Stent thrombosis
Future directions

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Disclosures

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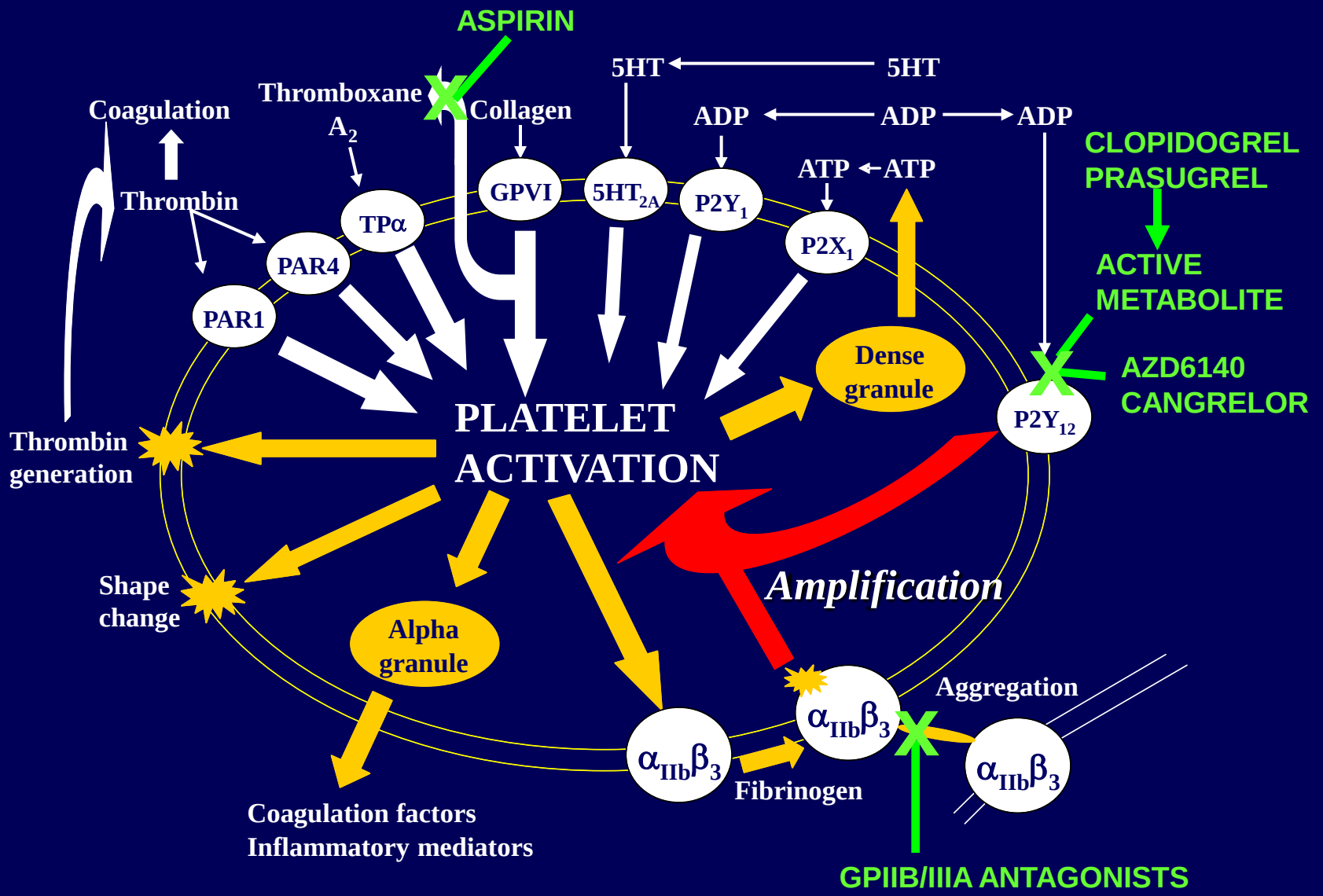
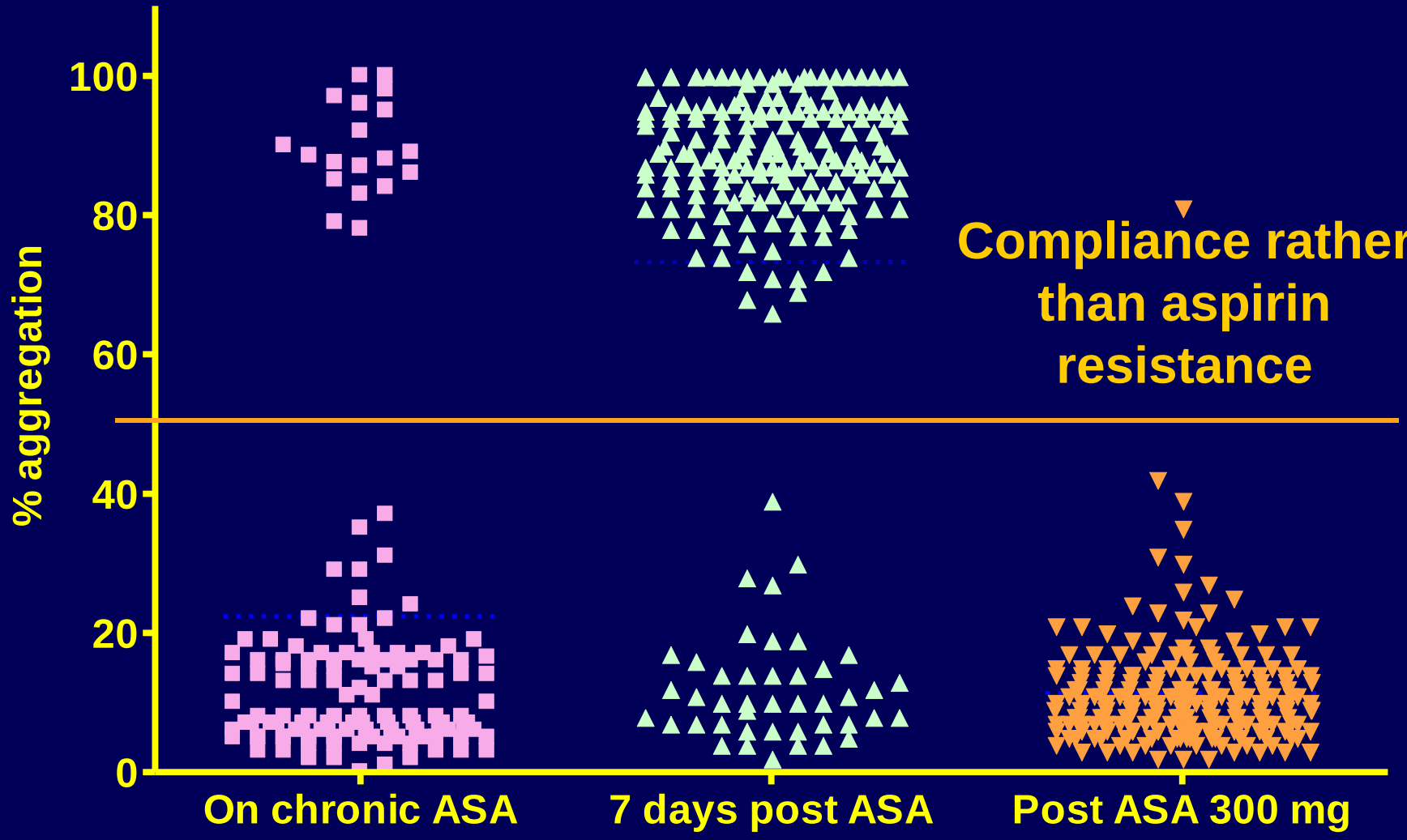
Platelet Activation Mechanisms



