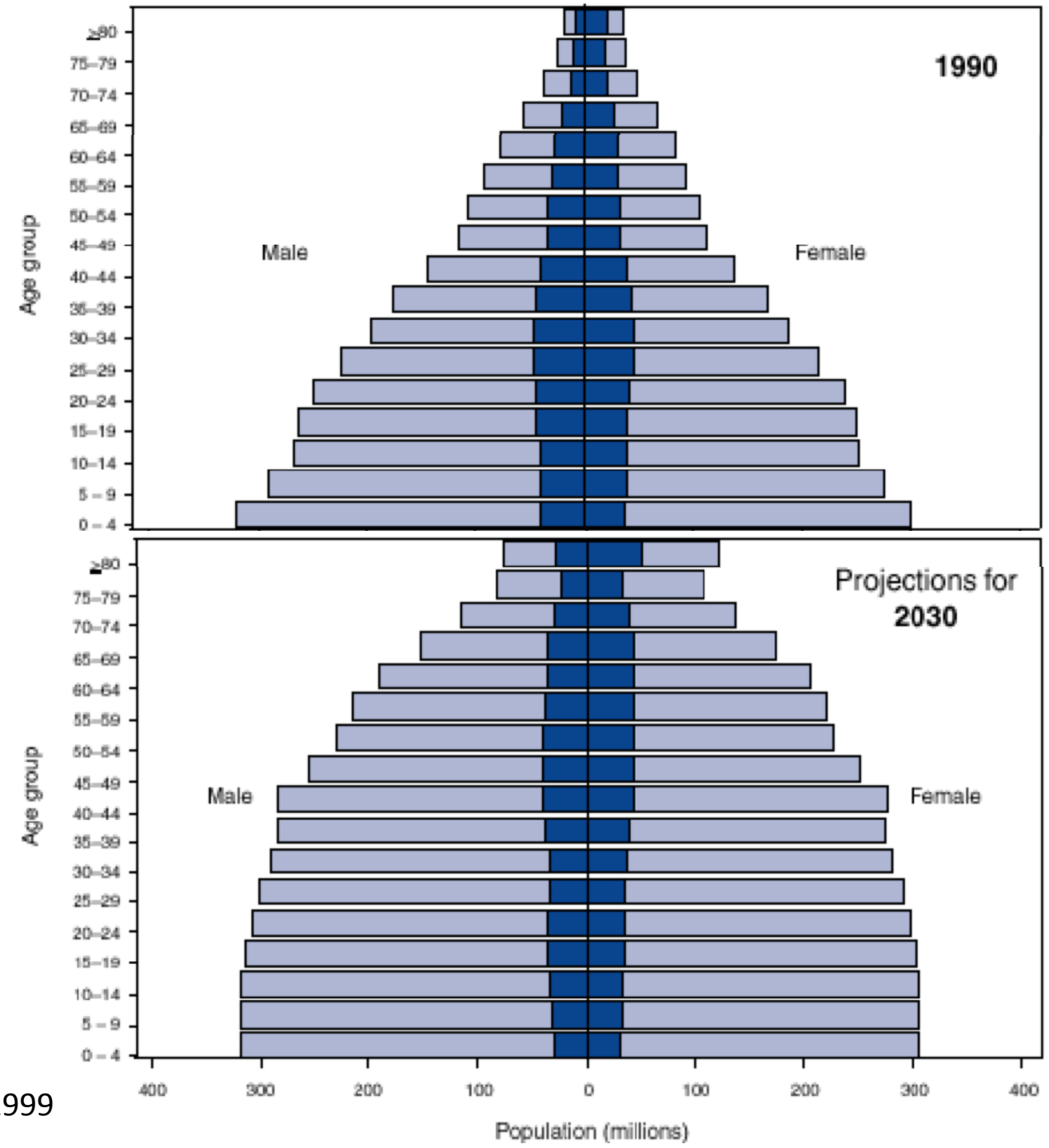
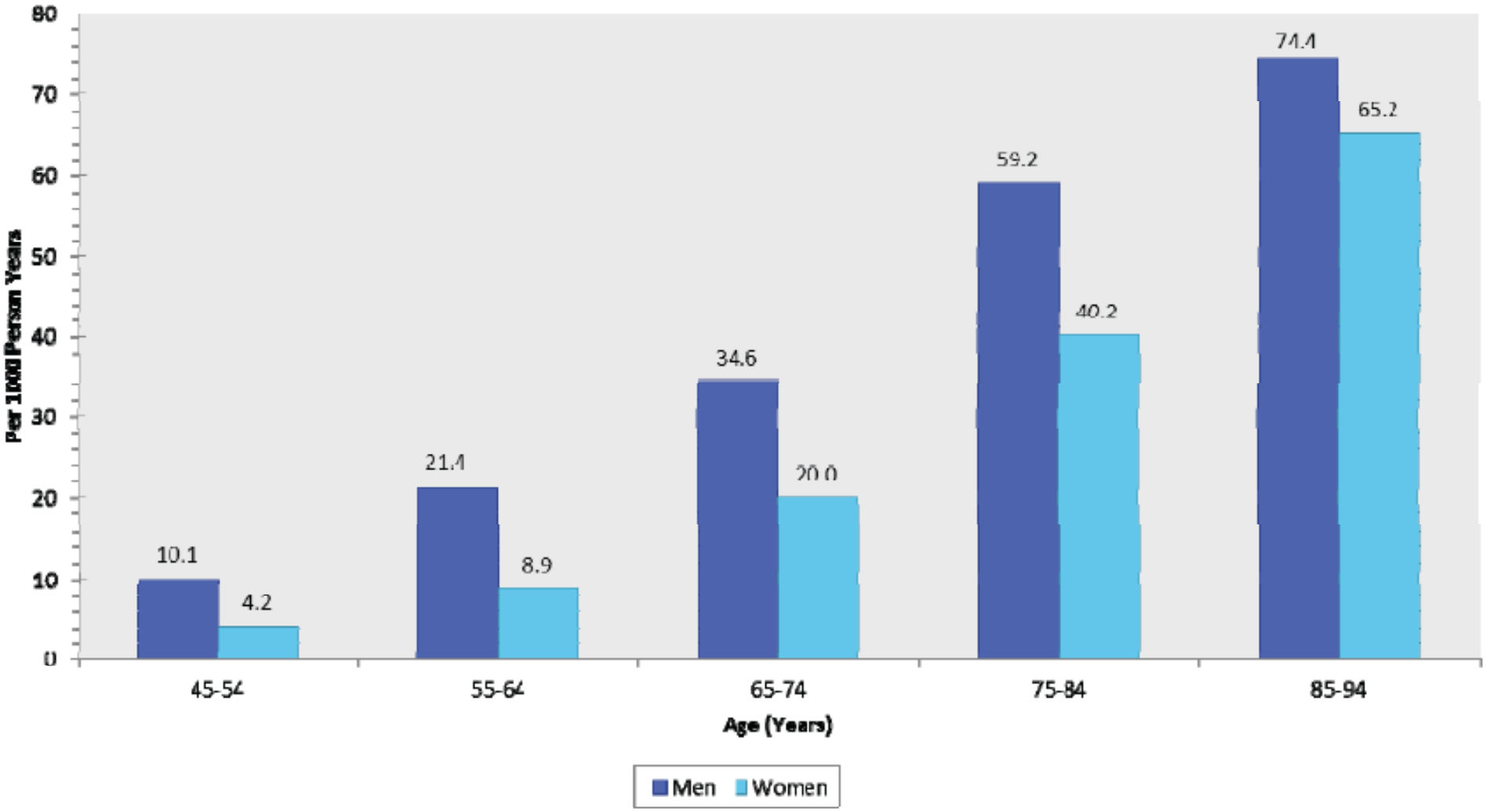
PROBLEMÁTICA DEL TRATAMIENTO FARMACOLÓGICA CARDIOVASCULAR EN EL ANCIANO

Dr. D. Antonio Salvador Sanz



Fuente: ONU 1999

Incidence of cardiovascular disease by age and sex (FHS 1980-2003)



*Source: Incidence and Prevalence: 2006 Chart Book on Cardiovascular and Lung Diseases.*Bethesda, MD: National Heart, Lung, and Blood Institute; 2006.

Tratamiento farmacológico CVasc en p. con edad avanzada

- Los fármacos CVasc son los más frecuentemente prescritos.
- Suelen tener estrecho margen terapeutico: Efectos Adversos.
- Su uso apropiado requiere conocer:
  - Cambios de la fisiología relacionados con la edad.
  - Comorbilidades que alteren la FK y FD de los fármacos.
  - Interacciones medicamentosas.

Distribución de los fármacos: Cambios con la edad

< masa corporal total. >proporción de grasa corporal.

↓

> Vd de drogas liposolubles.

↓

< Betabloqueantes

< proporción de agua corporal.

↓

< Vd de drogas hidrosolubles.

↓

> Digoxina y IECAs

< albúmina plasm.

< perfusión tejidos.

↓

> % droga libre

< Vd.

↓

> Acenocumarol

Metabolismo y Excreción de fármacos: Cambios con la edad

Hígado: < masa, flujo sang. y capacidad metabólica.

Acumulación de drogas metabolizadas en hígado.

> Acenocumarol, propranolol, nitratos, diltiazem, verapamil.

Riñón: < filtración glomerular, función tubular y flujo sanguíneo.

Acumulación de drogas eliminadas por el riñón.

> Digoxina, atenolol, antiarrítmicos, IECAs.

