ANTICOAGULACIÓN ORAL

NUEVOS ESCENARIOS EN EL MANEJO DE LA FIBRILACIÓN AURICULAR (Moderador Dr. Pepe Zamorano)

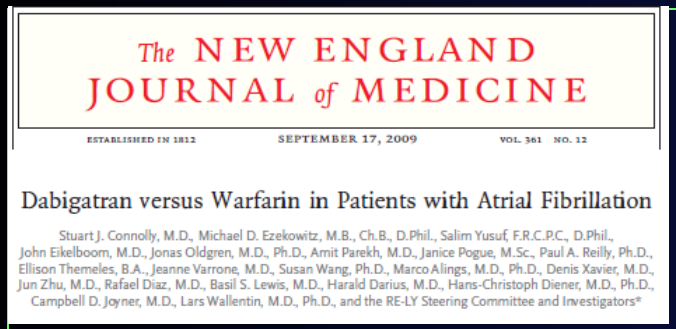
- Como es el paciente con fibrilación auricular en el siglo XXI (Dr. Antoni Martínez Rubio)
- Los nuevos anticoagulantes en la tromboprofilaxis de pacientes con fibrilación auricular sometidos a cardioversión, ablación y dispositivos (Dr. Xavier Viñolas)
- Nuevas evidencias en la prevención del ictus en pacientes con fibrilación auricular (Dr. Gonzalo Barón)

Nuevas evidencias en la prevención del ictus en pacientes con fibrilación auricular

Gonzalo Barón y Esquivias.
Servicio de Cardiología
Hospital Universitario Virgen del Rocío
Sevilla

20 de Octubre de 2011

NUEVAS EVIDENCIAS EN LA PREVENCIÓN DE ICTUS EN LA F.A.

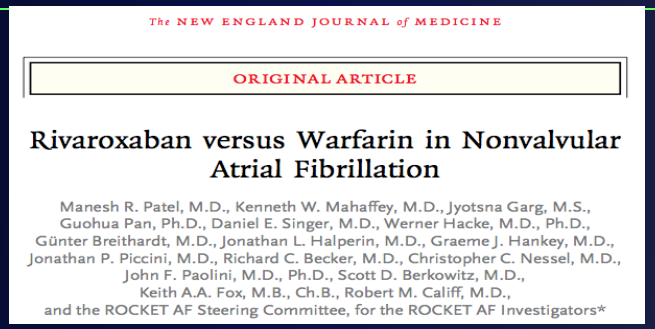


The NEW ENGLAND JOURNAL of MEDICINE

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*

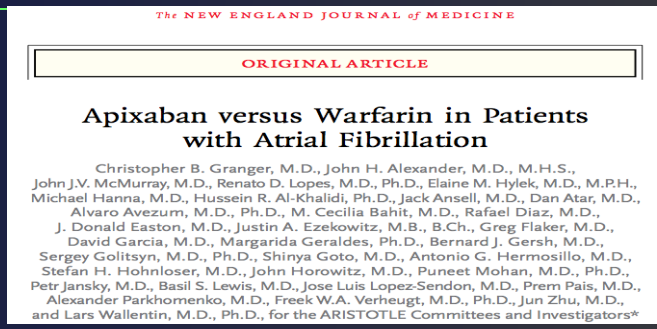


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Can We Rely on RE-LY?

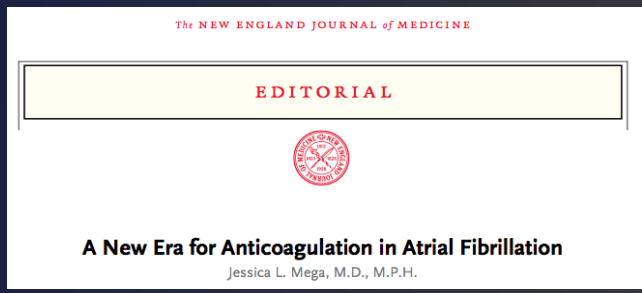
Brian F. Gage, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

New Options in Anticoagulation for Atrial Fibrillation

Gregory J. del Zoppo, M.D., and Misha Eliasziw, Ph.D.



The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

A New Era for Anticoagulation in Atrial Fibrillation

Jessica L. Mega, M.D., M.P.H.

N Engl J Med 2009; 361:1139-51

N Engl J Med 2011; 365: 883-891

N Engl J Med 2011; 365: 981-992

ROCKET AF
Diseño del estudio

Rivaroxaban—Once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: Rationale and Design of the ROCKET AF study

The Executive Steering Committee, on behalf of the ROCKET AF Study Investigators[a] *Durham, NC*

Submitted July 1, 2009;

Patel et al,Am Heart J, 2010; 159(3): 340-7

ROCKET AF

Diseño del estudio

Factores de Riesgo
- ICC
- Hipertension
- Edad ≥ 75
- Diabetes

Al menos 2 ó 3 requeridos*

OR
- AVC, AIT o Embolia Sistemica

Fibrilación Auricular

Rivaroxaban

20 mg daily
15 mg for Cr Cl 30-49 ml/min

Randomizado
Doble Ciego/
Doble Enmascaramiento
(n ~ 14,000)

Warfarina

INR target - 2.5
(2.0-3.0 inclusive)

Monitorización mensual
Adherencia a los estándares de cuidados recomendados en las guías

Objetivo Primario: AVC o Embolismo sistémico no-SNC

* Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%

Patel et al,Am Heart J, 2010; 159(3): 340-7

ROCKET AF:
Metodología estadística

Statistical analysis plan

- Ensayo comparado con placebo: No ético
- Se comparará con Warfarina a una INR de 2 a 3
- Potencia estadística adecuada para comprobar no-inferioridad
- Si se satisface la no inferioridad, se evaluará luego la posibilidad de superioridad
- El análisis de no-inferioridad se realizará en la población de análisis por protocolo
- Si se cumple el criterio de no inferioridad se analizará superioridad en la población de seguridad
- Si se cumple la no inferioridad se llevará a cabo pruebas cerradas para otras variables
- Un estadístico independiente llevará a cabo todos los análisis

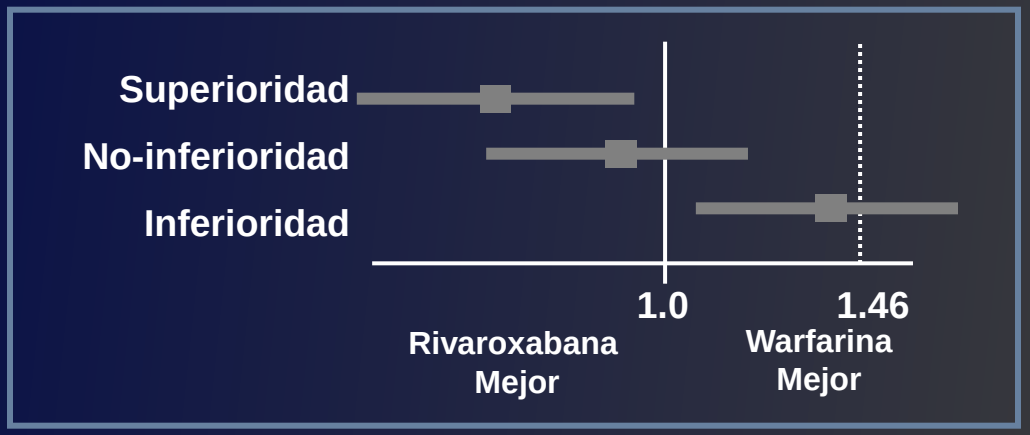
Noninferiority design consideration

- No-inferioridad implica que la eficacia de Rivaroxaban es similar o superior a warfarina (prueba unilateral en vez de bilateral)
- El margen que corresponde a la preservación del 50% del efecto de warfarina es 1,82 (IC del 95% 1,46-2,29)
- Se optó por un límite más conservador, se eligió 1,46:→ 363 episodios→405 episodios para tener una evaluación robusta.
- Estimándose una tasa de abandono del 14%:→ 14.000 pacientes. 40 meses

Patel et al,Am Heart J, 2010; 159(3): 340-7

ROCKET AF:
Metodología estadística

- Tamaño de la muestra
  - Tasa de eventos (Warfarina) ~2.3
  - Error Tipo 1 0.05 (2-sided)
  - 405 eventos; >95% potencia
  - ~14,000 pacientes



- Evaluación de la eficacia primaria:

  Stroke o embolismo no-SNC

  - Non-Inferiority: Protocol Compliant on treatment
  - Superiority: On Treatment and then by Intention-to-Treat

- Evaluación de seguridad primario: Sangrado mayor o no-mayor clínicamente relevante

