Antithrombotic therapy in patients with transient ischemic attack / stroke

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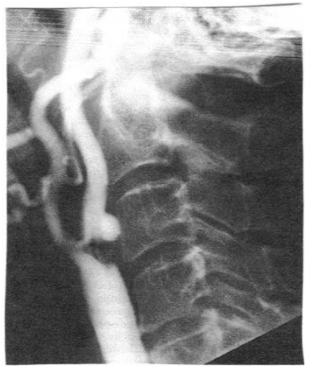
Stroke classification

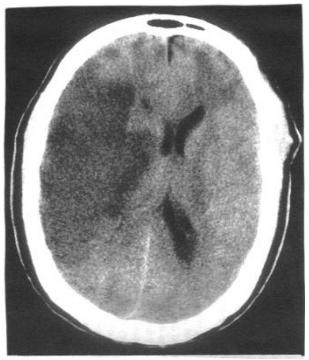
(based on etiology)

Ischemic 80%

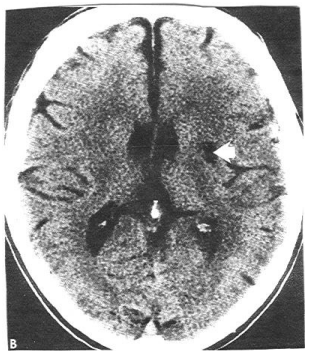
Large vessel Atherosclerosis 15-30%



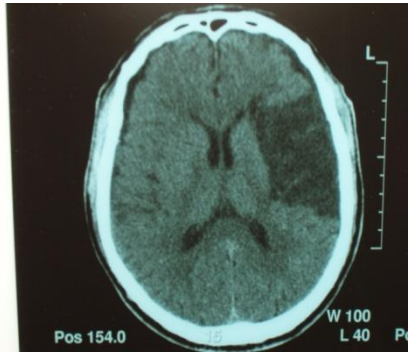
Cardioembolic 18-33%



Small vessel (lacunes) 17-25%

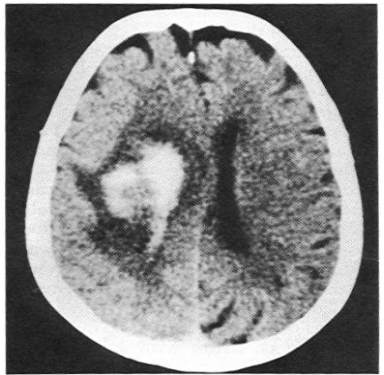


Cryptogenic 12-37%

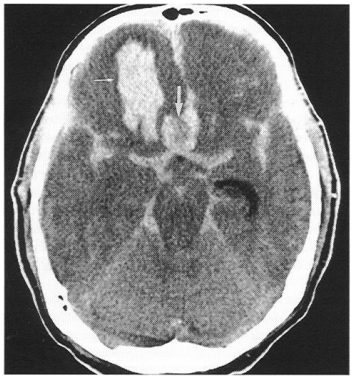


Hemorrhagic 20%

Intracerebral hemorrhage 15%



Subarachnoid hemorrhage 5-7%



Transient ischemic attack (TIA)

- **a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without evidence of acute infarction**

American Heart Association/American Stroke Association: Scientific Statement, *Stroke May 2009*

Pathophysiology of TIAs

1. Large vessel atherosclerosis

low-flow TIAs, true TIAs

2. Embolism

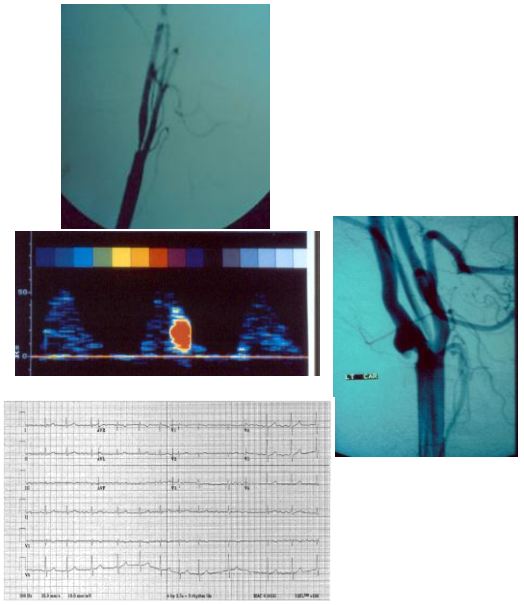
-artery to artery embolism

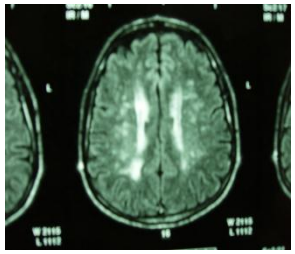
-cardioembolism

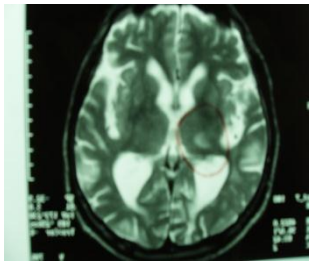
3. Small vessel diseases (Lacunes)

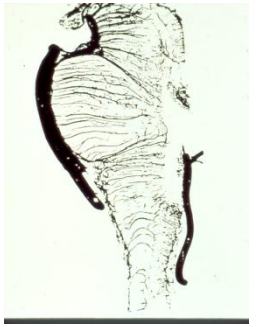
Lipohyalinosis

Microatheroma



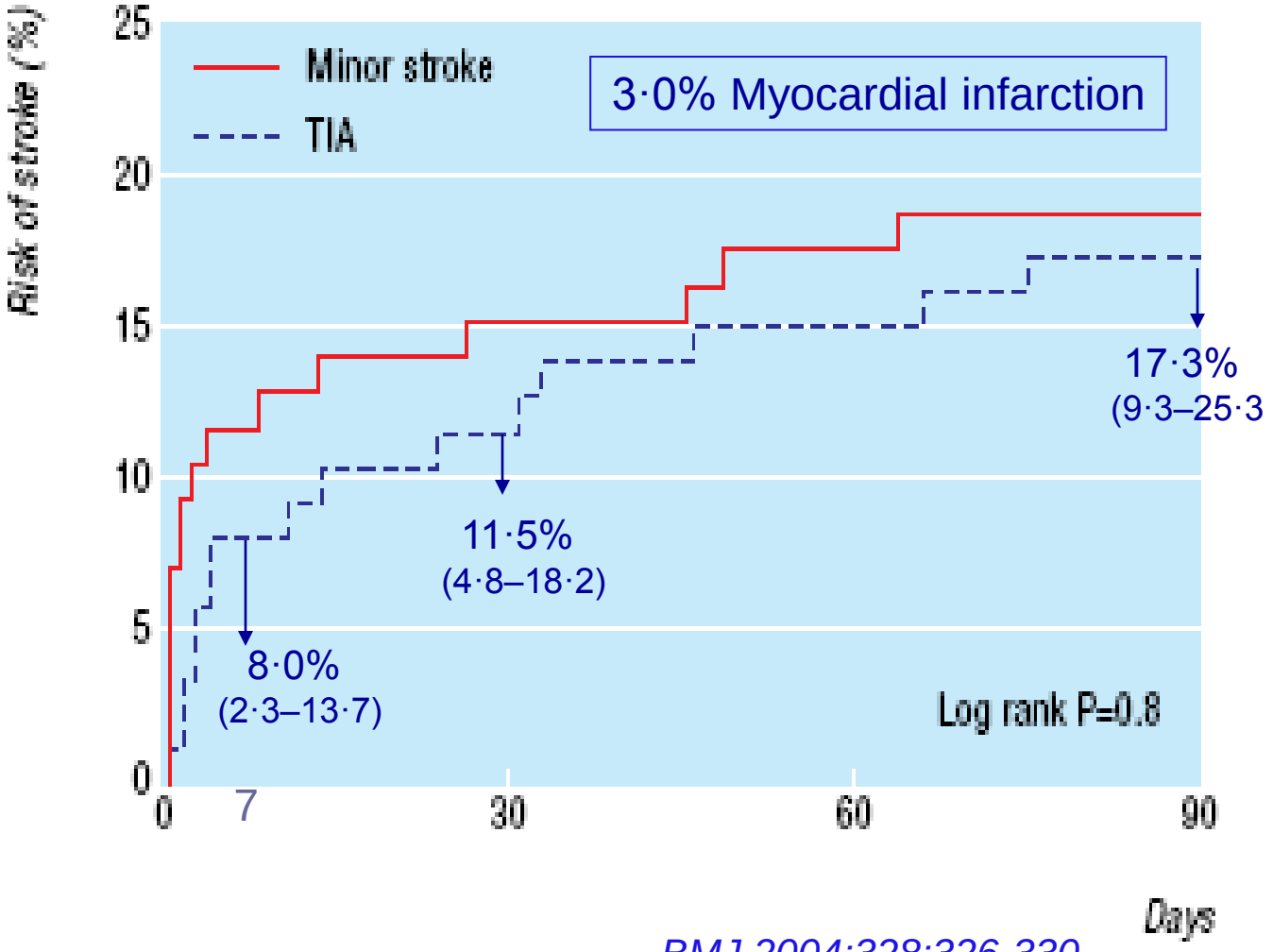






Stroke risk after TIAs or Minor Stroke

Oxford Vascular Study (2002–2003)



BMJ 2004;328;326-330

Antiplatelet therapy in acute stroke (<48h)

Aspirin (160-325 mg)

(IST και CAST trials, 40 000 ασθενείς)

- death and dependency (NNT 70)
- recurrence of stroke (NNT 140)

