TRATAMIENTO ANTICOAGULANTE Y FIBRILACION AURICULAR

ANTI-VITAMINAS K EN FIBRILACION AURICULAR

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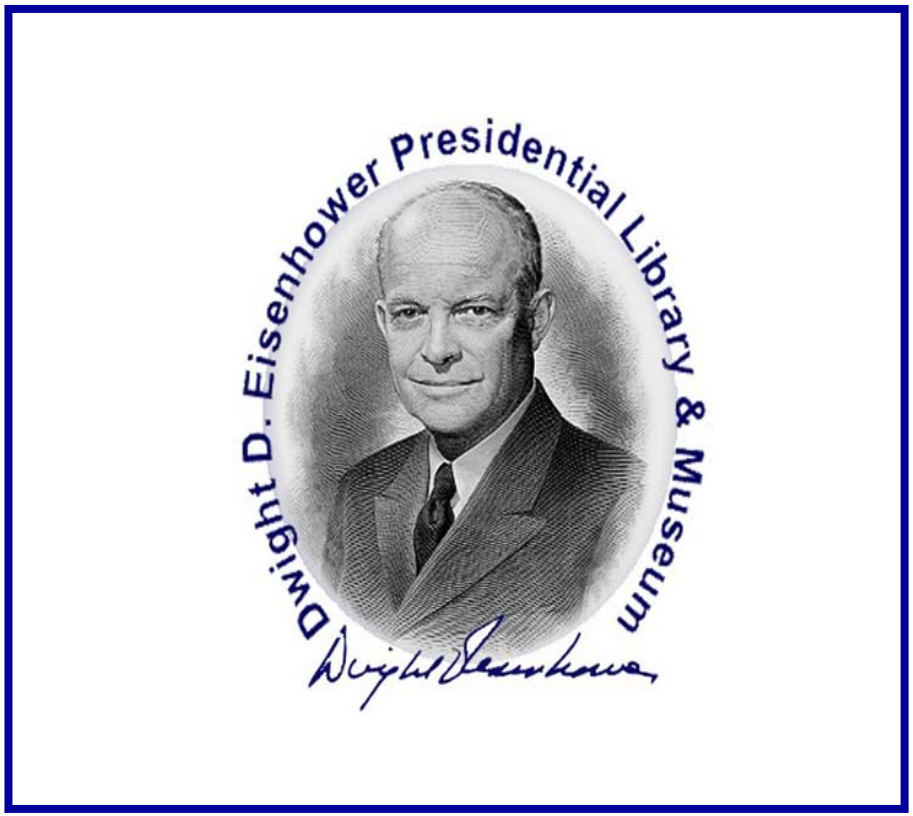
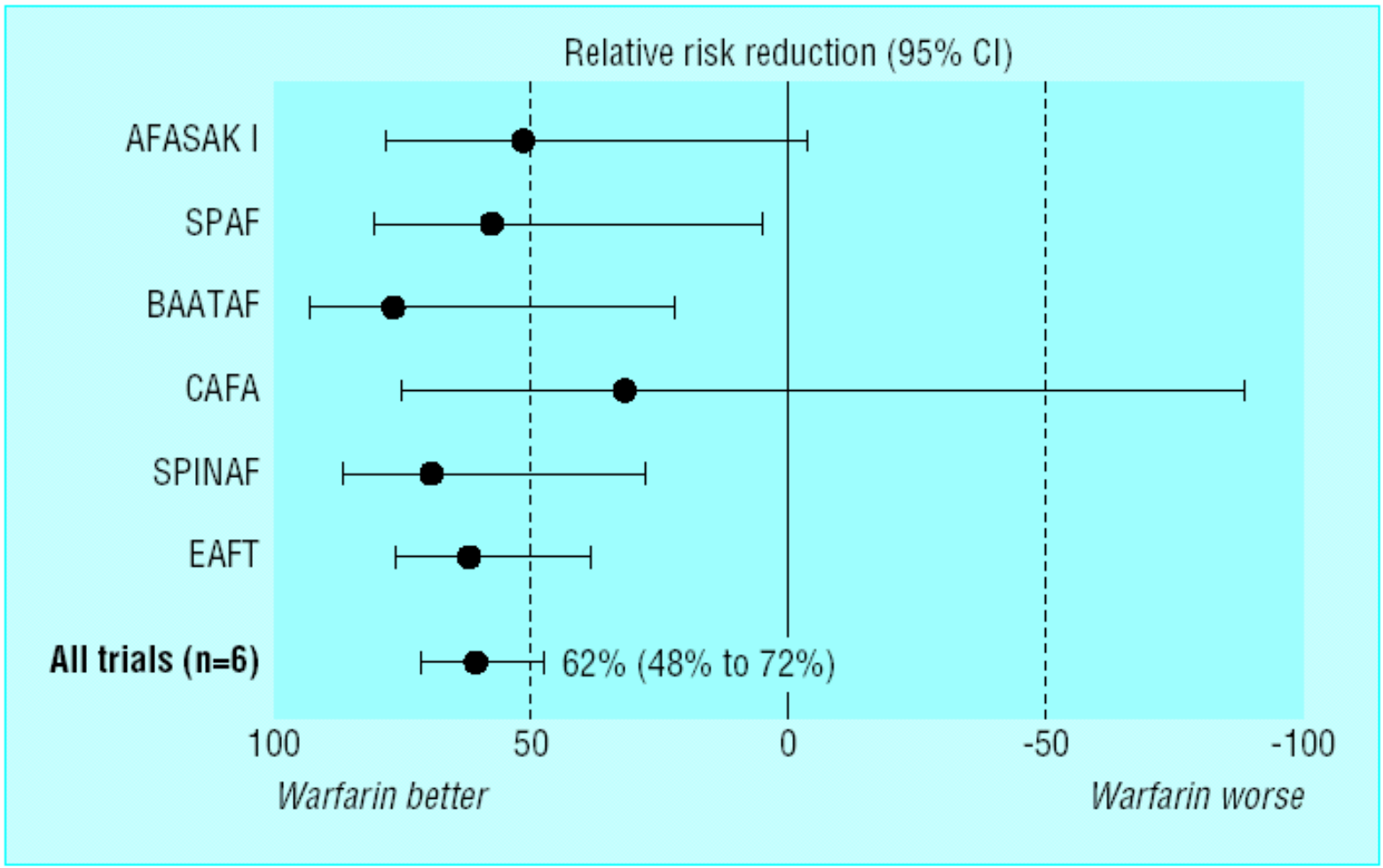

Dwight D. Eisenhower Presidential Library & Museum

BENEFICIO DE LA ANTICOAGULACION



Hart, Ann Intern Med 1999

Table 2. Crude Rates of Thromboembolism and Major Hemorrhage During Follow-up by Warfarin Exposure*

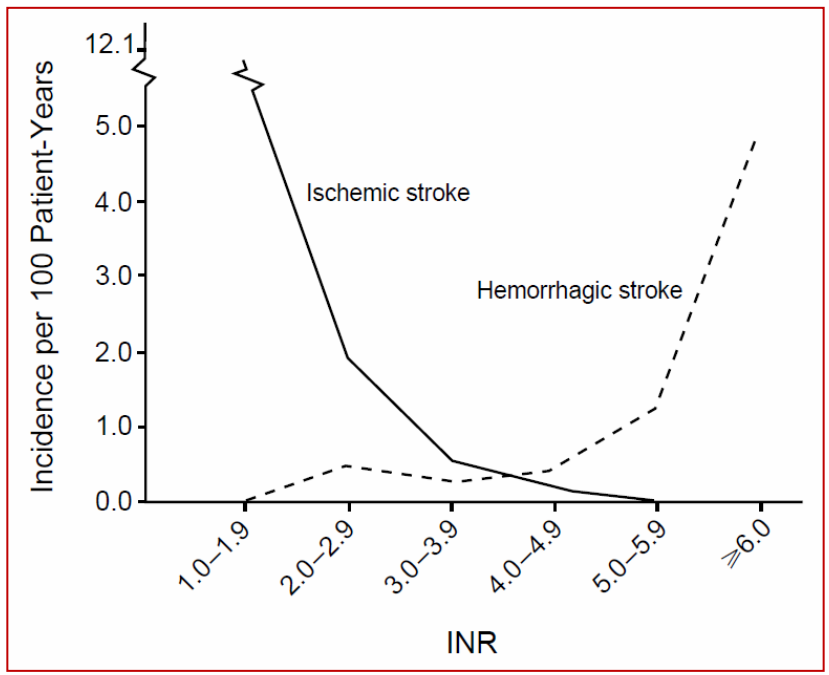
Event Type	Warfarin Status: Taking	Warfarin Status: Not Taking	Crude Rate Ratio (95% CI)
Ischemic stroke			
No. of events	141	231	
Event rate (95% CI)†	1.11 (0.94-1.31)	1.88 (1.65-2.14)	0.59 (0.48-0.73)
Other thromboembolism			
No. of events	7	18	
Event rate (95% CI)†	0.05 (0.03-0.11)	0.15 (0.09-0.23)	0.37 (0.16-0.89)
Intracranial hemorrhage			
No. of events	59	29	
Event rate (95% CI)†	0.46 (0.35-0.59)	0.23 (0.16-0.34)	1.94 (1.25-3.03)
Gastrointestinal hemorrhage			
No. of events	118	119	
Event rate (95% CI)†	0.91 (0.76-1.09)	0.96 (0.80-1.15)	0.95 (0.73-1.22)
Other hemorrhage			
No. of events	19	11	
Event rate (95% CI)†	0.15 (0.09-0.23)	0.09 (0.05-0.16)	1.65 (0.79-3.47)

Abbreviation: CI, confidence interval.
*Represents analyses of 11 526 patients with nonvalvular atrial fibrillation and no known contraindications to anticoagulation at baseline.
†The event rate is per 100 person-years.