Patel et al,Am Heart J, 2010; 159(3): 340-7

ROCKET AF
Arbol de Pacientes & Población

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

-20 -8 -103 79 -91

ROCKET AF

RESULTADOS

1) DATOS DE RECLUTAMIENTO Y SEGUIMIENTO
2) CARÁCTERÍSTICAS BASALES Y TRATAMIENTOS
3) OBJETIVO PRIMARIO
4) OBJETIVOS DE SANGRADO
5) OBJETIVOS DE EFICACIA SECUNDARIOS
6) ANÁLISIS DE EFICACIA EN SUBGRUPOS PREDEFINIDOS

N Engl J Med 2011; 365:883-91

ROCKET AF

DATOS DE RECLUTAMIENTO Y SEGUIMIENTO

	Rivaroxaban	Warfarina
Randomizados, n	7131	7133
Perdidos en el seguimiento, n	18	18
Retirada prematura, n (%)	1693 (23.7%)	1589 (22.2%)
Retirada de Consentimiento, n	626	620
Exposición Mediana días (25^{th}, 75^{th})	589 (396, 805)	593 (404, 810)
Seguimiento Mediana días (25^{th}, 75^{th})	706 (522, 884)	708 (518, 886)

N Engl J Med 2011; 365:883-91

ROCKET AF

CARÁCTERÍSTICAS BASALES Y TRATAMIENTOS

	Rivaroxaban (N=7081)	Warfarina (N=7090)
Edad (años)	73 (65, 78)	73 (65, 78)
Mujeres (%)	39,7	39,7
Raza (%)		
Blanco	83	83
Negros	1	1
Asiáticos	13	13
Region (%)		
Norte america	19	19
Latin America	13	13
Asia-Pacifico	15	15
Europa Central	38	38
Europa del Oeste	15	15
Aclaramiento Creatinina (ml/min) (%)		
30 - <50	21	21
50 - ≤80	47	48
> 80	32	31

Values are median (IQR)
Based on Intention-to-Treat Population

N Engl J Med 2011; 365:883-91

ROCKET AF

CARÁCTERÍSTICAS BASALES Y TRATAMIENTOS

	Rivaroxaban(N=7081)	Warfarin (N=7090)
$CHADS_2$ Score (media)	3.48	3.46
2 (%)	13	13
3 (%)	43	44
4 (%)	29	28
5 (%)	13	12
6 (%)	2	2
Uso previo de AVK (%)	62	63
ICC (%)	63	62
Hipertension (%)	90	91
Diabetes Mellitus (%)	40	39
AVC/AIT/Embolismo previo (%)	55	55
IAM previo (%)	17	18

Based on Intention-to-Treat Population

N Engl J Med 2011; 365:883-91

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CARÁCTERÍSTICAS BASALES Y TRATAMIENTOS

Warfarina

Among patients in the warfarin group, INR values were within the therapeutic range (2.0 to 3.0) a mean of 55% of the time (median, 58%; interquartile range, 43 to 71).

Based on Rosendaal method with all INR values included

Based on Safety Population

N Engl J Med 2011; 365:883-91

ROCKET AF
Objetivo 1ª(AVC y embolismo no-SNC)

Table 2. Primary End Point of Stroke or Systemic Embolism.*

Study Population	Rivaroxaban			Warfarin			Hazard Ratio (95% CI)†	P Value	
	No. of Patients	No. of Events	Event Rate *no./100 patient-yr*	No. of Patients	No. of Events	Event Rate *no./100 patient-yr*		Noninferiority	Superiority
Per-protocol, as-treated population‡	6958	188	1.7	7004	241	2.2	0.79 (0.66–0.96)	<0.001	
Safety, as-treated population	7061	189	1.7	7082	243	2.2	0.79 (0.65–0.95)		0.02
Intention-to-treat population§	7081	269	2.1	7090	306	2.4	0.88 (0.75–1.03)	<0.001	0.12
During treatment		188	1.7		240	2.2	0.79 (0.66–0.96)		0.02
After discontinuation		81	4.7		66	4.3	1.10 (0.79–1.52)		0.58

Event Rates are per 100 patient-years
Based on Safety on Treatment or Intention-to-Treat thru Site Notification populations

N Engl J Med 2011; 365:883-91

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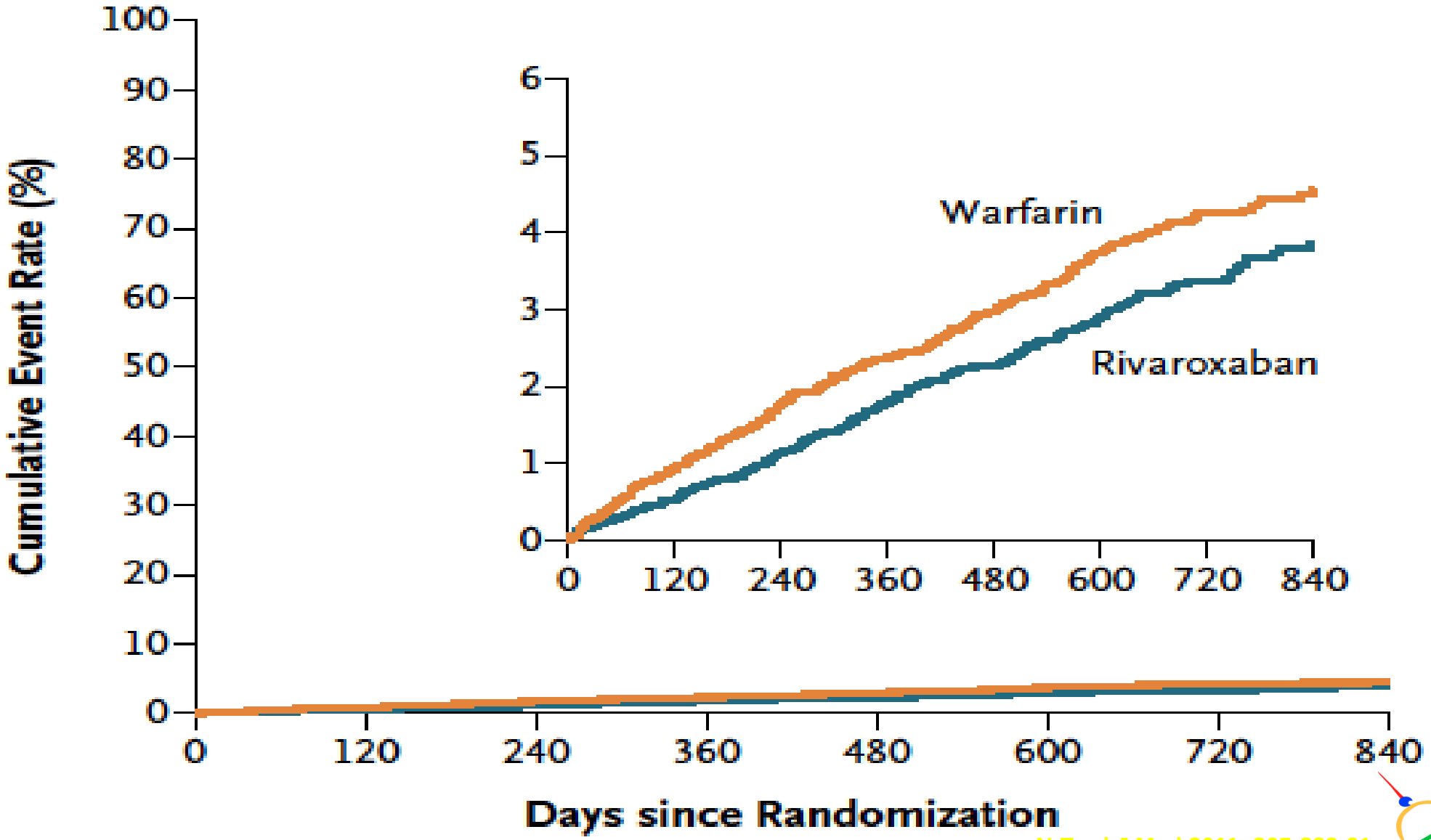
Objetivo 1ª(AVC y embolismo no-SNC)



Population

N Engl J Med 2011; 365:883-91

ROCKET AF
Objetivos de sangrado

Table 3. Rates of Bleeding Events.*

Variable	Rivaroxaban (N=7111)		Warfarin (N=7125)		Hazard Ratio (95% CI)†	P Value‡
	Events	Event Rate	Events	Event Rate		
	no. (%)	*no./100 patient-yr*	*no. (%)*	*no./100 patient-yr*		
Principal safety end point: major and nonmajor clinically relevant bleeding§	1475 (20.7)	14.9	1449 (20.3)	14.5	1.03 (0.96–1.11)	0.44
Major bleeding						
Any	395 (5.6)	3.6	386 (5.4)	3.4	1.04 (0.90–1.20)	0.58
Decrease in hemoglobin ≥2 g/dl	305 (4.3)	2.8	254 (3.6)	2.3	1.22 (1.03–1.44)	0.02
Transfusion	183 (2.6)	1.6	149 (2.1)	1.3	1.25 (1.01–1.55)	0.04
Critical bleeding¶	91 (1.3)	0.8	133 (1.9)	1.2	0.69 (0.53–0.91)	0.007
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5	0.50 (0.31–0.79)	0.003
Intracranial hemorrhage	55 (0.8)	0.5	84 (1.2)	0.7	0.67 (0.47–0.93)	0.02
Nonmajor clinically relevant bleeding	1185 (16.7)	11.8	1151 (16.2)	11.4	1.04 (0.96–1.13)	0.35

