

Advances in atherothrombosis management in the complex patients

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Case

M/70

Gangrenous wound, right leg

Rutherford 5

Risk factors:

Hypertension (+)

Smoking (-)

DM (+), 15 years, insulin treatment

Dyslipidemia (+)

Peripheral angiography



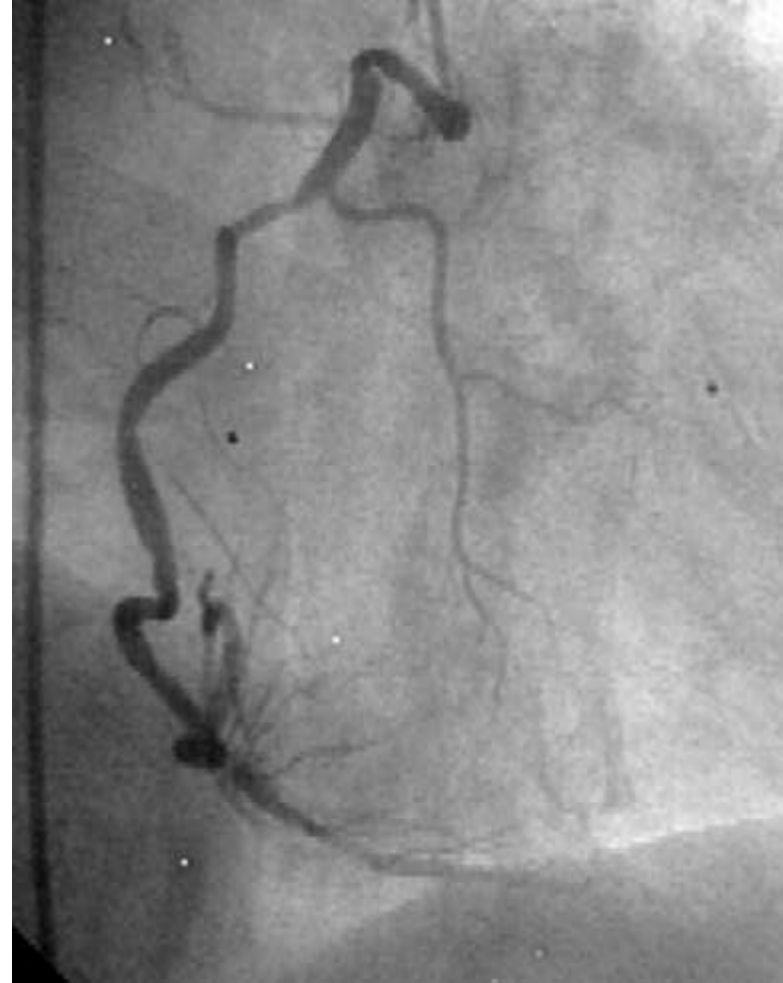
Total occlusion of right SFA

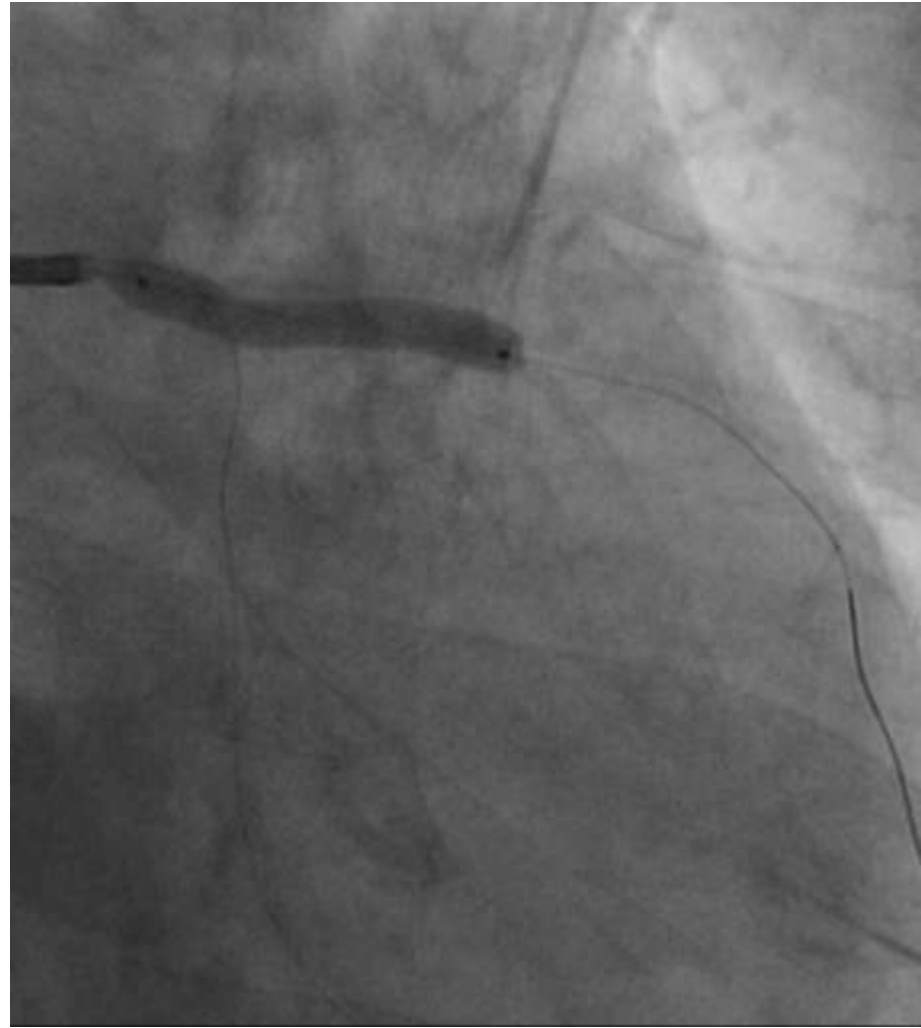
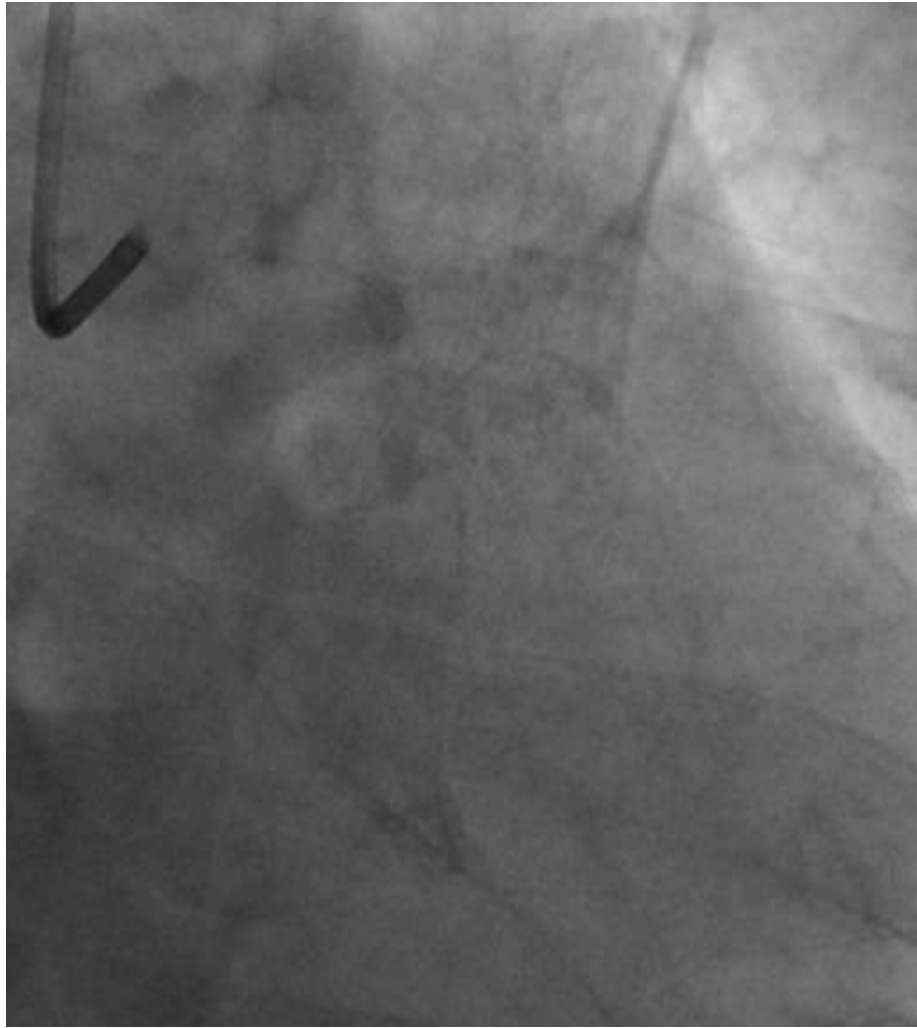
**Right popliteal artery
puncture**