Storey RF. *Current Pharmaceutical Design 2006*

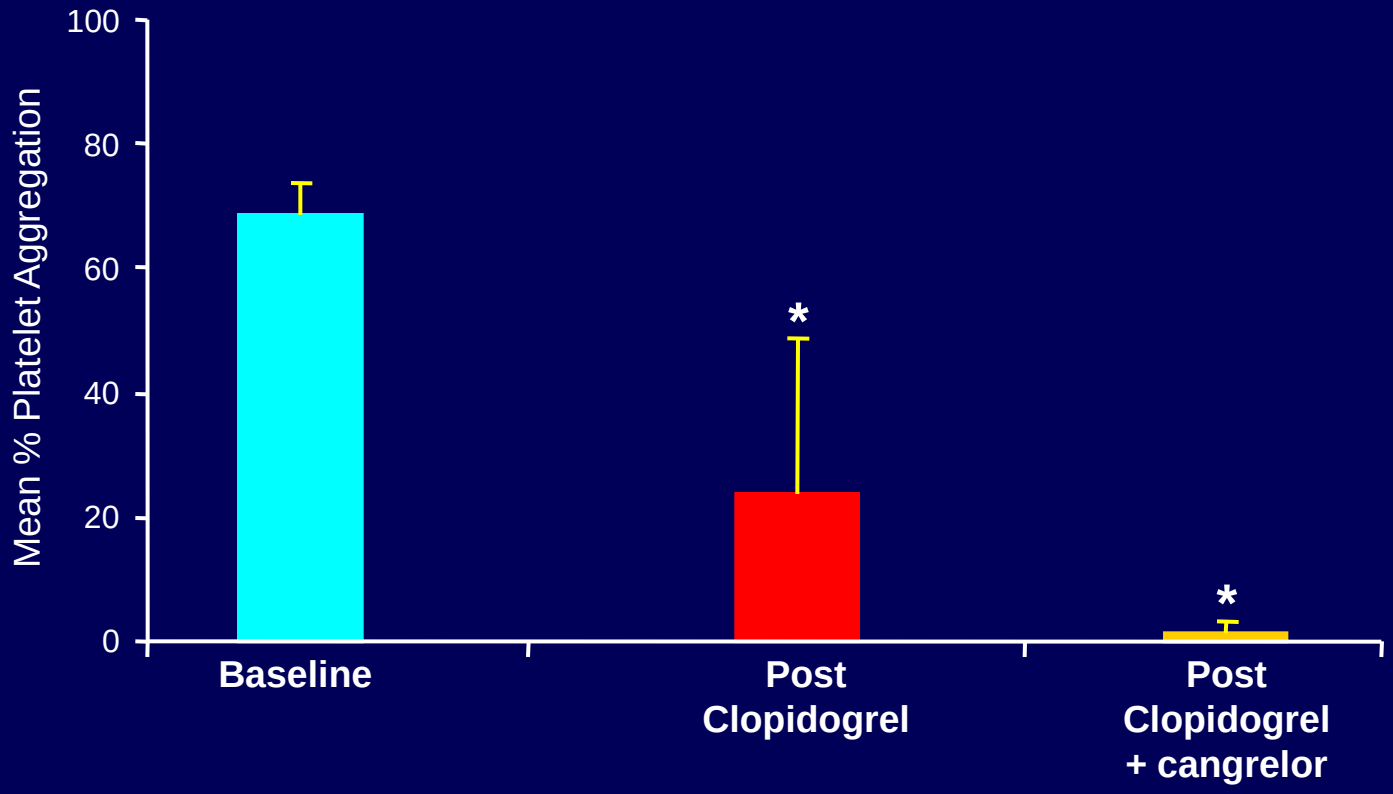
Arachidonic acid-induced platelet aggregation in 190 IHD patients



