Tratamiento de la enfermedad arterial periférica sintomática

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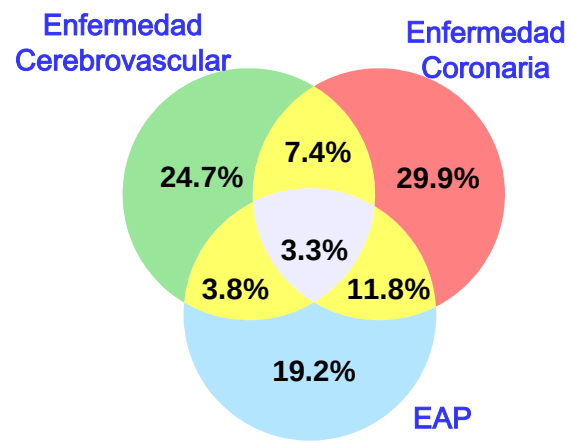
Enfermedad arterial periférica



1. La EVP es una enfermedad muy prevalente
   - Aumenta con la edad – ~20% en > 70 años[1]
   - 8 millones de pacientes en EEUU[1]
   - 2010 - ~650.000 personas padecen CI en España (30% >70 años)[2]

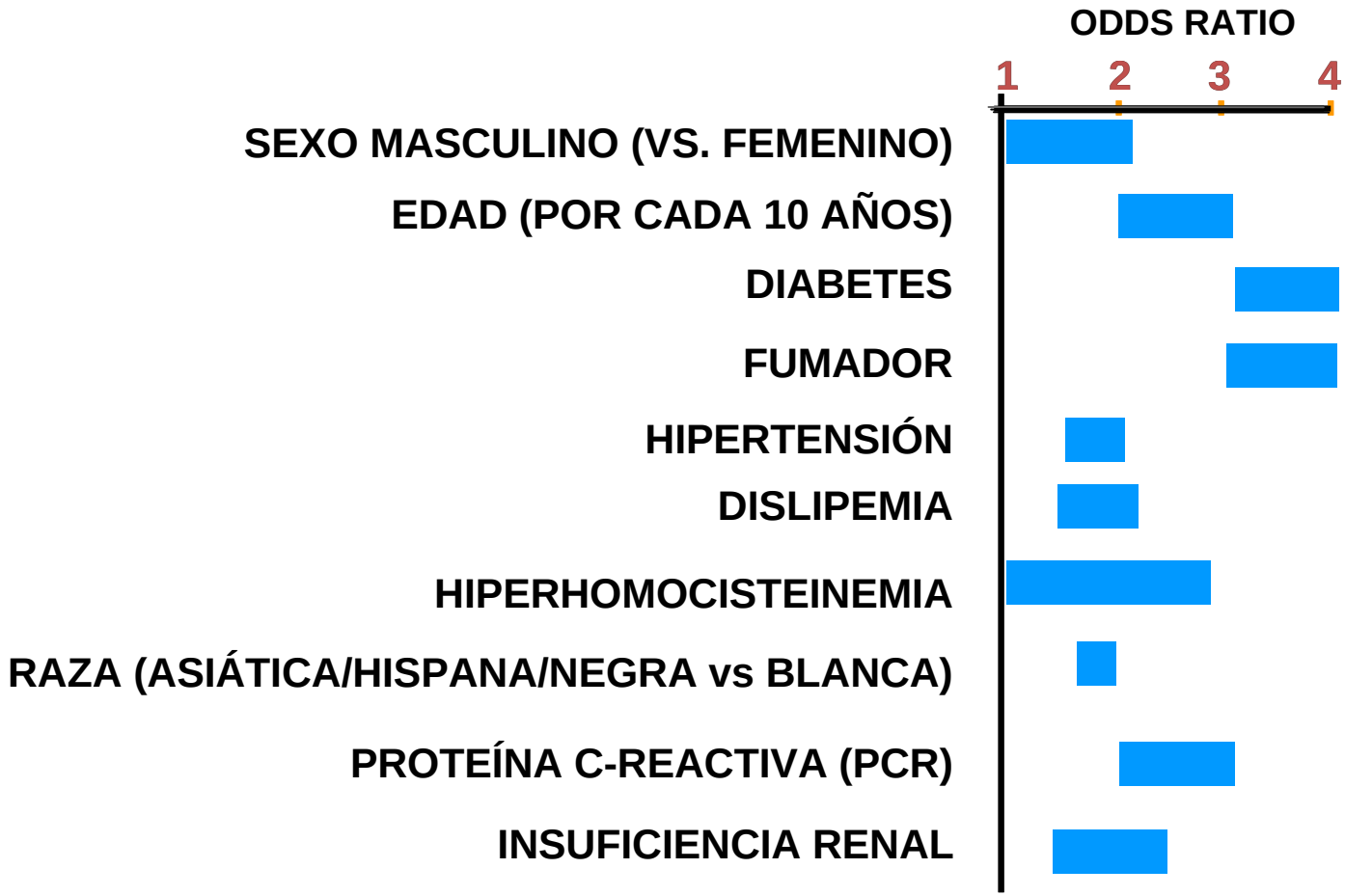
2. Placas de ateroma que ocluyen la luz vascular → isquemia M Esq
   - 25-68% de los pacientes presenta CAD y el 35-50% ECV
   - Es un buen indicador de aterosclerosis generalizada

3. Disminuye la QoL y conlleva una importante morbimortalidad
   - Aumenta 3-6 x la mortalidad CV a 10 años
   - 20-30% desarrollan IM no fatal, ictus o muerte vascular en 5 años

4. Poco diagnosticada y "maltratada"

(1) Olin et al. ACCF/AHA/ACR/SCAI/SIR/SVM/SVN/SVS 2010
(2) http://www.ine.es/jaxi/tabla.do?path=/t20/p251/proy_2001/l0/&file=01002.px&type=pcaxis

FACTORES RIESGO EAP



TASC II. Eur J Vasc Endovasc Surg Vol 33, Suplemento 1, 2007.

Objetivos del tratamiento

1. Reducir el riesgo de eventos cardiovasculares y mortalidad asociada
2. Reducir los síntomas, mejorar la capacidad funcional (aumentar la distancia que pueden caminar sin dolor) y la QoL del paciente con CI.

- Disponemos de tres alternativas terapéuticas:
- Programas de ejercicio físico para incrementar la DM caminada (IA)
  - Mejora función endotelial, metabolismo del MEq y función mitocondrial y disminuye la inflamación
- Modificar los factores de riesgo para evitar la progresión de la enfermedad isquémica y reducir el riesgo cardiovascular
  - Tabaco, diabetes, hiperlipidemias, hipertensión arterial, obesidad, hiperhomocisteinemia
  - No produce una mejoría importante en la sintomatología
- Fármacos que alivian los síntomas y mejoran la distancia que el paciente puede caminar sin dolor y la distancia total caminada

Modificar los factores de riesgo

1. Abandono del hábito tabáquico (IA)

- Tratamiento (Bupropion, Varenicline) si fuera necesario (IB)

2. Control lipídico

- Reducir LDL-C < 100 mg/dL (<2.59 mmol/L) (IA)
- EAP + otra ECV: LDL-C < 70 mg /dL (IIa,A)
- Estatinas para reducir los niveles de LDL-C (30-50%) y el riesgo de eventos CVs (IA)
- Fibratos y/o ácido nicotínico para elevar los niveles de HDL-C y disminuir los de triglicéridos (IIa,B)

3. Hipertensión arterial:

- < 140/90 mmHg (< 130/80 mmHg si tienen DM o insuficiencia renal) (IA)
- Primera elección un IECA
- Los β-bloqueantes no están contraindicados (CAD, HF, arritmias)

4. Diabetes mellitus:

- Niveles de Hb1AC < 7% (IIa, B)

Lipid-lowering for peripheral arterial disease of the lower limb

Aung et al. *Cochrane Database Syst Rev* 2007;(4):CD000123

Main results

- 18 RCTs involving a total of 10,049 participants
  - Different inclusion criteria, outcomes and lipid-lowering drugs
- Improved total walking distance (152 m; 95% CI 32.1-271.8) and pain-free walking distance (89.76 m; 95% CI 30.0-149.7)
- Significantly reduced the risk of total CV events due to a positive effect on total coronary events (OR 0.76; 95% CI 0.67 to 0.87)
- No effect on overall mortality (OR 0.86; 95% CI 0.49 to 1.50)
- No prospective, randomized trial of LDL reduction in patients with PAD has been performed (Weinberg. Nature Rev Cardiol 2010)

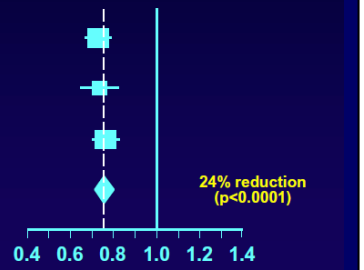
Conclusions

- Statins are effective in reducing CV events
- They may also improve local symptoms and QoL
- Statins are not prescribed with the same frequency as CAD patients

HPS - Effects on vascular events

SIMVASTATIN: MAJOR VASCULAR EVENTS

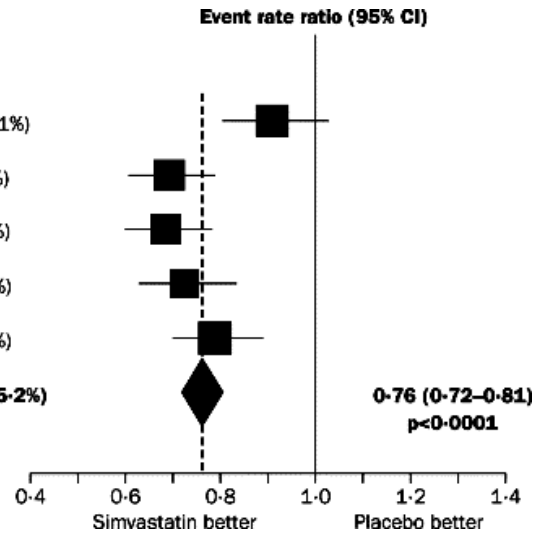
Vascular event	Simvastatin (10269)	Placebo (10267)
Major coronary event	898	1212
Any stroke	444	585
Any revascularisation	939	1205
MAJOR VASCULAR EVENT	2033 (19.8%)	2585 (25.2%)