ROCKET AF
Objetivos de sangrado

	Rivaroxaban	Warfarina		
	Event Rate or N (Rate)	Event Rate or N (Rate)	HR (95% CI)	P-value
Major	3.60	3.45	1.04 (0.90, 1.20)	0.576
caida ≥2 g/dL Hbna	2.77	2.26	1.22 (1.03, 1.44)	**0.019**
Tranfusion (> 2 unidades)	1.65	1.32	1.25 (1.01, 1.55)	**0.044**
sangrado critico	0.82	1.18	0.69 (0.53, 0.91)	**0.007**
sangrado causa exitus	0.24	0.48	0.50 (0.31, 0.79)	**0.003**
Hemorragia intracraneal	55 (0.49)	84 (0.74)	0.67 (0.47, 0.94)	**0.019**
Intraparenquimatosa	37 (0.33)	56 (0.49)	0.67 (0.44, 1.02)	0.060
Intraventricular	2 (0.02)	4 (0.04)		
Subdural	14 (0.13)	27 (0.27)	0.53 (0.28, 1.00)	0.051
Subaracnoidea	4 (0.04)	1 (0.01)		

Event Rates are per 100 patient-years
Based on Safety on Treatment Population

N Engl J Med 2011; 365:883-91

ROCKET AF

Objetivo de eficacia secundarios

	Rivaroxaban	Warfarin		
	Event Rate	Event Rate	HR (95% CI)	P-value
Muerte Vascular, AVC, Embolismo	3.11	3.63	0.86 (0.74, 0.99)	**0.034**
Tipo de AVC				
Hemorrágico	0.26	0.44	0.59 (0.37, 0.93)	**0.024**
Isquémico	1.34	1.42	0.94 (0.75, 1.17)	0.581
No conocido	0.06	0.10	0.65 (0.25, 1.67)	0.366
Embolismo no-SNC	0.04	0.19	0.23 (0.09, 0.61)	**0.003**
Infarto de Miocardio	0.91	1.12	0.81 (0.63, 1.06)	0.121
Mortalidad total	1.87	2.21	0.85 (0.70, 1.02)	0.073
Vascular	1.53	1.71	0.89 (0.73, 1.10)	0.289
No-vascular	0.19	0.30	0.63 (0.36, 1.08)	0.094
Causa desconocida	0.15	0.20	0.75 (0.40, 1.41)	0.370

Event Rates are per 100 patient-years
Based on Safety on Treatment Population

N Engl J Med 2011; 365:883-91

ROCKET AF
Conclusiones

In conclusion, in this trial comparing a once-daily, fixed dose of rivaroxaban with adjusted-dose warfarin in patients with nonvalvular atrial fibrillation who were at moderate-to-high risk for stroke, rivaroxaban was noninferior to warfarin in the prevention of subsequent stroke or systemic embolism. There were no significant differences in rates of major and clinically relevant nonmajor bleeding between the two study groups, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.

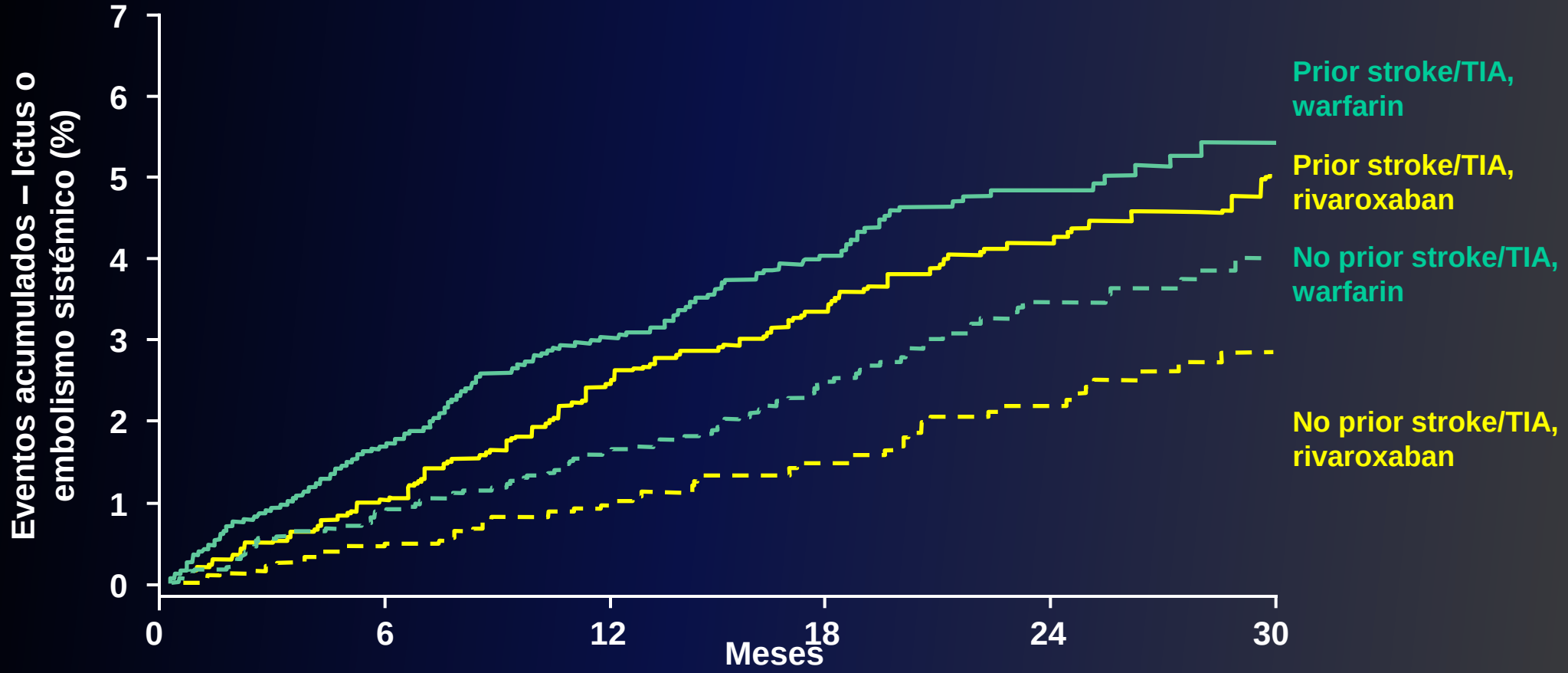
N Engl J Med 2011; 365:883-91

ROCKET AF
Cohorte de Prevención secundaria

- El porcentaje de pacientes incluidos en el estudio con historia previa de Ictus, AIT o embolismo sistémico fue del 55%
  - La mayoría tenía una historia de AIT (22%) e Ictus (~34%)
- El protocolo de estudio definía que los objetivos de seguridad y eficacia de ROCKET AF deberían ser analizados en la cohorte de prevencion secundaria (AIT/Ictus previo)
  - Rationale: Los pacientes con Ictus/AIT previo puden tener un riesgo específio para un elevado rango de recurrencia y mayor número de complicaciones hemorrágicas intracraneales
  - Objetivo: Comparar la eficacia y la seguridad de Ricaroxaban con warfarina en los pacientes con AIT/Ictus previo
- Cohortes:
  - Historia de AIT/Ictus (Cohorte Ictus) versus
  - No historia de AIT/Ictus (Cohorte non-Ictus)

ROCKET-AF-PREVENCIÓN 2ª

Resultados: Objetivo 1ª



- **El uso de Rivaroxaban es eficaz tanto en prevención 1ª como 2ª**

20th European Stroke Conference (Hamburg - May 2011)