TRATAMIENTO ANTICOAGULANTE

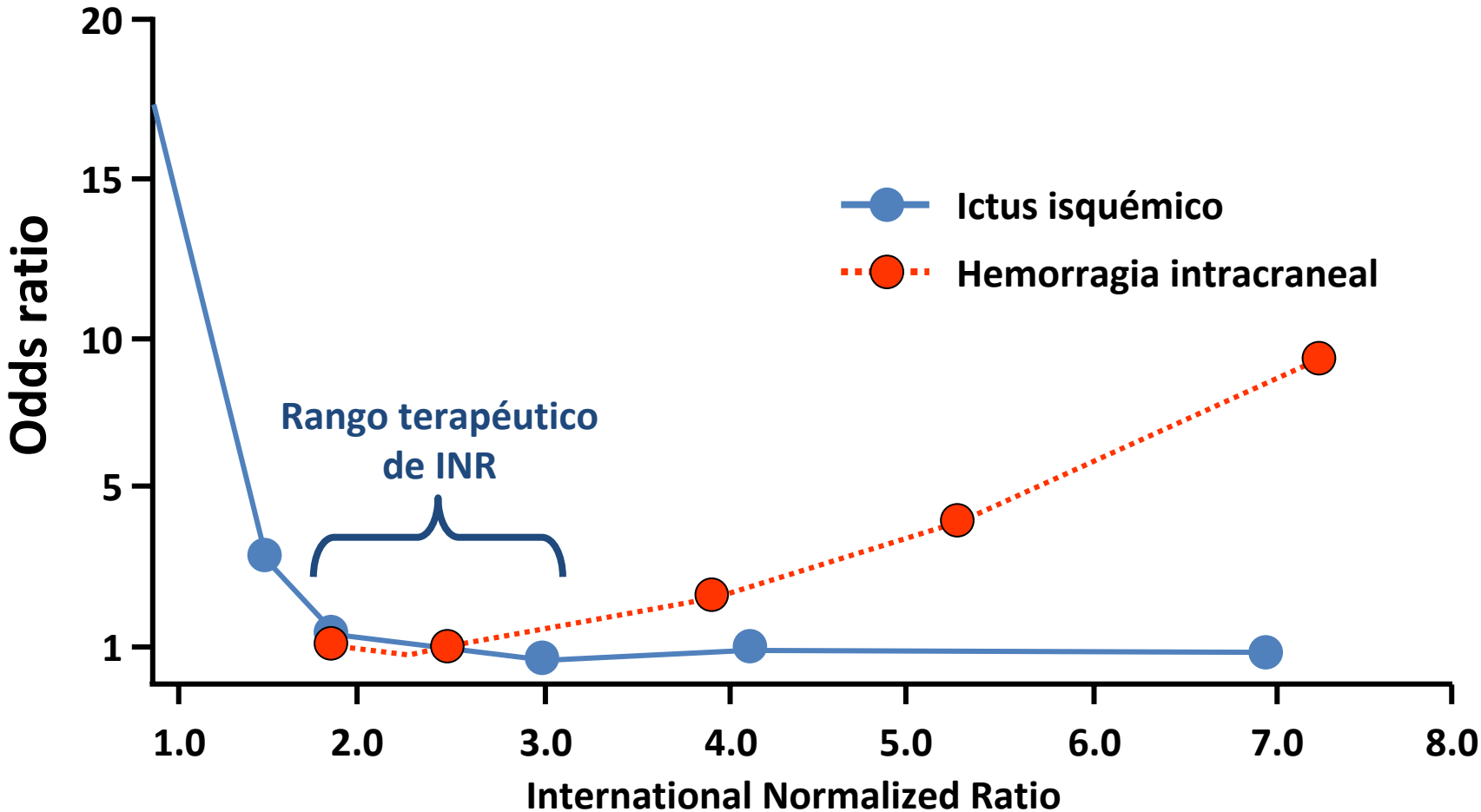
Reducción de eventos trombóticos

Incremento del riesgo hemorrágico



Rango terapéutico de la anticoagulación

Valor del INR en el momento del ictus o hemorragia intracraneal en pacientes con FA



Hylek, NEJM 2005

Antivitaminas K: Mecanismo de acción

Vitamina K

Anticoagulantes orales

Disponibilidad de Vit K reducida

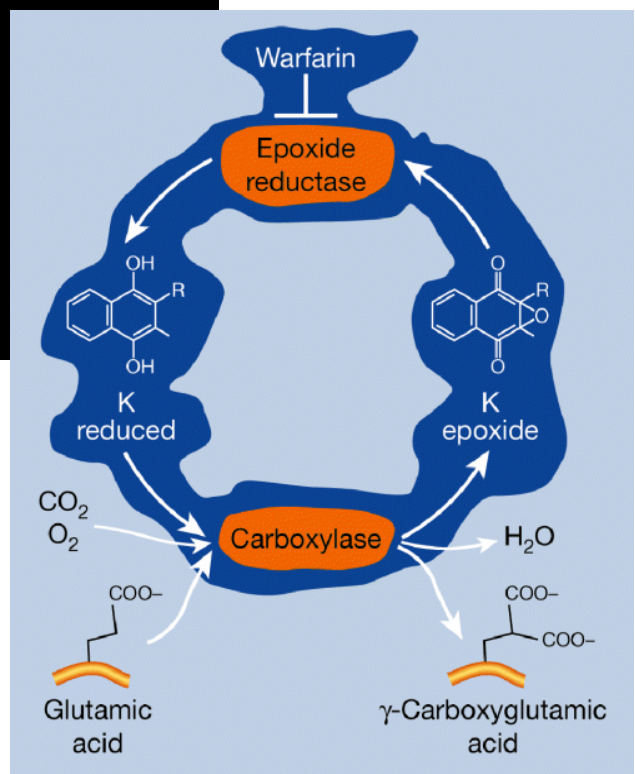
VII

IX

X

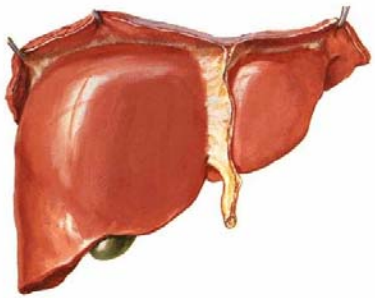
II

Síntesis de factores de coagulación no funcionantes

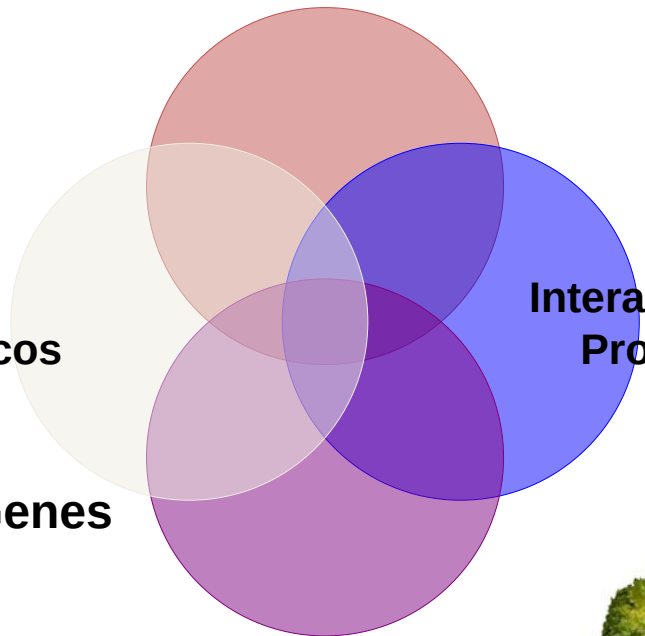


Fármacos Antivitaminas K

FACTORES QUE INFLUYEN SOBRE EL EFECTO DE ANTICOAGULANTES ORALES



Comunicación médico/paciente
Edad y peso



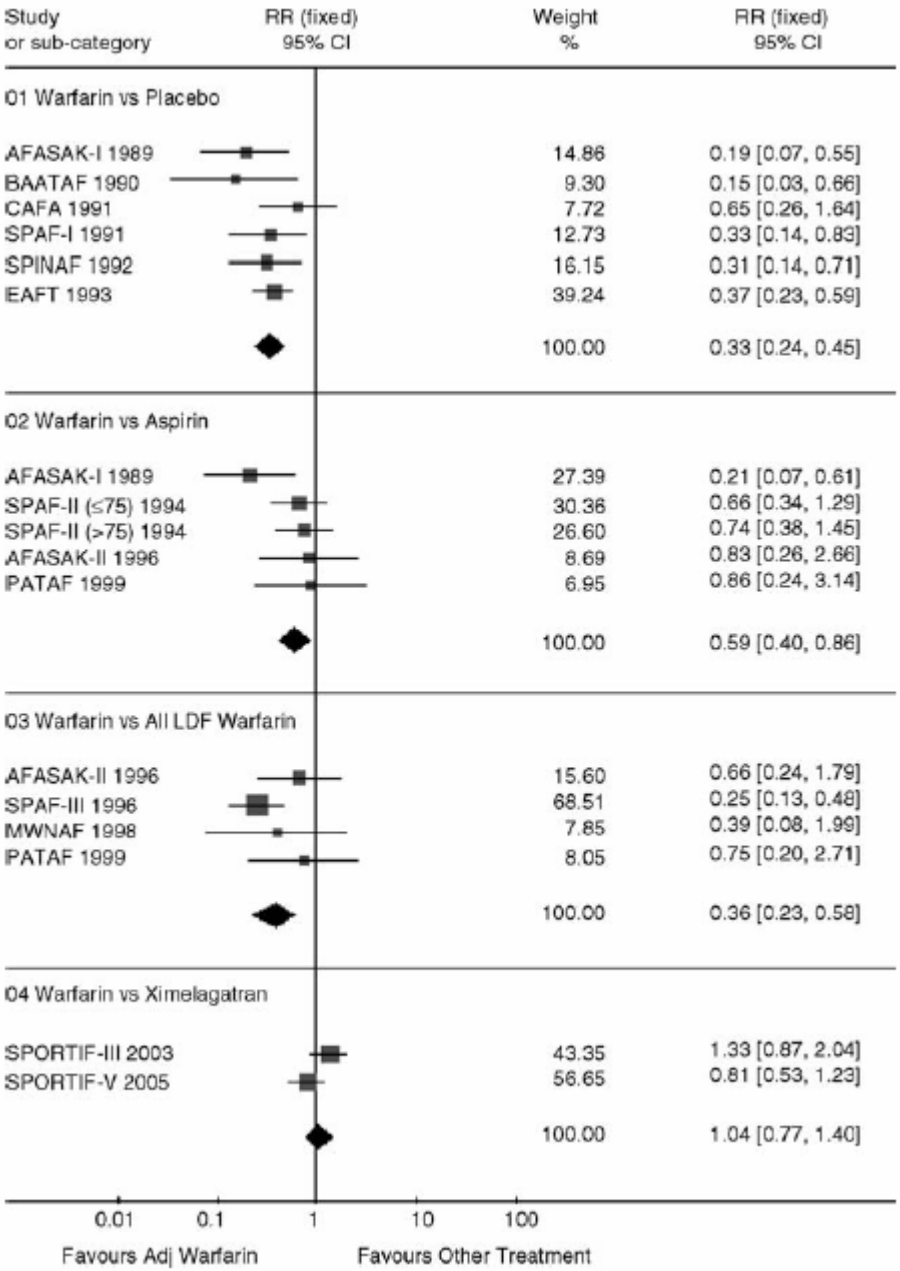
Disfunción hepática
Estados hipermetabólicos