Source: Heart Protection Study Collaborative Group, Lancet 2002;360:7-22

- Patients with CAD, cerebrovascular disease or PAD, and high-risk individuals, with diabetes or multiple risk factors
- 40 mg of simvastatin or placebo
- A subgroup analysis of 6,748 patients with PAD alone revealed a 22% reduction in the rate of first major vascular event

Year of follow-up	Simvastatin-allocated	Placebo-allocated
1	481/10 269 (4·7%)	527/10 267 (5·1%)
2	377/9745 (3·9%)	538/9683 (5·6%)
3	359/9288 (3·9%)	509/9055 (5·6%)
4	331/8818 (3·8%)	436/8463 (5·2%)
5+	485/8358 (5·8%)	575/7897 (7·3%)
ALL FOLLOW-UP	**2033/10 269 (19·8%)**	**2585/10 267 (25·2%)**



Treatment of low extremity PAD with statins

Study type	No. of participants	Statin used	Follow-up time	End-points	Results
Observational, longitudinal	544	Any statin, any dose	3 years	Walking distance, walking velocity, summary performance score	Slower functional decline in statin treated PAD patients
Cross-sectional	641	Any statin, any dose	N/A	Walking distance, walking velocity, summary performance score	Better scores in statin treated patients; benefit attenuated after adjustment for CRP levels
Randomized, double-blind, placebo-controlled trial	LE-PAD at baseline: 123/2223 placebo, 130/2221 simvastatin	Simvastatin	Median, 5.4 years	2′: new or worsening intermittent claudication (per Hx)	For simvastatin users, RR = 0.62 ($p = 0.008$)
Randomized, placebo-controlled	69	Simvastatin 40 mg	12 months	Pain free treadmill exercise time	Improvement in statin treated group
Randomized, double-blind, placebo-controlled	86	Simvastatin 40 mg	6 months	Pain free walking distance, total walking distance, ABI, claudication self-assessment	Improvement in all of the above measures in the statin treated group
Randomized, double-blind, placebo-controlled, parallel group	354	Atorvastatin 10 or 80 mg	12 months	1st: maximal walking time (MWT)2nd: pain-free walking time (PFWT), quality of life	PFWT but not MWT improved by statin treatment; on measure of quality of life also improved

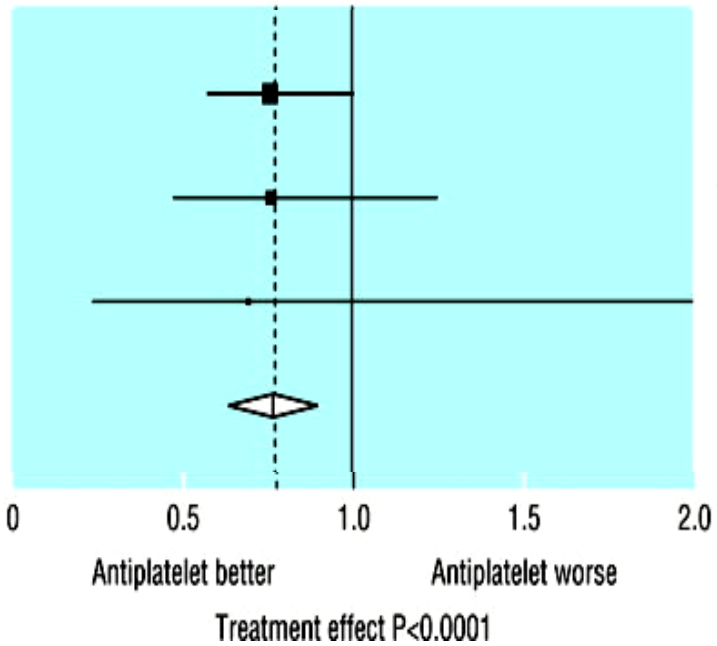
Abbreviations: ABI = ankle-brachial index.

(1) Griri et al. JACC 2006. (2) McDermott et al. Circulation 2003. (3) Pedersen et al. Am J Cardiol 1998. (4) Aronow et al. Am J Cardiol 2003. (5) Mondillo et al. Am J Med 2003. (6) Mohler et al. Circulation 2003

Effects of antiplatelet therapy on vascular events in 195 trials in high risk patients

Category of trial	No of trials with data	No (%) of vascular events: Allocated antiplatelet	No (%) of vascular events: Adjusted control	Observed-expected	Variance	% Odds reduction (SE)
Peripheral arterial disease:						
Intermittent claudication	26	201/3123 (6.4)	249/3140 (7.9)	-22.3	86.6	23 (9)
Peripheral grafting	12	67/1249 (5.4)	81/1248 (6.5)	-7.3	29.1	22 (16)
Peripheral angioplasty	4	12/472 (2.5)	17/474 (3.6)	-2.0	5.8	29 (35)
Subtotal	42	280/4844 (5.8)	347/4862 (7.1)	-31.6	121.5	23 (8)

Heterogeneity between 7 subtotals other than acute stroke: χ^2=15.4, df=6; P=0.02

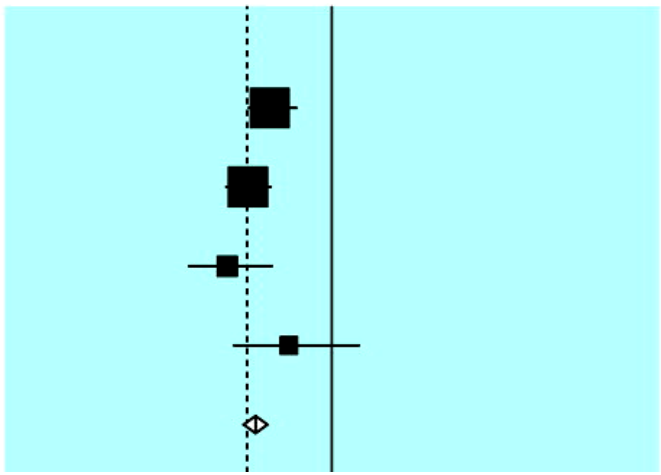


Antithrombotic Trialist´s Collaboration, A. T. BMJ 2002;324:71-86

BMJ

Effects of different doses of aspirin on vascular events in high risk patients (excluding those with acute stroke).

Category of trial	No of trials with data	No (%) of vascular events: Allocated antiplatelet	No (%) of vascular events: Adjusted control	Observed-expected	Variance	% Odds reduction (SE)
Aspirin alone (mg daily):						
500-1500	34	1621/11 215 (14.5)	1930/11 236 (17.2)	-147.1	707.8	19 (3)
160-325	19	1526/13 240 (11.5)	1963/13 273 (14.8)	-219.9	742.6	26 (3)
75-150	12	366/3370 (10.9)	517/3406 (15.2)	-72.0	183.8	32 (6)
<75	3	316/1827 (17.3)	354/1828 (19.4)	-18.9	136.5	13 (8)
Any aspirin*	65	3829/29 652 (12.9)	4764/29 743 (16.0)	-452.3	1717.0	23 (2)



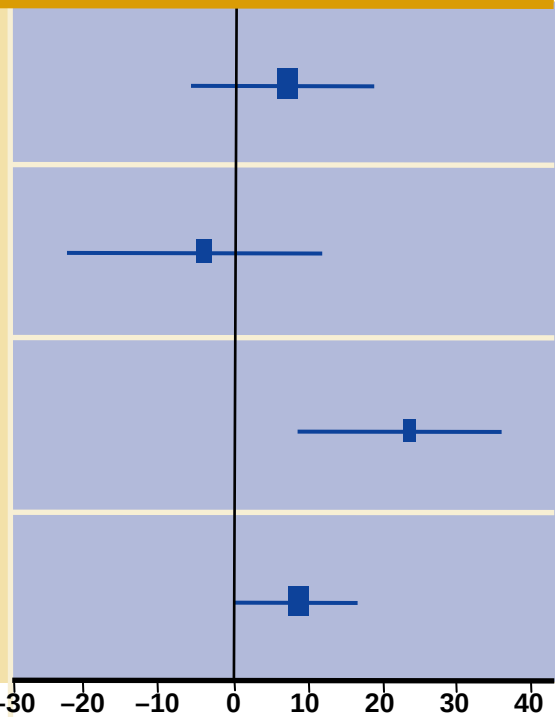
Aspirin 75 to 300 mg started prior to femoropopliteal endovascular treatment can cause a 66% reduction of recurrents obstruction at 12 months[2]

(1) Antithrombotic Trialist´s Collaboration, A. T. BMJ 2002;324:71-86
(2) Dorffler-Melly et al. Cochrane Database Syst 2005:CD002071

BMJ

CAPRIE: Clopidogrel versus Aspirin in Patients at risk of Ischemic Events

Subgroup	Treatment group (patient years at risk)	Events per year (%)	Relative risk reduction (95% CI)	p
Stroke	Clopidogrel (6054) Aspirin (5979)	7.15 7.71	7.3% (–5.7 to 18.7)	0.26
MI	Clopidogrel (5787) Aspirin (5843)	5.03 4.84	–3.7% (–22.1 to 12.0)	0.66
Peripheral arterial disease	Clopidogrel (5795) Aspirin (5797)	3.71 4.86	23.8% (8.9 to 36.2)	0.0028
All patients	Clopidogrel (17,636) Aspirin (17,519)	5.32 5.83	8.7% (0.3 to 16.5)	0.043



