

# Prophylaxis of cerebrovascular accidents with antiplatelet agents

**Marco Cattaneo**

**Unità di Medicina III**



**UNIVERSITÀ DEGLI STUDI DI MILANO  
DIPARTIMENTO DI MEDICINA CHIRURGIA E ODONTOIATRIA  
Polo Universitario San Paolo  
Milano - ITALY**



# Cerebral Ischemia of Arterial Origin

**1**

## **TRADITIONAL ANTICOAGULANT DRUGS**

- **Unfractionated heparin (UH)**
- **Warfarin and other vitamin-K antagonists**
- **Low molecular weight heparins (LMWH)**
- **Fondaparinux**
- **(Bivalirudin)**
- **(Lepirudin)**

## Vitamin K antagonists (VKA) vs ASA in patients with Cerebral Ischemia of Arterial Origin

Year	Trial	INR	Outcome	HR AC vs. ASA
1997	SPIRIT	3.0-4.5	VE + MB	2.3 (1.6-3.5)
2001	WARSS	1.4-2.8	IS + D	1.13 (0.92-1.38)
2007	ESPRIT	2.0-3.0	VE + MB	1.02 (0.77-1.35)

*VE, vascular event; MB, major bleeding; IS, ischaemic stroke; D, death*

**Major/fatal bleedings:**  
**SPIRIT = 53 (VKA) vs 6 (ASA);**  
**WARSS = 44 (VKA) vs 30 (ASA);**  
**ESPRIT = 55 (VKA) vs 22 (ASA)**

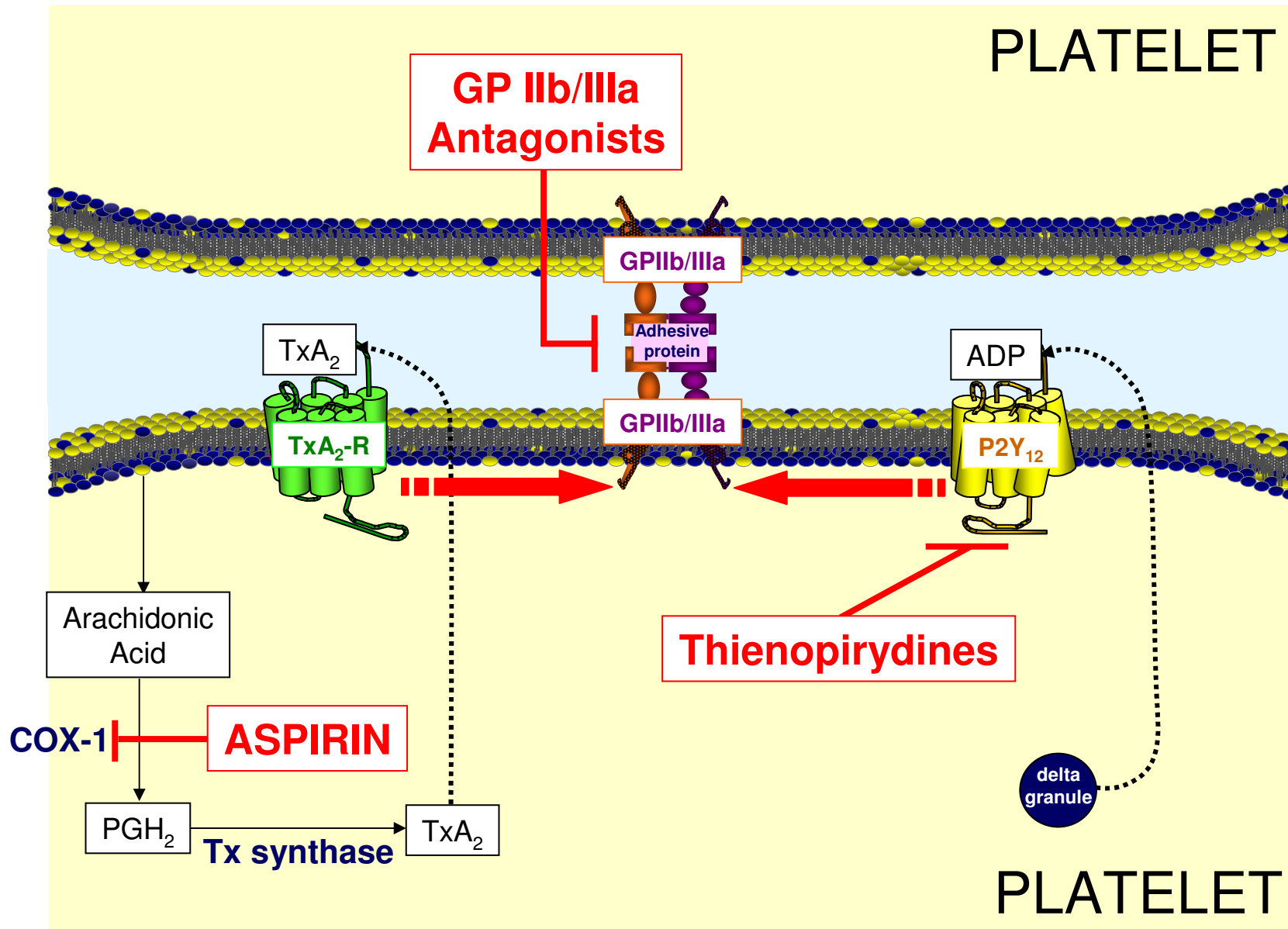
*SPIRIT, Ann Neurol 1997;42:857-65*

*WARSS, N Engl J Med 2001;345:1444-51*

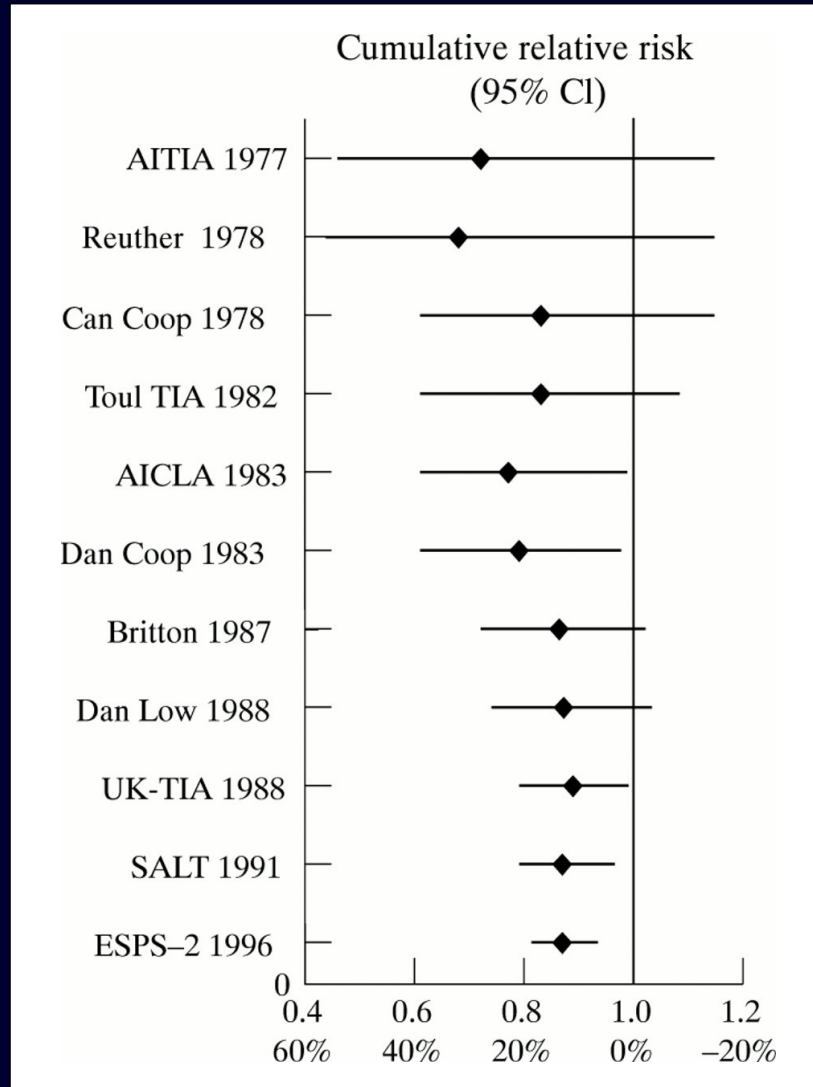
*ESPRIT, Lancet Neurol 2007;6:115-24*

## TRADITIONAL ANTIPLATELET DRUGS

- Aspirin
- Dipyridamole
- Clopidogrel and ticlopidine
- **Glycoprotein IIb/IIIa inhibitors**



