Perspectivas de futuro

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Perspectivas de futuro

- **Criterios de tratamiento antitrombótico**
- **Nuevos fármacos anticoagulantes**

Table 9. Stroke Risk in Patients With Nonvalvular AF Not Treated With Anticoagulation According to the $CHADS_2$ Index

$CHADS_2$ Risk Criteria	Score
Prior stroke or TIA	2
Age >75 years	1
Hypertension	1
Diabetes mellitus	1
Heart failure	1

TABLE 13. Antithrombotic Therapy for Patients With Atrial Fibrillation

Risk Category	Recommended Therapy
No risk factors	Aspirin, 81 to 325 mg daily
One moderate-risk factor	Aspirin, 81 to 325 mg daily, or warfarin (INR 2.0 to 3.0, target 2.5)
Any high-risk factor or more than 1 moderate-risk factor	Warfarin (INR 2.0 to 3.0, target 2.5)*

	Score
CHA_2DS_2-VASc[10]	
Congestive heart failure	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke, transient ischaemic attack, or thromboembolism	2
Vascular disease (previous myocardial infarction, peripheral artery disease, or aortic plaque)	1
Age 65–74 years	1
Sex category (ie, female sex)	1
Maximum score	9
HAS-BLED[9]	
Hypertension (systolic blood pressure >160 mm Hg)	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	1
Bleeding tendency or predisposition	1
Labile international normalised ratios (if on warfarin)	1
Elderly (eg, age >65 years)	1
Drugs or alcohol (1 point each)	1 or 2
Maximum score	9

CHA_2DS_2-VASc score=0: recommend no antithrombotic therapy. CHA_2DS_2-VASc score=1: recommend antithrombotic therapy with oral anticoagulation or antiplatelet therapy, but preferably oral anticoagulation. CHA_2DS_2-VASc score ≥2 recommend oral anticoagulation.[2,10] HAS-BLED score of ≥3 suggests that caution is warranted when prescribing oral anticoagulation and regular review is recommended.[2,9]

Table: **Assessment of stroke and bleeding risk in patients with atrial fibrillation**

Table 9 Approach to thromboprophylaxis in patients with AF

Risk category	CHA_2DS_2-VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥2 'clinically relevant non-major' risk factors	≥ 2	OAC[a]
One 'clinically relevant non-major' risk factor	1	Either OAC[a] or aspirin 75–325 mg daily. Preferred: OAC rather than aspirin.
No risk factors	0	Either aspirin 75–325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin.

Nuevos anticoagulantes en fibrilación auricular

	RE-LY	ROCKET	ARISTOTLE	AVERROES
Drug	Dabigatran	Rivaroxaban	Apixaban	Apixaban
Blinding	Single	Double	Double	Double
Dosing regimen	bid	od	bid	bid
Doses	110 or 150 mg	20 mg or 15mg (moderate renal impairment)	5 mg	5 mg 2.5 mg
Control	Open-label warfarin	Double-blind warfarin	Double-blind warfarin	Double-blind ASA
INR	Range 2–3	Range 2–3	Range 2–3	–
No. of patients	15,000	14,000	15,000	5600
Duration	25 months	33 months	–	–
Outcome	Efficacy and safety	Efficacy and safety	Efficacy	Efficacy and safety
Start date	Nov-05	Dec-06	Dec-06	Aug-07

Nuevos anticoagulantes en fibrilación auricular

RE-LY	ROCKET AF	ARISTOTLE	AVERROES
Dabigatran	Rivaroxaban	Apixaban	Apixaban
And one of the following: -Previous ischaemic stroke -TIA -Systemic embolism -LVD -Age ≥75 years -Age ≥ 65 with either diabetes mellitus, history of coronary artery disease or hypertension	And history of stroke, TIA, systemic embolism Or at least 2 of the following: - Heart failure - Hypertension - Age >75 years - Diabetes mellitus	And 1 or more of the following: - History of stroke, transient ischaemic attack - Embolism - Age ≥ 75 years - Symptomatic HF or LVD with LVEF≤ 40% - Diabetes or hypertension requiring pharmacological treatment	And at least 1 of the following: - Previous ischaemic stroke - Transient ischaemic attack or systematic embolism - Age ≥75 years - NYHA HF Class 2 or greater at time of enrollment - LVEF ≤ 35%, documented within 6 months of enrolment
$CHADS_2$ ≥1	$CHADS_2$ ≥2	$CHADS_2$ ≥1	$CHADS_2$ ≥1