Cambios en la farmacodinámica con la edad

< sensibilidad de los barorreceptores	Tendencia a Hipotensión Ortostática
< respuesta cardiaca y vascular de recept. ß	< efecto betabloqueante
> Sensibilidad a anticoagulantes	> efecto del acenocumarol
Comorbilidades	> interacciones fármaco-enfermedad
Polifarmacia	> interacciones fármaco-fármaco
Disfunción sinusal y del nodo AV	Tendencia al bloqueo cardiaco

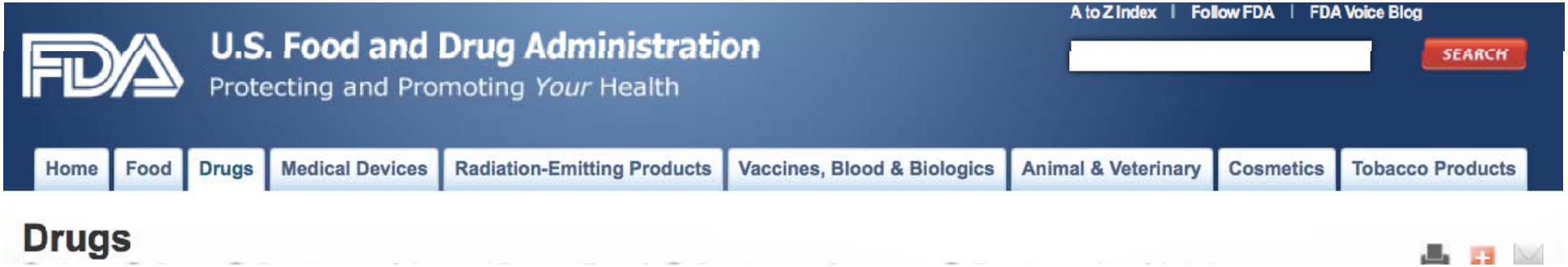
Fármacos culpables de síntomas frecuentes en edad avanzada

Estados confusionales	Digoxina, betabloqueantes
Vértigo, tinnitus	Aspirina, Furosemida
Depresión	Betabloqueantes
Caídas	Nitratos, fármacos productores de hipotensión postural
Hipotensión postural	Antihipertensivos, antianginosos, betabloq., diuréticos
Estreñimiento	Diltiazem, Verapamil, Diuréticos
Incontinencia urinaria	Betabloqueantes, Diuréticos

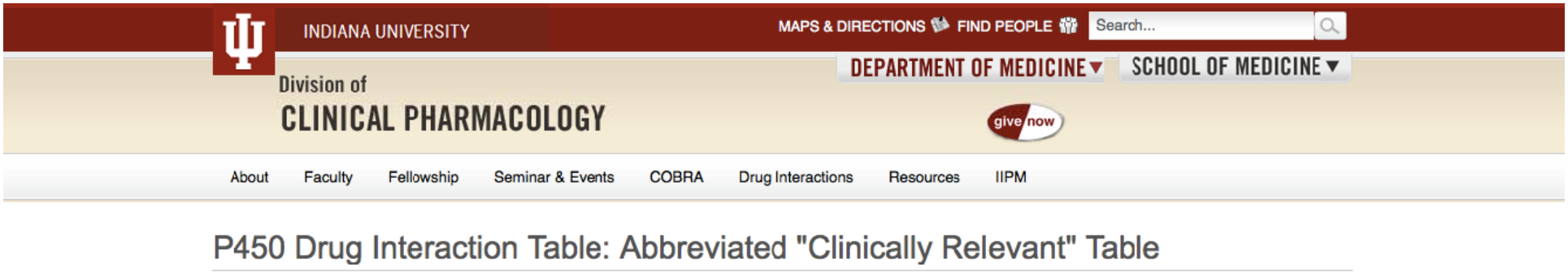
Interacciones fármaco-enfermedad en edad avanzada

Enfermedad	Fármacos	Efecto Adverso
ICC	Verapamil	Descompensación IC aguda
Alter. Conducción	Antidepres. Tricíclicos	Bloqueo Cardiaco
Hipertensión	AINES	Aumento de Presión Arterial
Arteriop. Per. Crón.	Betabloqueantes	Claudicación Intermitente
EPOC	Betabloqueantes	Broncoconstricción
IRC	AINES	Insuf. Renal Aguda
Diabetes	Diuréticos	Hiperglucemia
Depresión	Betabloqueantes	Exacerban la Depresión
Hipokaliemia	Digoxina	Arritmias cardiacas
Ulcera Péptica	ACO, NACO, Salicilatos	Hemorragia Gastrointestinal

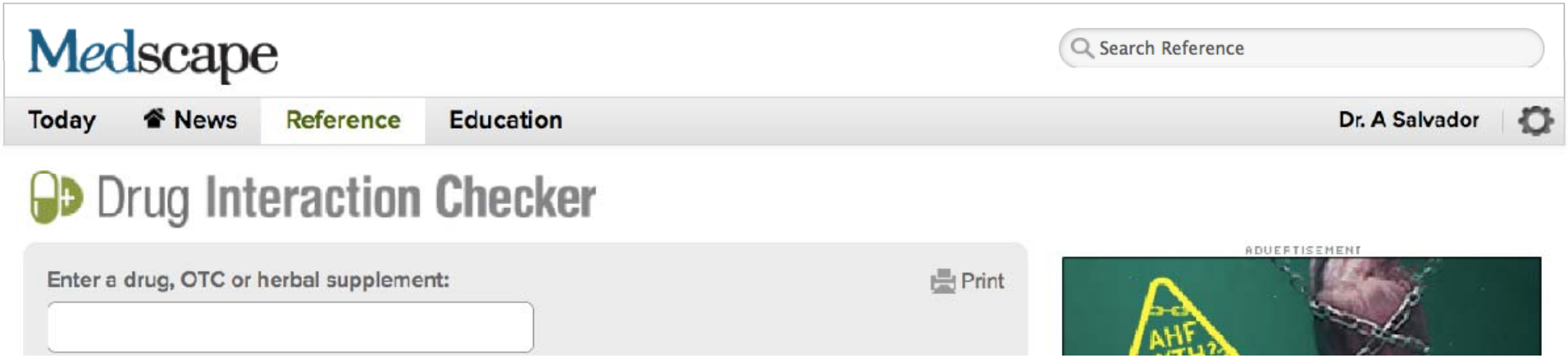
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm



http://medicine.iupui.edu/clinpharm/ddis/clinical-table/

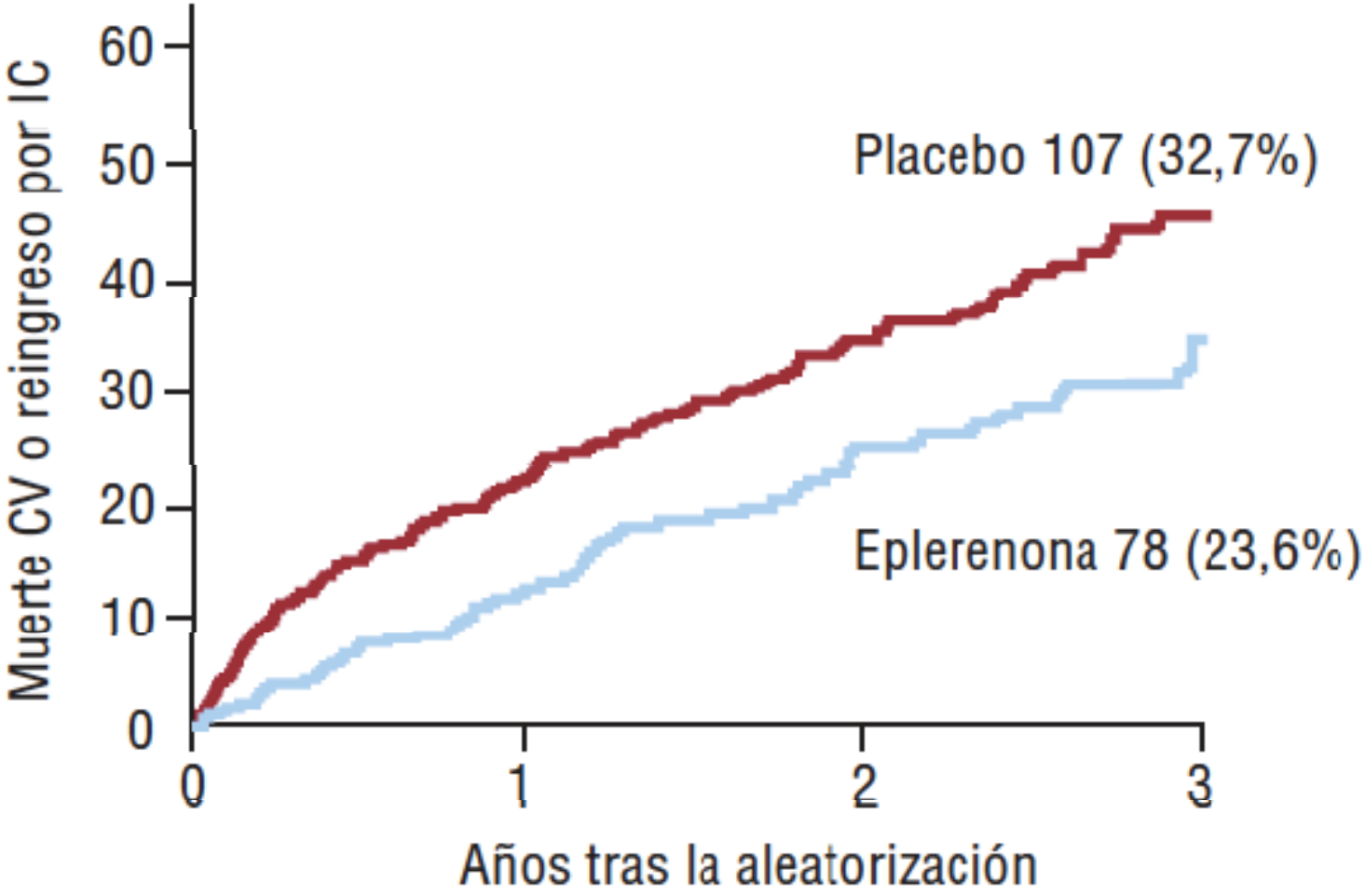


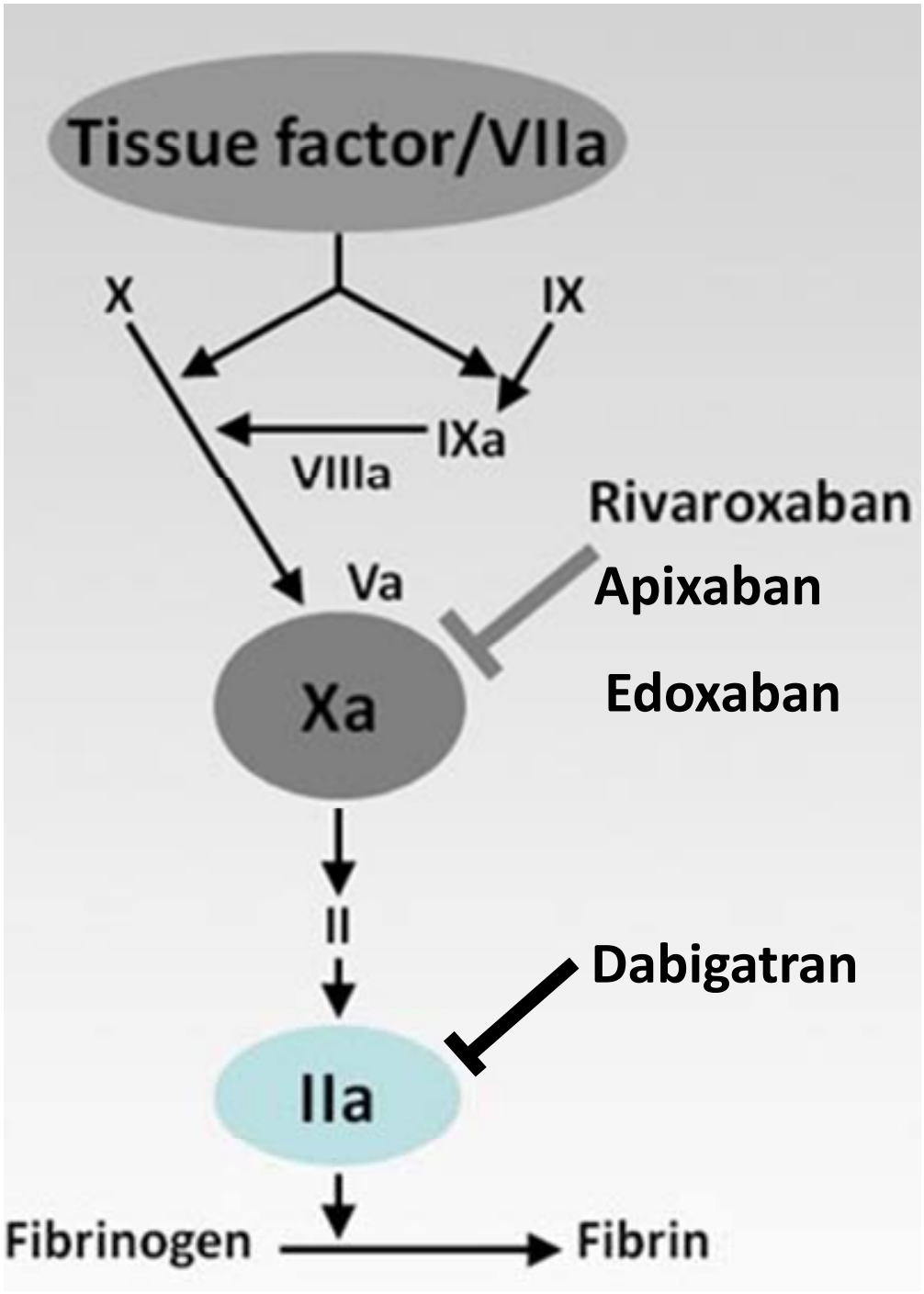
http://reference.medscape.com/drug-interactionchecker



EMPHASIS en edad ≥ 75 años

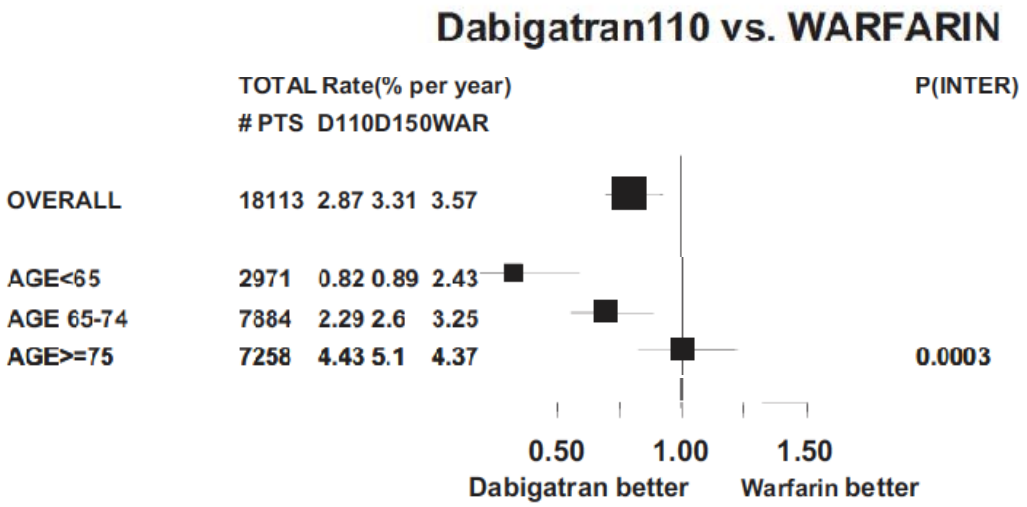
HR (IC95%) = 0,66 (0,49-0,88) p = 0,0044

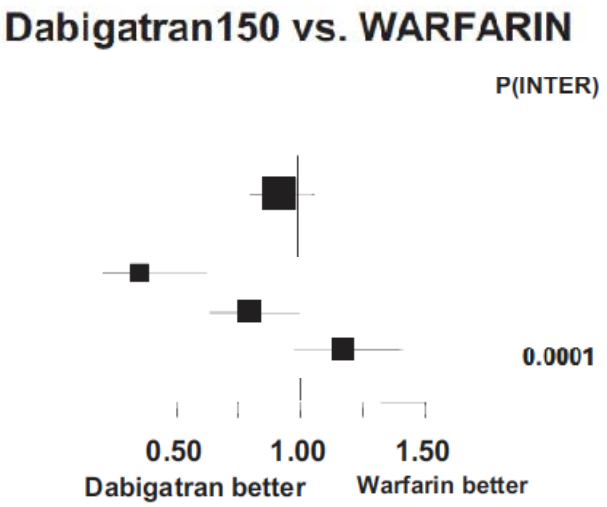



Tissue factor/VIIa
X
IX
IXa
VIIIa
Va
Xa
II
IIa
Fibrinogen
Fibrin
Rivaroxaban
Apixaban
Edoxaban
Dabigatran

