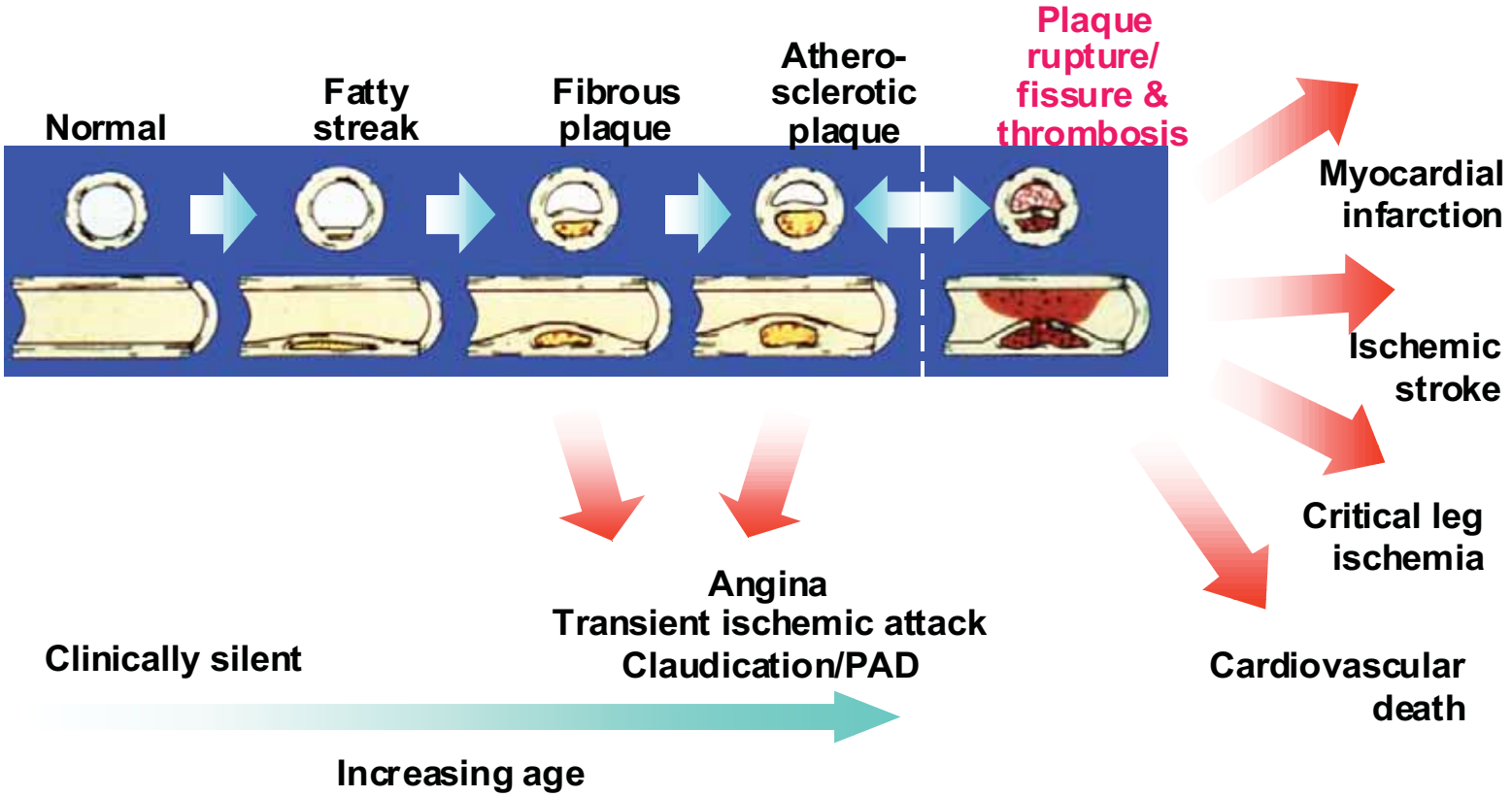
New Developments in Antiplatelet Therapy

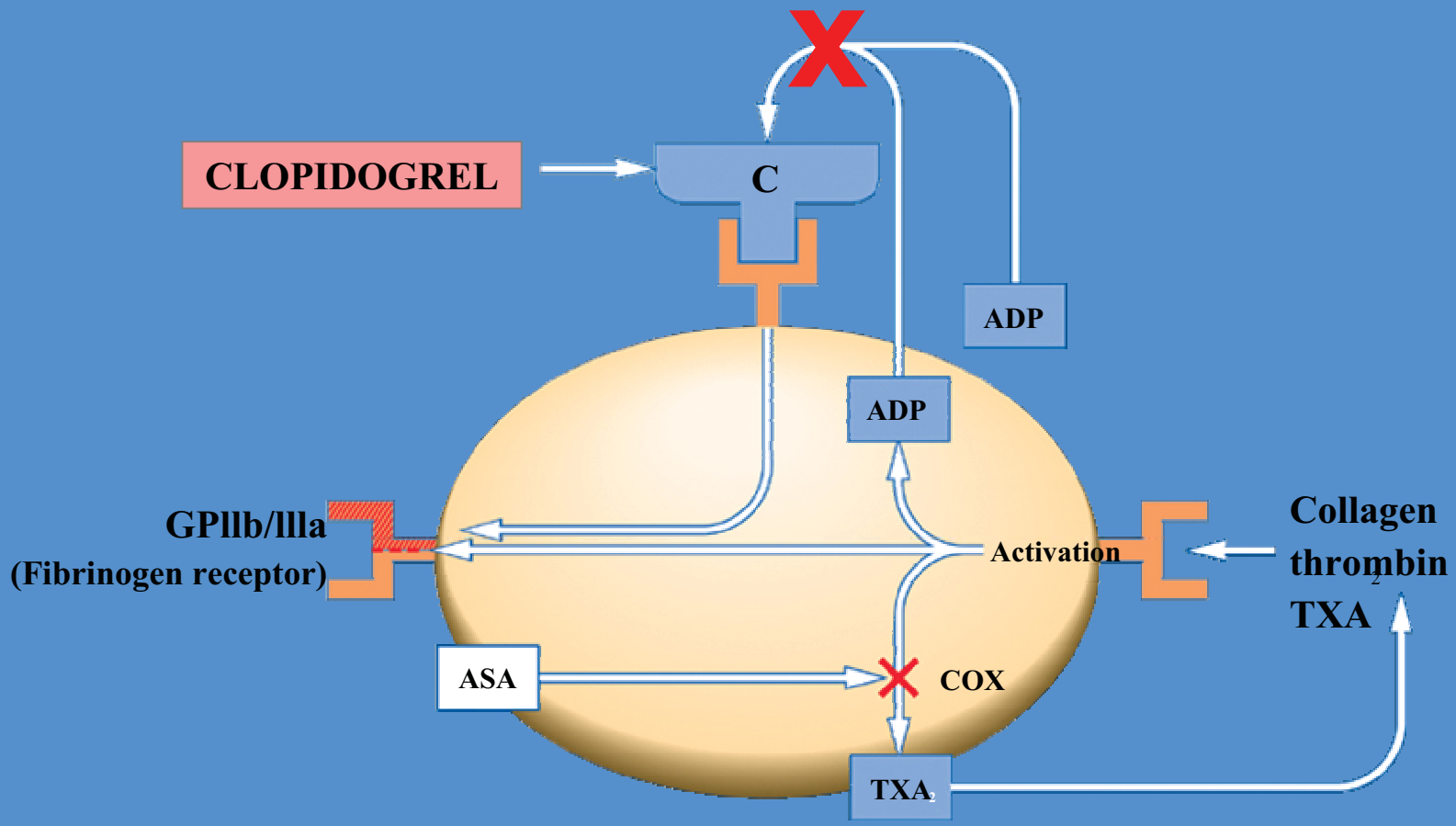
29 April 2004 *Seoul, Korea*

Mel Blumenthal, M.D., F.A.C.C.
Executive Director, Clinical Design & Evaluation
Bristol-Myers Squibb Pharmaceutical Research Institute
Princeton, N.J. USA