RELY®
Study of stroke prevention in atrial fibrillation

Characteristics	Dabi 110 mg	Dabi 150 mg	Warfarin	P-value 110 vs. W	P-value 150 vs. W
Number of patients (n)	6015	6076	6022		
Net Clinical Benefit	**7.09**	**6.91**	**7.64**	**0.10**	**0.04**
- Stroke / SSE	1.53	1.11	1.69	<0.001 (NI) 0.34 (sup)	<0.001 (NI) <0.001 (sup)
- Death	3.75	3.64	4.13	0.13	0.051
- Major bleeding	2.71	3.11	3.36	0.003	0.31
- Pulmonary embolism	0.12	0.15	0.09	0.56	0.21
- Myocardial infarction	0.72	0.74	0.53	0.07	0.048

All data represents %/year

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PRADAXA safely and effectively. See full prescribing information for PRADAXA.

PRADAXA® (dabigatran etexilate mesylate) capsules for oral use
Initial U.S. Approval: 2010

----------INDICATIONS AND USAGE----------

PRADAXA is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (1)

----------DOSAGE AND ADMINISTRATION----------

- For patients with CrCl >30 mL/min: 150 mg orally, twice daily (2.1)
- For patients with CrCl 15-30 mL/min: 75 mg orally, twice daily (2.1)
- Instruct patients not to chew, break, or open capsules (2.1)
- Review recommendations for converting to or from other oral or parenteral anticoagulants (2.2, 2.3)
- Temporarily discontinue PRADAXA before invasive or surgical procedures when possible, then restart promptly (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 75 mg and 150 mg (3)

ROCKET AF: Rivaroxabán vs. warfarina

Ensayo aleatorizado Fase III, a doble ciego, con doble enmascaramiento

FA no valvular *más* historia de ictus, AIT o ES

***o* ≥2* de los siguientes factores de riesgo:**
ICC
HTA
Edad ≥ 75 años
Diabetes

N=14,269

R

Mes 0

Rivaroxabán 20 mg od

CrCl 30–49 ml/min:
Rivaroxabán 15 mg od

INR objetivo de warfarina 2,5
(rango 2–3)