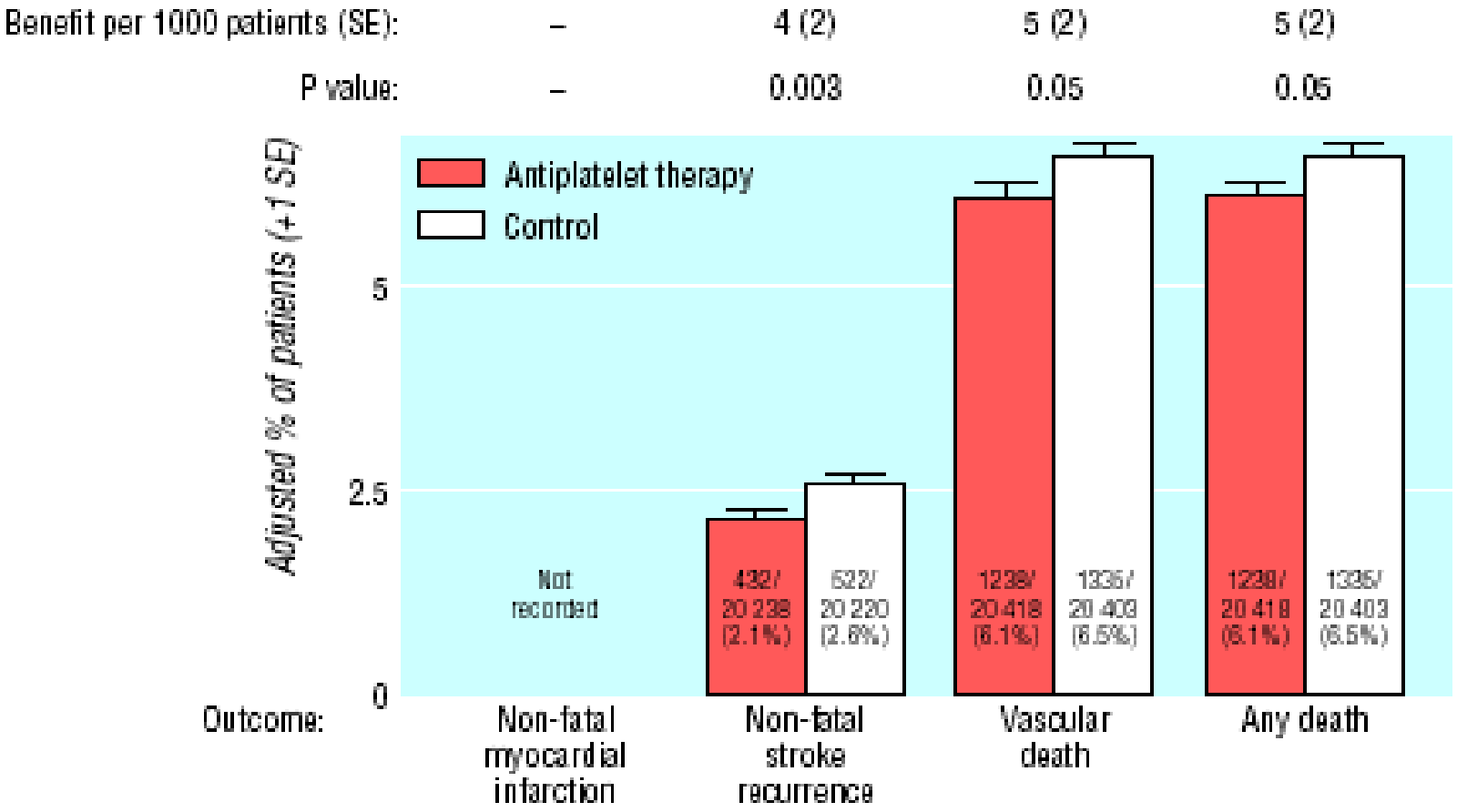
Lancet 1997;349:1569-1581

Antithrombotic Trialists' Collaboration. BMJ 2002; 324: 71–86

Acute Ischemic Stroke

Antithrombotic Trialists' Collaboration

(therapy <3 weeks)



Antithrombotic Trialists' Collaboration, BMJ 2002

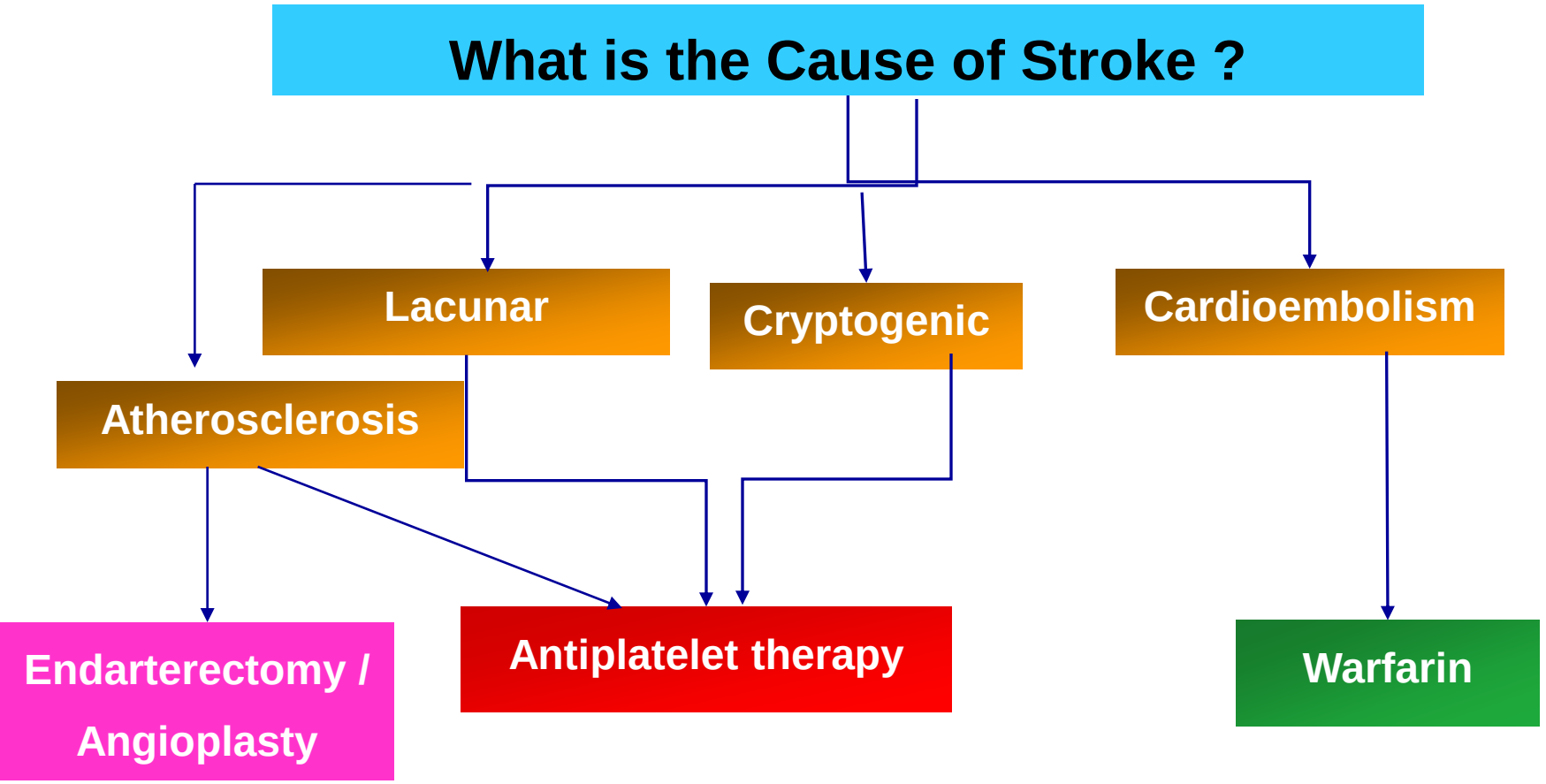
Antiplatelet Therapy in Acute Ischemic Stroke

European Stroke Organization Guidelines 2008

Recommendations

- **Aspirin** (160–325 mg loading dose) should be given within 48 hours after ischaemic stroke (Class I, Level A)
- If thrombolytic therapy is planned or given, aspirin or other antithrombotic therapy should not be initiated within 24 hours (Class IV, GCP)
- The use of other antiplatelet agents (single or combined) is not recommended in the setting of acute ischaemic stroke (Class III, Level C)

Secondary Stroke Prevention



Albers GW, et al. Chest 1998;114:683S-698S.
Barnett HJ, et al. N Engl J Med 1998;339:1415-1425.

Antithrombotic Therapy

Background:

- **Aspirin**
  - **13%** relative risk reduction for stroke after TIA or stroke

    Antithrombotic Trialists' Collaboration. BMJ 2002; 324: 71–86
- **Dipyridamole plus aspirin**
  - Relative risk reduction of vascular death, stroke or myocardial infarction with the combination is significantly greater

    (**RR 0.82;** 95%CI 0.71-0.91) than with aspirin alone

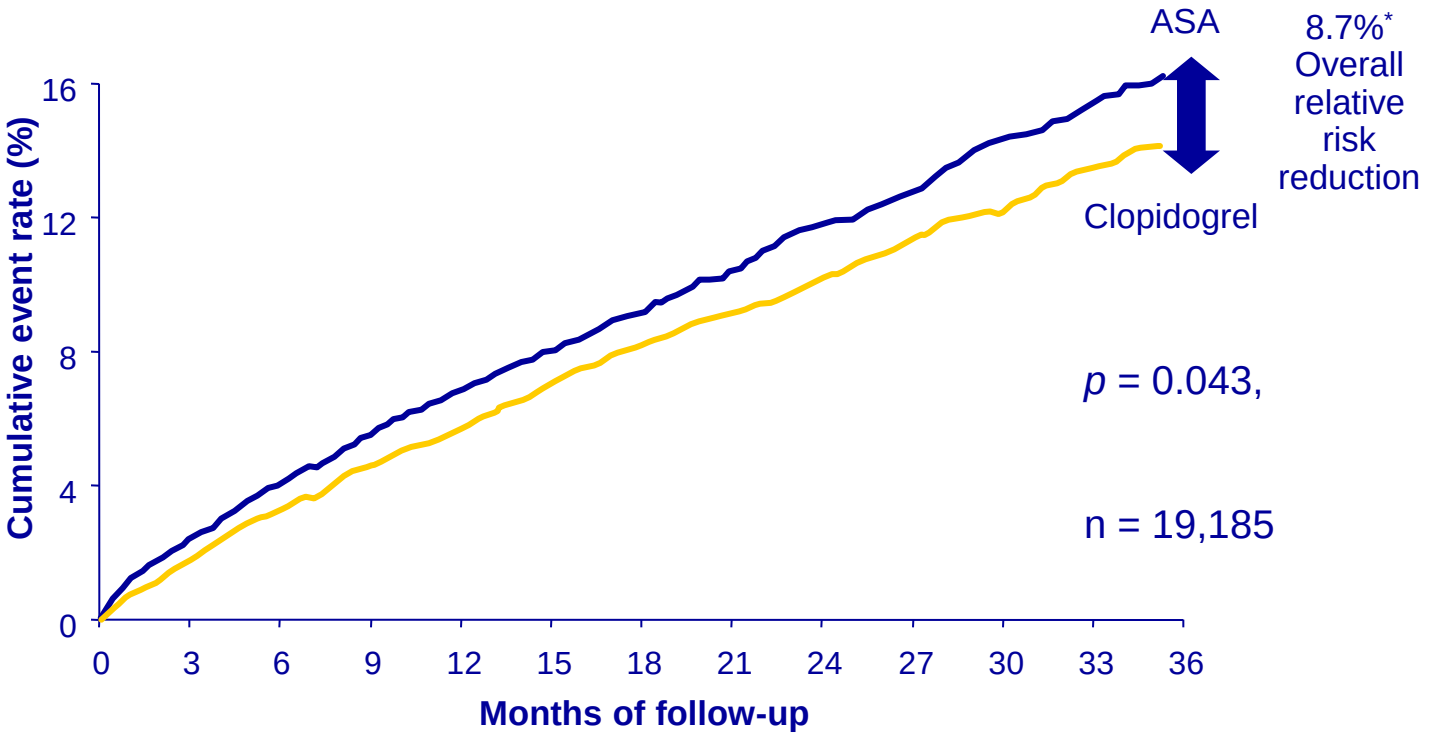
    ESPS2, J Neurol Sci 1996;143:1-13
- **Clopidogrel:**
  - Clopidogrel is slightly but significantly more effective than medium-dose aspirin (**RRR 8.7%,** ARR 0,5%) in preventing vascular events in patients with previous stroke, MI or PAD

    CAPRIE trial Lancet 1996;348:1329-39

1996

CAPRIE Study (Clopidogrel vs Aspirin, 1996)

Cumulative Event Rate
(Myocardial Infarction, Ischemic Stroke or Vascular Death)



