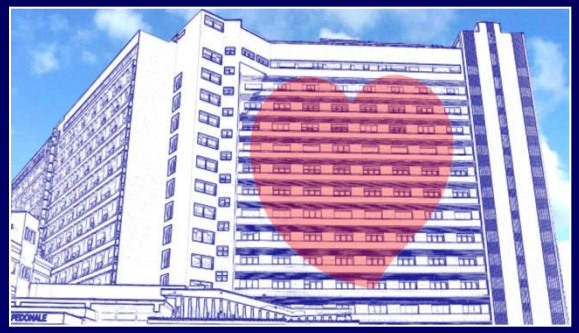
I NUOVI ANTICOAGULANTI NELLA FIBRILLAZIONE ATRIALE

Simposio SIGG – SICGe
"Unmet needs nel cardiopatico anziano: FA e scompenso"
57° Congresso Nazionale SIGG

Milano, 23 Novembre 2012

Giuseppe Di Pasquale
Direttore Dipartimento Medico ASL Bologna
Direttore UO Cardiologia
Ospedale Maggiore, Bologna

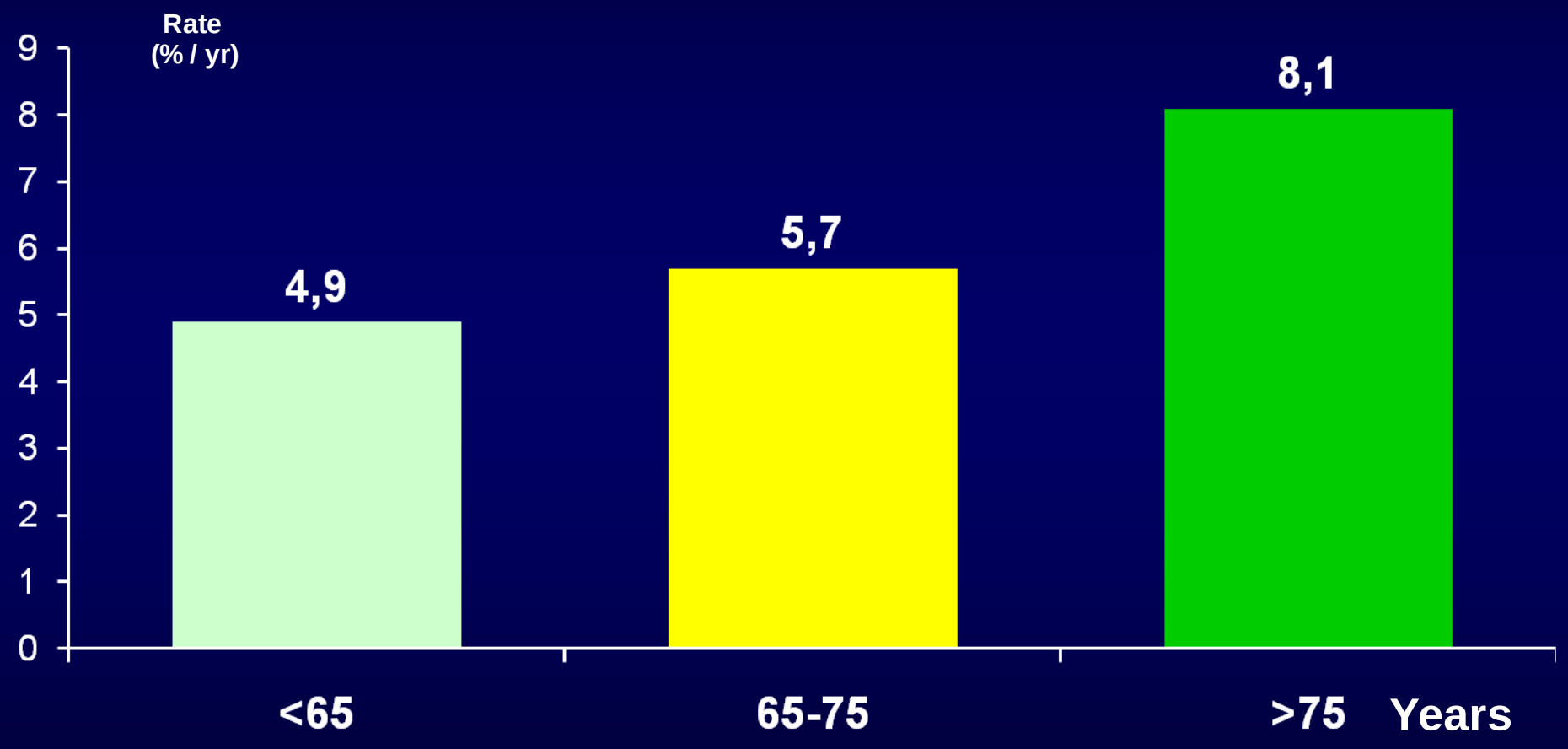


Disclosures

- Member of the Steering Committee of the RELY and PALLAS trials
- Member of Advisory Board of Dabigatran, Rivaroxaban, Apixaban, Dronedarone
- Consulting fees / honoraria
  - Boehringer Ingelheim
  - Bayer AG
  - Sanofi Aventis
  - BMS / Pfizer

Stroke Risk in Atrial Fibrillation

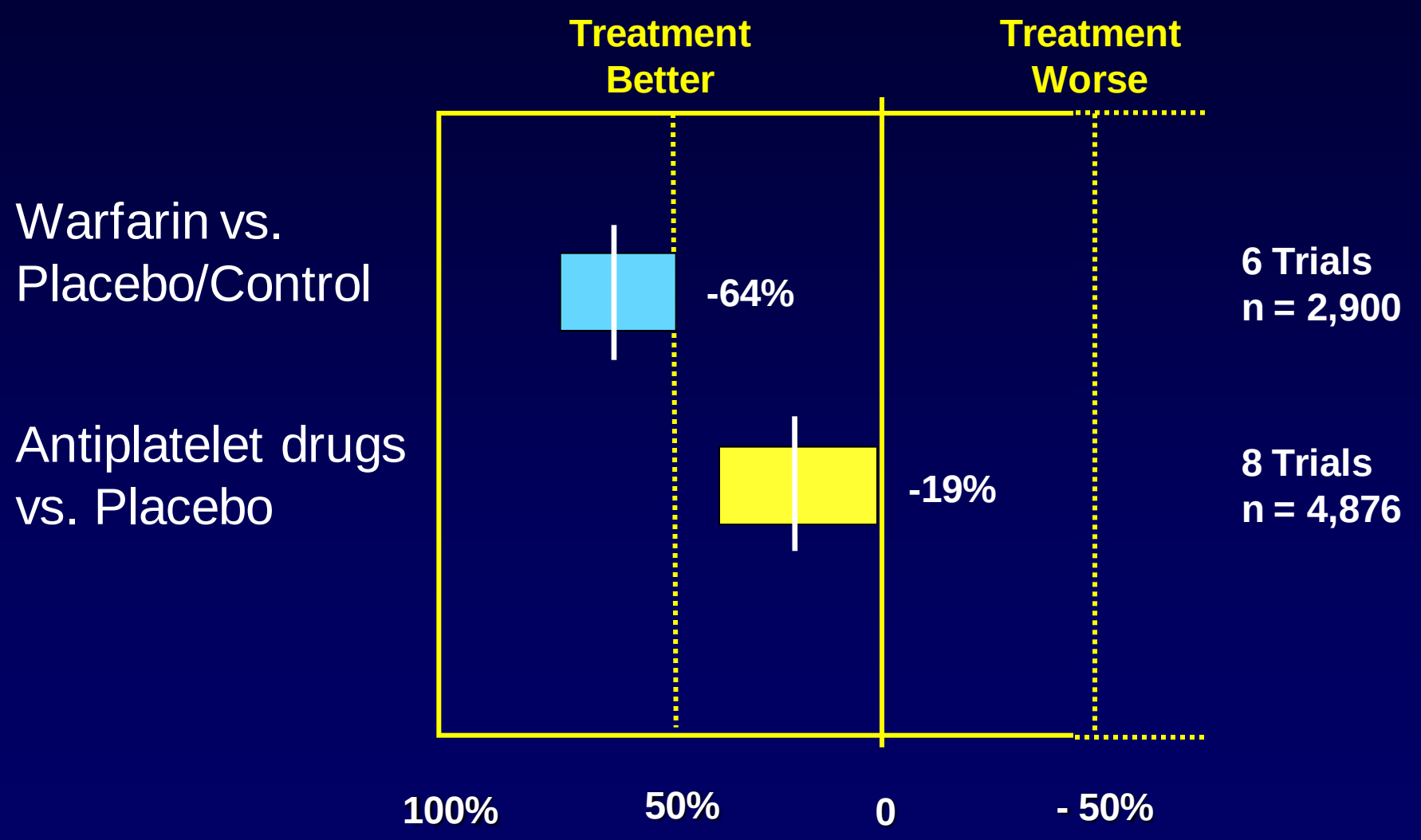
Untreated Control Groups of Randomized Trials



Atrial Fibrillation Investigators, Arch Intern Med 1994;154:1449.