## Cumulative meta-analysis of aspirin efficacy after cerebral ischaemia of arterial origin



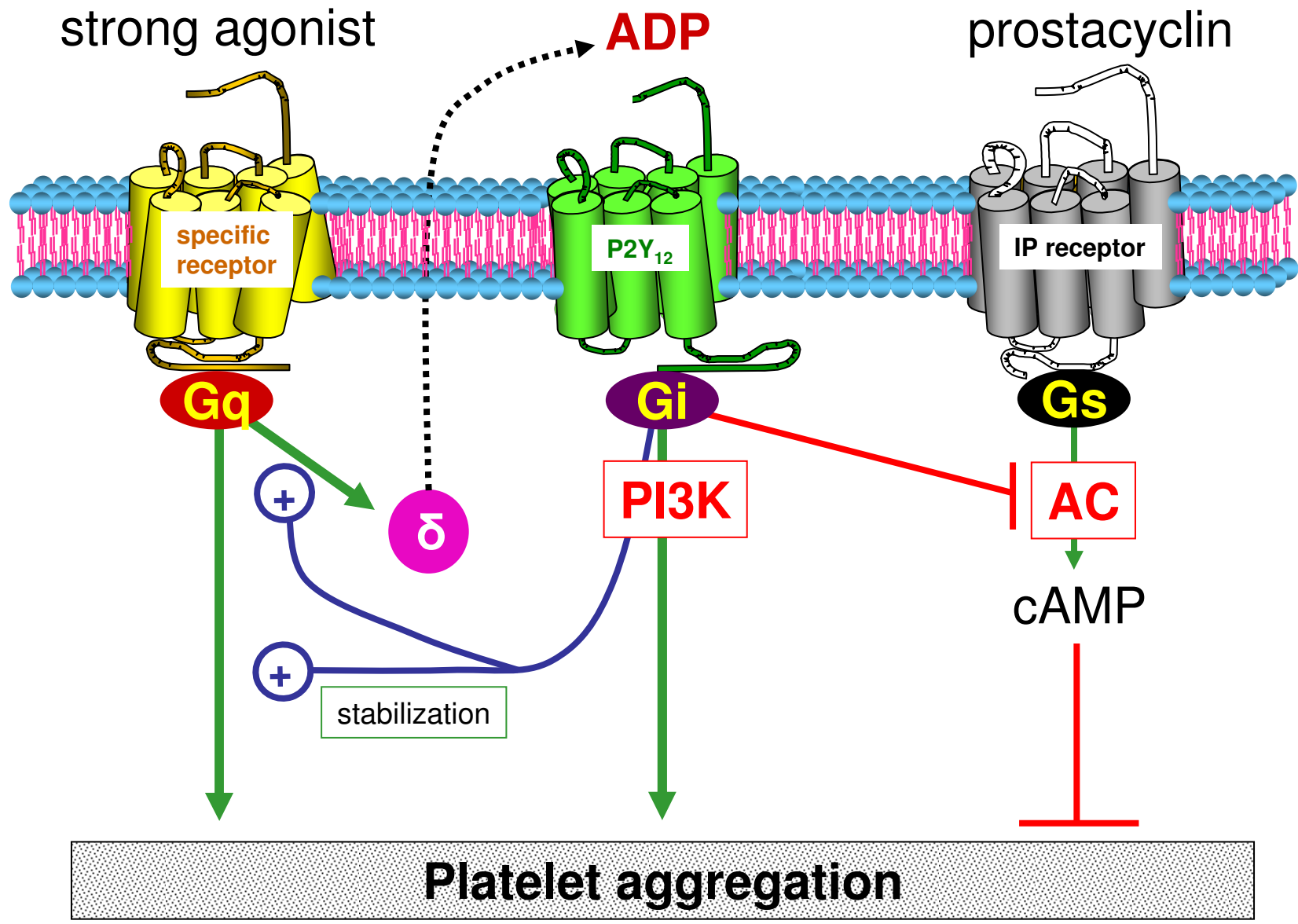
**OVERALL RRR: 13%**

No difference in relative risk reduction for doses of ASA:  
low (<100 mg/day),  
medium (300-325 mg/day),  
high (>900 mg/day)

## Risk of stroke with various NSAIDs

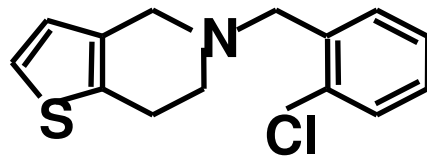
NSAID	HR (95% CI) for risk of stroke
Ibuprofen	1.28 (1.14–1.44)
Diclofenac	1.86 (1.58–2.19)
Rofecoxib	1.61 (1.14–2.29)
Celecoxib	1.69 (1.11–2.26)
Naproxen	1.35 (1.01–1.79)

Gislason G. European Society of Cardiology 2010 Congress; August 29-September 1, 2010; Stockholm, Sweden.

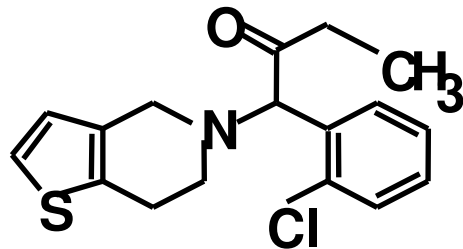
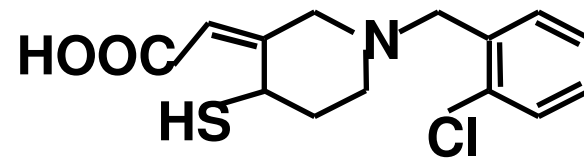


