Clopidogrel, P2Y12 receptor inhibitor in Polyvascular Disease

일석삼조

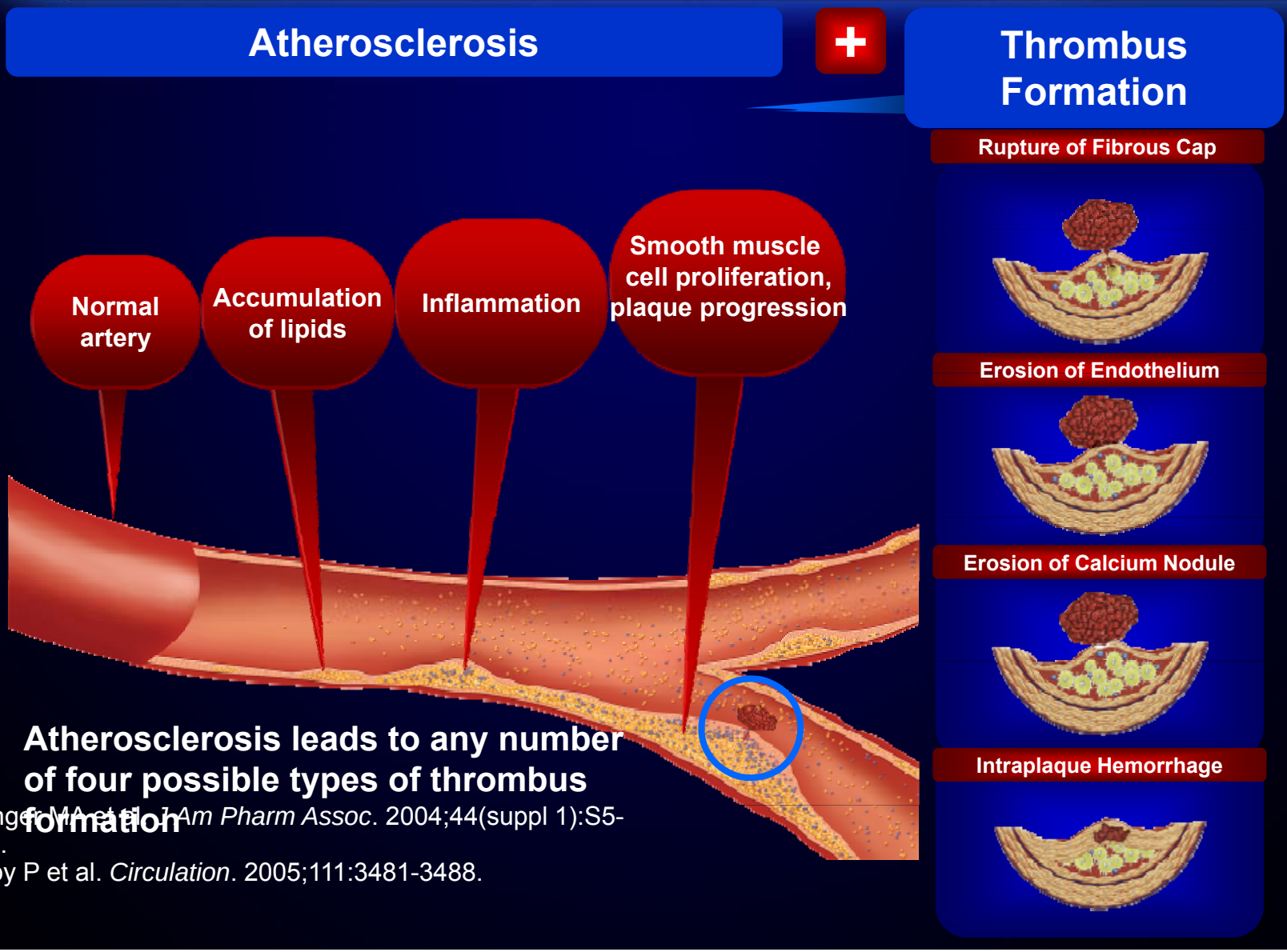
一石三鳥

Three birds in a throw

Contents

- Atherothrombosis and polyvascular disease
- REACH Registry “Polyvascular Disease” and Recent Update
- Clinical Trials: Clopidogrel in Polyvascular Disease
- Indication of Clopidogrel, Prasugrel, and Ticagrelor
- International Guidelines related to “Clopidogrel”
- Conclusions

Pathophysiology of Atherothrombosis



1. Munger MA et al. *J Am Pharm Assoc*. 2004;44(suppl 1):S5-S13.
2. Libby P et al. *Circulation*. 2005;111:3481-3488.

Atherothrombosis Manifestations: Stroke, CAD, and PAD

Prevalence of Atherothrombosis[1] (In Millions)

- IS 5.0
- CAD 15.8
- PAD 8.0

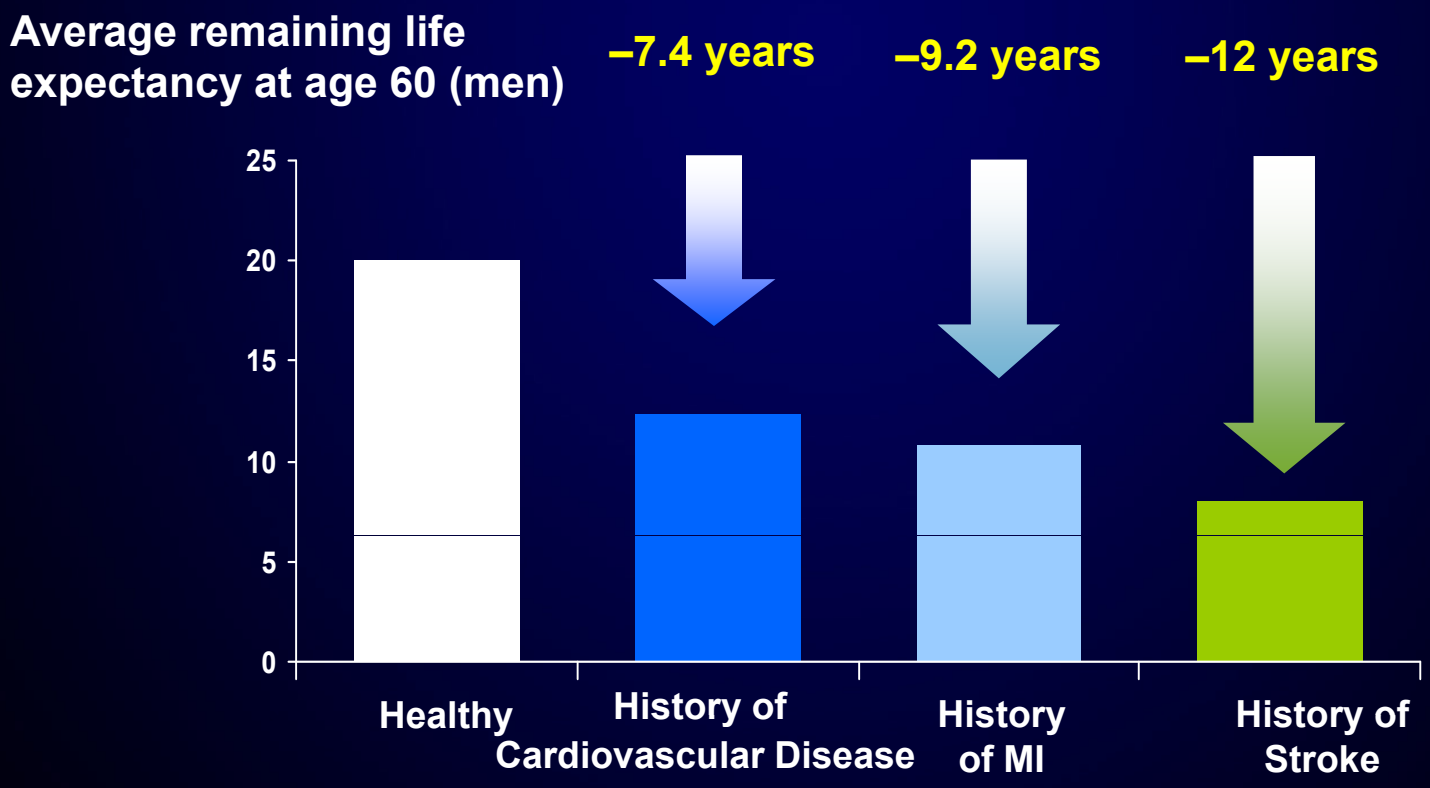
Mortality

Patients with a history of atherothrombosis are most likely to die of a future atherothrombotic event[2–4]

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.

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



***Analysis of data from the Framingham Heart Study.**

Peeters A, et al. *Eur Heart J* 2002; 23: 458-466.

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.

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The REduction in Atherothrombotic Events for Continued Health (REACH) Registry:

Objectives of the REACH Registry

- Primary objectives
  - to generate an **international data** set to extend knowledge of atherothrombotic risk factors and ischemic events in the **real world, outpatient setting**.
  - to improve our understanding of the prevalence and clinical consequences of atherothrombosis in patients across different parts of the world.

- Additional aim
  - to assess use of risk management strategies and 1-, 2-, 3- and 4-year outcomes in a broad outpatient population encompassing various geographical regions and physician specialties.

[1]Ohman EM et al. *Am Heart J* 2006;151(4):786.e1.

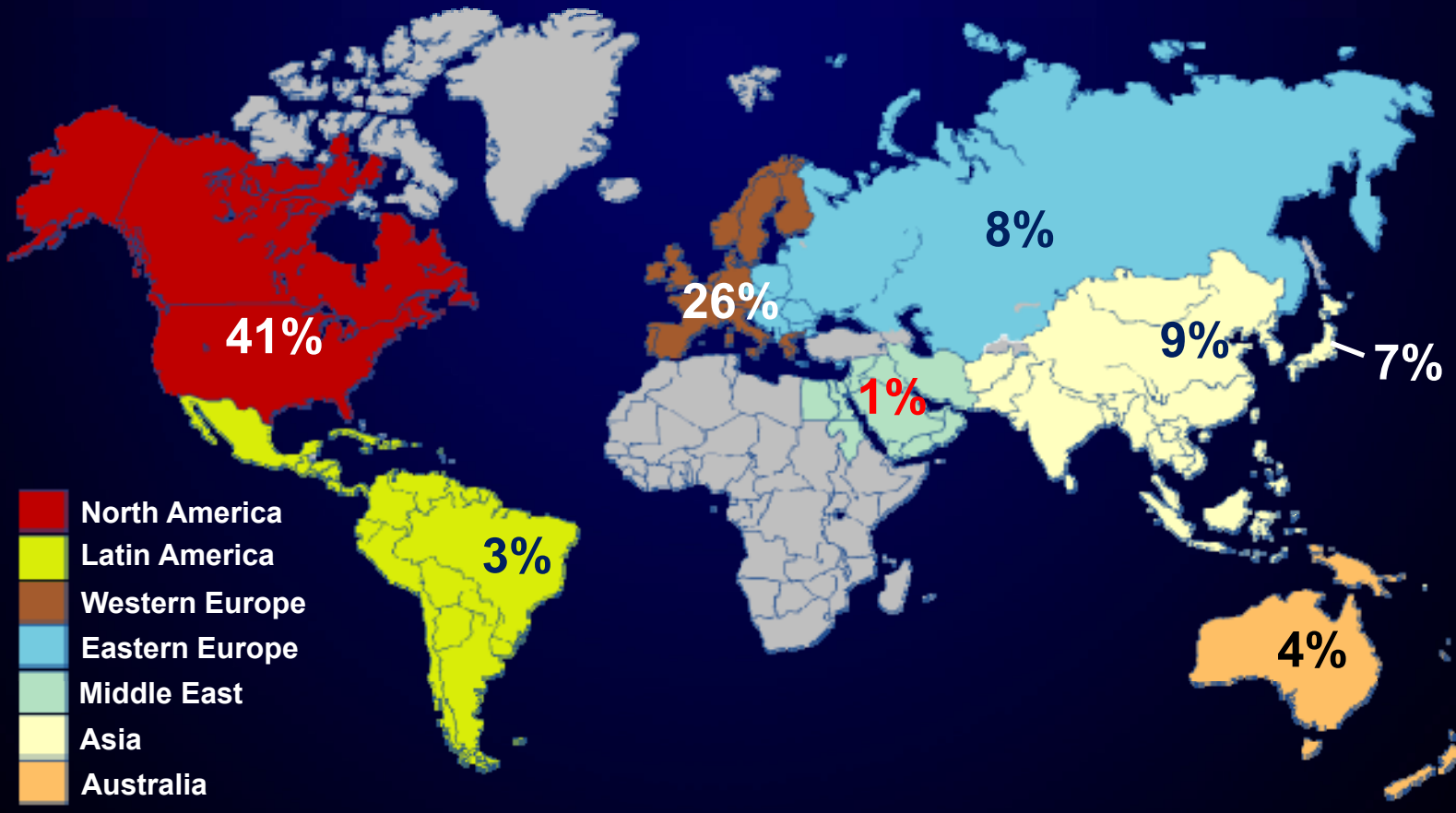
REACH Registry inclusion criteria

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. Ohman EM et al, on behalf of the REACH Registry Investigators. *Am Heart J* 2006;151(4):786.e1-10.

Global population coverage within REACH Registry at baseline



- 67,888 patients enrolled at 5,587 centres in 44 countries were included in the baseline analysis[1]

[1]Bhatt DL, et al. JAMA. 2006;295:180.

Patient enrollment

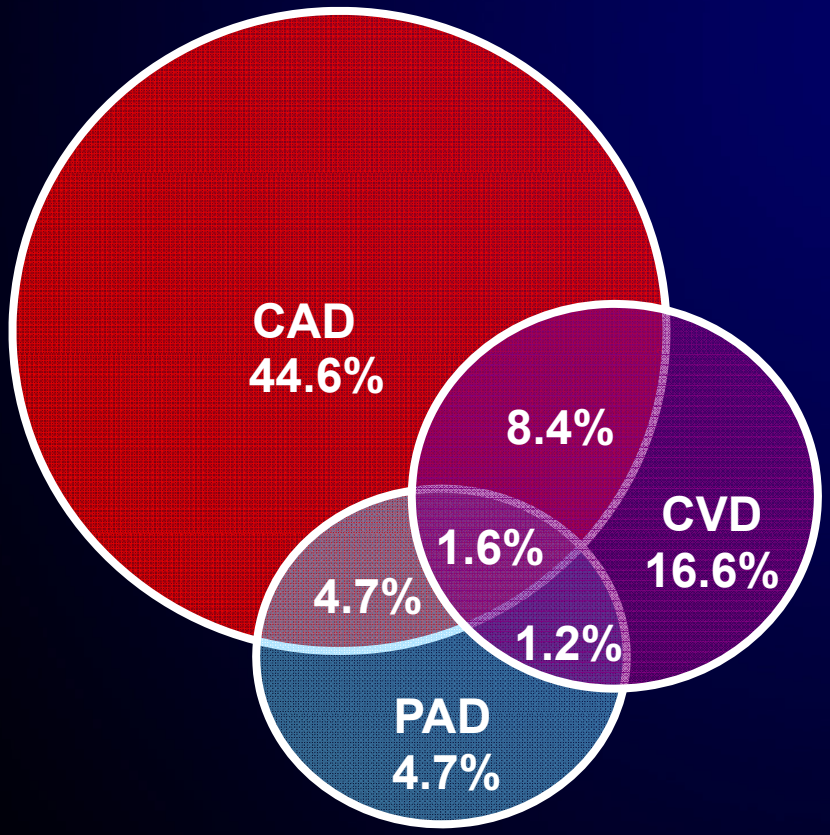
- At the time of the announcement of the REACH Registry, the initial goal was to enroll >50,000 patients across 35 countries
- In total, 69,005 patients were enrolled between December 2003 and December 2004 at 5,587 centres across 44 countries
  (at the time of the baseline analyses and publication, 67,888 enrolled patients had baseline data. Baseline data and enrolment eligibility for additional patients confirmed at the time of the 1-year analyses therefore the number of patients with baseline data differs in the 1-year vs. baseline publications)
- The initial follow-up period was 2 years, but centres were later invited to participate in an extension of the study to monitor and record patient outcomes at 3 years and 4 years after enrolment.

[1]Bhatt DL, et al. JAMA. 2006;295:180.
[2]Bhatt DL, et al. JAMA 2010;304:1350.