***ITT analysis**

CAPRIE Steering Committee. *Lancet* 1996; 348: 1329–39

CAPRIE: similar safety for clopidogrel compared with ASA*

Adverse events†	ASA (n=9,586)	Clopidogrel (n=9,599)	*p*-value
Diarrhoea (severe)[1]	0.11%	0.23%	ns
Gastritis[2]	1.32%	0.75%	<0.001
Gastrointestinal ulcer[2]	1.15%	0.68%	0.001
Gastrointestinal haemorrhage (severe)[1]	0.71%	0.49%	<0.05
Intracranial haemorrhage[1]	0.49%	0.35%	ns
Rash (severe)[1]	0.10%	0.26%	<0.05
Neutropenia[2]	0.17%	0.10%	ns

*Patients with ASA intolerance were excluded
†Clinically severe or resulting in early drug discontinuation

ASA = acetylsalicylic acid
CAPRIE = Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events

1. CAPRIE Steering Committee. *Lancet* 1996; 348: 1329–1339.
2. Harker LA *et al*. *Drug Saf* 1999; 21: 325–335.

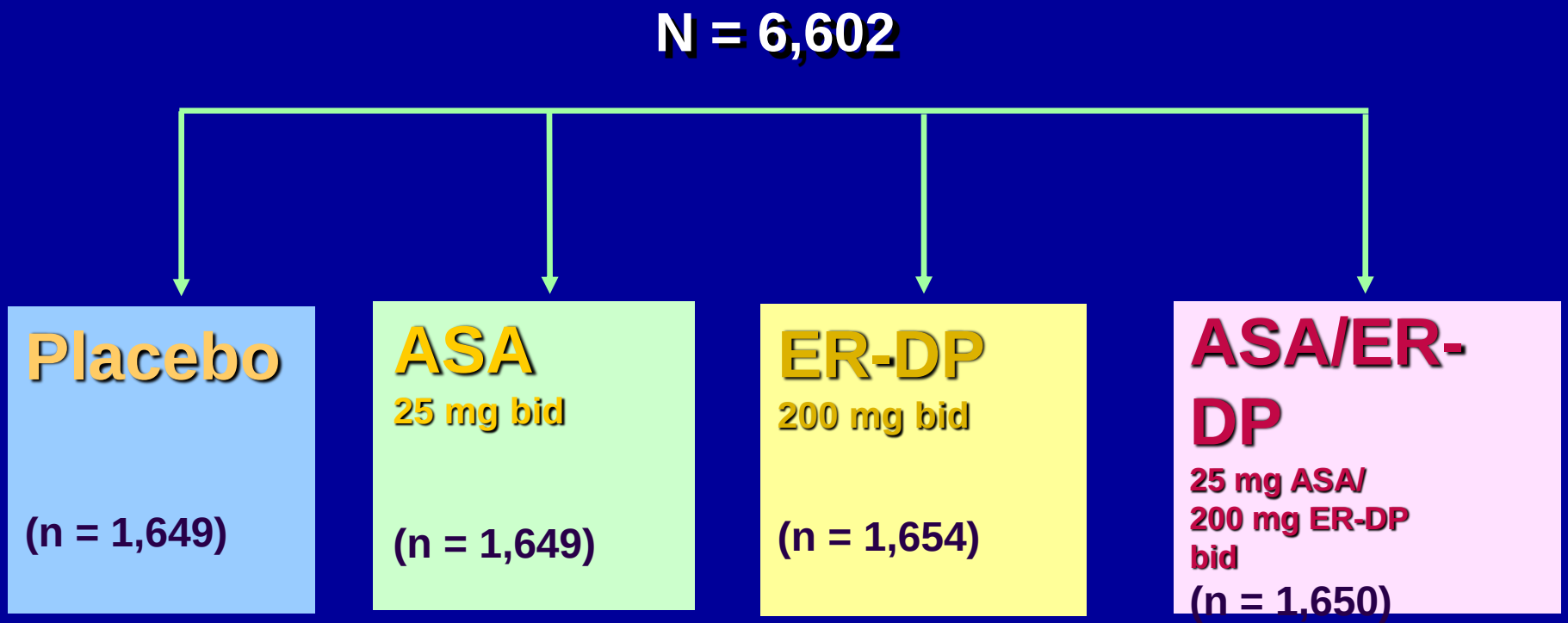
1997

ESPS-2 : (1997)
The Second European Stroke Prevention Study

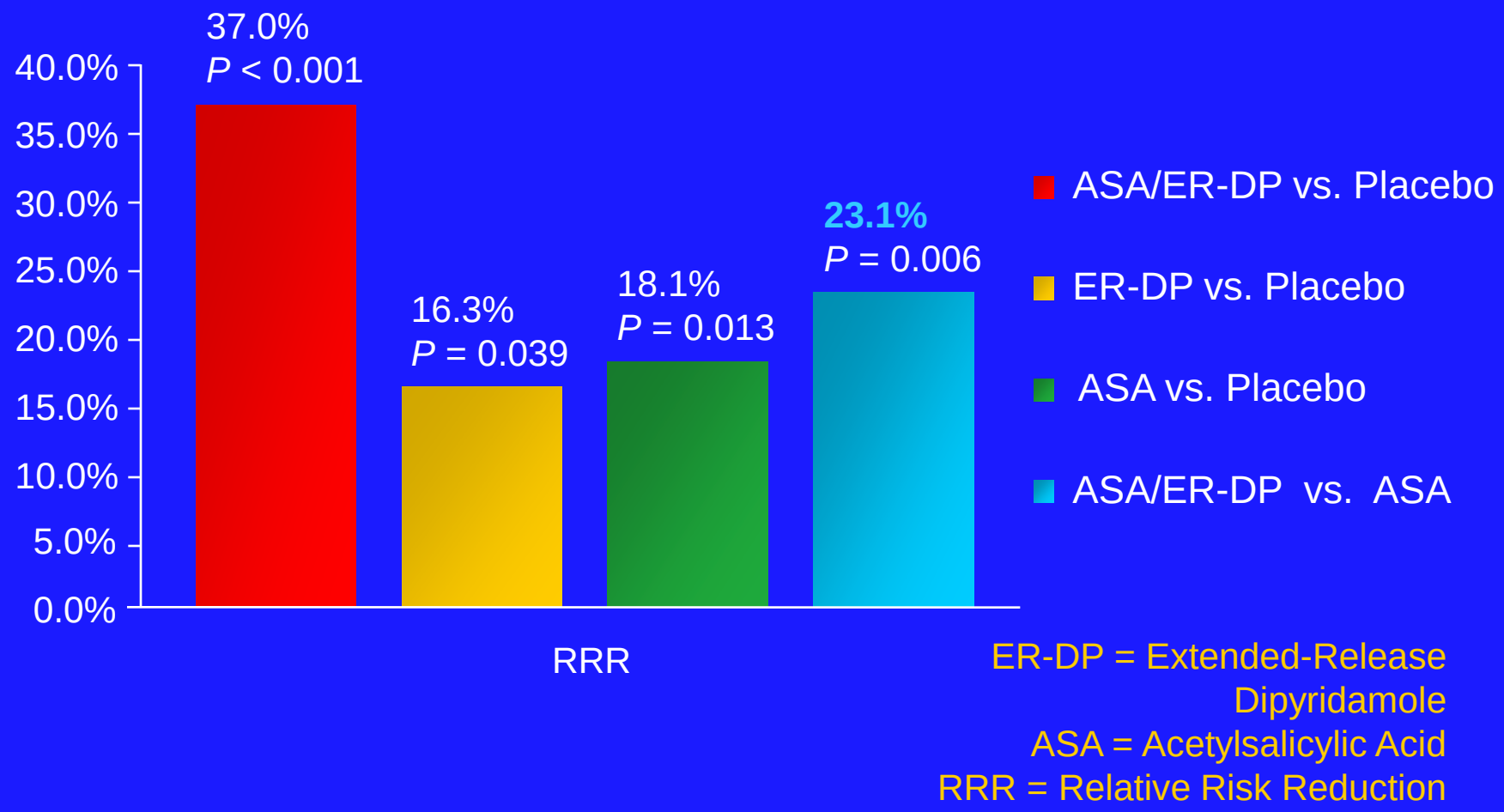
- **Tested efficacy of ASA/ER-DP for secondary stroke prevention**
- **Addressed clinical questions**
  - ***Does low-dose ASA prevent stroke?***
  - ***Does ER-DP prevent stroke?***
  - ***Is ASA/ER-DP superior to ASA alone? To ER-DP alone?***
  - ***Is ASA/ER-DP well tolerated?***

The ESPS-2 Group. *J Neurol Sci*. 1997;151:S3. Diener et al. *J Neurol Sci*. 1996;143:1.

ESPS-2: Treatment Arms



ESPS 2: Effects on Stroke—Relative Risk Reduction
(Pairwise Comparisons)



ER-DP = Extended-Release Dipyridamole
ASA = Acetylsalicylic Acid
RRR = Relative Risk Reduction

[15] **ESPS 2 Group. *J Neurol Sci.* 1997**; 151(suppl):S1-S77.

ESPS 2: Adverse Events

(Percent within each group)

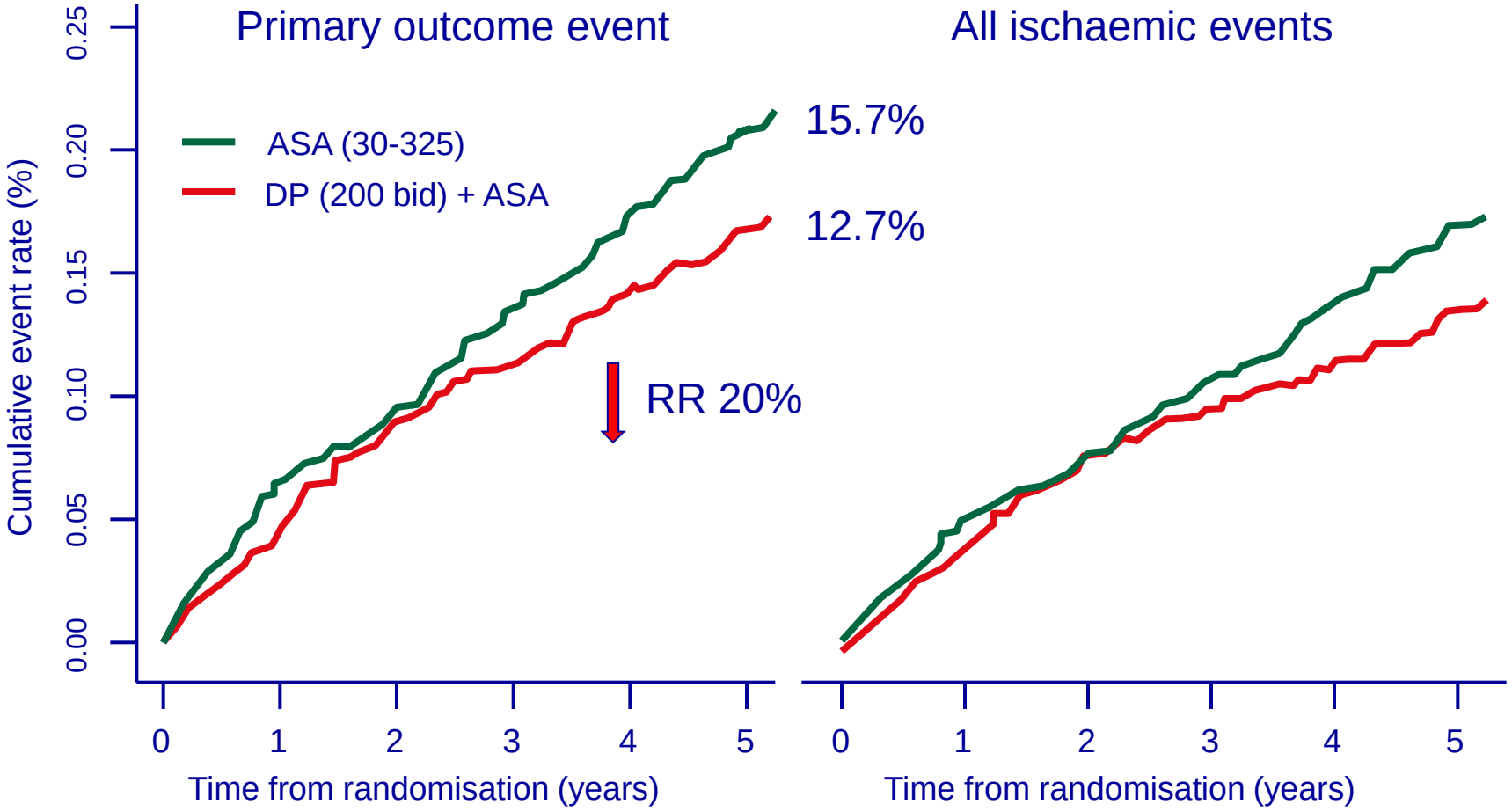
Treatment group	Dyspepsia	GI Bleeding	Headache
ASA/ER-DP	18.4	4.1*	39.2
Placebo	16.7	2.1	32.9
ASA	18.1	3.2	33.8
ER-DP	17.4	2.2	38.3