Schwartz et al. Am J Cardiol 2005

Variable response to clopidogrel with incomplete $P2Y_{12}$ receptor blockade

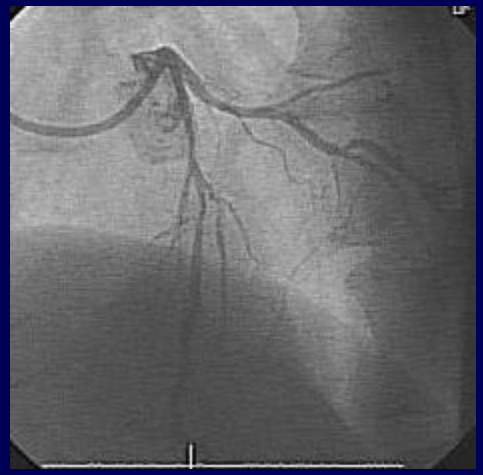
Final response to 20 µM ADP before and after clopidogrel 300 mg followed by 75 mg daily for 4-7 days in patients undergoing PCI +/- 150 nM cangrelor added in vitro

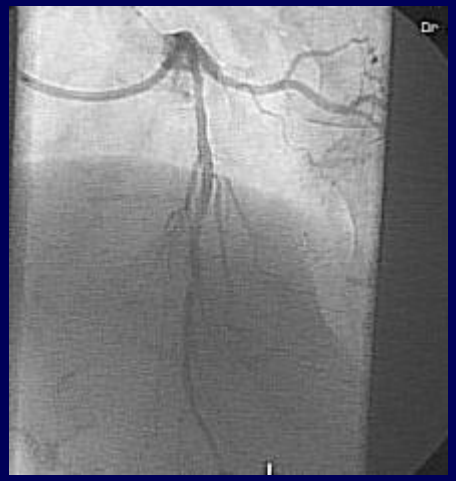


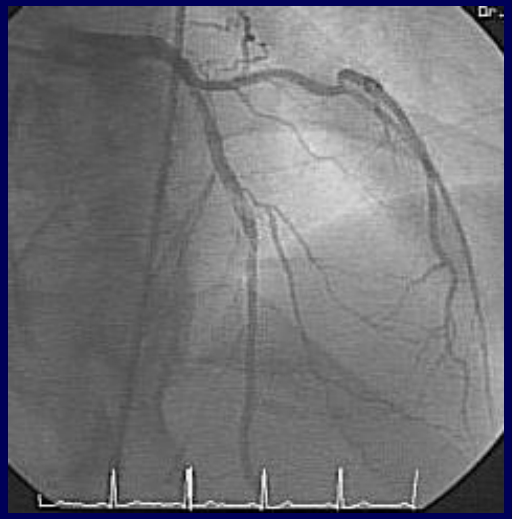
Storey RF et al. *Platelets* 2002; 13: 407-413