# THIENOPYRIDINES

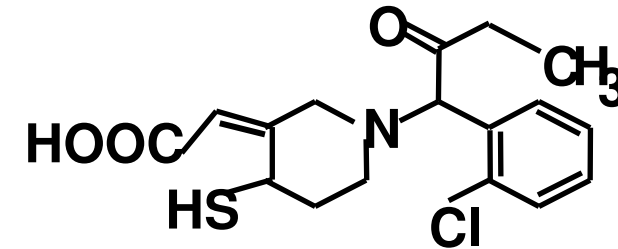
## ACTIVE METABOLITES

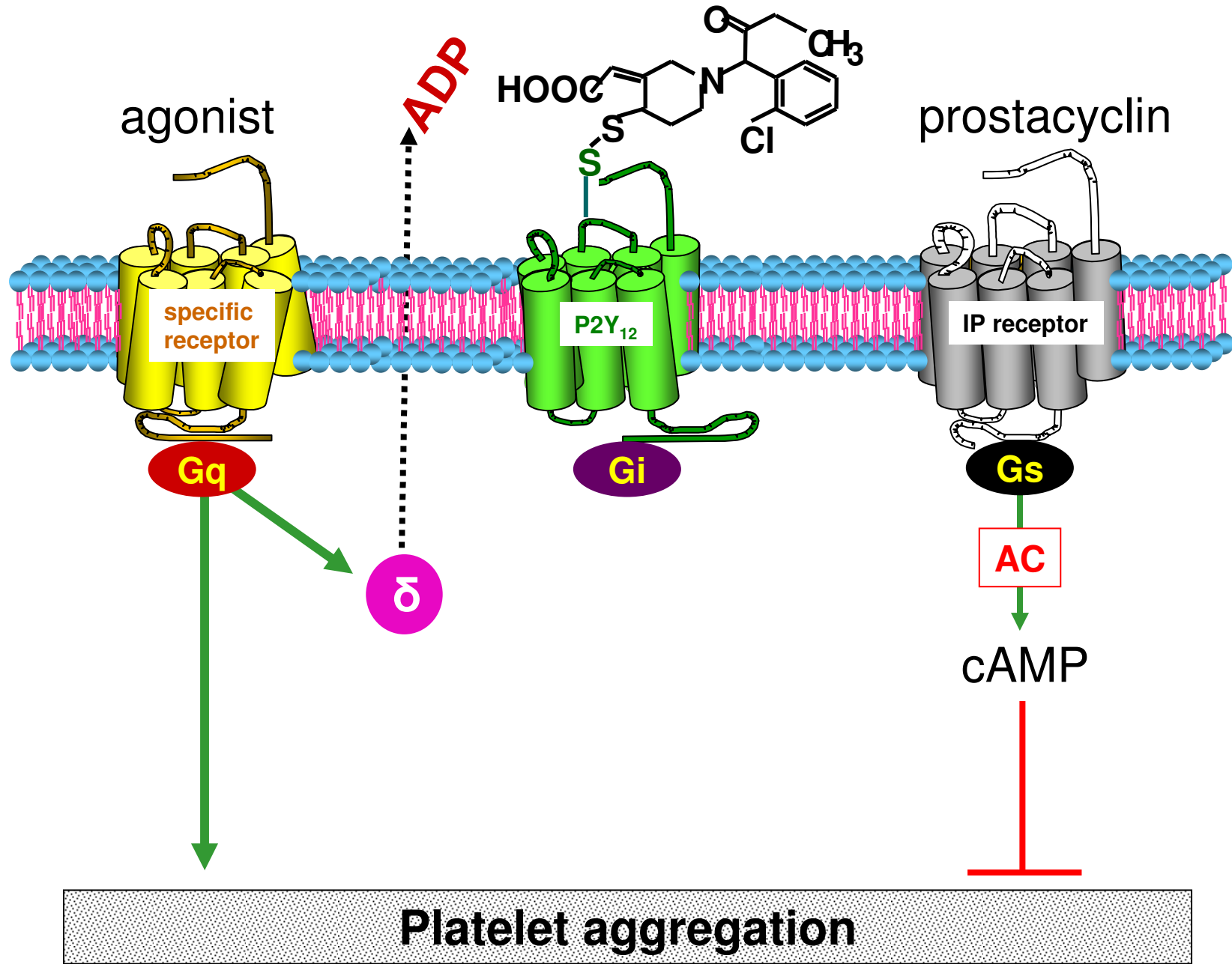


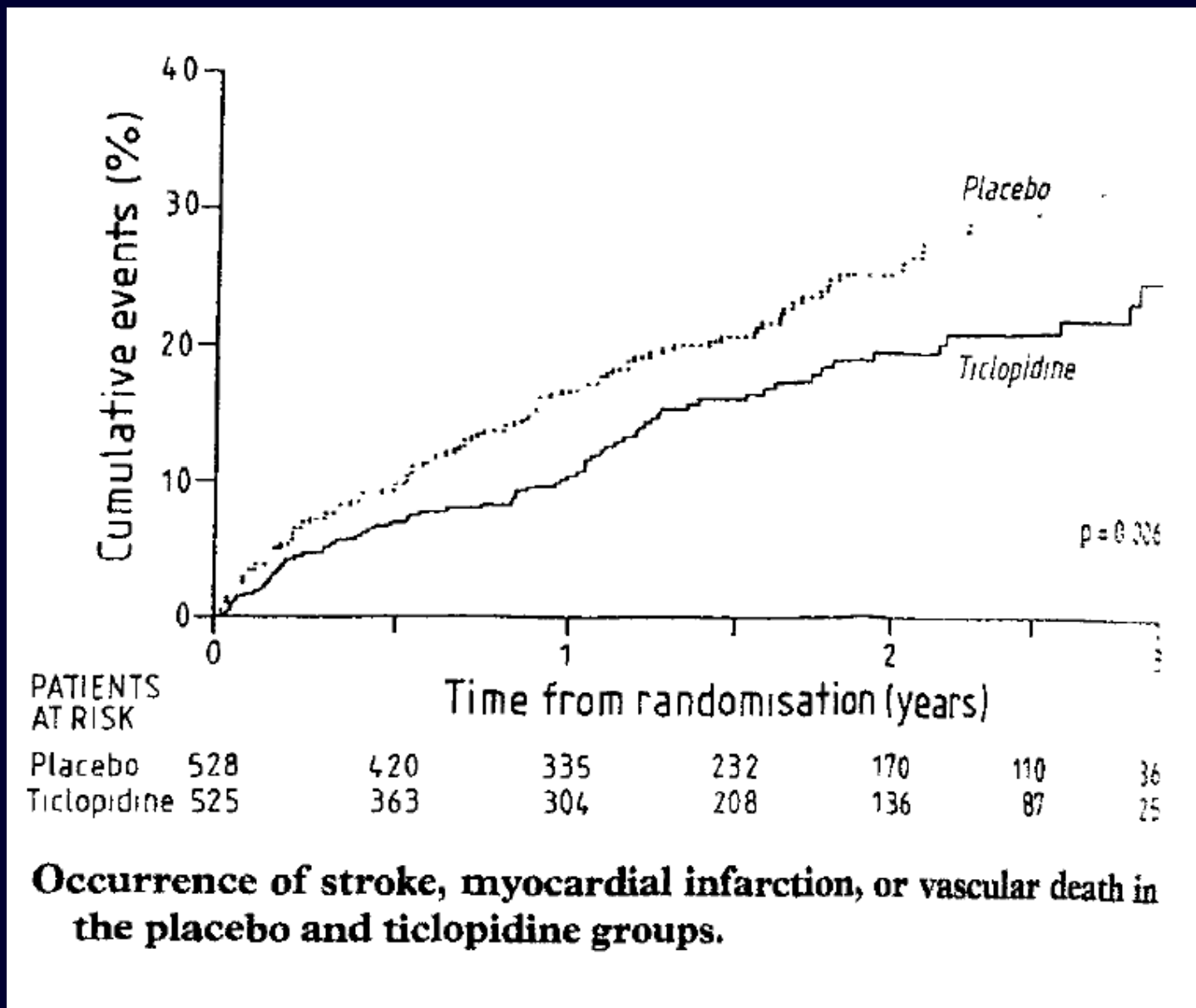
**Ticlopidine**



**Clopidogrel**







# Ticlopidine vs Aspirin in stroke (TASS Study)

- Patients: 3069 patients with recent transient or mild persistent focal cerebral or retinal ischemia
- Treatments: Ticlopidine hydrochloride (250 mg b.i.d.) vs aspirin (1300 mg q.d.)
- End points: stroke or death.
- Follow-up: two to six years.

# Ticlopidine vs Aspirin in stroke (TASS Study): main results

End point	Ticlopidine	ASA	RRR (95% CI)
<b>Non-fatal stroke or death</b>	<b>17%</b>	<b>19%</b>	<b>12% (-2/26)</b>
<b>Fatal and non-fatal stroke</b>	<b>10%</b>	<b>13%</b>	<b>21% (4/38)</b>

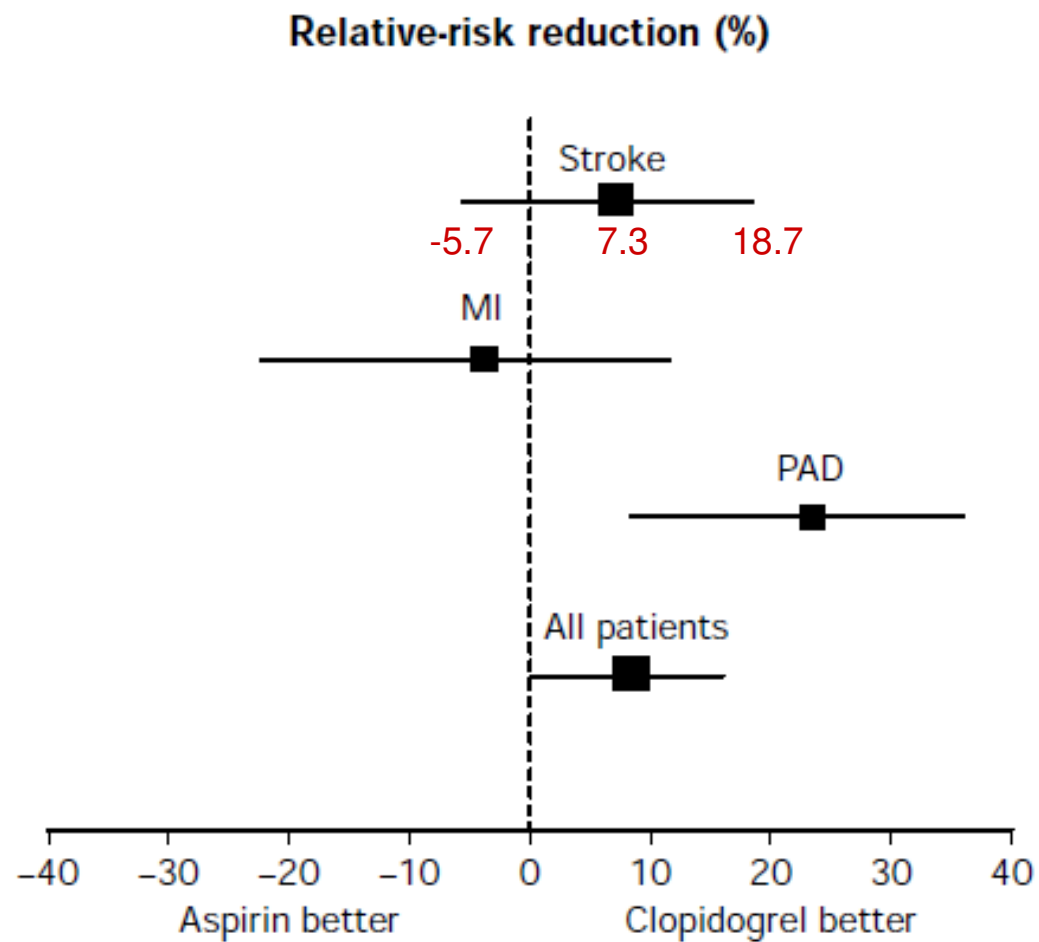


Figure 4: **Relative-risk reduction and 95% CI by disease subgroup**

MI=myocardial infarction; PAD=peripheral arterial disease.

