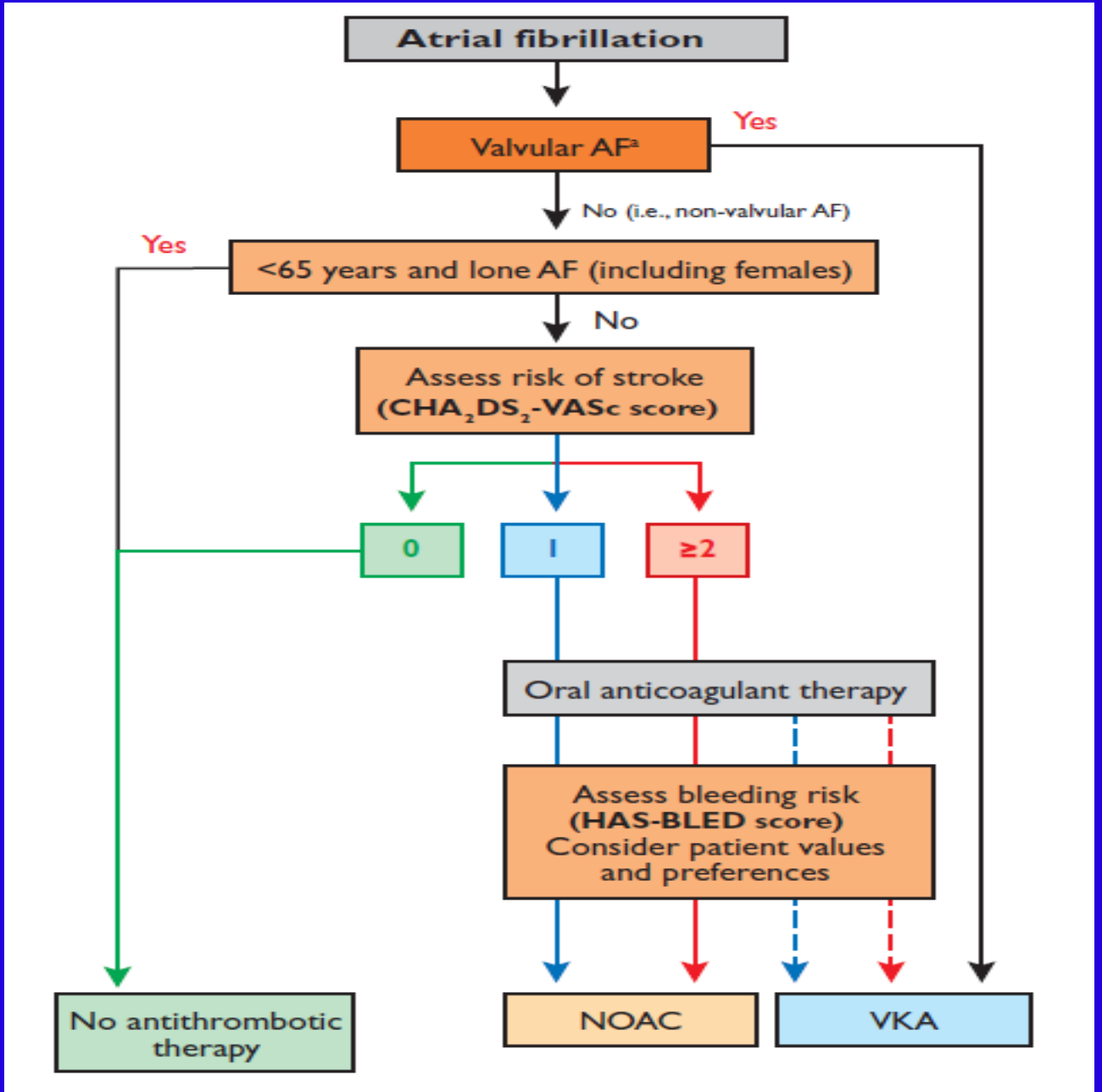


Figure. Sites of intracranial bleeding.

FLOWCHART OF AF TREATMENT
ESC Guidelines 2012



Limiti della Terapia Anticoagulante Orale

Conseguenze

nella FA

Un significativo numero di pazienti con FA a rischio di stroke

- **non riceve la TAO**
- **non la riceve in un range ottimale**

Limiti della terapia con antagonisti della Vitamina K

- Risposta non prevedibile
- Finestra di trattamento stretta (INR range 2-3)
- Monitoraggio routinario dei fattori della coagulazione
- Lente insorgenza/termine d'azione

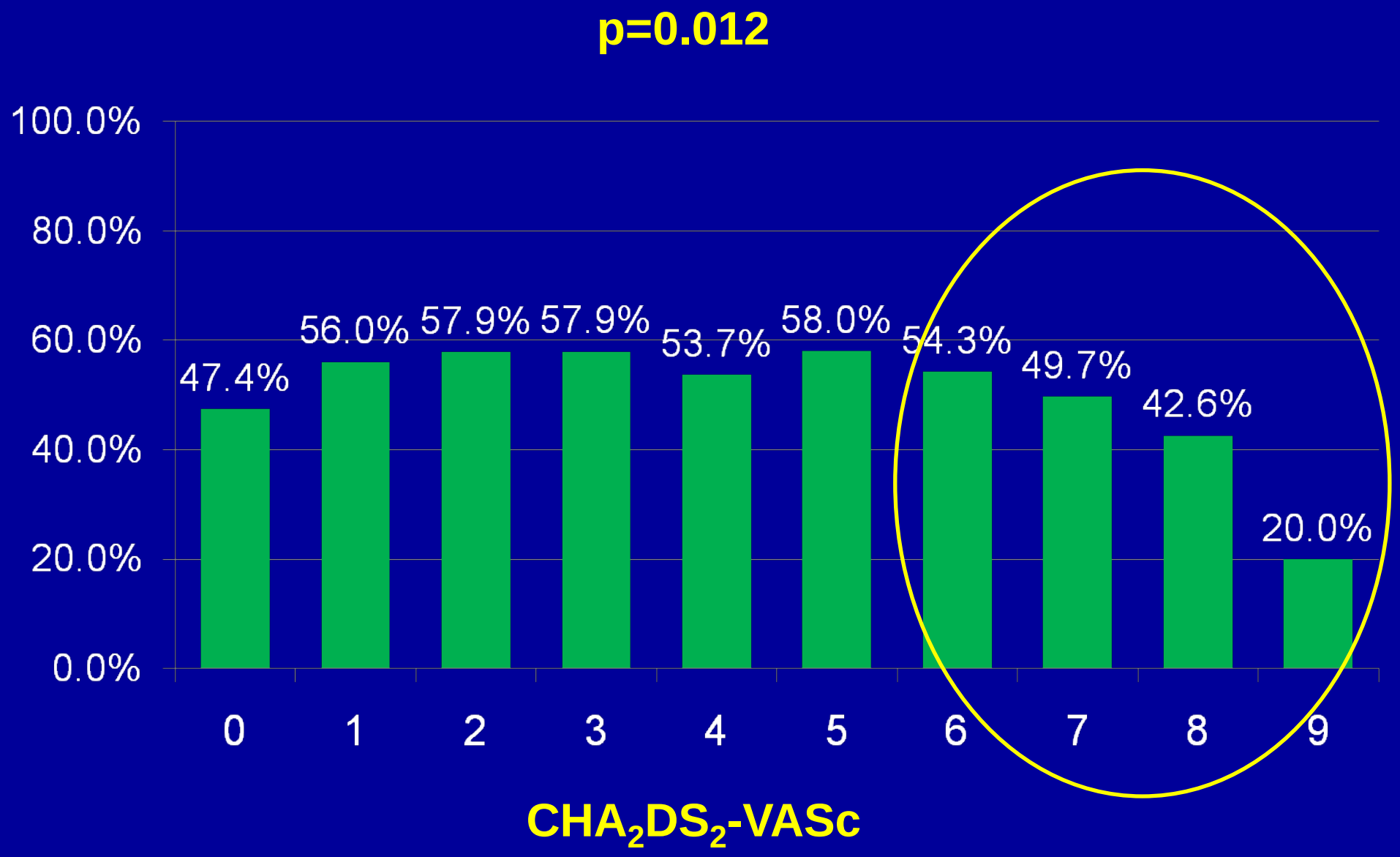
limiti che rendono difficoltoso l'impiego nella pratica clinica

- Frequenti aggiustamenti della dose
- Numerose interazioni alimentari
- Numerose interazioni con altri farmaci
- Resistenza al Warfarin

1. Ansell J, et al. *Chest* 2008;133;160S-198S; 2. Umer Ushman MH, et al. *J Interv Card Electrophysiol* 2008; 22:129-137; Nutescu EA, et al. *Cardiol Clin* 2008; 26:169-187.

Prescription of OAC by CHA_2DS_2-VASc

(non valvular AF, 4845 pts)

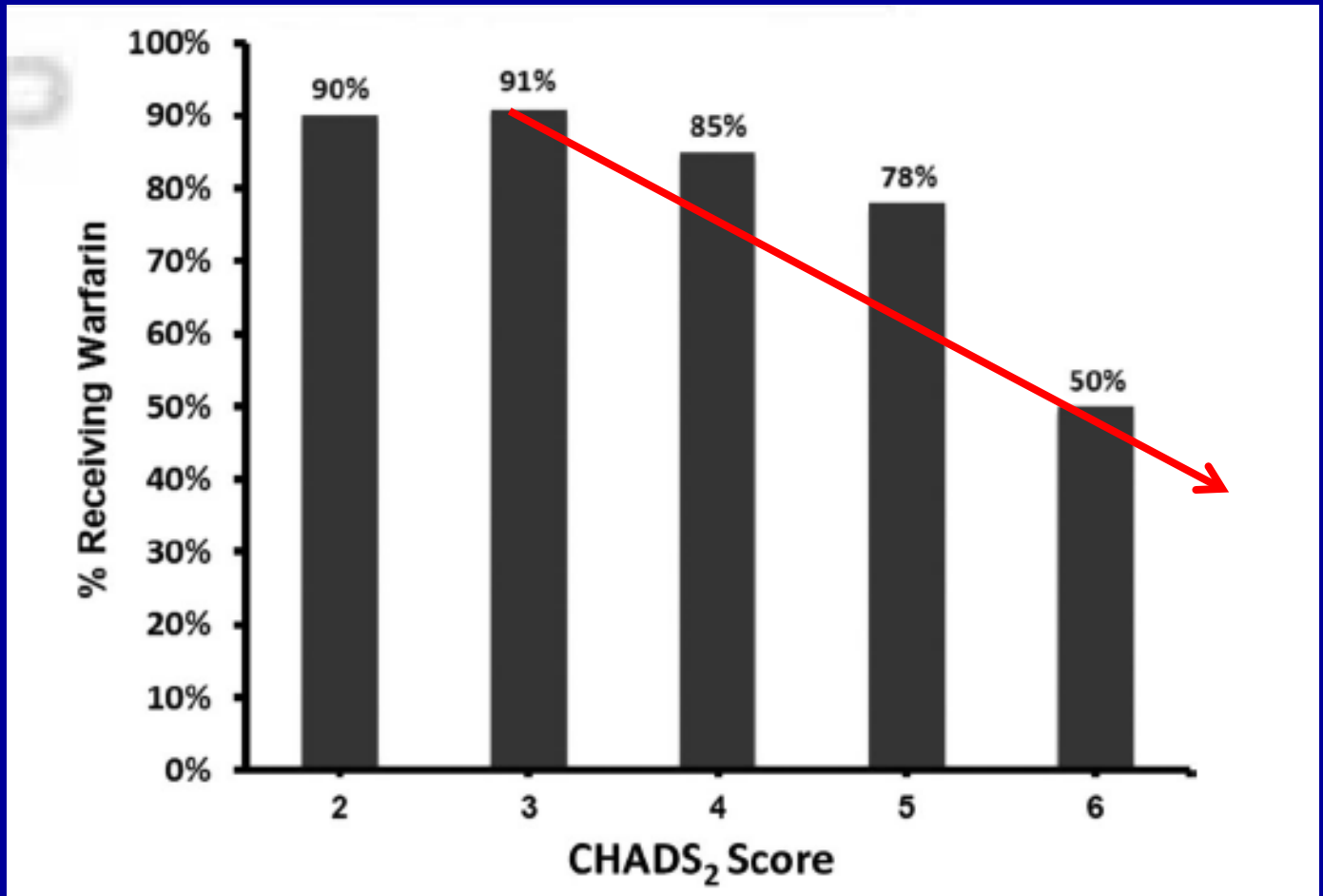


Antithrombotic Therapy Use at Discharge and 1 Year in Patients With Atrial Fibrillation and Acute Stroke

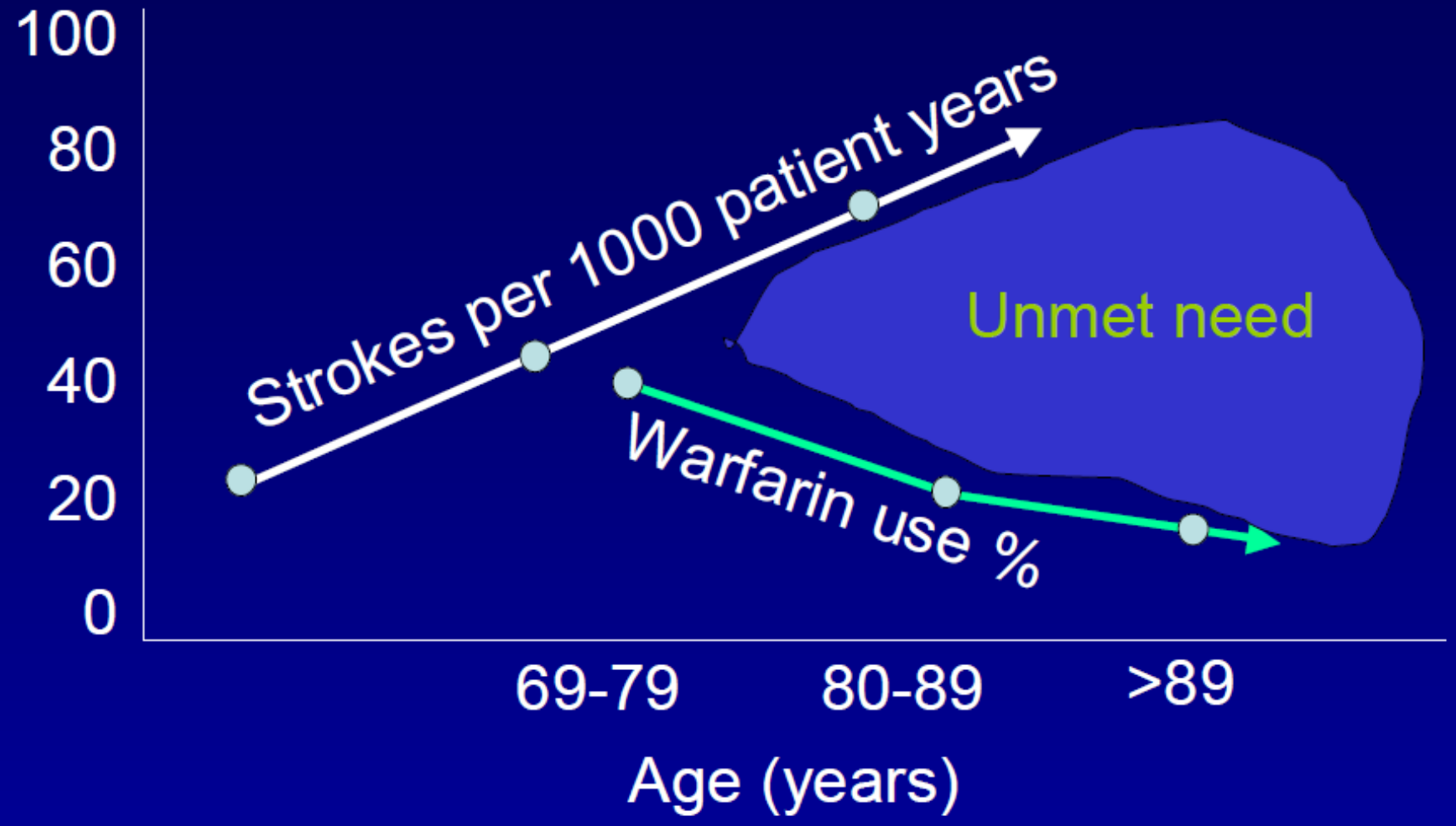
Results From the AVAIL Registry

Renato D. Lopes, MD, PhD; Bimal R. Shah, MD, MBA; DaiWai M. Olson, PhD, RN; Xin Zhao, MS; Wenqin Pan, PhD; Cheryl D. Bushnell, MD, MHS; Eric D. Peterson, MD, MPH

(*Stroke*. 2011;42:00-00.)



