Polyvascular Disease and the Broad Indication of Clopidogrel

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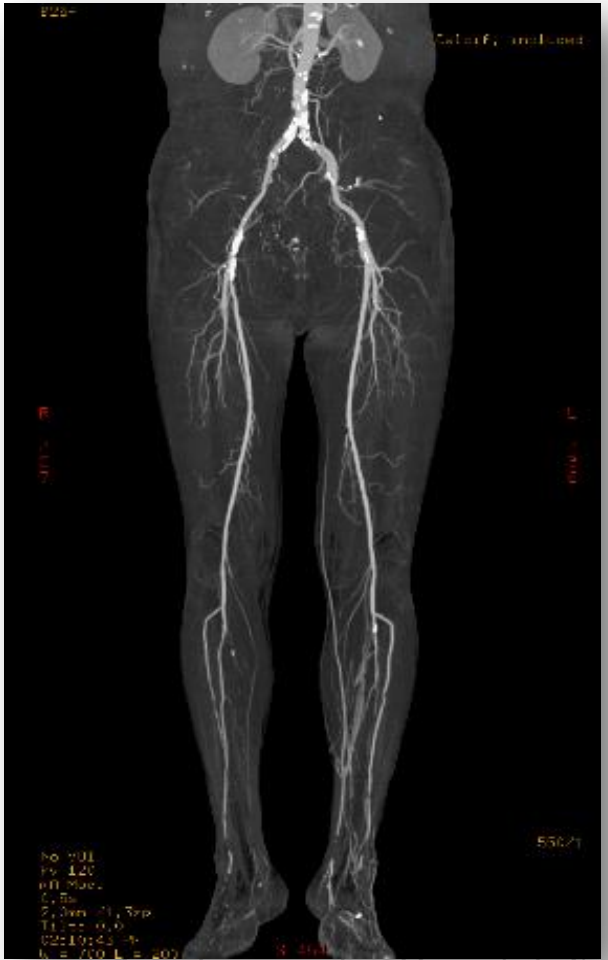
M/66(KJN, #5388620)

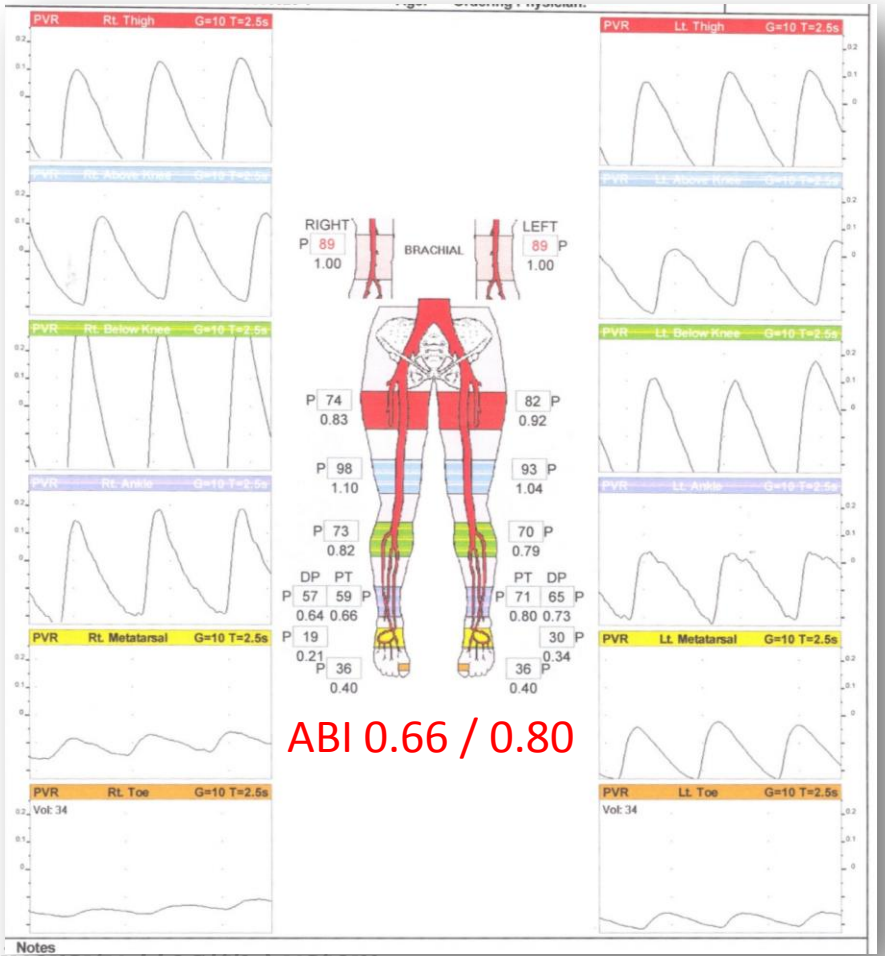
- CC: Severe claudication, Rt leg (100M)
- PHx:

  HTN (+), DM (-)

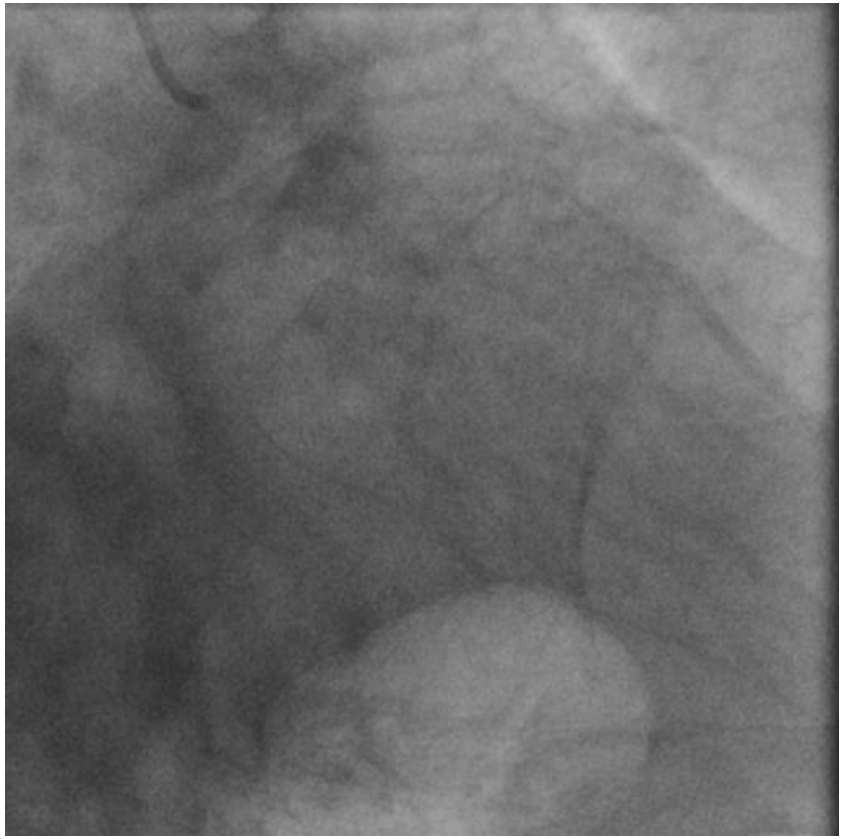
  Current smoker – 50 Pys

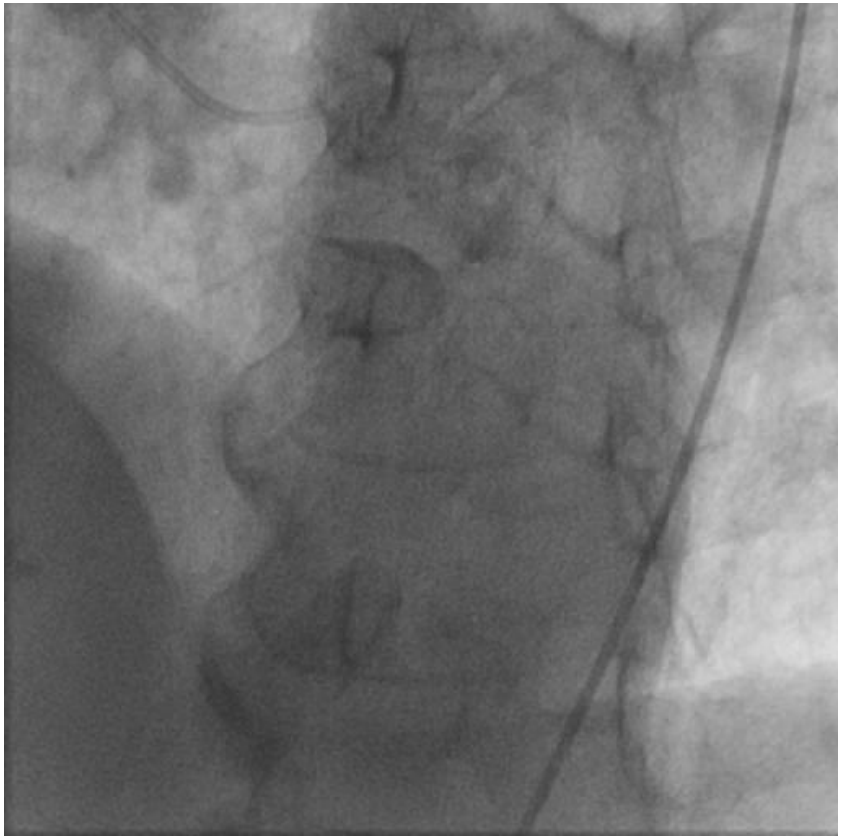
CT & PVR



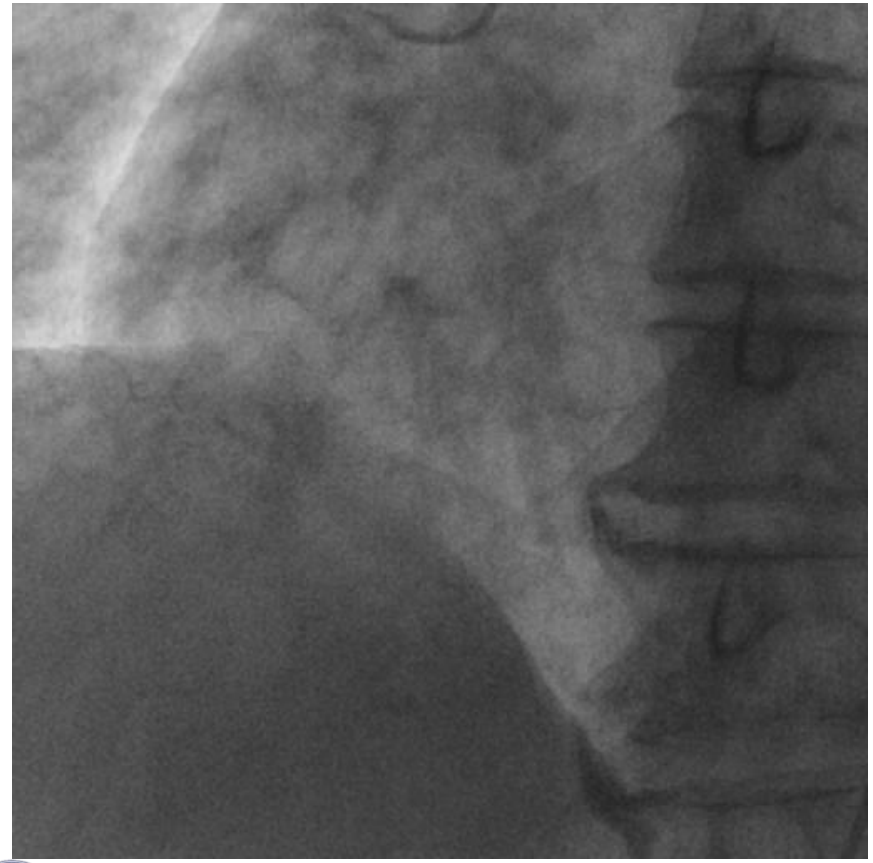

PVR Rt. Thigh G=10 T=2.5s
PVR Lt. Thigh G=10 T=2.5s
PVR Rt. Above Knee G=10 T=2.5s
PVR Lt. Above Knee G=10 T=2.5s
PVR Rt. Below Knee G=10 T=2.5s
PVR Lt. Below Knee G=10 T=2.5s
PVR Rt. Ankle G=10 T=2.5s
PVR Lt. Ankle G=10 T=2.5s
PVR Rt. Metatarsal G=10 T=2.5s
PVR Lt. Metatarsal G=10 T=2.5s
PVR Rt. Toe G=10 T=2.5s
PVR Lt. Toe G=10 T=2.5s
Vol: 34
Vol: 34
RIGHT
LEFT
BRACHIAL
P 89 1.00
89 P 1.00
P 74 0.83
82 P 0.92
P 98 1.10
93 P 1.04
P 73 0.82
70 P 0.79
DP PT
P 57 59 P
0.64 0.66
PT DP
P 71 65 P
0.80 0.73
P 19 0.21
30 P 0.34
P 36 0.40
36 P 0.40
ABI 0.66 / 0.80
Notes

