Ferrara, 24 Settembre 2011

I nuovi farmaci anticoagulanti nella fibrillazione atriale

Gualtiero Palareti

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Policlinico S. Orsola-Malpighi

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VKAs or ASA vs placebo for stroke prevention in AF

	Trials	N. Pts	Dose	RRR %	ARR % y
VKAs	6	2900	1.4 - 4.5 INR	64 (49 – 74)	Primary 2.7 Secondary 8.4 prevention
Aspirin	9	3990	50-1200 mg/d	19 (-1 - 35)	Primary 0.8 Secondary 2.5 prevention

Problemi con la gestione della TAO

Elevata variabilità inter/intra-individuale

Necessari frequenti controlli INR

Necessari “esperti” adattamenti posologici

Difficile e a maggior rischio la fase iniziale

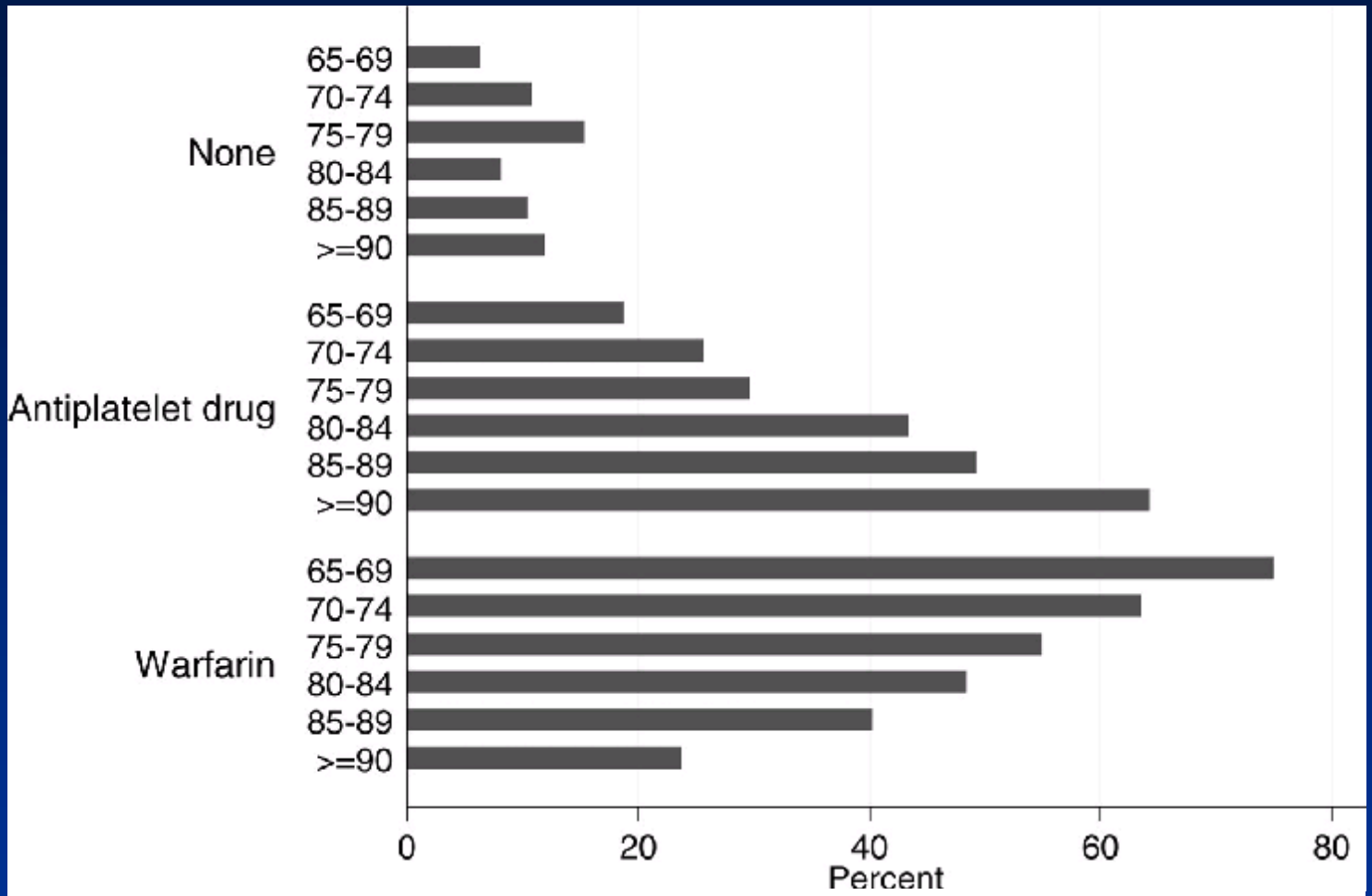
Consistente rischio emorragico

Rischio emorragico cresce con l’età

Necessari servizi dedicati (impegno sanitario)

Una importante porzione di pazienti con FA non vengono trattati o sono trattati in modo incongruo

Euro Heart Survey (2003-2004) =
intorno al 28% la percentuale di pazienti
con FA ad alto rischio “undertreated”



Antithrombotic therapy at hospital discharge by patient age.