Age-related Trends in AF

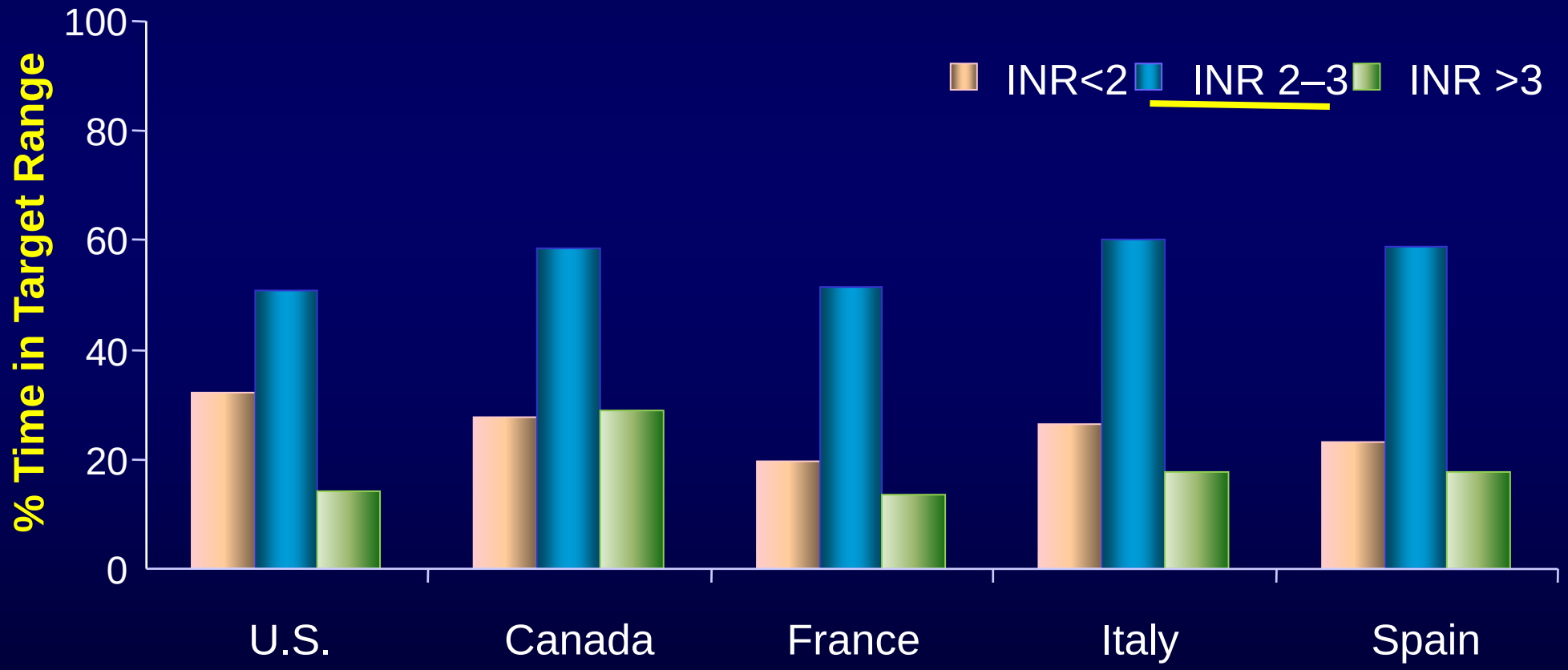


Wolf PA, Arch Intern Med 1987; 147:1561-4
White RH, Am J Med 1999; 106:165-71

Anticoagulation with Warfarin

Intensity Often Outside the Target Range

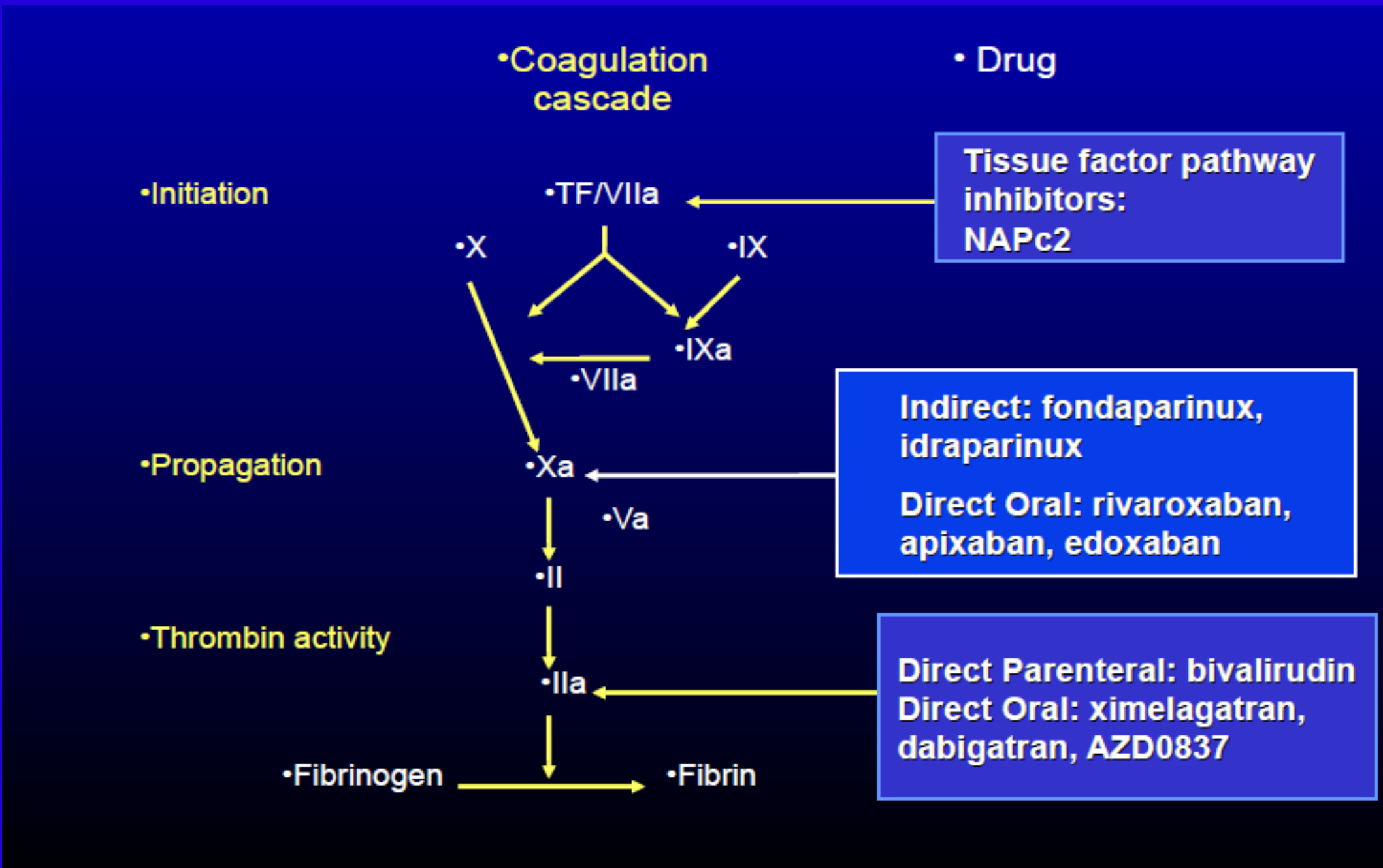
International Study of Anticoagulation Management



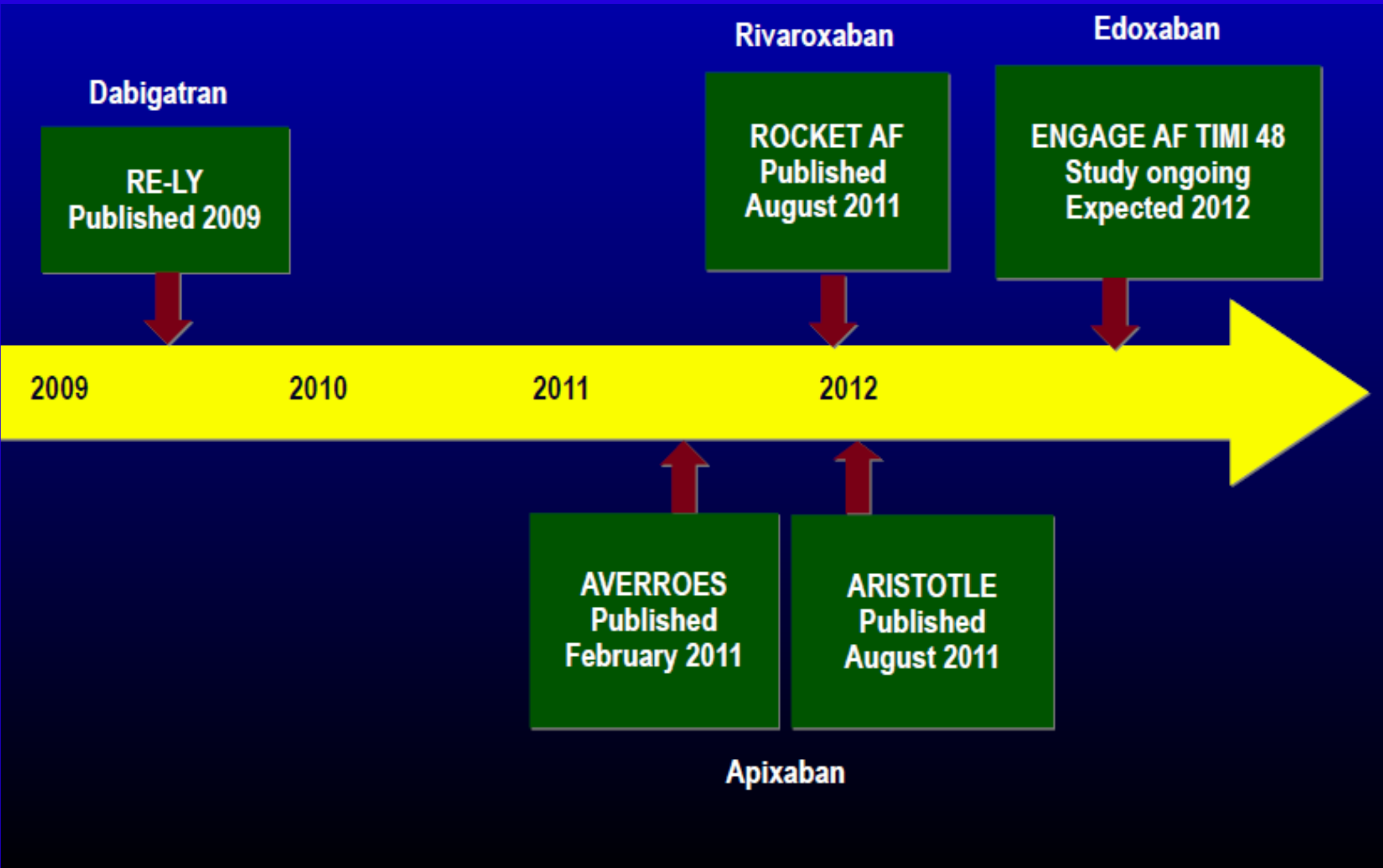
Ansell J, et al. J Thromb Thrombolysis 2007; 23: 83.

…..fratelli…..

Nuovi anticoagulanti orali



FA e nuovi anticoagulanti orali



RE-LY® – Disegno dello studio

RELY®
Study of stroke prevention
in atrial fibrillation

Fibrillazione atriale
con ≥1 fattore di rischio
Assenza di controindicazioni

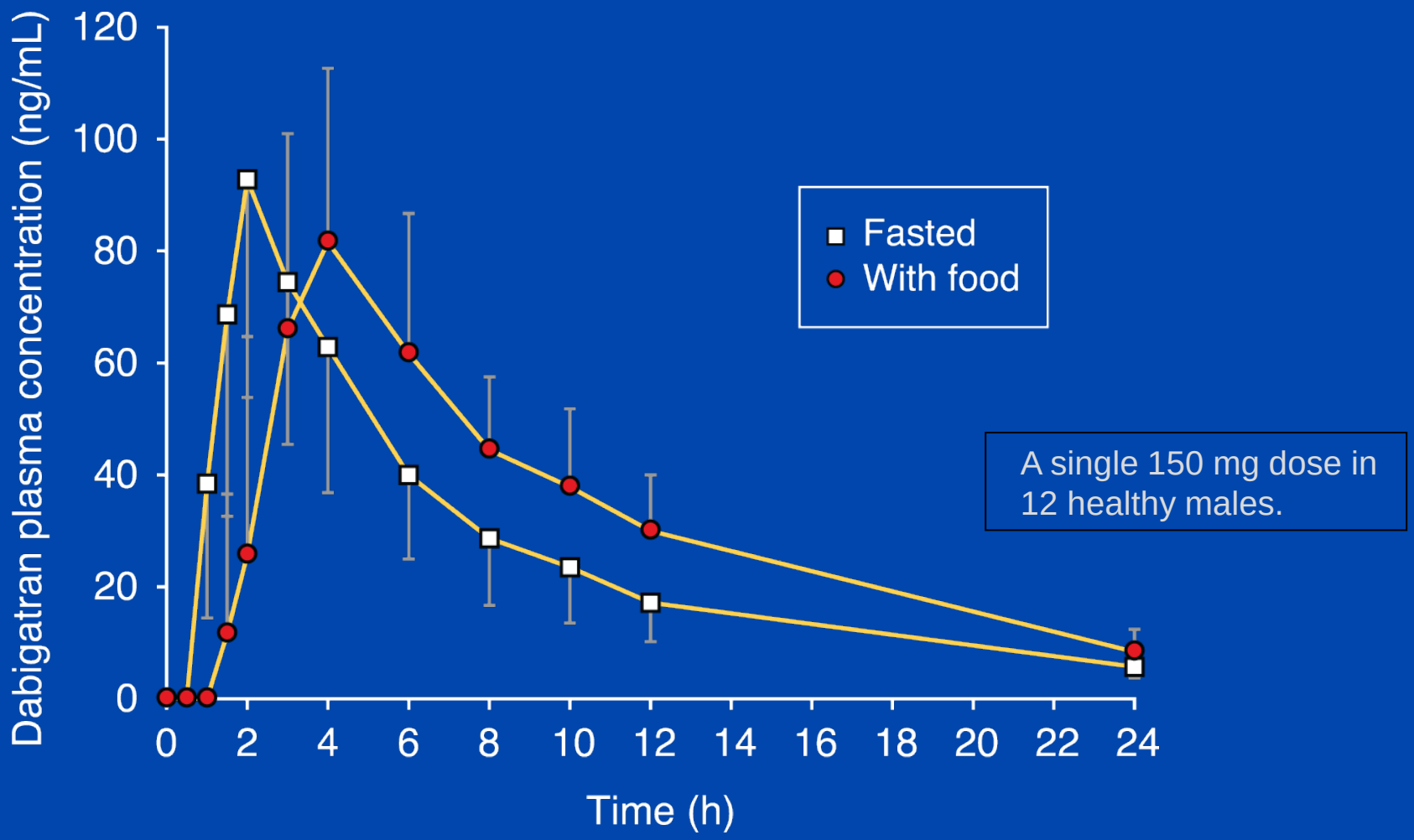
Dabigatran etexilato	**Dabigatran etexilato**	**Warfarin**
150 mg bid	**110 mg bid**	**1 mg, 3 mg, 5 mg**
N=6.000	N=6.000	(INR 2,0–3,0) N=6000

Obiettivo primario: stabilire la non-inferiorità di dabigatran etexilato vs warfarin;
Minimo 1 anno di follow-up, massimo 3 anni e in media 2 anni di follow-up

Dabigatran etexilato ha ricevuto approvazione EMA nella prevenzione dello stroke nei pazienti con fibrillazione atriale il 4 Agosto 2011.

Ezekowitz MD, et al. *Am Heart J* 2009;157:805-810.
Connolly SJ, et al. *N Engl J Med* 2009;361:1139-1151.

Rapid Absorption

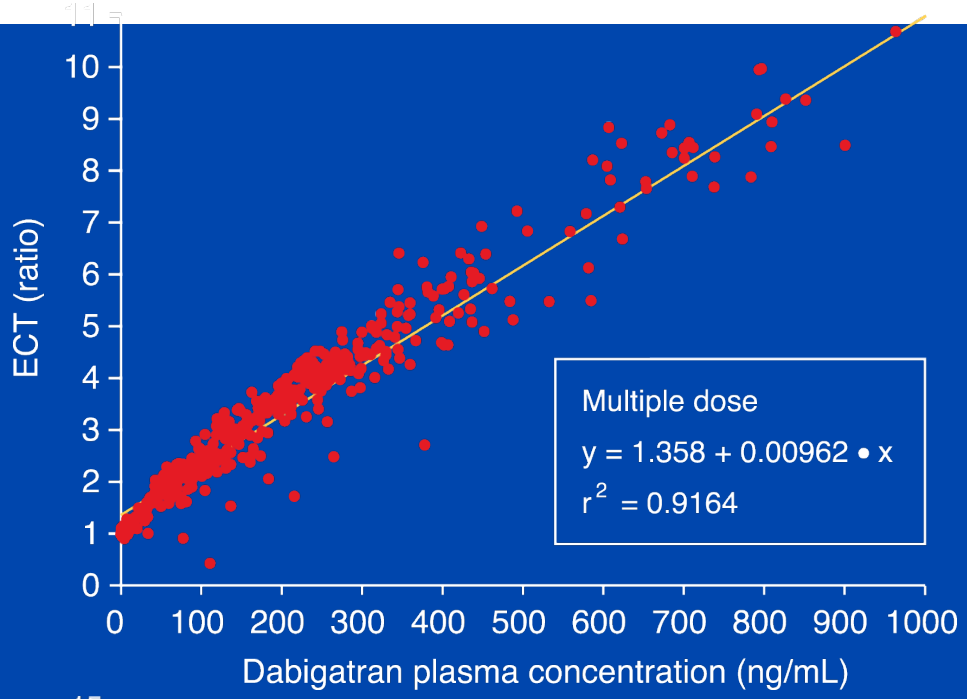


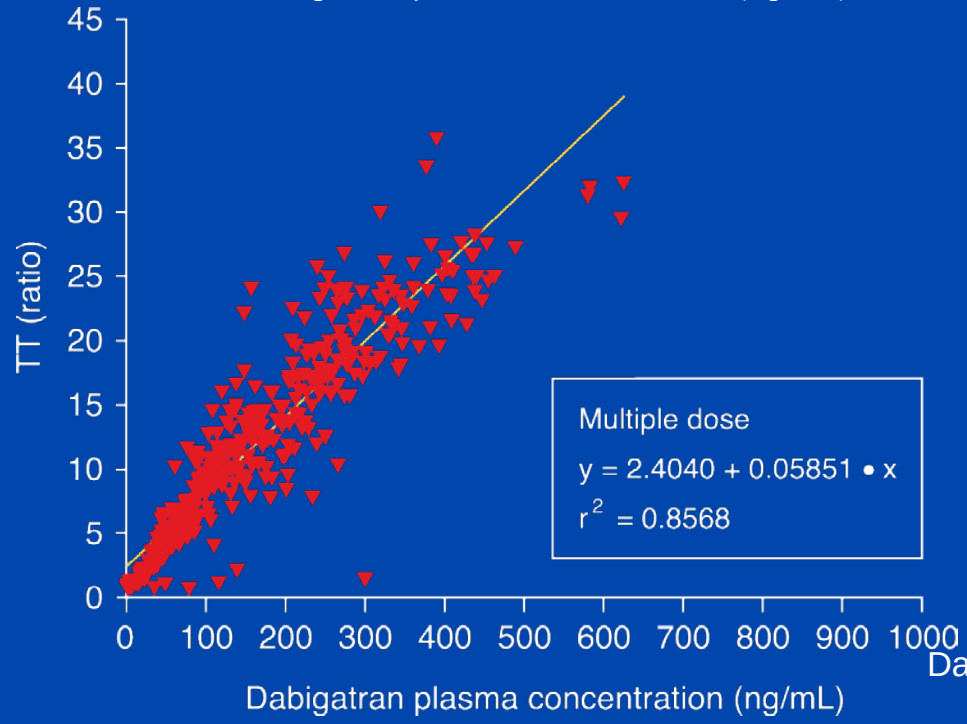
- Rapid absorption (C_{max} in up to 2 hours)
  - Food delayed C_{max} by 2 hours
  - Surgery delayed C_{max} by 4 hours