Antithrombotic Therapy for AF

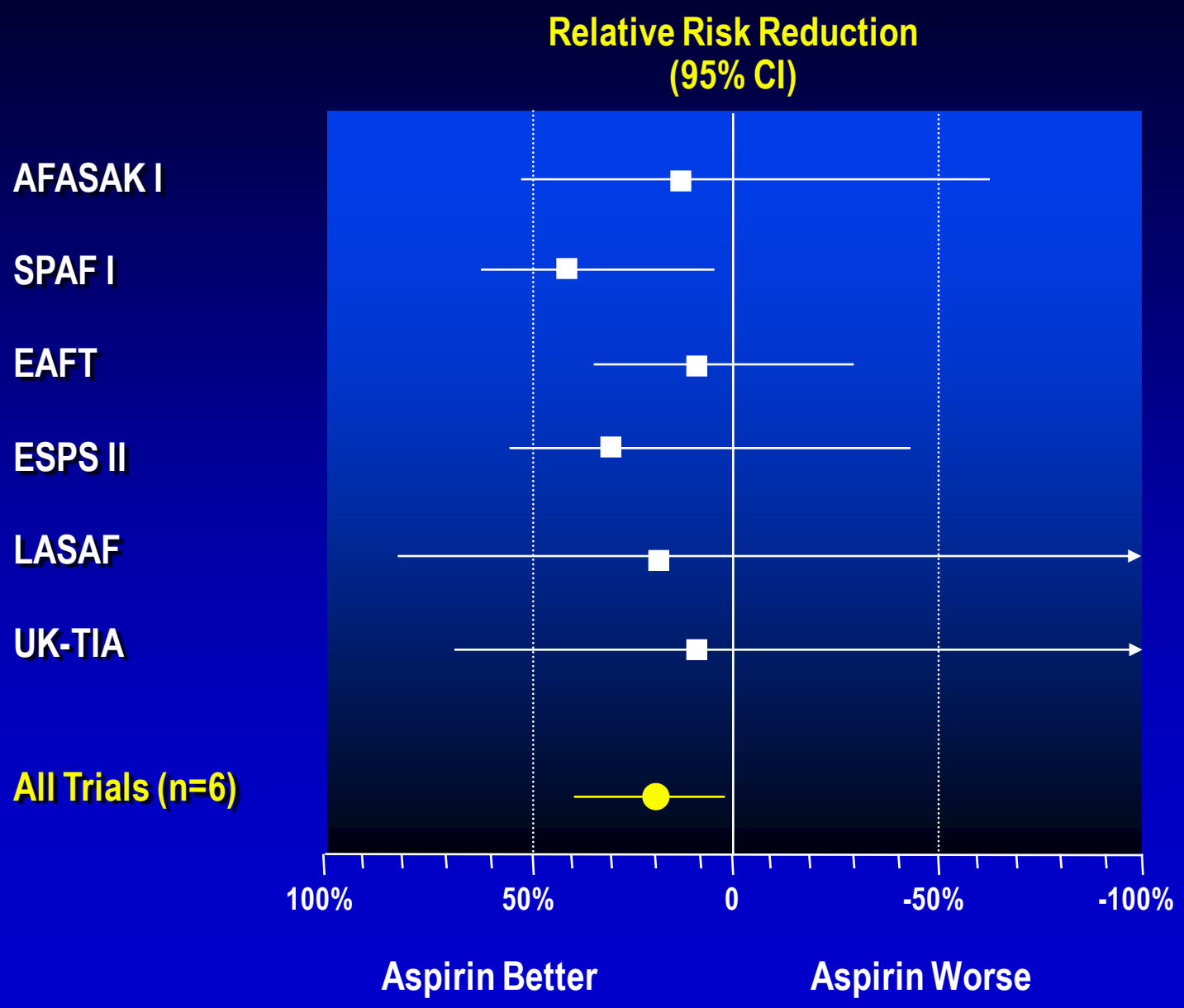
Stroke Risk Reduction



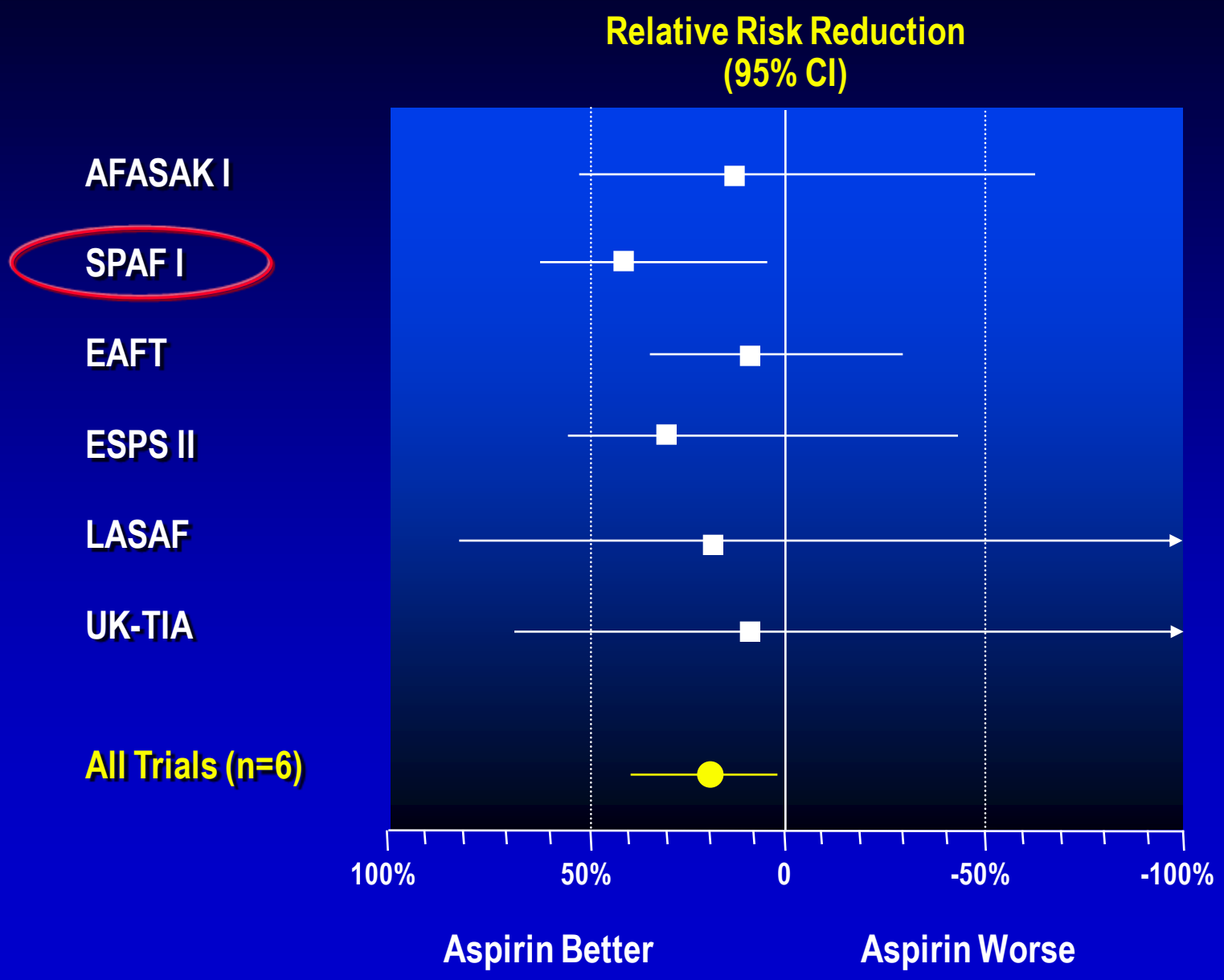
Hart RG et al. Ann Intern Med 2007;146:857

Aspirin as a compromise……..

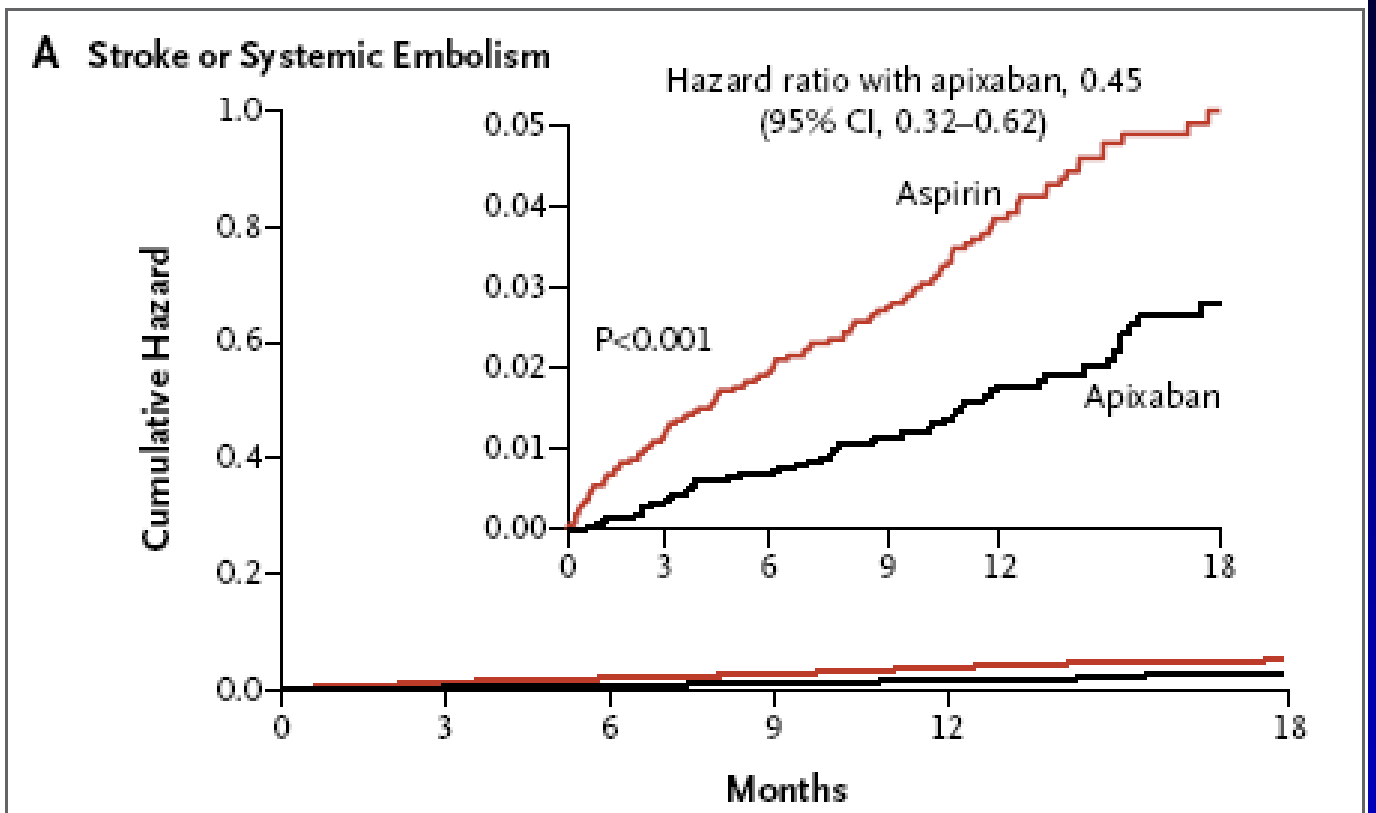
Aspirin for stroke prevention in AF



Aspirin for stroke prevention in AF



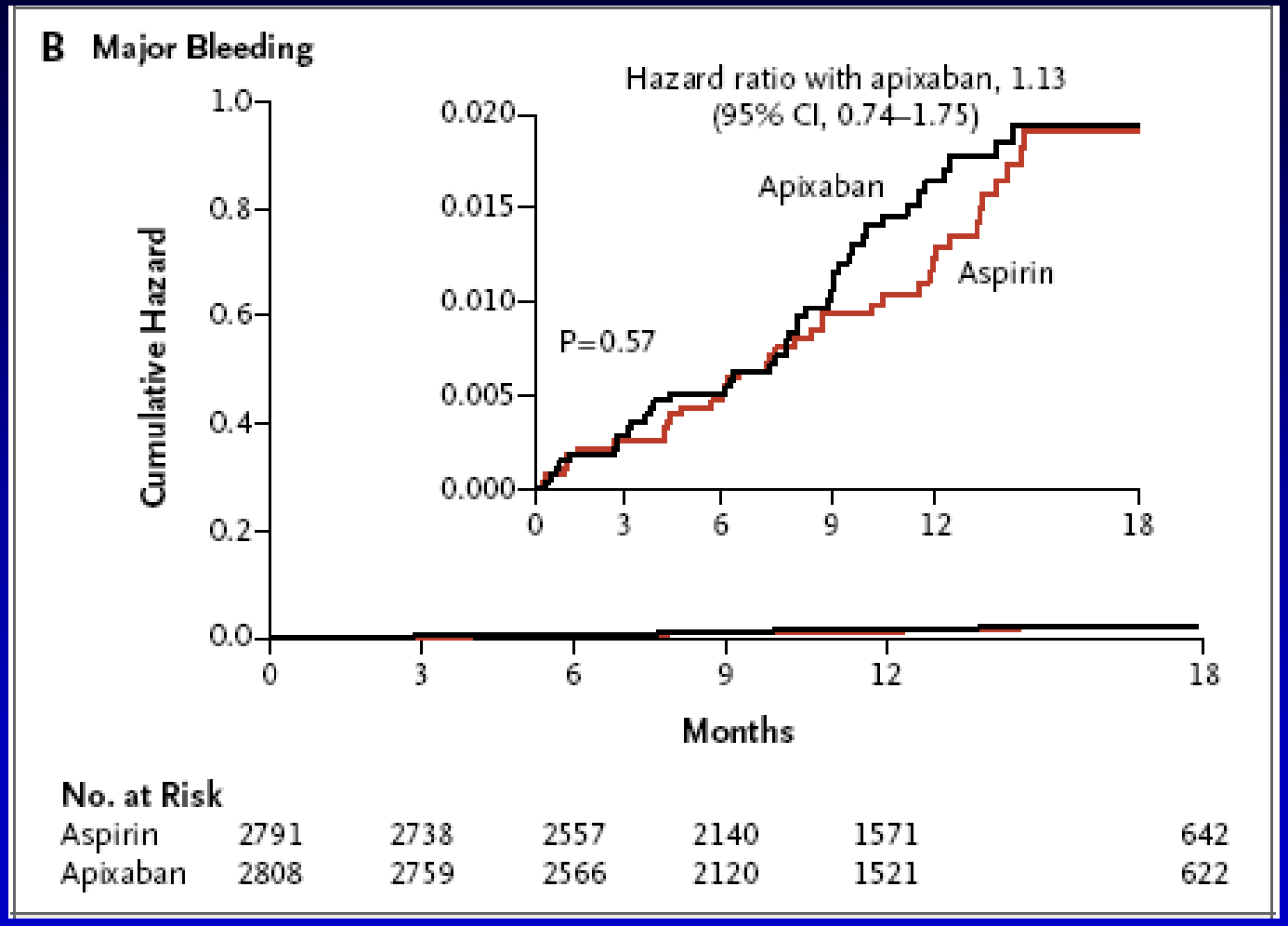
AVERROES - Primary Efficacy Outcome



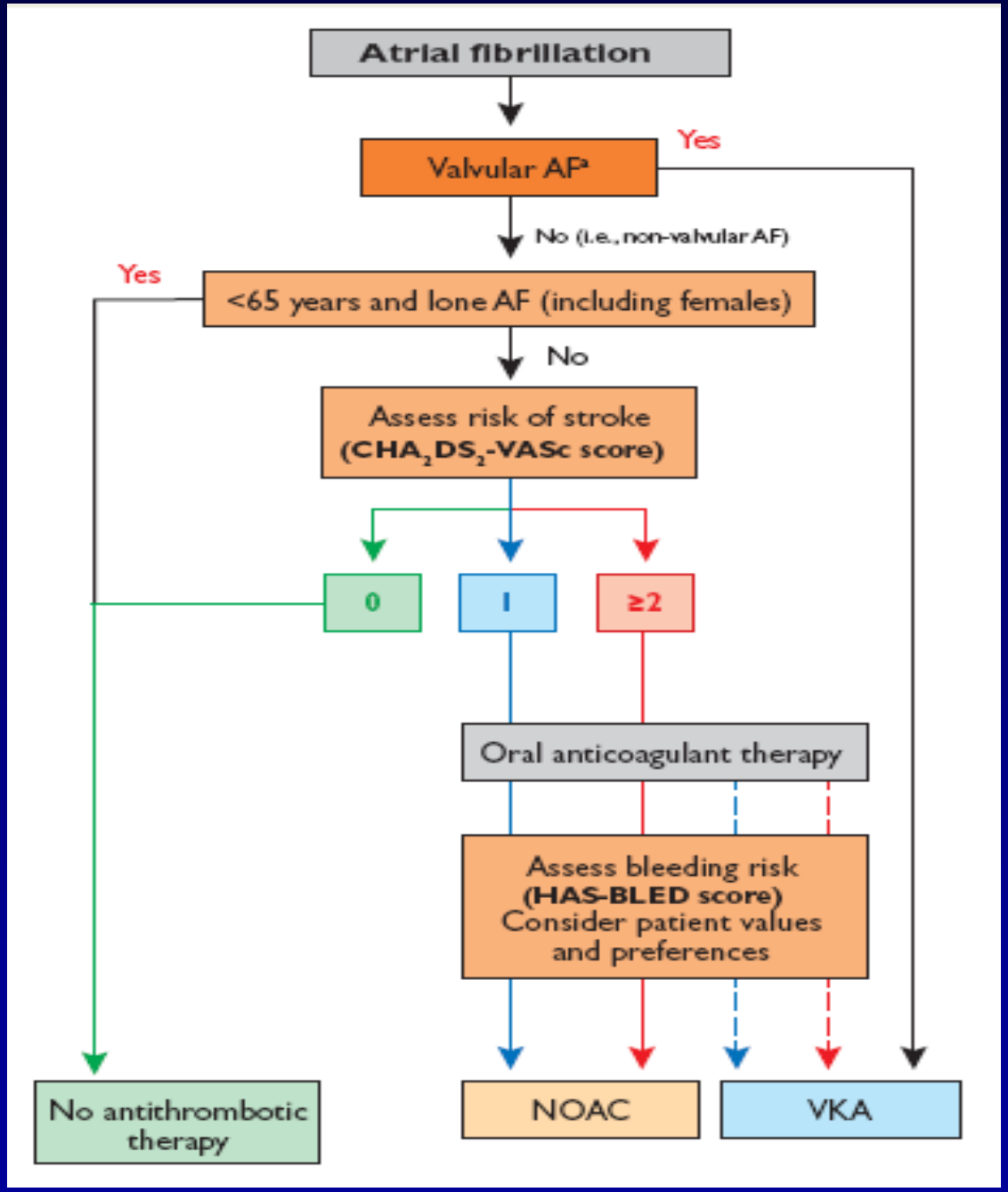
No. at Risk						
Aspirin	2791	2716	2530	2112	1543	628
Apixaban	2808	2758	2566	2125	1522	615