The REACH Registry

5 KEY FINDINGS

Prevalence of atherothrombosis at baseline



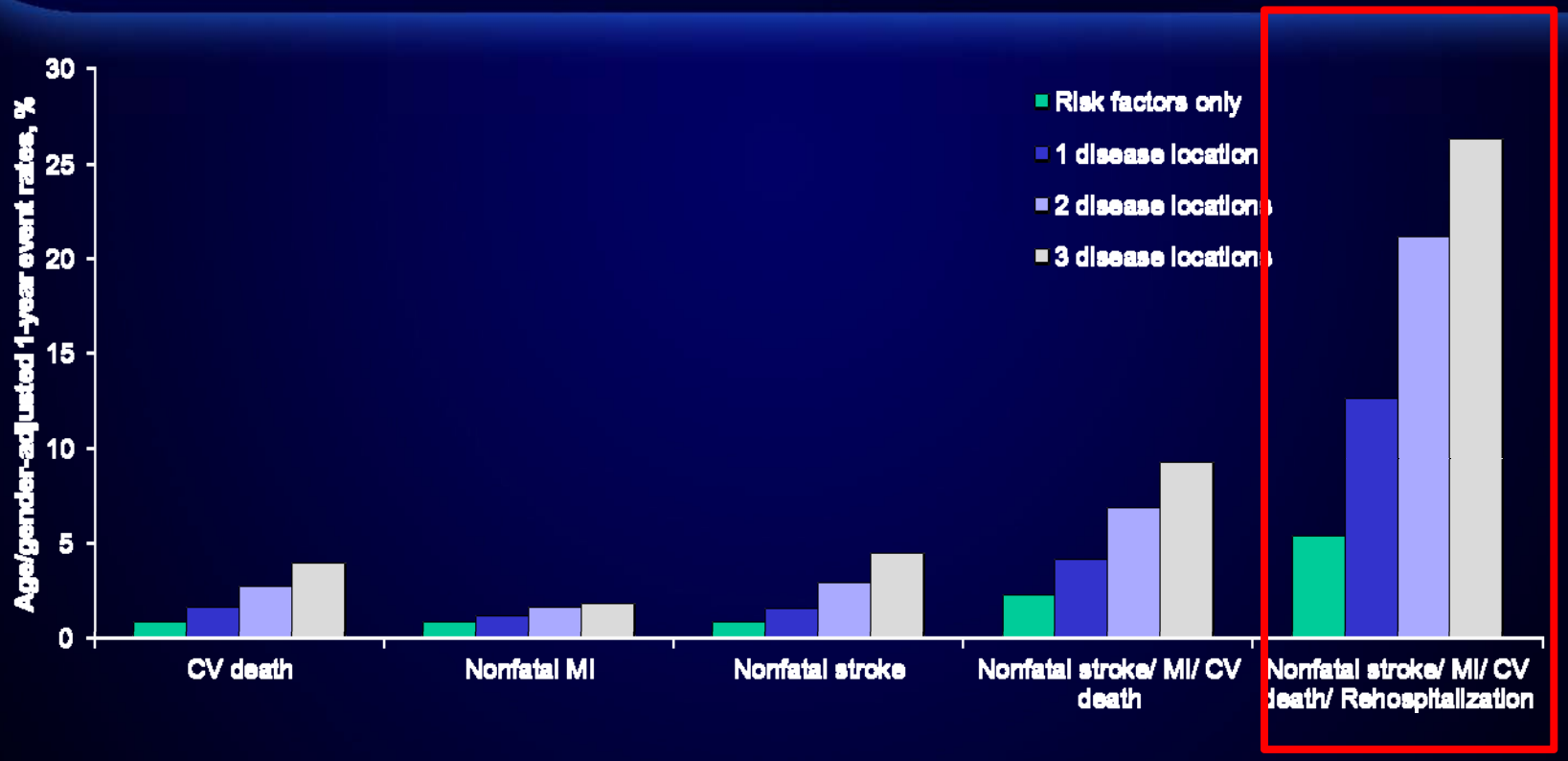
- Atherothrombotic status of REACH Registry patients at baseline:
  - 18.2% RFO (n=12 389)
  - 59.3% CAD (n=40 258)
  - 27.8% CVD (n=18 843)
  - 12.2% PAD (n=8273)

  (single bed disease and overlap in patients with polyvascular disease shown to left)
- Cardiovascular risk-factor profiles were consistent across patient types and across all participating regions.[1]

CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral artery disease; RFO, Risk Factors Only.

[1]Bhatt DL, et al. JAMA 2006;296:180.

Patient outcomes at 1 year after enrolment

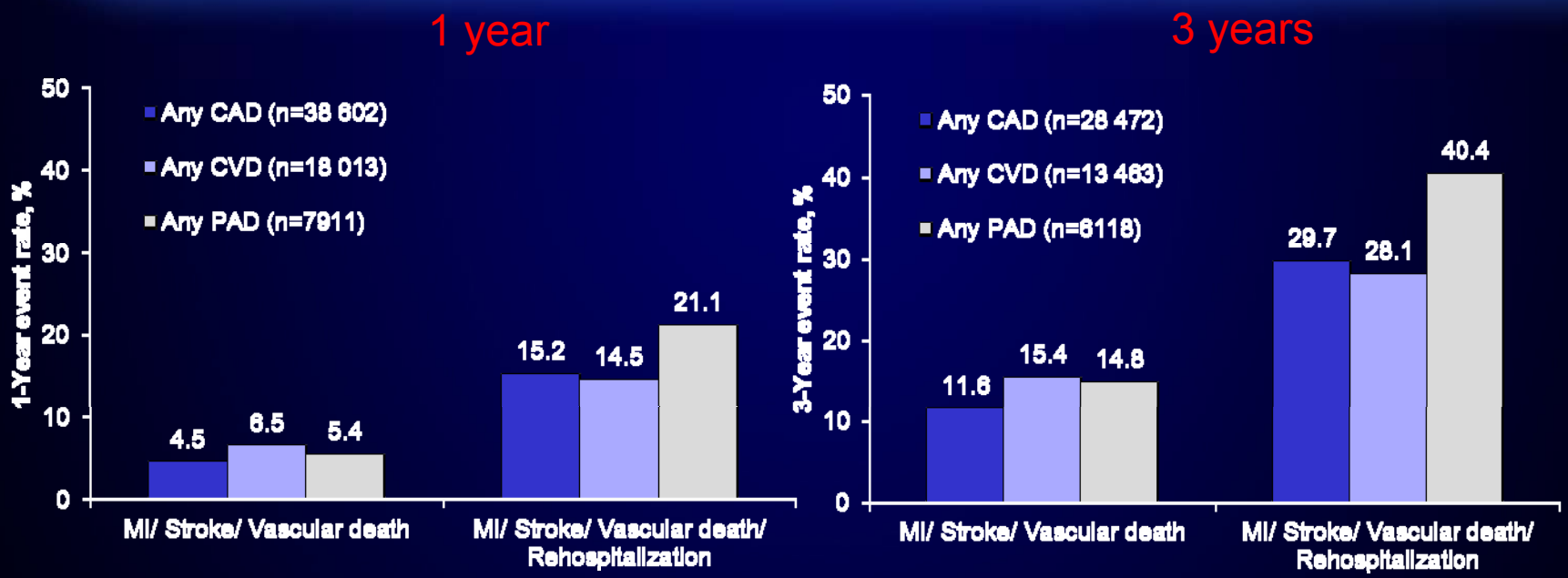


- 1 in 7 patients with symptomatic disease at baseline had a major vascular event or were rehospitalized for a vascular event / intervention procedure.[1]
- CV event rates increased according to number of disease beds.[1]

CV, cardiovascular; MI, myocardial infarction.

[1]Steg PG et al. JAMA 2007;297:1197.

Event rates at 1 and 3 years according to disease

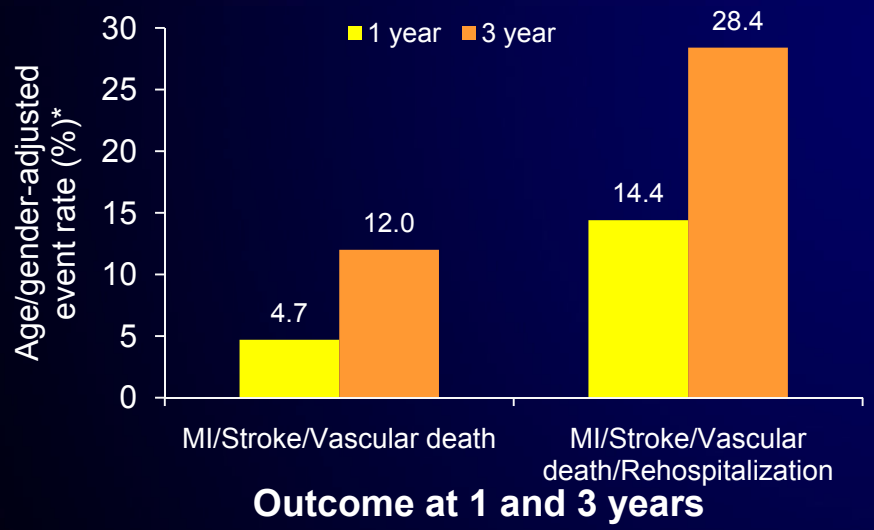


- At enrolment, 53.7% of CVD patients had stroke only, 27.7% had a history of TIA only, 18.5% had experience both a stroke and TIA.[1]
- By the 3-year follow-up, 40% of PAD patients had experienced a CV/ ischemic event or been rehospitalized for another event.[2]

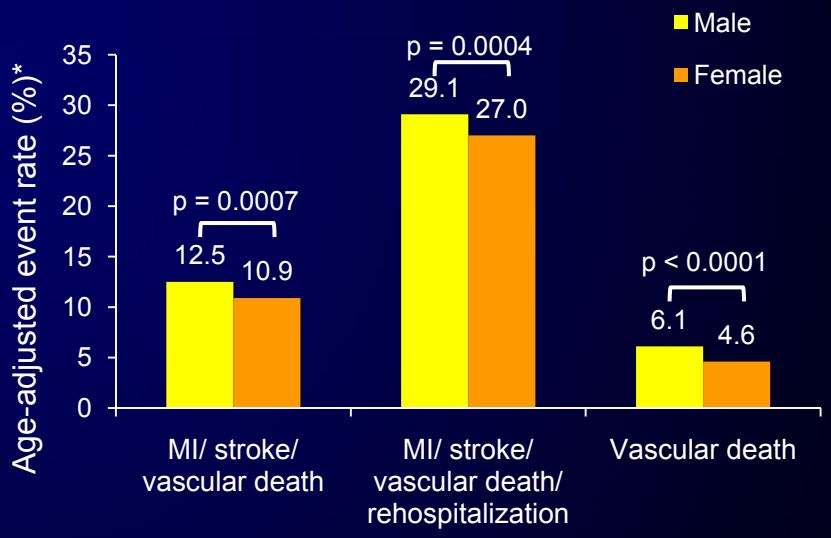
TIA, Transient Ischemic Attack.

[1]Roether J et al. Cerebrovasc Dis. 2008;25:366.
[2]Alberts MJ et al. Eur Heart J 2009;30:2318.

3-year outcomes in patients with symptomatic atherothrombosis



Outcome at 1 and 3 years

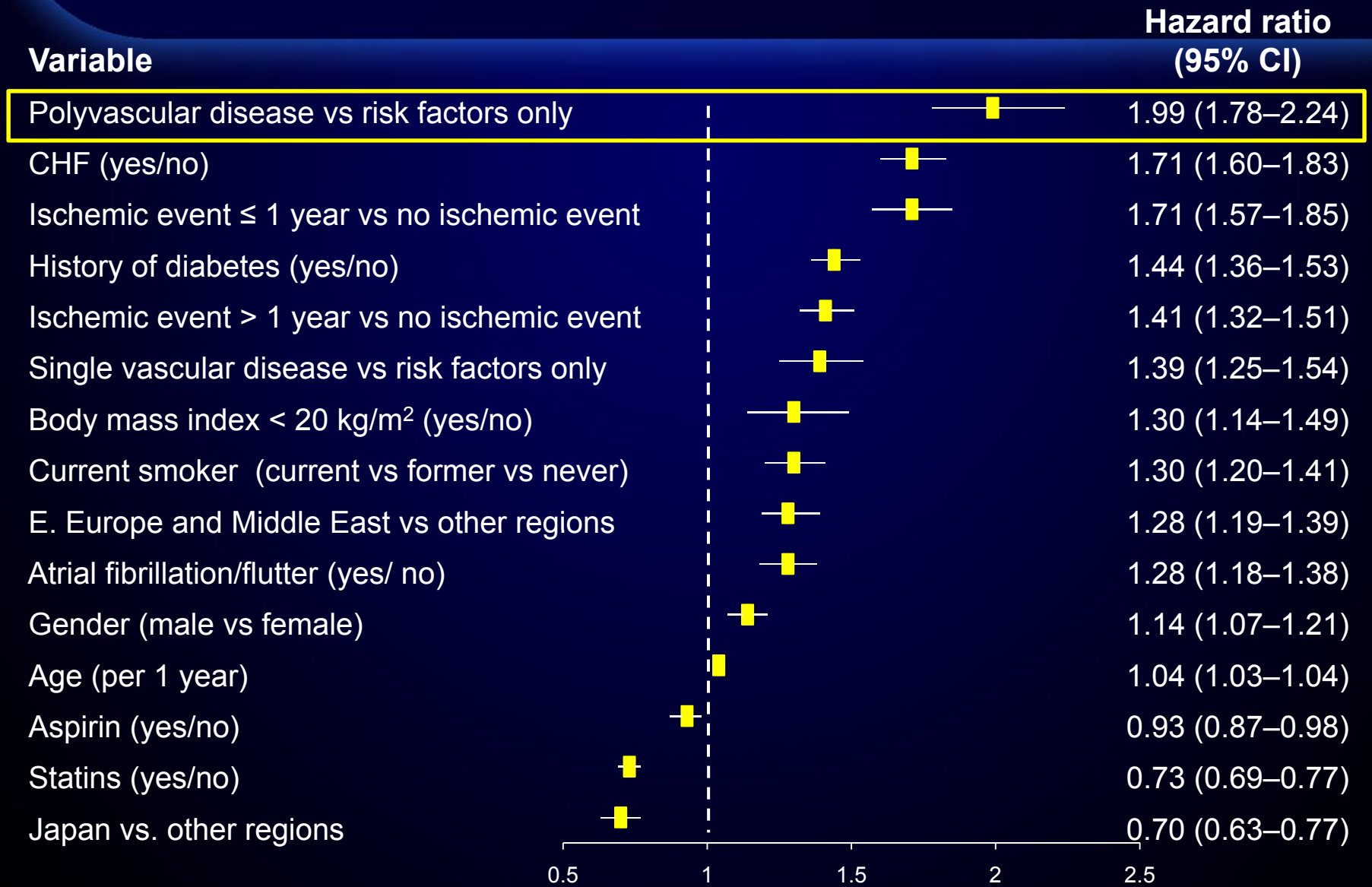


Outcome at 3 years

- Patients with symptomatic disease at baseline had high rates of the combined endpoint of vascular death, MI, stroke and re-hospitalisation, despite currently available medications.[1]
- 3-Year event rates appeared to be higher in men then women, driven mostly by higher rates of vascular death.[2]

[1]Alberts MJ et al. Eur Heart J 2009;30:2318;
[2]Alberts MJ on behalf of the REACH Registry investigators presented at Hotline Sessions at ESC 2009.

Predicting CV event rates at 4 years

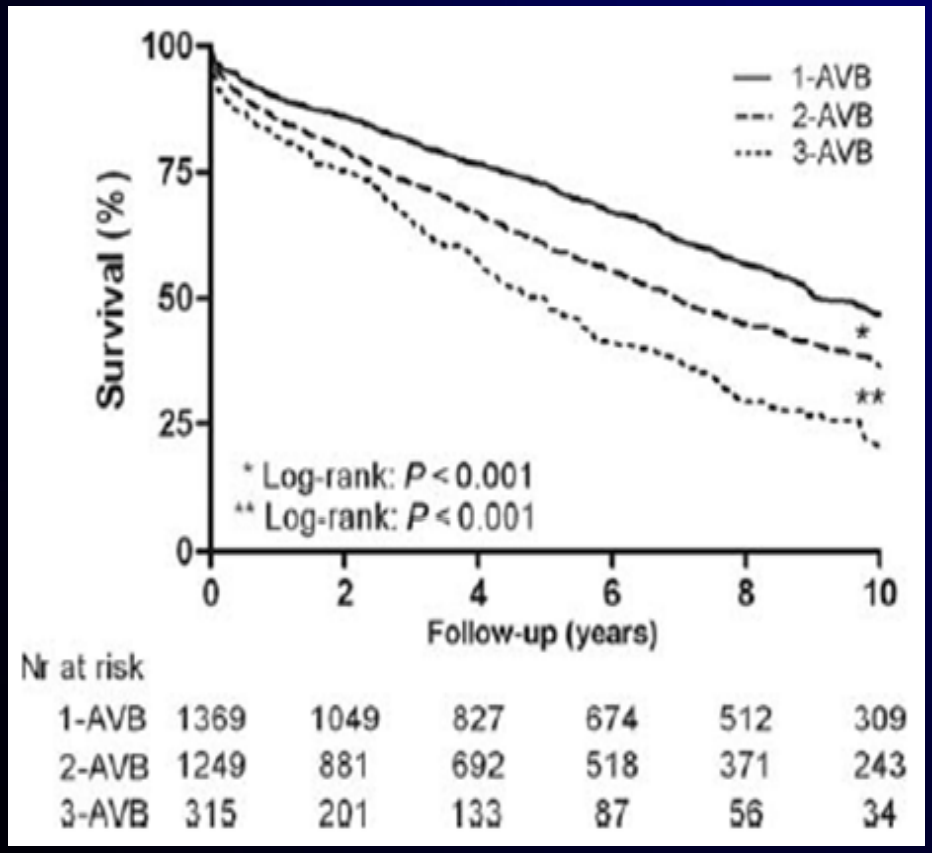


[1]Bhatt DL on behalf of the REACH registry Investigators. Presented at Clinical Trial Update session at ESC 2010.

