Madrid, 29 de Noviembre de 2013

V JORNADAS CIENTÍFICAS DEL

CEIPC

Comité Español Interdisciplinario para la Prevención Cardiovascular

GOBIERNO DE ESPAÑA | MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD | MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

LA PREVENCIÓN CARDIOVASCULAR EN ESPAÑA. OPORTUNIDADES Y BARRERAS

Nuevos Anticoagulantes Orales. Implicaciones en la Práctica clínica

José Vivancos Mora

Unidad de Ictus y Servicio de Neurología

Hospital Universitario de la Princesa. Madrid

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Anticoagulantes Orales de 2ª Generación.

Implicaciones en la Práctica clínica

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Servicio de Neurología

Declaración de Conflicto de Intereses

El Dr. José Vivancos Mora ha desempeñado funciones de asesor científico, y ha percibido honorarios por ello, o ha tomado parte en estudios investigación financiados en todo o en parte por las siguientes entidades:

Almirall

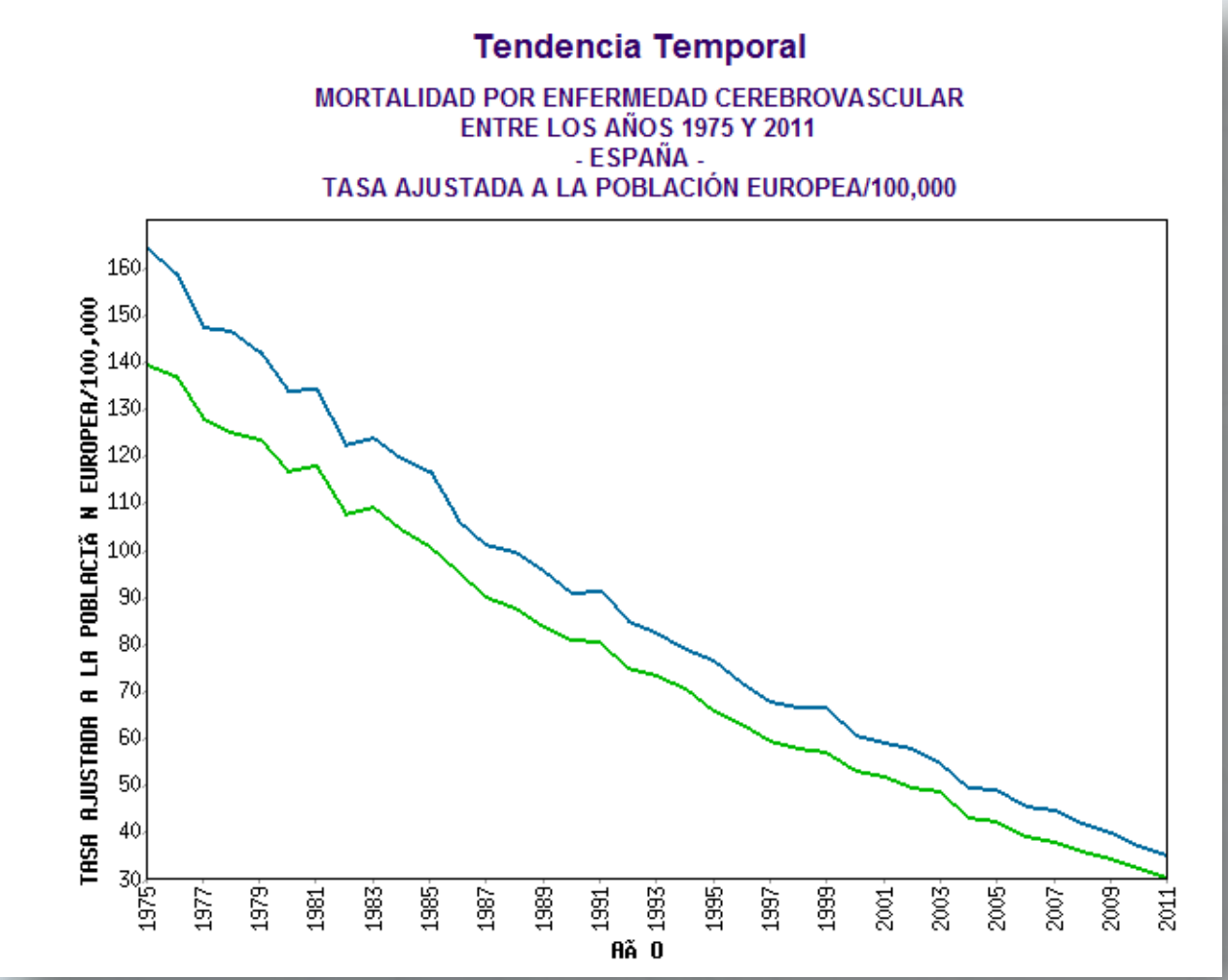
Bayer

Boeringher Ingelheim

Pfizer

BMS

El ictus en España





Fuente: INE 2012 (www.ine.es)

El Ictus en España…



- 1ª causa de mortalidad en la mujer[2006] (19.038)[1] (16,703)[2011]
- 2ª causa de mortalidad[2006] (32.887)[1] (28.885)[2011]
- 1ª causa de discapacidad, 2ª de demen (12,2%)
- Morbilidad hospitalaria[2006] :

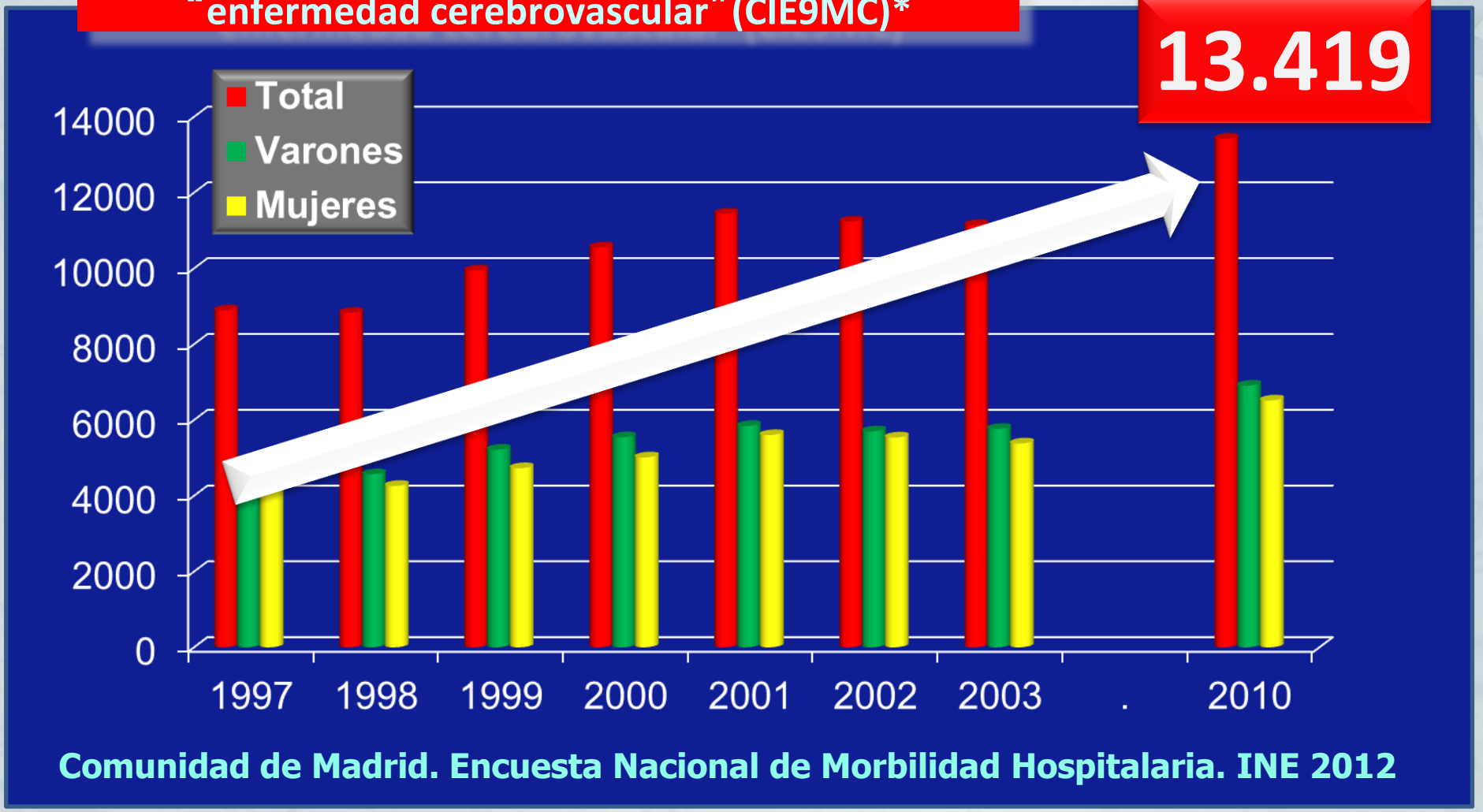
  $69266^{ictus}+15.194^{AIT}$ (114.807)[2]
- Incidencia[2008]: ictus y AIT[3] (84.460 nuevos anuales)
- Prevalencia[2008]: 3.5 % > 64 a[4] (265.604*)

Fuentes: INE 2008-2013 (mortalidad y morbilidad 2006[1,2], *censo 2001,estimada 2008) [3]IBERICTUS ,[4]J Díaz Tesis doctoral 1998

Población 44.687.483
≥ 65 a → 7.588.686 *

Altas Hospitalarias por Ictus en La Comunidad de Madrid

Altas hospitalarias con el diagnóstico principal de "enfermedad cerebrovascular" (CIE9MC)*



Comunidad de Madrid. Encuesta Nacional de Morbilidad Hospitalaria. INE 2012

REGISTRO EPICES

EPidemiología del ICtus en ESpaña

SOCIEDAD ESPAÑOLA DE NEUROLOGÍA

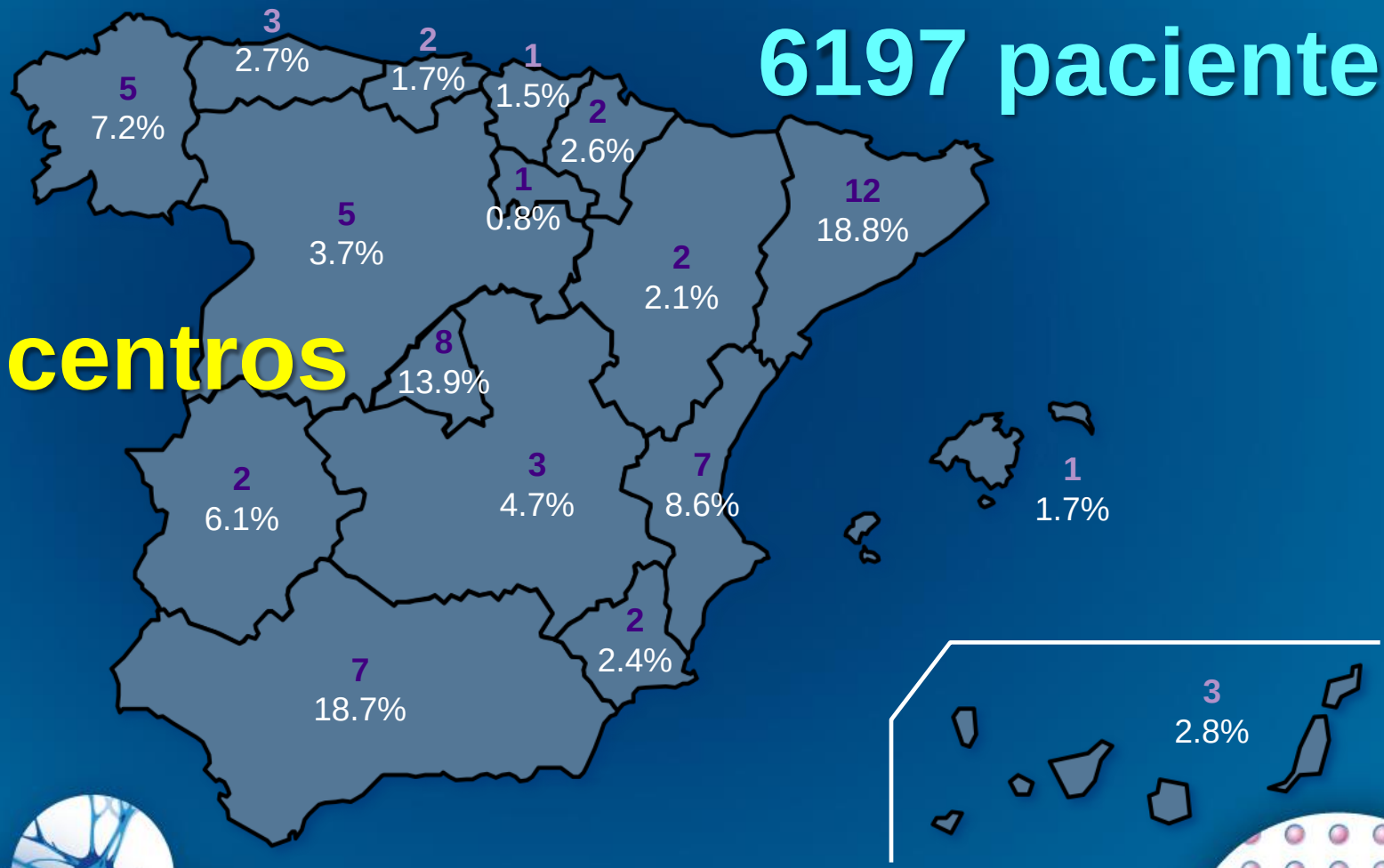
- Blanco M, Vivancos-Mora J, Castillo J. Rev Neurol. 2012 May 1;54(9):523-9.
- Castillo J, Vivancos-Mora J. Rev Neurol. 2012 Apr 16;54(8):461-7.
- Arias-Rivas S, Vivancos-Mora J, Castillo J. Rev Neurol. 2012 Apr 1;54(7):385-93.

SOCIEDAD ESPAÑOLA DE NEUROLOGÍA

CENTROS Y PACIENTES INCLUIDOS

6197 pacientes

66 centros



REGISTRO EPICES
EPidemiología del ICtus en ESpaña

SOCIEDAD ESPAÑOLA DE NEUROLOGÍA

DIAGNÓSTICO DE LOS ICTUS ISQUÉMICOS

	N	%
Aterotrombótico	**1.543**	**28.4**
Cardioembólico	**1.424**	**26.2**
Lacunar	**1.202**	**22.5**
Indeterminado	**1.125**	**20.7**
- Diagnóstico insuficiente	806	14.8
- Varias causas	319	5.9
Poco frecuente	**132**	**2.4**

	N	%
TACI	867	16.0
PACI	2.213	40.8
LACI	1.402	25.8
POCI	944	17.4

REGISTRO EPICES

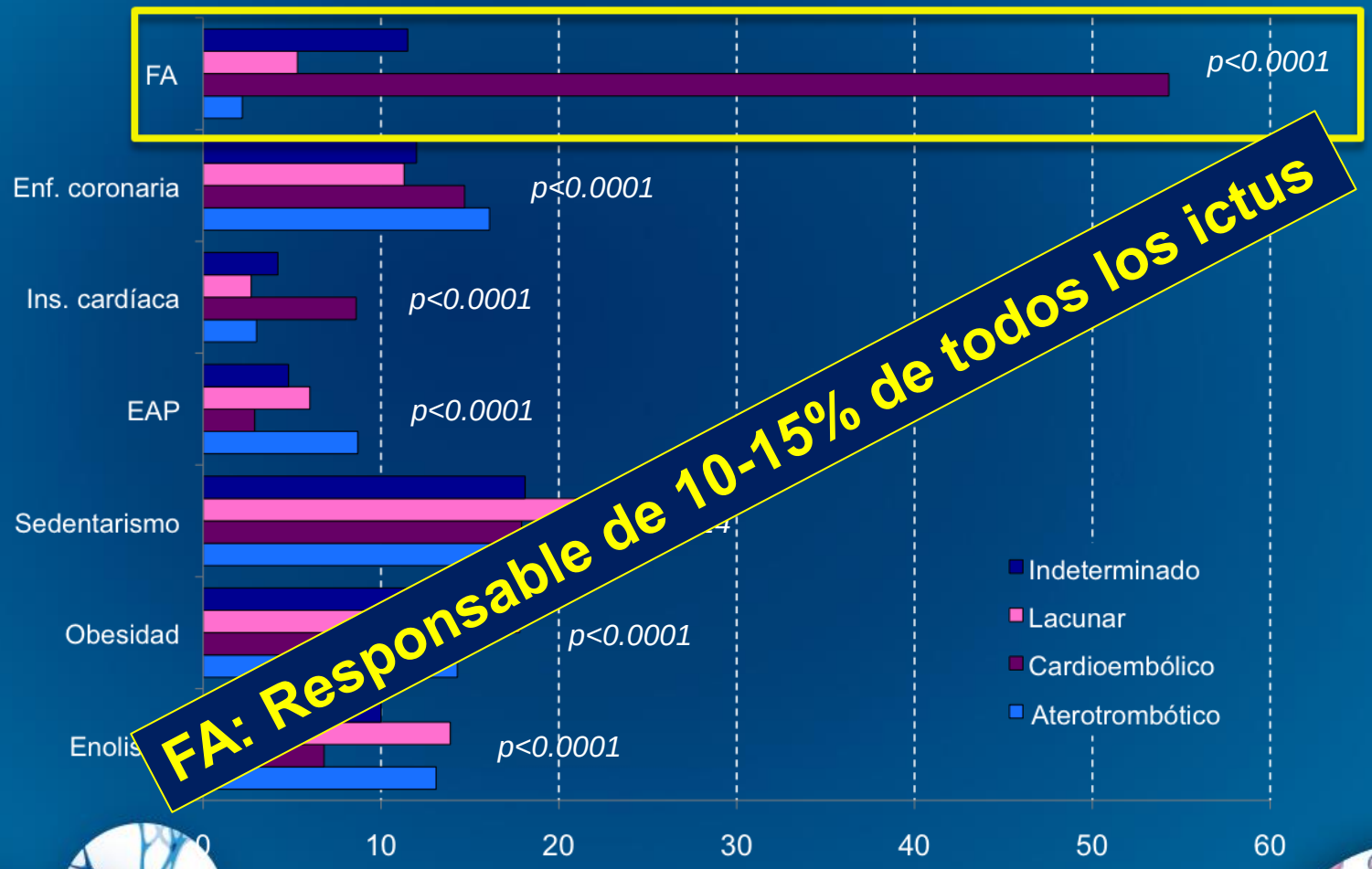
- Blanco M, Vivancos-Mora J, Castillo J. Rev Neurol. 2012 May 1;54(9):523-9.
- Castillo J, Vivancos-Mora J. Rev Neurol. 2012 Apr 16;54(8):461-7.
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REGISTRO EPICES
EPidemiología del ICtus en ESpaña

