Insights into Antiplatelet Therapy
From CAPRIE to TRITON-TIMI 38

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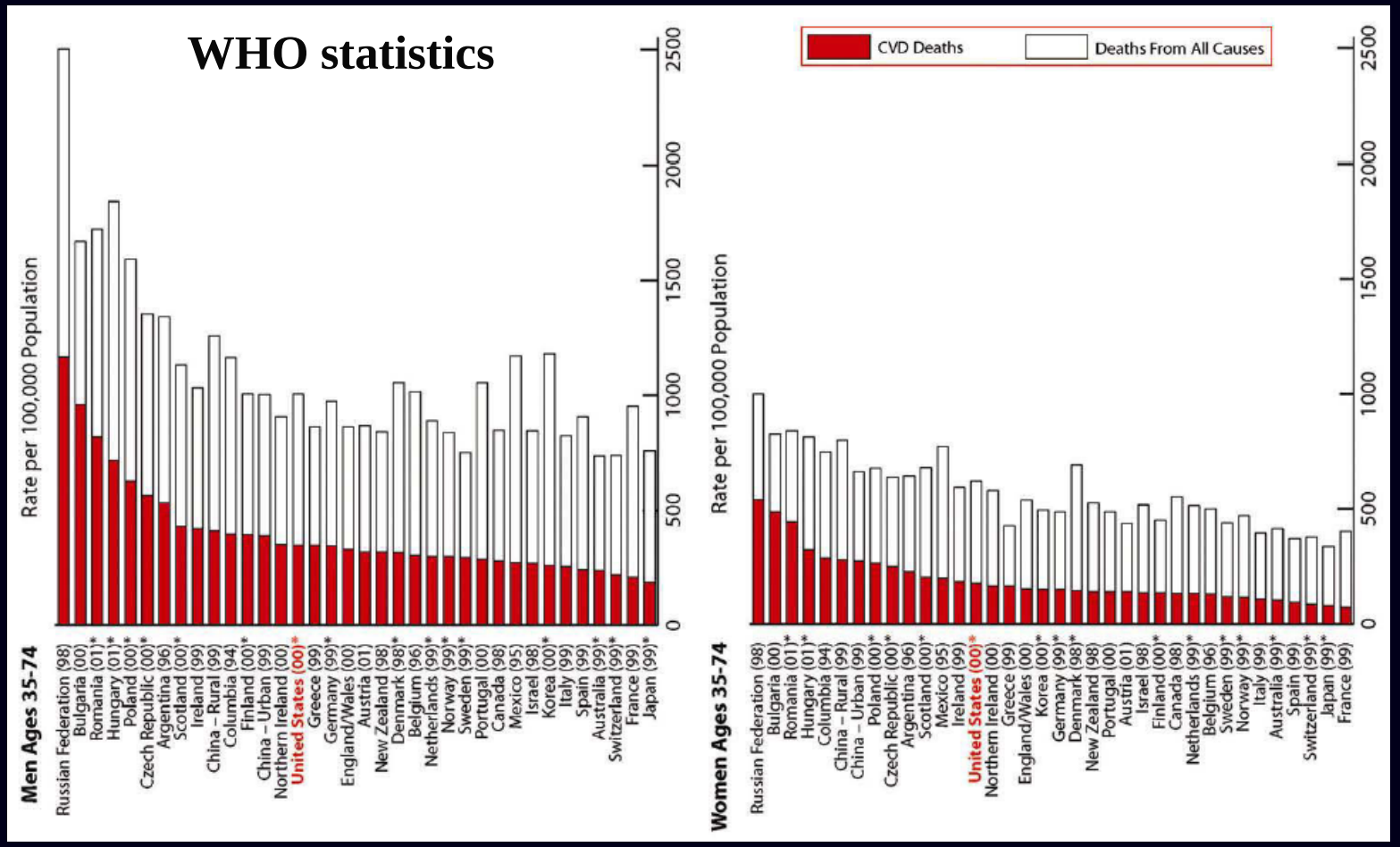
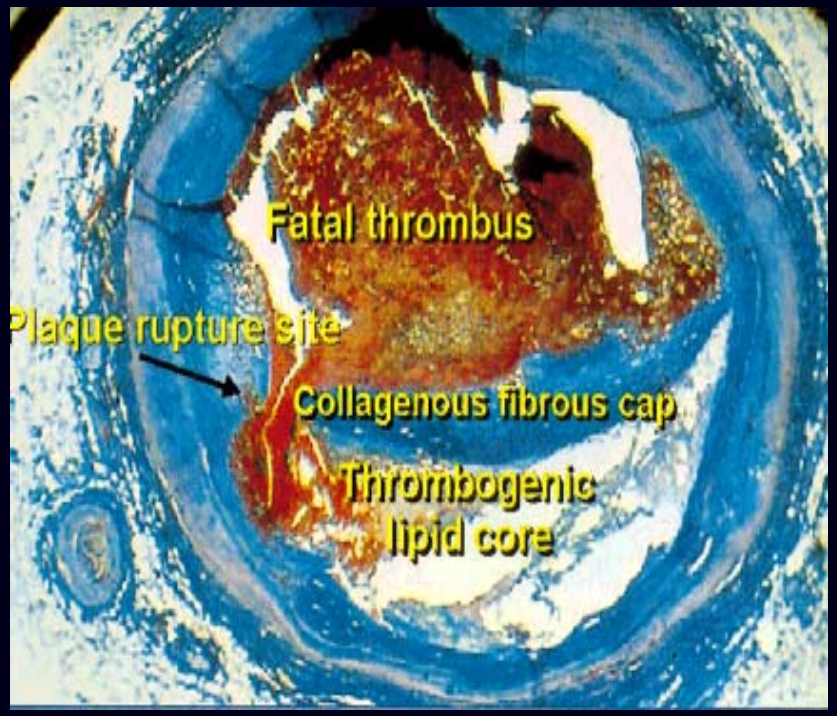
Causes of Global Death, 2004

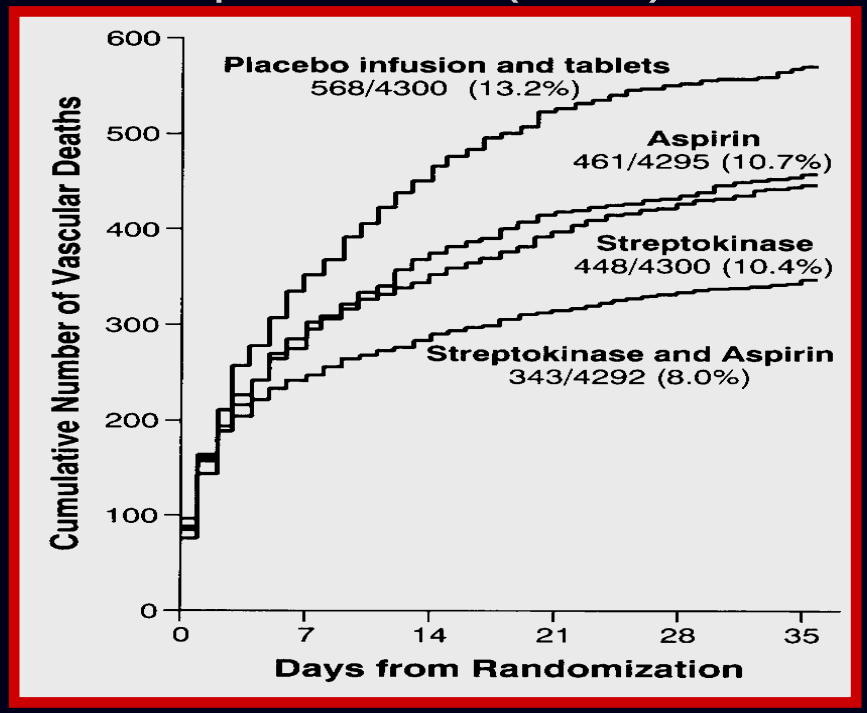


By 2020, chronic disease will account for ~3/4 of all deaths. Heart disease has no geographic, gender or socioeconomic boundaries.