atran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation

Stangier J.: *Clin Pharmacokinet* 2008:47:285-295

Assessing Dabigatran's Effect on Thrombin Inhibition



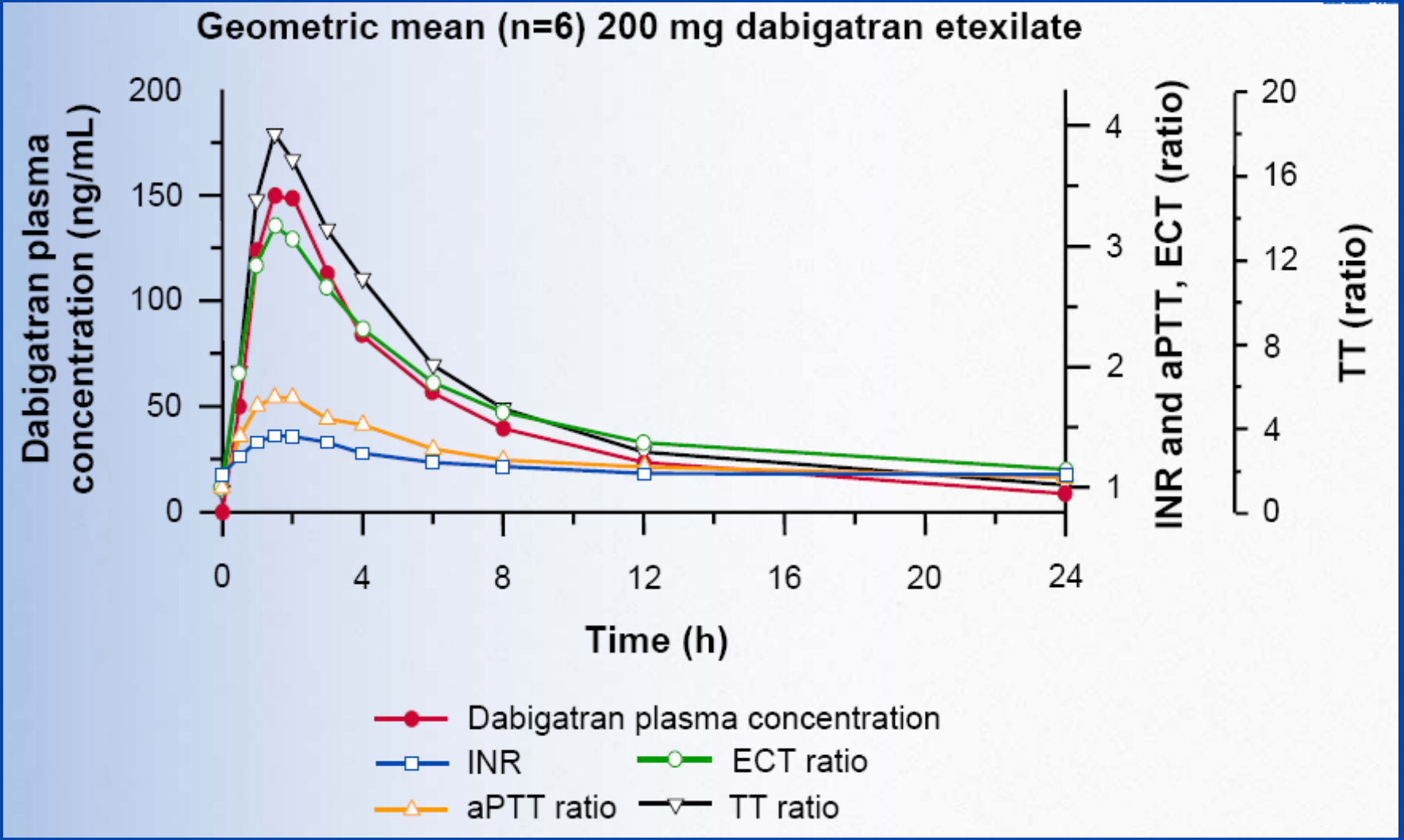


- Thrombin is the central player in clot formation
- Thrombin clotting time (TT) and ecarin clotting time (ECT) directly reflect thrombin inhibition
- Dabigatran has a very predictable, dose-linear, direct effect on coagulation via thrombin

Stangier J.: *Clin Pharmacokinet* 2008:47:285-295

Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation

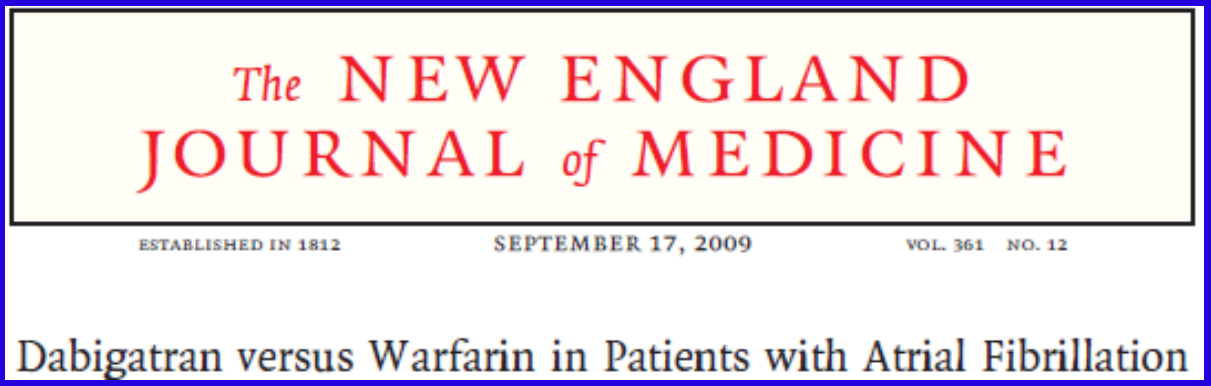
Correlation of plasma concentration with coagulation parameters



Time curve for INR, aPTT, ECT and TT (ratios) parallel dabigatran plasma concentration-time curves.

atran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation

Stangier *et al. Br J Clin Pharmacol* 2007;64:292-303

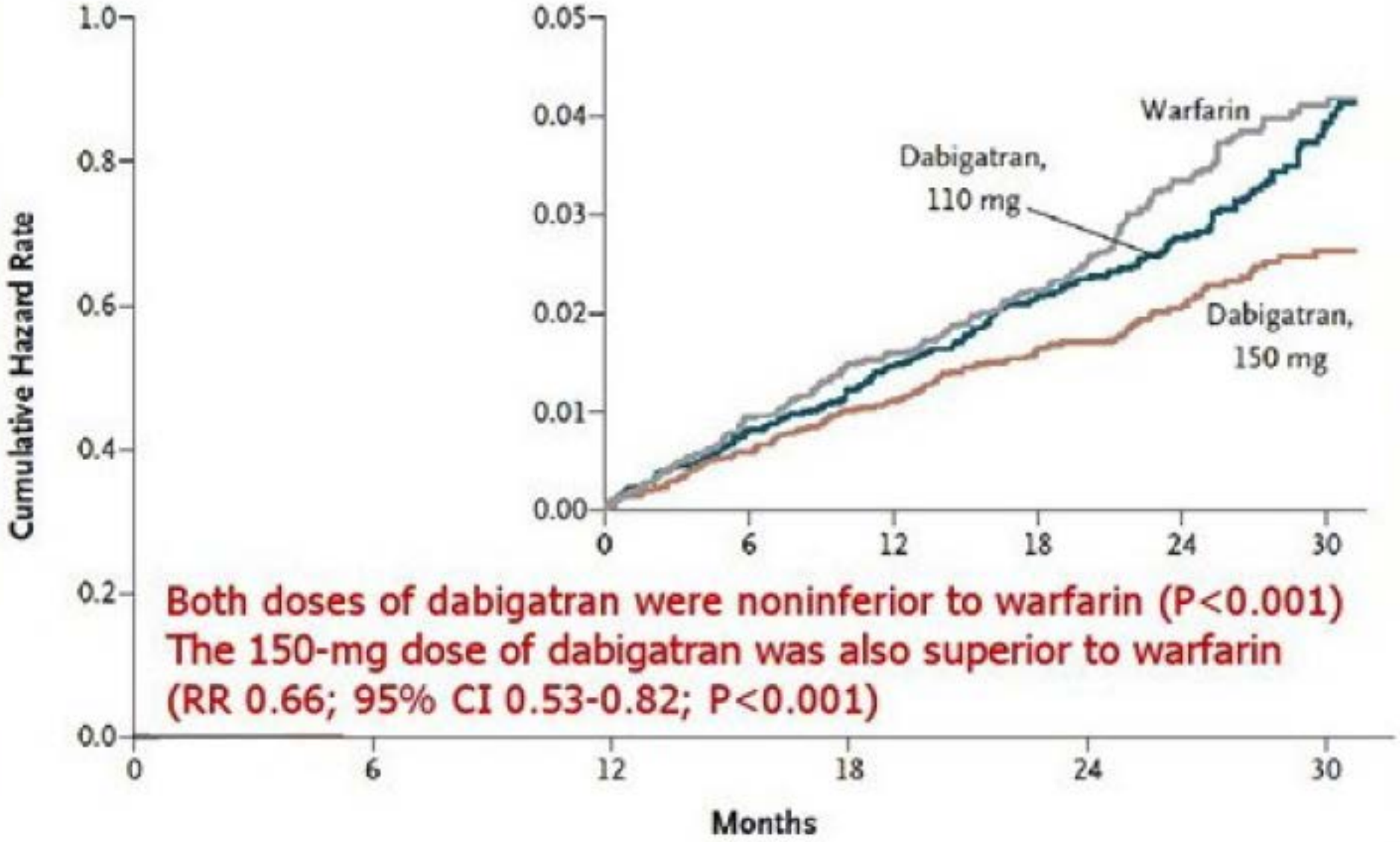


- Trial randomizzato di non inferiorità
- 18.113 pz con FA non valvolare
- Studio in doppio cieco per il dabigatran (110mg,150mg bd) e aperto per il warfarin

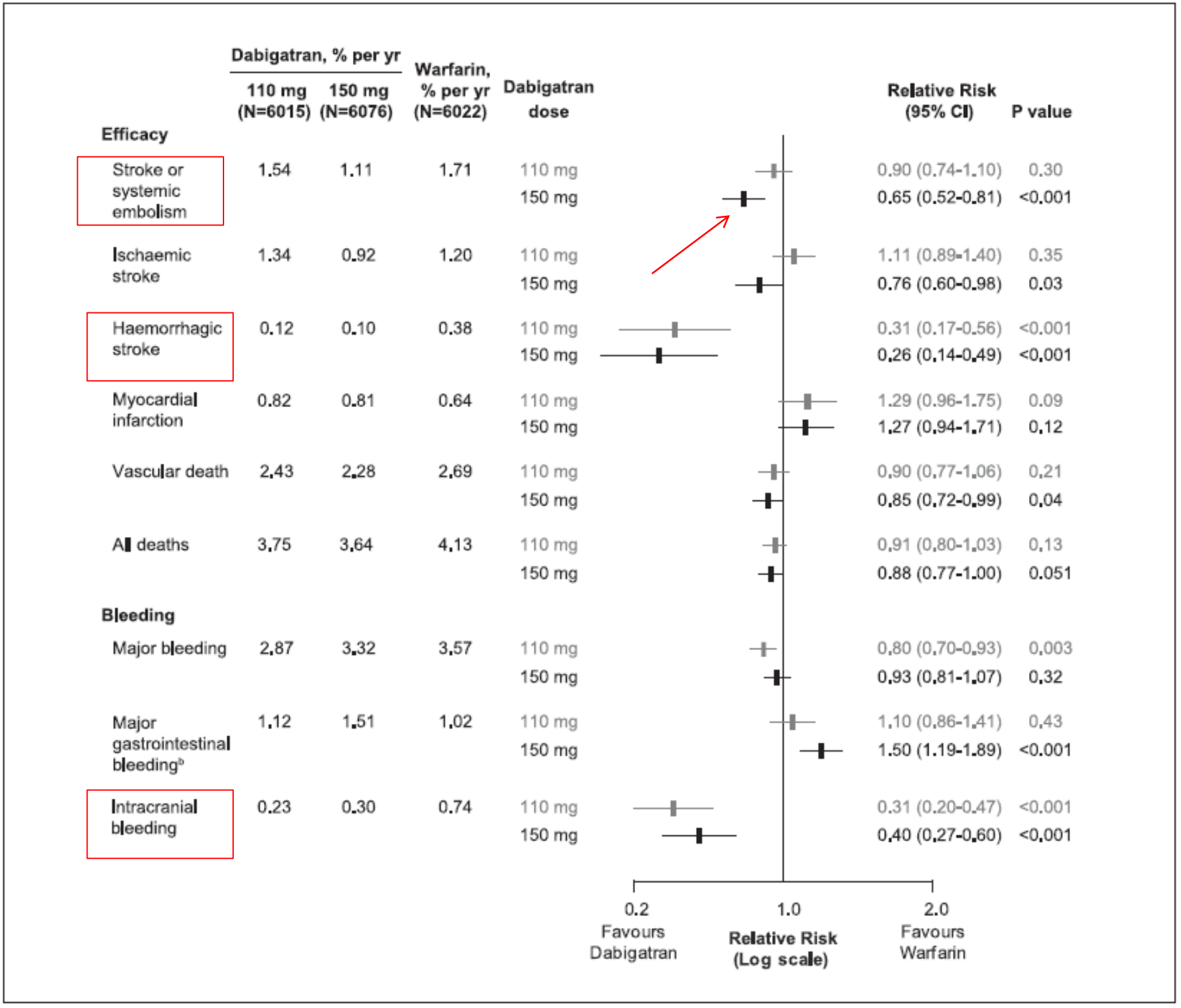
Characteristic	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
Age	71.4±8.6	71.5±8.8	71.6±8.6
$CHADS_2$ score	2.1±1.1	2.2±1.2	2.1±1.1
Previous stroke or TIA (%) 3600 pz	19.9	20.3	19.8
Diabetes mellitus (%)	23.4	23.1	23.4
Hypertension (%)	78.8	78.9	78.9

NEJM 2009;361:1139-1151

STROKE o embolia sistemica



NEJM 2009;361:1139-1151

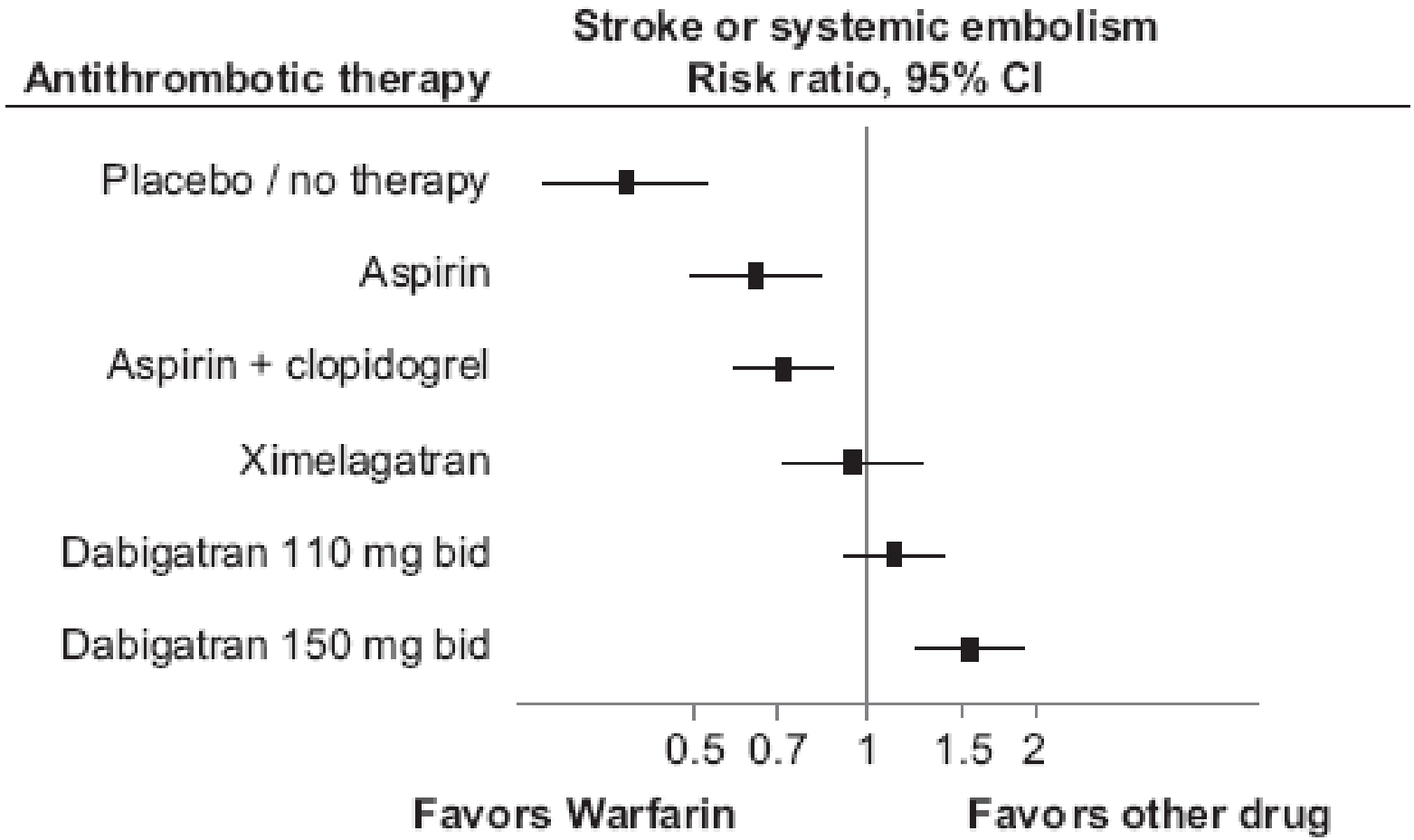

Dabigatran, % per yr
110 mg (N=6015)
150 mg (N=6076)
Warfarin, % per yr (N=6022)
Dabigatran dose
Relative Risk (95% CI)
P value
Efficacy
Stroke or systemic embolism
1.54
1.11
1.71
110 mg
0.90 (0.74-1.10)
0.30
150 mg
0.65 (0.52-0.81)
<0.001
Ischaemic stroke
1.34
0.92
1.20
110 mg
1.11 (0.89-1.40)
0.35
150 mg
0.76 (0.60-0.98)
0.03
Haemorrhagic stroke
0.12
0.10
0.38
110 mg
0.31 (0.17-0.56)
<0.001
150 mg
0.26 (0.14-0.49)
<0.001
Myocardial infarction
0.82
0.81
0.64
110 mg
1.29 (0.96-1.75)
0.09
150 mg
1.27 (0.94-1.71)
0.12
Vascular death
2.43
2.28
2.69
110 mg
0.90 (0.77-1.06)
0.21
150 mg
0.85 (0.72-0.99)
0.04
All deaths
3.75
3.64
4.13
110 mg
0.91 (0.80-1.03)
0.13
150 mg
0.88 (0.77-1.00)
0.051
Bleeding
Major bleeding
2.87
3.32
3.57
110 mg
0.80 (0.70-0.93)
0.003
150 mg
0.93 (0.81-1.07)
0.32
Major gastrointestinal bleeding[b]
1.12
1.51
1.02
110 mg
1.10 (0.86-1.41)
0.43
150 mg
1.50 (1.19-1.89)
<0.001
Intracranial bleeding
0.23
0.30
0.74
110 mg
0.31 (0.20-0.47)
<0.001
150 mg
0.40 (0.27-0.60)
<0.001
0.2
Favours Dabigatran
1.0
Relative Risk (Log scale)
2.0
Favours Warfarin