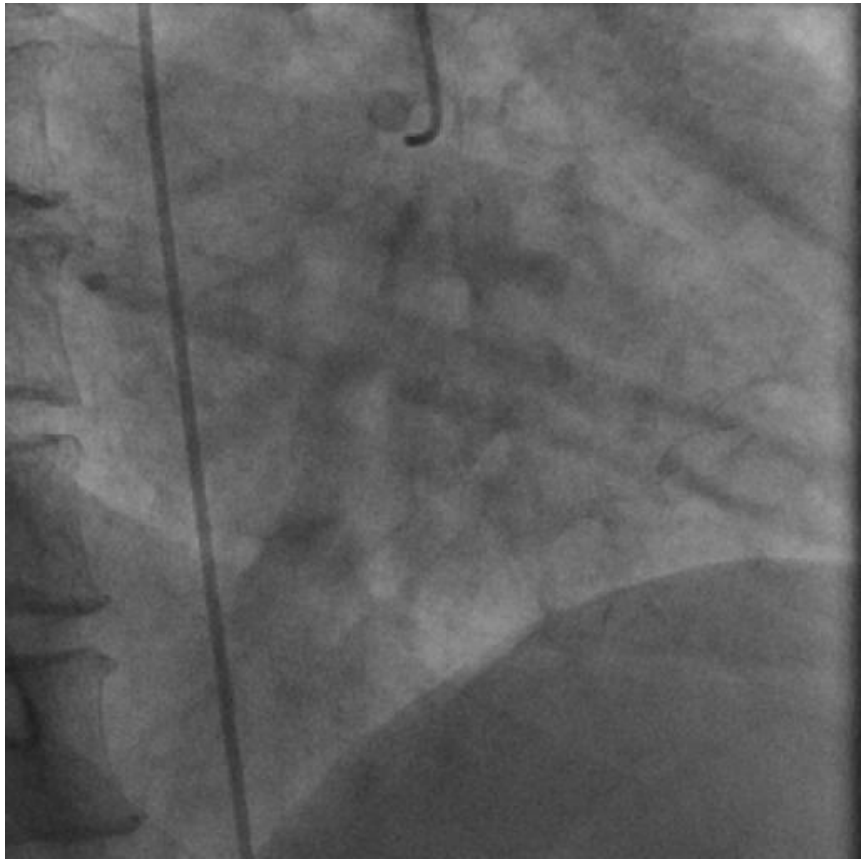
Coronary Angiogram



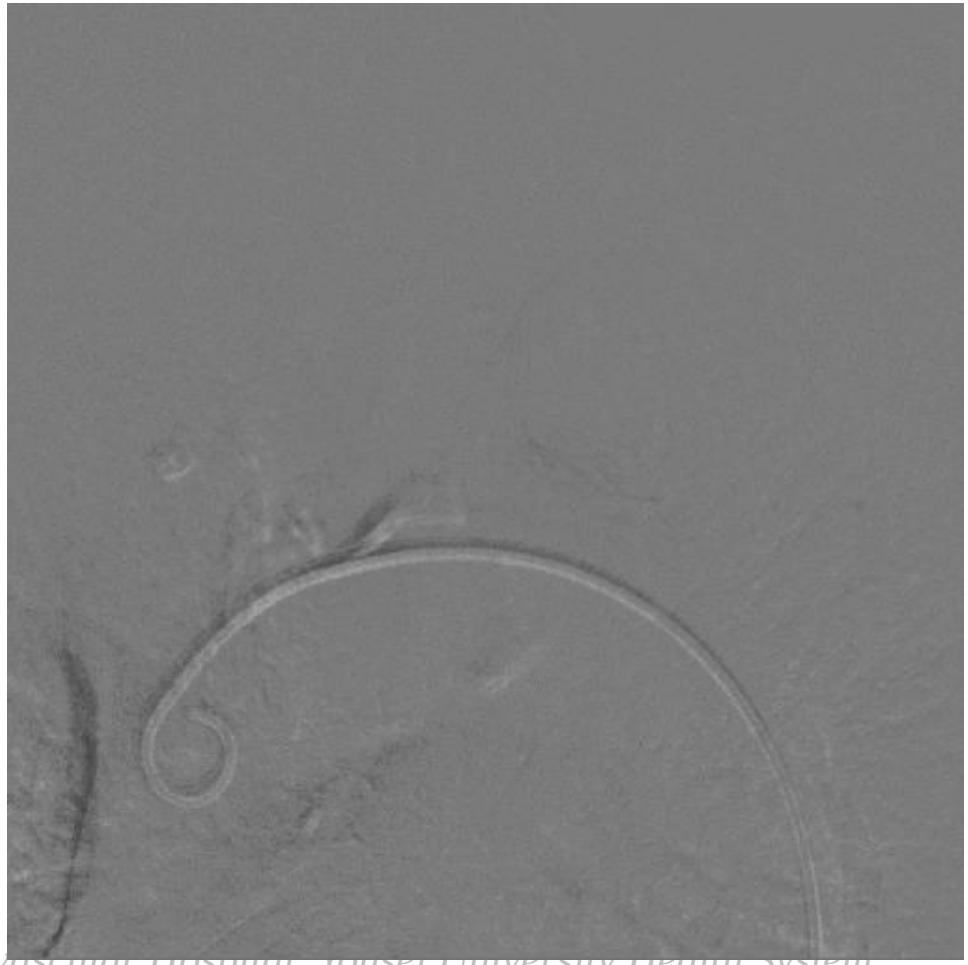


Coronary Angiogram



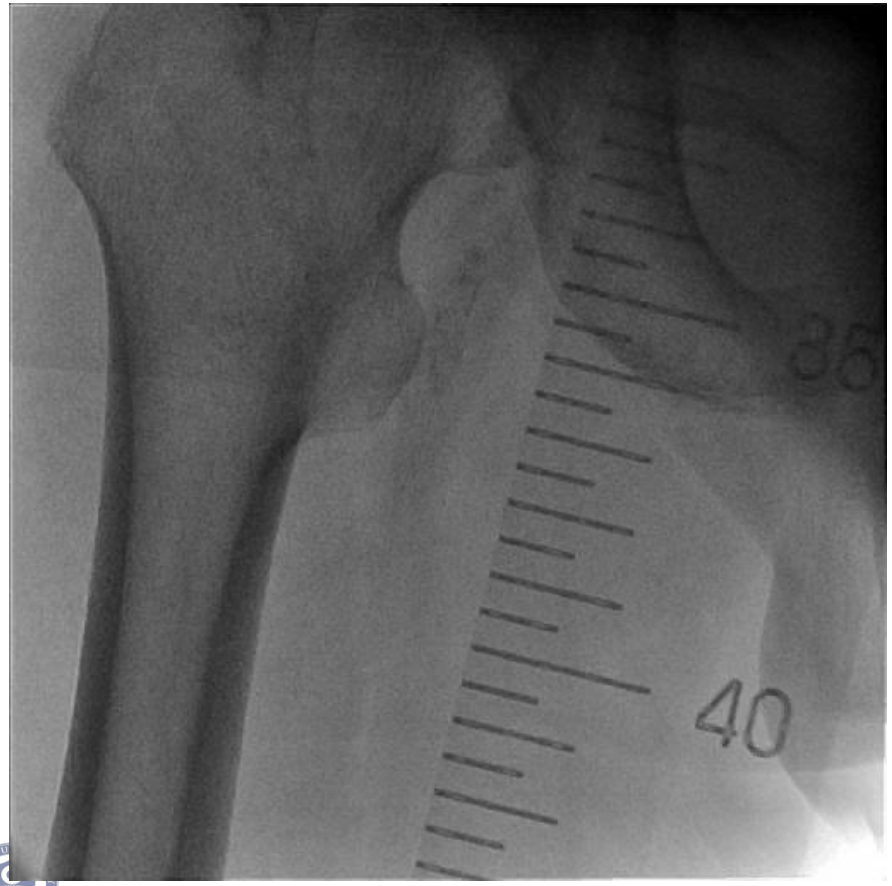


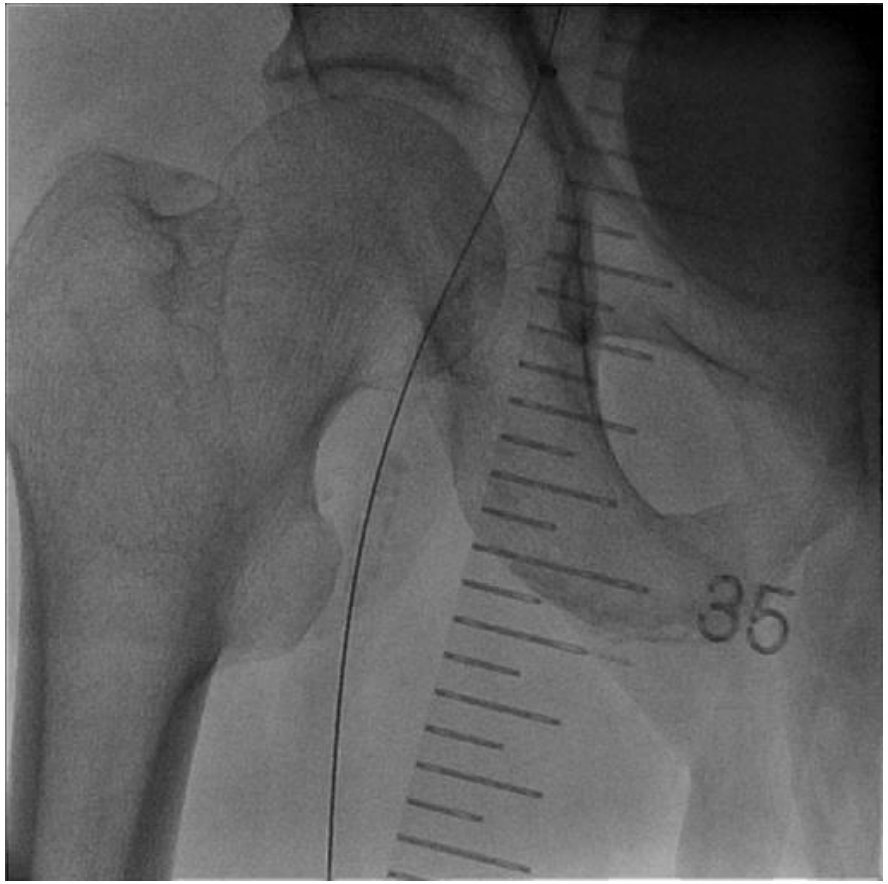
Aortogram



Rt. SFA

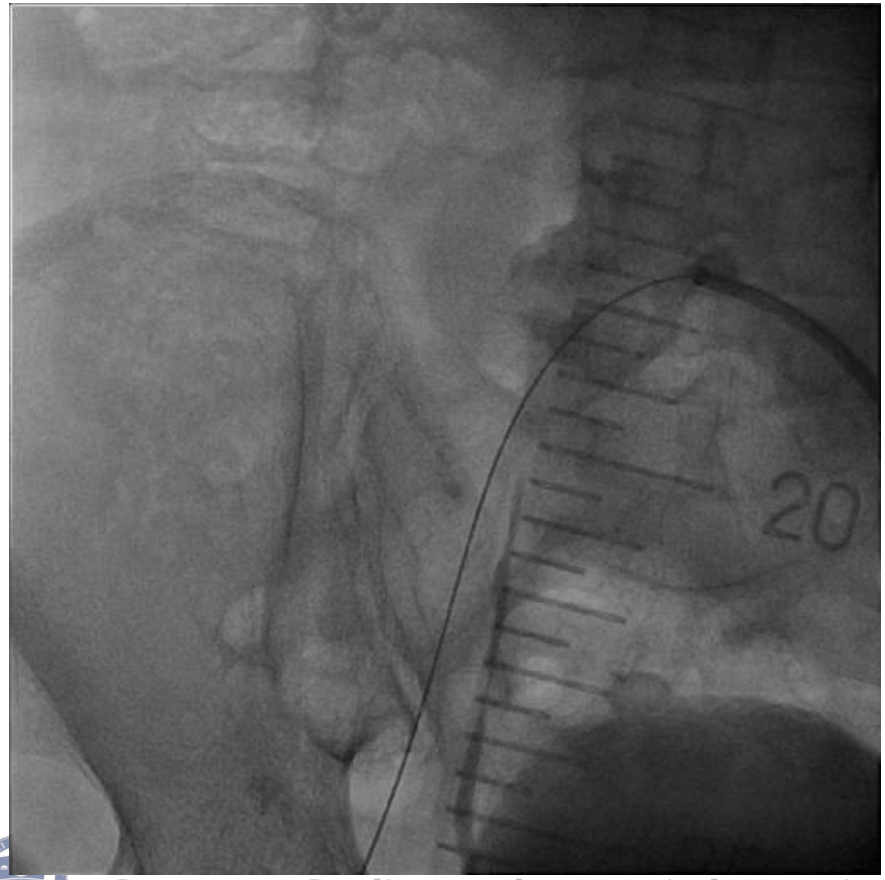
After balloon angioplasty (B. 6 x 40 mm)

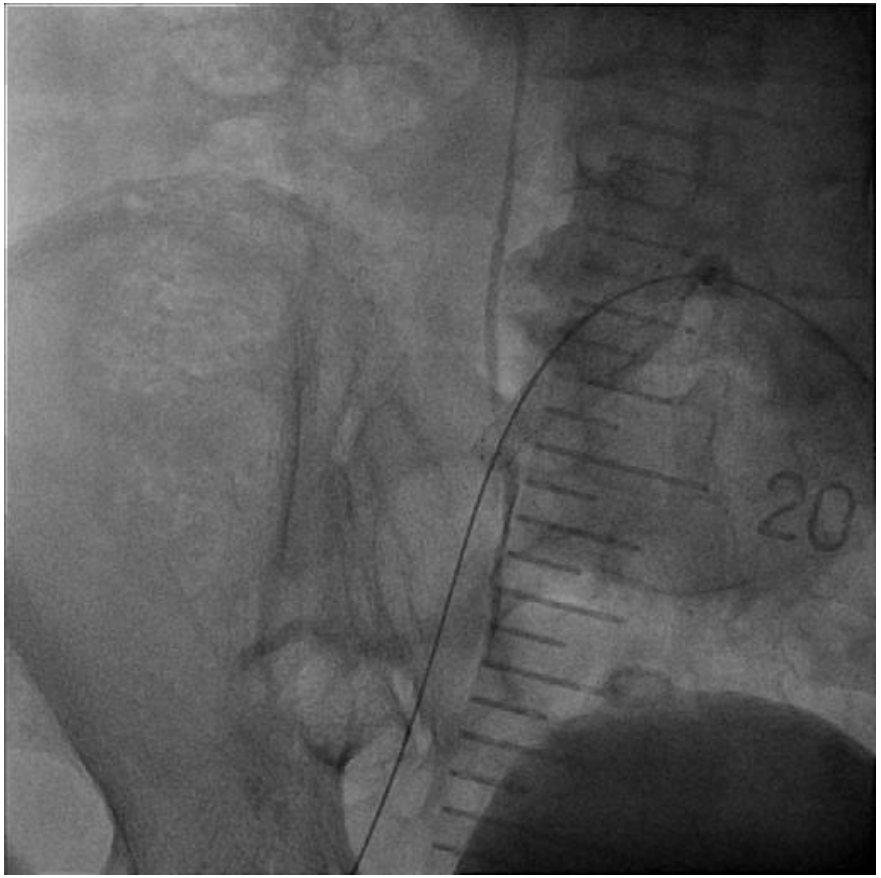




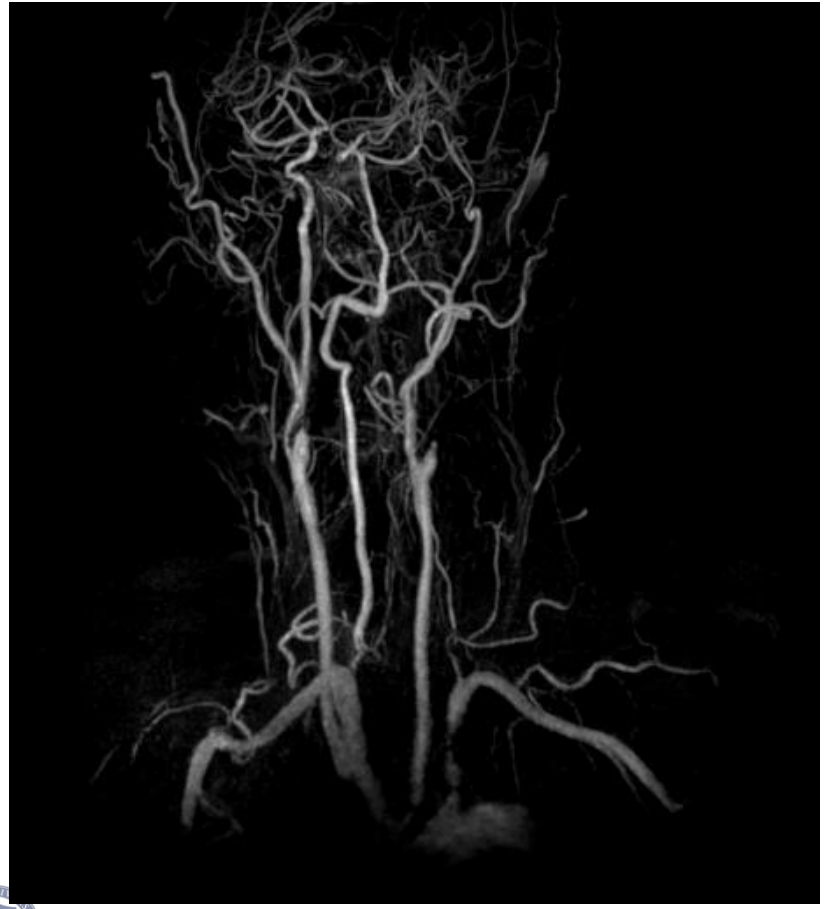
Rt. CIA

SMART 9 x 40 mm





MR angiogram

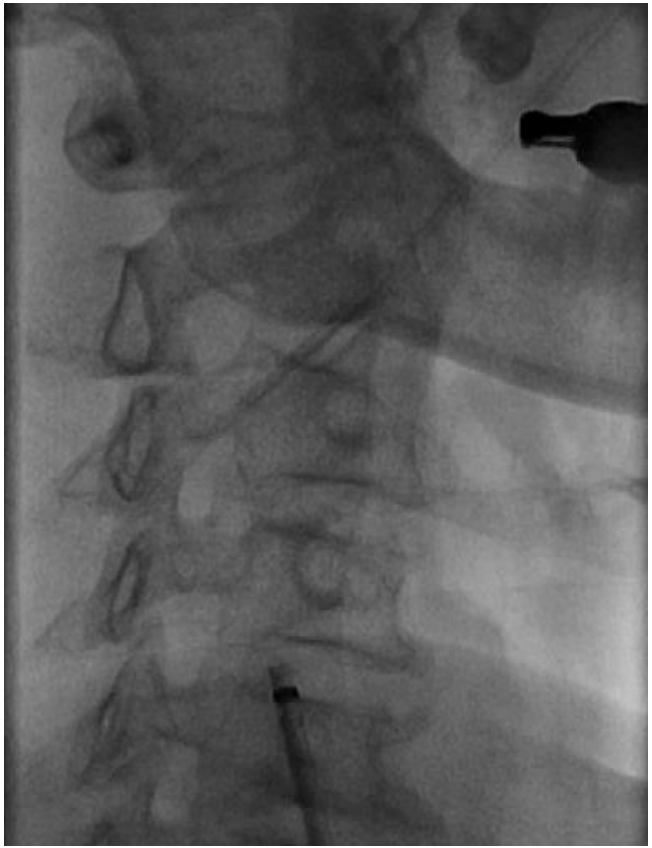


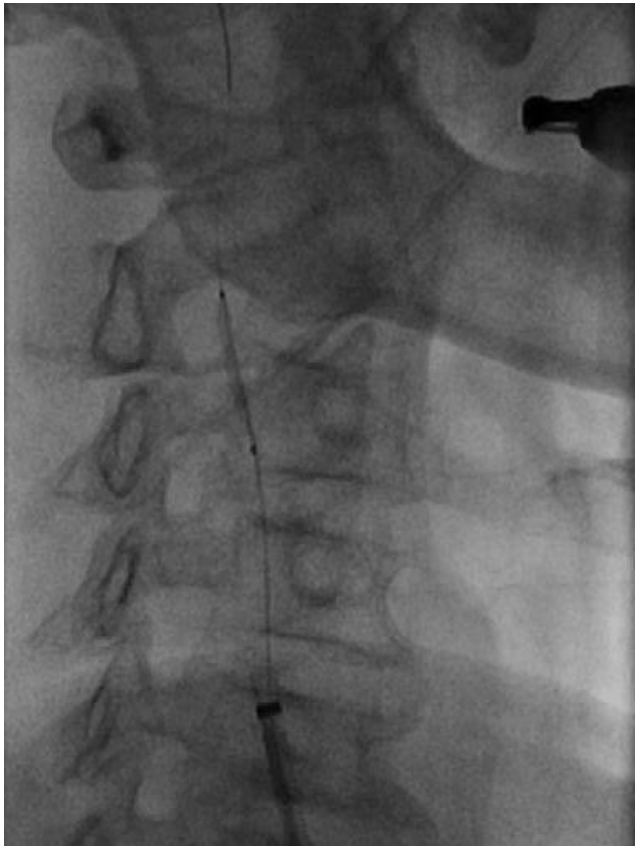
Radiological Report:

- Severe stenosis/occlusion, Lt. prox. VA.
- Occlusion, Lt. prox ICA.
- Severe focal stenosis, Rt. Prox ICA, Lt. prox CCA, & Lt. prox subclavian a.
- A few nonspecific T2 hyperintense lesions in the WM of brain.