~Mes 12–32#

Fin del estudio

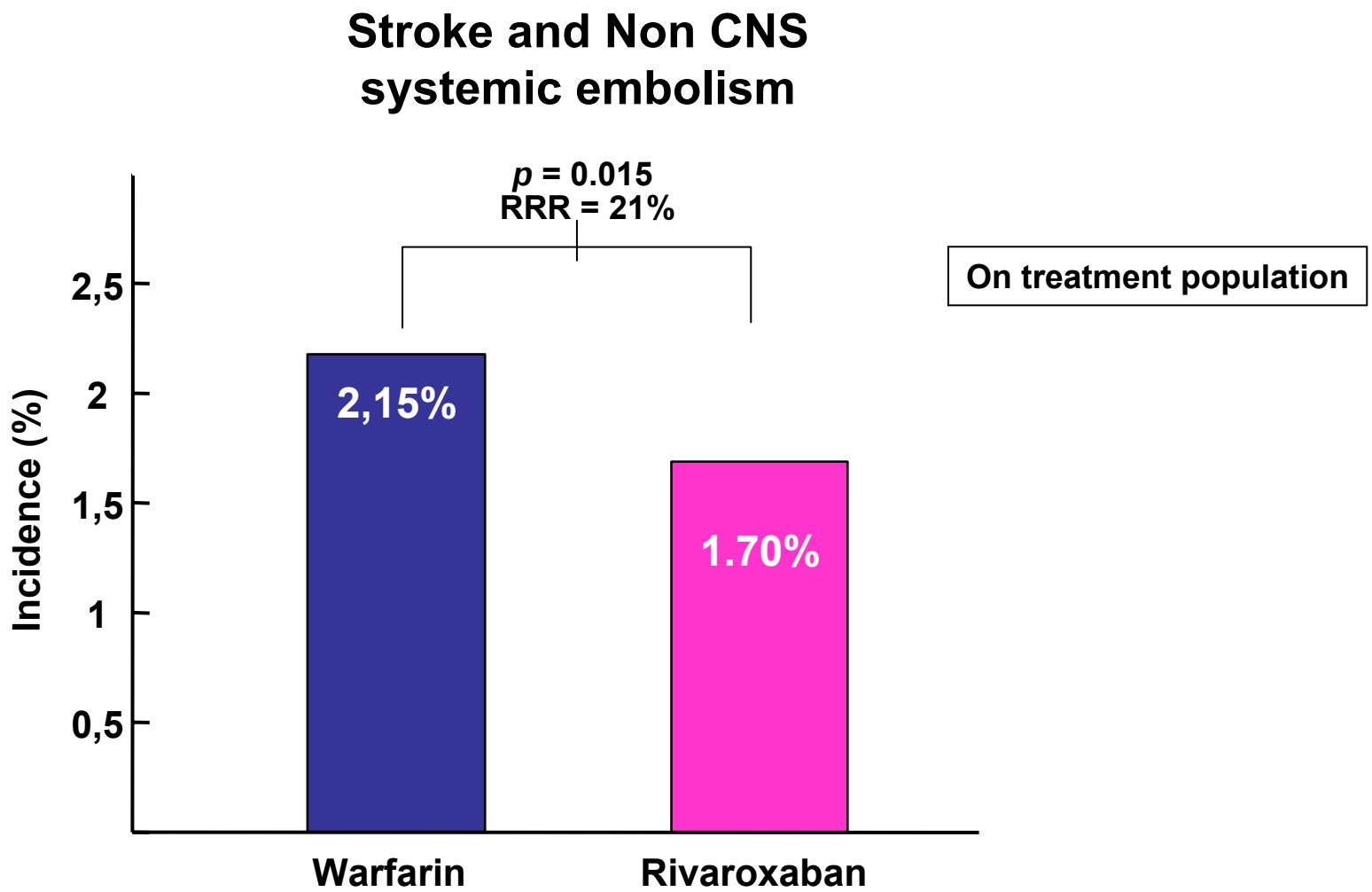
Mes 13–33

Seguimiento

*Tras un 10% de inclusión con 2 factores de riesgo, los siguientes pacientes debían presentar ≥3 factores de riesgo o ictus/AIT previos o ES fuera del SNC
#Al tratarse de un estudio en función de los acontecimientos, la duración del tratamiento varía para cada paciente. Se espera que el ensayo se prolongue alrededor de 42 meses