Prevalencia de FA según subtipos de ictus

SOCIEDAD ESPAÑOLA DE NEUROLOGÍA

PREVALENCIA DE LOS FACTORES DE RIESGO



FA: Responsable de 10-15% de todos los ictus

REGISTRO EPICES
EPidemiología del ICtus en ESpaña

El ictus cardioembólico

- Oclusión de grandes vasos cerebrales
- Infartos mas extensos
- Infartos múltiples
- Mayor probabilidad de transformación hemorrágica
- Pacientes mas ancianos
- Mayor gravedad neurológica (60%)
- Mayor morbi-mortalidad (20%)
- Mayor probabilidad de recurrencia
- Mayores costes sociosanitarios



Europace (2008) 10, 403–411
doi:10.1093/europace/eun048

EUROPEAN SOCIETY OF CARDIOLOGY®

Costs of atrial fibrillation in five European countries: results from the Euro Heart Survey on atrial fibrillation

Anna Ringborg[1,2]*, Robby Nieuwlaat[3], Peter Lindgren[1,2], Bengt Jönsson[4], Dogan Fidan[5], Aldo P. Maggioni[6], Jose Lopez-Sendon[7], Janina Stepinska[8], Dennis V. Cokkinos[9], and Harry J.G.M. Crijns[3]

[1]*i3 Innovus, Vasagatan 38, 2tr, 111 20 Stockholm, Sweden;* [2]*Institute of Environmental Medicine, Karolinska Institute, Solna, Sweden;* [3]*Department of Cardiology, University Hospital Maastricht, Maastricht, The Netherlands;* [4]*Centre for Health Economics, Stockholm School of Economics, Stockholm, Sweden;* [5]*Sanofi-Aventis, Bagneux, France;* [6]*ANMCO Research Center, Firenze, Italy;* [7]*Department of Cardiology, Hospital Universitario La Paz, Madrid, Spain;* [8]*Institute of Cardiology, Warsaw, Poland; and* [9]*First Department of Cardiology, Onassis Cardiac Surgery Center, Athens, Greece*

Received 8 October 2007; accepted after revision 14 January 2008; online publish-ahead-of-print 7 March 2008

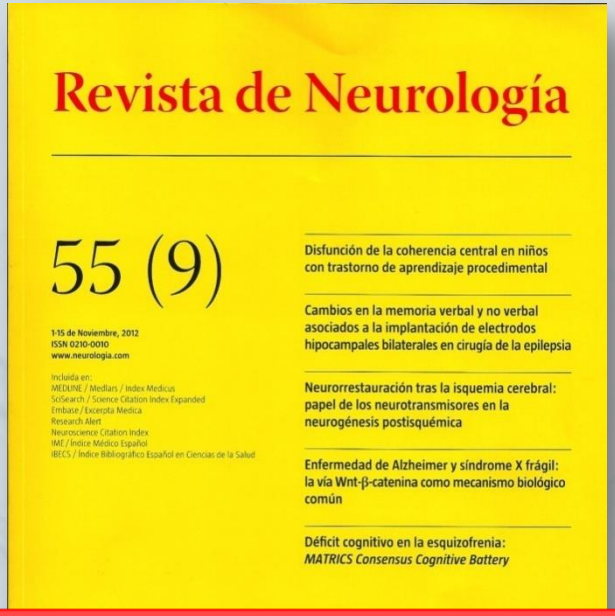
Table 6 Mean (SD) annual costs of AF patients, by resource category and country

Resource	Greece ($n = 251$)	Italy ($n = 645$)	Poland ($n = 203$)	Spain ($n = 720$)	The Netherlands ($n = 685$)
Diagnostics	45 (121)	147 (223)	28 (153)	104 (140)	160 (384)
Interventions	780 (3091)	851 (2441)	172 (456)	708 (2547)	798 (3488)
Drug therapy	159 (296)	199 (311)	96 (325)	237 (358)	87 (150)
Consultations	37 (46)	44 (88)	24 (26)	37 (67)	57 (56)
Inpatient care	352 (2248)	1778 (4075)	651 (1271)	987 (2234)	834 (3036)
Work loss	135 (999)	206 (1395)	39 (186)	242 (2253)	391 (3596)
Total annual cost	1507 (5238)	3225 (5975)	1010 (1667)	2315 (4931)	2328 (6834)

All costs are expressed in year 2006 Euros.
SD, standard deviation.

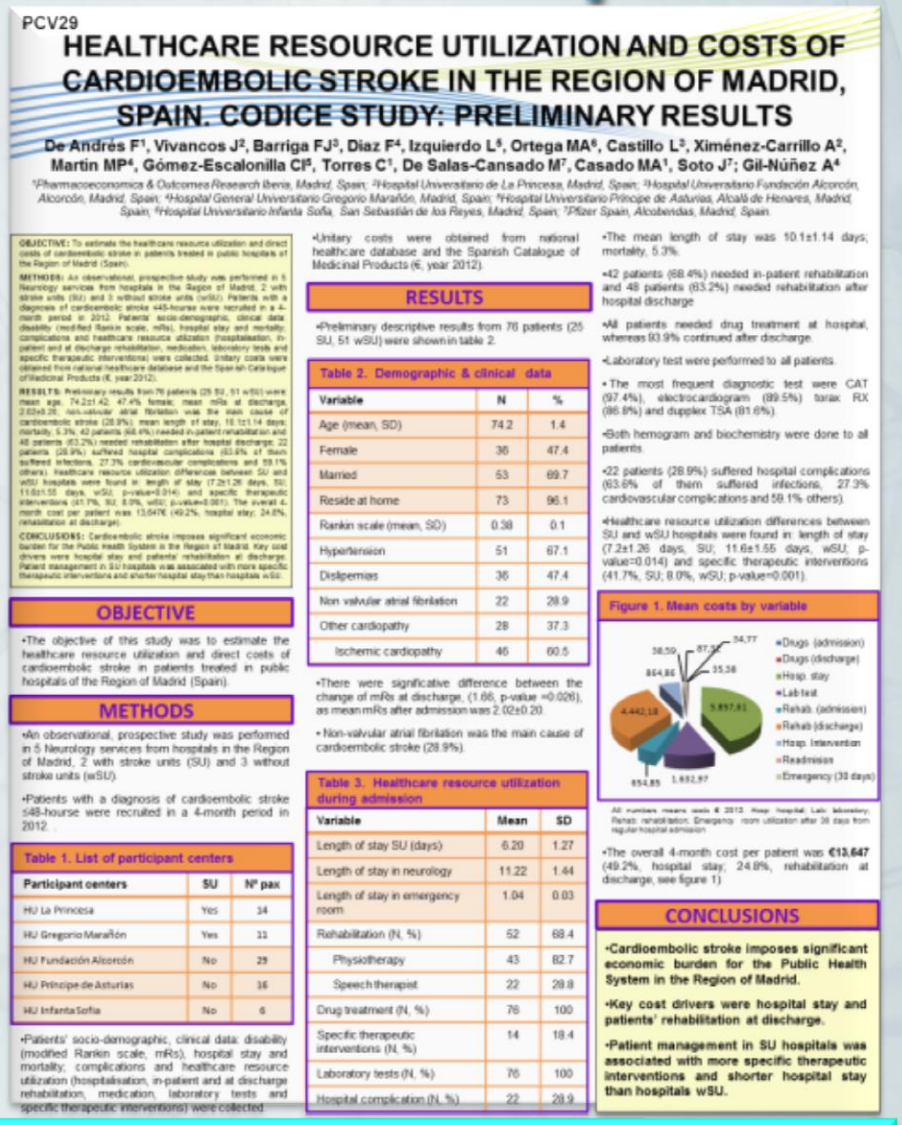
El coste del ictus cardioembólico en España

El estudio CODICE



13.130 €

- **45% c. hospitalización**
- **29% c. rehabilitación**



PCV29

HEALTHCARE RESOURCE UTILIZATION AND COSTS OF CARDIOEMBOLIC STROKE IN THE REGION OF MADRID, SPAIN. CODICE STUDY: PRELIMINARY RESULTS

De Andrés F[1], Vivancos J[2], Barriga FJ[3], Díaz F[4], Izquierdo L[5], Ortega MA[6], Castillo L[3], Ximénez-Carrillo A[2], Martín MP[4], Gómez-Escalonilla CI[5], Torres C[1], De Salas-Cansado M[7], Casado MA[1], Soto J[7]; Gil-Núñez A[4]

[1]Pharmacoeconomics & Outcomes Research Iberia, Madrid, Spain; [2]Hospital Universitario de La Princesa, Madrid, Spain; [3]Hospital Universitario Fundación Alcorcón, Alcorcón, Madrid, Spain; [4]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [5]Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid, Spain; [6]Hospital Universitario Infanta Sofía, San Sebastián de los Reyes, Madrid, Spain; [7]Pfizer Spain, Alcobendas, Madrid, Spain

OBJECTIVE: To estimate the healthcare resource utilization and direct costs of cardioembolic stroke in patients treated in public hospitals of the Region of Madrid (Spain).

METHODS: An observational, prospective study was performed in 5 Neurology services from hospitals in the Region of Madrid, 2 with stroke units (SU) and 3 without stroke units (wSU). Patients with a diagnosis of cardioembolic stroke ≤48-hourse were recruited in a 4-month period in 2012. Patients' socio-demographic, clinical data (disability (modified Rankin scale, mRs), hospital stay and mortality; complications and healthcare resource utilization (hospitalisation, in-patient and at discharge rehabilitation, medication, laboratory tests and specific therapeutic interventions) were collected. Unitary costs were obtained from national healthcare database and the Spanish Catalogue of Medicinal Products (€, year 2012).

RESULTS: Preliminary results from 76 patients (25 SU, 51 wSU) were: mean age, 74.2±11.42; 47.4% female; mean mRs at discharge, 2.02±0.28; non-valvular atrial fibrillation was the main cause of cardioembolic stroke (28.9%); mean length of stay, 10.1±1.14 days; mortality, 5.3%; 42 patients (68.4%) needed in-patient rehabilitation and 48 patients (63.2%) needed rehabilitation after hospital discharge; 22 patients (28.9%) suffered hospital complications (63.6% of them suffered infections, 27.3% cardiovascular complications and 59.1% others). Healthcare resource utilization differences between SU and wSU hospitals were found in: length of stay (7.2±1.26 days, SU; 11.6±1.55 days, wSU; p-value=0.014); and specific therapeutic interventions (41.7%, SU; 8.0%, wSU; p-value=0.001). The overall 4-month cost per patient was 13,647€ (49.2%, hospital stay; 24.8%, rehabilitation at discharge).

CONCLUSIONS: Cardioembolic stroke imposes significant economic burden for the Public Health System in the Region of Madrid. Key cost drivers were hospital stay and patients' rehabilitation at discharge. Patient management in SU hospitals was associated with more specific therapeutic interventions and shorter hospital stay than hospitals wSU.

OBJECTIVE

- The objective of this study was to estimate the healthcare resource utilization and direct costs of cardioembolic stroke in patients treated in public hospitals of the Region of Madrid (Spain).

METHODS

- An observational, prospective study was performed in 5 Neurology services from hospitals in the Region of Madrid, 2 with stroke units (SU) and 3 without stroke units (wSU).
- Patients with a diagnosis of cardioembolic stroke ≤48-hourse were recruited in a 4-month period in 2012.

Table 1. List of participant centers

Participant centers	SU	Nº pax
HU La Princesa	Yes	14
HU Gregorio Marañón	Yes	11
HU Fundación Alcorcón	No	29
HU Príncipe de Asturias	No	16
HU Infanta Sofía	No	6

- Patients' socio-demographic, clinical data: disability (modified Rankin scale, mRs), hospital stay and mortality; complications and healthcare resource utilization (hospitalisation, in-patient and at discharge rehabilitation, medication, laboratory tests and specific therapeutic interventions) were collected.
- Unitary costs were obtained from national healthcare database and the Spanish Catalogue of Medicinal Products (€, year 2012).

RESULTS

- Preliminary descriptive results from 76 patients (25 SU, 51 wSU) were shown in table 2.

Table 2. Demographic & clinical data

Variable	N	%
Age (mean, SD)	74.2	1.4
Female	36	47.4
Married	53	69.7
Reside at home	73	96.1
Rankin scale (mean, SD)	0.38	0.1
Hypertension	51	67.1
Dislipemias	36	47.4
Non valvular atrial fibrilation	22	28.9
Other cardiopathy	28	37.3
Ischemic cardiopathy	46	60.5

- There were significative difference between the change of mRs at discharge, (1.66, p-value =0.026), as mean mRs after admission was 2.02±0.20.
- Non-valvular atrial fibrilation was the main cause of cardioembolic stroke (28.9%).

Table 3. Healthcare resource utilization during admission

Variable	Mean	SD
Length of stay SU (days)	6.20	1.27
Length of stay in neurology	11.22	1.44
Length of stay in emergency room	1.04	0.03
Rehabilitation (N, %)	52	68.4
Physiotherapy	43	82.7
Speech therapist	22	28.8
Drug treatment (N, %)	76	100
Specific therapeutic interventions (N, %)	14	18.4
Laboratory tests (N, %)	76	100
Hospital complication (N, %)	22	28.9

- The mean length of stay was 10.1±1.14 days; mortality, 5.3%.
- 42 patients (68.4%) needed in-patient rehabilitation and 48 patients (63.2%) needed rehabilitation after hospital discharge.
- All patients needed drug treatment at hospital, whereas 93.9% continued after discharge.
- Laboratory test were performed to all patients.
- The most frequent diagnostic test were CAT (97.4%), electrocardiogram (89.5%) torax RX (86.8%) and dupplex TSA (81.6%).
- Both hemogram and biochemistry were done to all patients.
- 22 patients (28.9%) suffered hospital complications (63.6% of them suffered infections, 27.3% cardiovascular complications and 59.1% others).
- Healthcare resource utilization differences between SU and wSU hospitals were found in: length of stay (7.2±1.26 days, SU; 11.6±1.55 days, wSU; p-value=0.014) and specific therapeutic interventions (41.7%, SU; 8.0%, wSU; p-value=0.001).

Figure 1. Mean costs by variable

All numbers means costs € 2012. Hosp. hospital; Lab. laboratory; Rehab. rehabilitation; Emergency room utilization after 30 days from regular hospital admission

- The overall 4-month cost per patient was **€13,647** (49.2%, hospital stay; 24.8%, rehabilitation at discharge, see figure 1).

CONCLUSIONS

- **Cardioembolic stroke imposes significant economic burden for the Public Health System in the Region of Madrid.**
- **Key cost drivers were hospital stay and patients' rehabilitation at discharge.**
- **Patient management in SU hospitals was associated with more specific therapeutic interventions and shorter hospital stay than hospitals wSU.**

ISPOR 15th Annual European Congress, Berlin, Germany, Nov 3-7th, 2012

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CONOCES

COSTS IN PATIENTS ALONG FIRST YEAR POSTSTROKE IN SPAIN

Álvarez-Sabín J[1]; Masjuan J[2]; Casado MA[3]; Mar J[4]; Oliva J[5]; González-Rojas N[6]. **CONOCES** Study Investigators.

[1]Hospital Vall d´Hebron, Barcelona, Spain. [2]Hospital Ramón y Cajal, Madrid, Spain. [3]Pharmacoeconomics & Outcomes Research Iberia, Madrid, Spain. [4]Hospital Alto Deba, Mondragón, Spain. [5]Universidad de Castilla-La Mancha, Toledo, Spain. [6]Boehringer-Ingelheim, Barcelona, Spain.

INTRODUCTION

- Stroke is the 2nd cause of death in Spain, and the 3th in women[1]. The one-year mortality approaches 30%[2]. In addition, stroke is a prominent cause of disability and represents a high burden for the health care system and the society[3].
- Atrial fibrillation (AF) 5-folds the risk of stroke. Moreover, strokes in AF patients are more severe, with higher mortality and recurrence rates, and worse disability levels[4,5].
- Increased stroke severity in AF can represent an increase on resource use[6].
- CONOCES is the first costs of stroke study comparing patients with and without AF in Spain.