# Prevalence of resistance to antiplatelet agents

- Aspirin (serum TxB<sub>2</sub>) ≈ 0-5%\*
- Clopidogrel (P2Y<sub>12</sub>-specific assays) ≈ 30%

---

\*mostly associated with non-compliance

# Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial

*Hans-Christoph Diener, Julien Bogousslavsky, Lawrence M Brass, Claudio Cimminiello, Laszlo Csiba, Markku Kaste, Didier Leys, Jordi Matias-Guiu, Hans-Jürgen Rupprecht, on behalf of the MATCH investigators\**

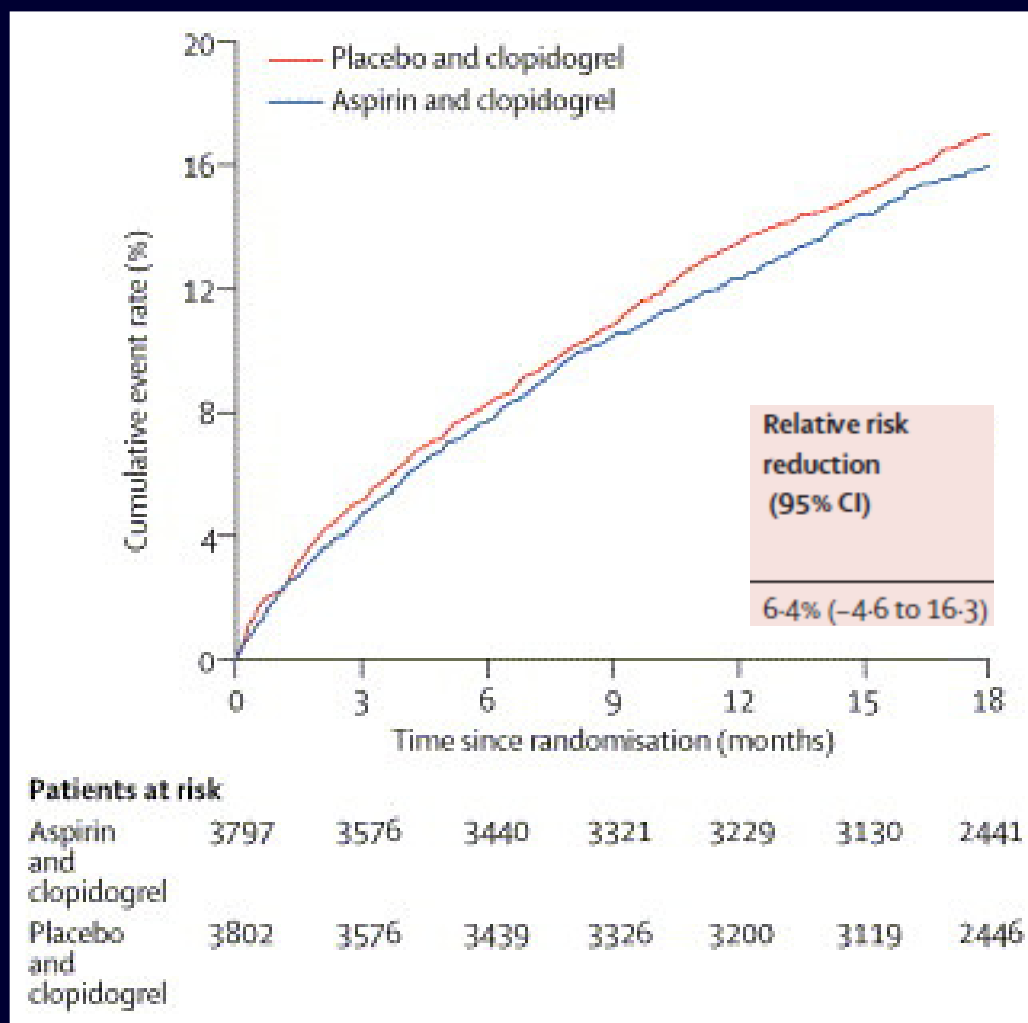
## Summary

**Background** Clopidogrel was superior to aspirin in patients with previous manifestations of atherothrombotic disease in the CAPRIE study and its benefit was amplified in some high-risk subgroups of patients. We aimed to assess whether addition of aspirin to clopidogrel could have a greater benefit than clopidogrel alone in prevention of vascular events with potentially higher bleeding risk.

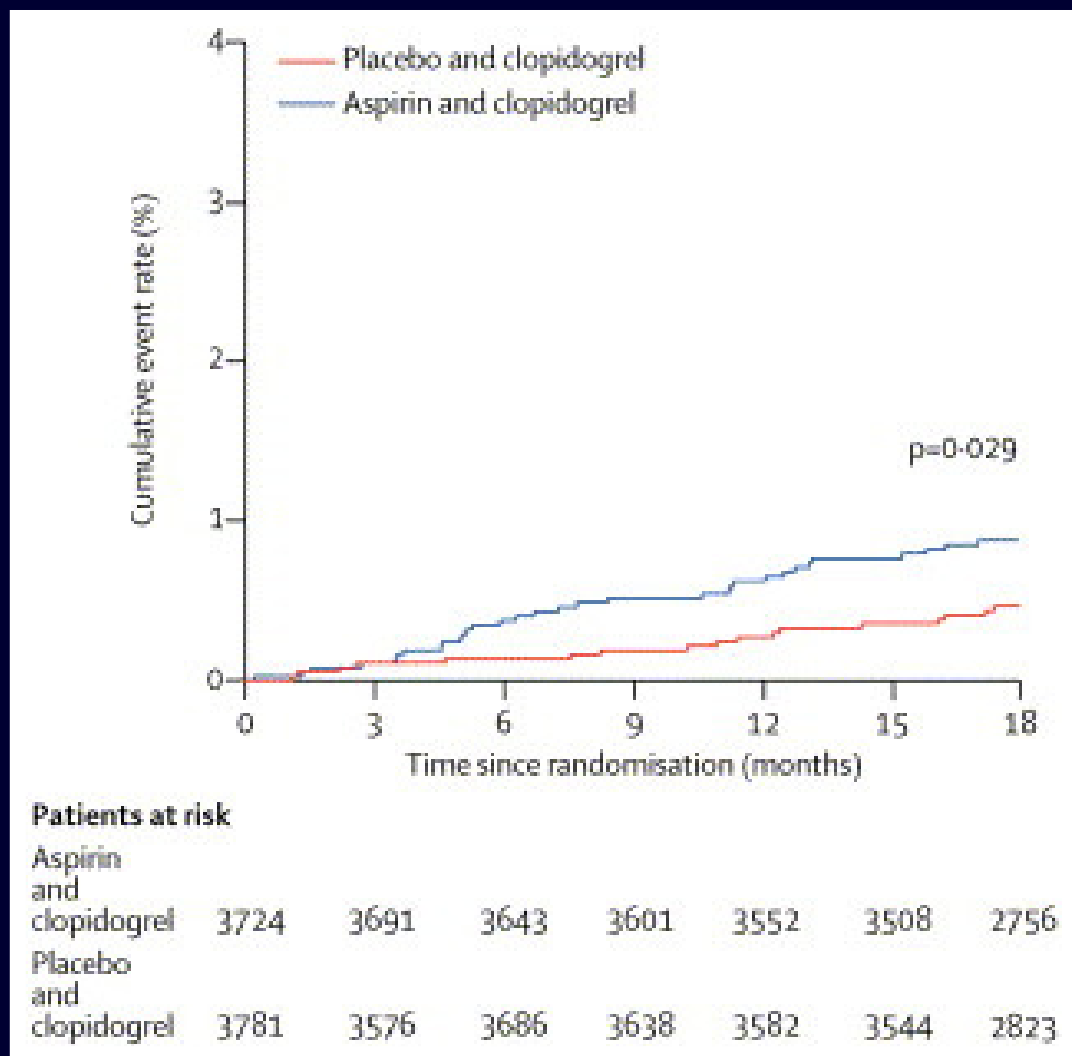
**Methods** We did a randomised, double-blind, placebo-controlled trial to compare aspirin (75 mg/day) with placebo in 7599 high-risk patients with recent ischaemic stroke or transient ischaemic attack and at least one additional vascular risk factor who were already receiving clopidogrel 75 mg/day. Duration of treatment and follow-up was 18 months. The primary endpoint was a composite of ischaemic stroke, myocardial infarction, vascular death, or rehospitalisation for acute ischaemia (including rehospitalisation for transient ischaemic attack, angina pectoris, or worsening of peripheral arterial disease). Analysis was by intention to treat, using logrank test and a Cox's proportional-hazards model.