N Engl J Med 2011;364(9): 806-17

AVERROES - Primary Safety Outcome



N Engl J Med 2011;364(9): 806-17



Eur Heart J Aug 2012

Limiti della Terapia Anticoagulante Orale

Conseguenze nella FA

- Un significativo numero di pazienti con FA a rischio di stroke non riceve la TAO

International Journal of Cardiology xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

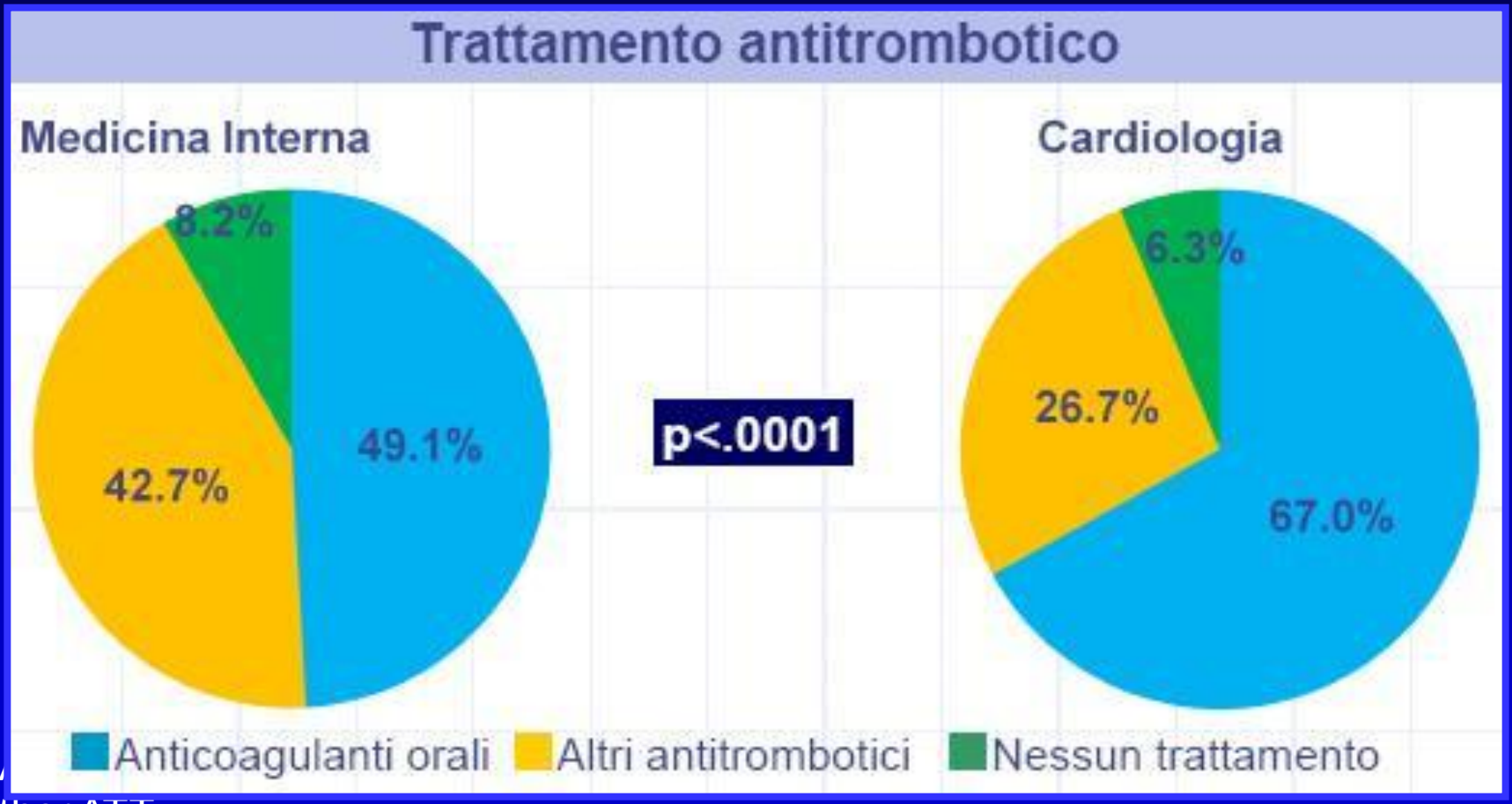
International Journal of Cardiology

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

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

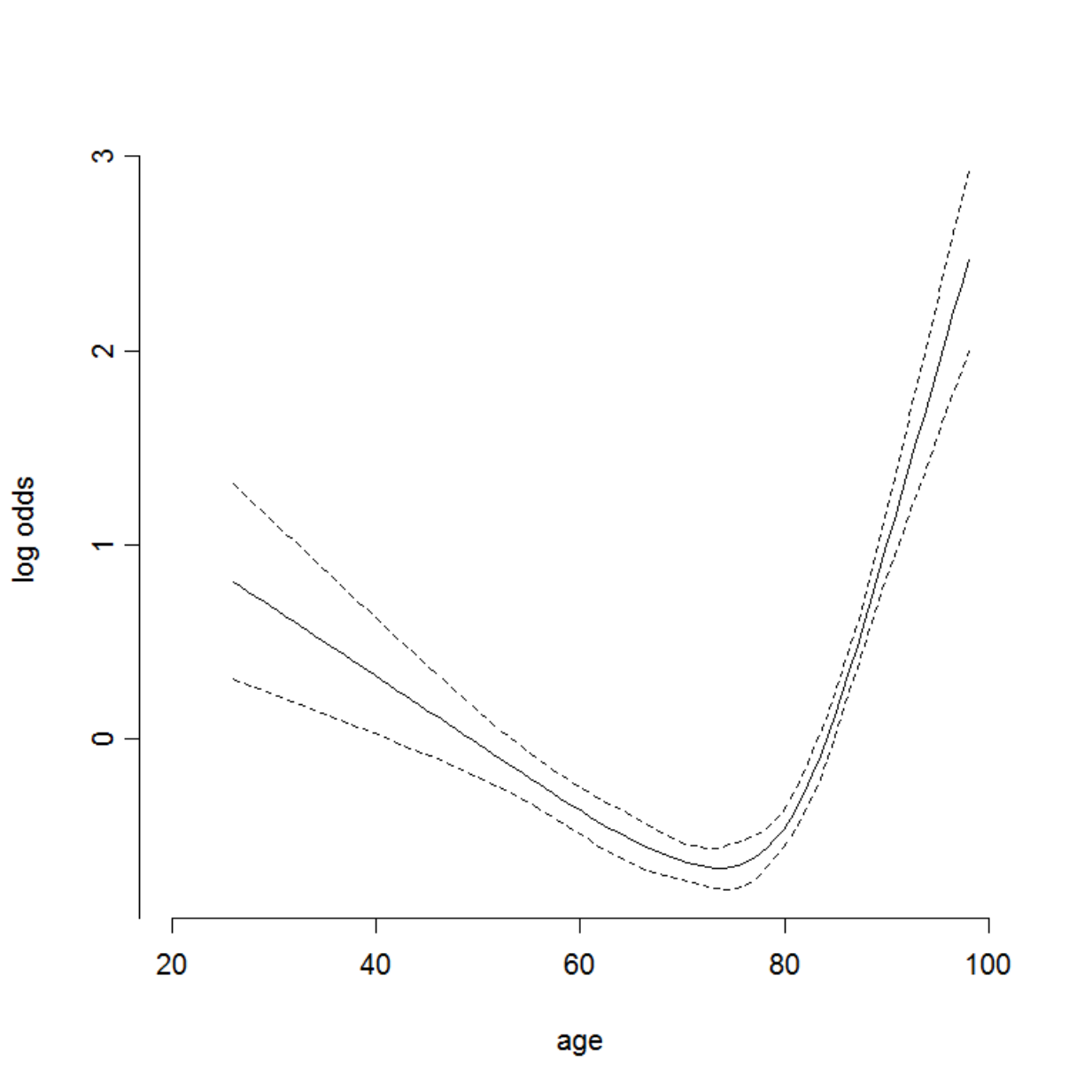
Giuseppe Di Pasquale [a], Giovanni Mathieu [b], Aldo Pietro Maggioni [c,*], Gianna Fabbri [c], Donata Lucci [c], Giorgio Vescovo [d], Salvatore Pirelli [e], Francesco Chiarella [f], Marino Scherillo [g], Michele Massimo Gulizia [h], Gualberto Gussoni [i], Fabrizio Colombo [j], Domenico Panuccio [k], Carlo Nozzoli [l], Massimo Zoni Berisso [m] on behalf of ATA-AF Investigators [1]

Antithrombotic Treatments in non valvular AF (4.845 pts)



O
Other ATT
None

Risk of non prescription of OAC by age



Limiti della Terapia Anticoagulante Orale

Conseguenze nella FA

- Un significativo numero di pazienti con FA a rischio di stroke non riceve la TAO
- L'intensità della scoagulazione è spesso al di fuori del range terapeutico (INR 2.0 – 3.0)

Adherence to treatment and anticoagulation control in vitamin K antagonists-treated patients: an administrative databases analysis in a large Italian population

RICERCA ORIGINALE

Luca Degli Esposti [1], Diego Sangiorgi [1], Giuseppe Di Pasquale [2], Gian Franco Gensini [3,4], Ido Iori [5], Stefano Buda [1], Ezio Degli Esposti [1] on the behalf of the Study Group

Farmeconomia e percorsi terapeutici 2011; 12(2): 69-75

Anticoagulation Control in Real Life in Italy

% of INR Determinations by Range in VKA Treated Patients

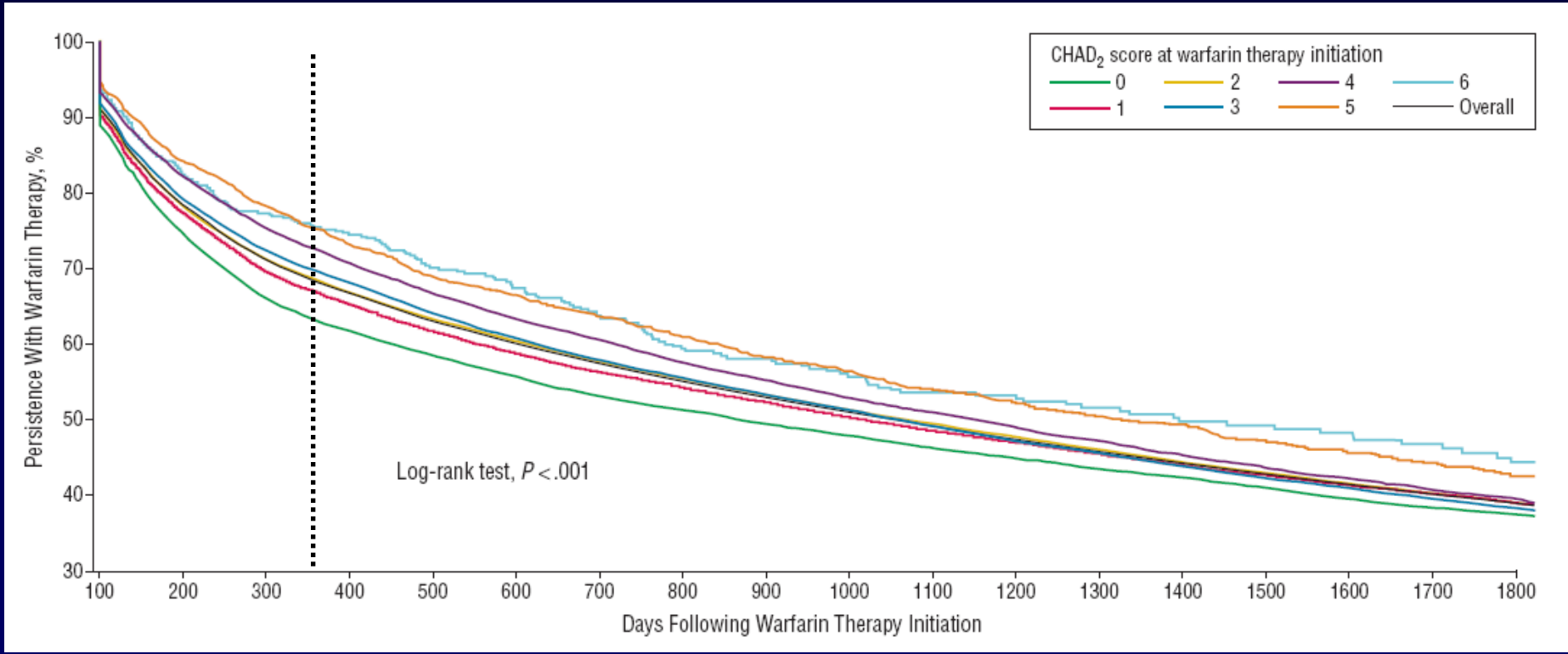
Range INR	*VKA Experienced*	*mean*	*median*	*(p25 - p75)*
% INR < 2	No	33.4%	28.8%	(15.4% - 47.9%)
% INR < 2	Yes	25.3%	20.0%	(7.7% - 36.4%)
% INR 2.0-3.0	No	47.9%	50.0%	(33.3% - 66.7%)
% INR 2.0-3.0	Yes	56.3%	58.3%	(42.5% - 73.1%)
% INR > 3	No	16.9%	13.3%	(0.0% - 25.0%)
% INR > 3	Yes	17.9%	14.3%	(4.0% - 26.7%)

