
بسم الله الرحمن الرحيم

Antiplatelet Resistance: A New Therapeutic Dilemma

By

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Introduction

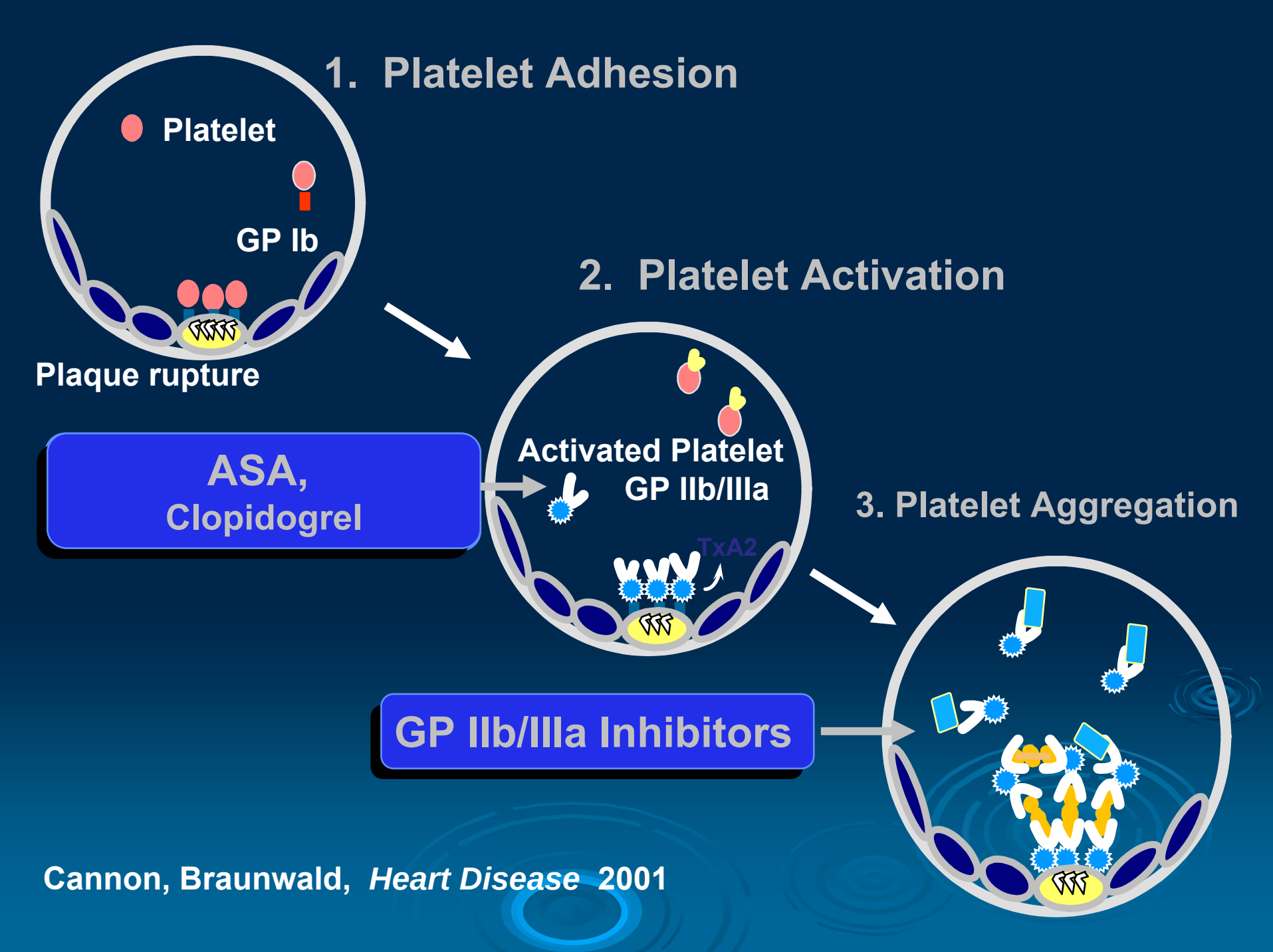
- Bayer Co patented acetyl-salicylic acid in 1899 under the trade name of aspirin (“a” stood for acetyl and “spir” stood for spirasaure, the German word for salicylic acid).
- Aspirin was used initially as an analgesic and an antipyretic; however its effects on haemostasis were recognized as early as 1945.
- The antithrombotic action of aspirin depends on the irreversible inhibition of arachidonate cyclo-oxygenase activity in platelets

Introduction

- Antiplatelet therapy is a cornerstone of cardiovascular medicine. Aspirin and clopidogrel have emerged as critical therapies in the treatment of cardiovascular disease
- Millions of patients are currently on low-dose antiplatelet therapy but it is unknown how many of these patients are under-treated or on the wrong medication.
- Aspirin and clopidogrel resistance are emerging clinical entities with potentially severe consequences such as recurrent MI, stroke, or death.

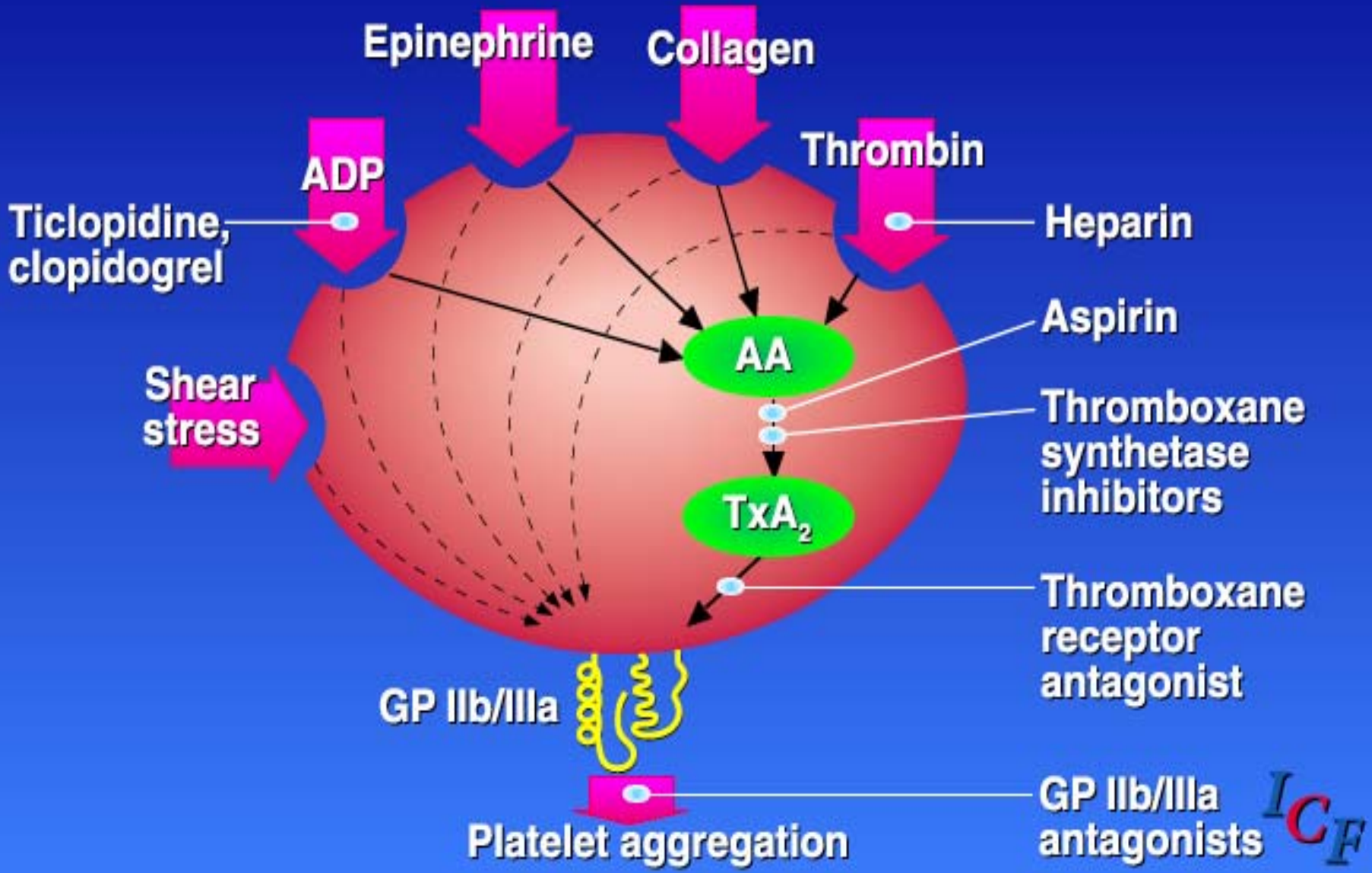
Key Questions About Antiplatelet Resistance

- Does a standardized definition exist?
- Are there is a reliable test to diagnose this phenomenon?
- What are the possible mechanism?
- Does it has any clinical implication?
- How do we can manage patients with antiplatelet resistance?



