The management of unstable angina and acute coronary syndrome

Acute Coronary Syndromes

- Unstable angina
- Non-Q-wave myocardial infarction
- Acute myocardial infarction
- Sudden cardiac death

Initial Assessment of Patients with Suspected Unstable Angina or Non-Q-wave MI

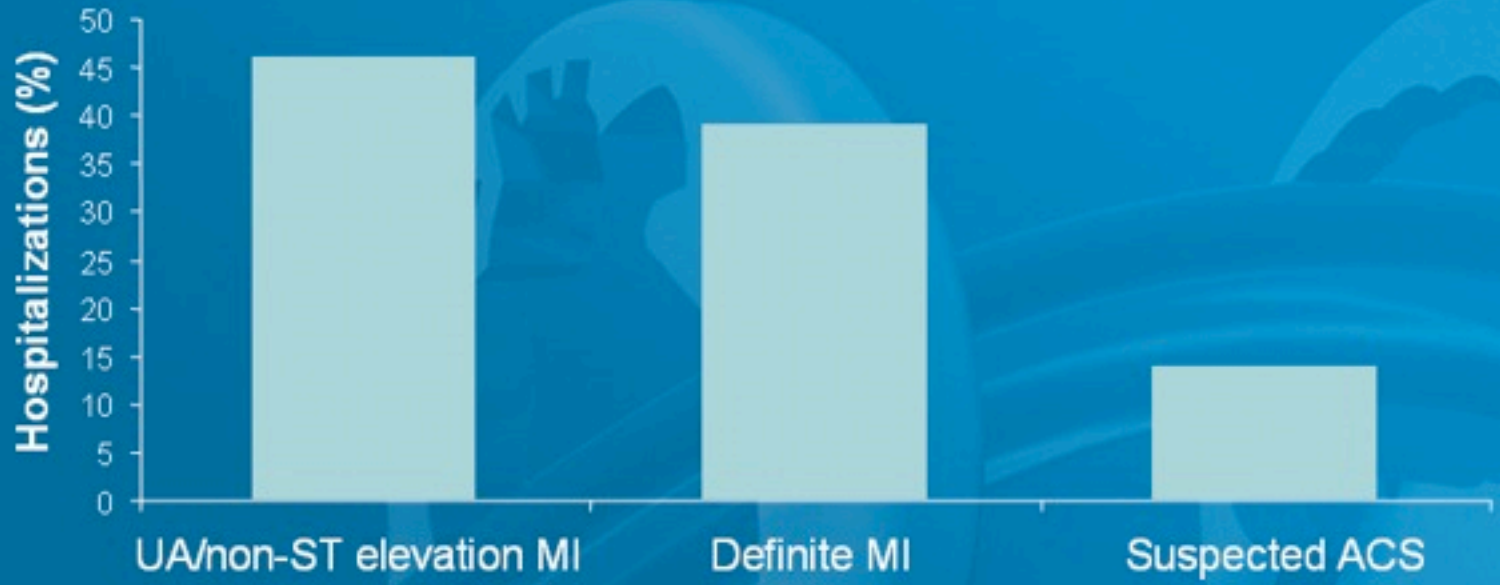
- Physical examination
  - chest examination
  - auscultation
  - heart rate/blood pressure
- 12-lead ECG
- Continuous ST-segment monitoring if available
- Troponin-I or -T measured on admission and at 6–12 hours
- CK and/or CK-MB
  - patients with recent symptoms
  - patients with post-MI angina

Diagnostic Criteria for Unstable Angina and Non-Q-wave MI

- Typical ischaemic cardiac pain
  - prolonged anginal pain at rest (80% of patients)
  - new-onset severe angina
  - increasing severity of previously stable angina
- ECG showing ST-segment and/or T-wave changes
  - ST depression >1 mm in 2 or more leads
  - T-wave inversion
- Elevated levels of biochemical markers
  - CK
  - CK-MB
  - troponin-I or -T

European Survey of Acute Coronary Syndromes: the ENACT Study[1]

Patient records from 3,092 ACS patients in the EU* (1999)



- Ratio of unstable angina (UA) to MI was 1.2:1.0 overall and was similar in all European countries
- In patients with diagnosis of UA on admission, 9% evolved to definite MI despite current treatment