*Not statistically different from aspirin

ER-DP = Extended-Release Dipyridamole
ASA = Acetylsalicylic Acid

[19] Aggrenox® (aspirin/extended-release dipyridamole) 25 mg/200 mg capsules product information, Boehringer Ingelheim Pharmaceuticals, Inc.

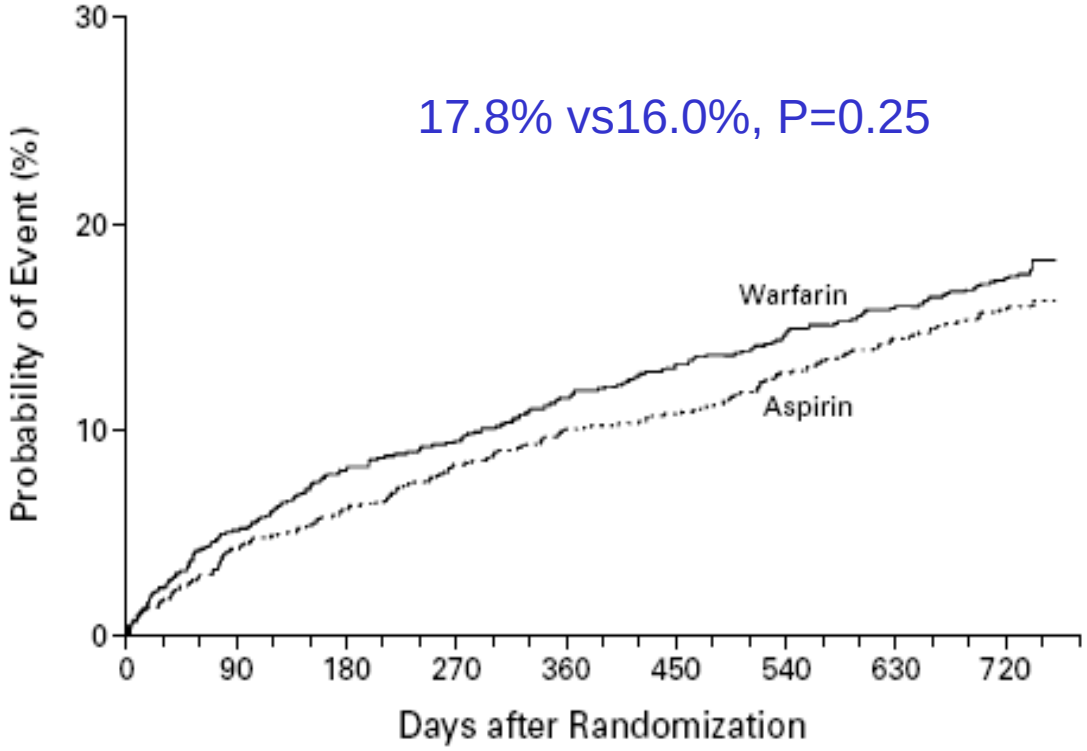
ESPRIT –
The European/Australasian Stroke Prevention in Reversible Ischaemia Trial



ESPRIT Study Group. *Lancet* 2006; 367 (9523): 1665–1673.

2001

A COMPARISON OF WARFARIN AND ASPIRIN FOR THE PREVENTION OF RECURRENT ISCHEMIC STROKE (WARRS study-2001)



No. at Risk

Warfarin	1103	1047	1013	998	972	956	939	924	885
Aspirin	1103	1057	1032	1004	984	974	951	932	900

N Engl J Med 2001;345:1444-51

2003

Comparison of Triflusal and Aspirin for Prevention of Vascular Events in Patients After Cerebral Infarction

The TACIP Study: A Randomized, Double-Blind, Multicenter Trial

Jordi Matías-Guiu, MD; José M. Ferro, MD; José Alvarez-Sabín, MD; Ferran Torres, MD; M. Dolores Jiménez, MD; Aida Lago, MD; Teresa Melo, MD; for the TACIP Investigators

Background and Purpose—The efficacy of the antiplatelet agent triflusal for prevention of vascular events after stroke has been reported in a pilot study. However, there is a need to confirm those results in a larger study.

Methods—We performed a randomized, double-blind, multicenter study to test the efficacy of triflusal (600 mg/d) versus aspirin (325 mg/d) for prevention of vascular events in patients with stroke or transient ischemic attack (Triflusal versus Aspirin in Cerebral Infarction Prevention [TACIP]). We assessed a combined end point (incidence of nonfatal ischemic stroke, nonfatal acute myocardial infarction, or vascular death) as well as the incidence of these events separately and the incidence of major hemorrhage.

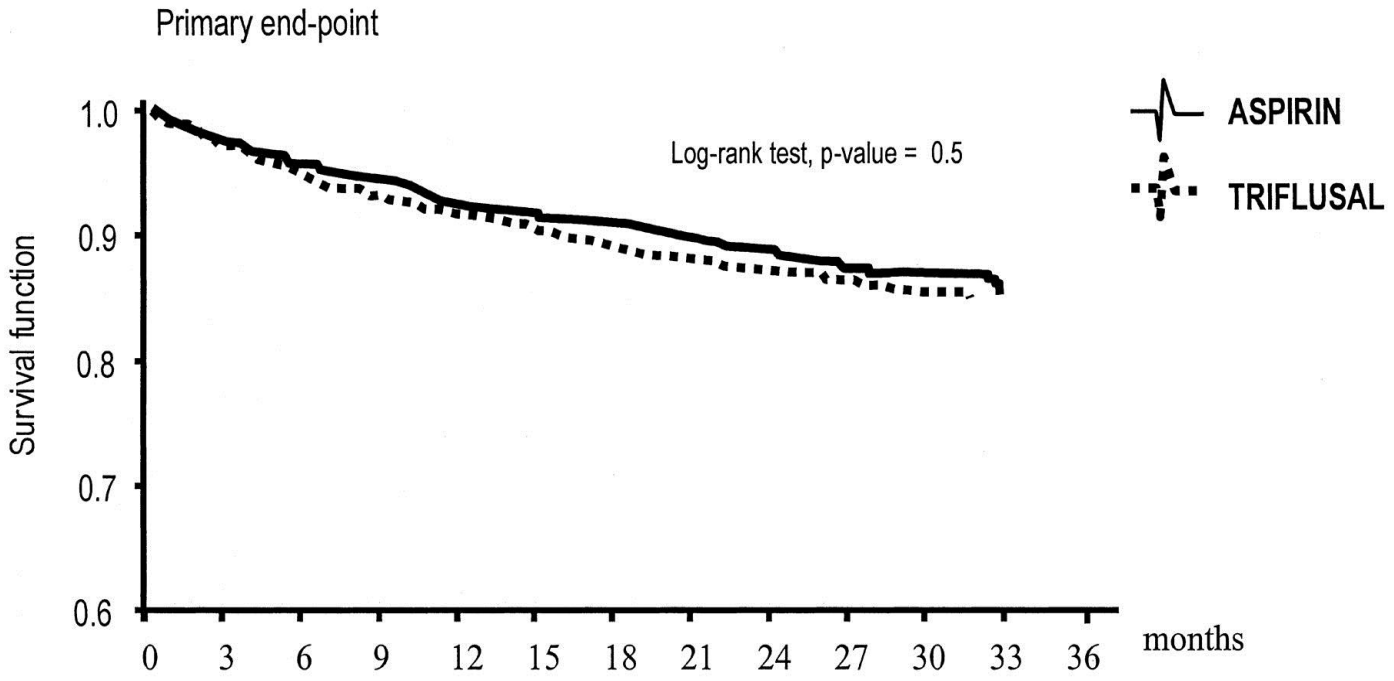
Results—Of 2113 patients, 1058 received triflusal and 1055 aspirin. The mean follow-up period was 30.1 months. The incidence of combined end point (13.1% for triflusal, 12.4% for aspirin) as well the survival analysis (hazard ratio [HR] for triflusal versus aspirin, 1.09; 95% CI, 0.85 to 1.38) showed no differences between groups. The incidence of nonfatal stroke (HR, 1.09; 95% CI, 0.82 to 1.44), nonfatal acute myocardial infarction (HR, 0.95; 95% CI, 0.46 to 1.98,) and vascular death (HR, 1.22; 95% CI, 0.75 to 1.96) was also similar. A significantly higher incidence of major hemorrhages in the aspirin group was recorded (HR, 0.48; 95% CI, 0.28 to 0.82). The overall incidence of hemorrhage was significantly lower in the triflusal group (16.7% versus 25.2%) (odds ratio, 0.76; 95% CI, 0.67 to 0.86; $P<0.001$).

Conclusions—This study failed to show significantly superior efficacy of triflusal over aspirin in the long-term prevention of vascular events after stroke, but triflusal was associated with a significantly lower rate of hemorrhagic complications.

(*Stroke*. 2003;34:840-848.)