5 Key Findings of the the REACH Registry

- A significant proportion of the symptomatic population have polyvascular disease. About 25% of patients with CAD have polyvascular disease.
- CV event rates increased in patients with the number of disease beds.
- 3-Year event rates appeared to be higher then 1-year.
- Patients with symptomatic disease at baseline had high rates of the combined endpoint of vascular death, MI, stroke and re-hospitalisation, despite currently available medications.
- Patients with polyvascular disease had much worse overall outcomes

Long-term prognosis of patients with PAD with or without polyVD

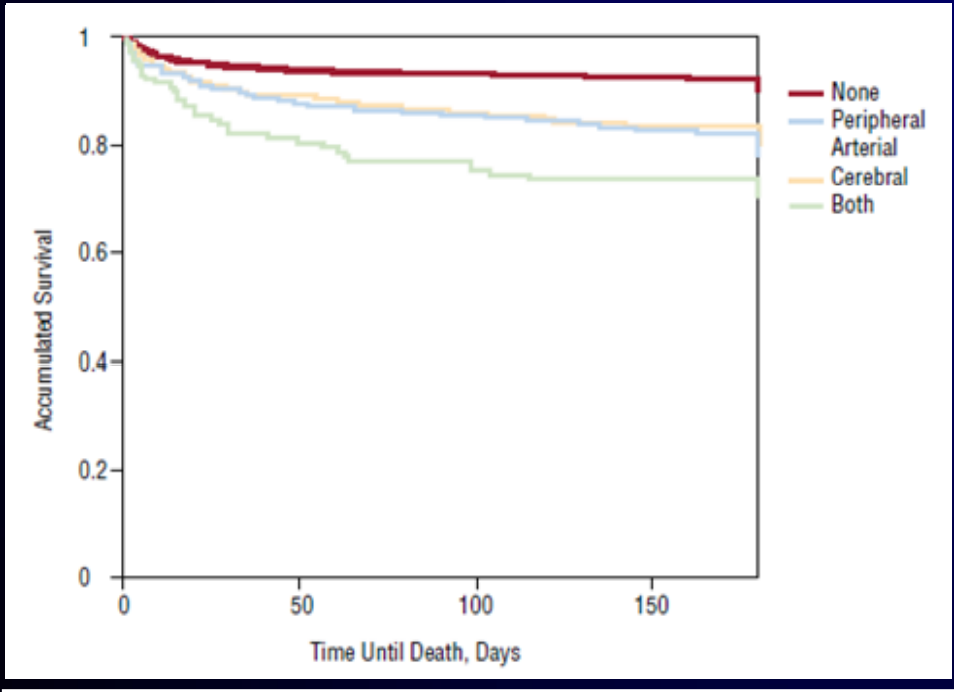


- 2933 PAD patients were screened prior to surgery for concomitant documented CV disease and coronary artery disease.
- The number of affected vascular beds (AVB) was determined.
- One-AVB: PAD
- 2-AVB: PAD + CAD or PAD + CVD
- 3-AVB: PAD + CAD + CVD

Polyvascular disease in PAD patients is independently associated with an increased risk for all-cause and cardiovascular mortality during long-term follow-up.

Kuijk JP et al., European Heart Journal (2010) 31, 992–999

MASCARA registry
: Patients With ACS and PolyVD



- Patients were stratified according to the presence of PAD, CVD, neither, or both. In-hospital management, treatment at discharge and outcomes at 6 months were recorded. (6745 patients)

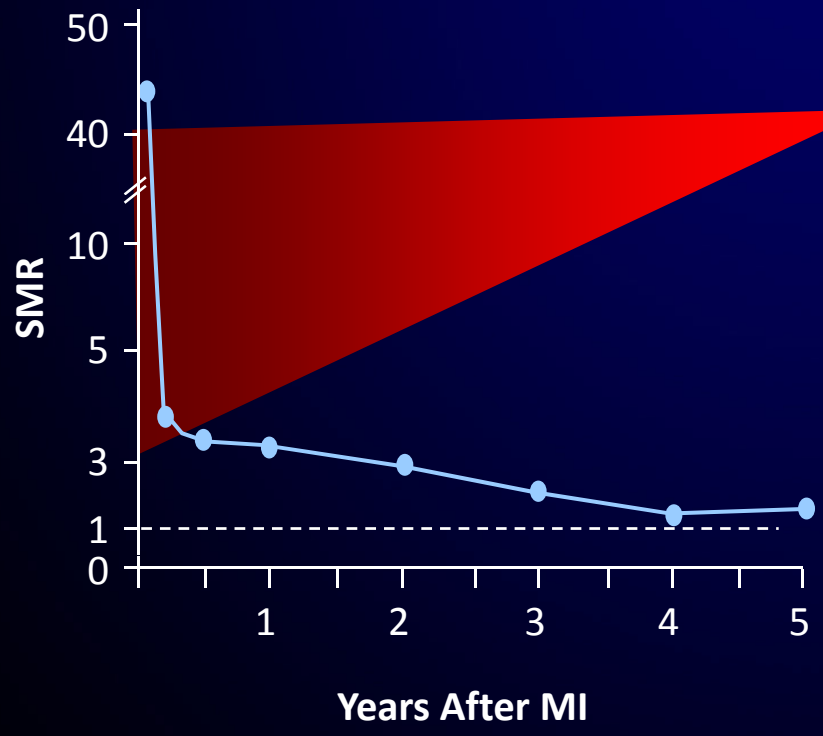
- 597 (8.85%) had PAD
- 392 (5.8%) had CVD
- 131 (1.94%) had both
- 5625 (83.4%) had neither.

Patients with acute coronary syndrome and concomitant arterial disease had more extensive coronary artery disease and poorer outcomes, both in hospital and at 6 months, but frequently did not receive regularly recommended treatment.

Ferreira-González I et al., the MASCARA Study investigators. Rev Esp Cardiol 2009 Sep;62(9):1012-21.

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.

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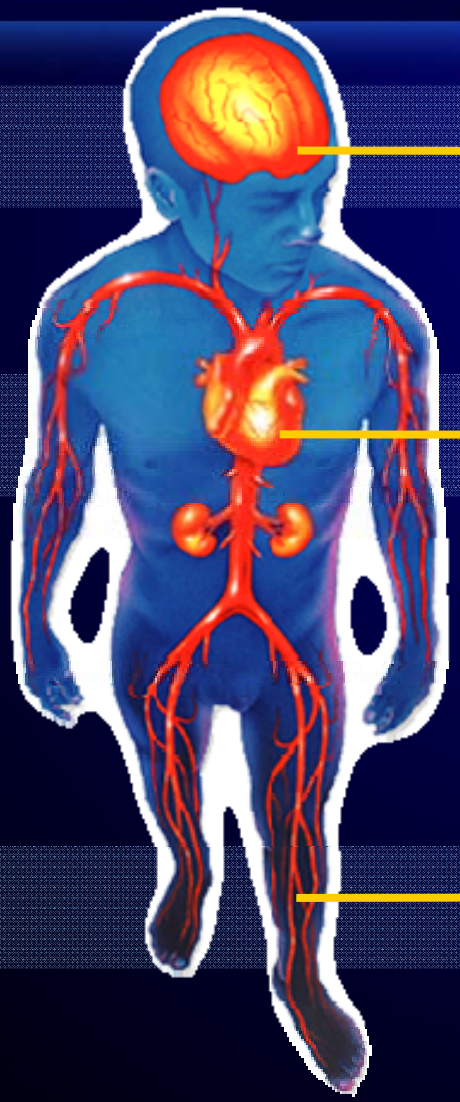
Proven Efficacy of Clopidogrel

Atrial Fibrillation ;Active A



Cerebrovascular disease (CVD)

Ischemic stroke, TIA

; CAPRIE, CARESS, MATCH

Coronary artery disease (CAD)

Acute coronary syndrome (**ACS** ; unstable angina, STEMI and non-STEMI)

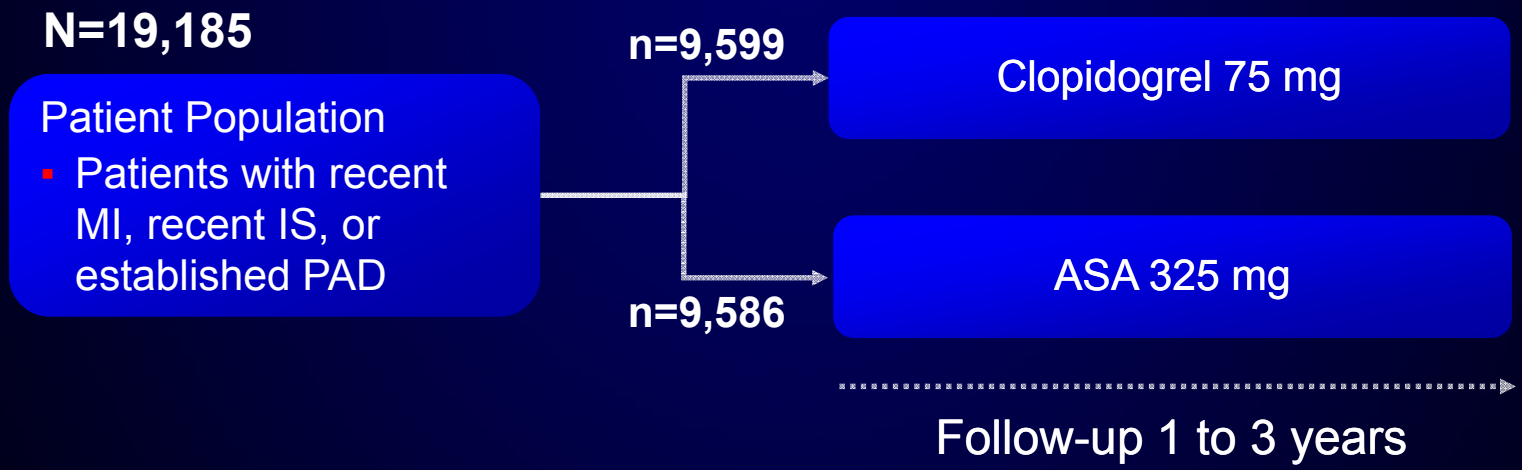
; CURE, PCI-CURE, CLARITY, CREDO CAPRIE

Peripheral arterial disease (PAD)

Critical limb ischemia, intermittent claudication, limb loss.

:CAPRIE, CASPAR

CAPRIE: Design

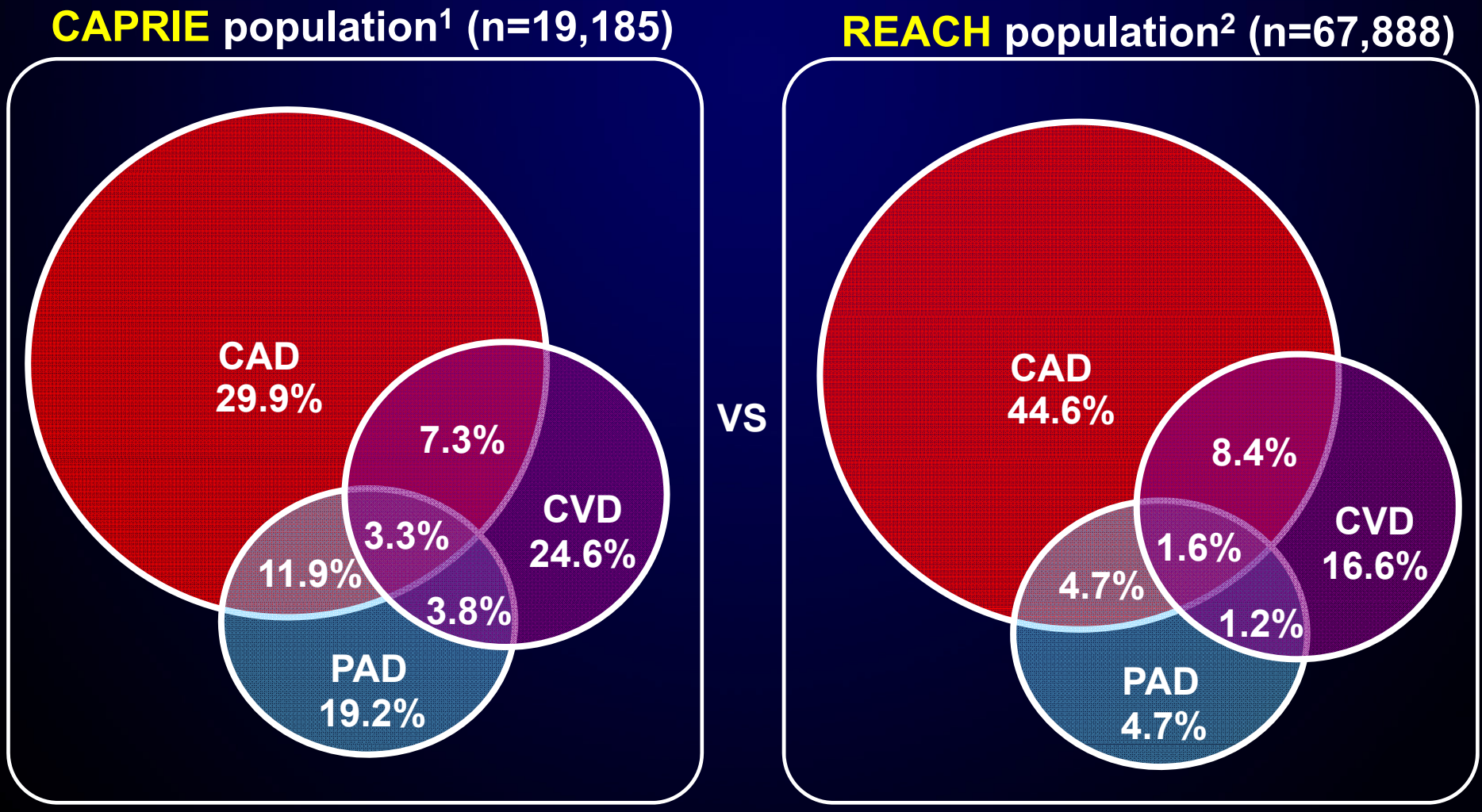


Primary End Point
- First occurrence of IS, MI, or vascular death

384 centers
16 countries

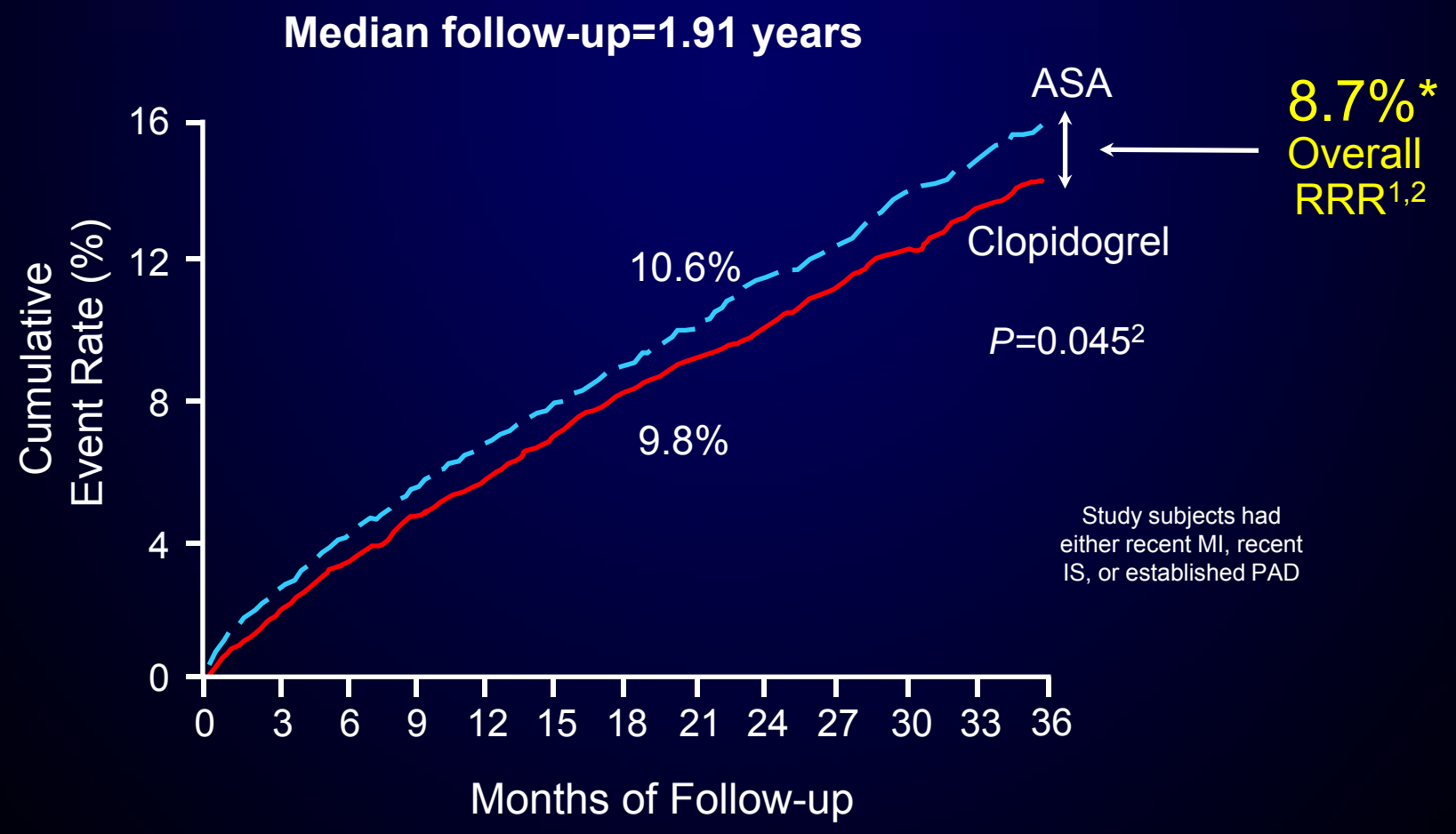
CAPRIE Steering Committee. *Lancet.* 1996;348:1329-1339.