Limiti della Terapia Anticoagulante Orale

Conseguenze nella FA

- Un significativo numero di pazienti con FA a rischio di stroke non riceve la TAO
- L'intensità della scoagulazione è spesso al di fuori del range terapeutico (INR 2.0 – 3.0)
- Un significativo numero di pazienti sospende la TAO entro un anno dall'inizio

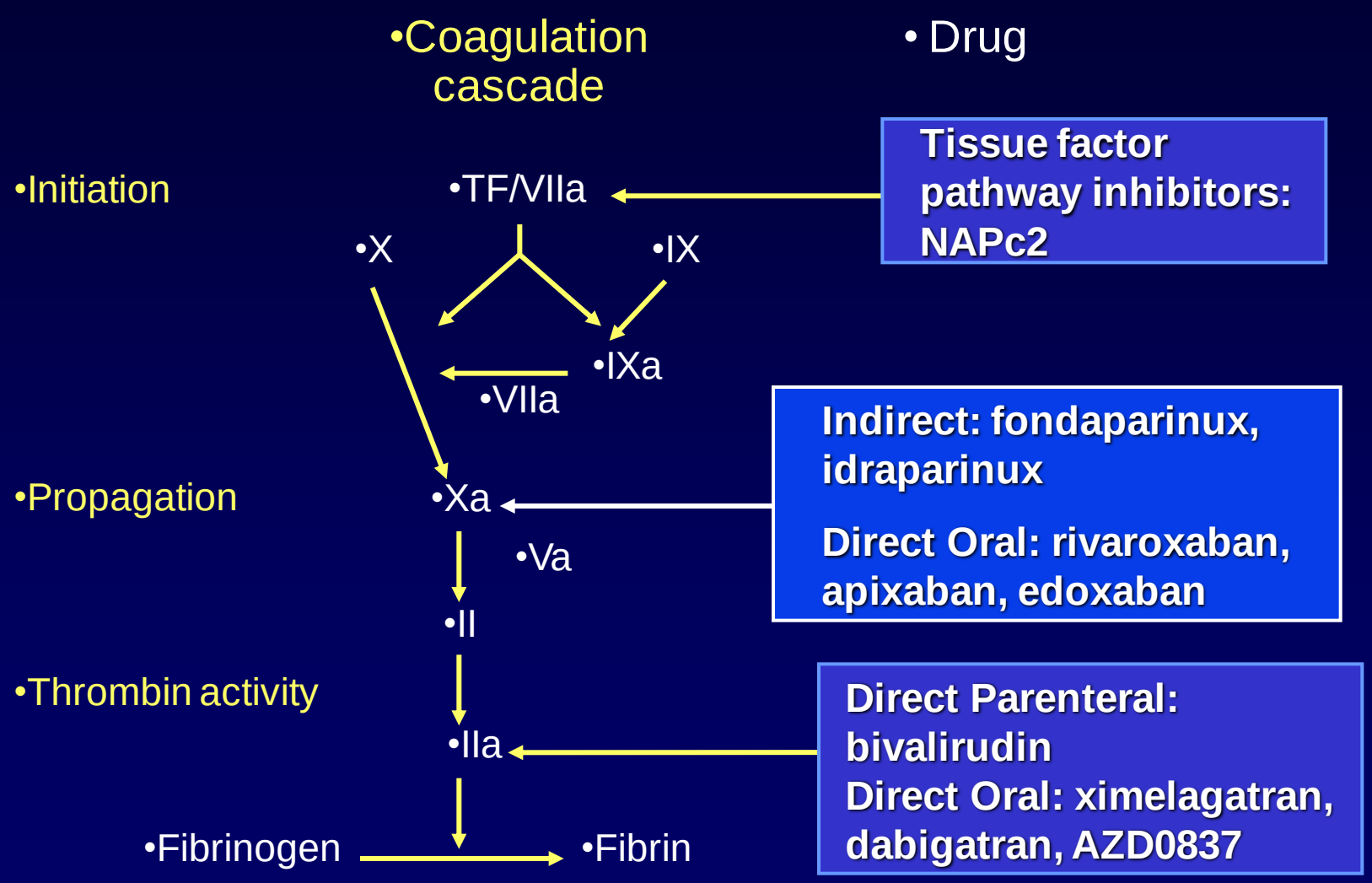
Warfarin Discontinuation Among AF Patients Stratified by $CHADS_2$ Score



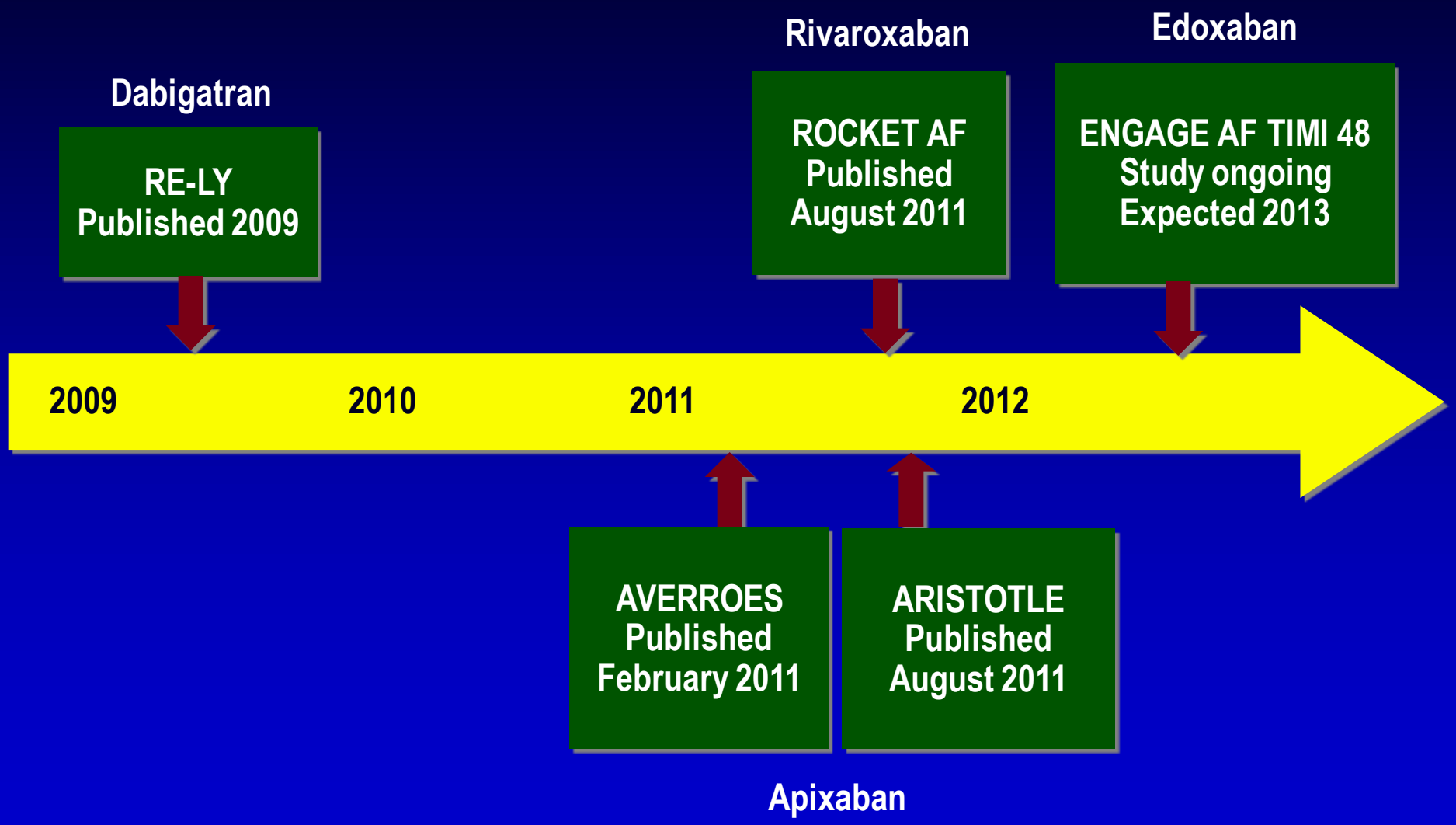
Gomes T et al. Arch Intern Med, 22 October 2012

The Promise of New Anticoagulants

New Anticoagulants



Atrial Fibrillation
NOAs Phase 3 Study Timelines



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

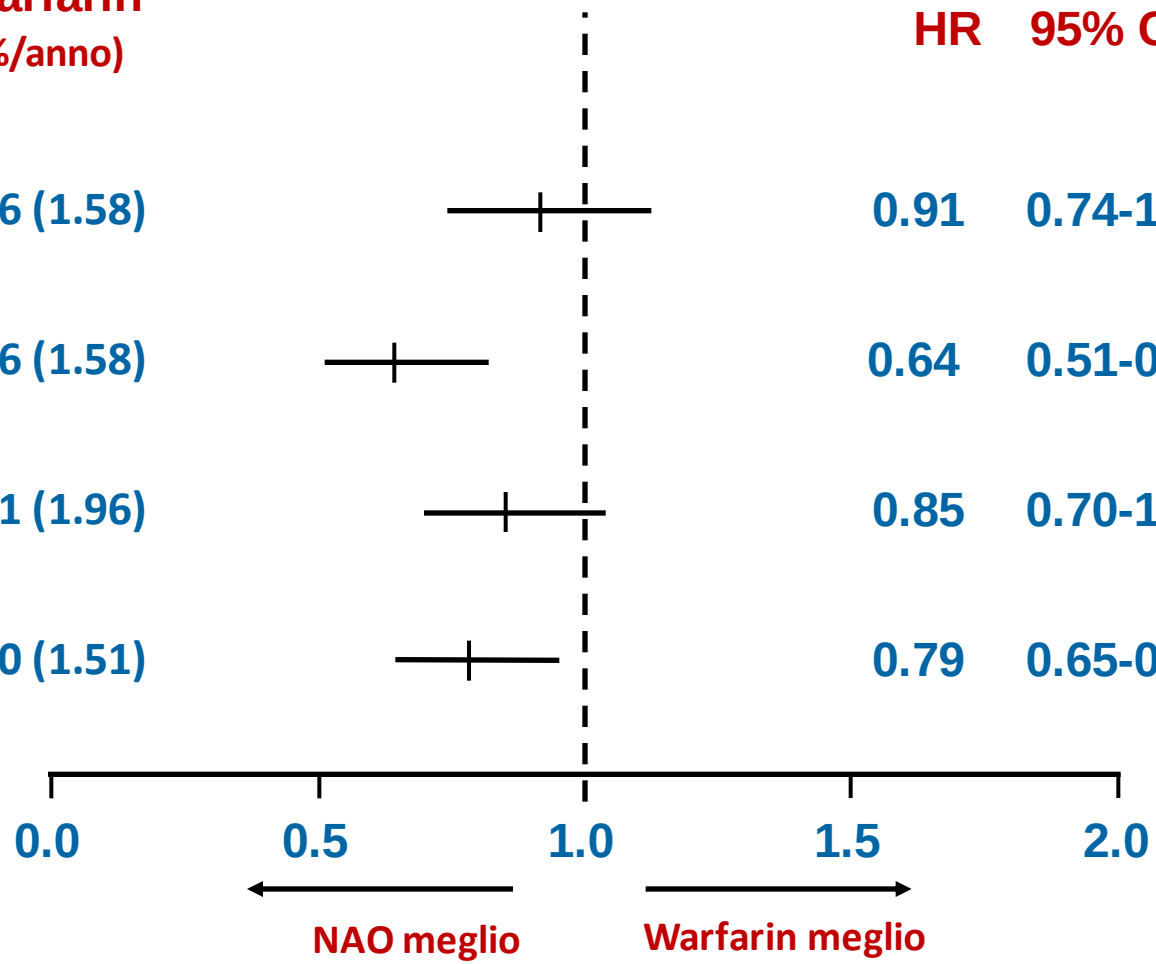
The NEW ENGLAND JOURNAL of MEDICINE

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

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Stroke (ischemico + emorragico)

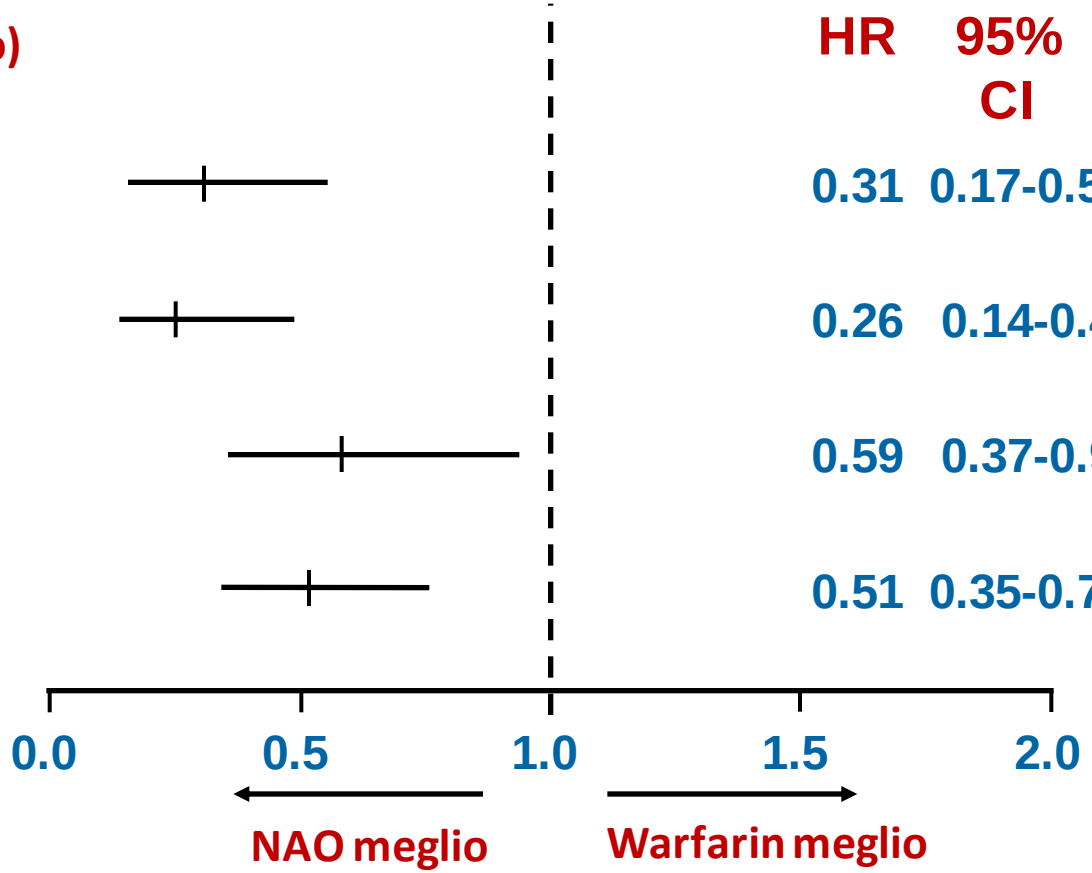
	NAO N° eventi (%/anno)	Warfarin N° eventi (%/anno)	HR	95% CI
Dabi 110 (ITT)	171 (1.44)	186 (1.58)	0.91	0.74-1.12
Dabi 150 (ITT)	122 (1.01)	186 (1.58)	0.64	0.51-0.81
Riva (safety AT)	184 (1.65)	221 (1.96)	0.85	0.70-1.03
Apixaban (ITT)	199 (1.19)	250 (1.51)	0.79	0.65-0.95