Cannon, Braunwald, *Heart Disease* 2001

Platelet Aggregation



Ideal antiplatelet

It is one that would exploit the unique metabolic features of platelets through a “hit and run” mechanism of action i. e. by permanently inactivating a platelet protein (an enzyme or receptor) that cannot be re-synthesized during a 24 h dosing interval thus limiting the extent and duration of any extra-platelet effect(s).

Two currently available antiplatelets (ASA & Clopidogril) meat this requirements

European antiplatelet guidelines 2004

Thromboxane suppression

- Thromboxane A_2
  - Potent platelet activator
  - Potent vasoconstrictor
  - Generated from arachidonic acid by the cyclo-oxygenase enzymes, COX-1 and COX-2
- Low-dose ASA blocks COX-1 in platelets, suppressing thromboxane A_2

Aspirin in Primary Prevention of IHD

*Physician Health Study**

- 22,000 healthy male physicians treated with ± 325mg ASA qod for 5 yrs
- ASA reduced 1st MI by 44% (absolute risk 0.2 vs 0.4 %/yr)
- benefit only for those age ≥ 50
- increased risk of hemorrhagic stroke and GI bleeding

Thrombosis Prevention Trial***

- only 0.23% absolute reduction

British Doctors' Trial**

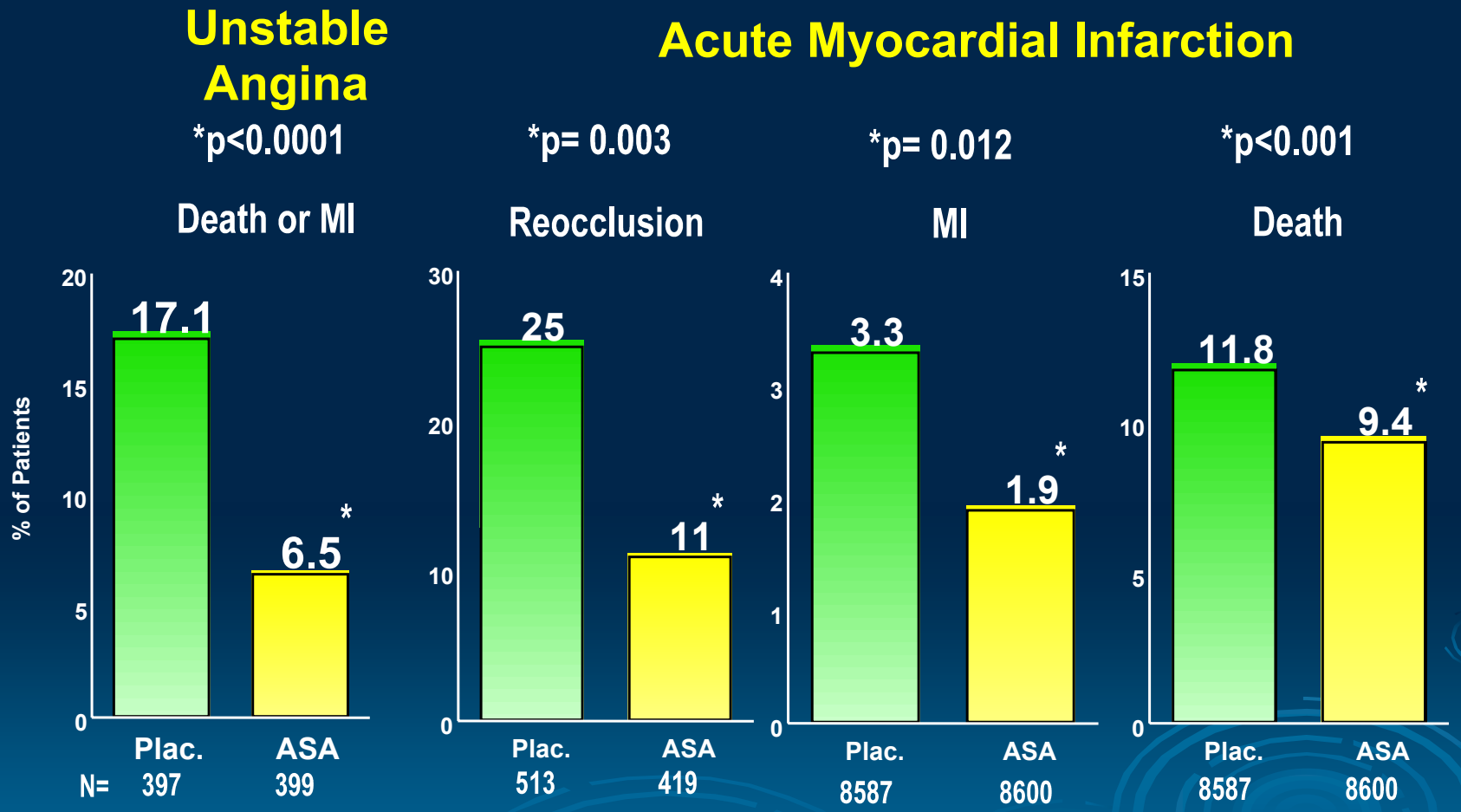
- 5139 male physicians treated with ± 500mg ASA qd for 6 yrs
- no difference in the rate of MI or cardiovascular deaths

Recommendation:

- ASA may have some modest benefit in selected high risk patients age > 45-50 years

NEJM 1989; 321:129-135. ** BMJ 198824;296:313-316. * Lancet 1998;351:233-241.*

Aspirin in Acute Coronary Syndromes



RISC Group. *Lancet* 1990;336:827-30.

Roux et al. *JACC* 1992;19:671-7.

ISIS-2. *Lancet* 1988;2:349-60.

ISIS-2. *Lancet* 1988;2:349-60.

Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients

Antithrombotic Trialists' Collaboration

Abstract

Objective To determine the effects of antiplatelet therapy among patients at high risk of occlusive vascular events.

Design Collaborative meta-analyses (systematic overviews).

Inclusion criteria Randomised trials of an antiplatelet regimen versus control or of one antiplatelet regimen versus another in high risk patients (with acute or previous vascular disease or some other predisposing condition) from which results were available before September 1997. Trials

bleeding. Aspirin was the most widely studied antiplatelet drug, with doses of 75-150 mg daily at least as effective as higher daily doses. The effects of doses lower than 75 mg daily were less certain. Clopidogrel reduced serious vascular events by 10% (4%) compared with aspirin, which was similar to the 12% (7%) reduction observed with its analogue ticlopidine. Addition of dipyridamole to aspirin produced no significant further reduction in vascular events compared with aspirin alone. Among patients at high risk of immediate coronary occlusion, short term addition of an intravenous glycoprotein IIb/IIIa antagonist to aspirin prevented a further 20 (4)

Editorial by FitzGerald

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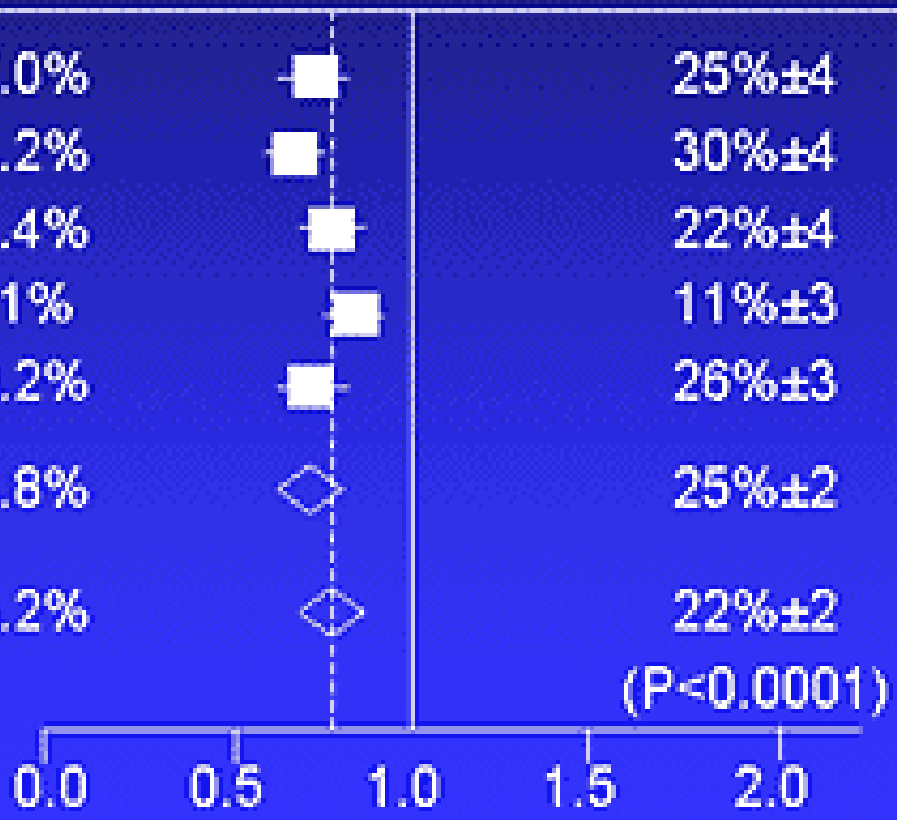
BMJ 2002;324:7