CAPRIE population (vs. REACH population)



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

CAPRIE: Efficacy of Clopidogrel vs Aspirin in MI, IS, or Vascular Death (N=19,185)



* ITT analysis.
RRR=Relative Risk Reduction; ITT=Intent-To-Treat.

1. CAPRIE Steering Committee. *Lancet*. 1996;348:1329-1339.
2. PLAVIX Prescribing Information, sanofi-aventis U.S. LLC.

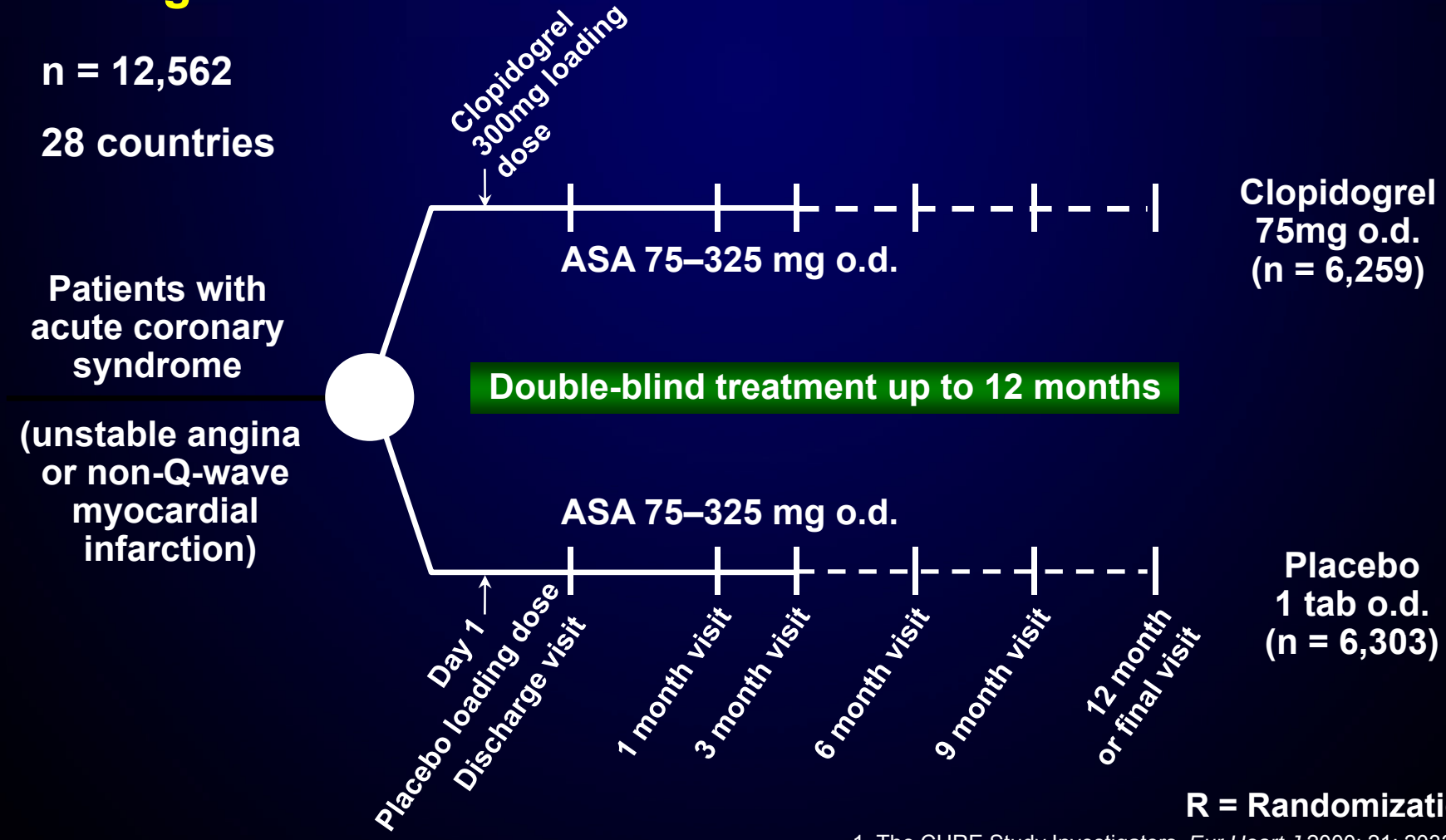
CURE (Clopidogrel in Unstable angina to prevent Recurrent Events)

ACS medical or PCI

: Design[1]

n = 12,562

28 countries

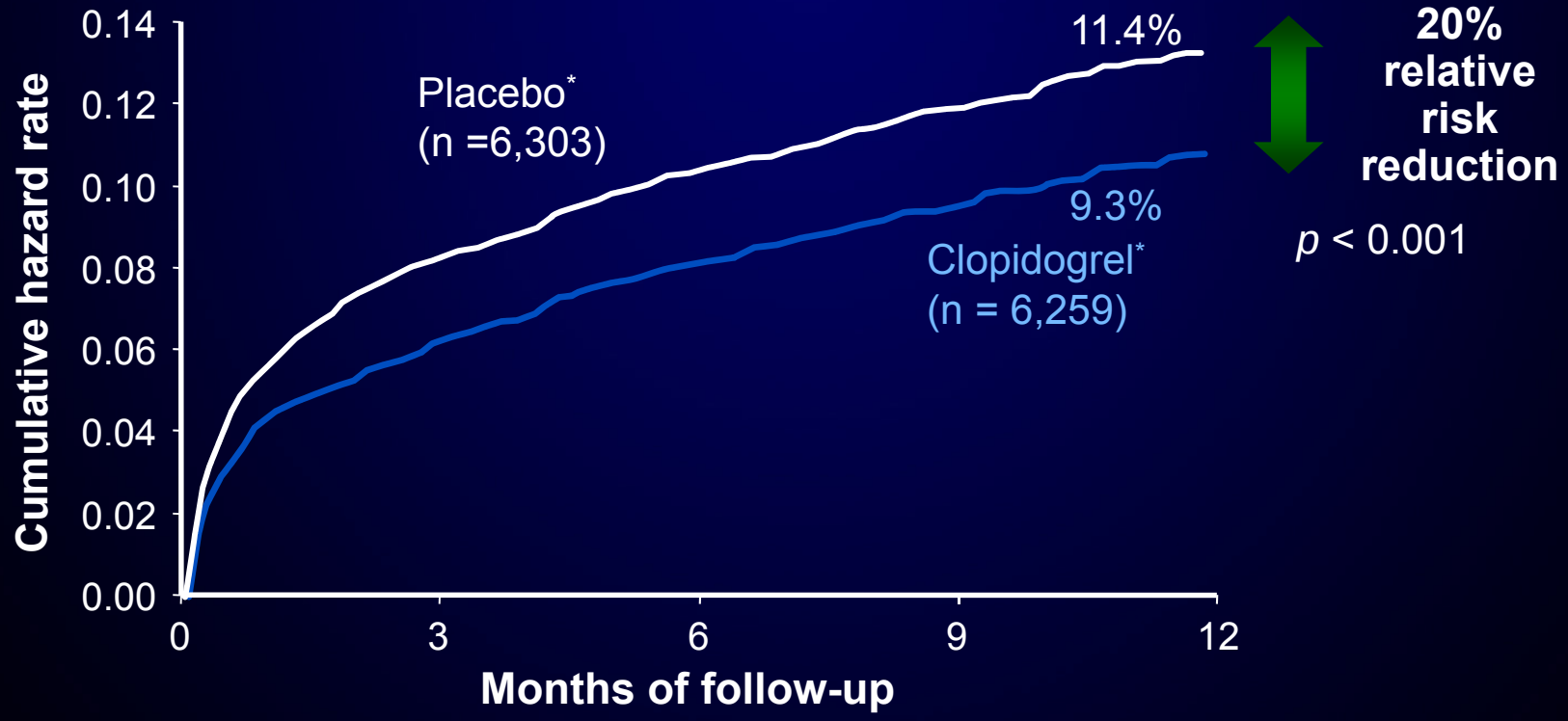


R = Randomization

1. The CURE Study Investigators. *Eur Heart J* 2000; 21: 2033–41.

CURE: Early and Long-term Efficacy of Clopidogrel[1,2]

Cumulative events
(myocardial infarction, stroke, or cardiovascular death)

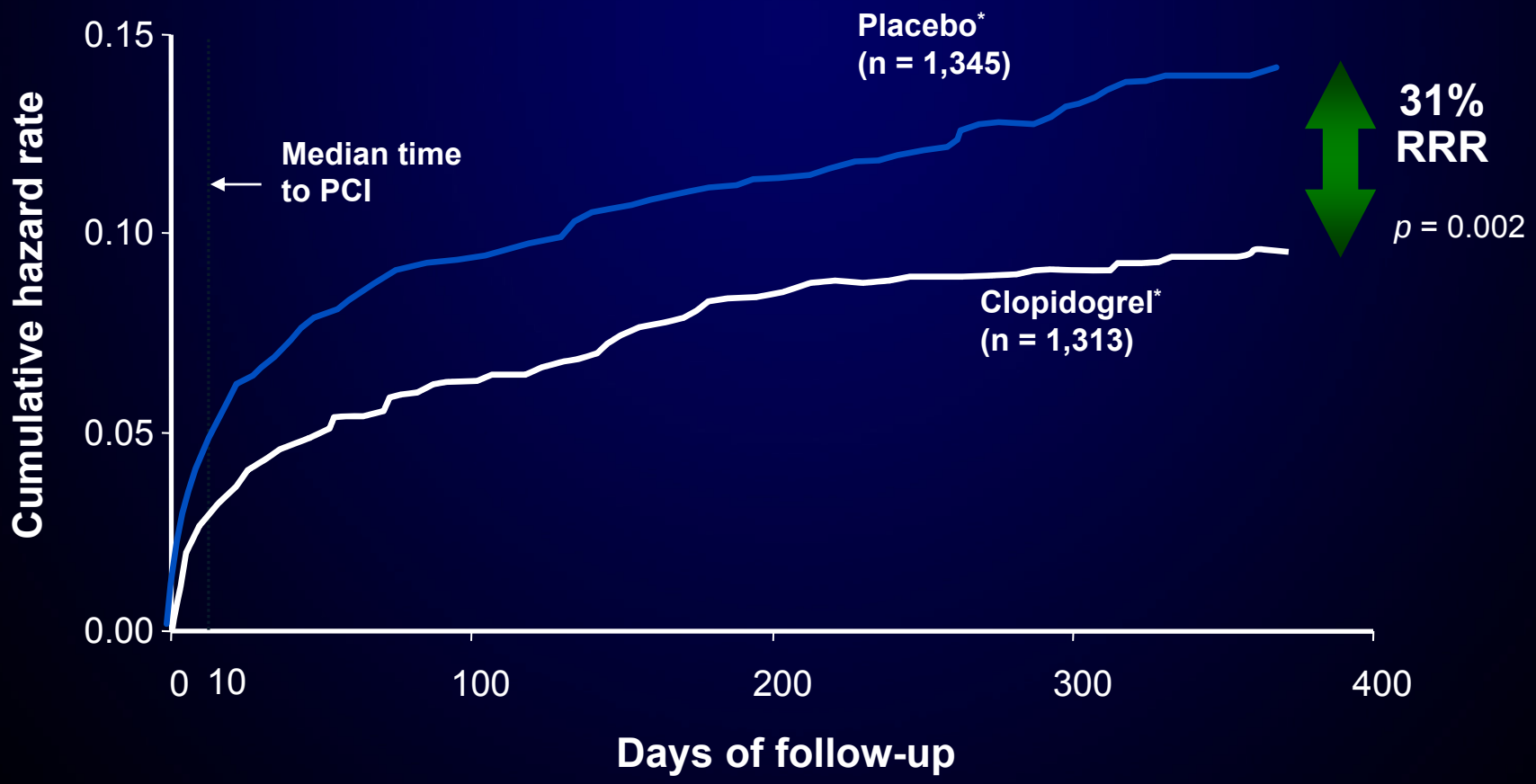


*On top of standard therapy (including acetylsalicylic acid)

1. The CURE Trial Investigators. *N Engl J Med* 2001; 345: 494–502
2. Data on file, 2002, p73 internal CSR-EFC 3307

PCI-CURE: 31% RRR at long-term [1]

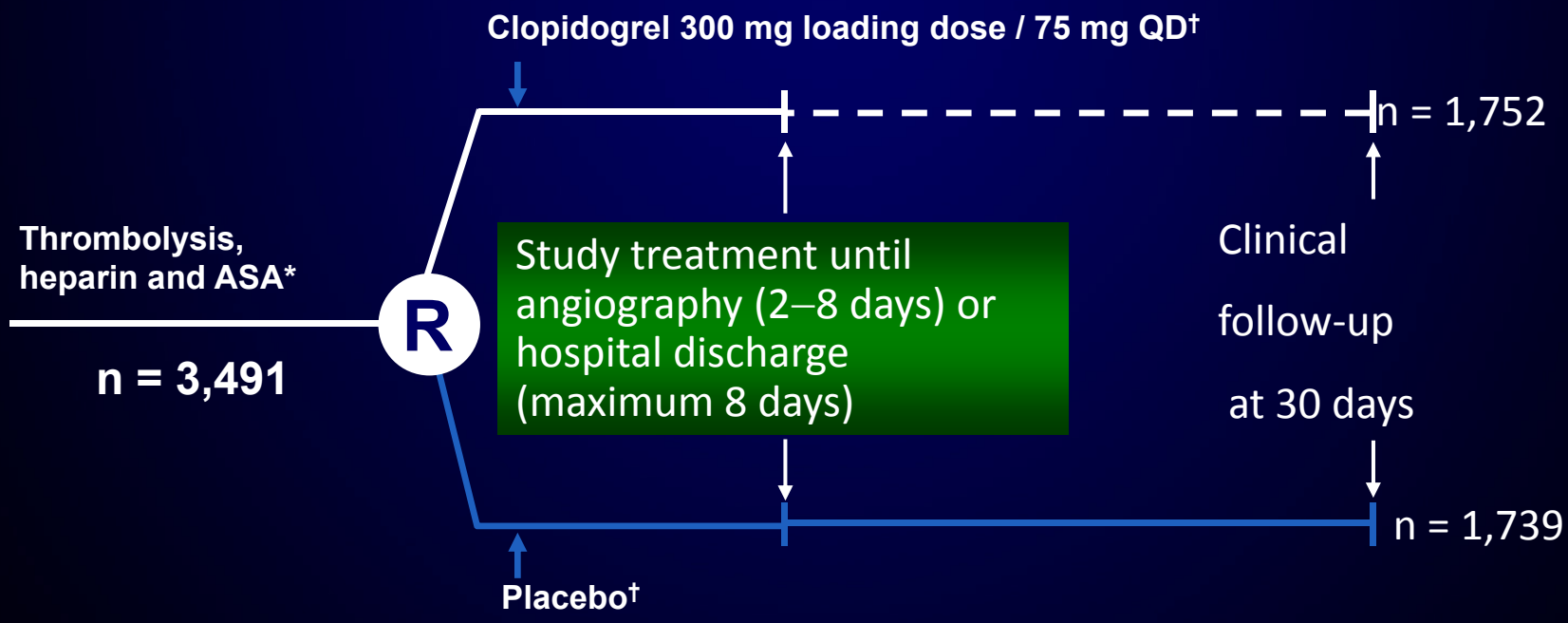
Endpoint: MI or CV death



*On top of standard therapy (including ASA)
[1]Overall (including events before and after PCI)
Mehta SR *et al*. *Lancet* 2001;358:527–533