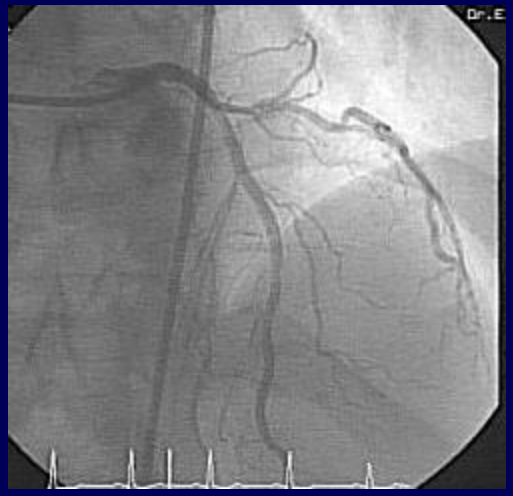
* *P*<0.05

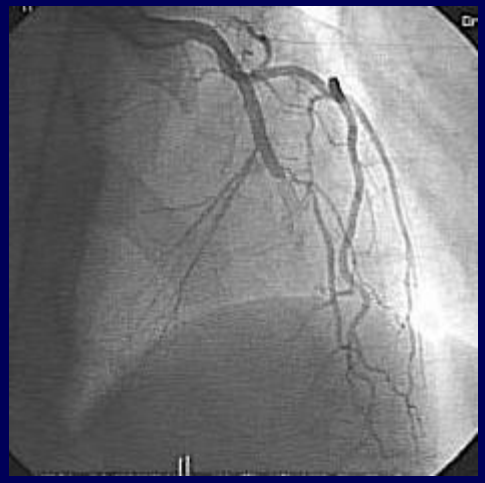
Subacute stent thrombosis

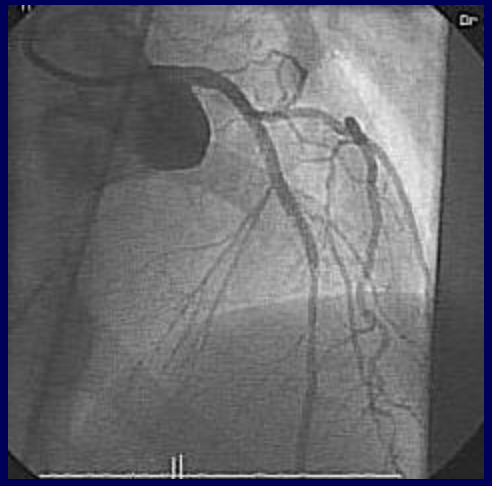






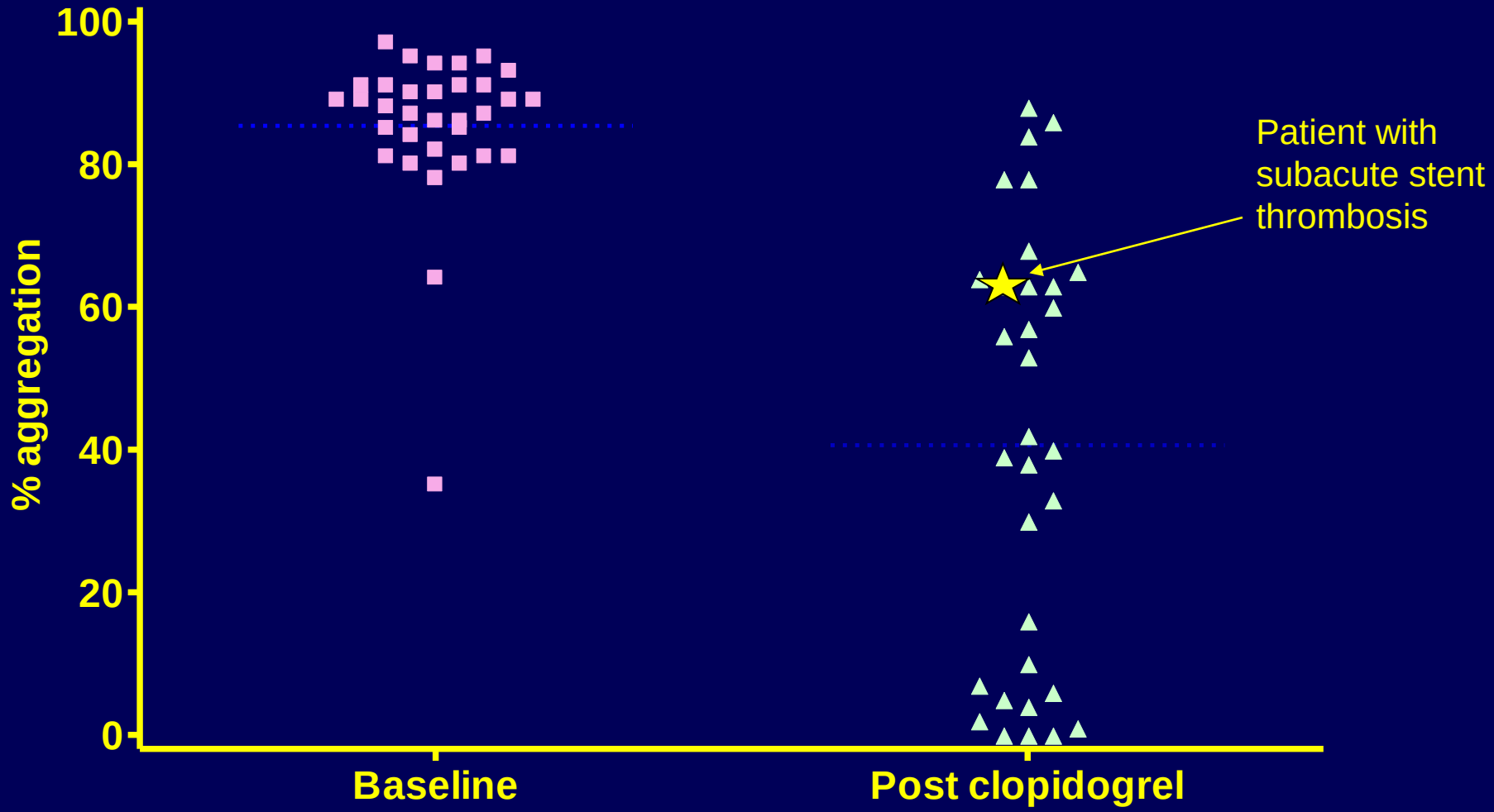






Platelet aggregation before and 4 hours after clopidogrel 600 mg in patients undergoing PCI