Interacciones farmacológicas y
Productos de herboristeria

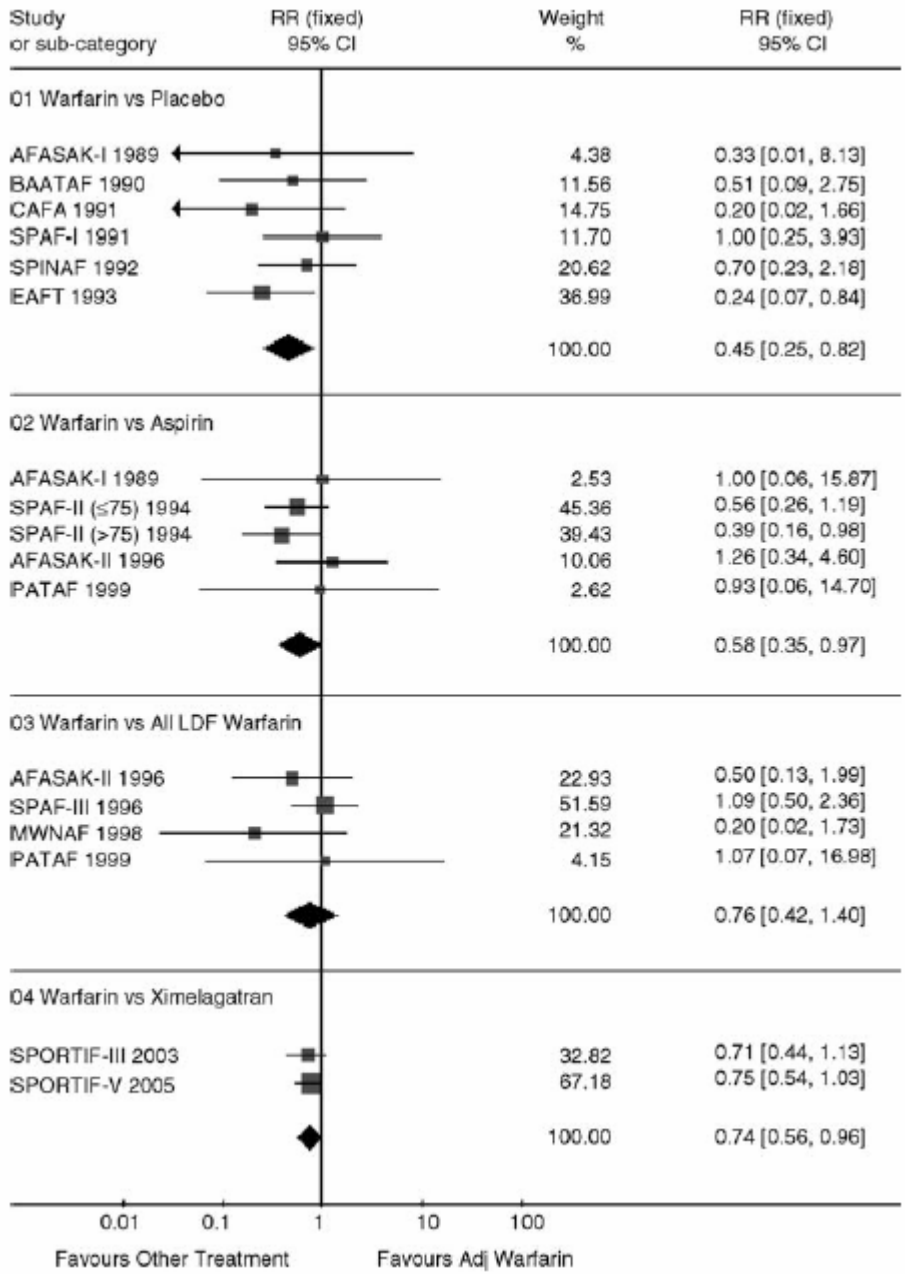
Genes

Dieta

ICTUS



HEMORRAGIA

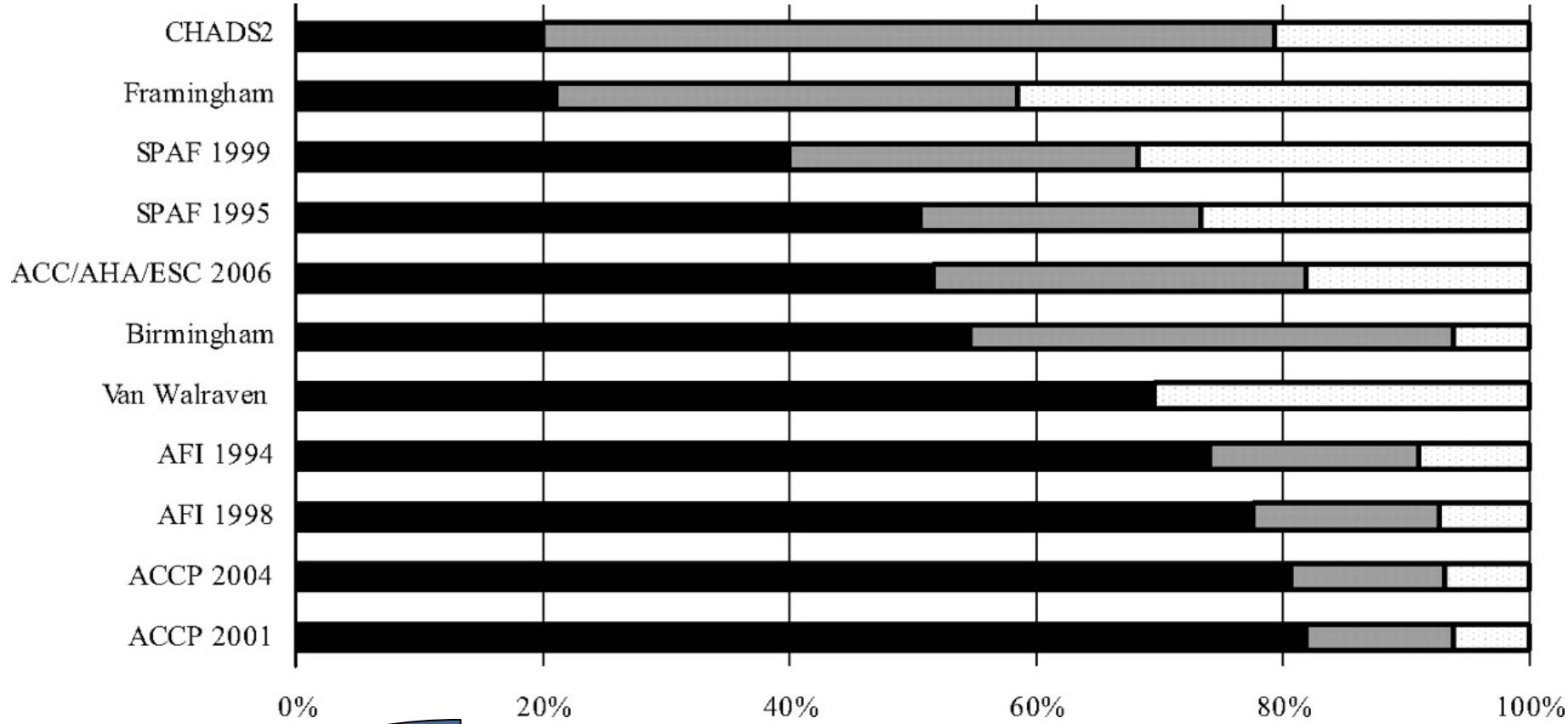


Lip, Thromb Res 2006

ESTRATIFICACION RIESGO

- Los esquemas actuales de estratificación del riesgo (RSS) categorizan los pacientes en 3 categorías: bajo-intermedio-alto

- Según las guías vigentes, se recomienda TAO en el alto riesgo y aspirina (o nada) en el bajo riesgo, siendo ambas opciones válidas para el riesgo intermedio



- **PREVIO ACV/AIT**
- **EDAD**
- **HTA**
- **DIABETES**
- **INSUFICIENCIA CARDIACA**

BAJO RIESGO
RIESGO INTERMEDIO
ALTO RIESGO

Stroke Risk in Atrial Fibrillation Working Group, Stroke 2008

JAMA®

Validation of Clinical Classification Schemes for Predicting Stroke: Results From the National Registry of Atrial Fibrillation

Brian F. Gage; Amy D. Waterman; William Shannon; et al.

JAMA. 2001;285(22):2864-2870 (doi:10.1001/jama.285.22.2864)

http://jama.ama-assn.org/cgi/content/full/285/22/2864

C Congestive heart failure

H Hypertension

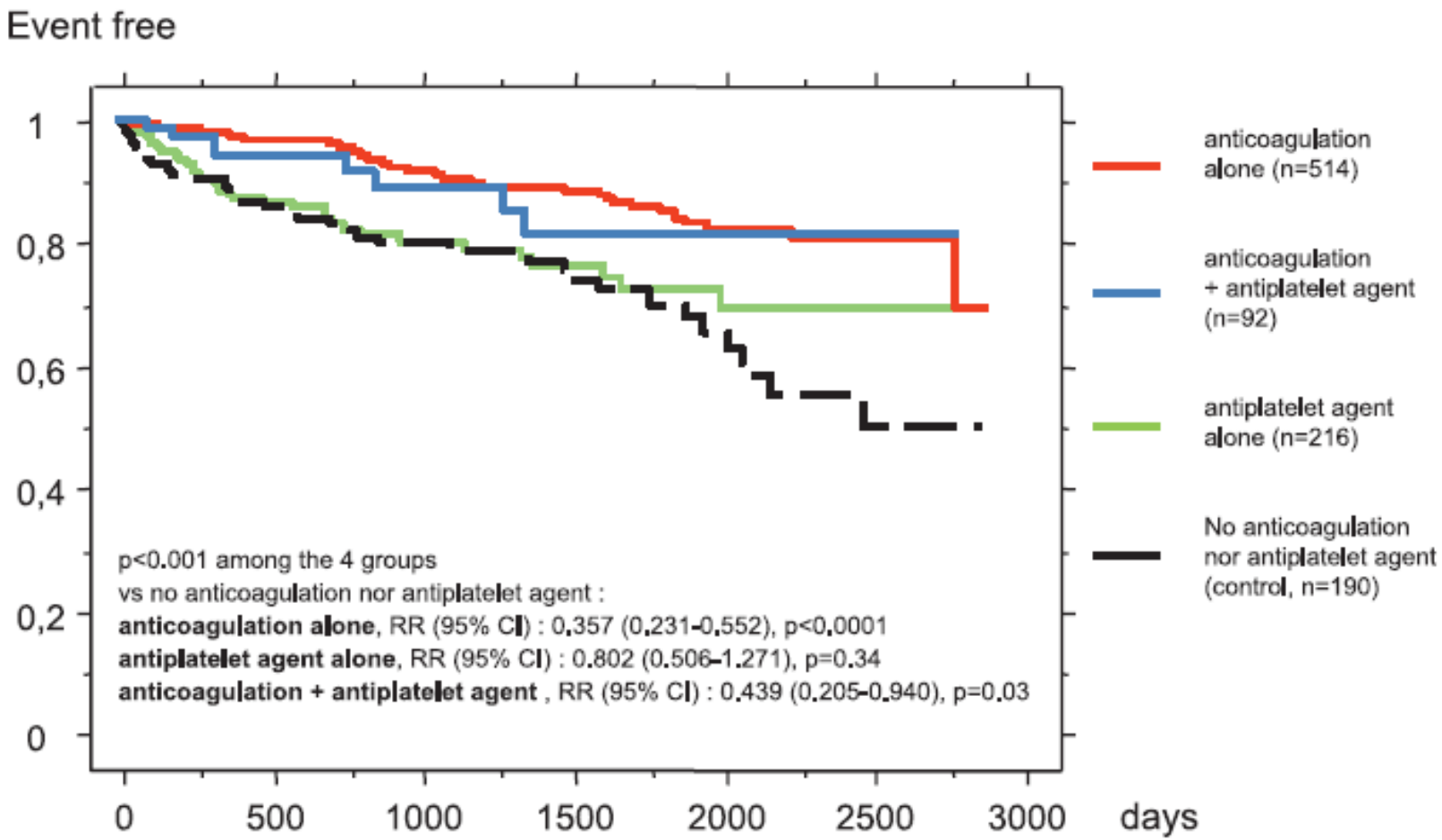
A Age ≥ 75 years

D Diabetes

S_2 Stroke or Transient ischaemic attack

0	RIESGO BAJO
1-2	RIESGO INTERMEDIO
3-6	ALTO RIESGO

POBLACIÓN CHADS$_2$ =1



Gorin, T&H 2010

ACTIVE-W

Table 2. $CHADS_2$-Specific Stroke Rates for Patients Treated With Clopidogrel Plus Aspirin vs Oral Anticoagulation (OAC)