Atherothrombosis : a progressive process



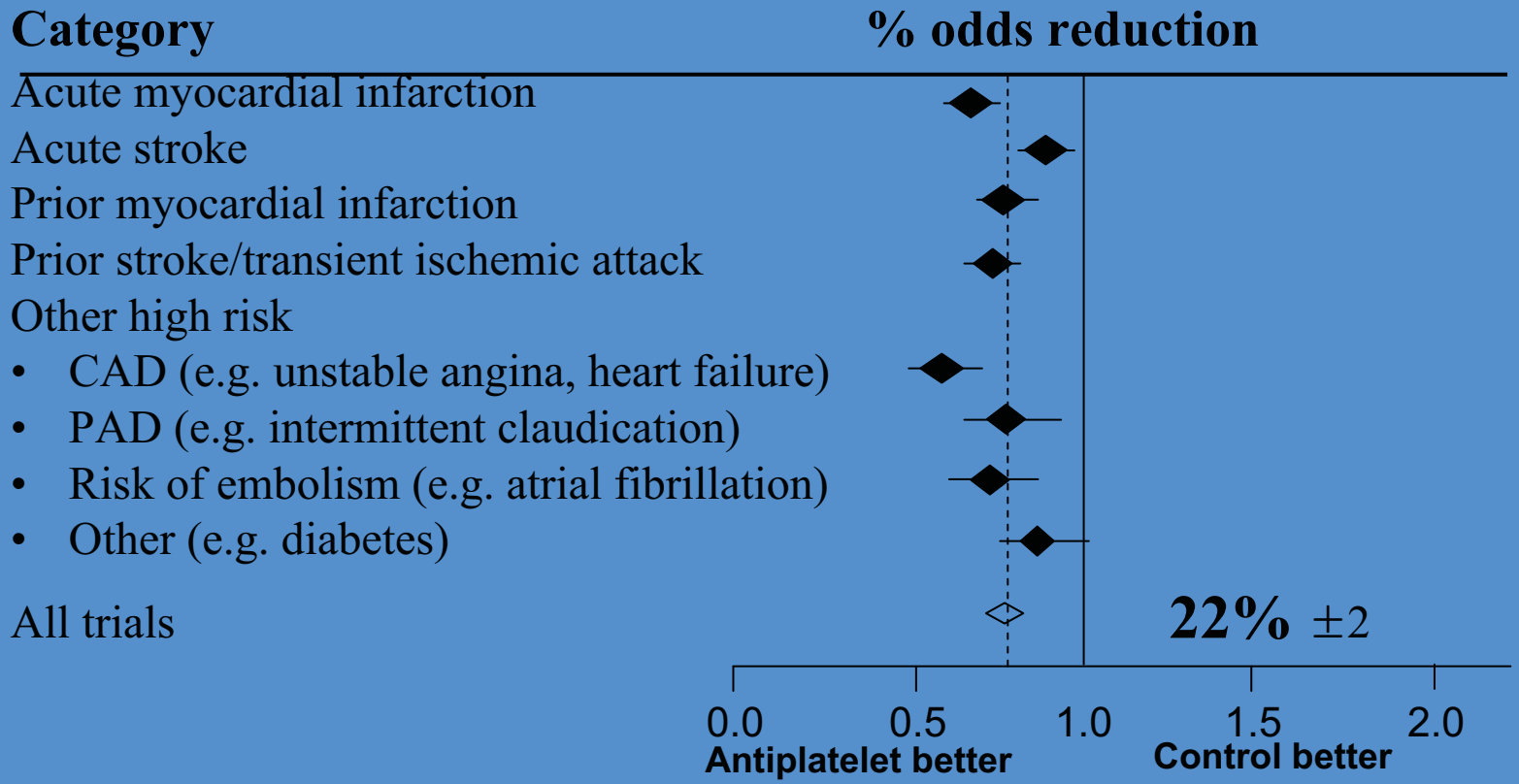
Modes of Action of Clopidogrel & ASA[1]



COX (cyclo-oxygenase)
ADP (adenosine diphosphate)
TXA_2 (thromboxane A_2)

1. Jarvis B, Simpson K. *Drugs* 2000; 60: 347–77.

Antithrombotic Trialists' Collaboration: Efficacy of Antiplatelet Therapy on Vascular Events*[1]