CAPRIE Steering Committee. Lancet 1996;348:1329-1339

Antiagregantes plaquetarios (ACC/AHA 2006)

Class I

- Antiplatelet therapy is indicated to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD *(A)*
- Aspirin (75 to 325 mg), is recommended *(A)*
- Clopidogrel (75 mg/d) is recommended *(B)*
- There is no evidence to support the combination of AAS and clopidogrel (CHARISMA trial. Bhatt et al. N Engl J Med 2006).
- These patients did not receive antiplatelet therapy with the same frequency as patients with CAD

Class III

- No benefit of heparin, LMWHs or oral anticoagulants (Anand et al. N Engl J Med 2007) has been established for IC *(C)*

Antihypertensive drugs

Lane and Lip. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD003075

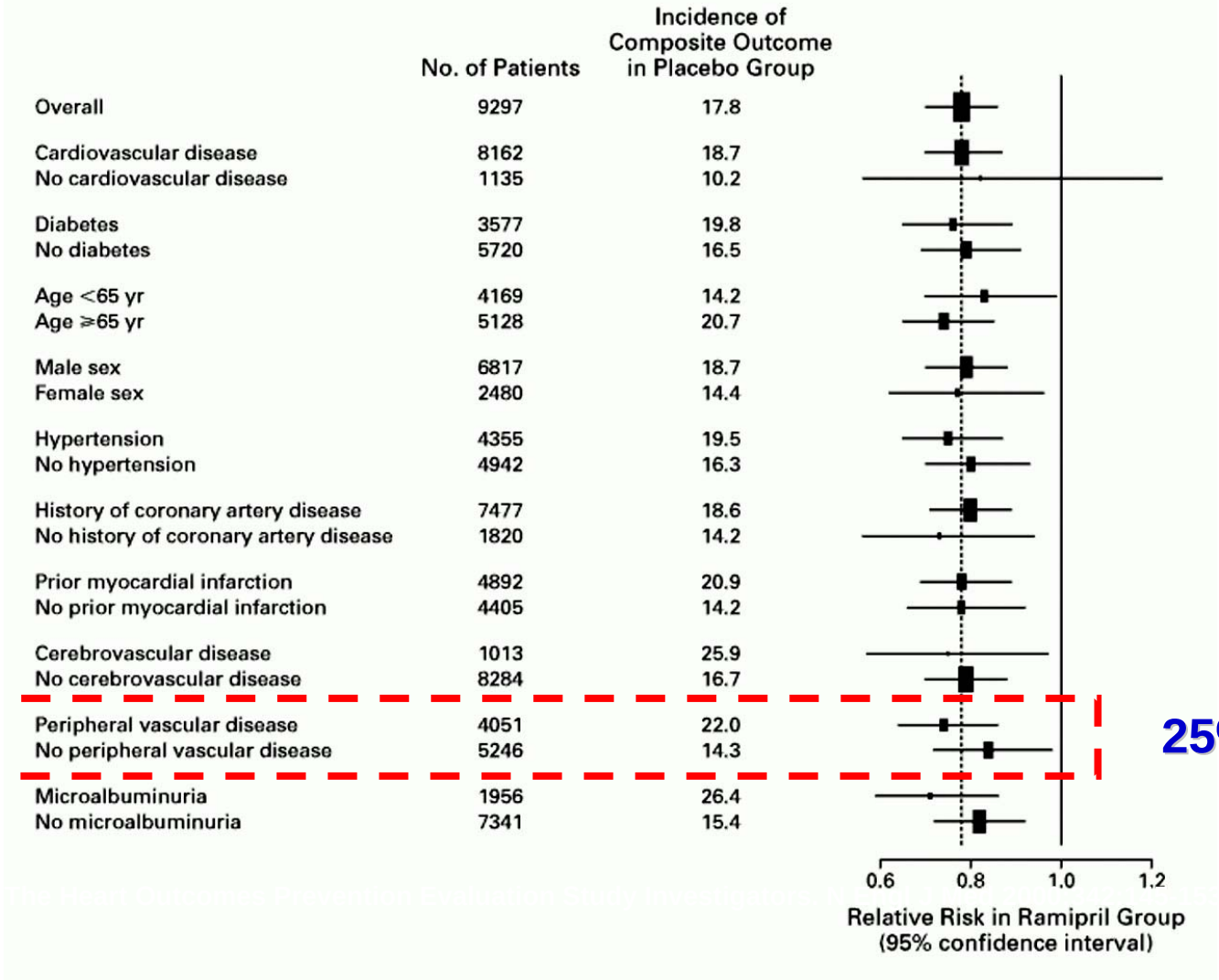
1. **4 studies were included**

- **2 trials compared ACEIs vs placebo (HOPE and EUROPA)**
- **Patients undergoing angioplasty - verapamil reduced restenosis, although this was not reflected in the maintenance of a high ABPI**
- **A small study - no differences in arterial intima-media thickness in men receiving hydrochlorathiazide or doxazosin**

CONCLUSIONS:

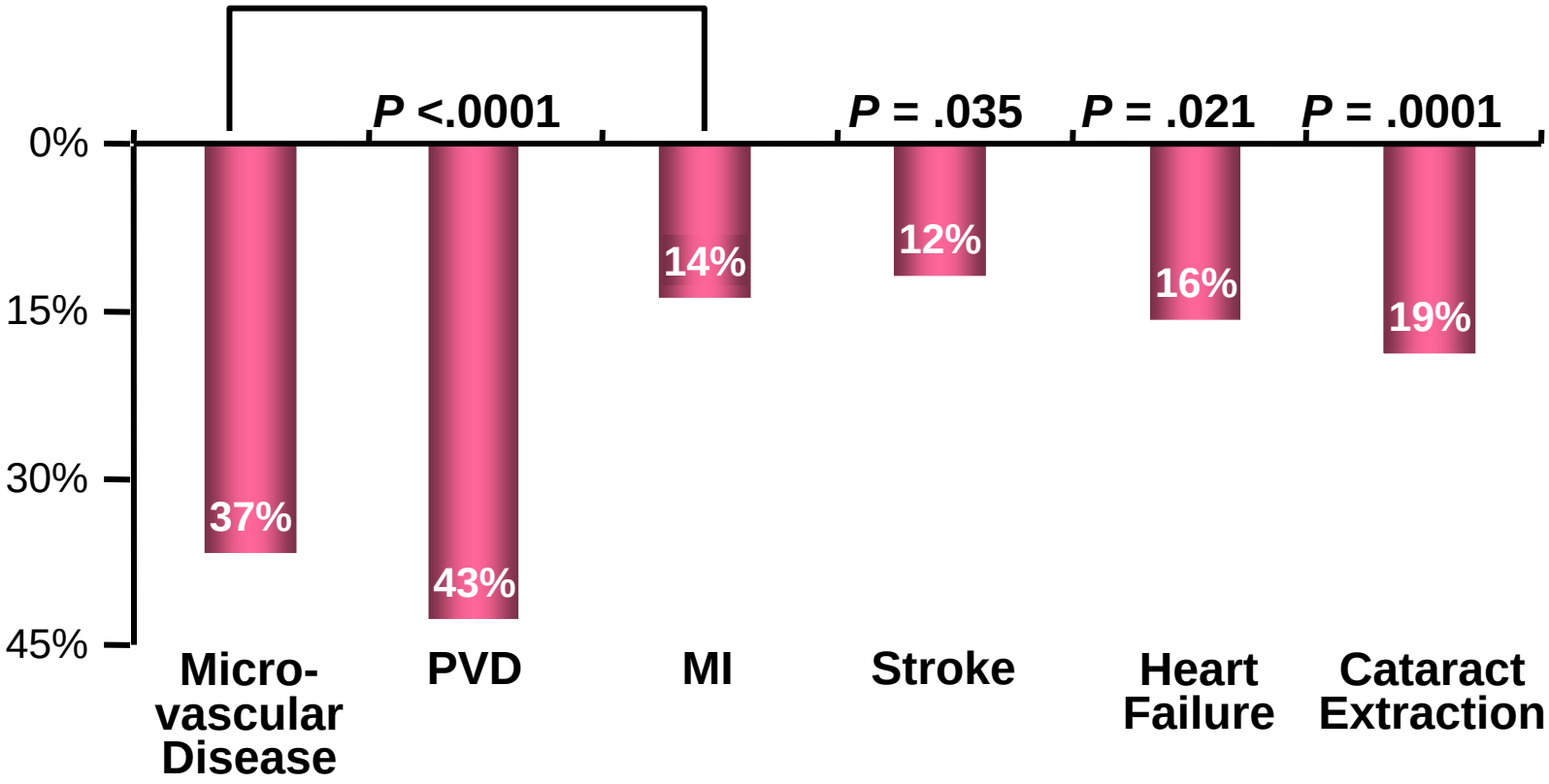
- **Evidence of anti-hypertensive drugs in PAD is poor**
- **Uncertain benefits or risks accrue from their use**
- **The lack of data should not detract from the compelling evidence of the benefit of lowering blood pressure.**

The Beneficial Effect of Treatment with Ramipril on the Composite Outcome of MI, Stroke, or Death from Cardiovascular Causes Overall and in Various Predefined Subgroups (HOPE Trial. Yusuf et al. NEJM 2000)



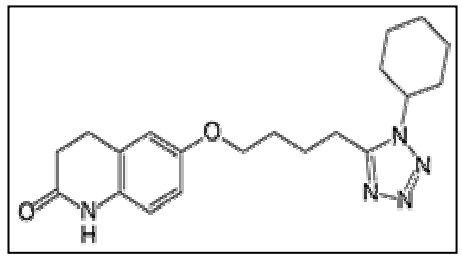
UKPDS 35: prospective observational study

RR with 1% decline in annual mean HbA1c is associated



Stratton IM, et al. *BMJ*. 2000;321:405-412.