*17 Western European countries

1. Fox KA *et al. Eur Heart J* 2000; 21: 1440–9.

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The Role of Antiplatelet Therapy in Unstable Angina and NSTEMI

- Atherothrombosis is a generalised disease affecting the coronary, cerebral and peripheral circulations
- Unstable angina/NSTEMI is one of the classic examples of the progression of atherothrombotic disease
- Platelets play a key role in thrombus formation associated with rupture of an unstable atherosclerotic plaque
- Angiographic findings show that unstable angina is due to the formation of a platelet-rich thrombus
- Consequently, antiplatelet therapy is recognised as the foundation of long-term management

Théroux P et al *Circulation* 1998; 97:1195–1206

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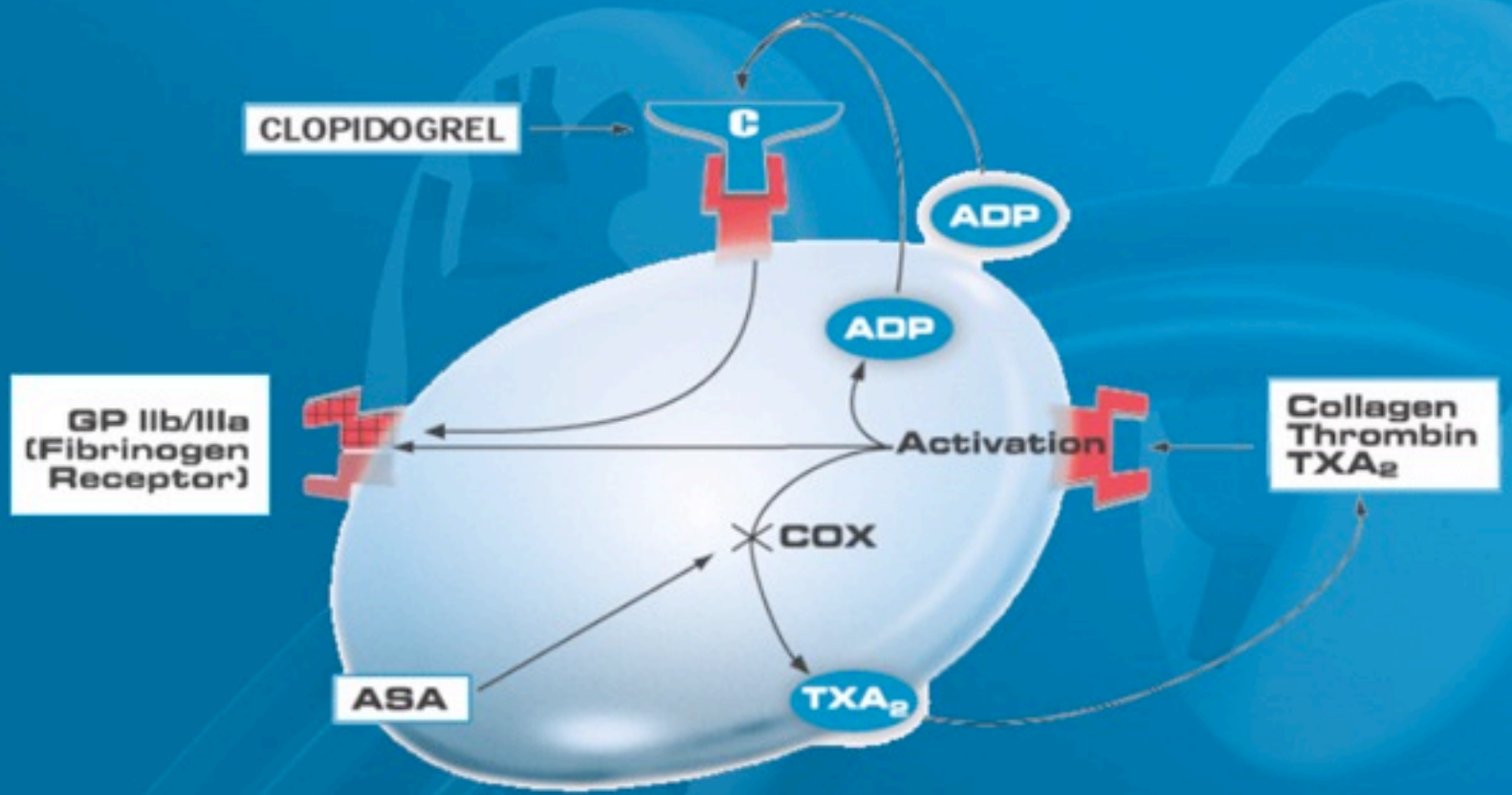
Complementary Mode of Action between Clopidogrel and ASA