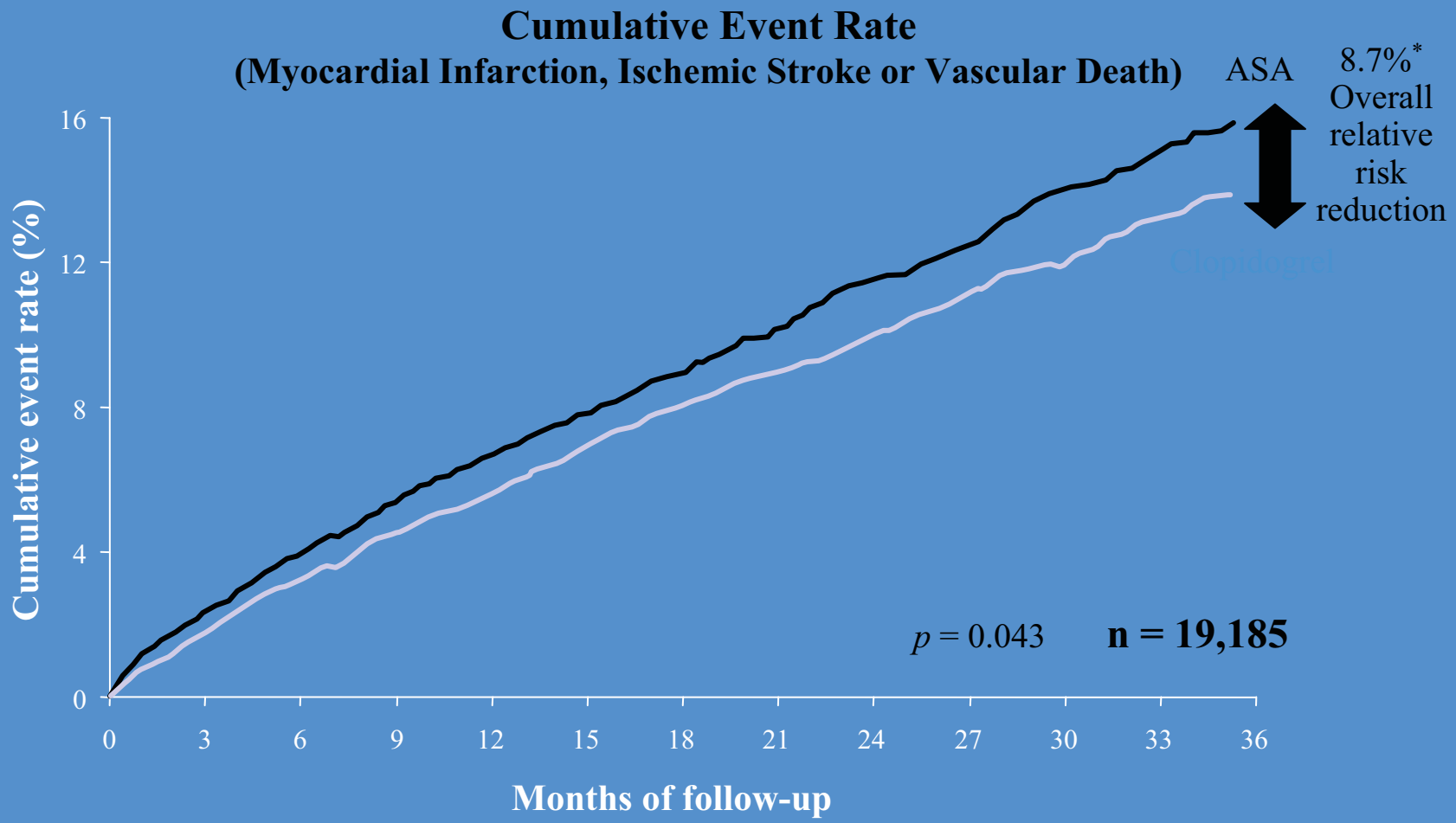


*Vascular events = myocardial infarction, stroke or vascular death

Data on 135,000 patients in 287 trials

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

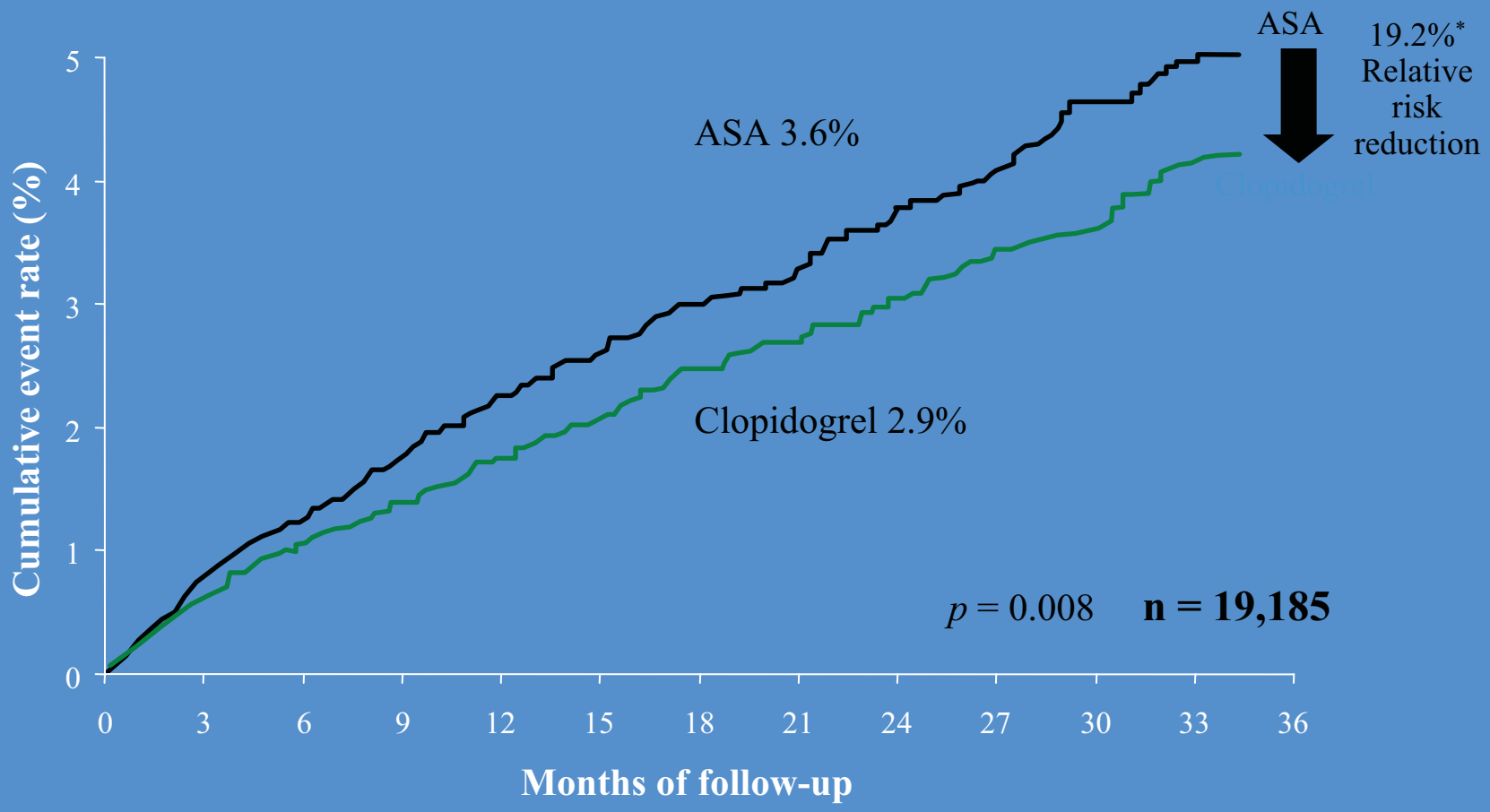
CAPRIE: Long-Term Benefit of Clopidogrel Compared with ASA[1]



*ITT analysis

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

CAPRIE: Benefit of Clopidogrel over ASA in the Reduction of Myocardial Infarction[1]



* ITT analysis

1. Cannon C. *Am J Cardiol*. 2002; 90; 760-762

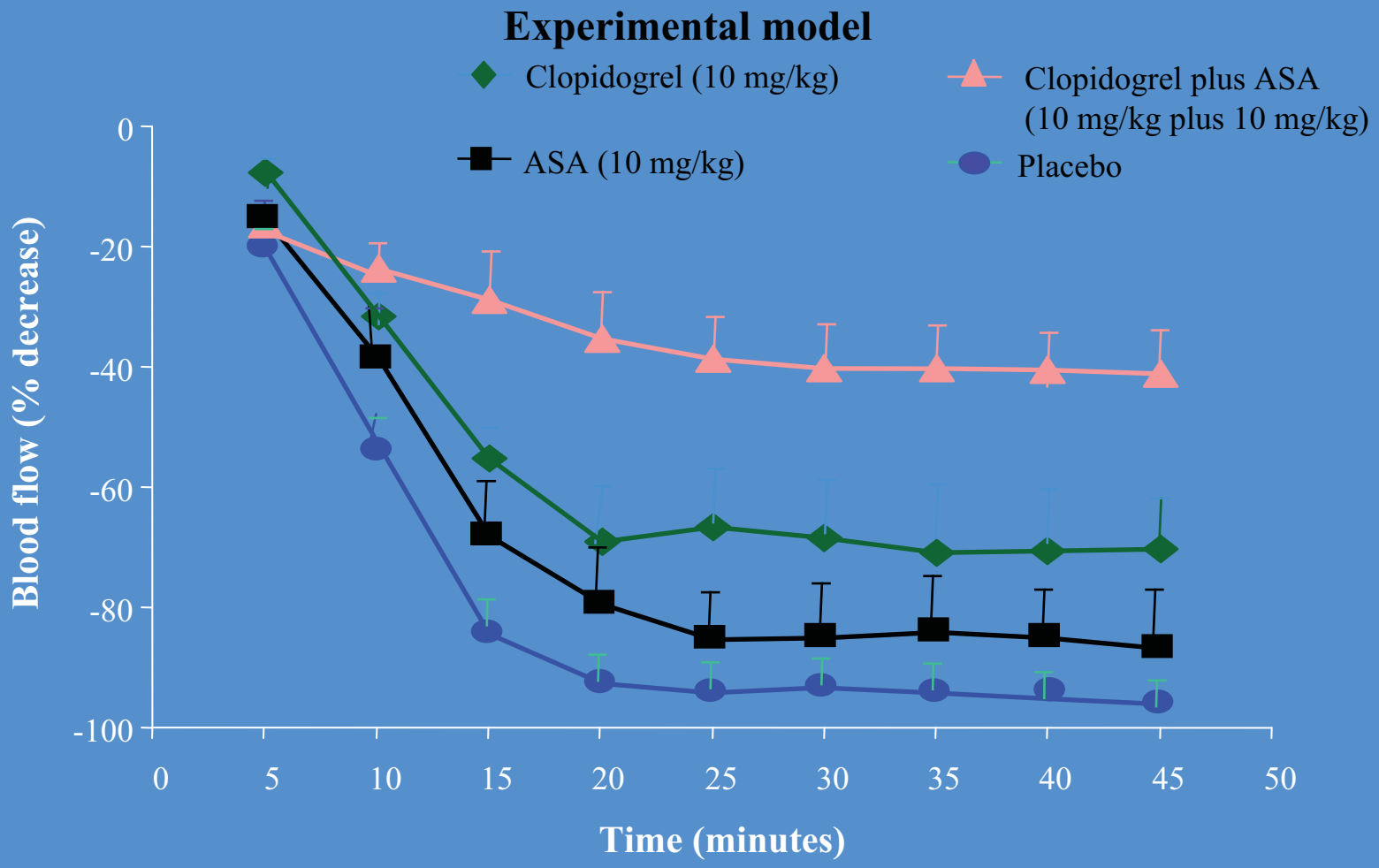
CAPRIE: Favorable Safety for Clopidogrel Compared with ASA*

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

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

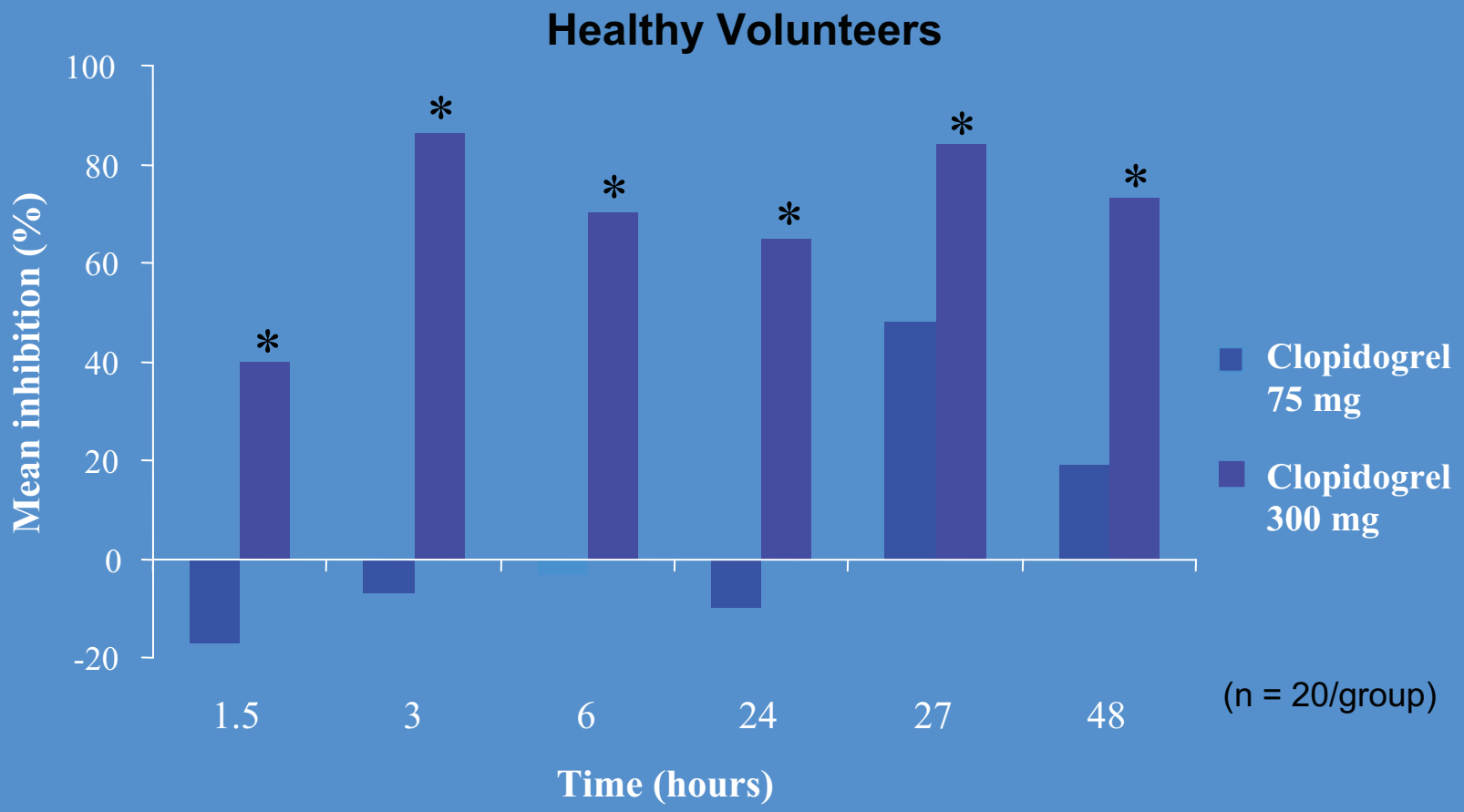
1. CAPRIE Steering Committee. *Lancet* 1996; 348; 1329–39.
2. Harker LA *et al*. *Drug Safety* 1999; 21; 325–35.