ITT: Intention to Treat – AT: as treated

Stroke emorragico

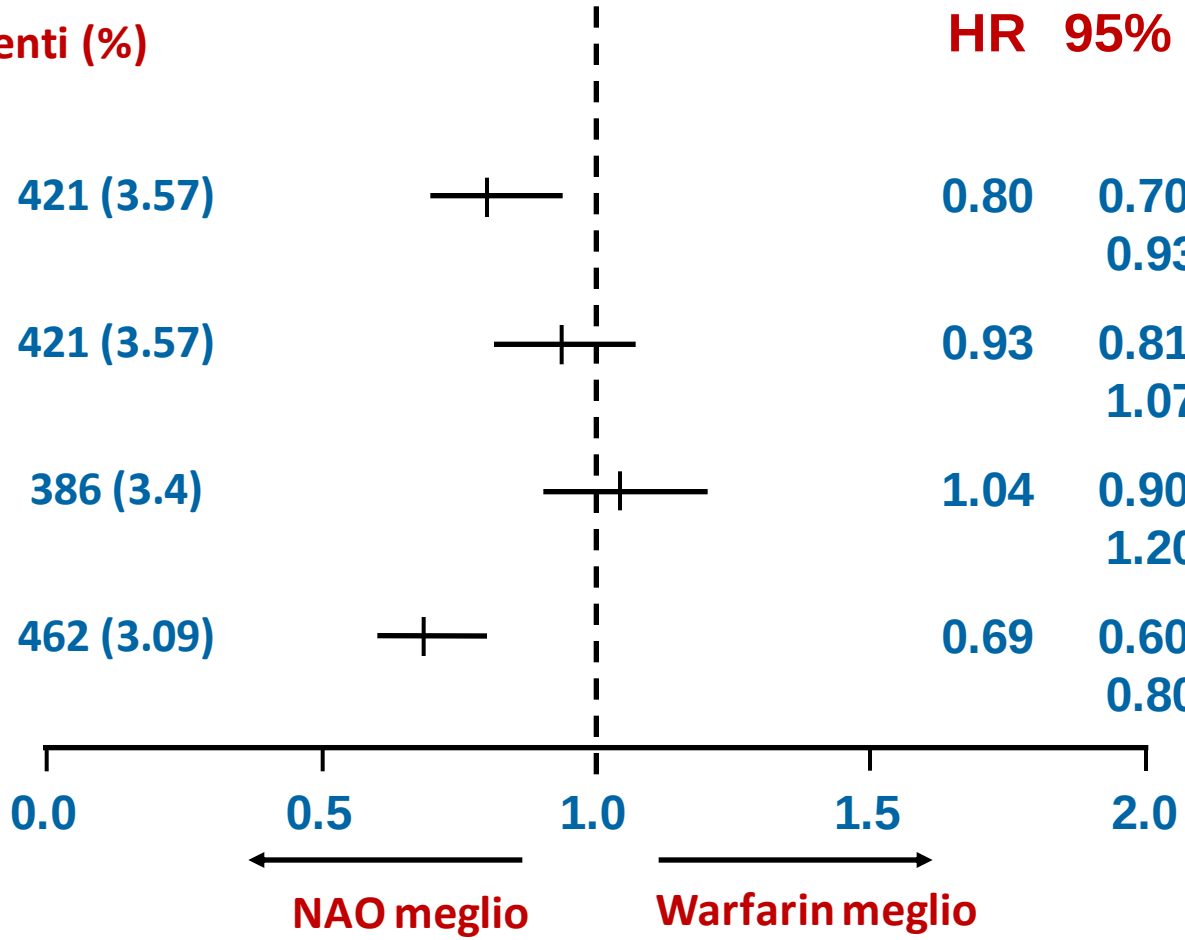
	NAO N° eventi (%/anno)	Warfarin N° eventi (%/anno)	HR	95% CI
Dabi 110 (ITT)	14 (0.12)	45 (0.38)	0.31	0.17-0.56
Dabi 150 (ITT)	12 (0.10)	45 (0.38)	0.26	0.14-0.49
Riva (safety AT)	29 (0.26)	50 (0.44)	0.59	0.37-0.93
Apixaban (ITT)	40 (0.24)	78 (0.47)	0.51	0.35-0.75



ITT: Intention to Treat – AT: as treated.

Emorragie maggiori

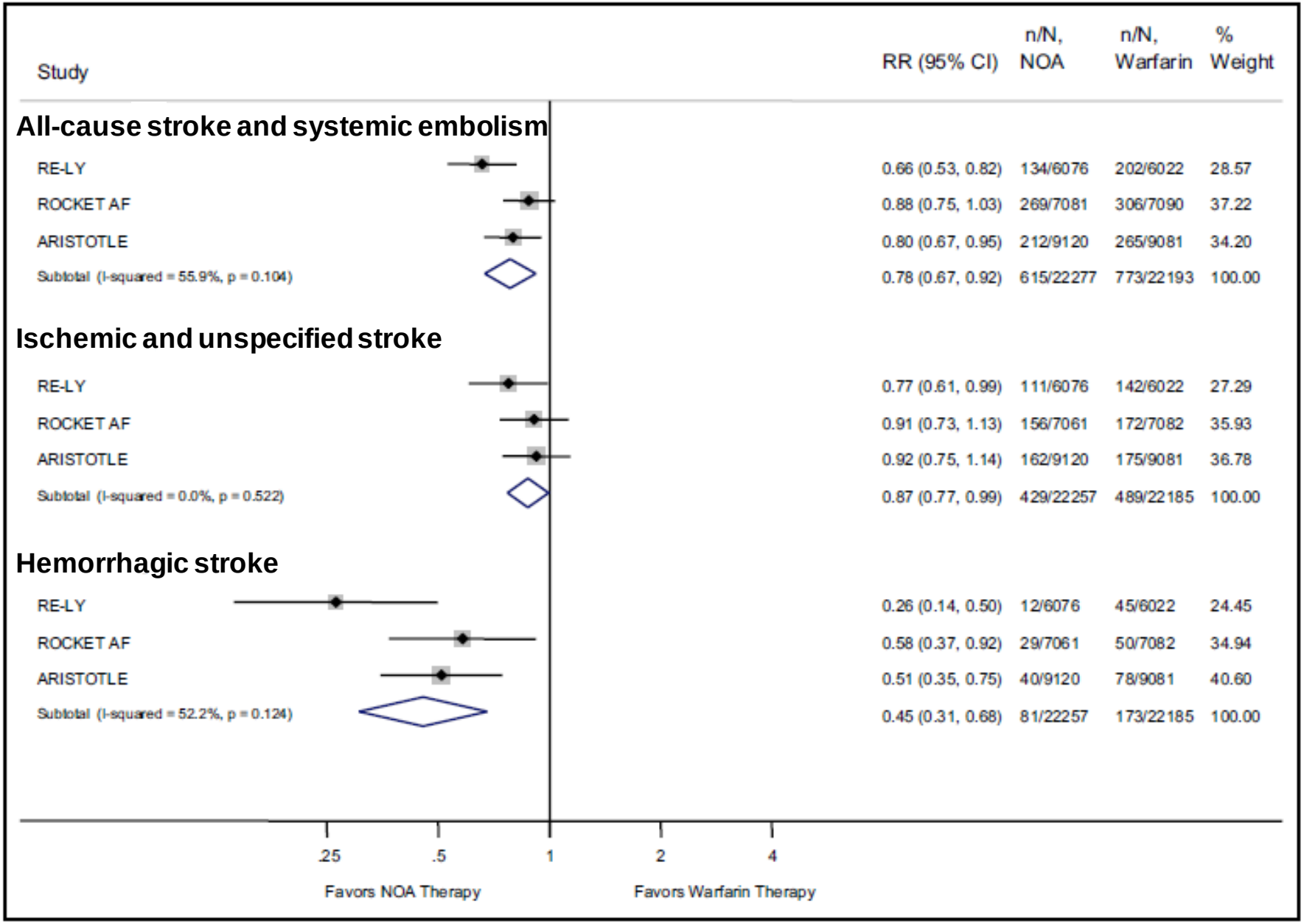
	NAO	Warfarin	HR	95% CI
	N° eventi (%)			
Dabi 110	342 (2.87)	421 (3.57)	0.80	0.70-0.93
Dabi 150	399 (3.32)	421 (3.57)	0.93	0.81-1.07
Riva	395 (3.6)	386 (3.4)	1.04	0.90-1.20
Apixaban	327 (2.13)	462 (3.09)	0.69	0.60-0.80



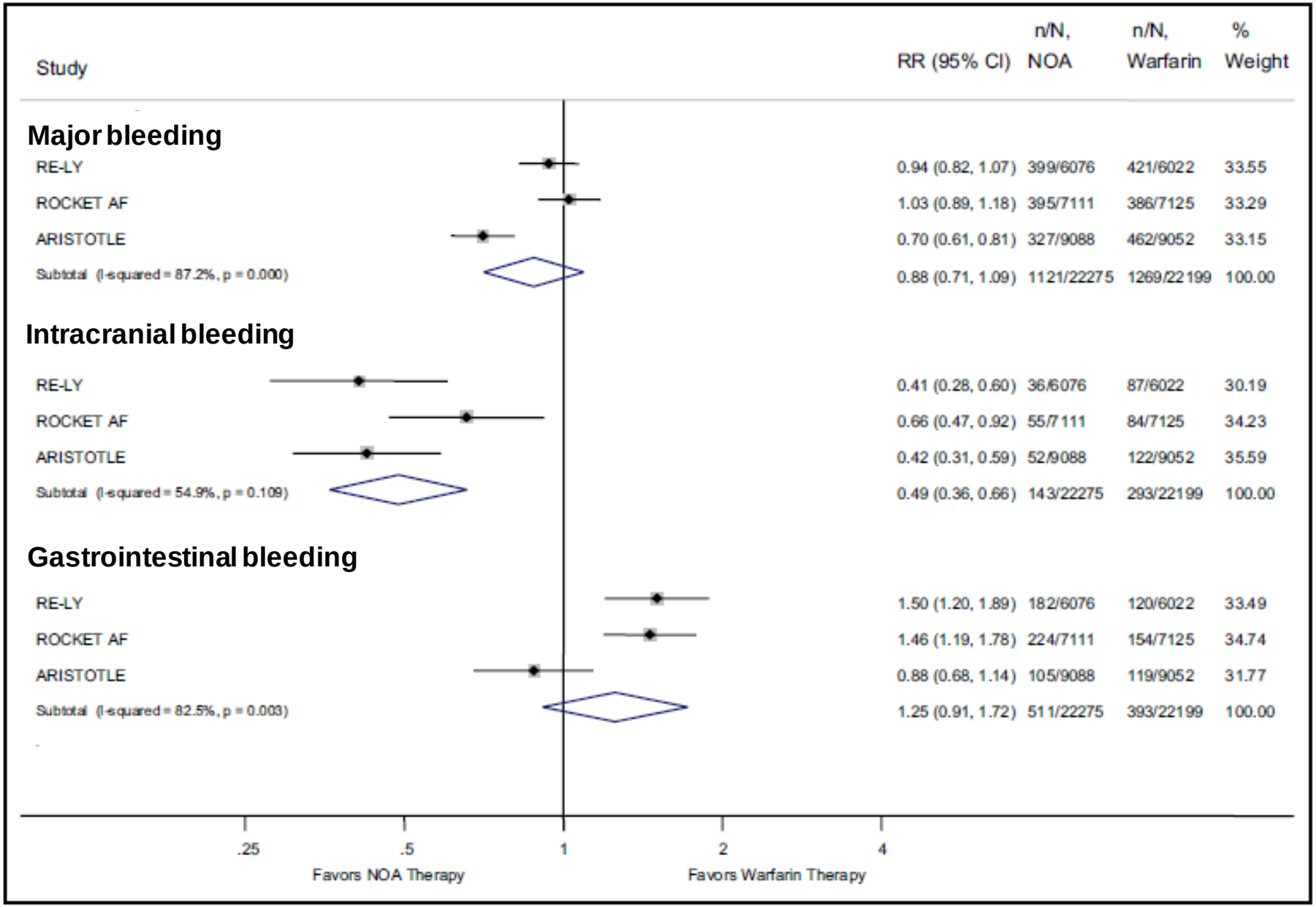
Meta-Analysis of Efficacy and Safety of New Oral Anticoagulants (*Dabigatran*, *Rivaroxaban*, *Apixaban*) Versus *Warfarin* in Patients With Atrial Fibrillation