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

Antithrombotic Trialists' Collaboration: VASCULAR EVENTS

Category	APT	CTRL	Reduction
Prior MI	13.5%	17.0%	25%±4
Acute MI	10.4%	14.2%	30%±4
Prior stroke/TIA	17.8%	21.4%	22%±4
Acute stroke	8.2%	9.1%	11%±3
Other high risk	8.0%	10.2%	26%±3
All except acute stroke	11.7%	14.8%	25%±2
All trials	10.7%	13.2%	22%±2



Absolute risk reduction in vascular events by antiplatelet therapy

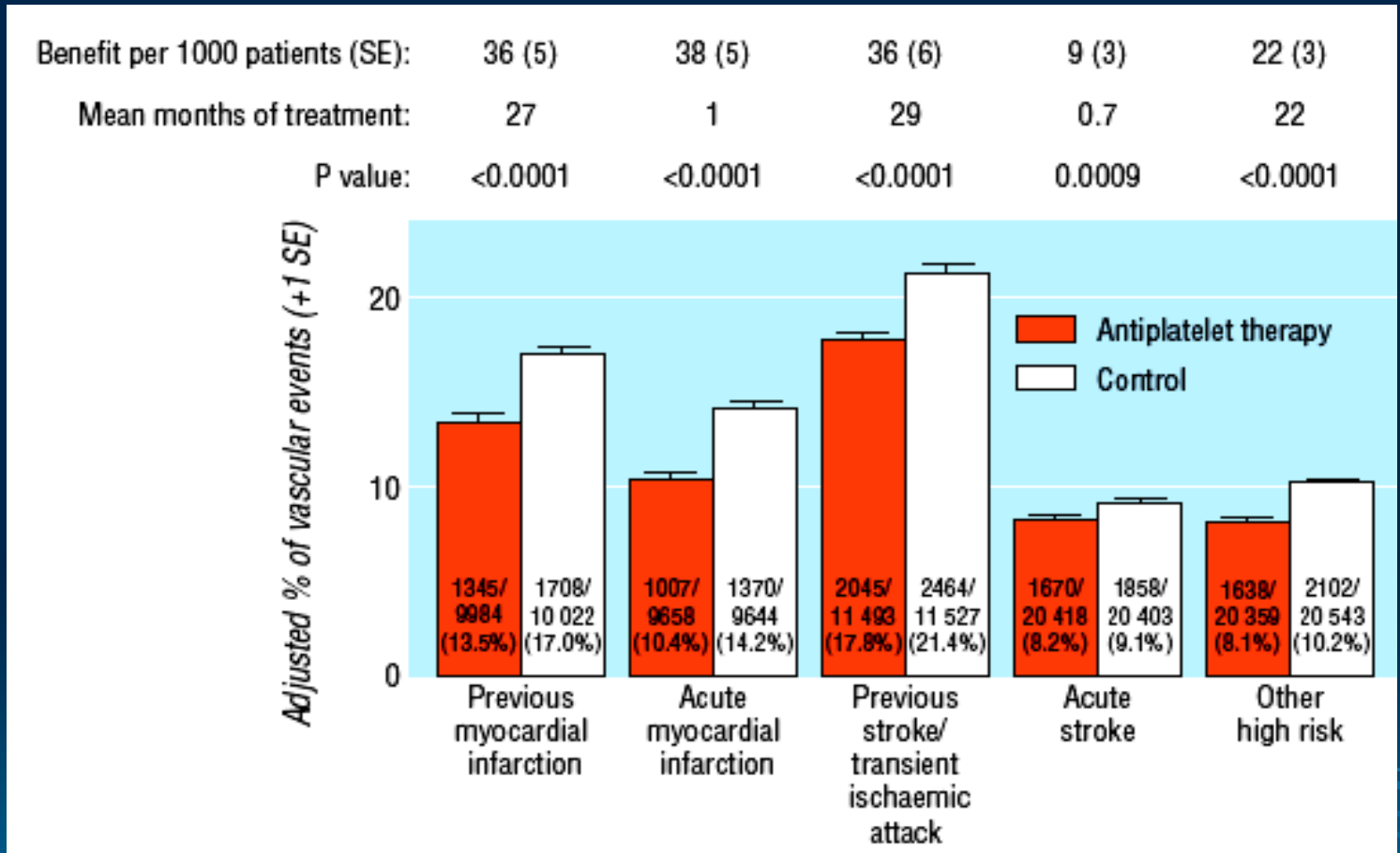


Fig 2 Absolute effects of antiplatelet therapy on vascular events (myocardial infarction, stroke, or vascular death) in five main high risk categories. Adjusted control totals have been calculated after converting any unevenly randomised trials to even ones by counting control groups more than once

Table 1. Benefit–Risk Ratio of Antiplatelet Prophylaxis with Aspirin in Different Settings

Clinical Setting	Benefit*	Risk†
Men at low to high CV risk	1–2	1–3
Essential hypertension	1–2	1–3
Chronic stable angina	10	1–3
Prior myocardial infarction	20	1–3
Unstable angina	50	1–3

CV = cardiovascular.

* Number of subjects in whom a major vascular event is avoided per 1,000/year.

† Number of subjects in whom a major bleeding event is caused per 1,000/year.

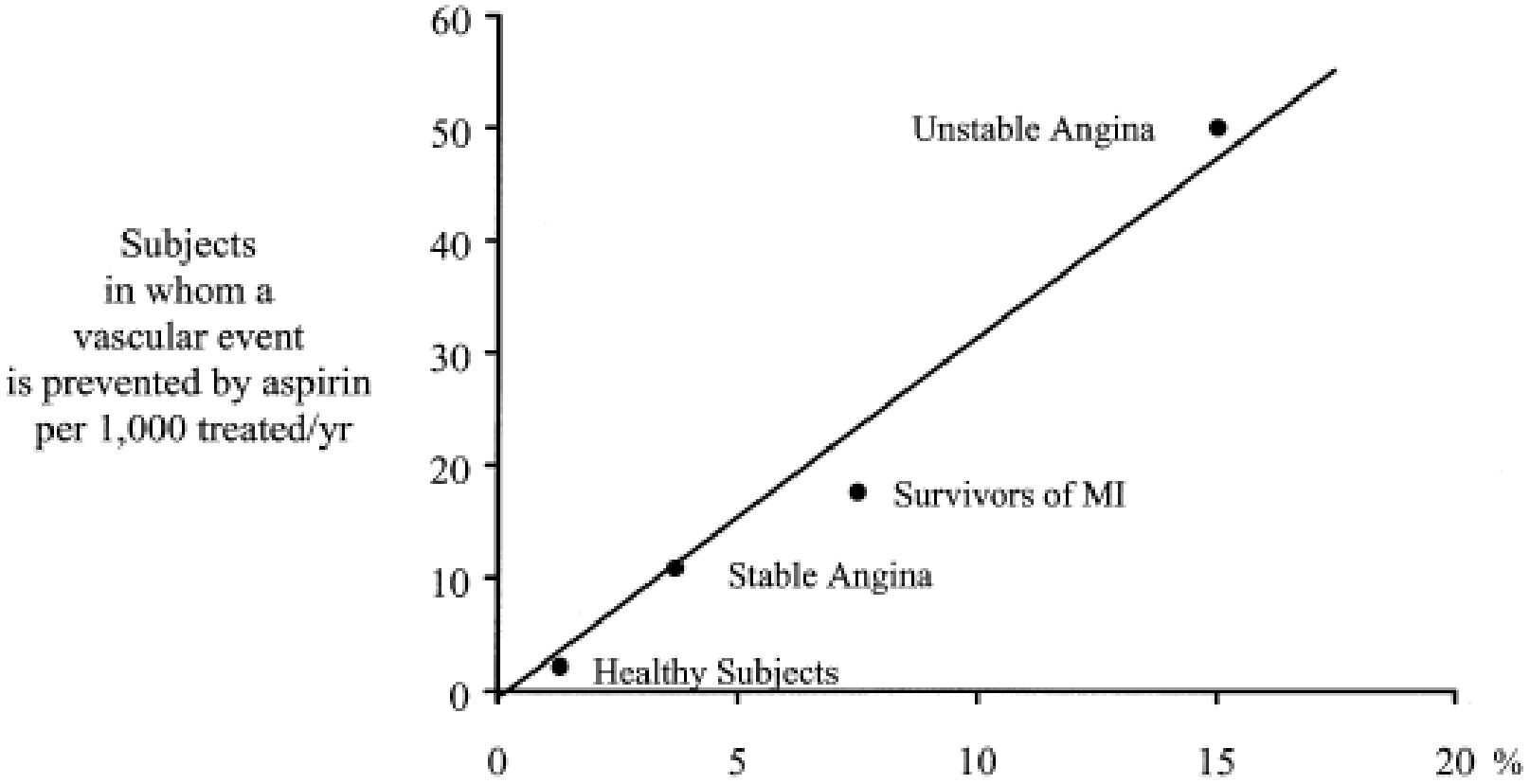
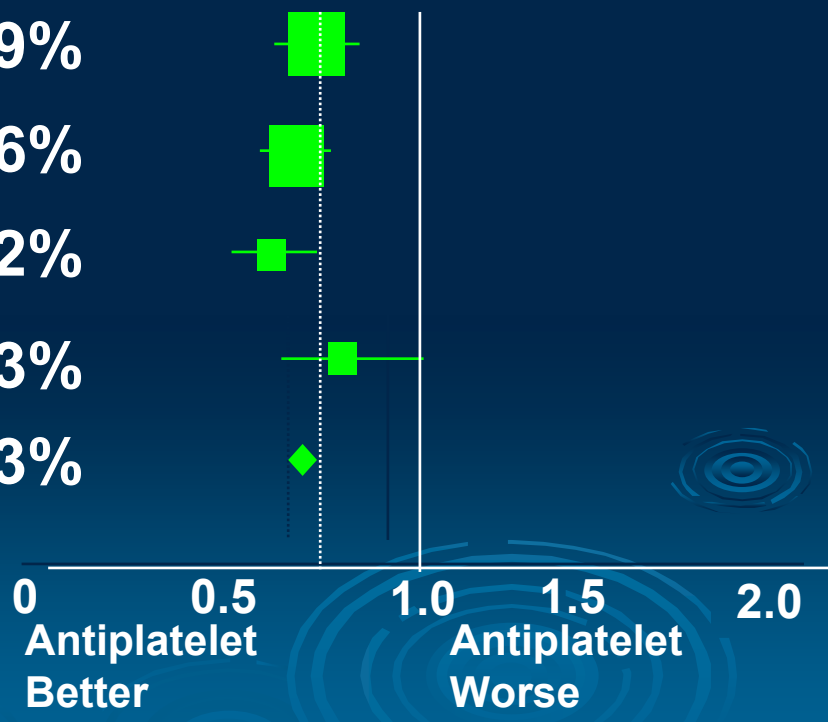