CHADS Score	Stroke Rate With ASA (/100 pt-yrs)*[4]	No. of Patients in ACTIVE-W	Stroke Rate C+A (/100 pt-yrs)	Stroke Rate OAC (/100 pt-yrs)	Relative Risk (C+A vs OAC)†
0	0.8	178 (3%)	1.90	0.80	3.02
1	2.2	2436 (36%)	1.21	0.40	3.11
2	4.5	2286 (34%)	1.93	1.86	1.04
3	8.6	1107 (17%)	2.79	1.72	1.62
4	10.9	490 (7%)	6.73	3.25	2.07
5	12.3	183 (3%)	11.65	2.69	7.01
6	13.7	26 (0.4%)	0	0	NA

Healey, Stroke 2008

CHA_2DS_2VASC

	Score
CHA_2DS_2-VASc	
Congestive heart failure	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (previous MI, PAD, or aortic plaque)	1
Aged 65–74 years	1
Female	1
Maximum score	9

BAJO RIESGO

RIESGO INTERMEDIO

ALTO RIESGO

	N	Number of TE events	TE rate during 1 year (95% CI)
0	103	0	0% (0 – 0)
1	162	1	0.6% (0.0 – 3.4)
2	184	3	1.6% (0.3 – 4.7)
3	203	8	3.9% (1.7 – 7.6)
4	208	4	1.9% (0.5 – 4.9)
5	95	3	3.2% (0.7 – 9.0)
6	57	2	3.6% (0.4 – 12.3)
7	25	2	8.0% (1.0 – 26.0)
8	9	1	11.1% (0.3 – 48.3)
9	1	1	100% (2.5 - 100)
Total	1084	25	P value for trend 0.003

Hemorrhagic Complications of Anticoagulant and Thrombolytic Treatment*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

Sam Schulman, MD, PhD; Rebecca J. Beyth, MD, MSc; Clive Kearon, MD, PhD; and Mark N. Levine, MD, MSc

- Los principales factores predisponentes del sangrado son:
  - La intensidad del tratamiento anticoagulante
  - Las características del paciente: EDAD
  - Fármacos concomitantes

Advanced Age, Anticoagulation Intensity, and Risk for Intracranial Hemorrhage among Patients Taking Warfarin for Atrial Fibrillation

Margaret C. Fang, MD, MPH; Yuchiao Chang, PhD; Elaine M. Hylek, MD, MPH; Jonathan Rosand, MD; Steven M. Greenberg, MD, PhD; Alan S. Go, MD; and Daniel E. Singer, MD

Ann Intern Med. 2004;141:745-752.

Figure 1. Adjusted relative odds of intracranial hemorrhage by age in 145 case-patients and 870 controls, overall (*top*) and

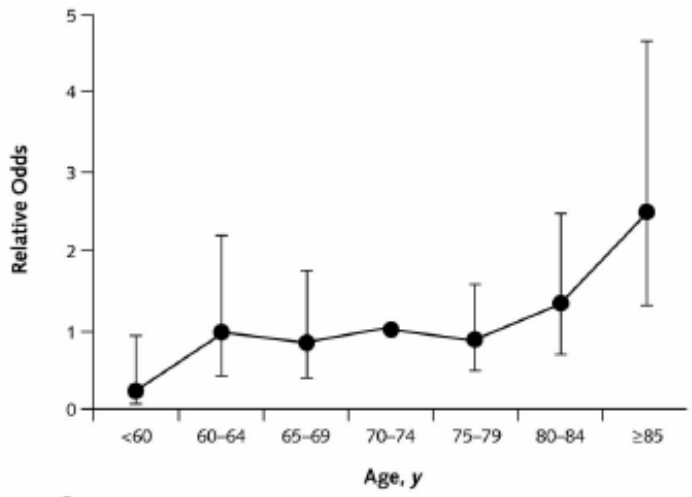
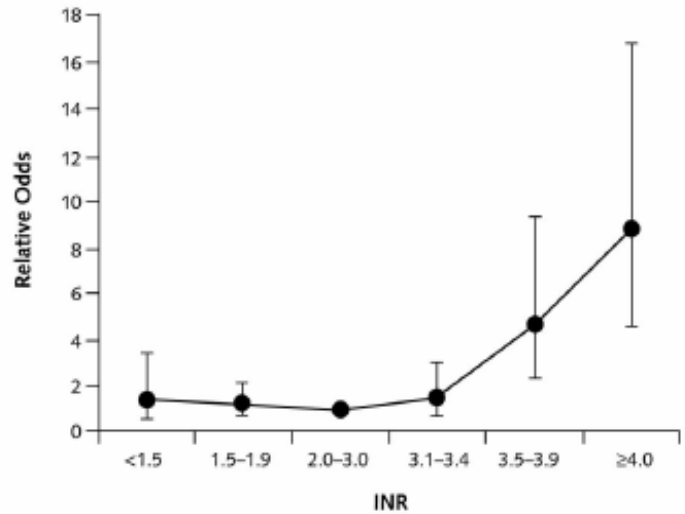
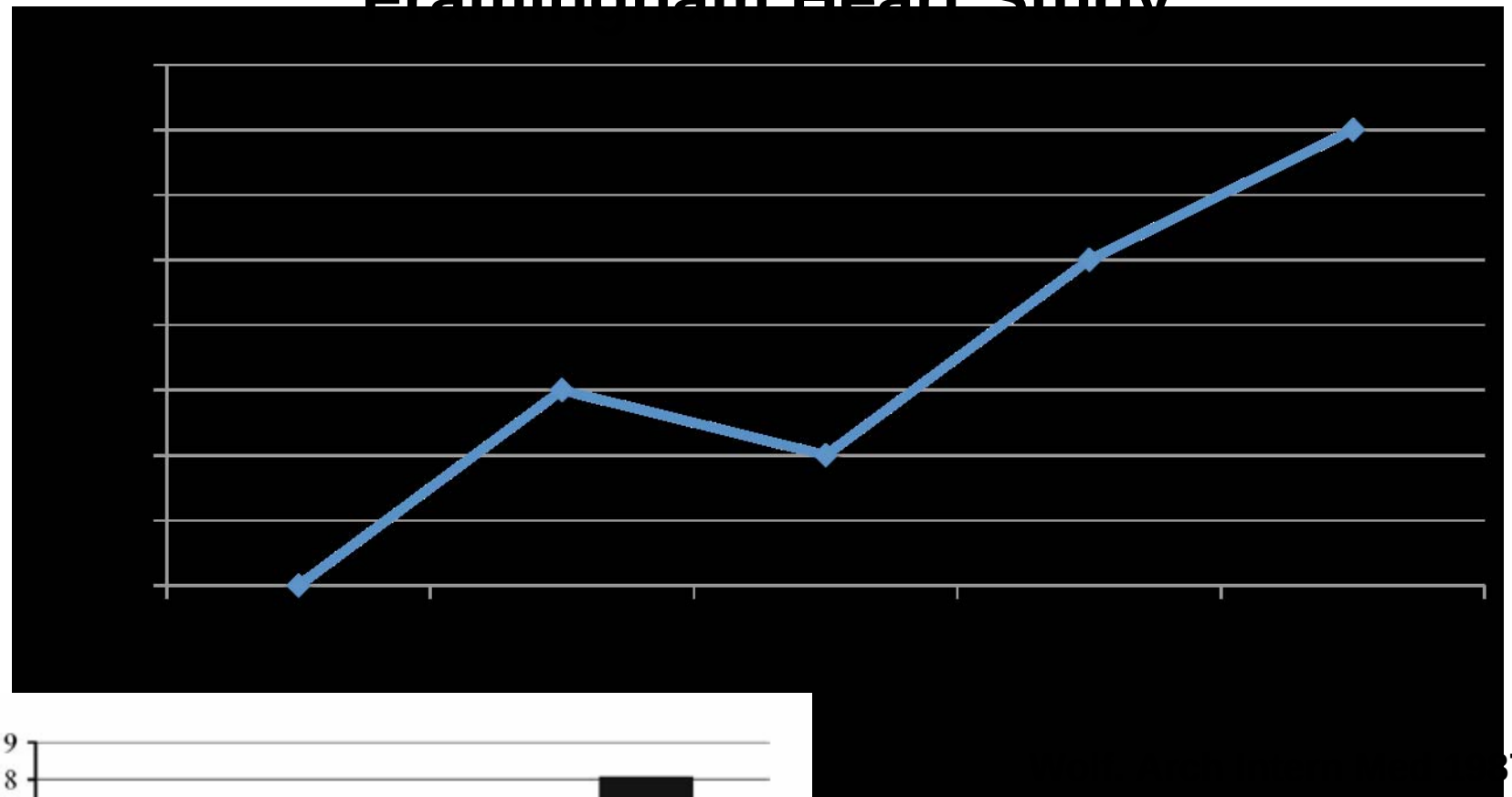
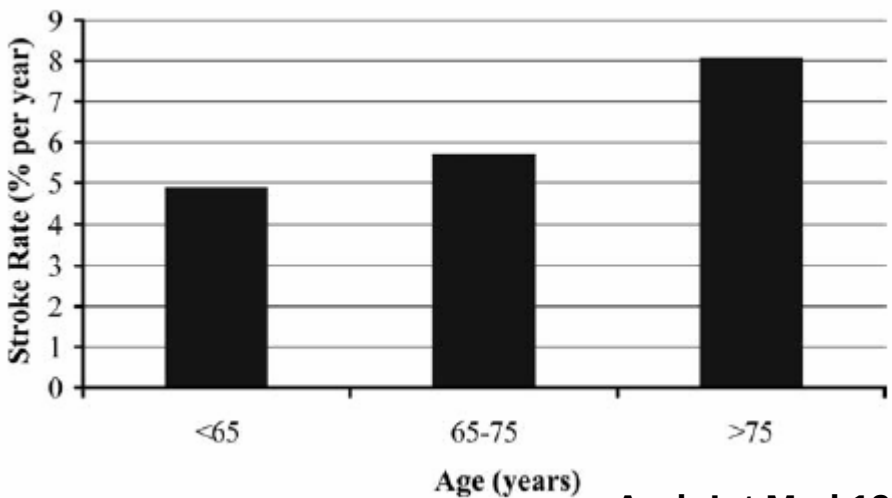


Figure 2. Adjusted relative odds of intracranial hemorrhage by international normalized ratio (*INR*) in 145 case-patients and



Framingham Heart Study





Arch Int Med 1994

Major Hemorrhage and Tolerability of Warfarin in the First Year of Therapy Among Elderly Patients With Atrial Fibrillation

Elaine M. Hylek, MD, MPH; Carmella Evans-Molina, MD; Carol Shea, RN; Lori E. Henault, MPH; Susan Regan, PhD