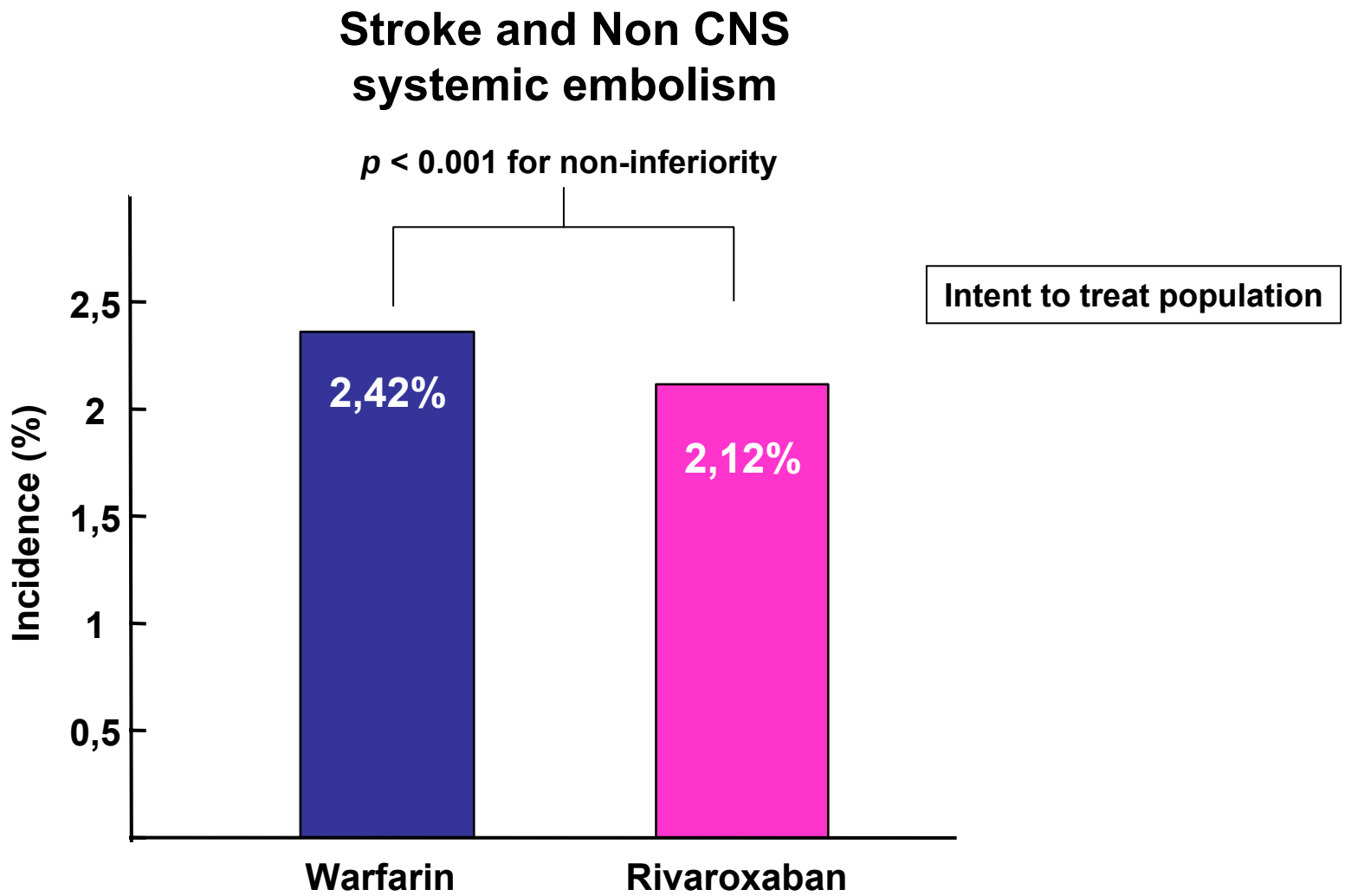
Patel *et al*, 2010

ROCKET AF: Primary Efficacy Endpoint



Event rates are per 100 patient years
Late Breaking Scientific Session, AHA, Chicago 2010

