ANTIPLATELETS IN STROKE

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CEREBROVASCULAR DISEASE

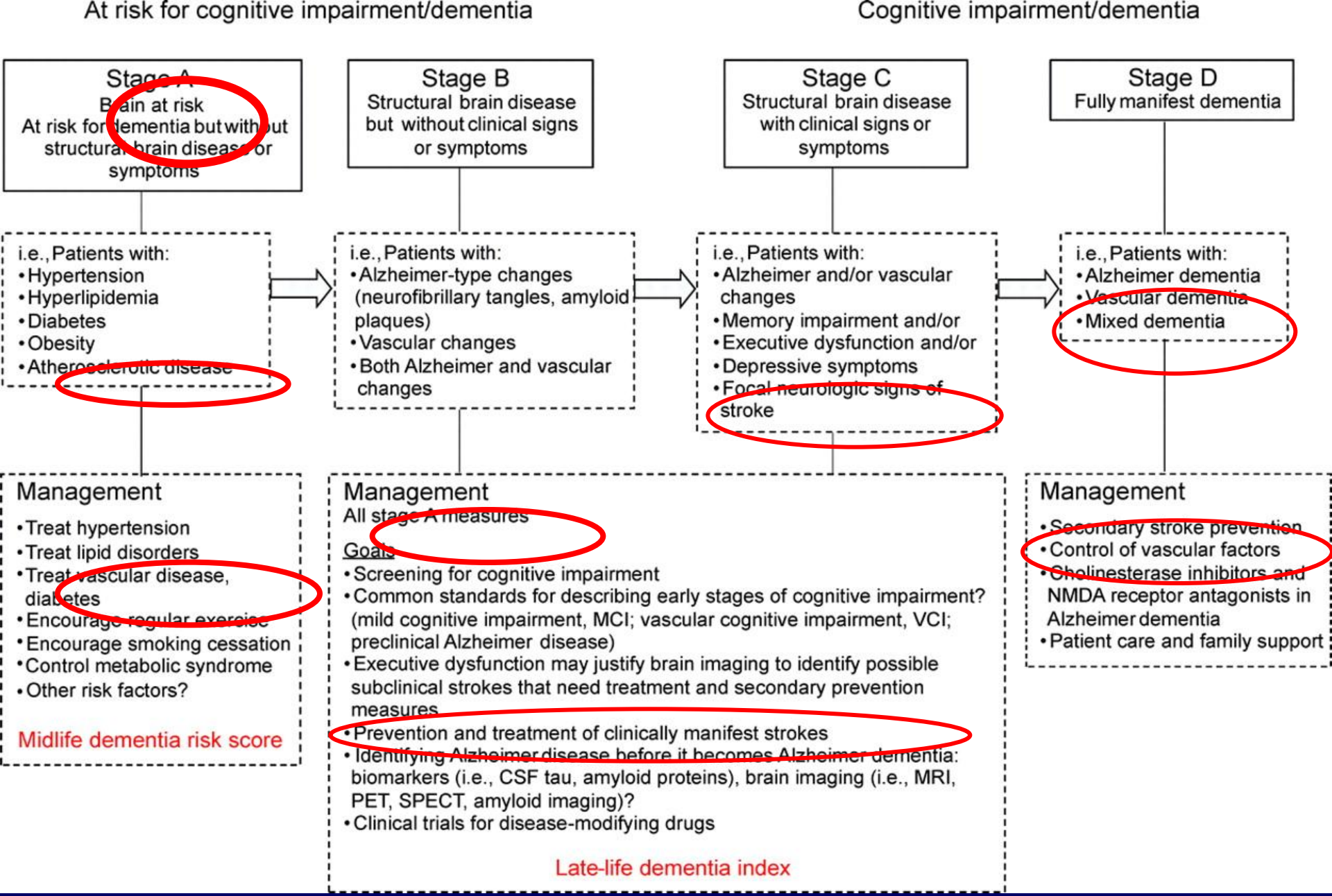
- major cause of morbidity and mortality

  * 2-nd cause of mortality worldwide
    (Romania: 1-st cause of mortality!)

  * FIRST CAUSE of MORBIDITY ALL OVER THE WORLD ("Silent" strokes are x5 more frequent than other strokes !)

    Prof.V. Hachinski – WCN, Bangkok 2009

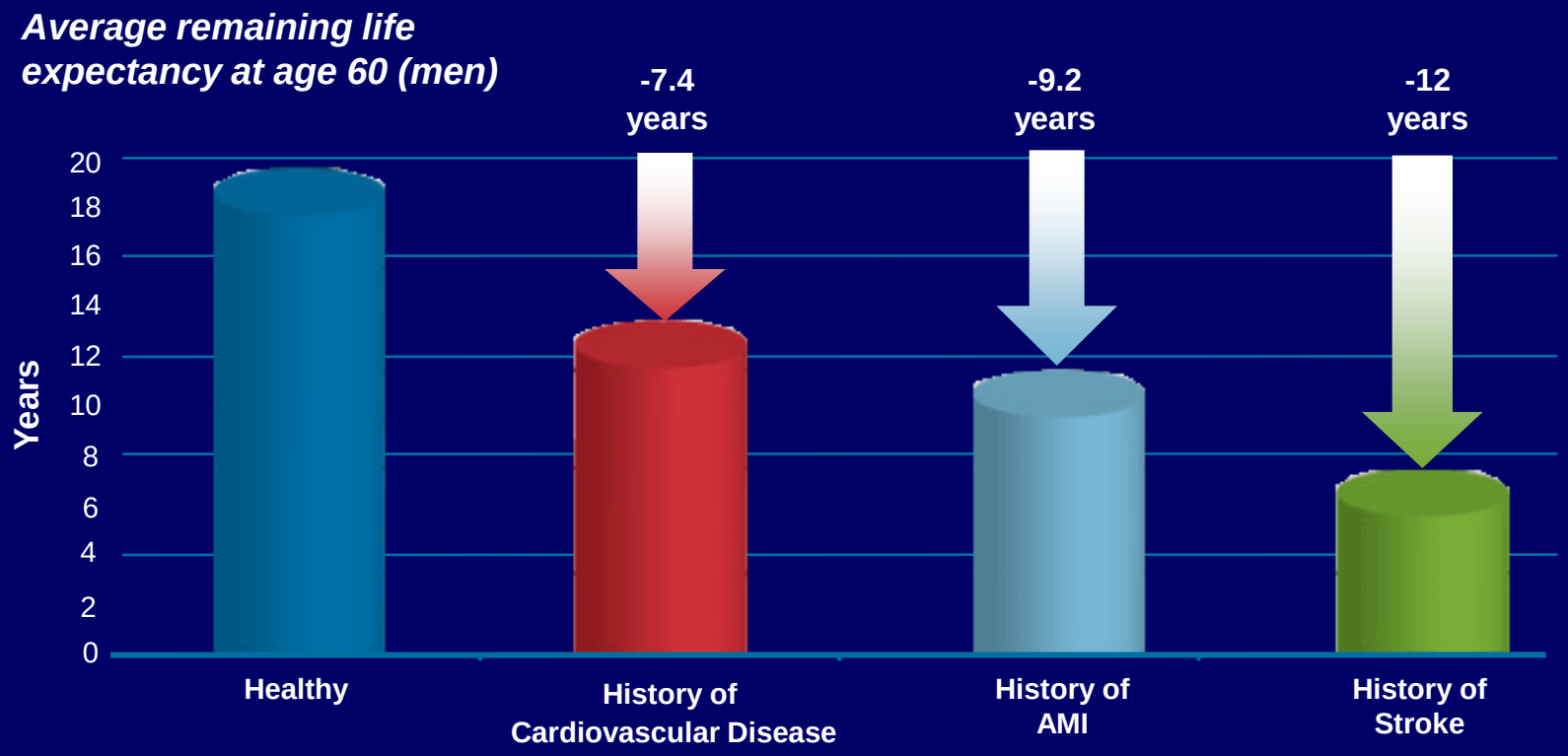
  * 1-st cause of long-term physical and / or mental handicap *(20 – 25% among the survivors of a first stroke develop a form of dementia during the next 5 years)*



modified after **Miia Kivipelto, MD, PhD and Alina Solomon, MD - NEUROLOGY 2009;73:168-169**

Impact of Atherothrombosis on Life Expectancy

Atherothrombosis reduces life expectancy by approximately 8–12 years in patients aged over 60 years*



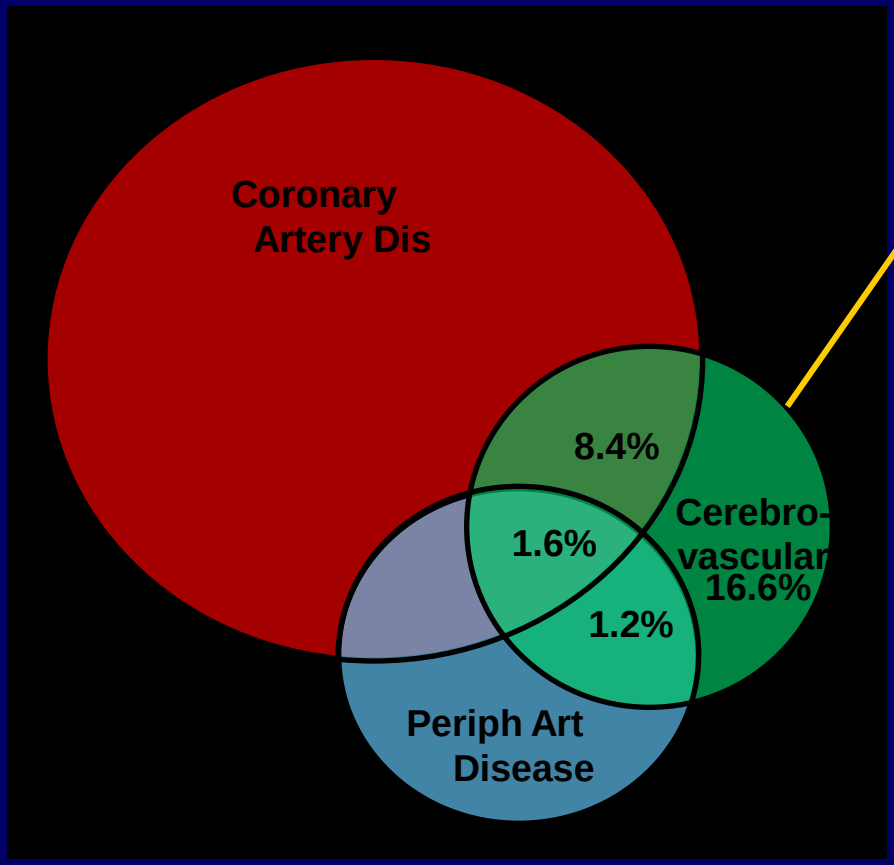
Analysis of data from the Framingham Heart Study
AMI = Acute myocardial infarction

**Peeters et al. Eur Heart J 2002; 23: 458–466*

~ 2/5 of Patients with Cerebrovascular Disease Have Polyvascular Disease[1]

~ 2/5 of the 18,843 patients with Cerebrovascular Disease also have atherothrombotic disease in other arterial territories

(%s are of total population)[1]



Patients with Cerebrovasc Dis = 27.8% of the REACH Registry population

1. Bhatt DL et al, on behalf of the REACH Registry Investigators. JAMA 2006; 295(2): 180-189.

Risk of a Second Vascular Event

	Increased risk vs general population (%)	
Original event	**Myocardial infarction**	**Stroke**
Myocardial infarction	**5–7 x greater risk[1]** (includes death)	**3–4 x greater risk[2]** (includes TIA)
Stroke	**2–3 x greater risk[2]** (includes angina and sudden death*)	**9 x greater risk[3]**
Peripheral arterial disease	**4 x greater risk[4]** (includes only fatal MI and other CHD death†)	**2–3 x greater risk[3]** (includes TIA)

***Sudden death defined as death documented within 1 hour and attributed to coronary heart disease (CHD)**
†Includes only fatal MI and other CHD death; does not include non-fatal MI

1. Adult Treatment Panel II. Circulation 1994; 89:1333–63. 2. Kannel WB. J Cardiovasc Risk 1994; 1: 333–9.
3. Wilterdink JI, Easton JD. Arch Neurol1992; 49: 857–63. 4. Criqui MH et al. N Engl J Med 1992; 326: 381–6.