Circulation 2007

TABLE 3. Distribution of Major Hemorrhagic Events and Warfarin Terminations Due to Perceived Safety Concerns by $CHADS_2$ Score

	Overall		Major Bleed			Taken Off Therapy		
$CHADS_2$ Score	N	Person-Years	N	Rate (per 100 Person-Years)	95% CI	N	Rate (per 100 Person-Years)	95% CI
0	42	32	1	3.12	0.08 to 17.38	5	15.59	5.06 to 36.39
1	121	93	4	4.28	1.17 to 10.96	16	17.12	9.79 to 27.81
2	181	147	3	2.04	0.42 to 5.96	19	12.92	7.78 to 20.18
3	94	61	12	19.54	10.10 to 34.13	20	32.56	19.89 to 50.29
≥4	34	26	6	23.42	8.59 to 50.97	9	35.12	16.06 to 66.68
Total	472		26			69		

Tasas de sangrado: 13.08/100 pac/año vs 4.75/100 pac/año

Bleeding Risk During Oral Anticoagulation in Atrial Fibrillation Patients Older Than 80 Years

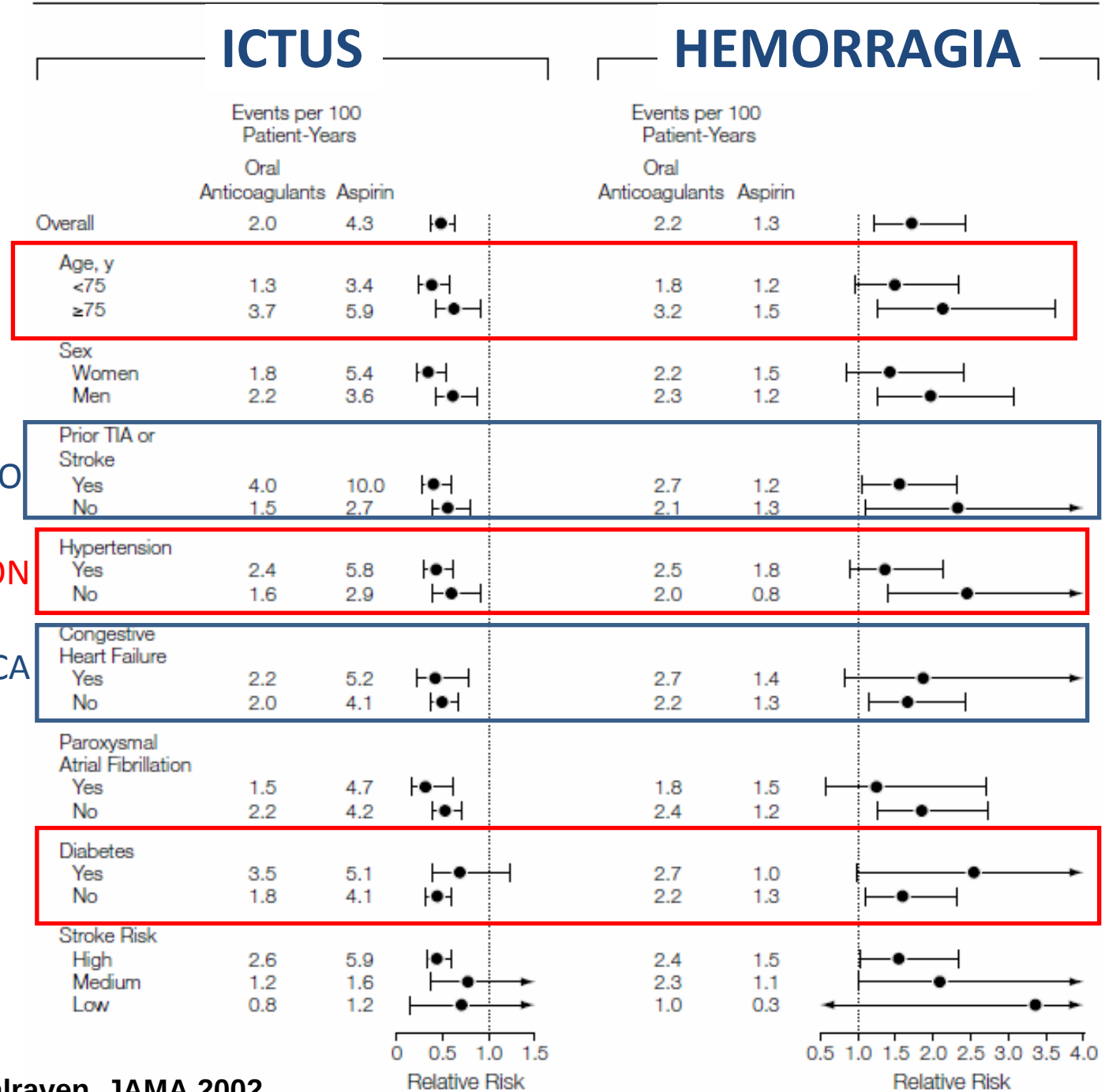
Daniela Poli, MD,*† Emilia Antonucci, MS,*† Elisa Grifoni, MD,*† Rosanna Abbate, MD,*† Gian Franco Gensini, MD,*†‡ Domenico Prisco, MD*†

JACC Vol. 54, No. 11, 2009
September 8, 2009:999–1002

	Age <80 Yrs (1,738 Patient/Yrs)		Age ≥80 Yrs (829 Patient/Yrs)			
	n	Rate	n	Rate	RR (95% Confidence Interval)	p Value
Major bleeding	16	0.9	21	2.5	1.9 (1.2–2.8)	0.004
Cerebral	10	0.5	10	1.2	2.1 (0.8–5.5)	0.1
Gastrointestinal	6	0.3	9	1.1	3.1 (1.0–10.7)	0.03
Other	—	—	2	0.2	—	—
Fatal	3	0.2	6	0.7	4.2 (0.9–26.0)	0.04
Minor bleeding	31	1.8	26	3.1	1.7 (1.0–3.0)	0.03

Table 3 Odds Ratios Associated With Bleeding Risk

	Odds Ratio	95% Confidence Interval	p Value
Age ≥80 yrs	3.1	1.5–6.2	0.002
Stroke/TIA	2.5	1.3–4.8	0.007
Hypertension	1.3	0.6–2.7	0.5
Previous bleeding	1.0	0.1–6.9	0.9
$CHADS_2$ score	1.3	1.0–1.7	0.03