(from Hylek EM, et al *Stroke* 2006; 37: 1077)

The NEW ENGLAND JOURNAL of MEDICINE

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

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

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

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The NEW ENGLAND JOURNAL of MEDICINE

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

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NOACs for AF: 3 studies at a glance (1)
(1st target: non-inferiority vs warfarin)

	RE-LY (dabigatran-anti-IIa)	Rocket (rivaroxaban-anti-Xa)	Aristotle (apixaban-anti-Xa)
Design	Open warfarin blind 2 doses NOAC	Double-blind Double-dummy	Double-blind Double-dummy
Doses	110 mg BID 150 mg BID warfarin 2-3 INR	20 mg OID (15 mg OID if CrCl 30-49 ml/min)	5 mg BID (2.5 mg BID if >80y, <60Kg, creat.>1.5 mg
Patients	6000 x 3	7130 x 2	9100 x 2

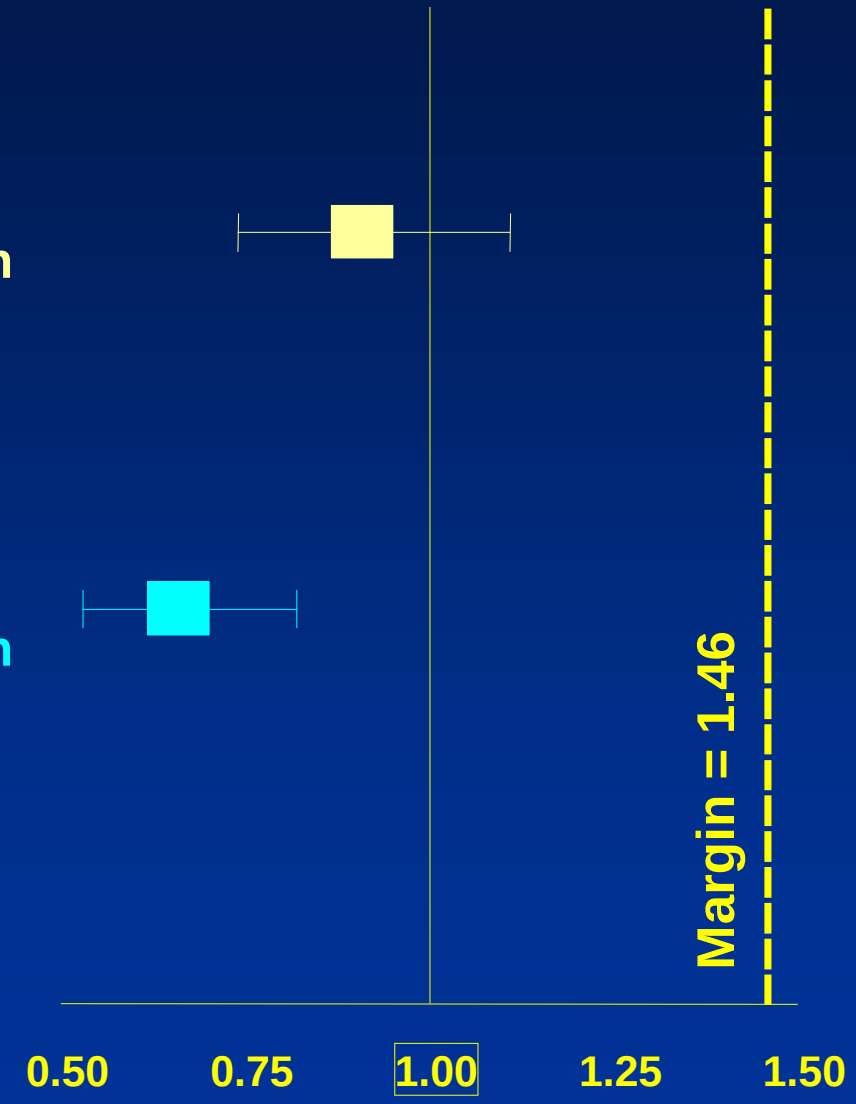
NOACs for AF: 3 studies at a glance (2) outcome measures

Primary efficacy endpoint	Secondary efficacy endpoints	Safety criteria include
• All stroke (ischaemic + haemorrhagic) and systemic embolism	• All stroke (ischaemic + haemorrhagic) • Systemic embolism • All death	• Bleeding events (major and minor) (RE-LY)
	• All stroke (ischaemic + haemorrhagic) • Systemic embolism • Pulmonary embolism • Acute MI • Vascular death (incl. deaths from bleeding)	• major or non-major clinically relevant bleeds (ROCKET)

NOACs for AF: 3 studies at a glance (3)