retrograde approach

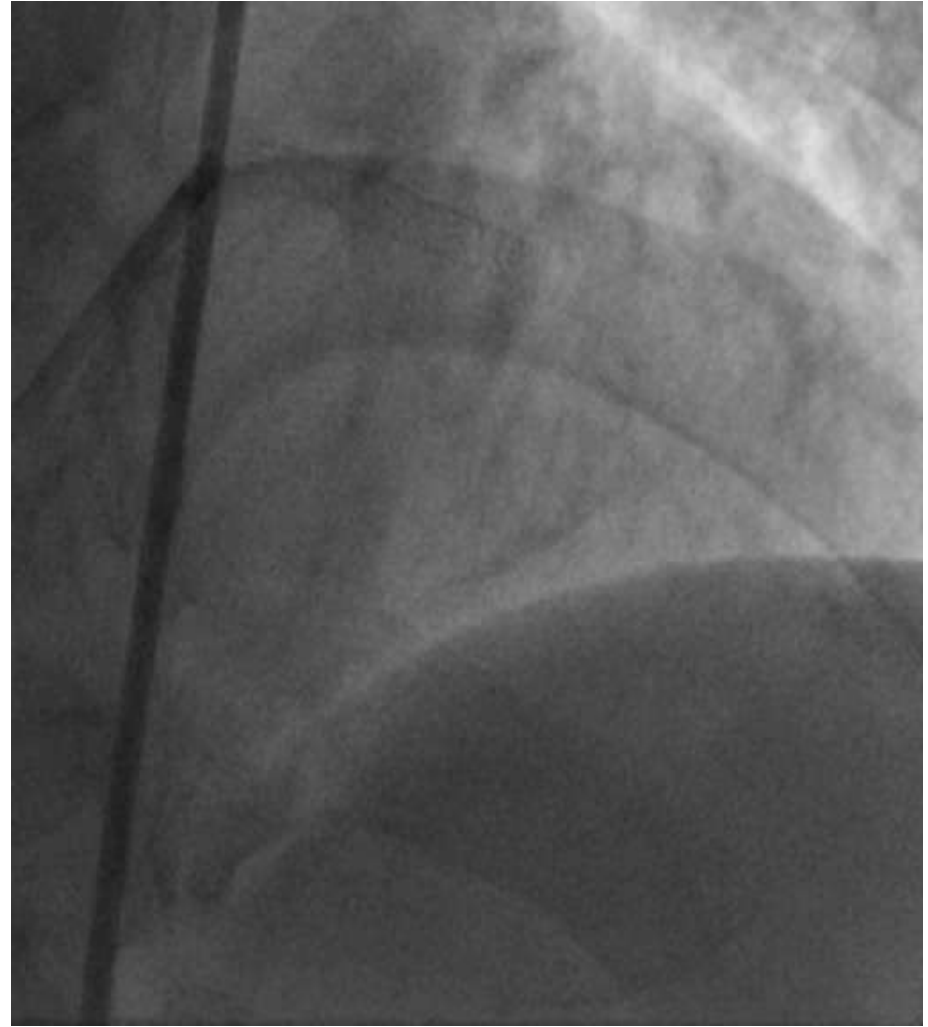
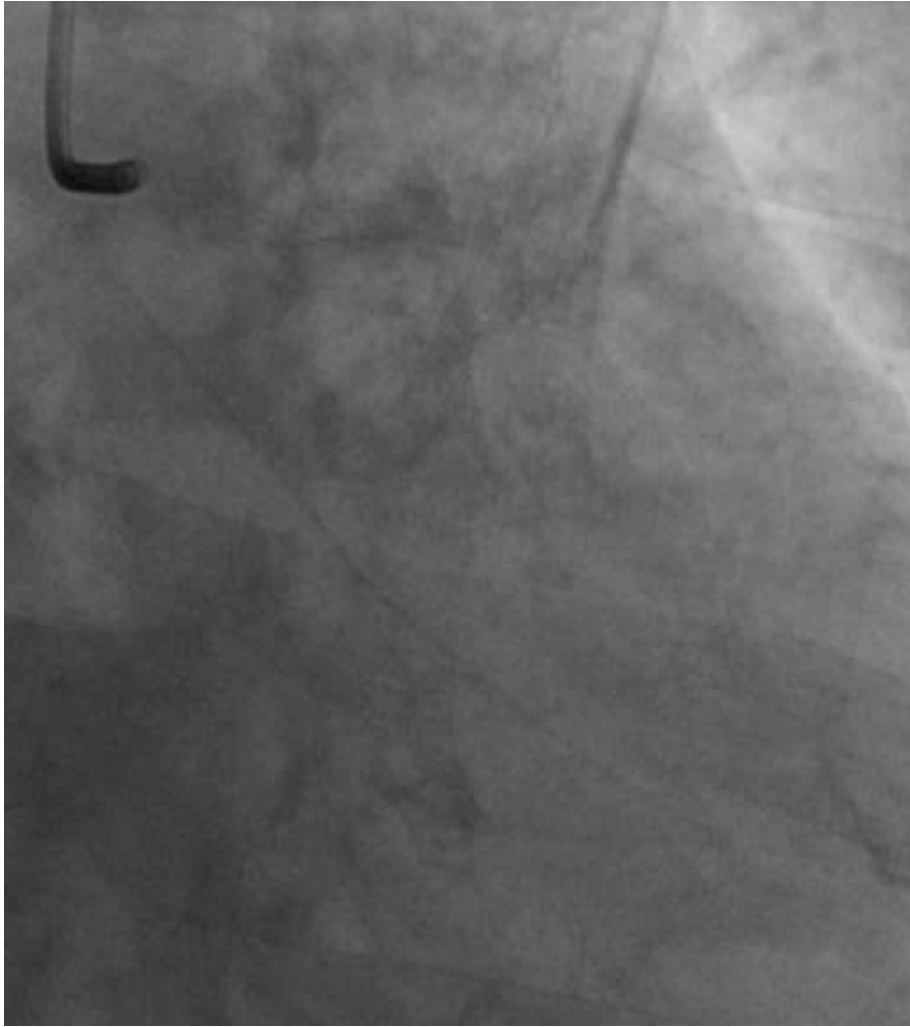
SMART 7x10 mm stent

Coronary angiography after peripheral intervention





FINAL ANGIOGRAPHY



Discharged after

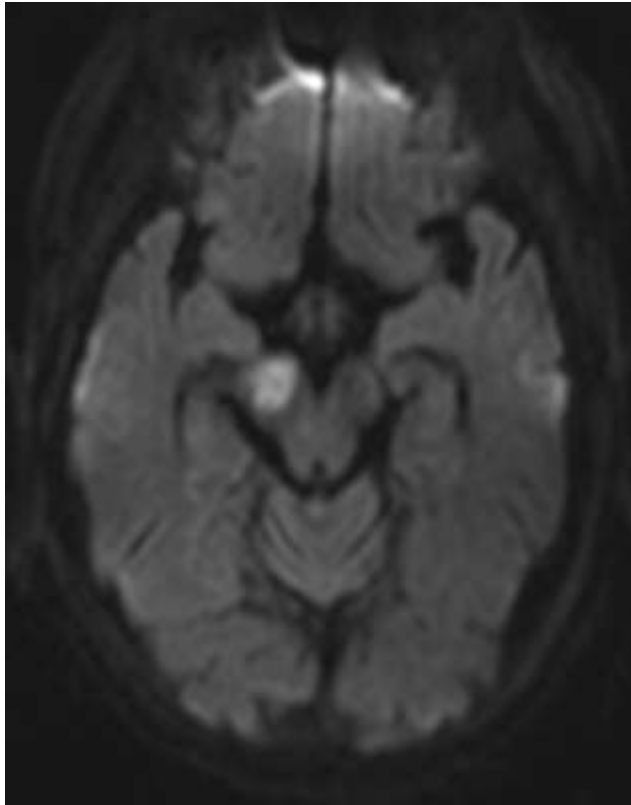
Peripheral stenting at right SFA

Coronary stenting at LM

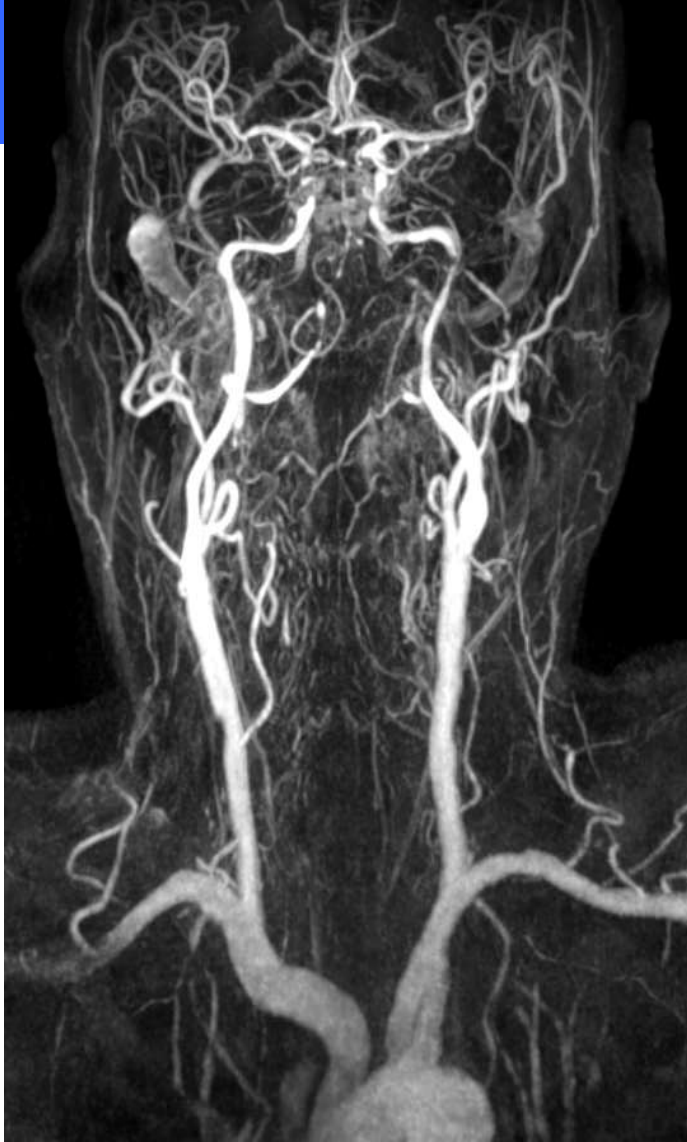
1 month later

Admitted to Emergency Room

**because of left side weakness and
dysarthria**



Acute infarction at right midbrain and splenium of corpus callosum on DWI

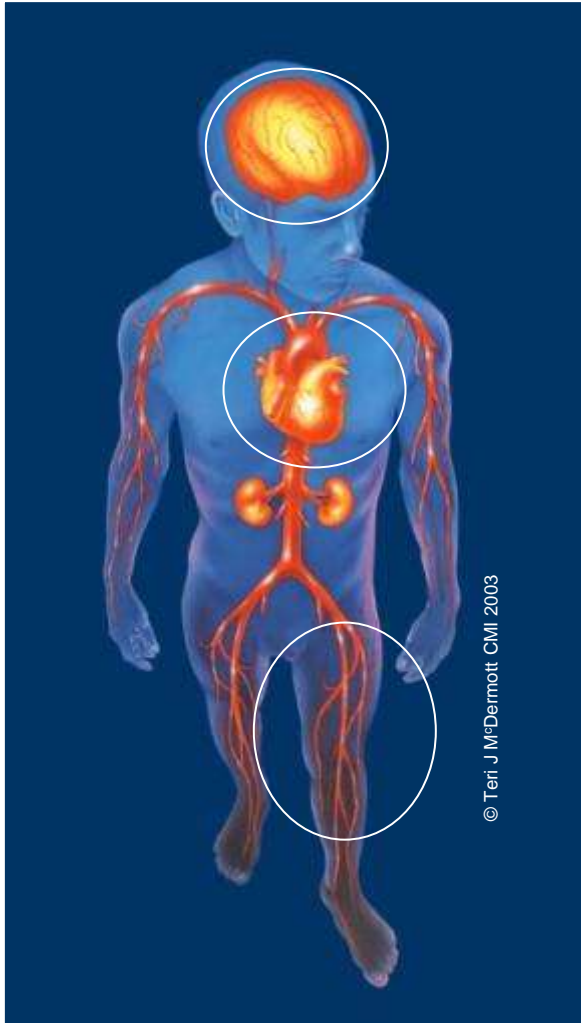


Multifocal significant stenosis or near total occlusion at bilateral proximal VAs and BA.
Multifocal significant stenosis at left petrous ICA, right cavernous ICA.
Multifocal mild stenoses with irregularities at bilateral carotid bulbs, left cavernous ICA and right proximal PCA.