ROCKET-AF
Subestudio en pacientes con Insuficiencia Renal

EUROPEAN SOCIETY OF CARDIOLOGY®

European Heart Journal
doi:10.1093/eurheartj/ehr342

FASTTRACK
ESC CLINICAL TRIAL UPDATE

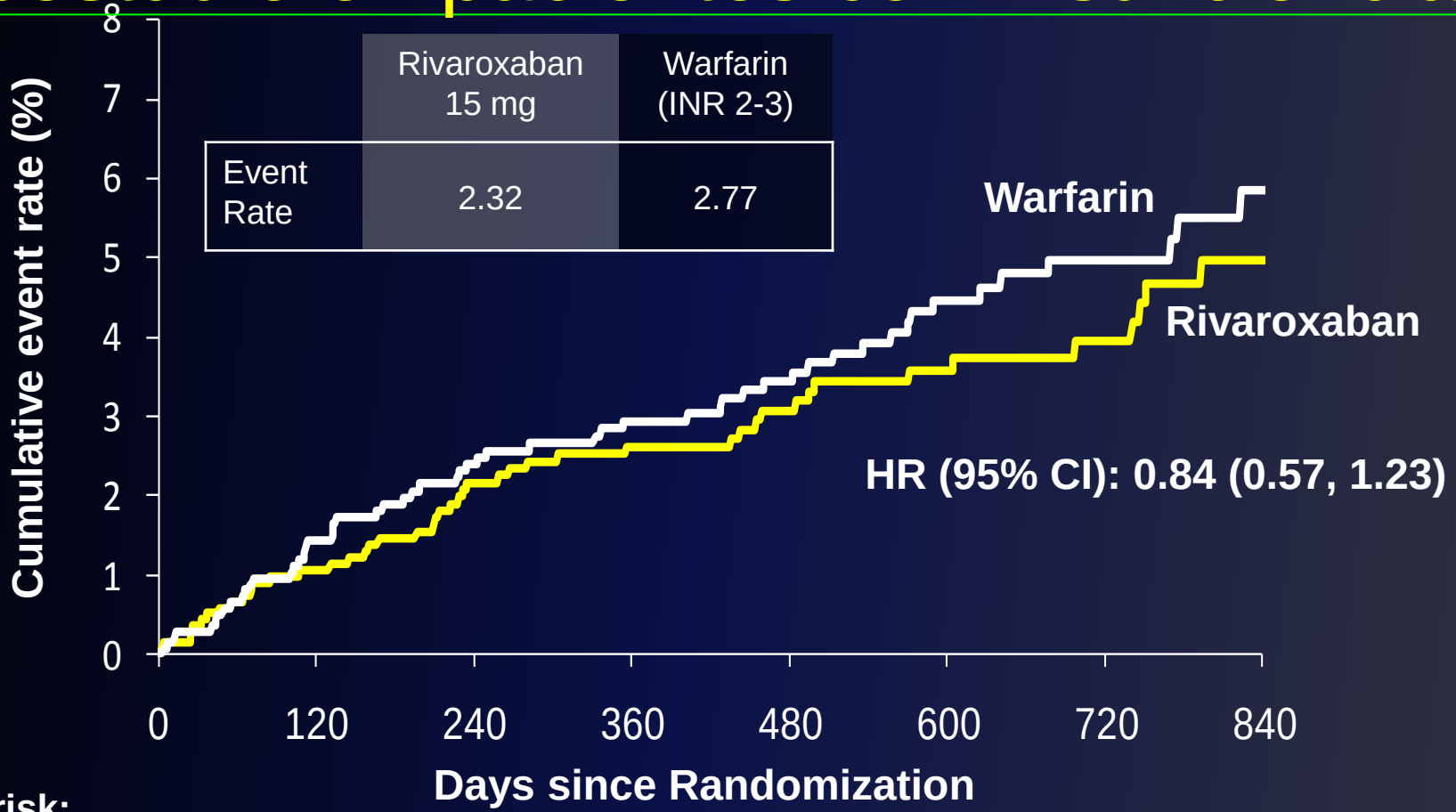
Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment

Keith A.A. Fox*, Jonathan P. Piccini, Daniel Wojdyla, Richard C. Becker, Jonathan L. Halperin, Christopher C. Nessel, John F. Paolini, Graeme J. Hankey, Kenneth W. Mahaffey, Manesh R. Patel, Daniel E. Singer, and Robert M. Califf

Fox KAA et al. Eur Heart J, 2011, 32(19): 2387-94

ROCKET-AF

Subestudio en pacientes con Insuficiencia Renal



No. at risk:

Rivaroxaban	**1434**	**1226**	**1103**	**1027**	**806**	**621**	**442**	**275**
Warfarin	**1439**	**1261**	**1140**	**1052**	**832**	**656**	**455**	**272**

Event rates are % per year
Based on Protocol Compliant on Treatment Population

Fox KAA et al. Eur Heart J, 2011, 32(19): 2387-94

RIVAROXABAN
Perspectiva editorial

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Evaluating Rivaroxaban for Nonvalvular Atrial Fibrillation — Regulatory Considerations

Thomas R. Fleming, Ph.D., and Scott S. Emerson, M.D., Ph.D.

NEJM, 2011, October 5, 2011 (10.1056/NEJMp1110639)

heartwire

Arrhythmia/EP

Rivaroxaban should be approved for stroke prevention in AF, panel tells FDA

September 8, 2011 Michael O'Riordan

5-11-2011

FDA decision?

Cardiovascular and Renal Drugs Advisory Committee > Briefing Information for the September 8, 2 - Windows Internet Explorer

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm270795.htm

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Committees & Meeting Materials

Drugs

Cardiovascular and Renal Drugs Advisory Committee

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- 2010 Meeting Materials, Cardiovascular and Renal Drugs Advisory Committee
- 2009 Meeting Materials, Cardiovascular and Renal Drugs Advisory Committee
- Cardiovascular and Renal Drugs Advisory Committee Charter
- Cardiovascular and Renal Drugs Advisory Committee Roster

Briefing Informati or the September 8, 20 M ng of Cardiovascular an Drugs Advisory Commit

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FDA

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Errata to the FDA Briefing Information for the September 8, 2011 Meeting of the Cardiovascular and Renal Drugs Advisory Committee (PDF – 134KB)

Johnson & Johnson Pharmaceutical Research & Development

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 September 2011
EMA/CHMP/753436/2011
Committee for Medicinal Products for Human Use (CHMP)

Summ inion[1] (po horisation)

Xarelto
rivarox

On 22 mber 2011 Comm for Medic roducts for H n Use (CHMP) adopted two pos inions for the dina duct Xarelto recommendi extension to the terms of the ma ion a r reco at of the marketing authorisation.

The marketing authorisation holder for this medicinal product is Bayer Schering Pharma AG. They may request a re examination of the CHMP opinion, provided that they notify the European Medicines Agency in writing of their intention within 15 days of receipt of the opinion.

The CHMP adopted a new indication for two new strengths as follows:
Treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.

Furthermore in parallel the CHMP adopted another a new indication for the same strengths as follows:
Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

Detailed conditions for the use of this product will be described in the updated summary of product characteristics (SmPC), which will be published in the revised European public assessment report (EPAR), and will be available in all official European Union languages after the variation to the marketing authorisati as been granted by the E an Commission.

For information, the full indications for Xarelto will be as follows[2]:

0 mg et

P tion of venous mboe m (VTE) in ad atie ndergoin ang replac t s ry

Xare 5 m d 20 mg tablet

[1] Summaries of positive opinion are published without prejudice to the Commission decision, which will normally be issued within 44 days (Type II variations) and 67 days (Annex II applications) from adoption of the opinion.
[2] The text in bold represents the new or the amended indication.

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ARISTOTLE
Diseño del estudio

Apixaban for Reduction In Stroke and Other ThromboembolLic Events in Atrial Fibrillation (ARISTOTLE) trial: Design and rationale

Renato D. Lopes, MD, PhD,[a] John H. Alexander, MD, MHS,[a] Sana M. Al-Khatib, MD, MHS,[a] Jack Ansell, MD,[b] Raphael Diaz, MD,[c] J. Donald Easton, MD,[d] Bernard J. Gersh, MB, ChB, DPhil,[e] Christopher B. Granger, MD,[a] Michael Hanna, MD,[f] John Horowitz, MD,[g] Elaine M. Hylek, MD, MPH,[h] John J. V. McMurray, MD,[i] Freek W. A. Verheugt, MD, PhD,[j] and Lars Wallentin, MD, PhD[k] on behalf of the ARISTOTLE Investigators

Durham, NC; New York, NY; Santa Fe, Argentina; Providence, RI; Rochester, MN; Princeton, NJ; Adelaide, Australia; Boston, MA; Glasgow, United Kingdom; Nijmegen, The Netherlands; and Uppsala, Sweden

Submitted February 6, 2009;

Lopes RD et al, Am Heart J, 2010; 159(3): 331-9

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

N Engl J Med 2011; 365: 981-992

Fibrilación auricular con al menos un factor de riesgo de ictus

Criterios de inclusión
- Edad ≥ 75 años
- Ictus previo, AIT, o ES
- IC o FEVI ≤ 40%
- Diabetes mellitus
- Hipertensión

Aleatorizado doble ciego, doble enmascaramiento (n = 18,201)

Criterios de exclusión
- Válvulas cardíacas mecánicas
- Insuficiencia renal grave
- Necesidad de Aspirina® más tienopiridina (Effient®, Plavix®)

Apixabán 5 mg oral c/12h
(2,5 mg BID en poblacion especial)

Warfarina
(INR 2-3)

Warfarina/warfarina placebo ajustado por INR/INR ficticio basado en un dispositivo de evaluación de punto de cuidado encriptado

Varible primaria: Ictus o embolia sistémica

Evaluación jerárgica: no-inferioridad de la variable primaria, superioridad para la varioable primaria, sangrado grave, muerte