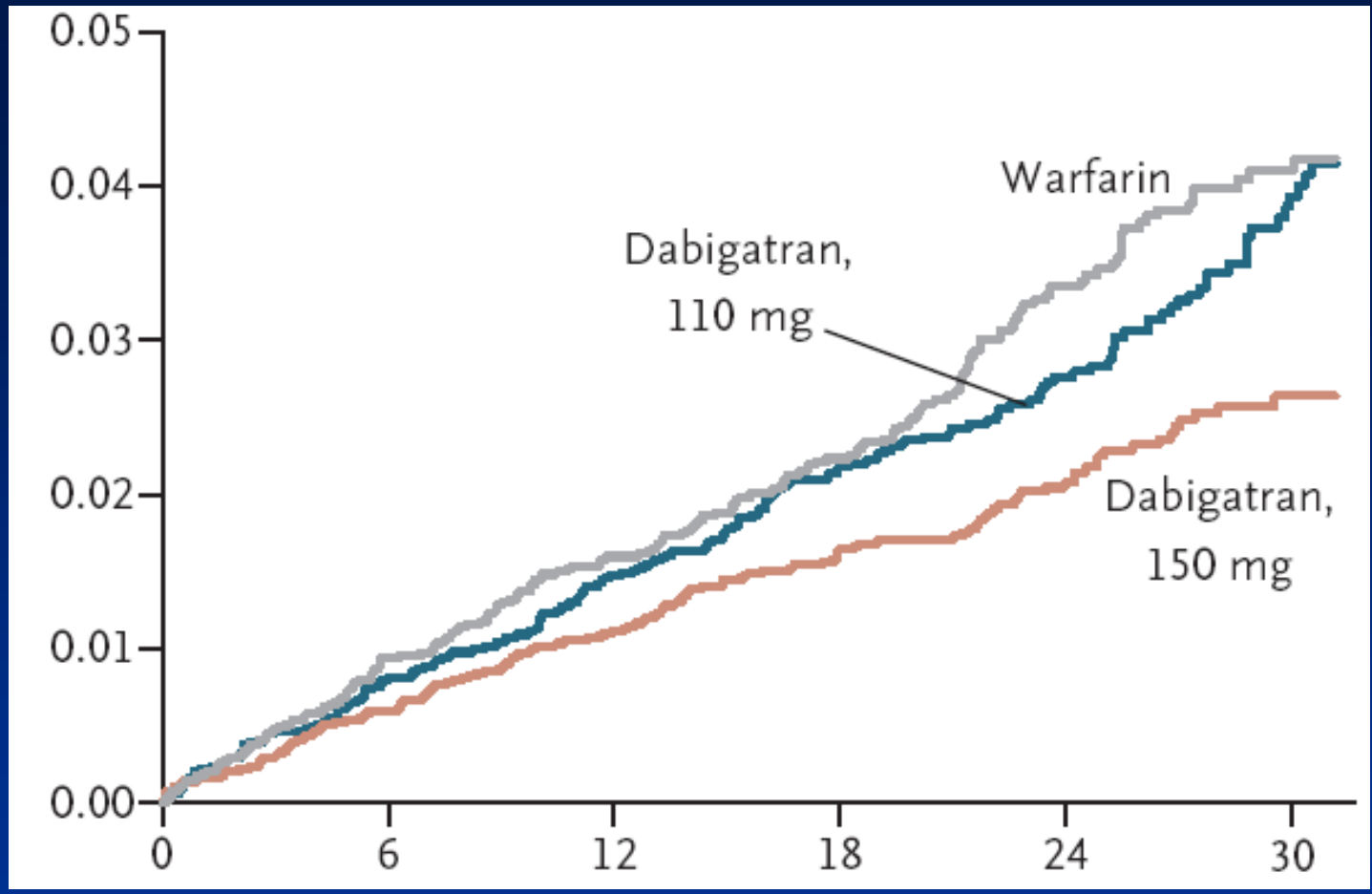
	RE-LY (dabigatran-anti-IIa)	Rocket (rivaroxaban-anti-Xa)	Aristotle (apixaban-anti-Xa)
Age y	71 (mean)	73 (median)	70 (median)
CHADS2	2.1±1.1	3.48±0.94	2.1±1.1
Previous Warfarin	≅ 50%	≅ 62%	≅ 57%
ASA during trial	≅ 20%	≅35%	≅ 31%
TTR warfarin	64%	55%	66%

Stroke or systemic embolism (SSE)



	Noninferiority p-value	Superiority p-value
Dabigatran 110 mg vs. warfarin	<0.001	0.34
Dabigatran 150 mg vs. warfarin	<0.001	<0.001