- **What is Polyvascular Disease ?**
 - **Pathogenesis**
 - **Prevalence**
 - **Prognosis**

Polyvascular Disease

: Disease in more than one Arterial Bed



Polyvascular disease is defined as presence of more than one affected vascular bed.

That is,

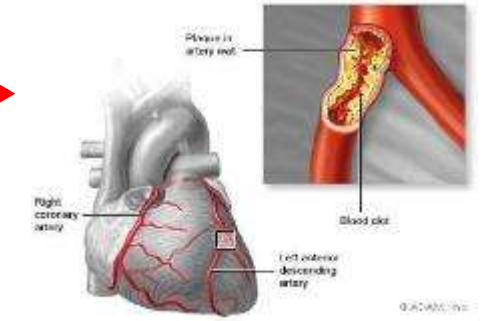
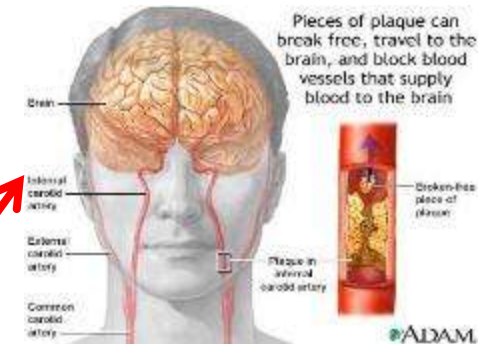
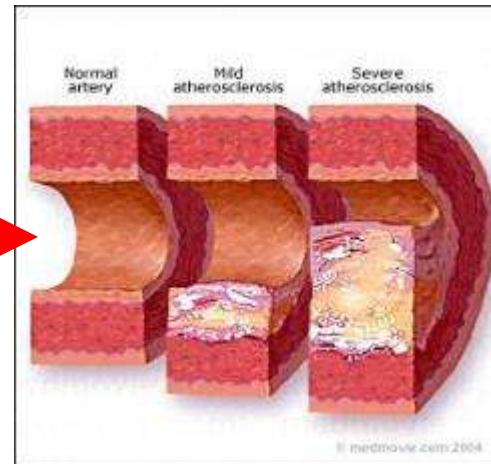
- Cerebrovascular disease (CVD)
- Coronary artery disease (CAD)
- Peripheral arteries (PAD)

Common Pathophysiology

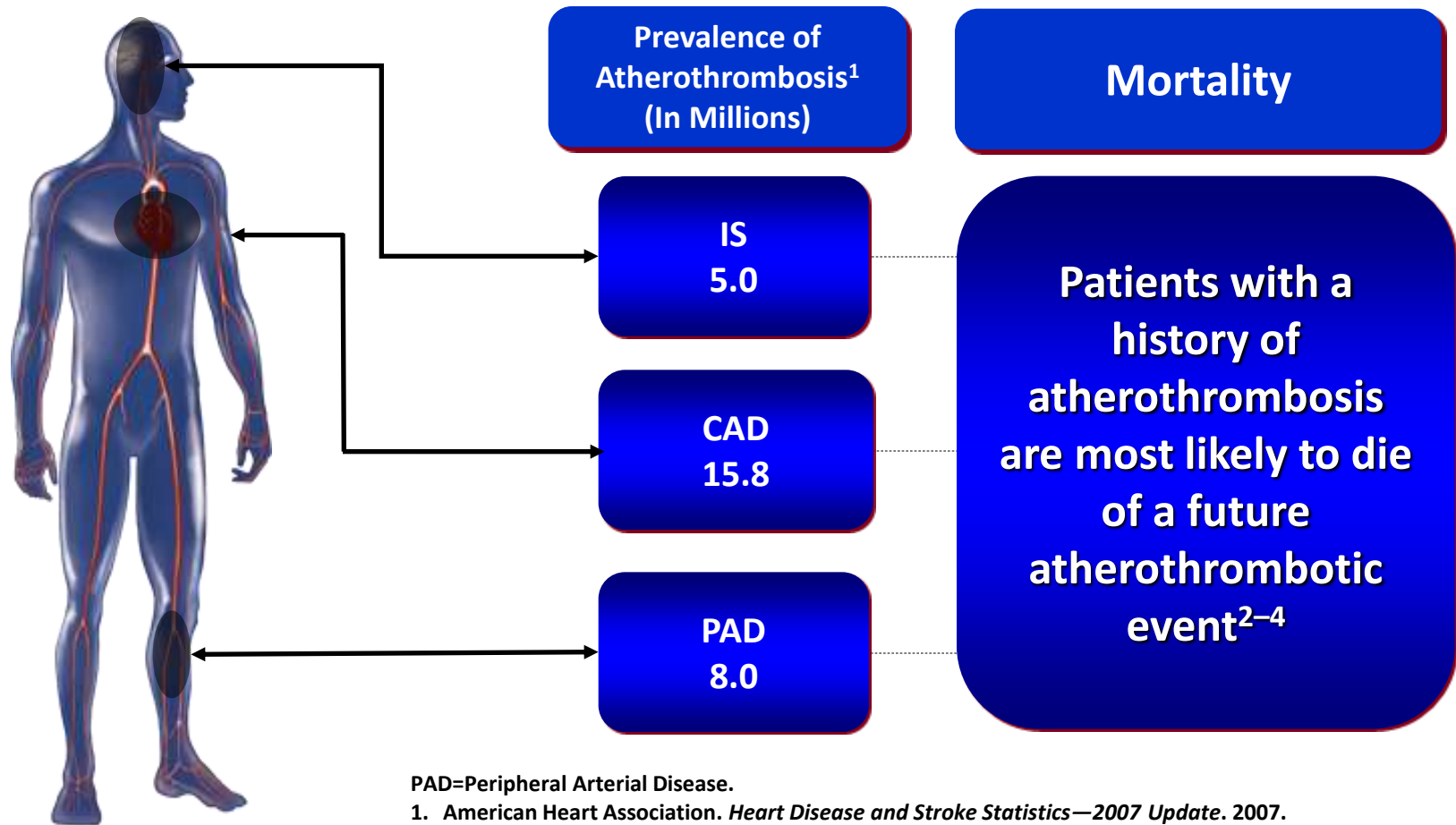
Risk Factors

- Gender (male)
- Age
- Smoking
- Hypertension
- Diabetes
- Hyperlipidaemia
- Fibrinogen
- Homocysteinaemia

Atherosclerosis



Atherothrombosis Manifestations: Stroke, CAD, and PAD



PAD=Peripheral Arterial Disease.

1. American Heart Association. *Heart Disease and Stroke Statistics—2007 Update*. 2007.
2. Hardie K et al. *Stroke*. 2003;34:1842-1846.
3. Taneja AK et al. *Eur Heart J*. 2004;25:2013-2018.
4. Hirsch AT et al. Executive Summary. Available at: <http://www.acc.org>. Accessed December 7, 2007.

Patients with previous atherothrombotic events are at increased risk of further events

Increased risk versus general population

Previous event	MI	Stroke
Ischemic stroke	2–3 X (includes angina and sudden death*) ¹	9 X ²
MI	5–7 X (includes death) ³	3–4 X (includes TIA) ¹
PAD	4 X (includes only fatal MI and other CHD death [†]) ⁴	2–3 X (includes TIA) ¹

*Sudden death defined as death documented within one hour and attributed to coronary heart disease (CHD)

[†]Includes only fatal MI and other CHD death; does not include non-fatal MI

1. Kannel WB. *J Cardiovasc Risk*,1994;1:333–339.
2. Wilterdink JI et al. *Arch Neurol*,1992;49:857–863.
3. Adult Treatment Panel II. *Circulation*,1994;89:1333–1363.
4. Criqui MH et al. *N Engl J Med*,1992;326:381–386.

● REACH Registry

REACH: Overview of the REduction of Atherothrombosis for Continued Health Registry

REACH Registry

- Objective**
 - To establish contemporary international CV event rates in outpatients
- Design**
 - Outpatients aged 45 years or older with established CAD, CVD, or PAD, or with at least three atherothrombotic risk factors (n=68,236 patients)
- Primary endpoint**
 - Cumulative incidence of CV death, MI or stroke
- Follow-up**
 - 4 years

CAD=Coronary Artery Disease; CVD=CerebroVascular Disease.

Steg PG. *JAMA*. 2007;297:1197-1206.

The REACH registry is sponsored by Sanofi-Aventis and Bristol-Meyers Squibb.

The REACH registry includes patients with conditions for which PLAVIX may not be indicated.

REACH Registry inclusion criteria

Must include:

Signed
written
informed
consent

Patients aged
≥45 years

At least
1 of four
criteria

1. Documented cerebrovascular disease
Ischemic stroke or TIA
2. Documented coronary disease
Angina, MI, angioplasty/
stent/bypass
3. Documented historical
or current intermittent
claudication associated
with ABI <0.9

4. At least
3 atherothrombotic
risk factors

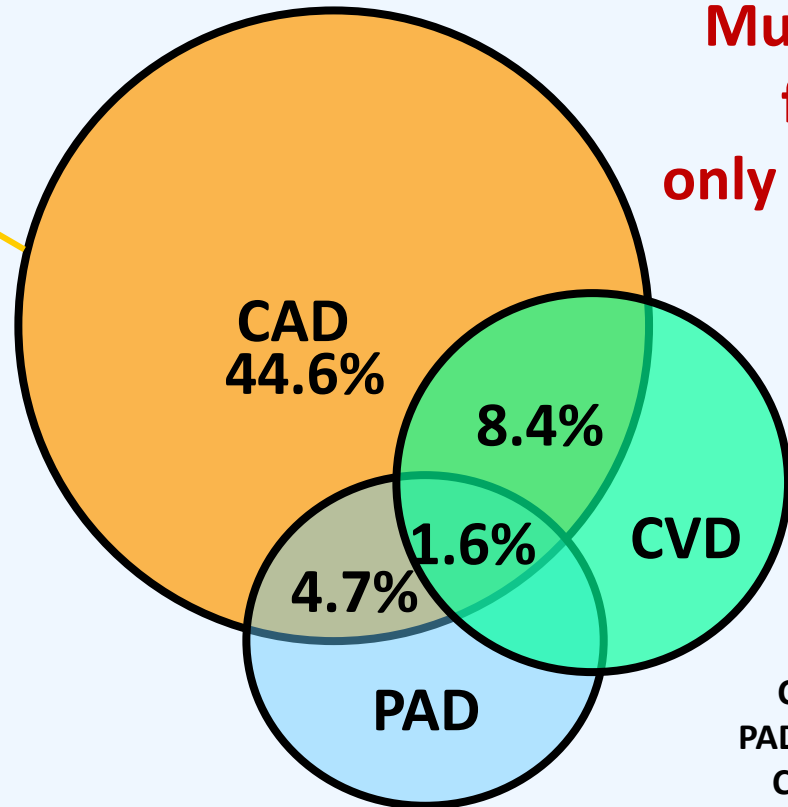
1. Male aged ≥65 years
or female aged ≥70 years
2. Current smoking
>15 cigarettes/day
3. Type 1 or 2
diabetes
4. Hypercholesterolemia
5. Diabetic nephropathy
6. Hypertension
7. ABI <0.9 in either
leg at rest
8. Asymptomatic carotid
stenosis ≥70%
9. Presence of at least
one carotid plaque