*Lancet 2004; 364: 331-37*

Kaplan-Meier curves for cumulative rates of primary endpoint events (composite of ischaemic stroke, myocardial infarction, vascular death, or rehospitalisation for acute ischaemia)



## Kaplan-Meier curves for cumulative rates of primary intracranial haemorrhage in the MATCH trial



# The CHARISMA Trial

- *Background.* Dual antiplatelet therapy with clopidogrel plus low-dose aspirin has not been studied in a broad population of patients at high risk for atherothrombotic events.
- *Methods.* 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors were randomly assigned to receive clopidogrel (75 mg per day) plus low-dose aspirin (75 to 162 mg per day) or placebo plus low-dose aspirin
- *Follow up.* a median of 28 months
- *Primary efficacy end point.* A composite of myocardial infarction, stroke, or death from cardiovascular causes
- *Secondary efficacy end points* included hospitalization

## Composite and Individual Primary and Secondary End Points.

**Table 4. Composite and Individual Primary and Secondary End Points.**

End Point	Clopidogrel plus Aspirin (N=7802)	Placebo plus Aspirin (N=7801)	Relative Risk (95% CI)*	P Value
	no. (%)			
<b>Efficacy end points</b>				
Primary efficacy end point	534 (6.8)	573 (7.3)	0.93 (0.83–1.05)	0.22
Death from any cause	371 (4.8)	374 (4.8)	0.99 (0.86–1.14)	0.90
Death from cardiovascular causes	238 (3.1)	229 (2.9)	1.04 (0.87–1.25)	0.68
Myocardial infarction (nonfatal)	146 (1.9)	155 (2.0)	0.94 (0.75–1.18)	0.59
Ischemic stroke (nonfatal)	132 (1.7)	163 (2.1)	0.81 (0.64–1.02)	0.07
Stroke (nonfatal)	150 (1.9)	189 (2.4)	0.79 (0.64–0.98)	0.03
Secondary efficacy end point†	1301 (16.7)	1395 (17.9)	0.92 (0.86–0.995)	0.04
Hospitalization for unstable angina, transient ischemic attack, or revascularization	866 (11.1)	957 (12.3)	0.90 (0.82–0.98)	0.02
<b>Safety end points</b>				
Severe bleeding	130 (1.7)	104 (1.3)	1.25 (0.97–1.61)	0.09
Fatal bleeding	26 (0.3)	17 (0.2)	1.53 (0.83–2.82)	0.17
Primary intracranial hemorrhage	26 (0.3)	27 (0.3)	0.96 (0.56–1.65)	0.89
Moderate bleeding	164 (2.1)	101 (1.3)	1.62 (1.27–2.08)	<0.001

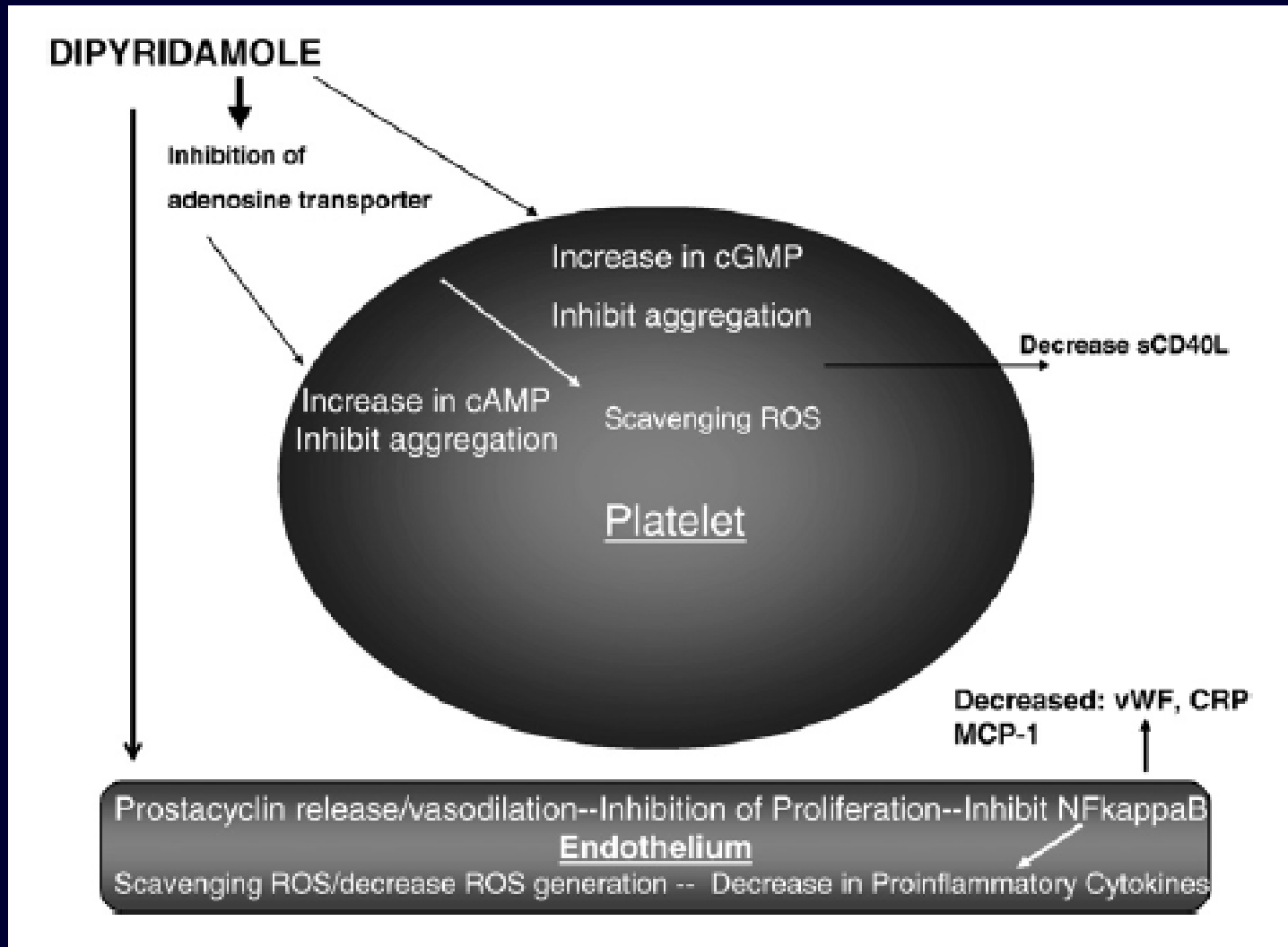
\* CI denotes confidence interval.

† The secondary efficacy end point was the first occurrence of myocardial infarction, stroke, death from cardiovascular causes, or hospitalization for unstable angina, a transient ischemic attack, or a revascularization procedure (coronary, cerebral, or peripheral).