Corey S. Miller, BA[a,c], Sonia M. Grandi, MSc[a], Avi Shimony, MD[a,b,d], Kristian B. Filion, PhD[a], and Mark J. Eisenberg, MD, MPH[a,b,c,*]

Am J Cardiol 2012;110:453-60



Am J Cardiol 2012;110:453-60



Am J Cardiol 2012;110:453-60

Survival benefit of new anticoagulants compared with warfarin in patients with atrial fibrillation: A meta-analysis

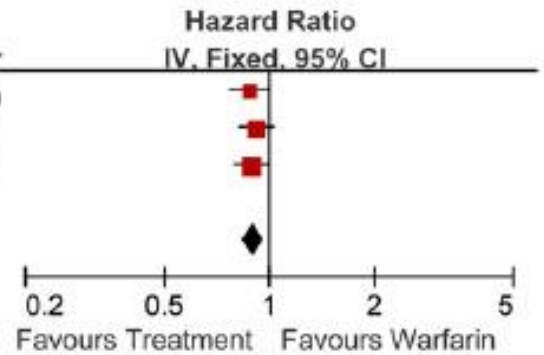
Tong Liu [a], Panagiotis Korantzopoulos [b], Lijian Li [c], Guangping Li [a,*]

[a] Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin 300211, China
[b] Department of Cardiology, University of Ioannina Medical School, 45110 Ioannina, Greece
[c] Graduate School, Tianjin Medical University, Tianjin, 300211, China

A

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
RELY	-0.128	0.067	26.6%	0.88 [0.77, 1.00]	2009
ROCKET AF	-0.083	0.058	35.4%	0.92 [0.82, 1.03]	2011
ARISTOTLE	-0.117	0.056	38.0%	0.89 [0.80, 0.99]	2011
Total (95% CI)			**100.0%**	**0.90 [0.84, 0.96]**	

Heterogeneity: $Chi^2 = 0.30$, df = 2 (P = 0.86); $I^2 = 0\%$
Test for overall effect: Z = 3.12 (P = 0.002)



B

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
RELY (2)	-0.094	0.064	28.4%	0.91 [0.80, 1.03]	2009
ARISTOTLE	-0.117	0.056	37.1%	0.89 [0.80, 0.99]	2011
ROCKET AF	-0.083	0.058	34.6%	0.92 [0.82, 1.03]	2011
Total (95% CI)			**100.0%**	**0.91 [0.85, 0.97]**	

Heterogeneity: $Chi^2 = 0.19$, df = 2 (P = 0.91); $I^2 = 0\%$
Test for overall effect: Z = 2.90 (P = 0.004)

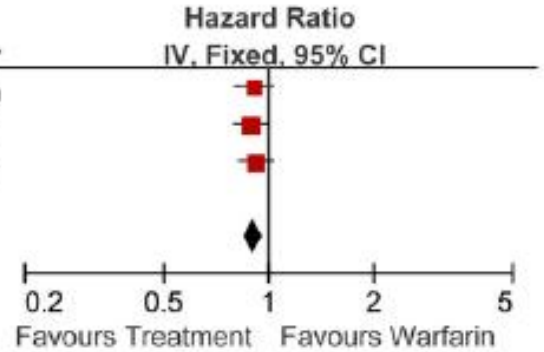


Fig. 1. Effects of the 3 new anticoagulants on all-cause mortality compared with dose-adjusted warfarin.

Int J Cardiol 2012;156(1):96-7

Quale NAO scegliere ?

Journal of the American College of Cardiology
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ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.03.019

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Antithrombotic Therapy

Indirect Comparisons of New Oral Anticoagulant Drugs for Efficacy and Safety When Used for Stroke Prevention in Atrial Fibrillation

Gregory Y. H. Lip, MD,*† Torben Bjerregaard Larsen, MD, PhD,†‡ Flemming Skjøth, PhD,†‡ Lars Hvilsted Rasmussen, MD, PhD†‡
Birmingham, United Kingdom; and Aalborg, Denmark

J Am Coll Cardiol 2012;60:738-46

Systematic Review and Adjusted Indirect Comparison Meta-Analysis of Oral Anticoagulants in Atrial Fibrillation

William L. Baker, PharmD, BCPS; Olivia J. Phung, PharmD

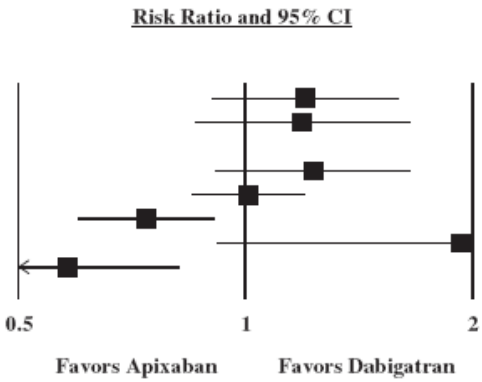
Background—Oral anticoagulants such as apixaban, dabigatran, and rivaroxaban are alternatives to warfarin for preventing events in patients with atrial fibrillation. Direct comparative studies between agents are unavailable. Our objective was to conduct an adjusted indirect comparison meta-analysis between new oral agents in atrial fibrillation.

Methods and Results—We searched MEDLINE and Cochrane Central through February 2012 for randomized, controlled trials in patients with atrial fibrillation evaluating apixaban, dabigatran, or rivaroxaban versus warfarin. For dabigatran, only data from the Food and Drug Administration–approved dose were included. Outcomes included the composite of stroke or systemic embolism, any stroke, and major bleeding among, others. Outcomes were initially pooled using standard random-effects methods, producing risk ratio and 95% confidence intervals. Adjusted indirect comparisons using these pooled estimates were then performed. A total of 44 733 patients from 4 studies were analyzed. Most analyses yielded no differences between agents. Dabigatran lowered risk of composite outcome (risk ratio, 0.75; 95% confidence interval, 0.57–1.00), ischemic stroke (0.67; 0.48–0.93), and hemorrhagic stroke (0.45; 0.45–0.99) versus rivaroxaban. No differences in all strokes or mortality were seen. Apixaban lowered the risk of major bleeding (0.74; 0.60–0.91) and gastrointestinal bleeding (0.58; 0.41–0.82) versus dabigatran and major bleeding versus rivaroxaban (0.68; 0.55–0.83), but increased systemic emboli versus rivaroxaban (3.86; 1.17–12.75).

Conclusions—Significant differences in efficacy and safety parameters may exist between oral anticoagulant agents in patients with atrial fibrillation. Apixaban lowers the risk of major and gastrointestinal bleeding versus dabigatran and rivaroxaban. Dabigatran lowers the composite of stroke or systemic emboli, and ischemic stroke versus rivaroxaban. Head-to-head clinical trials are required to confirm these findings. (***Circ Cardiovasc Qual Outcomes*. 2012;5:711-719.**)

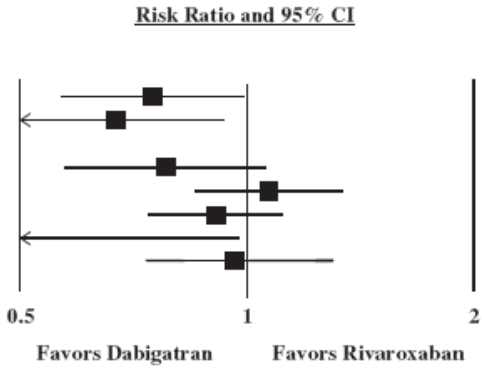
A Forest Plots Comparing Apixaban vs Dabigatran

Outcome	Statistics For Each Outcome		
	Risk ratio	Lower limit	Upper limit
Stroke or Systemic Emboli	1.193	0.902	1.579
Ischemic Stroke	1.190	0.860	1.645
Systemic Emboli	Not Available		
Any Stroke	1.213	0.907	1.622
Mortality	1.007	0.855	1.185
Major Bleed	0.753	0.619	0.916
Hemorrhagic Stroke	1.933	0.929	4.017
GI Bleed	0.603	0.434	0.838



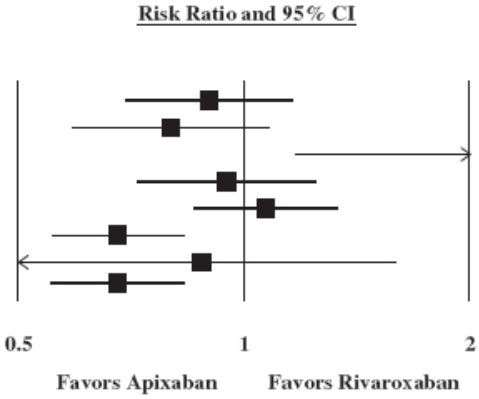
B Forest Plots Comparing Dabigatran vs Rivaroxaban

Outcome	Statistics For Each Outcome		
	Risk ratio	Lower limit	Upper limit
Stroke or Systemic Emboli	0.758	0.580	0.992
Ischemic Stroke	0.676	0.490	0.933
Systemic Emboli	Not Available		
Any Stroke	0.783	0.582	1.053
Mortality	1.069	0.859	1.331
Major Bleed	0.913	0.753	1.107
Hemorrhagic Stroke	0.454	0.210	0.983
GI Bleed	0.970	0.715	1.314



C Forest Plots Comparing Apixaban vs Rivaroxaban

Outcome	Statistics For Each Outcome		
	Risk ratio	Lower limit	Upper limit
Stroke or Systemic Emboli	0.905	0.712	1.150
Ischemic Stroke	0.804	0.598	1.082
Systemic Emboli	3.854	1.202	12.356
Any Stroke	0.949	0.727	1.238
Mortality	1.077	0.873	1.328
Major Bleed	0.688	0.566	0.835
Hemorrhagic Stroke	0.878	0.487	1.583
GI Bleed	0.585	0.414	0.826



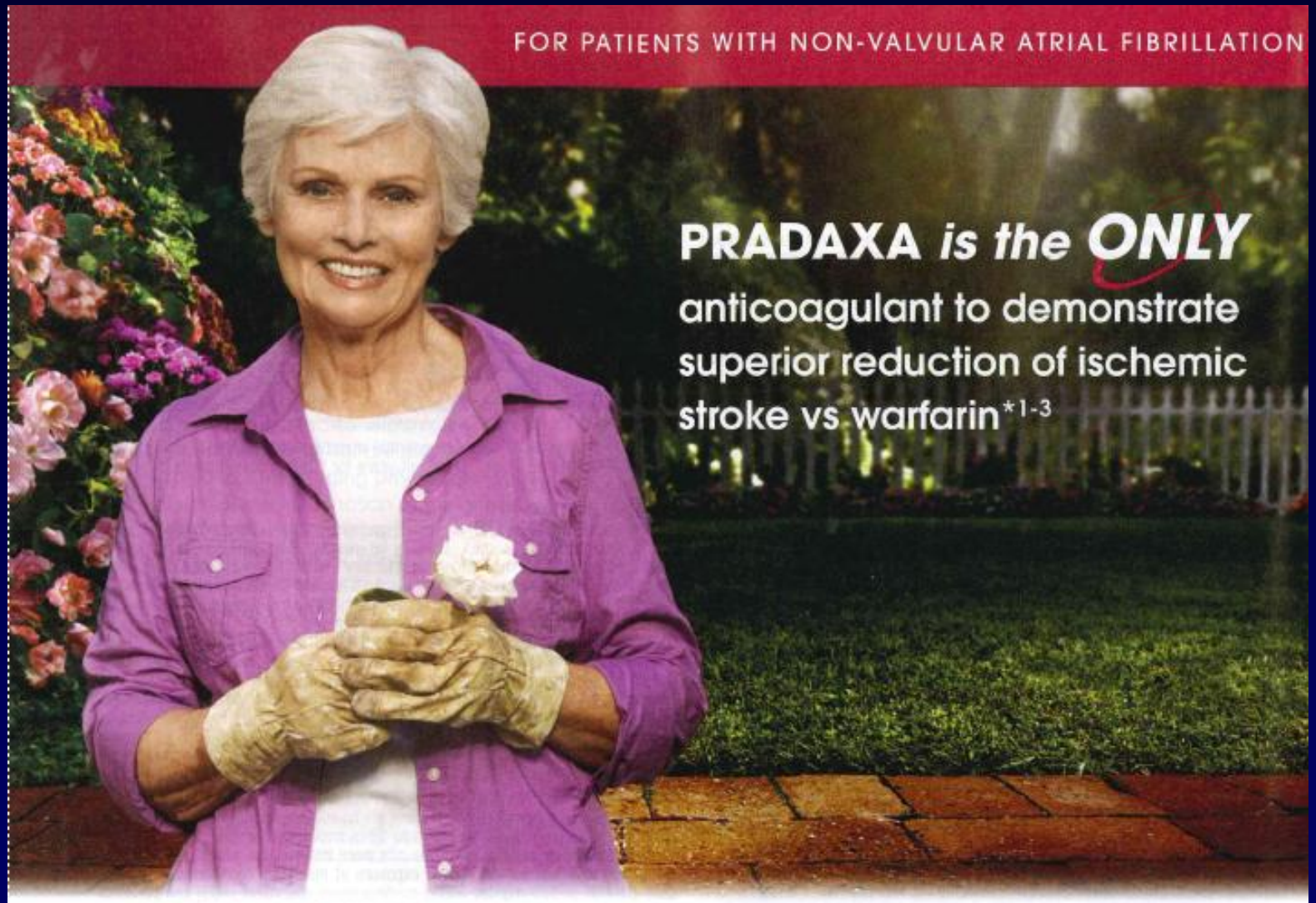
Circ Cardiovasc Qual Outcomes 2012;5:711-19

The only once-daily fixed-dose anticoagulant
to reduce stroke risk in nonvalvular AF patients—

PROTECTION IN ACTION...