Primary prevention

Management of vascular risk factors

Antithrombotic therapy

Surgery and angioplasty

Treatment Options for Long-Term Prevention

- **Risk Factor Management**
  - Increase physical activity, blood pressure control, smoking cessation, diabetes control, lipid reduction
- **Surgical Treatment**
  - Carotid Endarectomy (CEA): if symptomatic and substantial carotid stenosis
  - Carotid Stenting: investigating angioplasty + stenting
- **Antithrombotic - pharmacologic management**
  - Antiplatelets
    - Clopidogrel
    - Aspirin
    - Extended-release dipyridamole + aspirin
  - Anticoagulants
    - Warfarin

PRIMARY PREVENTION

- **U.S.Physician's Health Care (1989)**
  - **randomised, double-blind, placebo-controlled trial**
  - **22071 physicians**
  - **325 mg ASA / day vs. PLACEBO**
  - **Results:**
    - *** RR for MI cu 44%**
    - **** non-significant increase for stroke !***
      (non-significant association with hemorrhagic stroke)

- **British Doctor's Trial (1988)**
  - **5139 physicians**
  - **500 mg ASA / day or no treatment**
  - ***increased risk for stroke*** *(no stroke subtype correlation)*

Both trials combined:

**increase by 21% (± 13%) of STROKE RISK in subjects with low risk (ns.)*

- **Nurses Health Study:**

  ** does not modify the STROKE RISK in women (?)*

- **Hypertension Optimal Study (HOT):**

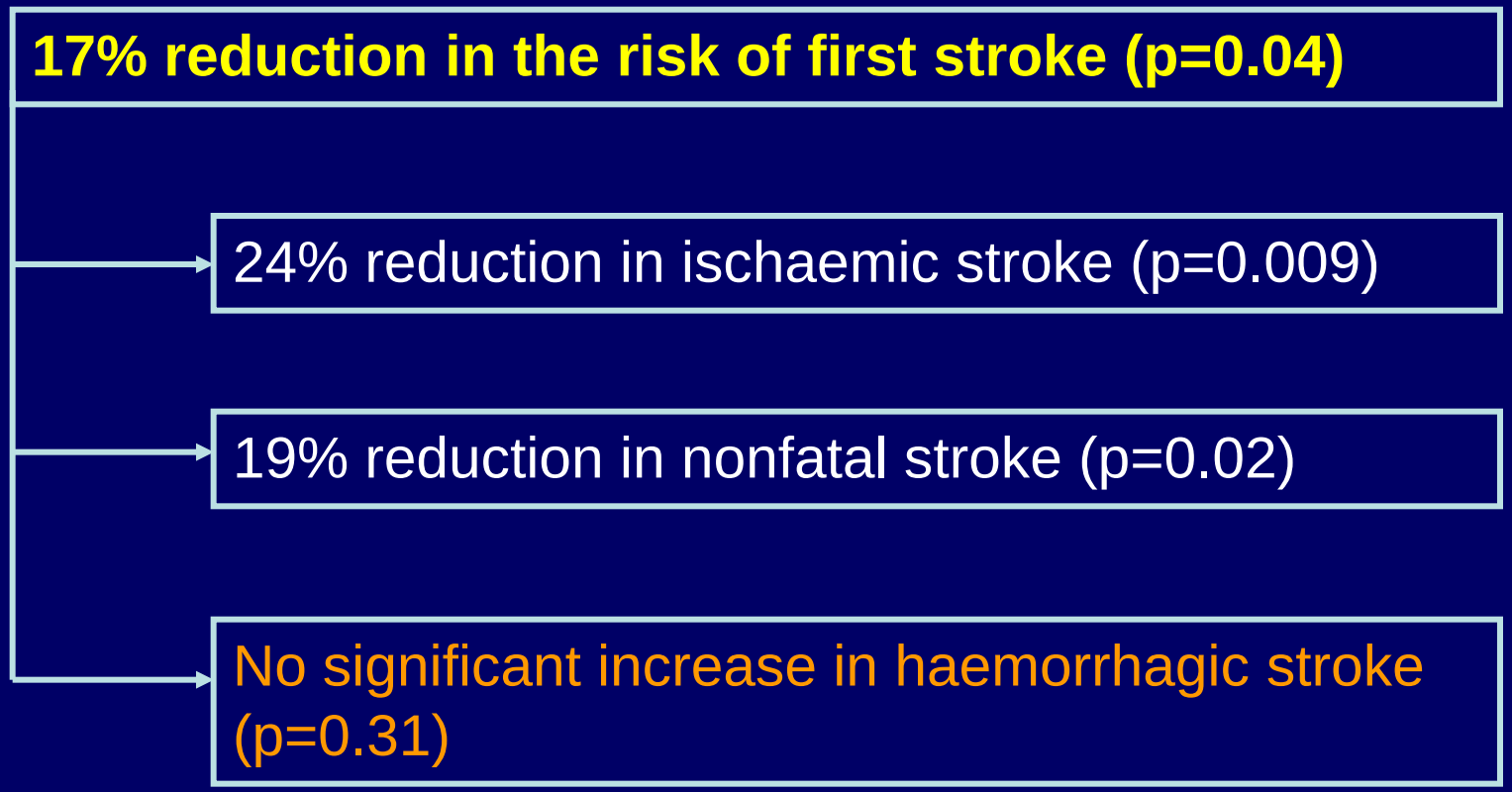
  - 75 mg ASA / day vs. PLACEBO

  - ~ 20.000 patients with high BP

  ** does not modify the STROKE RISK*

THERE IS NO INDICATION TO PRESCRIBE ASA IN PRIMARY PREVENTION for STROKE ***(before Women's Health Study, 2005)*** **!**

WHS: Aspirin® reduced risk of first stroke in women aged ≥45 years



Ridker PM, et al. N Engl J Med 2005;352:1293–304.

WHS: Aspirin® reduced risk of first major CV events in women aged ≥65 years

26% reduction in the risk of first CV events (p=0.008)

- 34% reduction in fatal and nonfatal MI (p=0.04)
- **30% reduction in ischaemic stroke (p=0.05)**
- 22% reduction in total stroke (p=0.13; NS)

Ridker PM, et al. N Engl J Med 2005;352:1293–304.

Antithrombotic Therapy

ESO Guidelines Ischaemic Stroke - 2009

Recommendations

- **Low-dose aspirin is recommended in women aged 45 years or more who are not at increased risk for intracerebral haemorrhage and who have good gastro-intestinal tolerance; however, its effect is very small (Class I, Level A)**

- **Low-dose aspirin may be considered in men for the primary prevention of myocardial infarction; however, it does not reduce the risk of ischaemic stroke (Class I, Level A)**

Antithrombotic Therapy

ESO Guidelines Ischaemic Stroke - 2009

Recommendations

- Antiplatelet agents **other than aspirin** are **not recommended for primary stroke prevention** **(Class IV, GCP)**

- **Aspirin** may be recommended for patients with non-valvular **AF who are younger than 65 years and free of vascular risk factors** **(Class I, Level A)**

ASA in the treatment of ACUTE STROKE

ANTITHROMBOTIC TRIALISTS' COLLABORATION
(meta-analysis, 2002): ***IST, CAST, MAST-1, other smaller trials:***

*** 40821 patients receiving oral ASA during the first 48 h**
*** averrage follow-up: 3 – 4 weeks**
*** conclusions of IST and CAST become statisticaly significant**

Antithrombotic Therapy

ESO Guidelines Ischaemic Stroke - 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)**

- **The administration of glycoprotein-IIb-IIIa inhibitors is not recommended (Class I, Level A)**

FASTER Trial

(Fast assessment of stroke and transient ischaemic attack to prevent early recurrence)

- a randomised controlled pilot trial
- within 24 h of symptom onset
- randomly assigned, in a factorial design, 392 patients with TIA or minor stroke to:
  - * clopidogrel (300 mg loading dose then 75 mg daily (198 patients) or placebo (194 patients),
    and
  - * simvastatin (40 mg daily; 199 patients) or placebo (193 patients)
- All patients were also given aspirin and were followed for 90 days
- The primary outcome was total stroke (ischaemic and haemorrhagic) within 90 days
- Safety outcomes included haemorrhage related to clopidogrel *(and myositis related to simvastatin)*
- RESULTS:
  - * Immediately after TIA or minor stroke, patients are at high risk of stroke, which might be reduced by using clopidogrel in addition to aspirin
  - * The interaction between clopidogrel and simvastatin was not significant (p=0.64)
  - * The haemorrhagic risks of the combination of aspirin and clopidogrel do not seem to offset this potential benefit
  - * There was no difference between groups for the simvastatin safety outcomes
  - * *This aggressive prevention approach merits further study*

Kennedy J et al (Oxford Univ., UK)- Lancet Neurol. 2007

SECONDARY PREVENTION

- **ANTIPLATELET TRIALIST COLLABORATION**

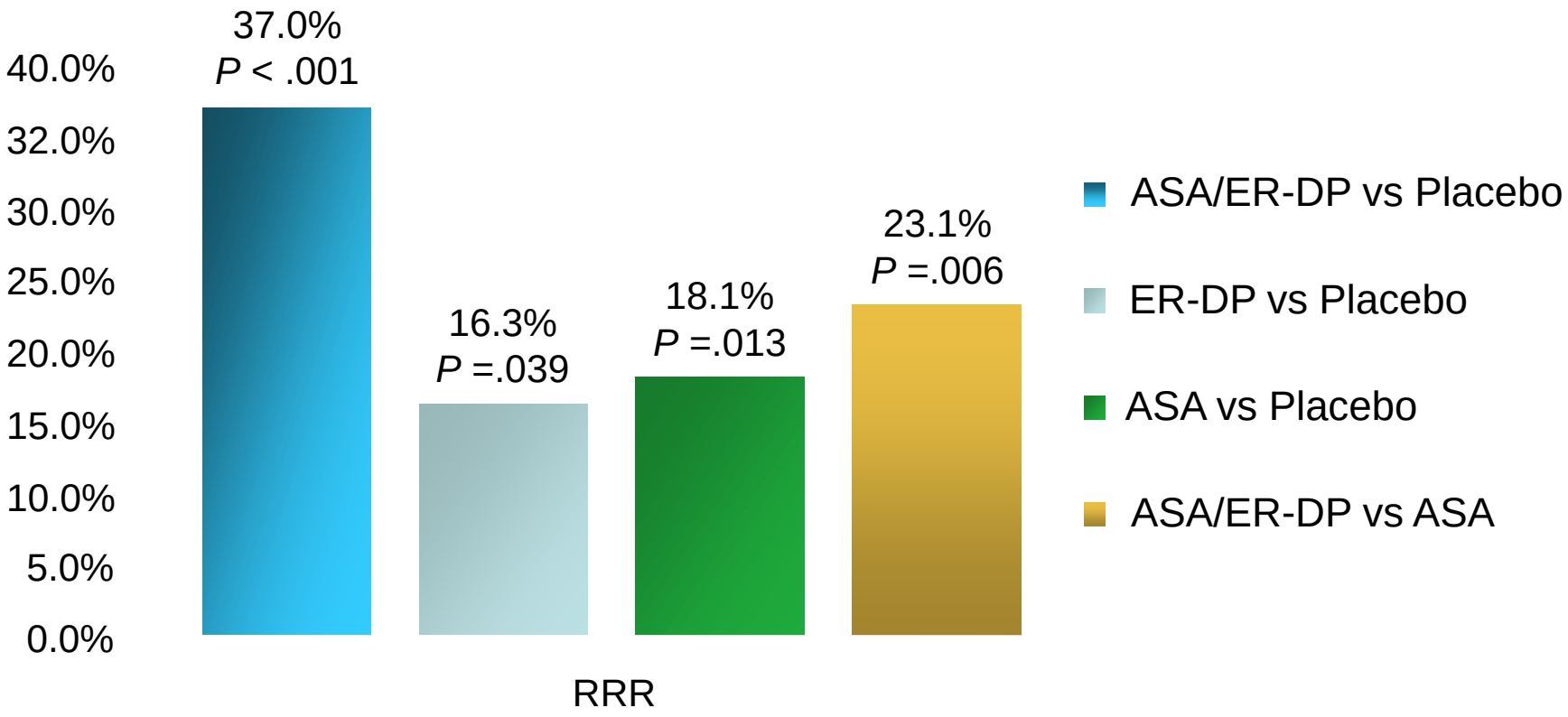
  - META-ANALYSIS on 145 trials including 51.144 patients:

  **** ASA reduces by 25% the RECCURENCE RISK of***

  STROKE in patients with increased risk (TIA, STROKE,

  MI or history of MI), but only by 13% after a stroke / TIA

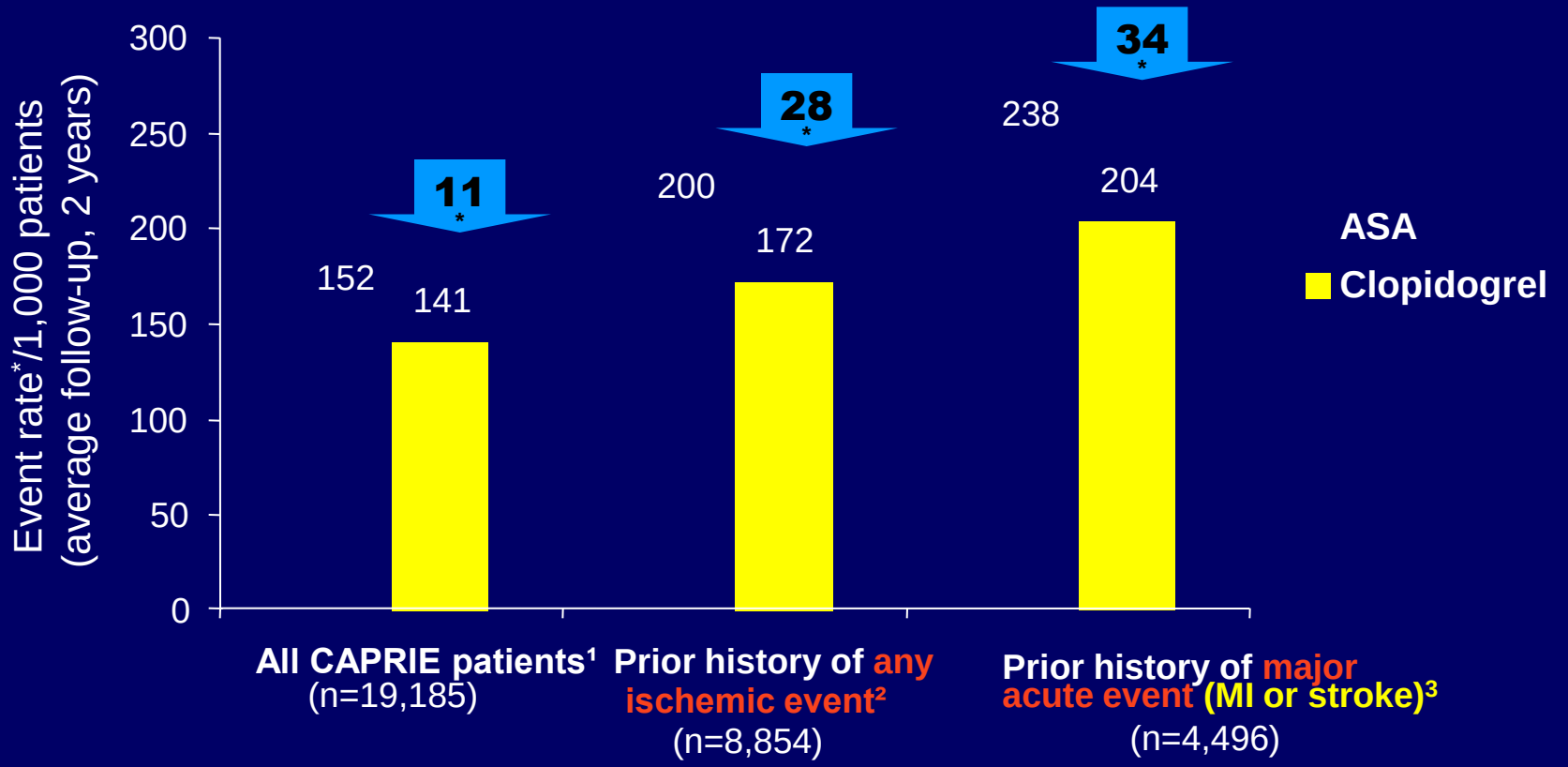
ESPS 2: Effects on Stroke–RRR (Pairwise Comparisons)



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

CAPRIE: Clopidogrel Is Shown to Provide Amplified Benefits in Patients with Higher Vascular Risk[1–3]

***Event rate of myocardial infarction, ischemic stroke, or vascular death over a 3-year period**



***Events Prevented/1,000 Patients/3 Years over ASA**

1. CAPRIE Steering Committee. *Lancet* 1996; 348: 1329–1339. 2. Jarvis B, Simpson K. *Drugs* 2000; 60: 347–377. 3. Ringleb. Stroke 2004;35:528-532

Antithrombotic Therapy

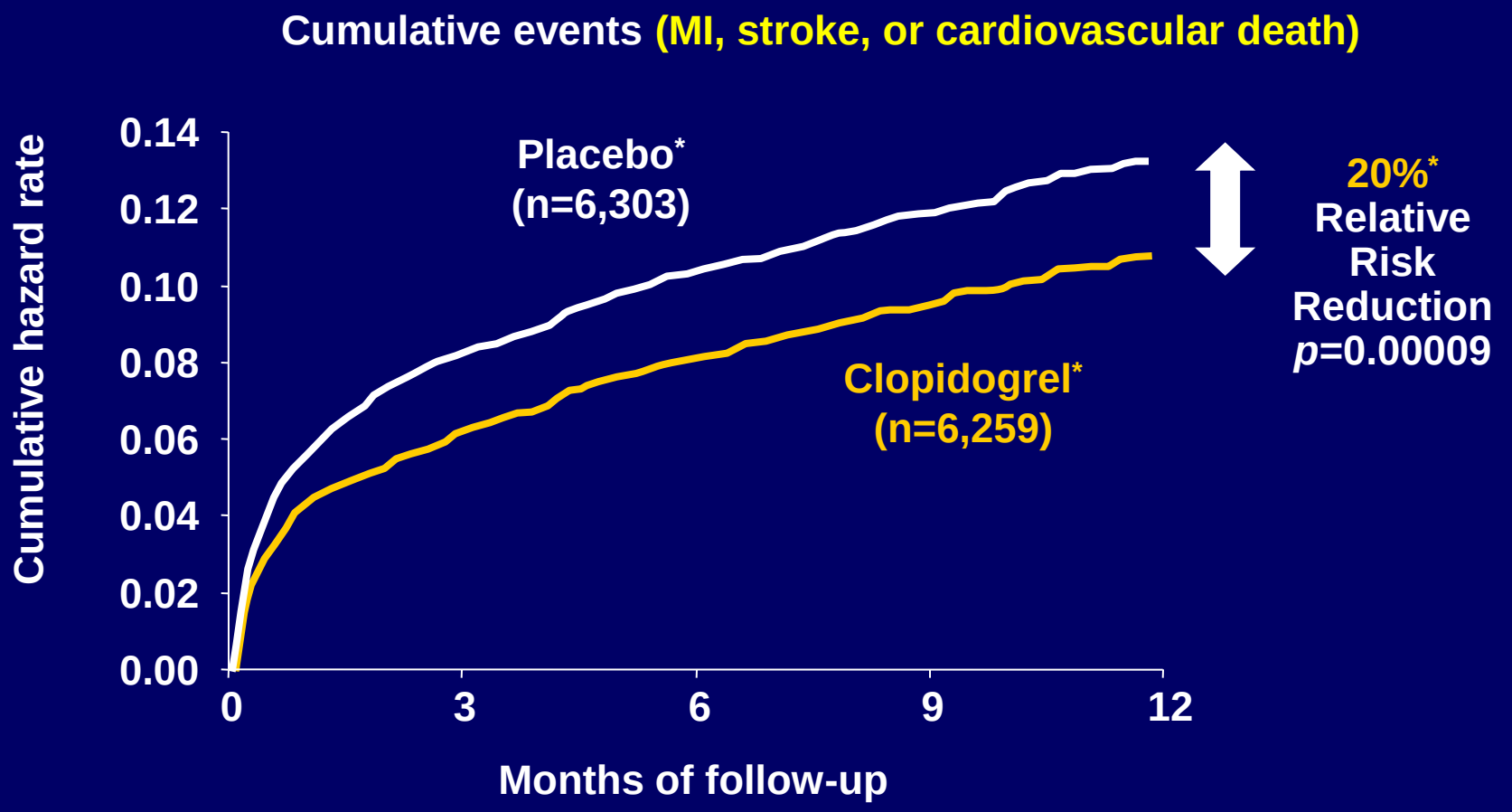
ESO Guidelines Ischaemic Stroke

Recommendations

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)**

Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) Trial[1,2]

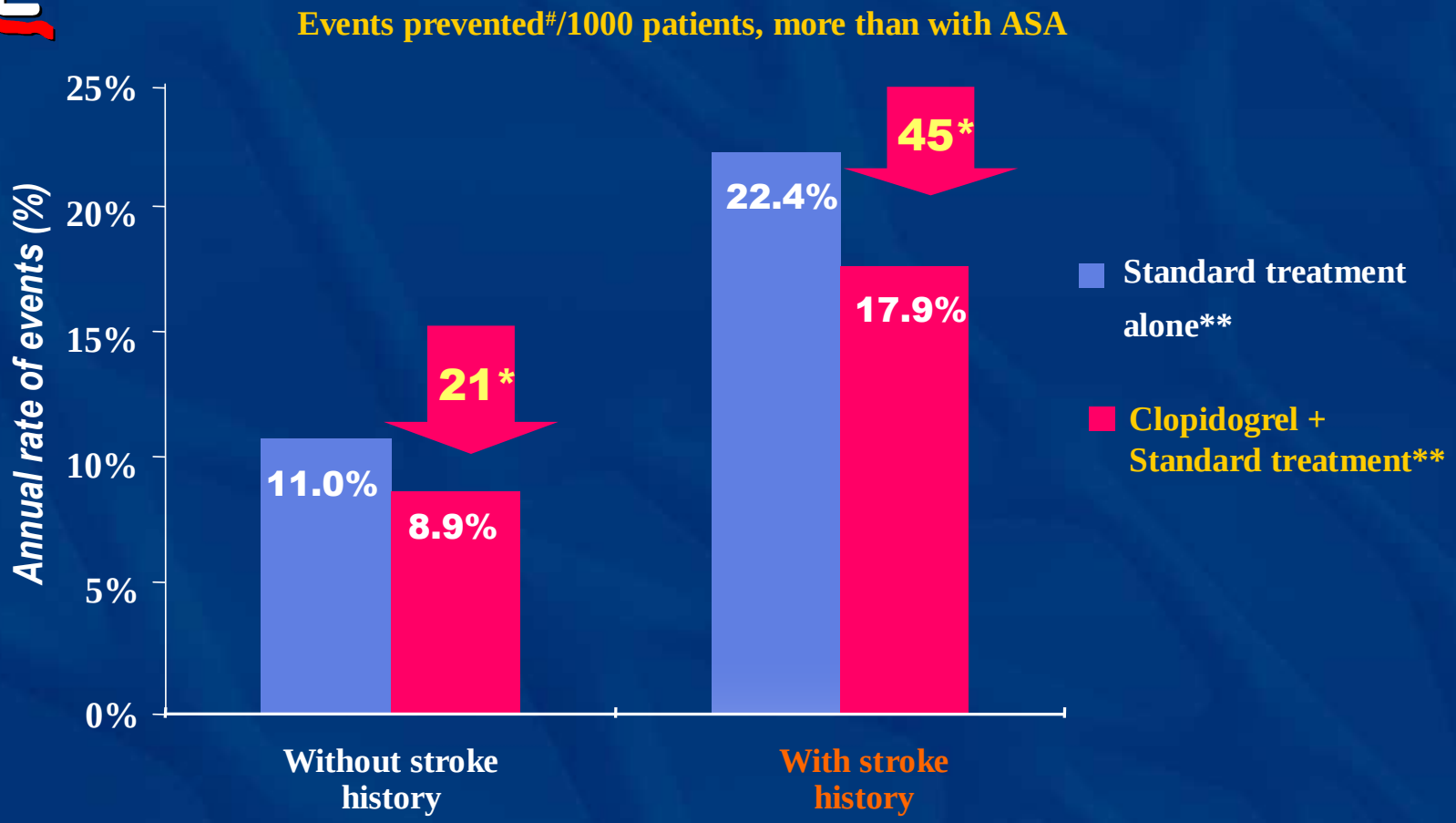


*On top of standard therapy (including ASA)

1. The CURE Trial Investigators. *N Engl J Med* 2001; **345:** 494–502.
2. Yusuf S *et al*. *Circulation* 2003; **107:** 966–972.