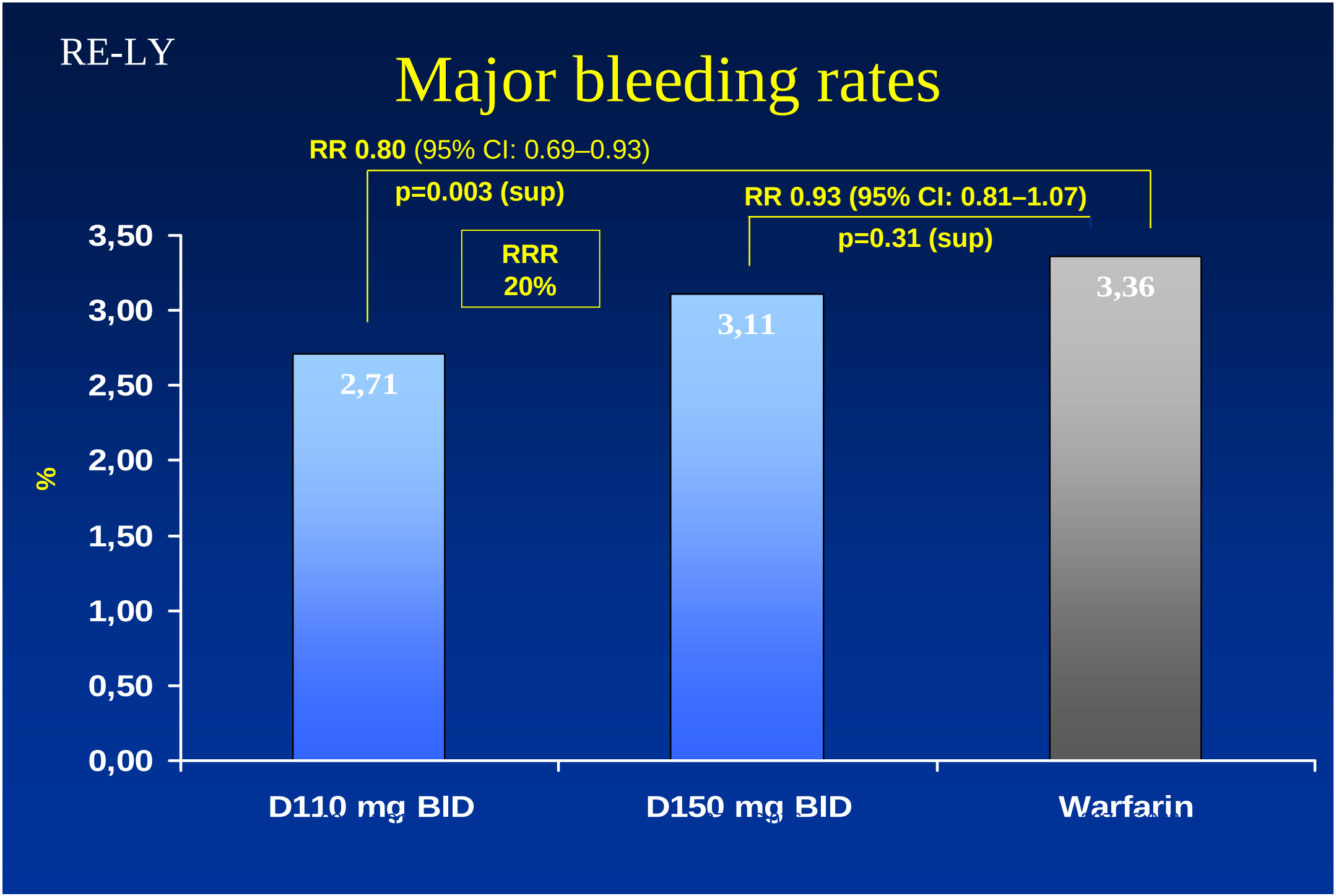
RE-LY



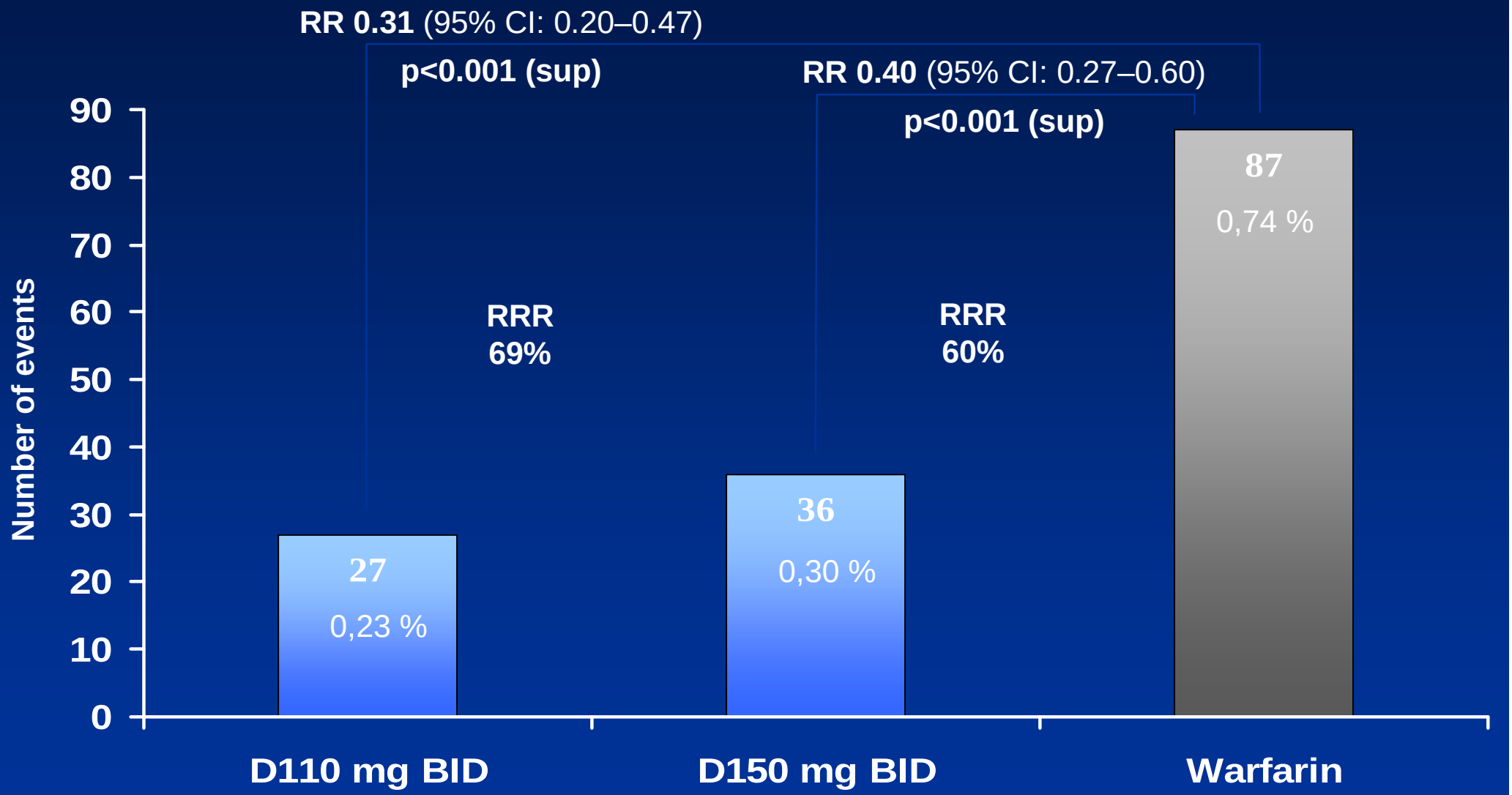
Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group (Connolly et al., NEJM 2009)

RE-LY

Major bleeding rates



Intra-cranial bleeding rates



Connolly SJ., et al. NEJM 2009.