Survival analysis of primary end point (nonfatal ischemic stroke, nonfatal AMI, vascular death)

The TACIP study

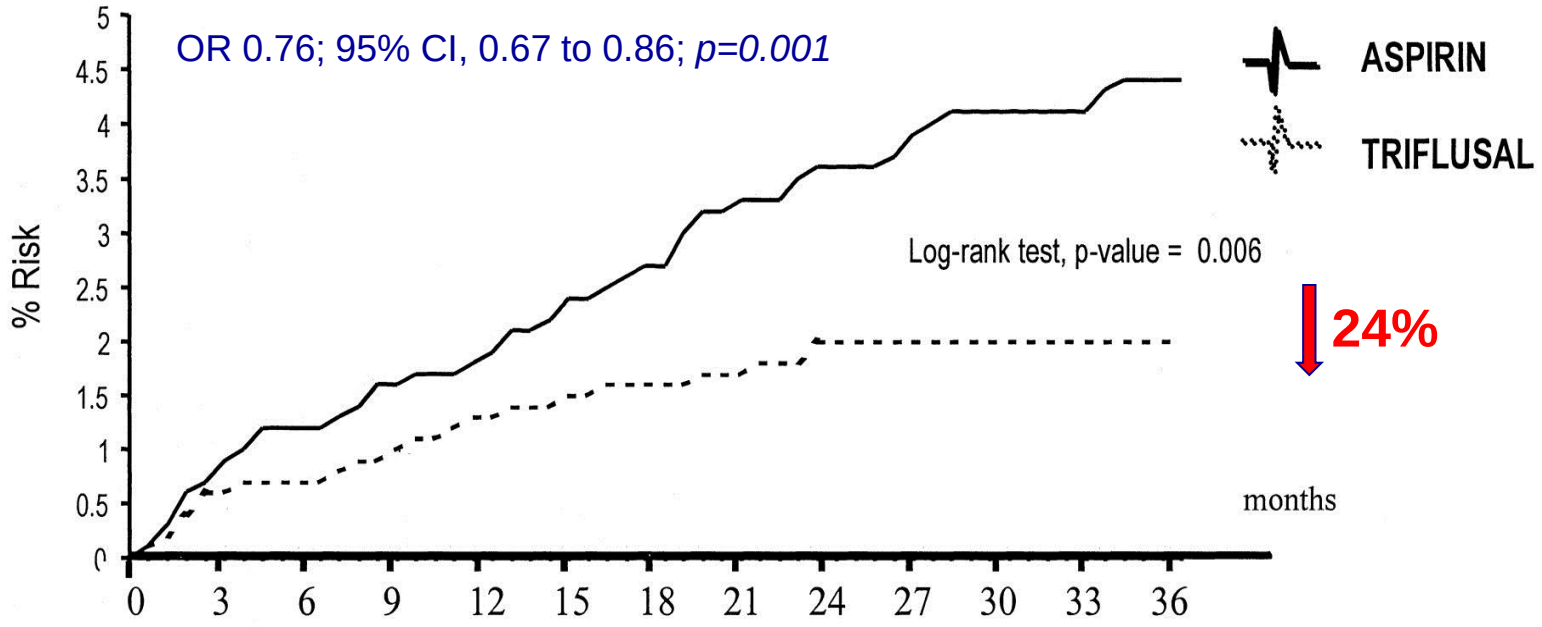


Patients at risk:

Time	Baseline	6 months	12 months	18 months	24 months	30 months	36 months
Aspirin	1052	1007	974	948	915	698	301
Triflusal	1055	996	960	931	904	624	300

Matias-Guiu, J. et al. Stroke 2003;34:840-848

Cumulative risk of any cerebral or major systemic Hemorrhages (The TACIP study)



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Matias-Guiu, J. et al. Stroke 2003;34:840-848

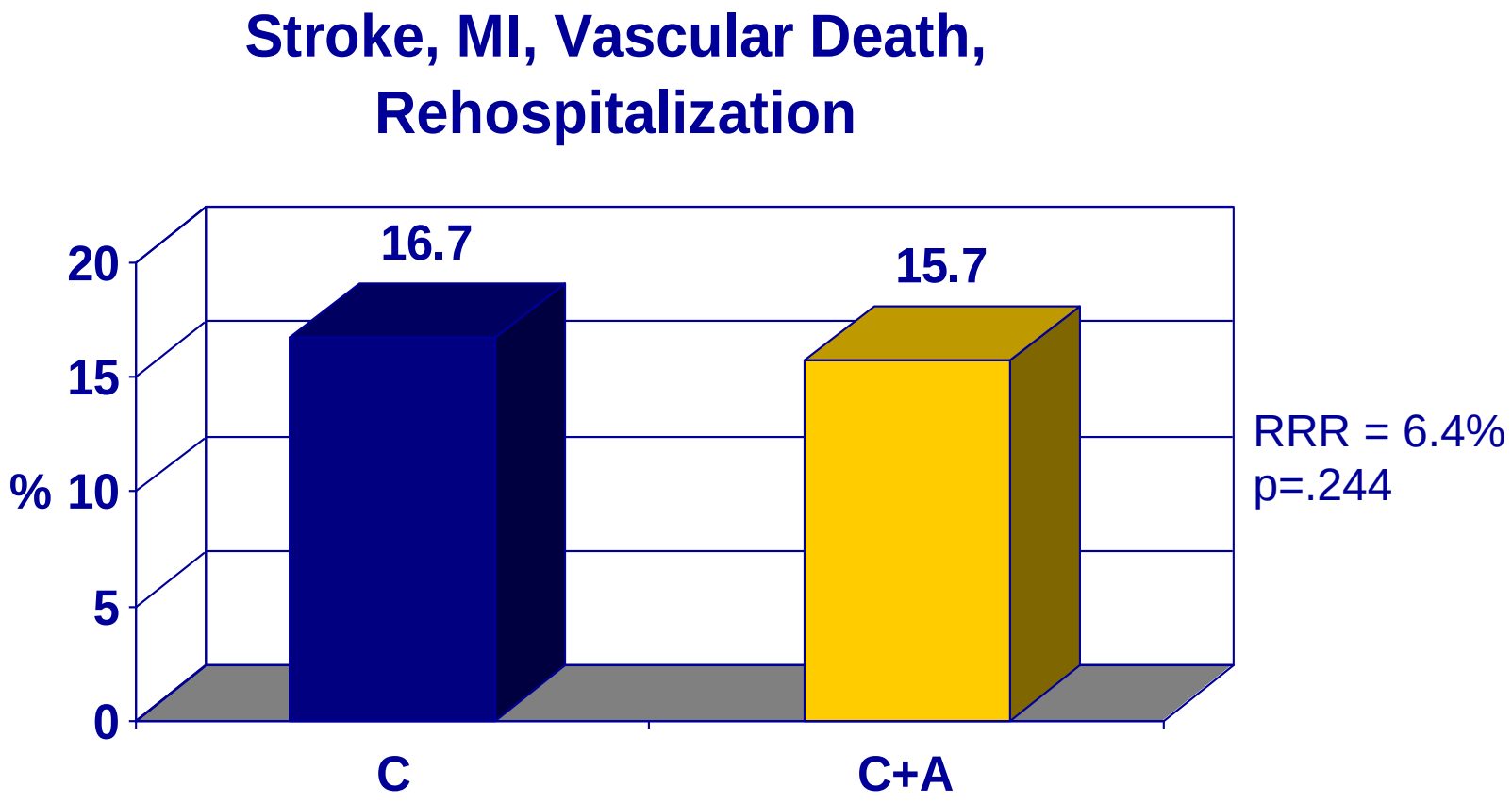
2004

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

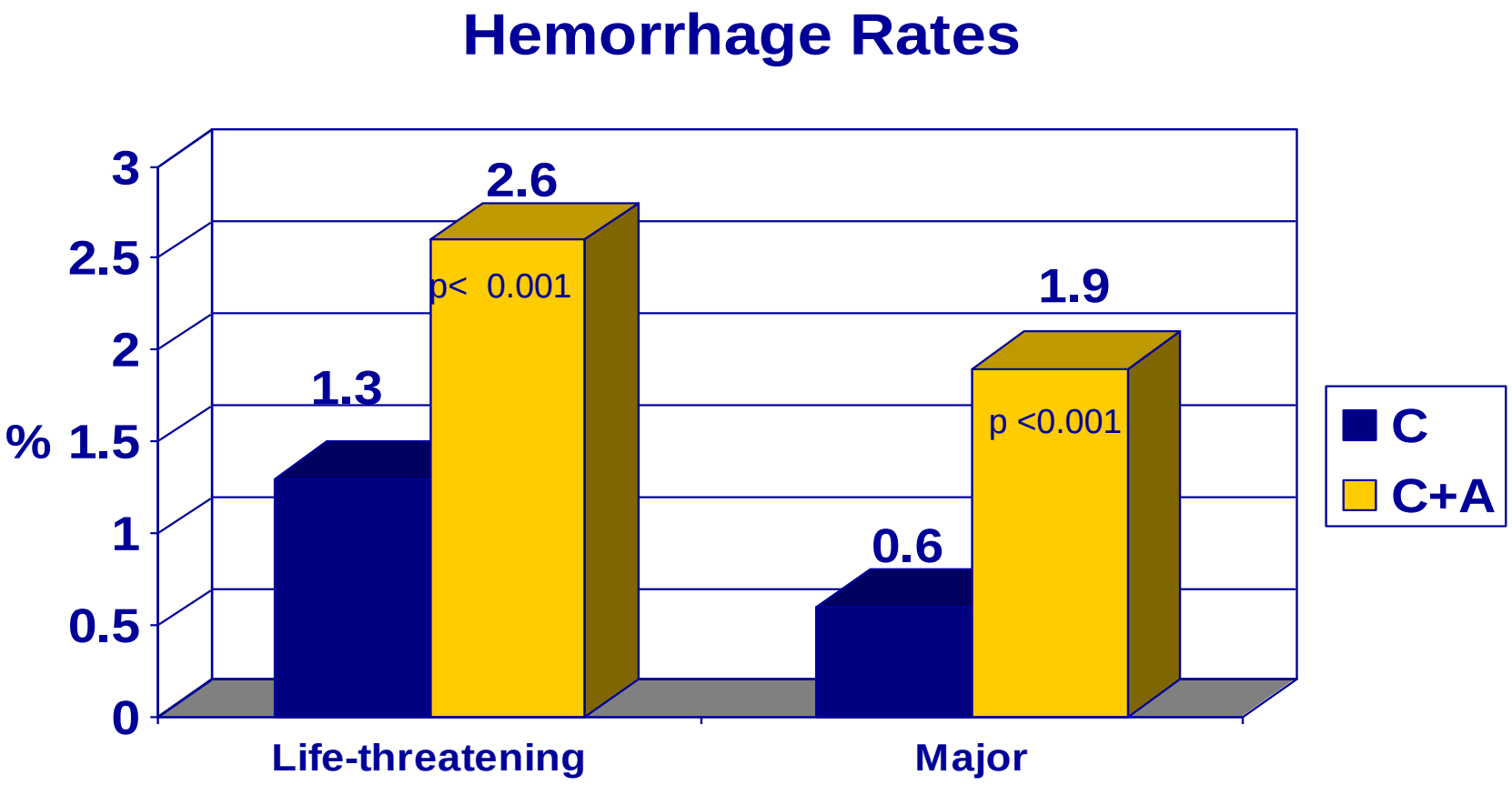
Hans-Christoph Diener, Julien Bogousslavsky, Lawrence M Brass, Claudio Cimminiello, Laszlo Csiba, Markku Kaste, Didier Leys, Jordi Matias-Guiu, Hans-Jürgen Rupprecht, on behalf of the MATCH investigators*