Anti-platelet Therapy



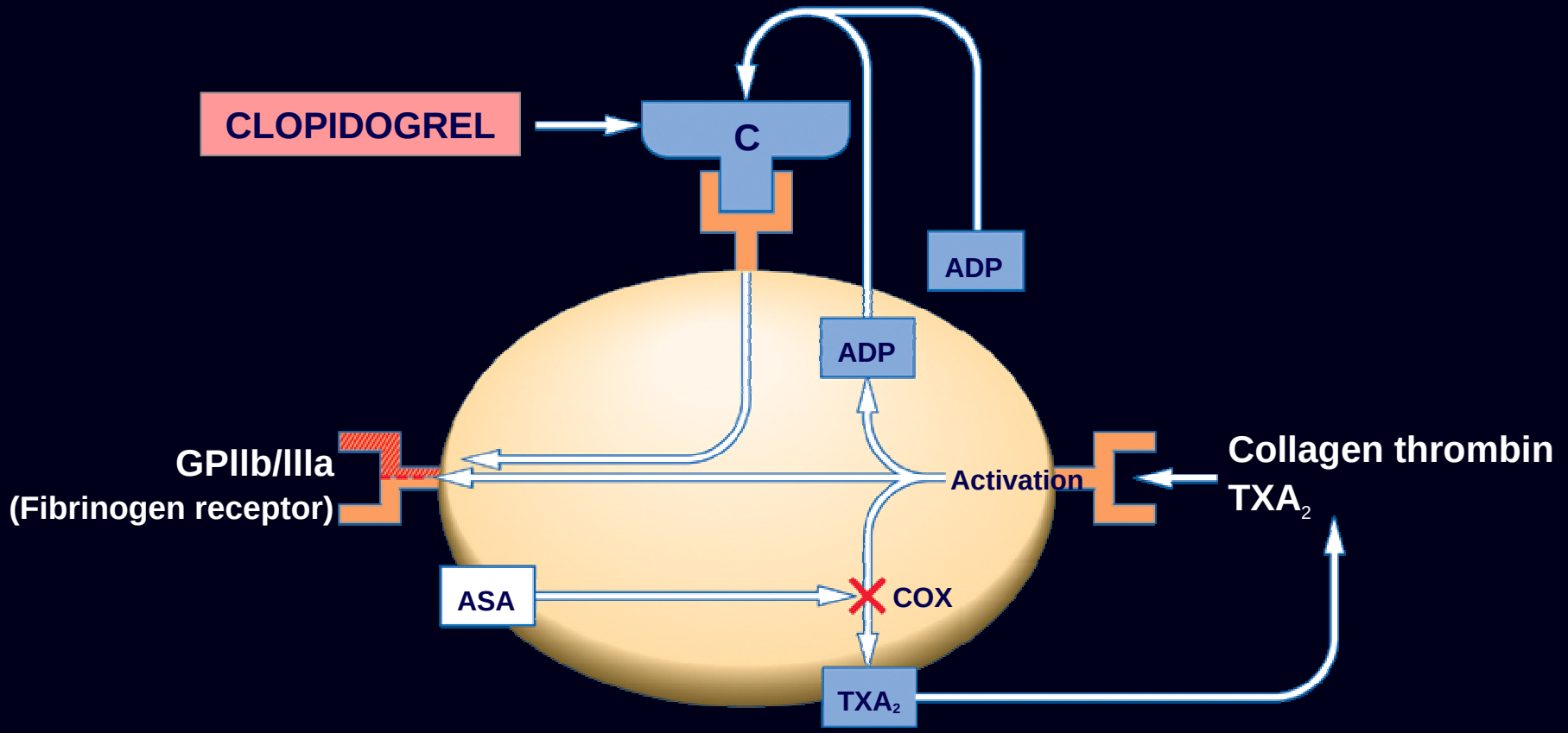
Aspirin in AMI (ISIS-2)



Platelets play a central role in the pathophysiology of arterial thrombosis, & the importance of platelet inhibition in ACS was confirmed in the ISIS-2 trial trial. Use of aspirin dramatically increased after publication of ISIS-2 (1988).

Lancet 1988;2:349

Beyond Aspirin



The constant need for better clinical efficacy beyond aspirin monotherapy lead to the production of different molecules, such as clopidogrel.

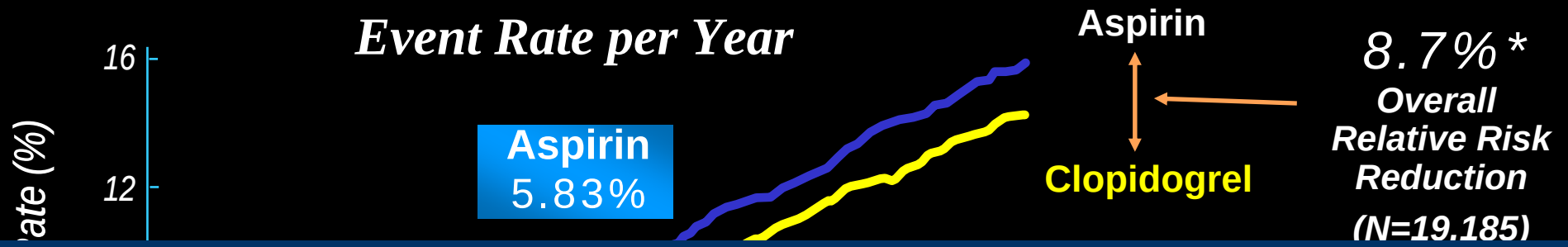
CAPRIE Study

The 1st RCT to evaluate the efficacy & safety of clopidogrel in the prevention of arterial ischemic events.

Study design	**Multicenter, prospective, randomized, blinded**
Study population	**19,185 patients with atherosclerotic vascular disease**
Qualifying conditions	**Ischemic stroke (1 week and 6 months)** **Myocardial infarction (MI) (≤ 35 days)** **Established peripheral arterial disease**
Study drugs	**Clopidogrel 75 mg once daily** **Aspirin 325 mg once daily**
Primary end point	**MI, ischemic stroke, or vascular death**
Treatment duration	**Up to 3 years (mean 1.6 years)**
Investigational sites	**384 in 16 countries**

Lancet 1996;348:1329-1339.