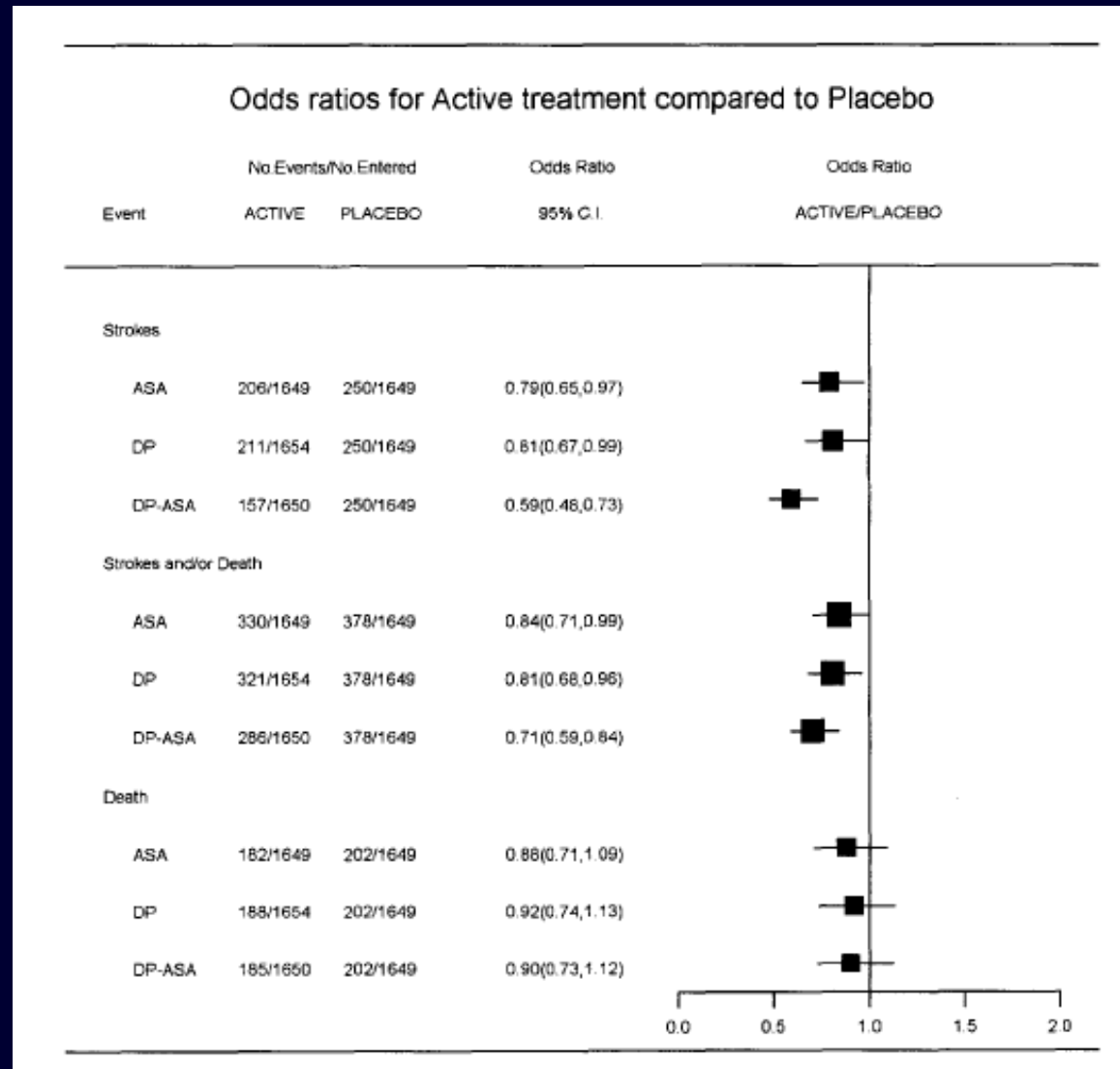
## TRADITIONAL ANTIPLATELET DRUGS

- Aspirin
- Dipyridamole
- Clopidogrel and ticlopidine
- Glycoprotein IIb/IIIa inhibitors

# Mechanisms of action of dipyridamole



## OR and 95% CI for the effect of active treatment vs placebo on the principal end-points of the ESPS-2 trial



# Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial

*The ESPRIT Study Group\**

## **Summary**

**Background** Results of trials of aspirin and dipyridamole combined versus aspirin alone for the secondary prevention of vascular events after ischaemic stroke of presumed arterial origin are inconsistent. Our aim was to resolve this uncertainty.

**Methods** We did a randomised controlled trial in which we assigned patients to aspirin (30–325 mg daily) with (n=1363) or without (n=1376) dipyridamole (200 mg twice daily) within 6 months of a transient ischaemic attack or minor stroke of presumed arterial origin. Our primary outcome event was the composite of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication, whichever happened first. Treatment was open, but auditing of outcome events was blinded. Primary analysis was by intention to treat. This study is registered as an International Standard Randomised Controlled Trial (number ISRCTN73824458) and with ClinicalTrials.gov (NCT00161070).

*Lancet 2006; 367: 1665–73*

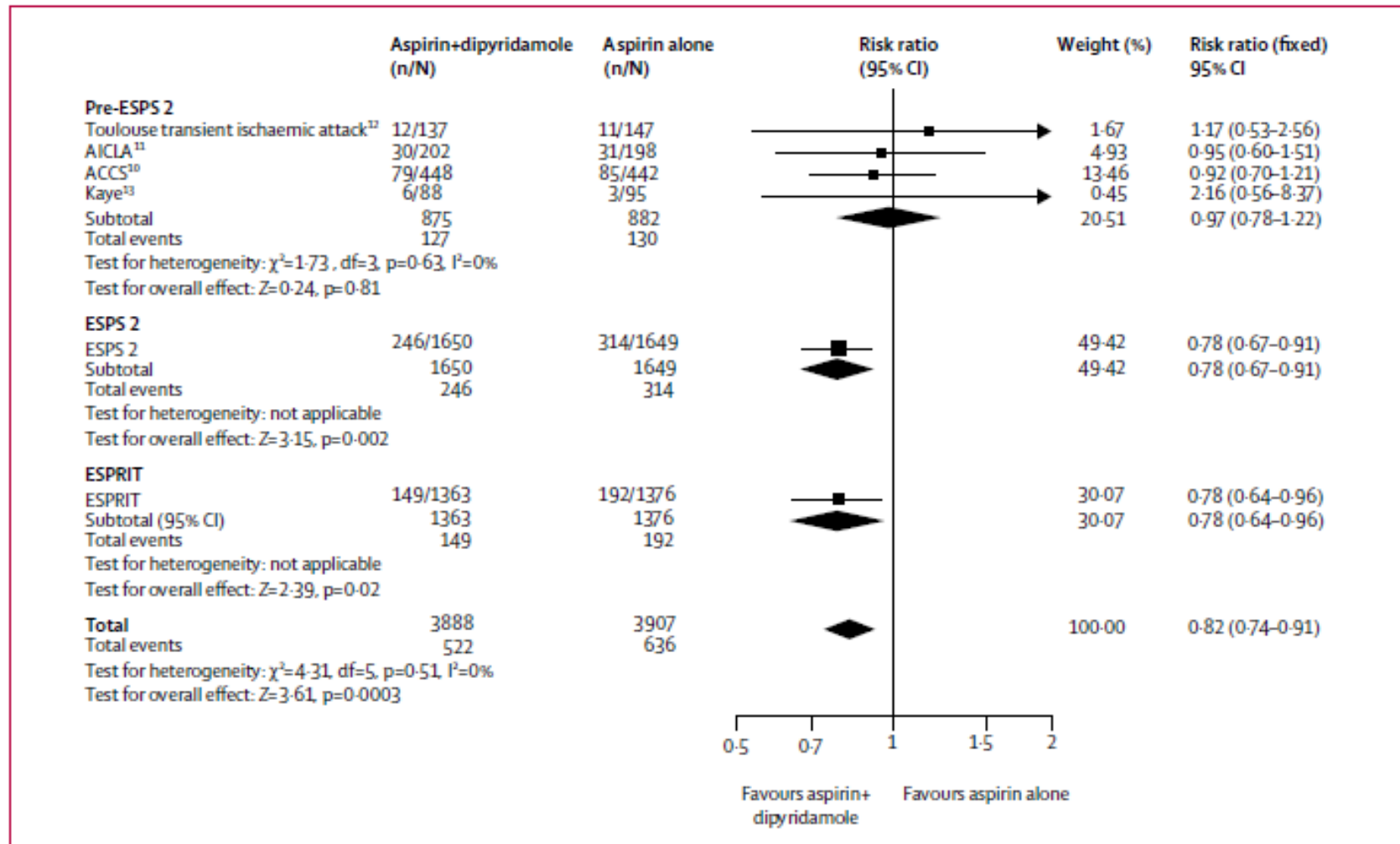
## Occurrence of first outcome events, according to treatment

	Intention to treat		On treatment	
	Aspirin+dipyridamole (n=1363)	Aspirin alone (n=1376)	HR (95% CI)	HR (95% CI)
Person-years of observation*	4498	4495		
Death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, non-fatal major bleeding complication†	173	216	0.80 (0.66-0.98)	0.82 (0.66-1.02)
Death from all causes	93	107	0.88 (0.67-1.17)	0.98 (0.72-1.35)
Death from all vascular causes	44	60	0.75 (0.51-1.10)	0.86 (0.55-1.34)
Death from all vascular causes, non-fatal stroke†	132	171	0.78 (0.62-0.97)	0.83 (0.65-1.06)
Major bleeding complication	35	53	0.67 (0.44-1.03)	0.58 (0.35-0.97)
Non-fatal extracranial	21	32		
Fatal extracranial	2	0		
Non-fatal intracranial	9	17		
Fatal intracranial	3	4		
All major ischaemic events: non-haemorrhagic death from vascular causes, non-fatal ischaemic stroke, non-fatal myocardial infarction†	140	174	0.81 (0.65-1.01)	0.88 (0.69-1.12)
Death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction†	149	192	0.78 (0.63-0.97)	0.82 (0.65-1.04)
First ischaemic stroke	96	116	0.84 (0.64-1.10)	0.91 (0.68-1.22)
First cardiac event	43	60	0.73 (0.49-1.08)	0.87 (0.56-1.37)

\*Years of follow-up until primary outcome event or end of follow-up. †Whichever event occurred first.