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

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

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CURE – Objectives

- Primary
  - evaluate the efficacy of clopidogrel compared with placebo in preventing ischemic complications in patients with unstable angina or non-Q-wave MI receiving standard therapy (including ASA)
- Secondary
  - evaluate safety of clopidogrel in these patients

CURE – Endpoints

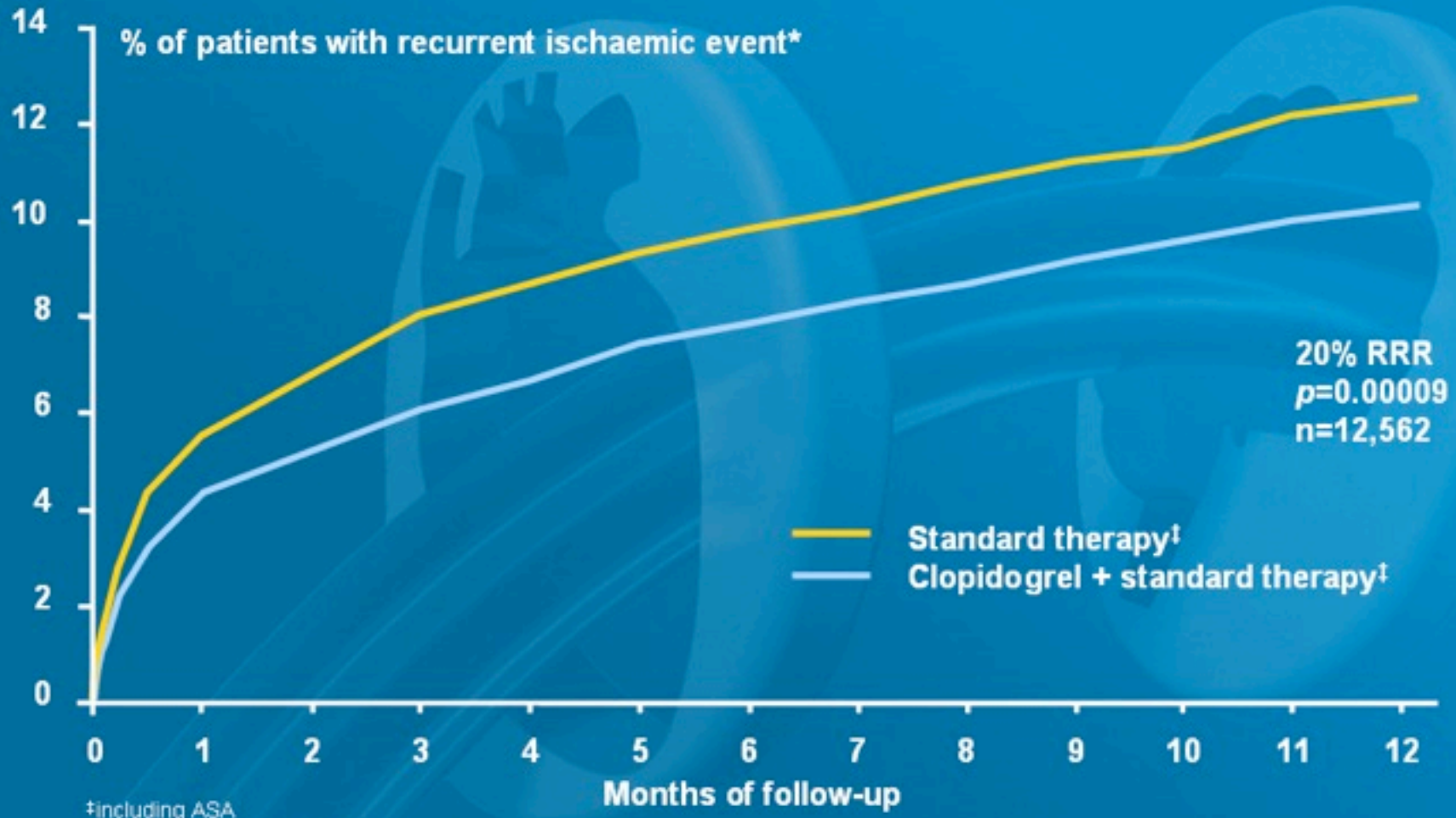
Primary endpoint

- First occurrence of any component of the cluster of:
  - cardiovascular death
  - myocardial infarction
  - stroke (ischaemic, haemorrhagic, or of uncertain type)