N Engl J Med 2011; 365: 981-992

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RESULTADOS

1) PACIENTES Y SEGUIMIENTO
2) FÁRMACOS DEL ESTUDIO
3) OBJETIVO PRIMARIO
4) OBJETIVOS CLAVES SECUNDARIOS DE EFICACIA
5) SANGRADO
6) SUBGRUPOS
6) OBJETIVOS DE SEGURIDAD EN GENERAL

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ARISTOTLE

PACIENTES Y SEGUIMIENTO

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Apixaban (N=9120)	Warfarin (N=9081)
Age — yr		
Median	70	70
Interquartile range	63–76	63–76
Female sex — no. (%)	3234 (35.5)	3182 (35.0)
Region — no. (%)		
North America	2249 (24.7)	2225 (24.5)
Latin America	1743 (19.1)	1725 (19.0)
Europe	3672 (40.3)	3671 (40.4)
Asian Pacific	1456 (16.0)	1460 (16.1)
Systolic blood pressure — mm Hg		
Median	130	130
Interquartile range	120–140	120–140
Weight — kg		
Median	82	82
Interquartile range	70–96	70–95
Prior myocardial infarction — no. (%)	1319 (14.5)	1266 (13.9)
Prior clinically relevant or spontaneous bleeding — no. (%)	1525 (16.7)	1515 (16.7)
History of fall within previous year — no. (%)	386 (4.2)	367 (4.0)
Type of atrial fibrillation — no. (%)		
Paroxysmal	1374 (15.1)	1412 (15.5)
Persistent or permanent	7744 (84.9)	7668 (84.4)
Prior use of vitamin K antagonist for >30 consecutive days — no. (%)	5208 (57.1)	5193 (57.2)
Qualifying risk factors		
Age ≥75 yr — no. (%)	2850 (31.2)	2828 (31.1)
Prior stroke, TIA, or systemic embolism — no. (%)	1748 (19.2)	1790 (19.7)
Heart failure or reduced left ventricular ejection fraction — no. (%)	3235 (35.5)	3216 (35.4)
Diabetes — no. (%)	2284 (25.0)	2263 (24.9)
Hypertension requiring treatment — no. (%)	7962 (87.3)	7954 (87.6)
$CHADS_2$ score		
Mean	2.1±1.1	2.1±1.1
Distribution — no. (%)		
≤1	3100 (34.0)	3083 (34.0)
2	3262 (35.8)	3254 (35.8)
≥3	2758 (30.2)	2744 (30.2)

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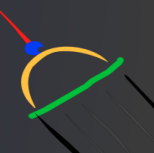
FÁRMACOS DEL ESTUDIO

	Apixaban	Warfarina
Randomizados, n	9120	9081
Perdidos en el seguimiento, n	35	34
Retirada de Consentimiento, n (%)	92 (1,0%)	107 (1,2%)
Retirada prematura, % ★	25.3%	27.5%
Debida a fallecimiento	3.6%	3,8%
Mediana de Tiempo INR en rango 2-3		66%

★ **p=0,001**



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ARISTOTLE

OBJETIVO 1ª (ICTUS O EMBOLISMO SISTÉMICO)

Outcome	Apixaban Group (N=9120)		Warfarin Group (N=9081)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	*%/yr*	*no.*	*%/yr*		
Primary outcome: stroke or systemic embolism	212	1.27	265	1.60	0.79 (0.66–0.95)	0.01
Stroke	199	1.19	250	1.51	0.79 (0.65–0.95)	0.01
Ischemic or uncertain type of stroke	162	0.97	175	1.05	0.92 (0.74–1.13)	0.42
Hemorrhagic stroke	40	0.24	78	0.47	0.51 (0.35–0.75)	<0.001
Systemic embolism	15	0.09	17	0.10	0.87 (0.44–1.75)	0.70

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ARISTOTLE

OBJETIVO CLAVE 2ª DE EFICACIA

Variable	Apixabán (N=9120) Tasa de eventos (%/año)	Warfarina (N=9081) Tasa de eventos (%/año)	HR (95% IC)	Valor P
Todas las causas de muerte*	3,52	3,94	0,89 (0,80, 0,998)	0,047
Muerte cardiovascular	1,80%	2,02%	0,89 (0,76, 1,04)	
Muerte no cardiovascular	1,14%	1,22%	0,93 (0,77, 1,13)	
Ictus, ES o todas las causas de muerte	4,49	5,04	0,89 (0,81, 0,98)	0,019
Infarto del miocardio	0,53	0,61	0,88 (0,66, 1,17)	0,37

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ARISTOTLE

SANGRADO

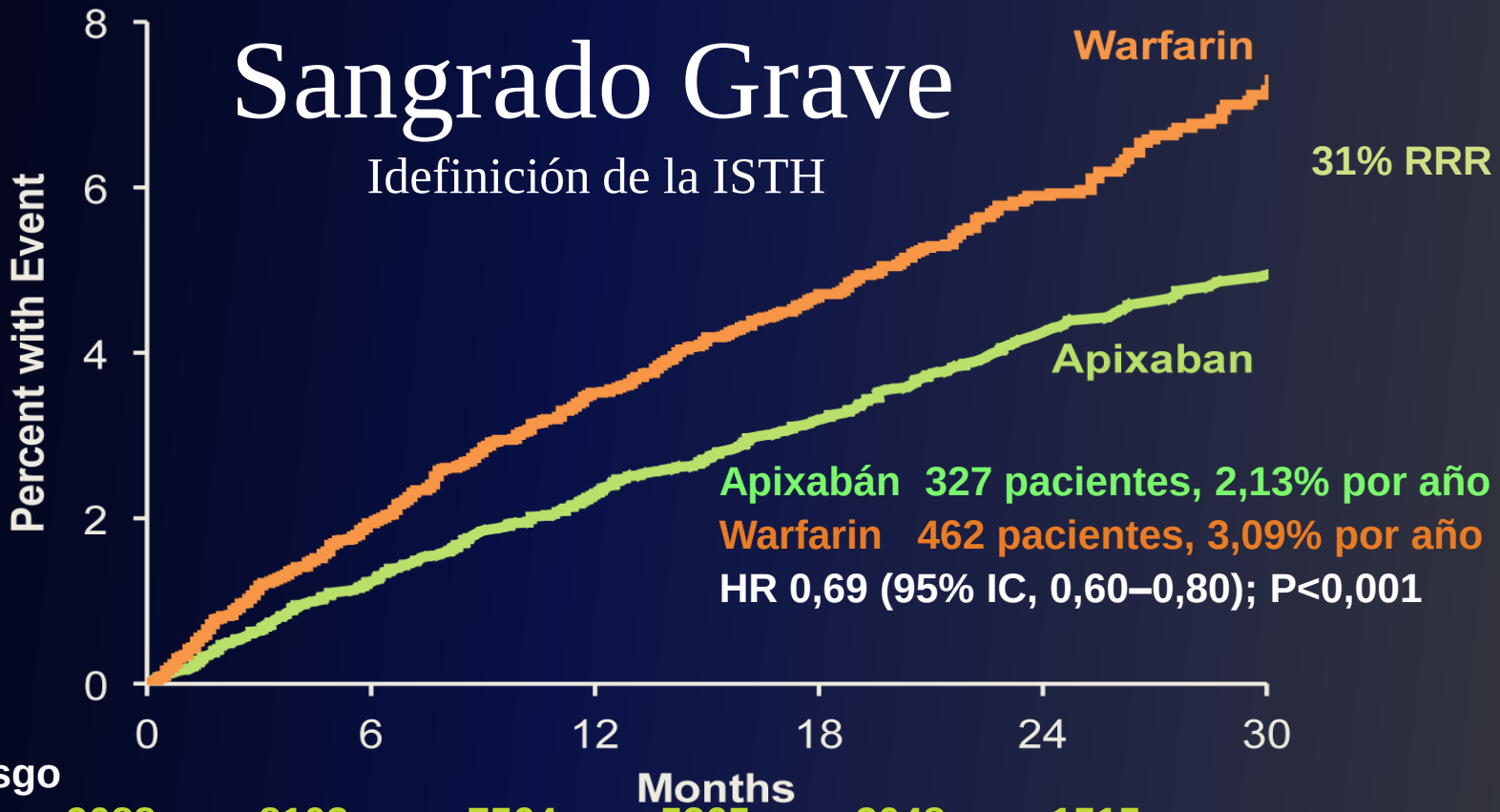
Outcome	Apixaban Group (N=9088)		Warfarin Group (N=9052)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	%/yr	*no.*	%/yr		
Primary safety outcome: ISTH major bleeding†	327	2.13	462	3.09	0.69 (0.60–0.80)	<0.001
Intracranial	52	0.33	122	0.80	0.42 (0.30–0.58)	<0.001
Other location	275	1.79	340	2.27	0.79 (0.68–0.93)	0.004
Gastrointestinal	105	0.76	119	0.86	0.89 (0.70–1.15)	0.37
Major or clinically relevant nonmajor bleeding	613	4.07	877	6.01	0.68 (0.61–0.75)	<0.001
GUSTO severe bleeding	80	0.52	172	1.13	0.46 (0.35–0.60)	<0.001
GUSTO moderate or severe bleeding	199	1.29	328	2.18	0.60 (0.50–0.71)	<0.001
TIMI major bleeding	148	0.96	256	1.69	0.57 (0.46–0.70)	<0.001
TIMI major or minor bleeding	239	1.55	370	2.46	0.63 (0.54–0.75)	<0.001
Any bleeding	2356	18.1	3060	25.8	0.71 (0.68–0.75)	<0.001