Mecanismo de acción del cilostazol



↑ adenosine levels

↓ adenosine uptake

Cilostazol

FDE3

Adenilil ciclasa → AMPc → 5´-AMPc

PKA

↑ Contractilidad y frecuencia cardiacas

A1R

↓ Lípidos plasmáticos

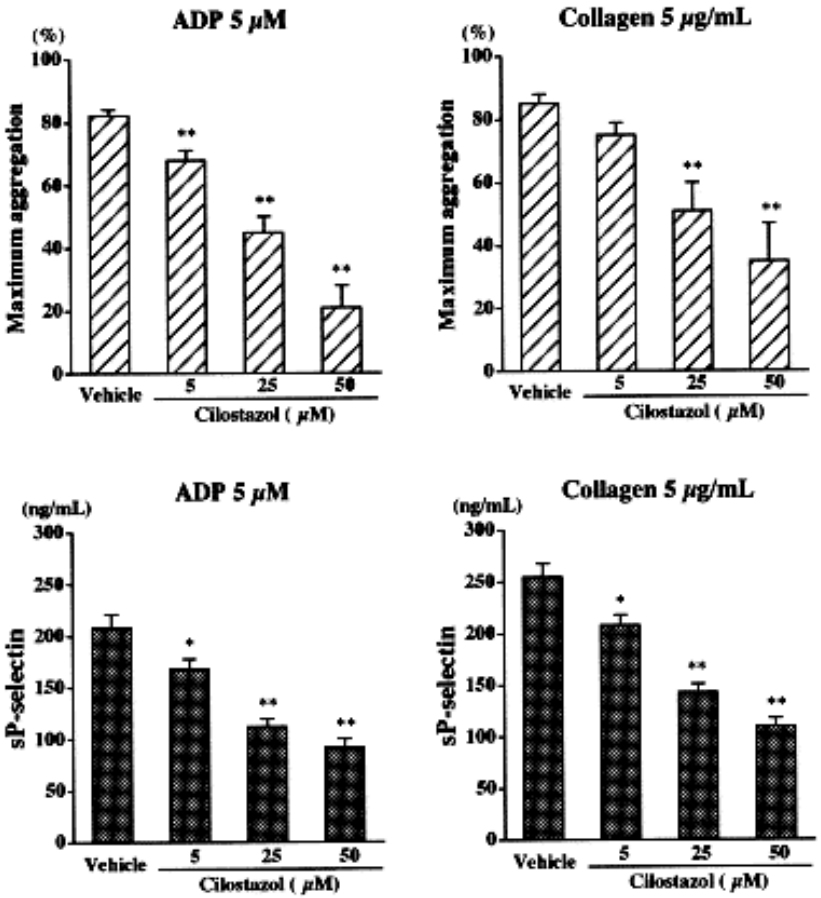
A2AR

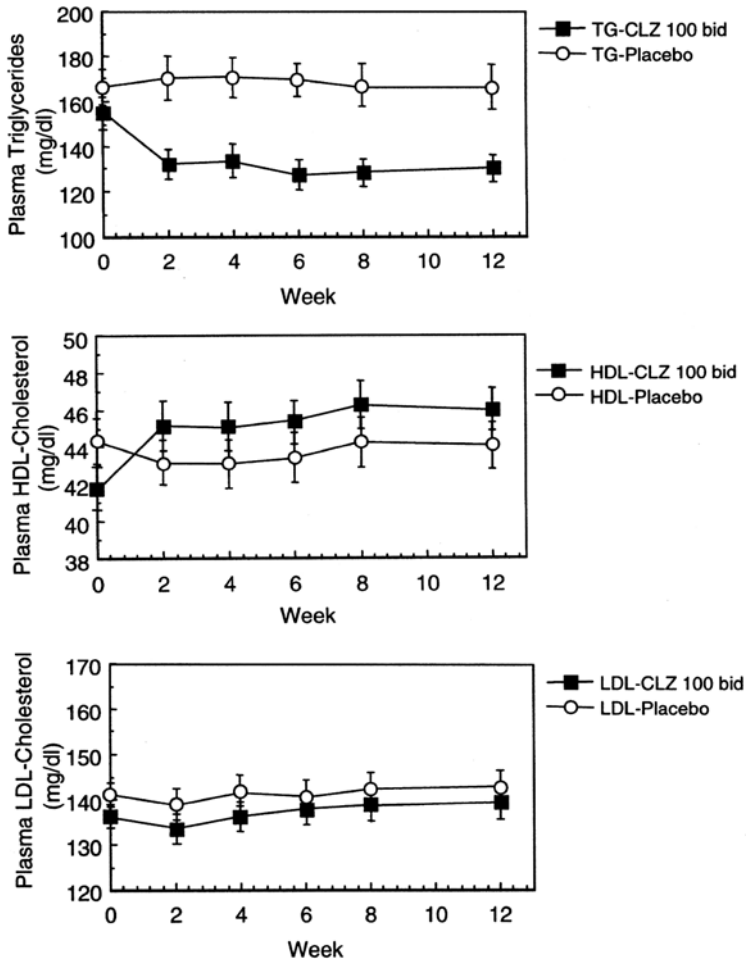
↓ Proliferación de las CMLV

Vasodilatación

↓ Agregación plaquetaria

Cilostazol inhibited platelet aggregation[1,2] and improved lipid profile[3]

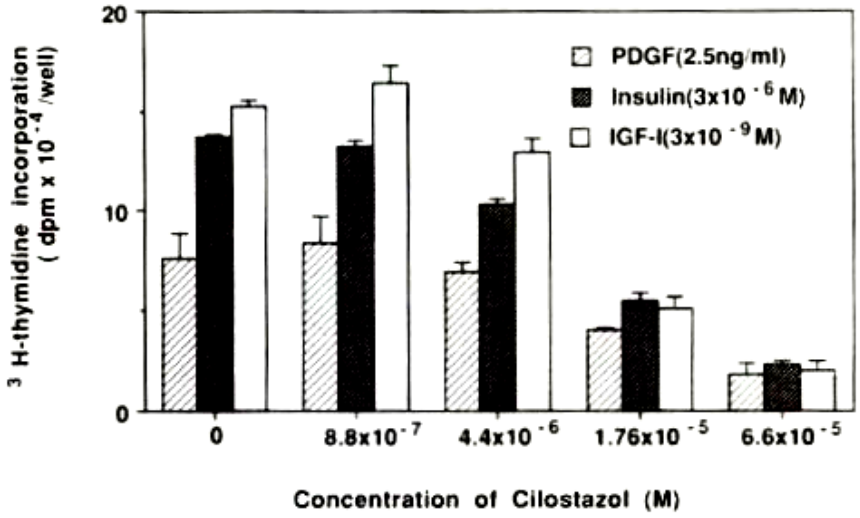


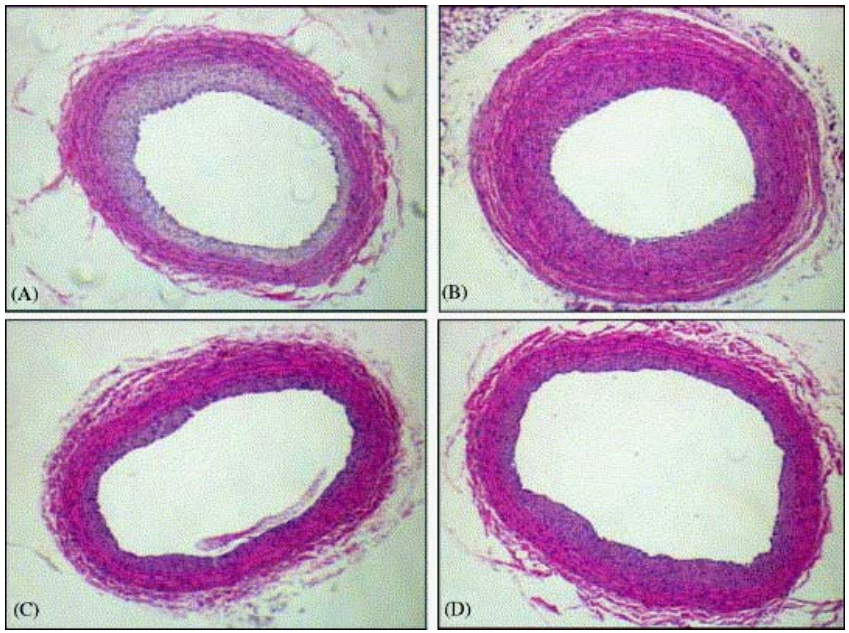


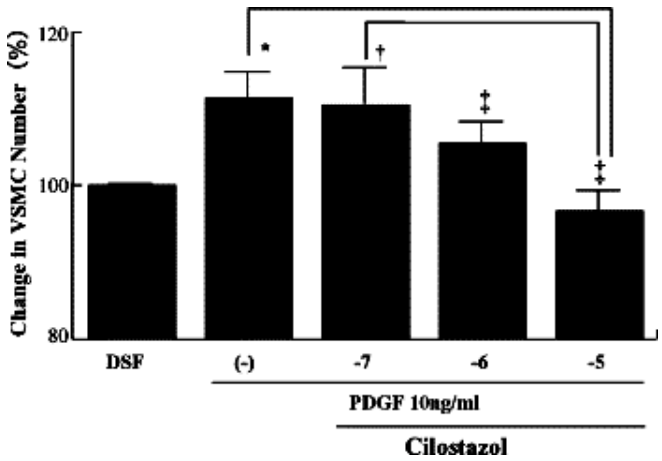
1. Suppress VLDL synthesis, increase LPL activity
2. Inhibition of cholesteryl ester transfer protein (CETP)

(1) Matsumoto et al. Thromb Res 1999. (2) Kariyazono et al. Thromb Res 2001. (3) Elam et al. Arteriosclerosis Thromb Vasc Biol 1998