Table 3: Occurrence of first outcome events, according to treatment

# Meta-analysis of RCT comparing ASA-Dipyridamole to ASA in Patients with Cerebral Ischemia of Arterial Origin



**Table 1. Aspirin and Dipyridamole: Total Daily Dose and Formulation**

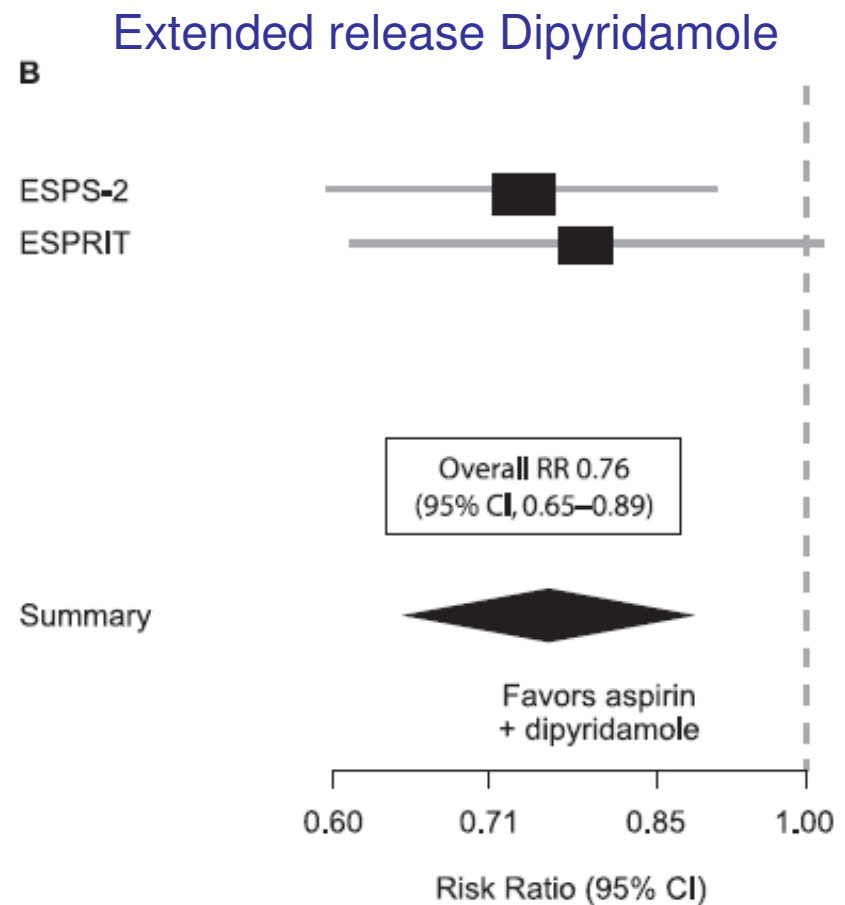
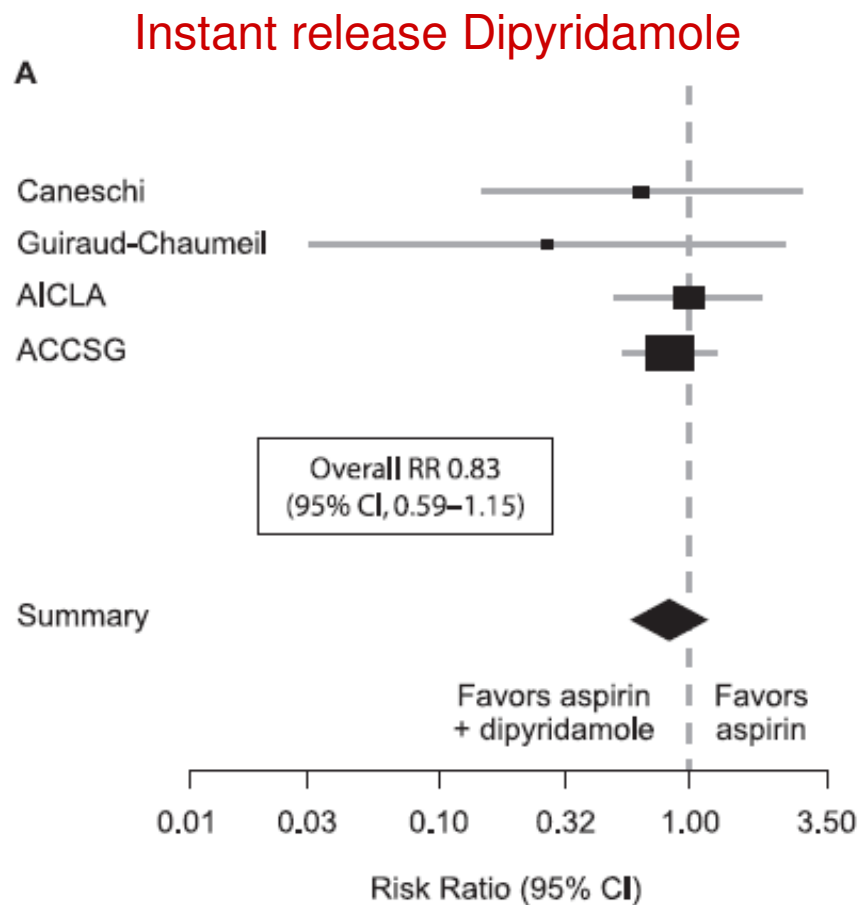
	ASA	ASA+DP
Caneschi et al <sup>20</sup>	300 mg	ASA 150 mg+IR-DP 225 mg
Guiraud-Chaumeil et al <sup>17</sup>	990 mg	ASA 990 mg+IR-DP 150 mg
AICLA <sup>18</sup>	990 mg	ASA 990 mg+IR-DP 225 mg
ACCSG <sup>19</sup>	1300 mg	ASA 1300 mg+IR-DP 300 mg
ESPS-2 <sup>9</sup>	50 mg	ASA 50 mg+ER-DP 400 mg
ESPRIT <sup>10</sup>	75 mg†	ASA 75 mg†+DP‡ 400 mg

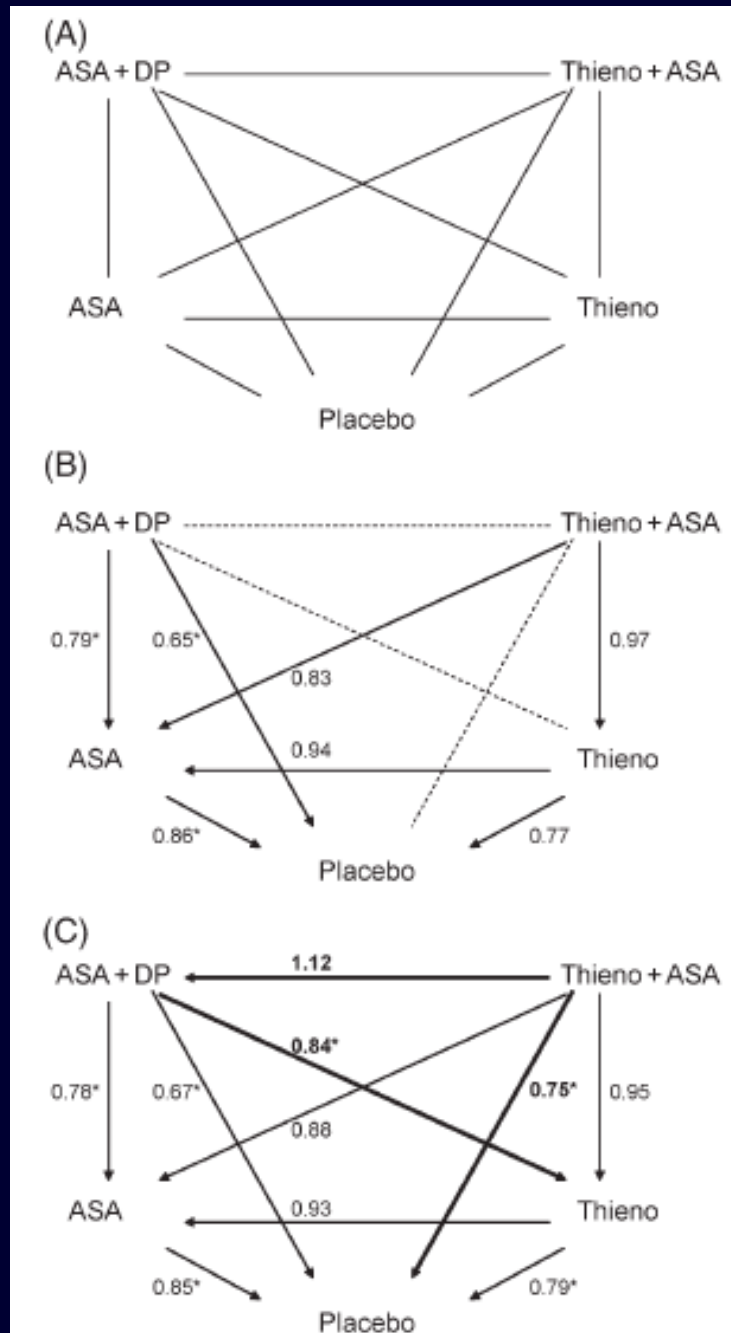
ASA indicates aspirin; IR-DP, immediate-release dipyridamole; ER-DP, extended-release dipyridamole.

