Optimising antiplatelet therapy in patients with STEMI: Main findings of CLARITY & COMMIT

Zhengming Chen MD PhD
CTSU, Nuffield Department of Medicine,
University of Oxford, UK

Angioplasty Summit 2006-TCT Asia Pacific,
Soul, South Korea, 26-28 April, 2006

commit CCS-3

Management perspectives for acute MI

Main aims:

- to prevent death
- to limit the infarct size
- to prevent re-MI & complications

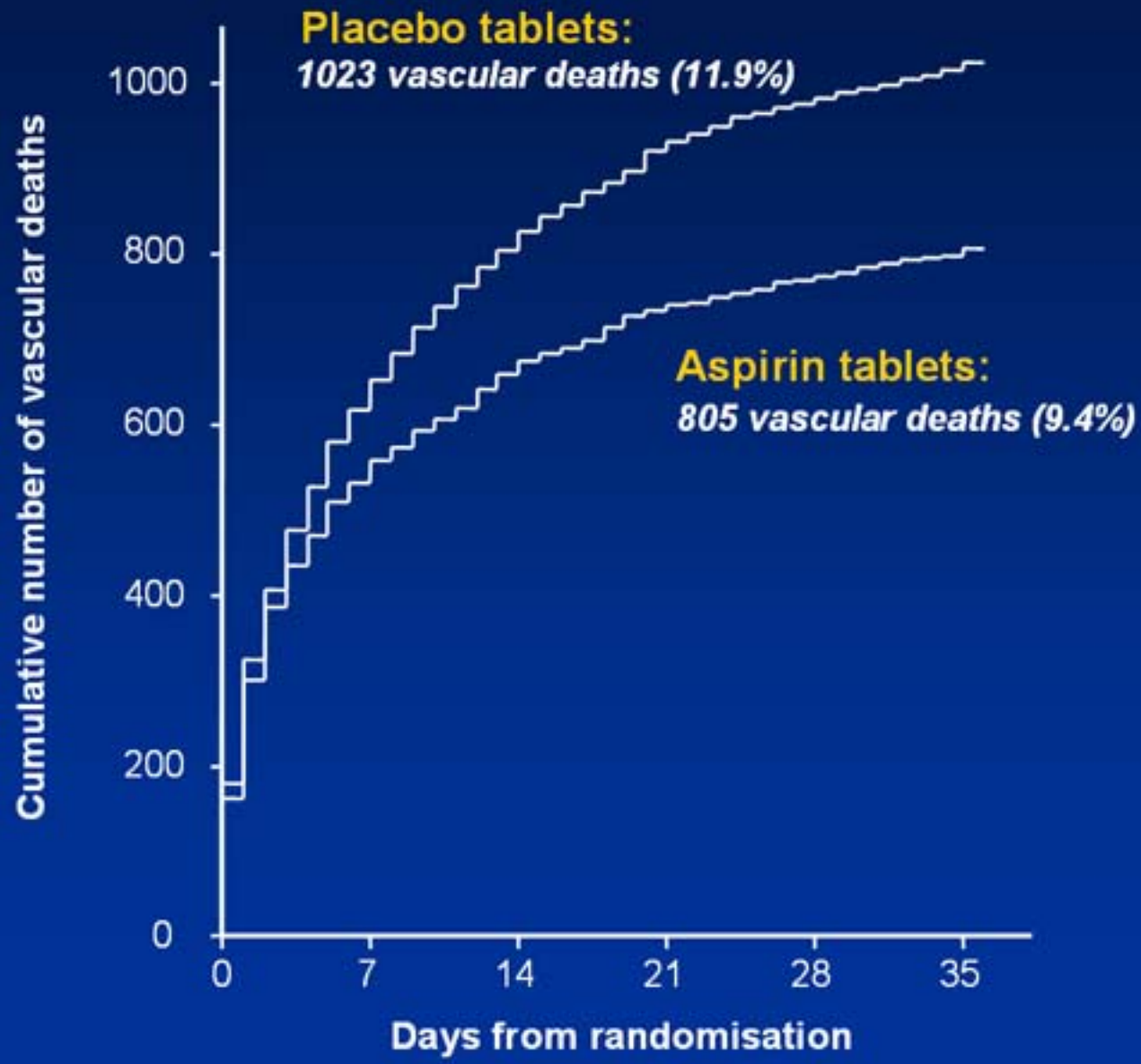
Strategy:

- Reperfusion (PCI or lytic agents)
- Anti-platelet therapy (e.g. ASA, clopidogrel)
- Anti-thrombotic therapy (LMWH)
- Anti-ischaemic (i.v. beta-blocker)

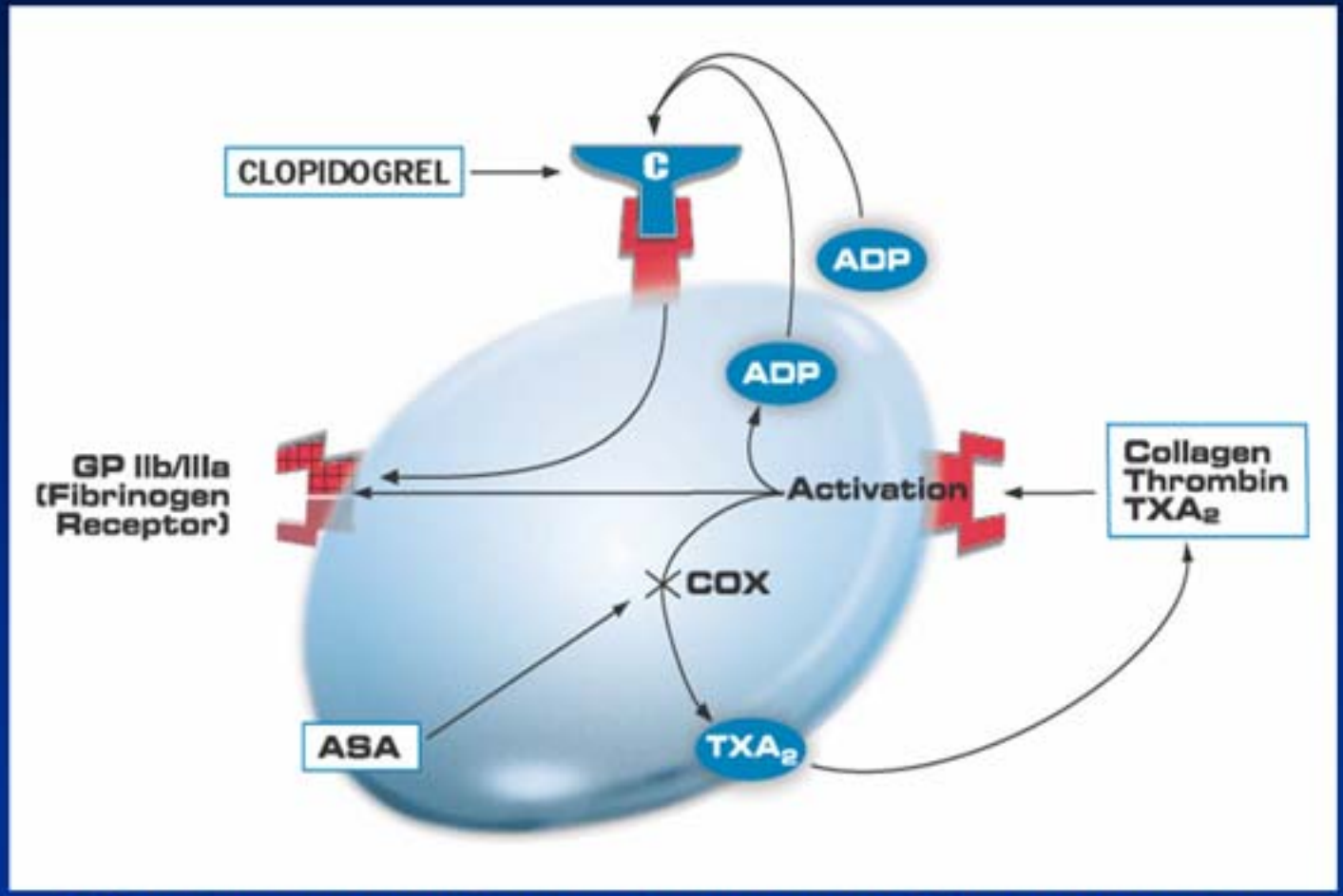
The Aspirin Story

- First suggested as an anti-thrombotic drug in 1953 by Lawrence Craven in Los Angeles
- The anti-platelet effects of aspirin was not discovered until late 1960s by John Vane
- The first landmark Canadian trial of aspirin in stroke prevention was reported in 1978
- Really large ISIS-2 trial of aspirin in acute MI was reported in 1988