Parte de la evaluación secuencial preservando el error tipo I

N Engl J Med 2011; 365: 981-992

ARISTOTLE

SANGRADO



No. en Riesgo						
Apixabán	9088	8103	7564	5365	3048	1515
Warfarina	9052	7910	7335	5196	2956	1491

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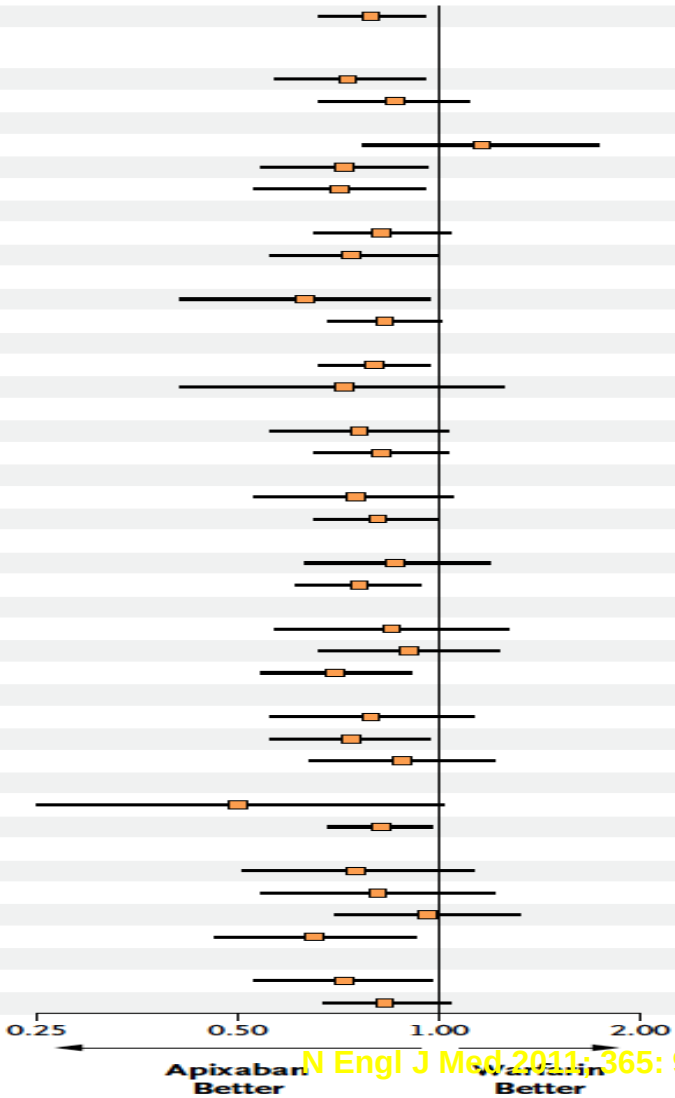
ARISTOTLE

SUBGRUPOS

A Primary Efficacy Outcome: Stroke and Systemic Embolism

Subgroup	No. of Patients	Apixaban	Warfarin	P Value for Interaction
		no. of events (%/yr)		
All patients	18,201	212 (1.27)	265 (1.60)	
Prior use of warfarin or other vitamin K antagonist				0.39
Yes	10,401	102 (1.1)	138 (1.5)	
No	7,800	110 (1.5)	127 (1.8)	
Age				0.12
<65 yr	5,471	51 (1.0)	44 (0.9)	
65 to <75 yr	7,052	82 (1.3)	112 (1.7)	
≥75 yr	5,678	79 (1.6)	109 (2.2)	
Sex				0.60
Male	11,785	132 (1.2)	160 (1.5)	
Female	6,416	80 (1.4)	105 (1.8)	
Weight				0.26
≤60 kg	1,985	34 (2.0)	52 (3.2)	
>60 kg	16,154	177 (1.2)	212 (1.4)	
Type of atrial fibrillation				0.70
Permanent or persistent	15,412	191 (1.4)	235 (1.7)	
Paroxysmal	2,786	21 (0.8)	30 (1.1)	
Prior stroke or TIA				0.71
Yes	3,436	73 (2.5)	98 (3.2)	
No	14,765	139 (1.0)	167 (1.2)	
Diabetes mellitus				0.71
Yes	4,547	57 (1.4)	75 (1.9)	
No	13,654	155 (1.2)	190 (1.5)	
Heart failure				0.50
Yes	5,541	70 (1.4)	79 (1.6)	
No	12,660	142 (1.2)	186 (1.6)	
$CHADS_2$ score				0.45
≤1	6,183	44 (0.7)	51 (0.9)	
2	6,516	74 (1.2)	82 (1.4)	
≥3	5,502	94 (1.9)	132 (2.8)	
Level of renal impairment				0.72
Severe or moderate	3,017	54 (2.1)	69 (2.7)	
Mild	7,587	87 (1.2)	116 (1.7)	
No impairment	7,518	70 (1.0)	79 (1.1)	
Apixaban dose				0.22
2.5 mg twice daily or placebo	831	12 (1.7)	22 (3.3)	
5 mg twice daily or placebo	17,370	200 (1.3)	243 (1.5)	
Geographic region				0.44
North America	4,474	42 (1.0)	56 (1.3)	
Latin America	3,468	43 (1.4)	52 (1.8)	
Europe	7,343	75 (1.1)	77 (1.1)	
Asian Pacific	2,916	52 (2.0)	80 (3.1)	
Aspirin use at randomization				0.44
Yes	5,632	70 (1.3)	94 (1.9)	
No	12,569	142 (1.2)	171 (1.5)	

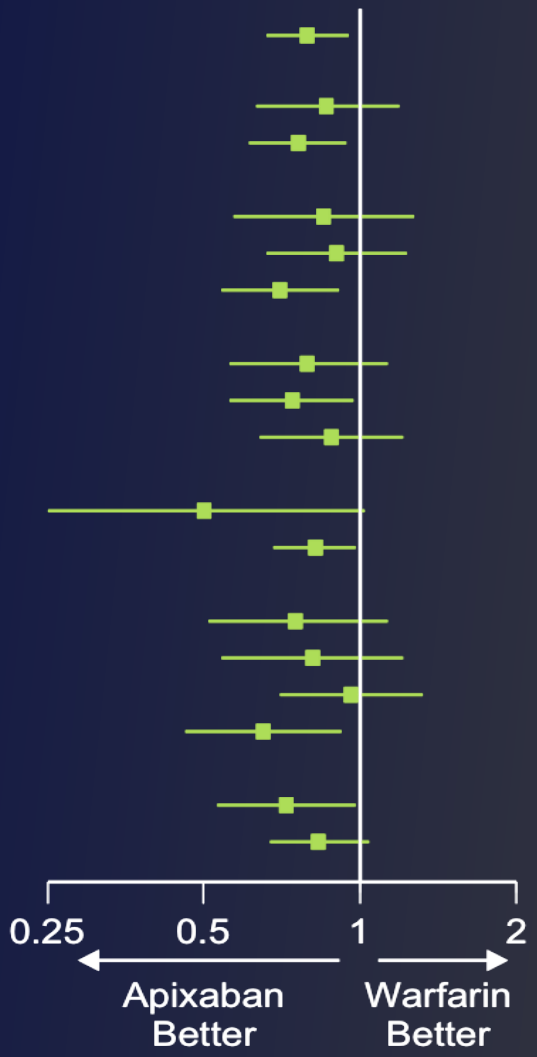


N Engl J Med 2011; 365: 981-992

ARISTOTLE

SUBGRUPOS

Characteristics	No. of Patients	Apixaban no. of events (%/yr)	Warfarin no. of events (%/yr)	P-value for Interaction
All Patients	18201	212 (1.27)	265 (1.60)	
Heart Failure				0.50
Yes	5541	70 (1.4)	79 (1.6)	
No	12660	142 (1.2)	186 (1.6)	
CHADs Score				0.45
≤ 1	6183	44 (0.7)	51 (0.9)	
=2	6516	74 (1.2)	82 (1.4)	
≥3	5502	94 (1.9)	132 (2.8)	
Level of Renal Impairment				0.72
Severe or Moderate	3017	54 (2.1)	69 (2.7)	
Mild	7587	87 (1.2)	116 (1.7)	
No impairment	7518	70 (1.0)	79 (1.1)	
Apixaban Dose				0.22
2.5 mg BID or placebo	831	12 (1.7)	22 (3.3)	
5 mg BID or placebo	17370	200 (1.3)	243 (1.5)	
Geographic Region				0.44
North America	4474	42 (1.0)	56 (1.3)	
Latin America	3468	43 (1.4)	52 (1.8)	
Europe	7343	75 (1.1)	77 (1.1)	
Asia/Pacific	2916	52 (2.0)	80 (3.1)	
Aspirin at Randomization				0.44
Yes	5632	70 (1.3)	94 (1.9)	
No	12569	142 (1.2)	171 (1.5)	



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ARISTOTLE

CONCLUSIÓN

In conclusion, in patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.