~ 1/4 of patients with CAD have polyvascular disease

~ 1/4 of the 40,258 patients with CAD also have atherothrombotic disease
in other arterial territories
(%s are of total population)

Patients with
CAD = 59.3%
of the REACH
Registry
population

Multiple risk
factors
only population

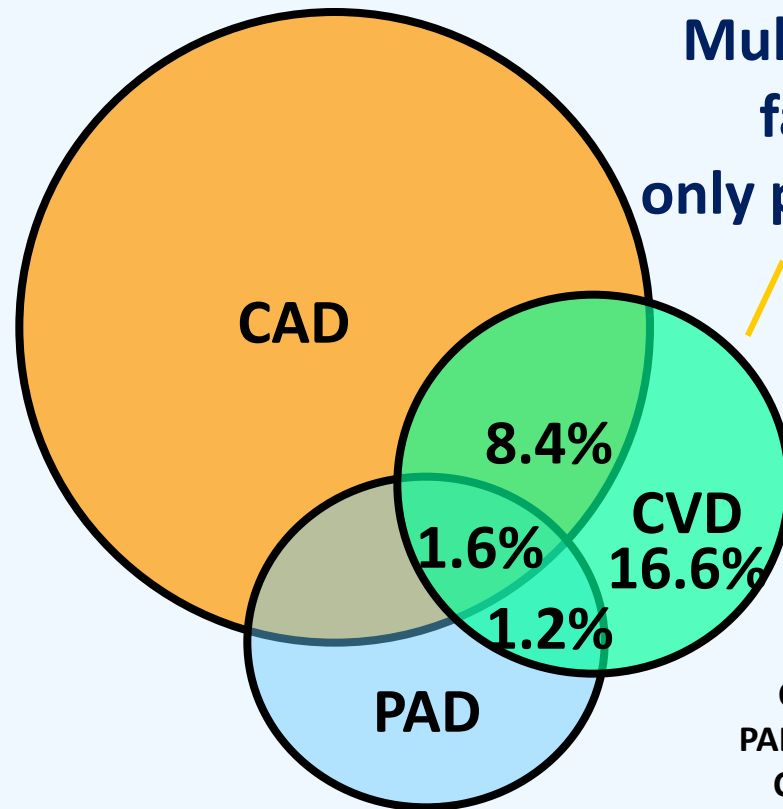


CAD=coronary artery disease
PAD=peripheral arterial disease
CVD=cerebrovascular disease



~ 2/5 of patients with CVD have polyvascular disease

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



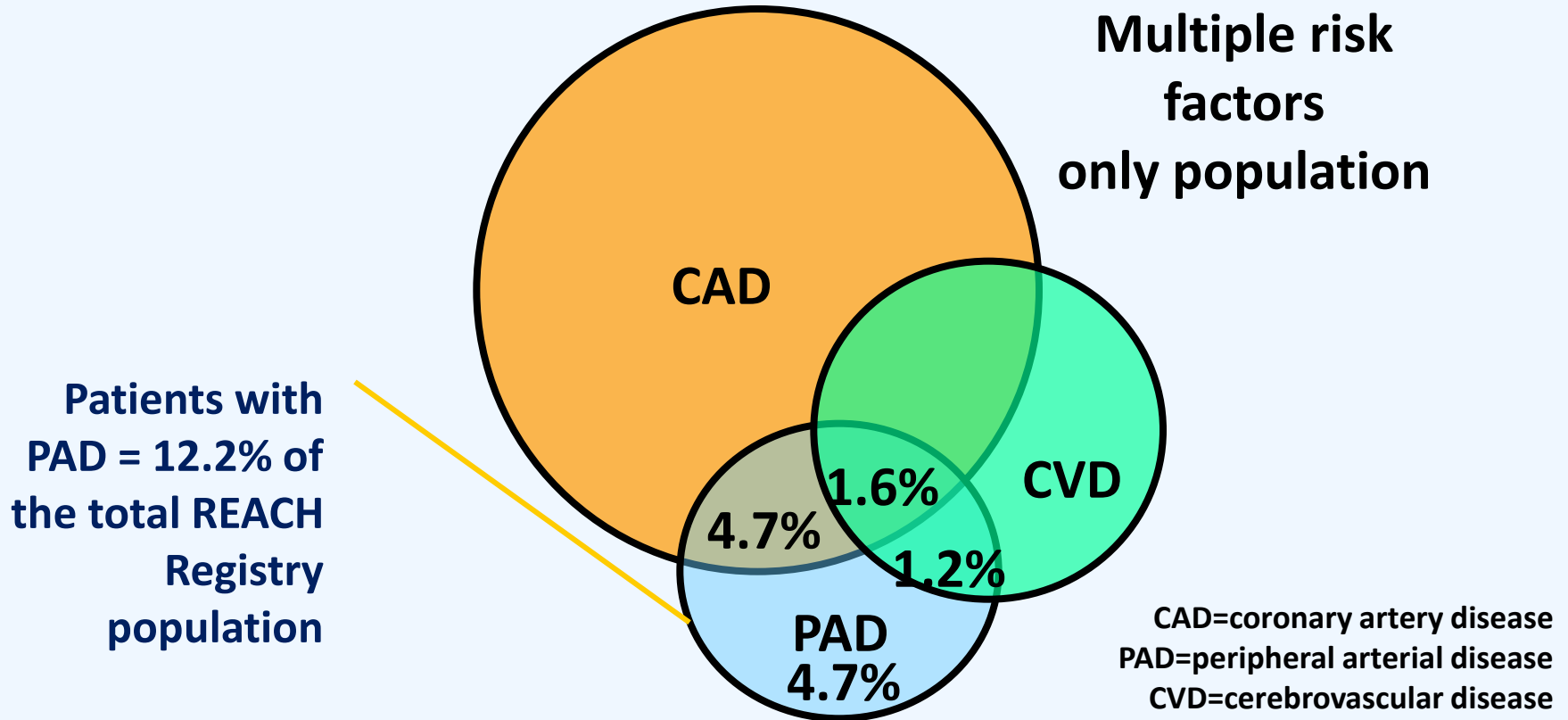
Multiple risk factors only population

Patients with CVD = 27.8% of the REACH Registry population

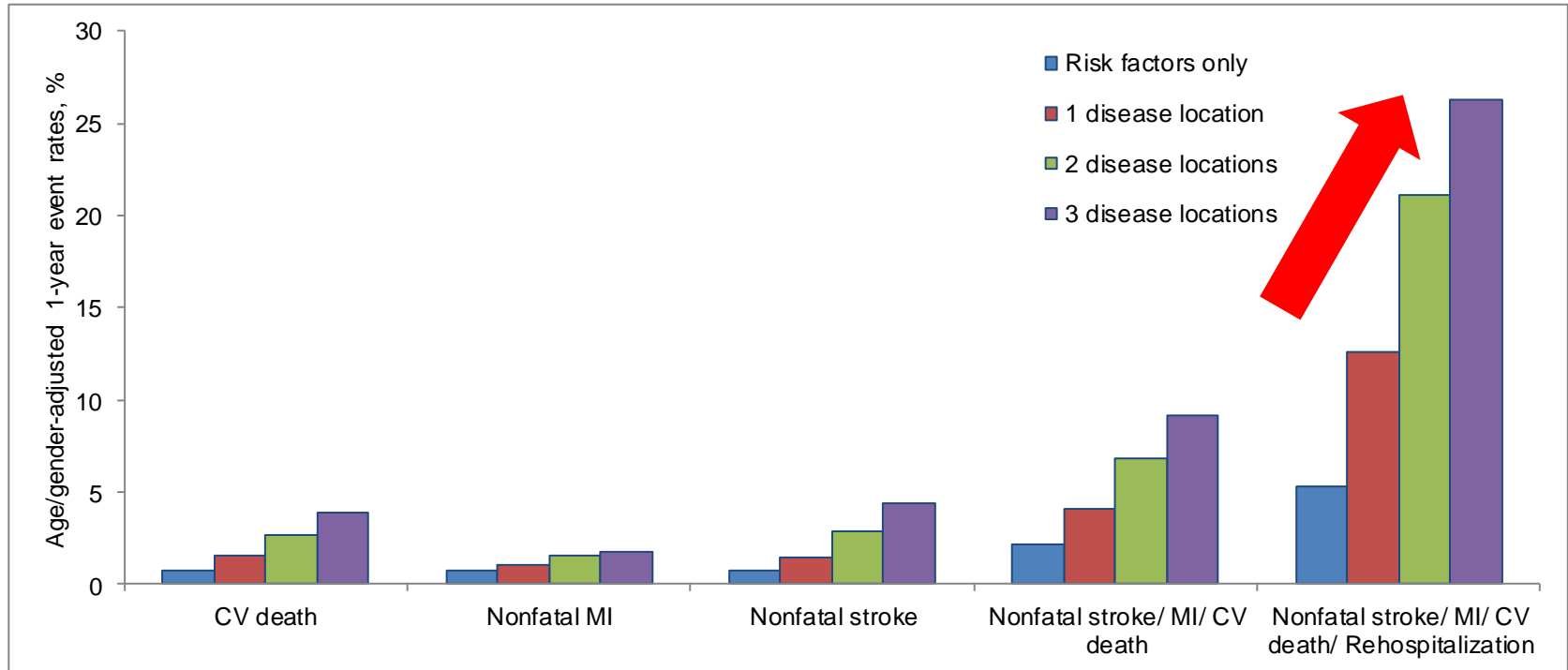
CAD=coronary artery disease
PAD=peripheral arterial disease
CVD=cerebrovascular disease

~ 3/5 of patients with symptomatic PAD have polyvascular disease

~ 3/5 of the 8,273 patients with PAD also have
atherothrombotic disease in other arterial territories



Patient outcomes at 1 year after enrolment



- CV event rates increased according to number of disease beds.

CV, cardiovascular; MI, myocardial infarction.