Figure 1. The absolute risk of vascular complications is the major determinant of the absolute benefit of antiplatelet prophylaxis. Data are plotted from placebo-controlled aspirin trials in different clinical settings. For each category of patients, the abscissa denotes the absolute risk of experiencing a major vascular event as recorded in the placebo arm of the trial(s). The absolute benefit of antiplatelet treatment is reported on the ordinate as the number of subjects in whom an important vascular event (nonfatal MI, non-fatal stroke, or vascular death) is actually prevented by treating 1,000 subjects with aspirin for 1 year. (Reproduced with permission from *Chest*.[8])

ATC 2002: Indirect Comparisons ASA Doses on Vascular Events in High Risk Patients

ASA Dose	# Trials	OR
500-1500 mg	34	19%
160-325 mg	19	26%
75-150 mg	12	32%
<75 mg	3	13%
Overall	65	23%



Antithrombotic Trialists' Collaboration *BMJ* 2002;324:71-86

Conclusions of the meta-analysis

- **Aspirin (or another oral antiplatelet drug) is protective in most types of patient at increased risk of occlusive vascular events, including those with an acute myocardial infarction or ischemic stroke, unstable or stable angina, previous myocardial infarction, stroke or cerebral ischemia, peripheral arterial disease, or atrial fibrillation.**

Conclusions of the meta-analysis

- Low dose aspirin (75-150 mg daily) is an effective antiplatelet regimen for long term use, but in acute settings an initial loading dose of at least 150 mg aspirin may be required.
- Adding a second antiplatelet drug to aspirin may produce additional benefits in some clinical circumstances, but more research into this strategy is needed.

Possible causes of recurrent ischemic vascular events among patients taking ASA

- **Non-atherothrombotic causes of vascular events**
  - Embolism from the heart (red, fibrin thrombi; vegetations; calcium; tumor; prostheses)
  - Arteritis
- **Reduced bioavailability of aspirin**
  - Inadequate intake of aspirin (poor compliance)
  - Inadequate dose of aspirin
  - Concurrent intake of certain non steroidal anti-inflammatory drugs (for example ibuprofen, indomethacin), possibly preventing the access of aspirin to cyclo-oxygenase-1 binding site

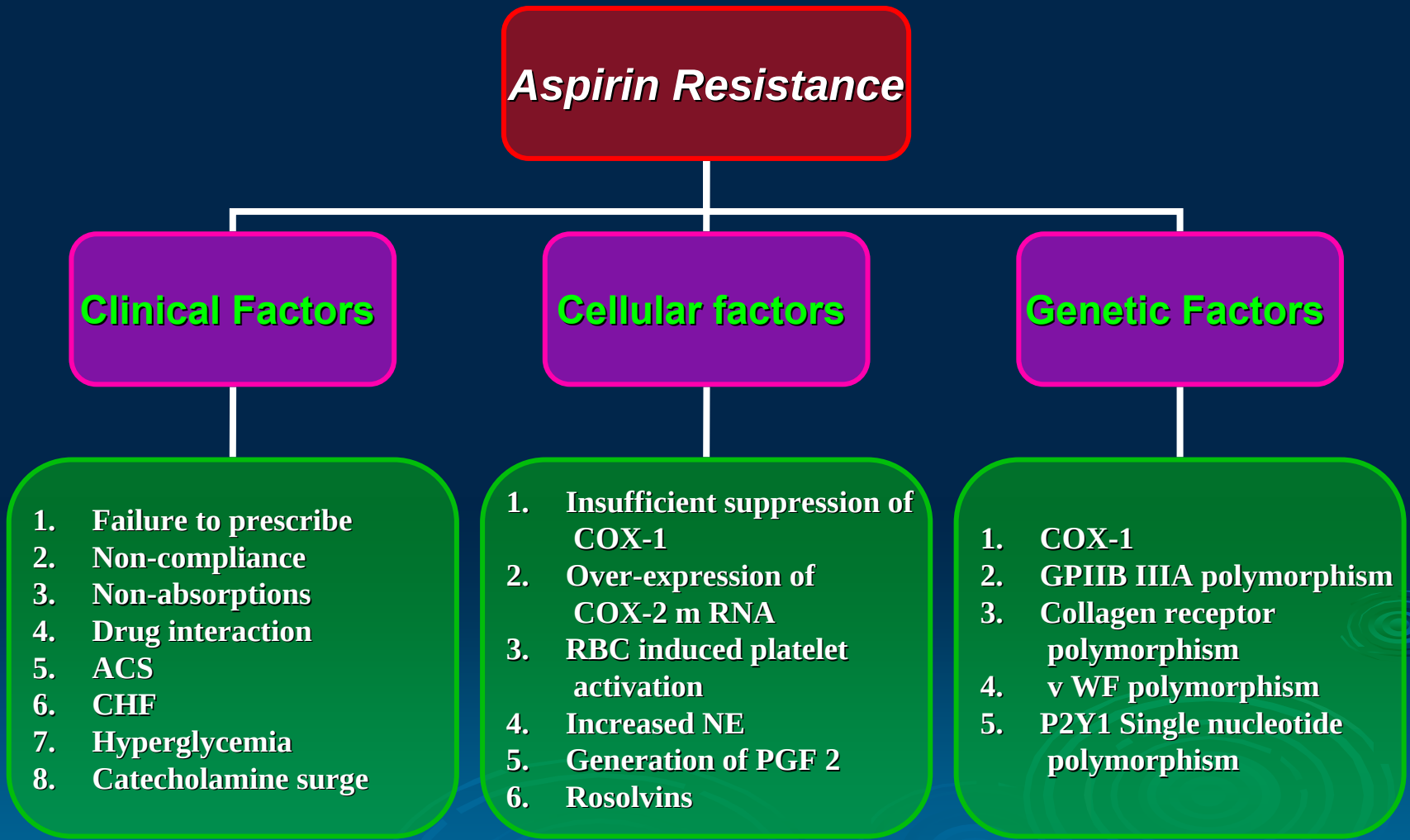
Possible causes of recurrent ischemic vascular events among patients taking ASA