Superiority of Clopidogrel in patients with ACS with stroke history

CURE



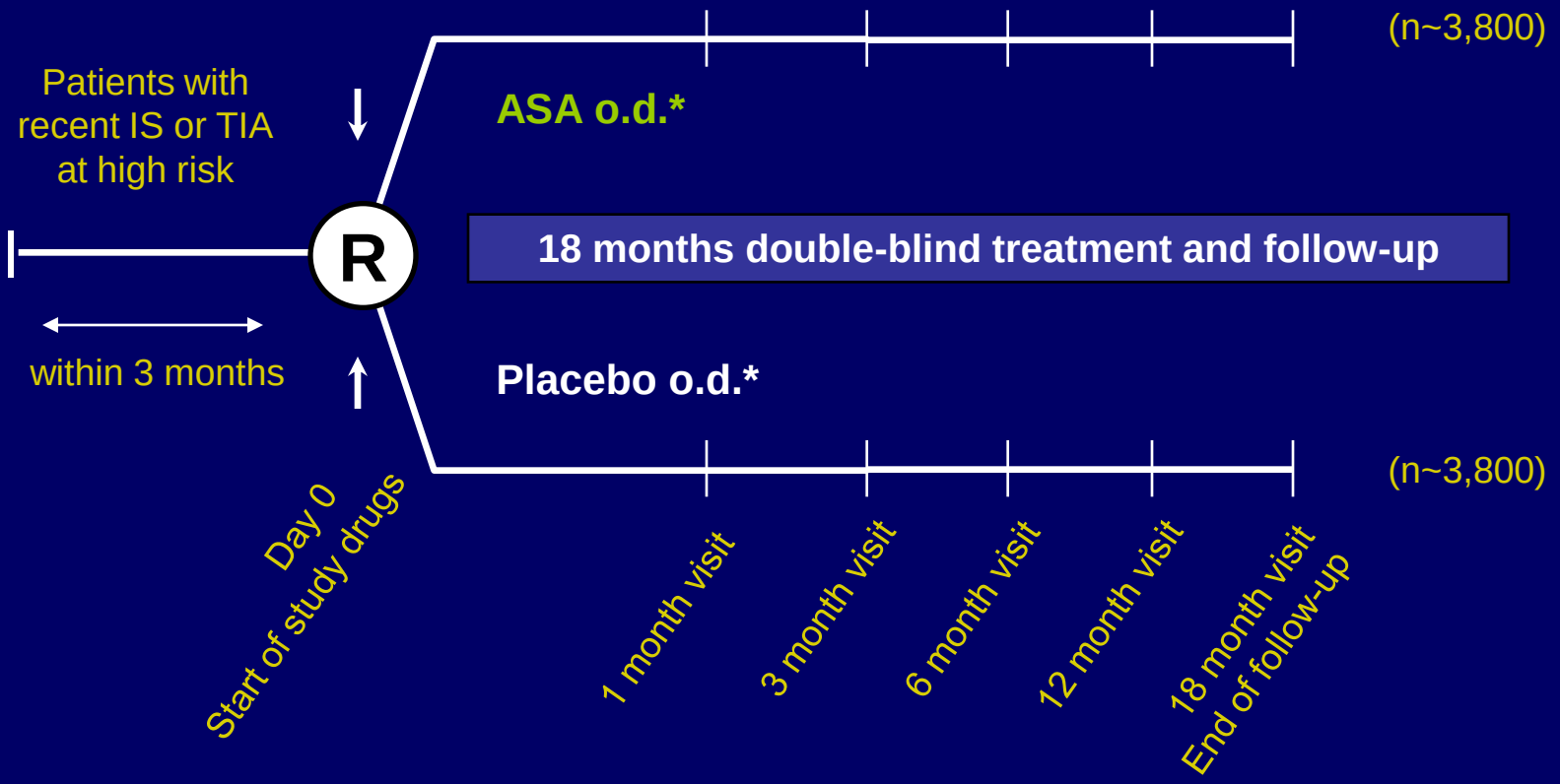
*Number of events prevented/1,000 patients treated
**Terapia standard (inclusiv ASA)
1. Data on file, 2002, p87 internal CSR-EFC 3307.

Stroke, Mi, vascular death

Study Objectives and Design

The MATCH trial was designed to determine:

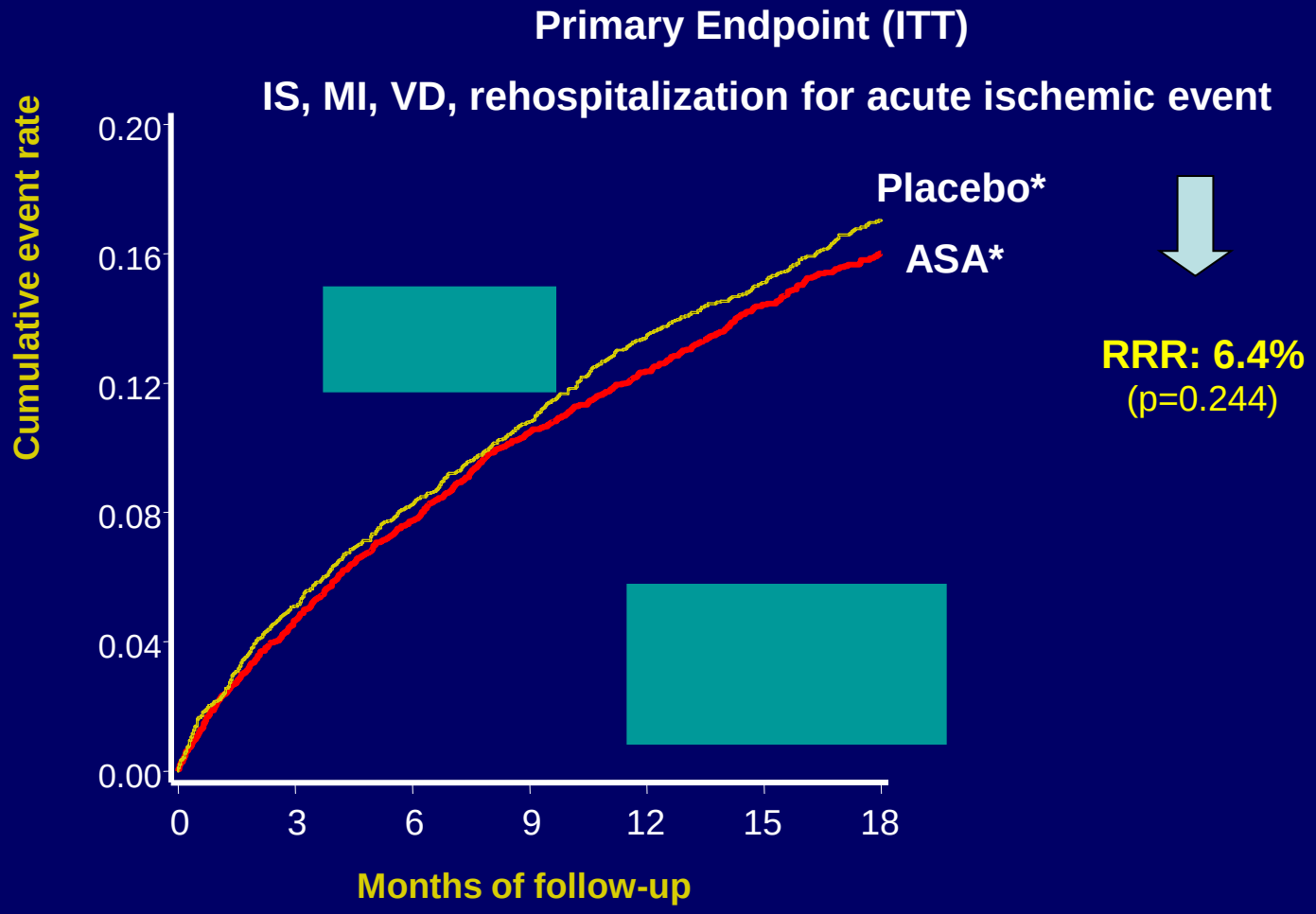
- **The efficacy and safety of ASA compared to placebo in high-risk cerebrovascular patients receiving clopidogrel 75mg**



R = Randomization

*** All patients received clopidogrel 75 mg and other standard therapies**

ASA showed a non-significant trend for the reduction in major vascular events of in specific high risk cerebrovascular patients*



* All patients received clopidogrel and other standard therapies

Overall Benefit Risk

- **Efficacy:**
  - **In absolute terms:**
    - **10 events prevented per 1000 patients (ITT)**

- **Safety**
  - **In absolute terms , *increased risk of life-threatening bleeding of 13 additional events (including 4 PICH)* per 1000 patients**

MATCH (2004):

In secondary preventions in patients with stroke,

association of ASA over CLOPIDOGREL

does not bring supplemental benefits !

Particular post-hoc observations, without statistical significance: patients receiving CLO+ASA earlier after a stroke had a better evolution !

Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA)

Inclusion Criteria

Patients aged ≥45 years

with

at least one of the following:

1) Documented coronary disease

and/or

2) Documented cerebrovascular disease

and/or

3) Documented symptomatic PAD

and/or

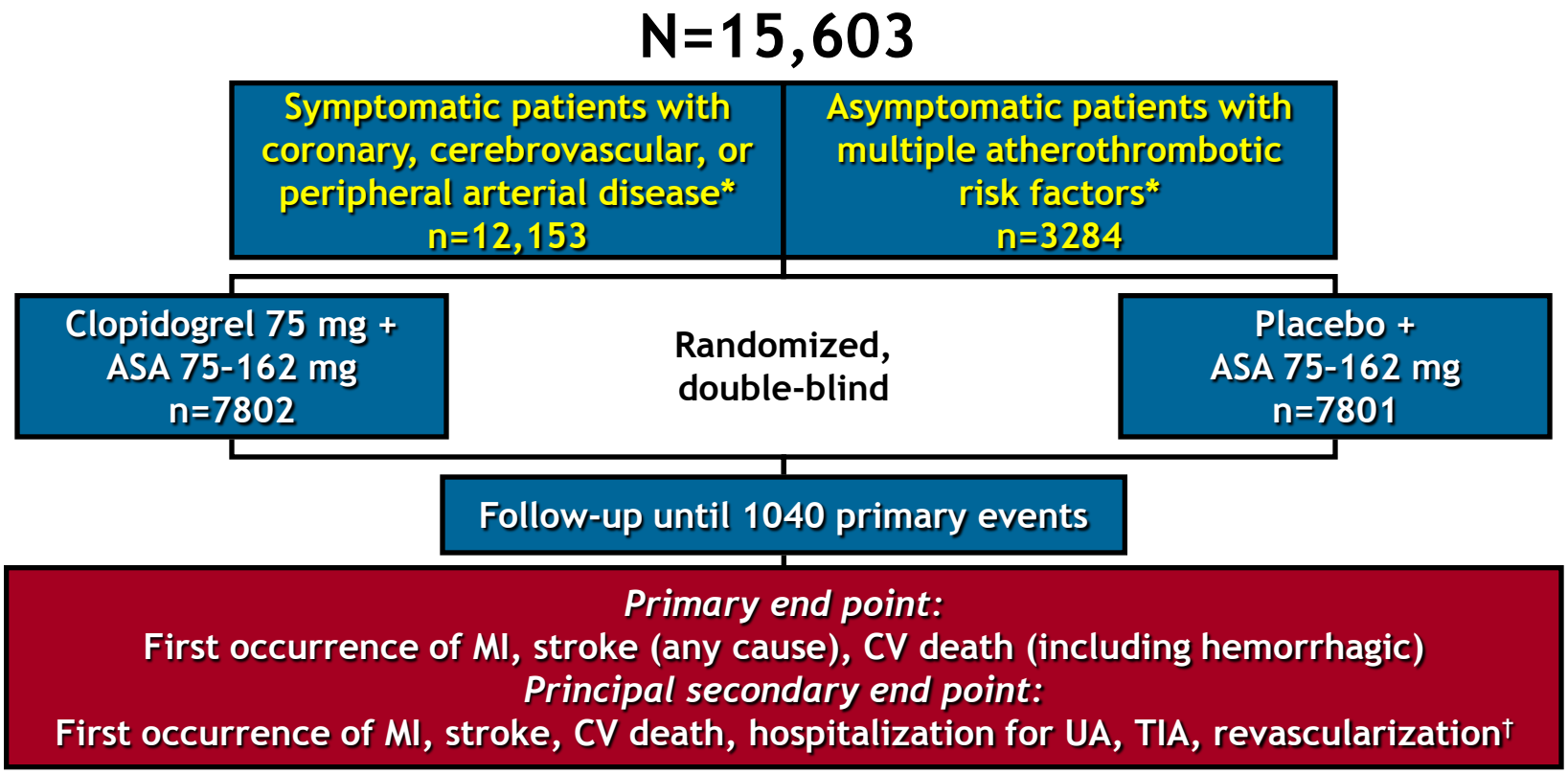
4) Two major or one major and two minor or three minor risk factors

With written informed consent

Without Exclusion criteria

Bhatt DL, Topol EJ, et al. Am Heart J 2004; 148: 263–268.