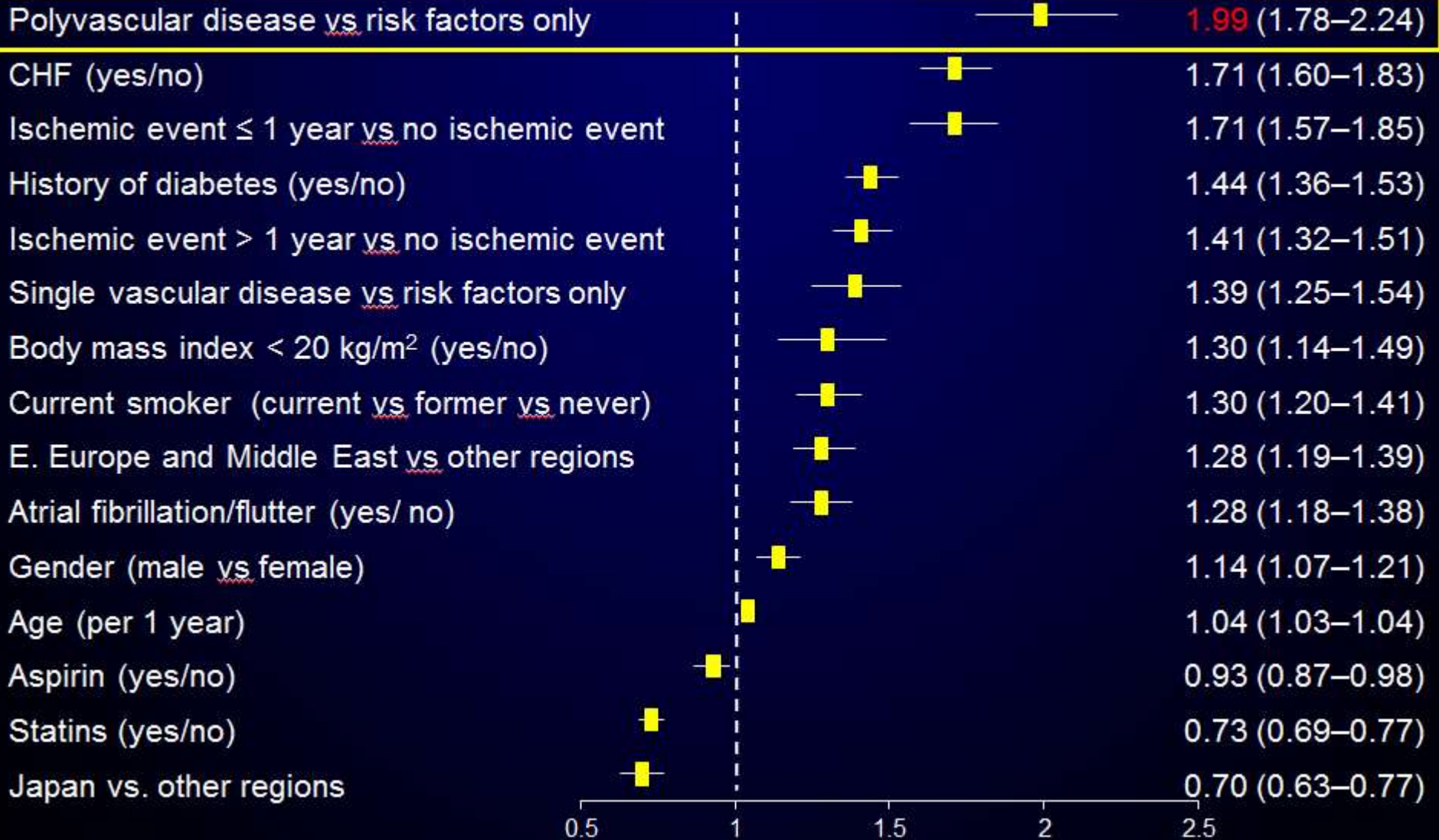
¹Steg PG et al. JAMA 2007;297:1197.

Predicting CV event rates at 4 years

¹Bhatt DL on behalf of the REACH registry Investigators. Presented at Clinical Trial Update session at ESC 2010.

**Hazard ratio
(95% CI)**

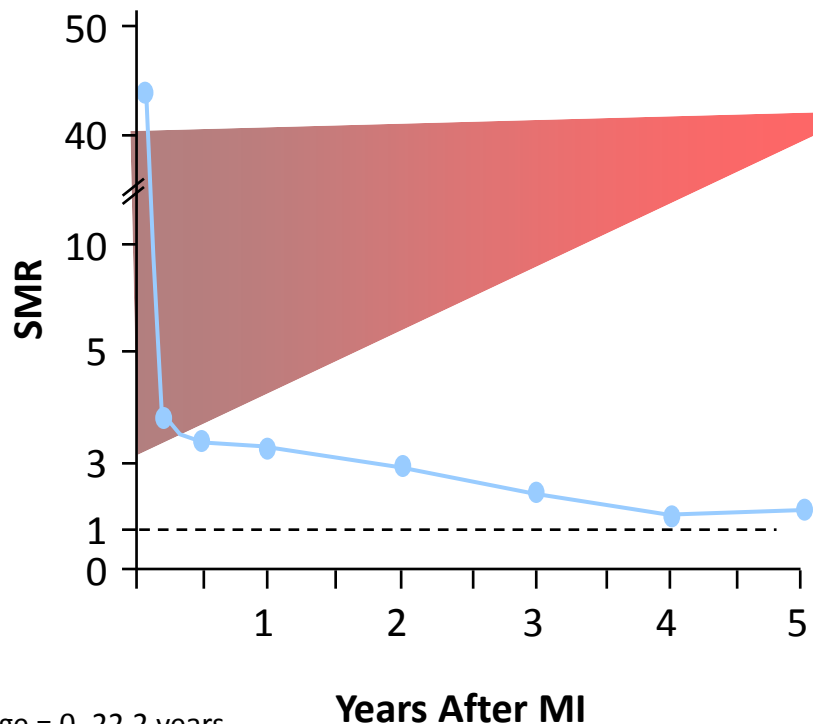
Variable



- **Are each vascular disease related with others ?**

Relative Risk of Stroke after MI : Highest in the First Month

Patients (N=2,160) hospitalized for MI
were followed for a median of 5.6 years*



The risk of stroke after MI in the first month is **44x** that of the general population

The risk for stroke remained **2–3x** higher than expected during the **first 3** years after MI. The unadjusted risk reduction for death was calculated to be **3.94** (3.32–4.67, $P<0.001$).

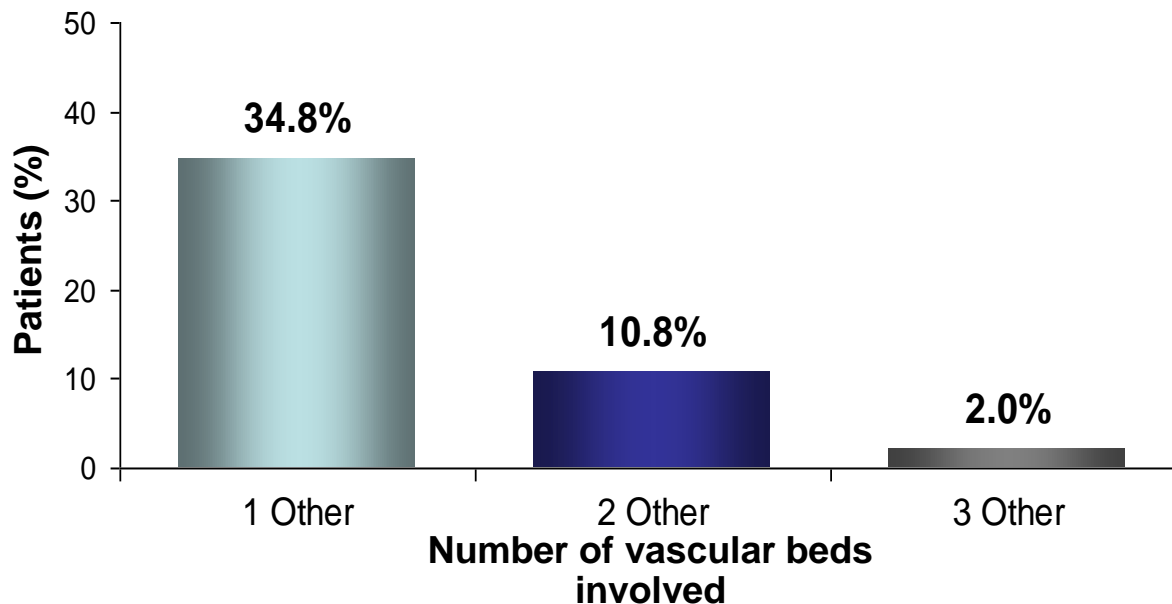
* Range = 0–22.2 years.

SMR=Standardized Mortality Ratio.

Witt BJ et al. *Ann Intern Med.* 2005;143:785-792.

DETECT: Nearly 50% of Ischemic Stroke Patients Had at Least One Other Form of Vascular Disease

- In the DETECT (Diabetes Cardiovascular Risk-Evaluation: Targets and Essential Data for Commitment of Treatment) survey, 753 patients admitted for IS were assessed for evidence of disease in other vascular beds*
- 358 of 753 (47.5%) had at least one other manifestation of atherothrombosis

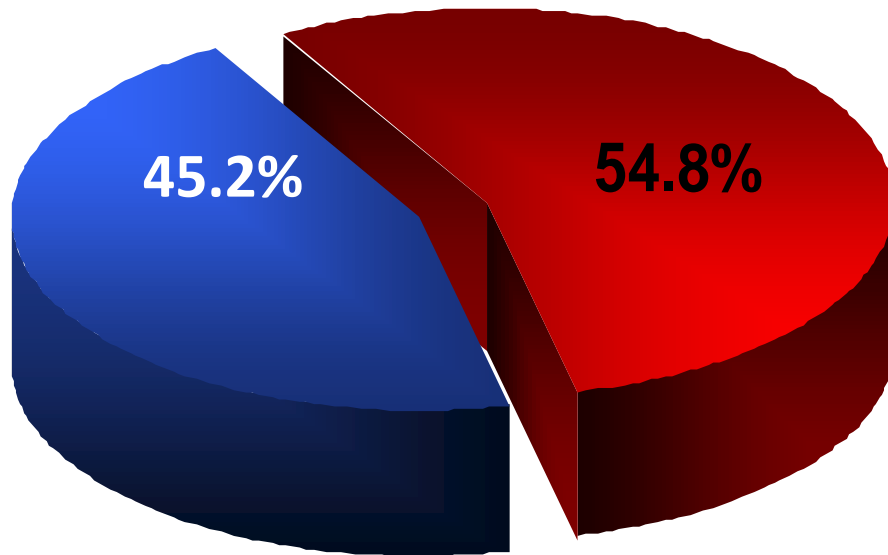


* CAD, aortic atheroma, or PAD, as defined by history and assessment of other vascular beds.