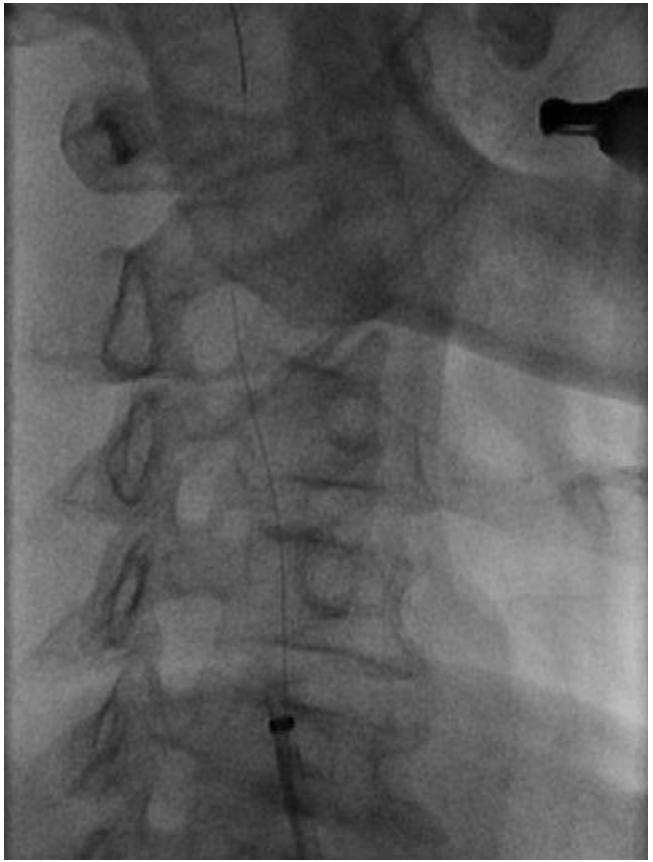
Rt. Carotid Artery

EZ filter + Balloon 4 x 30 mm

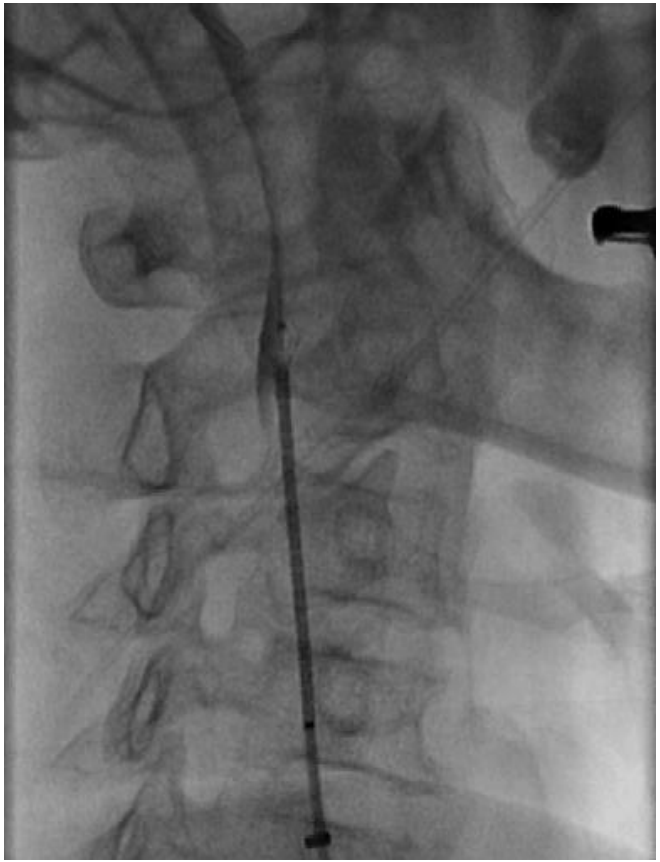




Carotid Stenting: Rt ICA

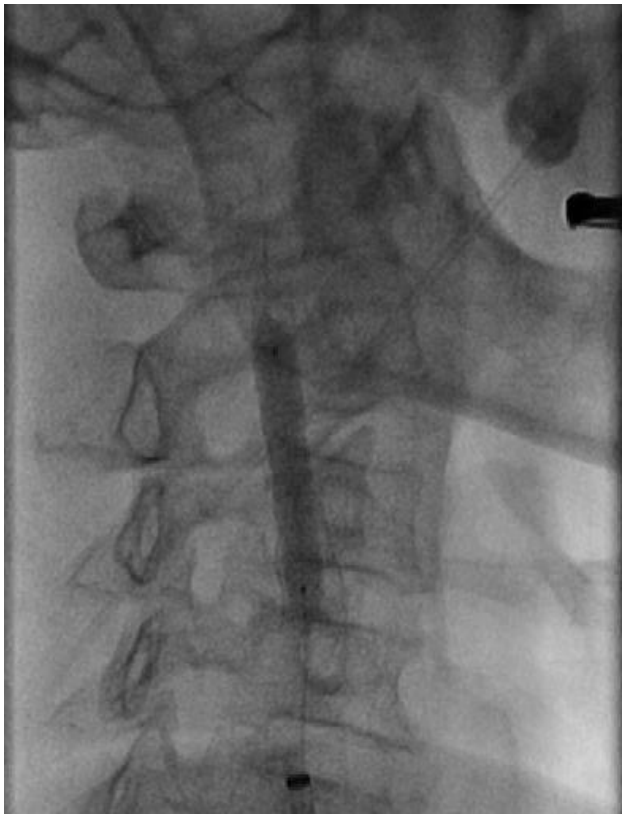


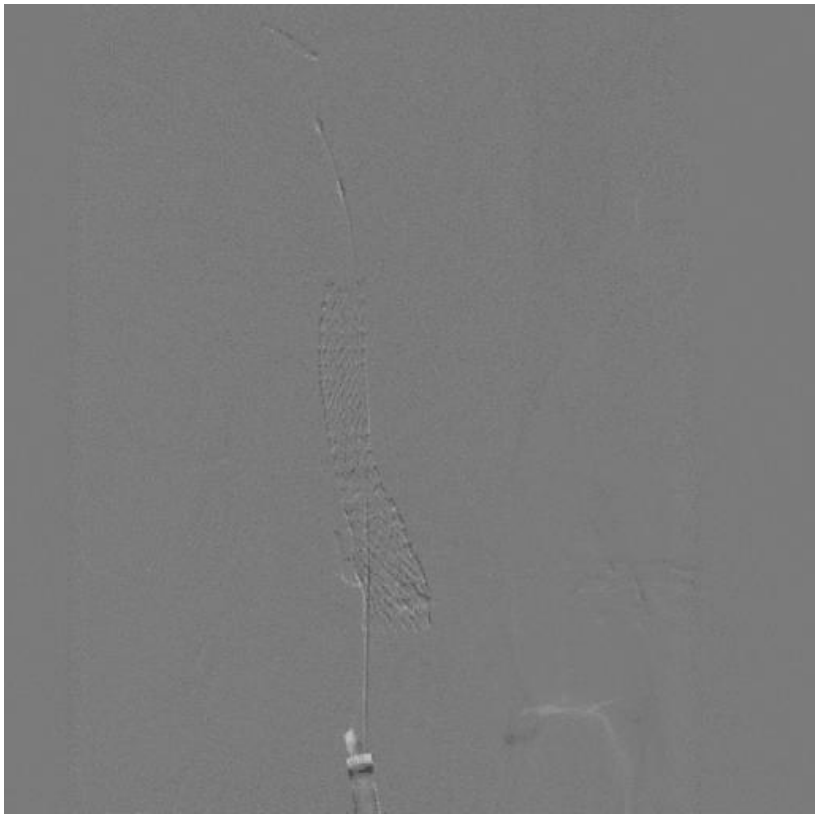
Precise 8 x 40 mm



Carotid Stenting

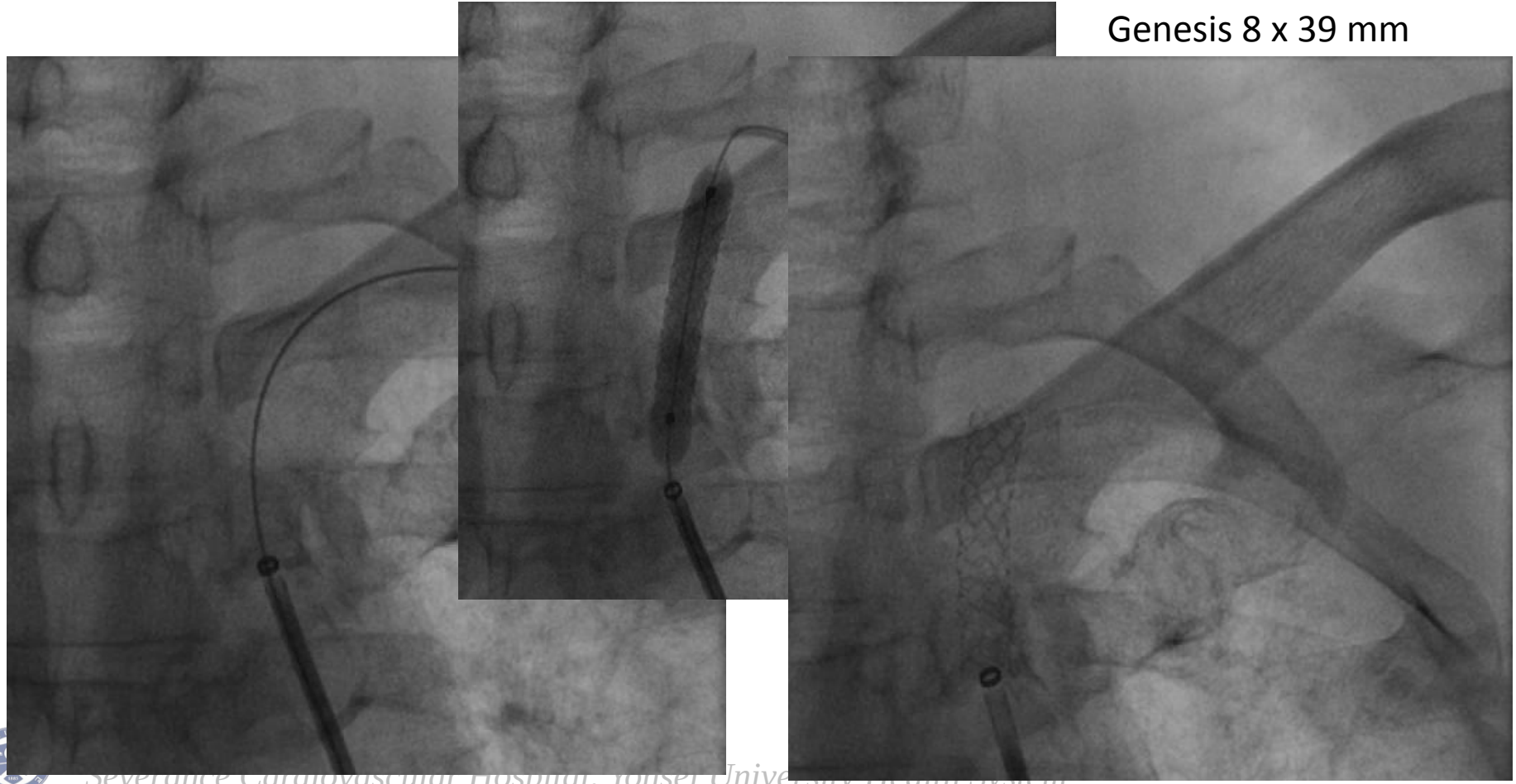
Balloon 5 x 40 mm





Lt. Subclavian Artery

Genesis 8 x 39 mm

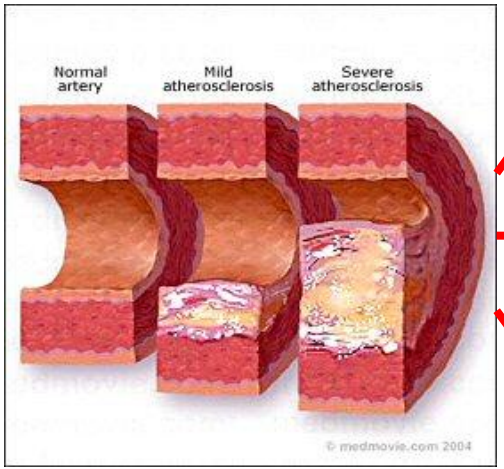


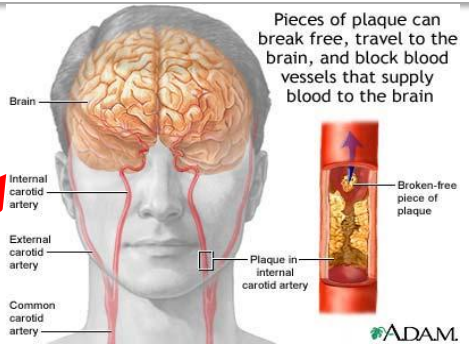
Common Pathophysiology

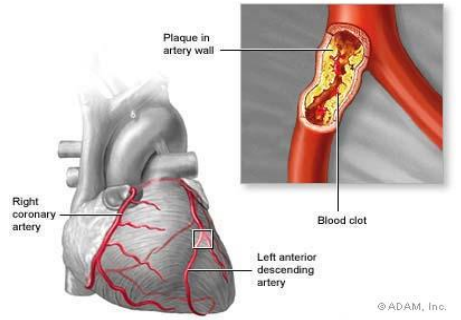
Risk Factors

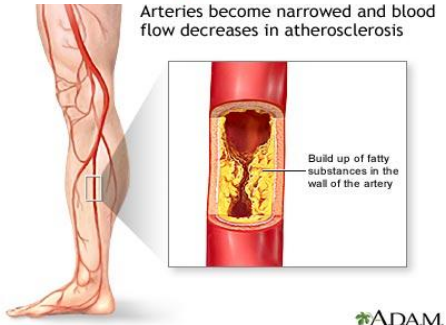
- Gender (male)
- Age
- Smoking
- Hypertension
- Diabetes
- Hyperlipidaemia
- Fibrinogen
- Homocysteinaemia

Atherosclerosis









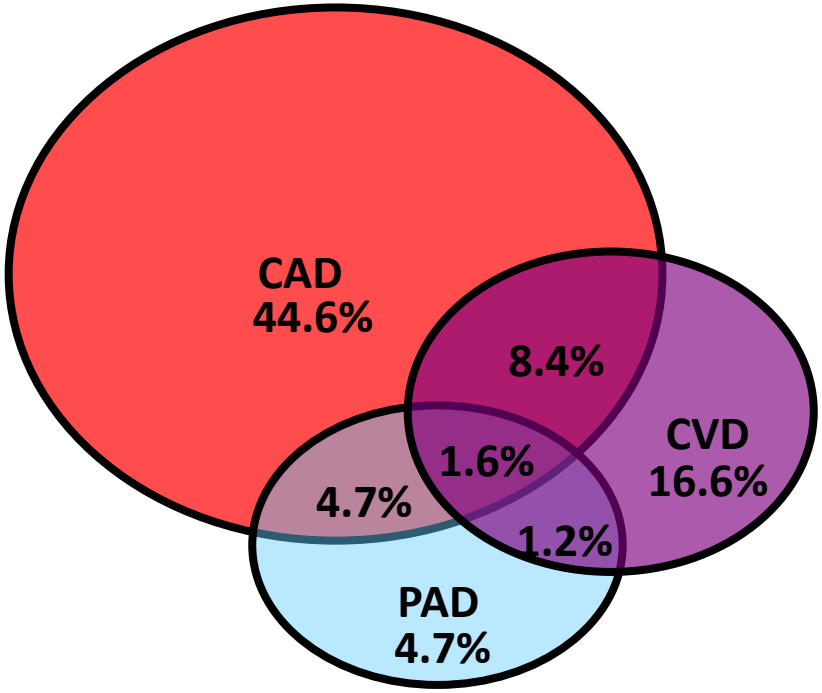
REACH: Overview of the REduction of Atherothrombosis for Continued Health Registry

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

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

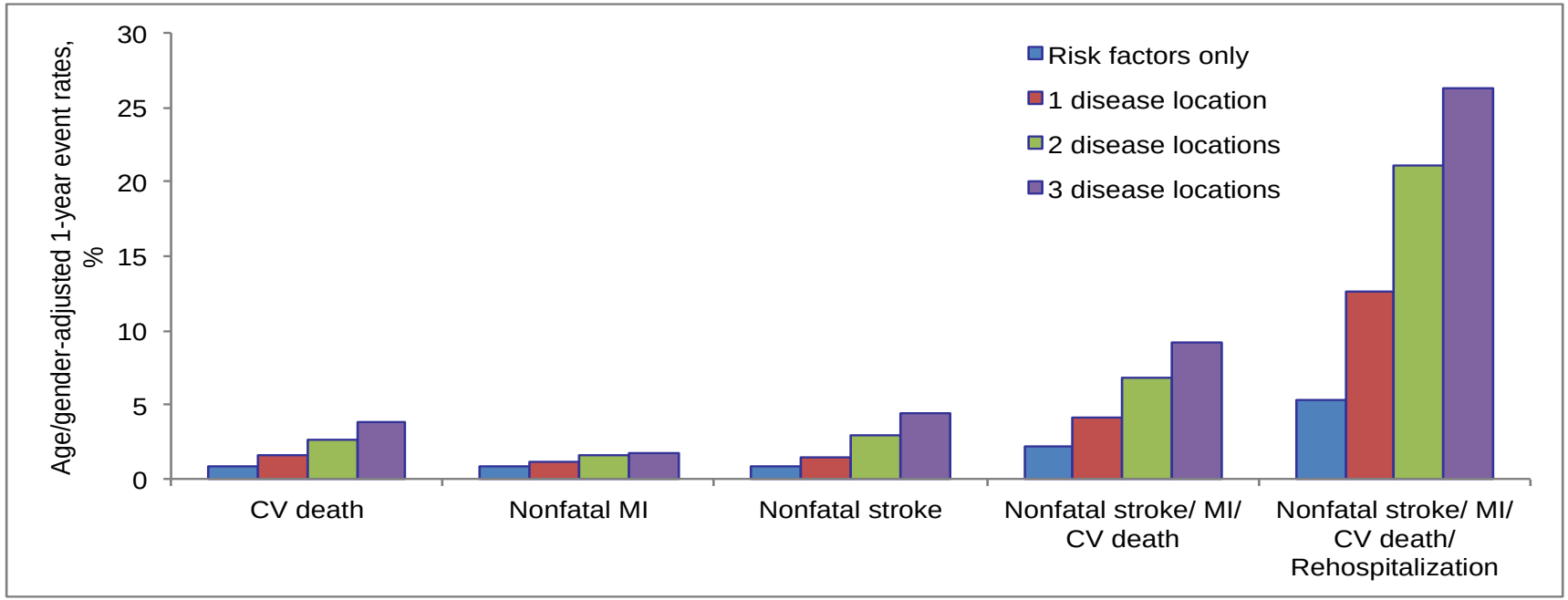
Prevalence of Atherothrombosis in REACH Registry



- Atherothrombotic status of REACH Registry patients at baseline:
  - 18.2% RFO (n=12 389)
  - 59.3% CAD (n=40 258)
  - 27.8% CVD (n=18 843)
  - 12.2% PAD (n=8273)

RFO, Risk Factors Only.