Estudio RELY: Hemorragias

Eikelboom JW y cols. Circulation 2011

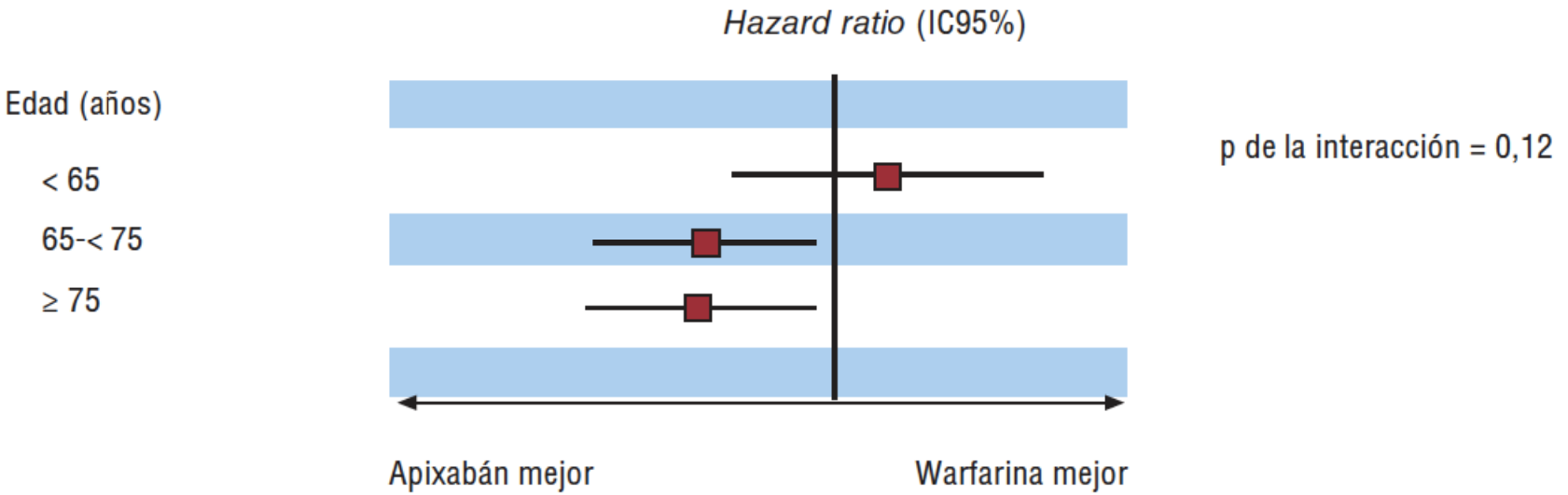




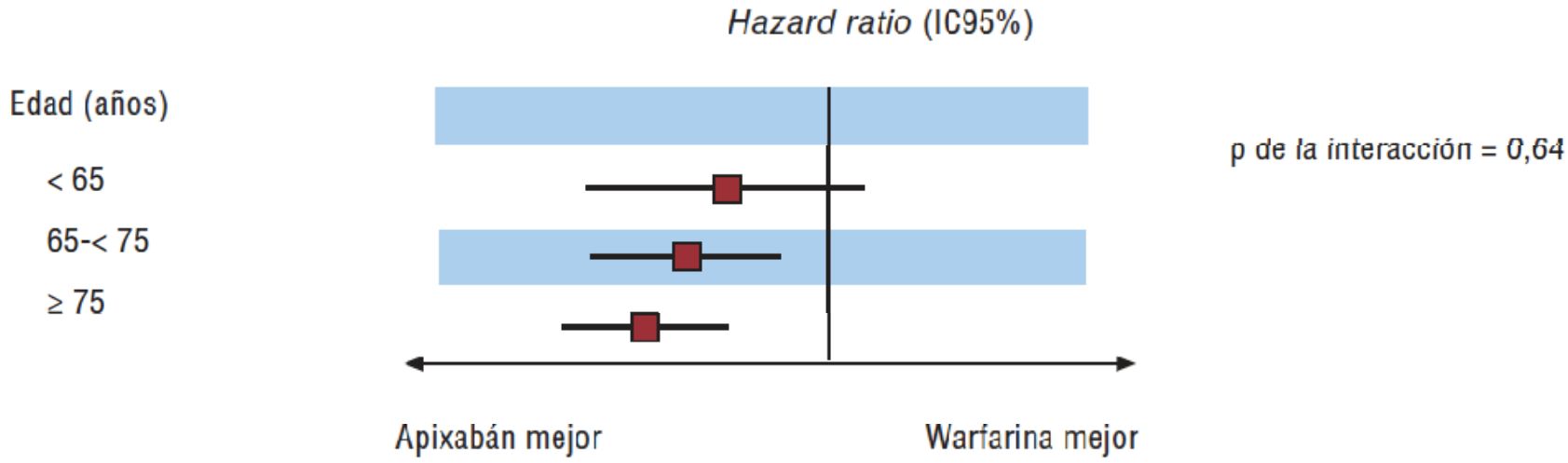
Apixaban vs Warfarina en edad avanzada: Eficacia y Seguridad