†Median dose. Allowable dose of ASA 30–325 mg.

‡83% ER-DP, 17% IR DP.

# Meta-analysis for non-fatal stroke for subsets of trials, based on the type of dipyridamole used





Network of antiplatelet regimens after TIA or stroke

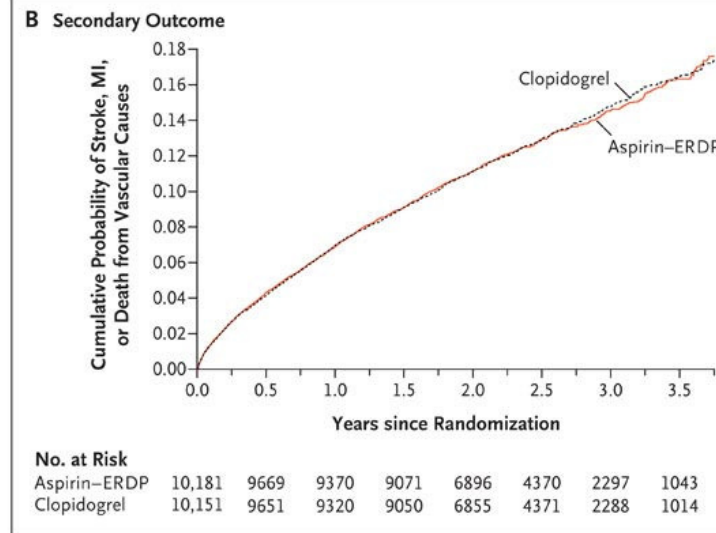
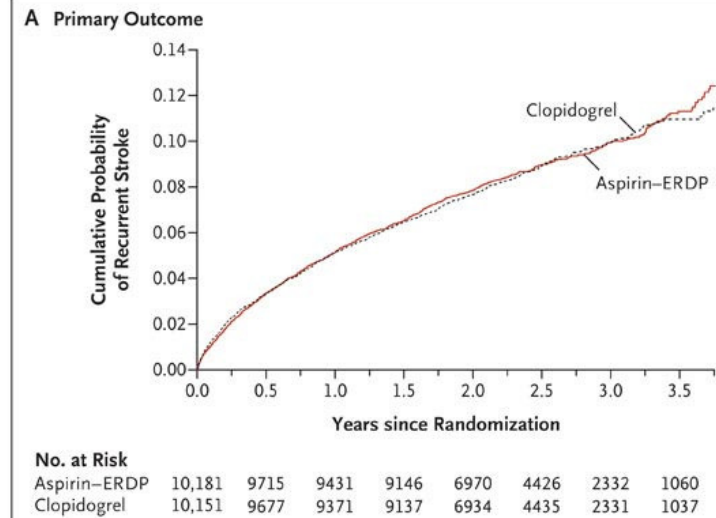
**Table 2** Results for direct comparison and network meta-analysis

	Placebo	ASA	Thieno	ASA + DP	Thieno + ASA
Placebo		0.86 (0.78–0.96)	0.77 (0.58–1.03)	0.65 (0.57–0.76)	–
ASA	0.85 (0.78–0.93)		0.94 (0.85–1.04)	0.79 (0.70–0.90)	0.83 (0.67–1.03)
Thieno	0.79 (0.70–0.89)	0.93 (0.85–1.02)		–	0.97 (0.84–1.10)
ASA + DP	0.67 (0.60–0.75)	0.78 (0.70–0.87)	<b>0.84 (0.73–0.97)</b>		–
Thieno + ASA	0.75 (0.64–0.88)	0.88 (0.77–1.00)	0.95 (0.84–1.07)	1.12 (0.95–1.33)	

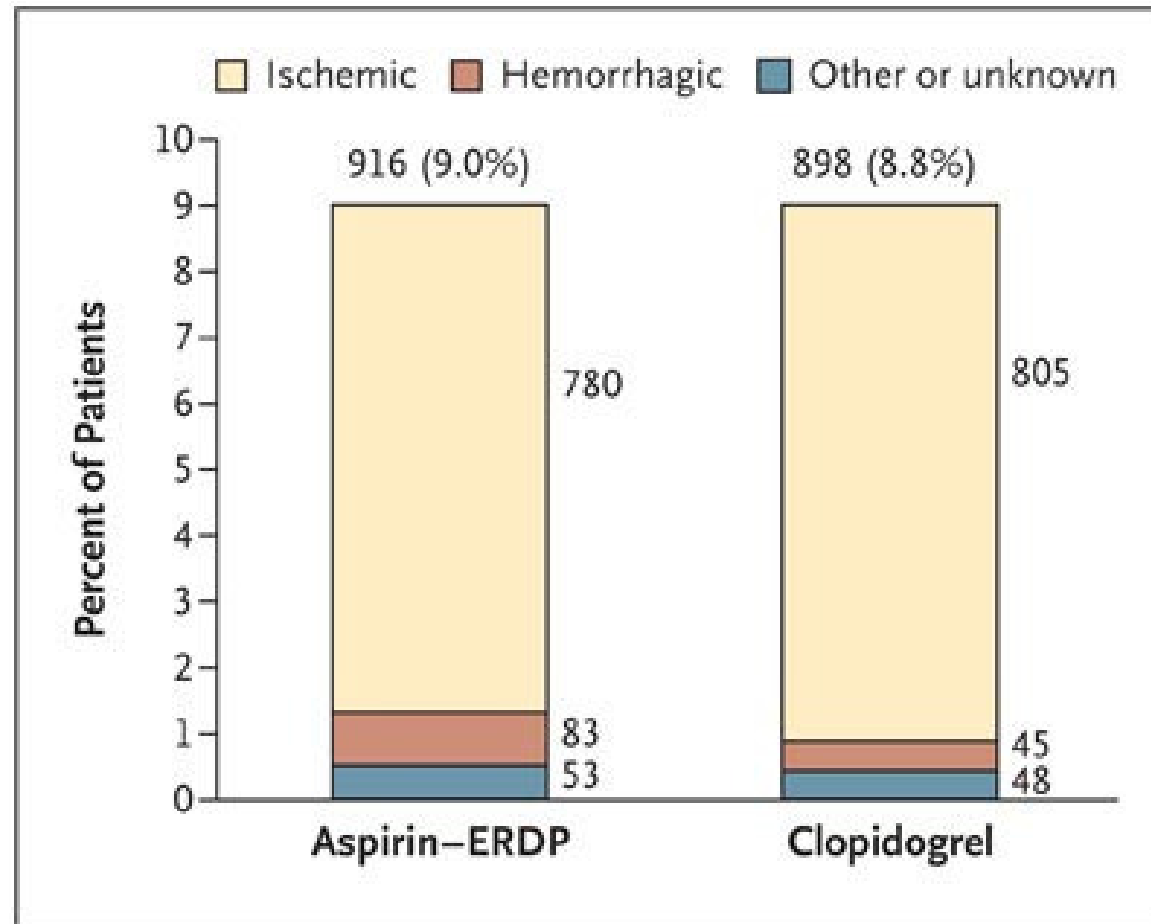
Comparison of results of direct comparisons (upper diagonal part) and the results from a network meta-analysis combining both direct and indirect comparisons (lower diagonal part). Each cell gives an odds ratio (and 95% confidence interval); in the lower diagonal part, this OR compares the row condition with the column condition, and in the upper diagonal part, the OR compares the column condition with the row condition.

'–' pertains to direct comparisons for which no trials are available, italic font refers to indirect comparisons in the network.

# Kaplan-Meier Estimates of the Cumulative Probability of Primary and Secondary Outcomes, According to Treatment Group



## Frequency of Types of Recurrent Stroke among the Study Patients, According to Treatment Group



## Other antiplatelet agents tested in Cerebral Ischemia of Arterial Origin

- Triflusal (COX-1 inhibitor)
- Cilostazol (PD3 inhibitor)
- Terutroban (TP receptor antagonist)

# Guidelines for secondary prevention Cerebral Ischemia of Arterial Origin

- It is recommended that patients not requiring anticoagulation should receive antiplatelet therapy (Class I, Level A).
- Where possible, combined aspirin and dipyridamole, or clopidogrel alone, should be given. Alternatively, aspirin alone, or triflusal alone, may be used (Class I, Level A)

# Guidelines for secondary prevention Cerebral Ischemia of Arterial Origin

- The combination of aspirin and clopidogrel is not recommended in patients with recent ischaemic stroke, except in patients with specific indications (e.g. unstable angina or non-Q-wave MI, or recent stenting); treatment should be given for up to 9 months after the event (Class I, Level A)