REACH: Patient Outcomes at 1 year



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

Steg PG et al. JAMA 2007;297:1197.

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

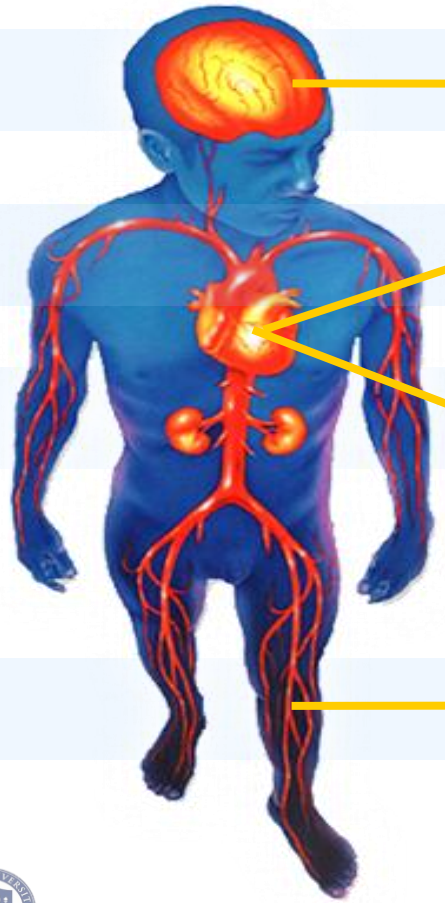
Increased risk versus general population

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.

Efficacy of Clopidogrel in Atherothrombotic Diseases



Cerebrovascular disease

CAPRIE, CHARISMA, CARESS, CLAIR, MATCH

Atrial Fibrillation

Active A

Coronary artery disease

CURE, PCI-CURE, COMMIT, CLARITY, CREDO, CURRENT
OASIS 7, CAPRIE, CHARISMA

Peripheral arterial disease

CAPRIE, CHARISMA, CASPAR

CAPRIE: Clopidogrel vs Aspirin in Patients at Risk of Ischaemic Events

N=19,185

Patient Population

- Patients with recent MI, recent IS, or established PAD

n=9,599 → **Clopidogrel 75 mg**

n=9,586 → **ASA 325 mg**

Follow-up 1 to 3 years

Primary End Point

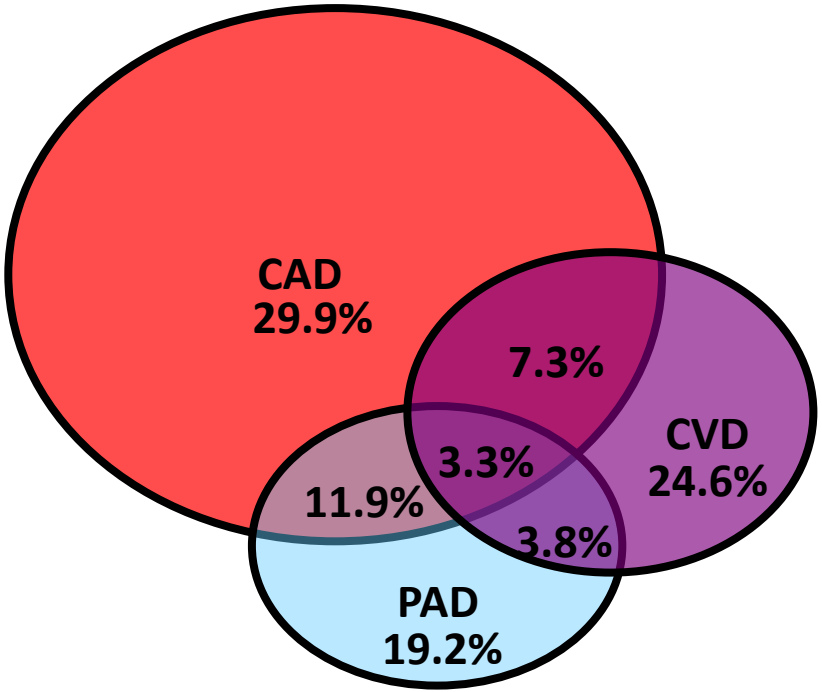
- First occurrence of IS, MI, or vascular death

384 centers
16 countries

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

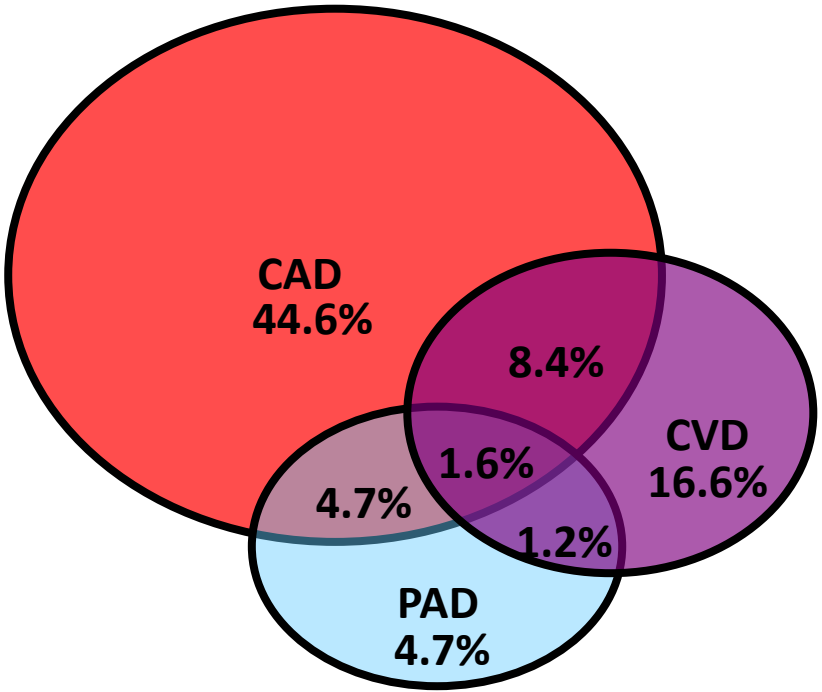
CAPRIE vs. REACH Study Population

CAPRIE population[1] (n=19,185)



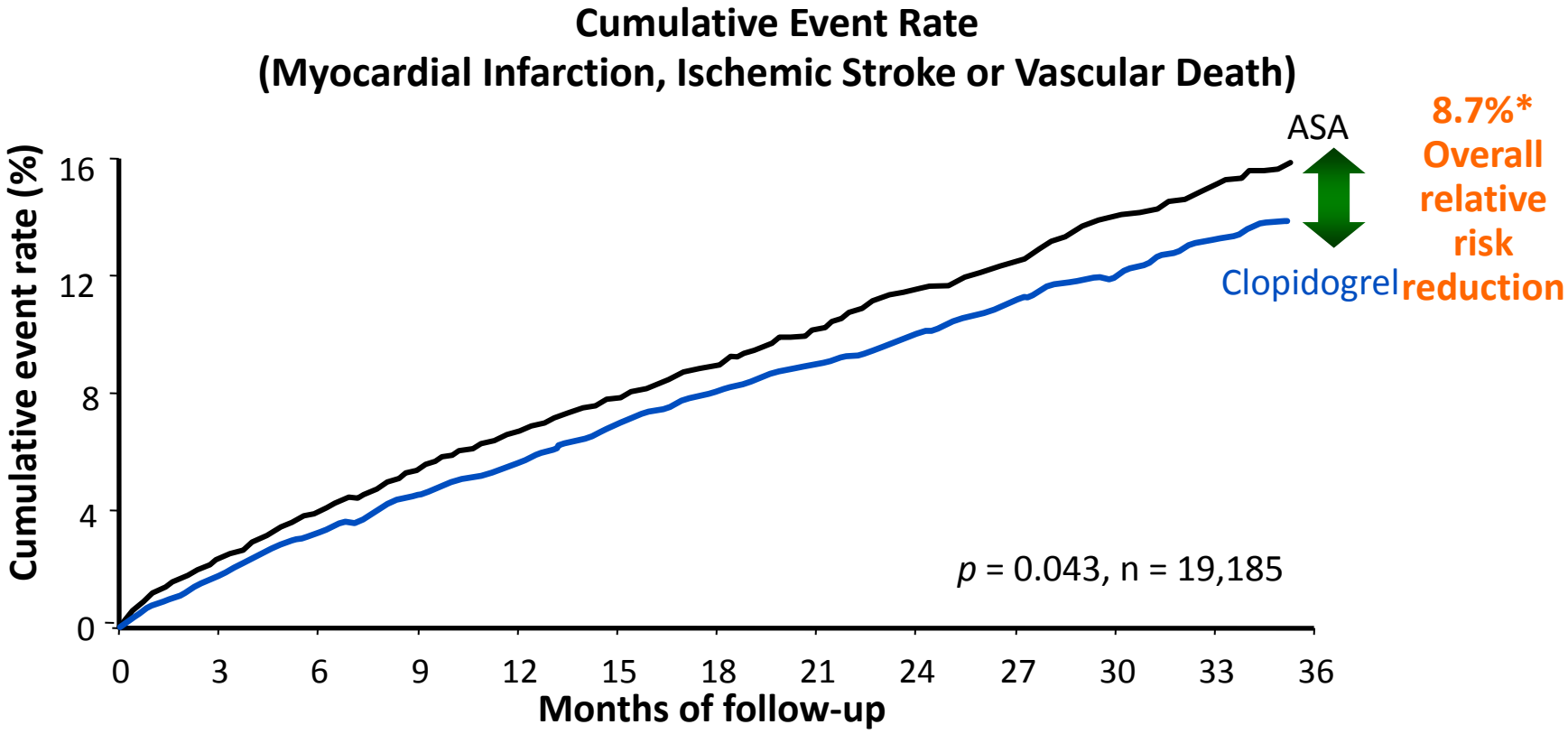
vs

REACH population[2] (n=67,888)



1.CAPRIE Steering Committee. *Lancet.* 1996;348:1329-1339.
2.Bhatt DL, et al. JAMA 2006;296:180

CAPRIE: Long-Term Benefit of Clopidogrel Compared with ASA

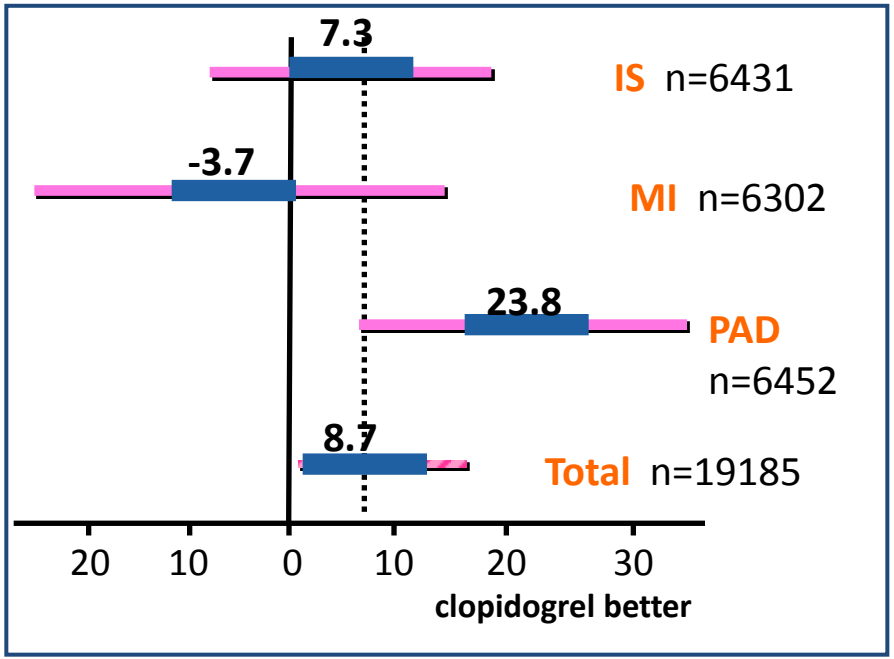


*ITT analysis

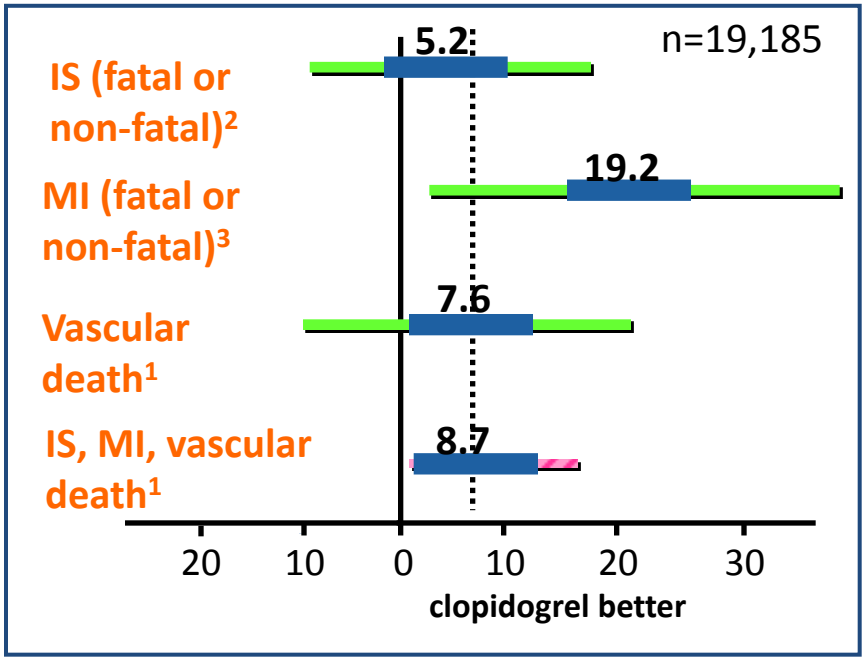
1. CAPRIE Steering Committee. *Lancet* 1996; 348: 1329–39.

CAPRIE: Benefit in specific subgroups

Relative Risk Reduction* by Qualifying Entry Criteria[1]



Relative Risk Reduction of Individual End Points



*Cluster of IS, MI, or vascular death.

1. CAPRIE Steering Committee. Lancet 1996;348:1329-1339.
2. Easton. Neurology 1998;50(suppl 4):A157.
3. Gent. Circulation. 1997;96(suppl):I-467.

