CONTROVERSIE SULL'USO DEI FARMACI ANTITROMBOTICI
7-8 ottobre 2016 - Hotel Lloyd's Baia - Via Enrico de Marinis, 2 - 84019 Vietri sul Mare

Arteriopatie periferiche

Trattamento delle arteriopatie periferiche: AVK versus **Antiaggregante**

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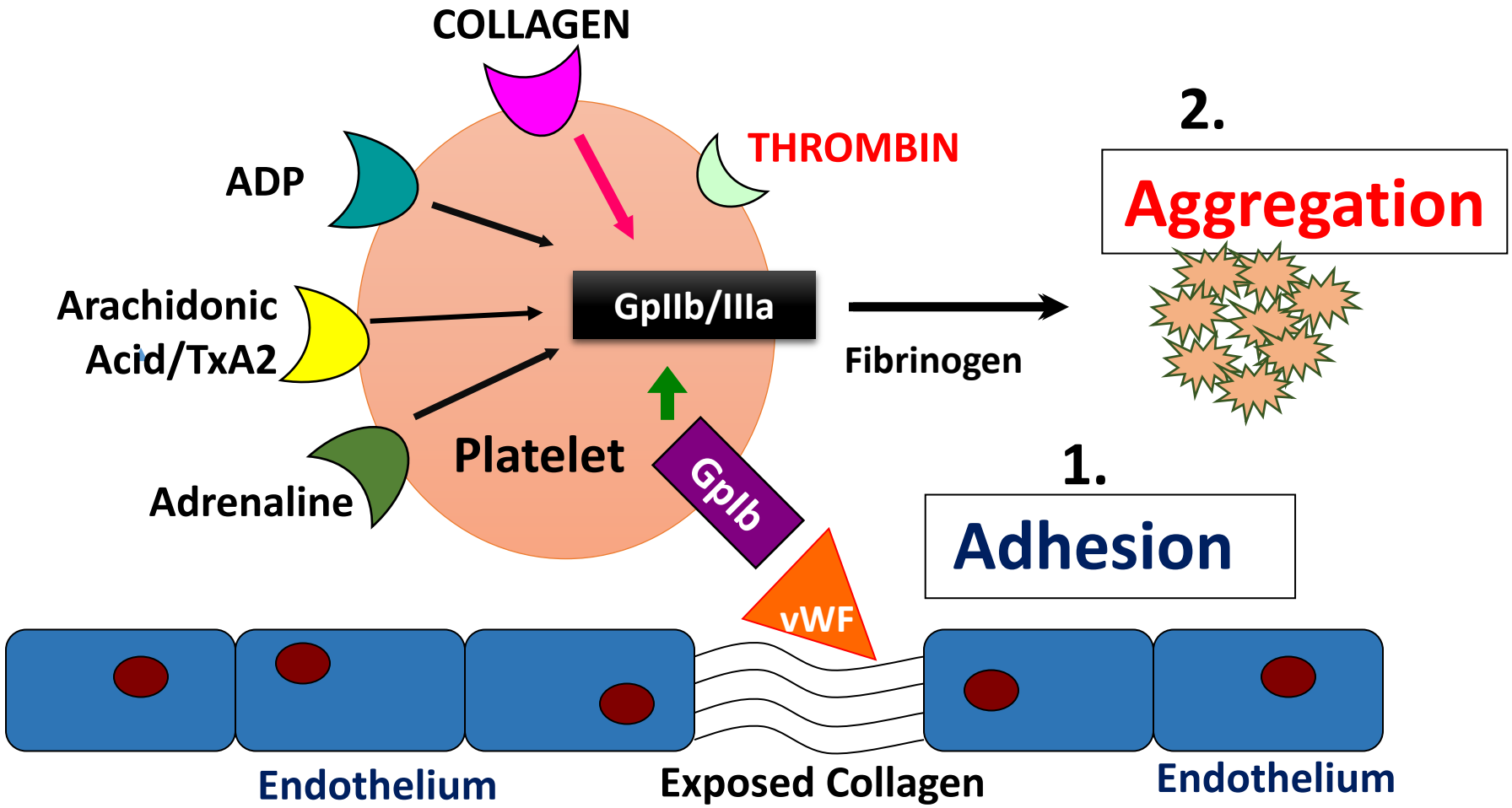
Obiettivi della terapia nei pazienti con PAOD

- Ridurre l'incidenza di complicanze cardiovascolari
- Ritardare il peggioramento della malattia
- Evitare la trombosi dopo la rivascolarizzazione
- Migliorare la capacità di deambulare