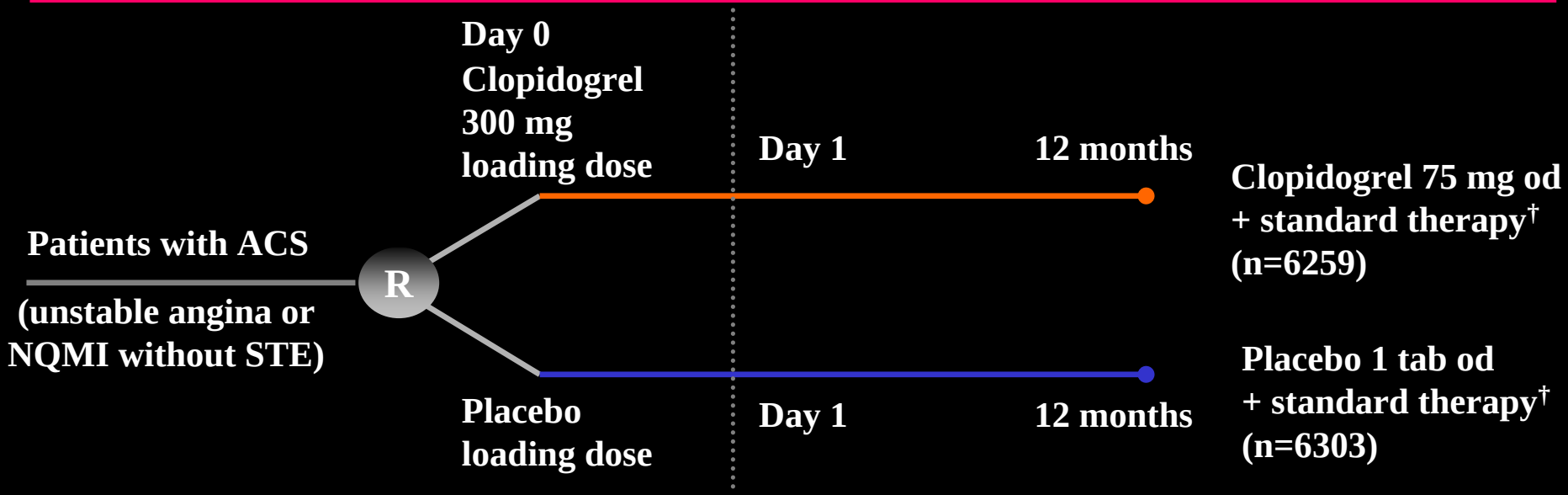
Cumulative Risk of Stoke, MI or Vascular Death in Patients in the CAPRIE Trial



Conclusion

Clopidogrel is more effective than aspirin in reducing the risk of ischemic event in patients with MI, stroke & established PAD, suggesting clopidogrel as the best alternative to aspirin in pts with aspirin allergy.

Effects of Clopidogrel in Addition to Aspirin in Patients with ACS without STE (CURE Trial)



R=Randomization, occurred within 24 hours of symptom onset

† Standard therapy always included ASA, and could also include heparin, LMWH, GP IIb/IIIa inhibitors post-randomization, beta-blockers, ACE-inhibitors, lipid-lowering agents, and/or other therapies or interventions (e.g. PTCA, CABG) at physician's discretion.

Primary endpoint: first occurrence of cardiovascular death, MI or stroke

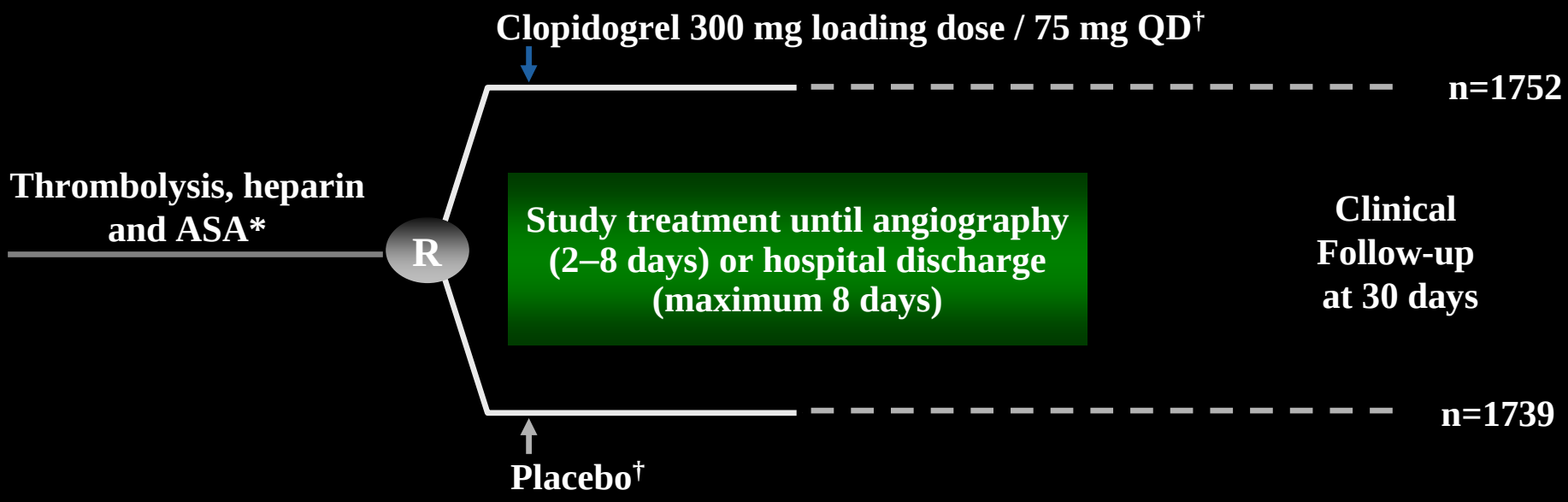
Primary Endpoint

Conclusion

Clopidogrel on top of standard therapy (including ASA) demonstrates an early effect and sustained long-term benefit throughout the entire trial period of 12 months.

CLopidogrel as Adjunctive ReperfusIon TherapY (CLARITY) – TIMI 28 Trial Results

a randomized, double-blind, placebo-controlled trial comparing clopidogrel plus ASA vs. ASA alone in patients with acute STEMI treated with fibrinolytic therapy (onset ≤12 h)



Primary endpoint: Composite of occluded infarct related artery (TFG 0/1) on pre-discharge angiogram, or death or MI before angiography

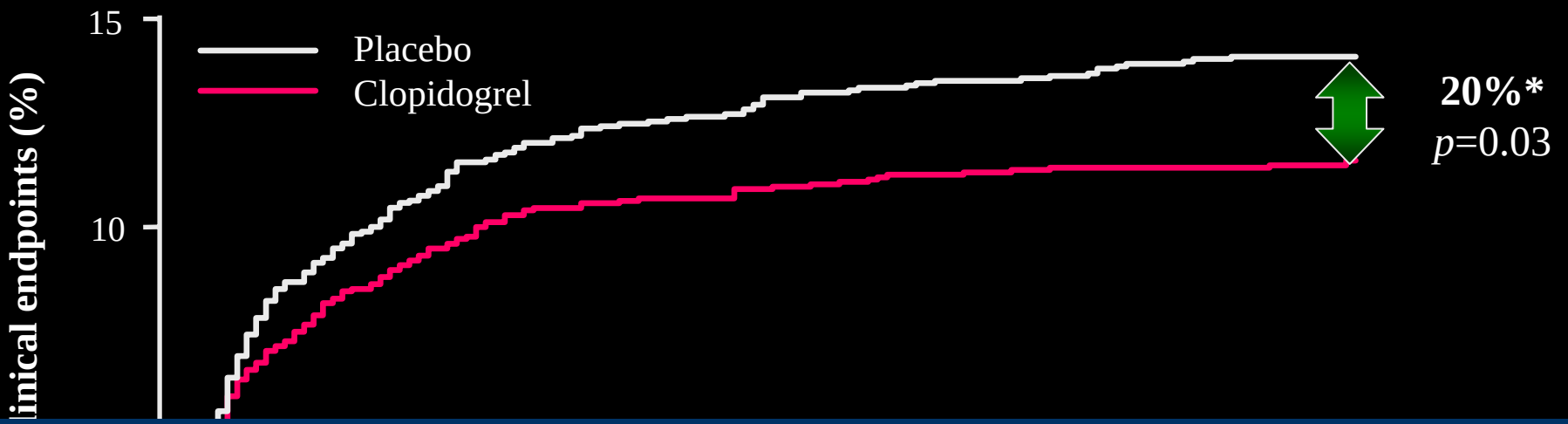
*ASA=150–325 mg (if no ASA within prior 24 hours) as loading dose. Patients received heparin if they received a fibrin specific thrombolytic
†All patients received ASA 75–162 mg/day plus other standard care

New Engl J Med 2005; 352: 1179

Clopidogrel reduced primary endpoint by 36%.