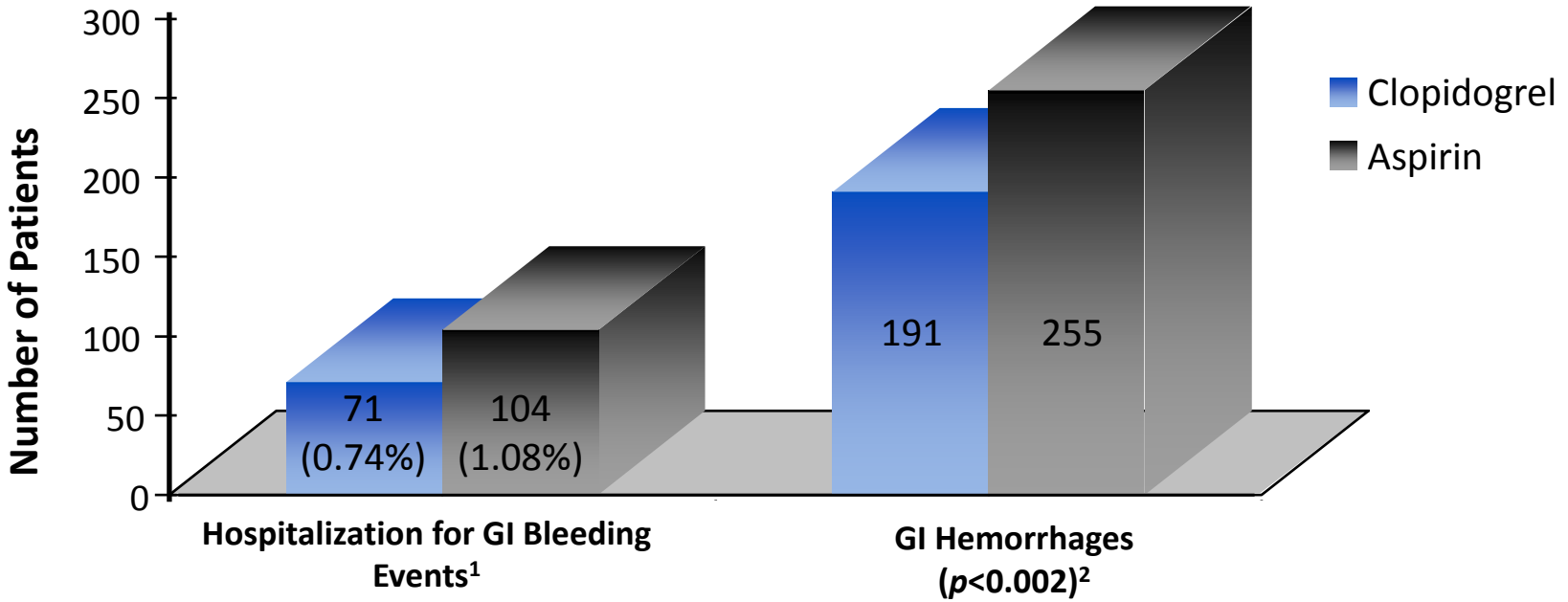
CAPRIE Safety: Hemorrhagic Events

Adverse experience	Patients ever reporting		Severe		Study drug permanently discontinued	
	Clopidogrel	Aspirin	Clopidogrel	Aspirin	Clopidogrel	Aspirin
Rash	578 (6·02%)	442 (4·61%)*	25 (0·26%)	10 (0·10%)*	86 (0·90%)	39 (0·41)*
Diarrhoea	428 (4·46%)	322 (3·36%)*	22 (0·23%)	11 (0·11%)	40 (0·42%)	26 (0·27%)
Indigestion/nausea/vomiting	1441 (15·01%)	1686 (17·59%)*	93 (0·97%)	118 (1·23%)	182 (1·90%)	231 (2·41%)*
Any bleeding disorder	890 (9·27%)	890 (9·28%)	132 (1·38%)	149 (1·55%)	115 (1·20%)	131 (1·37%)
Intracranial haemorrhage	34 (0·35%)	47 (0·49%)	30 (0·31%)	41 (0·43%)	20 (0·21%)	32 (0·33%)
Gastrointestinal haemorrhage	191 (1·99%)	255 (2·66%)*	47 (0·49%)	68 (0·71%)*	50 (0·52%)	89 (0·93%)*
Abnormal liver function	285 (2·97%)	302 (3·15%)*	11 (0·11%)	9 (0·09%)	22 (0·23%)	28 (0·29%)

*Statistically significant, p<0·05.

1. Bogousslavsky. Cerebrovasc Dis 1998;8(suppl 4):43. Abstract CLI 76.
2. CAPRIE Steering Committee. Lancet 1996;348:1329-1339.

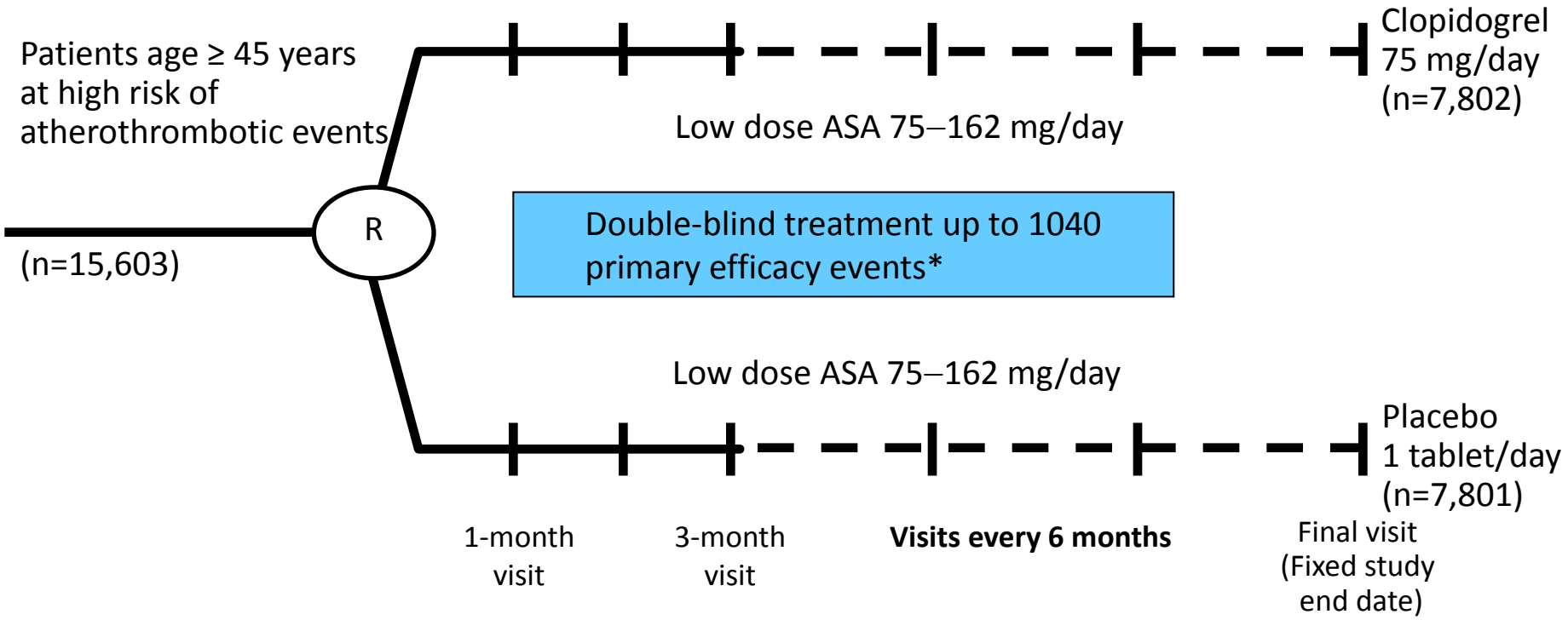
CAPRIE Safety: Hemorrhagic Events



- Trend to more cerebral hemorrhages, fatal or non-fatal, and more hemorrhagic deaths in aspirin group: 37 versus 51 (0.39% vs. 0.53%)

1. Bogousslavsky. Cerebrovasc Dis 1998;8(suppl 4):43. Abstract CLI 76.
2. CAPRIE Steering Committee. Lancet 1996;348:1329-1339.

CHARISMA: Study Design

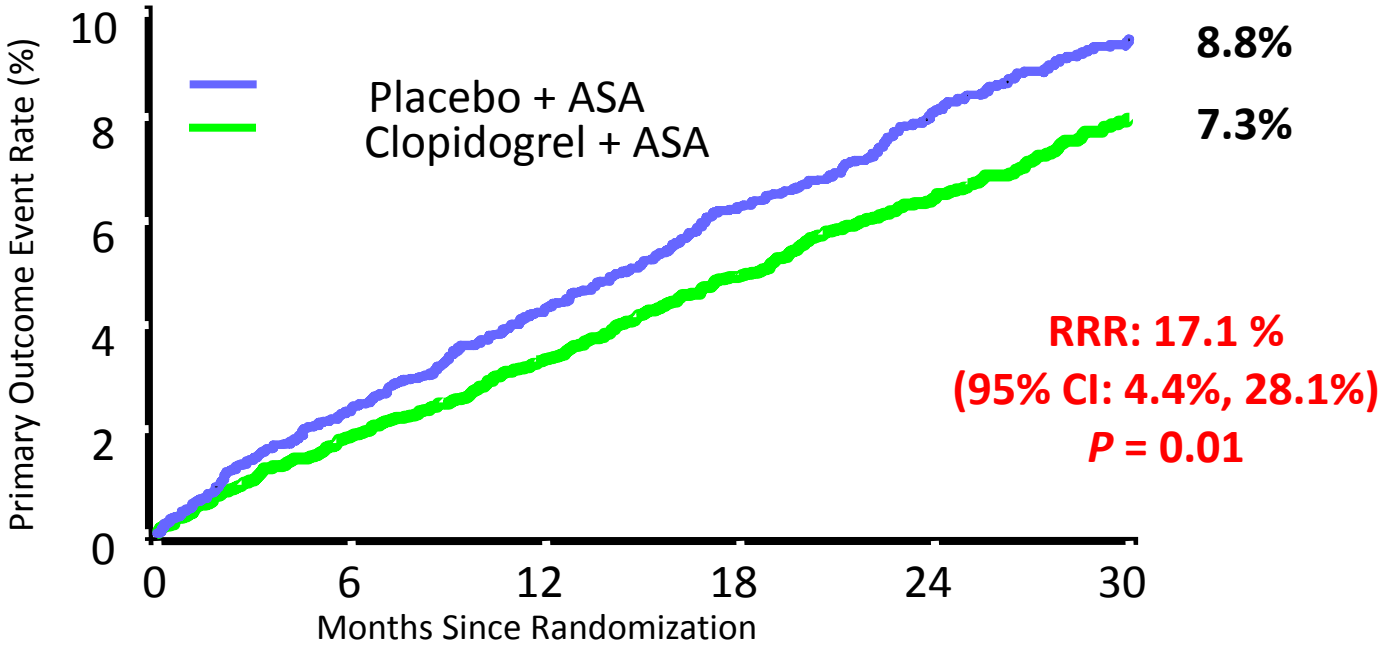


*** MI (fatal or non-fatal), stroke (fatal or non-fatal), or cardiovascular death**

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

CAPRIE-like CHARISMA study
PEP (Composite of CV death, MI, or stroke)

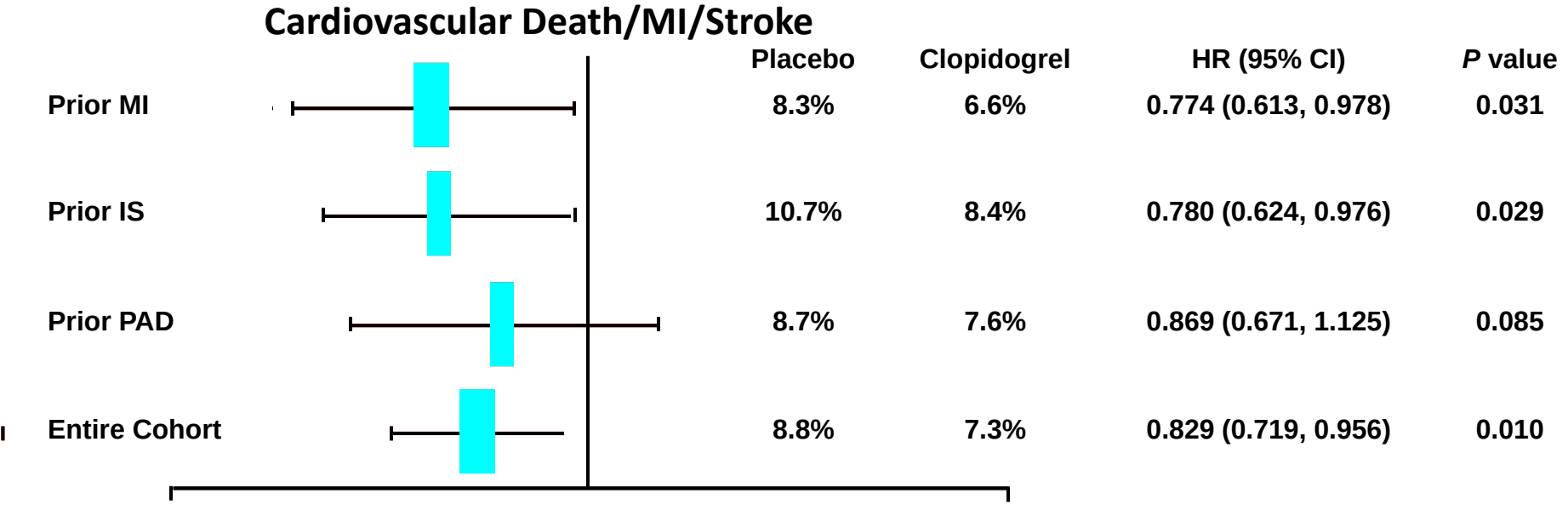
A post-hoc analysis in 9,478 patients of subgroup
in the CHARISMA trial who were enrolled with MI, IS, or PAD



Bhatt DL, JACC 2007;49:1982-1988

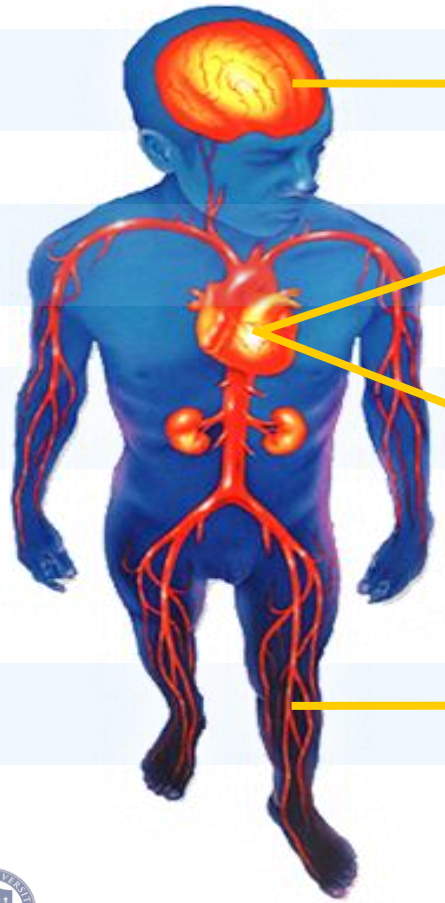
Primary Endpoint (MI/Stroke/CV Death) in Patients with Previous MI, IS, or PAD

"CHARISMA - CAPRIE-like Cohort"



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

Efficacy of Clopidogrel in Atherothrombotic Diseases



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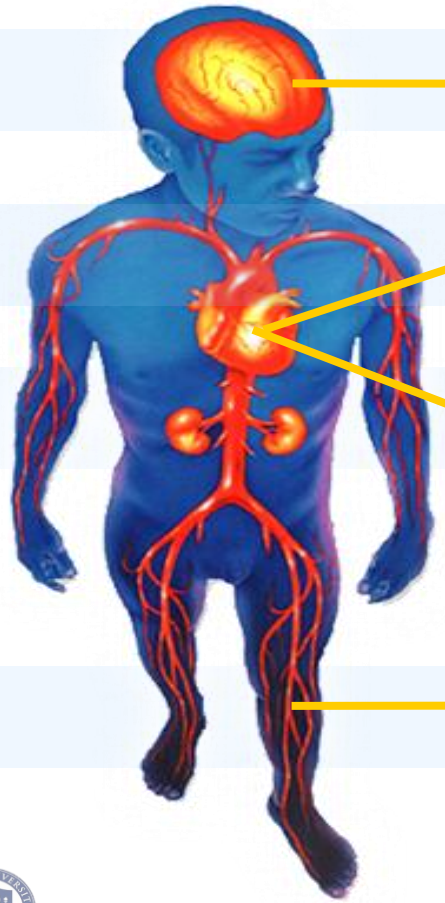