ISIS-2: Aspirin in 17,000 suspected acute MI



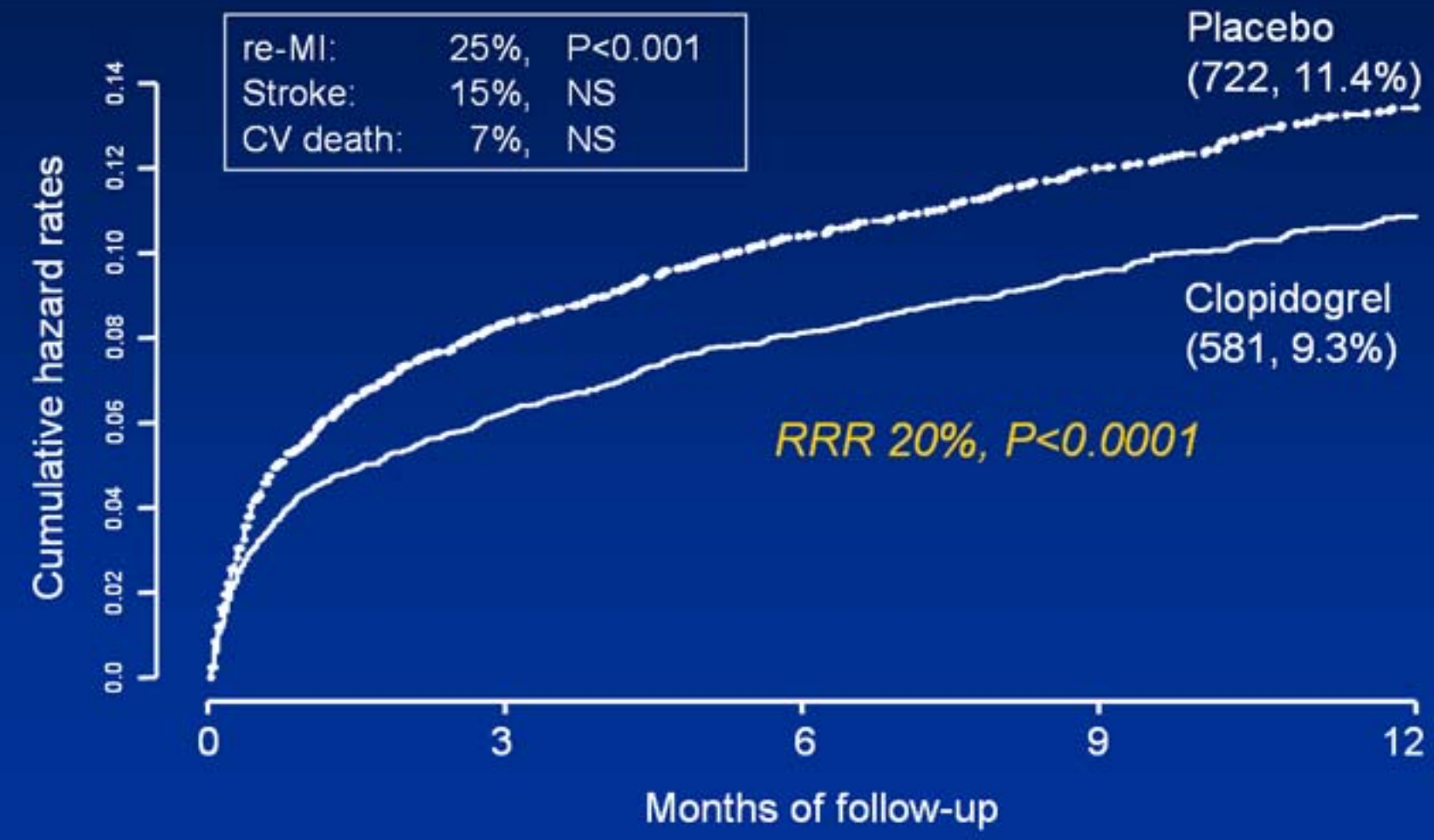
Clopidogrel and aspirin: complementary mode of antiplatelet action



COX: cyclooxygenase; ADP: adenosine diphosphate; TxA_2 thromboxane A_2

Schafer AI *Am J Med* 1996;101:199–209

Effects of adding clopidogrel to aspirin on major vascular events in patients with ACS



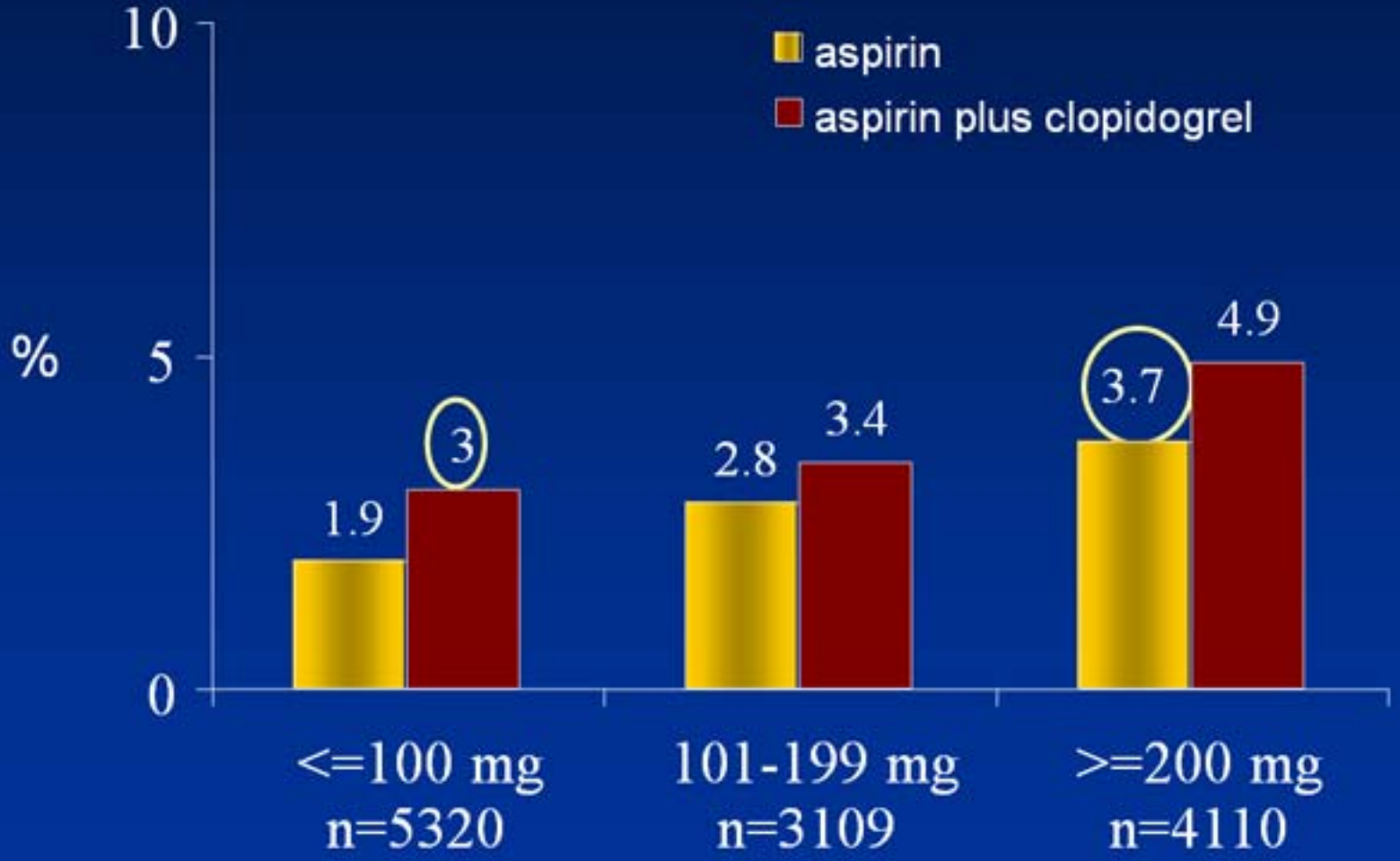
Yusuf S. et al., *N Engl J Med* 2001;345 494-502