- **Alternative pathways of platelet activation**
  - Platelet activation by pathways that are not blocked by aspirin (for example, red cell induced platelet activation: stimulation of collagen, ADP, epinephrine, and thrombin receptors on platelets)
  - Increased platelet sensitivity to collagen and ADP
  - Biosynthesis of thromboxane by pathways that are not blocked by aspirin (for example, by COX2 in monocytes and macrophages, and vascular endothelial cells)

Possible causes of recurrent ischemic vascular events among patients taking ASA

- **Increased turnover of platelets**
  - Increased production of platelets by the bone marrow in response to stress (for example, after CABG), introducing into blood stream newly formed platelets unexposed to aspirin during the 24 hour dose interval (aspirin is given once daily and has only a 20 minute half life)
- **Genetic polymorphisms**
  - Polymorphisms involving platelet glycoprotein Ia/IIa, Ib/V/IX, and IIb/IIIa receptors, and collagen and von Willebrand factor receptors
  - Polymorphisms of COX1, COX2 and TX A2-synthase, or other arachidonate metabolism enzymes
  - Factor XIII Val34Leu polymorphism, leading to variable inhibition of factor XIII activation by low dose aspirin

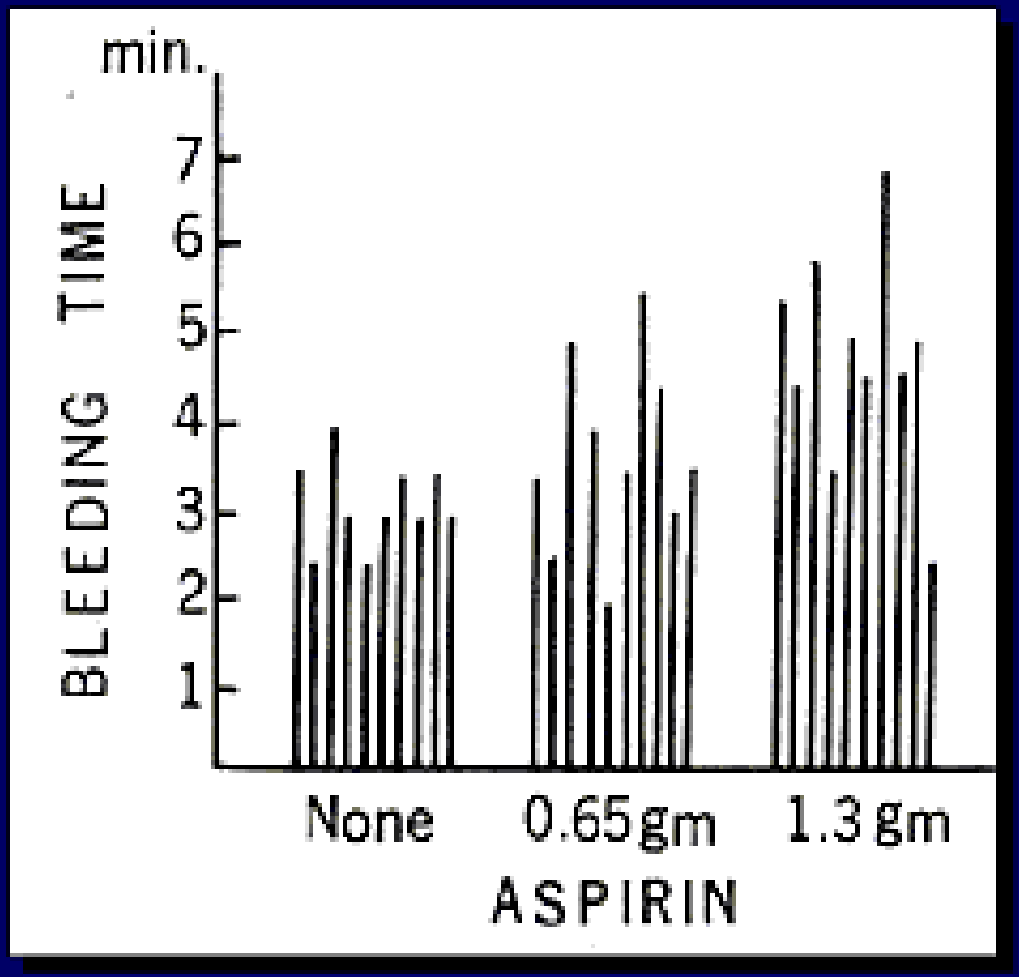
Possible Mechanisms of Aspirin Resistance



Possible mechanisms of Clopedogril Resistance

- Failure of activation by cytochrome P 450 3A4 (CYP450 3A4) to active drug
- Drug interaction (atorvastatin)
- Clinical factors like aspirin
- Genetic factors P_2Y_{12} receptors polymorphism

Inter-Individual Variability in Response to Aspirin



Variability in bleeding time response to aspirin in 10 healthy college and medical students.

Quick AJ.
American Journal of Medical Science
Sept 1966:265-9

Definitions

Aspirin resistance is defined as:

- ***Clinical ASA Resistance:***

  Inability of ASA to prevent thrombotic ischemic events in treated patients

  However, this definition is non-specific

Graeme J Hankey and John W Eikelboom *BMJ* 2004

Definitions

Biochemical ASA resistance:

1. Inability of ASA to prolong the bleeding time
2. Incomplete suppression of thromboxane – A_2 formation by use of ASA
3. Inability of ASA to inhibit platelet aggregation
4. Inability of ASA to achieve a predefined effect on platelet function

However, the precise abnormalities of platelet function which define biochemical aspirin resistance have not been established. So the prevalence of ASA resistance ranged from 5 to 45 %

Graeme J Hankey and John W Eikelboom *BMJ* 2004

Definitions

- An appropriate definition of aspirin resistance may be: the lack of anticipated response to a therapeutic dose of aspirin (75-150 mg per day for at least five days in a compliant patient) that can be demonstrated by a specific, valid, and reliable laboratory measure of the antiplatelet effects of aspirin and which correlates significantly, independently, and consistently with an increased incidence of atherothrombotic vascular events.

Graeme J Hankey and John W Eikelboom *BMJ* 2004

Laboratory tests used to measure the antiplatelet effects

Test	Method	Advantages	limitations
Platelet aggregation	Optical platelet aggregation	Widely available Correlated with clinical events Gold standard	Not specific Uncertain sensitivity Labor intensive Operator and interpreter dependent
	Semi-automated platelet aggregometry (PFA-100, Ultegra RPFA)	Simple Rapid	Not specific Uncertain sensitivity Uncertain correlation with clinical events
Bleeding time	Skin bleeding time	Simple Widely available	Not specific Not sensitive Operator dependent Limited reproducibility Uncertain correlation with clinical events
Thromboxane generation	Urinary thromboxane metabolite excretion	Correlated with clinical events	Uncertain specificity Uncertain sensitivity Uncertain reproducibility Not widely evaluated

PFA=platelet function analyzer; RPFA=rapid platelet function analyzer.

Ideal test of ASA Resistance

- It must be associated independently and consistently with the occurrence of recurrent vascular events in patients taking aspirin
- It must be standardized and valid
- Clinical management should be altered on the basis of the results of testing—for example, it should be shown in randomized controlled trials that reversing the laboratory abnormality (with treatment) is followed by a reduction in the incidence of recurrent vascular events while taking aspirin.
- The overall benefits of testing should outweigh any adverse consequences and costs.

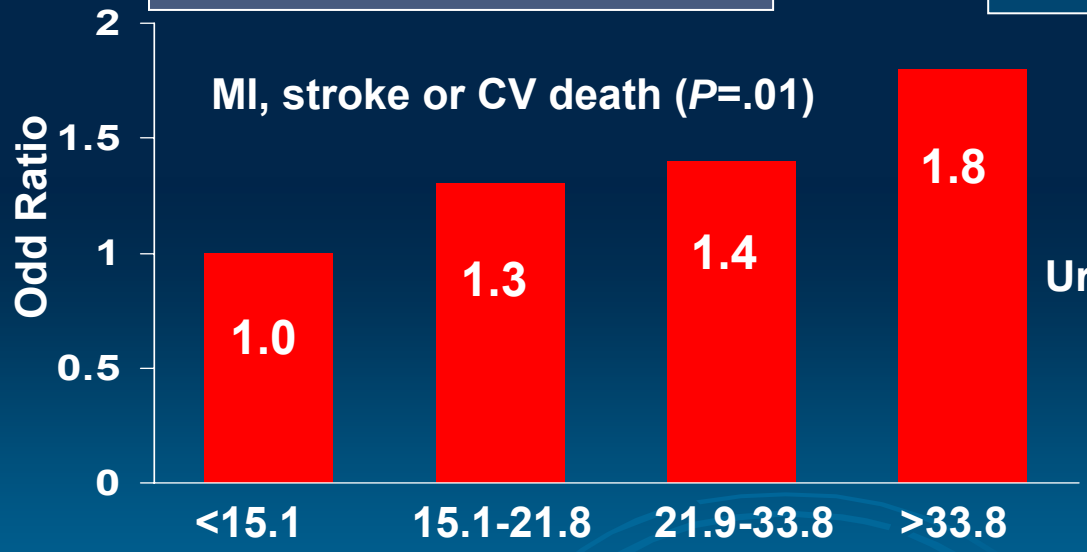
Aspirin Resistance and the Risk of Cardiovascular Events in High Risk Patients

Hypothesis: Incomplete inhibition of thromboxane B2 increases risk of cardiovascular event

5529 pts from HOPE study with baseline urine samples

Case (n=488)
Pts with CV events after randomization

Controls (n=488)
Pts without CV events after randomization



Adapted from Eikelboom JW, et al. Circulation. 2002;105:1650-1655.