Second primary endpoint

- First occurrence of any component of the cluster of:
  - cardiovascular death
  - myocardial infarction
  - stroke (ischaemic, haemorrhagic, or of uncertain type)
  - refractory ischaemia

CURE – Main Efficacy Results
Primary endpoint (1)



‡including ASA

*cardiovascular death, MI, or stroke

The CURE Investigators. *N Eng J Med* August 2001

Data on file

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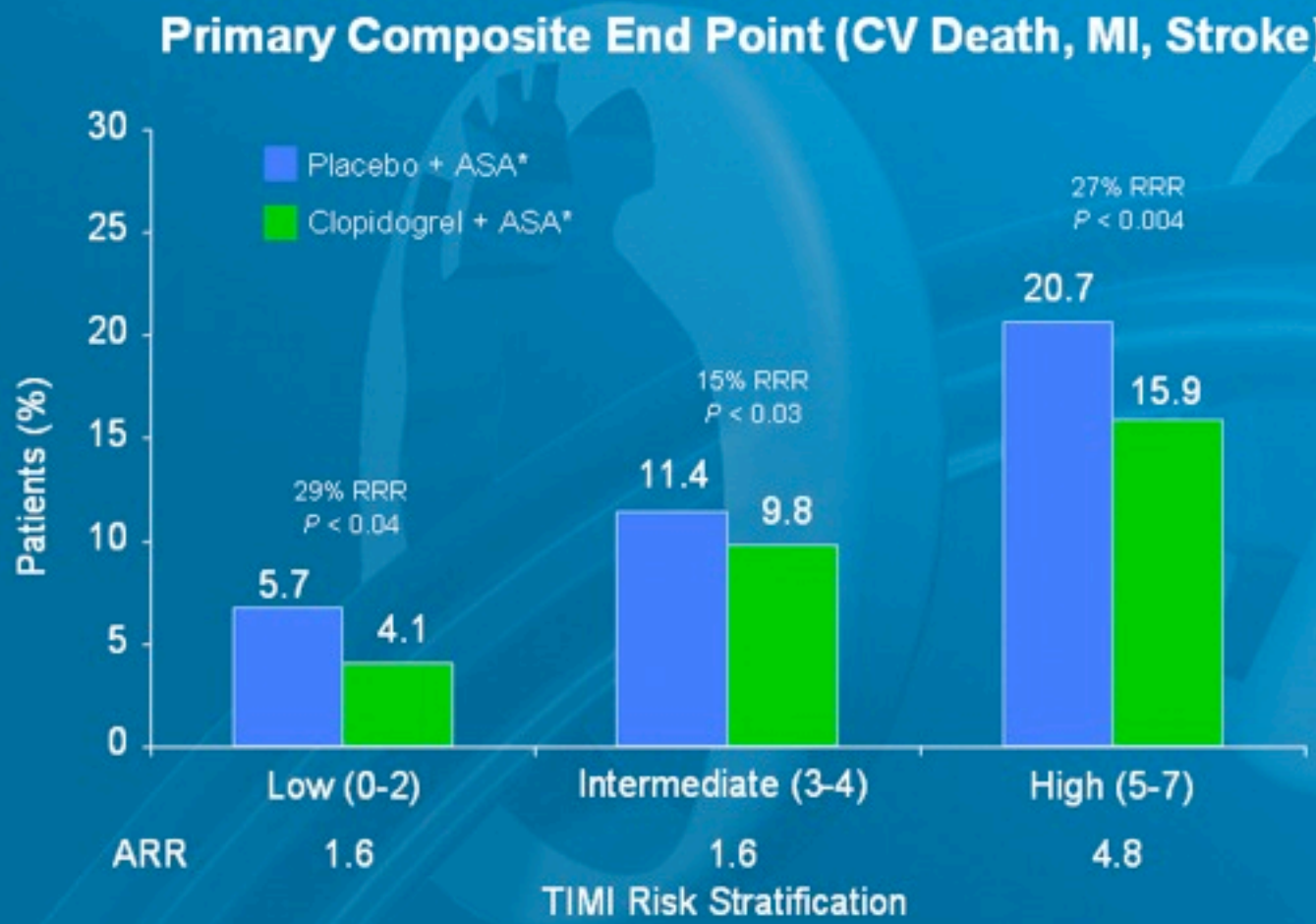
Rates of Primary Outcome in the Clopidogrel and Placebo Group According to TIMI Risk Stratification