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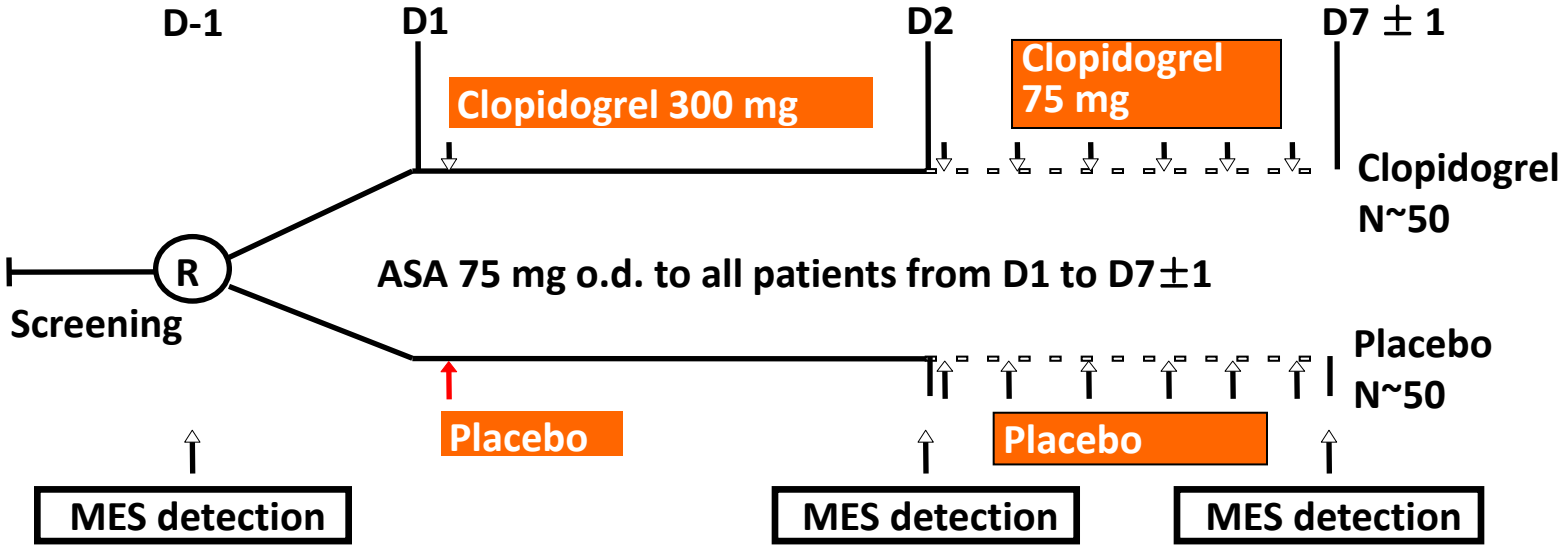
CURE, PCI-CURE, COMMIT, CLARITY, CREDO, CURRENT
OASIS 7, CAPRIE,CHARISMA

Peripheral arterial disease

CAPRIE, CHARISMA, CASPAR

CARESS: Study Design

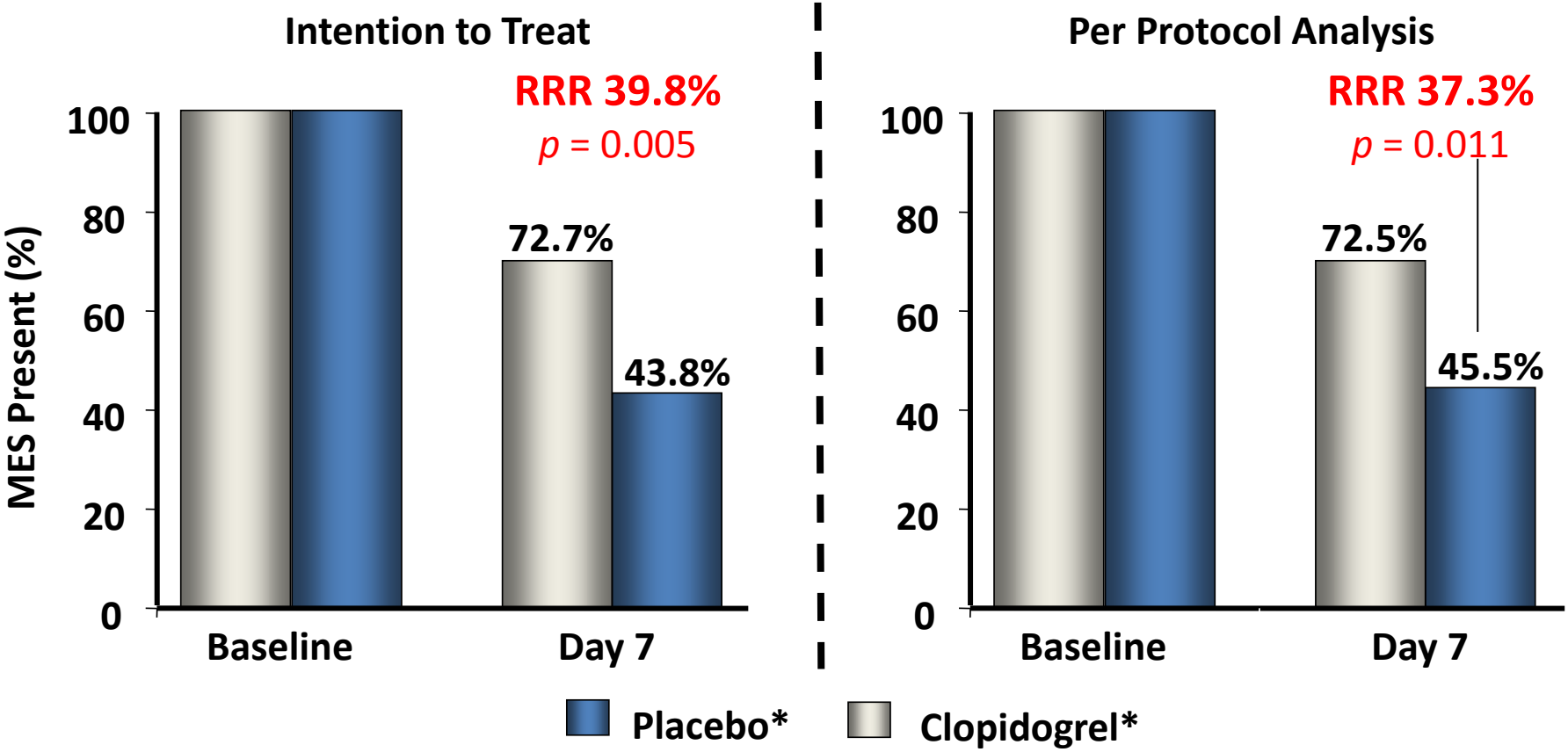
- **Subjects: Symptomatic patients with carotid stenosis >50%**



MES: microembolic signals by transcranial Doppler

Markus H, Circulation. 2005;111: 2233–40.

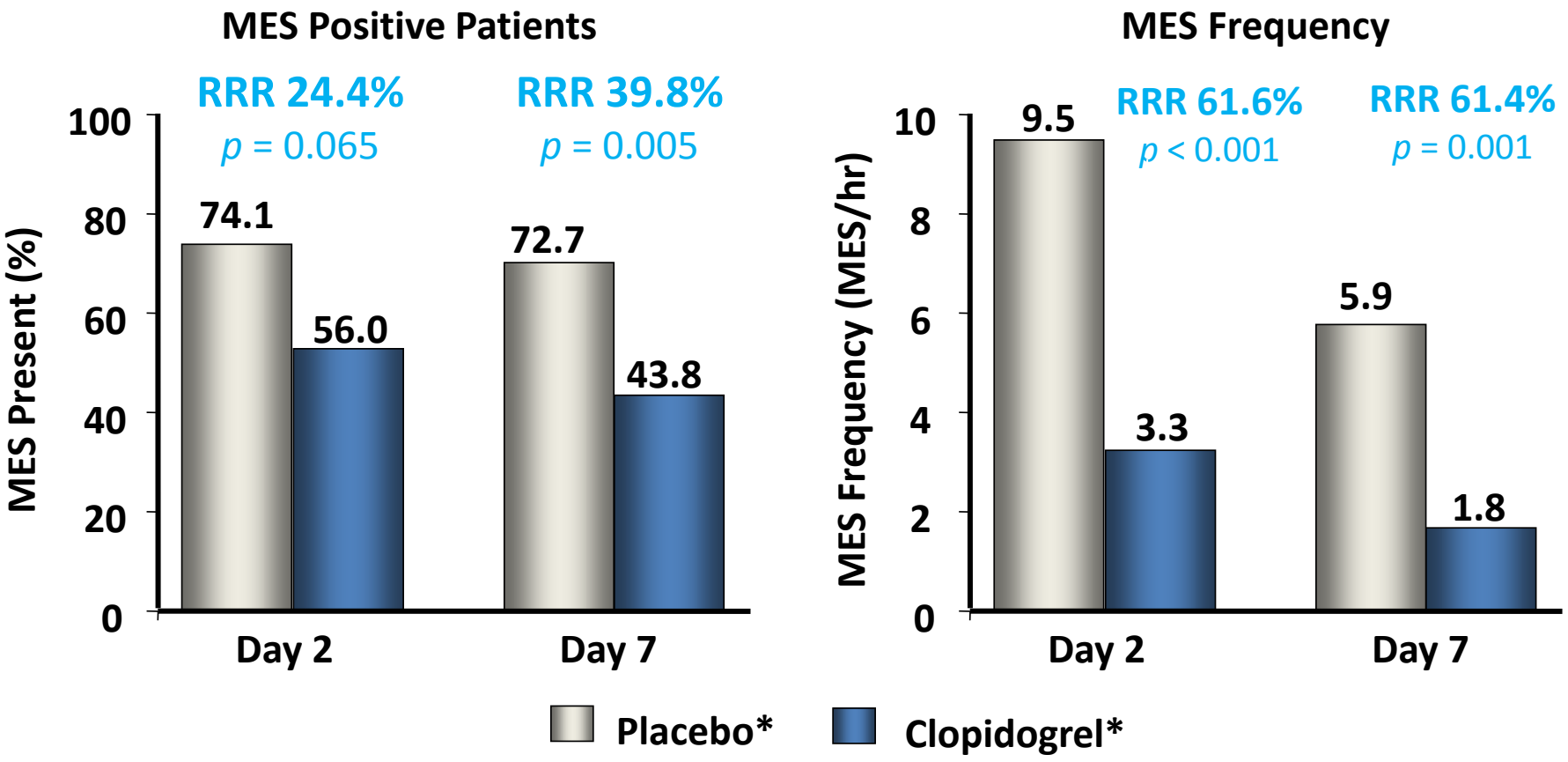
CARESS: Primary Results



*All patients received ASA 75 mg daily

Markus H, Circulation. 2005;111: 2233–40.

CARESS: Secondary Analyses



*All patients received ASA 75 mg daily

Markus H, Circulation. 2005;111: 2233–40.

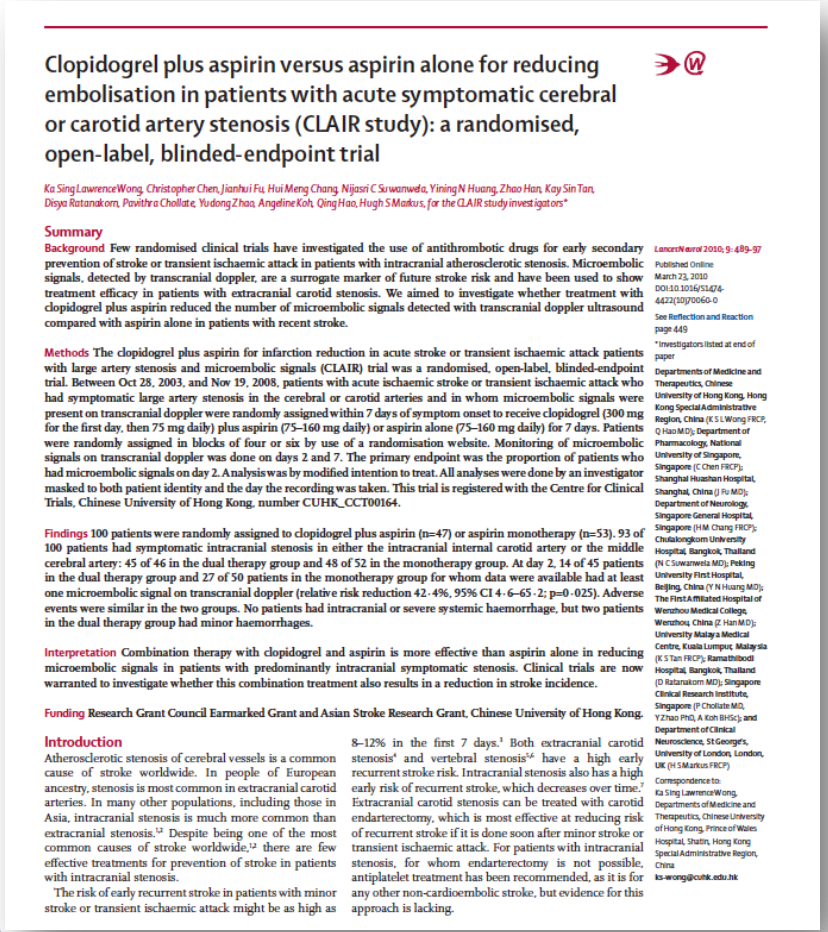
CARESS: Bleeding Events

	Placebo* (n = 56)	Clopidogrel* (n = 51)	
Any Bleeding, N (%)	1 (1.8)	2 (3.9)	NS
Life-threatening bleeding, N (%)	0	0	
Major bleeding including ICH, N (%)	0	0	
Minor bleeding, N (%)	1 (1.8)	2 (3.9)	NS

*All patients received ASA 75 mg daily

Markus H, et al. Circulation. 2005;111(17): 2233–40.

CLAIR Study



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

Ka Sing Lawrence Wong, Christopher Chen, Jianhui Fu, Hui Meng Chang, Nijasri C Suwanwela, Yining N Huang, Zhao Han, Kay Sin Tan, Disya Ratanakorn, Pavithra Chollate, Yudong Zhao, Angeline Koh, Qing Hao, Hugh S Markus, for the CLAIR study investigators*

Summary

Background Few randomised clinical trials have investigated the use of antithrombotic drugs for early secondary prevention of stroke or transient ischaemic attack in patients with intracranial atherosclerotic stenosis. Microembolic signals, detected by transcranial doppler, are a surrogate marker of future stroke risk and have been used to show treatment efficacy in patients with extracranial carotid stenosis. We aimed to investigate whether treatment with clopidogrel plus aspirin reduced the number of microembolic signals detected with transcranial doppler ultrasound compared with aspirin alone in patients with recent stroke.

Methods The clopidogrel plus aspirin for infarction reduction in acute stroke or transient ischaemic attack patients with large artery stenosis and microembolic signals (CLAIR) trial was a randomised, open-label, blinded-endpoint trial. Between Oct 28, 2003, and Nov 19, 2008, patients with acute ischaemic stroke or transient ischaemic attack who had symptomatic large artery stenosis in the cerebral or carotid arteries and in whom microembolic signals were present on transcranial doppler were randomly assigned within 7 days of symptom onset to receive clopidogrel (300 mg for the first day, then 75 mg daily) plus aspirin (75–160 mg daily) or aspirin alone (75–160 mg daily) for 7 days. Patients were randomly assigned in blocks of four or six by use of a randomisation website. Monitoring of microembolic signals on transcranial doppler was done on days 2 and 7. The primary endpoint was the proportion of patients who had microembolic signals on day 2. Analysis was by modified intention to treat. All analyses were done by an investigator masked to both patient identity and the day the recording was taken. This trial is registered with the Centre for Clinical Trials, Chinese University of Hong Kong, number CUHK_CCT00164.

Findings 100 patients were randomly assigned to clopidogrel plus aspirin (n=47) or aspirin monotherapy (n=53). 93 of 100 patients had symptomatic intracranial stenosis in either the intracranial internal carotid artery or the middle cerebral artery: 45 of 46 in the dual therapy group and 48 of 52 in the monotherapy group. At day 2, 14 of 45 patients in the dual therapy group and 27 of 50 patients in the monotherapy group for whom data were available had at least one microembolic signal on transcranial doppler (relative risk reduction 42·4%, 95% CI 4·6–65·2; p=0·025). Adverse events were similar in the two groups. No patients had intracranial or severe systemic haemorrhage, but two patients in the dual therapy group had minor haemorrhages.

Interpretation Combination therapy with clopidogrel and aspirin is more effective than aspirin alone in reducing microembolic signals in patients with predominantly intracranial symptomatic stenosis. Clinical trials are now warranted to investigate whether this combination treatment also results in a reduction in stroke incidence.

Funding Research Grant Council Earmarked Grant and Asian Stroke Research Grant, Chinese University of Hong Kong.

Introduction

Atherosclerotic stenosis of cerebral vessels is a common cause of stroke worldwide. In people of European ancestry, stenosis is most common in extracranial carotid arteries. In many other populations, including those in Asia, intracranial stenosis is much more common than extracranial stenosis.[1,2] Despite being one of the most common causes of stroke worldwide,[1,2] there are few effective treatments for prevention of stroke in patients with intracranial stenosis.

The risk of early recurrent stroke in patients with minor stroke or transient ischaemic attack might be as high as 8–12% in the first 7 days.[3] Both extracranial carotid stenosis[4] and vertebral stenosis[5,6] have a high early recurrent stroke risk. Intracranial stenosis also has a high early risk of recurrent stroke, which decreases over time.[7] Extracranial carotid stenosis can be treated with carotid endarterectomy, which is most effective at reducing risk of recurrent stroke if it is done soon after minor stroke or transient ischaemic attack. For patients with intracranial stenosis, for whom endarterectomy is not possible, antiplatelet treatment has been recommended, as it is for any other non-cardioembolic stroke, but evidence for this approach is lacking.