OBJECTIVE

The objective of the present study was to compare the first year post-stroke costs in patients with or without AF in spanish stroke units using a societal perspective

METHODS

The CONOCES study "Socioeconomic Stroke Costs in Spain" is an observational, multicenter, naturalistic and prospective study on stroke socioeconomic costs.

The study included 16 hospitals (stroke units of National Health System hospitals) from 16 different Spanish regions. Patients were recruited during November 2010 to May 2011.

Patient inclusion criteria: older than 18, diagnostic of clinical ischemic or hemorrhagic stroke with less of 24 hours evolution. We included 50% of patients with AF and 50% with non-AF. Patient exclusion criteria was ischemic attack, stroke history, intrahospitalary stroke. They were recruited at first stroke hospitalization (1st visit), and monitoring was at 3 and 12 months post-stroke.

The information was collected for patients and caregiver through direct physician interviews. We analyzed sociodemographic and clinical patients characteristics; and patient neurologic status, disability, dependency and QoL (NIH scale, Rankin scale, Barthel index and EQ-5D), and caregiver Zarit scale.

The study took into account consumption of direct healthcare and non-healthcare costs, societal costs (formal and informal care) and indirect costs (productivity lost and early mortality costs) during the first year post-stroke. Unit costs (€2013) were obtained from different Spanish sources (official published data).

RESULTS

321 post-stroke patients were recruited, 160 with AF and 161 without AF. 291 had an ischemic stroke (IS) and 30 an intracraneal hemorrhage (ICH) (table 1). The most predominant comorbidity was arterial hypertension (AHT). The time between stroke episode and neurology assistance was 4.96±4.85 hours. Stroke Code Activation took place in 52% of the patients. 7.8% of patients had stroke recurrences with no differences between AF and non-AF. Patients exitus one year post-stroke was 13.0% non-AF vs 21.9% AF (statistically significant, p=0.026).

NIH value improved between hospital entry and exit and it showed differences statistically significant between non-AF and AF patients at hospital entry (p <0.001) and at hospital exit (p=0.005) (table 1). Barthel index and Rankin scale improved along the year (table 1). Barthel index showed statistically significant differences between non-AF and AF patients in all visits. Also, Rankin scale showed the same profile as Barthel index between non-AF and AF patients. The global patients status one year post-stroke was mild disability and dependence.

Table 1. Patients Clinical and Sociodemographic characteristics.

	non-AF N=160	AF N=161	Total patients N=321	p-value
Age (years±SD)	67.78±14.54	76.46±9.97	72.12±13.19	<0.001
Male	60.9%	48.8%	54.8%	0.03
Ischemic stroke	86.3%	95.0%	90.7%	0.01
Intracraneal hemorrhage	13.7%	5.0%	9.3%	
Rankin scale hospital exit >2	41.0%	56.3%	48.6%	0.004
Rankin scale 2nd visit >2	29.0%	41.8%	35.0%	0.016
Rankin scale 3th visit >2	22.5%	36.4%	28.9%	0.01
Barthel index hospital exit (mean)	71.18	59.17	65.33	0.003
Barthel index 2nd visit (mean)	81.74	71.93	77.08	0.005
Barthel index 3th visit (mean)	84.27	76.21	80.56	0.014
NIH scale at hospital entry (mean±SD)	7.39±5.53	10.84±7.48	9.11±6.79	<0.001
NIH scale at hospital exit (mean±SD)	4.25±5.73	6.45±7.84	5.31±6.91	0.005
Stroke risk factors (%)	74.5%	81.9%	78.2%	–
INR value in OAC patients (mean±SD)	1.75±0.21	1.86±1.17	1.85±1.12	–
Exitus during first year post-stroke	13.0%	21.9%	17.4%	0.026
Recurrences	6.2%	9.4%	7.8%	0.198

OAC: Oral anticoagulants. INR: International Normalized Ratio index of blood coagulability.

The overall cost per year and patient was 27,711€. Direct healthcare costs were 30.6% of total costs (table 2). Intrahospital costs were 68.7% and extrahospital costs were 31.2% of total direct healthcare costs. The mainly direct cost was hospital stay which represented 70.1% of total intrahospital costs. Mean of hospital stay was 10.47±7.79 days.

Table 2. Stroke total costs.

	non-AF N=155 mean	AF N=151 mean	Total patients N=306 mean	p-value
Direct healthcare costs	8,077 €	8,915 €	8,491 €	0.291
Direct non-healthcare costs	17,797 €	19,512 €	18,643 €	0.560
Indirect costs	691 €	458 €	576 €	0.264
TOTAL COSTS	26,566 €	28,886 €	27,711 €	0.465

Direct non-healthcare costs were 67.3% of total costs, and informal care supposed… these costs (table 2-3). Only, 5.4% of patients received formal care. The inform… provided 46.42 hours per week in the 2nd visit and 42.19 hours per week … There were no significant differences between non-AF and AF patients. In… 2.1% of total costs (table 3).

AF costs were higher than non-AF but only formal care and support therapy co… statistically significant (table 2). The most explicative variables for these results were… male sex, NIH stroke scale, AHT comorbidity, and exitus along study.

Table 3. Stroke intrahospital and extrahospital costs.

	non-AF N=155 mean	AF N=151 mean	Total patients N=306 mean	p-value
INTRAHOSPITAL COSTS				
Direct healthcare costs	5,642 €	6,040 €	5,838 €	0.387
Direct non-healthcare costs	10 €	14 €	12 €	0.085
Total intrahospital costs	5,652 €	6,054 €	5,850 €	0.384
EXTRAHOSPITAL COSTS				
Direct healthcare costs	2,436 €	2,876 €	2,653 €	0.438
Direct non-healthcare costs	17,787 €	19,498 €	18,631 €	0.561
Indirect costs	691€	458 €	576€	0.264
Total extrahospital costs	20,913 €	22,832 €	21,860 €	0.538

CONCLUSIONS

- The management of stroke patients has improved in terms of mortality and recurrence.
- Stroke and its consequences represent an important use of healthcare and social resources during the first year post-stroke (hospital stay and informal care costs mainly).
- The costs are higher in AF patients than in non-AF patients, although global study do not show statistical significance. We obtain significance in formal care costs and support therapy costs.
- Several studies from others countries showed similar healthcare costs but lower informal care costs, which where more than two-thirds of total costs in our study, with a very high burden over the family or informal caregiver.

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PCV61

ISPOR 16TH ANNUAL EUROPEAN CONGRESS 2-6 November 2013 The Convention Centre Dublin

Boehringer Ingelheim

CONOCES

28.886 €
Primer año
Ictus + FA

unidad de Ictus
Hospital Universitario de la Princesa
Servicio de Neurología

Gentileza del Dr. Jaime Masjuan

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Annals of Internal Medicine | Review

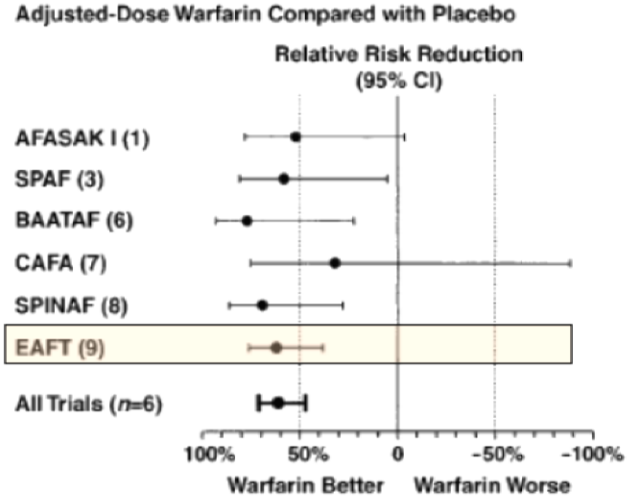
Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation

Robert G. Hart, MD; Lesly A. Pearce, MS; and Maria I. Aguilar, MD

Ann Intern Med. 2007;146:857-867.

Meta-análisis: warfarina vs placebo

Reducción R.R. Ictus 64%



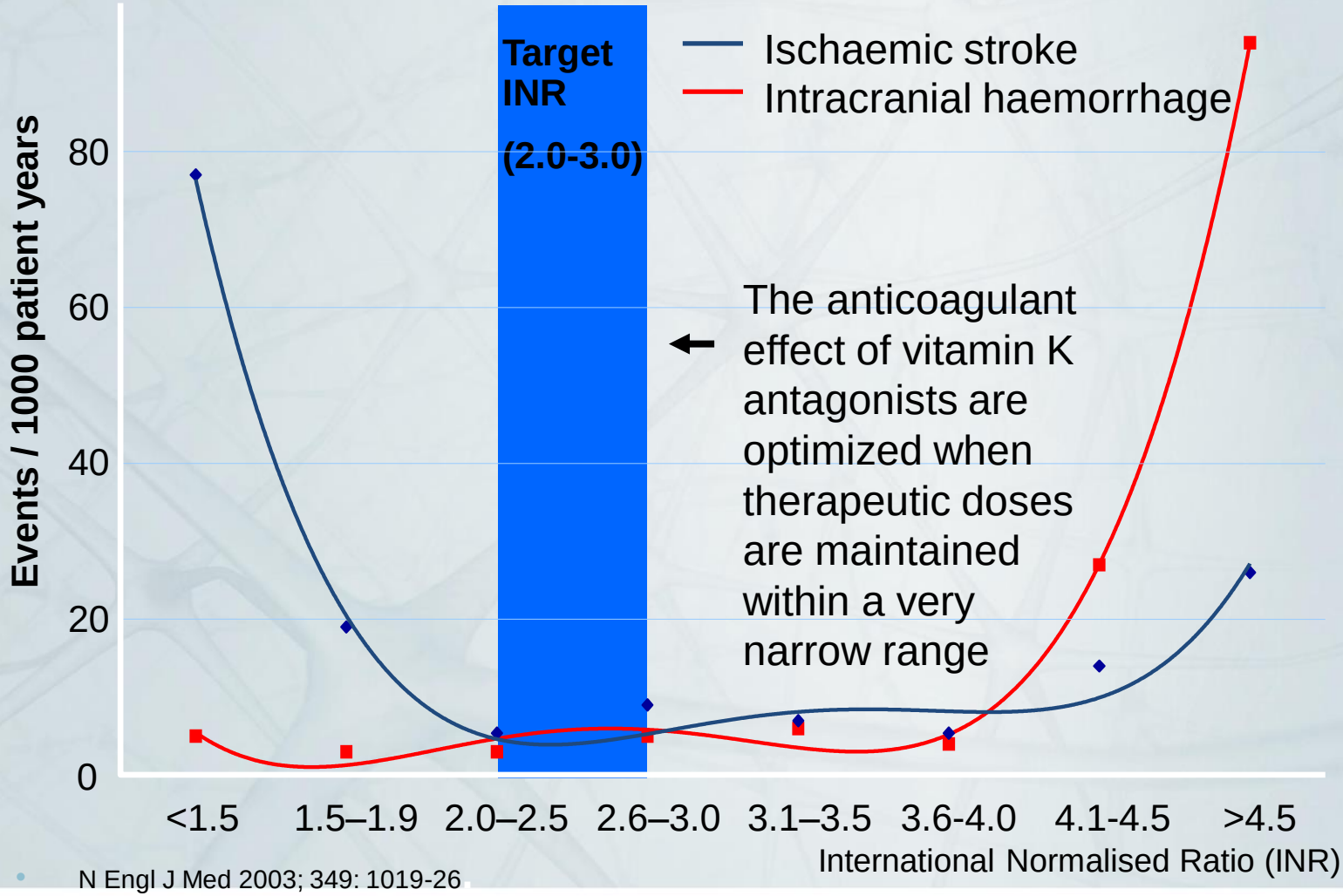
Reducción del riesgo relativo de ictus del **64%**

NNT (evento vascular mayor):
-Prevención primaria: 37
-Prevención secundaria: 14

Reducción riesgo relativo de **mortalidad** de cualquier causa del 26% con NNT=62

Stroke Prevention in Atrial Fibrillation

Limitations of Warfarin Therapy in AF: Narrow Therapeutic Window



- N Engl J Med 2003; 349: 1019-26

Pacientes con FA con AVK en rango terapéutico

- **Metaanálisis ensayos clínicos**
  - **66,4%**

  • Van Walraven C et al. Chest 2006; 129: 1155-1166

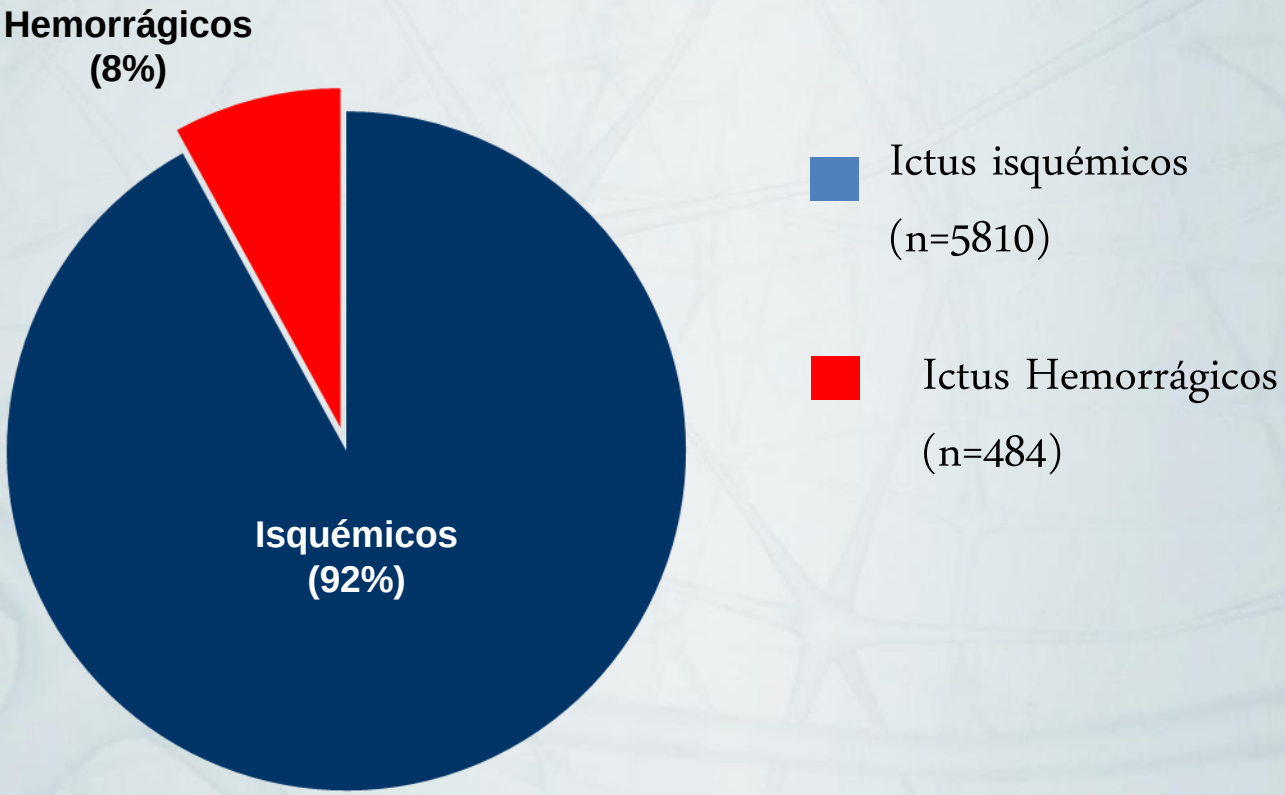
- **Práctica clínica habitual**
  - **56,7%**

  • Baker WL et alJ Manag Care Pharm 2009; 15: 244-252

- **Unidad de Ictus HULP (2012)**
  - **Ictus cardioembólicos x FA + INR fuera de rango: 67%**
  - **Ictus hemorrágicos en FA tratada con Sintrom: 21%**

La mayoría de los Ictus que se asocian con FA son Isquémicos

Tipos de Ictus en los Pacientes con FA



Basado en los datos obtenidos del Proyecto Nacional Indicadot Danés con 39.484 pacientes hospitalizados por Ictus (incluidos 6.294 pacientes con FA) Andersen KK et al. Stroke 2009;40:2068–72

Hemorragias intracerebrales

SOCIEDAD ESPAÑOLA DE NEUROLOGÍA

DIAGNÓSTICO DE LAS HEMORRAGIAS INTRACEREBRALES

	N	%
Hipertensivas	**435**	**56.4**
Secundarias	**98**	**12.7**
- Anticoagulantes	65	8.4
- Malformaciones AV	17	2.2
- Drogas	3	0.4
- Discrasias sanguíneas	9	1.2
- Tumores	4	0.5
Amiloideas	**107**	**13.9**
Indeterminadas	**131**	**17.0**

REGISTRO EPICES
EPidemiología del ICtus en ESpaña

FANV, Anticoagulación con AVK y Riesgo Hemorrágico

Risk of Stroke or Systemic Embolism in Atrial Fibrillation Patients Treated With Warfarin

A Systematic Review and Meta-analysis

Ida Ehlers Albertsen, BSc; Lars Hvilsted Rasmussen, MD, PhD; Thure Filskov Overvad, BSc; Tina Graungaard, MSc; Torben Bjerregaard Larsen, MD, PhD; Gregory Y.H. Lip, MD

Background and Purpose—Although oral anticoagulants (OACs) are highly effective in reducing stroke risk in atrial fibrillation, some patients still sustain stroke despite being on an OAC. Our aim was to identify the risk factors that contribute to stroke risk in atrial fibrillation, although patients were taking OACs in a clinical trial setting.