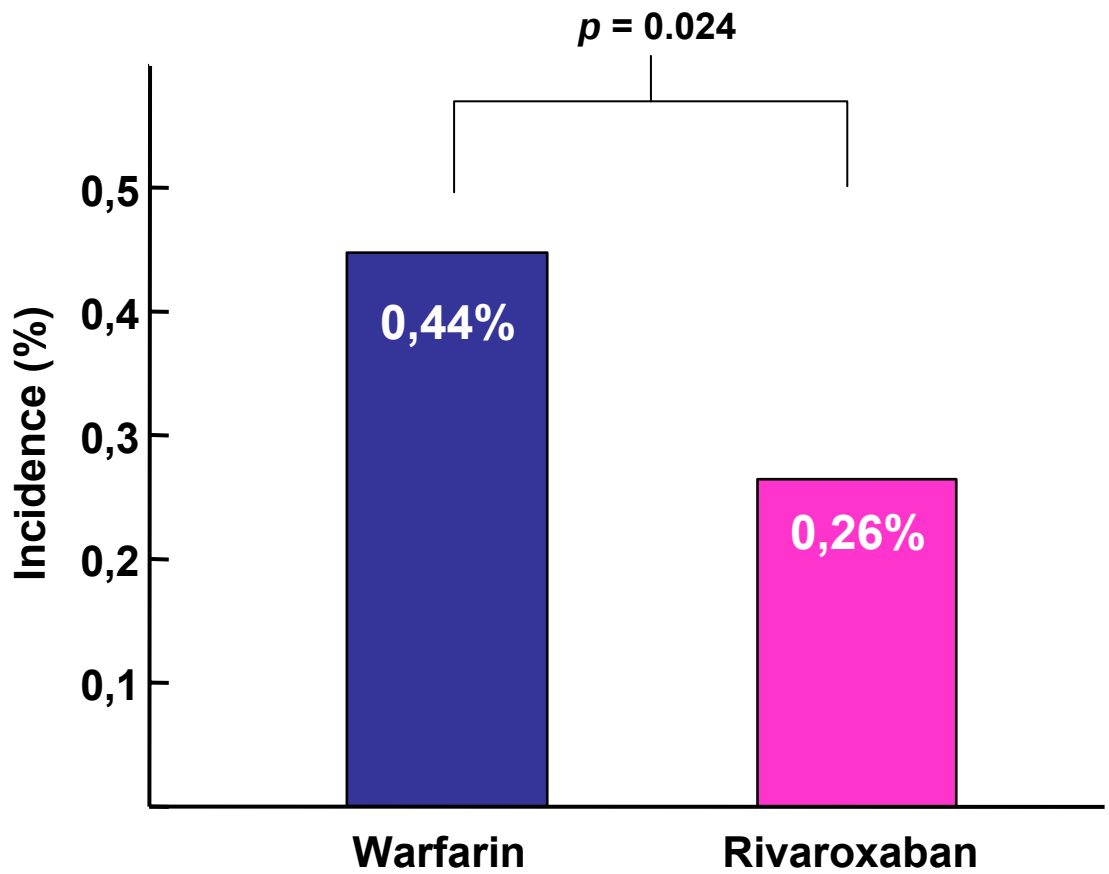
ROCKET AF: Primary Efficacy Endpoint



Event rates are per 100 patient years
Late Breaking Scientific Session, AHA, Chicago 2010