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See Reflection and Reaction page 449

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Patients with acute ischaemic stroke or TIA who had symptomatic cerebral or carotid artery stenosis

100 patients were randomly assigned to clopidogrel plus aspirin (n=47) or aspirin monotherapy (n=53).

The primary endpoint was the proportion of patients who had microembolic signals on day 2

Wong KSL, Lancet Neurol 2010; 9: 489–97

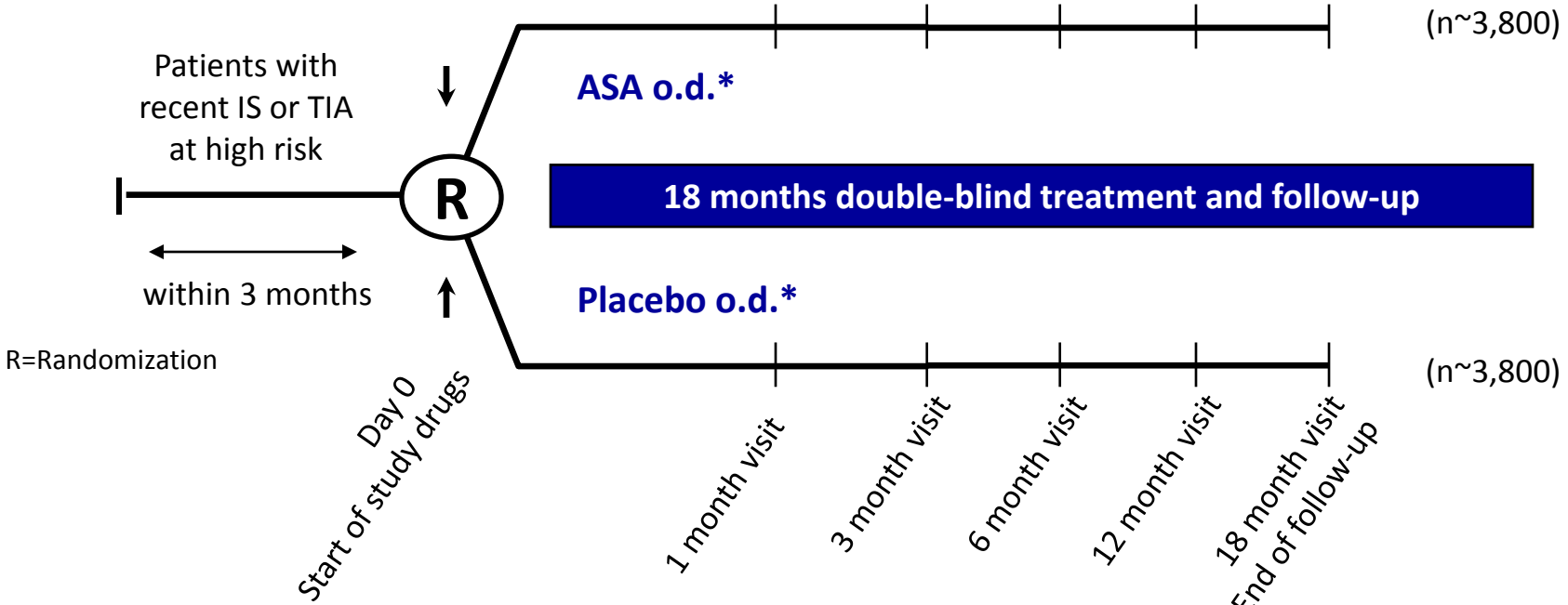
CLAIR : Main Results

	Dual therapy	Monotherapy	Relative risk reduction, % (95% CI)	p
Modified intention to treat	n=46	n=52		
Baseline	26/46 (57%)	35/52 (67%)	16·0% (–15·2 to 38·8)	0·272
Day 2	14/45 (31%)	27/50 (54%)	42·4% (4·6 to 65·2)	0·025
Day 7	10/43 (23%)	26/51 (51%)	54·4% (16·4 to 75·1)	0·006
Per protocol	n=25	n=31		
Baseline	25/25 (100%)	31/31 (100%)	..	..
Day 2	10/25 (40%)	22/30 (73%)	45·5% (7·7 to 67·8)	0·013
Day 7	8/24 (33%)	20/31 (65%)	48·3% (3·7 to 72·3)	0·022

	Estimated coefficient (SE)	Adjusted relative risk reduction, % (95% CI)	p
Day 2			
Treatment (dual vs monotherapy)	–0·528 (0·235)	41·0% (6·5 to 62·8)	0·025
Presence of microembolic signals at day 1	1·211 (0·383)	–235·6% (–610·9 to –58·5)	0·002
Day 7			
Treatment (dual vs monotherapy)	–0·696 (0·293)	50·2% (11·5 to 72·0)	0·018
Presence of microembolic signals at day 1	1·190 (0·427)	–228·6% (–685·1 to –42·4)	0·005

MATCH: Study Design

The MATCH Trial is designed to determine the efficacy and safety of ASA compared to placebo in high-risk cerebrovascular patients receiving clopidogrel 75 mg and other standard therapies

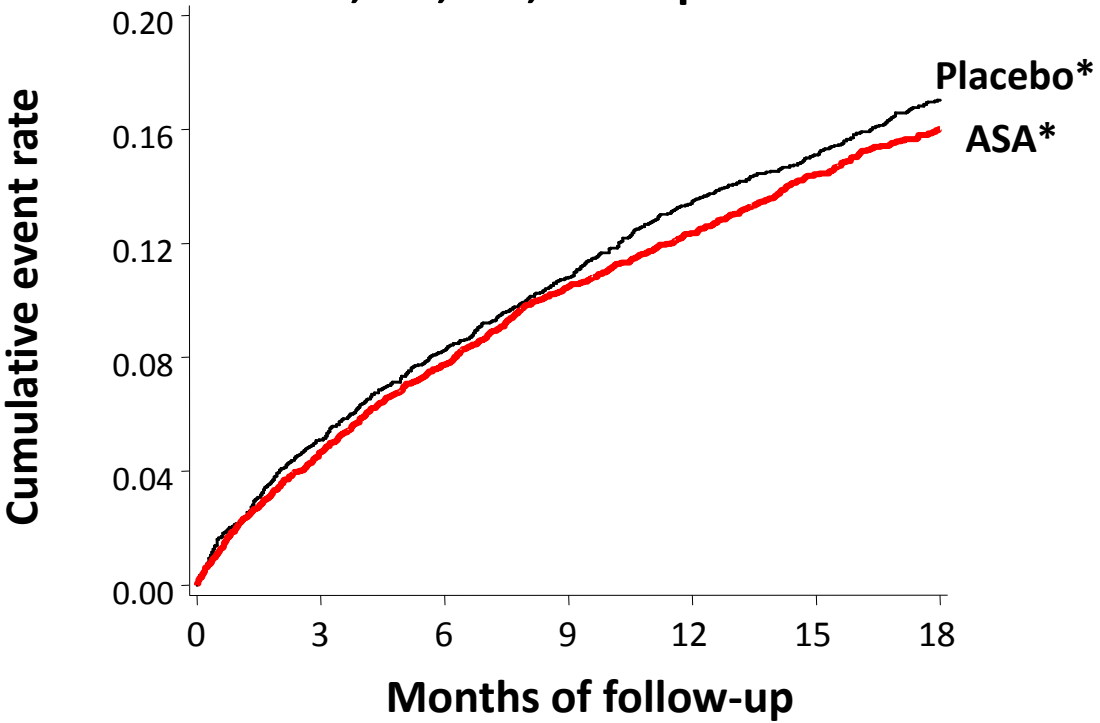


***All patients received clopidogrel and other standard therapies**

1. Diener H-C, *et al*. *Lancet* 2004; **364:** 331–337.

MATCH :Primary Endpoint

Primary Endpoint (ITT):
IS, MI, VD, rehospitalization for acute ischemic event



RRR: 6.4%
(p=0.244)

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

Diener H-C, *et al*. *Lancet* 2004; **364:** 331–337.

MATCH: Main Safety Outcomes

Type of Bleeding Events	ASA (n=3,759)		Placebo (n=3,781)		% Absolute Difference (95% CI)		*P* value
Life-Threatening* Bleeding Events (%)	96	(3%)	49	(1%)	1.26	(0.64 to 1.88)	<0.0001
Fatal	16	(<1%)	11	(<1%)	0.13	(–0.14 to 0.40)	
Nonfatal	81	(2%)	38	(1%)	1.15	(0.59 to 1.71)	
Major Bleeding† Events (%)	73	(2%)	22	(1%)	1.36	(0.86 to 1.86)	<0.0001

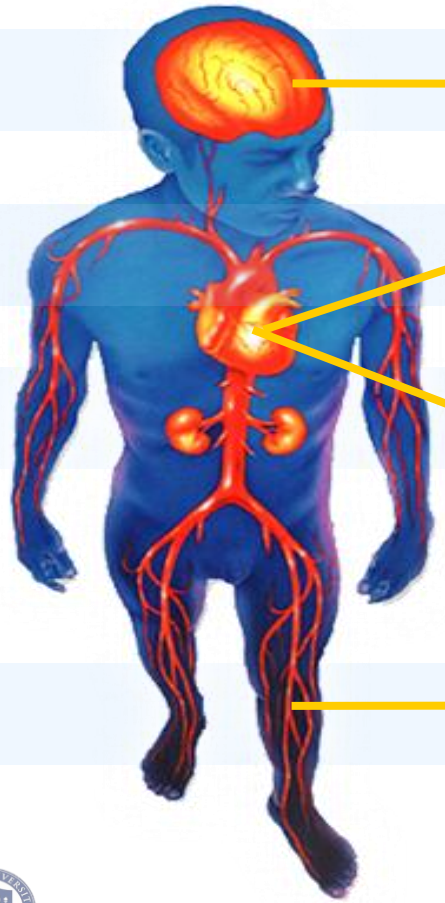
Life threatening: defined as any fatal bleeding event, or a drop in hemoglobin of ≥5 g/dL, or significant hypotension with the need for inotropes (hemorrhagic shock), or symptomatic intracranial hemorrhage, or requiring transfusion of ≥4 units of red blood cells or equivalent amount of whole blood.

† Major bleeding: defined as significantly disabling (with persistent sequelae), or intraocular bleeding leading to significant vision loss, or requiring transfusion of ≤3 units of red blood cells or equivalent amount of whole blood.

Adapted from Diener H-C et al for the MATCH Investigators. *Lancet*. 2004;364:331-337.

TIA is not a labeled indication in some countries.

Efficacy of Clopidogrel in Atherothrombotic Diseases



Cerebrovascular disease

CAPRIE, CHARISMA,CARESS, CLAIR, MATCH

Atrial Fibrillation

Active A

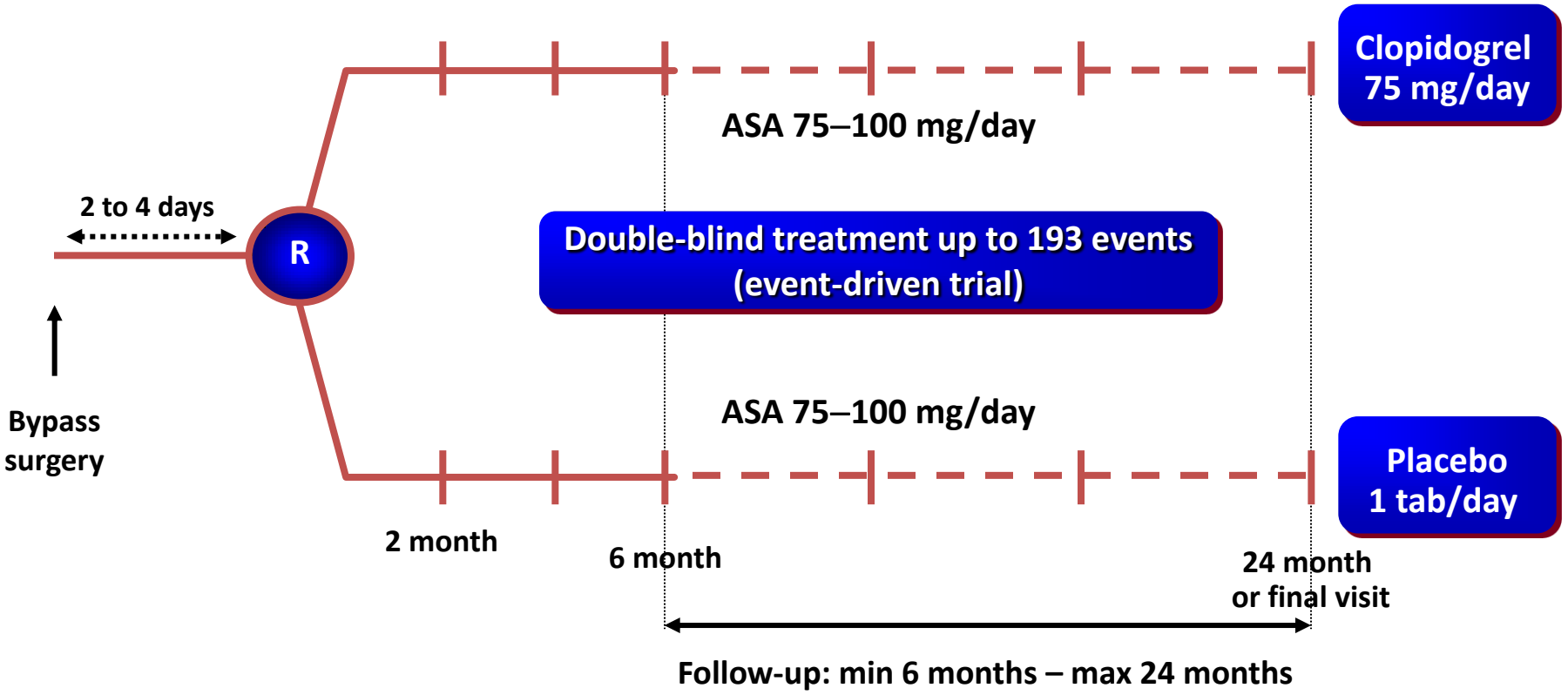
Coronary artery disease

CURE, PCI-CURE, COMMIT, CLARITY, CREDO, CURRENT
OASIS 7, CAPRIE, CHARISMA

Peripheral arterial disease

CAPRIE, CHARISMA, CASPAR

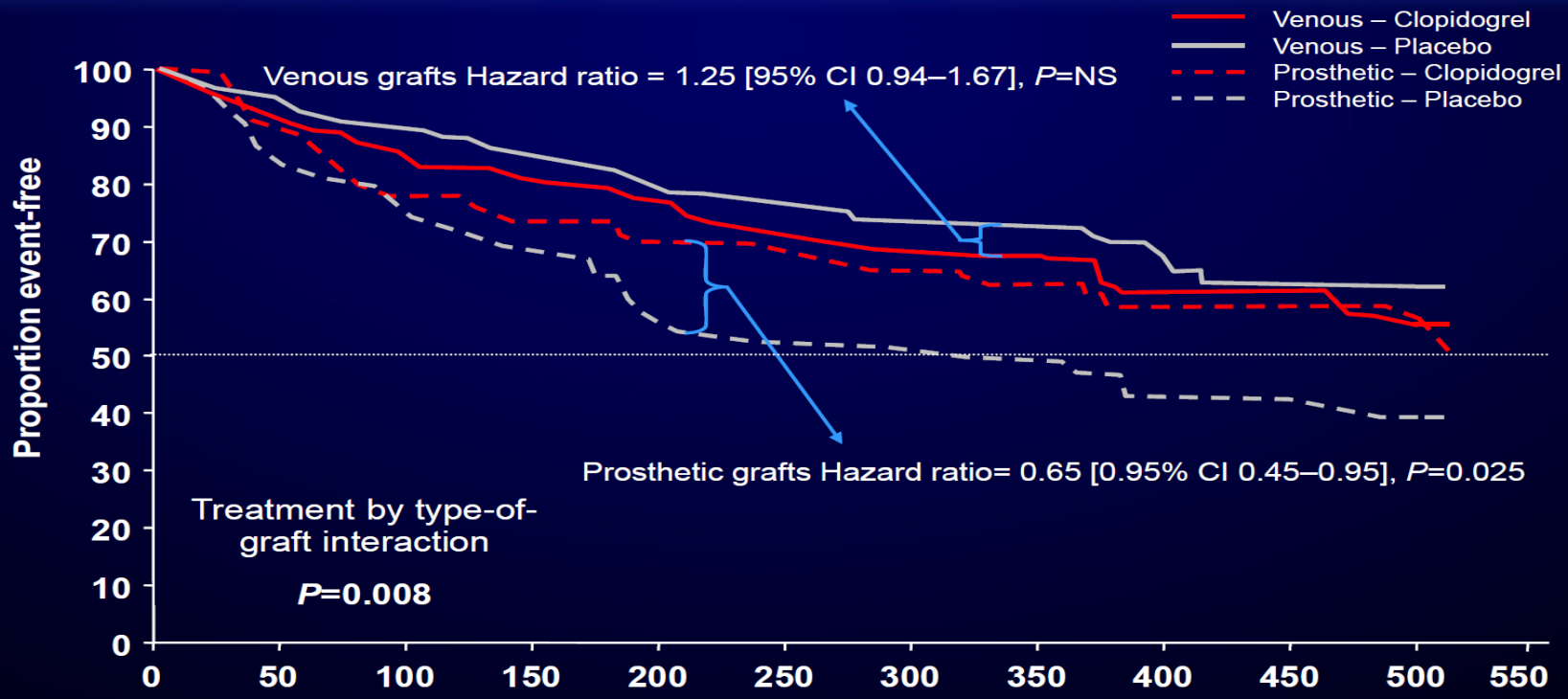
CASPAR: Study Design



R=Randomization stratified by type of graft (venous/prosthetic).