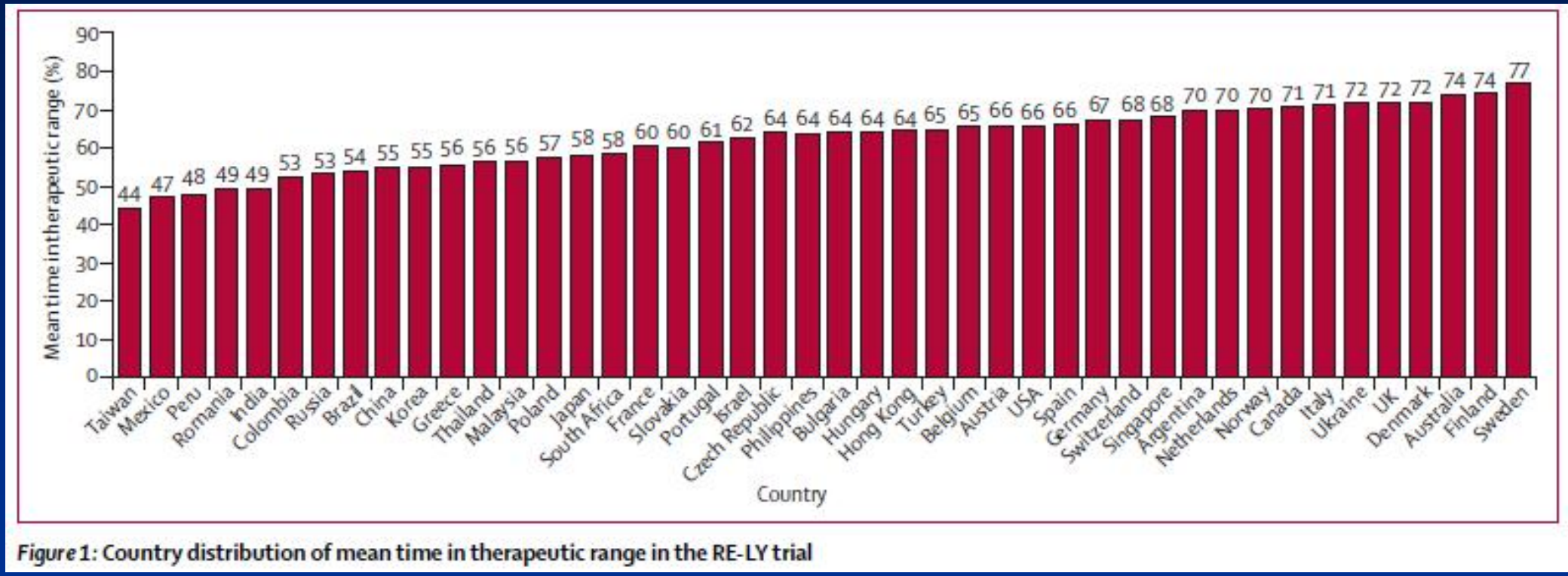


Figure 1: **Country distribution of mean time in therapeutic range in the RE-LY trial**

(From Wallentin et al., Lancet 2010)

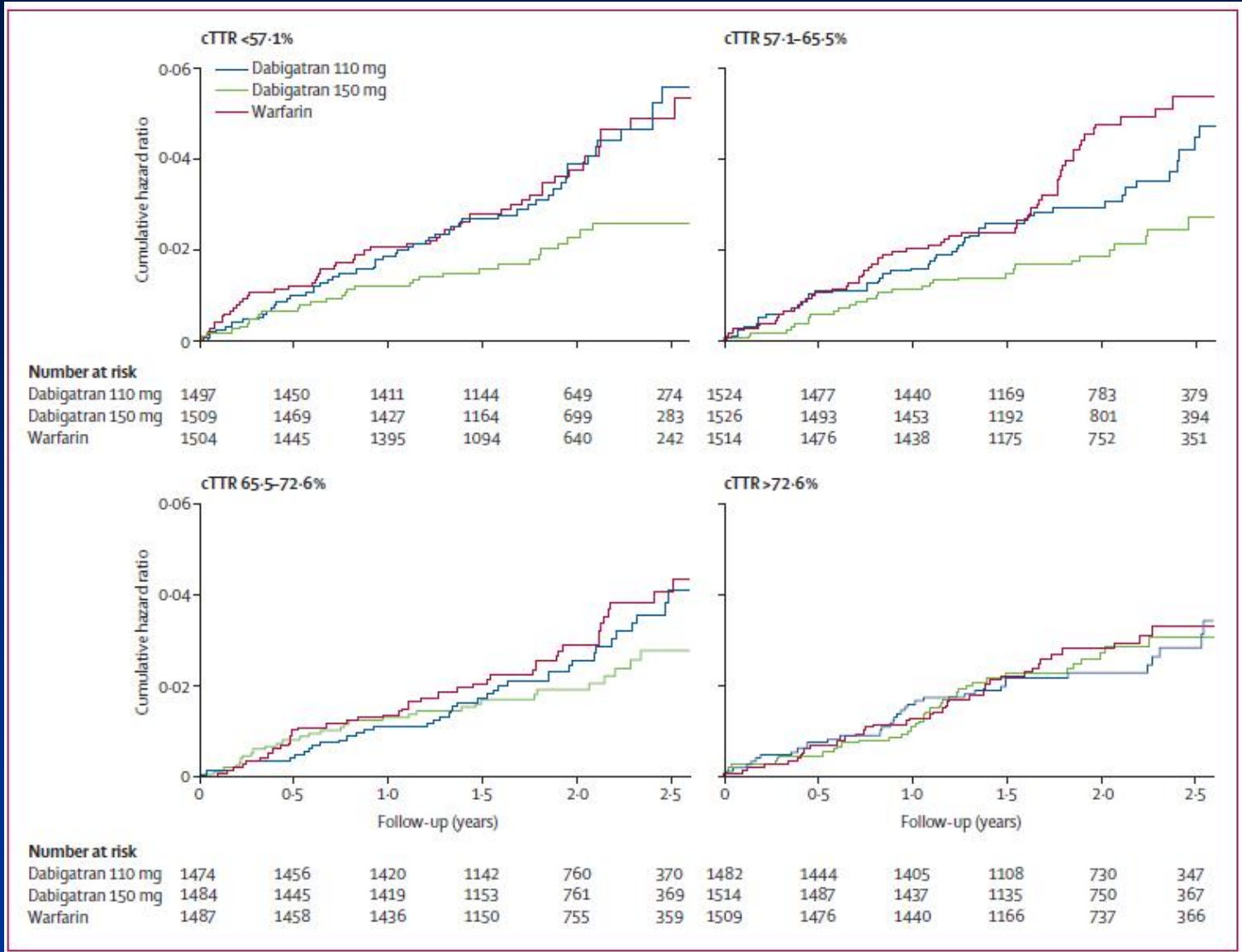


Figure 2: **Time to primary outcome in each quartile of centre's mean time in therapeutic range**
cTTR=centre's mean time in therapeutic range.