Antiplatelet therapy

Platelet Functions in Hemostasis

Activation Pathways



Falanga A., 2013

Farmaci antipiastrinici

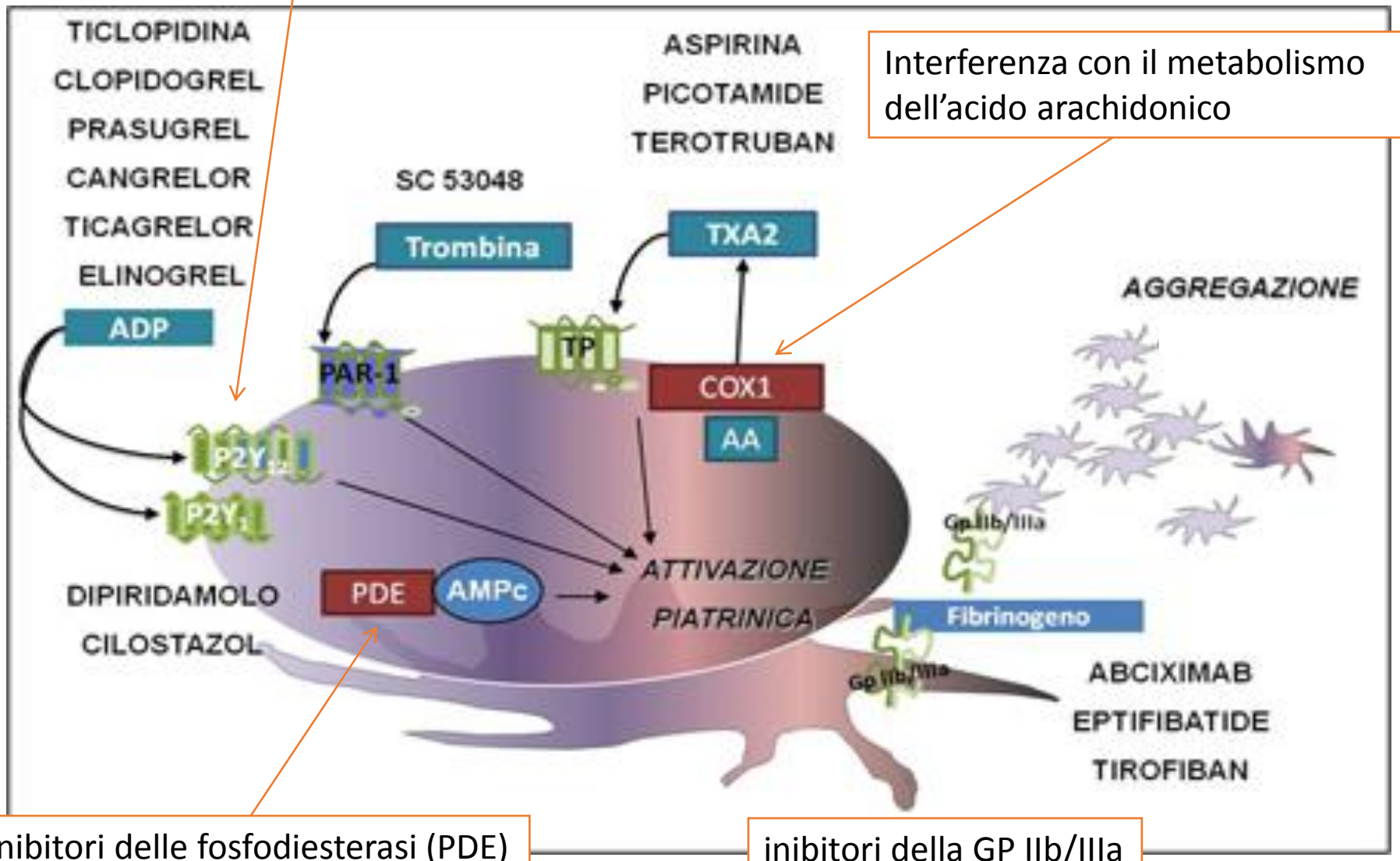
- Interferenza con il metabolismo dell'acido arachidonico
- Interferenza con la via adenosina difosfato (ADP)-dipendente dell'attivazione piastrinica
- Inibitori delle fosfodiesterasi (PDE)
- Inibitori del recettore per la trombina (PAR)