Methods—We identified contemporary clinical trials that investigated OACs in patients with atrial fibrillation. Event rates per year from each study and pooled event rates and relative risks, all with a 95% confidence interval, were calculated. Statistical heterogeneity was assessed using the I^2 test.

Results—Six trials were included in the meta-analysis, with a total of 58 883 patients randomized. Characteristics associated

Conclusions—Stroke rates are higher on OACs with some patient clinical characteristics, that is, older age, female sex, previous stroke/transient ischemic attack, vitamin K-antagonist naive status, renal impairment, previous aspirin use, and higher $CHADS_2$ score. The identified risk factors for stroke while on an OAC could potentially be used to consider a risk assessment tool to flag up high-risk patients while on an OAC (in this case, warfarin). Whether these risk factors apply to novel OACs is uncertain. (***Stroke*. 2013;44:1329-1336.**)

higher $CHADS_2$ score. The identified risk factors for stroke while on an OAC could potentially be used to consider a risk assessment tool to flag up high-risk patients while on an OAC (in this case, warfarin). Whether these risk factors apply to novel OACs is uncertain. (***Stroke*. 2013;44:1329-1336.**)

Key Words: atrial fibrillation ■ oral anticoagulation ■ stroke ■ warfarin

Stroke 2013; 44: 1329

Los Anticoagulantes Orales de 2ª Generación (AO2G)







AO2G: Eficacia y seguridad

Resultados de Eficacia (nACOs)

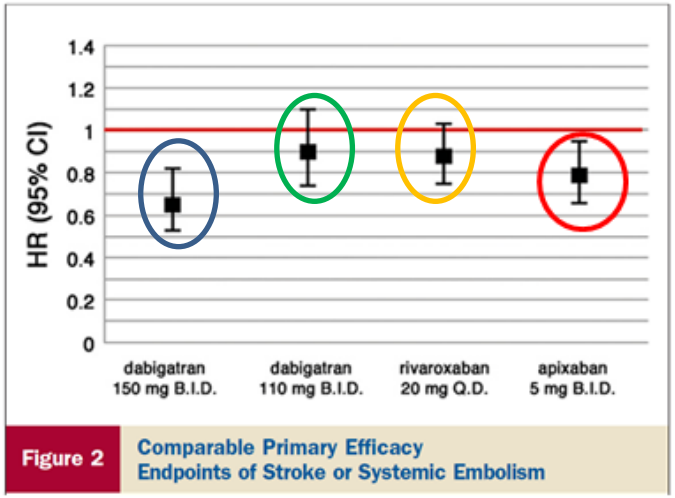


Figure 2 Comparable Primary Efficacy Endpoints of Stroke or Systemic Embolism

De Caterina R, et al. JACC 2012;59:1413–25

Resultados de Seguridad (nACOs)

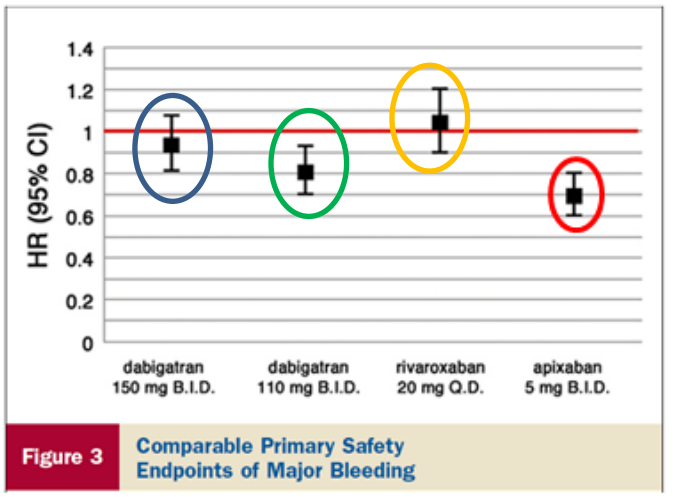


Figure 3 Comparable Primary Safety Endpoints of Major Bleeding

De Caterina R, et al. JACC 2012;59:1413–25

AO2G: Eficacia y seguridad

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

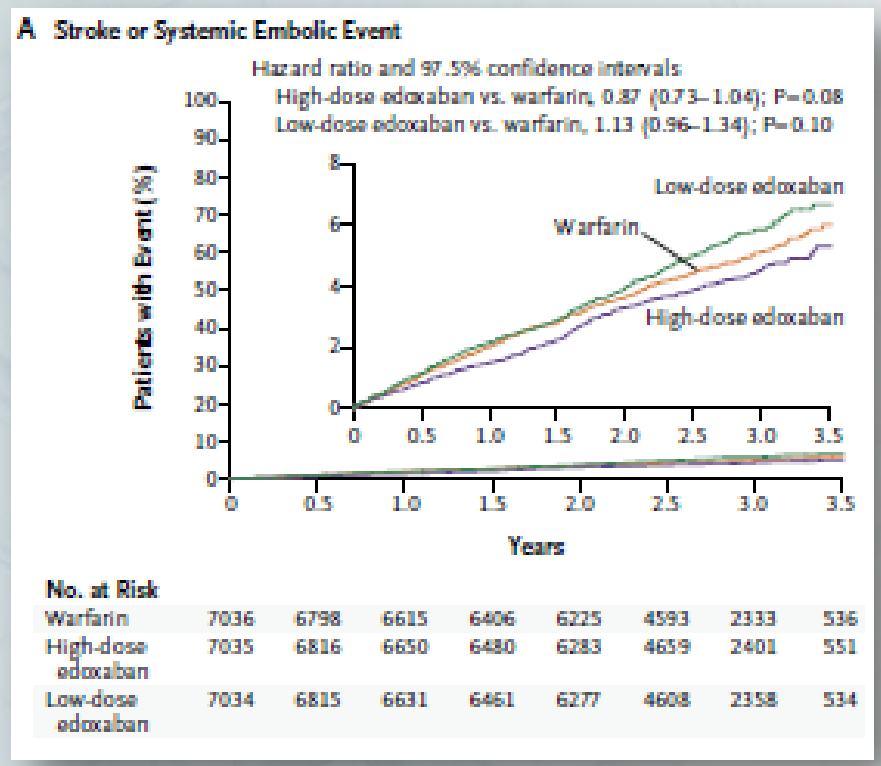
Edoxaban versus Warfarin in Patients with Atrial Fibrillation

Robert P. Giugliano, M.D., Christian T. Ruff, M.D., M.P.H., Eugene Braunwald, M.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Jonathan L. Halperin, M.D., Albert L. Waldo, M.D., Michael D. Ezekowitz, M.D., D.Phil., Jeffrey I. Weitz, M.D., Jindřich Špinar, M.D., Witold Ruzyllo, M.D., Mikhail Ruda, M.D., Yukihiro Koretsune, M.D., Joshua Betcher, Ph.D., Minggao Shi, Ph.D., Laura T. Grip, A.B., Shirali P. Patel, B.S., Indravadan Patel, M.D., James J. Hanyok, Pharm.D., Michele Mercuri, M.D., and Elliott M. Antman, M.D., for the ENGAGE AF-TIMI 48 Investigators*

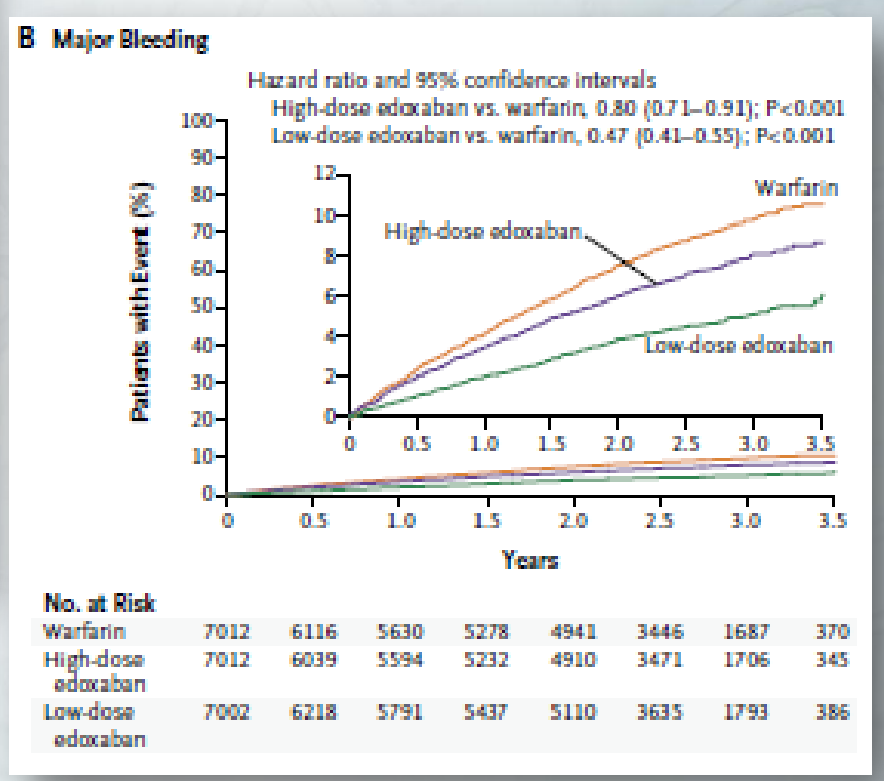
N Engl J Med 2013.
DOI: 10.1056/NEJMoa1310907

Edoxaban

Eficacia



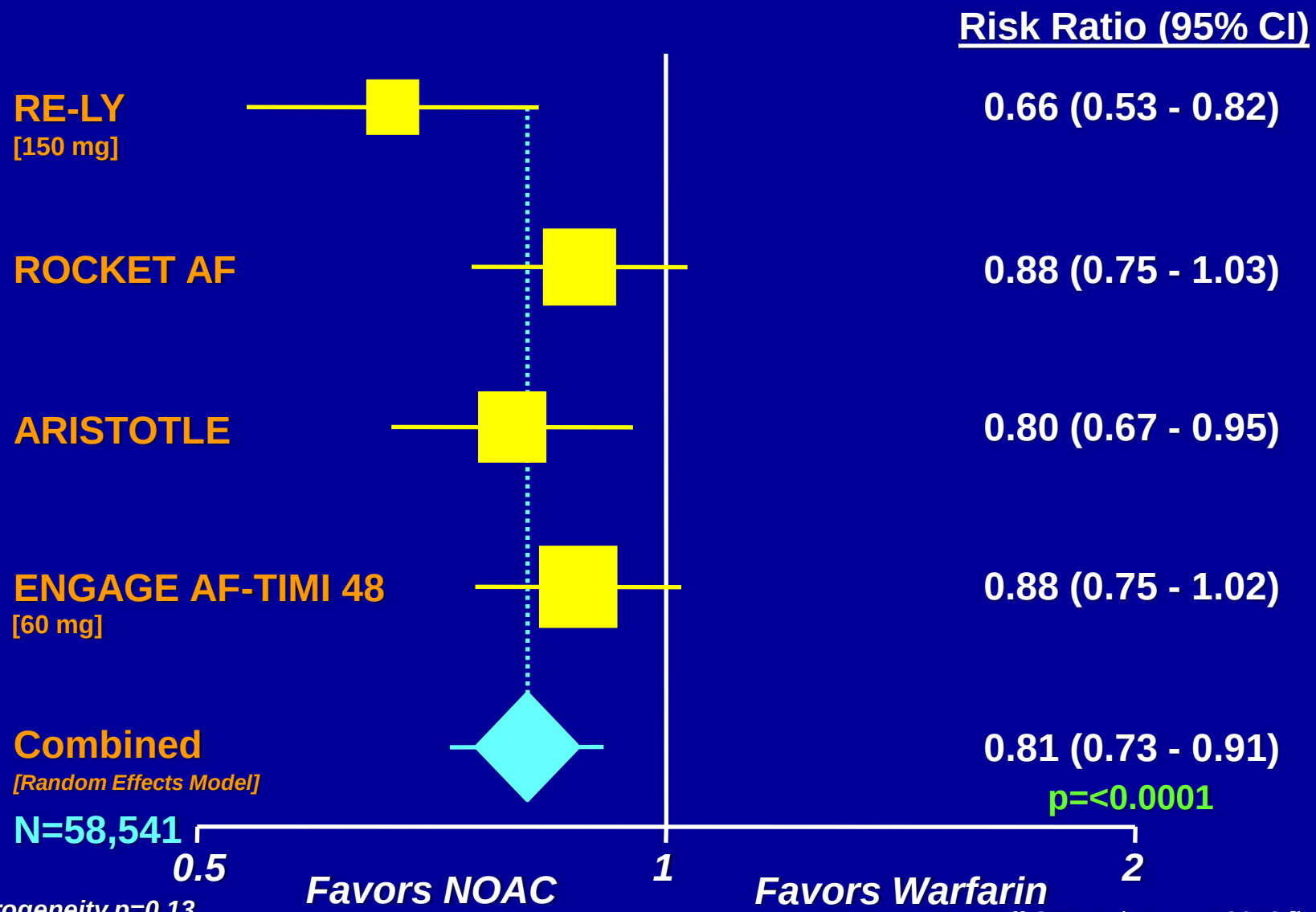
Seguridad



N Engl J Med 2013.
DOI: 10.1056/NEJMoa1310907

Gentileza del Dr. José Mª Lobos

All NOACS: Stroke or SEE



Ruff CT, et al. Lancet 2013 [in-press]

Garfield

global anticoagulant registry in the field

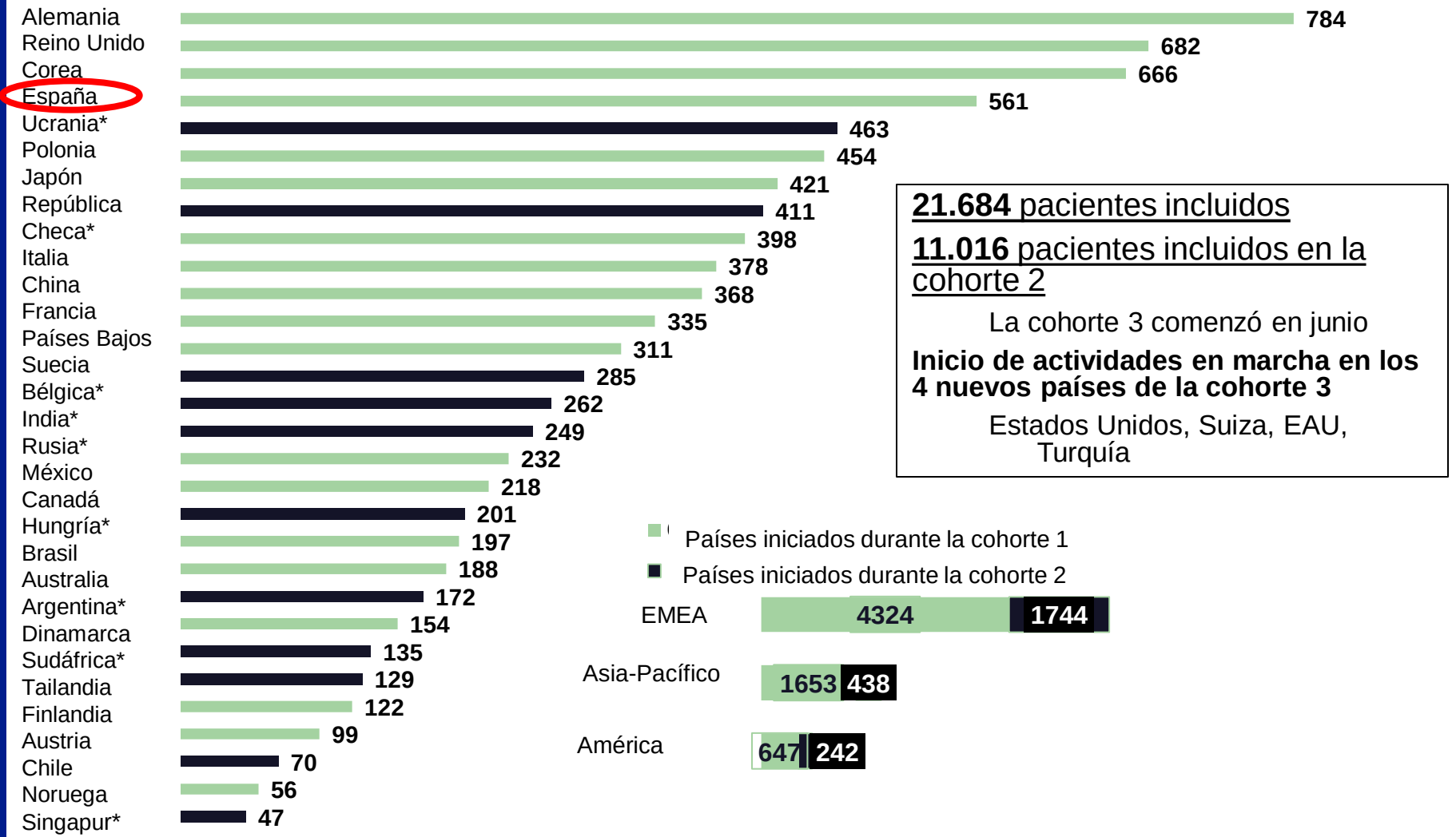
Registro internacional, multicéntrico y prospectivo de pacientes de ambos sexos con diagnóstico reciente de fibrilación auricular