CURE Bleeding risk of adding clopidogrel to ASA

Event	Clopidogrel + ASA* (n = 6,259)	Placebo + ASA* (n = 6,303)	*P* value
Major bleeding†	3.7%	2.7%	0.001
Life-threatening bleeding	2.2%	1.8%	0.13
Other major bleeding	1.6%	1.0%	0.005
Minor bleeding	5.1%	2.4%	<0.001

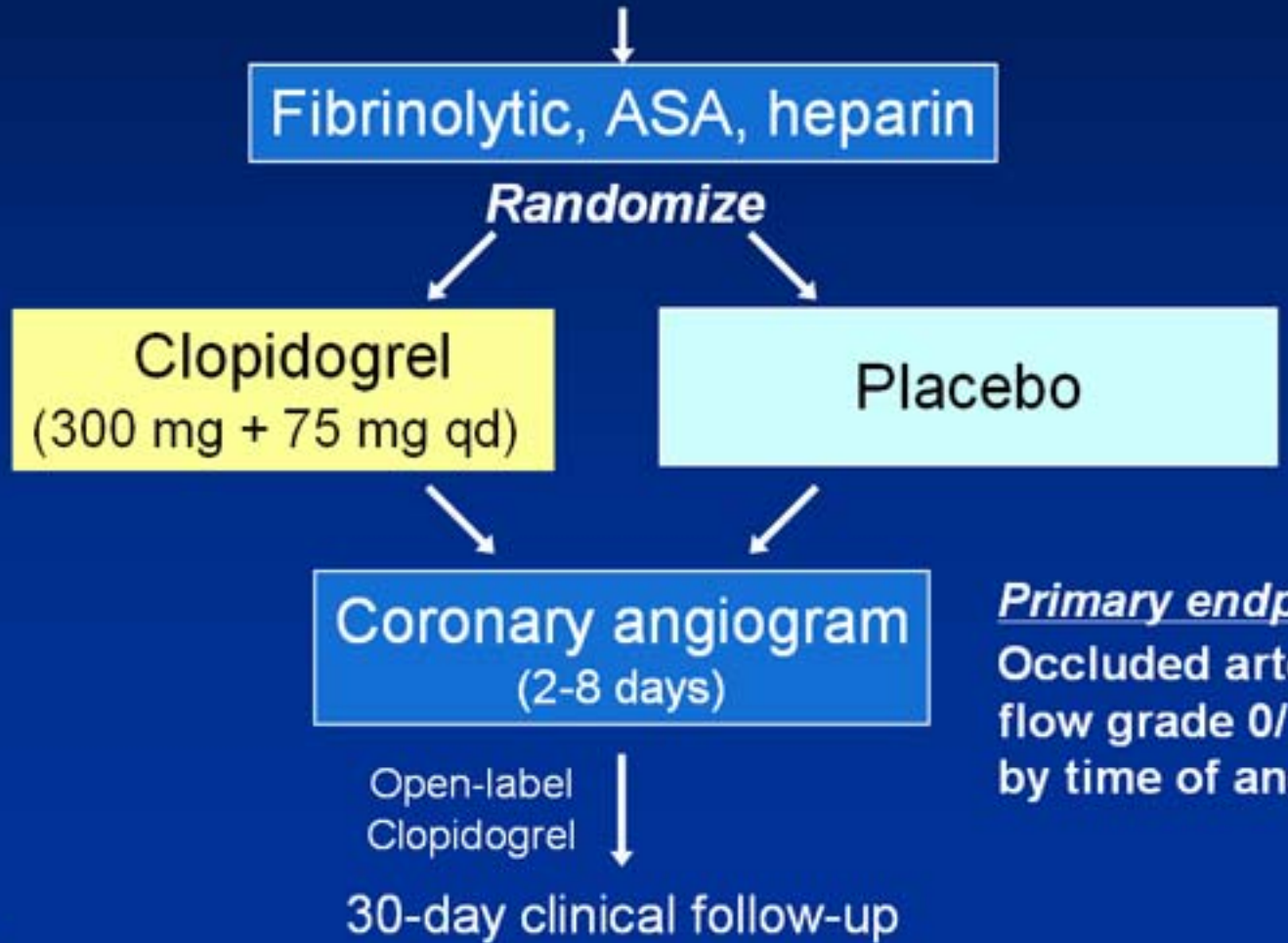
* Other standard therapies were used as appropriate.
† Life-threatening and other major bleeding.

Aspirin dose and major bleeding



CLARITY-TIMI 28: Study design

Double-blind, randomized, placebo-controlled trial in 3491 patients, age 18-75 years with STEMI <12 hours

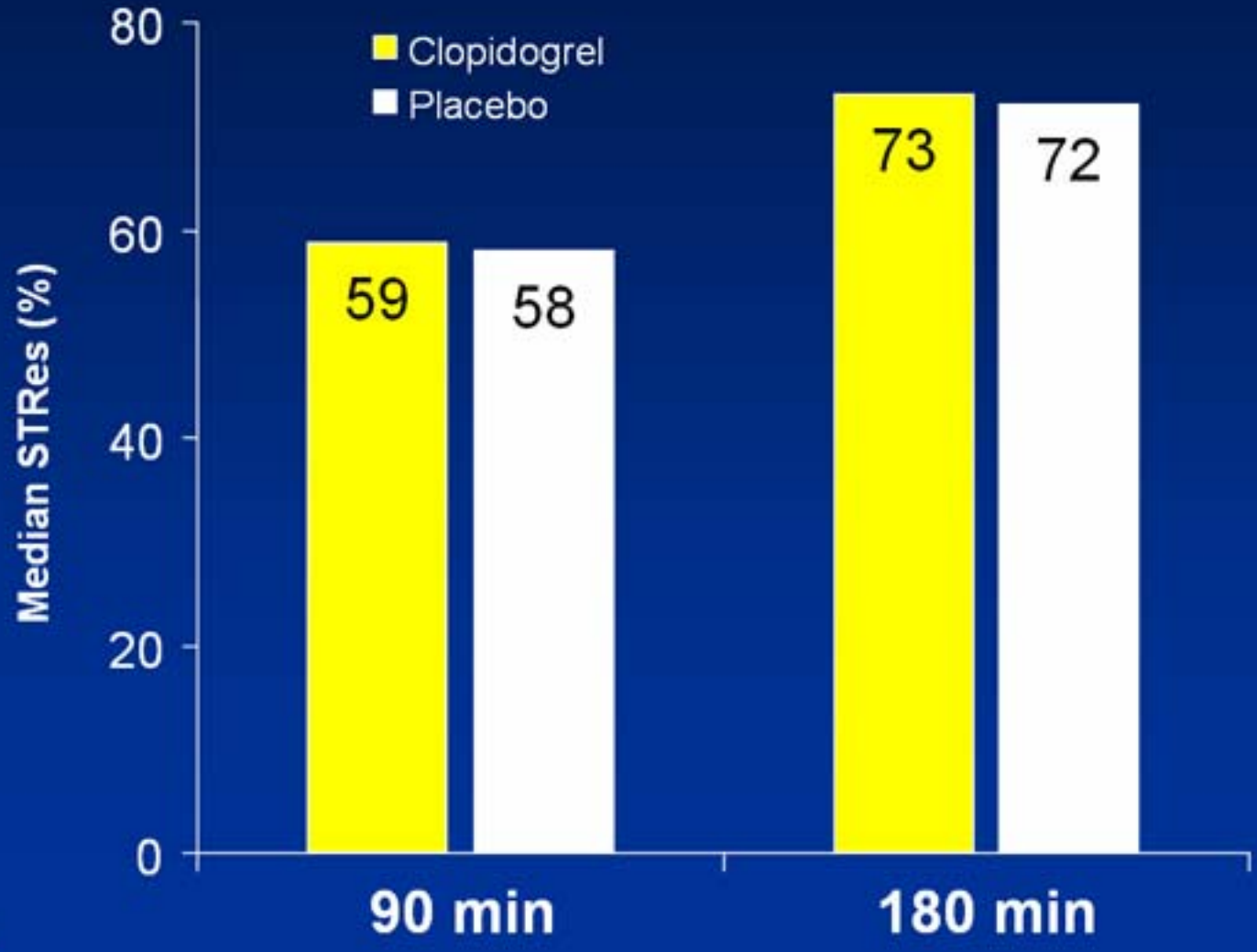


Primary endpoint:

Occluded artery (TIMI flow grade 0/1) or D/MI by time of angio

CLARITY TIMI 28

CLARITY: No effects on early ST segment resolution with loading dose of CLOPIDOGREL



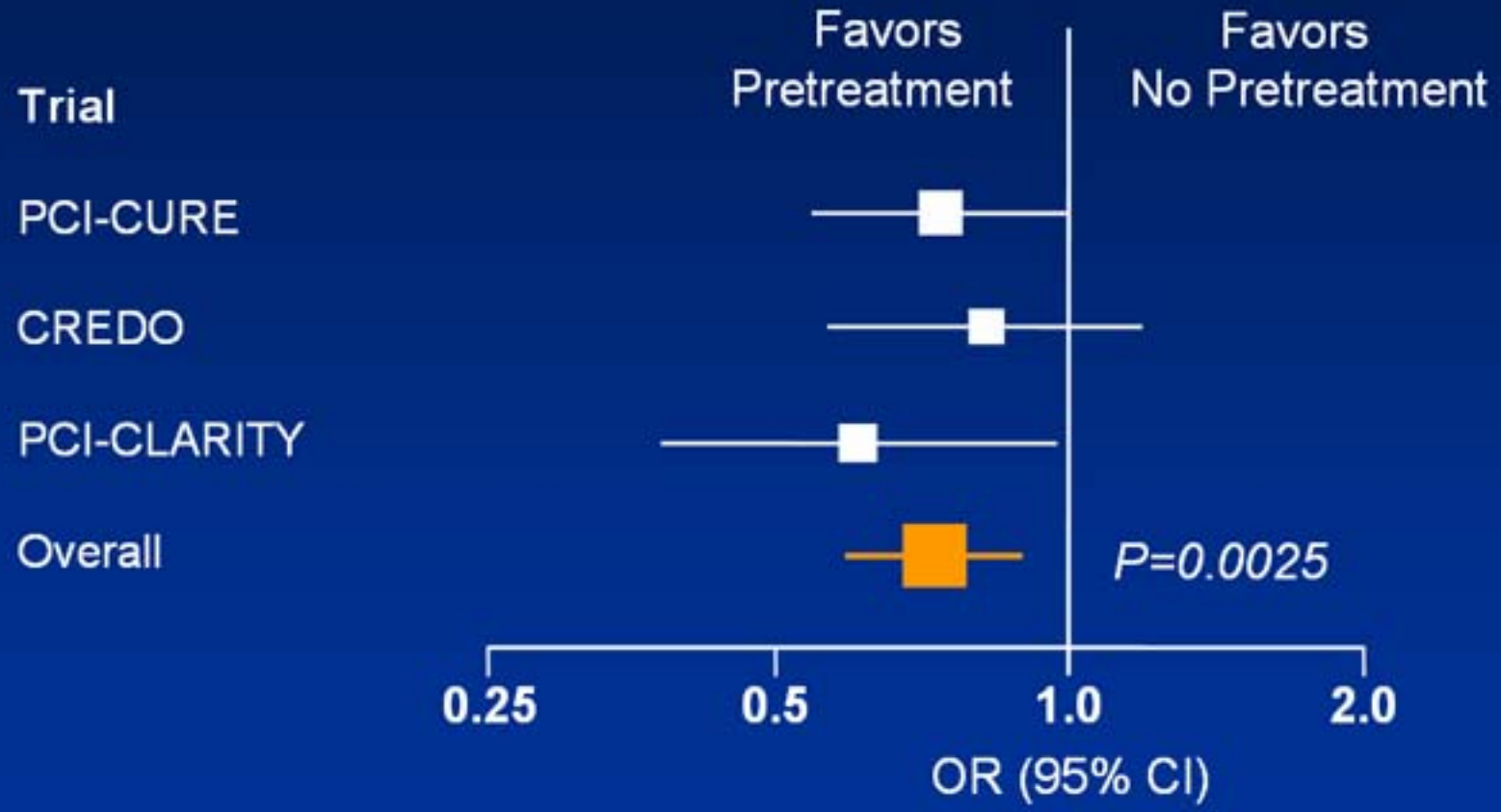
CLARITY TIMI 28

CLARITY: Effects of CLOPIDOGREL, starting with 300 mg of loading dose, on artery patency

Outcome	Clopidogrel (n=1752)	Placebo (n=1739)	OR	2P value
TIMI Flow 0/1	11.7	18.4	0.59	<0.001
Re-MI	2.5	3.6	0.70	0.08
Death	2.6	2.2	1.17	0.49
Any event	15.0	21.7	0.64	<0.001

CLARITY-PCI substudy

CV death or MI after PCI to 30 days



CLARITY TIMI 28

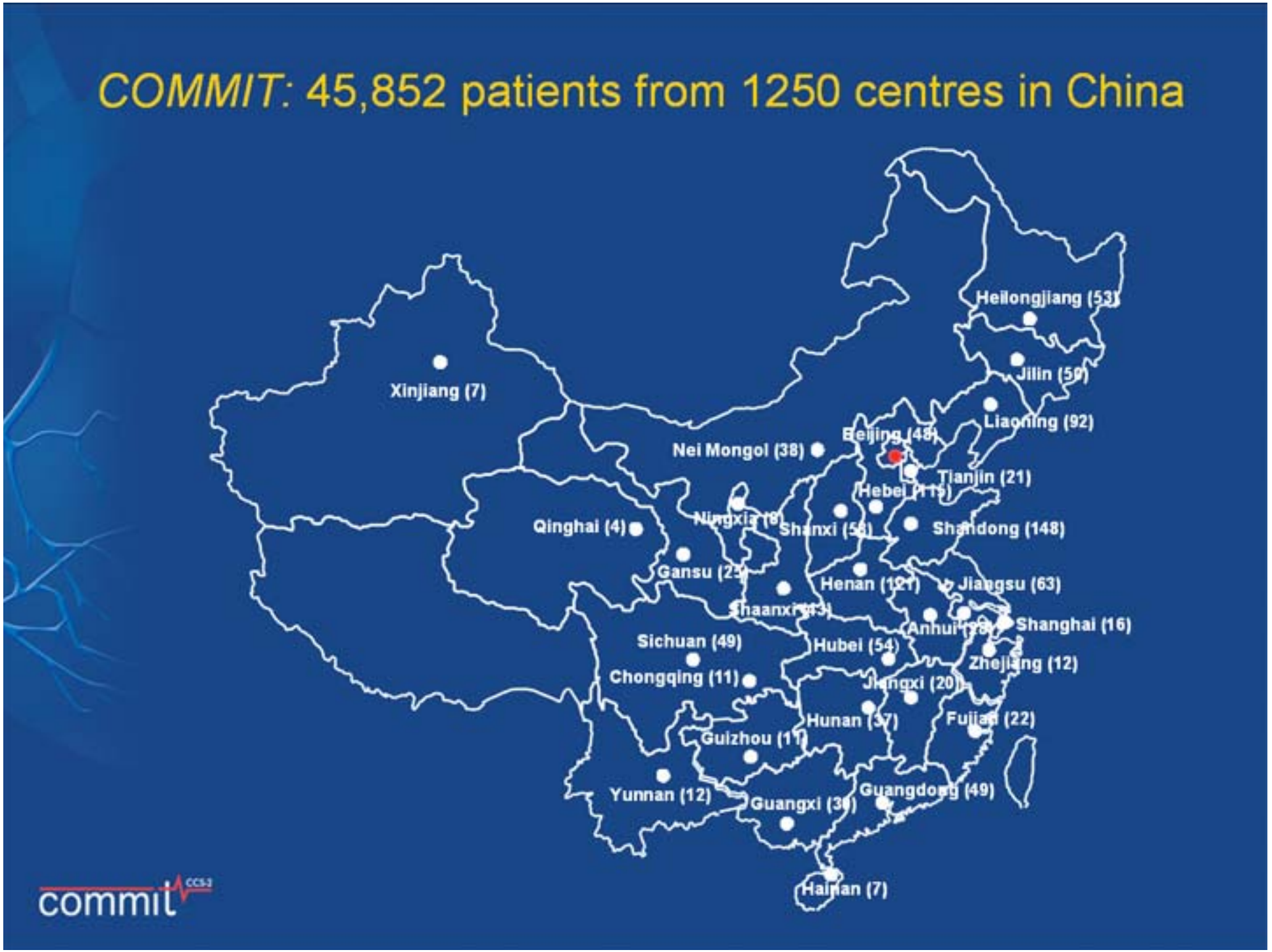
COMMIT: Objectives

(**Cl**O**O**pidogrel & **M**etoprolol in **M**yocardial **I**nfarction **T**rial)