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association
Learn and Live

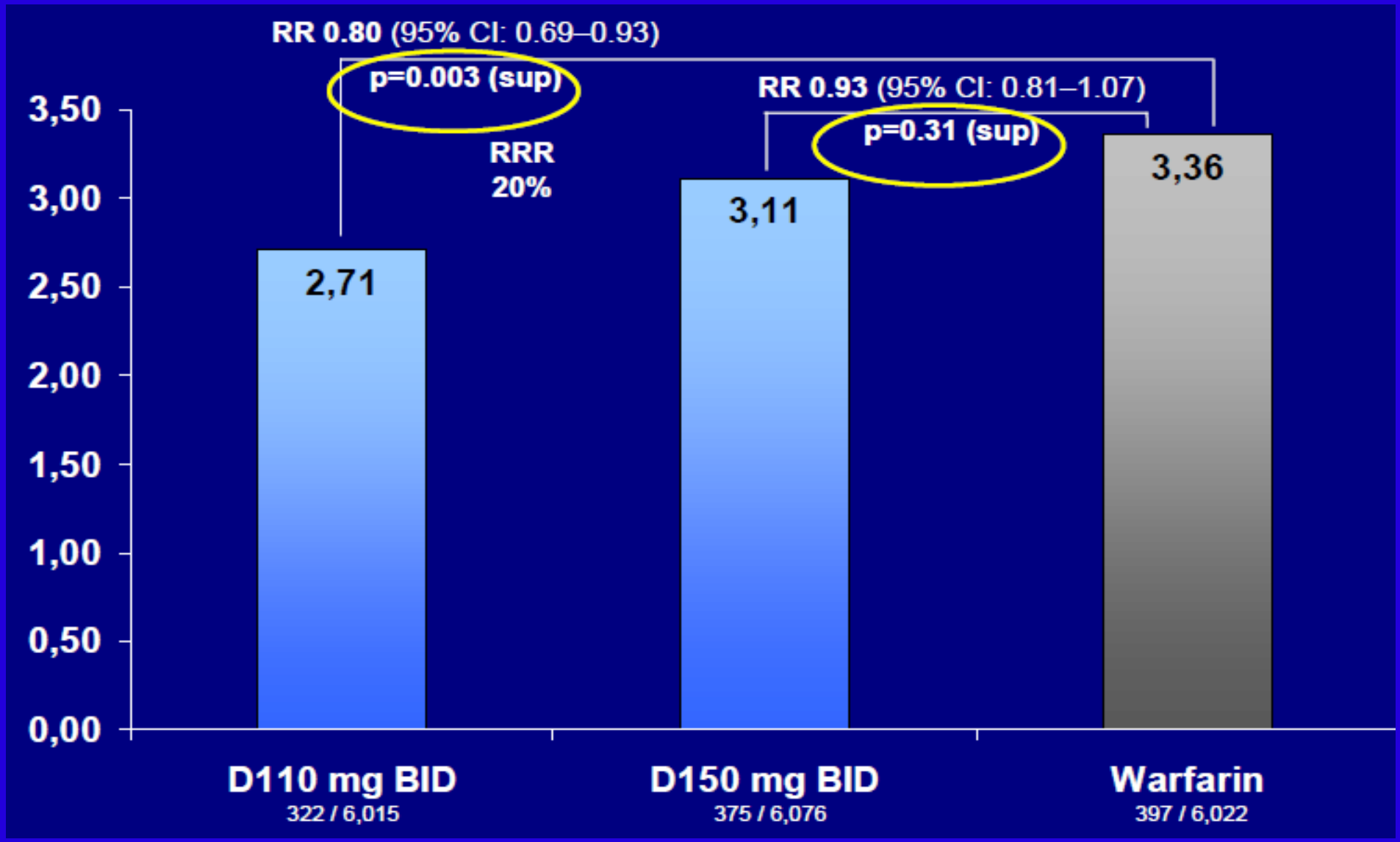
Dabigatran Etexilate: A New Oral Thrombin Inhibitor

Graeme J. Hankey and John W. Eikelboom

Circulation 2011;123;1436-1450
DOI: 10.1161/CIRCULATIONAHA.110.004424
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

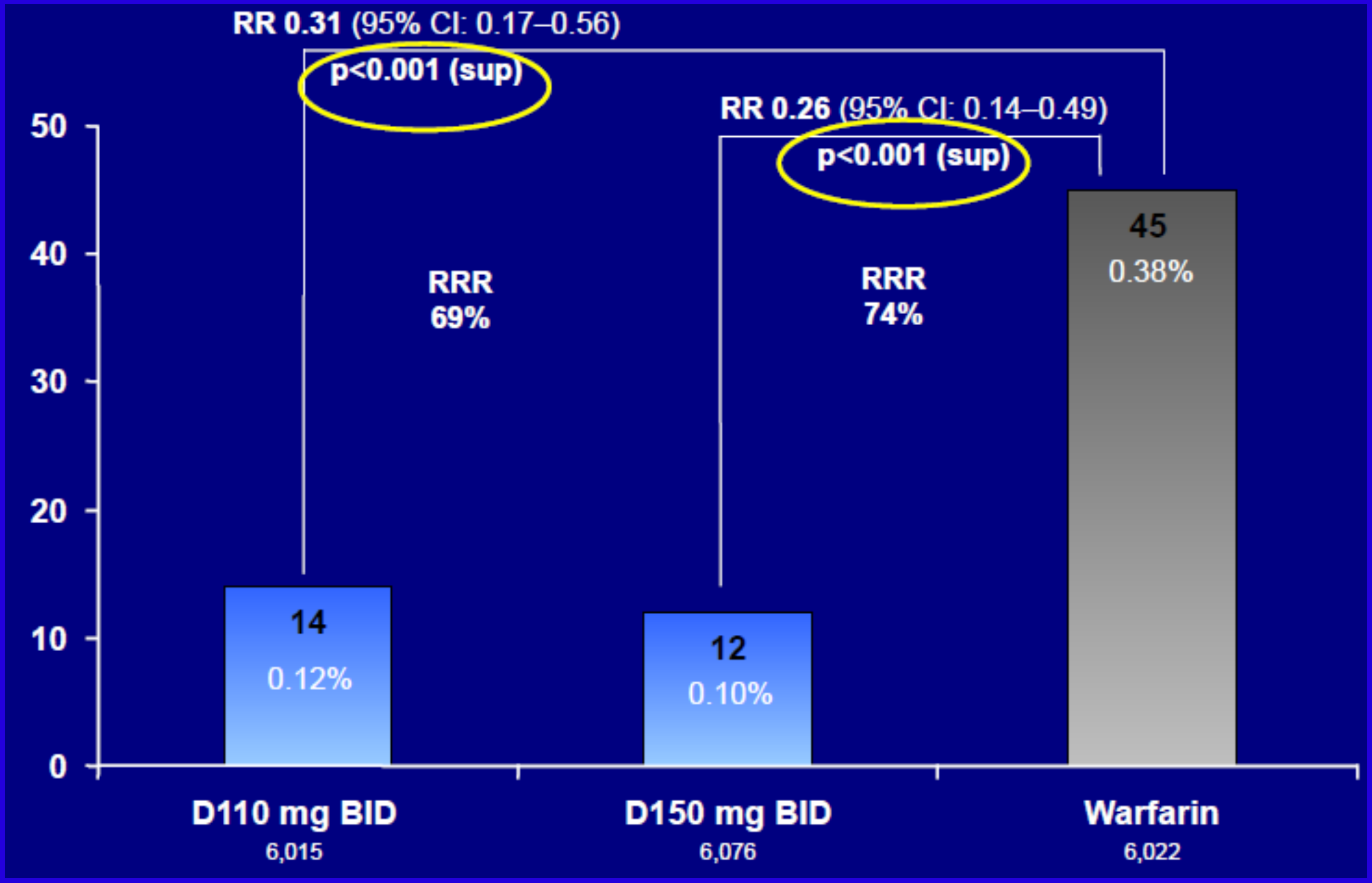


EMORRAGIE MAGGIORI



NEJM 2009;361:1139-1151

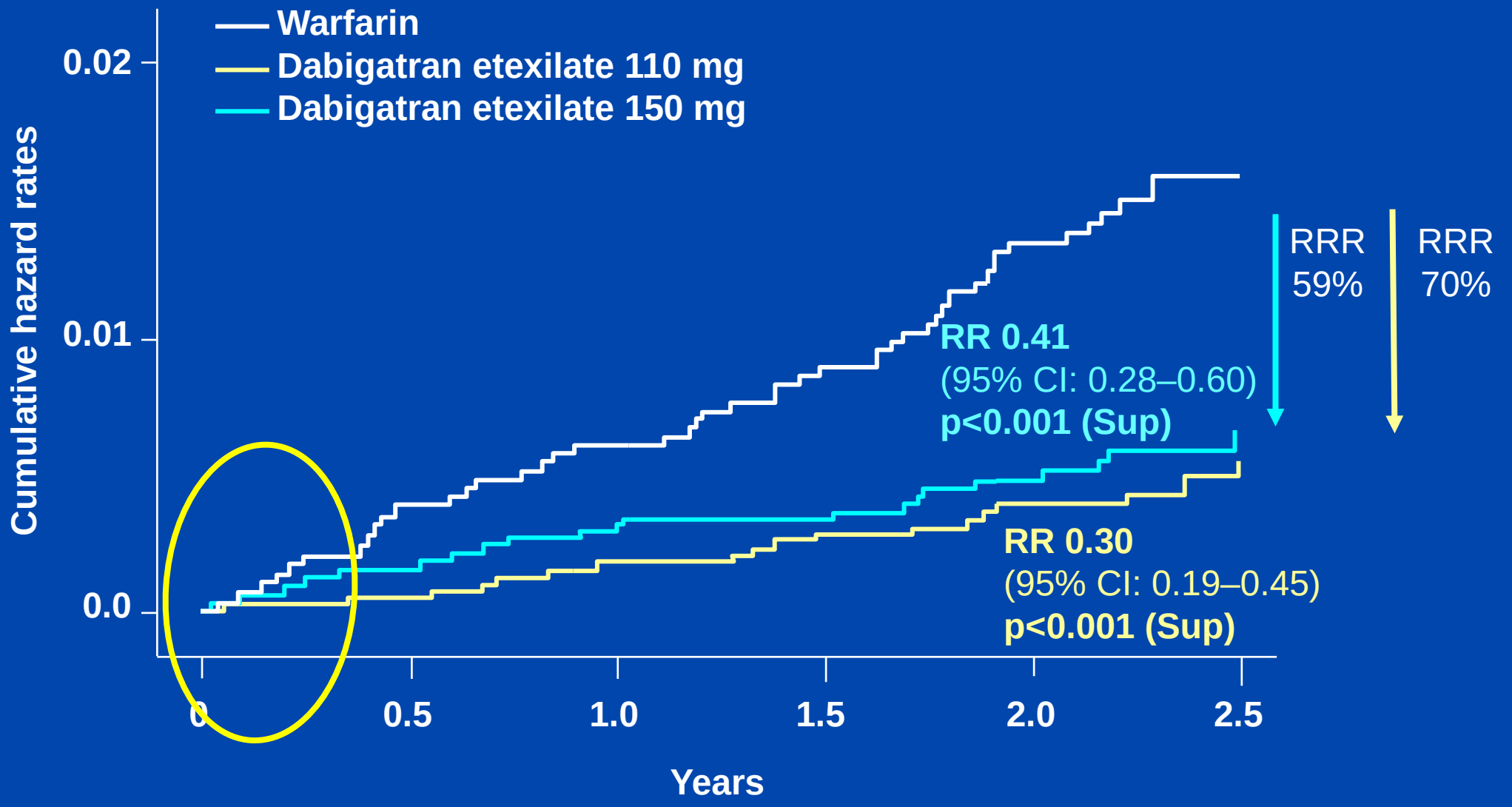
STROKE EMORRAGICO



NEJM 2009;361:1139-1151

Tempo al primo sanguinamento intracranico

RELY®
Study of stroke prevention in atrial fibrillation



RR, Relative risk; CI, confidence interval; Sup, superior

Connolly SJ., et al. *N Engl J Med* 2009; 361:1139-1151.
Connolly SJ., et al. *N Engl J Med* 2010; 363 (19):1875-76

Dabigatran etexilato ha ricevuto approvazione EMA nella prevenzione dello stroke nei pazienti con fibrillazione atriale il 4 Agosto 2011.

Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial

*Hans-Christoph Diener, Stuart J Connolly, Michael D Ezekowitz, Lars Wallentin, Paul A Reilly, Sean Yang, Denis Xavier, Giuseppe Di Pasquale, Salim Yusuf, for the RE-LY study group**

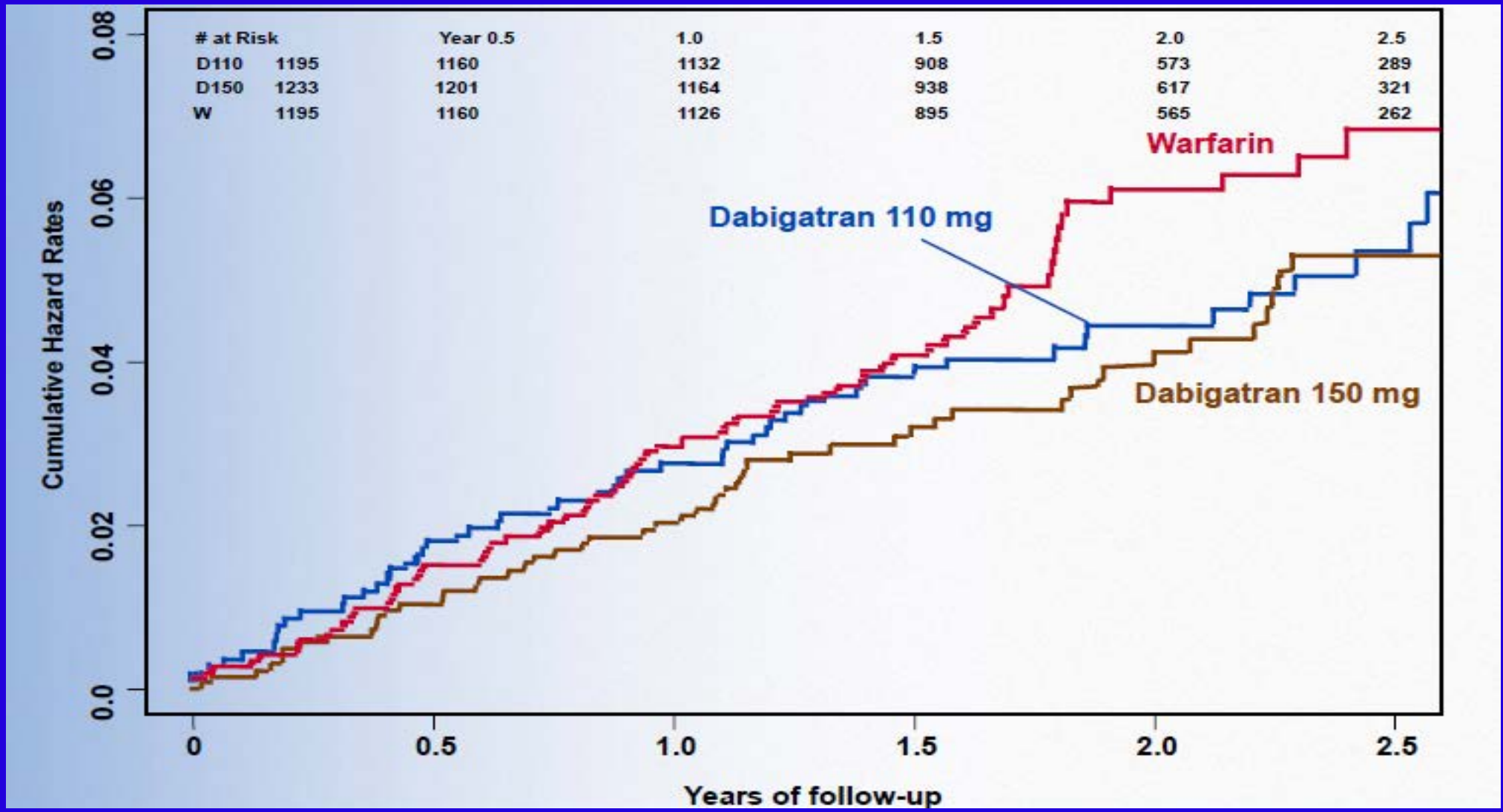
Summary

Background In the Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, dabigatran reduced occurrence of both stroke and haemorrhage compared with warfarin in patients who had atrial fibrillation and were at increased risk of stroke. We aimed to assess the effects of dabigatran compared with warfarin in the subgroup of patients with previous stroke or transient ischaemic attack.