Diseño del estudio GARFIELD AF

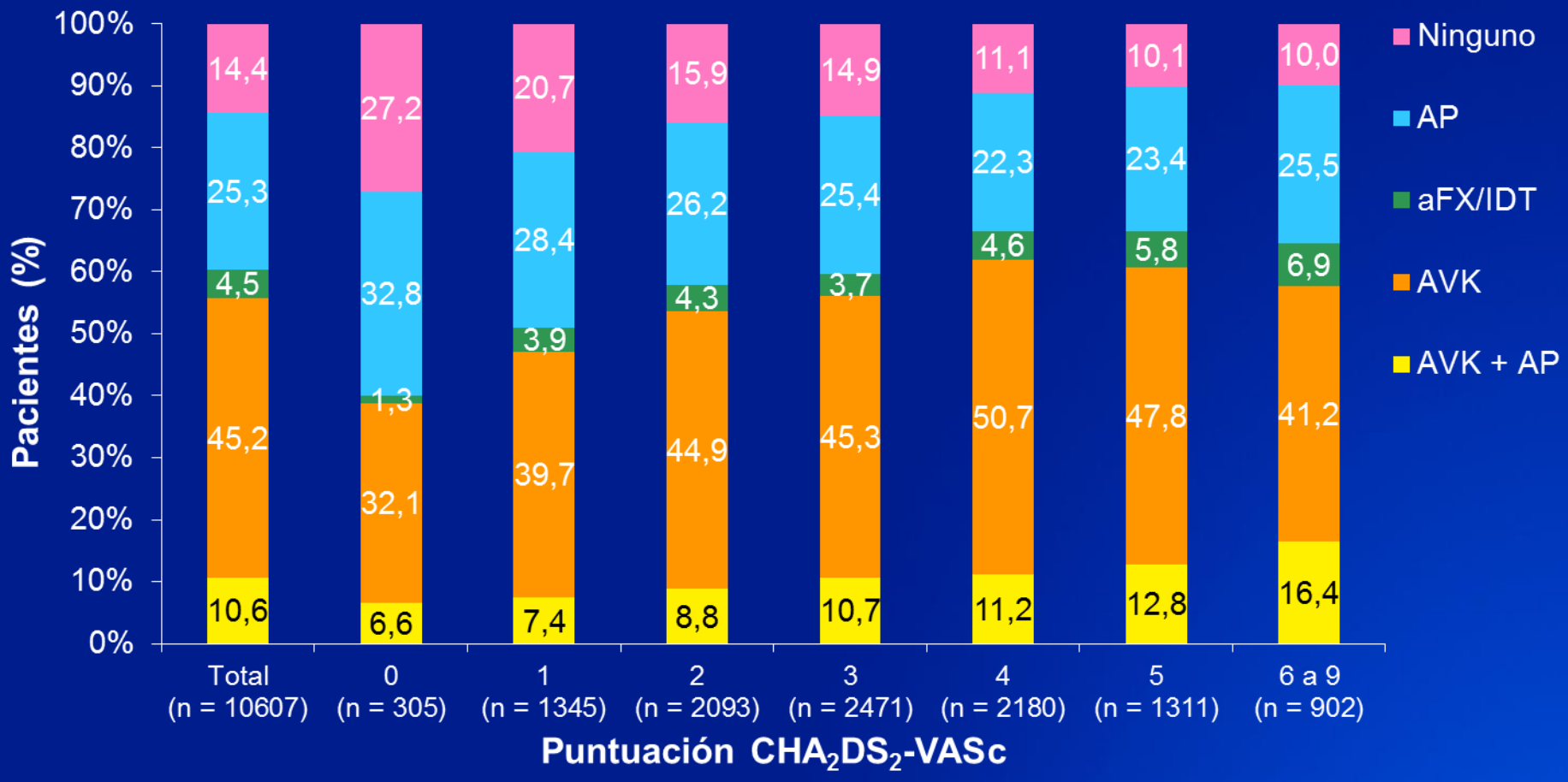
- Estudio observacional en adultos con FA no valvular de reciente diagnóstico y ≥ 1 factor de riesgo de ictus adicional definido por el investigador
- Centros representativos de ámbitos de atención sanitaria de la FA en cada país
- Sin intervención terapéutica
- Pacientes consecutivos reclutados en cinco cohortes secuenciales:
  - Objetivo de 55.000 pacientes (50.000 prospectivos y 5.000 retrospectivos)
  - > 1.000 centros seleccionados de forma aleatoria en ≥ 35 países
- Período de seguimiento de al menos 2 años

Kakkar y cols., 2013; Apenteng y cols., 2013

Estado de países de la cohorte 2 de GARFIELD - inicio de la cohorte 3 (junio de 2013)



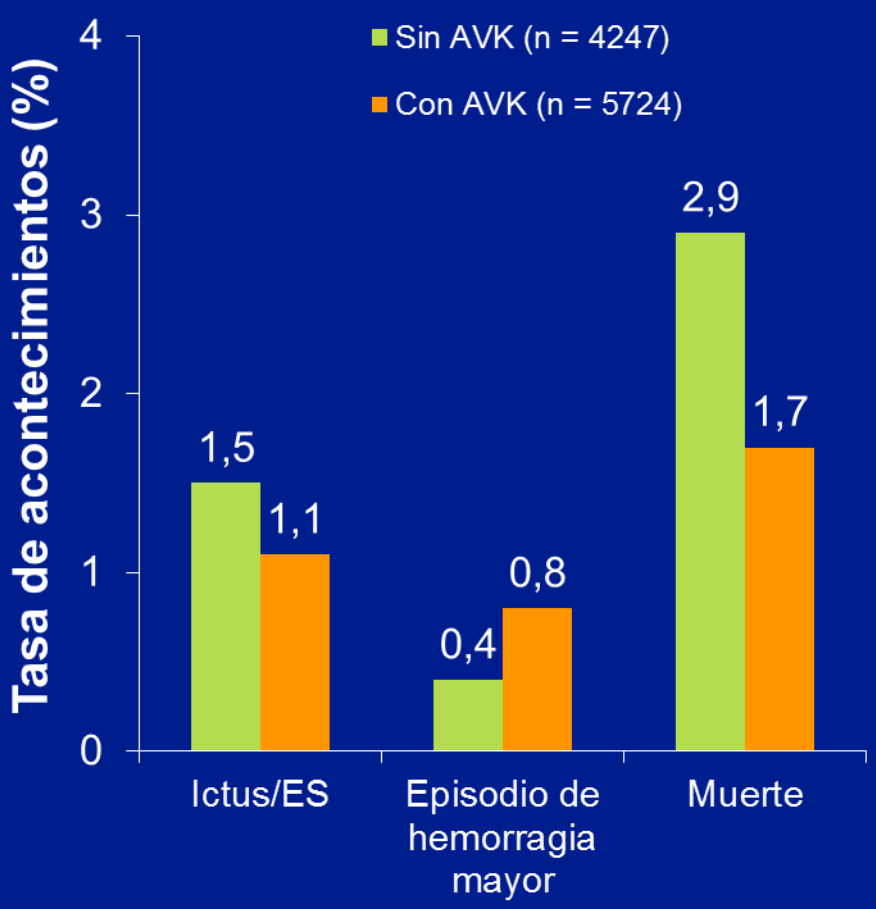
Cohorte 1: uso de anticoagulantes por puntuación CHA_2DS_2-VASc

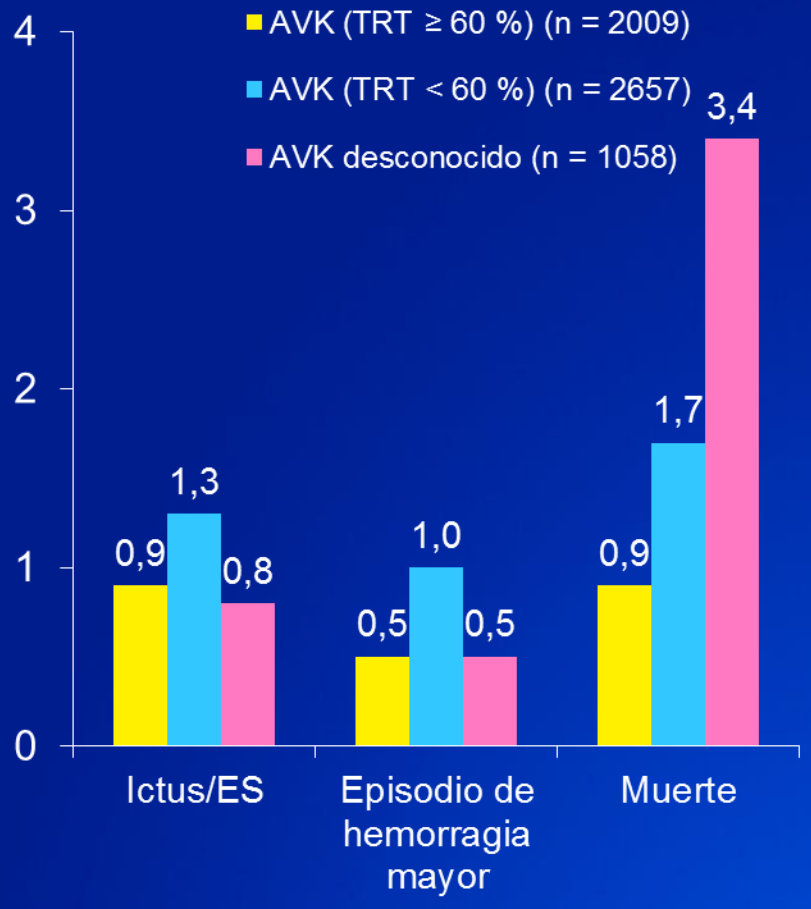


- Sin prescripción de anticoagulantes un importante % de los pacientes con puntuación CHA_2DS_2-VASc ≥ 2.

Kakkar y cols., 2013

Cohorte 1: tasas de eventos durante el primer año en función del control con AVK*





*Recopilación de datos en curso

Kakkar y cols., 2012b

RELY®

Study of stroke prevention in atrial fibrillation

RELY-ABLE™

RE-LY® and RELY-ABLE™ Long-term Follow-up of Patients with Non-valvular Atrial Fibrillation Receiving Dabigatran Etexilate for up to 6.7 Years

Michael D Ezekowitz[1], Anthony P Kent[1], Janice Pogue[2], Paul A Reilly[3], Martina Brueckmann[4], Christine Duffy[3], Andreas Clemens[4], Salim Yusuf[2], Lars Wallentin[5], and Stuart J Connolly[2]

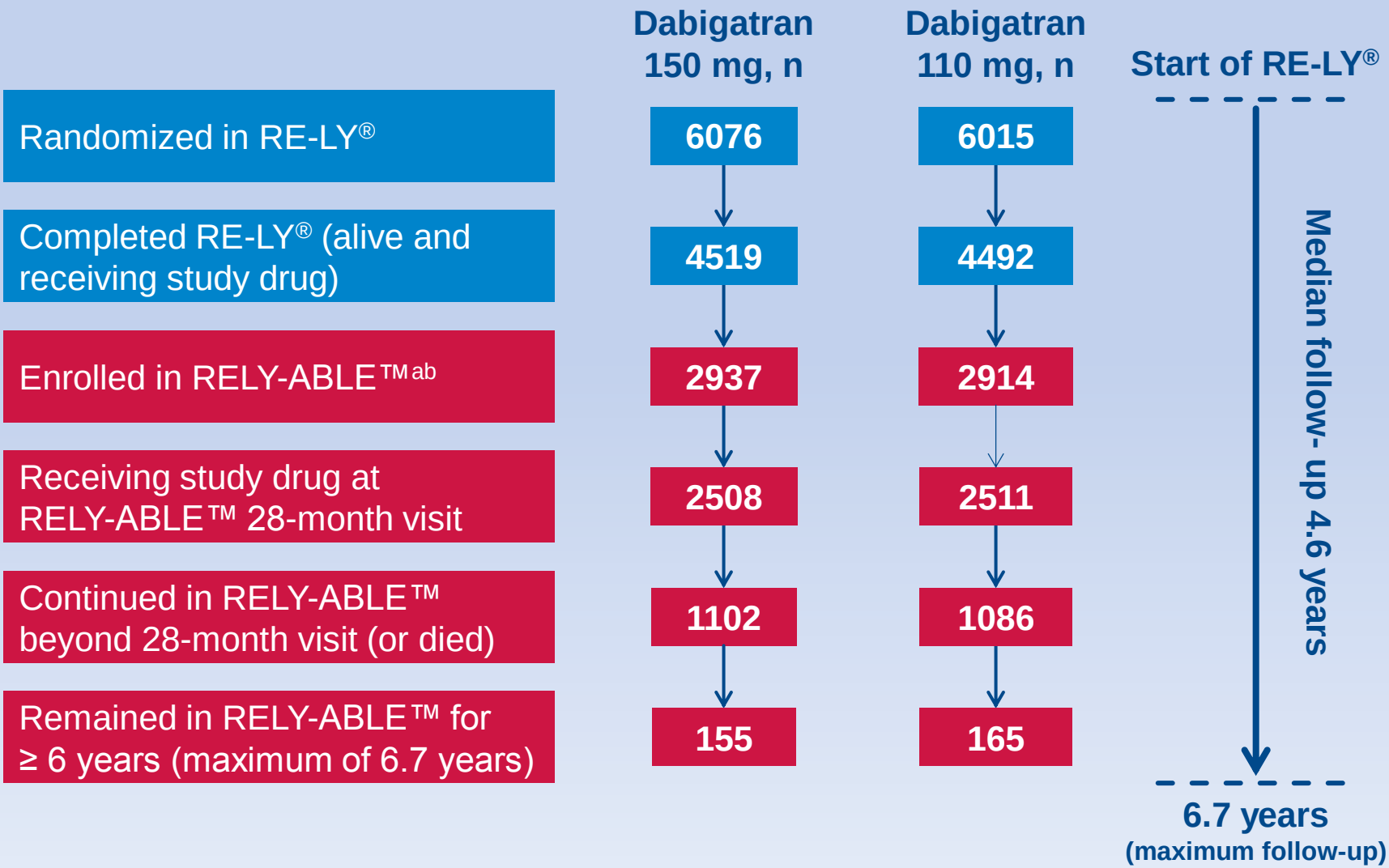
[1]Jefferson Medical College, Philadelphia, PA, USA; [2]McMaster University, Hamilton, ON, Canada; [3]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; [4]Boehringer Ingelheim GmbH & Co. KG, Ingelheim am Rhein, Germany; [5]University Hospital Uppsala, Uppsala, Sweden

AHA 2013, November 16–20 2013, Dallas, Texas

Patient Flow Through RE-LY® and RELY-ABLE™

RELY® Study of stroke prevention in atrial fibrillation

RELY-ABLE™

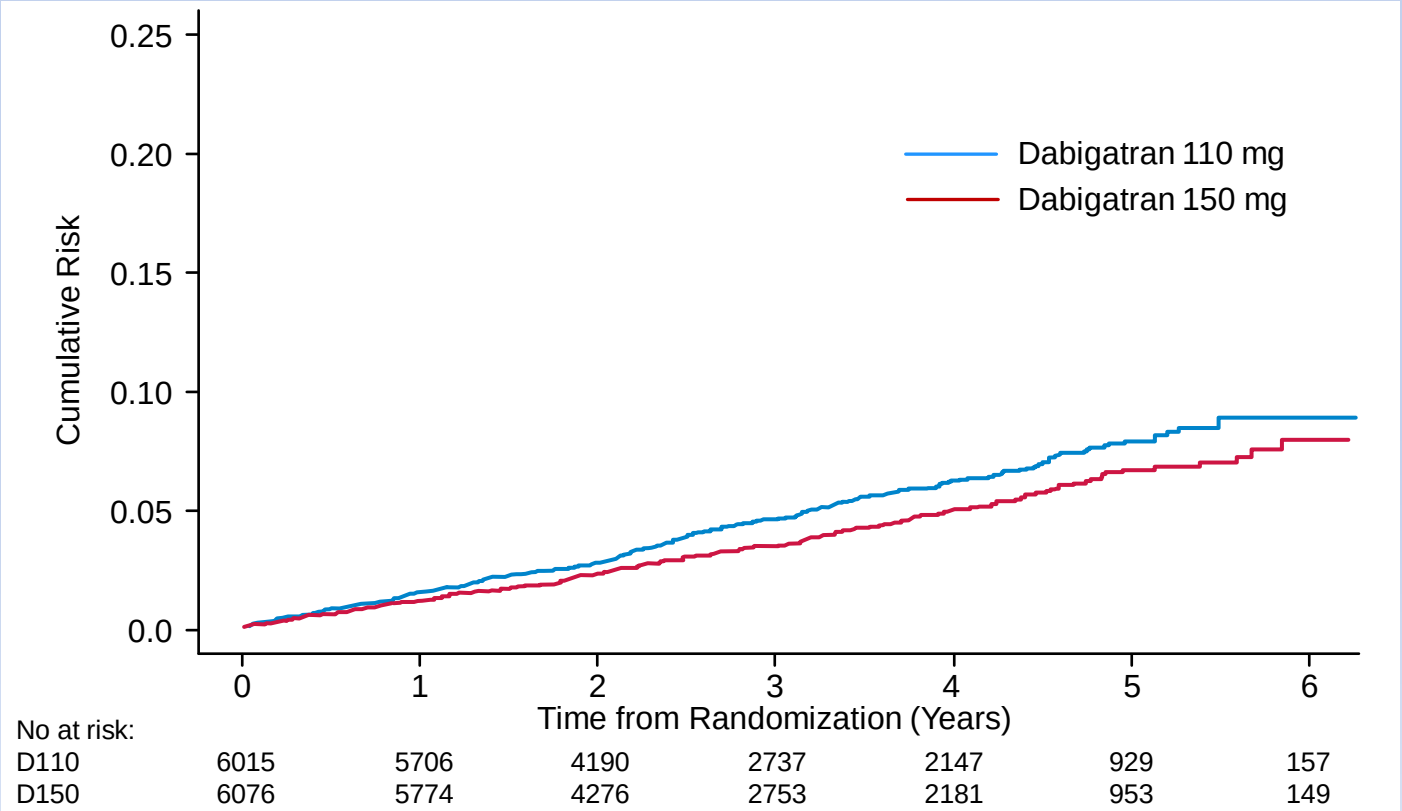


[a]Patients randomized to warfarin in RE-LY® were not eligible for RELY-ABLE™; [b]Excluding 40 patients who did not receive study drug or for whom there were serious protocol violations at their center.