Whole blood single platelet counting in response to ADP 10 uM

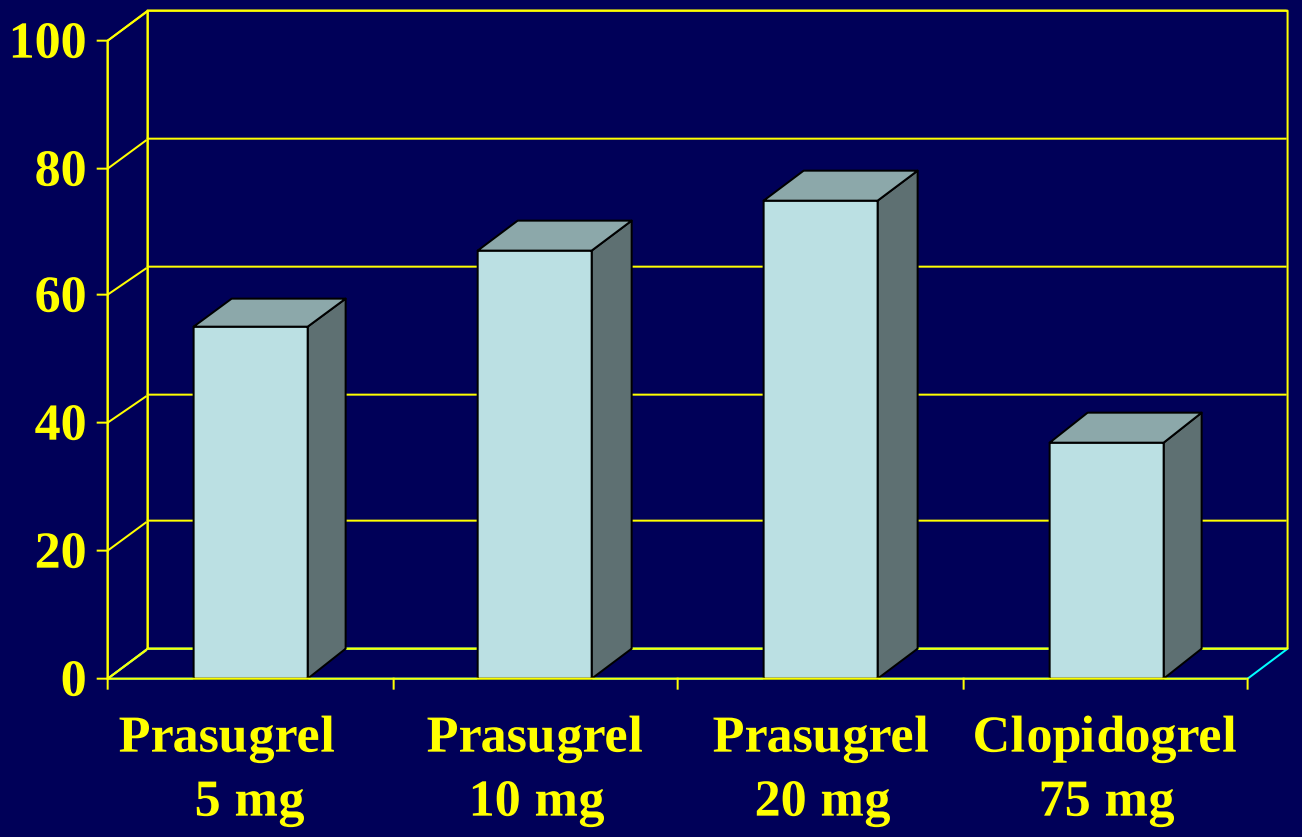


Smith SMG et al. *Platelets* 2006; 17: 250-258

Prasugrel

- Novel thienopyridine (CS-747) in phase III development (PCI in ACS patients)
- Different pathways of metabolism to clopidogrel and higher potency probably related to more efficient production of active metabolite

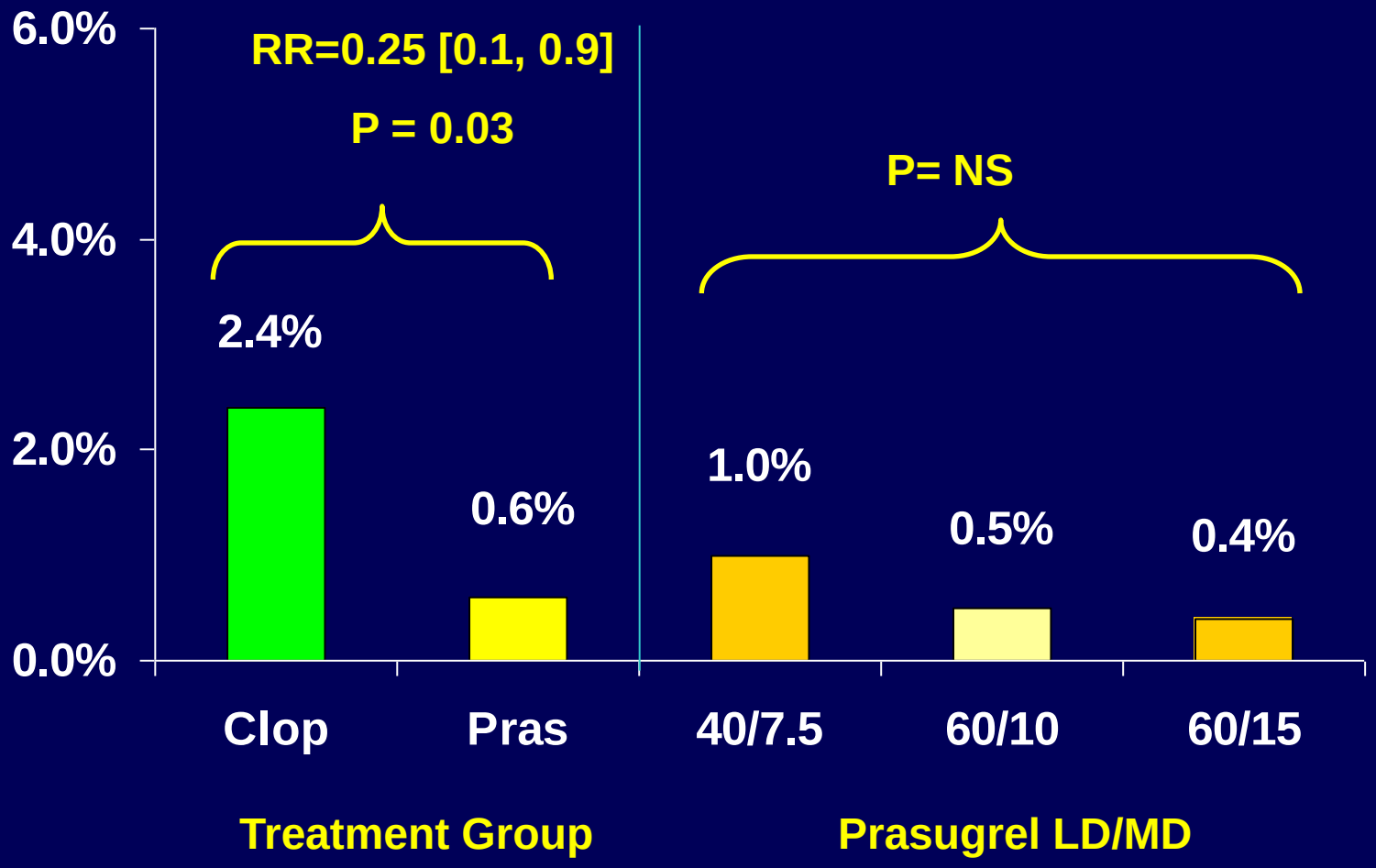
Prasugrel 5-20 mg daily vs clopidogrel 75 mg daily in healthy volunteers – inhibition of ADP induced platelet aggregation at 10 days