Cilostazol inhibe la síntesis de ADN inducida por PDGF, insulina o IGF y la proliferación neointimal







A. STZ –
B. B) STZ +
C. Cilostazol STZ –
D. Cilostazol STZ +

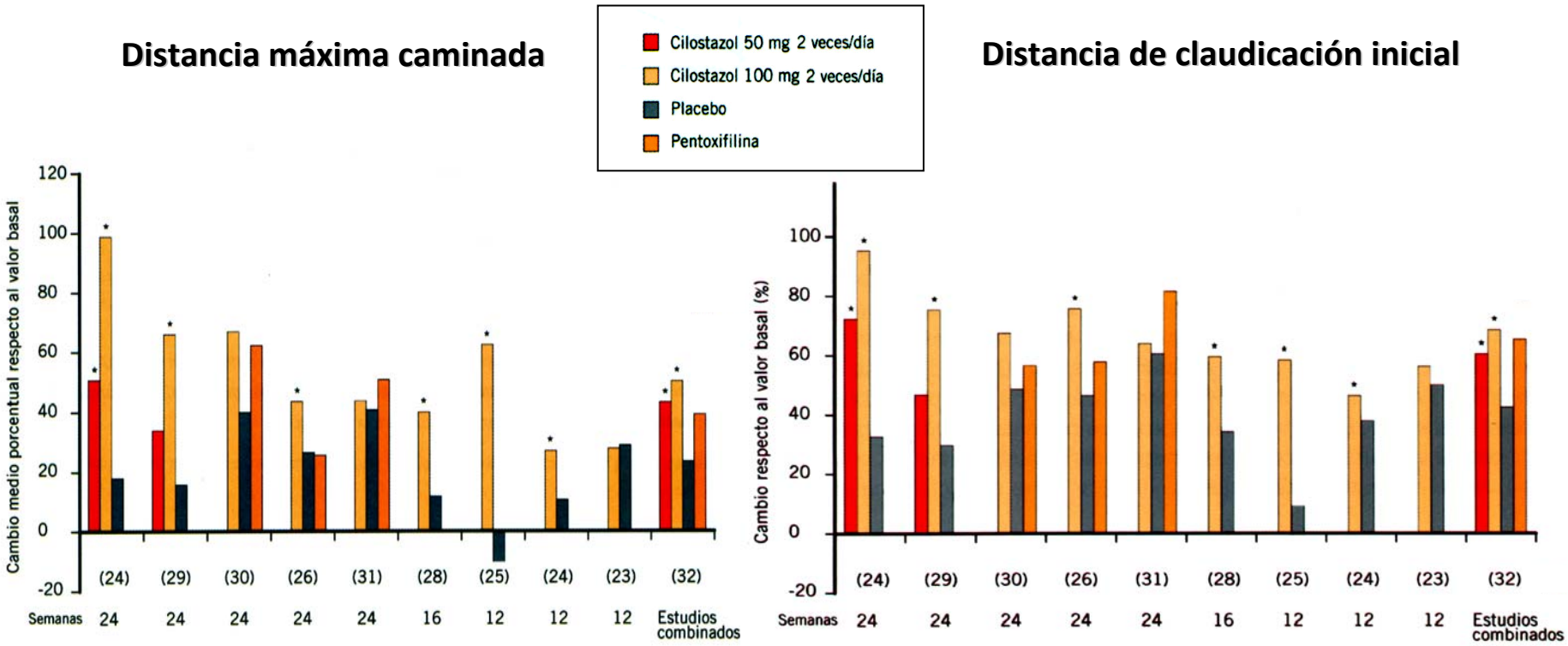
- Takahashi S et al. J Cardiovasc Pharmacol 1992;20:900-906.
- Morishita. Atheroscleoris 2006
- Hayashi, S.-i. et al. Hypertension 2000;35:237-243

Cilostazol – Resultados

(Revisión Cochrane, Robless et al 2009)

- 7 ECRs y 2.702 pacientes con claudicación intermitente moderada o severa de más de 5 años de existencia
- 65 años, 75% varones, 25% diabéticos e ITB <0.9
- Dosis - 100 mg dos veces al día, durante **12-24 semanas**
- OP: distancia de claudicación absoluta (DCA):
  - Cilostazol la aumenta un **62%** vs placebo (10-28%, P < 0.05)
- OS: distancia de claudicación inicial (hasta la aparición del dolor) y cambios en QoL y estado funcional (WIQ, *COM,* SF-36)
  - Aumenta un **86%** (58-96% vs 8-48% en el grupo placebo, P < 0.05)
- No se produjo ningún aumento de los RAMs graves (eventos CVs o muerte) en los tratados con cilostazol vs placebo

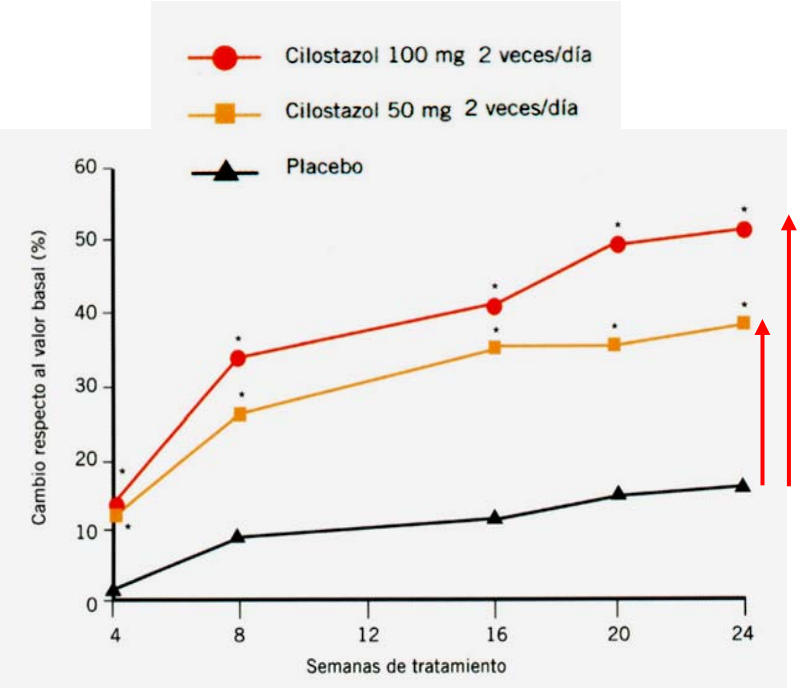
Efectos del cilostazol sobre la distancia máxima caminada y la distancia de claudicación inicial

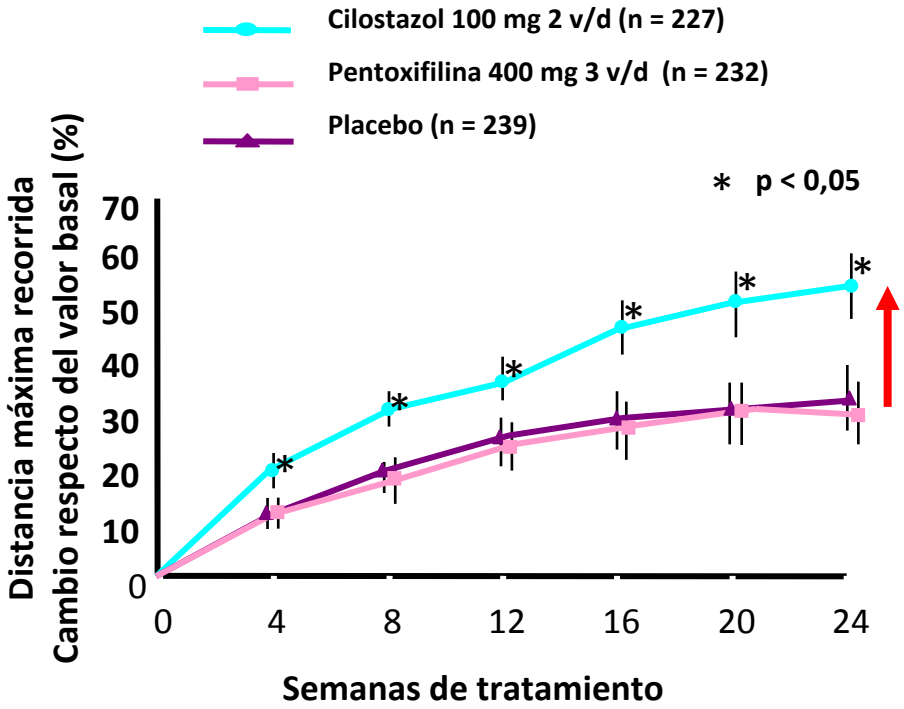


- **Los cambios aparecen a las 4 semanas de trat. Y se mantienen en el tiempo**
- **Beneficio independientemente de edad, sexo, raza, tabaquismo o historia de DM2, así como de la duración de la EAP o del uso concomitante de calcioantagonistas o beta-bloqueantes**

Thompson et al. Am J Cardiol 2002; 90:1314-1319

Comparison of cilostazol (100 mg bid), pentoxifylline (400 mg tid), and placebo on maximal walking distance





- **La supresión del tratamiento con cilostazol producía un empeoramiento en la DCA y DCI que ya era evidente a las 2 semanas**

Beebe et al. Arch Intern Med 1999

Dawson et al. Am J Med. 2000

Mejoría (media e índice de confianza 95%) observada en los valores del cuestionario SF-36 en los pacientes con claudicación intermitente tratados con cilostazol