CHARISMA: Study Design



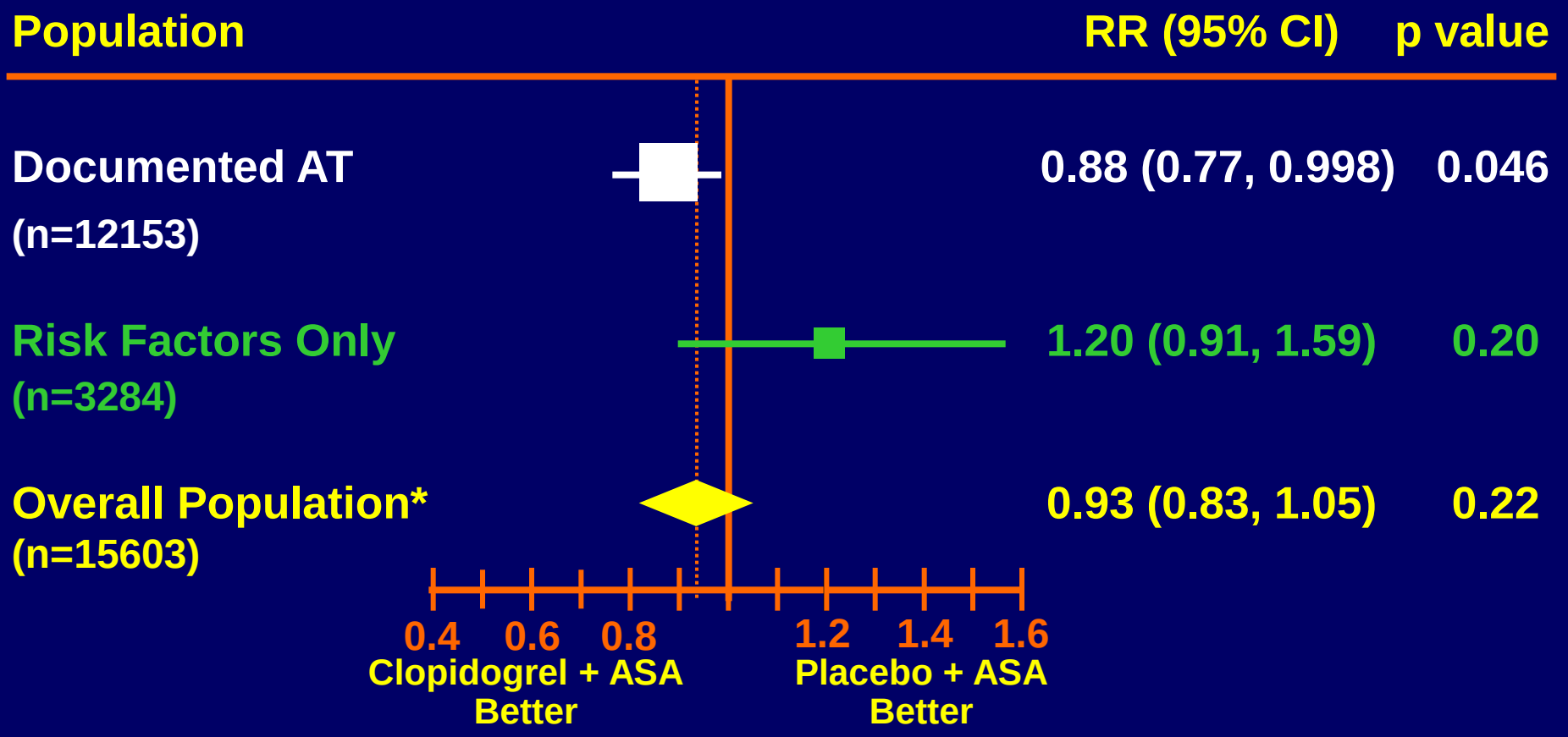
*n=166 not in either category, but included in overall analysis.

†Coronary, cerebral, or peripheral.

CHARISMA=Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance.

Bhatt DL et al. *N Engl J Med*. 2006;354:1706-1717.

Primary Efficacy Results (MI/Stroke/CV Death) by Pre-Specified Entry Category

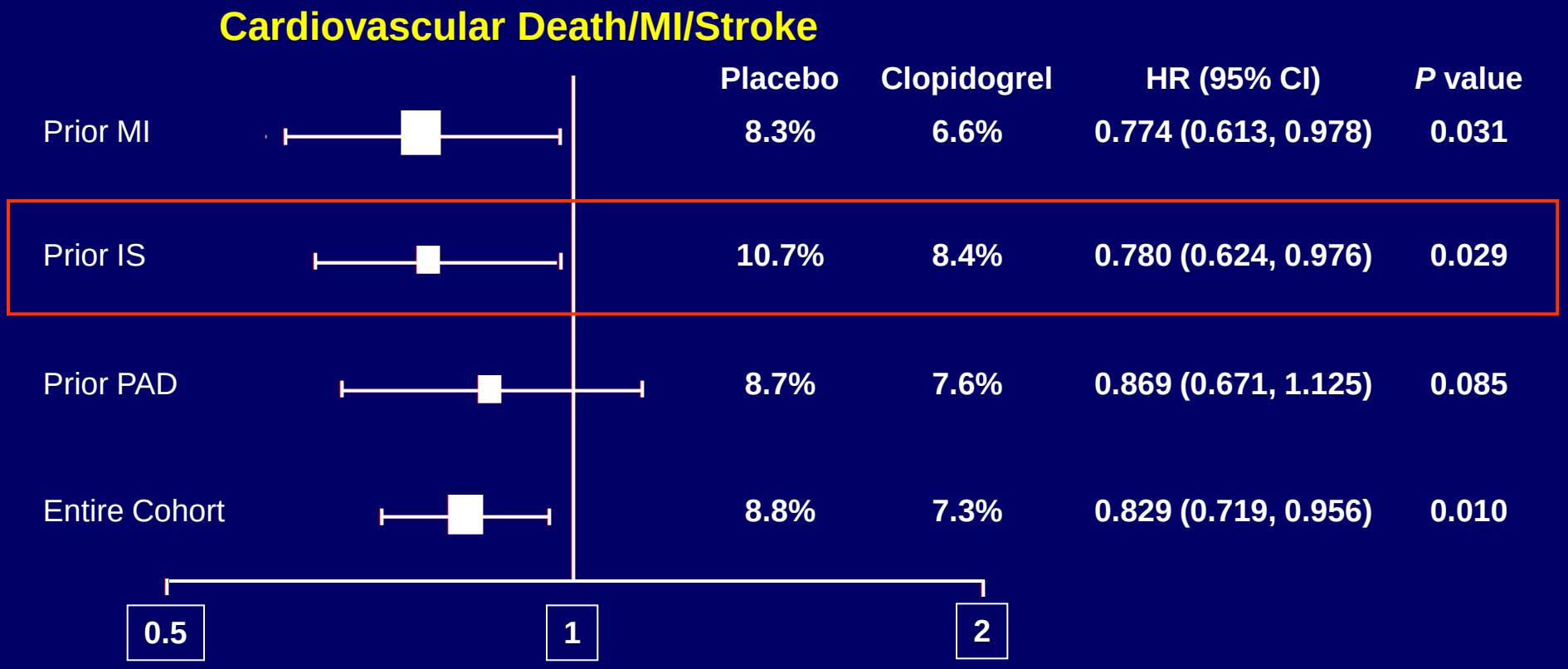


* A statistical test for interaction showed marginally significant heterogeneity (p=0.045) in treatment response for the pre-specified subgroups of symptomatic and asymptomatic patients

AT=Atherothrombosis

Adapted from Bhatt DL, Fox KA, Hacke W, et al. NEJM 2006 – In press

CHARISMA: (MI/Stroke/CV Death) in Patients With Previous MI, IS, or PAD* "CAPRIE-like Cohort"



***Post hoc analysis.**

Bhatt DL, Flather MD, Hacke W, et al. *J Am Coll Cardiol.* 2007;49:1982-1988.

Conclusions

- In patients with **multiple risk factors, without clearly established atherothrombotic disease, *dual antiplatelet was not beneficial;* an excess in CV mortality as well as an increase in bleeding was seen**

- In patients with **established atherothrombotic disease (CAD, cerebrovascular disease, or PAD) long-term clopidogrel plus ASA therapy resulted in a significant reduction in atherothrombotic events (MI/Stroke/CV Death/ hospitalization for vascular events) with no significant increase in severe bleeding compared to ASA alone**

Bhatt DL. Oral presentation at ACC 2006.

Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial

- a factorial design to address several questions

- in a large population of **20,332 patients** from ***695 sites*** in ***35 countries***

- a **noncardioembolic ischemic stroke** within the **previous 120 days**

- randomized to receive:

aspirin (25 mg) plus extended-release dipyridamole (200 mg) 2x / day

or,

clopidogrel (75 mg) once daily

-at the same time, patients were randomized to receive either

80 mg/day of telmisartan or **placebo**

Study design

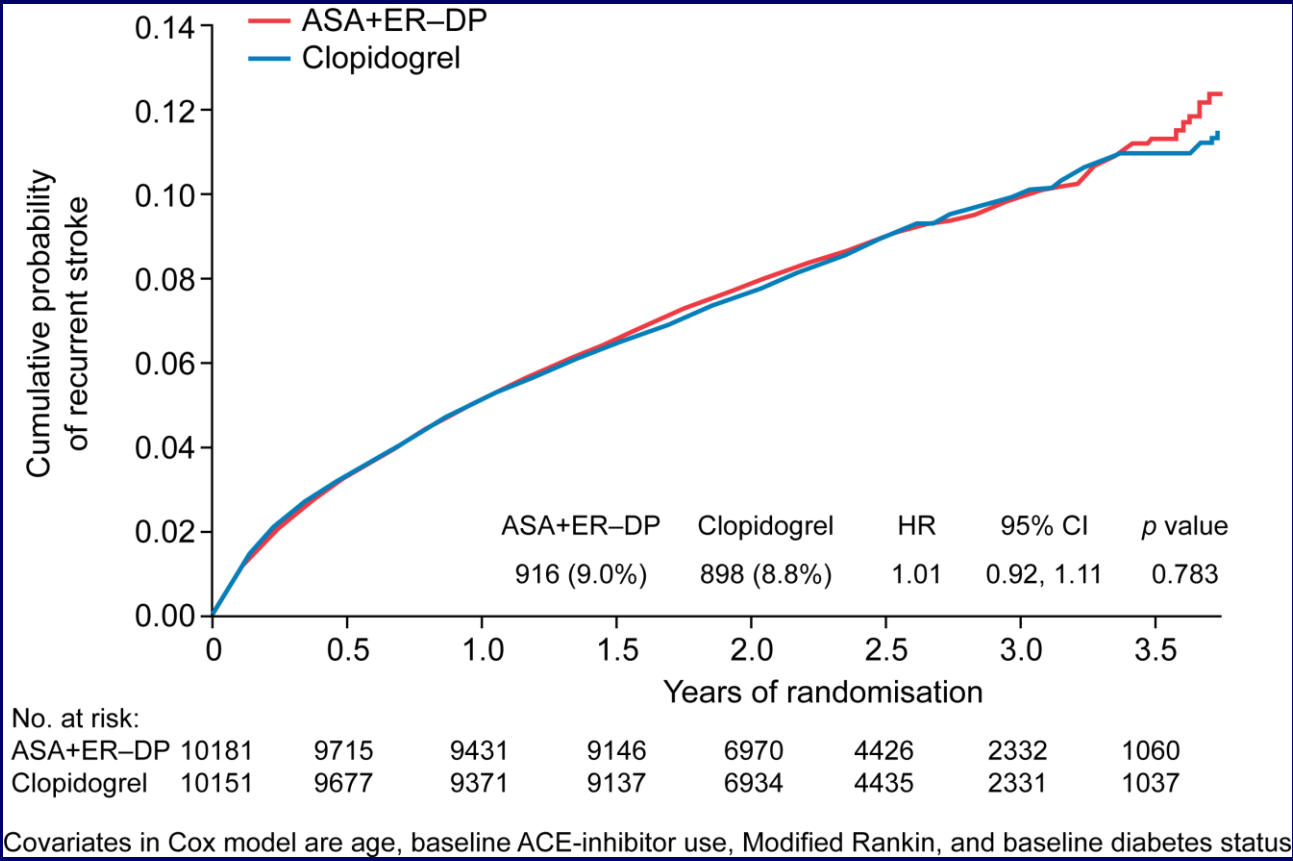
- **2X2 Factorial design 20,332 stroke patients over age 50**

	ER-DP + ASA	Clopidogrel
Telmisartan	ER-DP+ASA + Clopidogrel placebo + Telmisartan	Clopidogrel + ER-DP+ASA placebo + Telmisartan
Telmisartan placebo	ER-DP+ASA + Clopidogrel placebo + Telmisartan placebo	Clopidogrel + ER-DP+ASA placebo + Telmisartan placebo