Leys D et al. *Cerebrovasc Dis.* 2006;21:60-66.

The DETECT Study was sponsored by the Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership.

SCALA: The Prevalence of PAD in IS Patients



A study of 852 patients with TIA or ischemic stroke found **54.8%** patients had a form of PAD. This included:

- **50.8%** of the total population had an ABI ≤ 0.9
- **10.0%** of the total population had intermittent claudication

ABI=Ankle-Brachial Index.

TIA is not a labeled indication in some countries.

This study was funded by sanofi-aventis.

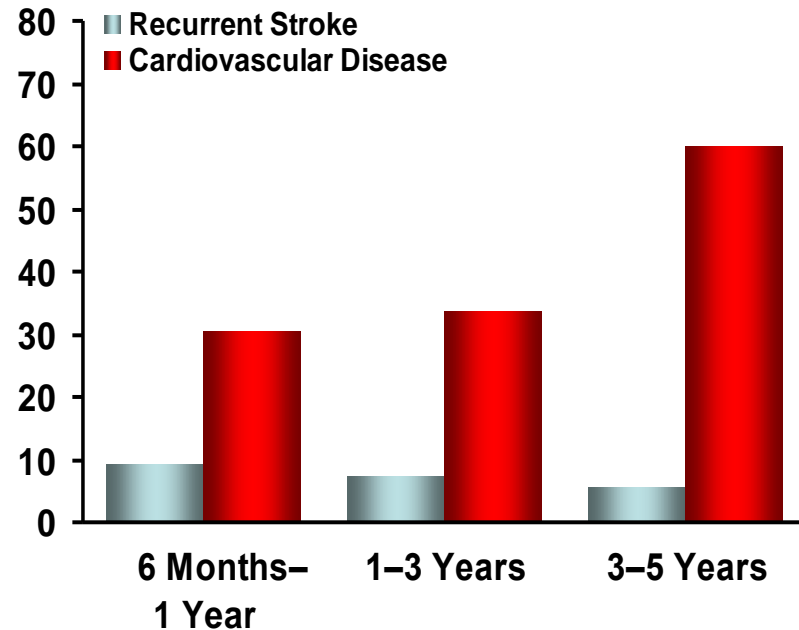
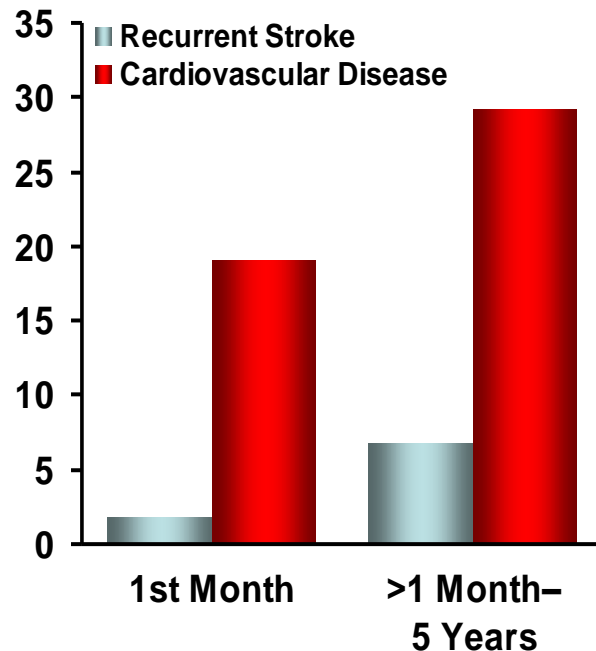
Weimar C et al. *J Neurol.* 2007 Aug 3; [Epub ahead of print].

Stroke patients have more risks to die from a MI rather than a stroke

Cardiovascular Disease as Cause of Death After First Ischemic Stroke

NOMASS¹

Perth²



NOMASS=Northern Manhattan Stroke Study.

1. Hartmann A et al. *Neurology*. 2001;57:2000-2005.

2. Hankey GJ et al. *Stroke*. 2000;31:2080-2086.

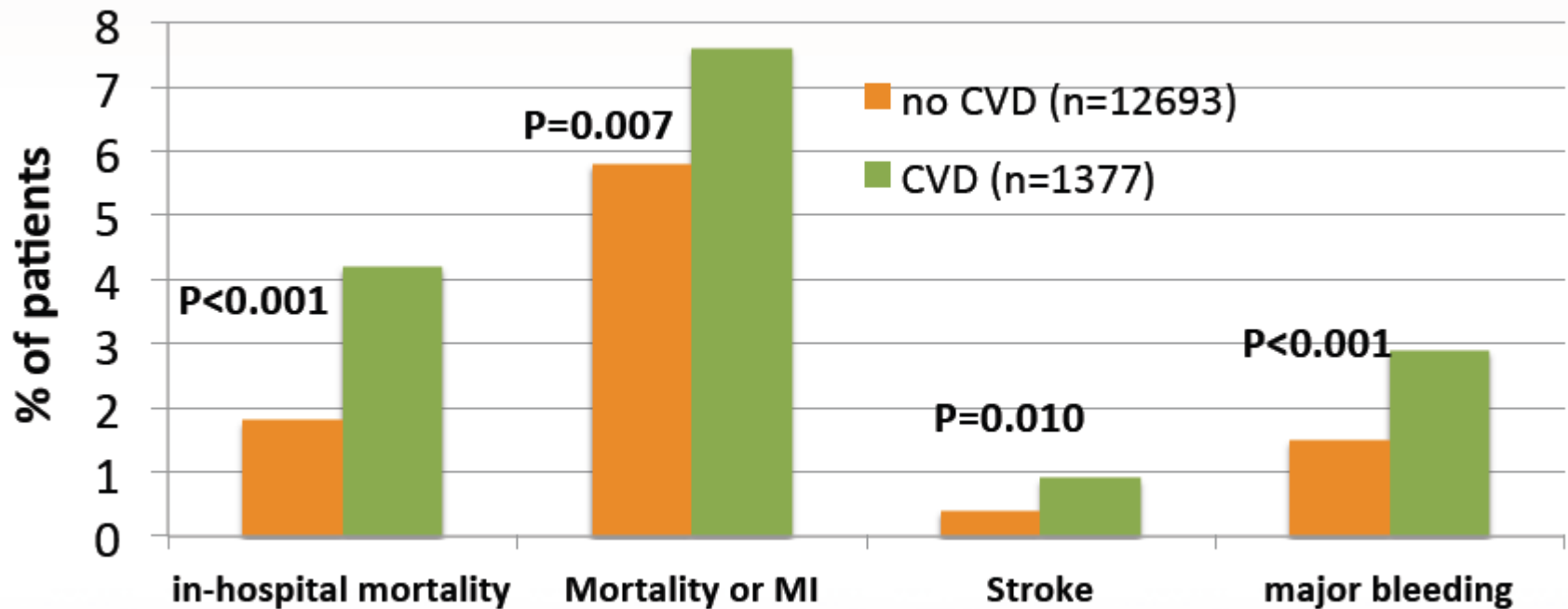
GRACE & CANRAC

Global Registry of Acute Coronary Events/Canadian Registry of Acute Coronary Events