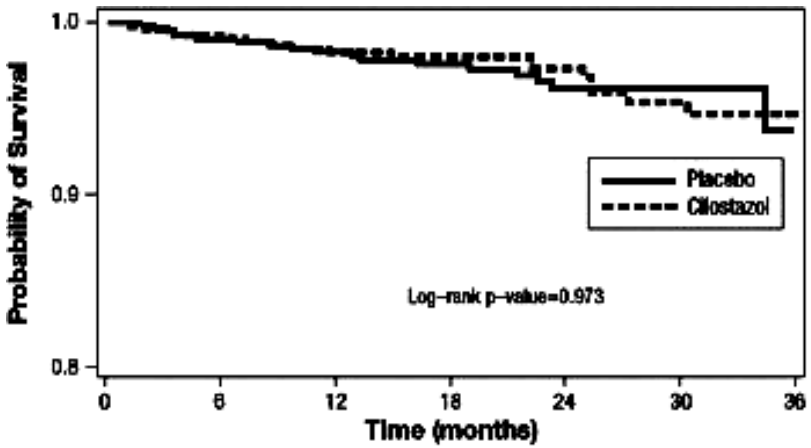
Salud Física/ Componentes	Mejoría neta (CI al 95%)	Salud mental/ componentes	Mejoría neta (IC al 95%)
Función física	+ 4,8 (2,9-6,8)*	Vitalidad	+ 2,3 (0,4-4,2)*
Limitaciones relacionadas con problemas físicos	+ 6,0 (2,2-9,7)*	Función social	+ 1,9 (-0,3-4,1)
Dolor corporal	+ 4,1 (1,9-6,3)*	Limitaciones del rol por problemas emocionales	+ 0,2 (-3-3,1)
Salud general	+ 1,1 (-0,4-2,7)	Salud mental	+ 0,07 (-1-1,6)
Salud física general	+ 2,2 (1,3-3,1)*	Salud mental general	- 0,4 (-1,0-0,5)

*p<0,05. IC= intervalo de confianza.

Resultados del estudio CASTLE

- 1899 pts con EVP y diagnóstico de CI
- Tratamiento durante 36 meses + 1

Parámetro	Placebo	Cilostazol	IC
Muerte	19	18	0.99 (0.52-1.88)
Muerte CV	52	49	0.94 (0.64-1.39
Sangrado	22	18	



Hiatt et al. J Vasc Surg 2008

Drugs for intermittent claudication

Cochrane Database of Systematic Reviews (CCDSR)

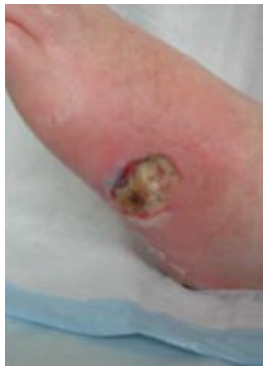
- **Naftidrofuryl (23/04/2008): this $5HT_2$RA has a clinically meaningful effect compared with placebo in improving walking distance**
- **Pentoxifylline (10/5/2011): The clinical effectiveness of pentoxifylline as therapy for claudication is marginal and not well established (IIb,A)**
- **Buflomedil (28/01/2008): benefit of this α-blockers is small in relation to safety issues (narrow therapeutic range)**
- **Prostanoids (20/10/2003): prostacyclin did not increase the walking distances significantly. ARs – 24%**
- **Omega-3 fatty acids (17/10/2007): no evidence of consistent improved clinical outcomes (QoL, PFWD, MWD, ABPI, angiographic findings)**
- **Ginkgo biloba (15/04/2009): No evidence of clinical benefit**
- **Anticoagulants (8/12/2009): No benefit of heparin, LMWHs or oral anticoagulants**

AHA-ACC Guidelines for pharmacological management of claudication

Medication and Class of Evidence	Level of Evidence	Dose	Side Effects
Class I			
Cilostazol	A	100 mg two times/day	Contraindicated in heart failure; headache, diarrhea, palpitations, dizziness
Class IIb			
Pentoxifylline	A	400 mg three times/day	Sore throat, dyspepsia, nausea, diarrhea
Arginine	B	3 g three times/day	Gastrointestinal distress, drop in hematocrit
Propionyl levocarnitine	B	1–2 g two times/ day	None or mild
Ginkgo biloba	B	120–160 mg/day	None or mild
Class III			
Prostaglandins	A	Beraprost: 40 μg three times/day	Headache, flushing gastrointestinal distress
Vitamin E	C	50 mg/day	None or mild
Chelation EDTA	A	1.5–3 g intravenously two times/wk	Hypocalcemia, renal failure, proteinuria, gastrointestinal distress

- Hirsch TA et al. JACC 2006;47:1239-1312
- TASC II. Eur J Vasc Endovasc Surg Vol 33, Suplemento 1, 2007

Recommended management of lower extremity PAD



Patient presentation

- Asymptomatic
- Claudication
- Critical limb ischemia
  - Chronic
  - Acute
- Prior limb arterial revascularization

- Smoking cessation
- Lipid modification (statin ± fibrate); target LDL cholesterol <2.59 mmol/l (<100 mg/dl) or <1.8 mmol/l (<70 mg/dl)[a]
- Treatment of hypertension; target BP <140/90 mmHg or <130/80 mmHg[b]
- Control of hyperglycemia; target HbA_{1c} <7.0%
- Antiplatelet therapy (aspirin [75–325 mg/day] or clopidogrel [75 mg/day])
- ACE inhibition (optional)

Appropriate foot care

Treatment of PAD

- Exercise rehabilitation
- Cilostazol (100 mg bid orally)

As indicated
- Revascularization (endovascular or surgical)

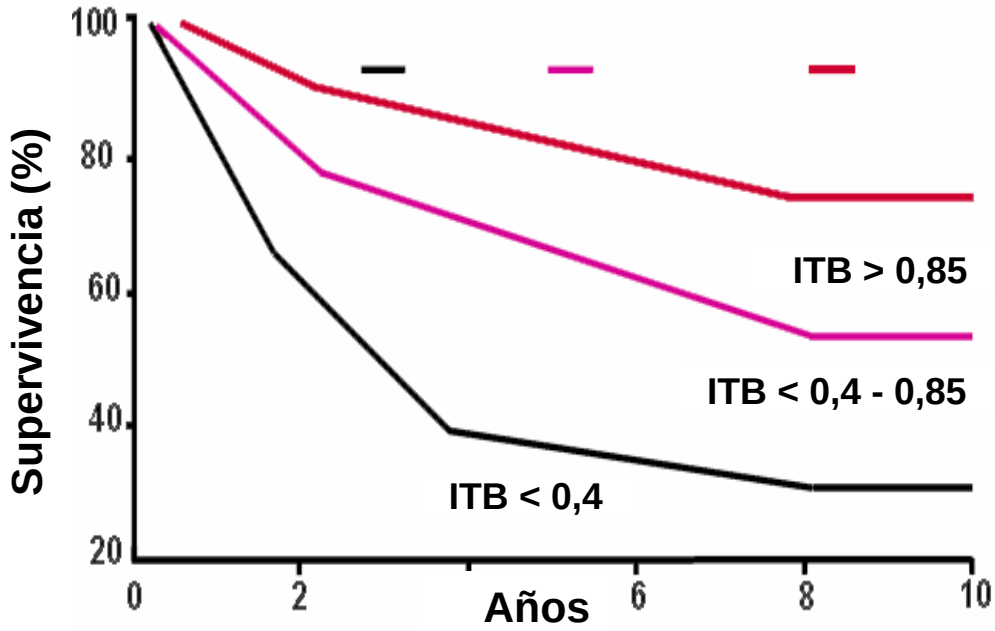
Anticoagulation (UFH or LMWH)

As indicated
- Revascularization (endovascular, thrombolytic or surgical)
- Amputation