(From Wallentin et al., Lancet 2010)

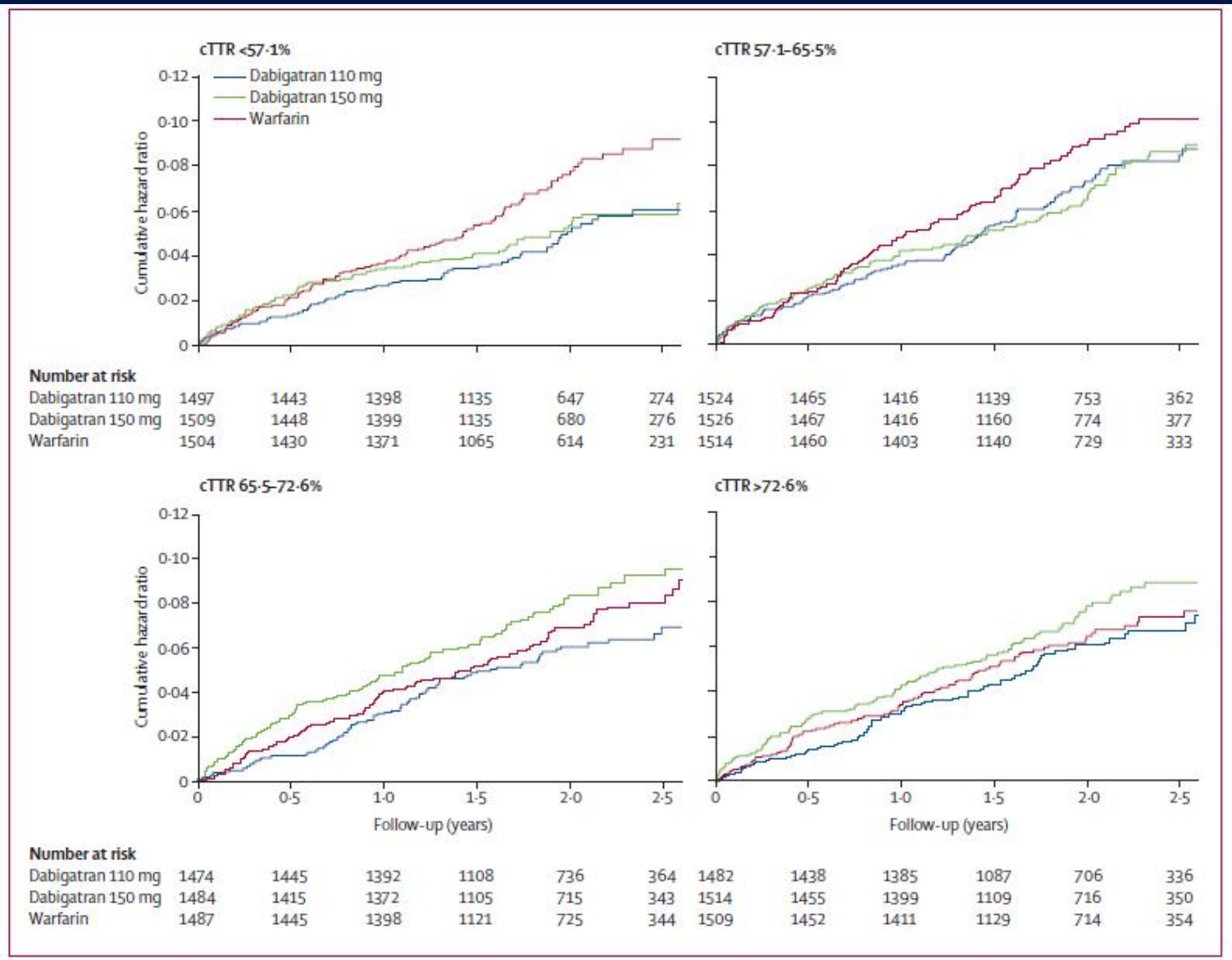


***Figure 3*: Time to major bleeding event in each quartile of centre's mean time in therapeutic range**
cTTR=centre's mean time in therapeutic range.

(From Wallentin et al., Lancet 2010)

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

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Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Primary End Point of Stroke or Systemic Embolism.*

Study Population	Rivaroxaban Event Rate *no./100 patient-yr*	Warfarin Event Rate *no./100 patient-yr*	Hazard Ratio (95% CI)†	P Value Noninferiority	P Value Superiority
Per-protocol, as-treated population‡	1.7	2.2	0.79 (0.66–0.96)	<0.001	
Safety, as-treated population	1.7	2.2	0.79 (0.65–0.95)		0.02
Intention-to-treat population§	2.1	2.4	0.88 (0.75–1.03)	<0.001	0.12
During treatment	1.7	2.2	0.79 (0.66–0.96)		0.02

Patel et al., NEJM 2011

Rocket

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Rates of Bleeding Events.*

Variable	Rivaroxaban (N=7111) Event Rate *no./100 patient-yr*	Warfarin (N=7125) Event Rate *no./100 patient-yr*	Hazard Ratio (95% CI)†	P Value
Principal safety end point: major and nonmajor clinically relevant bleeding§	14.9	14.5	1.03 (0.96–1.11)	0.44
Major bleeding				
Any	3.6	3.4	1.04 (0.90–1.20)	0.58
Decrease in hemoglobin ≥2 g/dl	2.8	2.3	1.22 (1.03–1.44)	0.02
Transfusion	1.6	1.3	1.25 (1.01–1.55)	0.04
Critical bleeding¶	0.8	1.2	0.69 (0.53–0.91)	0.007
Fatal bleeding	0.2	0.5	0.50 (0.31–0.79)	0.003
Intracranial hemorrhage	0.5	0.7	0.67 (0.47–0.93)	0.02
Nonmajor clinically relevant bleeding	11.8	11.4	1.04 (0.96–1.13)	0.35