*In addition to other standard therapies.

Budaj A, et al, for The CURE Trial Investigators. *Circulation*. 2002;106:1622-1626.

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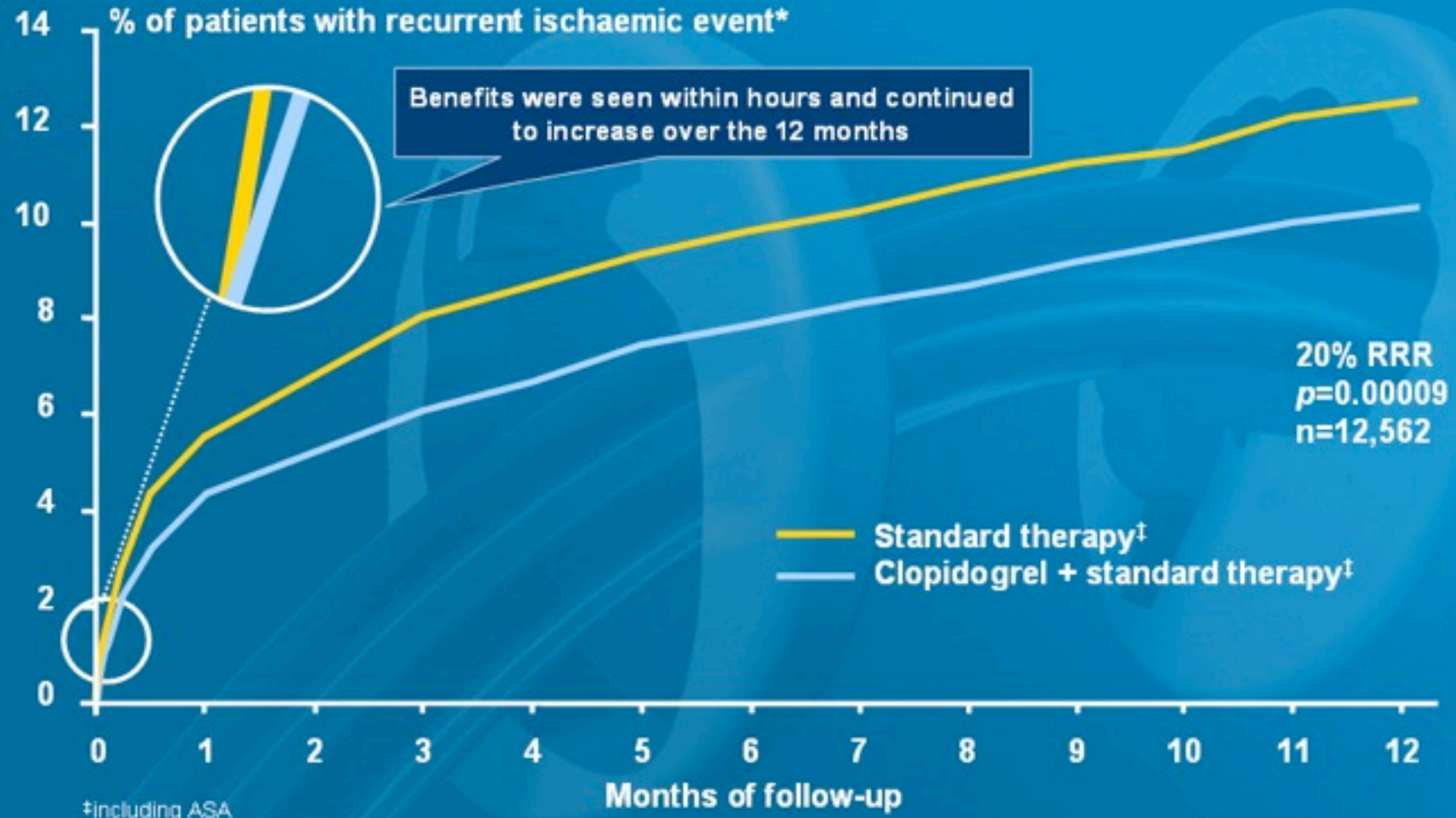
CURE – Main Efficacy Results
Primary endpoint (2)