Lancet Neurol 2010; 9: 1157–63

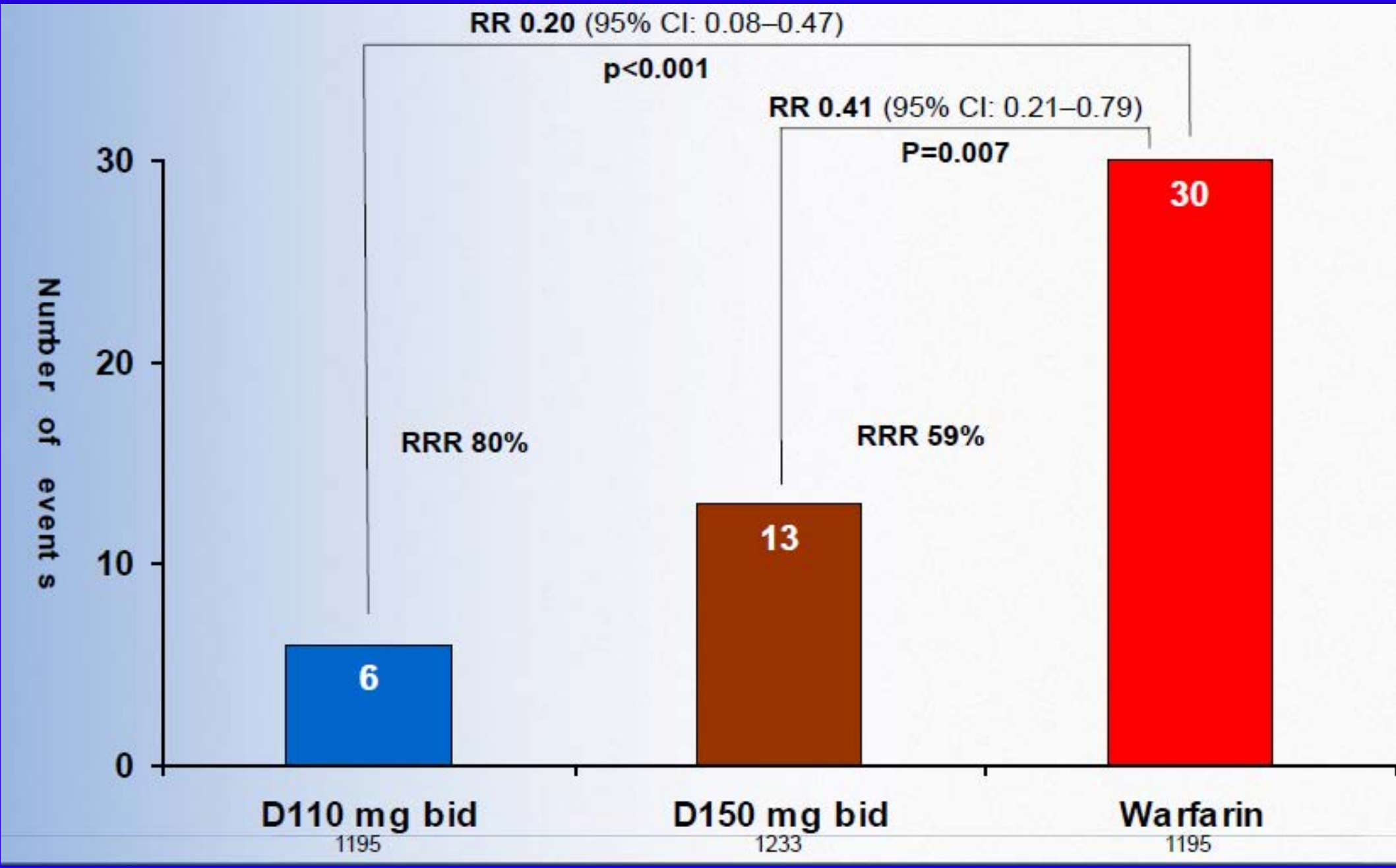
Published Online November 8, 2010 DOI:10.1016/S1474-4422(10)70274-X

Precedente Stroke e/o TIA: 3600 pz



NEJM 2009;361:1139-1151

Sanguinamenti intracranici in pz con pregresso Stroke e/o TIA



NEJM 2009;361:1139-1151

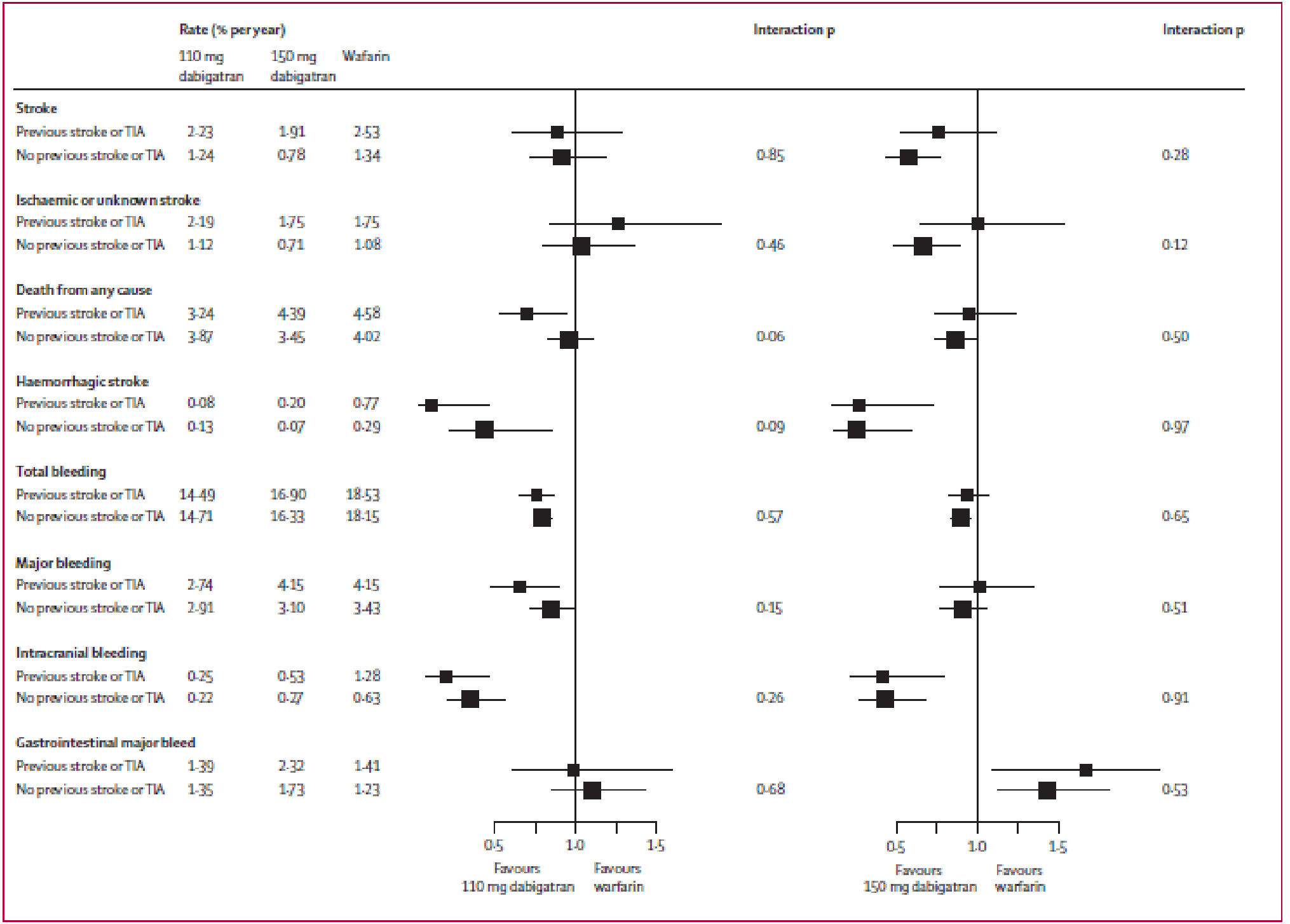


Figure 2: Subgroup analyses of stroke, ischaemic or unknown stroke, haemorrhagic stroke, and major bleeding
TIA=transient ischaemic attack.

RE-LY® – Riassunto dei risultati

RELY®
Study of stroke prevention in atrial fibrillation

150 mg vs. warfarin

- Riduzione statisticamente significativa dell'ictus / embolia sistemica
- Riduzione statisticamente significativa dell'ictus emorragico
- Riduzione statisticamente significativa della mortalità vascolare
- Tassi di sanguinamento maggiore sovrapponibili
- Riduzione significativa del numero totale di sanguinamenti, dei sanguinamenti che hanno messo in pericolo di vita e dei sanguinamenti intracranici

110 mg vs. warfarin

- Tassi sovrapponibili di ictus / embolia sistemica
- Riduzione statisticamente significativa dell'ictus emorragico
- Riduzione statisticamente significativa dei tassi di sanguinamento importante
- Riduzione significativa del numero totale di sanguinamenti, dei sanguinamenti che hanno messo in pericolo di vita e dei sanguinamenti intracranici

Connolly SJ, et al. *N Engl J Med* 2009;361:1139-1151.

Dabigatran etexilato ha ricevuto approvazione EMA nella prevenzione dello stroke nei pazienti con fibrillazione atriale il 4 Agosto 2011.

Conclusioni

RELY®
Study of stroke prevention in atrial fibrillation

Entrambi i dosaggi di dabigatran forniscono **vantaggi diversi e complementari** rispetto a warfarin

- **150 mg** due volte al giorno presenta **una efficacia superiore** con un'incidenza di sanguinamento maggiore sovrapponibile
- **110 mg** due volte al giorno presenta **un'incidenza significativamente inferiore di sanguinamenti maggiori** con efficacia sovrapponibile
- E' stato osservato un **beneficio clinico netto** sovrapponibile con i due dosaggi di dabigatran

Connolly SJ, et al. *N Engl J Med* 2009;361:1139-1151.

Dabigatran etexilato ha ricevuto approvazione EMA nella prevenzione dello stroke nei pazienti con fibrillazione atriale il 4 Agosto 2011.

ACC.11
60th Annual Scientific Session & Expo

E62
JACC April 5, 2011
Volume 57, Issue 14

CARDIAC ARRHYTHMIAS

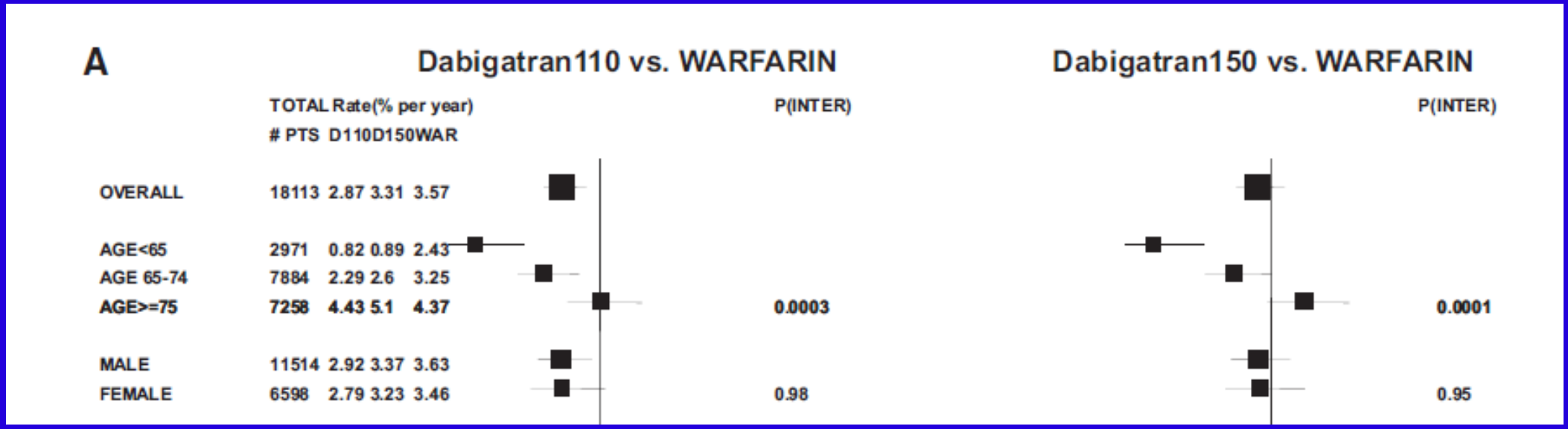
DABIGATRAN ETEXILATE VERSUS WARFARIN IN PATIENTS WITH DIFFERENT TYPES OF ATRIAL FIBRILLATION: A RE-LY® SUBGROUP ANALYSIS

ACC Poster Contributions
Ernest N. Morial Convention Center, Hall F
Sunday, April 03, 2011, 3:30 p.m.-4:45 p.m.

Risk of Bleeding With 2 Doses of Dabigatran Compared With Warfarin in Older and Younger Patients With Atrial Fibrillation

An Analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) Trial

John W. Eikelboom, MBBS; Lars Wallentin, MD; Stuart J. Connolly, MD; Mike Ezekowitz, MD; Jeff S. Healey, MD; Jonas Oldgren, MD; Sean Yang, BComSc; Marco Alings, MD; Scott Kaatz, DO; Stefan H. Hohnloser, MD; Hans-Christoph Diener, MD; Maria Grazia Franzosi, PhD; Kurt Huber, MD; Paul Reilly, MD; Jeanne Varrone, MD; Salim Yusuf, MD



Risk of Bleeding With 2 Doses of Dabigatran Compared With Warfarin in Older and Younger Patients With Atrial Fibrillation

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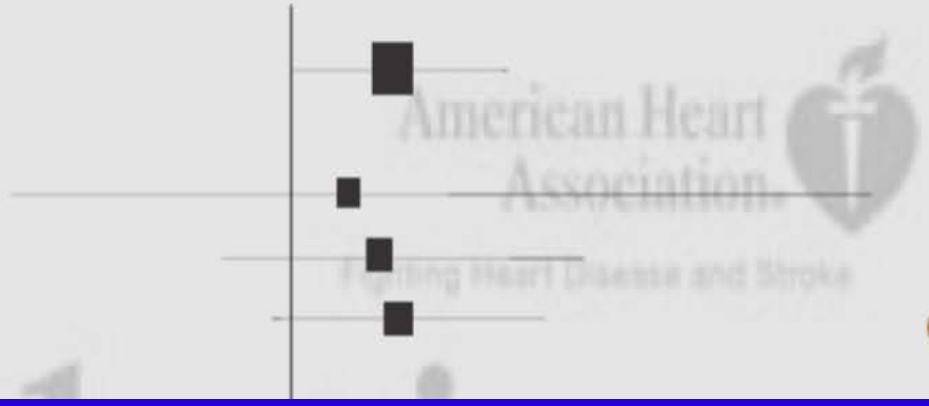
B

Dabigatran150 vs. Dabigatran110

	TOTAL # PTS	Rate(% per year) D110	D150	P(INTER)
OVERALL	12091	2.87	3.31	
AGE<65	2019	0.82	0.89	
AGE 65-74	5244	2.29	2.6	
AGE>=75	4828	4.43	5.1	0.98



Stroke
Journal of the American Heart Association

Intracranial Hemorrhage in Atrial Fibrillation Patients During Anticoagulation With Warfarin or Dabigatran: The RE-LY Trial

Robert G. Hart, Hans-Christoph Diener, Sean Yang, Stuart J. Connolly, Lars Wallentin, Paul A. Reilly, Michael D. Ezekowitz and Salim Yusuf

Stroke. 2012;43:1511-1517; originally published online April 5, 2012;
doi: 10.1161/STROKEAHA.112.650614
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