Baseline urinary 11-dehydro-TXB2 levels (ng/mmol creatinine)

Outcome	cases*	controls †	p
Stroke	25.0 (n=80)	27.4 (n=80)	0.47
CV death	25.6 (n=244)	20.4 (n=244)	<0.001
MI	24.5 (n=378)	20.9 (n=378)	0.003
MI, stroke, or CV death	24.5 (n=488)	21.5 (n=488)	0.01

* geometric mean in HOPE subjects taking ASA who had CV events following randomization

† geometric mean in HOPE subjects taking ASA who had no CV events following randomization

Alternate thromboxane-generation pathway

- Nucleated cells (monocytes and vascular endothelial cells) are able to
  - Supply prostaglandin H_2 to platelets
  - Synthesize their own thromboxane A_2 from prostaglandin H_2 (a precursor of thromboxane)
  - Produce prostaglandin H_2 via COX-2
- COX-2 expression is augmented by inflammatory stimuli

Failure of suppression of COX-1 vs upregulation of COX-2?

- Upregulation of COX-2 in atherosclerotic tissue
  - May increase prostaglandin H2 transfer to platelets
  - Bypasses platelet COX-1-mediated thromboxane synthesis
  - Thus, ASA-insensitive thromboxane biosynthesis occurs in some patients
- The study does not differentiate between failure of suppression of COX-1 vs upregulation of COX-2

Eikelboom JW et al. Circulation 2002;105:1650-1655

Study conclusions

- Persistent thromboxane generation predicts the risk of composite CV outcome in high-risk patients taking ASA, independent of other CV risk factors
- High urinary levels of 11-dehydro-TXB2 may prospectively identify patients resistant to conventional antithrombotic doses of ASA
- Such patients may benefit from
  - Additional antiplatelet therapies, or
  - Treatments that more effectively block thromboxane production or activity

Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA)

- Inclusion Criteria

Patients aged ≥45 years with at least one of the following:

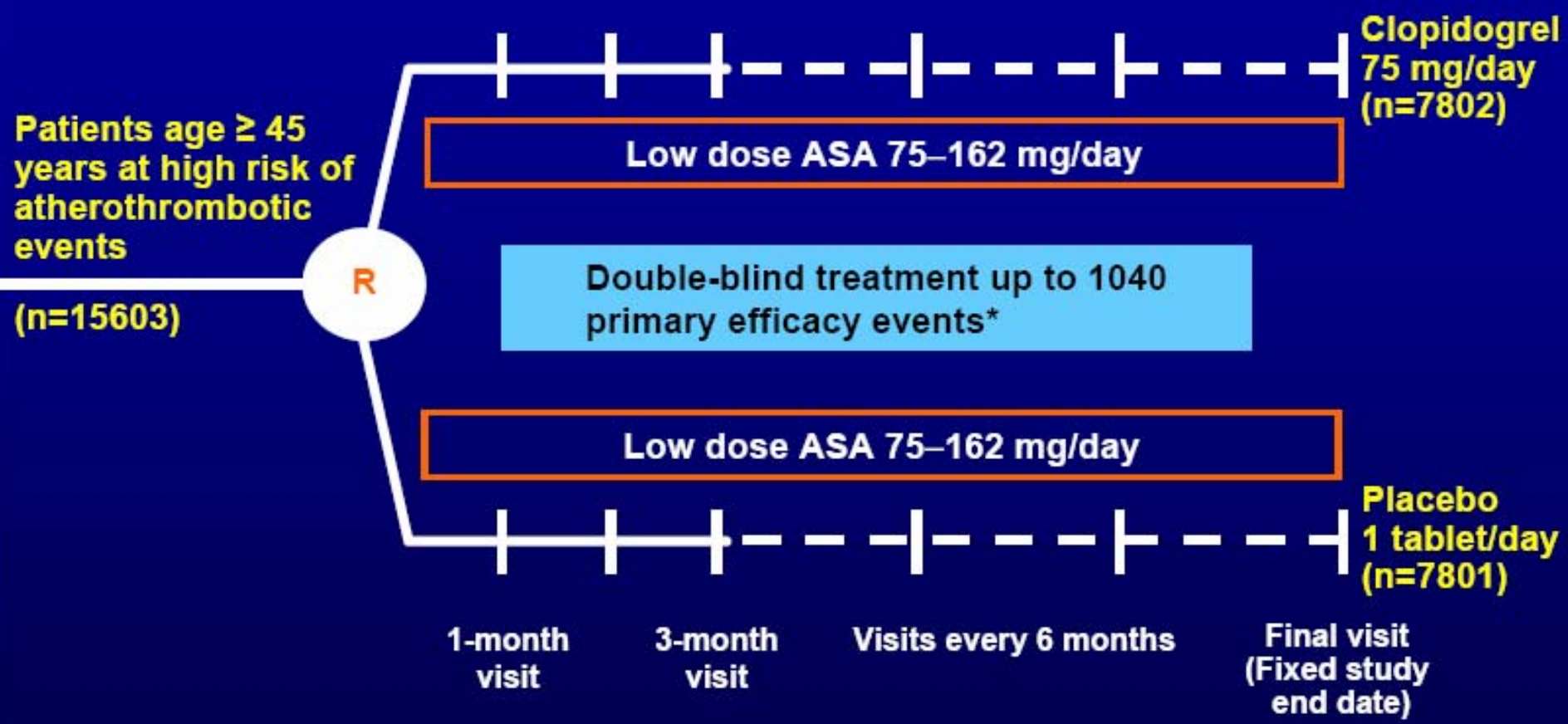
1. Documented coronary diseaseand/or
2. Documented cerebrovascular disease and/or
3. Documented symptomatic PADand/or
4. Two major or one major and two minor or three minor risk factors

Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA)

- ***Exclusion Criteria***

1. **Requirement for clopidogrel such as:**
   - **Recent acute coronary syndrome without ST-segment elevation**
   - **investigator's assessment clopidogrel required long-term**
   - **Need for chronic therapy with high dose (> 162 mg/day) ASA or NSAID (exceptCOX-2 inhibitors)**
2. **Current use of other oral anti-thrombotic medications with intention for long term treatment (e.g. OAC)**
3. **Planned revascularization procedure (OK after the procedure if no open-label clopidogrel is needed)**