Inibizione dell'attivazione piastrinica

- Inibitori della glicoproteina (GP) IIb/IIIa

Inibizione dell'aggregazione piastrinica

Inibitori recettore P2Y12 dell'ADP



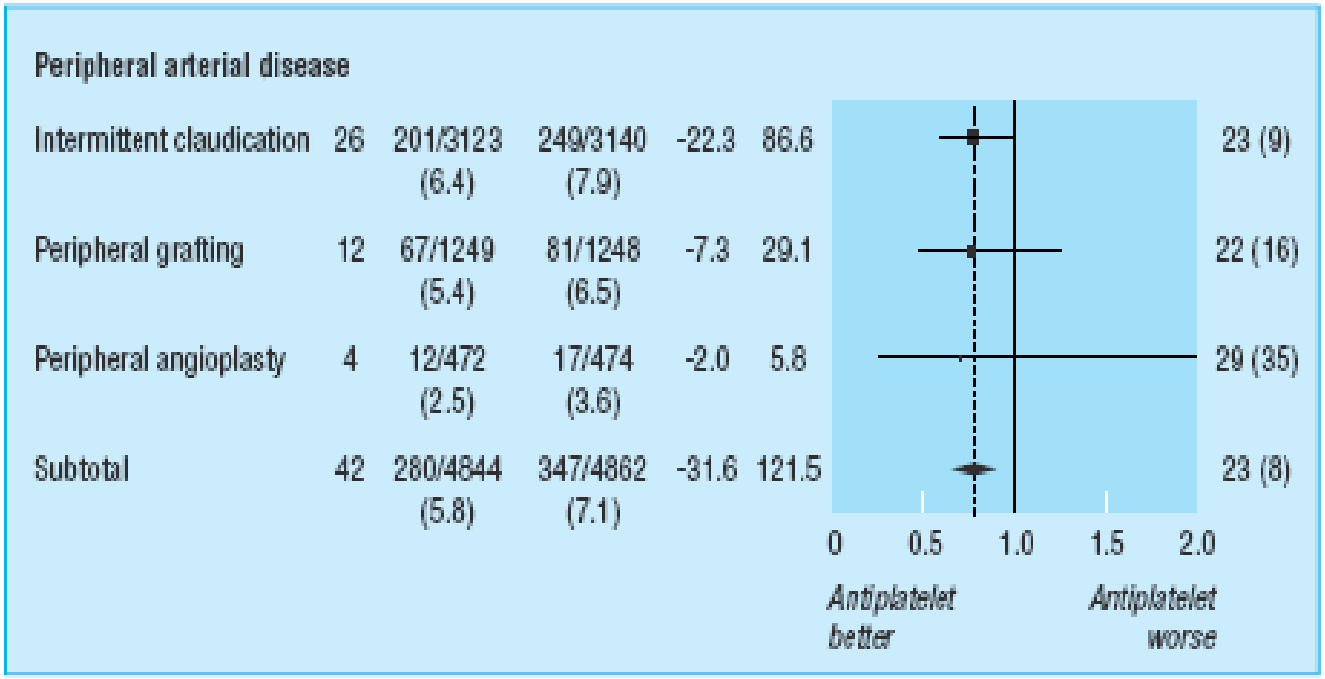
Interferenza con il metabolismo dell'acido arachidonico

inibitori delle fosfodiesterasi (PDE)

inibitori della GP IIb/IIIa

The Antithrombotic Trialists' Collaboration. BMJ 2012

Collaborative metanalysis of randomised trials of antiplatelet therapy for prevention of death, MI, and stroke among patients at high risk of occlusive vascular events*.



Overall, among 9214 patients with peripheral arterial disease in 42 trials there was a proportional reduction of 23% in serious vascular events (P = 0.004), with similar benefits among patients with intermittent claudication, those having peripheral grafting, and those having peripheral angioplasty.

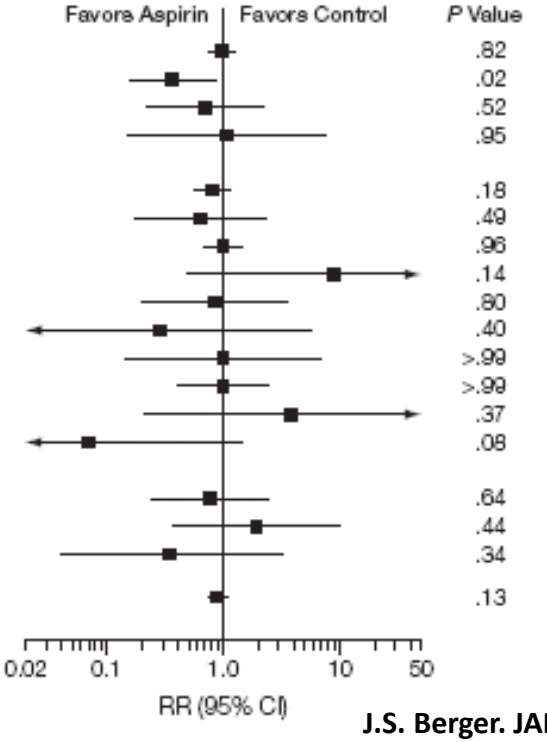
*acute MI, ischaemic stroke, unstable or stable angina, previous MI, stroke or cerebral ischaemia, peripheral arterial disease, or atrial fibrillation.