EDAD≥75

ICTUS PREVIO

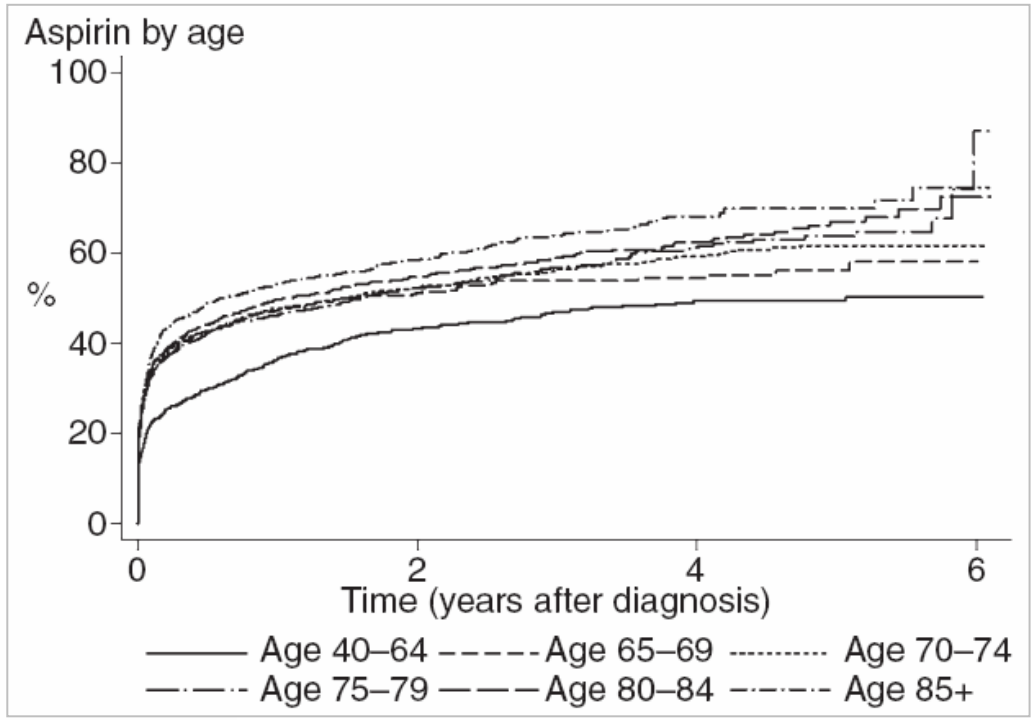
HIPERTENSIÓN

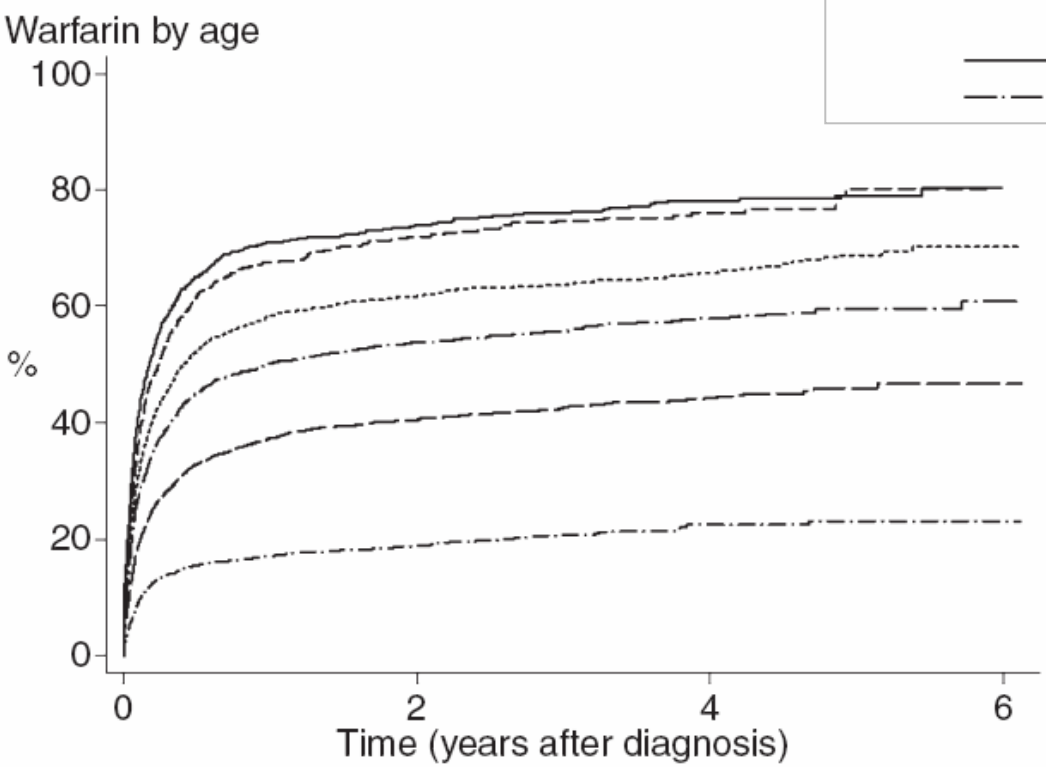
INS. CARDIACA

DIABETES

Van Walraven, JAMA 2002

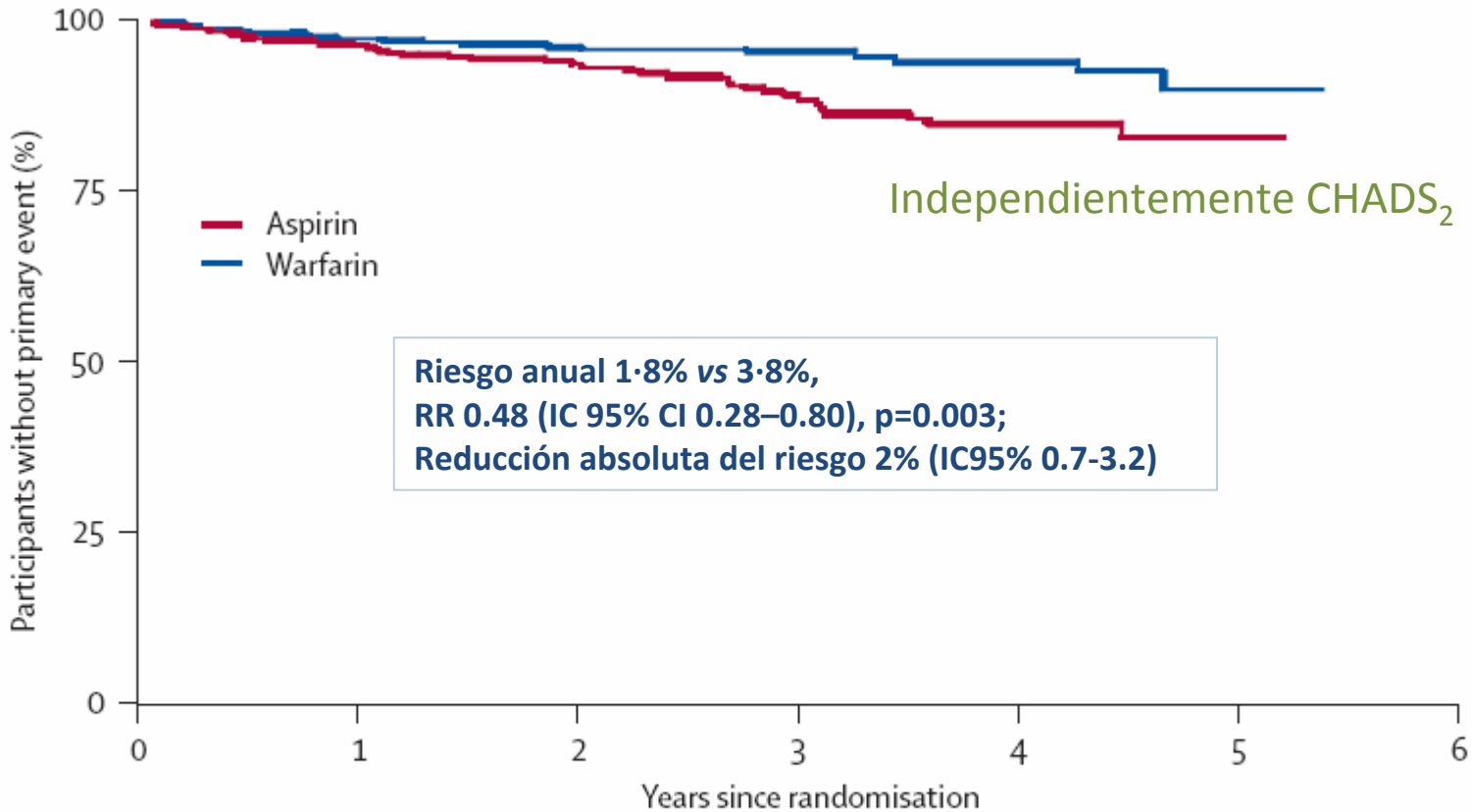
Proporción de pacientes con FA en quienes se inicia anticoagulación o aspirina dependiendo de la edad





Gallagher JTH 2008

BAFTA



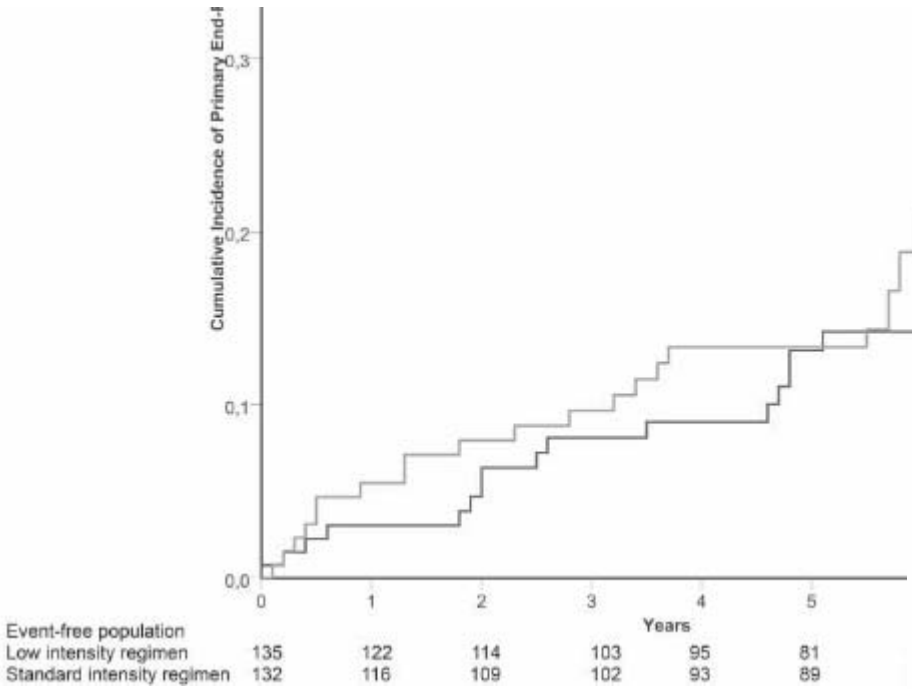
Mant, Lancet 2007

Lower versus standard intensity oral anticoagulant therapy (OAT) in elderly warfarin-experienced patients with non-valvular atrial fibrillation

A randomised primary prevention trial

Vittorio Pengo[1]; Umberto Cucchini[1]; Gentian Denas[1]; Bruce L. Davidson[2]; Filippo Marzot[1]; Seena Padayattil Jose[1]; Sabino Iliceto[1]

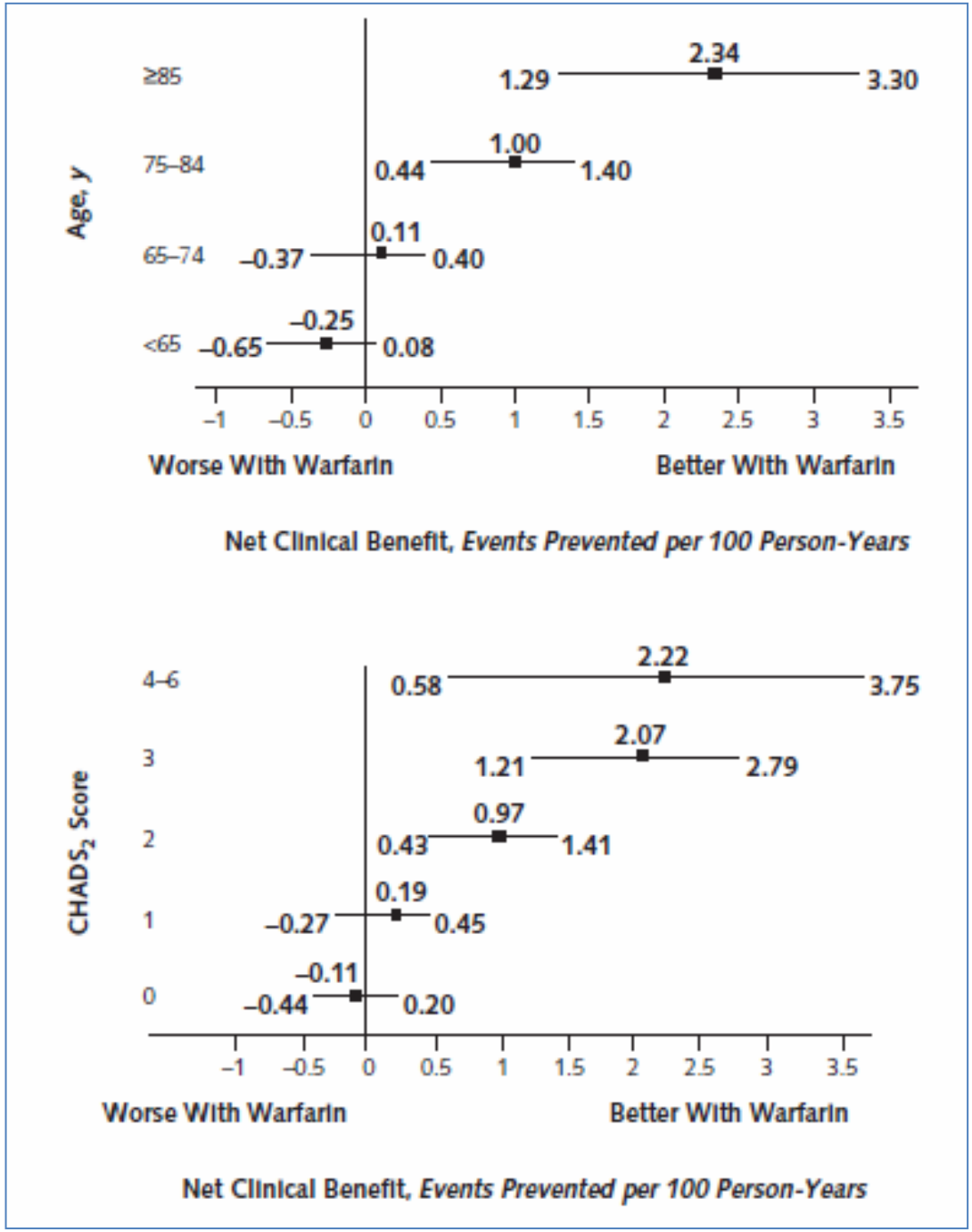
[1]Clinical Cardiology, Department of Cardiac Thoracic and Vascular Sciences, University of Padova School of Medicine, Padova, Italy; [2]Pulmonary Critical Care, University of Washington School of Medicine and Swedish Medical Center, Seattle, WA, USA



Events, n (per 100 patient-years)	INR 1,5–2 (n=135)	INR 2–3 (n=132)	HR (95% CI)	P-value
Primary end-points (ITT)	24 (3.5)	35 (5.0)	0.67 (0.39–1.13)	0.13
Stroke/Systemic thromboembolism	11 (1.6)	14 (2.0)	0.81 (0.37–1.78)	0.60
Major bleeding	13 (1.9)	21 (3.0)	0.57 (0.28–1.17)	0.12
Secondary end-points (ITT)				
Myocardial infarction	8 (1.2)	9 (1.3)	0.83 (0.31–2.23)	0.71
Cardiovascular deaths	52 (7.5)	47 (6.7)	1.1 (0.73–1.63)	0.67
Non-cardiovascular deaths	25 (3.6)	23 (3.3)	1.1 (0.63–1.96)	0.71
All cause death	78 (11.2)	70 (10.0)	1.1 (0.79–1.52)	0.57

ITT, intention to treat; HR, hazard ratio.