N Engl J Med 2011; 365: 981-992

Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: Design and rationale for the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation–Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF–TIMI 48)

Christian T. Ruff, MD,[a,c] Robert P. Giugliano, MD, SM,[a,c] Elliott M. Antman, MD,[a,c] Sharon E. Crugnale, MS,[a,c] Tomas Bocanegra, MD,[b,c] Michele Mercuri, MD, PhD,[b,c] James Hanyok, PharmD,[b,c] Indravadan Patel, MD,[b,c] Minggao Shi, PhD,[b,c] Dan Salazar, PhD,[b] Carolyn H. McCabe, BS,[a,c] and Eugene Braunwald, MD[a,c] *Boston, MA; and Parsippany, NJ*

ENGAGE AF-TIMI 48

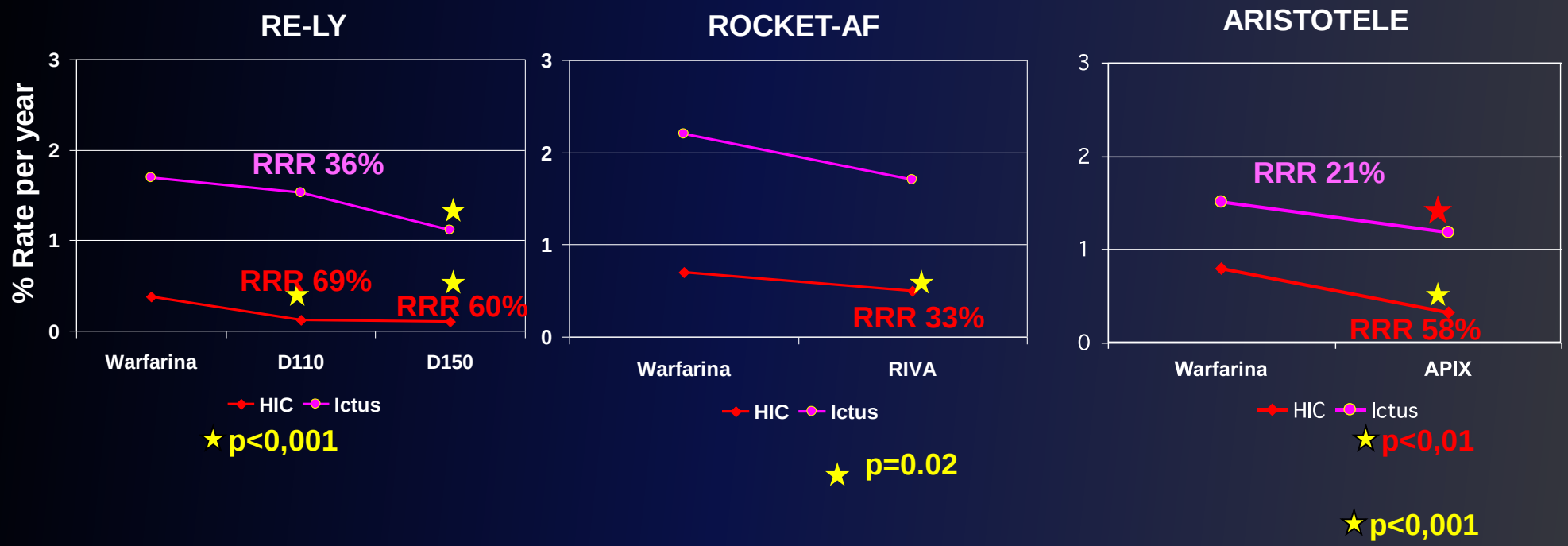
Table III. Baseline characteristics for 15 000 subjects

Demographics	
Age (y)	72 (64-77)
Age ≥75 y	39
Female	38
$CHADS_2$	
2-3	81
4-6	19
Warfarin naïve	39
Category of AF	
Paroxysmal	26
Persistent	23
Permanent	52
Any reason for dose adjustment	25
Weight ≤60 kg	10
CrCl ≤50 mL/min	19
Concomitant verapamil or quinidine	4

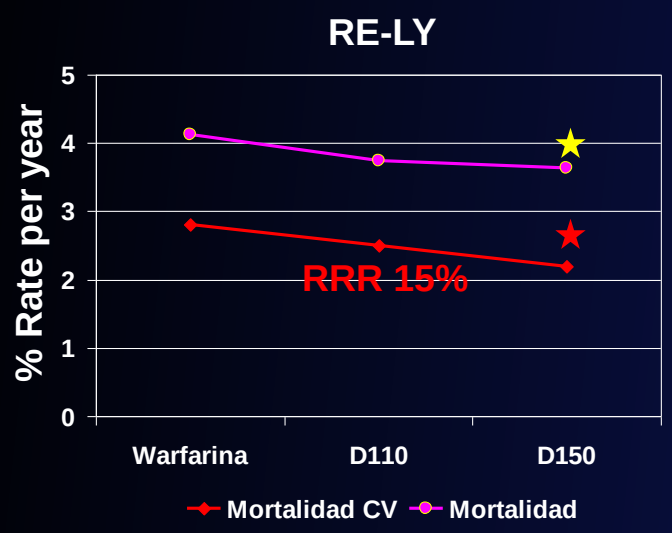
Ruff CT et al. Am Heart J, 2010; 160: 635-41