Aspirin for the prevention of cardiovascular events in patients with PAD: A meta-analysis of randomized trials

Berger et al. conducted a meta-analysis that compared outcomes with aspirin *vs* placebo in 3019 patients with **established PAD**

Figure 2. Effect of Any Aspirin on the Prevention of Composite Cardiovascular End Points

Source	No. of Cardiovascular Events/ Total No. of Patients: Aspirin	Control	Weight, %	RR (95% CI)[a]	*P* Value
Belch et al,[9] 2008	105/638	108/638	41.3	0.97 (0.76-1.24)	.82
Catalono et al,[21] 2007	7/185	19/181	3.5	0.36 (0.16-0.84)	.02
BMFT-II,[14] 1998	5/170	7/164	2.0	0.69 (0.22-2.13)	.52
Study group on pharmacological treatment after PTA,[20] 1994	2/108	2/115	0.7	1.06 (0.15-7.43)	.95
McCollum et al,[32] 1991	53/286	61/263	23.1	0.80 (0.58-1.11)	.18
Heiss et al,[28] 1990	5/132	4/67	1.5	0.63 (0.18-2.29)	.49
Colwell et al,[22] 1989	36/110	40/121	18.3	0.99 (0.68-1.43)	.96
Donaldson et al,[23] 1985	4/33	0/32	0.3	8.74 (0.49-155.97)	.14
Hess et al,[30] 1985	5/160	3/80	1.3	0.83 (0.20-3.40)	.80
Goldman and McCollum,[25] 1984	0/22	2/31	0.3	0.28 (0.01-5.53)	.40
Kohler et al,[31] 1984	2/50	2/50	0.7	1.00 (0.15-6.82)	>.99
Schoop and Levy,[33,34] 1984	14/200	7/100	3.2	1.00 (0.42-2.40)	>.99
Green et al,[26] 1982	3/32	0/17	0.3	3.82 (0.21-69.88)	.37
Harjola et al,[27] 1981	0/200	3/100	0.3	0.07 (0.00-1.38)	.08
Ehresmann et al,[24] 1977	0/215	0/213	0.0		
Hess and Keil-Kuri,[29] 1975	5/92	6/84	1.9	0.76 (0.24-2.40)	.64
Hess and Keil-Kuri,[29] 1975	4/42	2/40	0.9	1.90 (0.37-9.83)	.44
Zekert,[35] 1975	1/148	3/150	0.5	0.34 (0.04-3.21)	.34
Total	251/2823	269/2446		0.88 (0.76-1.04)	.13



J.S. Berger. JAMA 2009

Aspirin for the prevention of cardiovascular events in patients with PAD: a meta-analysis of randomized trials.

- In patients with PAD, treatment with aspirin alone or with dipyridamole resulted in a statistically non significant decrease in the primary end point of cardiovascular events and a significant reduction in nonfatal stroke.
- Results for the primary end point may reflect limited statistical power.
- The authors conclude that additional randomized controlled trials of aspirin therapy are needed to establish the net benefit and bleeding risks in PAD.

Berger, JAMA 2009

Antiplatelet therapy trials in patients with established PAD

Table 2. Antiplatelet therapy trials in patients with established peripheral artery disease

Trial	Design	Population	Endpoints	Results (treatment vs. control)
Antiplatelet monotherapy in asymptomatic PAD				
AAA (2010)	Aspirin ($n=1675$) vs. placebo ($n=1675$)	ABI $\leq$0.95	All-cause mortality, MI, stroke, any revascularization	HR: 1.03; 95% CI: 0.84–1.27 8.2 years average follow-up
POPADAD (2008)	Aspirin ($n=638$) vs. nonaspirin ($n=638$)	Diabetic patients with ABI $\leq$0.99	MI, stroke, above ankle amputation for CLI	HR: 0.98; 95% CI: 0.76–1.26 8 years follow-up
Antiplatelet monotherapy in symptomatic PAD				
DAVID (2004)	Picotamide ($n=603$) vs. aspirin ($n=606$)	Diabetic patients with ABI <0.9 or >1.3	Primary: all-cause mortality	Primary: 3.0 vs. 5.5%; $P=0.047$
			Secondary: MI, stroke, major amputation	Secondary: 7.1 vs. 8.7%; $P=0.300$
CLIPS (2007)	Aspirin ($n=185$) vs. nonaspirin ($n=181$)	ABI <0.85	MI, stroke, pulmonary embolus, or CLI	HR: 0.42; 95% CI: 0.21–0.83 2 years follow-up
CAPRIE (1996)	Clopidogrel ($n=3323$) vs. aspirin ($n=3229$)	ABI $\leq$0.85 or prior revascularization	Fatal or nonfatal MI or stroke	RRR: 23.8%; 95% CI: 8.9–36.2%
Dual antiplatelet therapy in symptomatic PAD				
CHARISMA (2006)	Clopidogrel + aspirin vs. placebo + aspirin ($n=2838$)[a]	ABI $\leq$0.85	Fatal or nonfatal MI or stroke	HR: 0.87; 95% CI: 0.67–1.13 30 months follow-up
MATCH (2004)	Clopidogrel + aspirin ($n=388$) vs. clopidogrel + placebo ($n=388$)[a]		Fatal or nonfatal MI or stroke, vascular death, hospitalization for ACS or PAD revascularization	19.1 vs. 24.0%; $P=$NS 18 months follow-up
TRA2P-TIMI 50 (2012)	Vorapaxar vs. placebo ($n=3787$)	ABI <0.85 or prior revascularization	Fatal or nonfatal MI or stroke, vascular death	HR: 0.94; 95% CI: 0.78–1.14 30 months median follow-up