Thrombosis & Haemostasis 2010



BENEFICIO CLINICO NETO DE LA ANTICOAGULACION

Singer, Ann Int Med 2009

bjh research paper

Risks factors for highly unstable response to oral anticoagulation: a case-control study

- Los pacientes más inestables de 35 clínicas de anticoagulación italianas comparados con un grupo control de pacientes estables.
- Las variables evaluadas:
  - Datos sociodemográficos.
  - Historia médica
  - Estilo de vida y dieta
  - Variantes del citocromo P450 CYP2C9
  - Parámetros analíticos.
  - Cuestionario para comprensión y cumplimiento (CCC).
  - *Abbreviated mental test* (AMT)

Palareti, BJH 2005

bjh research paper

Risks factors for highly unstable response to oral anticoagulation: a case-control study

- Más inestables
  - –Trabajadores más que pensionistas
  - –Acenocumarol más que warfarina
  - –*Score* bajo en AMT y en cuestionario CCC (comprensión/cumplimiento).
  - –Variantes citocromo P450 CYP2C9 *1/*3, *2/*3, y *3/*3
    - –casos 29,9%
    - –controles 15,0%

Palareti, BJH 2005

	Cases ($n = 77$)	Controls ($n = 80$)	P values
Type of coumarin drug; n (%)			
Warfarin	51 (66·2)	67 (83·7)	NS
Acenocoumarol	26 (33·8)	13 (16·3)	0·02
Duration of anticoagulation (median, months)	44	47	NS
Targeted therapeutic range; n (%)			
2·0–3·0 INR	36 (46·7)	48 (60·0)	NS
2·5–4·0 INR	41 (53·3)	32 (40·0)	NS
Indication for anticoagulation			
Mechanical valve prosthesis	33 (42·8)	25 (31·3)	NS
Heart disease	22 (28·6)	29 (36·2)	NS
Venous thromboembolism	14 (18·2)	14 (17·5)	NS
Others	8 (10·4)	12 (15·0)	NS
No. of visits during the period	9	6	0·0001
Mean interval between visits (d)	12·8	20·5	0·0001
Time in the therapeutic range; % (range)			
Within	38·8 (7·6–88·0)	100 (85–100)	0·0001
Below	33·3 (2–74·4)	0 (0–14·3)	0·0001
Above	24·7 (3–80·3)	0 (0–15·0)	0·0001
Percentage of visits with INR result >4·5	12·3	0·4	0·0001
Percentage of prescriptions changing the dose >15%	33·3 (2–100)	0 (0–40)	0·0001
Daily warfarin dose (mg)	3·05 (0·5–9·9)	3·75 (1·3–10·6)	0·012
Daily acenocoumarol dose (mg)	1·95 (0·5–7·7)	2·12 (1·2–4·7)	NS

NS, not satisfactory.

Palareti, BJH 2005

Bleeding with anticoagulation therapy – Who is at risk, and how best to identify such patients

Gualtiero Palareti; Benilde Cosmi

Department of Angiology and Blood Coagulation "Marino Golinelli", University Hospital S. Orsola-Malpighi, Bologna, Italy

Menor riesgo sangrado	Mayor riesgo sangrado
FACTORES ASOCIADOS AL TRATAMIENTO	
Duración y tiempo desde el inicio	
Periodos cortos	
	Primeros 3-6 meses
Intensidad de la anticoagulación	
INR diana moderado - bajo	INR diana alto
Calidad del control anticoagulante	
Clínicas de anticoagulación	
AVK larga vida media	AVK de vida media corta
Buen control anticoagulación	Control anticoagulación pobre
Auto control	
Uso de algoritmos	

Thrombosis & Haemostasis 2009

Bleeding with anticoagulation therapy – Who is at risk, and how best to identify such patients

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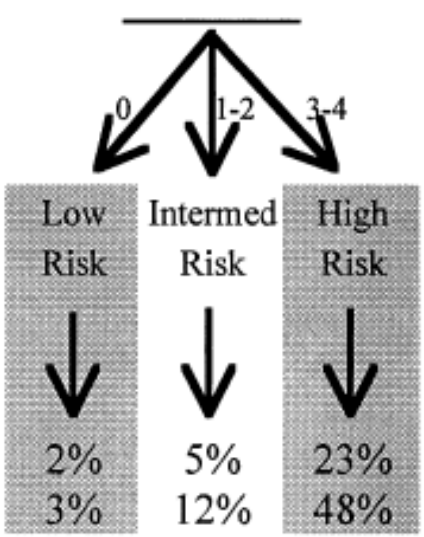
Menor riesgo sangrado	Mayor riesgo sangrado
FACTORES ASOCIADOS A LA PERSONA	
	Factores genéticos
	Sexo femenino, edad avanzada
	Tendencia a la caida
	Falta de información, ausencia de apoyo familiar
	Falta de adherencia
	Dieta pobre en vitamina K, productos de herboristería, alcoholismo
	Comorbilidades
	Polimedicación

Thrombosis & Haemostasis 2009

Prospective Evaluation of an Index for Predicting the Risk of Major Bleeding in Outpatients Treated with Warfarin*

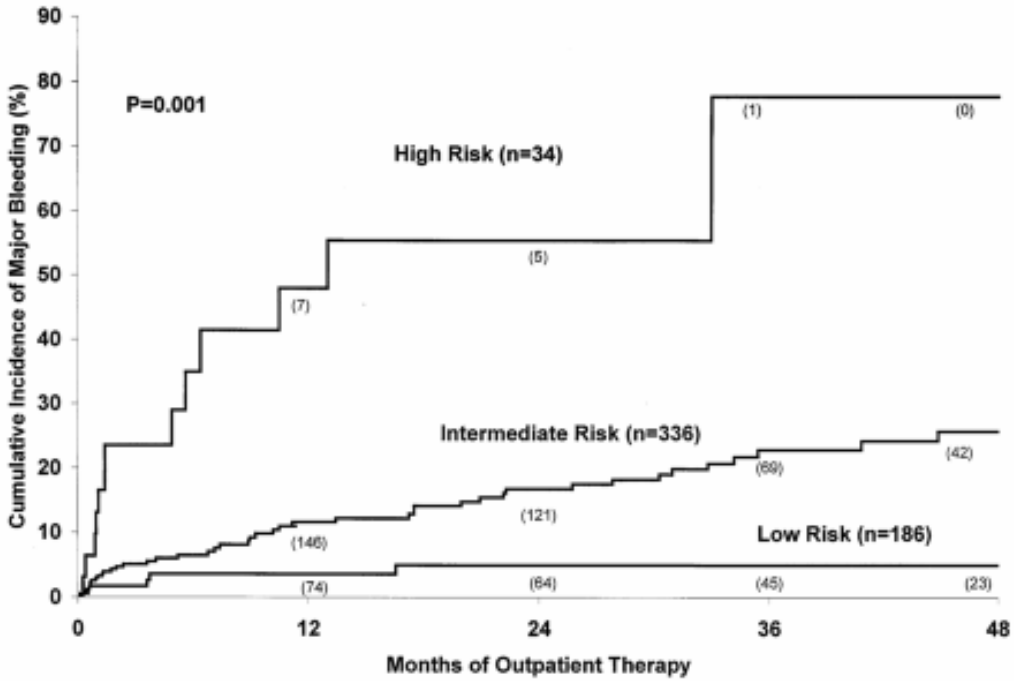
The Outpatient Bleeding Risk Index

1. What risk factors are present? (check all that apply)
   - ❑ Age ≥65 years
   - ❑ History of stroke
   - ❑ History of GIB
   - ❑ Recent MI, Hct<30% Cr>1.5 mg/dl, or Diabetes Mellitus
2. Sum the risk factors: _____
3. Classify your patient:



4. Estimated Risk for Major Bleeding*

	Low Risk	Intermed Risk	High Risk
- in 3 Months	2%	5%	23%
- in 12 Months	3%	12%	48%



Beyth, Am J Med 1998

Clinical classification schemes for predicting hemorrhage: Results from the National Registry of Atrial Fibrillation (NRAF)

American Heart Journal
March 2006

Brian F. Gage, MD, MSc,[a] Yan Yan, MD, PhD,[a,b] Paul E. Milligan, RPh,[a] Amy D. Waterman, PhD,[a] Robert Culverhouse, PhD,[a] Michael W. Rich, MD,[c] and Martha J. Radford, MD[d] *St. Louis, MO; and New Haven, CT*

HEMORR$_2$HAGES

- **H**epatic or renal disease
- **E**thanol abuse
- **M**alignancy **o**lder (age>75 years)
- **R**educed platelet count or function
- **R**e-bleeding risk (2 points)
- **H**ypertension (uncontrolled)
- **A**nemia
- **G**enetic factors
- **E**xcessive fall risk
- **S**troke

HEMORR$_2$HAGES score*	n	No. of bleeds	Bleeds per 100 point-years warfarin (95% CI)
0	209	4	1.9 (0.6-4.4)
1	508	11	2.5 (1.3-4.3)
2	454	20	5.3 (3.4-8.1)
3	240	15	8.4 (4.9-13.6)
4	106	9	10.4 (5.1-18.9)
≥5	87	8	12.3 (5.8-23.1)
Any score	1604	67	4.9 (3.9-6.3)

Scheme	*c* Indices (SD), stratified by cohort		
	Warfarin (n = 1604)	Aspirin (n = 660)	Neither (n = 1527)
Landefeld and Goldman[8] and Beyth et al[9]	0.65 (0.03)	0.69 (0.05)	0.65 (0.03)
Kuijer et al[10]	0.58 (0.03)	0.58 (0.05)	0.47 (0.03)
Kearon et al[11]	0.66 (0.03)	0.64 (0.05)	0.66 (0.04)
HEMORR$_2$HAGES	0.67* (0.04)	0.72* (0.05)	0.66 (0.04)