ONCE-DAILY
Xarelto®
rivaroxaban tablets

APPROVED FOR MULTIPLE INDICATIONS



Additional 35% risk reduction of stroke/systemic embolism vs warfarin

(primary efficacy endpoint; 134 vs 202 events, HR: 0.65, 95% CI [0.52, 0.81], *P*=0.0001)*1-3

Similar rate of major bleeds‡ with PRADAXA vs warfarin

(primary safety endpoint; 399 [3.3%] vs 421 [3.6%] events, HR: 0.93, 95% CI [0.81, 1.07])*1-3

Il valore aggiunto di Dabigatran

- Possibilità di individualizzare il dosaggio nel singolo paziente
- Unico tra i NAO che ha dimostrato una maggiore efficacia rispetto al warfarin nella prevenzione dello stroke ischemico
- Riduzione significativa rispetto al warfarin delle emorragie maggiori ed in particolare di quelle cerebrali
- Consistenza di beneficio dimostrata in numerosi sottogruppi prespecificati

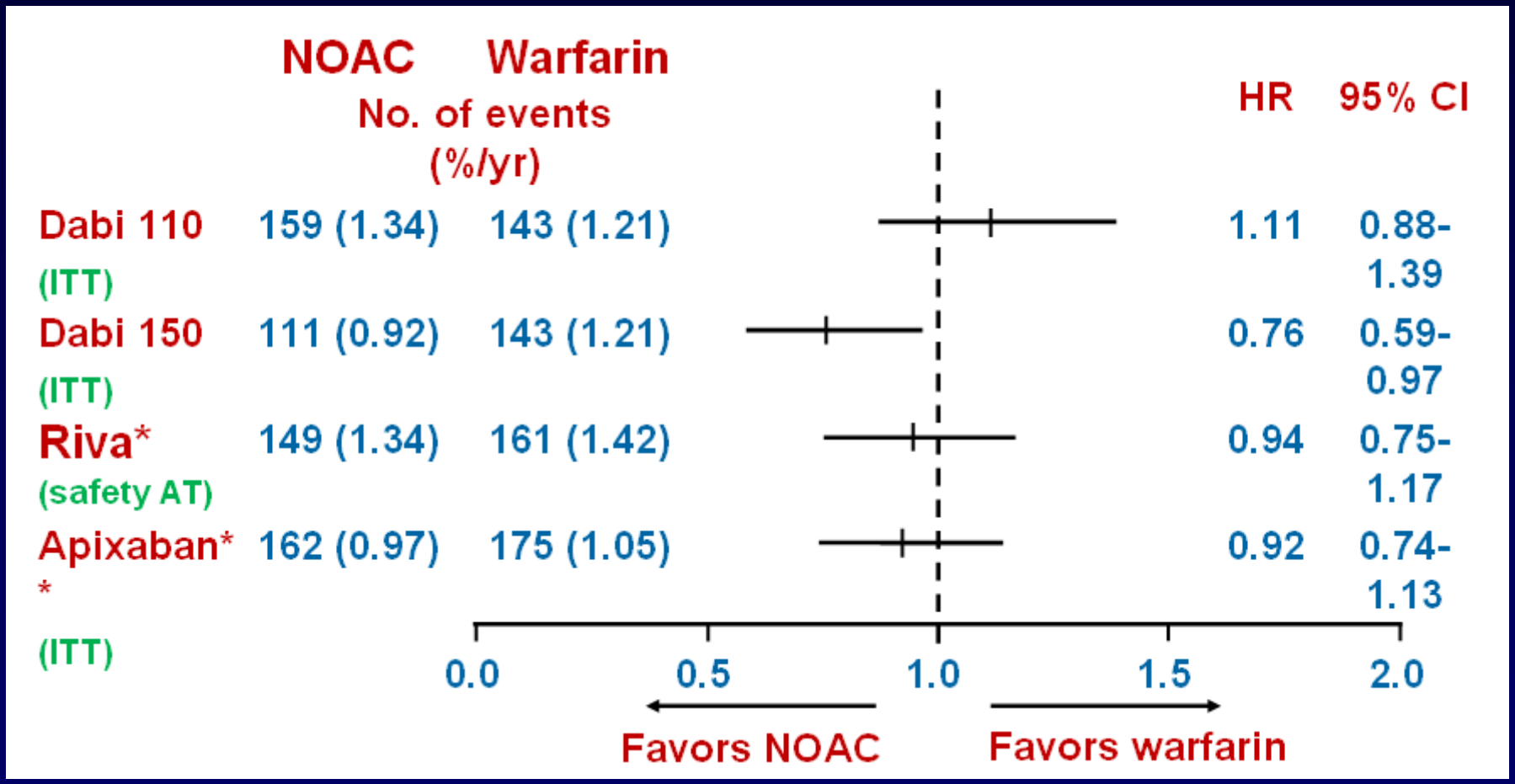
Dabigatran: individualizzazione dosaggio

- 150 mg bid nella maggior parte dei pazienti

- 110 mg bid nei soggetti:

✓ > 80 anni
✓ alto rischio emorragico
✓ con *clearance* creatinina 30-49 ml/min
✓ in terapia con verapamil

Dabigatran e Stroke Ischemico



1. Connolly et al. NEJM 2009; 361: 1139-51. 2. Connolly et al. NEJM 2010; 363: 1875-6.
3. Patel et al. NEJM 2011; 365: 883-91. 4. Granger et al. NEJM 2011; 365: 981-92.

CLINICAL OBSERVATION

The Use of Dabigatran in Elderly Patients

Matthieu Legrand, MD; Joaquim Mateo, MD; Alice Aribaud; Sixtine Ginisty, MD; Pirayeh Eftekhari, MD; Patrice Tran Ba Huy, MD, PhD; Ludovic Drouet, MD, PhD; Didier Payen, MD, PhD

Recent approval by the US Food and Drug Administration (FDA) of dabigatran etexilate, an oral direct thrombin inhibitor, for the prevention of stroke in patients with atrial fibrillation will likely extend its administration in elderly patients. The risk of major overdosage of dabigatran etexilate in this population is, however, much increased owing to frequent renal function impairment, low body weight, drug interactions that cannot be detected with a routine coagulation test, and no antagonist available. We report herein 2 clinical cases, including 1 fatal case, illustrating our concern regarding the risk of bleeding events in elderly patients.

Arch Intern Med. 2011;171(14):1285-1288

INVITED COMMENTARY

New Anticoagulant Drugs Among Elderly Patients Is Caution Necessary?

Arch Intern Med 2011;171(14):1287-88

NOTA INFORMATIVA IMPORTANTE CONCORDATA CON LE AUTORITÀ REGOLATORIE EUROPEE E L'AGENZIA ITALIANA DEL FARMACO (AIFA)

Milano, 27 ottobre 2011

In sintesi:

- **La funzionalità renale deve essere valutata in tutti i pazienti prima di iniziare la terapia con Pradaxa®.**
- **Pradaxa® è controindicato in pazienti con grave insufficienza renale.**
- **Durante il trattamento deve essere valutata la funzionalità renale in quelle condizioni cliniche che lascino prevedere un declino della funzionalità renale stessa.**
- **La funzionalità renale deve essere valutata almeno una volta l'anno nei pazienti di età superiore a 75 anni o in pazienti con insufficienza renale nota.**

Poiché i soli valori di creatininemia spesso non sono sufficienti per un'accurata valutazione della funzionalità renale, essa deve essere calcolata come clearance della creatinina, per escludere dal trattamento con Pradaxa i soggetti con un'insufficienza renale grave (cioè, con clearance della creatinina inferiore a 30 ml/min) che precluderebbe l'uso sicuro ed efficace di Pradaxa®.

Safety

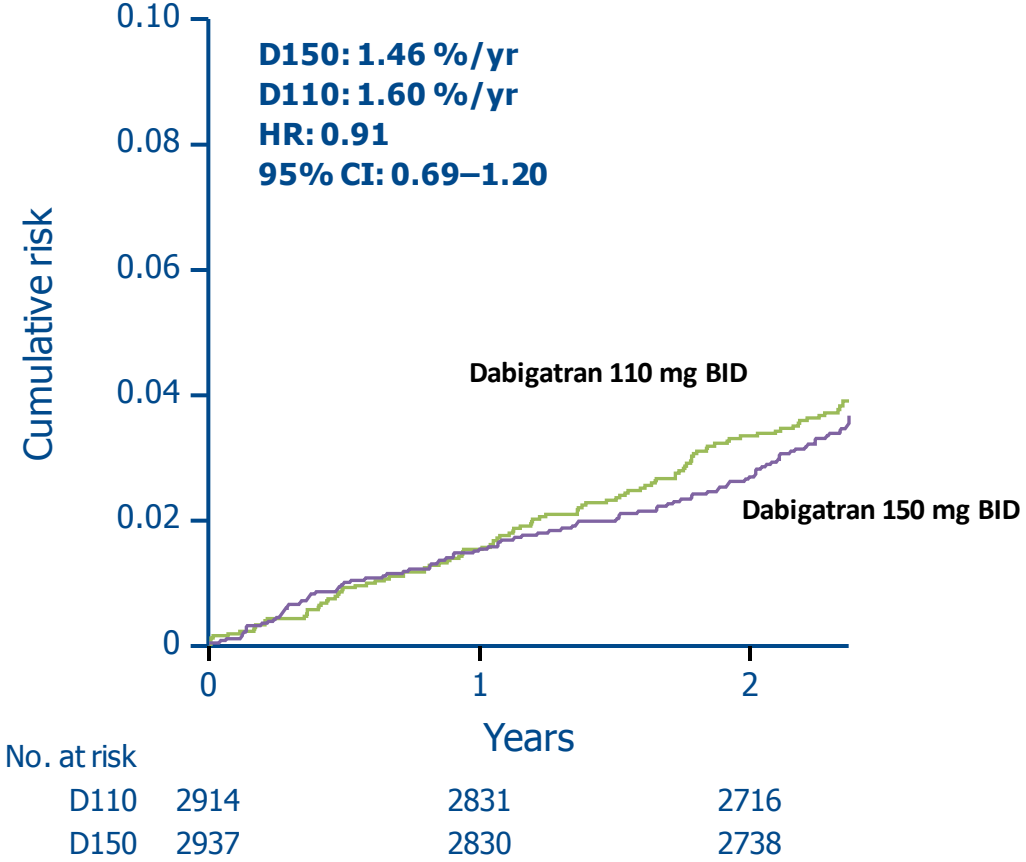
Pradaxa (dabigatran etexilate mesylate): Drug Safety Communication - Safety Review of Post-Market Reports of Serious Bleeding Events

UPDATED 11/02/2012. The FDA evaluated new information about the risk of serious bleeding associated with use of the anticoagulants (blood thinners) dabigatran (Pradaxa) and warfarin (Coumadin, Jantoven, and generics). This assessment was done using insurance claims and administrative data from FDA's Mini-Sentinel pilot of the Sentinel Initiative. The results of this assessment indicate that bleeding rates associated with new use of Pradaxa do not appear to be higher than bleeding rates associated with new use of warfarin, which is consistent with observations from the large clinical trial used to approve Pradaxa (the RE-LY trial). FDA is continuing to evaluate multiple sources of data in the ongoing safety review of this issue. See the Data Summary in the 11/02/2012 Drug Safety Communication below for additional information.

FDA has not changed its recommendations regarding Pradaxa. Pradaxa provides an important health benefit when used as directed. Healthcare professionals who prescribe Pradaxa should carefully follow the dosing recommendations in the drug label, especially for patients with renal impairment (when kidneys don't function normally) to reduce the risk of bleeding. Patients with atrial fibrillation should not stop taking Pradaxa without first talking to their healthcare professional. Stopping use of anticoagulant medications such as Pradaxa can increase the risk of stroke. Strokes can lead to permanent disability and death.

Posted 12/07/2011

Stroke/systemic embolism: RELY-ABLE®



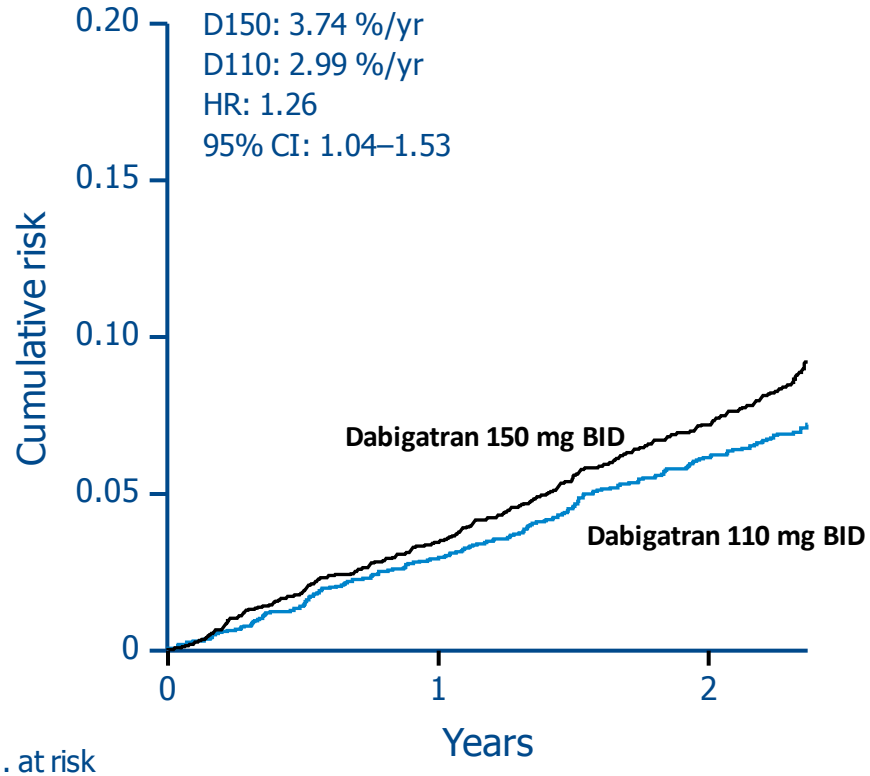
5851 patients followed for mean of 2.3 years

BID = twice daily; D150 and D110 = dabigatran 150 and 110 mg BID, respectively; HR = hazard ratio

Connolly SJ, et al. Randomized Comparison of the Effects of Two Doses of Dabigatran Etexilate on Clinical Outcomes Over 4.3 Years: Results of the RELY-ABLE Double-blind Randomized Trial. CS.04. Clinical Science: Special Reports: Valvular Heart Disease, PAD, Atrial Fibrillation: International Perspectives. Presented on 7 November 2012 at the American Heart Association Scientific Sessions 2012.

http://www.newshome.com/af-stroke/atrial-fibrillation-stroke/rely-able-webcast-connolly.aspx

Major bleeding: RELY-ABLE®



No. at risk			
D110	2914	2823	2692
D150	2937	2811	2692

5851 patients followed for mean of 2.3 years

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http://www.newshome.com/af-stroke/atrial-fibrillation-stroke/rely-able-webcast-connolly.aspx

Quanto sono rappresentati i pazienti over 75 negli studi dei NAO?