‡including ASA

*cardiovascular death, MI, or stroke

The CURE Investigators. *N Eng J Med* August 2001

Data on file

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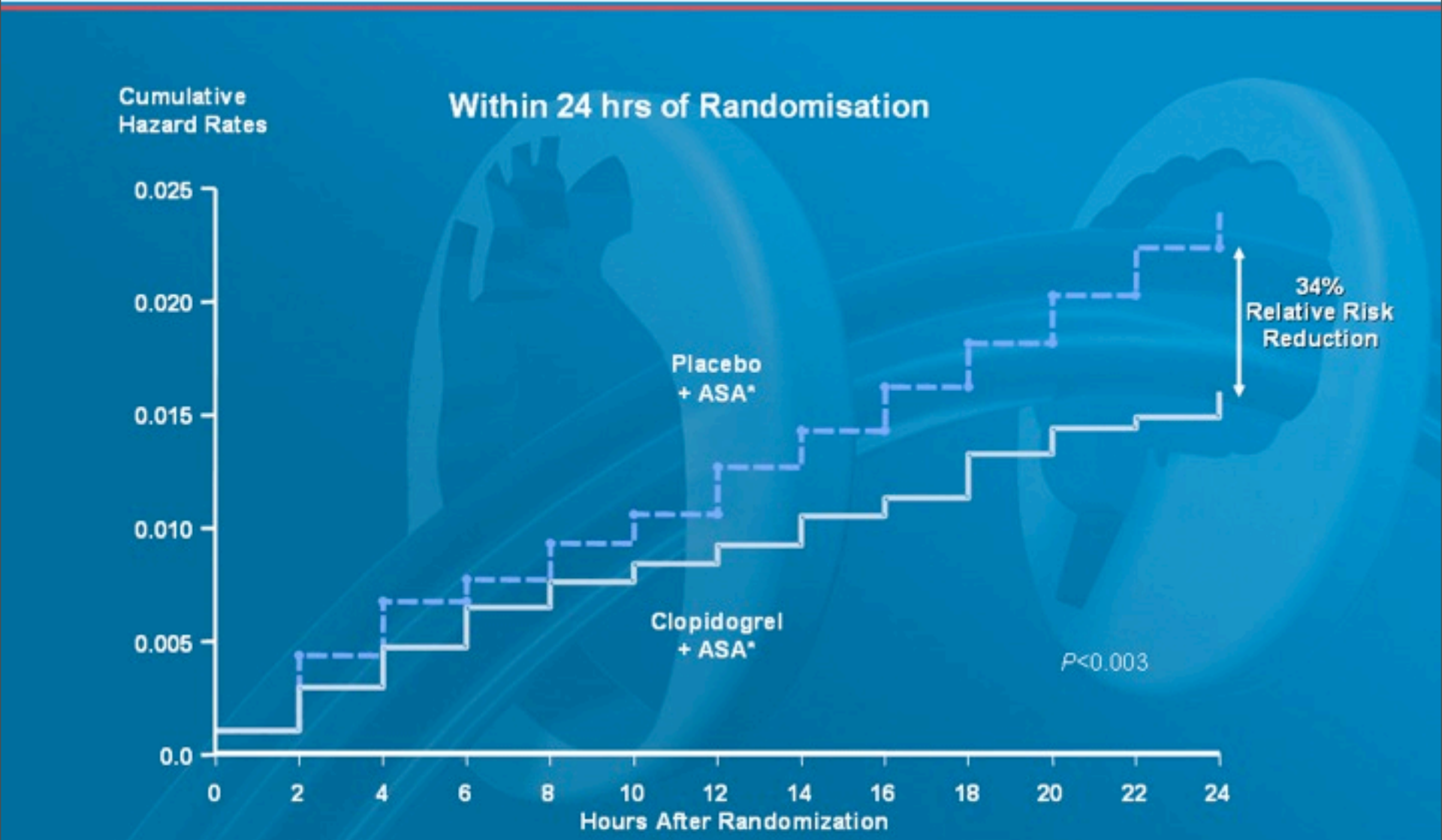
MI/Stroke/CV Death/Severe Ischaemia



* In addition to other standard therapies.