ARISTOTLE trial, NEJM 2011

Eficacia: Ictus o Embolia Sistémica

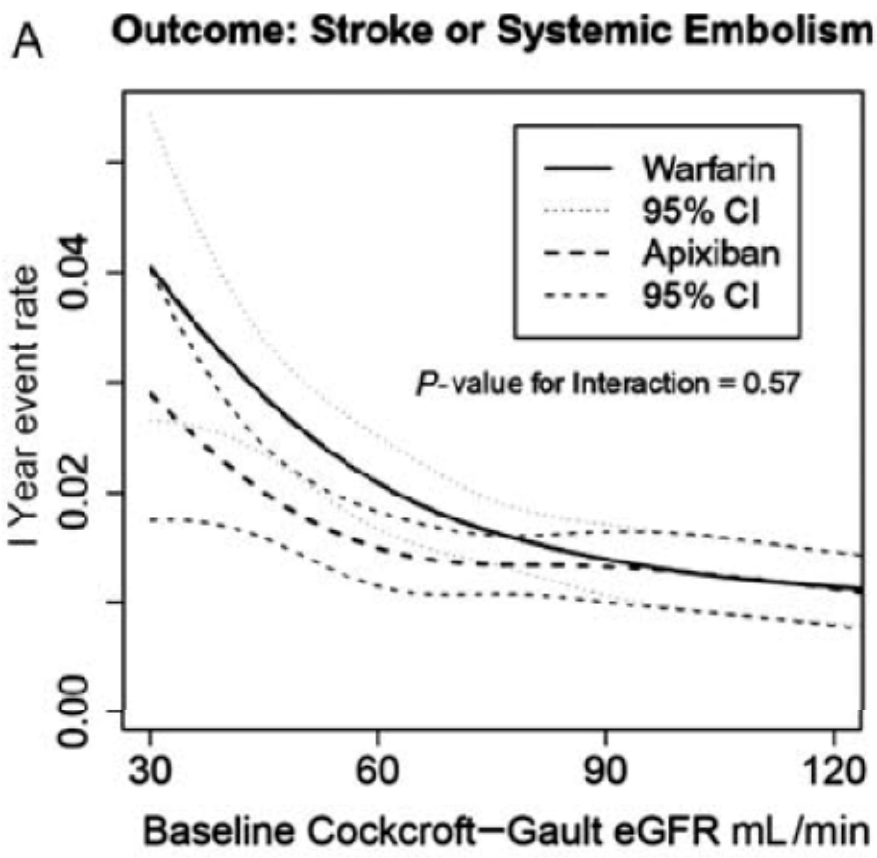


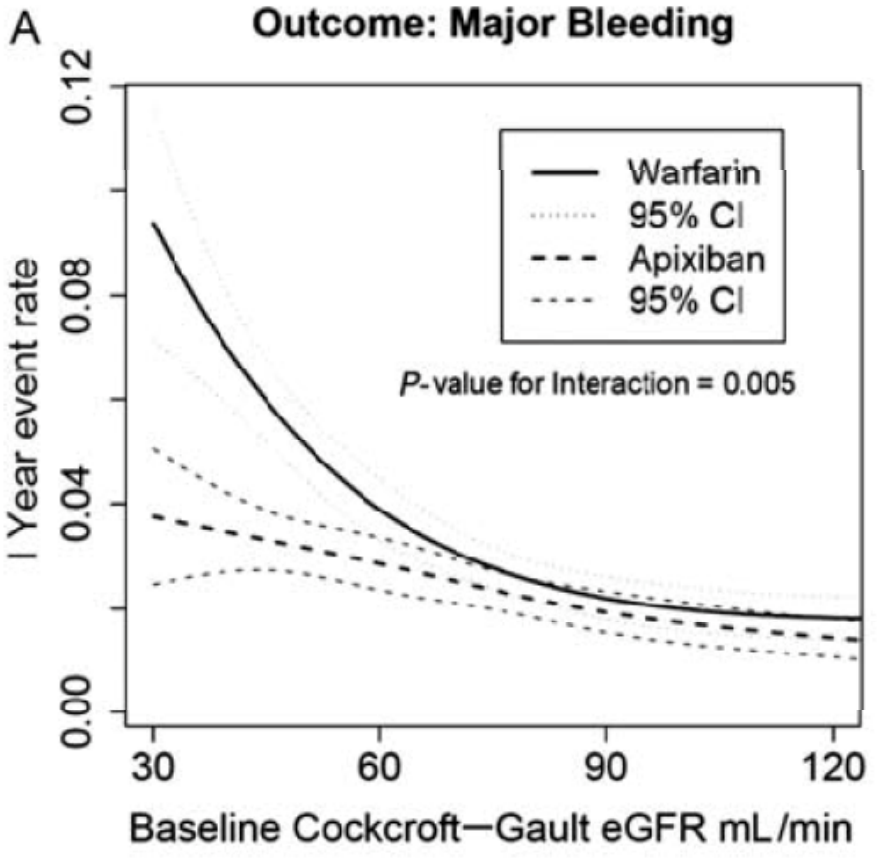
Seguridad: Hemorragia severa



Apixaban vs Warfarina en Eficacia y Seguridad. Función Renal

Hohnloser SH y cols. EHJ 2012

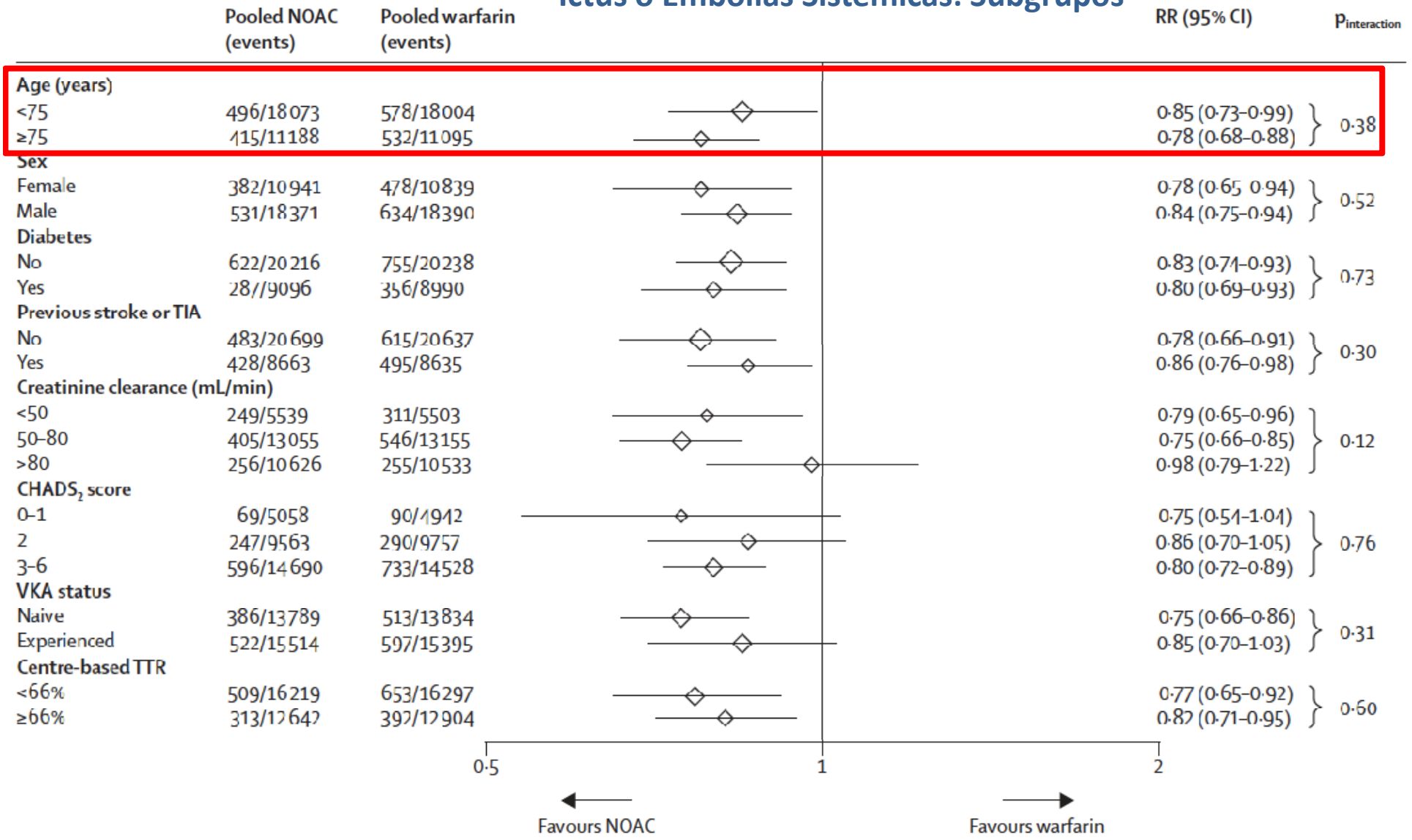




NACOs vs Warfarina en Eficacia. Metanálisis

Ruff CT y cols. *Lancet* 2013; DOI: 10.1016/S0140-6736(13)62376-4

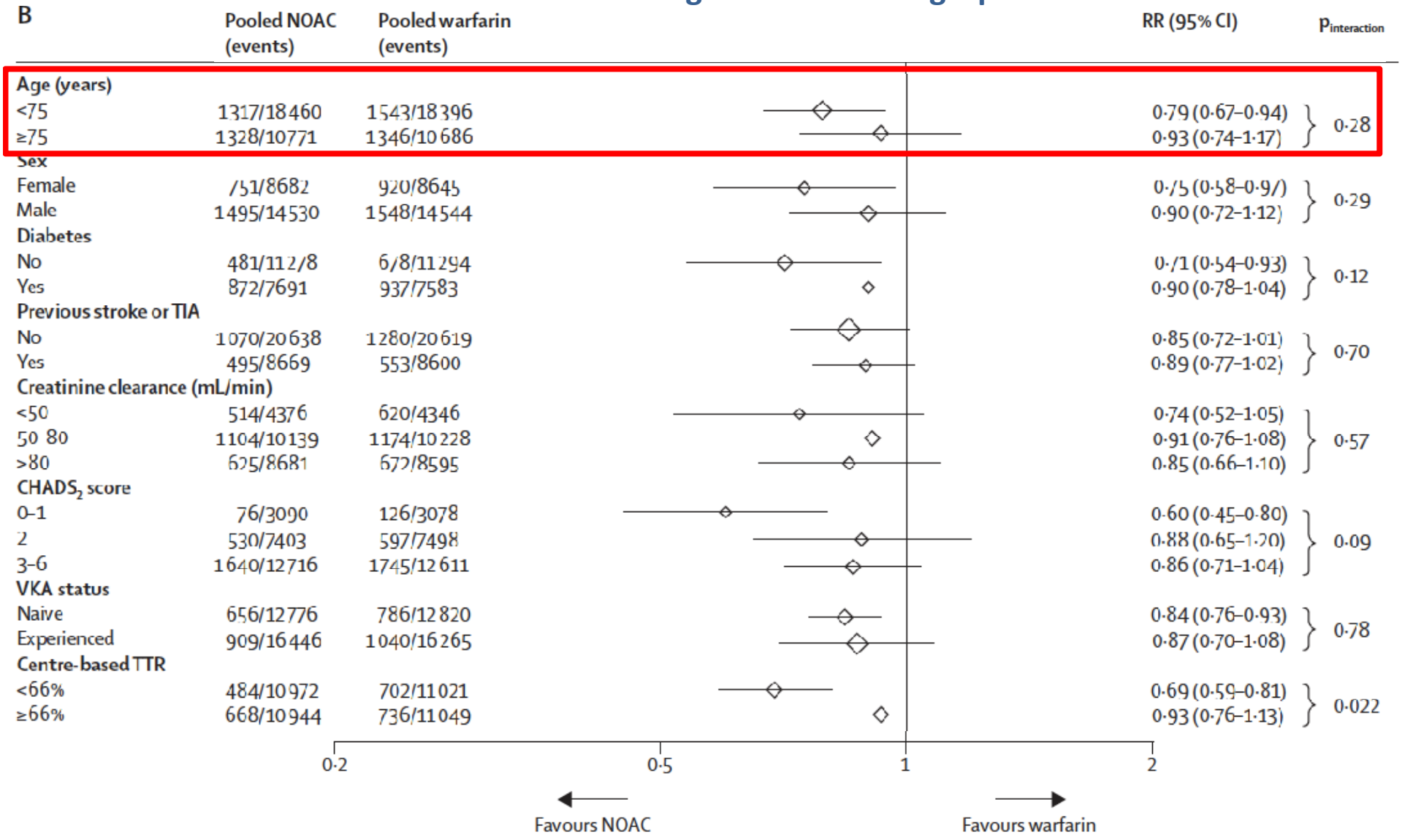
Ictus o Embolias Sistémicas: Subgrupos



NACOs vs Warfarina en Seguridad. Metanálisis

Ruff CT y cols. *Lancet* 2013; DOI: 10.1016/S0140-6736(13)62376-4

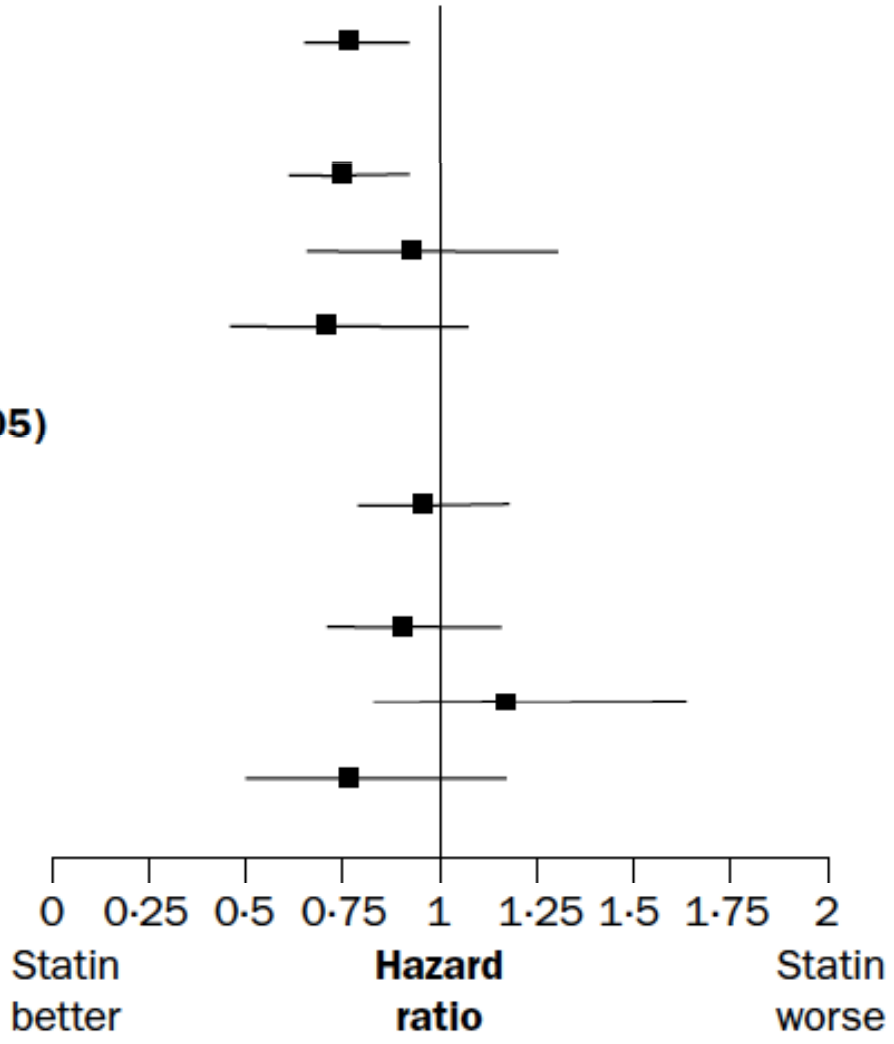
Hemorragias severas: Subgrupos



PROSPER: Estatinas en p. 70-82 a. con alto riesgo vascular

5800 p. Sepherd J y cols. Lancet 2002, 360: 1623-30

	Pravastatin	Placebo
Men	**(n=1396)**	**(n=1408)**
CHD death, non-fatal MI, and fatal or non-fatal stroke	222	279
CHD death, non-fatal MI	167	219
Fatal and non-fatal stroke	65	70
TIA	38	53
Women	**(n=1495)**	**(n=1505)**
CHD death, non-fatal MI, and fatal or non-fatal stroke	186	194
CHD death, non-fatal MI	125	137
Fatal and non-fatal stroke	70	61
TIA	39	49