To determine whether adding 75 mg clopidogrel to ASA (and early i.v. then oral metoprolol) can produce a further reduction in mortality and major vascular events in hospital for patients admitted with acute MI

commit CCS-2

COMMIT: 45,852 patients from 1250 centres in China



commit CCS-3

COMMIT: Randomisation by centrally pre-packed drug packs

commit CCS-2

COMMIT: Study medication for the combined anti-platelet agents

- 75 mg clopidogrel or placebo + 162 mg aspirin once daily, to be given immediately after entry
- Trial tablets continue for up to 4 weeks (or until discharge or death)
- But, no loading dose was used

commit CCS-2

COMMIT: Study design

TREATMENT:	Clopidogrel 75 mg daily vs placebo (aspirin 162mg daily in both groups)
INCLUSION:	Suspected acute MI (ST change or LBBB) within 24 h of symptom onset
EXCLUSION:	Primary PCI or high-risk of bleeding
1° OUTCOMES:	Death & death, re-MI or stroke up to 4 weeks in hospital (or prior discharge)

Mean treatment duration in survivors: 15 days

commit CCS-3

COMMIT: Baseline characteristics

Characteristic	Clopidogrel (22,961)	Placebo (22,891)
Age 70+ y	26.0%	26.0%
Female	27.7%	27.9%
Time delay <6 h	33.7%	33.7%
STEMI/LBBB	93.1%	93.1%
Killip class II/III	24.6%	24.5%
Fibrinolytic:		
All patients	49.7%	49.7%
STEMI <12h	67.8%	67.7%

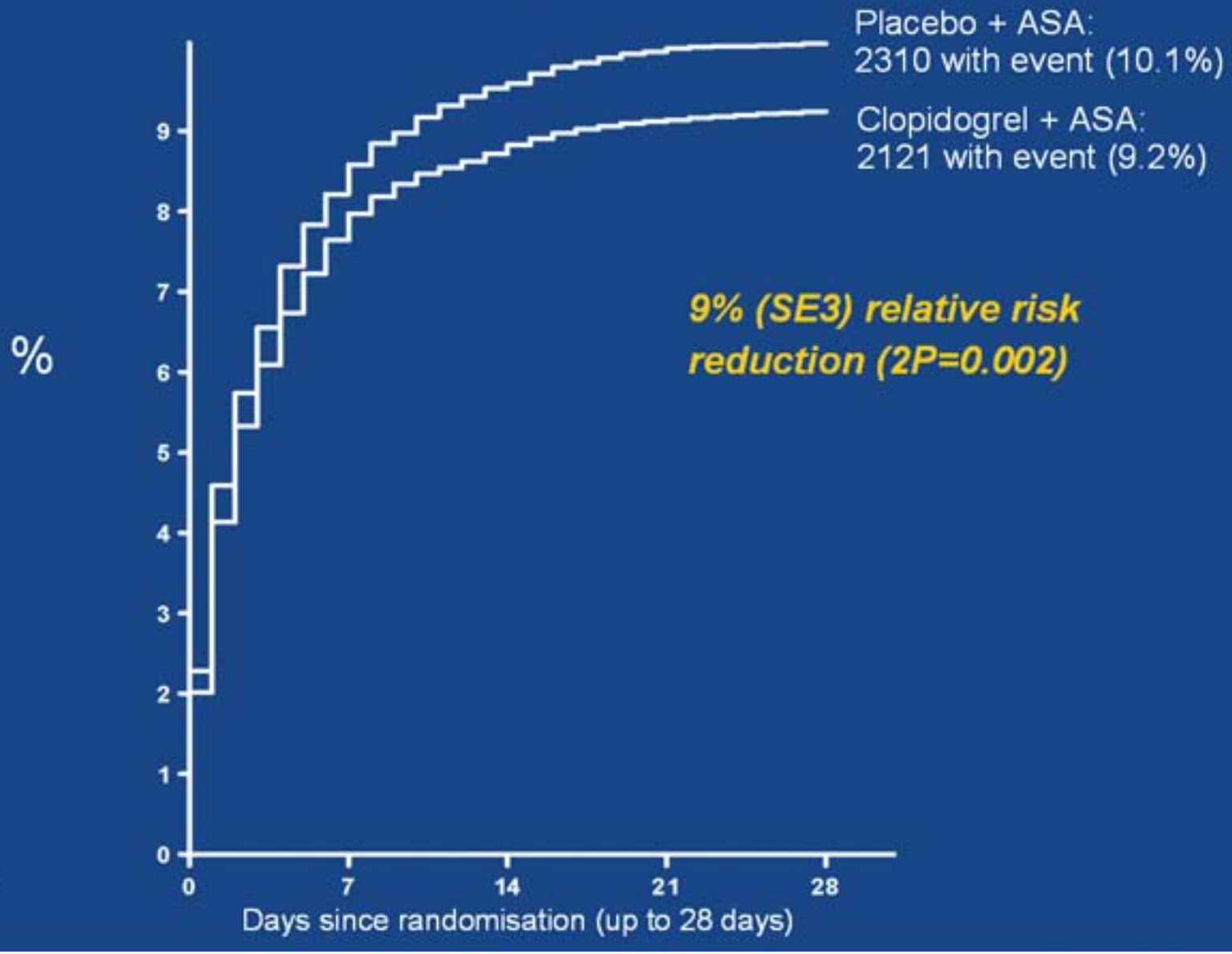
commit CCS-3

COMMIT: Concomitant therapy

Therapy	Clopidogrel (22,961)	Placebo (22,891)
Anticoagulant	74.1%	75.0%
ACE inhibitor	68.2%	68.3%
Antiarrhythmic	22.4%	22.2%
Nitrate (iv or oral)	94.1%	94.3%
Diuretic	23.3%	23.3%
Calcium antagonist	11.8%	11.8%