	Clopidogrel (n=1752)	Placebo (n=1739)	Odds ratio (95% CI)	p value
Primary composite endpoint (%)				
TFG 0/1, MI or death	15.0	21.7	0.64 (0.53–0.76)	<0.001
Individual components of primary endpoint (%)				
TFG 0/1	11.7	18.4	0.59 (0.48–0.72)	<0.001
Recurrent MI	2.5	3.6	0.70 (0.47–1.04)	0.08
Death	2.6	2.2	1.17 (0.75–1.82)	0.49

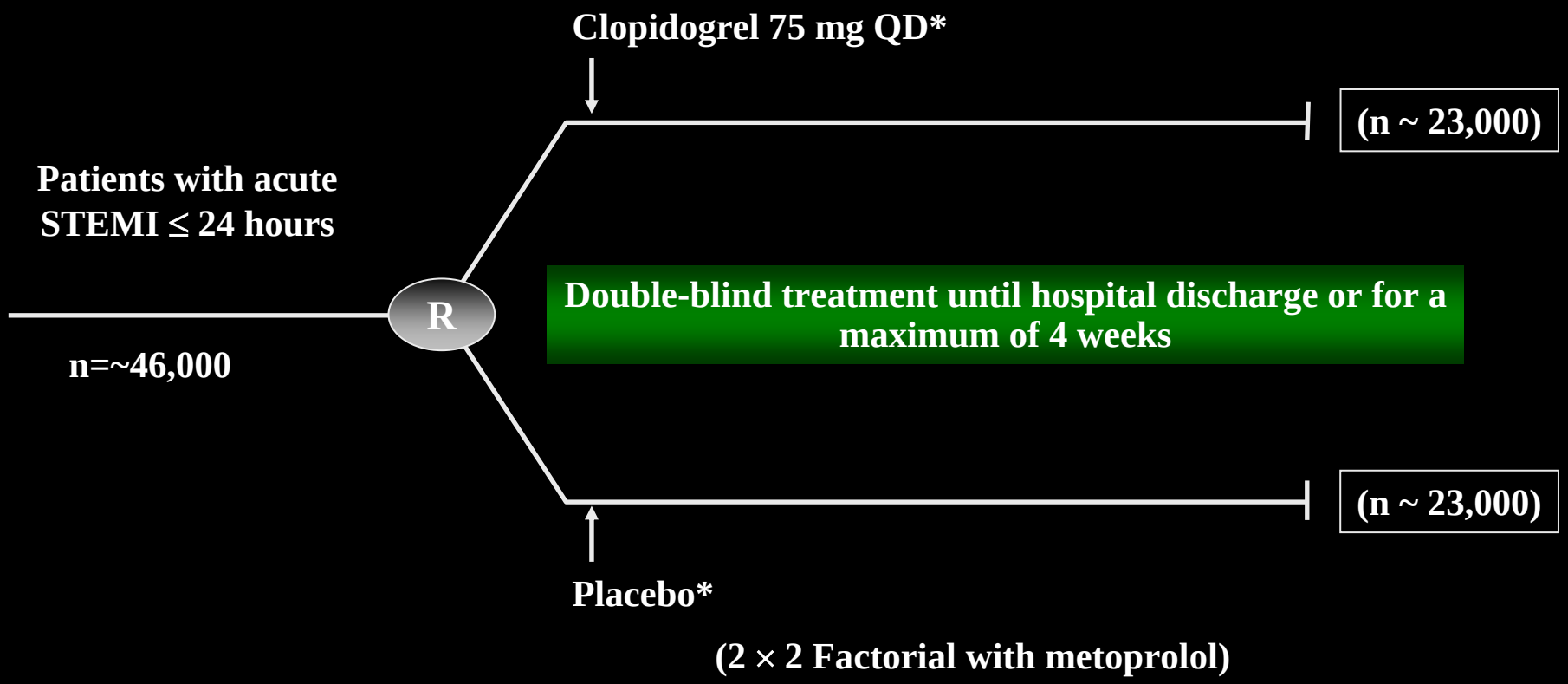
Clopidogrel reduced clinical events (death, MI) by 20% at 30 days



Conclusion

In patients with STEMI, who were receiving ASA & standard fibrinolytic therapy, clopidogrel therapy resulted in reduction of an occluded IRA, death or MI by the time of pre-discharge angiography and reduction in CV death, MI or recurrent ischemia at 30 days.

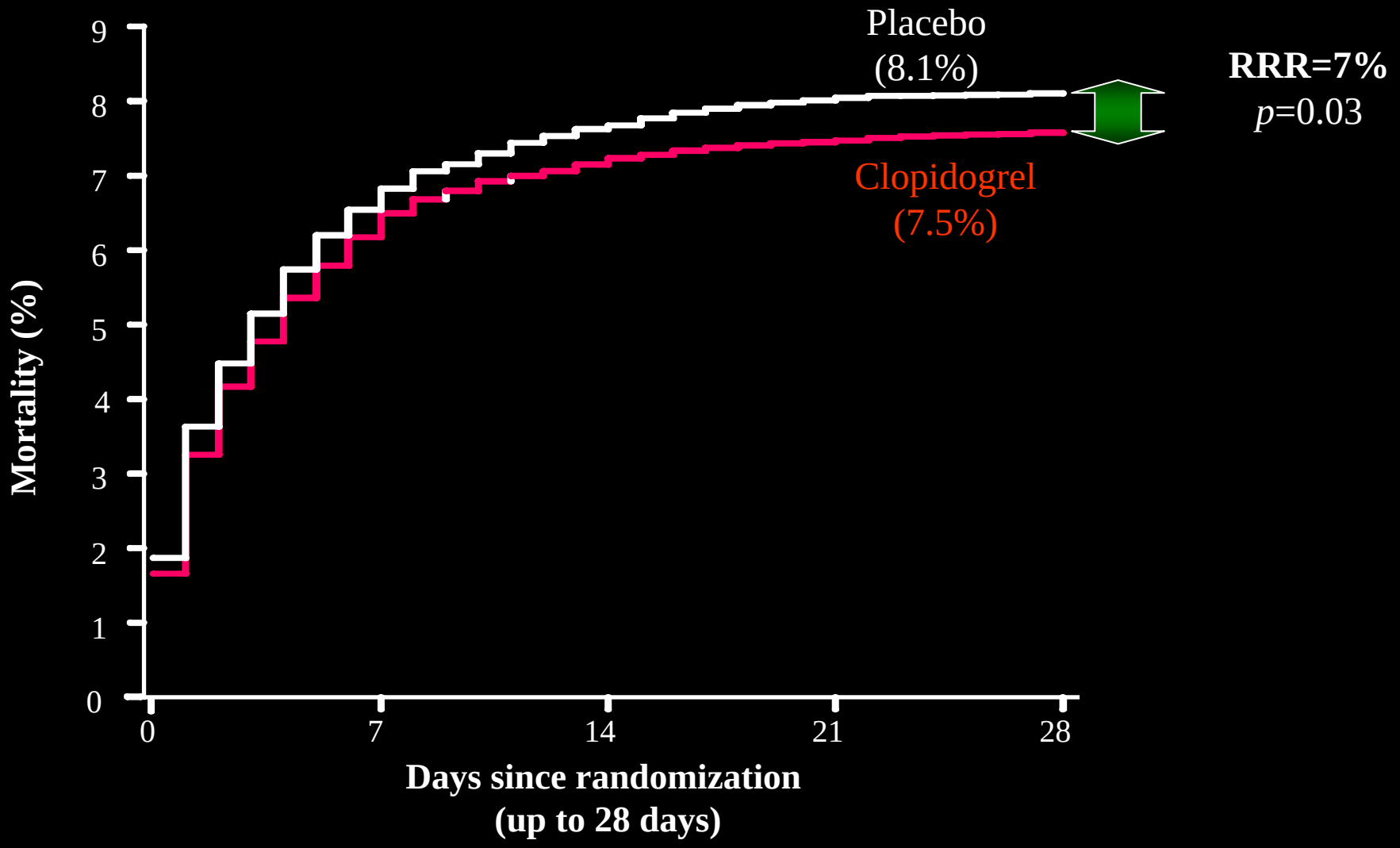
COMMIT/CCS-2:
ClOpidogrel & Metoprolol in Myocardial Infarction Trial