Synergistic Action of Clopidogrel on top of ASA in Thrombus Formation[1]



1. Herbert JM *et al. Thromb Haemost* 1998; 80; 512–18.

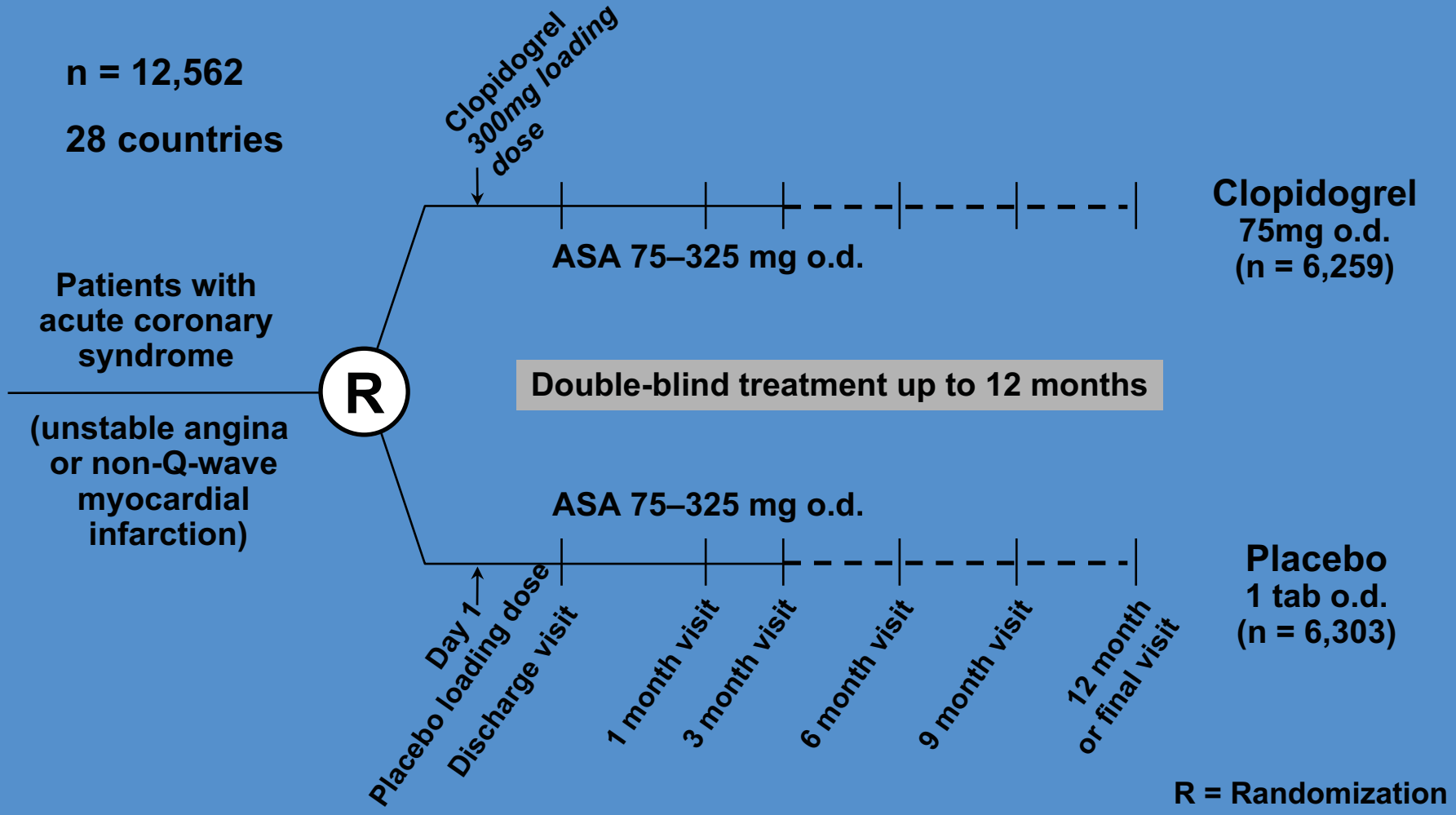
A Loading Dose of Clopidogrel Provides Rapid and Full Effect by 3 Hours[1]



p < 0.002 vs clopidogrel 75 mg

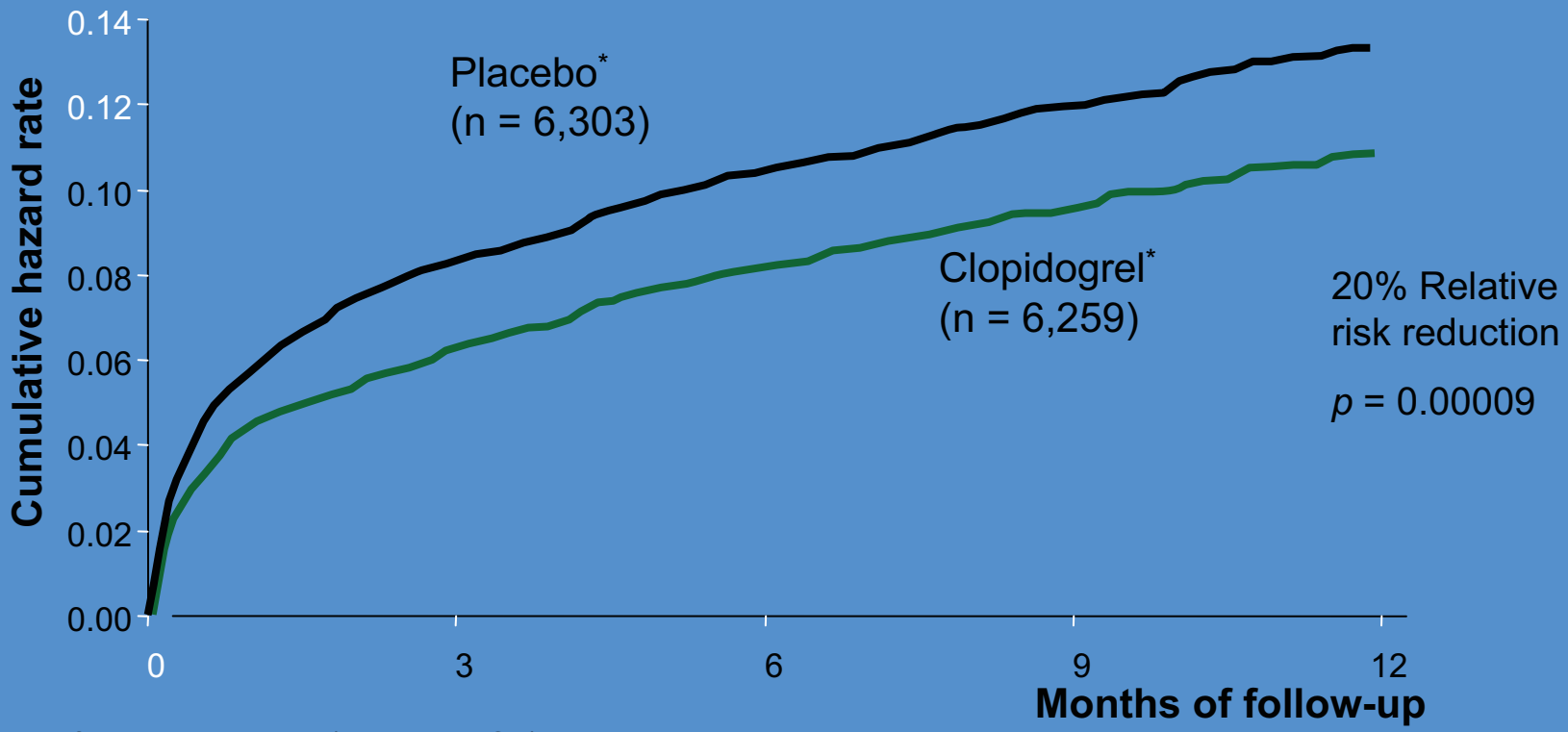
1. Data on file, Sanofi-Synthélabo, 1999, internal report PDY 3494.