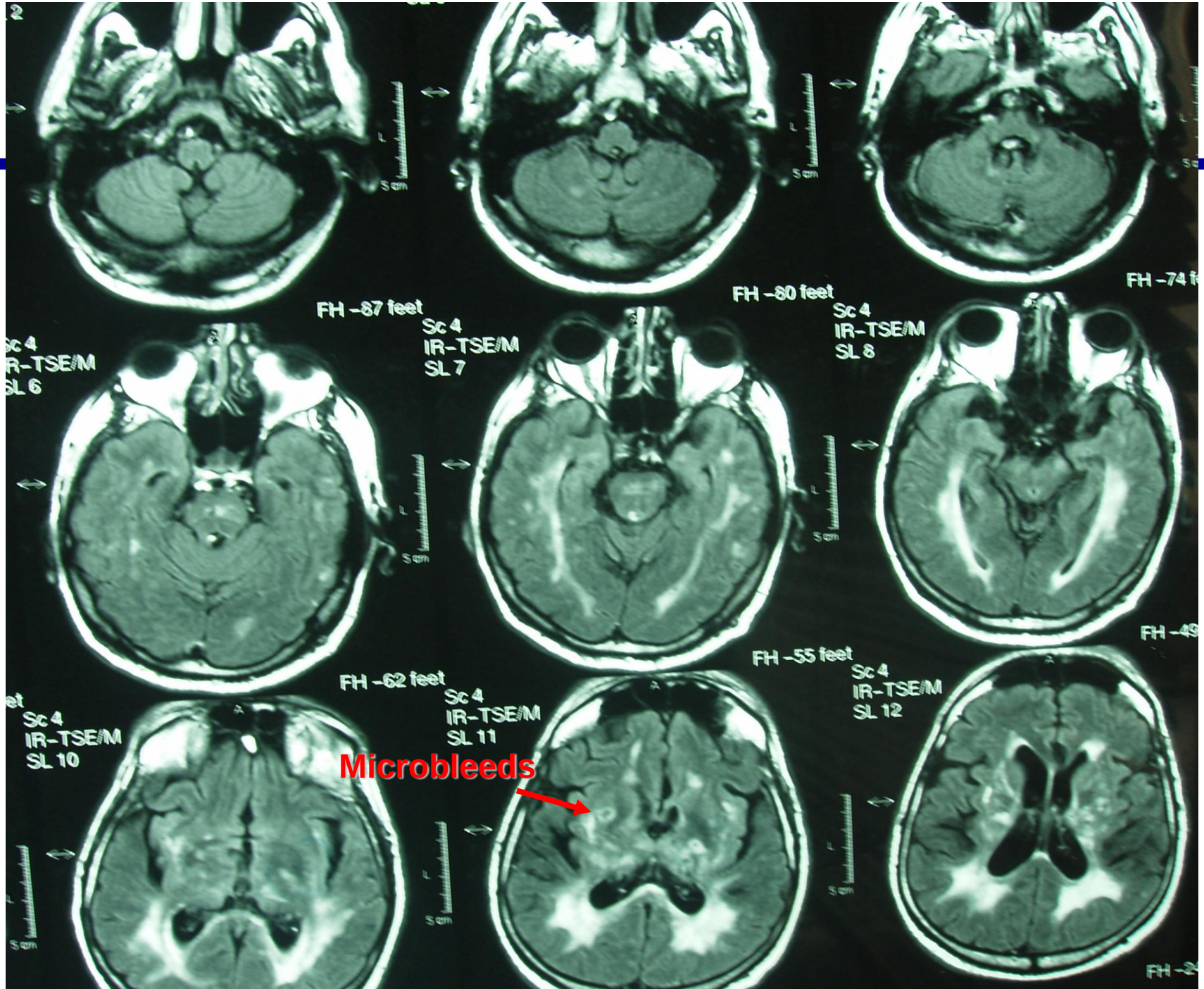
Lancet 2004; 364: 331–37

MATCH trial
Primary Endpoint



MATCH trial

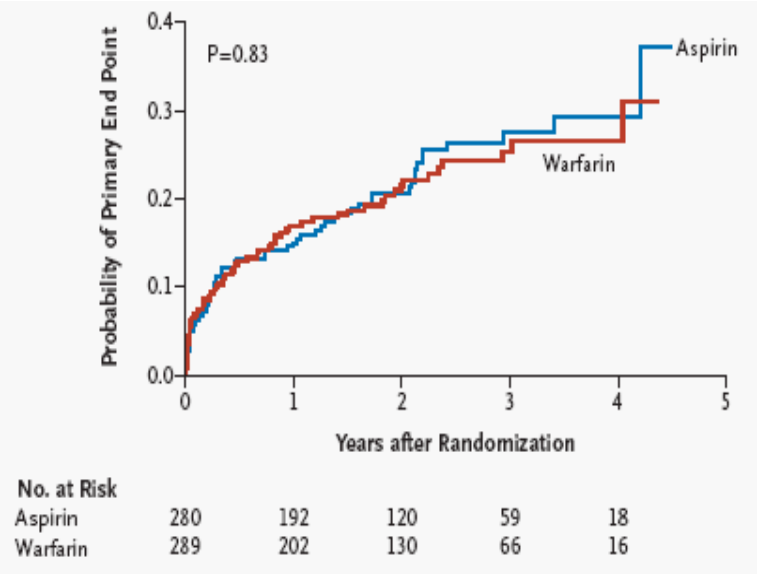

Hemorrhage Rates
3
2.5
2
1.5
1
0.5
0
%
2.6
1.3
1.9
0.6
p< 0.001
p <0.001
Life-threatening
Major
C
C+A

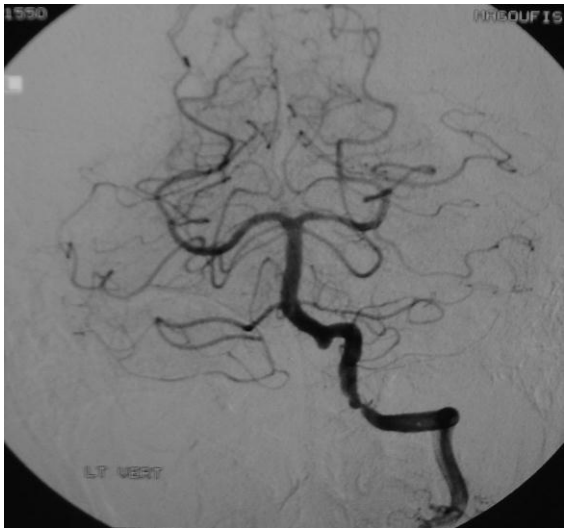

FH -87 feet
Sc 4
IR-TSE/M
SL 7
FH -80 feet
Sc 4
IR-TSE/M
SL 8
FH -74 f
Sc 4
IR-TSE/M
SL 6
FH -62 feet
Sc 4
IR-TSE/M
SL 11
FH -55 feet
Sc 4
IR-TSE/M
SL 12
Sc 4
IR-TSE/M
SL 10
Microbleeds

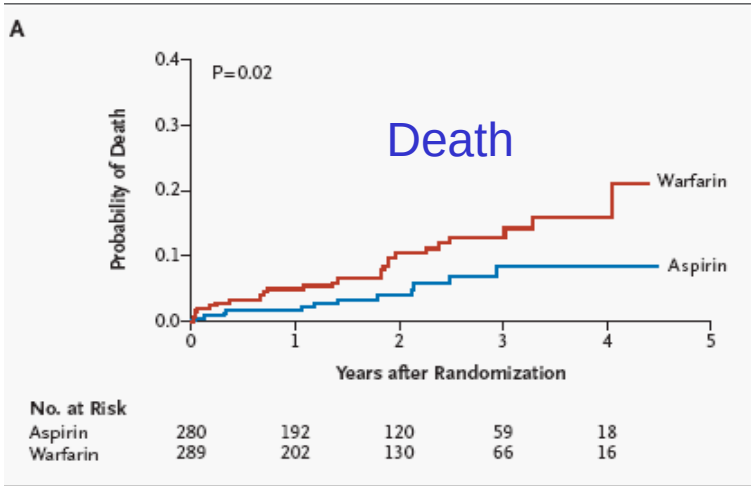
2005

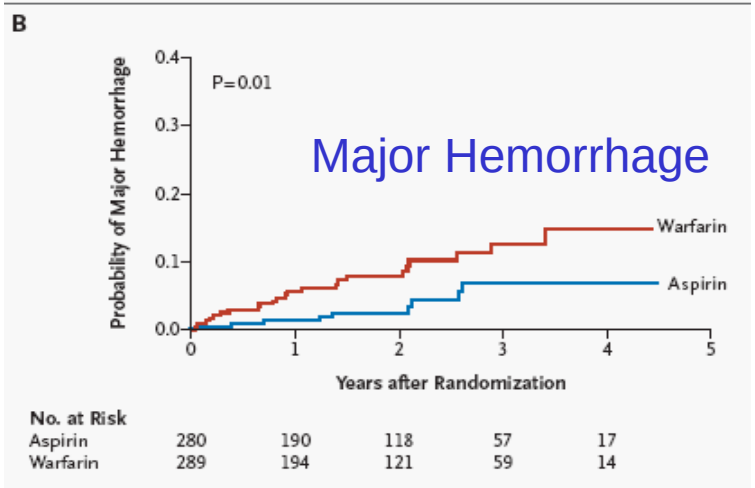
Comparison of Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis

WASID study (2005)