Mortalidad total y CV en pacientes con enfermedad arterial periférica

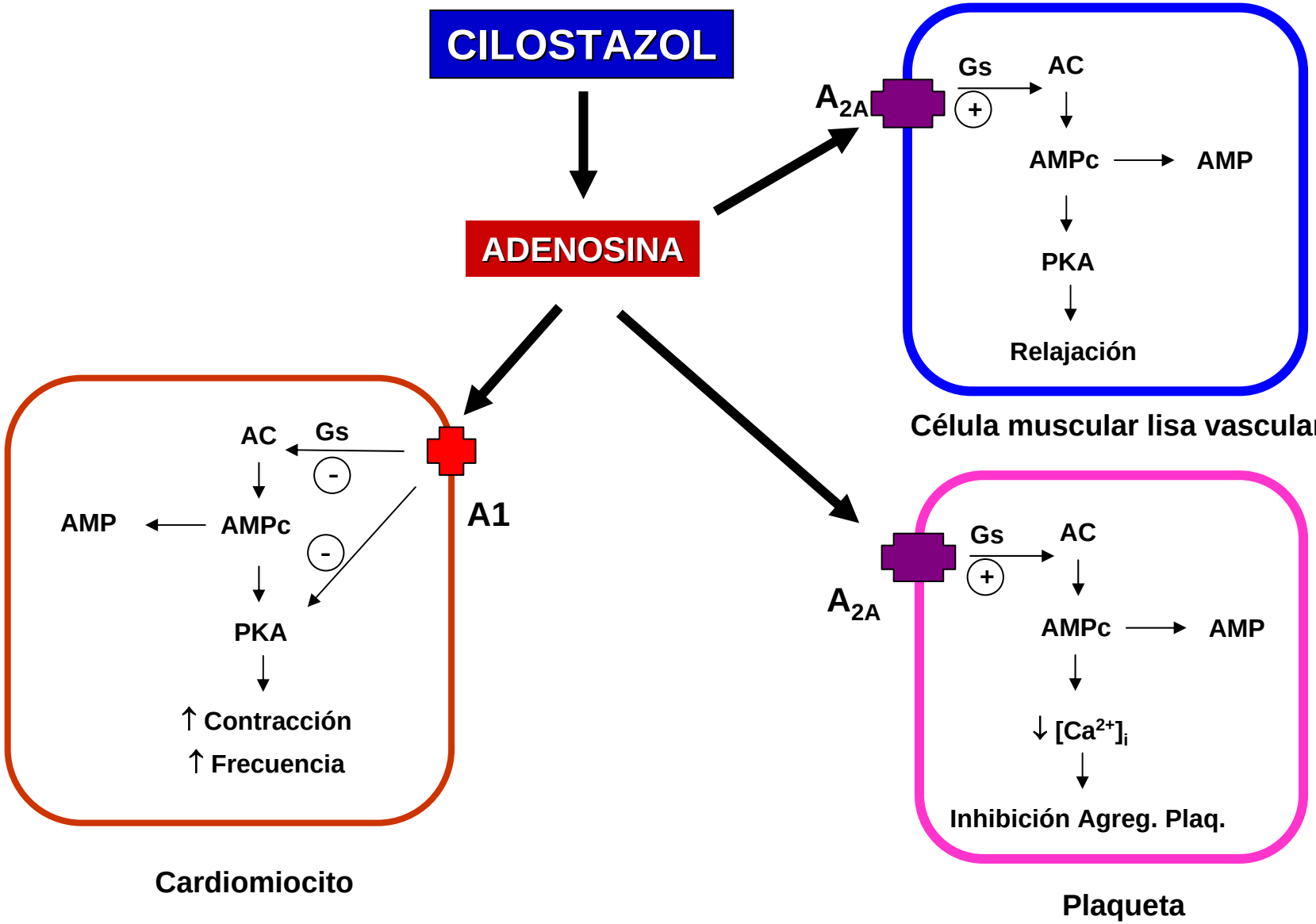
Study	No.	Age, y	Cardiovascular Death, RR (95% CI)
Criqui et al,[23] 1992	256	38-72	5.1 (2.4-10.8)
	309		4.8 (1.6-14.7)
Vogt et al,[24] 1993	1492	>65	4.0 (1.3-8.5)
Kornitzer et al,[25] 1995	2023	40-55	. . .
Leng et al,[18] 1996	1592	55-74	2.7 (1.3-5.3)
			2.1 (1.1-3.8)
Newman et al,[26] 1997	669	≥60	. . .
	868		. . .
Newman et al,[27] 1999	5714	≥65	2.0 (1.1-2.8)
Hooi et al,[28] 2004	3649	40-78	1.6 (1.2-2.1)
			1.6 (1.0-2.5)
			1.5 (1.1-2.2)

Hankey, G. J. et al. JAMA 2006;295:547-553

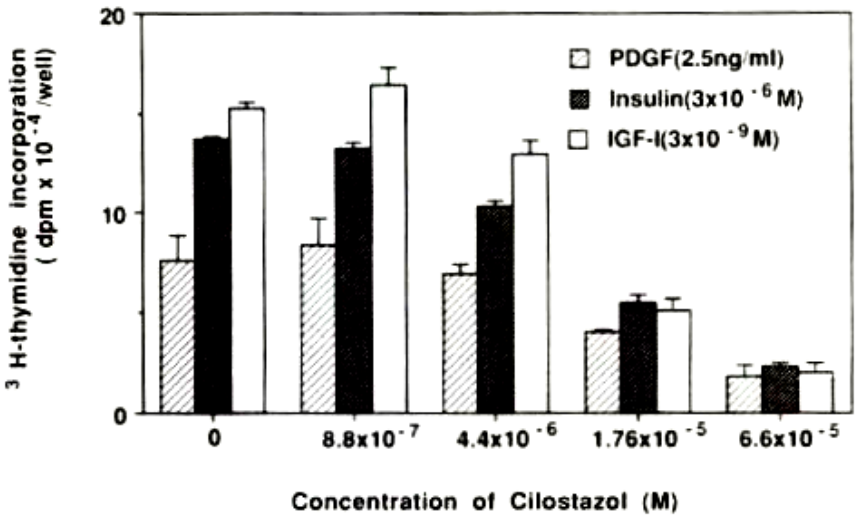


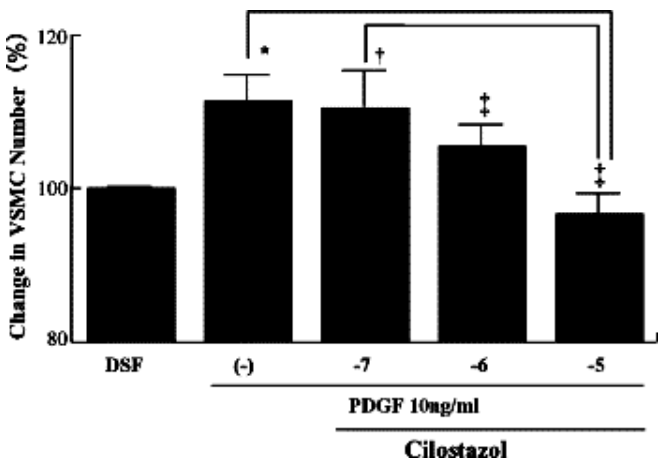
Donelly et al. BMJ 2000;8:259-302

Adenosina modula las acciones del cilostazol

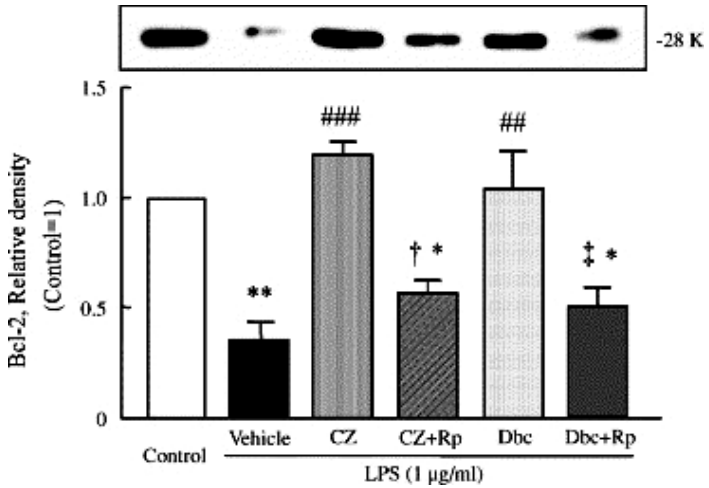


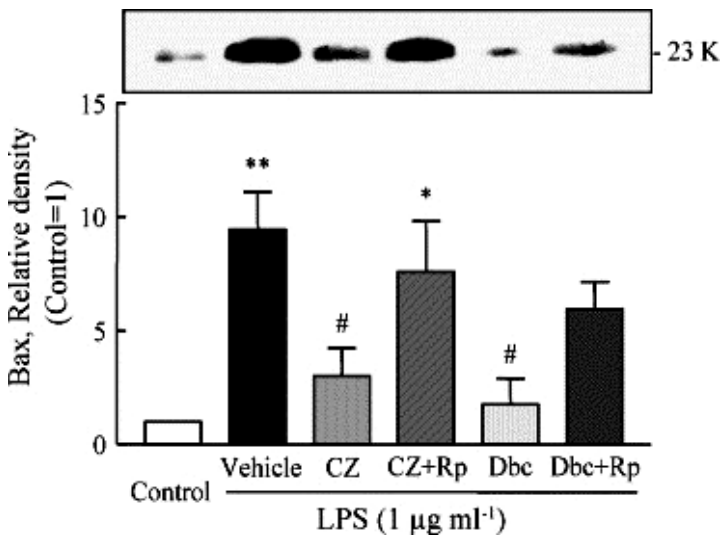
Effect of cilostazol on DNA synthesis in cultured arterial SMCs stimulated with PDGF, insulin or insulin growth factor (IGF)





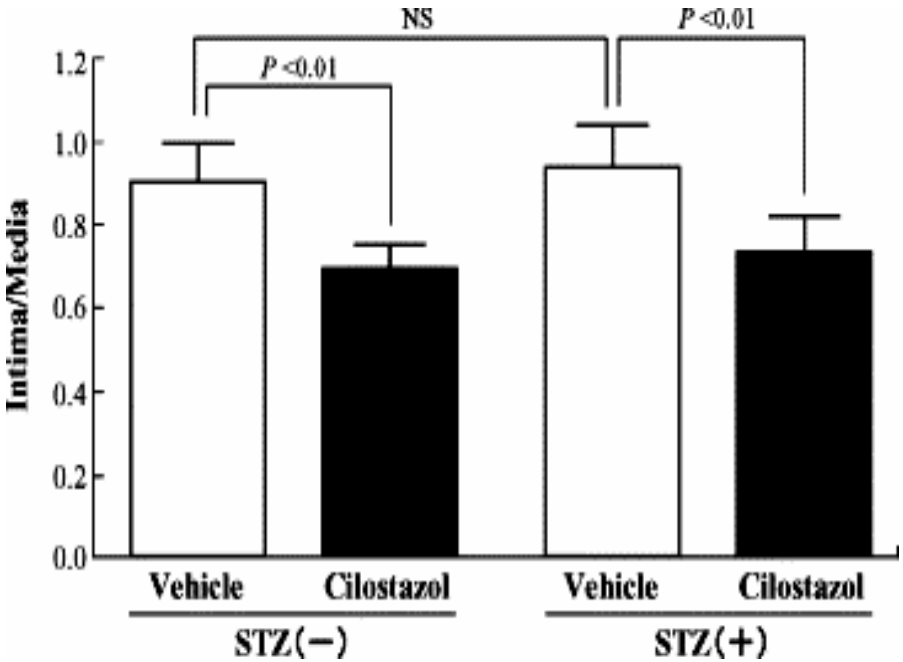
Takahashi S et al. J Cardiovasc Pharmacol 1992;20:900-906.