Patel et al., NEJM 2011

Rocket

The NEW ENGLAND JOURNAL of MEDICINE

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

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Apixaban vs warfarin in AF: Aristotle Study
(Granger et al. NEJM 2011)

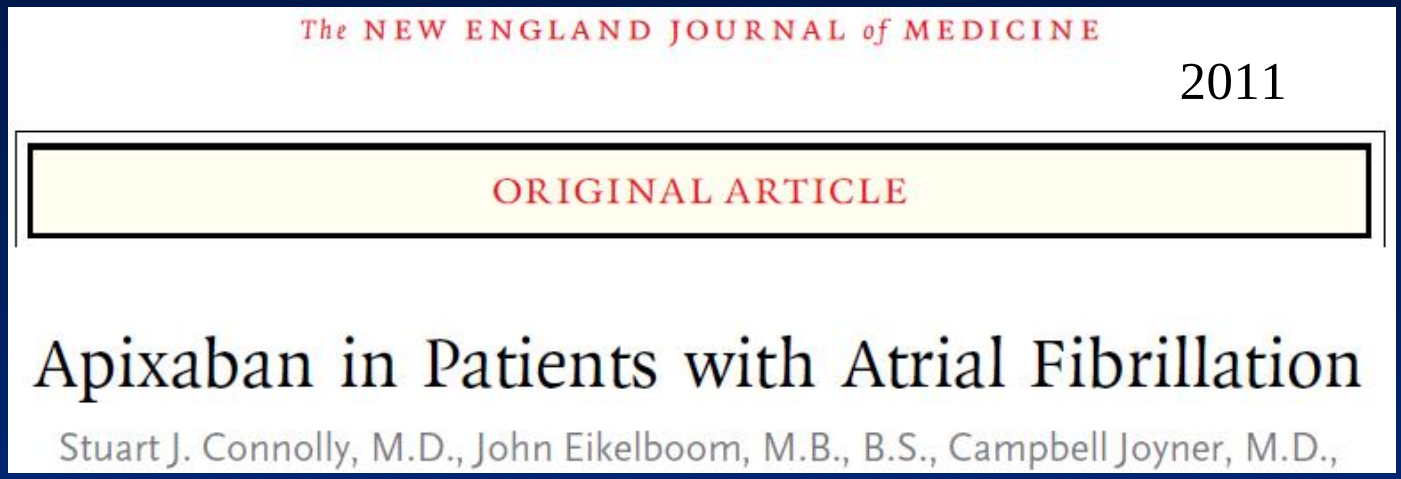
Table 2. Efficacy Outcomes.*

Outcome	Apixaban Group (N=9120) Event Rate %/yr	Warfarin Grou (N=9081) Event Rate %/yr	Hazard Ratio (95% CI)	P Value
Primary outcome: stroke or systemic embolism	1.27	1.60	0.79 (0.66–0.95)	0.01
Stroke	1.19	1.51	0.79 (0.65–0.95)	0.01
Ischemic or uncertain type of stroke	0.97	1.05	0.92 (0.74–1.13)	0.42
Hemorrhagic stroke	0.24	0.47	0.51 (0.35–0.75)	<0.001
Systemic embolism	0.09	0.10	0.87 (0.44–1.75)	0.70
Key secondary efficacy outcome: death from any cause	3.52	3.94	0.89 (0.80–0.998)	0.047
Other secondary outcomes				
Stroke, systemic embolism, or death from any cause	4.49	5.04	0.89 (0.81–0.98)	0.02
Myocardial infarction	0.53	0.61	0.88 (0.66–1.17)	0.37
Stroke, systemic embolism, myocardial infarction, or death from any cause	4.85	5.49	0.88 (0.80–0.97)	0.01
Pulmonary embolism or deep-vein thrombosis	0.04	0.05	0.78 (0.29–2.10)	0.63

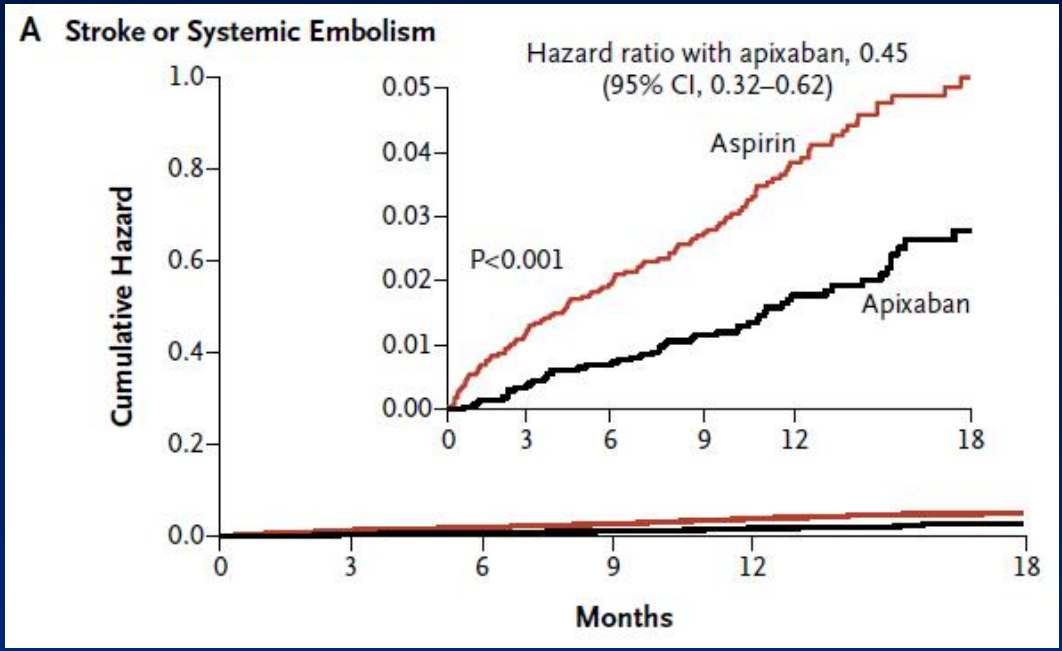
Apixaban vs warfarin in AF: Aristotle Study (Granger et al. NEJM 2011)