Yusuf, S et al for The CURE Trial Investigators. *Circulation.* 2003;107:966-972

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CURE – Main Efficacy Results
Primary endpoint (3)

	Clopidogrel + standard therapy‡ (n=6259) (%)	Standard therapy alone‡ (n=6303) (%)	RR	CI
Primary endpoint†	9.3	11.4	0.80	0.72–0.90*
CV death	5.1	5.5		
MI	5.2	6.7		
Strokes	1.2	1.4		

*p=0.00009

†CV death, MI, stroke

‡including ASA

The CURE Investigators. *N Eng J Med* August 2001
Data on file

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CURE – Safety
Bleeding definitions

- Bleeding was defined as "Major" and "Minor"
- Major bleeding was defined as follows:
  - life threatening: fatal, symptomatic intracranial haemorrhage, leading to a drop in haemoglobin of at least 5 g/dl, leading to the use of IV inotropes, requiring surgical intervention, or requiring transfusion of 4 or more units of blood
  - non-life-threatening: substantially disabling, intraocular bleeding leading to vision loss, or requiring at least 2 units of blood
- Minor
  - any other bleeds that led to interruption of study medication

The CURE Investigators. *N Eng J Med* August 2001

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CURE – Safety
Bleeding complications

	Clopidogrel + standard therapy including ASA (%)	Standard therapy alone including ASA (%)
Major	3.7	2.7*
life-threatening	2.2	1.8 ***(NS)***
non-life-threatening	1.5	0.9**
Transfusion	2.8	2.2***

The CURE Investigators. *N Eng J Med* August 2001
Data on file

*p=0.001; **p=0.002; ***p=0.02

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CURE – Conclusions

- In the CURE study of more than 12,500 unstable angina and NSTEMI patients:
  - clopidogrel demonstrated a 20% relative risk reduction in ischaemic events* with long-term use† (p=0.00009)
  - the Kaplan-Meier curves began to diverge within hours and continued to diverge over the course of 12 months
- Clopidogrel on top of standard therapy (including ASA) demonstrates an early effect (within hours) and sustained long-term benefit throughout the entire study period of 12 months

†up to 12 months
*cardiovascular death, MI and stroke
The CURE Investigators. *N Eng J Med* August 2001
Data on file

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NHS England and Wales NICE recommendations

NICE (National Institute for Clinical Excellence) has recently published its recommendations endorsing PLAVIX in ACS patients[1].

NICE guidance for ACS – www.nice.org.uk

Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome

Clopidogrel, in combination with low-dose asprin, is recommended for use in the management of non-ST-segment-elevation acute coronary syndrome (ACS) in people who are at moderate to high risk of myocardial infarction (MI) or death.

NHS England and Wales NICE recommendations

It is recommended that treatment with clopidogrel in combination with low-dose asprin should be continued for up to 12 months after the most recent acute episode of non-ST-segment-elevation ACS (as defined below). Thereafter, standard care, including treatment with low-dose aspirin alone, is recommended.

NHS England and Wales NICE recommendations

For the purposes of this guidance, moderate to high risk of MI or death in people presenting with non-ST-segment-elevation ACS can be determined by clinical signs and symptoms, accompanied by one or both of the following:

- The results of clinical investigations, such as new ECG changes (other than persistent ST-segment-elevation), indicating ongoing mycordial ischaemia, particularly dynamic or unstable patterns.
- The presence of raised blood levels of markers of cardiac cell damage such as troponin.