CASPAR: Primary Endpoint

K-M Curves of Time to Primary Outcome Event: Each Type Of Graft (ITT)

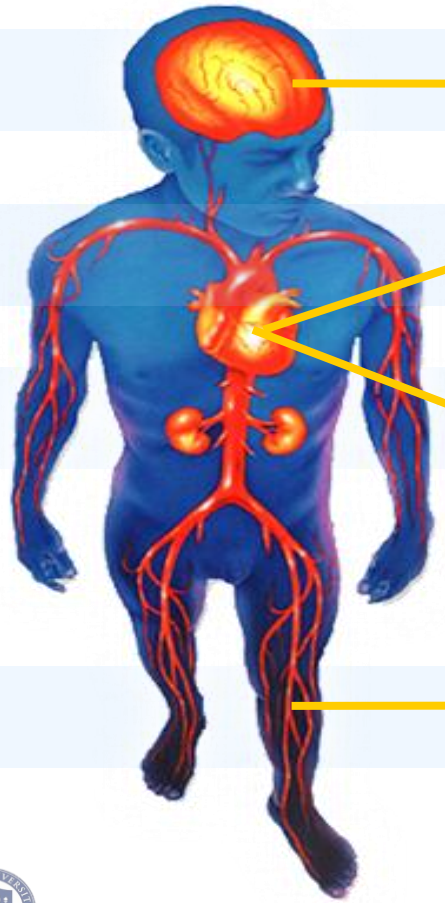


Bleeding: Total CASPAR Population (ITT)

	Placebo N=422	Clopidogrel N=426	*P*-value
Total bleeding, n (%)*	30 (7.1%)	71 (16.7%)	<0.001
Mild	21 (5.0%)	46 (10.8%)	<0.05
Moderate	4 (0.9%)	16 (3.8%)	0.007
Severe	5 (1.2%)	9 (2.1%)	NS
Fatal	1 (0.2%)	2 (0.5%)	—

* GUSTO definition (severe: ICH, HD compromise; moderate: transfusion but no HD compromise; mild: no transfusion).

Efficacy of Clopidogrel in Atherothrombotic Diseases



Cerebrovascular disease

CAPRIE, CHARISMA, CARESS, CLAIR, MATCH

Atrial Fibrillation

Active A

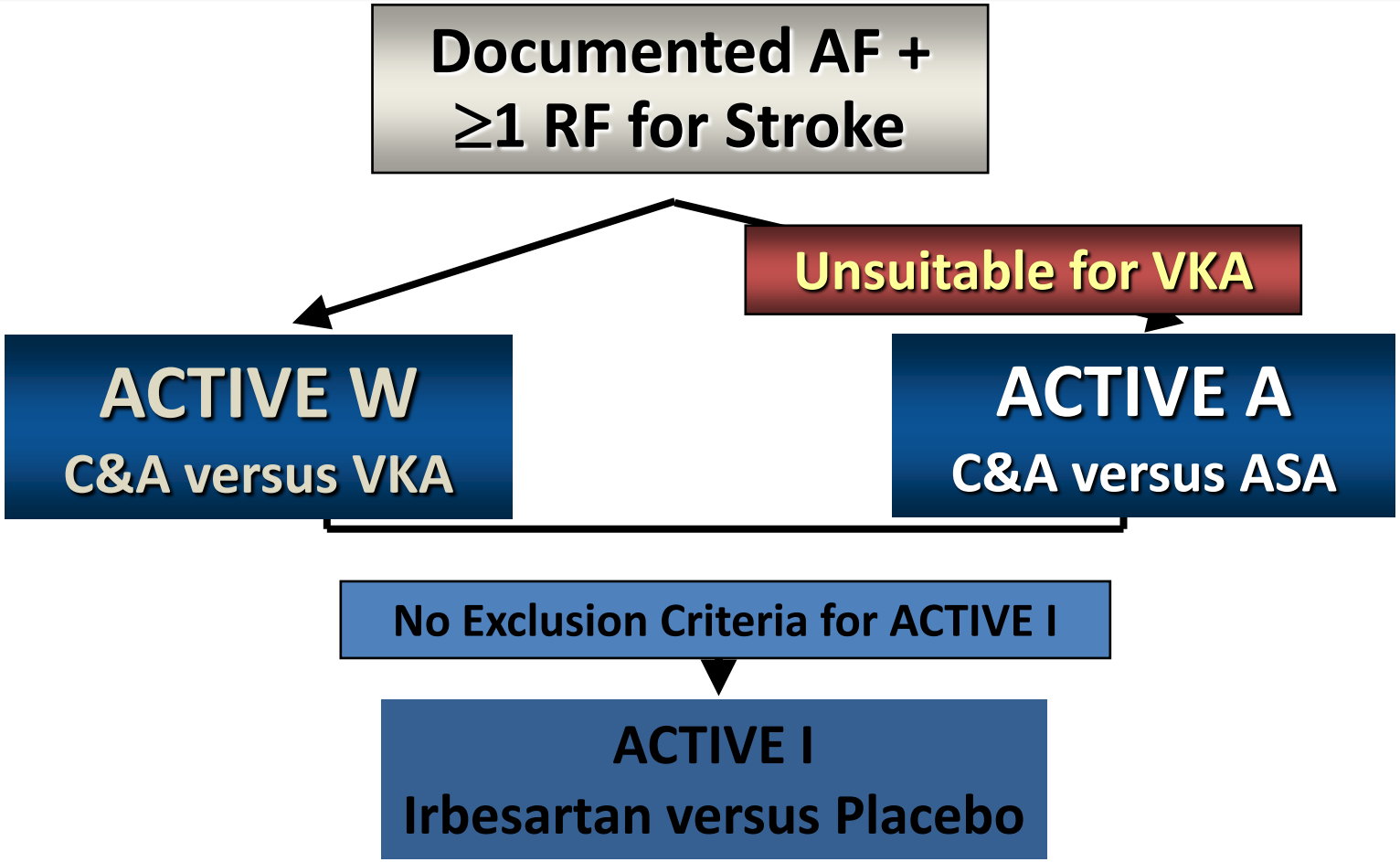
Coronary artery disease

CURE, PCI-CURE, COMMIT, CLARITY, CREDO, CURRENT OASIS 7, CAPRIE, CHARISMA

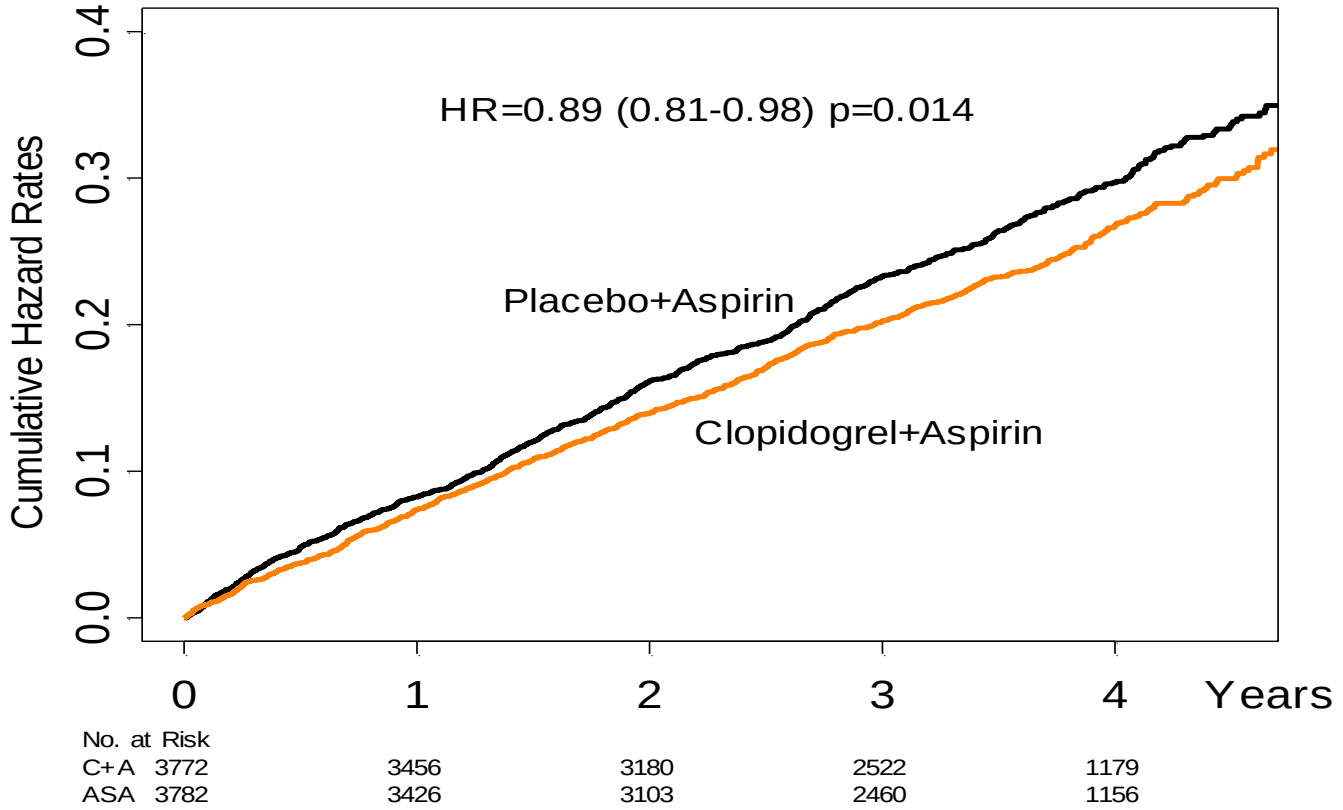
Peripheral arterial disease

CAPRIE, CHARISMA, CASPAR

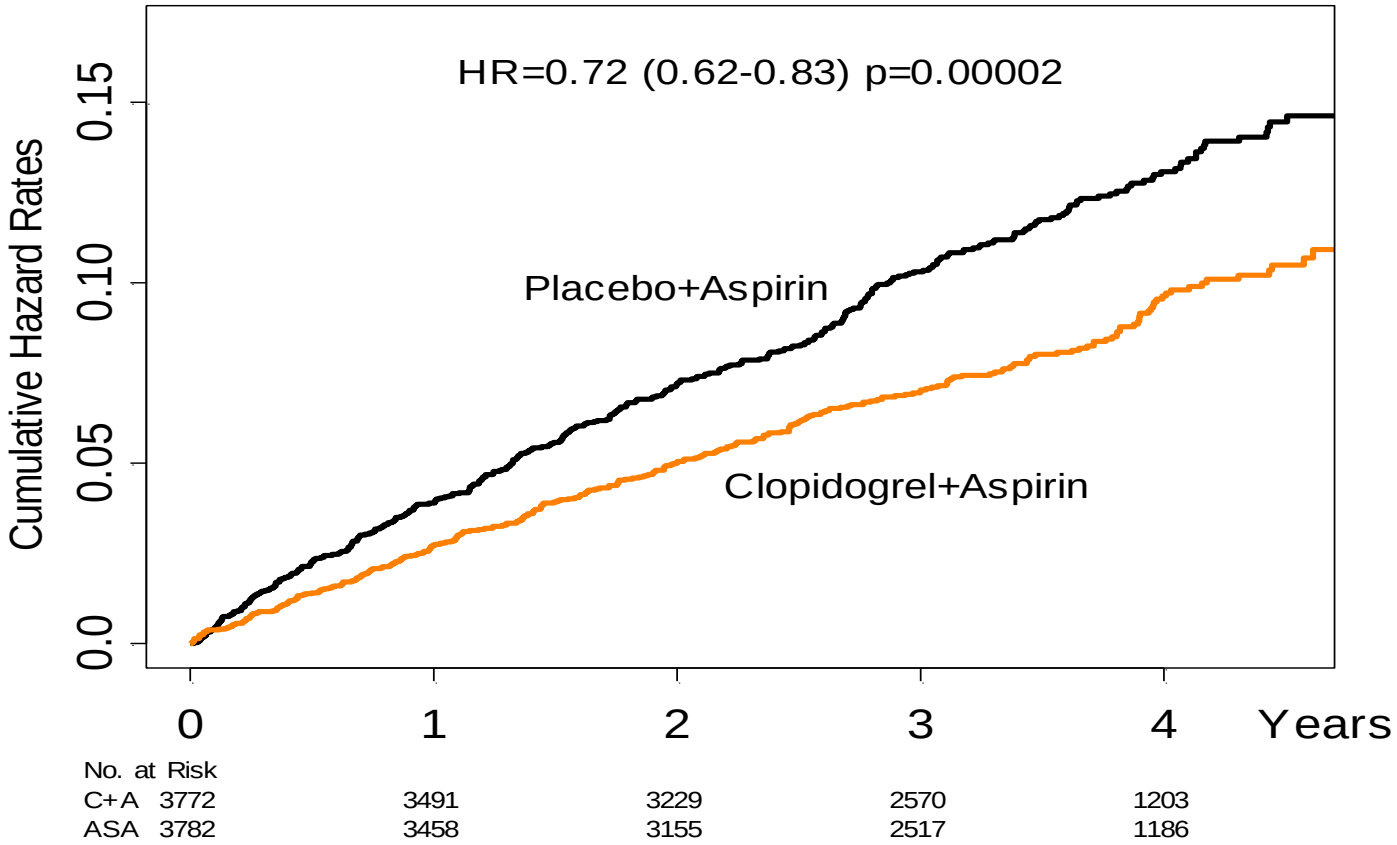
ACTIVE: Study Design



ACTIVE A: Primary Outcome
Vascuar death, Stroke, MI, non-CNS emoblism



ACTIVE A: Stroke



Safety : Bleeding

Outcome	Clopidogrel + Aspirin		Aspirin		Clopidogrel + Aspirin versus Aspirin		
	#	rate/ year	#	rate/ year	RR	95% CI	P
Major	251	2.0	162	1.3	1.57	1.29-1.92	<0.001
Severe	190	1.5	122	1.0	1.57	1.25-1.98	<0.001
Fatal	42	0.3	27	0.2	1.56	0.96-2.53	0.07
Intra-cranial	54	0.4	29	0.2	1.87	1.19-1.94	0.006
Extra-cranial	200	1.6	134	1.1	1.51	1.21-1.88	<0.001

AHA/ACCF Guidelines for PAD 2011

Class I

- Antiplatelet therapy is indicated to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD. (Level of Evidence: A)
- Aspirin, 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 atherosclerotic lower extremity PAD. (Level of Evidence: A)
- Clopidogrel (75 mg per day) is recommended as an effective alternative antiplatelet therapy to aspirin to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD. (Level of Evidence: B)

AHA/ACCF Guidelines for PAD 2011

New in 2011

Class IIa

- Antiplatelet therapy can be useful to reduce the risk of MI, stroke, or vascular death in asymptomatic individuals with an ABI less than or equal to 0.90. (Level of Evidence: C)

Class IIb

- The usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in asymptomatic individuals with borderline abnormal ABI, defined as 0.91 to 0.99, is not well established. (Level of Evidence: A)
- The combination of aspirin and clopidogrel may be considered to reduce the risk of cardiovascular events in patients with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia and who are not at increased risk of bleeding and who are at high perceived cardiovascular risk. (Level of Evidence: B)

AHA/ASA Guidelines for Secondary Prevention of Stroke 2011

Class I

- For patients with noncardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events (Level of Evidence A).
- Aspirin (50 mg/d to 325 mg/d) monotherapy (Class I; Level of Evidence A), the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily (Class I; Level of Evidence B), and clopidogrel 75 mg monotherapy (Class IIa; Level of Evidence B) are all acceptable options for initial therapy.

Class IIa

- For patients allergic to aspirin, clopidogrel is reasonable (Level of Evidence C).

Class III

- The addition of aspirin to clopidogrel increases the risk of hemorrhage and is not recommended for routine secondary prevention after ischemic stroke or TIA (Level of Evidence A).

AHA/ASA A-fib Guideline Update 2011

Class IIb

- The addition of clopidogrel to aspirin to reduce the risk of major vascular events, including stroke, might be considered in patients with AF in whom oral anticoagulation with warfarin is considered unsuitable due to patient preference or the physician's assessment of the patient's ability to safely sustain anticoagulation.(Level of Evidence: B)

Conclusions

1. High prevalence of polyvascuar disease : There is a substantial overlap between the various locations of atherothrombic disease
2. Clear evidences of Cross-Risk and high events rates especially in polyvascular patients : REACH registry & other studies
3. As well as detection of polyvascular diease, long term treatment and ,management of polyvascular disease patients need to be well established treatment guidelines.
4. Clopidogrel has shown clinical evidences and broad indication for atherothrombotic diseases and is currently recommended in various guidelines: ACS, Stroke, PAD & A-fib
5. Therefore, clopidogrel could be recommended as an effective medical therapy for patients with polyvascular diease.