S. Banerjee et al, Current Opinion Cardiol 2015

Antiplatelet therapy

Antiplatelet monotherapy for asymptomatic PAD

The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease.

- **Objective:** to determine whether aspirin and antioxidant therapy (*a-tocopherol, ascorbic acid, pyridoxine hydrochloride, zinc sulphate, nicotinamide, lecithin, and sodium selenite*), combined or alone, are more effective than placebo in reducing the development of cardiovascular events in patients with **diabetes mellitus** and **asymptomatic** PAD.

- Aspirin *vs* non-aspirin patients experienced similar rates of the primary endpoint of fatal or nonfatal MI, stroke, or above-ankle amputation for critical limb ischemia (CLI) over 8 years (HR: 0.98; 95% CI: 0.76–1.26).

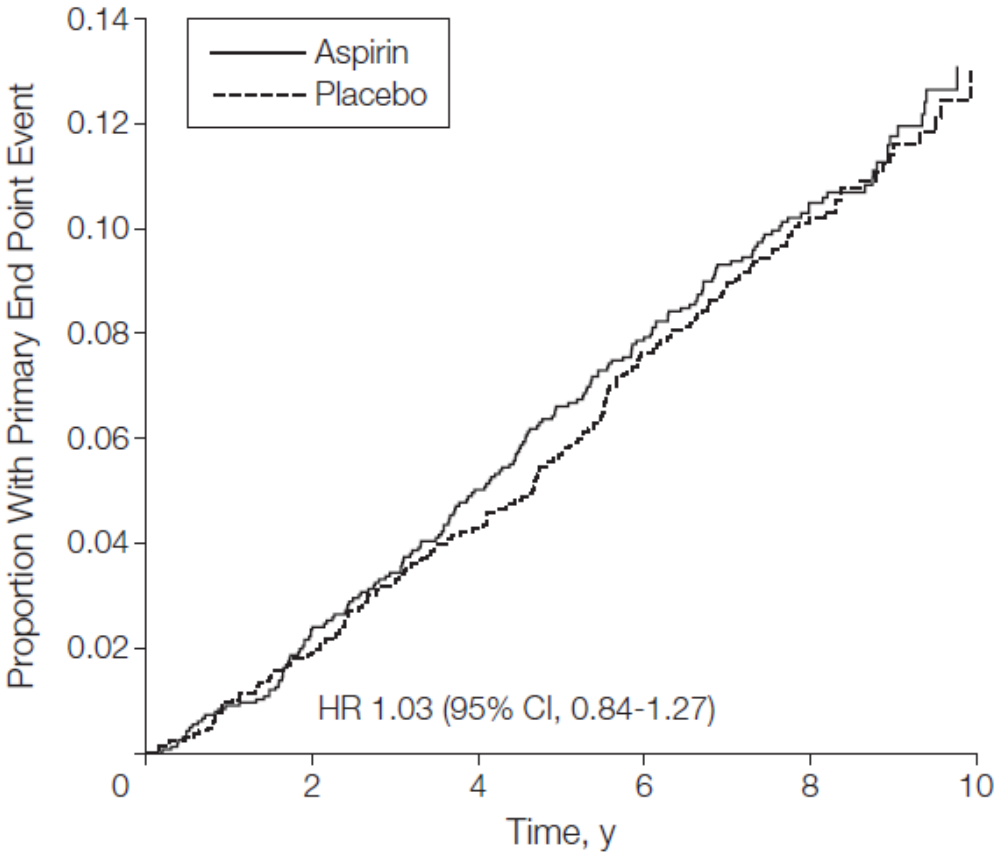
This trial **does not provide evidence to support** the use of aspirin or antioxidants in primary prevention of cardiovascular events and mortality in the population with diabetes studied.