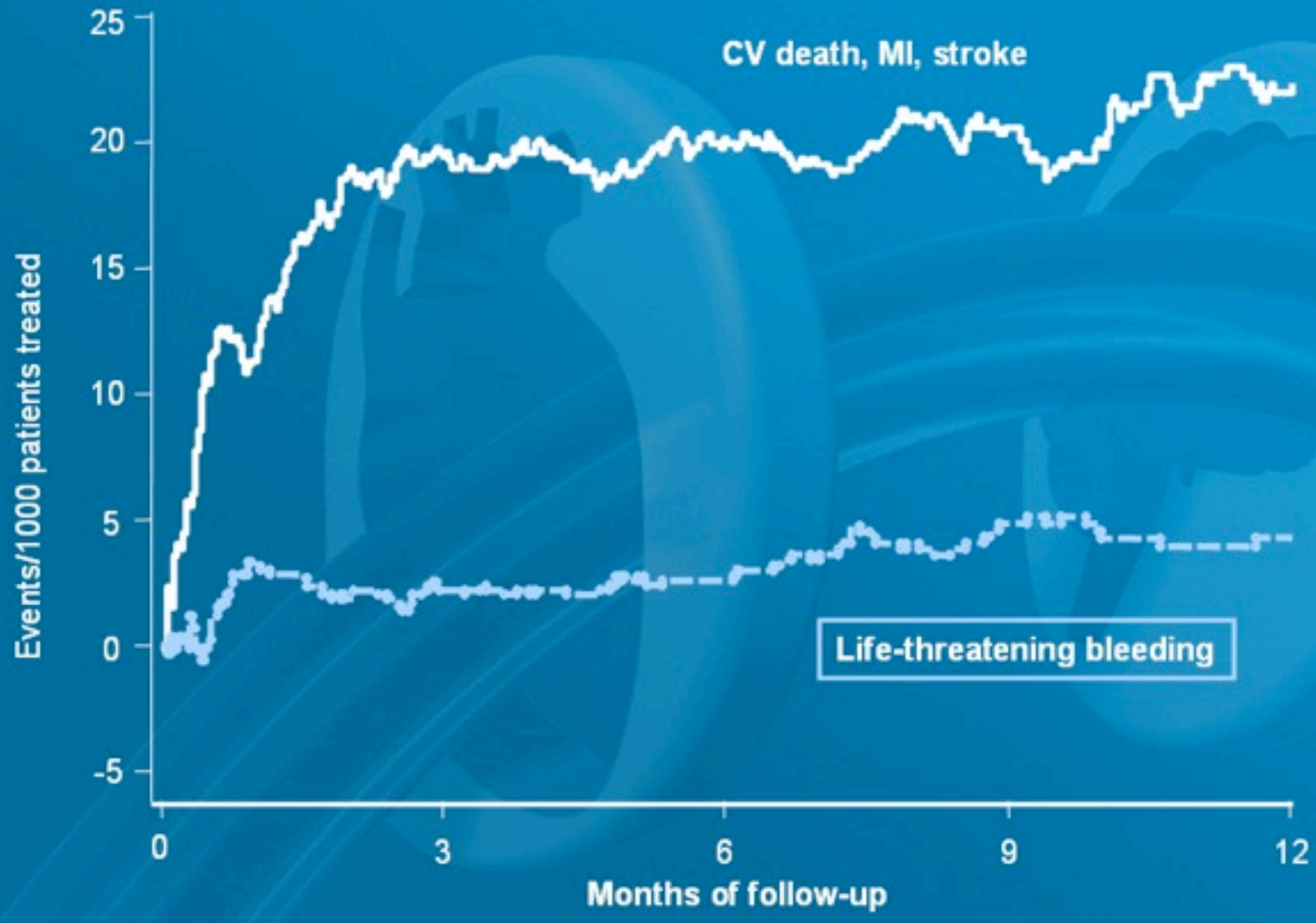
PRAIS-UK (Prospective Registry of Acute Ischaemic Syndromes in the UK)[3]

- Findings from PRAIS-UK showed that ACS patients without
- ST-elevation are at long-term risk of mortality. (The death rates for patients with ACS at 12, 24, 36 and 44 months after the qualifying event were 8.8%, 13.9%, 19.3% and 20.6% respectively).[3]

- This demonstrates a clear and consistent risk of subsequent events over time and the study concludes startegies to reduce this long-term risk are needed.[3]

CURE Post hoc analysis

Events Prevented vs Life-threatening Bleeding Over Time
Net Clinical Benefit of Clopidogrel + ASA*



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