Intracranial Hemorrhages in RE-LY

n = 154

Intracerebral	Subdural	Subarachnoid
46%	45%	8%

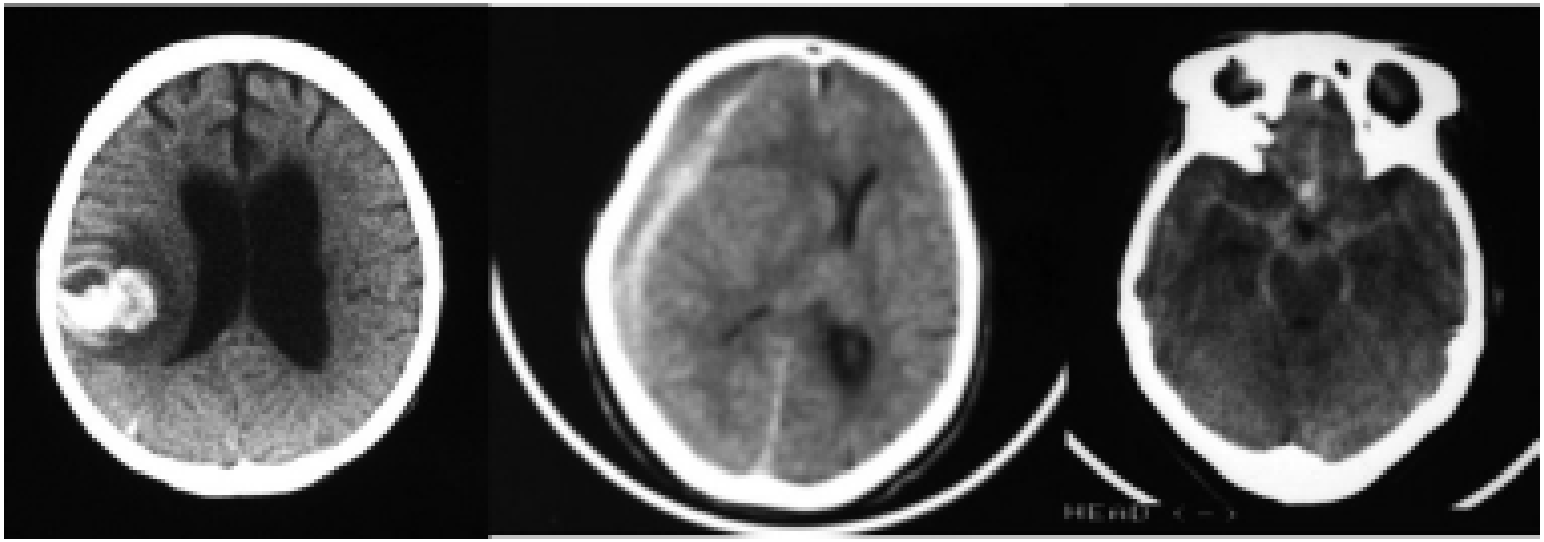
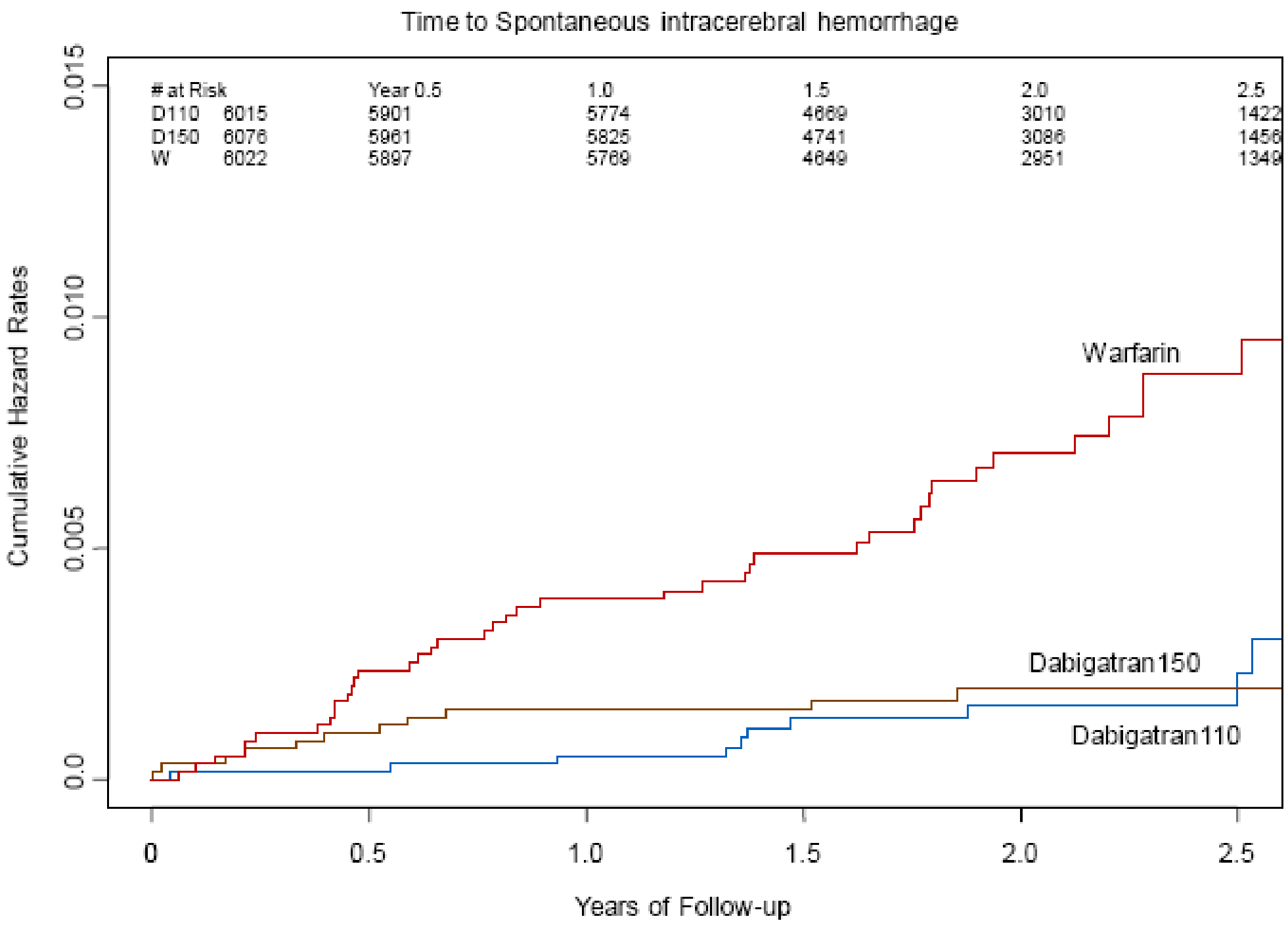
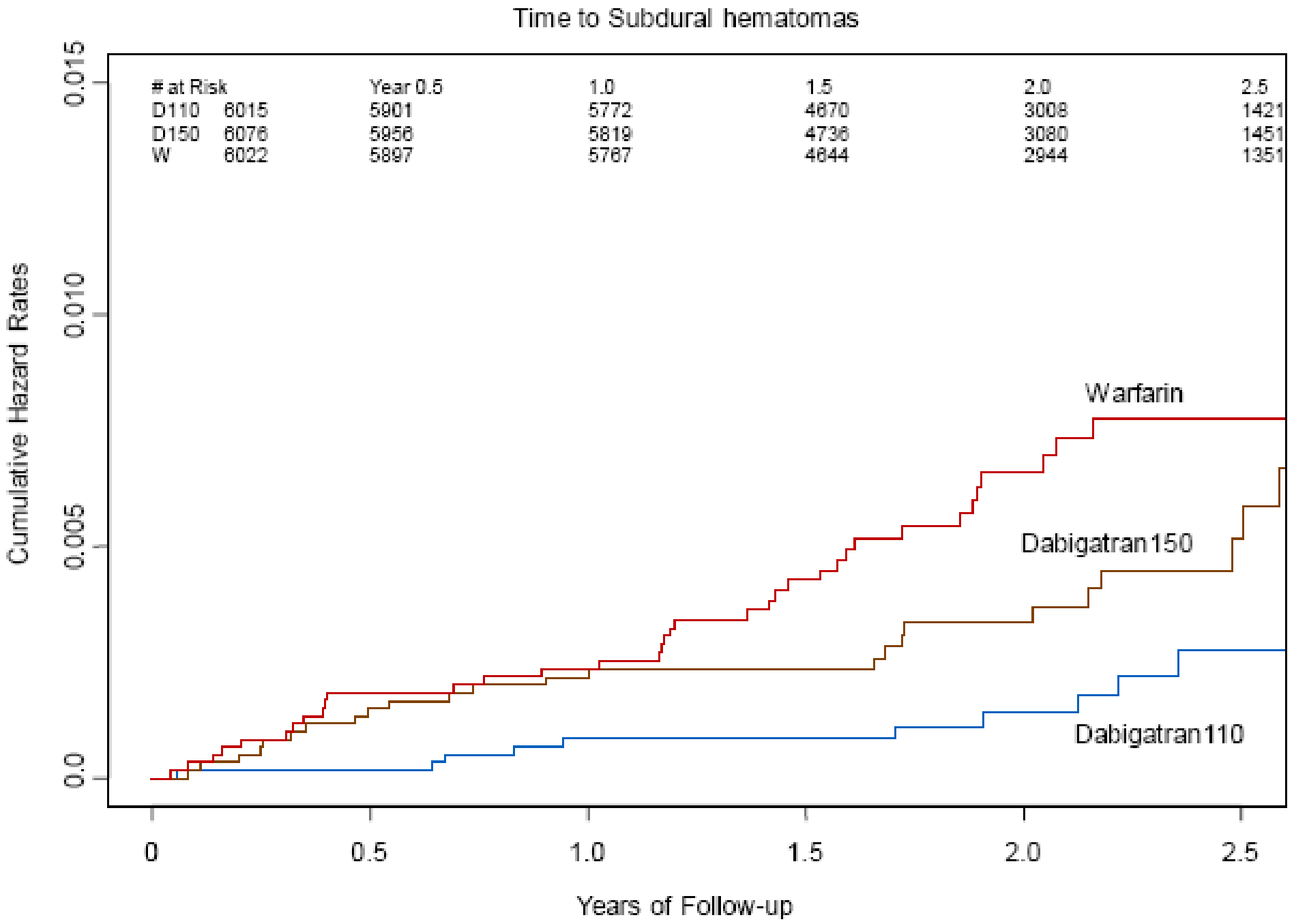


Figure. Sites of intracranial bleeding.

Table 1. Intracranial Hemorrhages In the RE-LY Trial: Sites of Bleeding and Associated Mortality*

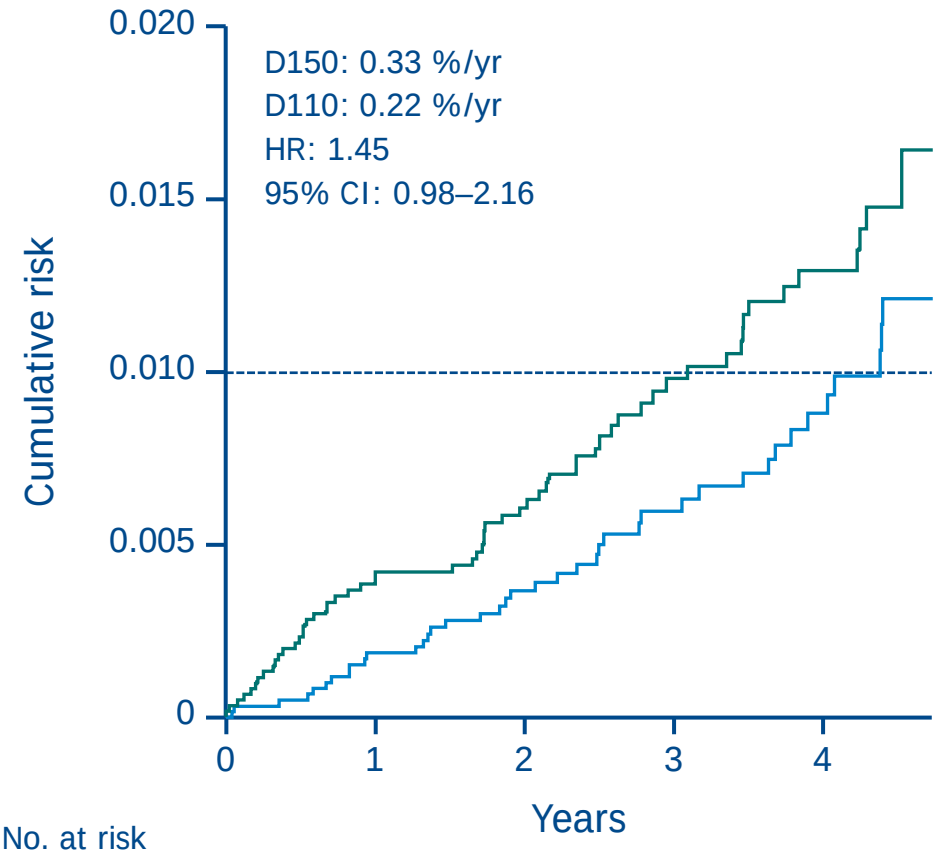
	All (Mortality)	Spontaneous (Mortality)	Traumatic (Mortality)
All sites	154 (36%)	108 (42%)	46 (24%)
Intracerebral	71 (49%)	63 (52%)	8 (25%)
Subdural	70 (24%)	39 (21%)	31 (29%)
Subarachnoid	13 (31%)	6 (67%)	7 (0%)


Time to Spontaneous intracerebral hemorrhage
at Risk
D110 6015 5901 5774 4669 3010 1422
D150 6076 5961 5825 4741 3086 1456
W 6022 5897 5769 4649 2951 1349
Year 0.5 1.0 1.5 2.0 2.5
Cumulative Hazard Rates
0.0
0.005
0.010
0.015
Warfarin
Dabigatran150
Dabigatran110
0
0.5
1.0
1.5
2.0
2.5
Years of Follow-up

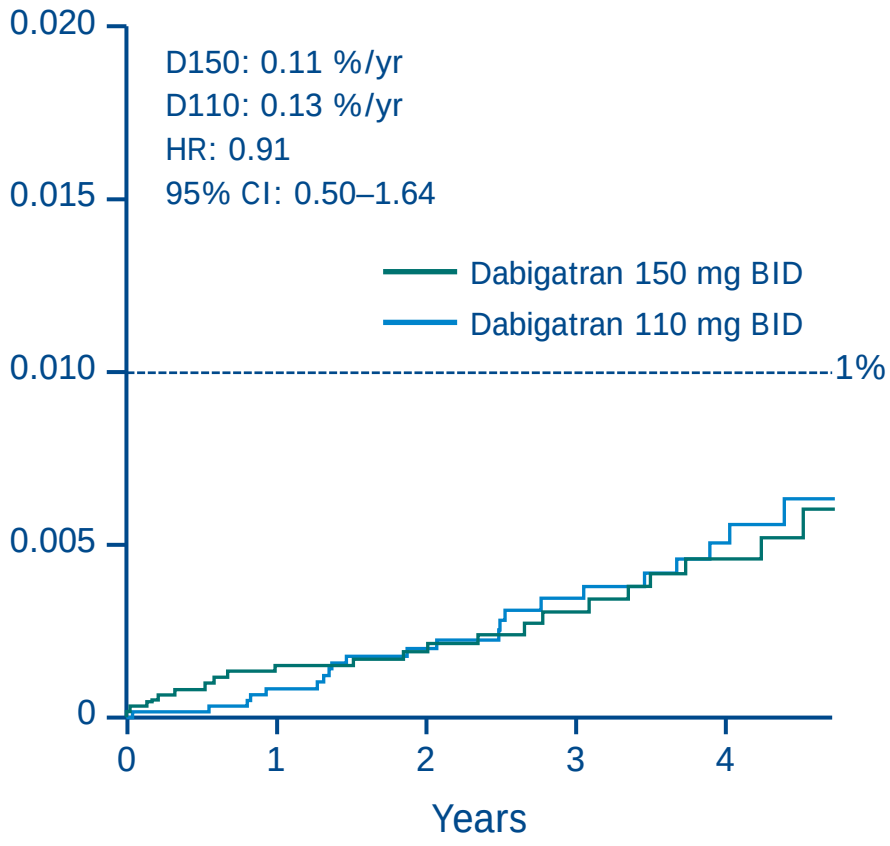

Time to Subdural hematomas
at Risk
D110 6015
D150 6076
W 6022
Year 0.5
5901
5956
5897
1.0
5772
5819
5767
1.5
4670
4736
4644
2.0
3008
3080
2944
2.5
1421
1451
1351
Cumulative Hazard Rates
0.0
0.005
0.010
0.015
Warfarin
Dabigatran150
Dabigatran110
0
0.5
1.0
1.5
2.0
2.5
Years of Follow-up

RE-LY® + RELY-ABLE®: all dabigatran patients

All intra-cranial haemorrhage



Intra-cerebral haemorrhage



No. at risk

D110	6015	5771	4277	2794	1974
D150	6076	5814	4350	2785	1975

6015	5774	4282	2799	1979	
6076	5825	4360	2790	1980	

12 091 patients, mean FU 3 yr; BID = twice daily; D150 and D110 = dabigatran 150 and 110 mg BID, respectively; FU = follow -up; HR = hazard ratio

Scene di vita quotidiana

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

- Trial randomizzato di non inferiorità in doppio cieco
- 14.264 pz con FA non valvolare
- Rivaroxaban (20mg o 15mg od) versus warfarin

Characteristic	Rivaroxaban (N = 7131)	Warfarin (N = 7133)
Age	73 (65 - 78)	73 (65 - 78)
$CHADS_2$ score	3.48±0.94	3.46±0.95
Previous stroke , systemic embolism or TIA (%)	54.9	54.6
Diabetes mellitus (%)	40.4	39.5
Hypertension (%)	90.3	90.8

NEJM 2011;365:883-891

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 15, 2011 VOL. 365 NO. 11

Apixaban versus Warfarin in Patients with Atrial Fibrillation

- Trial randomizzato di non inferiorità in doppio cieco
- 18,202 pz FA non valvolare
- Apixaban (5mg bd) versus warfarin

Characteristic	Apixaban (N = 9120)	Warfarin (N = 9081)
Age yrs (median)	70 (63 - 76)	70 (63 - 76)
$CHADS_2$ score	2.1±1.1	2.1±1.1
Previous stroke, systemic embolism or TIA (%)	19.2	19.7
Diabetes mellitus (%)	25	24.9
Hypertension requiring treatment (%)	87.3	87.6

In Sintesi....