- Patients with Acute MI within the previous 24 h received ASA 162 mg & either placebo or clopidogrel 75 mg/d with no loading dose of clopidogrel
- 2 primary endpoints: 1) death, 2) the composite of death, non-fatal MI, or non-fatal stroke.

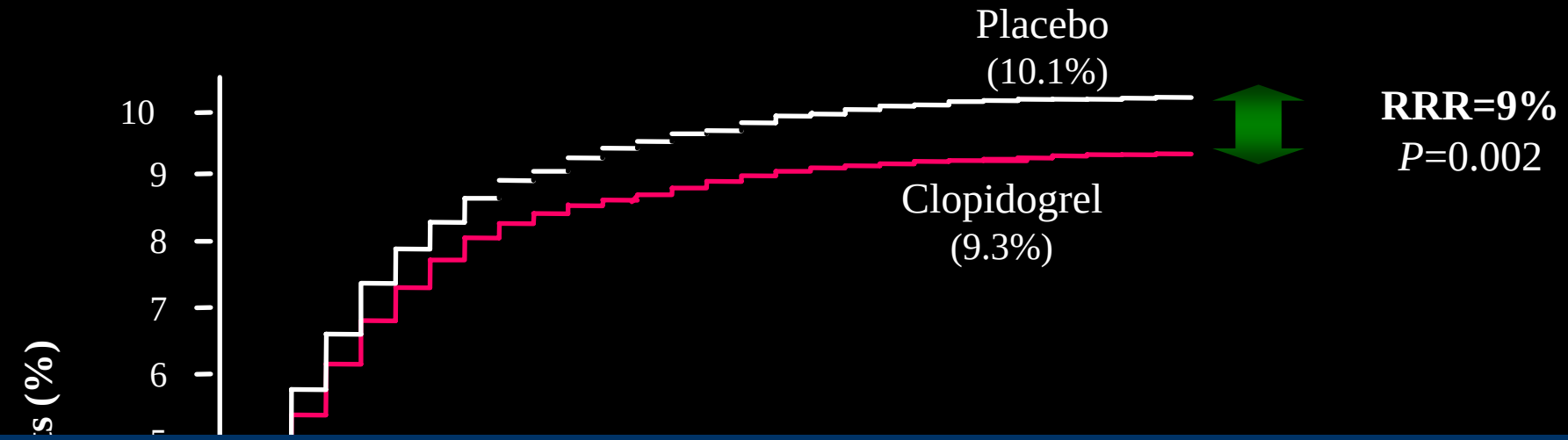
Lancet 2006;366:1607

Clopidogrel reduced mortality by 7%



Lancet 2006;366:1607

Clopidogrel Reduced the Composite of Death, MI, or Stroke by 9%

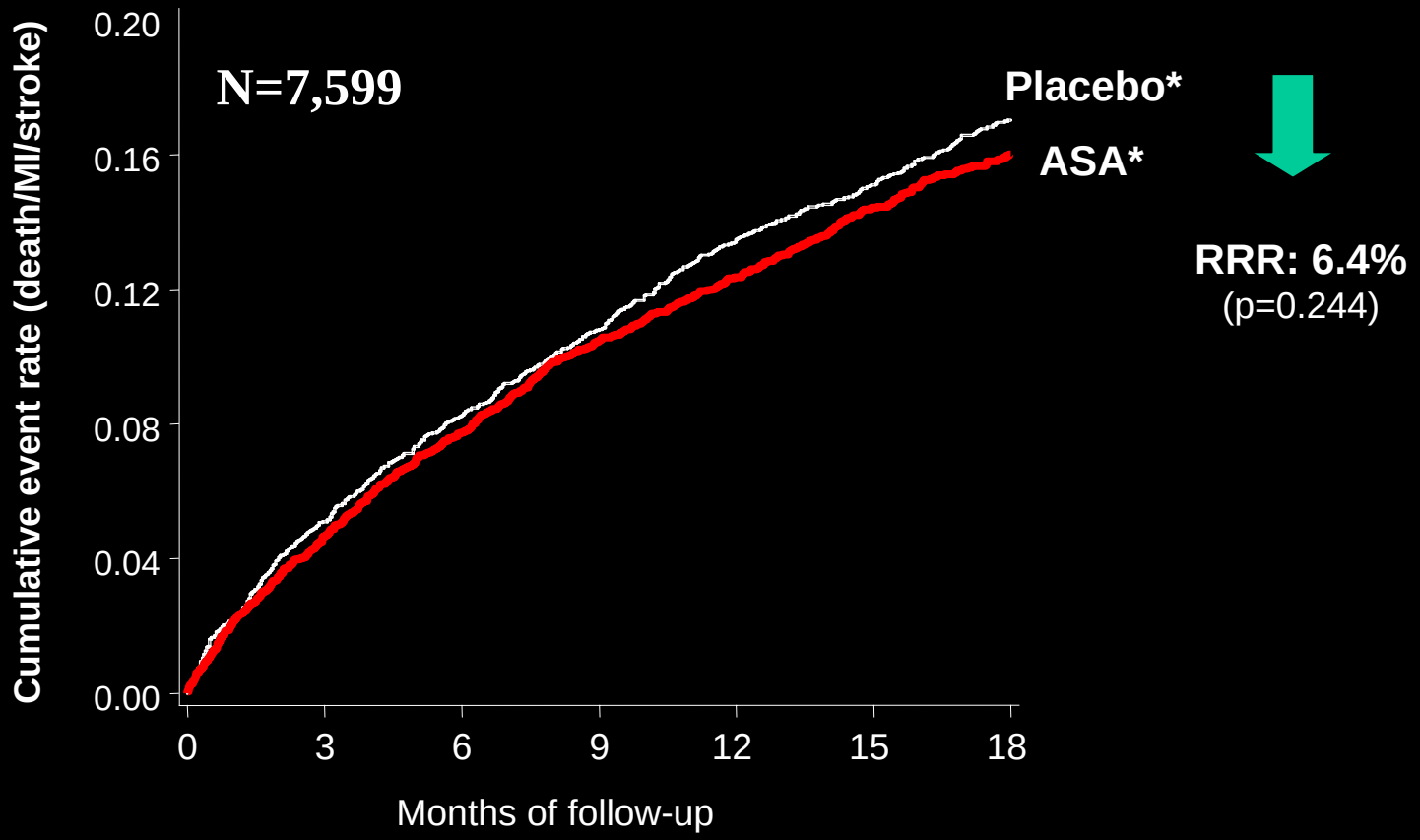