CLARITY(CLopidogrel as Adjunctive Reperfuslon TherapY) : Study design

Double-blind, randomized, placebo-controlled trial in patients aged 18–75 years with STEMI ≤ 12 hours



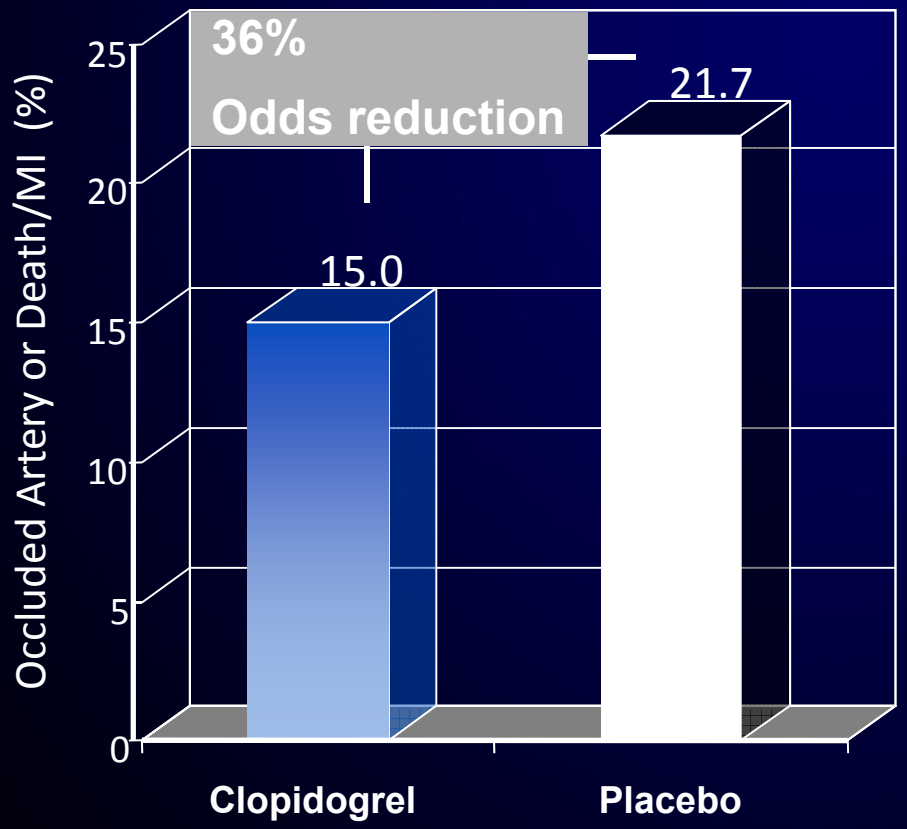
Primary endpoint: occluded artery (TIMI flow grade [TFG] 0/1), death/MI by time of angiography

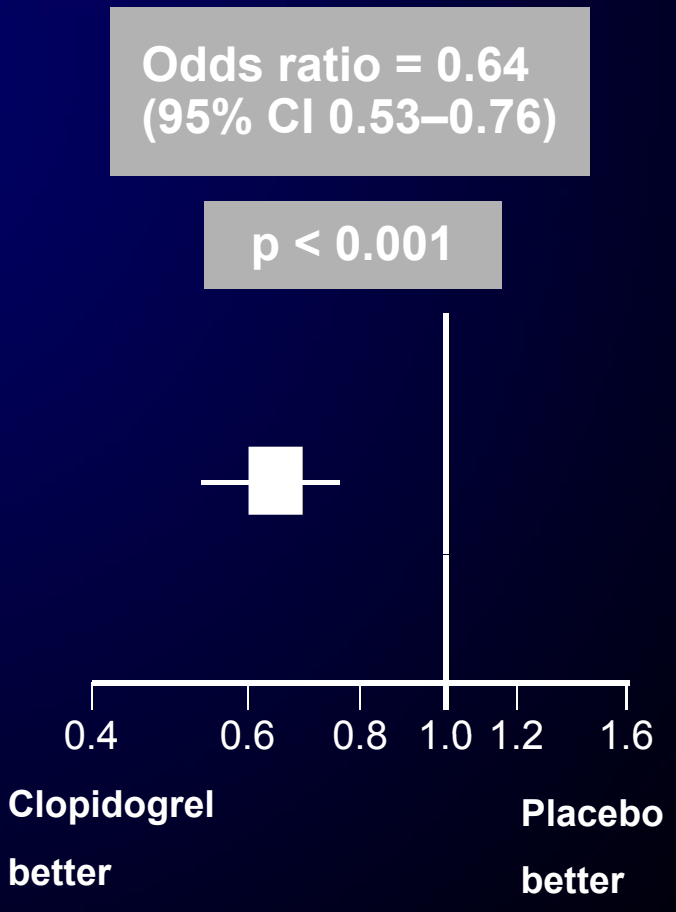
*ASA = 150–325 mg (if no ASA within prior 24 h). Heparin if fibrin-specific thrombolytic

†All patients: ASA 75–162 mg/day plus other standard care

Sabatine MS *et al*. *N Engl J Med* 2005;352:1179

CLARITY: Primary endpoint





Sabatine MS *et al*. *N Engl J Med* 2005;352:1179

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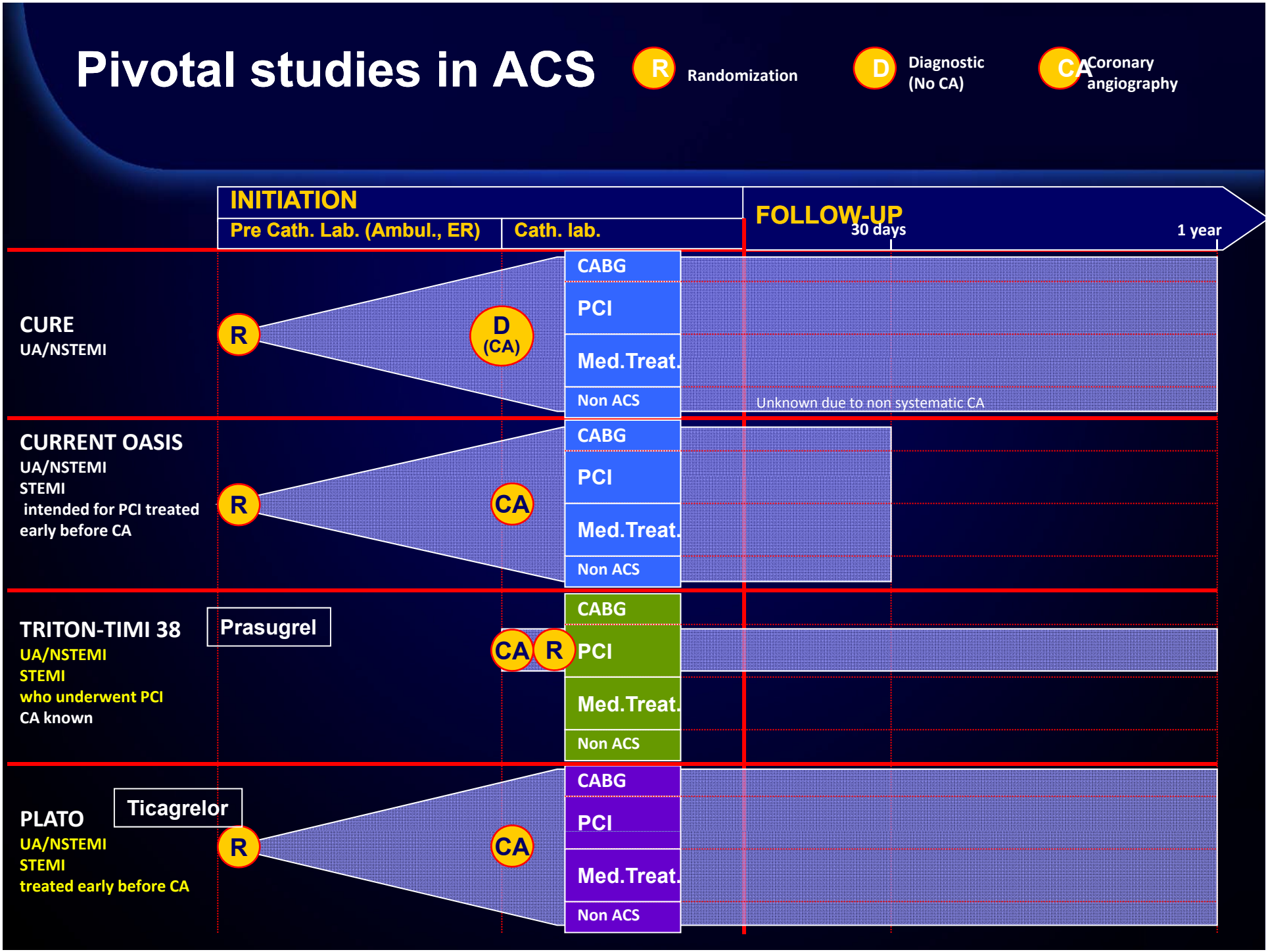
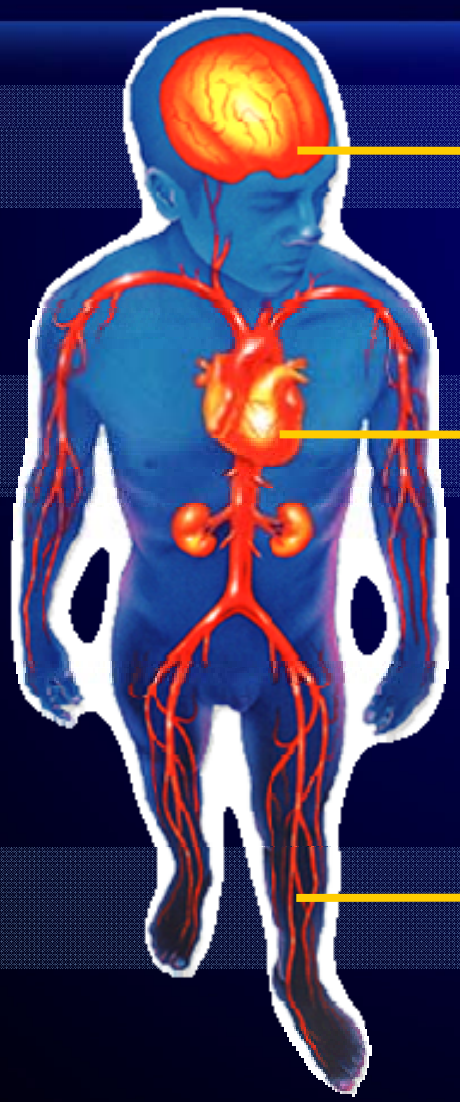
Pivotal studies in ACS



Proven Efficacy of Clopidogrel

Atrial Fibrillation
;Active A



Cerebrovascular disease (CVD)

Ischemic stroke, TIA
; CAPRIE, CARESS, MATCH

Coronary artery disease (CAD)

Acute coronary syndrome (**ACS** ; unstable angina, STEMI and non-STEMI)
; CURE, PCI-CURE, CLARITY, CREDO
CAPRIE

Peripheral arterial disease (PAD)

Critical limb ischemia, intermittent claudication, limb loss.
:CAPRIE, CASPAR

Indication coverage

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Stroke - International Guidelines

환자별	Class/ Level of Evidence	Recommendations
2011 AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update: A guideline from the AHA and ACCF[5]		
Ischemic Stroke 또는 TIA	IB	• 허혈성 뇌졸중 또는 TIA가 있었던 extracranial carotid or vertebral atherosclerosis 환자에게 아스피린 단독 75-325mg/d, 플라빅스 단독 75mg/d 또는 아스피린/디피리다몰 서방형 복합제 (25mg+200mg, 1일 2회)를 권장
2011 AHA/ASA Secondary Stroke Prevention Guidelines[6]		
Secondary Stroke Prevention	IIIB	• 아스피린과 플라빅스의 병용요법은 와파린과 유사한 출혈의 위험이 있어, 출혈 위험 때문에 와파린 사용이 금기인 환자에게 권장되지 않음
2010 AHA/ASA Guidelines for the Prevention of Stroke in Patients With Stroke or TIA[7]		
Ischemic Stroke (Secondary prevention)	IIIB	• 아스피린과 플라빅스의 병용요법은 와파린과 유사한 출혈의 위험이 있으므로, 출혈 위험 때문에 와파린 사용이 금기(hemorrhagic contraindication)인 환자에게 권장되지 않음
2008 ESO Guidelines for Management of Ischemic Stroke and TIA[8]		
Ischemic Stroke	IA IA IA	• 항응고요법이 필요하지 않은 환자에게 플라빅스 단독 투여 권장 • 플라빅스와 아스피린 병용투여는 권장되지 않음 (UA/NSTEMI/ 최근 stent 시술 환자 제외) • 아스피린에 알러지가 있는 환자에게 플라빅스 투여 권장
2008 ACCP - Antithrombotic and Thrombolytic Therapy for Ischemic Stroke[9]		
Ischemic Stroke	IA IIB IA	• 비심인성 뇌졸중 또는 TIA 환자에게 초기요법으로 플라빅스 75mg 투여 권장 • 비심인성 뇌졸중 또는 TIA 환자에게 아스피린보다 플라빅스 투여 권장 • 아스피린에 알러지가 있는 환자에게 플라빅스 투여 권장

ACS - International Guidelines

환자별	Class/ Level of Evidence	Recommendations
2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With UA/NSTEMI[1]		
UA/NSTEMI	IB IA IB	• 아스피린을 투여 받을 수 없는 환자*에게 플라빅스 부하용량 투여 후 유지용량 투여 * 과민반응 또는 주요위장장애가 있는 경우 • PCI 시술 예정인 환자에게 PCI 시술 전 또는 시술 시 최대한 빨리 플라빅스 부하용량 300mg 에서 600mg 까지 투여 권장 • PCI 시술 받은 환자에게 플라빅스 75mg을 적어도 12개월 투여권장
UA/NSTEMI (initial invasive strategy)	IB IA	• 초기 침습적 치료를 받는 중등도/고위험군 환자에게 이중항혈소판요법이 권장되며, 아스피린에 추가되는 두 번째 항혈전제로서 – PCI 시술 전, 플라빅스 권장 – PCI 시술 시, PCI 시술 전에 플라빅스 투여가 안 되었다면, 플라빅스 투여 권장
UA/NSTEMI (initial conservative strategy)	IB	• 항응고요법과 아스피린에 가능한 빨리 플라빅스(부하용량 투여 후 유지용량)를 추가해야 하며 적어도 1개월에서 가급적 1년까지 투여할 것을 권장
2011 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation[2]		
NSTEMI	IA	• 출혈 위험과 같은 투여 금기 사유를 제외하고 P2Y12 receptor 억제제는 아스피린에 가능한 빨리 추가되어야 하며 12개월 동안 유지
	IB	• 플라빅스를 포함한 초기치료요법에 상관 없이, 허혈성 사건의 중증–고위험군 환자에게 티카그렐러 (부하용량 180mg, 유지용량 90mg 1일 2회)가 권장 (플라빅스 투여 중단 후 티카그렐러 투여 시작)
	IB	• coronary anatomy가 확인되고 PCI 시술 예정인 P2Y12 receptor 억제제를 처음 사용하는 환자(특히 당뇨환자)에게 생명을 위협하는 출혈이나 투여 금기 사유가 없다면 프라수그렐 (부하용량 60mg, 유지용량 10mg)이 권장
	IA	• 티카그렐러나 프라수그렐을 투여할 수 없는 환자에게 플라빅스 부하용량 300mg, 유지용량 75mg/d 투여 권장
	IB	• 티카그렐러 또는 프라수그렐 투여가 가능하지 않은 침습적 치료 예정인 환자에게 플라빅스 부하용량 600mg(또는 300mg 부하용량 투여 후 PCI 시 300mg 추가)을 권장
	IIaB	• 출혈의 위험이 증가하지 않는 PCI 시술 환자에게 적어도 첫 7일 동안 플라빅스 유지용량 150mg 투여가 고려되어야 함