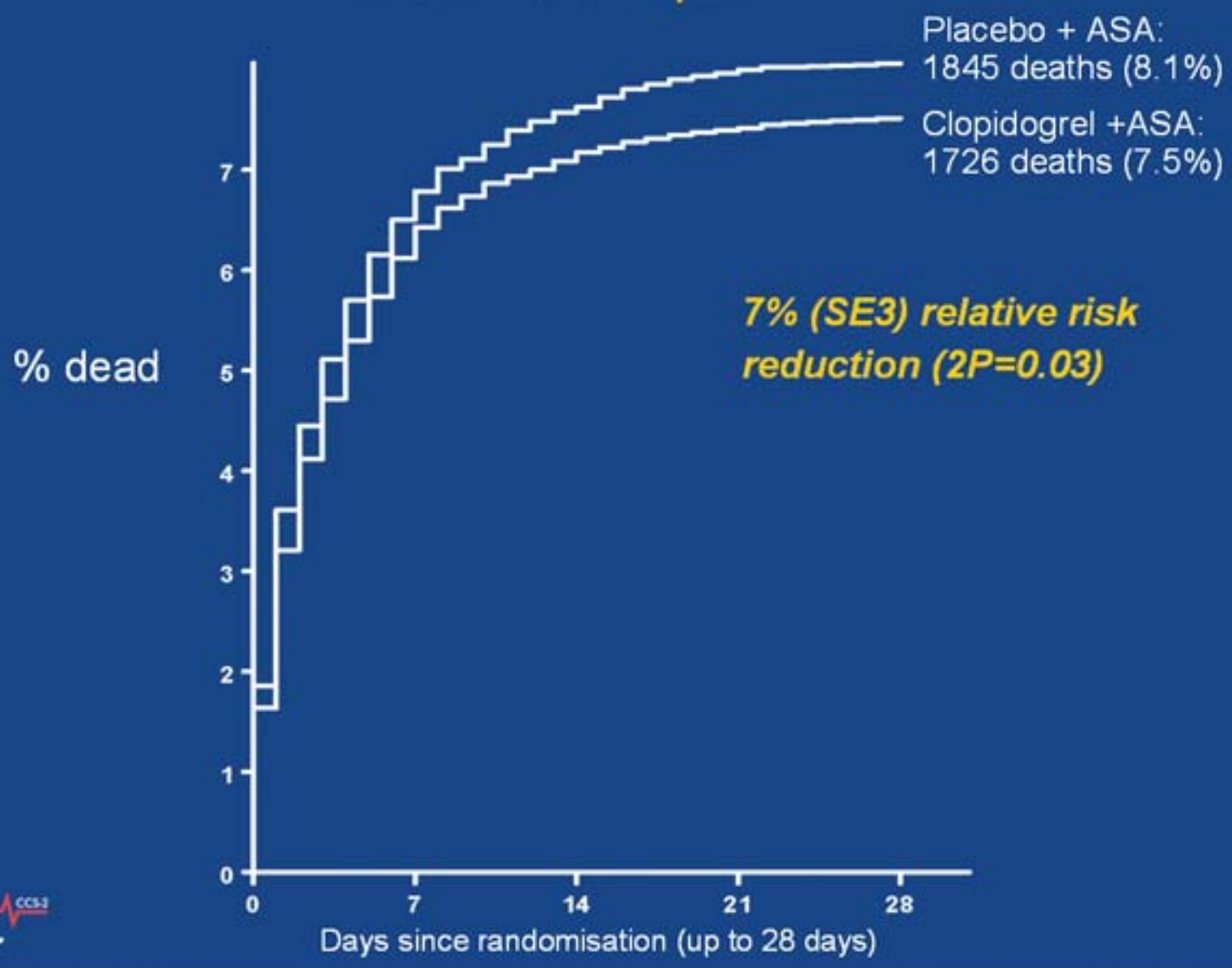
commit CCS-2

COMMIT: Effects of CLOPIDOGREL on Death, Re-MI or Stroke



commit CCS-2

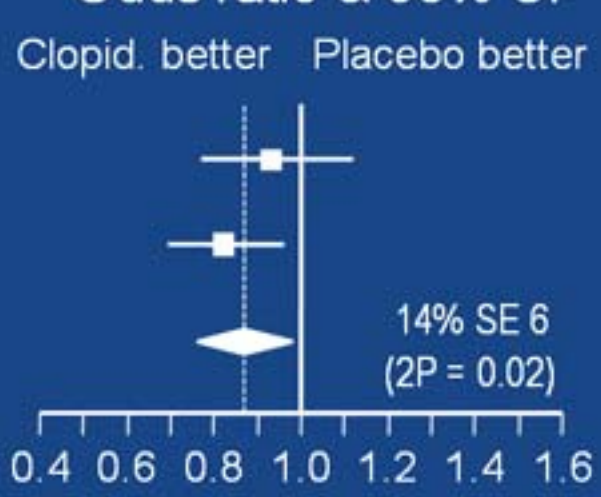
COMMIT: Effect of CLOPIDOGREL on Death in hospital



commit CCS-2

COMMIT: Effects of CLOPIDOGREL on Reinfarction

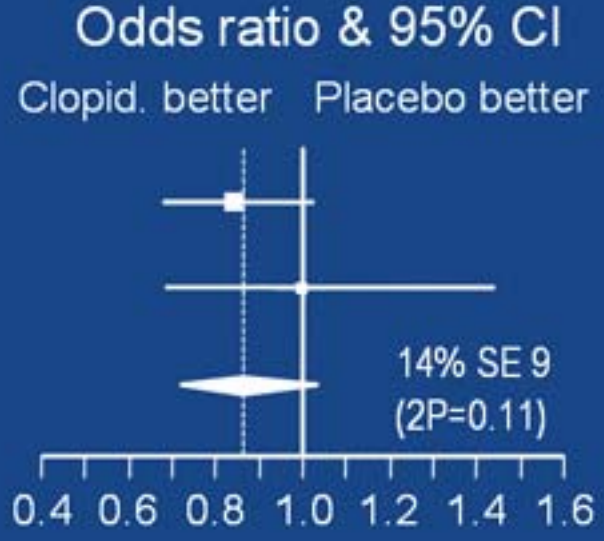
Outcome after Re-MI	Clopidogrel (22,961)	Placebo (22,891)
Died	209 (0.9%)	223 (1.0%)
Survived	270 (1.2%)	330 (1.4%)
ALL COMBINED	479 (2.1%)	553 (2.4%)



commit CCS-3

COMMIT: Effects of CLOPIDOGREL on any Stroke

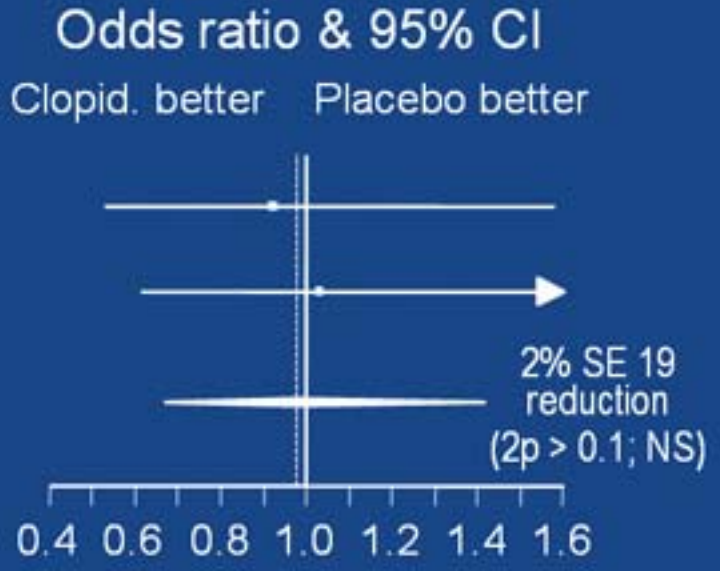
Types	Clopidogrel (22,961)	Placebo (22,891)
Ischaemic	164 (0.7%)	194 (0.8%)
Haemorrhagic	55 (0.2%)	56 (0.2%)
ALL COMBINED	217 (0.9%)	250 (1.1%)



commit ccs-2

COMMIT: Effects of CLOPIDOGREL on Haemorrhagic Stroke

Diagnostic criteria	Clopidogrel (22,961)	Placebo (22,891)
CT/MRI	25 (0.1%)	27 (0.1%)
Clinical	30 (0.1%)	29 (0.1%)
ALL COMBINED	55 (0.2%)	56 (0.2%)



commit CCS-2

COMMIT: Major bleed in hospital

Type	Clopidogrel (22,961)	Placebo (22,891)
Cerebral	**55**	**56**
Fatal	*39*	*41*
Non-fatal	*16*	*15*
Non-cerebral	**82**	**73**
Fatal	*36*	*37*
Non-fatal	*46*	*36*
Any	134 (0.58%)	125 (0.55%)