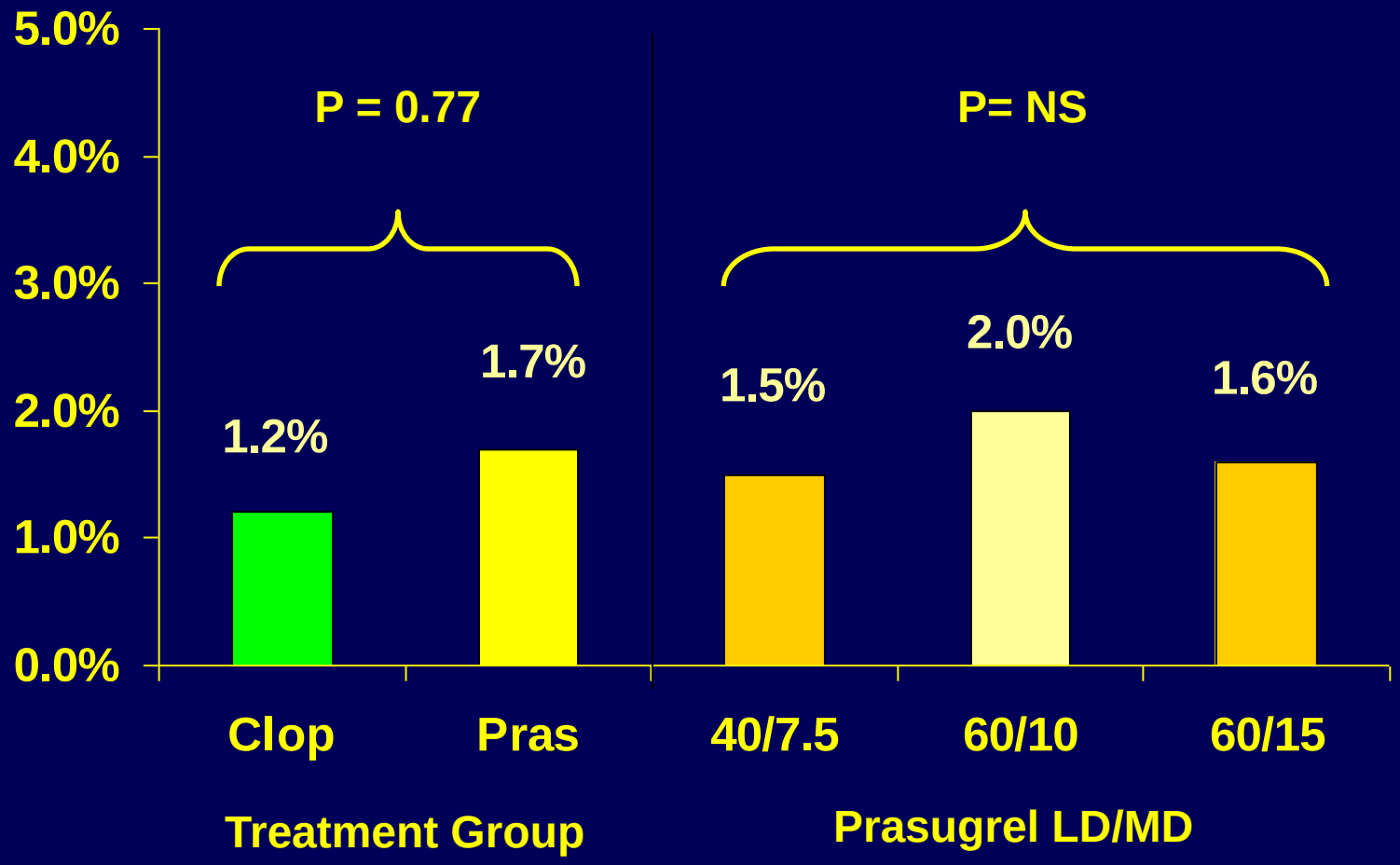
JA Jakubowski et al. ACC Annual Scientific Session 2005.