Conclusion

Clopidogrel (75 mg/day) on a background of standard therapy including ASA was beneficial for a wide range of acute STEMI patients.

Lancet 2006;366:1607

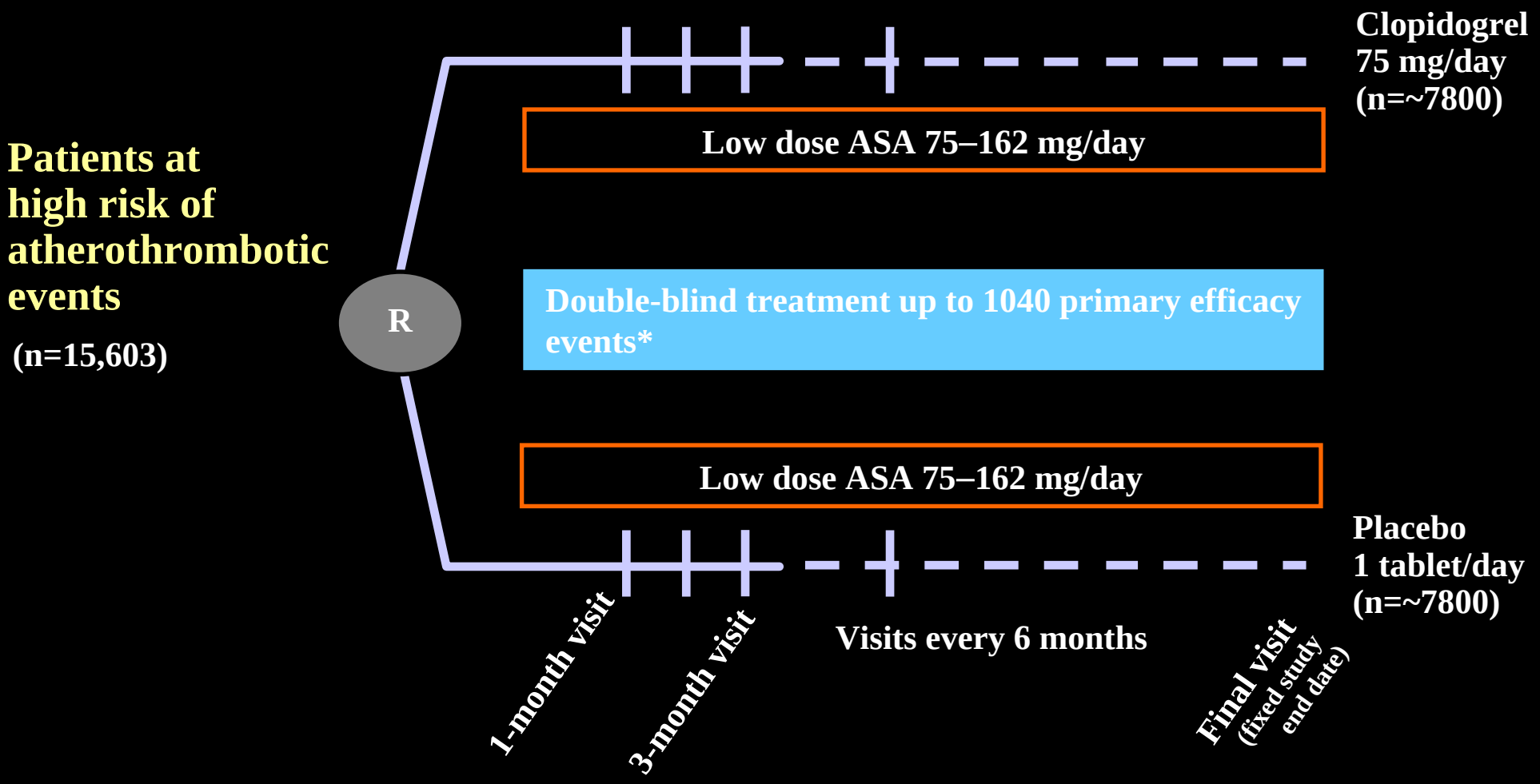
MATCH Management of Aterothrombosis with Clopidogrel in High-risk pts with recent TIA or IS



Adding ASA to clopidogrel provides a favorable non-significant trend in the reduction of atherothrombotic events in high-risk cerebrovascular patients.