GUIAS NICE

IDENTIFICA COMO FACTORES DE RIESGO

- EDAD ≥75
- TRATAMIENTO ANTIAGREGANTE
- HTA INCONTROLADA
- HISTORIA PREVIA SANGRADO
- ANEMIA
- POLIFARMACIA

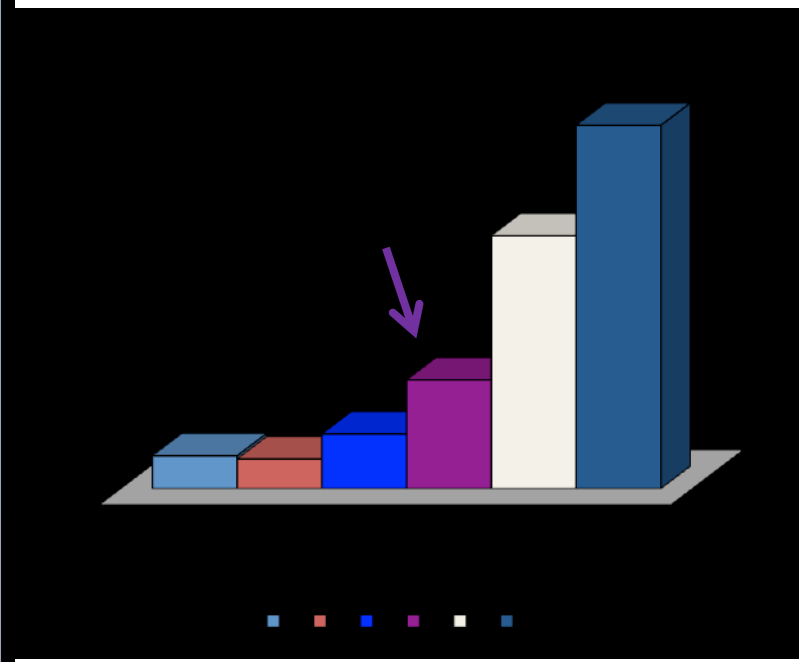
Hughes, QMJ 2007

CHEST

A novel user-friendly score (HAS-BLED) to assess one-year risk of major bleeding in atrial fibrillation patients: The Euro Heart Survey

Lip, 2010

	Clinical characteristic
H	Hypertension
A	Abnormal renal and liver function (1 point each)
S	Stroke
B	Bleeding
L	Labile INRs
E	Elderly (age >75)
D	Drugs or alcohol (1 point



Ciclo de la vitamina K

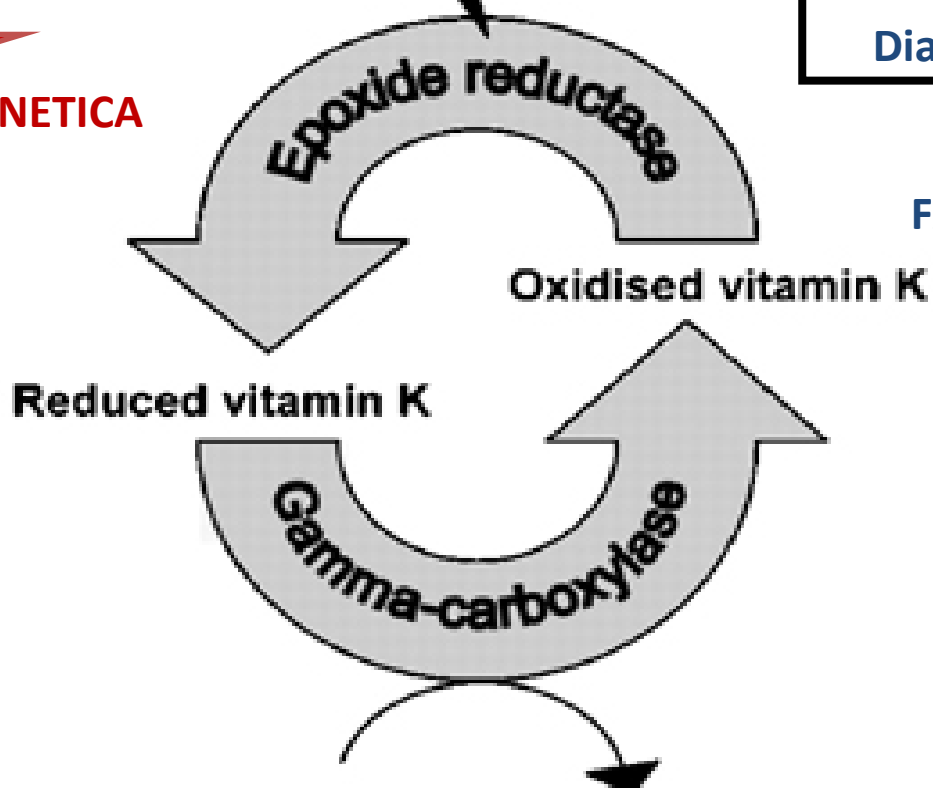
Citocromo P 4502C9
CYP2C9
Enzima metaboliza AVK

FARMACOCINETICA

Warfarin

Vitamina K epoxido reductasa
VKORC1
Diana enzimática de AVK

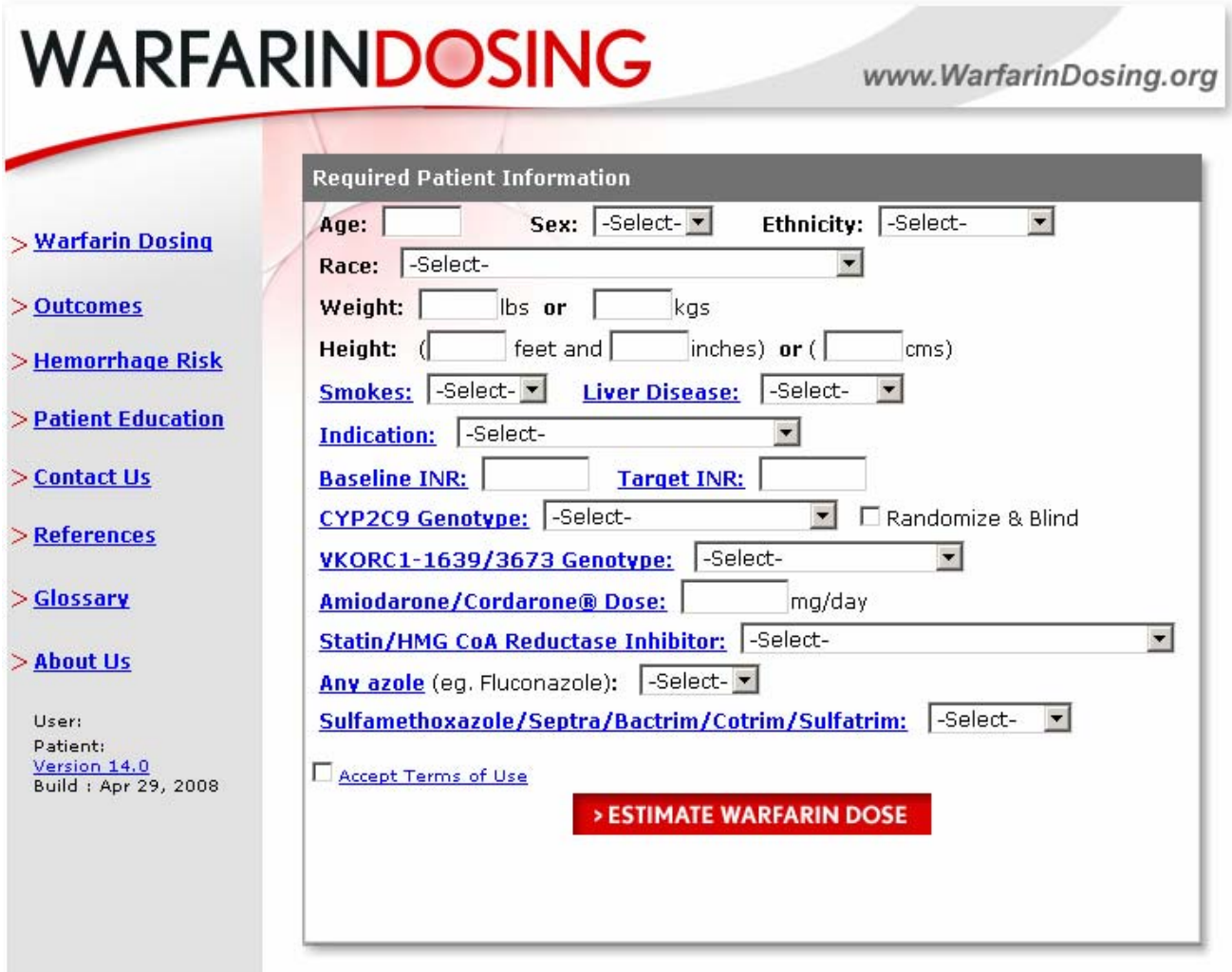
FARMACODINAMICA



Factors II, VII, IX, X

Proteins C, S, Z

Activated { Factors II, VII, IX, X ; Proteins C, S, Z }

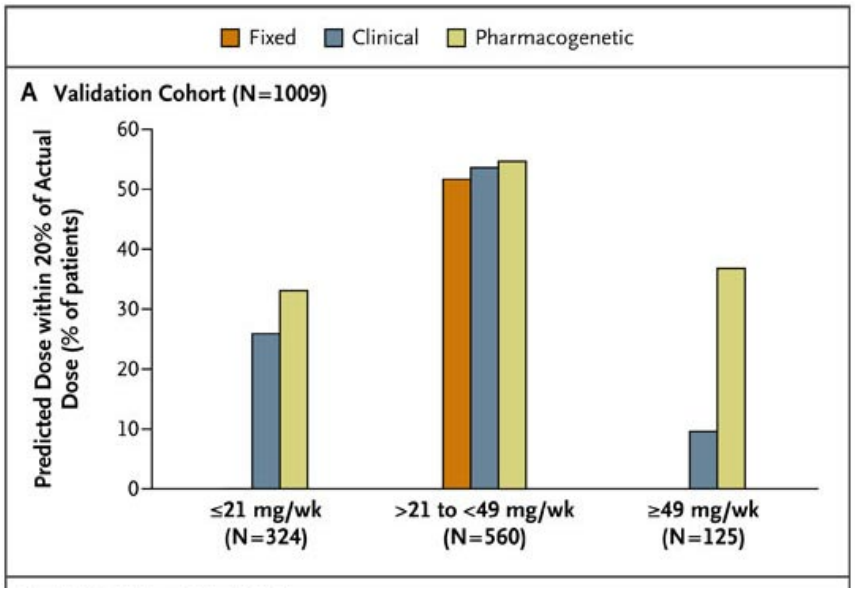


Los algoritmos clínicos son capaces de predecir entre el 17-22%
Los algoritmos genéticos el 50%

Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data

The International Warfarin Pharmacogenetics Consortium*

NEJM 2009



Actual Dose Required	No. of Patients	Ideal Dose	
		Percent	P Value†
Validation cohort only			
≤21 mg/wk	324		
Pharmacogenetic approach		33.0	0.008, <0.001
Clinical approach		25.9	<0.001
Fixed-dose approach		0	
>21 mg/wk to <49 mg/wk	560		
Pharmacogenetic approach		54.6	0.72, 0.31
Clinical approach		53.6	0.55
Fixed-dose approach		51.6	
≥49 mg/wk	125		
Pharmacogenetic approach		36.8	<0.001, <0.001
Clinical approach		9.6	<0.001
Fixed-dose approach		0	

Journal of Thrombosis and Haemostasis, **8**: 1012–1017 DOI: 10.1111/j.1538-7836.2010.03800.x

ORIGINAL ARTICLE

Pharmacogenetics of acenocoumarol in patients with extreme dose requirements

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TRATAMIENTO ANTICOAGULANTE

Reducción de eventos trombóticos

Incremento del riesgo hemorrágico

Mejorar la estratificación de los pacientes
- riesgo embólico
- riesgo hemorrágico

Clínicas anticoagulación:
- mejorar la educación pacientes
- algoritmos predictivos
- farmacogenética

Nuevos anticoagulantes