CURE: Design[1]



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

CURE: Early and Long-Term Benefits of Clopidogrel[1,2]

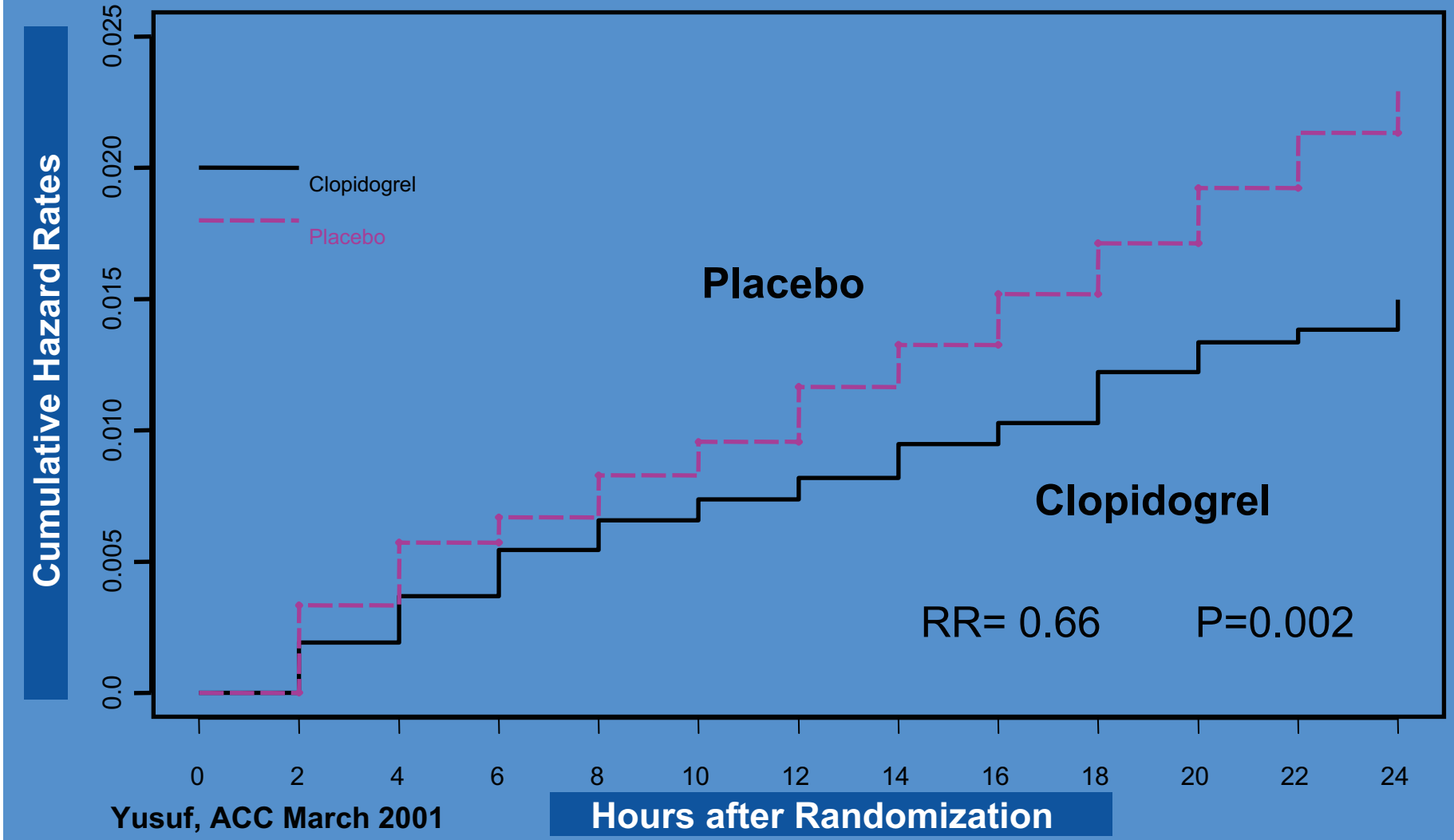


*On top of standard therapy (including ASA)

1.The CURE Trial Investigators. *NEJM* 2001; 345; 494–502.

2. Data on file, 2002, p73 internal CSR-EFC 3307.

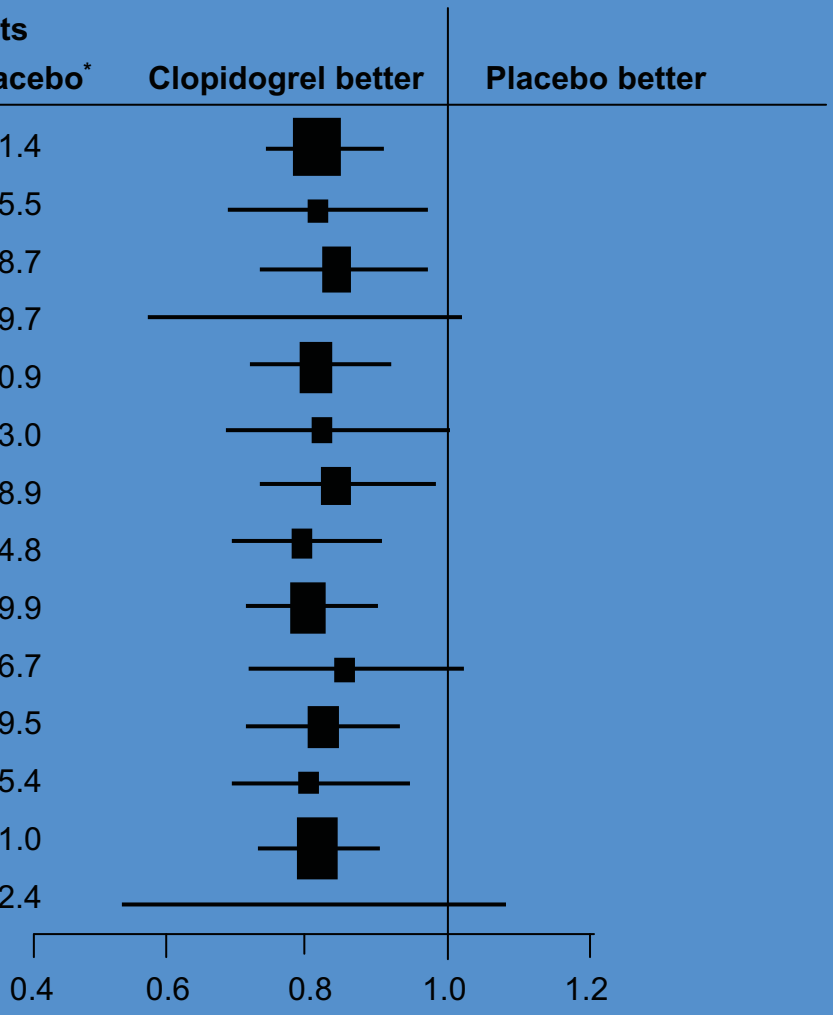
CV Death/MI/Stroke/Severe Ischemia Within 24 hrs of Randomization



Yusuf, ACC March 2001

CURE: Consistent Benefit Independent of Patient History[1]

Baseline characteristics		N	Percent events: Clopidogrel*	Percent events: Placebo*
Overall		12,562	9.3	11.4
Diagnosis	Non-Q-W MI	3,295	12.7	15.5
	Unstable angina	8,298	7.3	8.7
	Other	968	15.1	19.7
Elev card enzy	No	9,381	8.8	10.9
	Yes	3,176	10.7	13.0
ST depr >1.0 mm	No	7,273	7.5	8.9
	Yes	5,288	11.8	14.8
Diabetes	No	9,721	7.9	9.9
	Yes	2,840	14.2	16.7
Previous myocardial infarction	No	8,517	7.8	9.5
	Yes	4,044	12.5	15.4
Previous stroke	No	12,055	8.9	11.0
	Yes	506	17.9	22.4