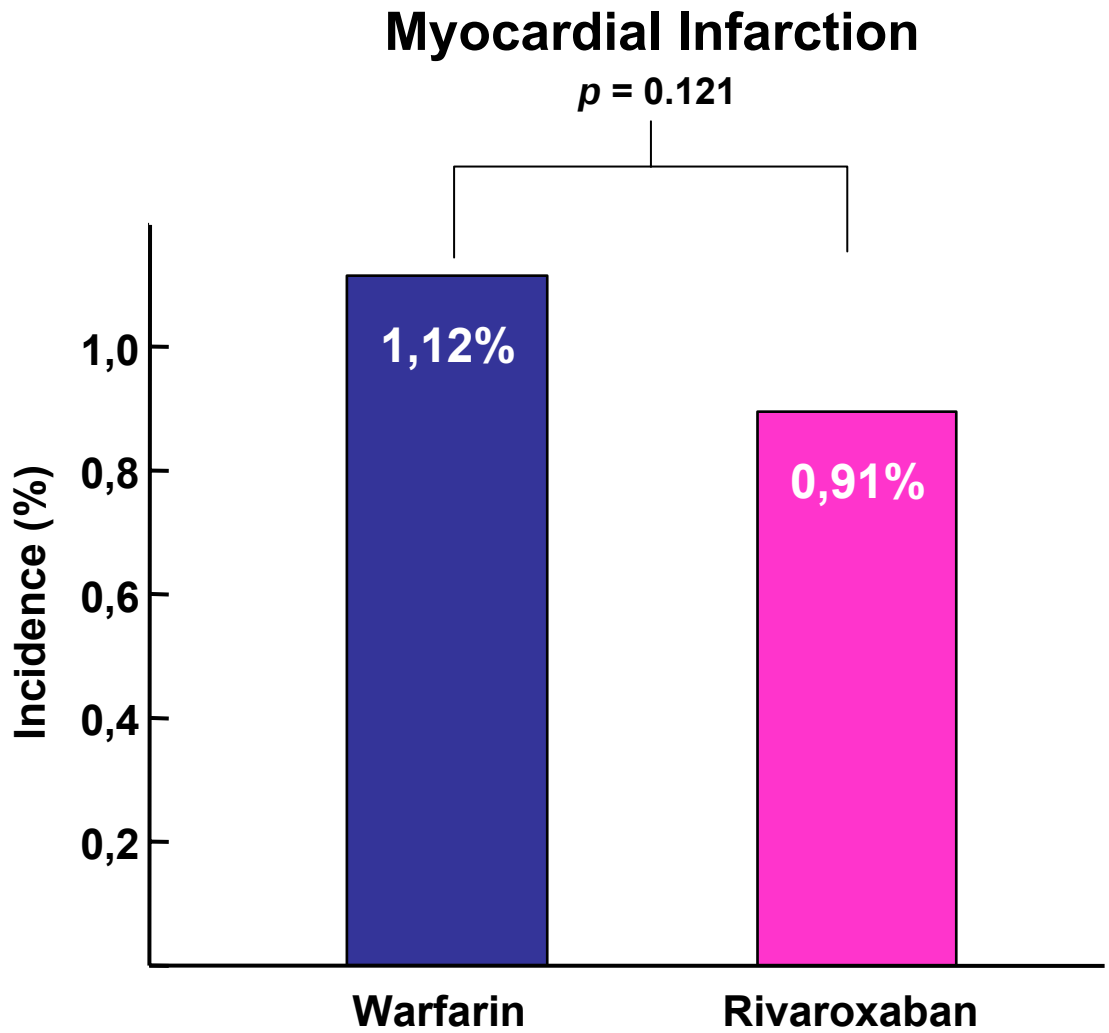
ROCKET AF: Efficacy Outcomes

Hemorragic Stroke



Event rates are per 100 patient years
Late Breaking Scientific Session, AHA, Chicago 2010

ROCKET AF: Efficacy Outcomes



Event rates are per 100 patient years
Late Breaking Scientific Session, AHA, Chicago 2010

Limitaciones al uso de los nuevos anticoagulantes

- Infarto de miocardio
- Coste económico
- Adherencia

Newly Identified Events in the RE-LY Trial

TO THE EDITOR: We wish to update our article about the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial (Sept. 17, 2009, issue).[1] After the database was locked on August 15, 2009, we identified several additional primary efficacy and safety outcome events during routine clinical site closure visits. These events included two systemic embolic events and nine major hemorrhages. Subsequently, after discussions with the Food and Drug Administration, the primary and secondary efficacy and safety data were checked for consistency, and the study database was reevaluated for possible underreporting of events. To achieve this, all free text, outcomes, and adverse events in the database were searched with the use of multiple algorithms to identify any symptom that might suggest the possibility of any primary or secondary event or bleeding. This included an examination of all decreases in the hemoglobin level by more than 2 g per deciliter between visits, other markers of potential bleeding, new pathologic Q waves on routine electrocardiography (ECG), and any report of weakness or other symptoms that might be potentially related to a stroke. This process resulted in the identification of 81 new events in 80 patients. These included 1 stroke, 1 systemic embolic event, 4 clinical myocardial infarctions, 1 pulmonary embolism, 5 transient ischemic attacks, and 69 major hemorrhages.

Although silent myocardial infarction, defined as the new appearance of pathologic Q waves on ECG, was part of the RE-LY definition of myocardial infarction, no cases of silent myocardial infarction were reported by investigators during the course of the study. However, review of the routine ECG reports revealed 28 cases fulfilling the criteria for silent myocardial infarction.

All these newly identified events were adjudicated in a blinded fashion and in accordance with the study protocol. Two rounds of data entry were performed for all data on the international normalized ratio (INR), for purposes of validation. This resulted in a change in the mean percentage

Table 1. Published and Revised Data for Primary Efficacy and Safety Outcomes and Myocardial Infarction, According to Treatment Group.*

Event	Dabigatran, 110 mg (N=6015)		Dabigatran, 150 mg (N=6076)		Warfarin (N=6022)		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	*%/yr*	*no. of patients*	*%/yr*	*no. of patients*	*%/yr*				
Stroke or systemic embolism										
Published	182	1.53	134	1.11	199	1.69	0.91 (0.74–1.11)	0.34	0.66 (0.53–0.82)	<0.001
Revised	183	1.54	134	1.11	202	1.71	0.90 (0.74–1.10)	0.30	0.65 (0.52–0.81)	<0.001
Major bleeding										
Published	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31
Revised	342	2.87	399	3.32	421	3.57	0.80 (0.70–0.93)	0.003	0.93 (0.81–1.07)	0.32
Myocardial infarction										
Published	86	0.72	89	0.74	63	0.53	1.35 (0.98–1.87)	0.07	1.38 (1.00–1.91)	0.048
Revised	98	0.82	97	0.81	75	0.64	1.29 (0.96–1.75)	0.09	1.27 (0.94–1.71)	0.12

* Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. P values are for superiority. CI denotes confidence interval.