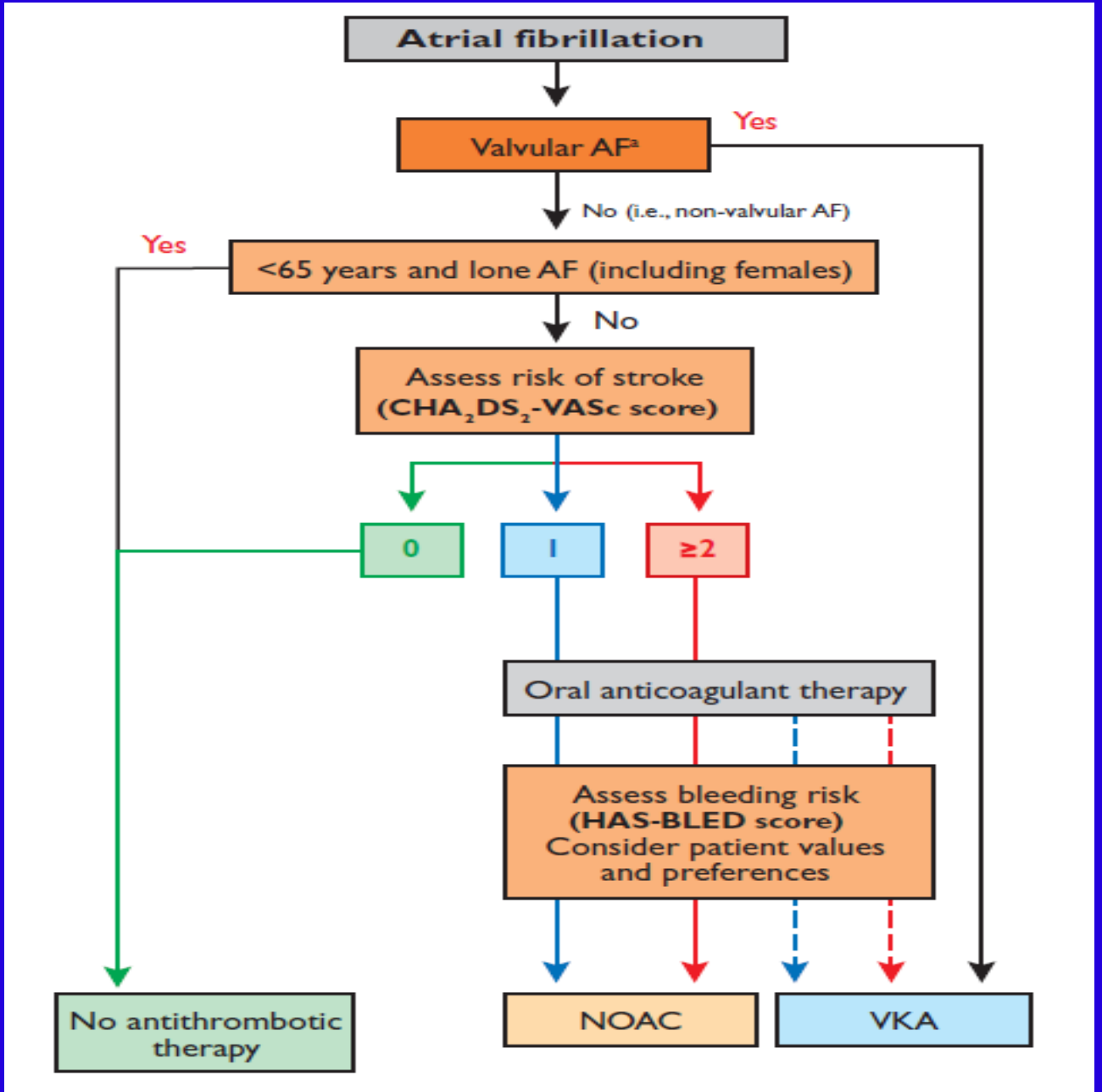
Feature	Dabigatran	Apixaban	Rivaroxaban
Target	Thrombin	Factor Xa	Factor Xa
Prodrug	Yes	No	No
Bioavailaibility	6%	60%	80%
Dosing	b.i.d.	b.i.d.	o.d.
Half life	12-14 hours	12 hours	7-11 hours
Renal	80%	25%	33% (66%)
Monitoring	No	No	No
Interactions	P-gp	3A4/P-gp	3A4/P-gp

Nuovi Anticoagulanti Orali a Confronto

	Dabigatran 110 mg	Dabigatran 150 mg	Rivaroxaban	Apixaban
Non-inferiorità vs W	✓	✓	✓	✓
Superiorità vs W		✓		✓
Riduzione stroke emorragico	✓	✓	✓	✓
Riduzione stroke ischemico		✓		
Riduzione emorragie maggiori	✓			✓
Aumento emorragie GI		✓		
Riduzione mortalità		(✓)		✓
Maggiore interruzione vs W	✓	✓		
Validazione in altro RCT				✓
Aumento infarto miocardico	(✓)	(✓)		

Di Pasquale G, G Ital Cardiol 2012

FLOWCHART OF AF TREATMENT
ESC Guidelines 2012



Drug interactions and dosing recommendation	Effect on dabigatran exposure due to drug interaction
No adjustment required	
Atorvastatin	↓ 18%
Diclofenac	No effect
Pantoprazole	↓ 30%[a]
Clopidogrel	↑ 30–40%[a]
Digoxin	No effect
Use lower dose (110 mg bid)	
Verapamil	↑ 20–150% [a,b]
Use with caution and assess bleeding risk	
Quinidine	↑ 50% [a]
Amiodarone	↑ 60% [a]
Clarithromycin	↑ 19% [a]
Not recommended	
Dronedarone	↑ 100%[a] (58)
Rifampicin	↓ 67%[a]
Carbamazepine, phenytoin	↓ (% not reported)
Protease inhibitors (e.g. ritonavir, tipranavir, nelfinavir and saquinavir)	Exposure not reported[c]
Contraindicated	
Systemic ketoconazole	↑ 150%[a]
Itraconazole, tacrolimus and cyclosporin	↑ (% not reported but likely to be similar to ketoconazole based on *in vitro* data)

European Heart Journal
doi:10.1093/eurheartj/ehs253

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

Dabigatran etexilate for stroke prevention in patients with atrial fibrillation: Resolving uncertainties in routine practice

Menno V. Huisman[1]; Gregory Y. H. Lip[2]; Hans-Christoph Diener[3]; Martina Brueckmann[4]; Joanne van Ryn[5]; Andreas Clemens[4]

[1]Departments of Thrombosis and Haemostasis, Leiden University Medical Center, Leiden, The Netherlands; [2]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; [3]Department of Neurology, University Hospital Essen, Essen, Germany; [4]Global Clinical Development and Medical Affairs, Boehringer Ingelheim GmbH & Co. KG, Ingelheim, Germany, [5]Department of CardioMetabolic Disease Research, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany

Summary

Dabigatran etexilate is a new oral anticoagulant recently approved in Europe for the prevention of stroke or systemic embolism in adult patients with non-valvular atrial fibrillation (AF) and at least one risk factor for stroke. With a fast onset of action and a predictable anticoagulant effect obviating the need for coagulation monitoring, dabigatran etexilate offers practical advantages over vitamin K antagonists in clinical practice. However, clinicians may have questions about practical aspects of dabigatran etexilate use including monitoring anticoagulant efficacy, interruption for surgical or invasive procedures and management of bleeding. This review article aims to address these concerns and provide guidance on the use of dabigatran etexilate in special situations, such as acute coronary syndromes and cardiac revascularisation. In addition, cut-off values for different coagulation assay results associated with an increased risk of bleeding are given.

Keywords

Dabigatran, atrial fibrillation, oral anticoagulant, bleeding

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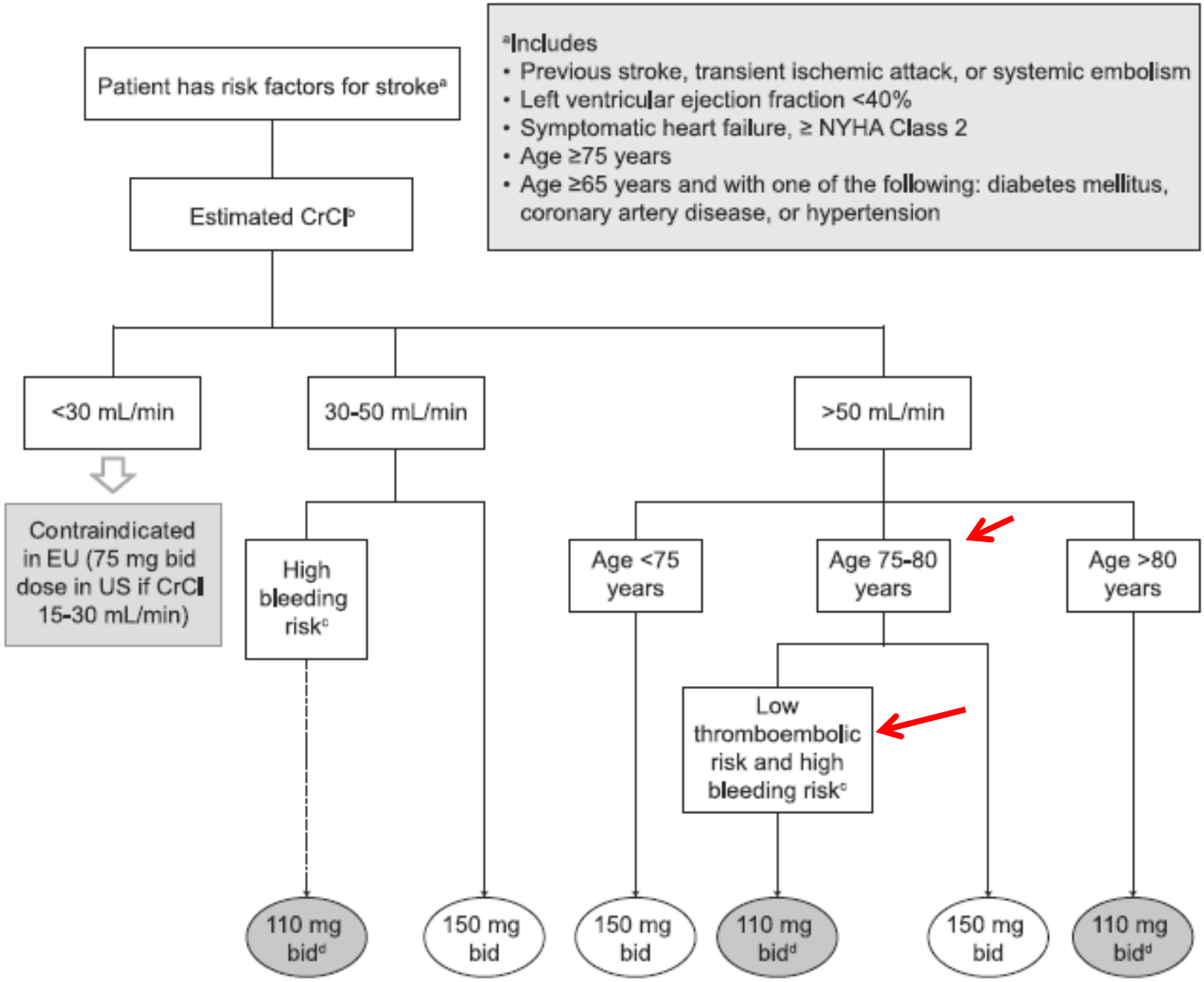
Received: October 18, 2011
Accepted after minor revision: January 29, 2011
Prepublished online: February 8, 2012

doi:10.1160/TH11-10-0718
Thromb Haemost 2012; 107: ■■■


[a]Includes
• Previous stroke, transient ischemic attack, or systemic embolism
• Left ventricular ejection fraction <40%
• Symptomatic heart failure, ≥ NYHA Class 2
• Age ≥75 years
• Age ≥65 years and with one of the following: diabetes mellitus, coronary artery disease, or hypertension
Patient has risk factors for stroke[a]
Estimated CrCl[b]
<30 mL/min
30-50 mL/min
>50 mL/min
Contraindicated in EU (75 mg bid dose in US if CrCl 15-30 mL/min)
High bleeding risk[c]
Age <75 years
Age 75-80 years
Age >80 years
Low thromboembolic risk and high bleeding risk[c]
110 mg bid[c]
150 mg bid
150 mg bid
110 mg bid[d]
150 mg bid
110 mg bid[d]
Recommended dose
Dose can be considered

Europace (2010) 12, 1360–1420
doi:10.1093/europace/euq350

Guidelines for the management of atrial fibrillation

The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)

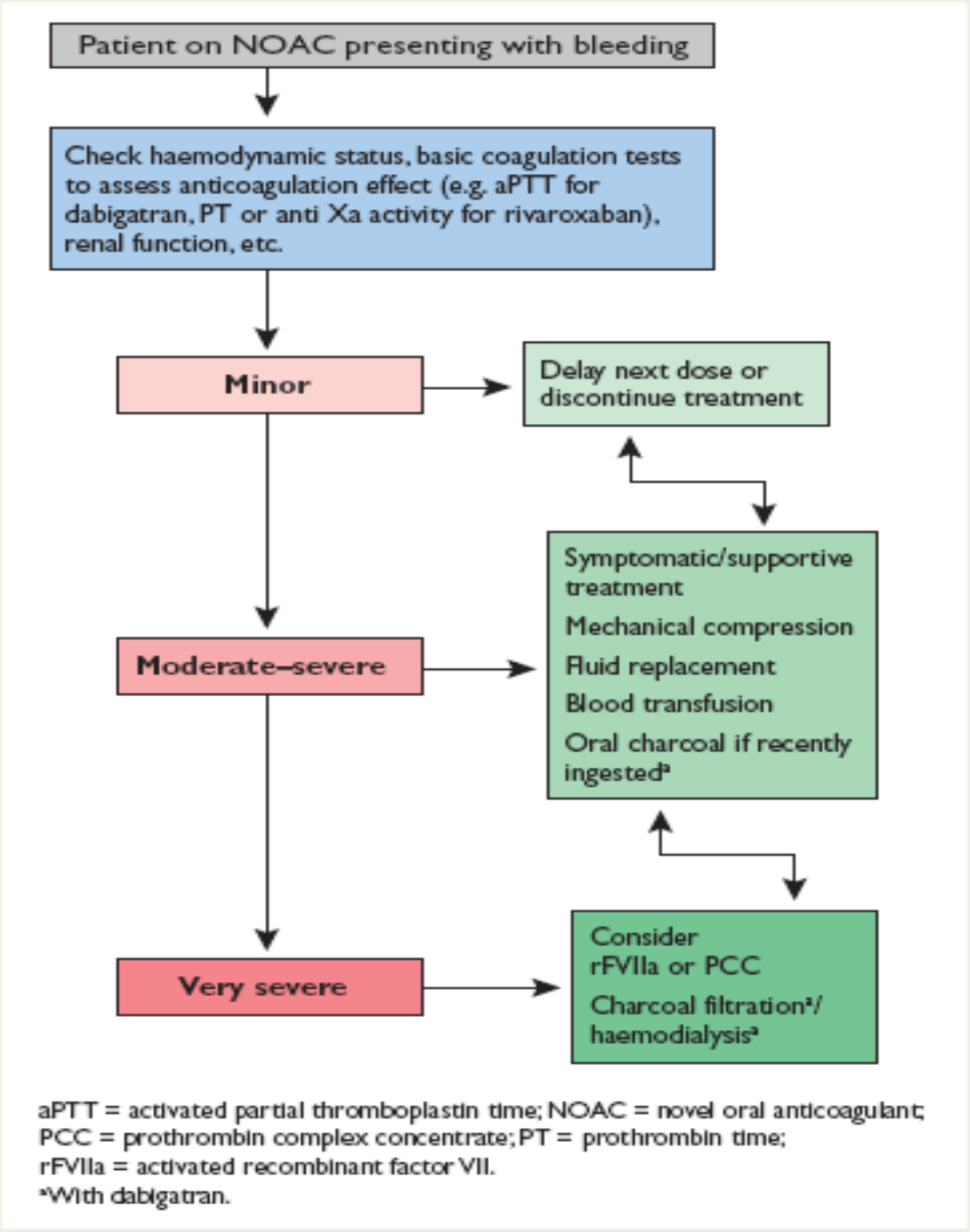
Table 10 Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

HAS-BLED score

- **0-2→ DABIG 150 mg x 2**
- **>3 →DABIG 110 mg x 2**

Cosa fare in caso di emorragia?



aPTT = activated partial thromboplastin time; NOAC = novel oral anticoagulant; PCC = prothrombin complex concentrate; PT = prothrombin time; rFVIIa = activated recombinant factor VII.
[a]With dabigatran.

Figure 2 Management of bleeding in patients taking novel oral anticoagulants.

grazie

Table 1: Limitations of vitamin K antagonists (VKA) in comparison with dabigatran.

	VKAs	Dabigatran
Onset of action	Slow (36 to 72 hours)	Rapid (2 hours)
Offset of action	Long (24 to 192 hours depending on type used)	Short, half-life dependent (12–14 hours)
Dosing	Individualised	Fixed dose
Dose adjustment	Frequent	Rare
Monitoring	Required; patient adherence and convenience can be problematic	Only in special situations
Food and alcohol	Interaction	No interaction
Drug interactions	Frequent	Few

Table 2: Factors identified in clinical trials which may increase the bleeding risk[a].

Demographic	Age ≥75 years
Factors increasing dabigatran plasma levels	Major: Moderate renal impairment (CrCL 30–50 ml/min) P-gp inhibitor co-medication Minor: Low body weight (<50 kg)
Pharmacodynamic interactions	ASA NSAID Clopidogrel
Diseases/procedures with special haemorrhagic risks	Congenital or acquired coagulation disorders Thrombocytopenia or functional platelet defects Active ulcerative GI disease Recent GI bleeding Recent biopsy or major trauma Recent ICH Brain, spinal, or ophthalmic surgery Bacterial endocarditis

[a]For special patient populations requiring a reduced 110 mg bid dose, see Figure 1. ASA, acetylsalicylic acid; CrCL, Creatinine clearance; P-gp, P-glycoprotein; GI, gastrointestinal; ICH, intracranial haemorrhage; NSAID, non-steroidal anti-inflammatory drug.

Table 3: Suggested approaches for switching to and from dabigatran (based on EU label) (5).