ACS - International Guidelines

2011 AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease[3]		
CAD	IA IB	• 아스피린에 투여 금기 사유가 있는 환자를 제외한 CAD 환자에게 아스피린 75-162mg/d 를 권장 • 아스피린에 과민증 또는 주요위장장애가 있는 환자에게 플라빅스 75mg/d가 대체요법으로 권장
ACS 환자 또는 스텐트 시술한 PCI 환자	IA IA	• ACS 환자 또는 스텐트 시술한 PCI 환자에게 아스피린과 P2Y12 receptor 억제제 병용요법을 권장 • BMS 또는 DES PCI 를 시술한 환자에게 플라빅스 75mg/d, 프라수그렐 10mg/d 또는 티카그렐러 90mg(1일 2회)을 적어도 12개월 투여 권장
CABG	IIaC	• 아스피린 75–162mg/d와 플라빅스 75mg/d 의 병용요법이 고려
Stable CAD	IIbB	• Stable CAD 환자에게 아스피린 1일 용량 75~162mg 과 플라빅스 1일 용량 75mg 의 병용요법이 고려
죽상동맥경화증	IIbA IIbA	• 죽상동맥경화증 환자의 치료를 위해 항응고요법(와파린 또는 비타민 K 길항제) 보다는 항혈소판제제를 권장 • 아스피린 (and/or 플라빅스)과 와파린의 병용투여는 출혈의 위험이 있고 면밀히 관찰 권장
2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With STEMI and ACC/AHA/SCAI Guidelines on PCI[4]		
Primary/non-primary PCI 예정인 STEMI 환자	IC	• PCI 시술 전 또는 시술 시에 적어도 플라빅스 부하용량 300mg에서 600mg 까지 투여
Non-primary PCI 예정인 STEMI 환자	IC IC	• 혈전용해제와 플라빅스를 모두 투여 받은 환자에게, 플라빅스 투여를 계속 권장 • Thienopyridine 계열 약물투여 없이 혈전용해제만 투여 받은 환자에게 플라빅스 부하용량 300mg 에서 600mg 까지 투여 권장
PCI (BMS 또는 DES) 시술 받는 ACS 환자	IB IIbC	• 플라빅스 75mg을 적어도 12개월 까지 투여 권장 • DES–PCI 시술받는 ACS 환자에게 플라빅스 15개월 이상 투여 고려 가능
UA/NSTEMI	IB	• 침습적 치료를 받는 환자에게 이중 항혈소판요법을 투여할 것을 권장 • 아스피린은 바로 투여하고, PCI 시술 전 또는 시술 시에 플라빅스가 두 번째 항혈전제로서 권장

A-Fib / PAD - International Guidelines

A-Fib

환자별	Class/ Level of Evidence	Recommendations
2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation[10]		
Atrial Fibrillation	IIbB	• 환자의 선호도 혹은 OAC를 안전하게 지속할 수 있는지에 대한 의사의 평가를 근거로 OAC(Warfarin) 투여가 적합하지 않은 심방세동 환자에서 뇌졸중을 포함한 주요 혈관성 사건들의 위험을 낮추기 위해 아스피린에 플라빅스를 추가하는 것을 고려
2010 ESC New Recommendation related to Antithrombotic agents in Guidelines for the Management of Atrial Fibrillation[11]		
Atrial Fibrillation	IIaB	• 환자가 OAC 복용을 거절하거나 OAC에 대해 명백한 금기사항이 있고 (항응고 모니터링 과정을 견디기 어렵거나 지속하기 어려운 경우), 출혈 위험이 낮은 심방세동 환자에게 뇌졸중 예방을 위해 아스피린 75–100mg 과 플라빅스 75mg 의 병용요법이 고려

PAD

환자별	Class/ Level of Evidence	Recommendations
2011 AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease[12]		
PAD	IA	• 증상이 있는 죽상혈전성 하지 PAD 환자에게 아스피린 75–325mg/d 또는 플라빅스 75mg/d 를 권장
2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease[13]		
PAD	B	• 죽상혈전성 하지 PAD 환자*에게 심근경색, 뇌졸중 또는 혈관성 사망의 위험을 감소시키는데 아스피린을 대체할 수 있는 항혈소판요법으로 플라빅스 권장 * Including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia
TASC II guideline 2007 Inter-Society Consensus for the Management of PAD Recommendation. Antiplatelet therapy in PAD[14]		
PAD	B	• Symptomatic PAD를 가진 환자에게 심혈관 사건의 감소에 플라빅스가 효과적

Take home messages

1. Patients with CAD or CVD or PAD have high risk for the development of another event or other diseases.
2. CV event rates increased in patients with the number of disease beds.

   → Comprehensive prevention of atherothrombotic polyvascular disease as a systemic vascular disease is importment for improving clinical prognosis.
3. Only clopidogrel has both evidence and a broad indication for polyvascular disease.

CRUSADE registry : Prior polyVD, risk factor for adverse ischemic outcomes in ACS

	Odds ratio	95% CI	χ^2	P-value
Age (per 10 years)	1.26	1.24, 1.28	605	<0.001
SBP (per 10 mm Hg)	0.94	0.93, 0.94	295	<0.001
Signs of CHF	2.32	2.06, 2.61	195	<0.001
Renal insufficiency	1.31	1.25, 1.37	119	<0.001
Positive cardiac marker	1.94	1.69, 2.24	84	<0.001
Heart rate (per 10 b.p.m.)	1.04	1.04, 1.05	83	<0.001
ST-depression[a]	1.32	1.25, 1.38	68	<0.001
Transient ST-elevation	1.31	1.19, 1.44		
Both	1.49	1.24, 1.79		
Diabetes	1.16	1.11, 1.20	48	<0.001
Polyvascular disease[a,b]			43	<0.001
One vascular bed	1.07	1.02, 1.12		
Two vascular beds	1.26	1.19, 1.34		
Three vascular beds	1.31	1.17, 1.48		
Dyslipidemia	0.88	0.85, 0.92	39	<0.001
Prior CHF	1.23	1.15, 1.32	33	<0.001
Male sex	0.91	0.87, 0.94	25	<0.001
Cardiologist	0.86	0.81, 0.92	19	<0.001
Hypertension	1.08	1.03, 1.12	11	<0.001

- Patients were categorized as having prior 0, 1, 2, or 3 affected arterial beds. (95749 patient)
- Factors associated with the composite outcome of in-hospital death, MI, stroke, or congestive heart failure

Identification of polyvascular patients in clinical trial and real world populations may provide an opportunity to reduce their excess risk with intensive secondary prevention efforts.

Bhatt DL et al., The CRUSADE Investigators. European Heart Journal (2009) 30, 1195–1202

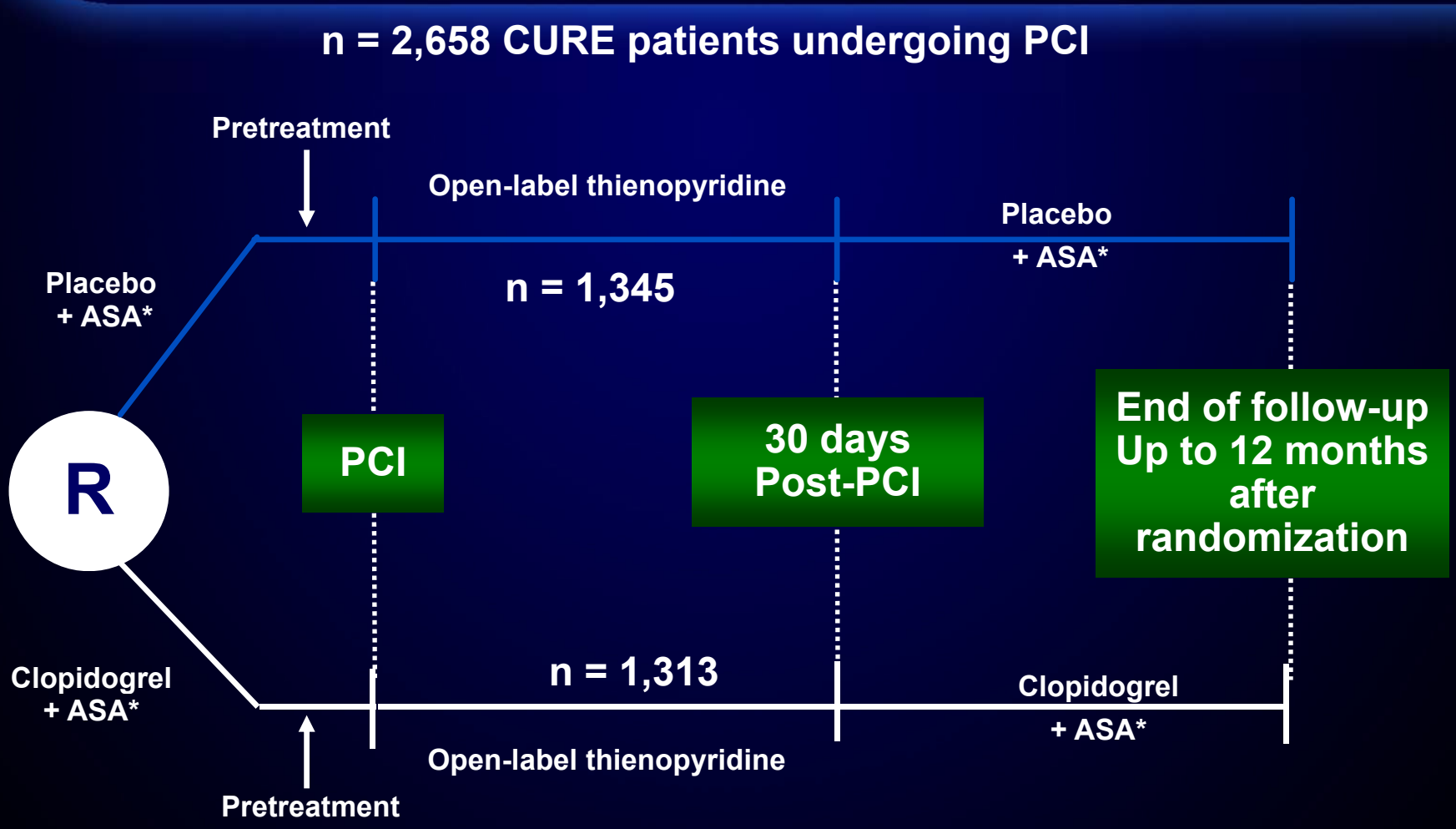
CAPRIE: Adverse Events

	% of Patients with Events	
	Aspirin (325 mg/day)	Clopidogrel (75 mg/day)
Intracranial hemorrhage[1]	0.49	0.35
Gastrointestinal bleeding[1]	2.66*	1.99
Gastrointestinal ulcers[2]	1.15*	0.68
Indigestion/nausea/vomiting[1]	17.59*	15.01
Diarrhea[1]	3.36	4.46*
Rash[1]	4.61	6.02*
Neutropenia[1]	0.17	0.10

[1]CAPRIE Steering Committee. Lancet 1996;348:1329-1339.
[2]Lok. Eur Heart J 1998;19(suppl):P487.