Limitaciones al uso de los nuevos anticoagulantes

- Infarto de miocardio
- **Coste económico**
- Adherencia

TO THE EDITOR: The editorial by Gage that accompanies the report by Connolly et al. highlights the difficulties associated with the use of warfarin therapy in the treatment of patients with atrial fibrillation and considers the use of the new thrombin inhibitor dabigatran.[1] But the author failed to highlight the significant difference in price between warfarin and dabigatran. In Ireland, a month's supply of warfarin in a dose of 5 mg per day costs approximately €2.13 (about $3.55), whereas a month's supply of dabigatran (Pradaxa, Boehringer Ingelheim) in a dose of 110 mg twice daily costs €143.70 (about $239.55). Warfarin has regularly been in the top 15 most frequently prescribed medicines, and more than 32,400 patients in Ireland take it. If just 50% of these patients were to switch to dabigatran, the drug acquisition cost would be roughly €27 million (about $45 million) per year, or about 10% of the total cost of cardiovascular medicines. Clearly, there will be cost offsets, since anticoagulation monitoring will not be necessary and the rate of clinical events will be reduced. Many countries will conduct a formal health technology assessment before providing reimbursement for the drug in the treatment of atrial fibrillation. The editorial suggests that we can rely on RE-LY, but many decision makers will ask, can we afford RE-LY?

Michael Barry, M.B., Ph.D.
Trinity College Dublin

THE EDITORIALIST REPLIES: Thank you for providing the cost of dabigatran in Ireland and for raising the issue of affordability. Dabigatran is not available in the United States, but a 1-month supply of dabigatran can be purchased through Canadian pharmacies for $339 (U.S. dollars) — about 10 times the monthly cost of warfarin therapy (including the cost of monitoring). For a typical participant in the RE-LY trial, the number needed to treat to prevent 1 (nonhemorrhagic) stroke with dabigatran (150 mg twice daily) is 357. Using these estimates, the cost per stroke averted with dabigatran (rather than warfarin) averages approximately $1.3 million (U.S. dollars). For patients with twice the average risk of stroke (e.g., CHADS2 score[1] of 3 to 4), the number needed to treat and the cost per stroke averted would be halved.

However, these calculations do not take into account the costs and morbidity associated with stroke. The cost of care for a stroke patient averages $28,500 in the initial 12 months,[2,3] and the lifetime cost of stroke is several times greater.[3] Thus, although dabigatran is unlikely to be cost-saving, it might be cost-effective, at least in carefully selected patients.

Brian F. Gage, M.D.
Washington University in St. Louis
St. Louis, MO

Limitaciones al uso de los nuevos anticoagulantes

- Infarto de miocardio
- Coste económico
- **Adherencia**

CONGRESO DE CARDIOLOGÍA EN BCN

Un fármaco abre grandes esperanzas en la mejora de la prevención del ictus

Los cardiólogos consideran que el paso del sintrom al dabigatrán puede ser revolucionario | El fármaco está en el mercado pero con otro uso, por lo que se necesita una nueva autorización

★★★★★ 7 votos | 14 comentarios

Barcelona. Redacción | 31/08/2009 | Actualizada a las 03:18h | Ciudadanos

Revolución en la prevención del **infarto cerebral**, el ictus, para los pacientes con fibrilación articular. Los entre **200.000 y 300.000 españoles** con esta dolencia podrán prescindir de los análisis cada cuatro semanas a los que les obliga el consumo de sintrom, si este medicamento es sustituido por el dabigatrán. Un estudio realizado entre **18.000 pacientes** en 44 países muestra una notable reducción de las complicaciones y un incremento de la eficacia del 30%, según informó Josep Brugada, jefe del servicio de Cardiología del **hospital Clínic de Barcelona** y coordinador de la investigación en España.

ATENCIÓ PRIMARIA

HOSPITAL TRIAS I PUJOL

Llista de VISITES (de més recent a més antiga)

Data	test / result. / fàrmac. / dosis / partic. / accidents					
11/11/10	INR	1.70	SI	27.50	27.50	
14/10/10	INR	2.50	SI	27.50	27.50	
16/09/10	INR	2.70	SI	27.50	27.50	
26/08/10	INR	2.40	SI	27.50	27.50	
12/08/10	INR	1.80	SI	27.50	27.50	
22/07/10	INR	2.10	SI	27.00	27.00	
09/07/10	INR	2.20	SI	27.00	27.00	
05/07/10	INR	1.60	SI	27.00	27.00	
01/07/10	INR	0.80	SI	27.00	27.00	
03/02/10	INR	2.70	SI	18.00	18.00	
29/01/10	INR	1.90	SI	18.00	18.00	
25/01/10	INR	2.10	SI	18.00	18.00	
21/01/10	INR	1.4 OT	SI	19.00	19.00	