J. Belch et al. BMJ 2008

The Aspirin for Asymptomatic Atherosclerosis (AAA) Trial

Aspirin for Prevention of Cardiovascular Events in a general population screened for a Low Ankle Brachial Index (ABI): a Randomized Controlled Trial

A low ABI indicates atherosclerosis and an increased risk of cardiovascular and cerebrovascular events.
Objective: to determine the effectiveness of aspirin in preventing events in people with a low ABI identified on screening the general population.



After a mean follow-up of 8.2 years, there was **no significant difference** in the primary endpoint of all-cause mortality, MI, stroke, or revascularization (HR: 1.03; 95% CI: 0.84–1.27)

Fowkes FGR et al., JAMA 2010

Antiplatelet therapy

Antiplatelet monotherapy in symptomatic PAD

Prevention of serious vascular events by aspirin amongst patients with PAD: randomized, double-blind trial (CLIPS study)

- The CLIPS RCT randomized **366** patients to receive aspirin (100 mg/d), or aspirin (100 mg/d) + antioxidant vitamins (Vitamin C, E, and b-carotene), or antioxidant vitamins alone, or placebo for up to 2 years.

Table 2a Aspirin versus nonaspirin: outcomes

	Aspirin (n = 185)	Nonaspirin (n = 181)	P-value[a]	HR (95% CI)
Stroke nonfatal plus fatal	2+2	6+1	0.33	0.54 (0.16–1.85)
Myocardial infarction nonfatal plus fatal	0+2	9+2	0.03	0.18 (0.04–0.83)
Pulmonary embolus nonfatal plus fatal	1+0	1+1	0.57	0.50 (0.05–5.54)
Vascular death	5	4	0.78	1.21 (0.32–4.52)
Nonvascular death[b]	2	0	0.99	–
Vascular event	7	20	0.02	0.35 (0.15–0.82)
Vascular event or critical limb ischaemia	12	28	0.01	0.42 (0.21–0.83)
Bleeding	4	0	0.99	–

–, Statistics could not be calculated because of the lack of events in the second group. [a]Aspirin versus nonaspirin groups P = 0.074 (chi-quadro = 3.18). [b]Both nonvascular deaths were from cancer.

For the first time direct evidence shows that **low-dose aspirin should routinely be considered for PAD patients**. However, a clear caveat is the study lack of power as evidenced by the poor enrollment numbers.

M. Catalano et al. J Intern Med 2007

A randomised, blinded, trial of clopidogrel *vs* aspirin in patients at risk of ischaemic events (CAPRIE)

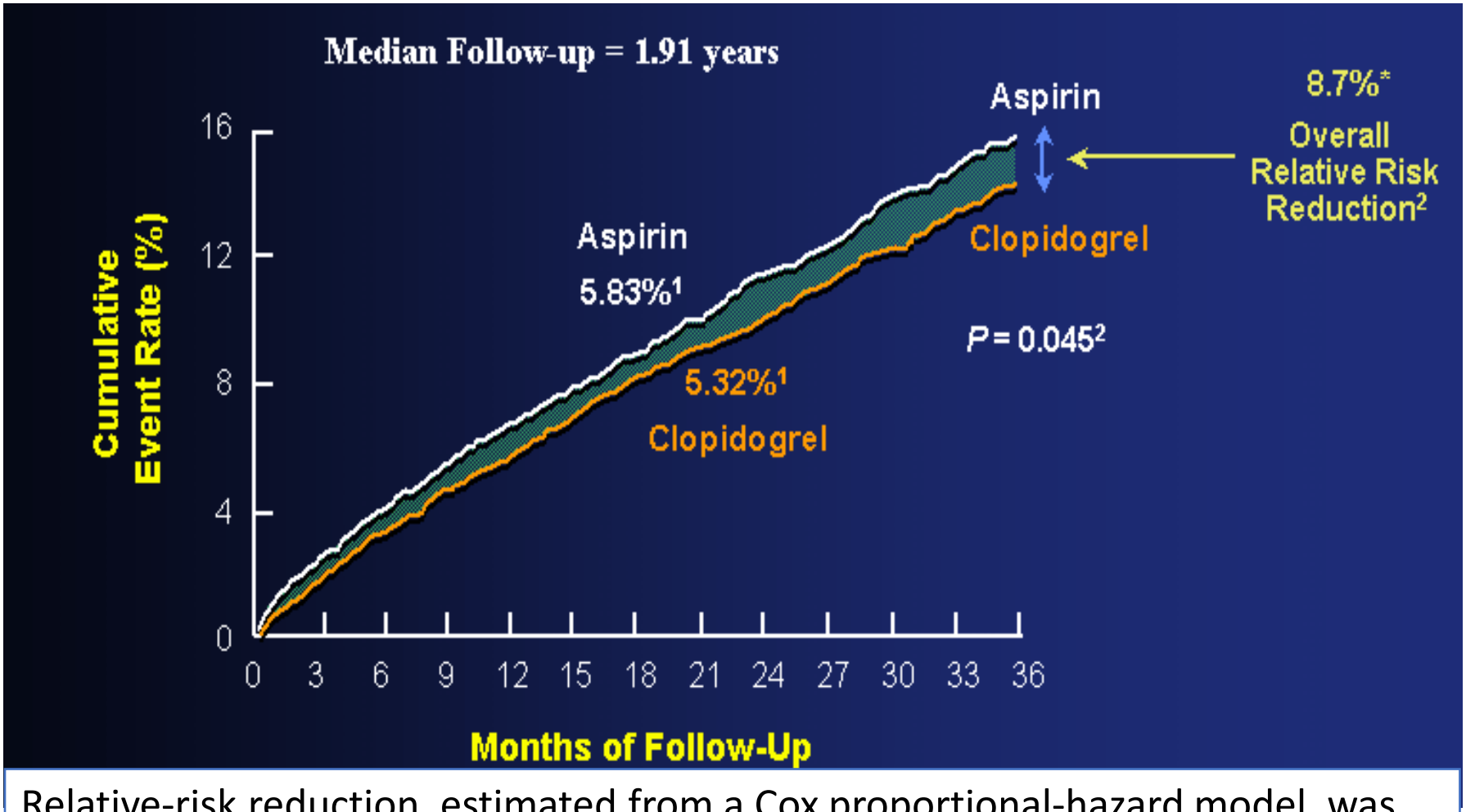
- In the Clopidogrel *vs* Aspirin in Patients at Risk of Ischemic Events (CAPRIE) RCT, clopidogrel was compared with aspirin for the secondary prevention of major adverse cardiovascular events (MACE) in 19.185 patients with prior stroke, MI, or established PAD.