- Pazienti ≥ 75 anni nello studio RELY 7258
- Pazienti ≥ 75 anni nello studio ROCKET 6164
- Pazienti ≥ 75 anni nello studio ARISTOTLE 5678

- Pazienti ≥ 75 anni esposti a DAB nello studio RELY 4828
- Pazienti ≥ 75 anni esposti a RIV nello studio ROCKET 3082
- Pazienti ≥ 75 anni esposti a API nello studio ARISTOTLE 2850

Distribuzione per età nello studio RE-LY

Table 1. Baseline Characteristics of the Study Participants, According to Treatment Group.*

Characteristic	Dabigatran, 110 mg	Dabigatran, 150 mg	Warfarin
Age — yr	71.4±8.6	71.5±8.8	71.6±8.6

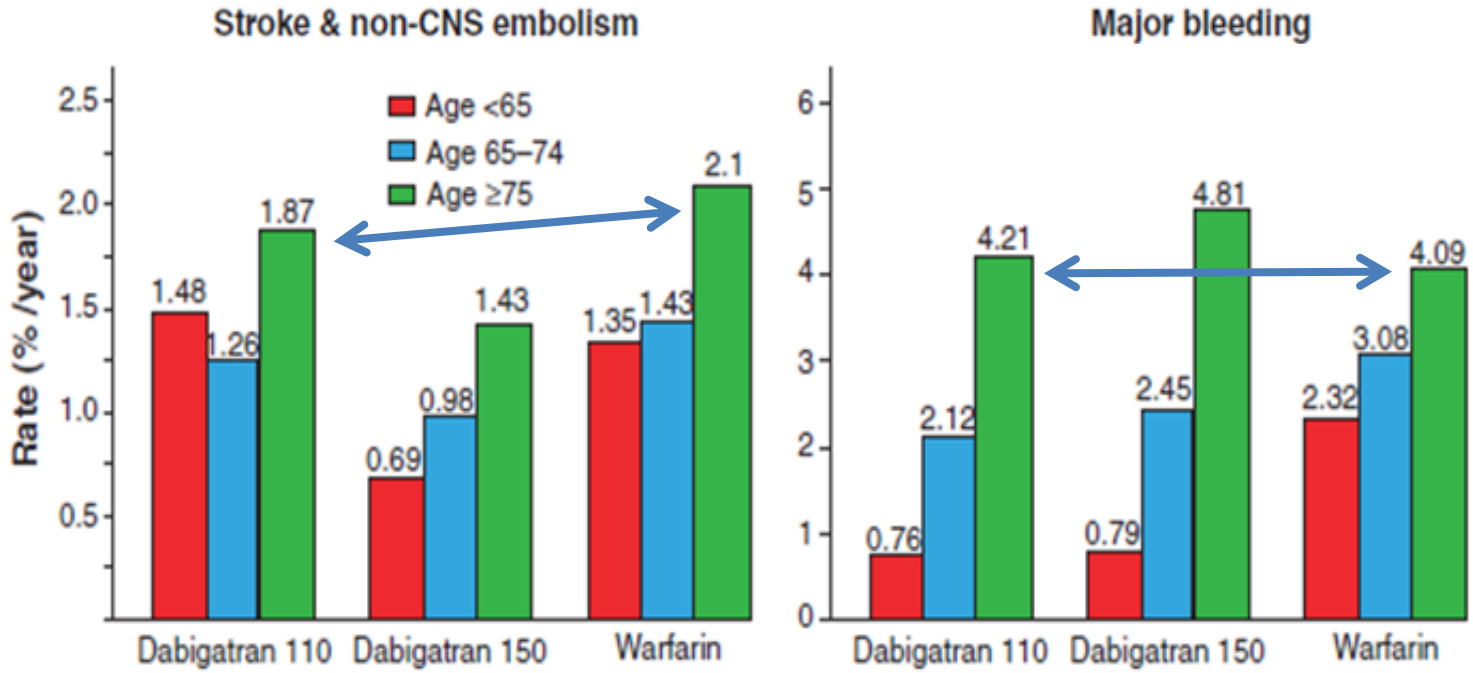
* Plus-minus values are means ±SD.

Age **7258 patients were ≥ 75 years**

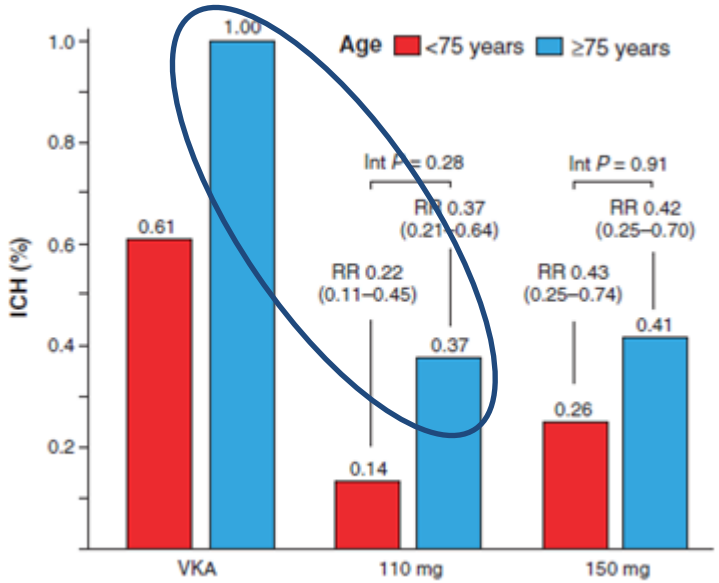
The mean age for subjects randomized in this trial was 71.5 years, ranging from 22 to 101 years of age. Overall, 16.4% of subjects were <65 years of age, 43.6% were ≥ 65 and <75 years of age, and 40.0% were ≥ 75 years of age (Table 15.1.4: 1).

Connolly SJ et al. N Engl J Med 2009;361:1139–51

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/cardiovascularandrenaldrugsadvisorycommittee/ucm226009.pdf
Tabella 7.1.3.8 Advisory Committee Briefing Document



Annual rates of ICH according to age in RE-LY



Intuitively, these results from RE-LY trial appear to be especially appealing for stroke prevention in an elderly AF population: the observation that 110 mg dabigatran bid is associated with similar efficacy to warfarin for preventing stroke and systemic emboli and significantly less ICH and haemorrhagic stroke without increasing major bleeding is of particular importance for elderly patients in need of effective anticoagulation. Especially elderly patients with AF now treated with antiplatelet agents or not receiving antithrombotic therapy at all might now be considered for stroke prophylaxis with dabigatran. As re-

Sinnaeve et al. Stroke prevention in elderly patients with atrial fibrillation: challenges for anticoagulationdoi: 10.1111/j.1365-2796.2011.02464.x

Distribuzione per età dello studio RE-LY: Pazienti over 80

- Age **3016 patiens were ≥ 80 years**

- Dabigatran 110 mg 971
- Dabigatran 150 mg 1057
- Warfarin 988

Connolly SJ et al. N Engl J Med 2009;361:1139–51

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/cardiovascularandrenaldrugsadvisorycommittee/ucm226009.pdf

Tabella 7.1.3.8 Advisory Committee Briefing Document

American Heart Association. SCIENTIFIC SESSIONS 2012

Dabigatran Versus Warfarin in Very Elderly Patients with Atrial Fibrillation: Results from the RE-LY Trial

Michiel Coppens, John Eikelboom, Michael Ezekowitz, Andreas Clemens, Jeff Healy, Lars Wallentin, Herbert Noack, Salim Yusuf, Stuart Connolly,

METHODS This post-hoc analysis compared outcomes of patients aged ≥ 80 years with patients < 80 years.The relative efficacy and safety of each dose of dabigatran versus warfarin was evaluated using an interaction p-value.

RESULTS Of the 18,113 patients in RE-LY, **3,016 (17%) patients were aged ≥80 years**, 720 (4%) patients were ≥85 years and 79 patients (0.4%) were ≥90 years of age. Elderly patients had higher risks of thromboembolic and bleeding outcomes compared with younger patients (Table). **The effects of both DE doses compared with warfarin on the primary efficacy outcome of SSE were consistent in those aged <80 and those ≥80**. Both DE doses provided large relative risk reductions in intracranial hemorrhage (ICH) compared with warfarin in all patients, including those over the age of 80. For major bleeding there was a significant interaction between age and treatment group due to relatively more major bleeding in patients aged ≥80 than in those < 80 years of age. The results were similar when patients ≥ 85 years of age were compared to those aged <85 years (data not shown in the table).

CONCLUSIONS The benefits in prevention of stroke and ICH with DE versus warfarin are preserved in those in the 9th decade compared to those younger except for major bleeding where, compared with warfarin, there is no difference with DE 110 and an increased bleeding rate with DE 150. Therefore a dose reduction should be considered in the very old patient population.

http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=e6243513-48ca-43a2-8b4c-f02a85db1cd6&cKey=445ef07e-8c16-4ac3-b0d6-10a06fc2f407&mKey=%7b14145D5B-F96B-4354-8237-8F0937744BA4%7d

Over 80

- "For those over the age of 80, DE 110 BID had similar efficacy to DE 150 BID with less bleeding and therefore had a better benefit/risk profile than both DE 150 BID and warfarin, and is thus most appropriate for use in this population. These results were robust with all sensitivity and subgroup analyses essentially having similar results."

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/cardiovascularandrenaldrugsadvisorycommittee/ucm226009.pdf Pag. 29

Over 80

- "Bleeding is increased in the elderly in all treatment groups. In subjects ≥80 years, the risk of major bleeding for DE 110 BID was reduced compared to DE 150 BID by approximately an absolute 1%/year from 6.24%/year on DE 150 BID to 5.25%/year on DE 110 BID and was more similar to the warfarin rate of 4.70%/year. The benefit of DE versus warfarin in this subgroup for ICH and hemorrhagic stroke was maintained."

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/cardiovascularandrenaldrugsadvisorycommittee/ucm226009.pdf Pag. 151

RASSEGNA

Profilassi cardioembolica 2011: siamo vicini al tramonto del warfarin?

Giuseppe Di Pasquale, Letizia Riva

U.O. di Cardiologia, Ospedale Maggiore, Bologna

Warfarin has been the effective treatment in the prophylaxis of cardioembolism, in particular in patients with atrial fibrillation, for more than 50 years. Nevertheless, many patients with atrial fibrillation are not currently treated because of the numerous limits of oral anticoagulation and in those treated the quality of anticoagulation is often poor.

Novel oral anticoagulant drugs, the direct thrombin antagonist dabigatran and factor Xa inhibitors such as rivaroxaban, apixaban, edoxaban, and betrixaban are more predictable and convenient anticoagulants in comparison with warfarin, mainly because of the non-requirement of regular laboratory monitoring and dose adjustments. Current data from phase III clinical trials are available for dabigatran and rivaroxaban, which show to be at least noninferior in efficacy to warfarin for the prevention of stroke in patients with atrial fibrillation.

This review focuses on the potential of novel anticoagulants to replace warfarin in patients with atrial fibrillation. Also the place in therapy and the potential limitations of the new agents in clinical practice represent important issues to be considered. The promise of new oral anticoagulants gives us the hope that warfarin will finally be replaced in a near future, but more importantly that anticoagulant undertreatment of atrial fibrillation will be partially overcome.

Key words. Atrial fibrillation; Oral anticoagulant therapy; Thromboembolic prophylaxis.

G Ital Cardiol 2011; 12(9): 556-65

Nuovi Anticoagulanti Orali non AVK

Vantaggi

- Dose – risposta prevedibile : dose fissa giornaliera
- Non necessità di monitoraggio dell'anticoagulazione
- Elevata efficacia e sicurezza
- Significativa riduzione del rischio emorragico
- Inizio e termine d'azione rapidi: non necessità di bridge con eparina
- Minime interazioni farmacologiche
- Assenza di interazioni alimentari

Di Pasquale G, Riva L. G Ital Cardiol 2011;12:556-65

Nuovi Anticoagulanti Orali non AVK

Potenziali criticità

- Aggiustamento empirico del dosaggio
- Necessità di nuovi test laboratoristici da eseguire in caso di eventi emorragici o trombotici
- Difficoltà di valutare l'aderenza del paziente alla terapia
- Mancanza di antidoto in caso di sovradosaggio o emorragie
- Inizio e termine d'azione rapidi: potenziale svantaggio nei pazienti con bassa aderenza terapeutica
- Possibile ridotta consapevolezza della terapia da parte del paziente
- Sostenibilità economica

Di Pasquale G, Riva L, G Ital Cardiol 2011; 12: 556-65