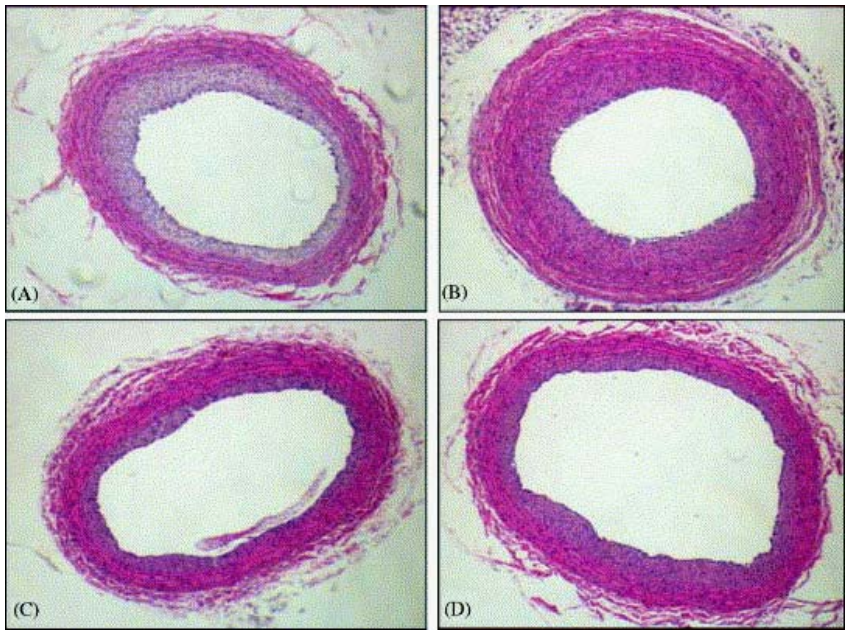




- Morishita T. Atheroscleoris 2006
- Hayashi SI. et al. Hypertension 2000;35:237-243

Cilostazol inhibits neointimal formation

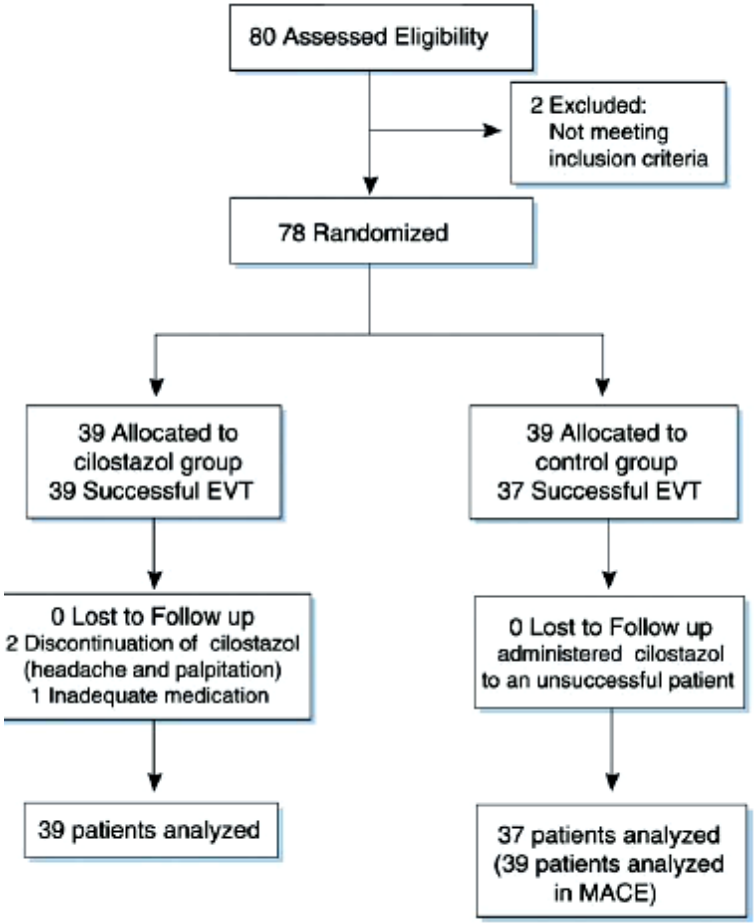




- Morishita. Atheroscleoris 2006
- Hayashi, S.-i. et al. Hypertension 2000;35:237-243

A. STZ –
B. B) STZ +
C. Cilostazol STZ –
D. Cilostazol STZ +

Efficacy of Cilostazol After Endovascular Therapy for Femoropopliteal Artery Disease in Patients With Intermittent Claudication

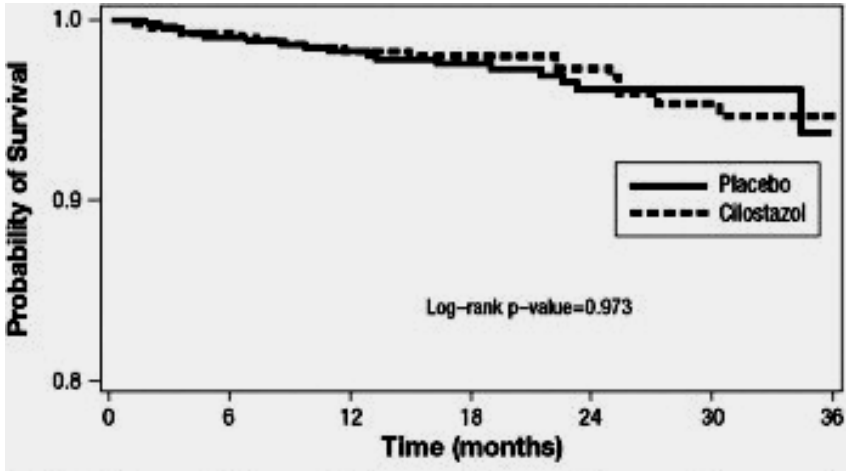


Soga Y et al. JACC 2009;53:48-53

Resultados del CASTLE

- Base de datos: 16 muertes en 2702 pts tratados 6 meses
- 1899 pts con EVP y diagnóstico de CI
- Tratamiento durante 36 meses + 1

Parámetro	Placebo	Cilostazol
Muerte	19	18
Muerte CV	52	49
Sangrado	22	18



- Sangrado (Serious Bleeding)

	Cilostazol	Placebo
AAS	2.5%	3.1%
AAS + Clopidogrel	2.1%	2.1%
Aos	0.4%	1.0%
	0.8%	1.3%

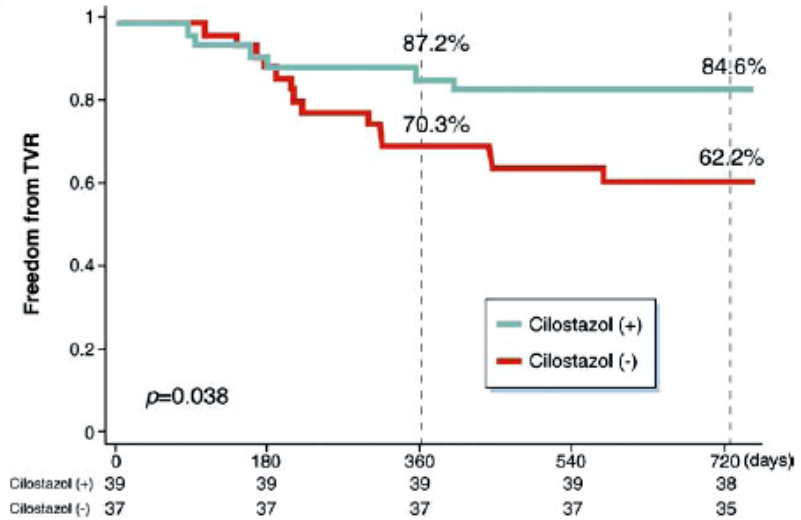


Figure 2 Freedom From TVR

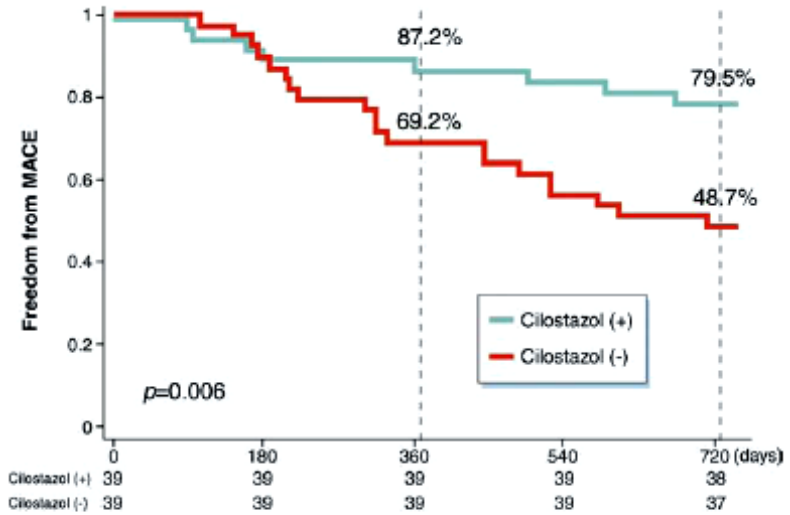


Figure 3 Freedom From MACE

Table 3 Major Adverse Cardiovascular Events in Patients Who Did and Did Not Receive Cilostazol

	Total	Cilostazol (+) (n = 39)	Cilostazol (−) (n = 39)	p Value
Death (cardiac death)	3 (1)	1 (0)	2 (1)	0.60
Nonfatal MI	0	0	0	0.99
Stroke	1	0	1	0.31
Repeat revascularization	24	7	17	0.014
TLR	17	5	12	
TVR	20	6	14	
Non-TVR	5	2	3	
Surgical revascularization	1	1	0	
Leg amputation	0	0	0	0.99
Major bleeding	0	0	0	0.99

MI = myocardial infarction; TLR = target lesion revascularization; TVR = target vessel revascularization.

Soga et al. JACC 2009;53:48-53