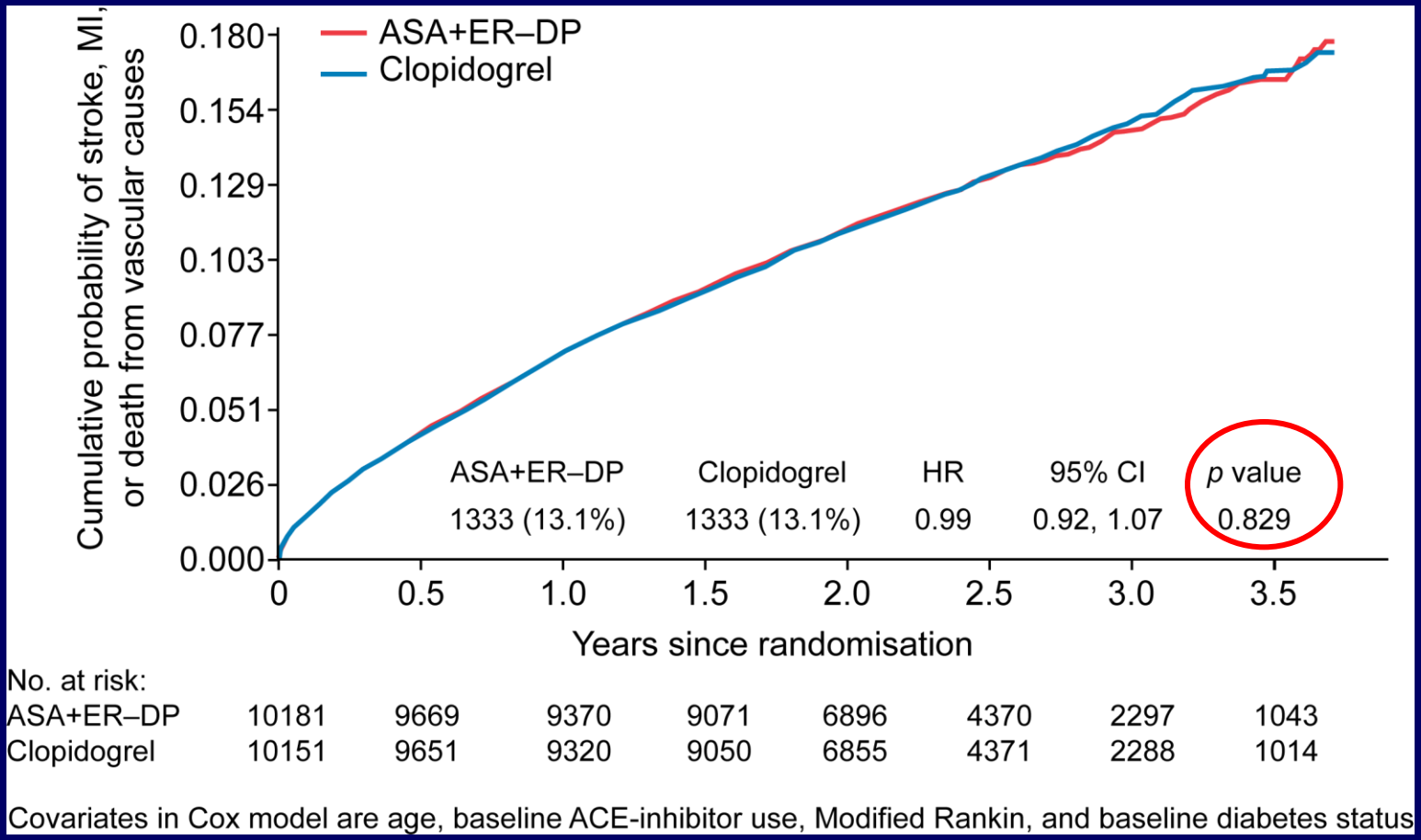
Sacco RL et al. *N Engl J Med* 2008;359: published online

PRoFESS: Primary Outcome for Comparison of Aspirin Plus Extended-Release Dipyridamole vs Clopidogrel

End point	Aspirin + ER-Dipyridamole	Clopidogrel	Hazard Ratio (95% CI)	*P*
Stroke recurrence, No. (%)	915 (9.0%)	898 (8.8)	1.01 (0.92 – 1.11)	.783



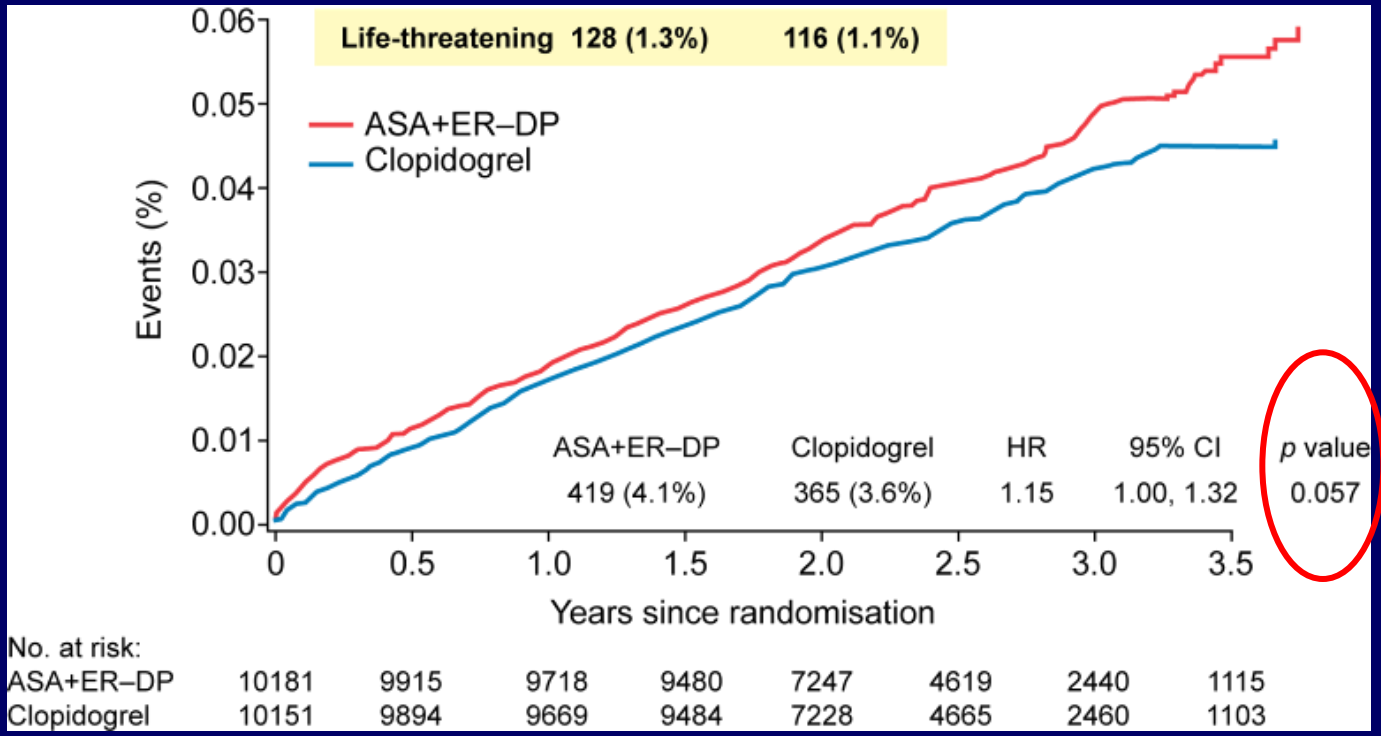
Secondary Outcome: Stroke, MI, Vascular Death



Sacco RL et al. *N Engl J Med* 2008;359: published online 27 August 2008.

PRoFESS: Major Hemorrhagic Events

End point	Aspirin + ER-Dipyridamole	Clopidogrel	Hazard Ratio (95% CI)	*P*
Major hemorrhagic event, No. (%)	419 (4.1)	365 (3.6)	1.15 (1.00 – 1.32)	.057
Life-Threatening hemorrhagic events	128 (1.3)	116 (1.1)	–	–

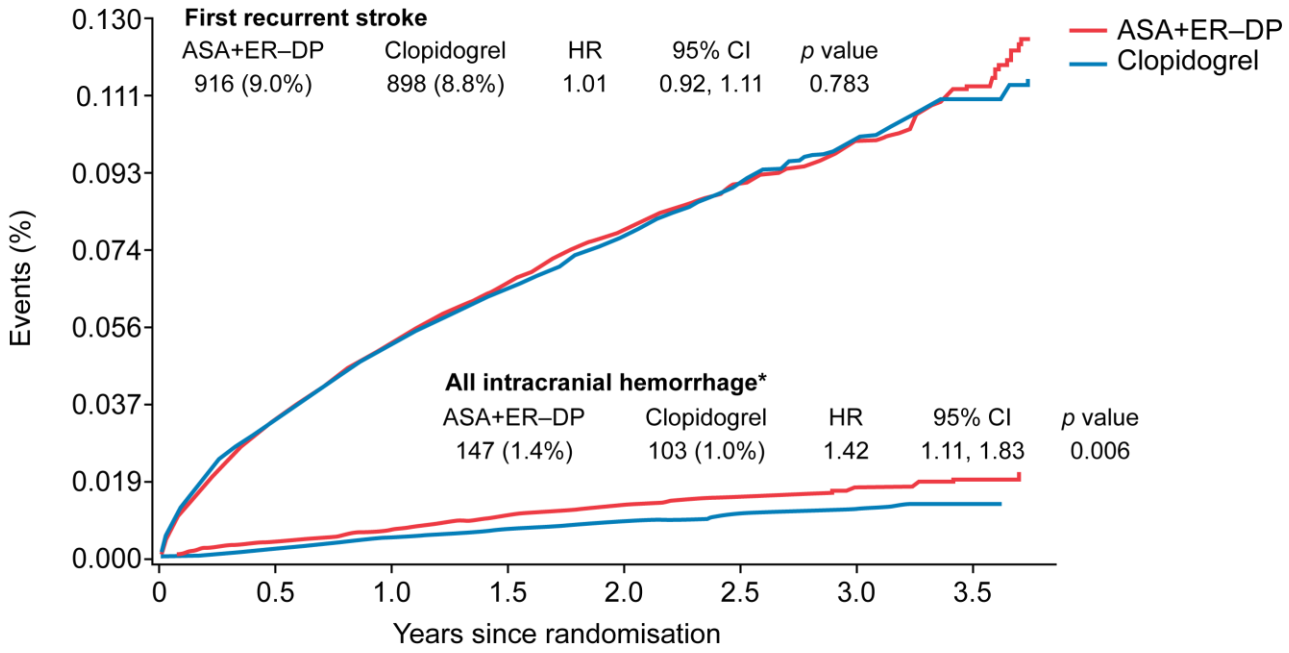


Recurrent Stroke or Intracranial Hemorrhage

PRoFESS: Safety

- **Major hemorrhagic events and intracranial bleeds occurred more frequently in the ER-DP plus ASA group compared with clopidogrel**

	ER-DP + ASA	Clopido-grel	Hazard Ratio (95% Confidence Interval)	*P* Value
Major hemorrhagic events	4.1%	3.6%	1.15 (1.00-1.32)	0.06
Intracranial hemorrhage*	1.4%	1.0%	1.42(1.11-1.83)	0.006



*128 of the 250 reported ICH events are also reported in the primary outcome

Sacco RL et al. *N Engl J Med* 2008;359

PRoFESS trial: summary of efficacy and safety

A) Efficacy endpoints

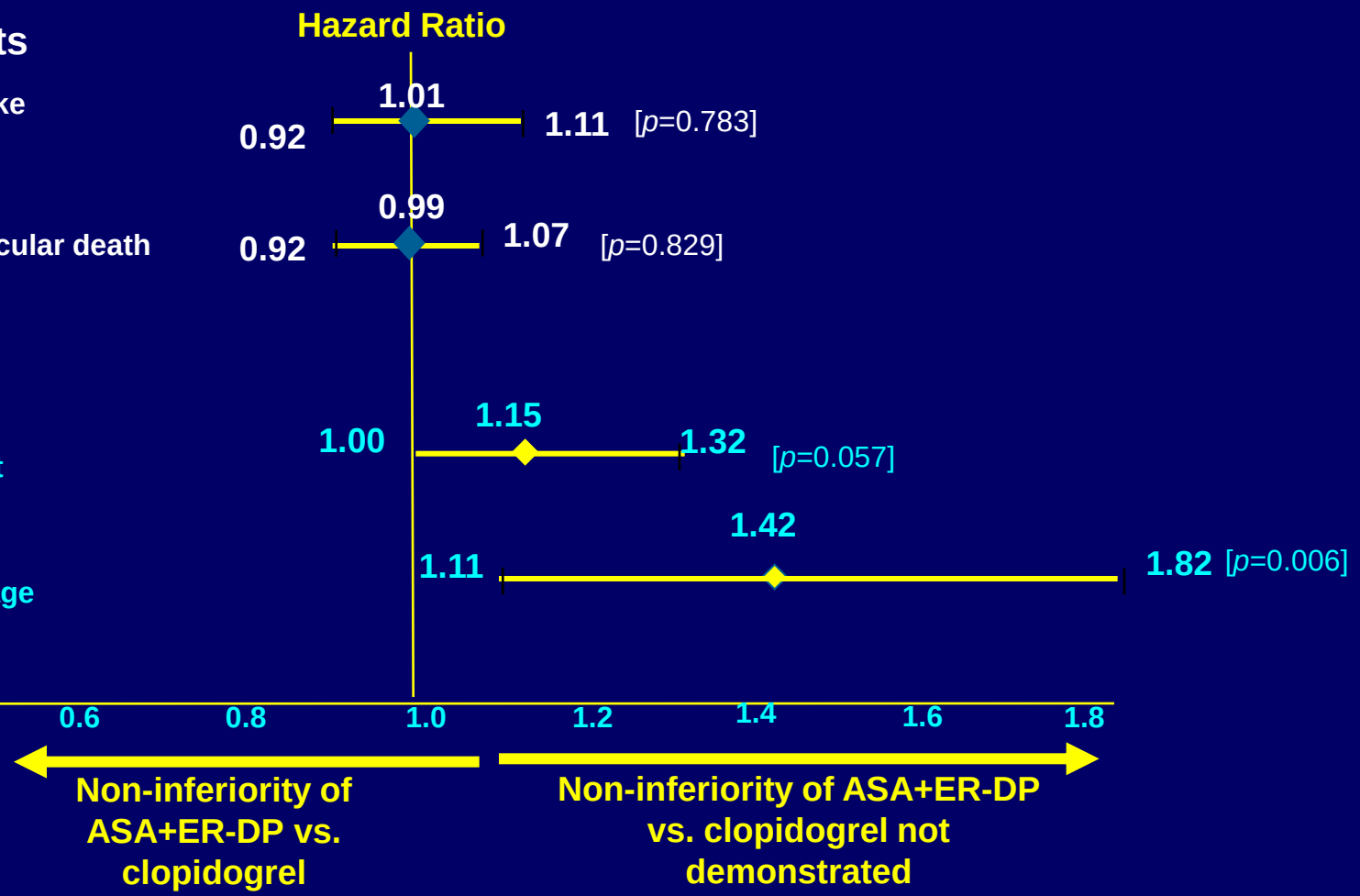
1º endpoint: recurrent stroke (non-inferiority test)