Worse outcome after ACS in patients with polyVD

Canadian ACS I, ACS II, GRACE/GRACE2 and CANRACE registries

A total 14,070 patients with NSTEMI-ACS from 1999 to 2008

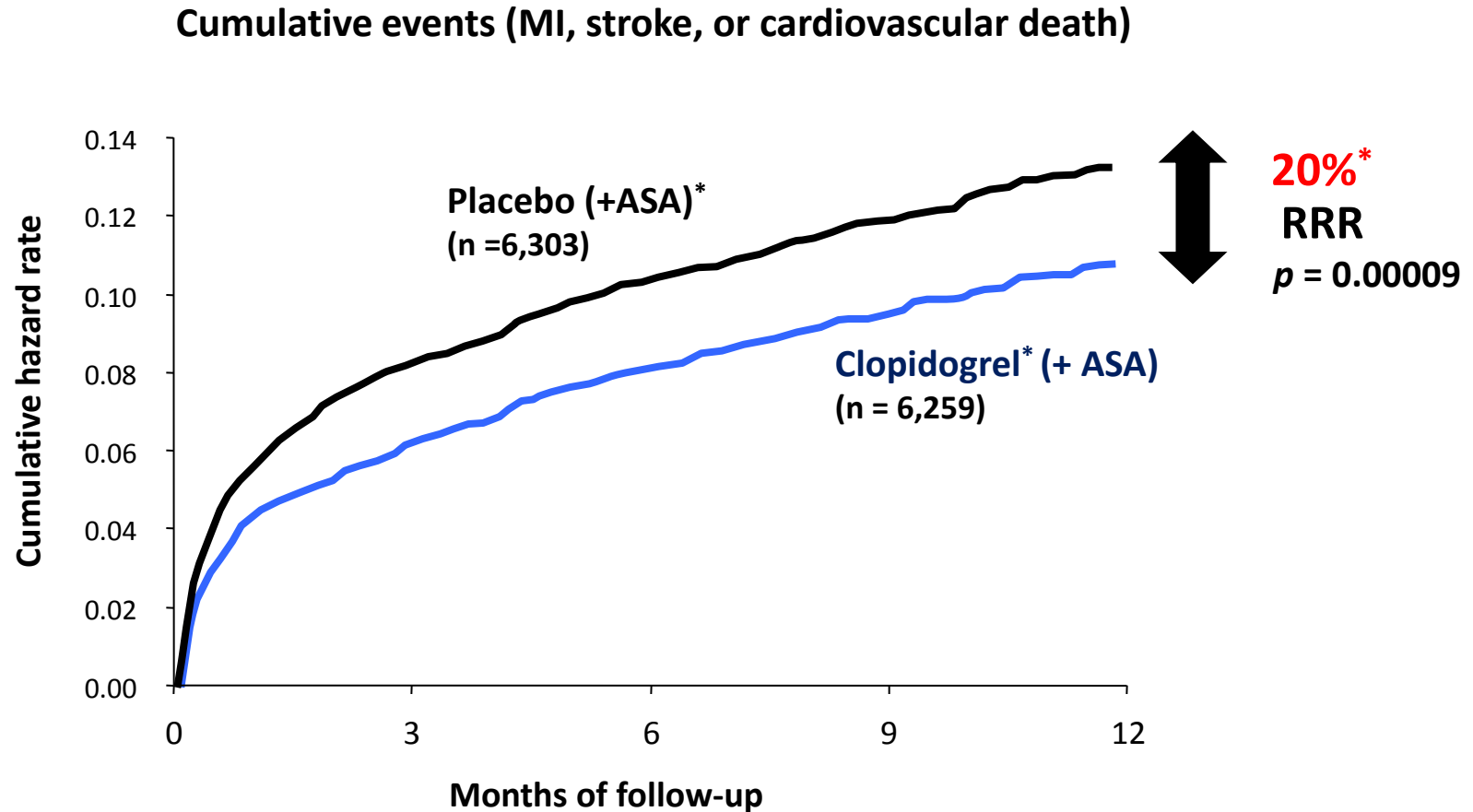


In CRACE & CANRACE: -31% of revascularization in ACS patients with CVD

Lee et al Am J Cardiol (2010) 105 1083-89

- **What is the evidence of clopidogrel ?**

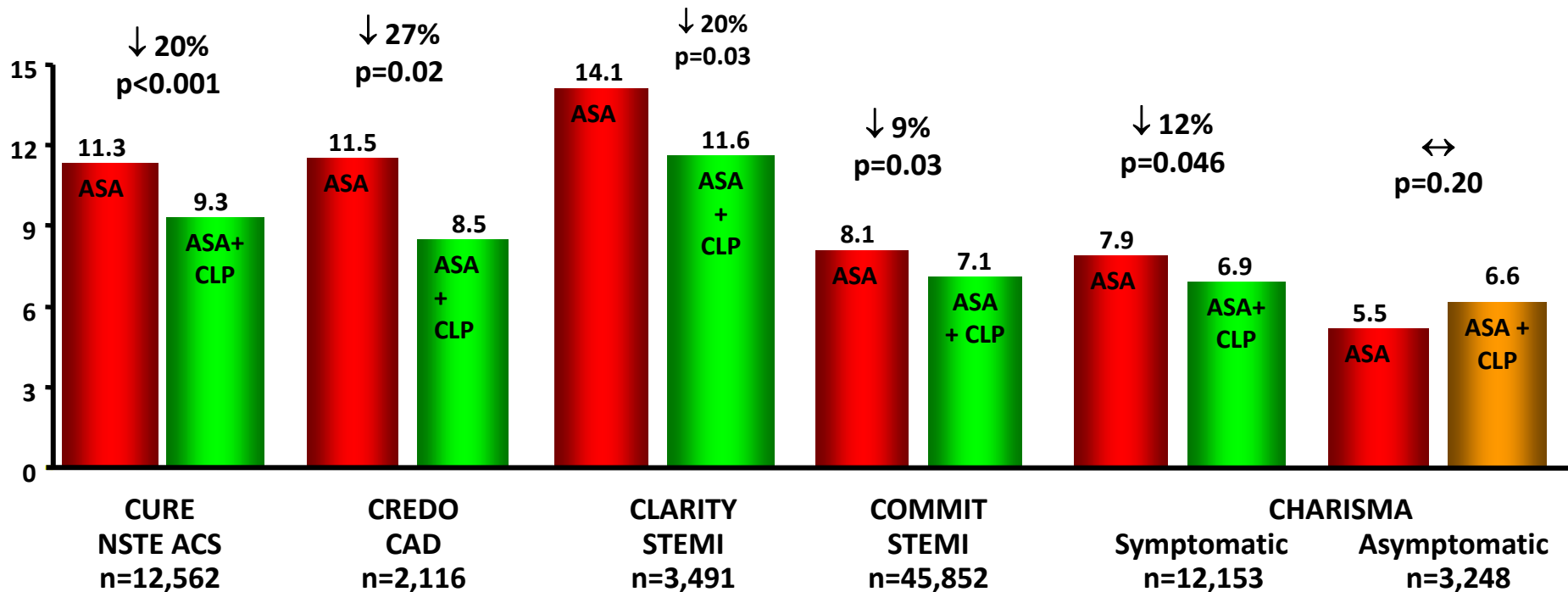
CURE: Long-Term Efficacy of Clopidogrel versus ASA



*On top of standard therapy (including ASA)

The CURE Trial Investigators. *N Engl J Med* 2001; 345: 494–502

Clopidogrel in CAD



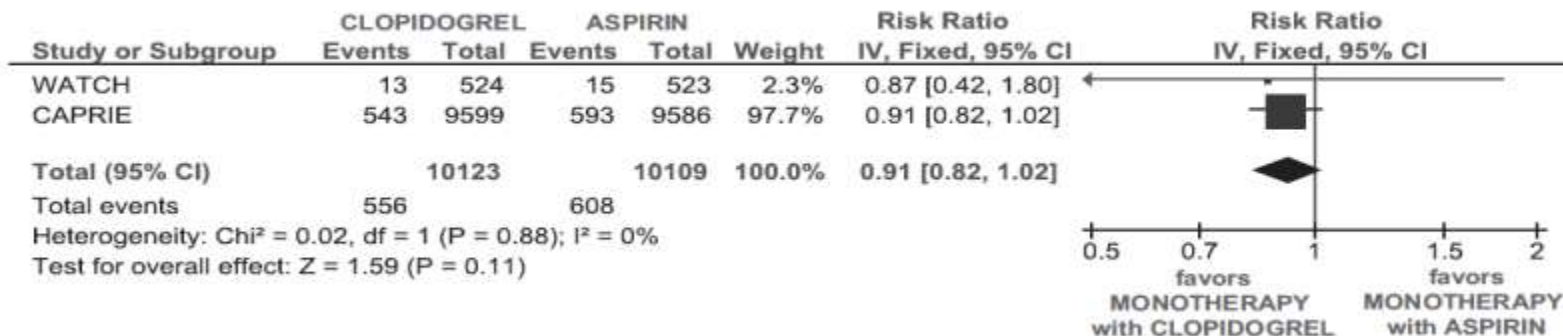
Post PCI

No Evidence of New Anti-Platelet Agent for elective PCI

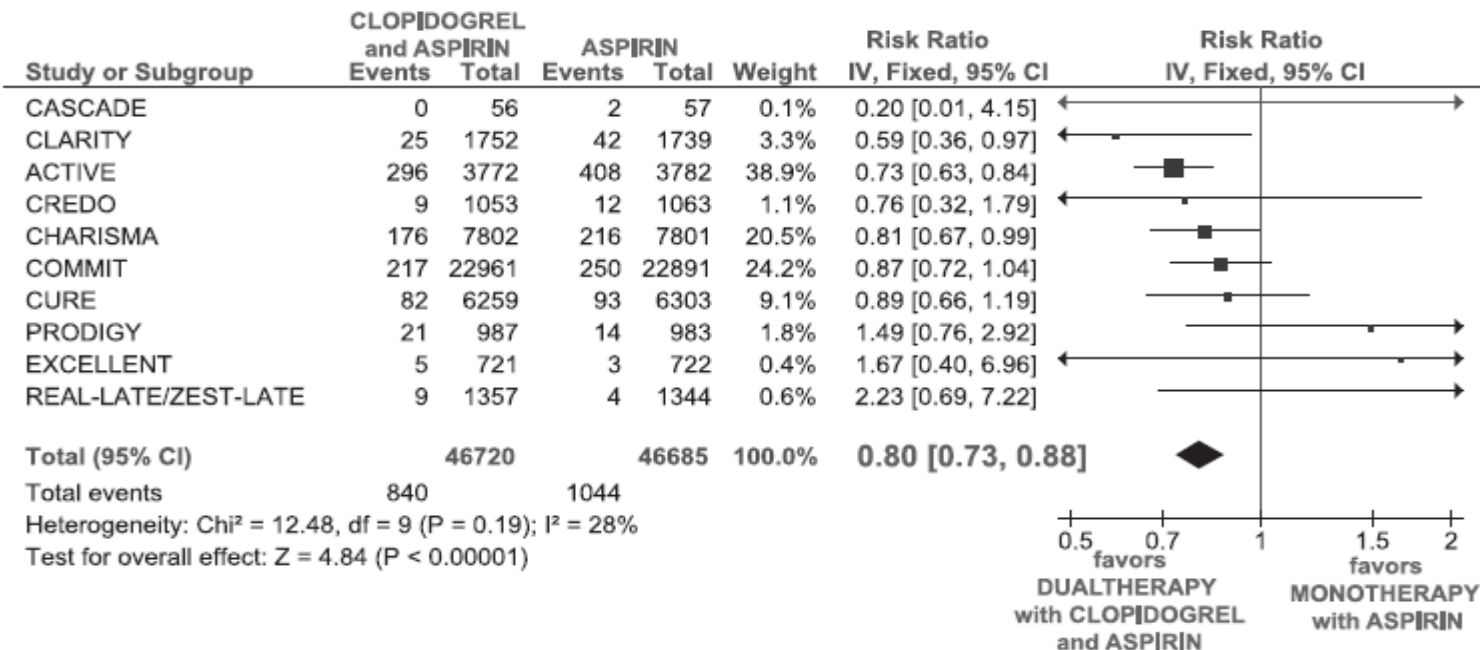
1. The CURE Trial Investigators. *N Engl J Med* 2001; 345: 494–502
2. The CREDO Trial Investigators. *JAMA* 2002;288:2411-2420
3. The CLARITY Trial Investigators. *JAMA* 2005;294:1224-32
4. The COMMIT Trial Investigators. *Lancet* 2005;366:1607-21
5. The CHARISMA Trial Investigators. *N Engl J Med* 2006; 354: 1706–17