Stroke or Systemic Embolism

RELY®
Study of stroke prevention in atrial fibrillation

RELY-ABLE™

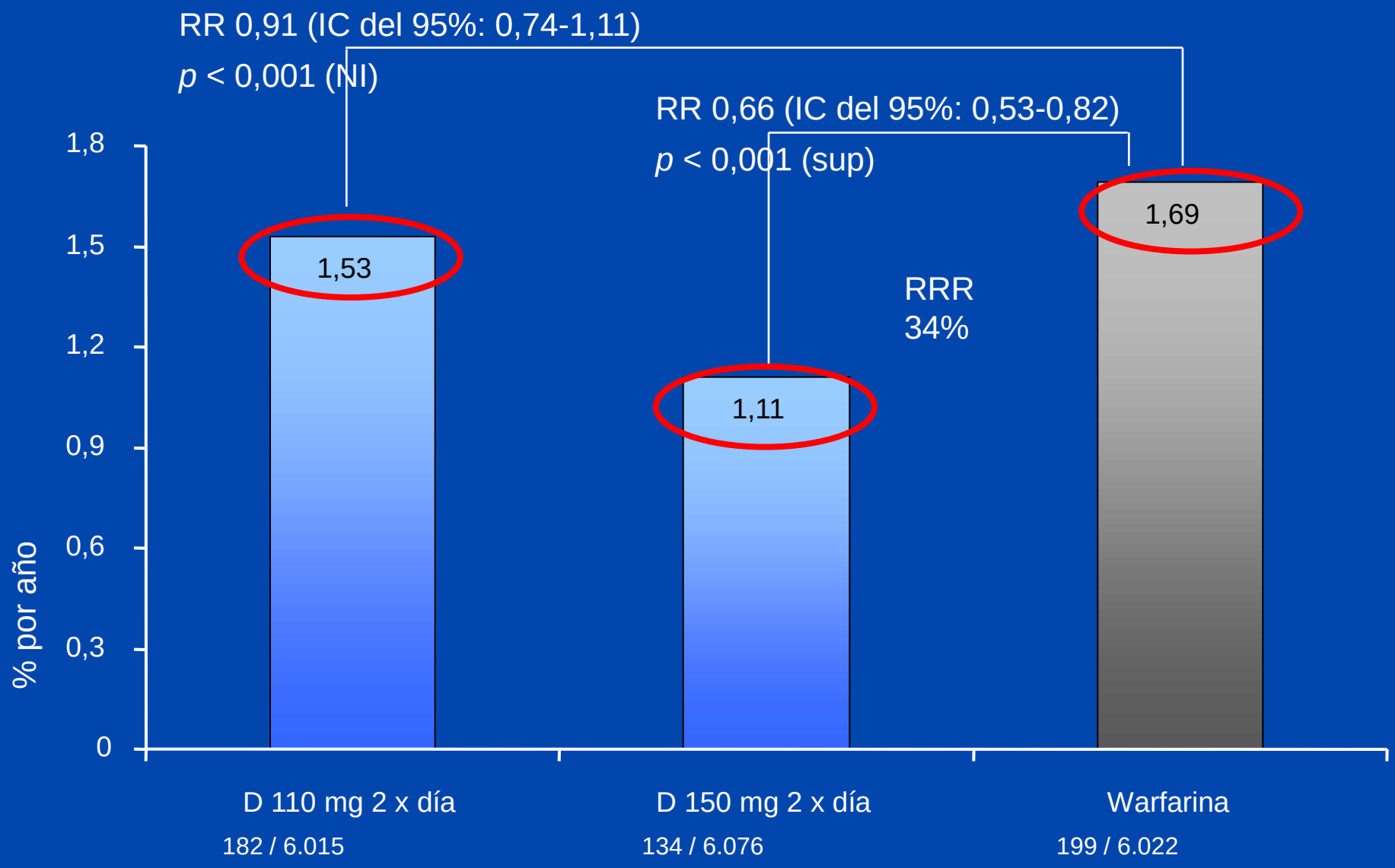


Annual rate of stroke or systemic embolization:
Dabigatran 150 mg, 1.25% per year; 110 mg, 1.54% per year
HR 0.81 (95% CI 0.68, 0.96)

D110 = Dabigatran 110 mg; D150 = Dabigatran 150 mg; HR: hazard ratio; CI = confidence interval.

Ictus o embolia sistémica

RELY®
Study of stroke prevention in atrial fibrillation



Connolly SJ, et al. *NEJM* 2009;361:1139-51

Major Bleeding

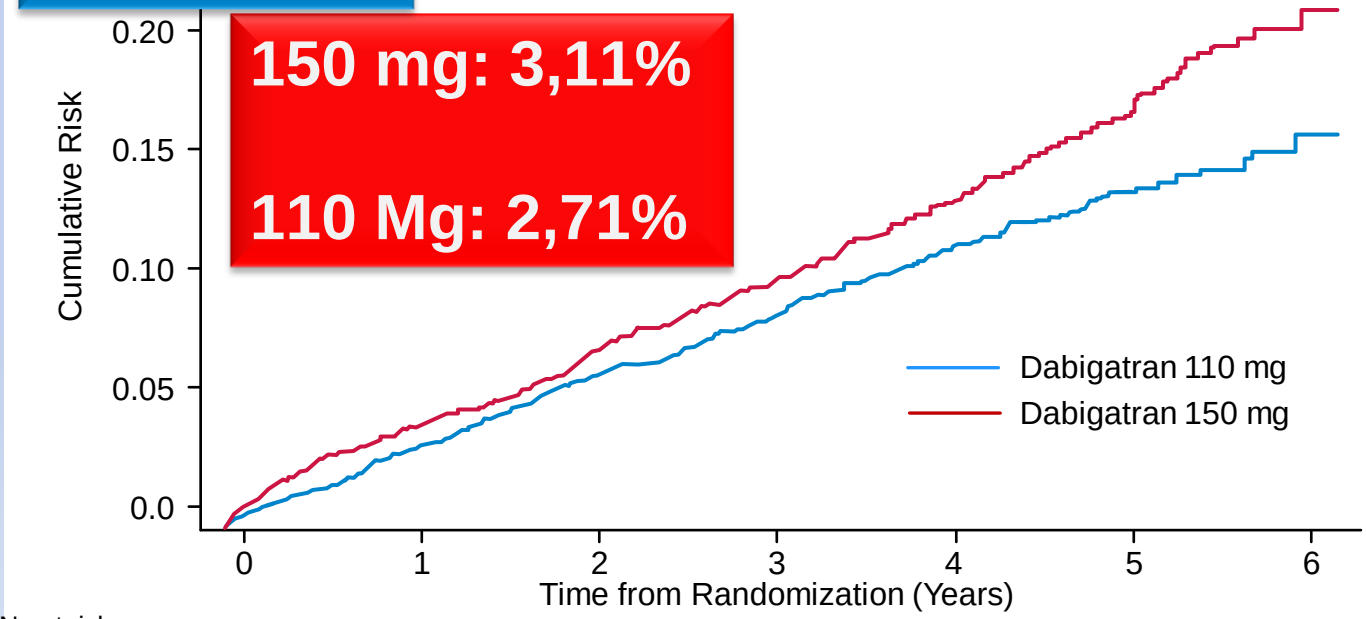
RELY® Study of stroke prevention in atrial fibrillation

RELY-ABLE™

RE-LY

150 mg: 3,11%

110 Mg: 2,71%



No at risk:

D110	6015	5616	4075	2658	2085	903	158
D150	6076	5622	4130	2638	2077	910	146

Annual rate of major bleeding:
Dabigatran 150 mg, 3.34% per year; 110 mg, 2.76% per year
HR 1.22 (95% CI 1.08, 1.37)

D110 = Dabigatran 110 mg; D150 = Dabigatran 150 mg; HR: hazard ratio; CI = confidence interval.

FDA Mini-Sentinel Data[1]

RE-LY

150 mg: 1,51%

110 Mg: 1,12%

	FDA Postmarketing Surveillance*			
	atran		Warfarin	
		Incidence (No. of events per 0,000 days at risk)	No. of events/ No. of patients	Incidence (No. of events per 100,000 days at risk)
GI major bleeding	16/10,599	1.6	160/43,541	3.5
Intracranial bleeding	8/10,587	0.8	109/43,594	2.4

ran and warfarin from the Mini-Sentinel distributed database, October 2010
11. Events were assessed during drug exposure, from inpatient or emergency
nly. Analysis with required diagnosis of atrial fibrillation.

RE-LY

150 mg: 0,30%

110 Mg: 0,23%

DA`s conclusion:

"Bleed ith new use of dabigatran do not appear to be h tes associated with new use of warfarin"

FDA = Food and Drug Administration; GI = gastrointestinal.

1. Southworth MR, Reichman ME, Unger EF. *NEJM* 2013;14:1272–1274.

Análisis del uso de nuevos anticoagulantes orales en un área sanitaria de Asturias

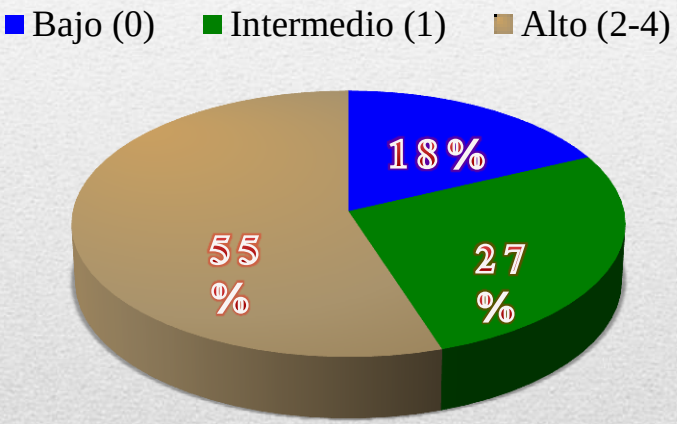
Pablo Sánchez Lozano
Sergio Calleja Puerta
Ángeles Fernández Rodríguez (1)
Marta Suárez Pinilla
Lorena Benavente Fernández
Davinia Larrosa Campo

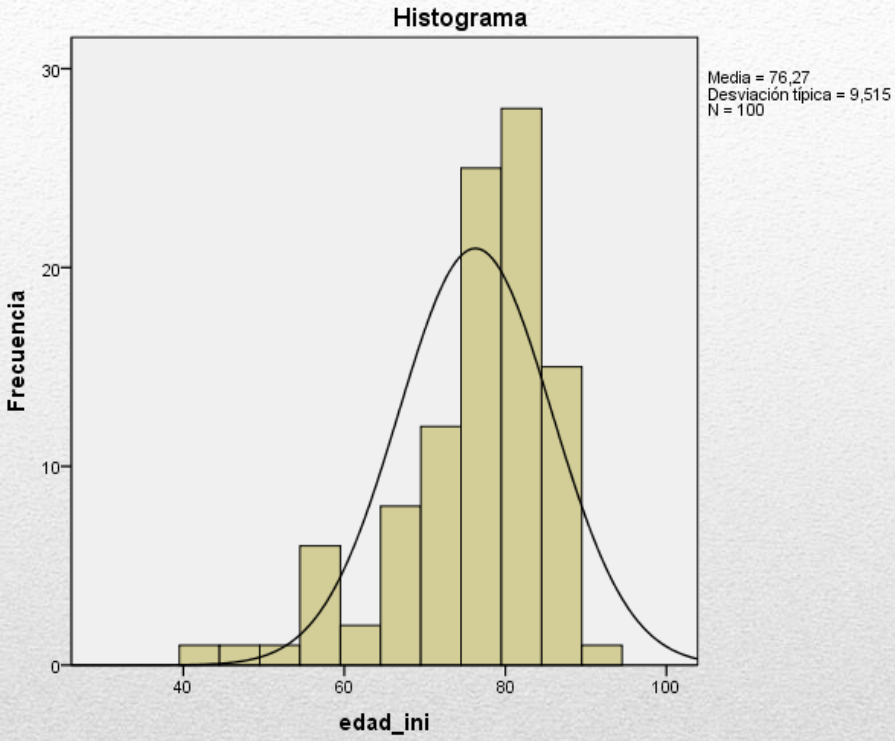
Servicios de Hematología (1) y Neurología