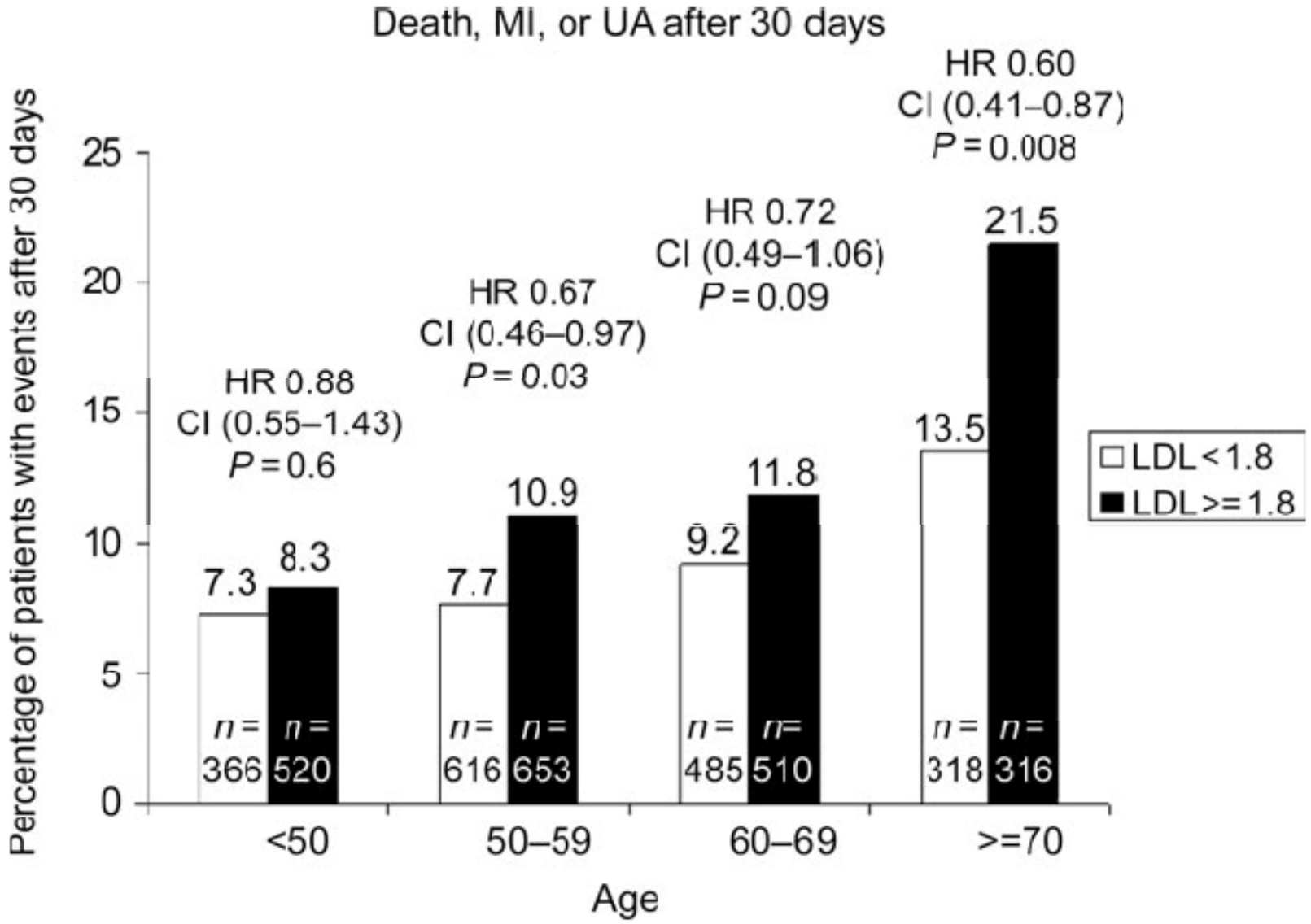
Benefits of β-Blockade Among Elderly Patients: Survival at 1 Year After Myocardial Infarction

Age over 75 years	Two or more comorbidities	Number of patients	Relative risk (95% CI)	p
Yes	Yes	1700	0·42 (0·32–0·54)	0·0001
Yes	No	5206	0·41 (0·35–0·48)	0·0001
No	Yes	1469	0·49 (0·37–0·65)	0·0001
No	No	5248	0·30 (0·24–0·37)	0·0001

REF: Rochon PA, et al. Lancet. 2000 Aug 19;356:639-44

PROVE IT-TIMI 22: Beneficio del trat. con Estatinas en SCASEST

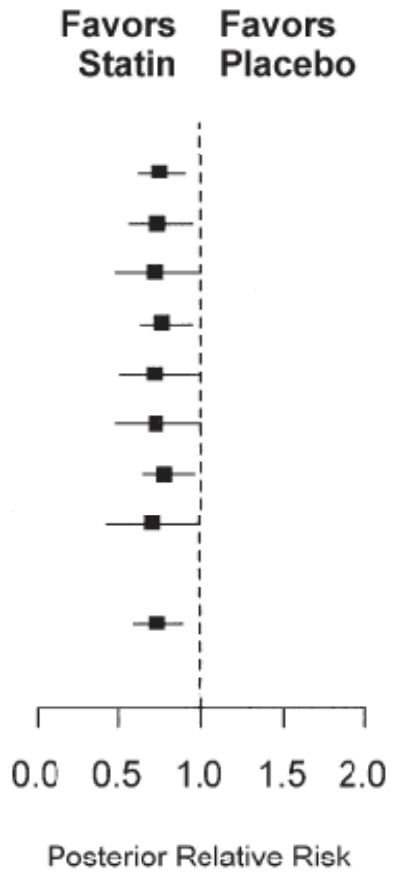
Ray KK y cols. European Heart Journal 2006, 27: 2310-6



Estatinas en Prevención Secundaria de p. con > 65 años. Metanálisis

Afilalo J y cols. J Am Coll Cardiol 2008;51:37–45

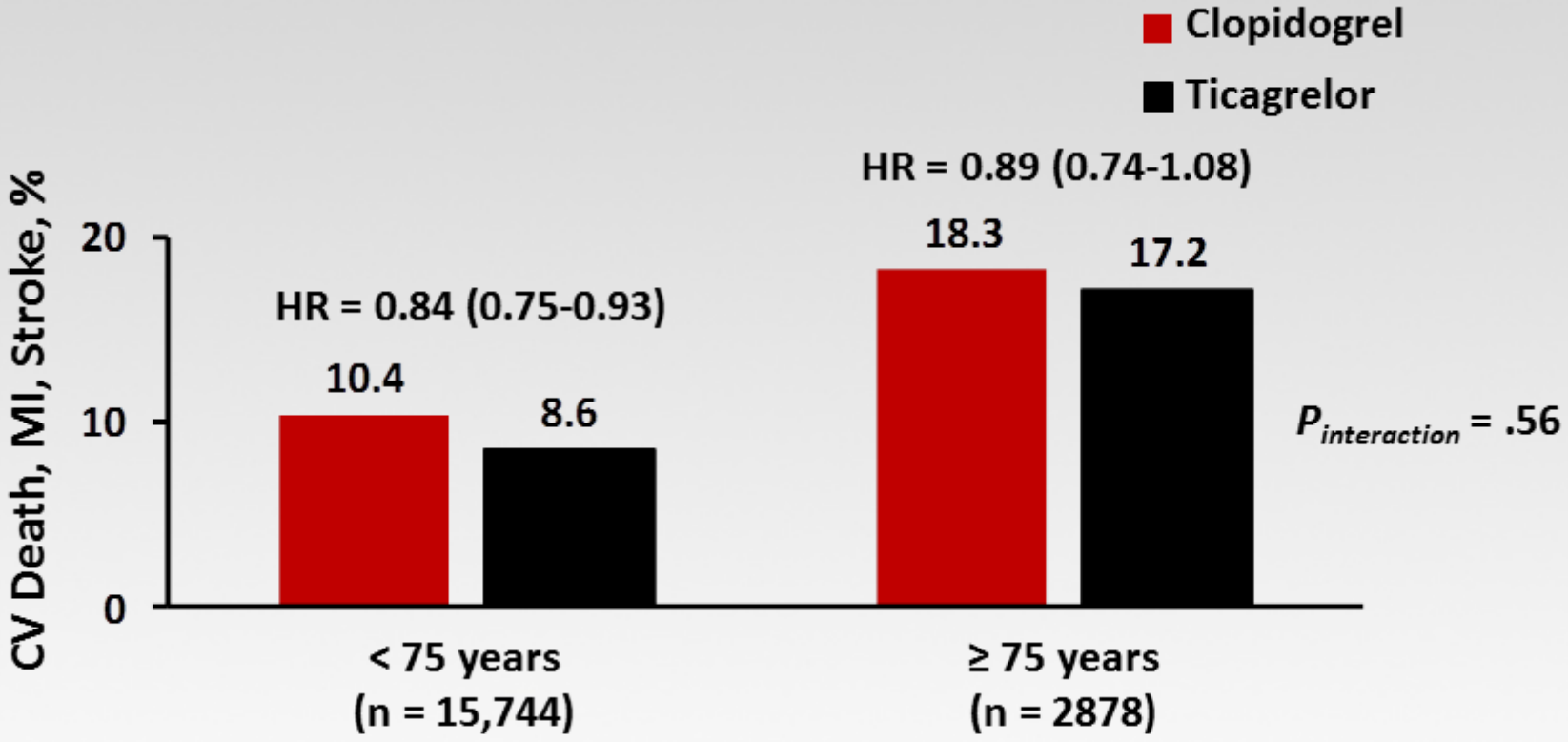
Study	No. Events/ Total No. of Patients: Statin	Placebo	Posterior Median Relative Risk (95% Credible Interval)
4S	89 / 518	122 / 503	0.75 (0.62 , 0.89)
CARE	41 / 640	57 / 643	0.73 (0.57 , 0.93)
FLARE	5 / 179	9 / 187	0.72 (0.49 , 0.98)
LIPID	110 / 1741	138 / 1773	0.77 (0.64 , 0.93)
LIPS	12 / 324	16 / 299	0.72 (0.51 , 0.97)
PLAC I	2 / 42	6 / 52	0.73 (0.48 , 0.99)
PROSPER	98 / 934	116 / 899	0.78 (0.64 , 0.95)
REGRESS	0 / 75	1 / 63	0.71 (0.43 , 0.97)
Pooled (5 year)	**357 / 4453**	**465 / 4419**	**0.74 (0.60 , 0.89)**