Clopidogrel is better than Aspirin for prevention of stroke

A OVERALL COHORT: TOTAL STROKE



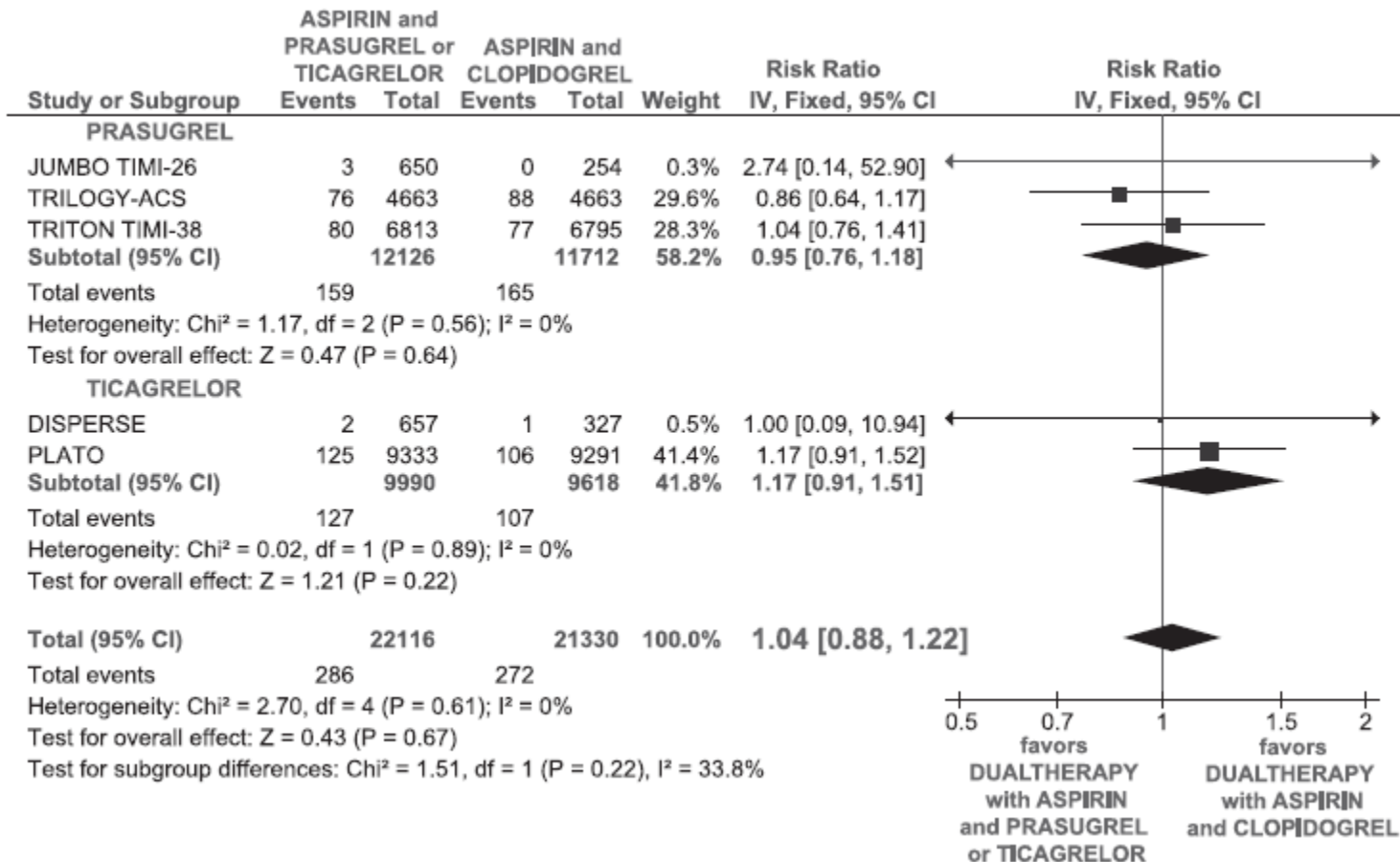
A OVERALL COHORT: TOTAL STROKE



Gouya G, et al. Stroke 2014;45(2):492-503

DAPT with prasugrel or ticagrelor and aspirin versus DAPT with clopidogrel and aspirin was not associated with a risk reduction of stroke

A OVERALL COHORT: TOTAL STROKE



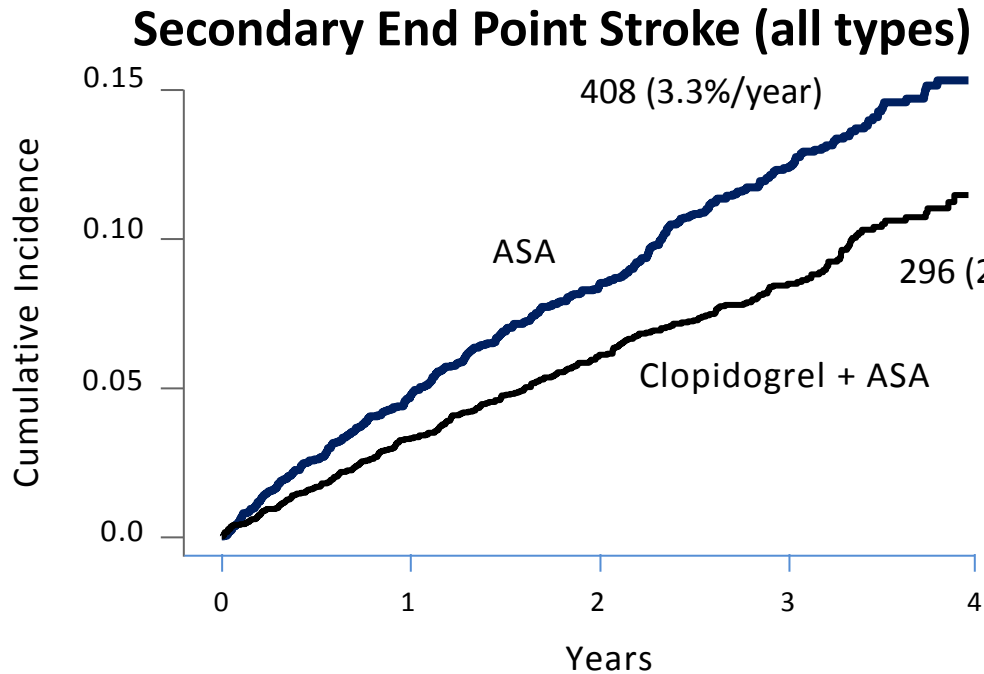
Gouya G, et al. Stroke 2014;45(2):492-503

Most recently added indication

ACTIVE-A

To prevent CVA in patients

with Atrial fibrillation in warfarin intolerant patients



28% RRR

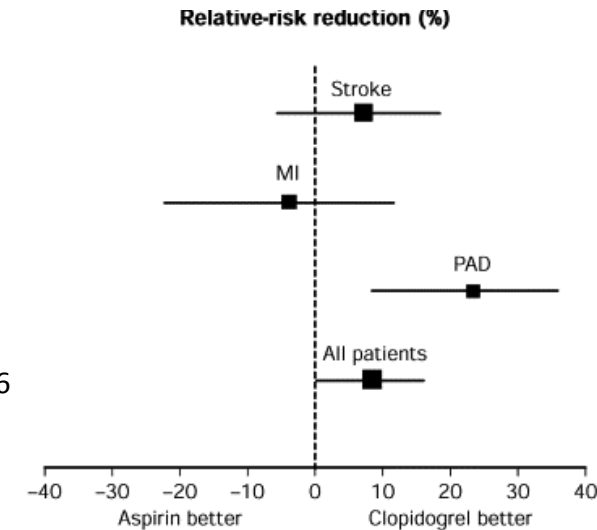
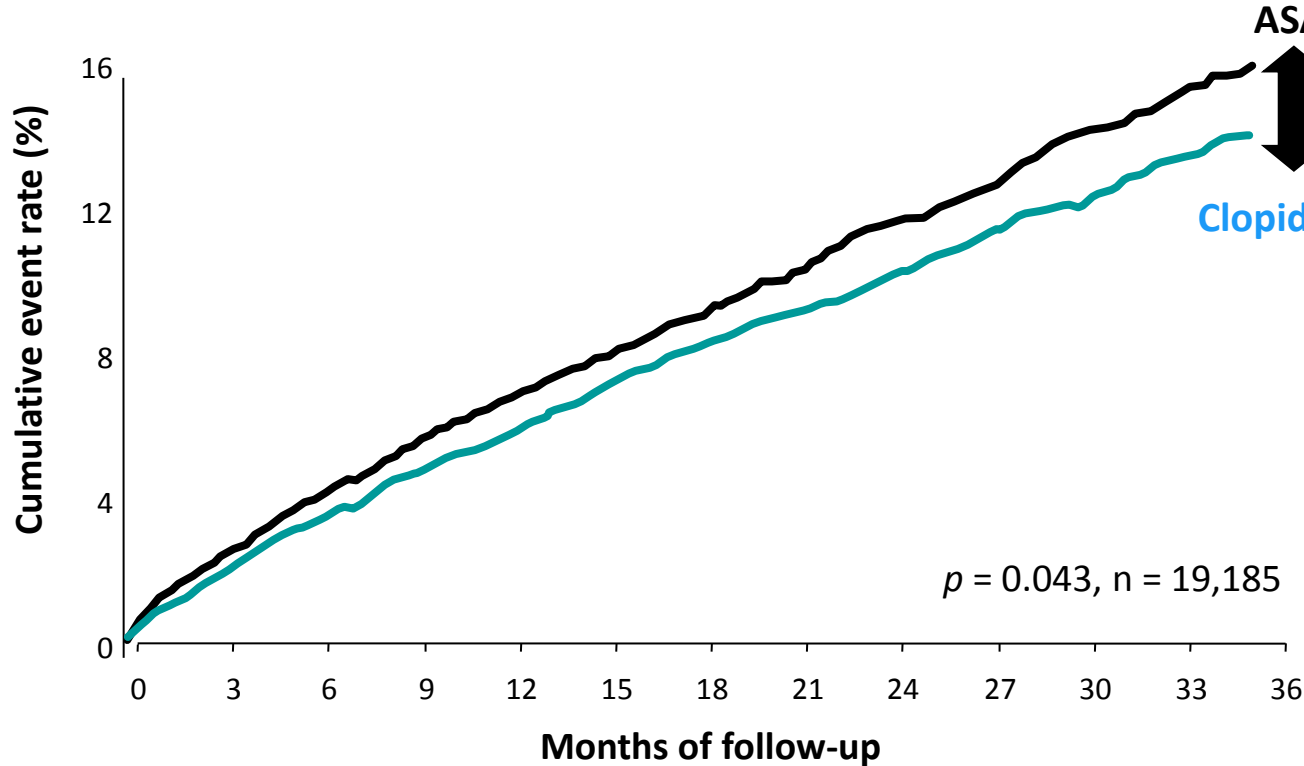
RR=0.72 (95%
CI, 0.62–0.83;
 $P < 0.001$)

Primary end point:
First occurrence of stroke, MI,
Non-CNS-embolism or
vascular death : 11 % RRR
(RR=0.89, 95% CI, 0.81-0.98)

The ACTIVE Investigators. *N Engl J Med.* 2009; 360(20):2066-2078

CAPRIE: Long-Term Efficacy of Clopidogrel versus ASA

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



ASA = acetylsalicylic acid MI = myocardial infarction *Intention to treat analysis

CAPRIE Steering Committee. *Lancet* 1996; 348: 1329–1339.

Peripheral Artery Disease and Clopidogrel

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, including those with intermittent claudication or CLI, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia. (*Level of Evidence: B*)

No Evidence for New Anti-platelet agent

2011 ACC/AHA Focus Update

SUMMARY

- Clinical Implication of “Polyvascular Disease”
 - ✓ Rates of CV death increase with the number of vascular beds with established atherothrombotic diseases
- Prognosis was worse in patients with polyvascular disease.
- Only Clopidogrel has both **clinical evidences and broad indication** & international guidelines for Atherothrombosis : **ACS, Stroke, PAD & A-fib.**
- Clopidogrel could recommend medical therapy for **atherthrombosis patients with Poly VD.**

Thanks for your Attention

Cardiovascular Hospital



Hybrid Cath Room



Preclinical Research Lab