Clinical Target Vessel Thrombosis

Target Vessel Revasc or Documented Total Occlusion



Significant Non-CABG Bleeding 30 d (%) (TIMI Major + Minor) – Primary Endpoint



TRITON – TIMI 38

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA

N= 13,000

Double-blind

PRASUGREL

CLOPIDOGREL

Median duration of therapy - 12 months

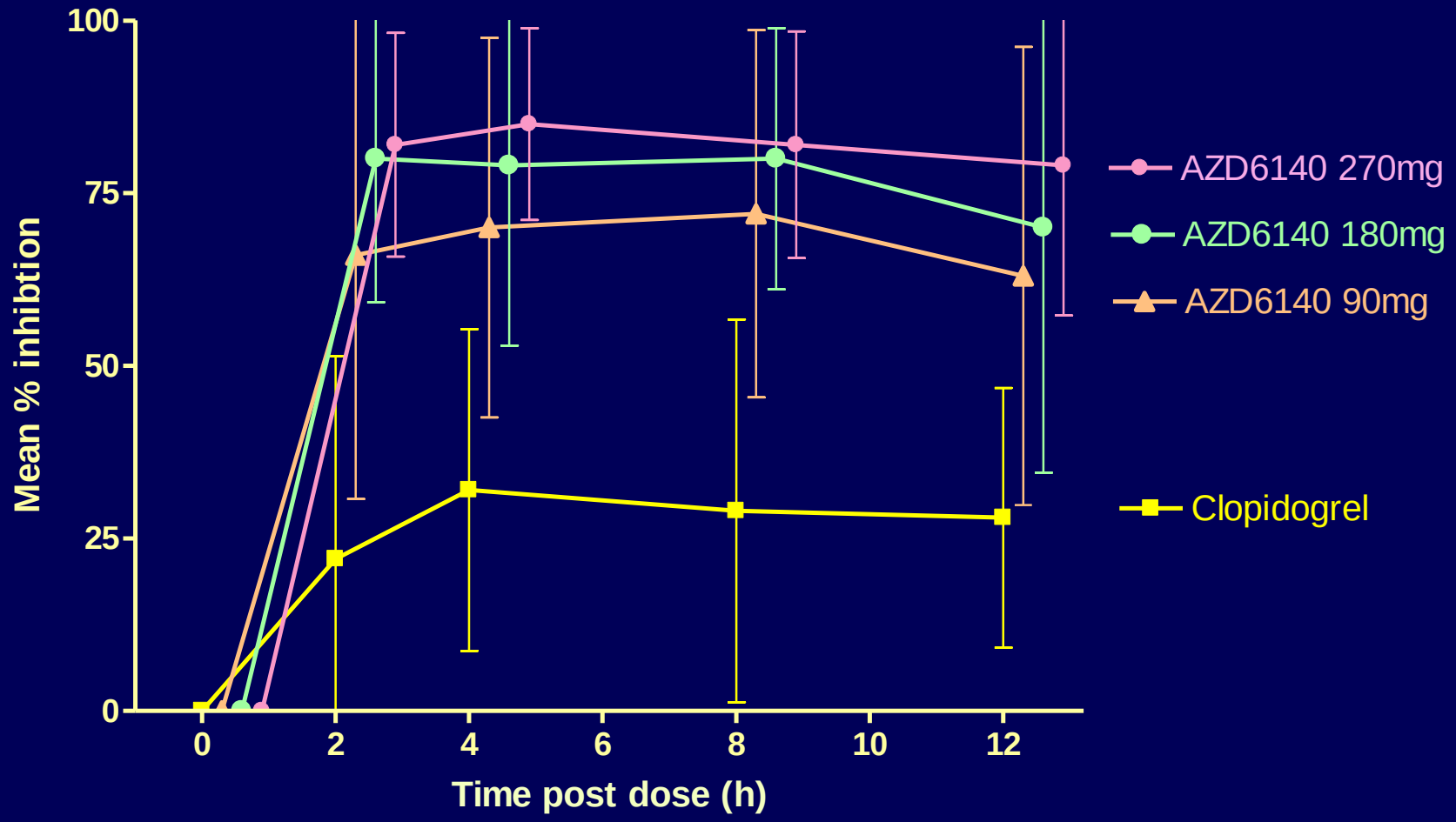
1º endpoint:	CV death, MI, Stroke
2º endpoints:	CV death, MI, Stroke, Re-ischemia
	CV death, MI, UTVR

AZD6140

- **Class: CPTP* (non-thienopyridine)**
- **Reversible platelet $P2Y_{12}$ receptor antagonist**
- **Orally active**
- **Rapid onset of action (2 h) with or without a loading dose**
- **Acts directly (no metabolic activation required)**
- **Plasma $t_{½}$ ~12 h**