Bayesian Forest Plot for Nonfatal Myocardial Infarction

PLATO Elderly: Primary End Point

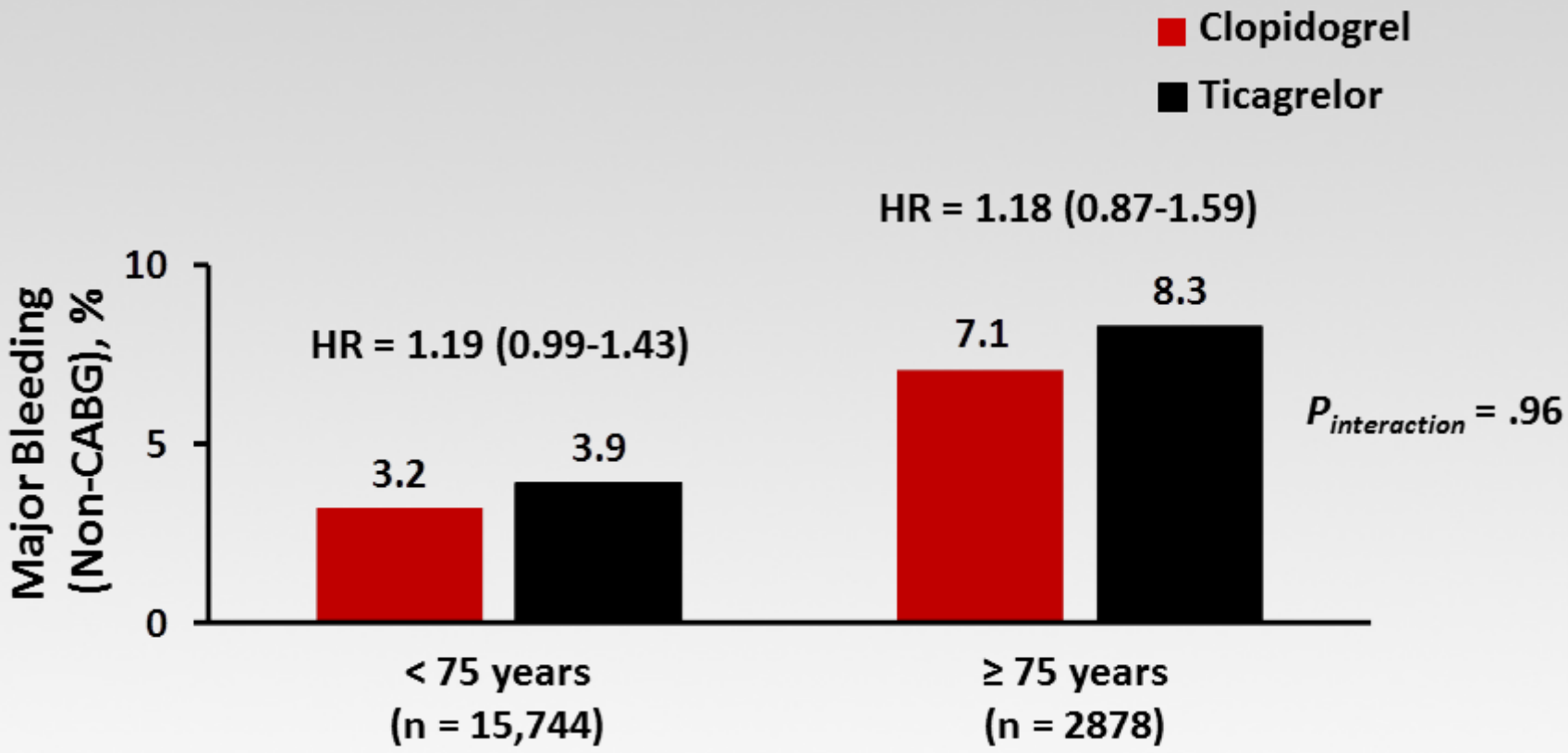
Absolute reduction in all-cause mortality greater in elderly vs younger patients (2.6% vs 1.2%)



Clopidogrel = 300-600 mg load, 75 mg daily
Ticagrelor = 180 mg load, 90 mg twice daily

Husted S, et al.[5]

PLATO Elderly: TIMI Major Bleeding (Non-CABG)



Clopidogrel = 300-600 mg load, 75 mg daily
Ticagrelor = 180 mg load, 90 mg twice daily

Husted S, et al.[5]

Fármacos para Prevención Secundaria de ECVAS en edad avanzada

Recom. de la AHA. Fleg JL y cols. Circulation 2013;128:2422-2446

Table 1. Selection of Antihypertensive Therapy for Older Adults Based on Comorbidities

Compelling Indication	Initial Therapeutic Choice
Heart failure	Thiazide, β-blocker, ACE inhibitor, angiotensin receptor antagonist, calcium channel blocker, aldosterone antagonist
Previous myocardial infarction	β-Blocker, ACE inhibitor, aldosterone antagonist, angiotensin receptor antagonist
CHD or high-risk CVD	Thiazide, β-blocker, ACE inhibitor, calcium channel blocker
Angina pectoris	β-Blocker, calcium channel blocker
Aortopathy/aortic aneurysm	β-Blocker, angiotensin receptor antagonist, ACE inhibitor, thiazide, calcium channel blocker
Diabetes mellitus	ACE inhibitor, angiotensin receptor antagonist, calcium channel blocker, thiazide, β-blocker
Chronic kidney disease	ACE inhibitor, angiotensin receptor antagonist
Recurrent stroke prevention	Thiazide, ACE inhibitor, angiotensin receptor antagonist, calcium channel blocker
Early dementia	Blood pressure control

Most patients will require combination therapy. ACE indicates angiotensin-converting enzyme; CHD, coronary heart disease; and CVD, cardiovascular disease.
Adapted from Aronow et al[37] with permission.

Fármacos para Prevención Secundaria de ECVAS en edad avanzada

Recom. de la AHA. Fleg JL y cols. Circulation 2013;128:2422-2446

Table 3. Common Iatrogenic Effects of Secondary Prevention Medications in Older Patients With ASCVD

Medication Class	Medication	General Side Effects in Older Cardiac Patients	Medication-Medication Side Effects	Comorbid Disease–Medication Interactions
Anti-ischemics and antihypertensives	β-Blockers	• Confusion, fatigue, dizziness, bronchospasm, conduction block, chronotropic incompetence, claudication, depression, cold sensitivity, incontinence • Hypoglycemia • Increased system absorption in body fat, with delayed metabolism	• Calcium channel blockers: conduction disease and chronotropic incompetence • Sulfonylureas: hypoglycemia	• COPD: bronchospasm • Depression or anxiety: ↑fatigue and depression • PAD: claudication • Raynaud syndrome: ↑symptoms • CHF: acute decompensation • Conduction disease: bradycardia, heart block
	ACE inhibitors	• Falls, dizziness, hypotension (orthostatic, postprandial), hyperkalemia, fatigue, azotemia, cough	• Diuretics (and other antihypertensives): ↑susceptibility to hypotension • NSAIDs: ↑susceptibility to renal failure	• CKD: hyperkalemia and ↑renal failure
	Nitrates	• Dizziness, hypotension, syncope, headache	• Diuretics: hypotension and low cardiac output • Phosphodiesterase inhibitors: severe hypotension • Alcohol: hypotension	• Aortic stenosis: hypotension
	Diuretics	• Urinary frequency and incontinence, electrolyte	• ACE inhibitors and other diuretics: hypotension	• CKD: ↑renal failure • Diabetes mellitus:

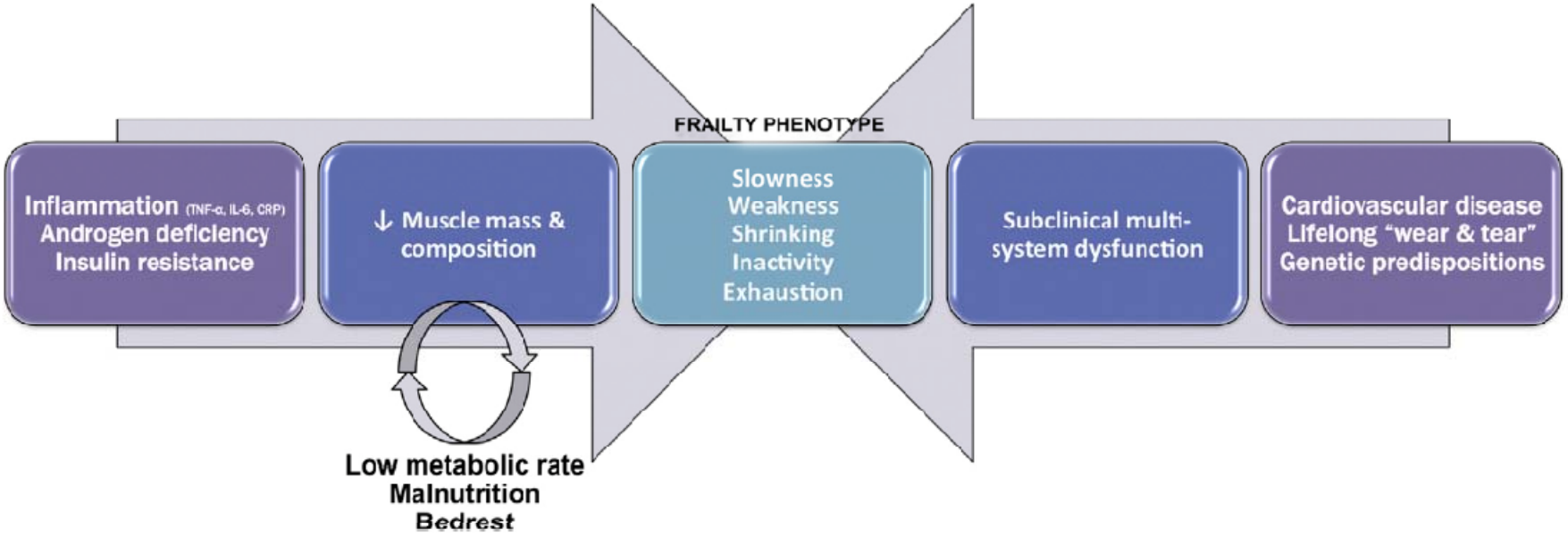
Fármacos para Prevención Secundaria de ECVAS en edad avanzada

Recom. de la AHA. Fleg JL y cols. Circulation 2013;128:2422-2446

Table 3. Common Iatrogenic Effects of Secondary Prevention Medications in Older Patients With ASCVD

Medication Class	Medication	General Side Effects in Older Cardiac Patients	Medication-Medication Side Effects	Comorbid Disease–Medication Interactions
	Calcium channel blockers	• Dizziness, flushing, and peripheral edema (dihydropyridines), constipation (verapamil)	• β-Blockers: conduction disease and chronotropic incompetence	• CHF: decompensation • Conduction disease: bradycardia, heart block
Antiplatelet	Aspirin	• GI bleeding, dyspepsia, tinnitus, skin reactions	• Warfarin, direct thrombin inhibitors, or thienopyridine: ↑bleeding	• GI bleeding history, hypertension: ↑bleeding risks
	Thienopyridines	• GI bleeding, bruising, rash	• Warfarin and ASA: ↑bleeding.	• GI bleeding history, anticipated surgery: ↑bleeding risks
Cholesterol reduction	Statins	• Myalgias, confusion, renal insufficiency, liver toxicity	• Meds metabolized by the cytochrome P450 system (fibrates, amiodarone, erythromycin, diltiazem, azole antifungals): ↑statin levels and ↑levels of the other meds • Grapefruit juice: ↑statin levels (via cytochrome P450 mechanism) • Fibric acids: myopathy (gemfibrazole>fenofibrate)	• Hypothyroidism, CKD, diabetes mellitus: ↑susceptibility to statin-induced myopathy
	Fibric acids	• Nausea, liver toxicity, gallstones	• Statins: myopathy • Warfarin: ↑warfarin levels	• CKD: ↑renal failure

Two of the Pathways Leading Toward the Phenotype of Frailty



Pasos para asegurar una prescripción cuidadosa

- Historia completa de hábitos y medicación del paciente.
- Considerar alternativas no farmacológicas.
- Comenzar con dosis baja y titular el fármaco lentamente.
- Titulación del fármaco adaptada a la respuesta del paciente.
- Minimizar el número de medicamentos a prescribir.
- Educar al paciente o cuidador sobre el uso apropiado de los fárm.
- Valorar coste: impacto sobre el cumplimiento.
- Insistir en listado de fármacos siempre con el paciente.
- Revisar tratamiento regularmente y retirar fármacos no precisos.

Fármacos para Prevención Secundaria de ECVAS en edad avanzada

Recom. de la AHA. Fleg JL y cols. Circulation 2013;128:2422-2446

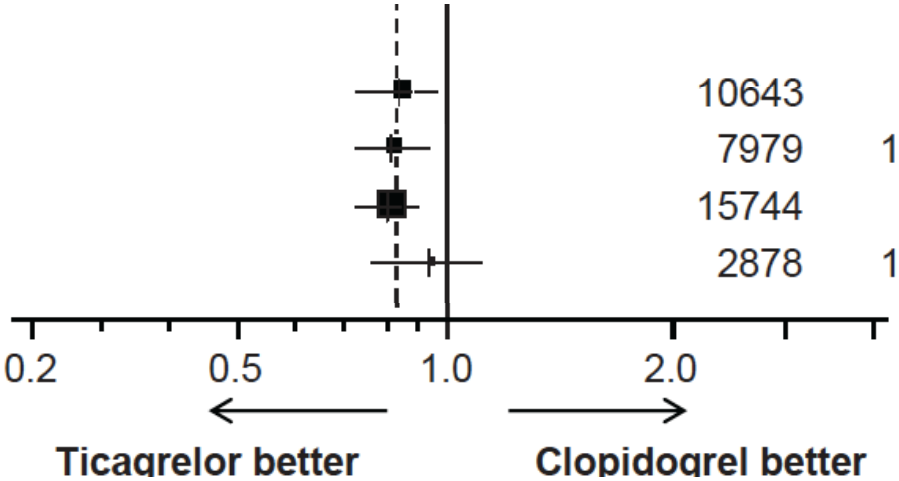
Table 2. Statin Trials for Secondary Prevention in Older Adults

Trial (ref)	Intervention	Age Subgroup (n)	All-Cause Death RRR%/ARR%	CHD Death RRR%/ARR%	CHD Events RRR%/ARR%	Stroke RRR%/ARR%	Comment
4S[53]	S20-40 vs PL	65–70 (1021)	34/6.2*	43/6.0	34/13.3 33/7.1†	NR	↓CV admissions by 21%
LIPID[54]	P40 vs PL	65–75 (3514)	21/4.5	24/2.9*	26/3.3	12/1.3	
CARE[55]	P40 vs PL	65–75 (1283)	NR	45/4.5	32/9* 39/6.7‡	40/2.9	32% RRR/5.2% ARR for PCI/CABG
HPS[56]	S40 vs PL	70–80 (5806)	NR	NR	18/5.1‡	NR	9.2% ARR in primary end point in patients 75–80 y (n=1263)
PROSPER[57]	P40 vs PL	70–82 (5804)	NS	24/0.9	19/2.1‡	NS	25% ↑ cancer risk with P40
PROVE-IT TIMI 22[58]	A80 vs P40	≥70 (634)	NR	NR	40/8 LDL-C < 70 vs LDL-C ≥70 mg/dL (in death/MI/UAP*)	NR	AE rate similar to young
TNT[59]	A80 vs A10	65–75 (3809)	NS	NS	19/2.3* (A80 vs A10)	21/0.9-NS	↑LFTs w A80 vs A10
SAGE[60]	A80 vs P40	65–85 (893)	67/2.7	67/0.9 based on 8 deaths	29/3.1‡ (*P*=0.11)	Too few to compare	↑LFTs w A80 vs P40
Meta-analysis[61]		65–82 (19 569)	22/3.1*	30/2.6	17/2.1‡ 26/2.3 NFMI	25/1.7	30%↓PCI/CABG

Estudio PLATO: Eficacia y seguridad en grupos preespecificados de edad

Wallentin L y cols. N Engl J Med 2009;361:1045-57 (append)

Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 Cl.	HR (95% CI)
Age Group					
<65 Years		10643	7.2	8.5	0.85 (0.74, 0.97)
≥65 Years		7979	13.2	16.0	0.83 (0.74, 0.94)
<75 Years		15744	8.6	10.4	0.82 (0.74, 0.91)
≥75 Years		2878	16.8	18.3	0.94 (0.78, 1.12)



Age Group				
<65 Years	10528	9.5	9.5	1.00 (0.87, 1.13)
≥65 Years	7892	14.4	13.6	1.07 (0.95, 1.22)
<75 Years	15574	11.1	10.8	1.04 (0.94, 1.15)
≥75 Years	2846	14.2	13.3	1.04 (0.84, 1.29)