*$p<0.05$

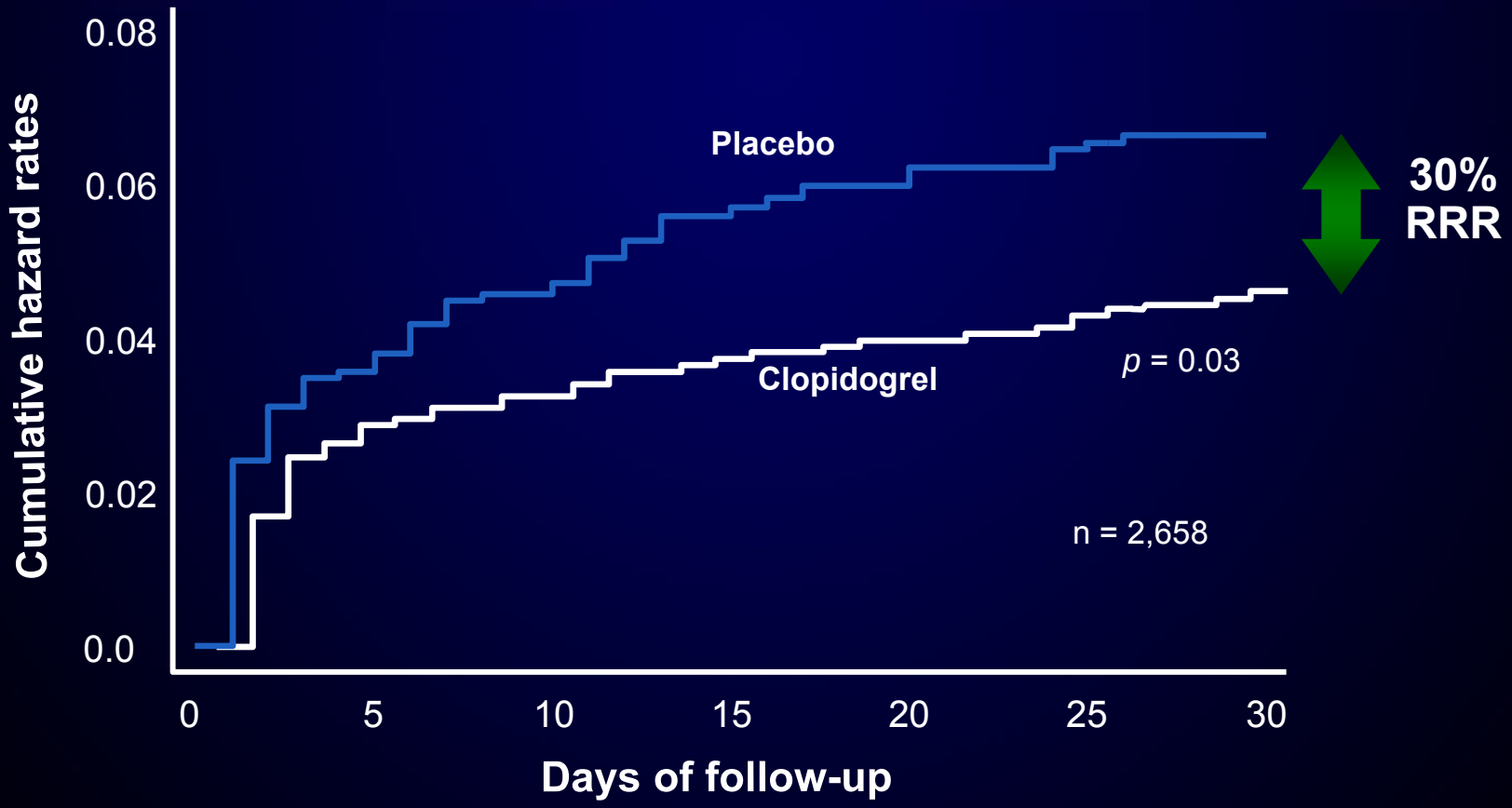
PCI-CURE: Study design



*In addition to other standard therapies

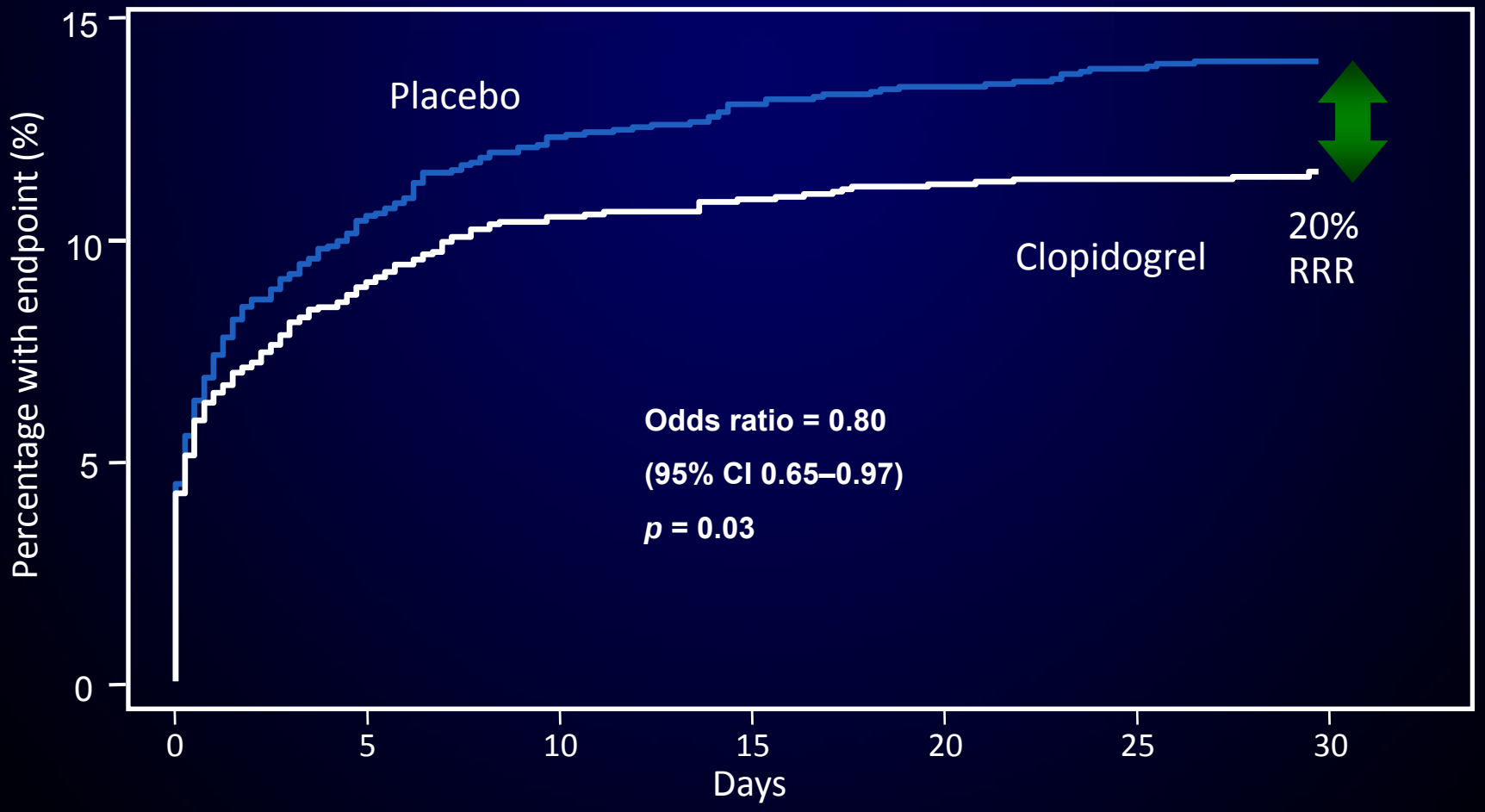
Mehta SR *et al*. *Lancet* 2001;358:527–533

PCI-CURE : 30-day results CV death, MI, or urgent revascularization



Mehta SR *et al*. *Lancet* 2001;358:527–533

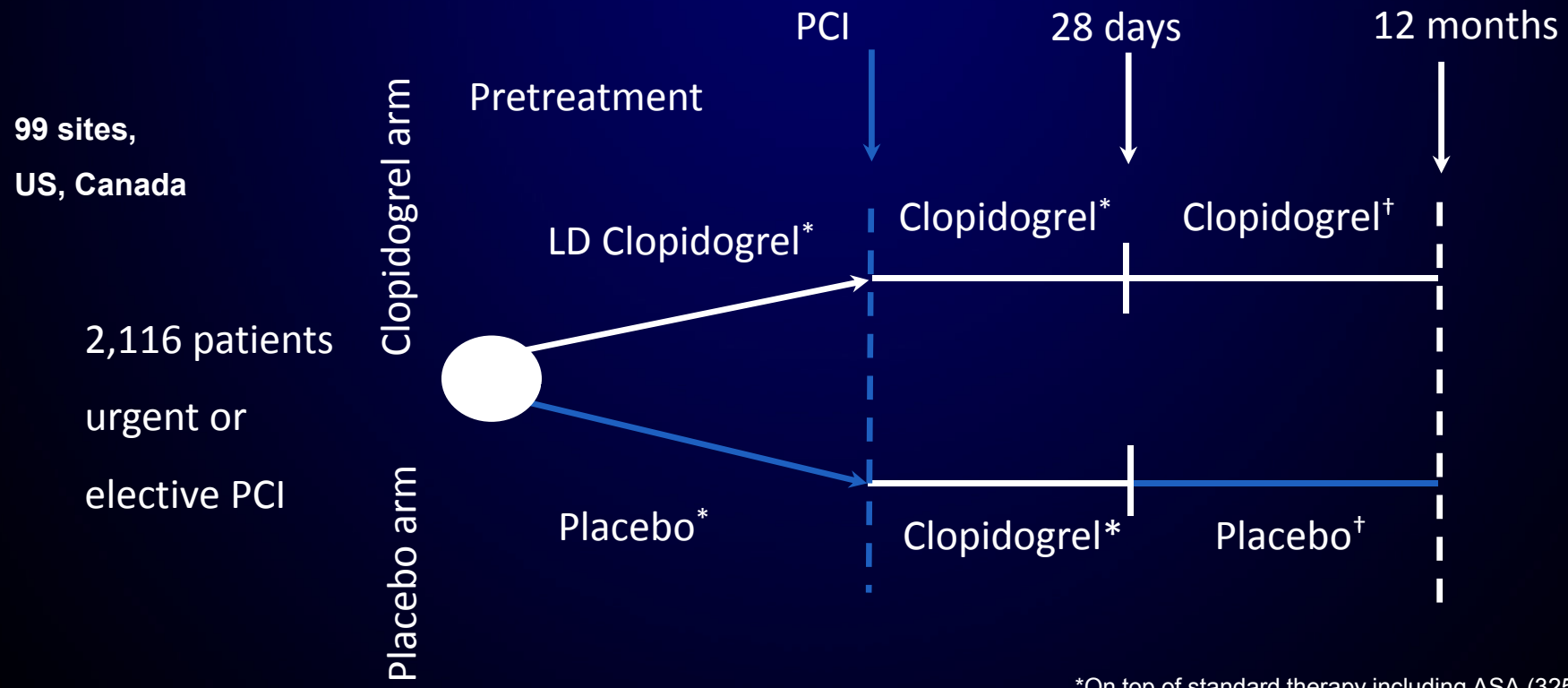
CV death, MI, RI → urgent revasc.



Sabatine MS *et al*. *N Engl J Med* 2005;352:1179

CREDO (Clopidogrel for Reduction of Events During Observation) PCI short vs long term DAPT : Design

Objective: evaluate efficacy and safety of clopidogrel 1 year vs 1 month in patients undergoing urgent or elective PCI; determine the benefit of a 300 mg LD 3–24 h prior to PCI

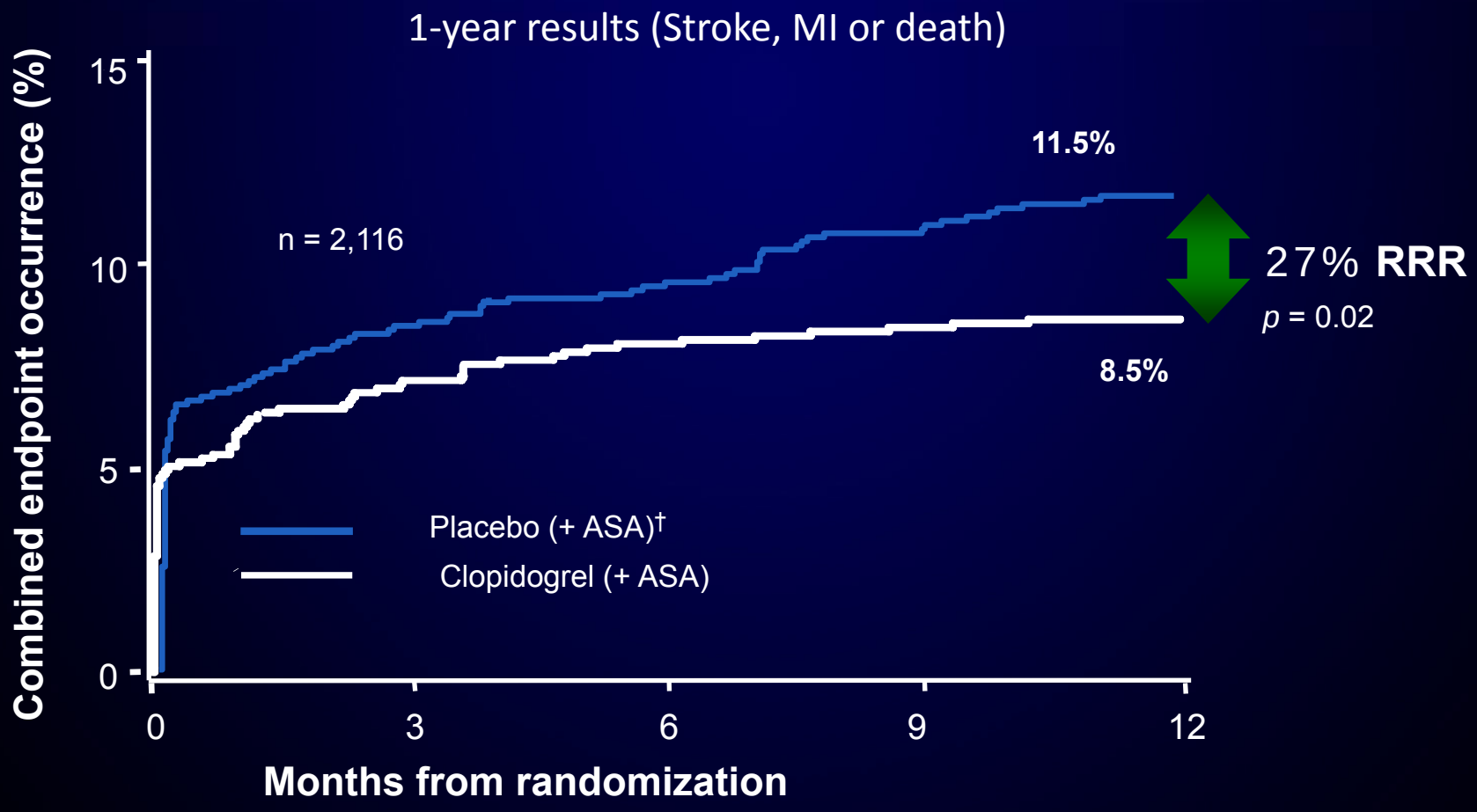


*On top of standard therapy including ASA (325 mg)

†On top of standard therapy including ASA (81–325 mg)

Steinhubl SR *et al*. *JAMA* 2002;288:2411–2420

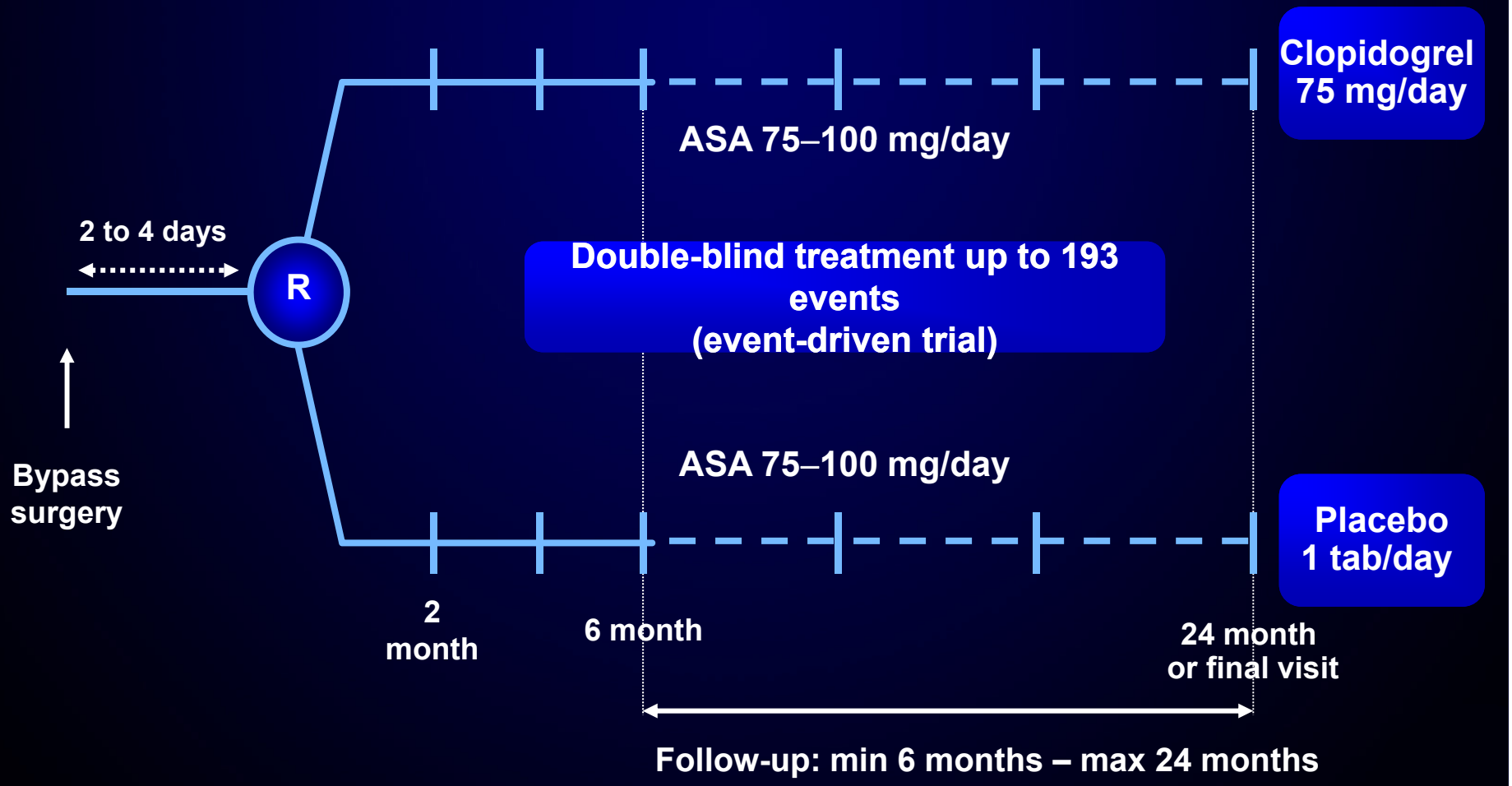
CREDO : Long-term efficacy of clopidogrel



†All patients received clopidogrel post-PCI up to Day 28

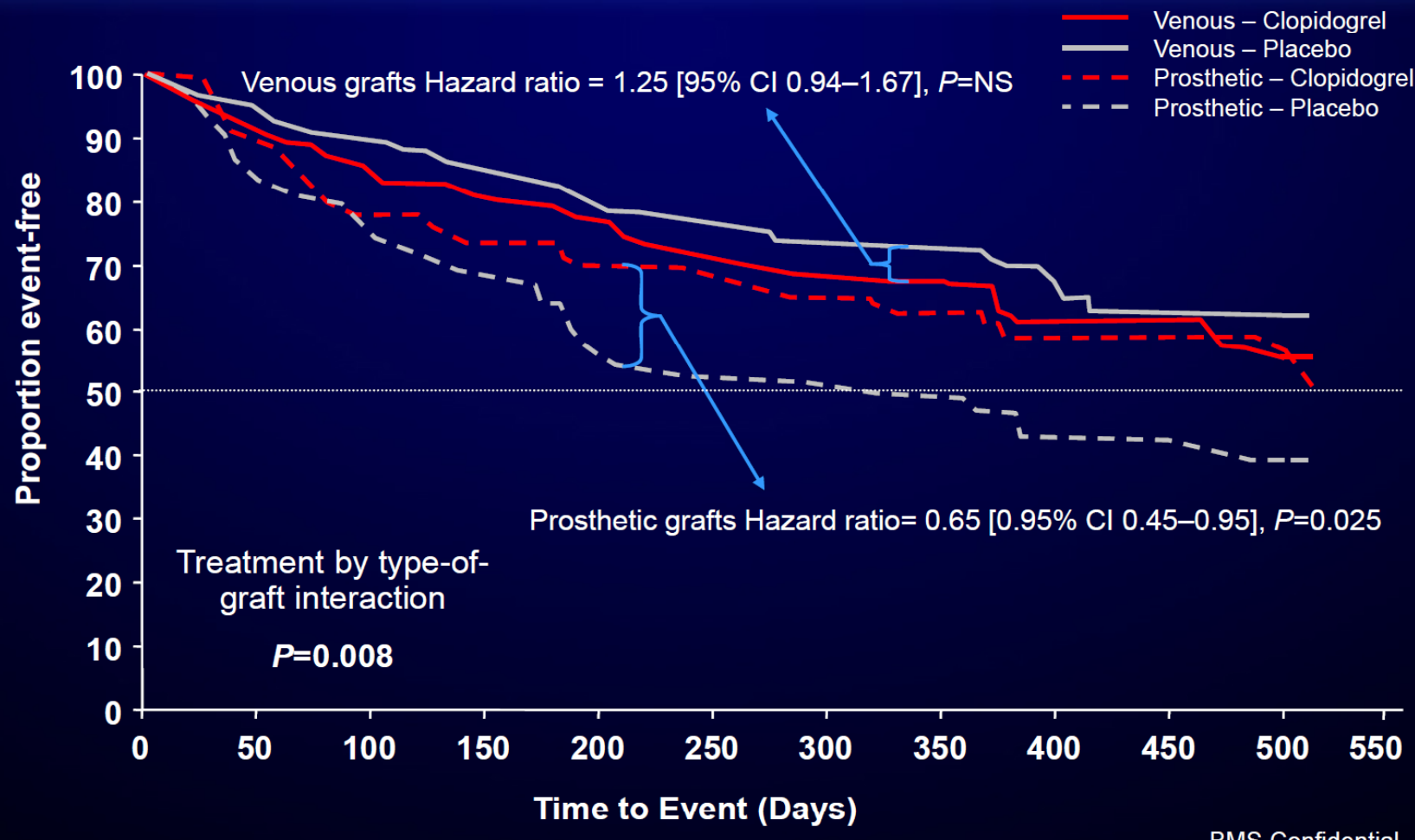
Steinhubl SR *et al*. *JAMA* 2002;288:2411–2420