Gentileza del Dr. Sergio Calleja

LVI Reunión Annual de la S.E.N. Barcelona 20-22 de Noviembre 2013

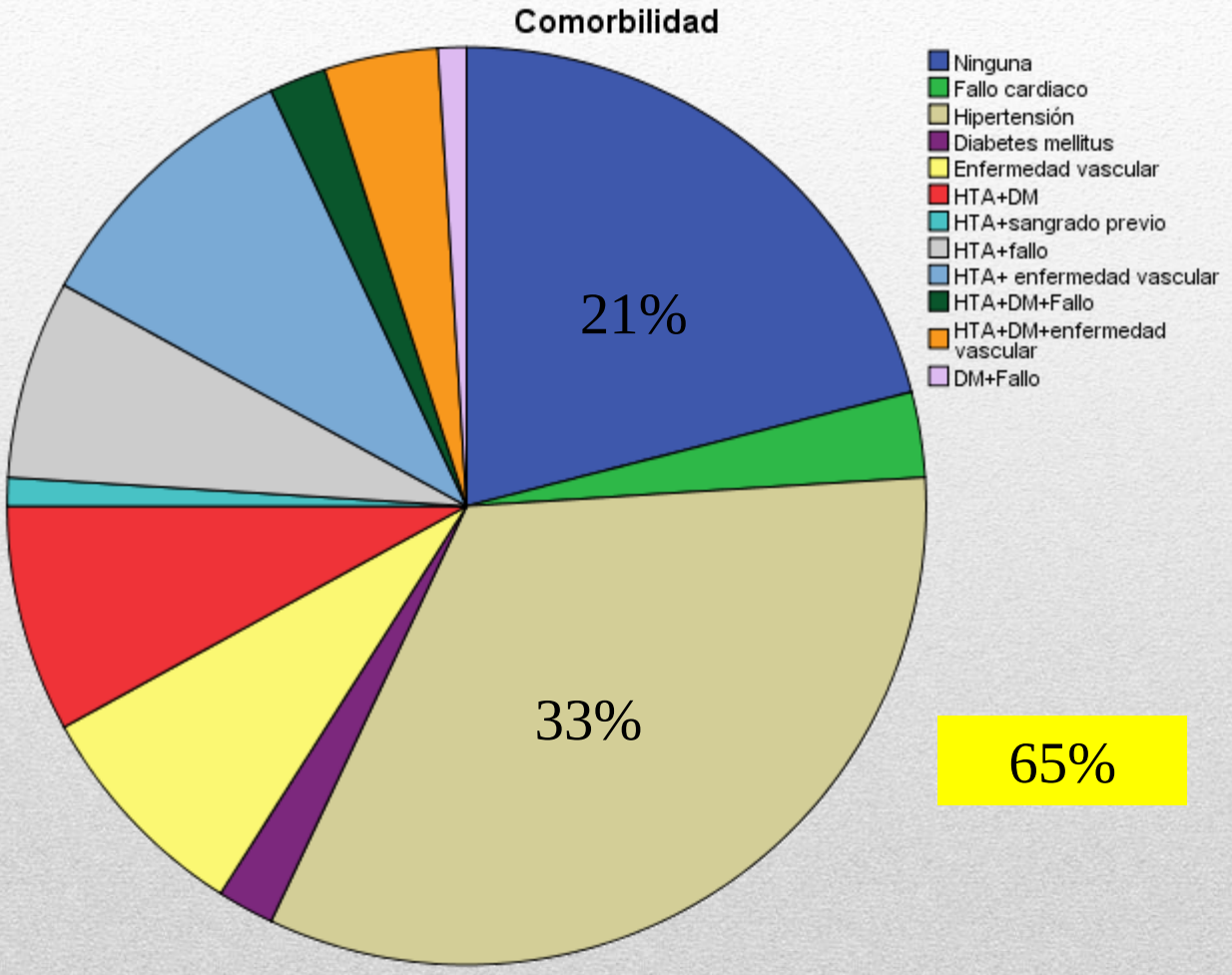
- Varones 49%
- Mujeres 51%





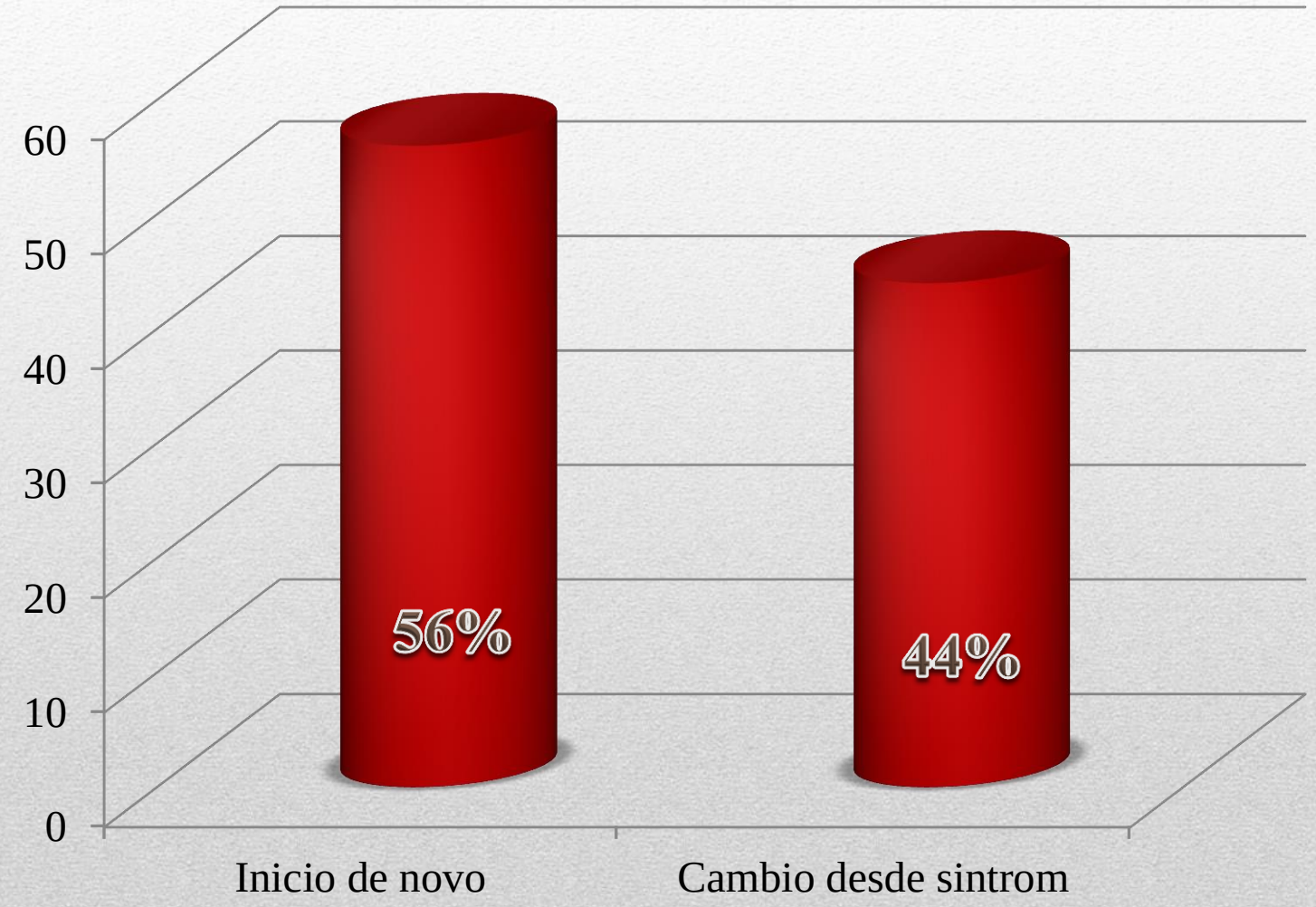
- CHADS VASC mayor de 2 en el 55% de la muestra
- 18% una puntuación de 0

- Edad media 76,27 años
- 38% de los pacientes son mayores de 80 años

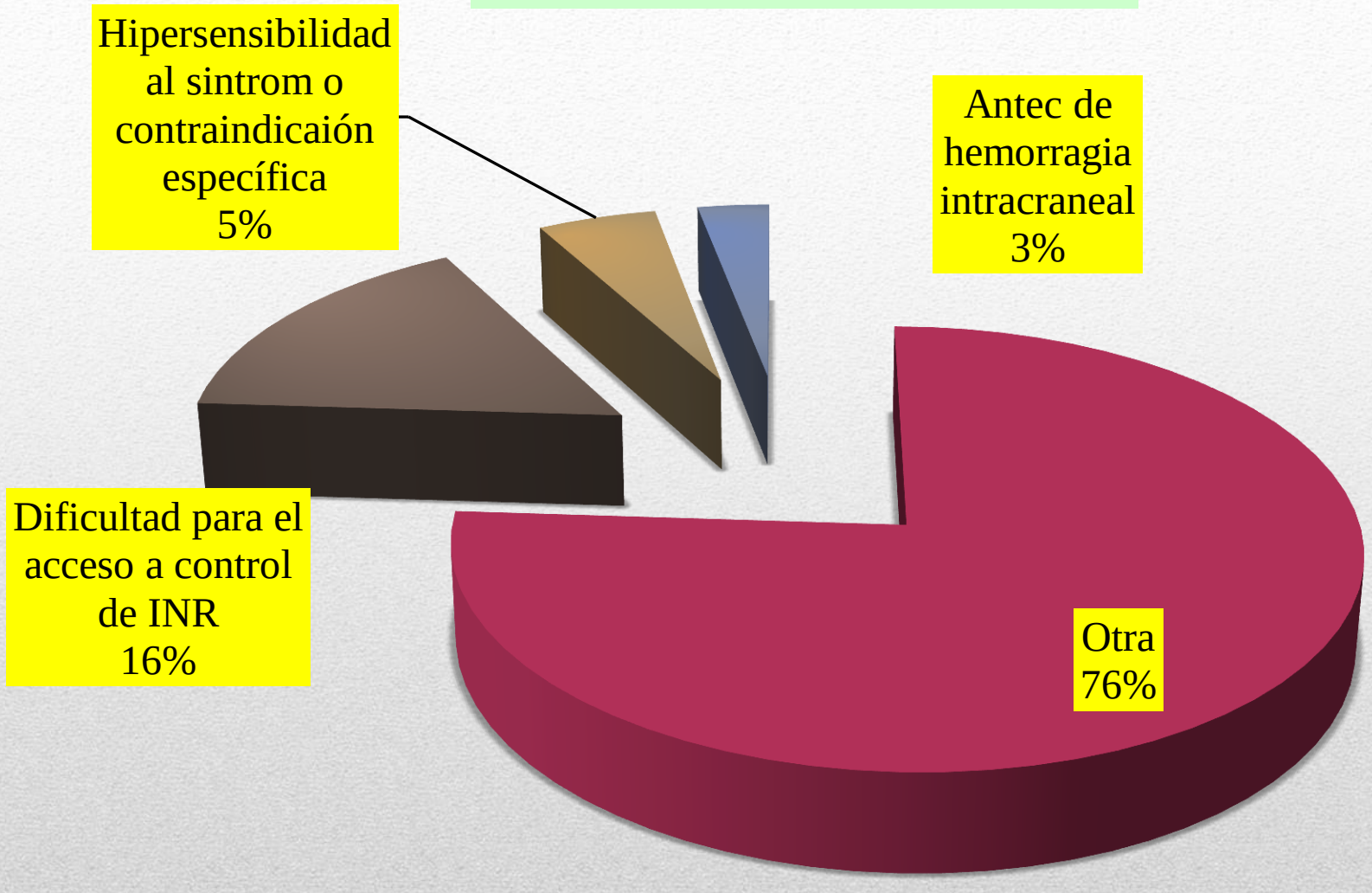

Comorbilidad
Ninguna
Fallo cardiaco
Hipertensión
Diabetes mellitus
Enfermedad vascular
HTA+DM
HTA+sangrado previo
HTA+fallo
HTA+ enfermedad vascular
HTA+DM+Fallo
HTA+DM+enfermedad vascular
DM+Fallo
21%
33%

65%

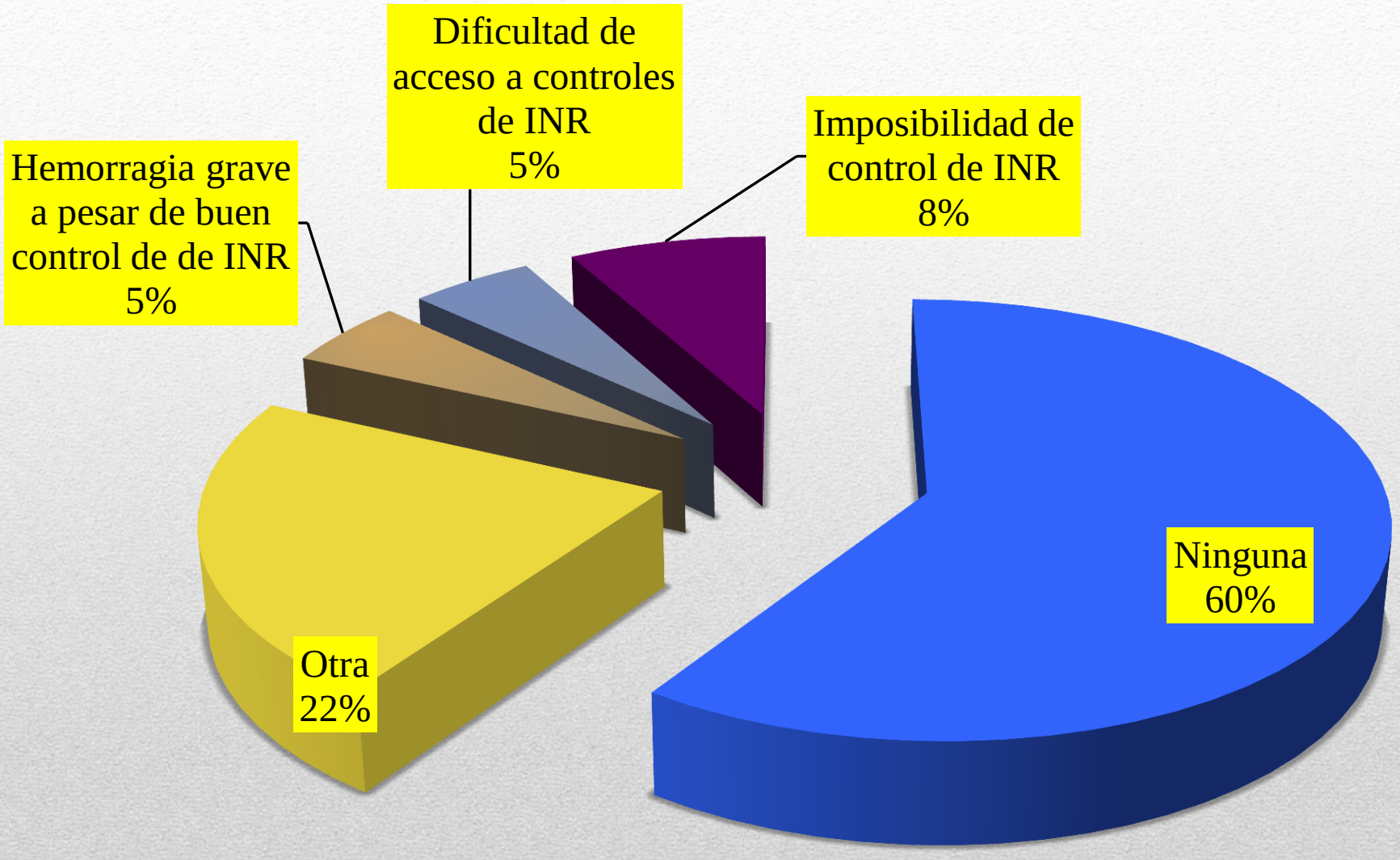
Tipo de tratamiento



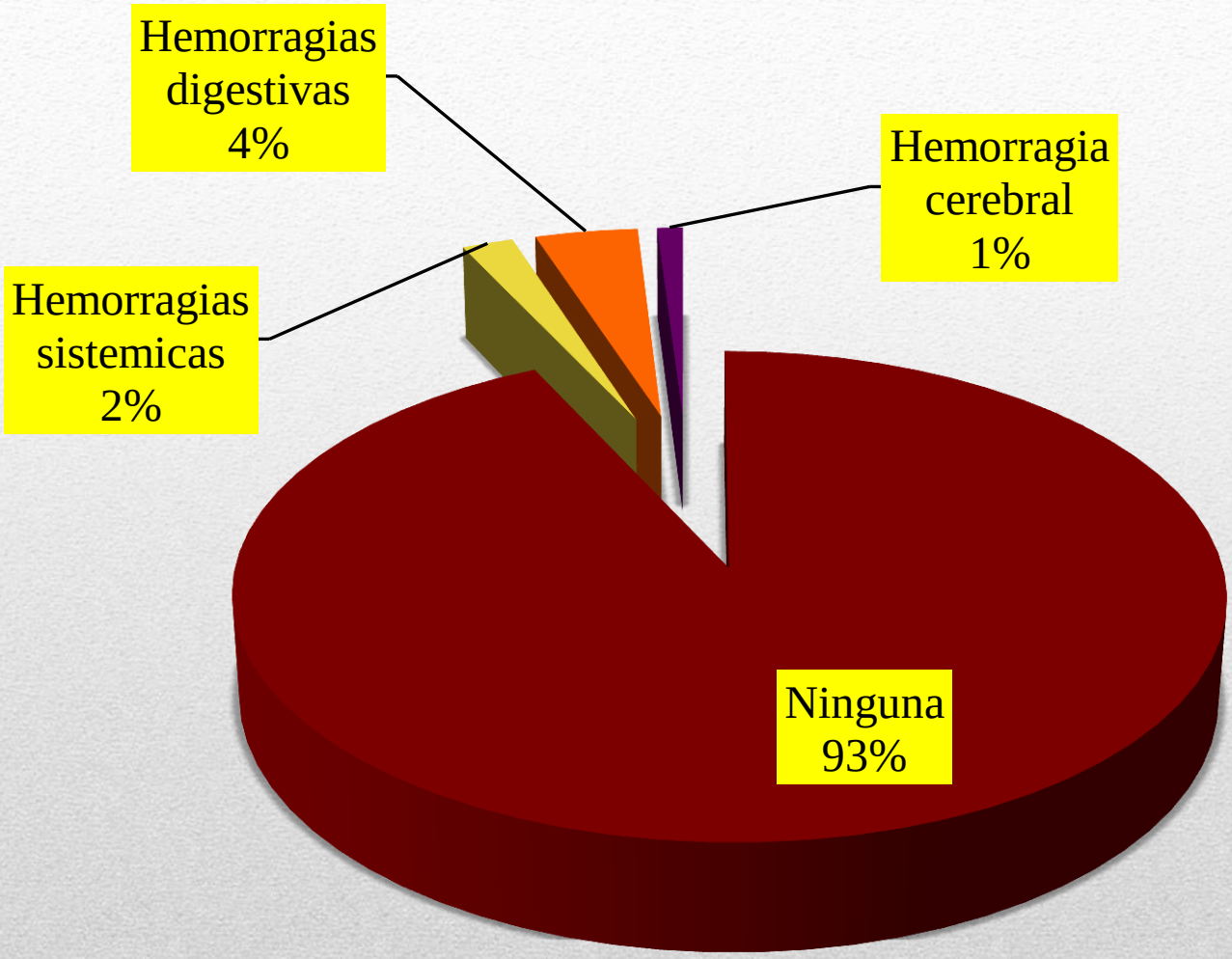
Indicación del tratamiento



Motivo de cambio



Complicaciones



Tiempo medio de seguimiento : 11,69 meses (0-26)

Prevención secundaria. Práctica Clínica



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SaludMadrid
Comunidad de Madrid
Servicio de Neurología

N:	43 pacientes
ACO2ªG	Dabigatrán
Edad Media:	79,7±6,1 años
Sexo Femenino:	74,4%
CHA2DS2-VASc:	6 (RIQ: 3)
HAS-BLED:	3 (RIQ: 2)
Media de seguimiento	451 días (IC95%: 369-533)

Prevención secundaria. Práctica Clínica



Hospital Universitario de La Princesa
SaludMadrid
Comunidad de Madrid
Servicio de Neurología

Tabla 1. Descripción de la muestra	
n	43
Sexo Femenino (%)	74,4
Edad (Media, SD)	79,7 (SD: 6,1)
HTA (%)	90,7
DM (%)	25,6
FA (%)	7
Dislipemia (%)	58,1
Enfermedad arterial periférica (%)	4,7
ICC (%)	9,3
AIT/Ictus previo (%)	34,9
IAM (%)	2,3
Cardiopatía isquémica crónica (%)	16,3
Tabaquismo (%)	2,3
Consumo de OH (%)	2,3
CHA2DS2-VASc (Mediana, RIQ)	6 (RIQ: 3)
HASBLED (Mediana, RIQ)	2 (RIQ: 1)
Creatinina (Mediana, SD)	0,96 (SD: 0,2)
AVK previo (%)	39,5