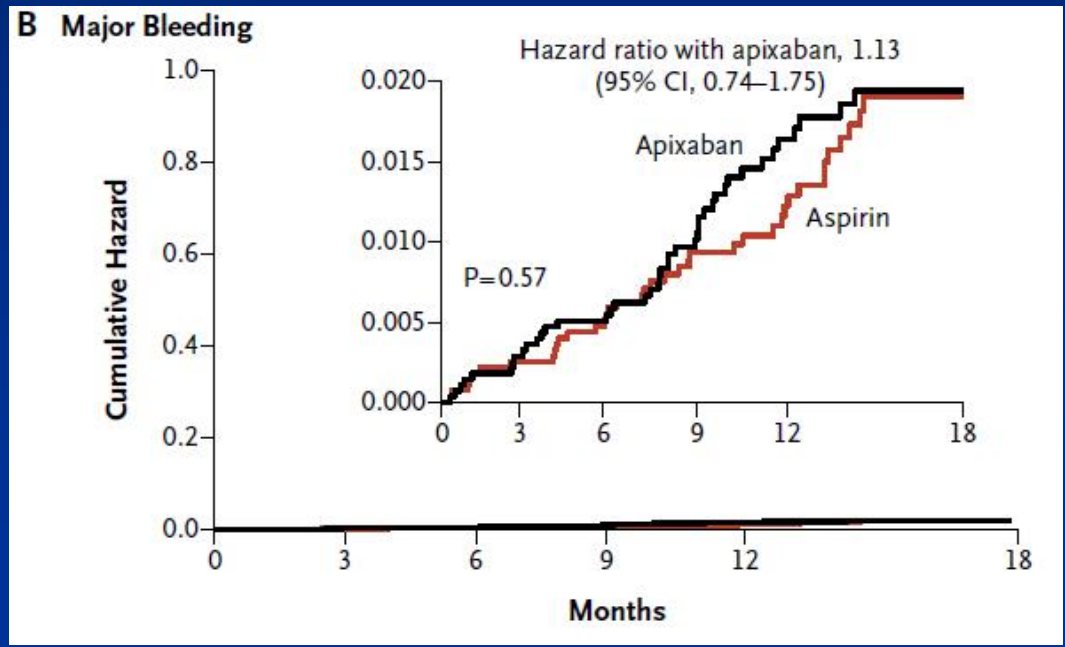
Bleeding Outcomes and Net Clinical Outcomes.*

Outcome	Apixaban Group (N=9088) Event Rate %/yr	Warfarin Group (N=9052) Event Rate %/yr	Hazard Ratio (95% CI)	P Value
Primary safety outcome: ISTH major bleeding†	2.13	3.09	0.69 (0.60–0.80)	<0.001
Intracranial	0.33	0.80	0.42 (0.30–0.58)	<0.001
Other location	1.79	2.27	0.79 (0.68–0.93)	0.004
Gastrointestinal	0.76	0.86	0.89 (0.70–1.15)	0.37



Double-blind study; 5599 patients with AF, for whom VKA therapy was unsuitable, were randomized to receive apixaban (5 mg twice daily) or aspirin (81 to 324 mg per day)


A Stroke or Systemic Embolism
Hazard ratio with apixaban, 0.45
(95% CI, 0.32–0.62)
Aspirin
Apixaban
P<0.001
Cumulative Hazard
Months


B Major Bleeding
Hazard ratio with apixaban, 1.13
(95% CI, 0.74–1.75)
Apixaban
Aspirin
P=0.57
Cumulative Hazard
Months

Obiettivi rilevanti per la sanità pubblica e per i singoli pazienti
(parere personale)

- Stessa efficacia e non più emorragie degli AVK (ma meno emorragie cerebrali)
- Rendere possibile un'efficace anticoagulazione in chi finora non poteva per problemi con AVK (specie anziani)
- Semplificare la conduzione dell'anticoagulazione
- Migliorare la qualità di vita dei pazienti
- Ridurre il carico di lavoro del sistema sanitario

NOA: important characteristics

- Selective, reversible, direct IIa or Xa inhibition
- Fast onset (~ 2 h) and offset of action
- Relatively short half-life (5-17 h)
- Predictable and linear dose-response
- No need for routine laboratory monitoring
- No need for skilful dosing
- Much less drug and food interactions
- Less ICH
- Renal clearance (different among NOAs)

NOAs: caveats

- No antidotes
- How to monitor their effects?
  (necessary in case of bleeding, emergency surgery)
- Possible other negative effects
- How to monitor compliance?
- Short half life, dis/advantage?
- “Extreme” types of pts not included in phase III studies
- Problems in pts with renal insufficiency

What is essential for NOA vs VKA treatment

- Appropriate indications (yes)
- Appropriate doses (yes)
- Skilful laboratory control (no)
- Skilful clinical monitoring and assistance (no)
- Education and compliance of patients (yes)
- Adequate services are crucial
  (much less and probably with different targets)

Patient education: NOA vs VKAs

- Effect of anticoagulant drugs (yes)
- Measure of anticoagulation level (no)
- Regular drug assumption (yes) and monitoring (no)
- Diet (no) and drug interactions (very few, the prescriber should be aware)
- Instruction about bleeding (yes), pregnancy (yes), etc

START–Register

SURVEY ON ANTICOAGULATED PATIENTS – REGISTER

Registro computerizzato per la raccolta dei dati di pazienti trattati cronicamente con anticoagulanti


START Register
Pagina
Strumenti
START Register
Registro pazienti in terapia anticoagulante cronica
Home
Utenti registrati
Chi siamo
Contatti