- Long-term administration of clopidogrel to patients with atherosclerotic vascular disease is more effective than aspirin in reducing the combined risk of ischaemic stroke, myocardial infarction, or vascular death. The overall safety profile of clopidogrel is at least as good as that of medium-dose aspirin.

- For the 6452 patients with PAD, clopidogrel use was associated with a 23.8% RR reduction of experiencing MACE, compared with a 7.3% RR reduction in the prior stroke subgroup and a 3.7% RR increase in the prior MI subgroup.

Committee CS. Lancet 1996

Cumulative risk of Ischaemic stroke, myocardial infarction, or vascular death



Relative-risk reduction, estimated from a Cox proportional-hazard model, was 8·7% (95% CI 0·3–16·5) in favour of clopidogrel (p=0·043)

Committee CS. Lancet 1996

Antiplatelet therapy

Dual Antiplatelet therapy in symptomatic PAD

Patients with peripheral arterial disease in the CHARISMA trial

- The effect of dual antiplatelet therapy in patients with PAD was examined in the Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events (CHARISMA) trial.
- Further analysis of the PAD cohort within CHARISMA identified 3096 patients that also failed to benefit from dual antiplatelet therapy compared to aspirin alone in reducing the composite endpoint of MI, stroke or death.

	Patients with PAD + Clopidogrel	on aspirin + Placebo	*P*-value
Efficacy endpoints			
Primary endpoint	117 (7.6)	138 (8.9)	0.183
Death from any cause	104 (6.7)	117 (7.5)	0.387
Death from cardiovascular causes	65 (4.2)	71 (4.6)	0.613
Myocardial infarction[b]	36 (2.3)	57 (3.7)	0.028
Ischaemic stroke[b]	32 (2.1)	39 (2.5)	0.416
Stroke[b]	36 (2.3)	46 (3.0)	0.275
Hospitalization[c]	255 (16.5)	331 (20.1)	0.011

There was a significant reduction in the rate of MI among patients with PAD randomized to clopidogrel and aspirin versus those receiving aspirin alone (2.3% vs 3.7%, HR 0.63; $p = 0.028$).

Cacoub et al., Eur Heart J 2009

CHARISMA trial

	Patients with PAD		P-value
	Aspirin + Clopidogrel	+ Placebo	
Safety endpoints			
Severe bleeding	26 (1.7)	27 (1.7)	0.901
Fatal bleeding	7 (0.5)	6 (0.4)	0.776
Primary intracranial haemorrhage	3 (0.2)	6 (0.4)	0.507
Moderate bleeding	38 (2.5)	29 (1.9)	0.259
Minor bleeding	531 (34.4)	323 (20.8)	<0.001

- Dual therapy provided some benefit over ASA alone in PAD patients for the rate of MI and of hospitalization for ischaemic events, **at the cost of an increase in minor bleeding**.
- Data on mortality rates suggest that dual antiplatelet therapy should not be used in patients without a history of established vascular disease.