Conversion	Start times recommenced
From VKAs to dabigatran	Discontinue VKA and start dabigatran when INR <2
From dabigatran to VKAs[a]	Start times for VKAs are based on renal function: – If CrCL ≥50 ml/min, start VKA 3 days before stopping dabigatran – If CrCL ≥30 to <50 ml/min, start VKA 2 days before stopping dabigatran – If CrCL 15–30 ml/min, start VKA 1 day before stopping dabigatran[b]
From dabigatran to parenteral	Start parenteral anticoagulant 12 h after last dose of dabigatran
From parenteral to dabigatran	Start dabigatran at the same time or up to 2 hours before the next parenteral drug dose. For continuous infusions of parenteral drugs, start dabigatran at the time of discontinuation of the continuous infusion.

[a]Because dabigatran may contribute to an elevated INR, the INR will better reflect the effect of the VKA after dabigatran has been stopped for at least 2 days; [b]Applies to patients treated in the US and for patients in whom the CrCL drops below 30 mL/min. CrCL, Creatinine clearance; h, hours; INR, International normalised ratio; VKA, vitamin K antagonists.

Table 4: Anticoagulation measurement for dabigatran in patients administered 150 mg twice-daily for AF[a].

Test	Increased risk of bleeding	Expected value at peak concentration (2 h post dose)
aPTT	>80 s at trough (2–3 x baseline value)	> 2–3 x baseline value
Hemoclot (diluted TT)	>65 s at trough	-
INR	Not applicable[b]	-
ECT	3–4 x baseline value	3 x baseline value

[a]Evidence based on post-hoc review of pharmacokinetic samples collected from patients enrolled in RE-NOVATE II (57) (aPTT and Hemoclot) and RE-LY (aPTT and ECT) (7) trials. After administration of dabigatran 150 bid, the 90th percentile of trough plasma concentration to double the risk of bleeding was ~215 ng/mL. Baseline aPTT range in RE-LY was 22–40 s. Baseline ECT range in healthy volunteer studies was 28–34 s (Boehringer Ingelheim, Data on file); [b]INR is insensitive and unreliable for dabigatran. aPTT, activated partial thromboplastin time; ECT, ecarin clotting time; h, hours; INR, international normalised ratio; s, seconds.

Renal function (CrCL in ml/min)	Estimated half-life (hours)	Timing of discontinuation after last dose of dabigatran before elective surgery	
		Standard bleeding risk	High bleeding risk[a]
≥80	~13	24 h before	2 days before
≥50 to <80	~15	1–2 days before	2–3 days before
≥30 to <50	~18	2–3 days before (>48 h)	4 days before

[a]Types of surgery associated with a high risk of bleeding (or major surgery where complete haemostasis may be required) including but not limited to cardiac surgery, neurosurgery, abdominal surgery, or surgeries involving a major organ. Other procedures such as spinal anaesthesia may also require complete haemostatic function. h, hour.

Table 6: Guidance for use of dabigatran with other drugs (as per E label) (5).

Drug interactions and dosing recommendation	Effect on dabigatran exposure due to drug interaction
No adjustment required	
Atorvastatin	↓ 18%
Diclofenac	No effect
Pantoprazole	↓ 30%[a]
Clopidogrel	↑ 30–40%[a]
Digoxin	No effect
Use lower dose (110 mg bid)	
Verapamil	↑ 20–150%[a,b]
Use with caution and assess bleeding risk	
Quinidine	↑ 50%[a]
Amiodarone	↑ 60%[a]
Clarithromycin	↑ 19%[a]
Not recommended	
Dronedarone	↑ 100%[a] (58)
Rifampicin	↓ 67%[a]
Carbamazepine, phenytoin	↓ (% not reported)
Protease inhibitors (e.g. ritonavir, tipranavir, nelfinavir and saquinavir)	Exposure not reported[c]
Contraindicated	
Systemic ketoconazole	↑ 150%[a]
Itraconazole, tacrolimus and cyclosporin	↑ (% not reported but likely to be similar to ketoconazole based on *in vitro* data)

Exposure refers to reported area under the plasma concentration curve. [a]Based on data in healthy volunteers. [b]Depends on timing of administration of and formulation of verapamil. Dabigatran exposure is 150% higher if the first dose of immediate release formulation verapamil is given 1 hour before dabigatran; lower if given as extended release formulation (70% higher) or with multiple doses of verapamil (50% increase); and negligible if given 2 hours after dabigatran (20% increase). Both medications should be taken at the same time. [c]Protease inhibitors including ritonavir and its combinations with other protease inhibitors affect P-gp (either as inhibitor or as inducer). They have not been studied and are therefore not recommended for concomitant treatment with dabigatran.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate : A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, Pieter W. Kamphuisen, Meertien K. Sijpkens, Joost C. Meijers, Harry R. Buller and Marcel Levi

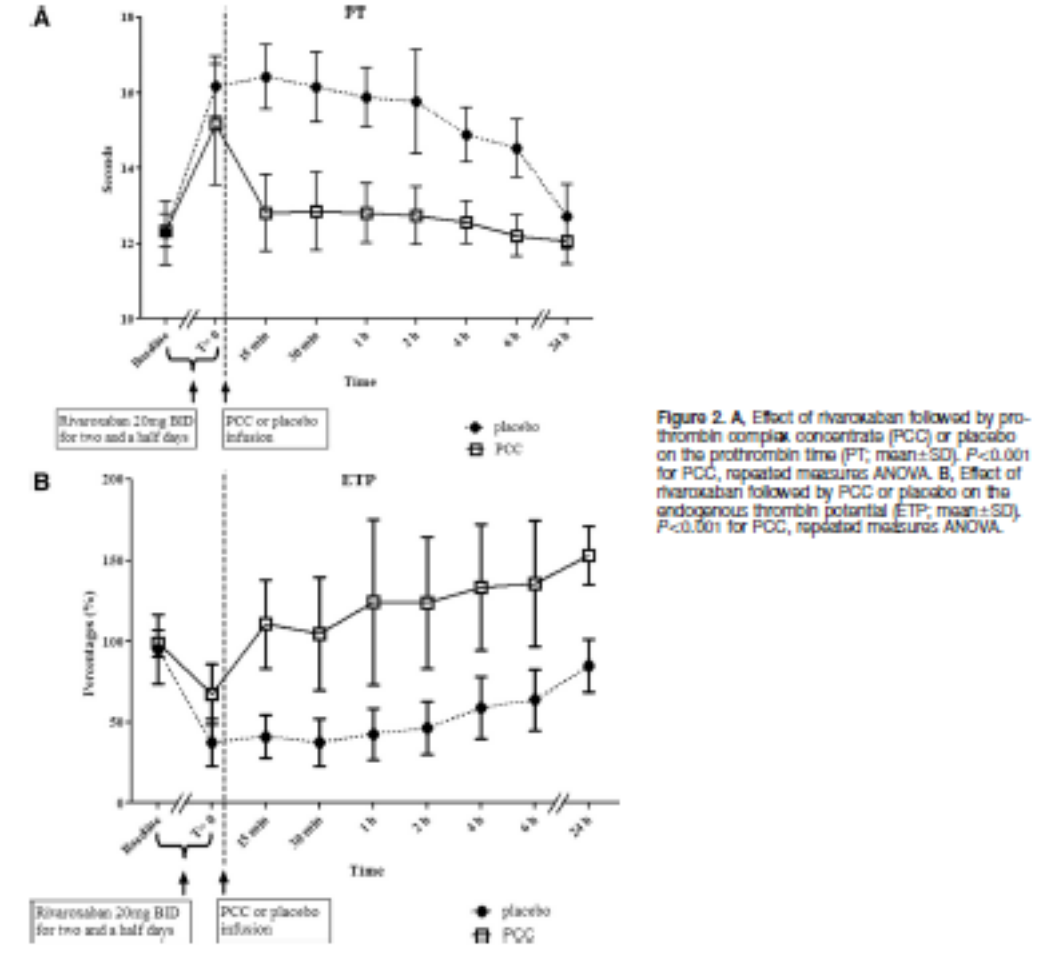


Figure 2. A, Effect of rivaroxaban followed by prothrombin complex concentrate (PCC) or placebo on the prothrombin time (PT; mean±SD). $P<0.001$ for PCC, repeated measures ANOVA. B, Effect of rivaroxaban followed by PCC or placebo on the endogenous thrombin potential (ETP; mean±SD). $P<0.001$ for PCC, repeated measures ANOVA.

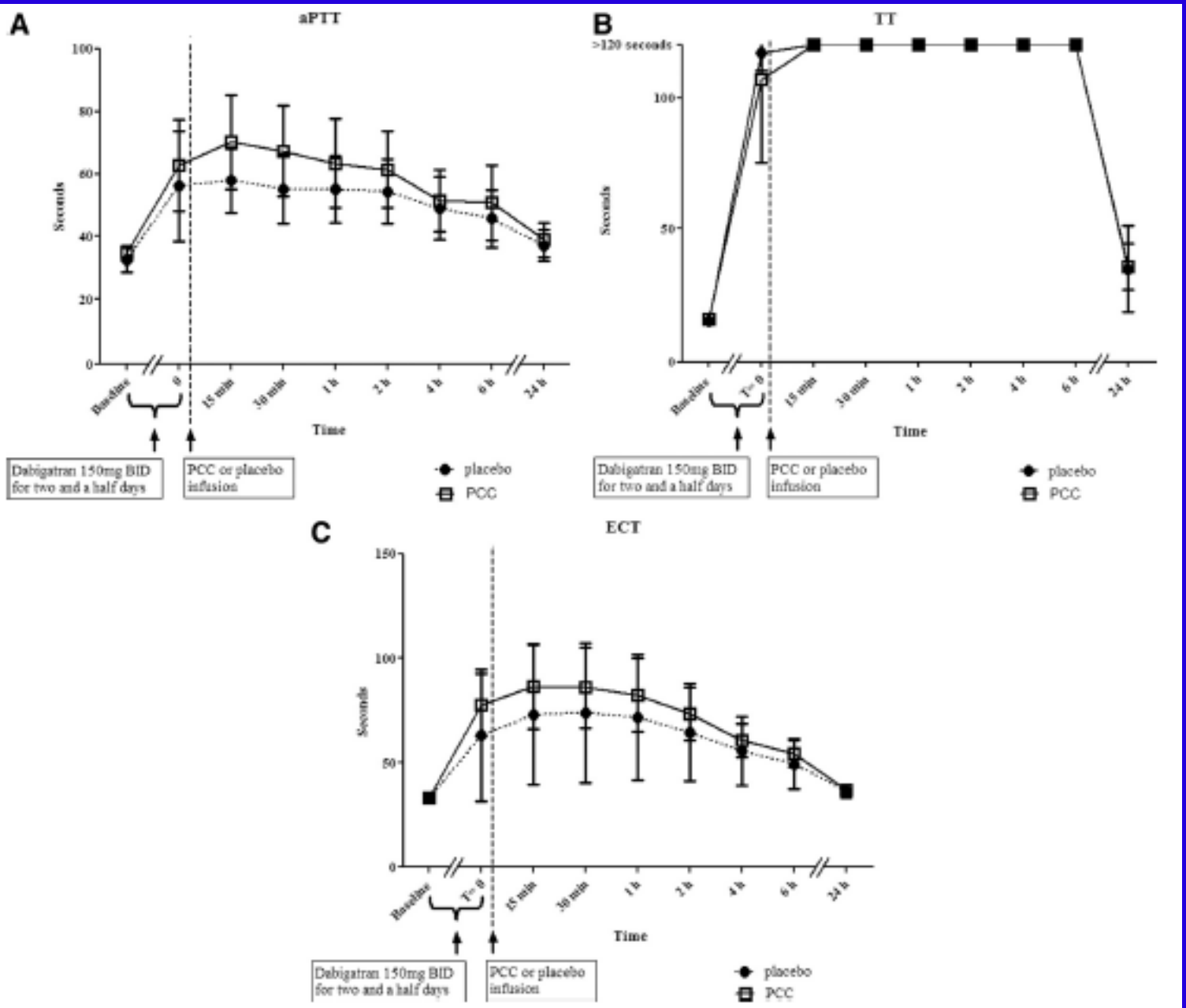


Figure 3. A, Effect of dabigatran followed by prothrombin complex concentrate (PCC) or placebo on the activated partial thromboplastin time (aPTT; mean ±SD). *P*=0.21 for PCC, repeated measures ANOVA. **B**, Effect of dabigatran followed by PCC or placebo on the thrombin time (TT; mean±SD). *P*=0.36 for PCC, repeated measures ANOVA. **C**, Effect of dabigatran followed by PCC or placebo on the ecarin clotting time (ECT; mean±SD). *P*=0.08 for PCC, repeated measures ANOVA.

Cosa fare in caso di emorragia in corso di dabigatran?

- **Plasma fresco congelato?**
  "Reversal of dabigatran-induced bleeding with a prothrombin complex concentrate and fresh frozen plasma" (Am J Health Syst Pharm2012 Oct)

- **PCCa?**
  "The use of FEIBA(®) in the correction of coagulation abnormalities induced by dabigatran" (Int J Lab Hematol2012 Sep)

- **FattoreVIIa?**

- **Emodialisi?**

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

Abstracts From the Emerging Science Series, June 20, 2012

Circulation. published online June 20, 2012;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Reversal of Apixaban Induced Alterations of Hemostasis By Different Coagulation Factor Concentrates: Studies In Vitro With Circulating Human Blood

apixaban

- 50 UI/kg di PCC
- 75 UI/kg di aPCC
- 270 mg/kg di fattore VII ricombinante

?

American Journal of Hematology

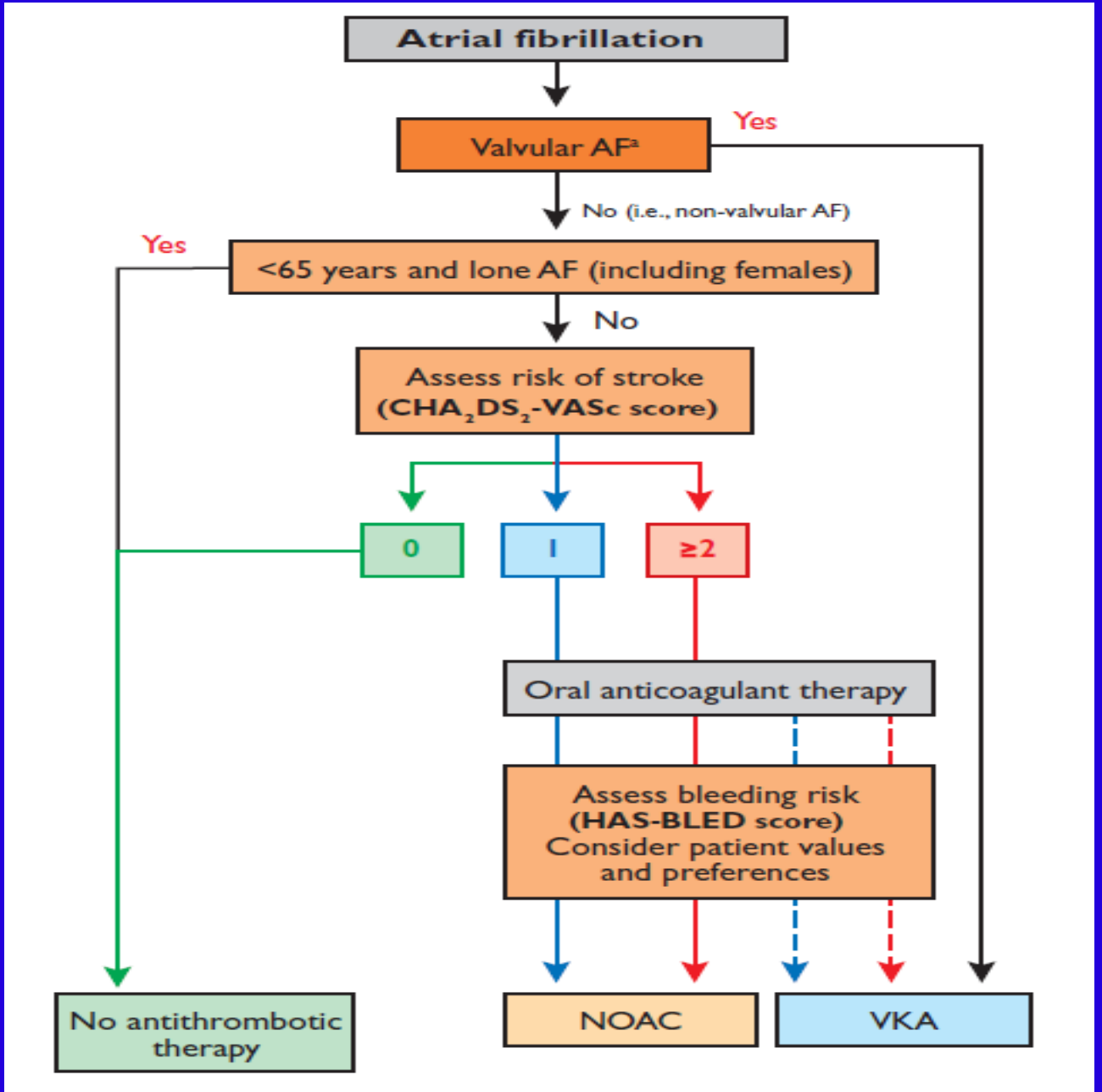
Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors

Scott Kaatz,[1]* Peter A. Kouides,[2] David A. Garcia,[3] Alex C. Spyropolous,[4] Mark Crowther,[5] Jim D. Douketis,[5] Anthony K. C. Chan,[6] Andra James,[7] Stephan Moll,[8] Thomas L. Ortel,[9] Elizabeth M. Van Cott,[10] and Jack Ansell[11]

	Apixaban	Dabigatran	Rivaroxaban
Oral activated charcoal	Yes	Yes	Yes
Hemodialysis	No	Yes	No
Hemoperfusion with activated charcoal	Possible	Yes	Possible
Fresh frozen plasma	No	No	No
Activated factor VIIa	Unclear	Unclear	Unclear
3-factor PCC	Unclear	Unclear	Unclear
4-factor PCC	Possible	Possible	Possible

Am. J. Hematol. 87:S141–S145, 2012

FLOWCHART OF AF TREATMENT
ESC Guidelines 2012



Perchè meno emorragie intracraniche?

FATTORE VIIa

- Attivazione fattore tissutale
- Riparazione del danno vascolare
- Aggregazione piastrinica

Circulation Journal, 2011