CHARISMA Trial Design

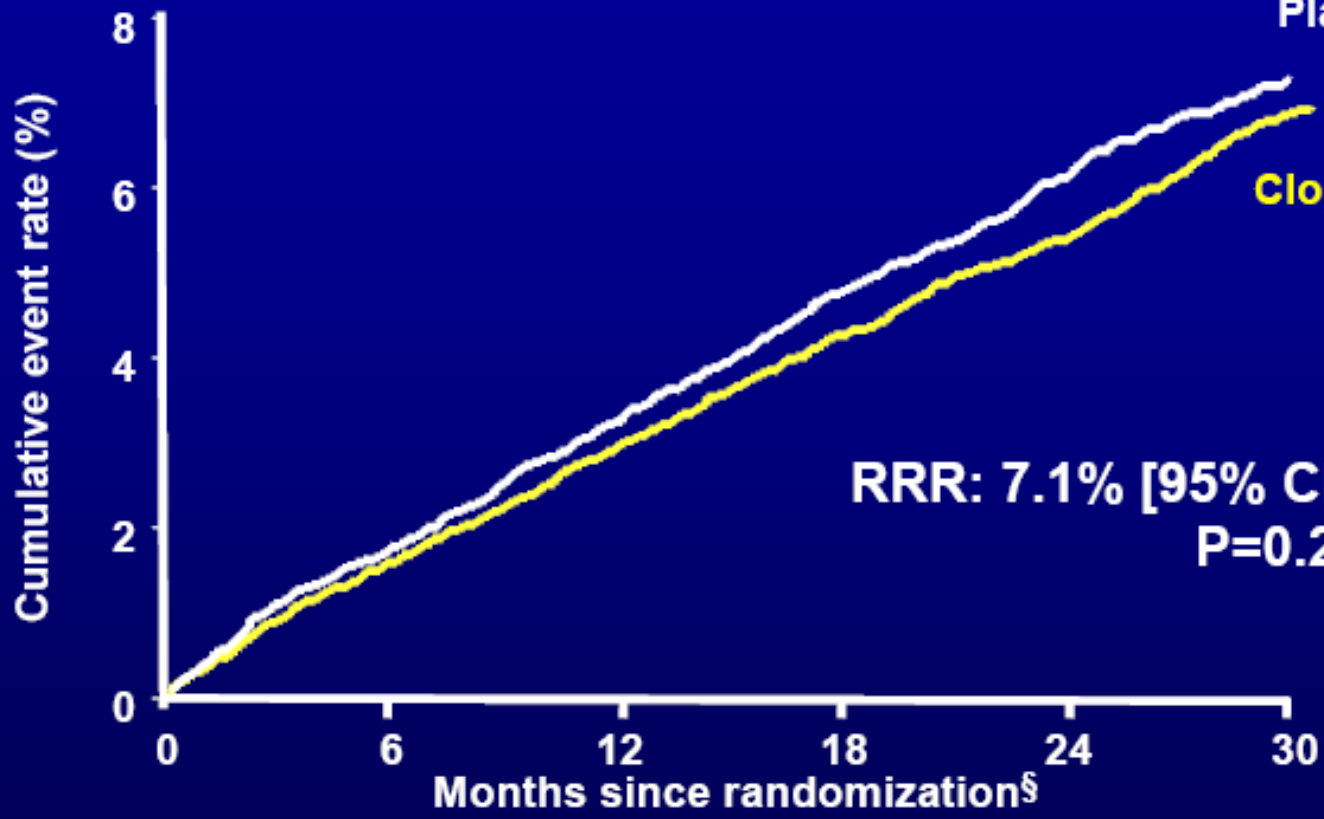


* MI (fatal or non-fatal), stroke (fatal or non-fatal), or cardiovascular death; event-driven trial

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

CHARISMA

Overall Population: Primary Efficacy Outcome (MI, Stroke, or CV Death)†



† First Occurrence of MI (fatal or non-fatal), stroke (fatal or non-fatal), or cardiovascular death

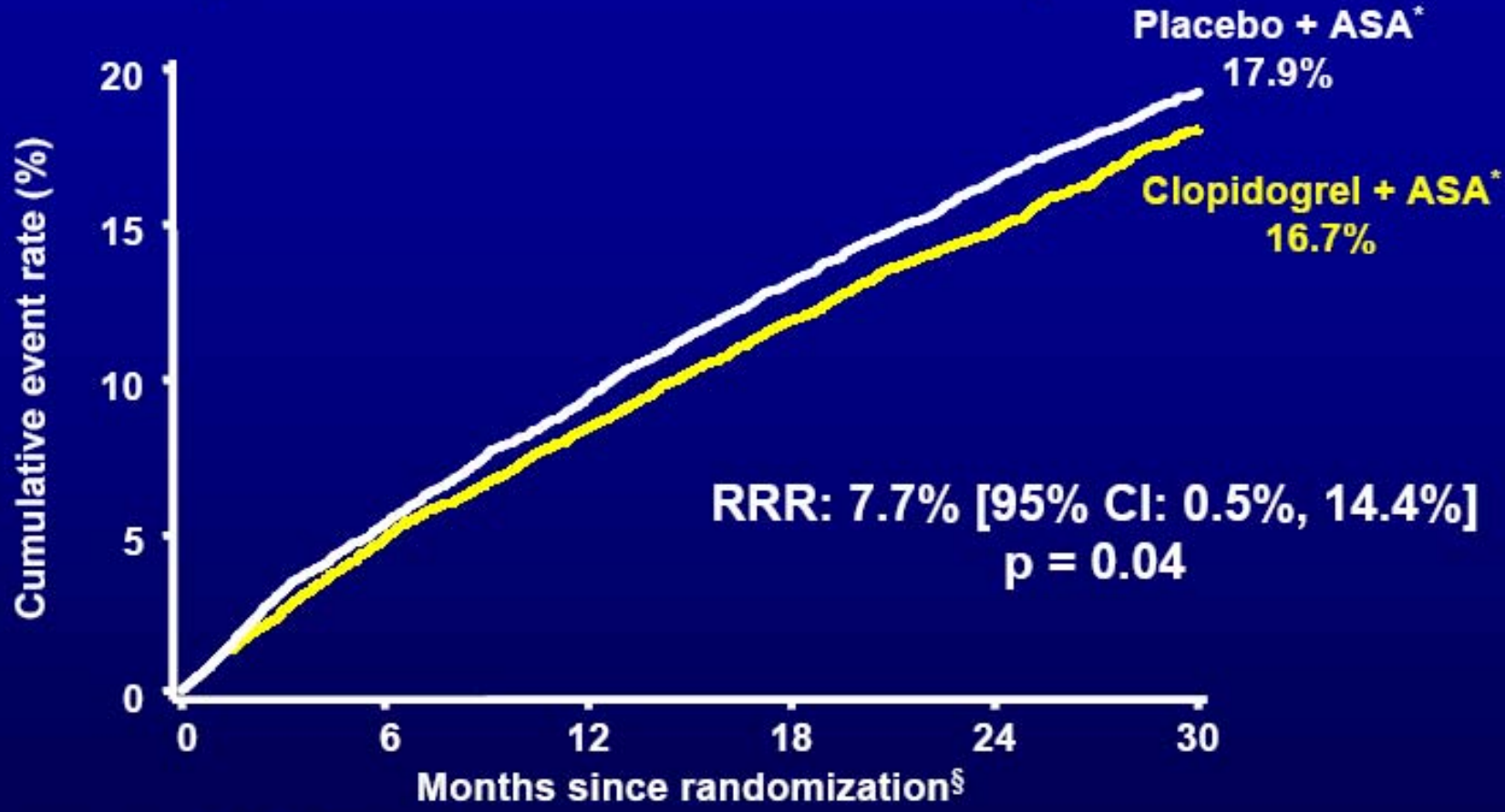
*All patients received ASA 75-162 mg/day

§The number of patients followed beyond 30 months decreases rapidly to zero and there are only 21 primary efficacy events that occurred beyond this time (13 clopidogrel and 8 placebo)

Bhatt DL, Fox KA, Hacke W, et al. NEJM 2006.

CHARISMA

Overall Population: Principal Secondary Efficacy Outcome (MI/Stroke/CV Death/Hospitalization)†



*All patients received ASA 75-162mg/day

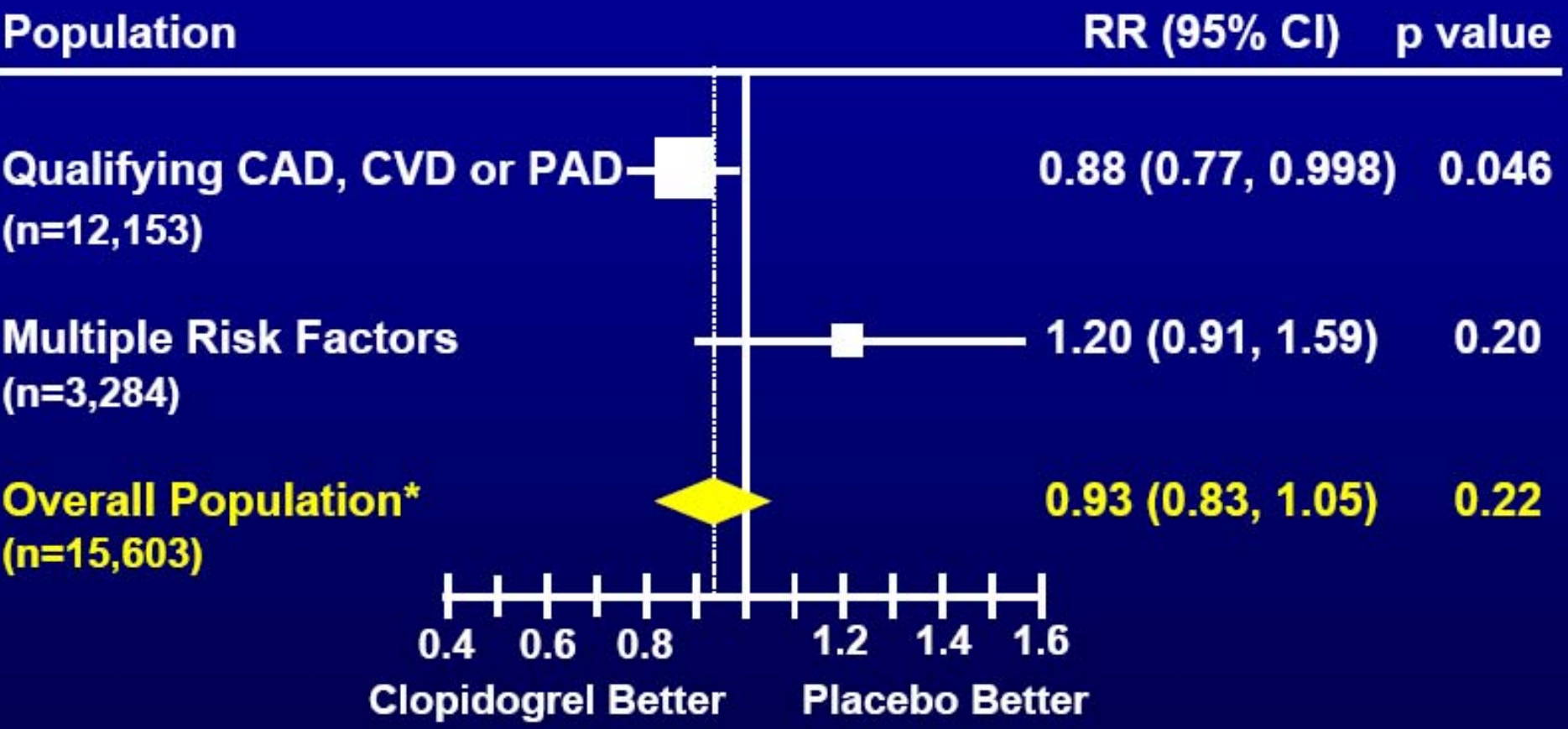
†First Occurrence of MI, Stroke, CV Death, or Hospitalization for UA, TIA, or Revascularization