CASPAR: Study Design



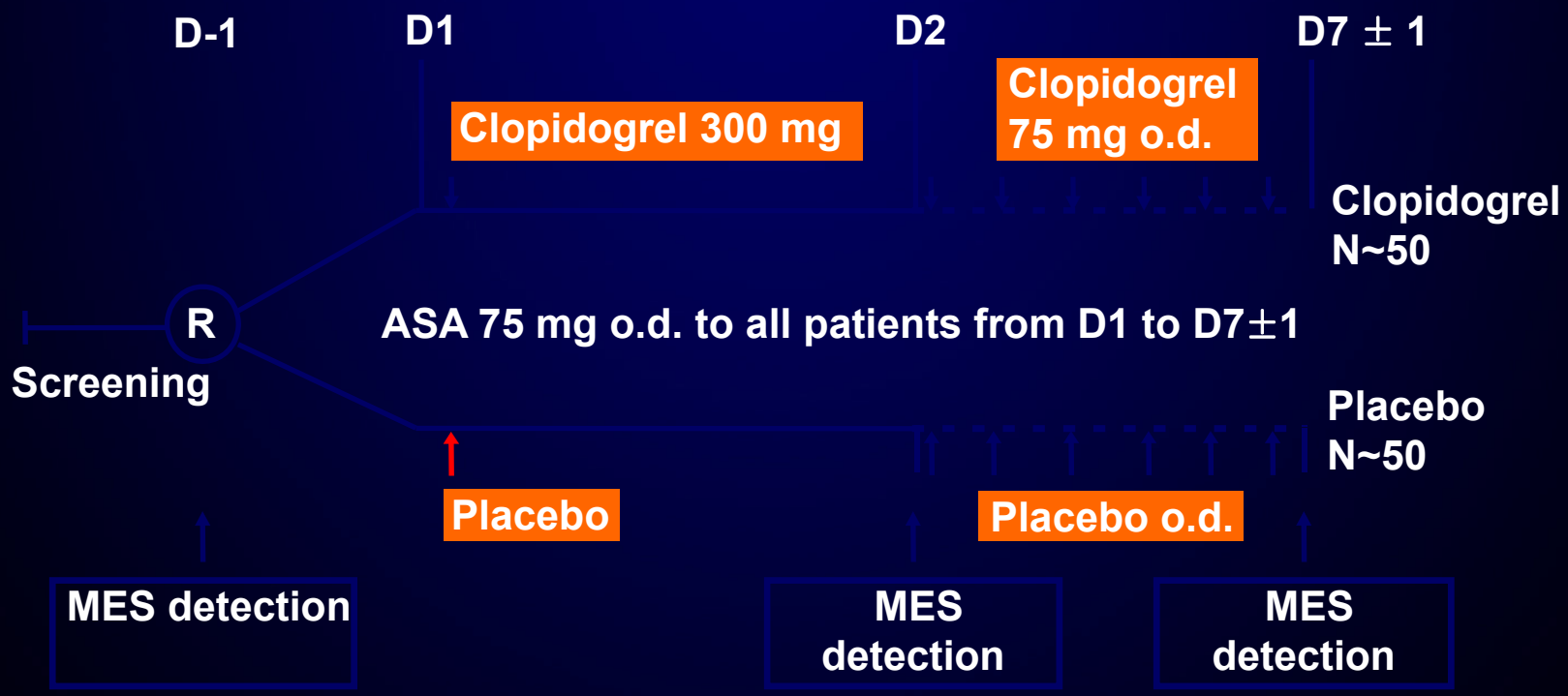
R=Randomization stratified by type of graft (venous/prosthetic).

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

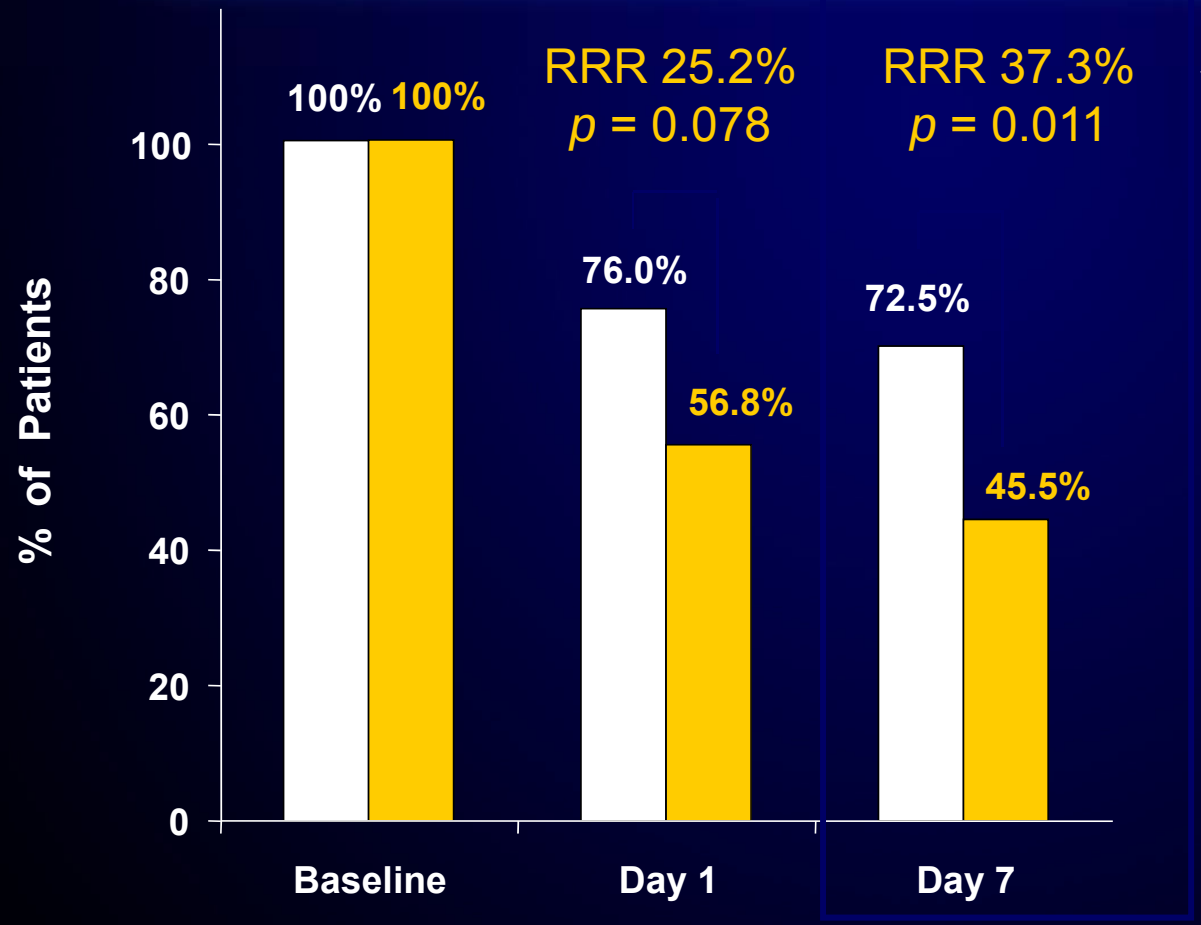


CARESS: Study Design

- Randomized, double-blind, placebo-controlled, parallel groups (n~100)



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



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

Placebo*

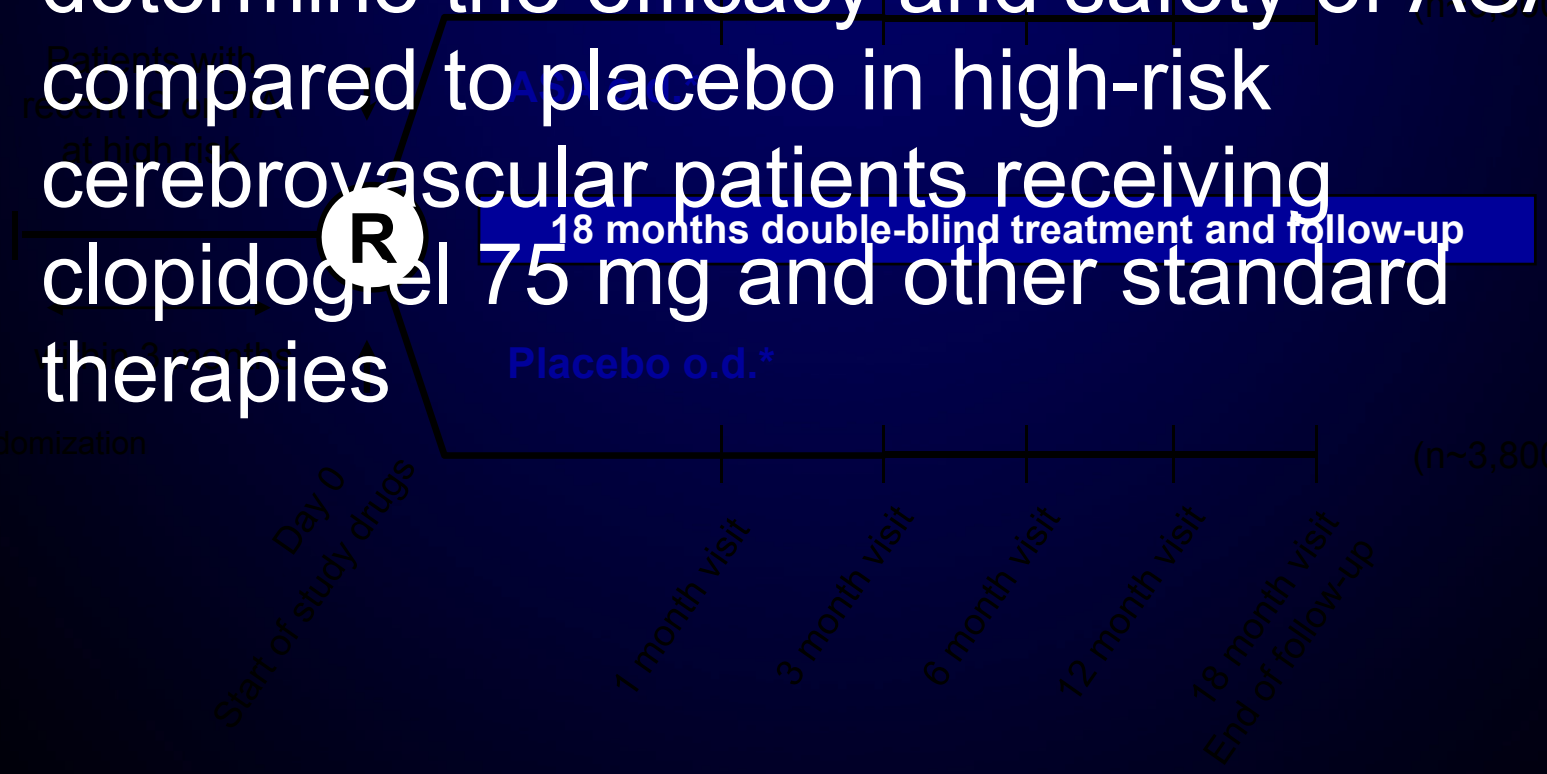
Clopidogrel*

*On a background of ASA 75 mg qd

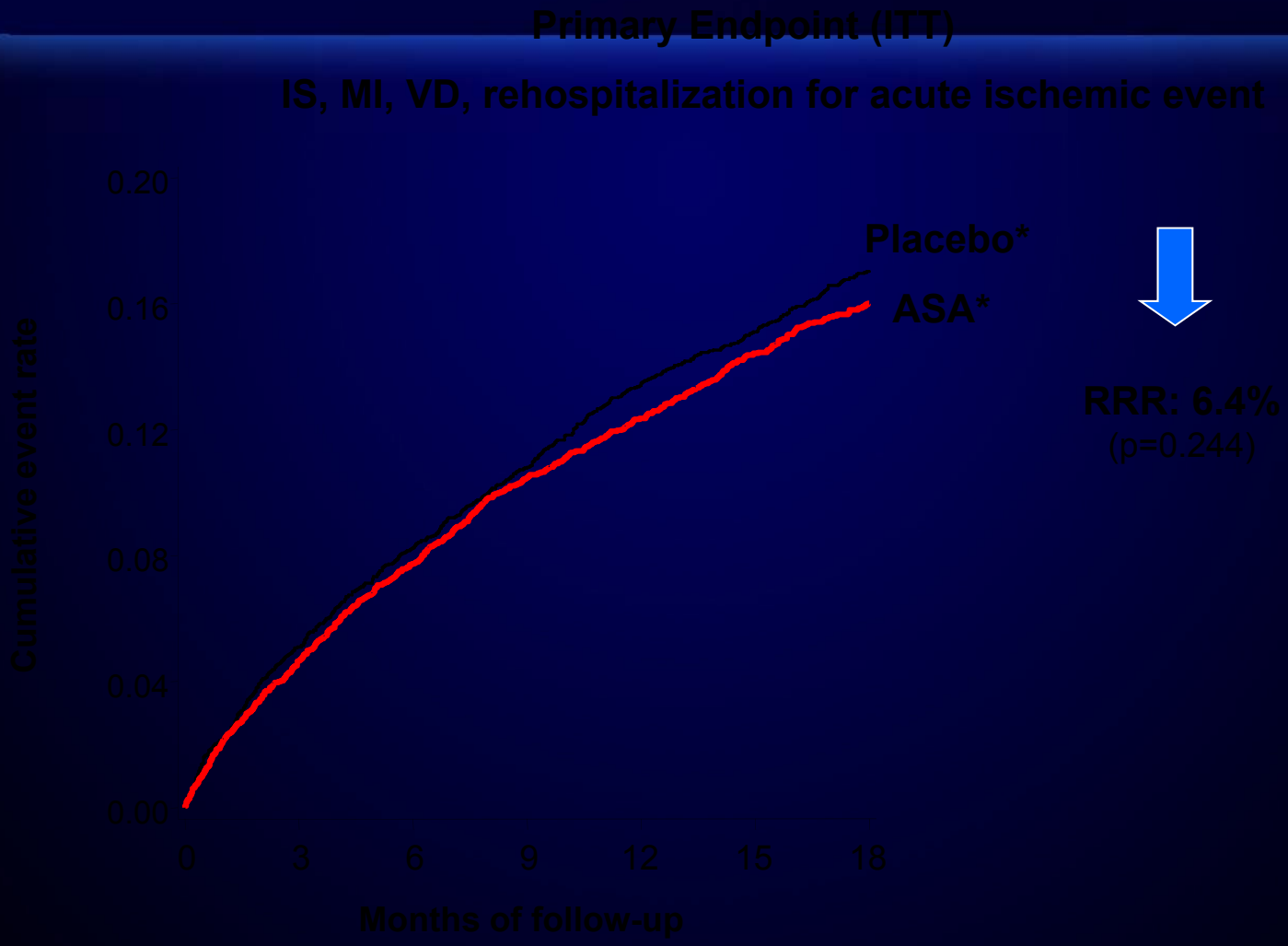
**Offline analysis

The MATCH Trial: Study Objectives and Design[1]

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



Adding ASA to Clopidogrel Shows a Non-Significant Trend for the Reduction of Major Vascular Events in High-Risk Cerebrovascular Patients[1]



All patients received clopidogrel and other standard therapies

1. Chen ZM, et al. Lancet 2004; 364: 331–337.