Prevención secundaria. Práctica Clínica



Tabla 2.	
Motivo de Indicación de Tratamiento con Dabigatrán	%
Ictus isquémico/AIT	74,4
Hemorragia por AVK	16,3
Otros	9,3

Hospital Universitario de La Princesa
Comunidad de Madrid
de Neurología

Tabla 3.	
Dosis de Dabigatrán Indicada	%
110 mg	76,7
150 mg	20,9
75 mg	2,3

Prevención secundaria. Práctica Clínica



Hospital Universitario de La Princesa
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Comunidad de Madrid
Servicio de Neurología

Tabla 4		
Eventos	%	Tasa porcentual anualizada
Infarto cerebral	4,65	3,77
AIT	4,65	3,77
Ictus hemorrágico	2,33	1,88
Hemorragias mayores (SNC y Digestivo)	4,65	3,76
Infarto del miocardio	2,33	1,88
Abandono el tratamiento sin eventos adversos	9,30	7,53
Mortalidad	2,32	1,27

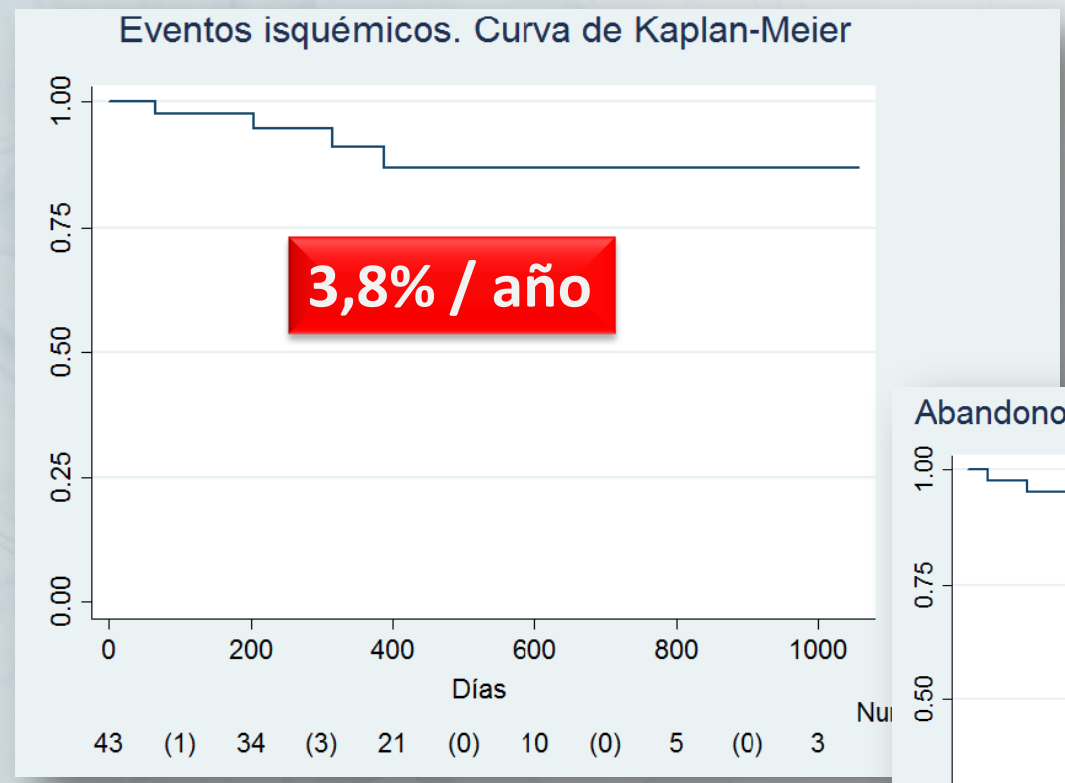
RE_LY 2,07-2,32 / año

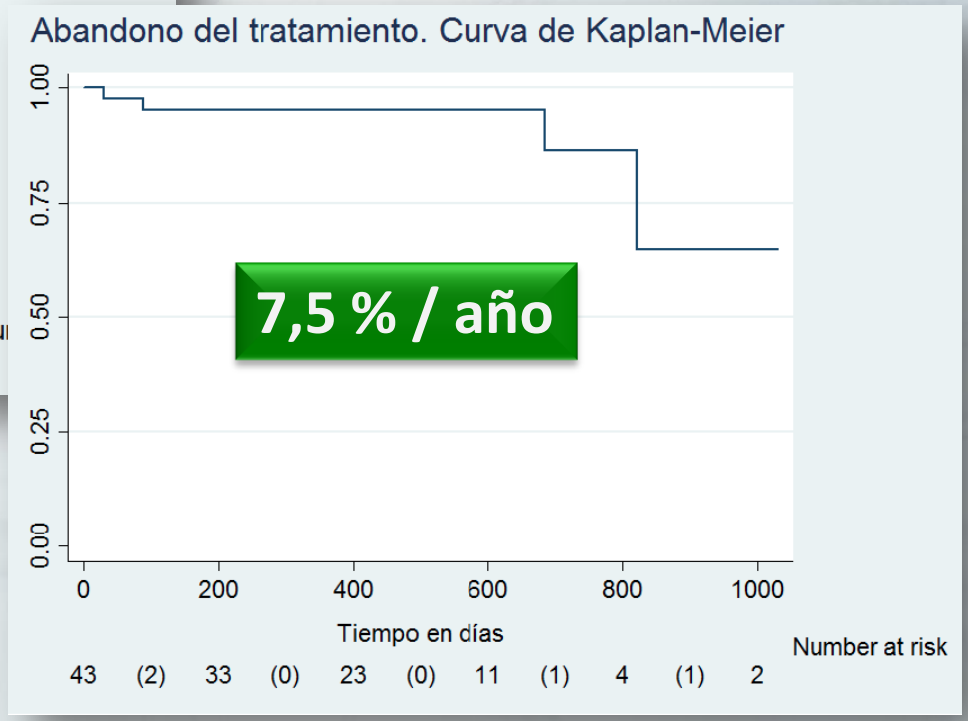
RE_LY 0,08-0,2 / año

Prevención secundaria. Práctica Clínica



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Comunidad de Madrid
Servicio de Neurología

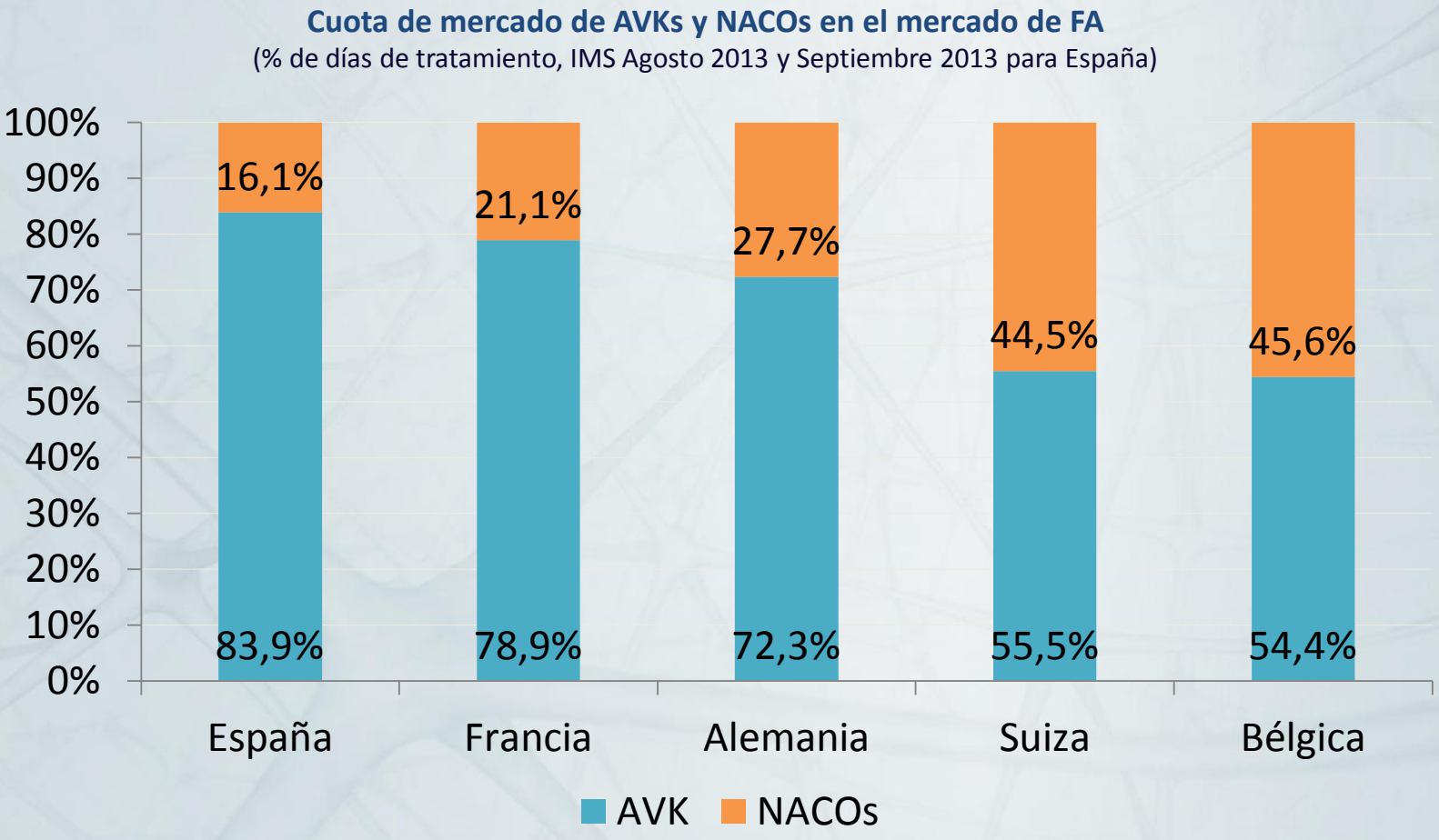




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Comunidad de Madrid
Servicio de Neurología

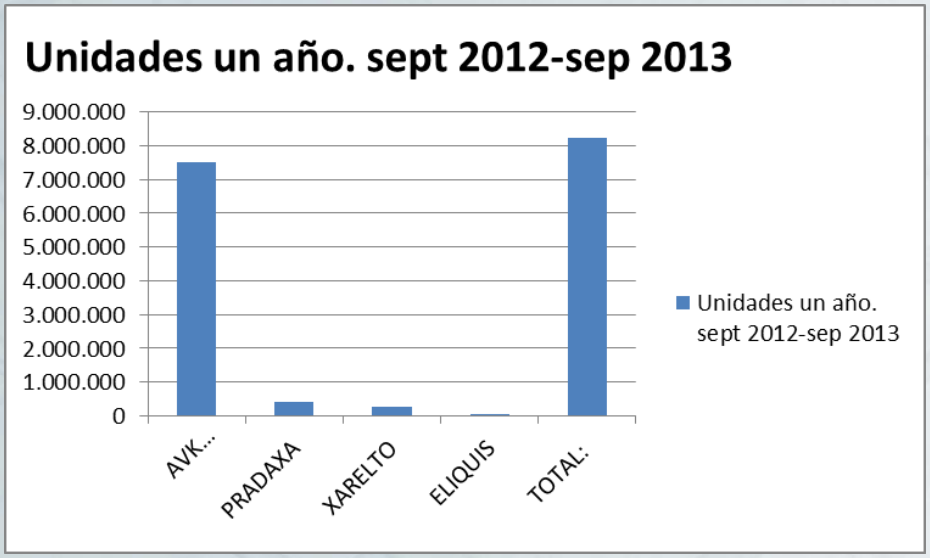
Introducción de NACOs en España y otros países europeos

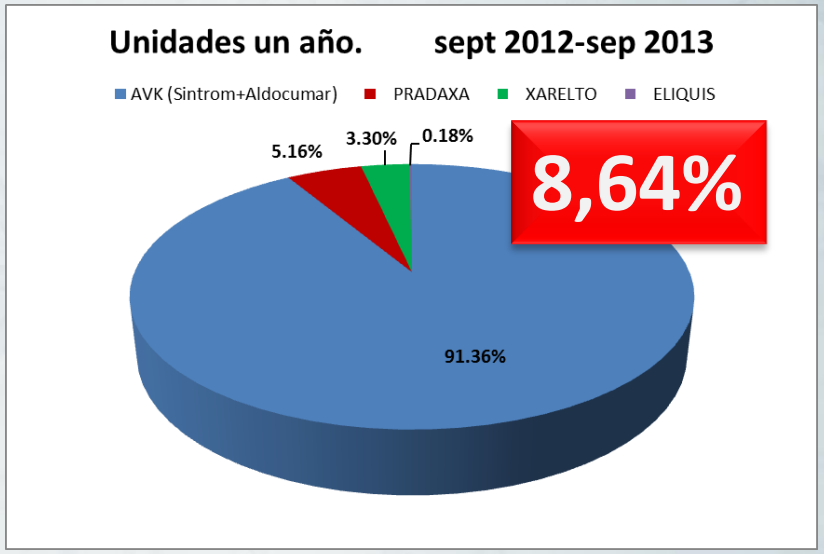


VENTAS ANTICOAGULANTES EN ESPAÑA.

Unidades. IMS últimos 12 meses.

De septiembre 2012 a septiembre 2013





	Unidades un año. sept 2012-sep 2013	%
AVK (Sintrom+Aldocumar)	7.508.185	91,36
PRADAXA	424.135	5,16
XARELTO	271.371	3,30
ELIQUIS	14.623	0,18
TOTAL:	8.218.314	

Fuente: datos IMS Sept. 2013

MINISTERIO
DE SANIDAD, SERVICIOS SOCIALES
E IGUALDAD

agencia española de
medicamentos y
productos sanitarios

INFORME DE UTILIDAD TERAPÉUTICA
UT/V1/26062012

Criterios y recomendaciones generales para el uso de nuevos anticoagulantes orales en la prevención del ictus y la embolia sistémica en pacientes con fibrilación auricular no valvular

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agencia española de medicamentos y productos sanitarios

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4.2. Situaciones en pacientes con fibrilación auricular no valvular en las que los nuevos anticoagulantes orales pueden presentar un mayor beneficio en comparación con los AVK y se justifica su elección en el marco del SNS (excluyendo las contraindicaciones generales para la TAO; ver sección 4.3);

4.2.1. Situaciones clínicas:

- **Pacientes con hipersensibilidad conocida o con contraindicación específica al uso de acenocumarol o de warfarina;**
- **Pacientes con antecedentes de hemorragia intracraneal (HIC)** en los que se valore que los beneficios de la anticoagulación superan el riesgo hemorrágico;
- **Pacientes con ictus isquémico que presenten criterios clínicos y de neuroimagen de alto riesgo de HIC**, definido como la combinación de HAS-BLED ≥ 3 y al menos uno de los siguientes: leucoaraiosis grado III-IV [29] y/o microsangrados corticales múltiples [30]. Los nuevos anticoagulantes podrían representar un beneficio en comparación con AVK en estos pacientes debido a su menor potencial para inducir HIC [20,21; ANEXO I];

Hospital Universitario de La Princesa

Informe clínico para la prescripción de Dabigatrán

PRADAXA 150 mg y PRADAXA 110mg sometidos a Visado de Inspección

1.- Filiación del paciente

ETIQUETA

NOMBRE .....
APELLIDOS .....
NUM. Hª Cª .....

2.- Indicaciones del Neurólogo para su Visado.

Según ficha técnica aprobada por la Agencia Española del Medicamento y Productos Sanitarios, se prescribe **DABIGATRAN** para una de las indicaciones siguientes.

☐ Para la prevención del ictus y de la embolia sistémica en pacientes adultos con fibrilación auricular no valvular, con uno o más de los siguientes factores de riesgo:

- ☐ Ictus, ataque isquémico transitorio o embolia sistémica (ES) previos
- ☐ Fracción de eyección ventricular izquierda < 40%
- ☐ Insuficiencia cardíaca sintomática ≥ Clase 2 escala New York Heart Association (NYHA)
- ☐ Edad ≥ 75 años

☐ Inicio del tratamiento anticoagulante

- ☐ Alergia a dicumarínicos
- ☐ Contraindicación para recibir tratamiento con warfarina o acenocumarol (especificar motivo)

_____

☐ Estimación de función renal por aclaramiento de creatinina $\frac{140 - \text{Edad} \times \text{Peso en kg}}{72 \times \text{creat. plasmática}} =$ _____

3.- Tipo farmacológico

PRESENTACIÓN .....
POSOLOGÍA .....
DURACIÓN DEL TTº .....

4.- Firma y sello del especialista

Nº COLEGIADO .....
APELLIDOS Y NOMBRE .....

5.- Fecha del Informe:

El ictus cardioembólico por FANV



Susceptibles de anticoagulación

- Incidencia del Ictus en España (Ibericus)
- Incidencia de la FANV en España (Prev-Ictus)
- Incidencia de Ictus Cardioembólico (EPICES)
- Incidencia del Ictus Cardioembolico-FANV

No susceptibles de Anticoagulación

- Ictus hemorrágico (EPICES)
- Mortalidad en fase aguda (EPICES)
- Contraindicaciones médicas y sociales

900 p / año

Muchas Gracias...