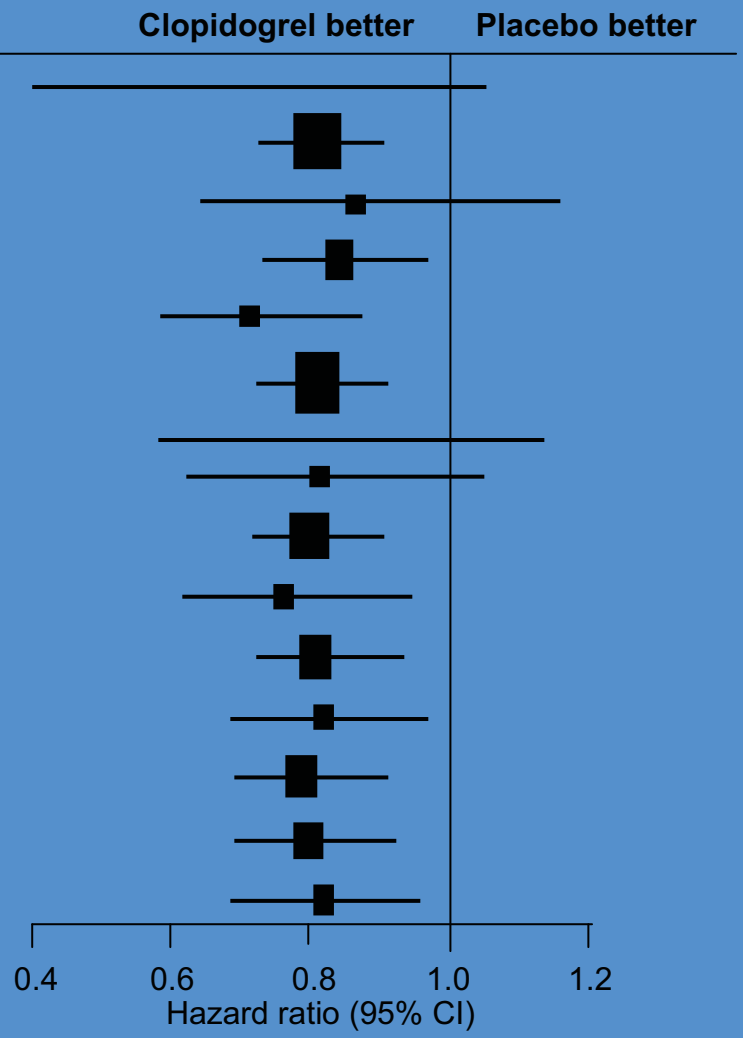


*On top of standard therapy (including ASA)

1. Clopidogrel Prescribing Information, USA, February 2002.

CURE: Consistent Benefit on Top of Various Standard Therapies[1]

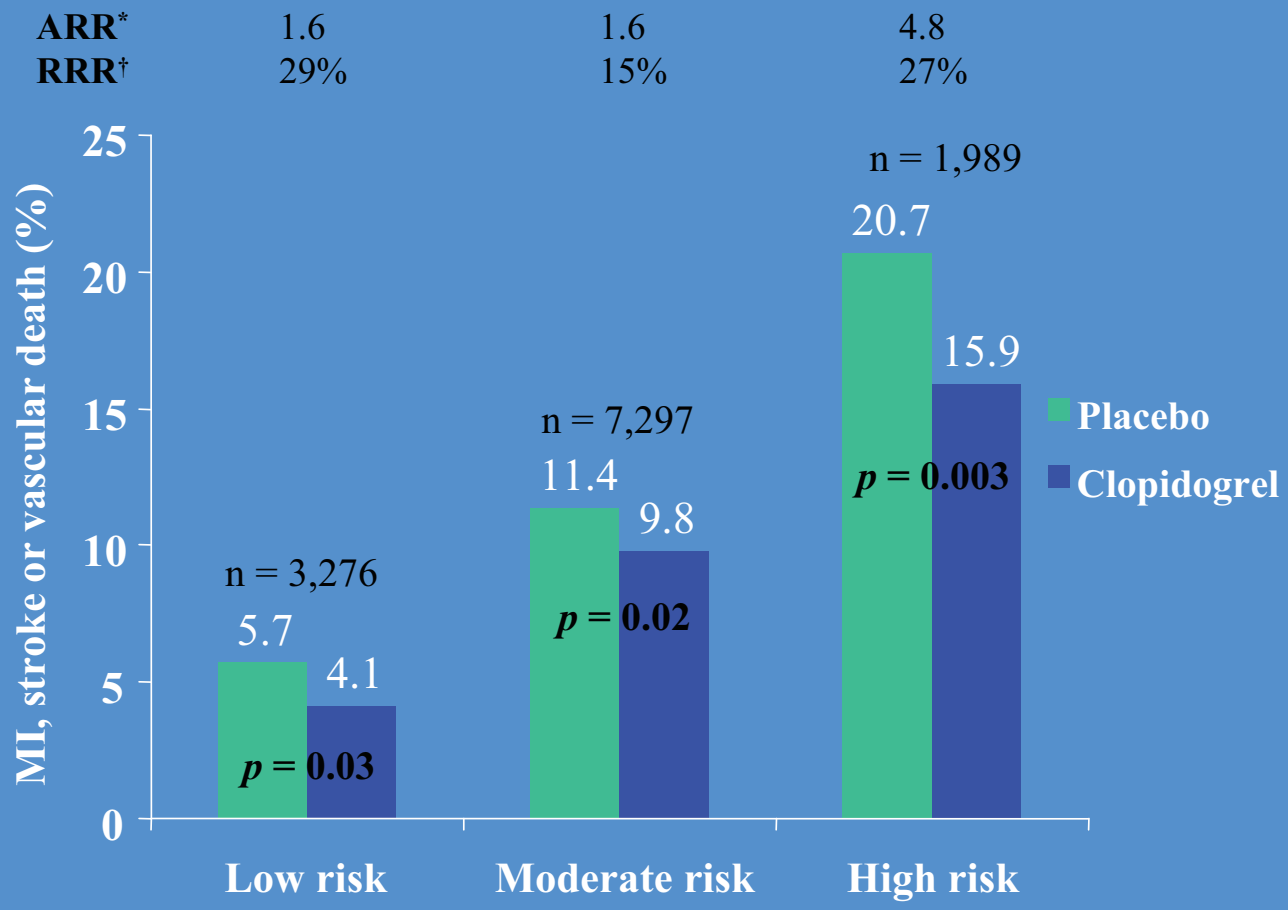
Concomitant medication/therapy		N	Events (%) Clopidogrel*	Placebo*
Heparin/LMWH	No	951	4.9	7.7
	Yes	11611	9.7	11.7
ASA	< 100 mg	1927	8.5	9.7
	100–200 mg	7428	9.2	10.9
	> 200 mg	3201	9.9	13.7
GPIIb/IIIa Antag	No	11739	8.9	10.8
	Yes	823	15.7	19.2
Beta-blocker	No	2032	9.9	12.0
	Yes	10530	9.2	11.3
ACEI	No	4813	6.3	8.1
	Yes	7749	11.2	13.5
Lipid-lowering	No	4461	10.9	13.1
	Yes	8101	8.4	10.5
PTCA/CABG	No	7977	8.1	10.0
	Yes	4585	11.4	13.8



*On top of standard therapy (including ASA)

1. Clopidogrel Prescribing Information, USA, February 2002.

CURE: Effects of Clopidogrel Stratified by TIMI Risk Score at 12 Months[1,2]



*Absolute risk reduction
†Relative risk reduction

1. The CURE Trial Investigators. *N EJM* 2001; 345: 494–502.
2. Budaj AJ *et al. Circulation 2002;106:1622-1626*

CURE: Bleeding Episodes

Event	Placebo* (n = 6,303)	Clopidogrel* (n = 6,259)	*p* value
Major bleeding[1]	2.7%	3.7%	0.001
• Life-threatening	1.8%	2.2%	NS
• Other major bleeding	0.9%	1.5%	0.002
Transfusions of ≥ 2 units of blood[1]	2.2%	2.8%	0.02
Minor bleeding[1]	2.4%	5.1%	< 0.001
Major bleeding by TIMI definition[2]	1.2%	1.1%	0.70
Major bleeding by GUSTO definition[3]	1.1%	1.2%	0.48