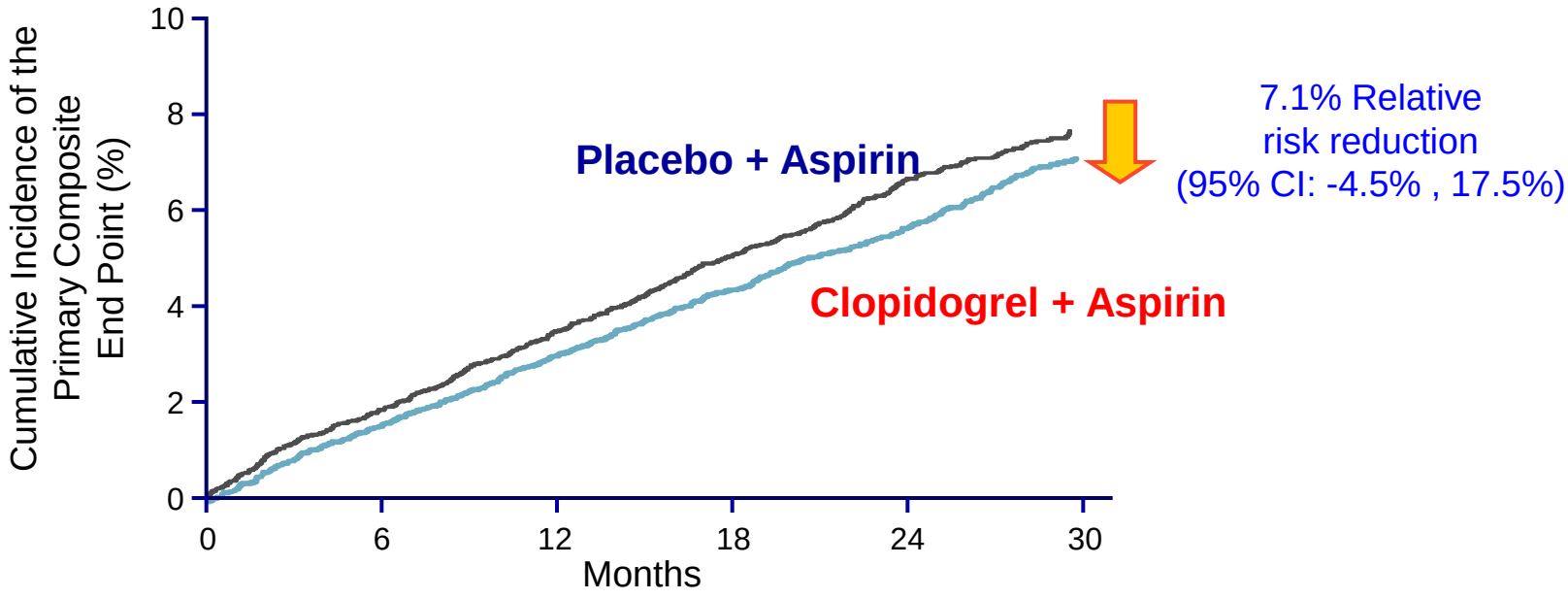




N Engl J Med 2005;352:1305-16

2006

CHARISMA 2006: Cumulative Incidence of the Primary Efficacy End Point

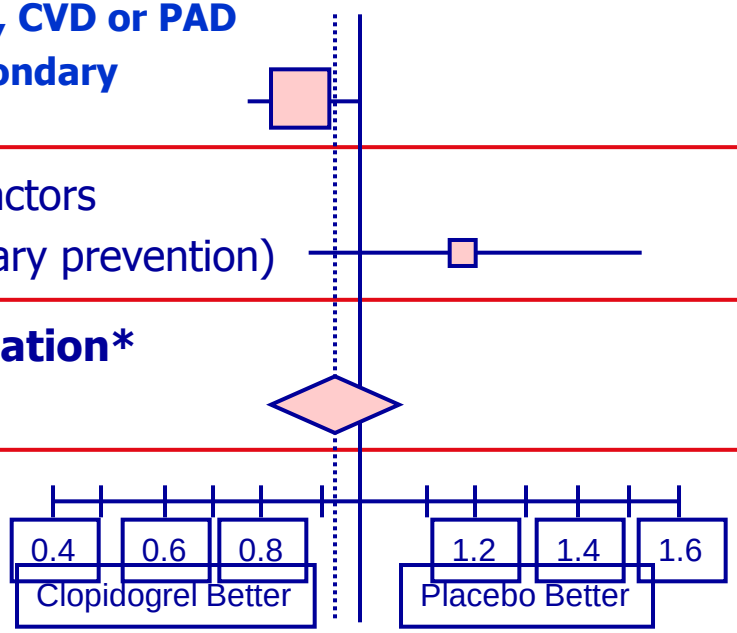


Bhatt et al. *N Engl J Med* 2006; 354.

CHARISMA Primary Efficacy Results

(MI/Stroke/CV Death)* by Pre-Specified Entry Category

Population	N	RR (95% CI)	*p*-Value
Qualifying CAD, CVD or PAD n=12,153 (secondary prevention)	**0.88**	**(0.77, 0.998)**	**0.046**
Multiple Risk Factors n=3,284 (primary prevention)	1.20	(0.91, 1.59)	0.20
Overall Population* n=15,603	**0.93**	**(0.83, 1,05)**	**0.22**



A statistical test for interaction showed marginally significant heterogeneity (p=0.045) in treatment response for these pre-specified subgroups of patients

Bhatt et al. The Main Results of the CHARISMA Trial.
Oral Presentation 402–410. ACC 2006. March 12th, 2006.
Bhatt et al. *N Engl J Med* 2006; 354.

2008

PROFESS

Aspirin and Extended-Release Dipyridamole versus Clopidogrel for Recurrent Stroke (2008)

2x2 factorial design involving 20,333 stroke patients, 2,5 y FU

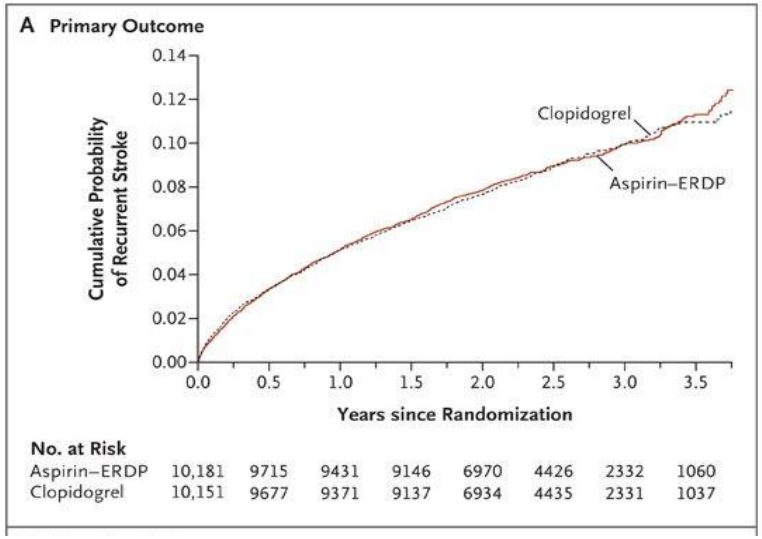
	ER-DP + ASA (400 mg/50 mg)	**Clopidogrel*** (75 mg)
Telmisartan (80 mg)	**ER-DP + ASA + Telmisartan** **(5,000 pts)**	**Clopidogrel* + Telmisartan** **(5,000 pts)**
Placebo	**ER-DP + ASA + Placebo** **(5,000 pts)**	**Clopidogrel + Placebo** **(5,000 pts)**

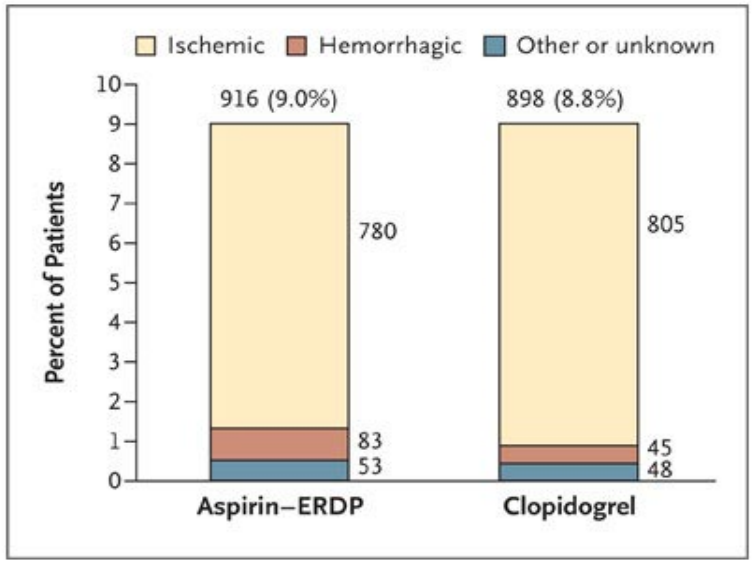
* Initially compared with ASA plus clopidogrel

Diener HC, Sacco R, Yusuf S. *Cerebrovasc Dis.* 2007; 23: 368–380.

PROFESS

Aspirin and Extended-Release Dipyridamole versus Clopidogrel for Recurrent Stroke (2008)





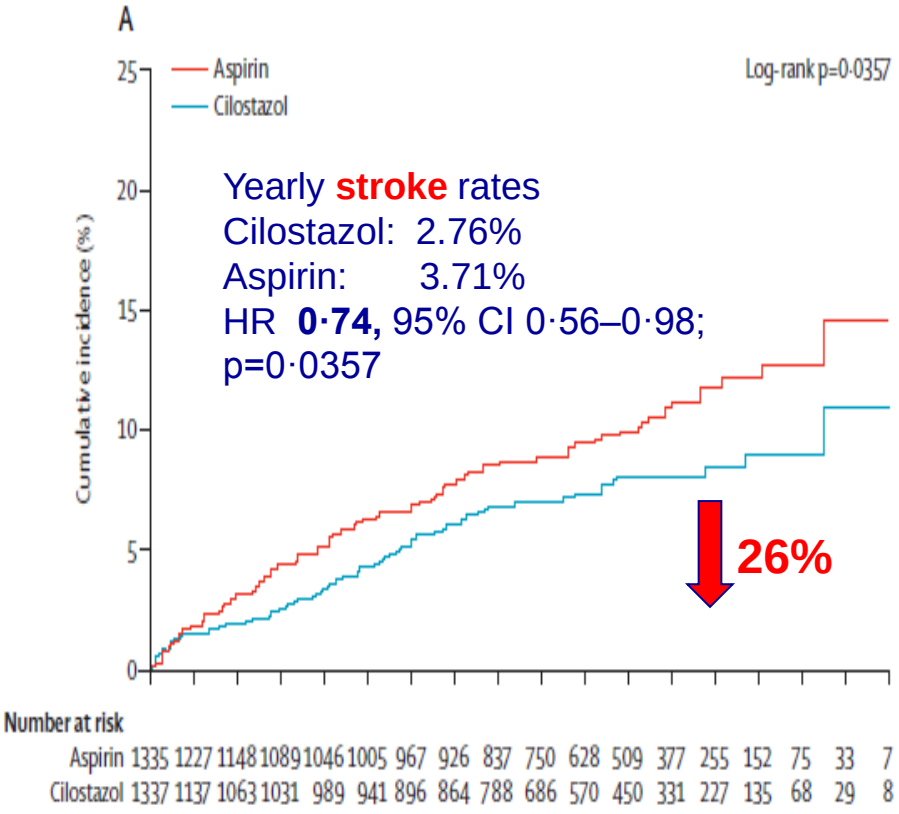
- **first recurrent stroke**
  - 9.0% ER-DP plus aspirin,
  - 8.8% clopidogrel
  - HR 1.01, 95%CI 0.92-1.11
- **stroke, MI or vascular death)**
  - 13.1% ER-DP plus aspirin
  - 13.1% clopidogrel
  - HR 0.99, 95% CI 0.92-1.07, p=0.83
- **Major haemorrhagic events**
  - 4.1% ER-DP plus aspirin
  - 3.6% clopidogrel
  - HR 1.15, 95% CI 1.00-1.32, p=0.06)
  - Intracerebral
  - (HR, **1.42**; 95% CI, 1.11 to 1.83).