commit CCS-2

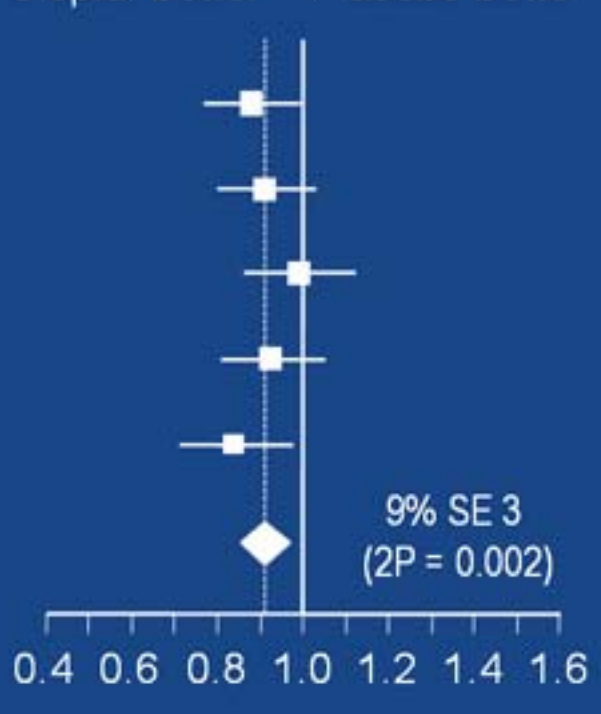
COMMIT: Major bleed by age & lytic use

Age & lytic use	Clopidogrel (22,961)	Placebo (22,891)
Age (years)		
<60	33 (0.3%)	36 (0.4%)
60-	51 (0.7%)	46 (0.6%)
70+	50 (0.8%)	43 (0.7%)
Lytic use		
Yes	74 (0.6%)	72 (0.6%)
No	60 (0.5%)	53 (0.5%
Any	134 (0.6%)	125 (0.5%)

commit CCS-2

COMMIT: Effects of CLOPIDOGREL on Death, Re-MI or Stroke by days of event

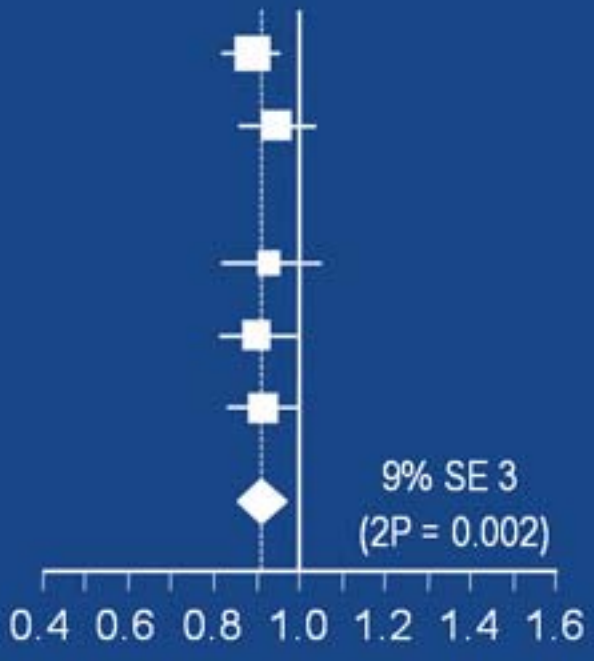
Days of event	Clopidogrel (22,961)	Placebo (22,891)
0	463 (2.0%)	524 (2.3%)
1	482 (2.1%)	525 (2.3%)
2-3	450 (2.0%)	451 (2.0%)
4-7	432 (1.9%)	463 (2.0%)
8-28	294 (1.3%)	347 (1.5%)
ALL PATIENTS	2121 (9.2%)	2310 (10.1%)



commit CCS-2

COMMIT: Effects of CLOPIDOGREL on Death, Re-MI or Stroke by sex and age

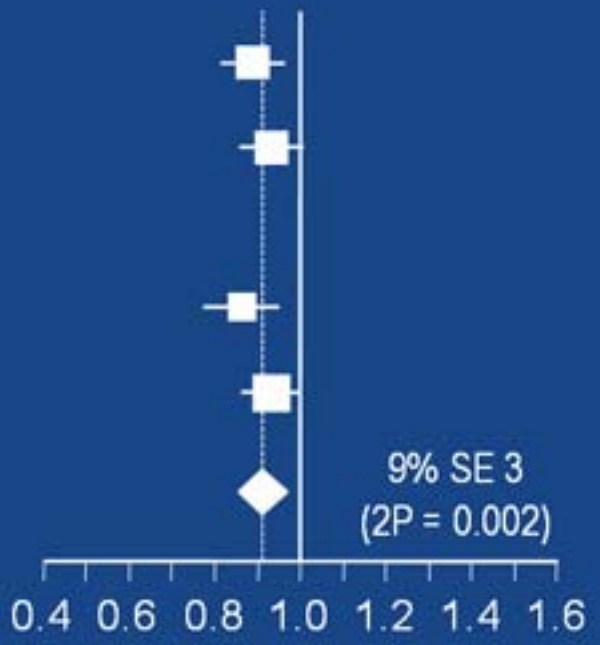
Baseline features	Clopidogrel (22,961)	Placebo (22,891)
Sex		
Male	1274 (7.7%)	1416 (8.6%)
Female	847 (13.3%)	894 (14.0%)
Age (years)		
<60	485 (5.0%)	512 (5.4%)
60-69	745 (10.1%)	835 (11.2%)
70+	891 (14.9%)	963 (16.2%)
ALL PATIENTS	2121 (9.2%)	2310 (10.1%)



commit CCS-3

COMMIT: Effects of CLOPIDOGREL on Death, Re-MI or Stroke by lytic use

Baseline features	Clopidogrel (22,961)	Placebo (22,891)
Lytic given		
Yes	1003 (8.8%)	1122 (9.9%)
No	1118 (9.7%)	1188 (10.3%)
CLARITY criteria*		
Yes	673 (8.4%)	785 (9.6%)
No	1448 (9.7%)	1525 (10.3%)
ALL PATIENTS	2121 (9.2%)	2310 (10.1%)



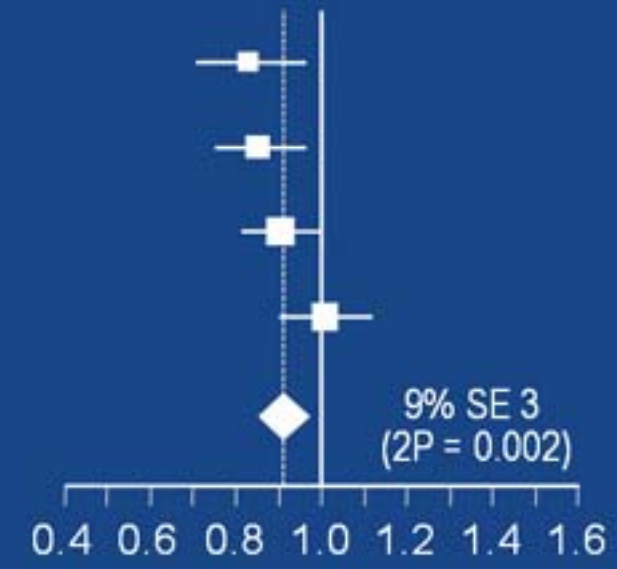
** age≤75, having ST↑, <12 h & lytic use*

commit CCS-3

COMMIT: Effects of CLOPIDOGREL on Death, Re-MI or Stroke by time delay

Hours from onset	Clopidogrel (22,961)	Placebo (22,891)
0-3	298 (8.4%)	361 (10.0%)
4-6	478 (9.9%)	542 (11.5%)
7-12	671 (9.7%)	735 (10.6%)
13-24	674 (8.8%)	672 (8.8%)
ALL PATIENTS	2121 (9.2%)	2310 (10.1%)