RE-LY & ROCKET-AF & ARISTOTLE

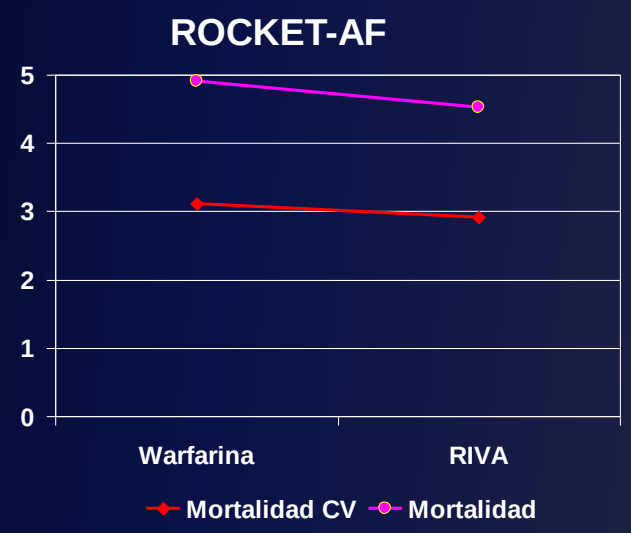
ICTUS & HEMORRAGIA INTRACRANEAL

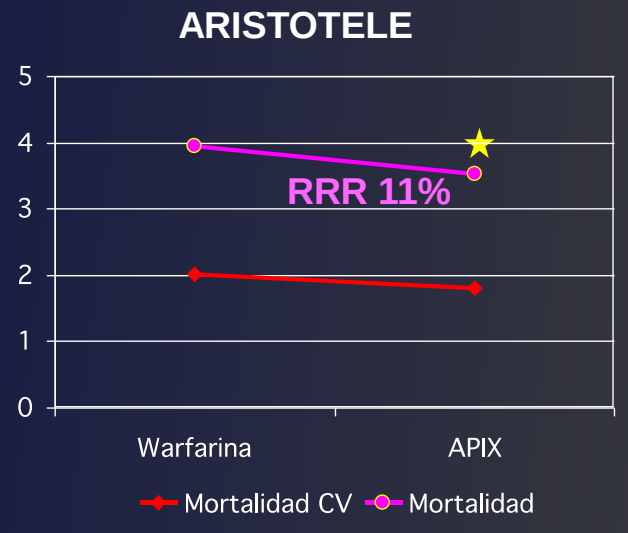


RE-LY & ROCKET-AF & ARISTOTLE
MORTALIDAD TOTAL & CARDIOVASCULAR



★ p=0,051 ★p=0,004



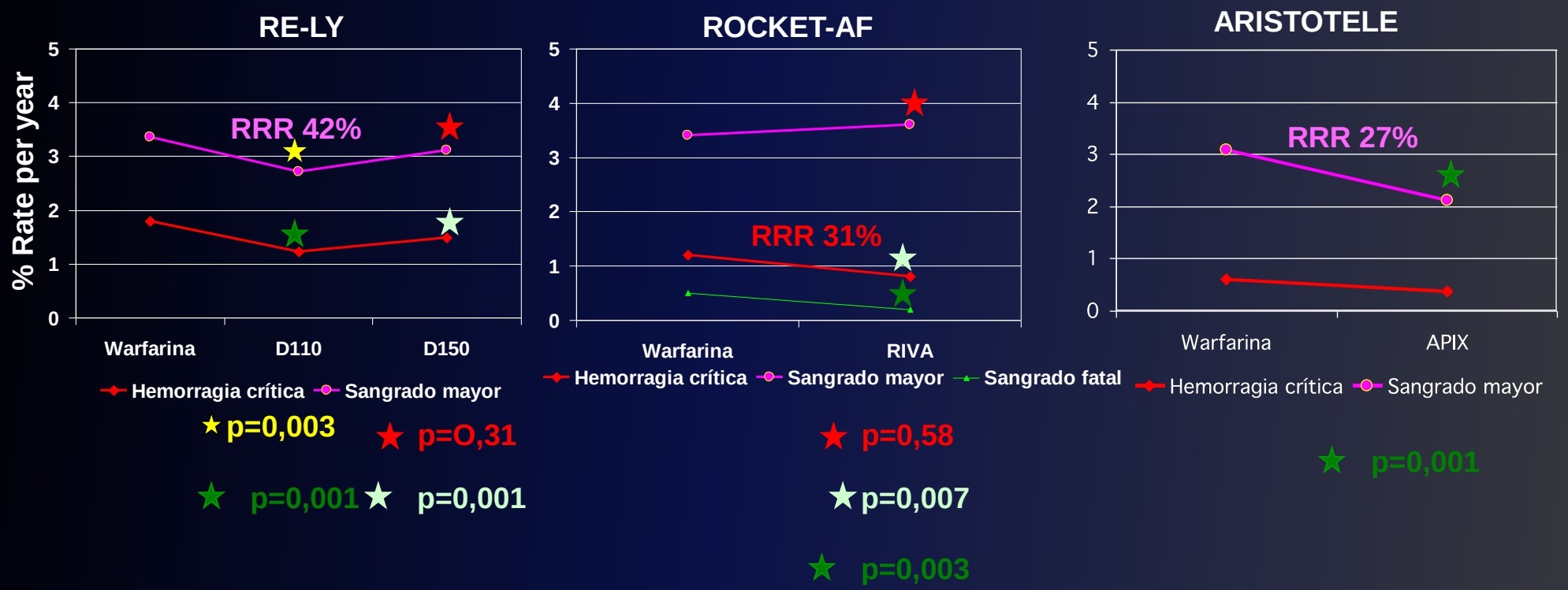


★ p=0,047

RRR ¿?

RE-LY & ROCKET-AF & ARISTOTLE

HEMORRAGIA CRÍTICA & SANGRADO MAYOR



Coste total por año por paciente Nuevos ACOs	Coste total por año por paciente AntiVitKs
???	661,77 €

Annals of Internal

RIGINAL RESEARCH

Cost-Effectivene Prevention in At

Warfarin for Stroke

James V. Freeman, MD, MPH; F
Alan S. Go, MD; Paul J. Wang,

, PhD; David W. Hutton, PhD;

68–70). We estimated a
dose dabigatran and $13.0
ran, on the basis of the do

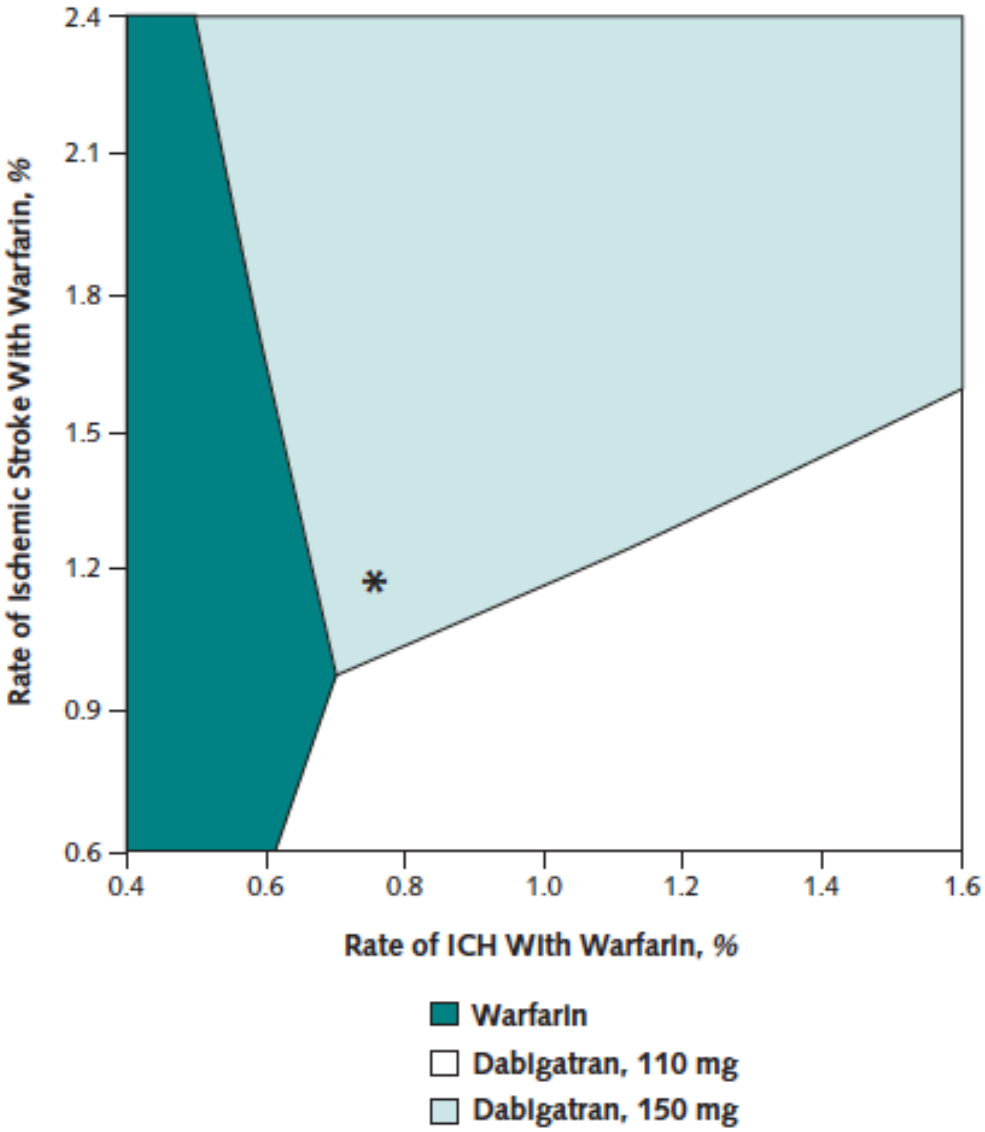
Ann Intern Med, 2011; 154: 1-11

OUTCOMES RES

Dabigatran Ap Warfarin

ternative to

Figure 2. Two-way sensitivity analysis demonstrating which therapy would be preferred for varying risks for ischemic stroke and ICH, using a willingness-to-pay threshold of $50 000 per quality-adjusted life-year.



Block JP. JCOM, 2011; 18(2): 64-5

NUEVOS ANTICOAGULANTES EN ESTUDIOS CLÍNICOS

1) Antivitamina K
   - Tercafarina

2) Inhibidores directos Orales del factor II (trombina):
   - Dabigatran etexilate (=BIBR 1048)
   - AZD0837
   - Argatroban (=SC201310) (sólo i.v.)
   - MCC 977

3) Inhibidores directos Orales del factor Xa:
   - Rivaroxaban (=BAY59-7939)
   - Apixaban (=BMS-562247-01)
   - Betrixaban (=PRT054021)
   - Edoxaban (=DU-176b)
   - Otamixaban (=PA151958300
   - Eribaxaban (=PD0348292**)**
   - LY-517717
   - YM150
   - GW813893
   - TAK-442
   - PD 0348292

NUEVOS ANTICOAGULANTES

CUESTIONES POR RESPONDER

- ¿Cómo podemos comparar los diferentes fármacos?
- ¿En cuál paciente se debe usar warfarina, Dabigatrán, Rivaroxaban, Apixaban, etc?
- ¿Son “mejores” los nuevos fármacos si los pacientes están bien controlados con Warfarina?
- ¿Se sentirán cómodos los médicos con la incapacidad de monitorizar el nivel de anticoagulación?
- ¿Cómo se manejan los nuevos fármacos en relación con las intervenciones?
- ¿Existe un problema con la rápida pérdida de efecto si el paciente es “no cumplidor”?
- ¿Cómo debemos evaluar el “coste-efectividad”?