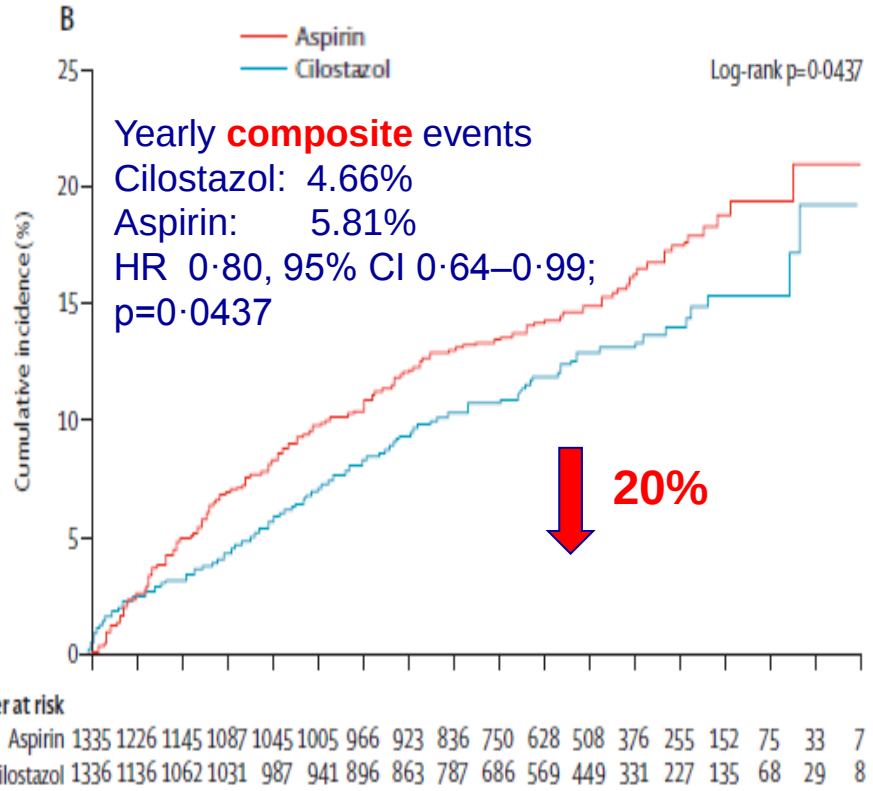
N Engl J Med. 2008;359:1238-51

2010

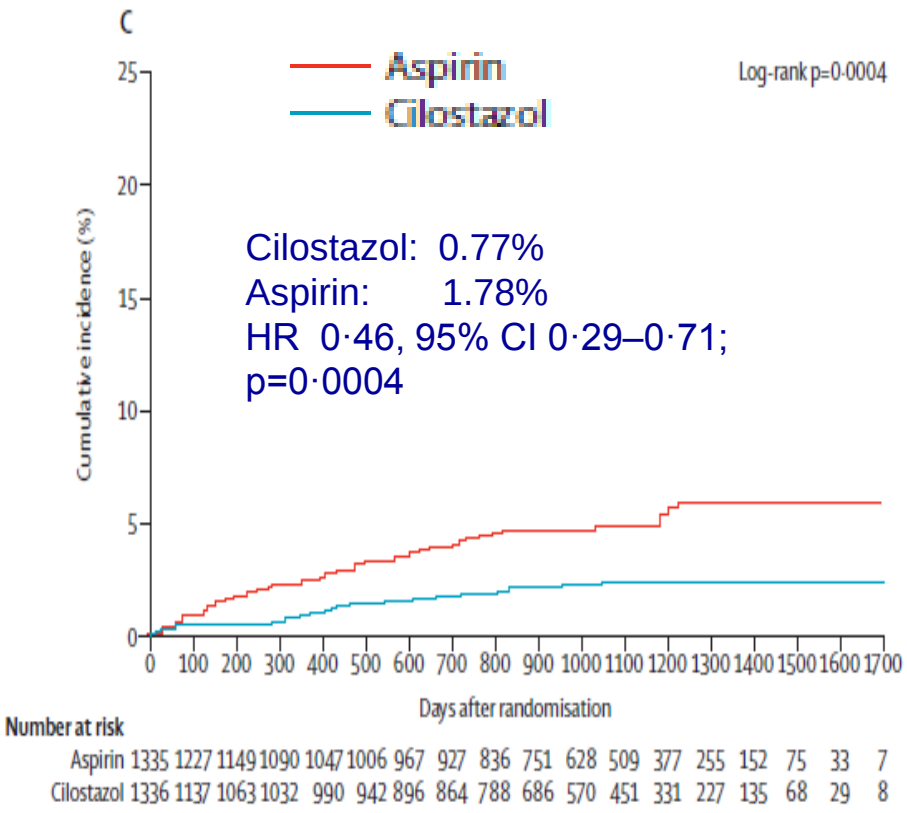
Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial

Lancet Neurol 2010; 9: 959–68





Adverse events in CSPS 2 study



Cilostazol: 0.77%
Aspirin: 1.78%
HR 0·46, 95% CI 0·29–0·71;
p=0·0004

Hemorrhages

	Cilostazol (n=1337)	Aspirin (n=1335)	p value*
Headache			
Events	313 (23%)†	217 (16%)	<0·0001
Discontinuations	64 (5%)	6 (<1%)	--
Diarrhoea			
Events	164 (12%)	85 (6%)	<0·0001
Discontinuations	4 (<1%)	1 (<1%)	--
Palpitations			
Events	156 (12%)	71 (5%)	<0·0001
Discontinuations	39 (3%)	2 (<1%)	--
Dizziness			
Events	129 (10%)‡	97 (7%)§	0·0268
Discontinuations	3 (<1%)	2 (<1%)	--
Tachycardia			
Events	89 (7%)	21 (2%)	<0·0001
Discontinuations	14 (1%)	0	--
Investigator-designated increase in blood pressure			
Events	120 (9%)	185 (14%)	<0·0001
Discontinuations	3 (<1%)	1 (<1%)	--
Constipation			
Events	110 (8%)	155 (12%)	0·0034
Discontinuations	0	0	--

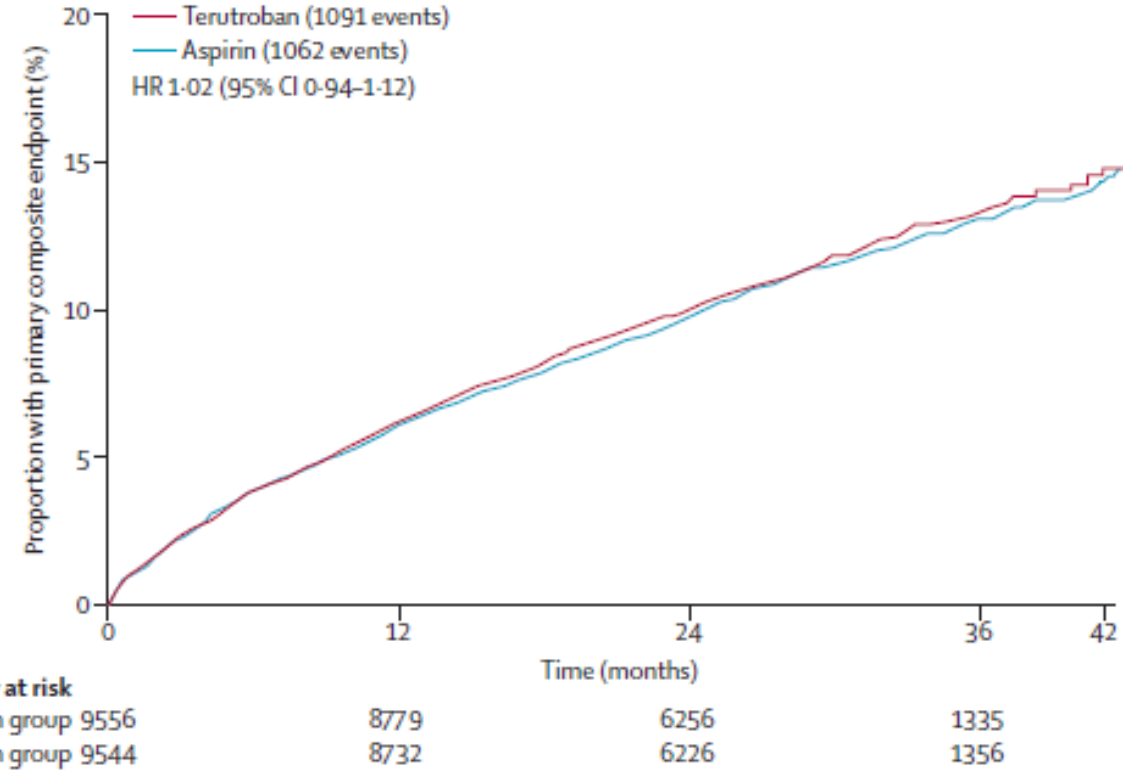
*χ^2 test. †One event was a serious adverse event. ‡Seven events were serious adverse events. §Six events were serious adverse events.

2011

Terutroban versus aspirin in patients with cerebral ischaemic events (PERFORM): a randomised, double-blind, parallel-group trial

Lancet 2011; 377: 2013–22

*Marie-Germaine Bousser, Pierre Amarenco, Angel Chamorro, Marc Fisher, Ian Ford, Kim M Fox, Michael G Hennerici, Heinrich P Mattle, Peter M Rothwell, Agnès de Cordoüe, Marie-Dominique Fratacci, on behalf of the PERFORM Study Investigators**



Number at risk				
Terutroban group	9556	8779	6256	1335
Aspirin group	9544	8732	6226	1356

Oral selective antagonist of thromboxane-prostaglandin receptors in platelets and in the vessel wall

Antiplatelet Therapy in Ischemic Stroke

European Stroke Organization Guidelines 2008

Recommendations -1

- Patients should receive antithrombotic therapy

  (Class I, Level A)

- 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)

Antiplatelet Therapy in Ischemic Stroke

European Stroke Organization Guidelines 2008

Recommendations - 2

- The **combination** of **aspirin** and **clopidogrel** is not recommended in patients with recent ischaemic stroke,
- Except in patients with specific indications:

  -unstable angina

  -non-Q-wave MI during the last 12 months

  -recent stenting (Class I, Level A)
- Patients who have a stroke on antiplatelet therapy should be **re-evaluated** for pathophysiology and risk factors

  (Class IV, GCP)

AHA/ASA Guidelines 2011

- **Aspirin** (50 mg/d to 325 mg/d) monotherapy

  (Class I; Level of Evidence A)

- *Aspirin 25 mg and extended-release* dipyridamole 200 mg twice daily *(Class I; Level of Evidence B)*
- *Clopidogrel 75 mg monotherapy* *(Class IIa; Level of Evidence B)*

  Are all acceptable options for initial therapy.

- The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, **cost**, tolerance, and other clinical characteristics.

Stroke. 2011 Jan;42:227-276

AHA/ASA Guidelines 2011

- The addition of aspirin to clopidogrel increases risk of hemorrhage and is not recommended for routine secondary prevention after ischemic stroke or TIA

  (Class III; Level of Evidence A)

- For patients allergic to aspirin, clopidogrel is reasonable

  (Class IIa; Level of Evidence C).

- For patients who have an ischemic stroke while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit.

  (Class IIb; Level of Evidence C).

Stroke. 2011 Jan;42:227-276

Antiplatelet treatment for secondary prevention

- Confusing and sometimes conflicting evidence
- Seems unlikely that one antiplatelet agent is really much superior to any another
- Consider side effects, general vascular risk profile (e.g. coexisting peripheral vascular disease)
- All agents have only a modest (but worthwhile) effect

How long to continue antiplatelet treatment?

- Apparent decline in benefit over many years of follow-up
- But likely decreasing adherence to treatment
- If the patient is still at risk of vascular events it seems reasonable to continue indefinitely

What if the stroke or TIAs occur despite antiplatelet treatment?

- Is the patient taking the tablets?
- Are the doses optimal?
- Is the diagnosis correct?
- Review the history again – are the attacks really typical of stroke/TIA?
- What is the mechanism?
- Repeat imaging or cardiac evaluation may be helpful
- Could leave unchanged, change to another agent or add another agent – temptation is always to make a change!

SPECIAL ARTICLE

Evidence and the Effective Clinical Neurologist

The 2009 H. Houston Merritt Lecture

Louis R. Caplan, MD

ARCH NEUROL/VOL 68 (NO. 10), OCT 2011

HOW DO TRIAL DATA RELATE TO TREATING INDIVIDUAL PATIENTS?

- This approach can be characterized as **"personalized medicine"** because it emphasizes the medical and personal details of each individual.

The most appropriate treatment:

- for a particular patient,
- with a particular stage of disease,
- with particular coexisting conditions,
- at a particular age.