p=0.02 for trend

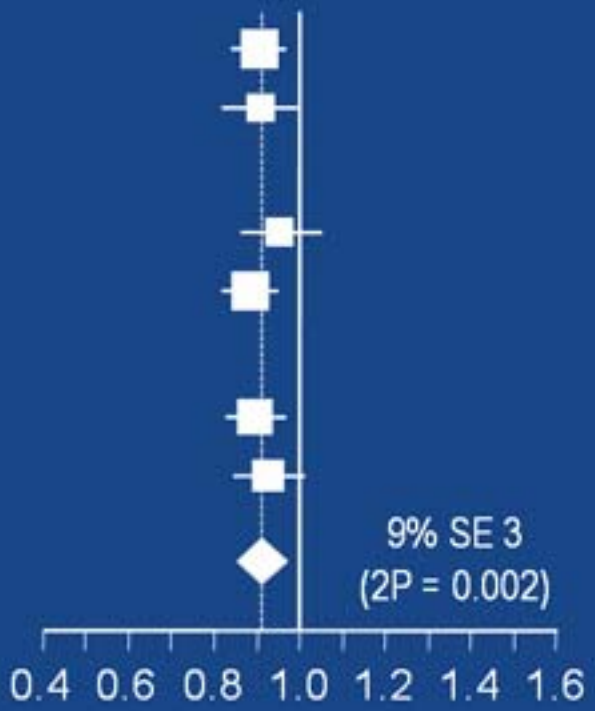


One of many subgroup results & not consistent with ISIS-2

commit CCS-2

COMMIT: Effects of CLOPIDOGREL on Death, Re-MI or Stroke by other therapy

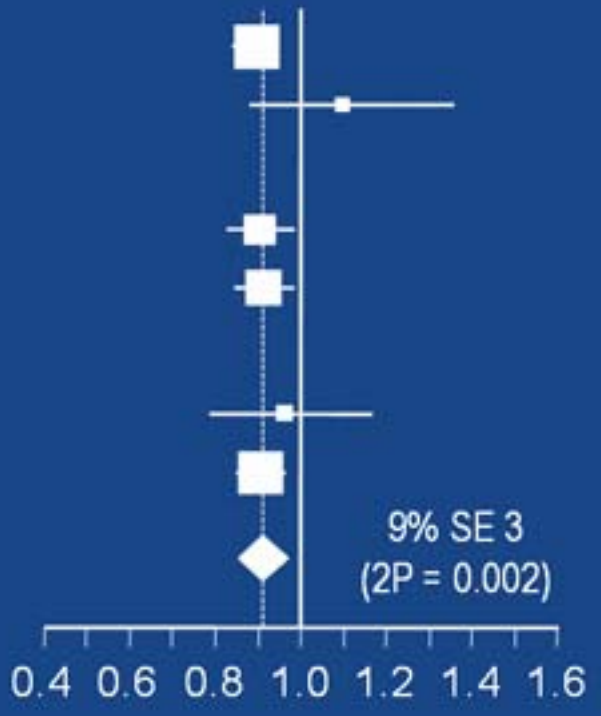
Concomitant therapy	Clopidogrel (22,961)	Placebo (22,891)
Anticoagulants		
Yes	1385 (8.1%)	1535 (8.9%)
No	736 (12.4%)	775 (13.5%)
Antiarrhythmic		
Yes	779 (15.1%)	804 (15.8%)
No	1342 (7.5%)	1506 (8.5%)
ACE inhibitors		
Yes	1151 (7.4%)	1279 (8.2%)
No	970 (13.3%)	1031 (14.2%)
ALL PATIENTS	**2121 (9.2%)**	**2310 (10.1%)**



commit CCS-2

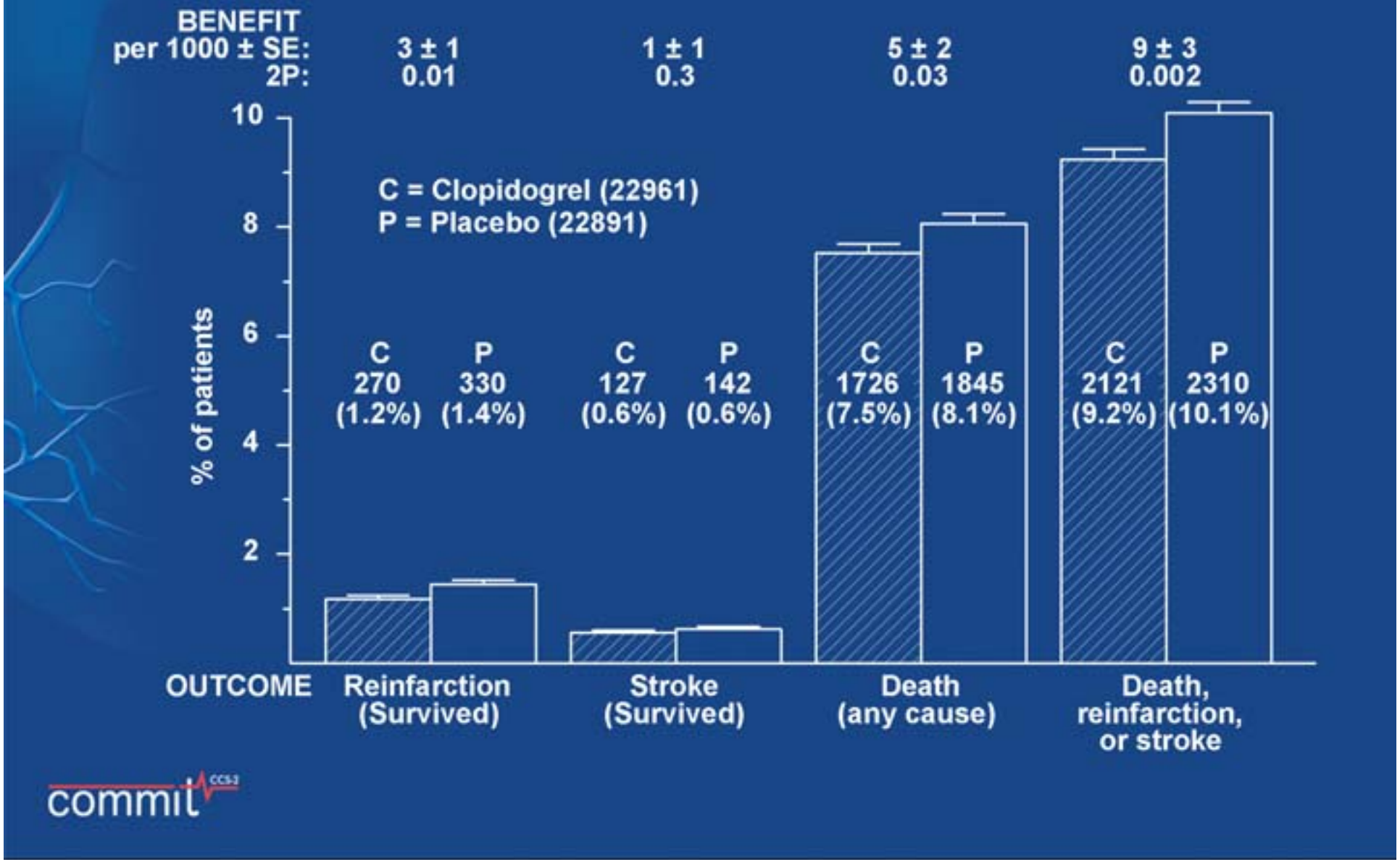
COMMIT: Effects of CLOPIDOGREL on Death, Re-MI or Stroke by other therapy

Concomitant therapy	Clopidogrel (22,961)	Placebo (22,891)
Nitrates		
Yes	1943 (9.0%)	2152 (10.0%)
No	178 (13.2%)	158 (12.1%)
Diuretics		
Yes	901 (16.9%)	987 (18.5%)
No	1220 (6.9%)	1323 (7.5%)
Ca++ antagonists		
Yes	197 (7.3%)	205 (7.6%)
No	1924 (9.5%)	2105 (10.4%)
ALL PATIENTS	**2121 (9.2%)**	**2310 (10.1%)**



commit CCS-3

COMMIT: Absolute effects of CLOPIDOGREL



commit CCS-2

From ISIS-2 to COMMIT: Effects of aspirin and clopidogrel on Death, Re-MI or Stroke

ISIS-2:	Placebo	14%	
		↓	~40 per 1000
	ASA	10%	
COMMIT:	ASA	10%	
		↓	~10 per 1000
	ASA + Clop.	9%	

ASA + Clopidogrel vs nil: ~50 per 1000 treated

commit CCS-2

COMMIT: Conclusions

- Adding 75 mg daily CLOPIDOGREL to aspirin in acute MI prevents ~10 major vascular events per 1000 treated
- No excess of cerebral, fatal or transfused bleeds (even with fibrinolytic therapy and in older people)
- Treating one million MI patients for ~2 weeks would avoid 5000 deaths and 5000 non-fatal events

Clopidogrel should be considered routinely in acute MI, perhaps starting with a loading dose of 300 mg

commit CCS-3