Cacoub et al., Eur Heart J 2009

Ongoing trials examining antiplatelet therapies for PAD

Trial (NCTID)	Design	Patient population	Primary endpoint
EUCLID	Ticagrelor vs. clopidogrel	Symptomatic PAD	MI, stroke, and cardiovascular death
NCT01732822			
TI-PAD EVR	Ticagrelor vs. aspirin	After infrainguinal endovascular procedure	Change in peak walking time
NCT02227368			
ASPIRE	1 month aspirin + clopidogrel vs. 12 months aspirin + clopidogrel	After infrainguinal endovascular procedure	Index limb occlusion, surgical or endovascular procedure, amputation, MI, stroke, or death

S. Banerjee. Current Opinion 2015

Antiplatelet therapy in PAD: conclusions

- In conclusion, aspirin has been shown to have little effect in trials examining patients with PAD, such as the POPADAD and AAA trials, which included patients with less severe ABI (<0.99 and 0.95, respectively).
- In a study population with more advanced PAD such as the CLIPS cohort, aspirin exhibited a benefit over placebo.
- Clopidogrel has also shown promise, and whether these benefits will translate to other thienopyridine derivatives remains to be explored.
- There is a demonstrable synergistic effect with the use of combination antiplatelet therapies. However, there is a relative lack of clinical trials examining DAPT in patients with established PAD.

Antiplatelet therapy

Guidelines

Summary of current antiplatelet guidelines for PAD

Guideline	Recommendation (in order of level of evidence)
Antiplatelet monotherapy for asymptomatic PAD	
AHA/ACC	Class IIa, level C: patients with asymptomatic PAD and an ABI <0.9
	Class IIb, level A: may or may not be useful in asymptomatic patients with a borderline ABI defined as >0.90 and <0.99
TASC II	Level A: all patients with PAD and established CAD or CVD
	Level C: aspirin for patients with PAD but without CAD or CVD
CHEST	Grade 2B: aspirin for asymptomatic PAD
Antiplatelet monotherapy for symptomatic PAD	
AHA/ACC	Class I, level A: patients with symptomatic PAD or prior revascularization or amputation
	Class I, level B: aspirin or clopidogrel for patients with symptomatic PAD or prior revascularization/amputation
TASC II	Level A: indefinitely following any endovascular or surgical procedure
	Level B: clopidogrel regardless of presence of other vascular diseases such as CAD or CVD
CHEST	Grade 1A: aspirin or clopidogrel for symptomatic PAD or following endovascular or surgical procedure
	Grade 2C: monotherapy rather than DAPT preferred for patients undergoing endovascular procedure
Dual antiplatelet therapy[a]	
AHA/ACC	Class IIb, level B: may be considered for patients with symptomatic PAD or prior revascularization, and who have high perceived risk for cardiovascular events
TASC II	No evidence for dual antiplatelet therapy for patients with stable PAD
CHEST	Grade 2B: recommend against DAPT with aspirin and clopidogrel in patients with symptomatic PAD

S. Banerjee. Current Opinion 2015

Antithrombotic Therapy in Peripheral Artery Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

P. Alonso-Coello et al. Chest 2012

ACCP guidelines 2012

- For persons with **asymptomatic** peripheral arterial disease (PAD), we **suggest aspirin 75 to 100 mg daily over no aspirin therapy** (Grade 2B).

- For **secondary prevention** patients with **symptomatic** PAD, we **recommend** one of the two following antithrombotic regimens to be continued long term over no antithrombotic treatment: **aspirin** 75 to 100 mg daily or **clopidogrel** 75 mg daily (all Grade 1A).

- We suggest ***not to use*** **dual antiplatelet therapy** with aspirin plus clopidogrel (Grade 2B) .

ACCP guidelines. CHEST 2012

ACCF/AHA Practice Guidelines

Management of Patients With Peripheral Artery Disease (Compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations)

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society for Vascular Medicine, and Society for Vascular Surgery

ACCF/AHA TASK FORCE MEMBERS

J. L. Anderson et al. Circulation 2013

2011 Updated Recommendation: Class I

- Antiplatelet therapy is indicated to reduce the risk of MI, stroke, and vascular death in individuals with symptomatic atherosclerotic lower extremity PAD. *(Level of Evidence: A)*
- Aspirin, typically in daily doses of 75 to 325 mg, is recommended as safe and effective antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD. *(Level of Evidence: B).*
- Clopidogrel (75 mg per day) is recommended as a safe and effective alternative antiplatelet therapy to aspirin to reduce the risk of MI, ischemic stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD. *(Level of Evidence: B)*

J. L. Anderson et al. Circulation 2013