§The number of patients followed beyond 30 months decreases rapidly to zero and there are only 38 primary efficacy events that occurred beyond this time (23 clopidogrel and 15 placebo)

Bhatt DL, Fox KA, Hacke W, et al. NEJM 2006.

CHARISMA

Primary Efficacy Results (MI/Stroke/CV Death) by Pre-Specified Entry Category



* A statistical test for interaction showed marginally significant heterogeneity (p=0.045) in treatment response for these pre-specified subgroups of patients

Bhatt DL, Fox KA, Hacke W, et al. NEJM 2006.

CHARISMA

Primary Efficacy Results (MI/Stroke/CV Death)* by Category of Inclusion Criteria

Population	N	RR (95% CI)	p value
Qualifying CV Disease	12,153	0.88 (0.77, 0.998)	0.046
Coronary	5,835	0.86 (0.71, 1.05)	0.13
Cerebrovascular	4,320	0.84 (0.69, 1.03)	0.09
PAD	2,838	0.87 (0.67, 1.13)	0.29
Multiple Risk Factors	3,284	1.20 (0.91, 1.59)	0.20
Overall Population	15,603	0.93 (0.83, 1.05)	0.22

* First Occurrence of MI (fatal or not), Stroke (fatal or not), or CV Death

Bhatt DL. Presented at ACC 2006.

CHARISMA

Conclusions

- In patients with multiple risk factors only, without clearly established CV disease, dual antiplatelet therapy was not beneficial - excess in CV mortality as well as an increase in bleeding
- In patients with documented CV disease (CAD, CVD, or PAD) long-term clopidogrel plus ASA resulted in a significant 12.5% RRR in MI/Stroke/CV Death with no significant increase in severe bleeding compared to ASA alone

Case Presentation

- A 58 year old man presented with hypercholesterolemia, +ve FH of CAD and HTN but no evidence of ischemia along the last 3 years.
- As many people he have tried diet control and life style modification but failed and he went statin.
- Amazingly when cholesterol went down the statin was stopped and he was admitted with rest pain and –ve markers but nonetheless had 3 vessel disease and went on for CABG

Case Presentation

- Is antiplatelet resistance can explain the case?
- If the patient has asprin resistance
  - To stop aspirin
  - Continue aspirin with the same dose
  - Continue aspirin with larger dose
  - Add clopidogrel or warfarin

Clinical implications

- ASA resistance is dose insensitive and increasing the dose increases bleeding especially GIT
- More ASA resistance seen in ACS & CHF patients
- A point-of-care rapid test for ASA resistance is needed
- Dual oral antiplatelet therapy with clopidogrel overrides ASA resistance as those patients have platelets that are more sensitive to ADP (CURE & CREDO Trials)

Clinical implications

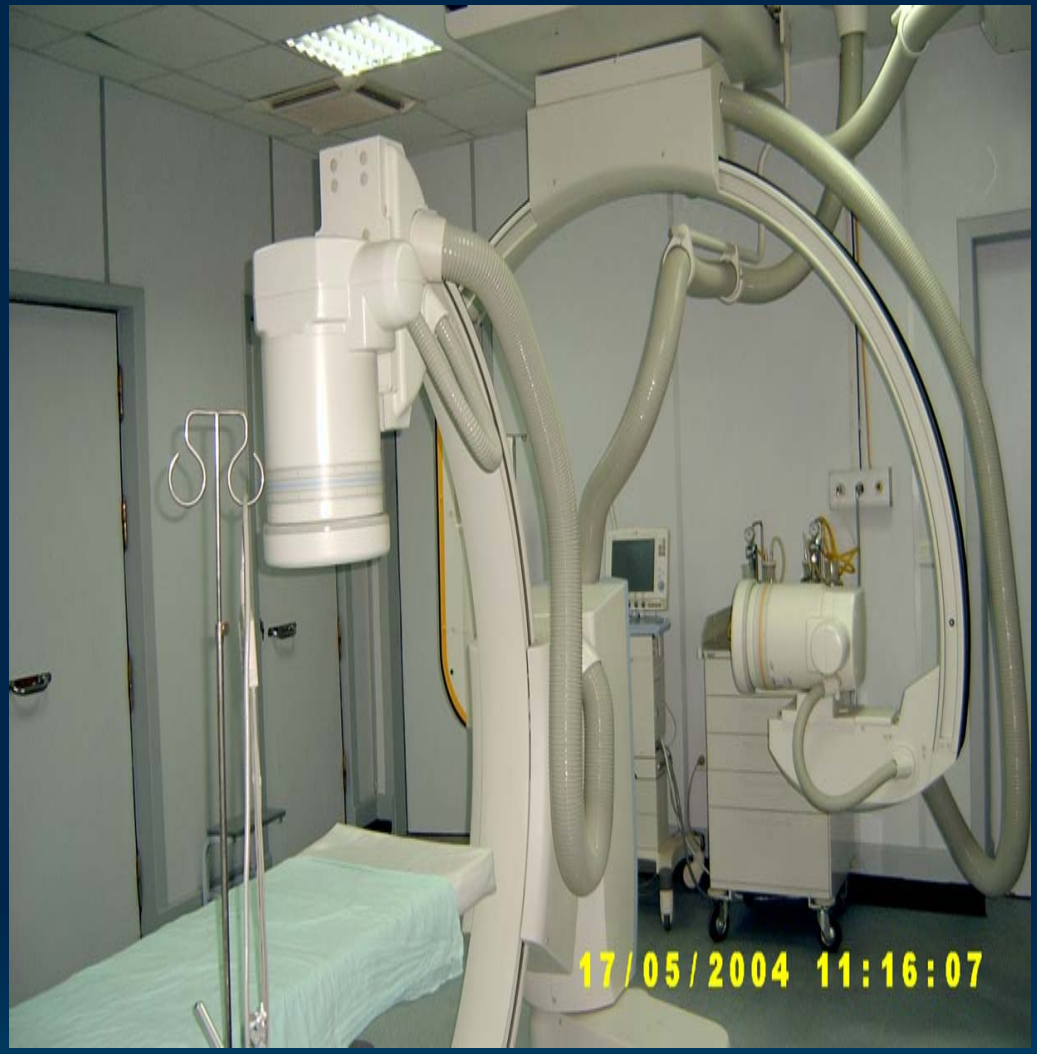
- Increasing the loading and maintenance doses of clopidogrel is to be considered (ARMYDA-2, ISAR-CHOICE & ALBION Trials)
- Alternative thienopyridine agents may overcome this problem [prasugrel (LY640315) or nonthienopyridine (cangrelor & AZD6140)]

Clinical implications

- The most efficient strategy for clinicians to prevent aspirin failure is
  - To make sure that the index event was atherothrombotic in origin
  - Use an appropriate dose of aspirin (75-150 mg daily)
  - Maintain a high level of compliance
  - Avoid combining aspirin with drugs such as ibuprofen that may reduce its effectiveness for the prevention of atherothrombotic vascular events

Future Perspectives

- The need for large trials that correlate clinical outcome data with laboratory assessment of platelet aggregability in patient with ASA or Clopidogrel resistance (CHARISMA, RESISTOR trials)
- Trial to compare the different ADP antagonists (TRITON-TIMI 38 & DISPERSE 2 trials)
- Routine use of platelet reactivity testing in the same way as cholesterol, BP and blood sugar waits the results of many of these trials.
- Also, these trials may set a new era of different antiplatelets with different dose regimen for the millions of patients receiving these treatments.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Thank You