2º endpoint: stroke MI, vascular death

B) Safety endpoints

Major haemorrhagic event

All Intracranial haemorrhage



MI, myocardial infarction; ASA, acetylsalicylic acid; ER-DP, extended release dipyridamole

PRoFESS: Conclusions

- The largest secondary stroke prevention trial comparing the combination of aspirin and extended-release dipyridamole vs clopidogrel

- Did not met prespecified noninferiority criteria for ER-dipyridamole + ASA vs clopidogrel in preventing stroke recurrence after a first event

Annual Incidence of Ipsilateral Stroke in Non-operated Patients with Carotid Stenosis >60%

- **Asymptomatic patients[1]**
  - **~2.2% per year**
- **Symptomatic patients[2]**
  - **13% per year during first 2–3 years**
  - **1–2% per year thereafter**

1. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA* 1995; **273:** 1421–1428. 2. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 1991; **325:** 445–453.

CARESS: Study Objectives

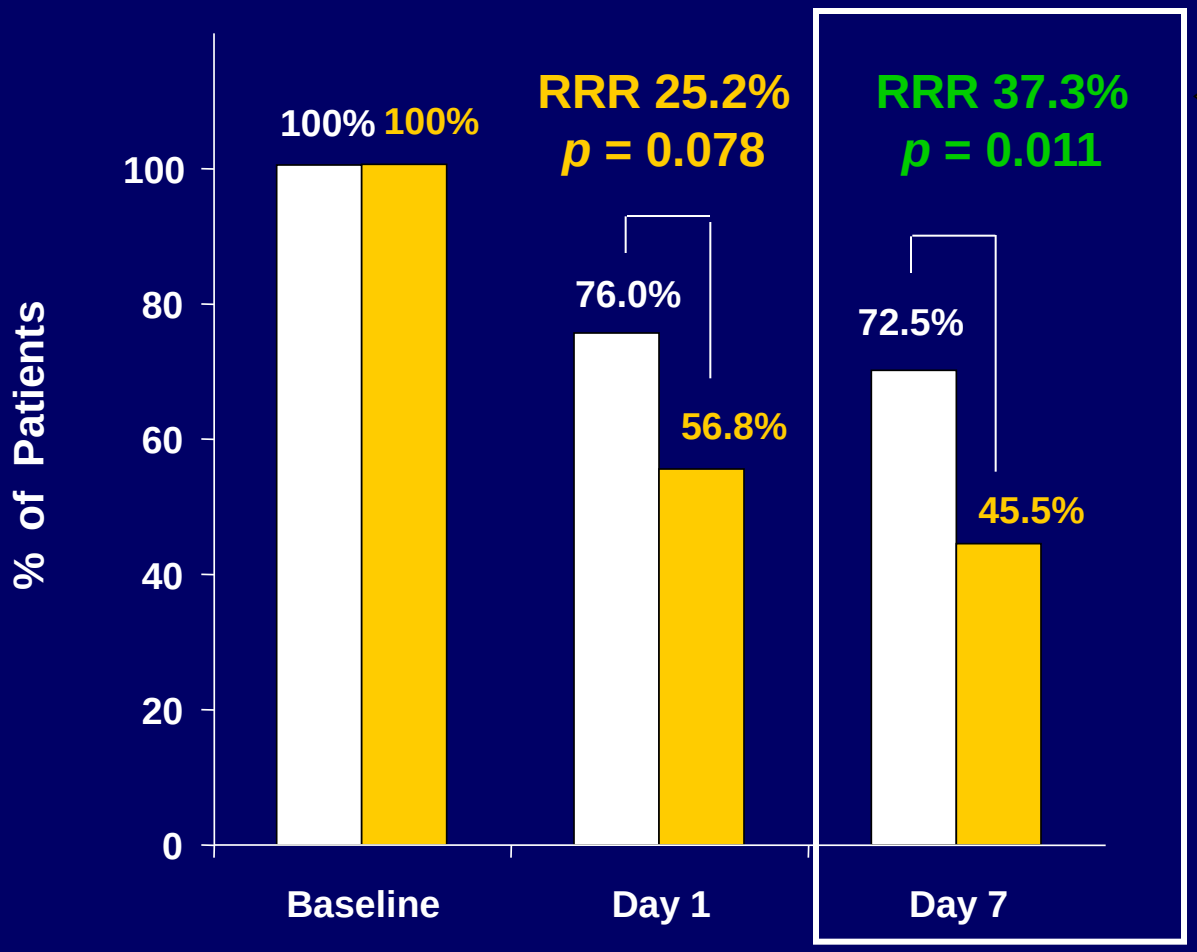
Primary

- **To evaluate whether clopidogrel added to ASA is superior to ASA alone in reducing the incidence of silent cerebral MES detected by TCD in patients with recently symptomatic carotid stenosis**

Secondary

- ***To compare the effects of the above regimens on platelet aggregation, platelet activation and platelet-dependent thrombin generation***
- ***To compare the safety of these two regimens***

Clopidogrel Significantly Reduces the Incidence of MES in Patients with Recent Symptomatic Carotid Stenosis



Primary Endpoint Results: Number of MES+ Patients at D7**

Placebo*

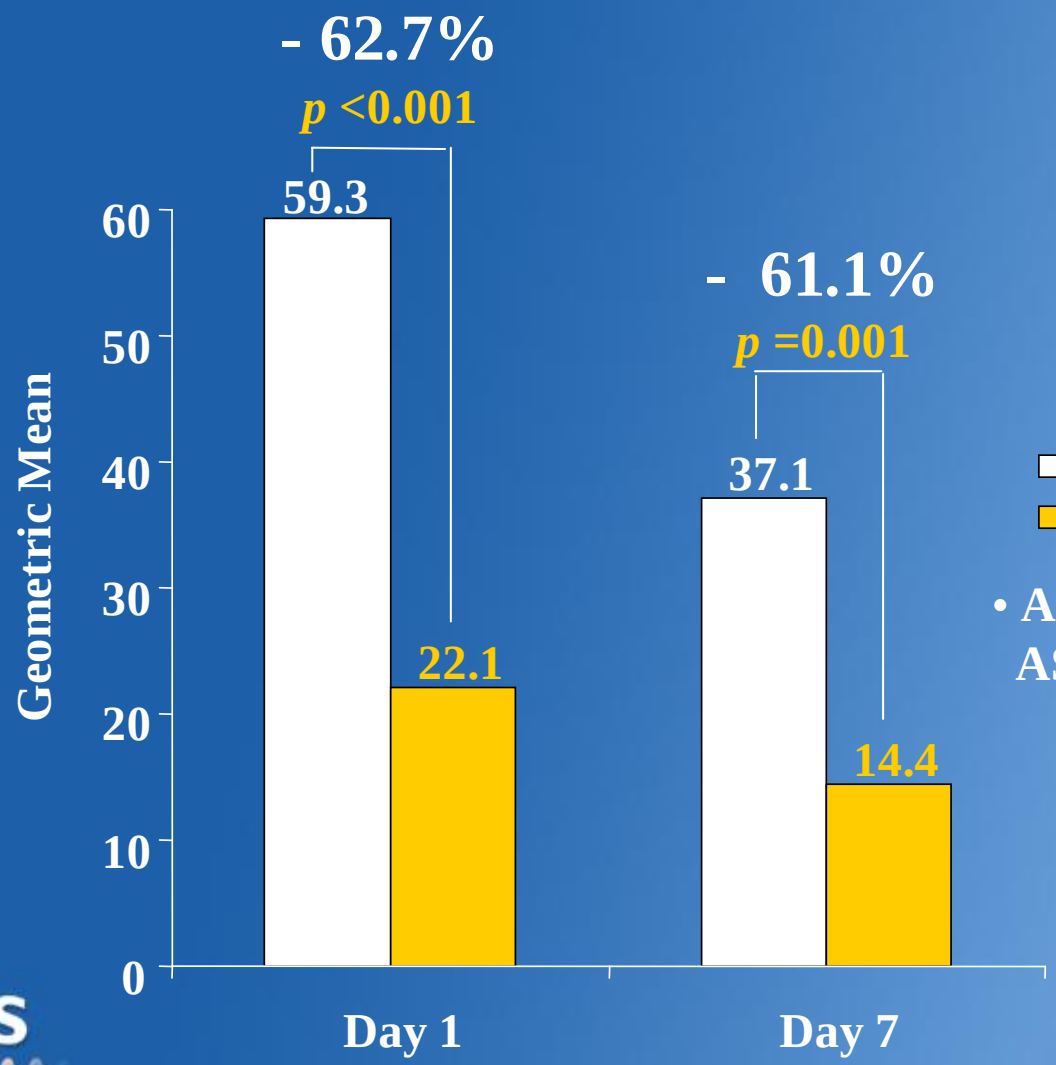
Clopidogrel*

*On a background of ASA 75 mg qd

**Off line analysis

CLOPIDOGREL significantly reduces the embolisation rate in patients with recently symptomatic carotid stenosis

Embolisation rate reduction



• All patients received ASA 75 mg/day

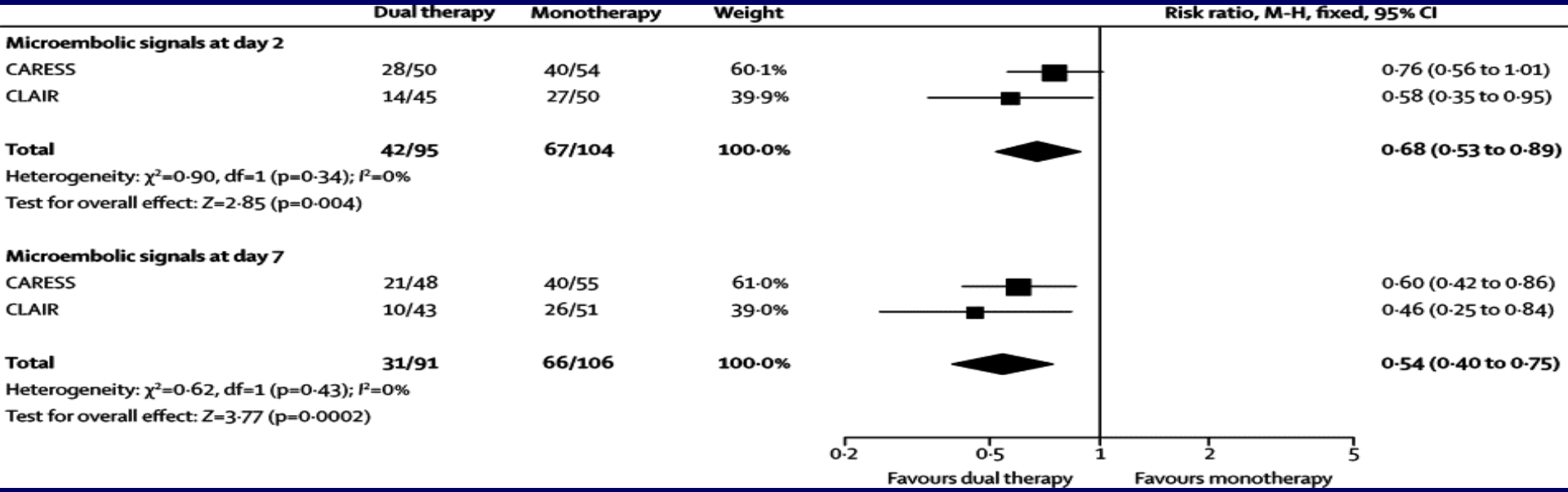
CARESS

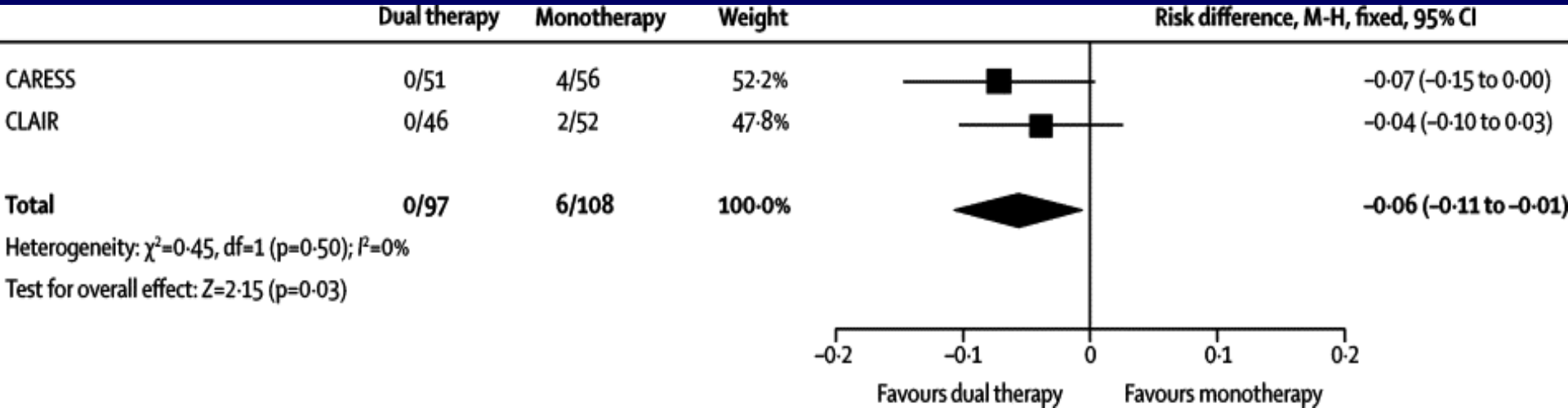
Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial

- randomised, open-label, blinded-endpoint trial
- 100 patients with recent stroke and with intracranial large artery stenosis and microembolic signals

Wong KSL et al - The Lancet Neurology 2010, 9(5): 489 - 497

Meta-analysis of number of patients with at least one microembolic signal (1) and of number of patients with recurrent stroke (2) in CARESS and CLAIR studies





RECEPTOR GP IIb / IIIa BLOCKERS

- oral: negative results in all trials

**** benefit: no greater than ASA***

**** more frequent hemorrhagic complications***

ANTIPLATELET ASSOCIATIONS

- do not activate GP IIb / IIIa

*** ASA (25 mg) + ER-DIPIRIDAMOL(200 mg) x 2/zi**

- superiority over ASA alone in patients with AVCI / AIT
(ESPS-2, ESPRIT)

- efficiency proved in patients with STROKE, not also in MI !

*** ASA + CLOPIDOGREL**

- CURE, CARESS

- MATCH (→→ NO !)

- CHARISMA

- SPS-3 (lacunar strokes) → results expected in 2012

HOW TO CHOOSE AN ANTIPLATELET TRATMENT FOR SECONDARY PREVENTION OF STROKE:

- GLOBAL CARDIOVASCULAR RISK EVALUATION

- ETIO-PATHOGENETIC STROKE SUBTYPE / TIA

- STROKE RISK EVALUATION

  * Clopidogrel: secondary prevention + HIGH RISK

    - stroke reccurence on ASA

    - ASA intolerance, bleeding

    - acute coronary syndrome (+ ASA)

    - more arterial teritories, including PAD

    - recent diagnosed carotid stenosis + MES (+ ASA)

Antithrombotic Therapy
ESO guidelines ischaemic stroke 2008

Recommendations

- **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 during the last 12 months, or recent stenting); treatment should be given for up to 9 months after the event (Class I, Level A)**

- **Patients who have a stroke on antiplatelet therapy should be re-evaluated for pathophysiology and risk factors (Class IV, GCP)**

Clopidogrel + aspirin combination in phase III ACTIVE programme in AF

Inclusion: documented AF + ≥ 1 risk factor for stroke

- Age ≥ 75 years
- On treatment of systemic hypertension
- Prior stroke, transient ischaemic attack, embolus
- Left ventricular (LV) dysfunction with LV ejection fraction < 45%
- Documented peripheral vascular disease
- 55-74 years with diabetes mellitus/post-MI/documented previous CAD

Contra-indications to OAC or unwilling

ACTIVE W
Open non-inferiority trial
6,706 patients randomised
- OAC (INR 2.0-3.0)
- Clopidogrel (75 mg od) + ASA (75-100 mg/d)

ACTIVE A
Double-blind RCT (superiority trial)
7,554 patients
- Placebo + ASA (75-100 mg/d)
- Clopidogrel (75 mg od) + ASA (75-100 mg/d)

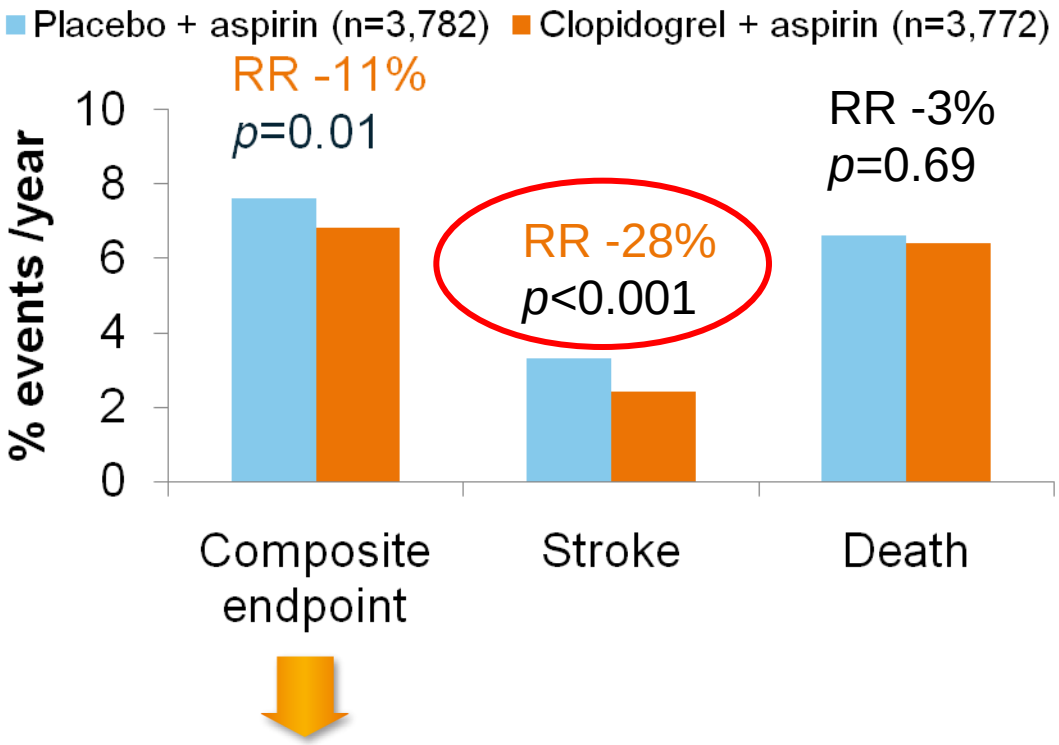
ACTIVE I (if SBP ≥ 110 mm Hg) ongoing

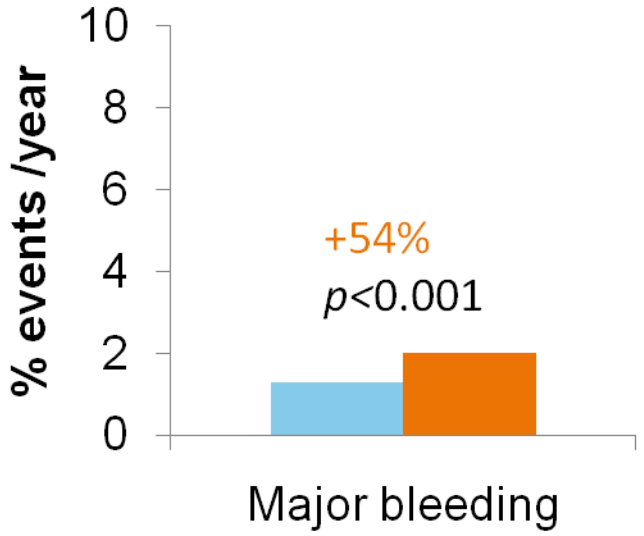
Primary outcome: composite endpoint of stroke, non-CNS systemic embolus, MI or vascular death

The Active Steering Committee. Am Heart J 2006;151:1187-93

ASA: aspirin; CAD: coronary artery disease

ACTIVE A: benefit in stroke reduction when adding clopidogrel to aspirin





Significant reduction by clopidogrel + aspirin versus aspirin alone is primarily due to reduction in stroke (no or only weak differential treatment effects for subgroups) after median follow-up of 3.6 years

Connolly SJ, et al. N Engl J Med 2009;360:2066-78

Conclusions

- While **antithrombotics are mainstay therapy in AF,** only **warfarin (for moderate-high risk)** or **aspirin (for low-moderate risk)** are recommended

- **Warfarin is more effective than aspirin** (when in targeted INR) but less convenient in use

- In **moderate to high-risk AF patients, clopidogrel + aspirin** is **less effective than OAC treatment** (ACTIVE W), but **more effective than aspirin alone** (ACTIVE A; ***OAC contra-indication***)

Sacco R, ESO Congress 2009, Stockholm

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Stroke Association
A Division of American Heart Association

Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack. A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Karen L. Furie, Scott E. Kasner, Robert J. Adams, Gregory W. Albers, Ruth L. Bush, Susan C. Fagan, Jonathan L. Halperin, S. Claiborne Johnston, Irene Katzan, Walter N. Kernan, Pamela H. Mitchell, Bruce Ovbiagele, Yuko Y. Palesch, Ralph L. Sacco, Lee H. Schwamm, Sylvia Wassertheil-Smoller, Tanya N. Turan, Deidre Wentworth and on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research

Stroke published online Oct 21, 2010;
DOI: 10.1161/STR.0b013e3181f7d043

1. **For patients with ischemic stroke or TIA with paroxysmal (intermittent) or permanent AF, anticoagulation with a vitamin K antagonist (target INR 2.5; range, 2.0 to 3.0) is recommended *(Class I; Level of Evidence A)*.**

2. **For patients unable to take oral anticoagulants, aspirin alone *(Class I; Level of Evidence A)* is recommended. The combination of clopidogrel plus aspirin carries a risk of bleeding similar to that of warfarin and therefore *is not recommended* for patients with a hemorrhagic contraindication to warfarin *(Class III; Level of Evidence B)*.** (New recommendation)

Authors' comment:
"On the basis of ***uncertainty of how to identify patients who are 'unsuitable' for anticoagulation***, as well as the ***lack of benefit in the analysis of vascular events plus major hemorrhage,*** **aspirin remains the treatment of choice** for AF patients who have a clear contraindication to vitamin K antagonist therapy but are able to tolerate antiplatelet therapy."

NB.
These new AF guidelines were written before recently regulatory approval of the oral thrombin inhibitor DABIGATRAN, based on encouraging results in the previously reported Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study.

PRACTICAL ATITUDE

(in agreement with ESO Guidelines for 2009):

- First TIA / stroke in a patient with low risk vascular profile, without significant comorbidities: ASA or *ER-Dipiridamole+ASA*

- TIA / stroke in a patient with vascular co-morbidities / high risk: CLOPIDOGREL

- New vascular event in a patient treated with ASA: CLOPIDOGREL or *ER-Dipiridamole+ASA*

- New event in a patient with CLOPIDOGREL / peri-stenting / particular group of pathology (CURE, CARESS, CLAIR): CLOPIDOGREL+ASA *(at least for a limited delay of 9 months)*

AHA / ASA Guidelines 2010

- Particular recommendations -

1. **In patients with prior stroke or transient cerebral ischemic attack in sinus rhythm who have cardiomyopathy characterized by systolic dysfunction (LVEF <35%), the benefit of warfarin has not been established *(Class IIb; Level of Evidence B)*.** (New recommendation)

2. **Warfarin (INR 2.0 to 3.0), aspirin (81 mg daily), clopidogrel (75 mg daily), or the combination of aspirin (25 mg twice daily) plus extended-release dipyridamole (200 mg twice daily) may be considered to prevent recurrent ischemic events in patients with previous ischemic stroke or TIA and cardiomyopathy *(Class IIb; Level of Evidence B)***

AHA / ASA Guidelines 2010

- Particular recommendations -

- **For patients with ischemic stroke or TIA and native aortic or nonrheumatic mitral valve disease who do not have AF, antiplatelet therapy may be reasonable *(Class IIb; Level of Evidence C)*.**

- **For patients with ischemic stroke or TIA and mitral annular calcification, antiplatelet therapy may be considered *(Class IIb; Level of Evidence C)*.**

- **For patients with mitral valve prolapse who have ischemic stroke or TIAs, long-term antiplatelet therapy may be considered *(Class IIb; Level of Evidence C)***