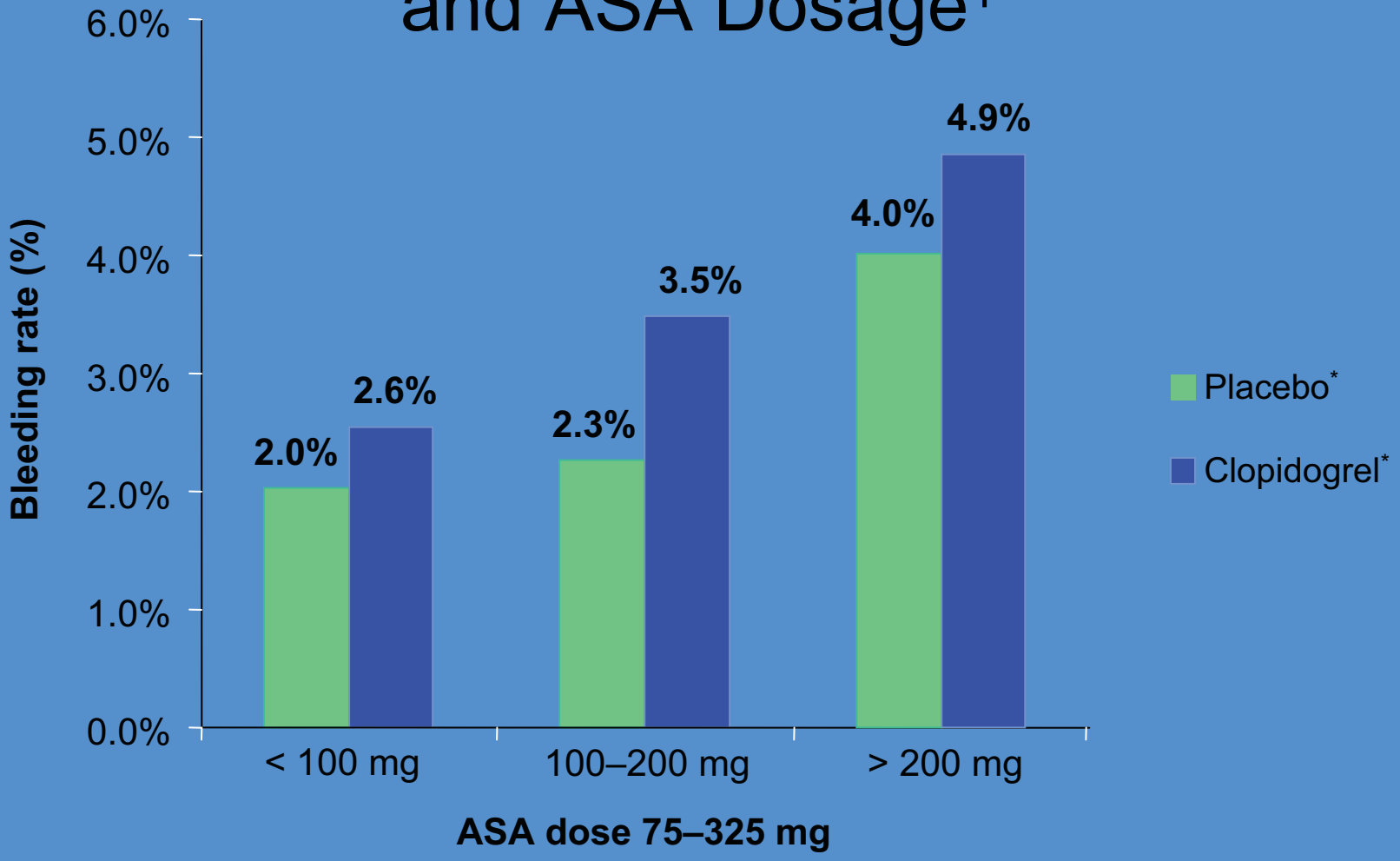
*On top of standard therapy (including ASA)

1. The CURE Trial Investigators. *NEJM* 2001; 345: 494–502.

2. Chesebro JH *et al. Circulation* 1987; 76: 142–54.

3. The GUSTO Investigators. *NEJM* 1993; 329: 673–82.

CURE: Relation Between Safety and ASA Dosage[1]



*On top of standard therapy (including ASA)

1. Clopidogrel Prescribing Information, USA, February 2002.

One of the Largest Clinical Trial Programs Ever Developed

More than 100,000 patients in studies with clopidogrel[1]

Study	Patients	Maximum follow-up	Number of patients	Status of study (data expected)
CAPRIE[2]	Ischemic stroke, MI or PAD	36 months	19,185	Published (*Lancet,* 1996)
CLASSICS[3]	Coronary stenting	4 weeks	1,020	Published (*Circulation,* 2000)
CREDO[4]	PCI	12 months	2,116	Published (*JAMA,* 2002)
CURE[5]	Unstable angina or NQWMI	12 months	12,562	Published (*N Engl J Med,* 2001)
PCI-CURE*[6]	CURE patients undergoing PCI	12 months	2,658	Published (*Lancet,* 2001)
ACTIVE	Atrial fibrillation	48 months	~14,000	Ongoing (2007)
CARESS	Carotid stenosis with MES	10 days	~100	Completed (2004)
CHARISMA	Coronary, cerebrovascular, PAD, or major risk factors	42 months	~15,200	Ongoing (2005/6)
COMMIT	Acute MI	4 weeks	~45,000	Ongoing (2005)
CLARITY	Acute MI (angiography)	4 weeks	3,000	Ongoing (2005)
MATCH	TIA or ischemic stroke	18 months	7,601	Completed (2004)

1) Bhatt D, Topol E. *Nature Rev (Drug Dis)* 2003; 3: 15–28
2) CAPRIE Steering Committee. *Lancet* 1996; 348: 1329–1339
3) Bertrand NE *et al. Circulation* 2000; 102: 624–629
4) Steinhubl S *et al. JAMA* 2002; 288(19): 2411–242
5) The CURE Trial Investigators. *NEJM* 2001; 345: 494–502
6) Mehta SR *et al. Lancet* 2001; 358: 527–533

* PCI-CURE is a substudy of the CURE study

Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance

CHARISMA: Inclusion Criteria

Patients aged 45 years and older

with

at least 1 of the following:

1) 2 major or 1 major and 2 minor or 3 minor risk factors

and/or

2) documented cerebrovascular disease

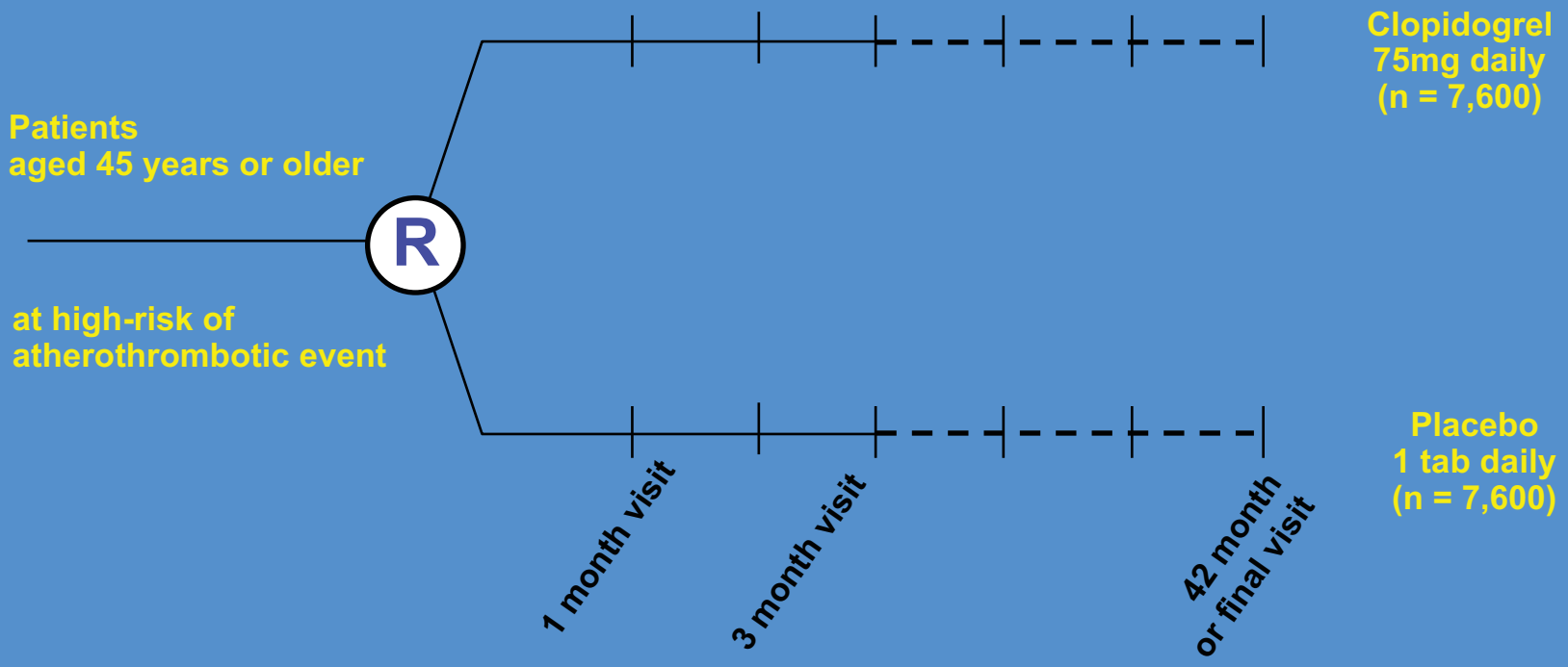
and/or

3) documented coronary artery disease

and/or

4) documented symptomatic peripheral arterial disease (PAD)