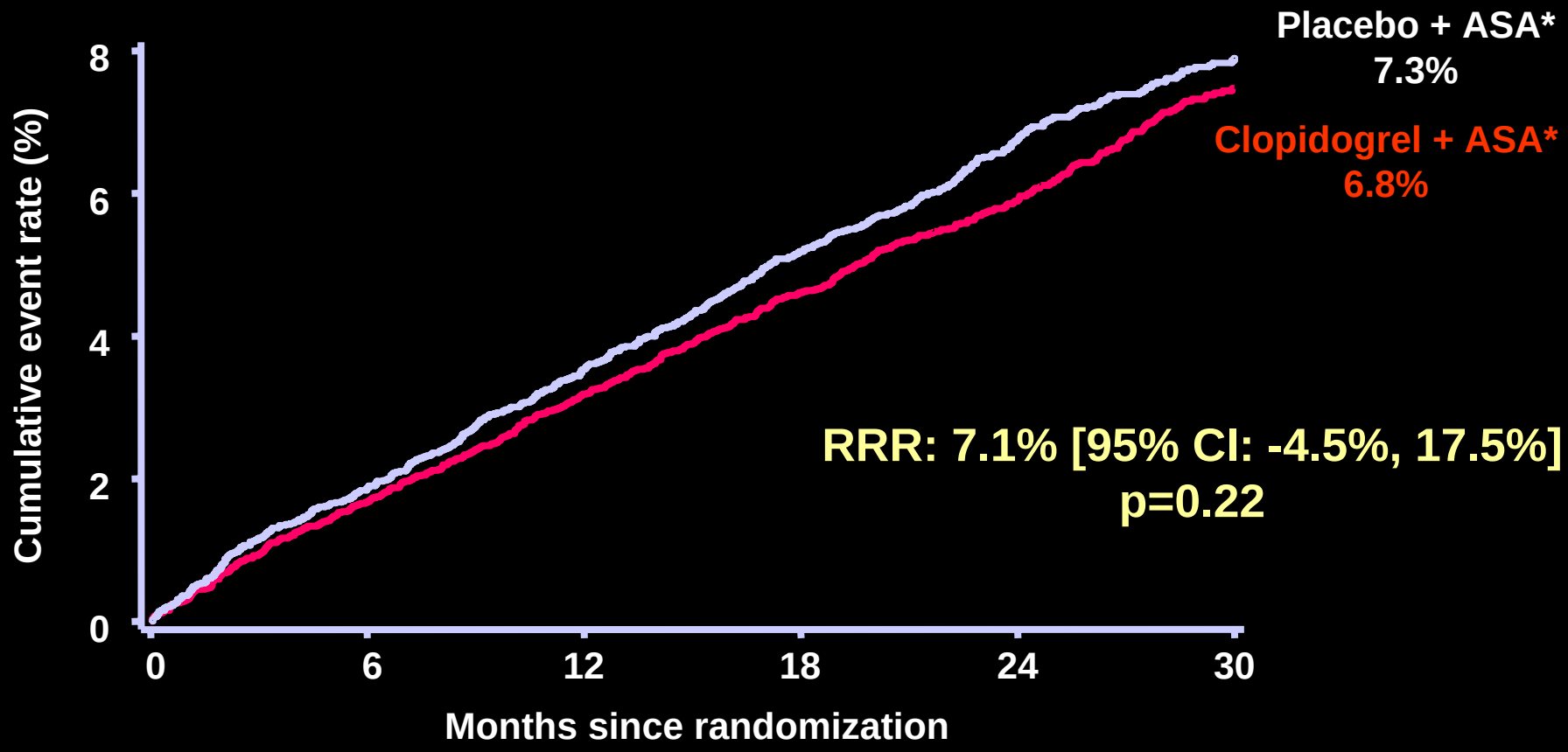
Lancet. 2004. **364:** 331

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



Primary endpoint: first occurrence of CV death, MI or stroke
Patients was followed until a fixed study end date, allowing at least 1040 primary efficacy endpoints.

Primary Outcome (MI, Stroke or CV Death)



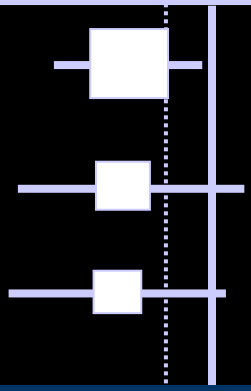
† First Occurrence of MI (fatal or non-fatal), stroke (fatal or non-fatal), or cardiovascular death

*All patients received ASA 75-162mg/day

Median follow-up was 28 months

Primary Outcome (MI/Stroke/CV Death) by Category of Inclusion Criteria

Population	N	RR (95% CI)	p value
Documented AT	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



Conclusion

In patients with atherothrombotic disease or multiple risk factors dual antiplatelet was not beneficial for prevention of CV events.

* First Occurrence of MI (fatal or not), Stroke (fatal or not), or CV Death
RF= Risk Factors, AT= Atherothrombosis

Bleeding Complications in Large RCTs

Trials	Ix	No	Duration	RR
Clopidogrel vs. ASA				
CAPRIE	High risk	19,185	1.9y	0.75 (0.63-0.90)
Dual vs. ASA				
CHARISTMA	High risk	15,603	28m	1.25 (0.97-1.61)
CLARITY	STEMI	3,491	8d	1.20 (0.66-2.20)
COMMIT	STEMI	45,852	28d	1.07 (0.84-1.36)
CREDO	PCI	2,116	12m	1.29 (0.86-1.93)
CURE	ACS	15,562	9m	1.38 (1.13-1.67)

Summary

From CAPRIE to CHARISMA

Clopidogrel monotherapy

- In CAPRIE, clopidogrel was more effective than ASA in reducing MI, stroke, or vascular death in patients with established atherosclerosis.

Dual therapy (aspirin plus clopidogrel)

- In CURE (UA/NSTEMI), clopidogrel on top of standard therapy demonstrate an early effect & sustained benefit throughout 12 month.

- In CHARISMA (high risk of atherosclerosis), aspirin plus clopidogrel was not effective in reducing death/MI/stroke compared to aspirin alone.

ACC/AHA Guidelines

Aspirin

Secondary prevention: IA, continued indefinitely
Primary prevention: 10-year CHD risk > 10%

Clopidogrel

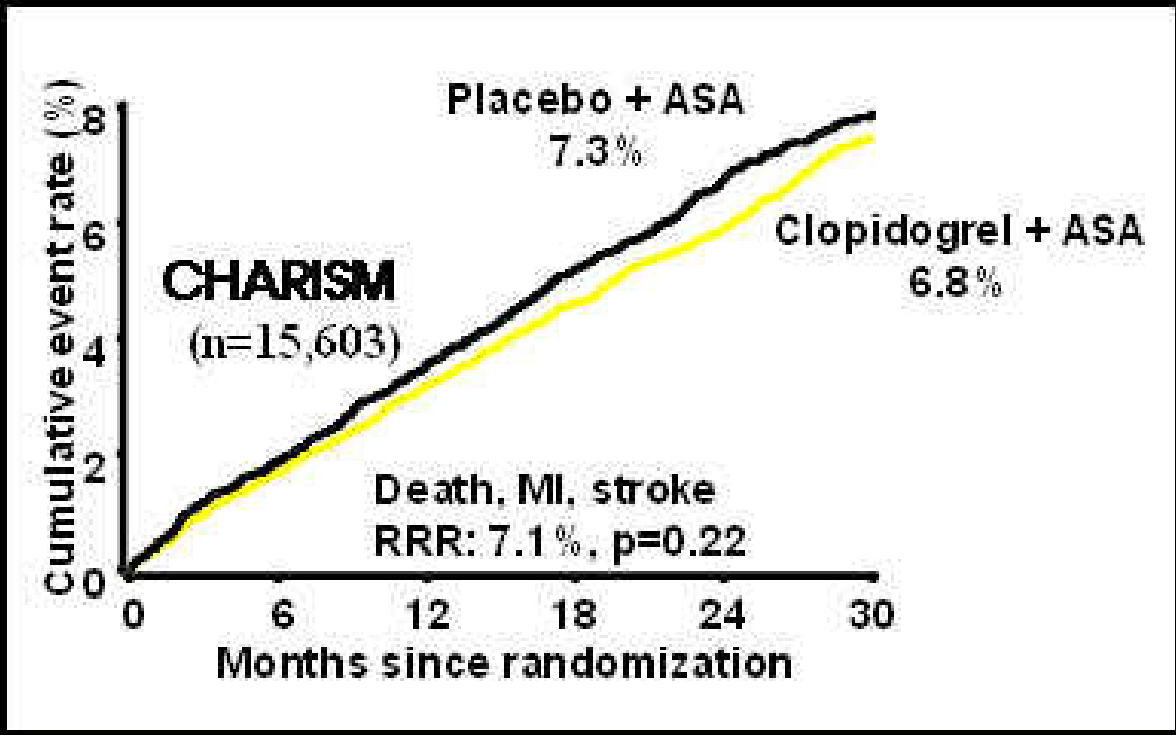
Dual therapy:

- PCI: IA (BMS, 1 month), IB (DES, 12 months)
- UA/NSTEMI: IA (1 month), IB (9 months)
- STEMI: IA (planned PCI), IA (medical therapy, 1 month)