CHARISMA: Study Design



R = Randomization
n = 15,200
Event driven trial

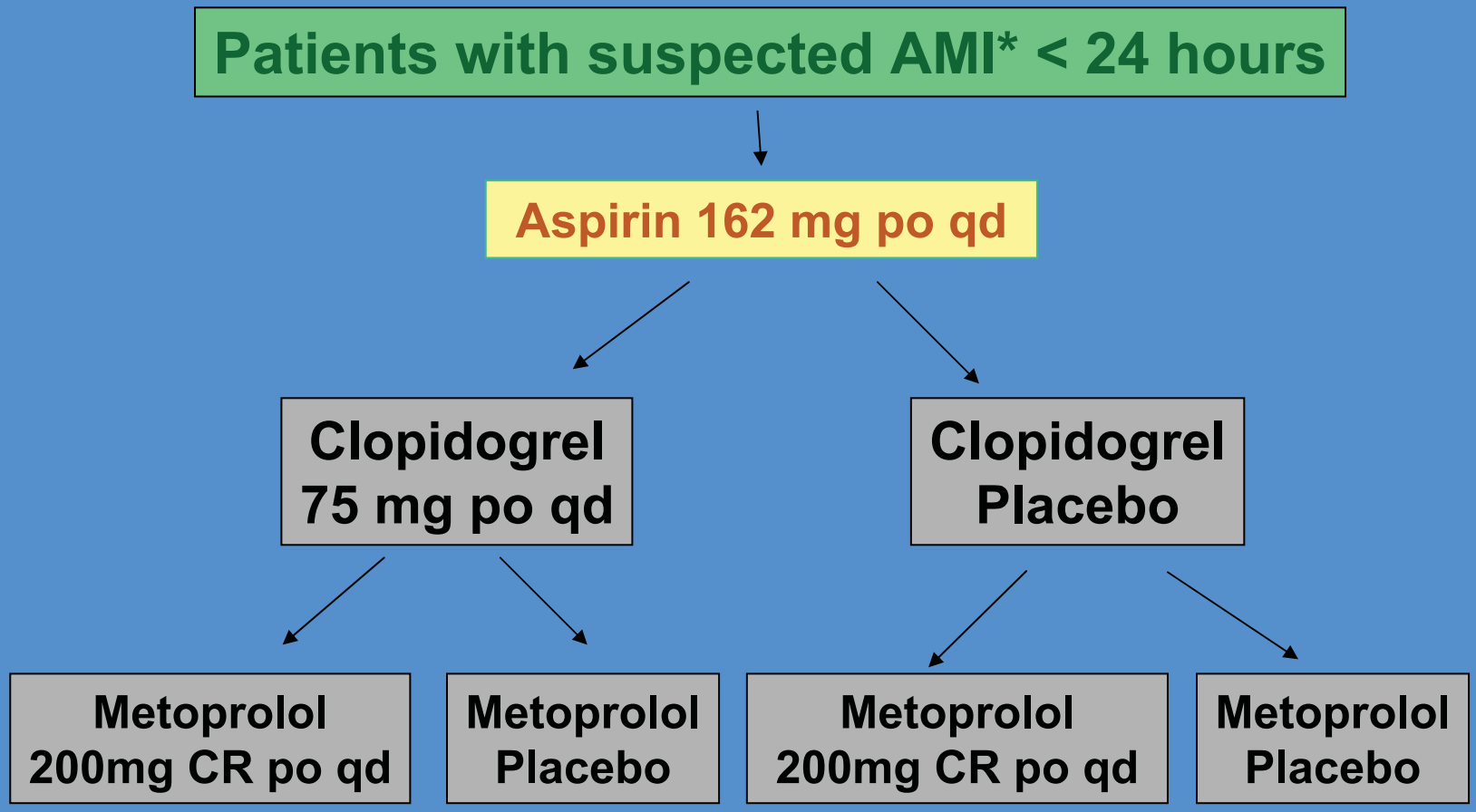
All patients receive low-dose ASA
(75-162 mg daily) as background therapy

COMMIT Trial
(CCS-2)

ClOpidogrel Metoprolol Myocardial Infarction Trial

COMMIT

Study Design



1^0 endpoint = death/death or MI

CR= controlled release

N = 45,000-48,000

* typical ECG changes

ACTIVE

Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events

ACTIVE : 3 Nested Trials

- ACTIVE-W
  - **Noninferiority** trial : clopidogrel + ASA vs. adjusted dose (INR 2.0-3.0) oral anticoagulation (OAC) [N=6500]
  - Open-label PROBE design
- ACTIVE-A
  - **Superiority** trial: clopidogrel vs. placebo on a background of standard care including ASA 75-100 mg (double-blind) [N=7500]

Common 1^{o} outcome = VD, MI, stroke, or peripheral embolism

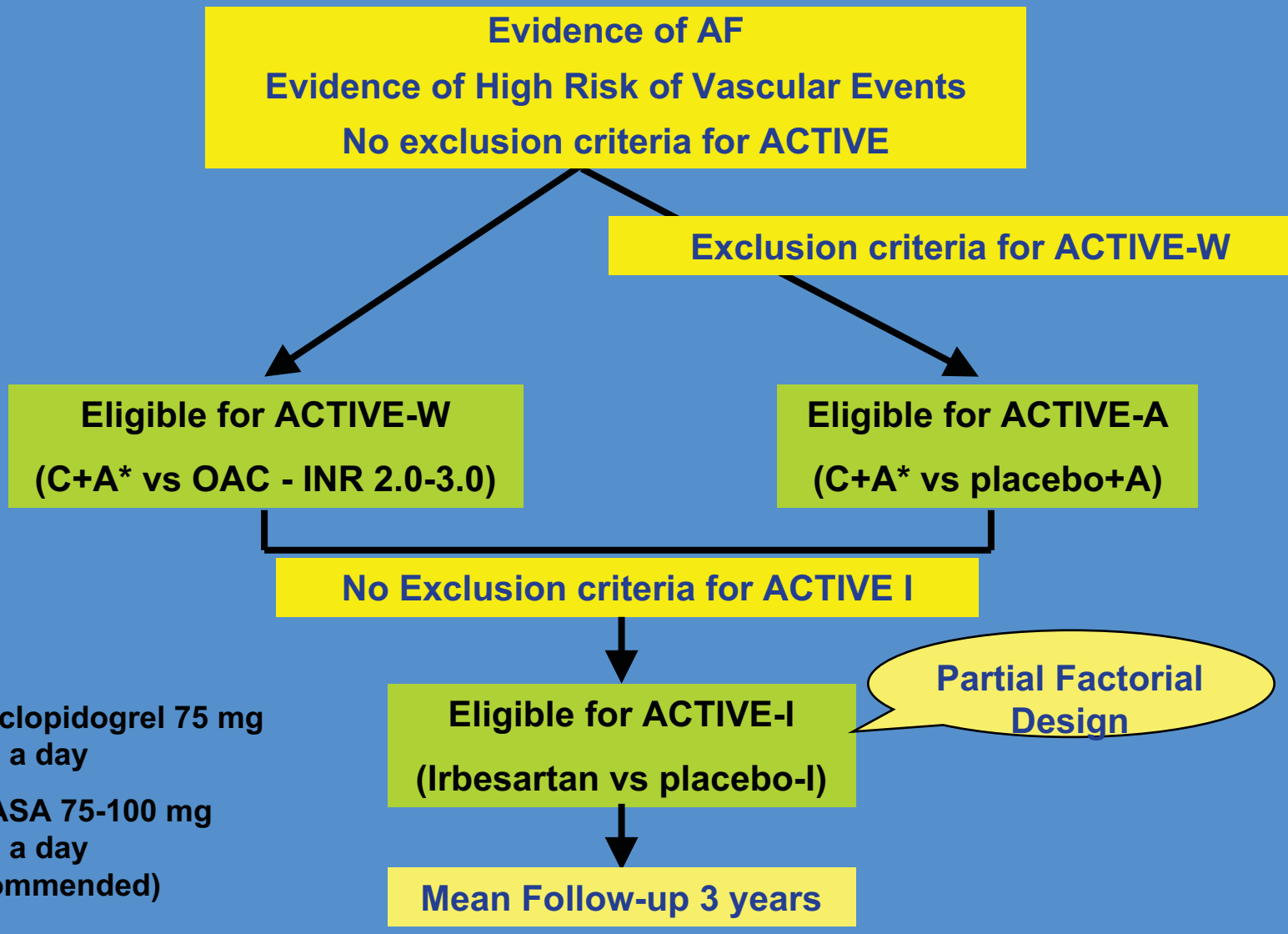
- ACTIVE-I
  - Factorial design: irbesartan (150 mg with forced titration to 300 mg) vs. placebo [N≈10,000]
  - 1^{o} outcome = VD, MI, or stroke

ACTIVE : Inclusion Criteria

- Evidence of Atrial Fibrillation:
  - Documented chronic AF or recurrent intermittent AF, and
  - No current plan to achieve sinus rhythm

- High risk of vascular events (any of):
  - Age ≥75 years
  - On treatment for systemic hypertension
  - Prior stroke, non-CNS systemic embolus or TIA
  - Left ventricular dysfunction, with left ventricular EF <45%
  - Age 65 to 74 years, **and** one of the following:
    - Diabetes mellitus requiring treatment
    - Coronary artery disease (coronary angiographic evidence or positive perfusion study)
    - Peripheral arterial disease

ACTIVE Design



New Developments in Antiplatelet Therapy

29 April 2004 *Seoul, Korea*

Mel Blumenthal, M.D., F.A.C.C.
Executive Director, Clinical Design & Evaluation
Bristol-Myers Squibb Pharmaceutical Research Institute
Princeton, N.J. USA