An alternative to aspirin: IIa

Platelet Hypothesis

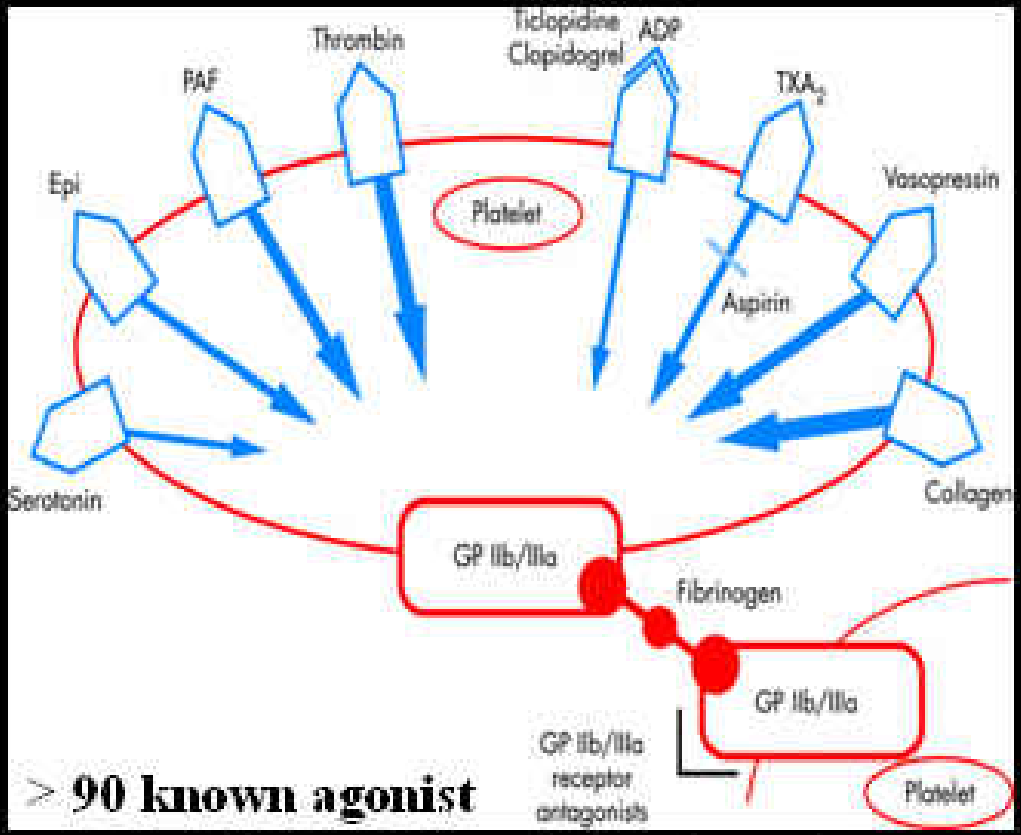
Axis of Evil, War Against The Platelet



Despite its proven benefits, many patients continue to suffer from acute vascular events.

Beyond Clopidogrel

The journey continue...



Potential limitations of clopidogrel
- incomplete inhibition
- variability to response
- prodrug

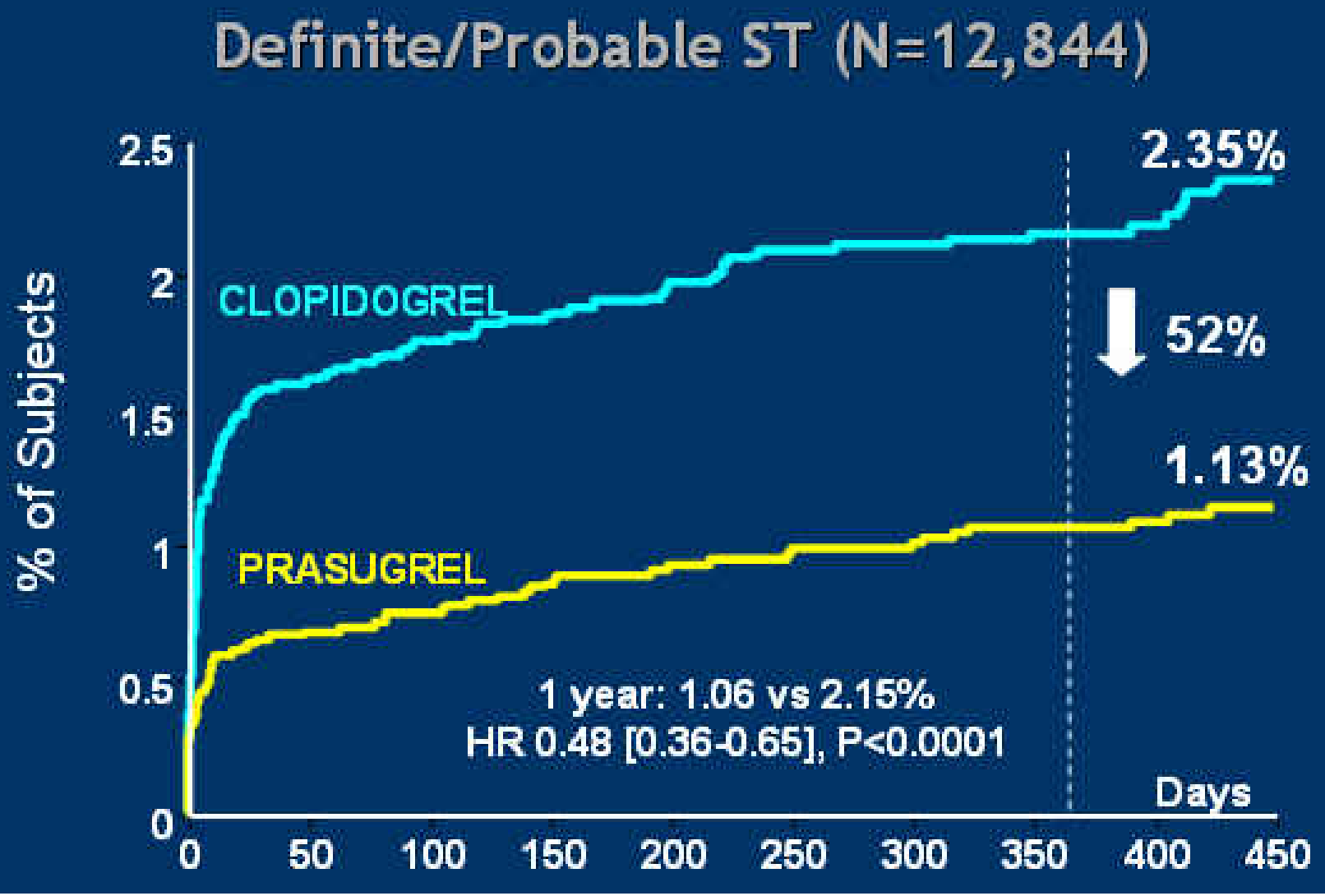
Rapid Action & Potent Effects

P_2Y_{12} blockers
- **prasugrel**
- **AZD6140**
- **cangrelol**

Other blockers

Early Benefits, Late Hazards!

TRITON-TIMI 38 Prasugrel Lowers Events but Ups Bleeding versus Clopidogrel in ACS



Conclusions

- Clopidogrel as anti-platelet monotherapy is beneficial for the secondary prevention in pts with documented atherosclerosis.
- Dual anti-platelet therapy is effective in secondary prevention after PCI and ACS. However, the overall benefit depends on a delicate balance between ischemic and bleeding risk.
- As new agents to overcome platelet resistance are available, clinical trials will be needed to define their place in therapy.