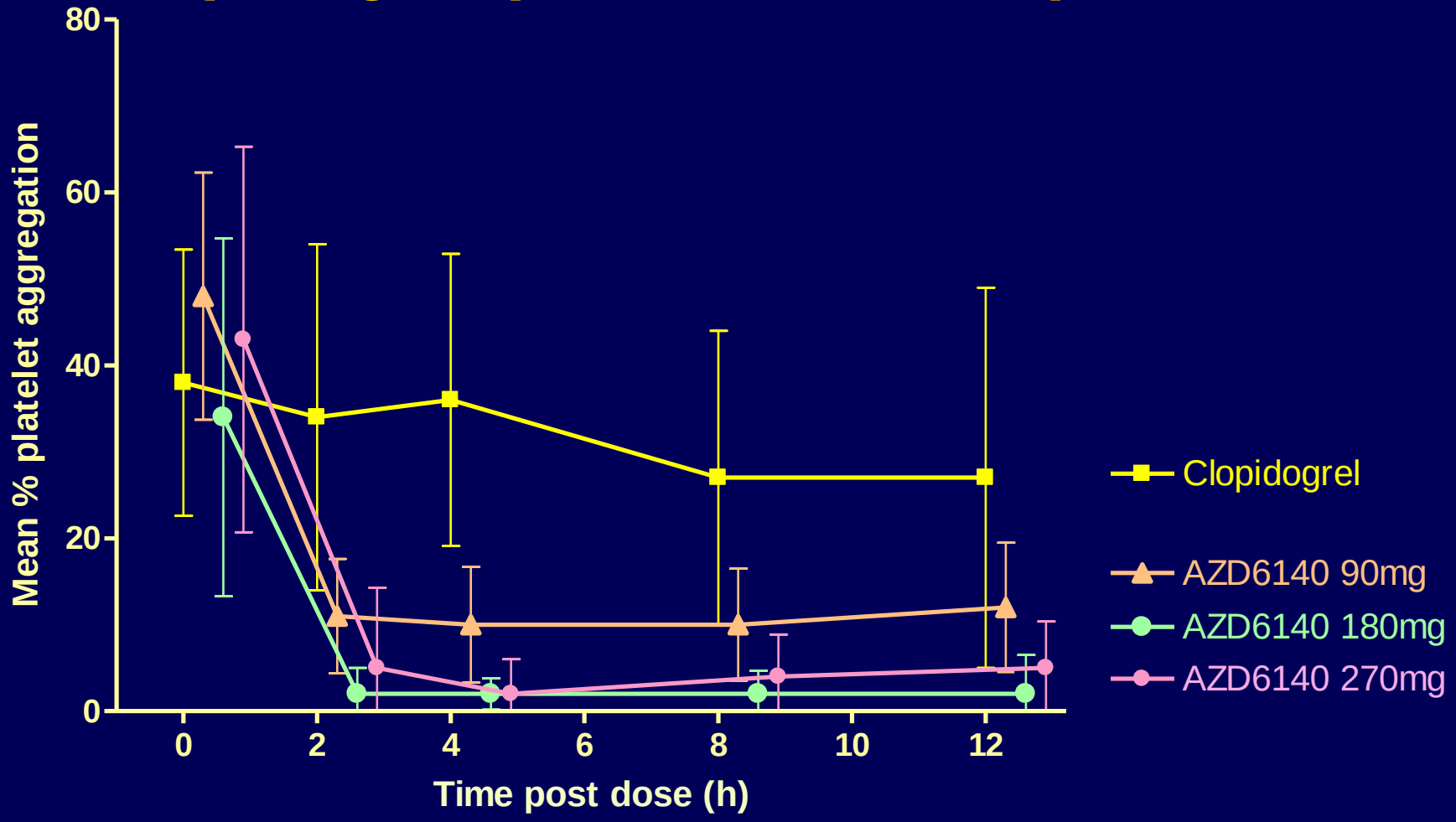
*cyclo-pentyl-triazolo-pyrimidine

Comparison of clopidogrel 300 mg loading dose vs AZD6140 90-270 mg loading doses in ACS patients



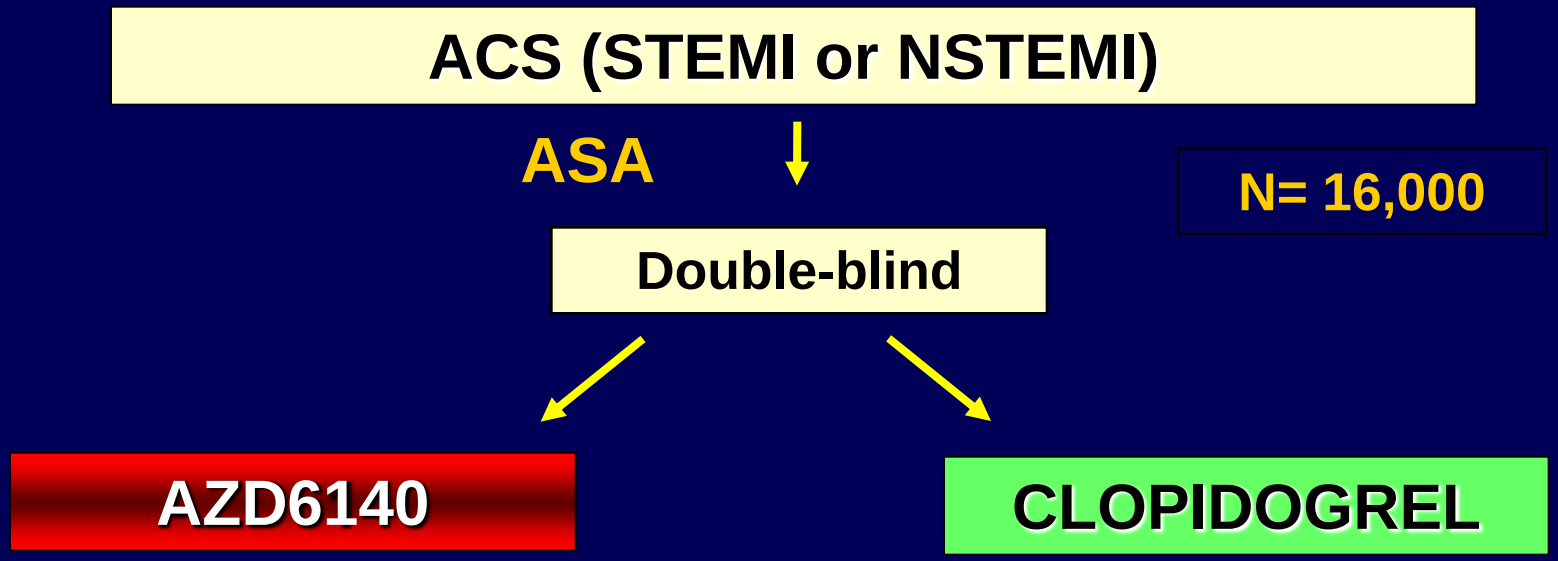
Inhibition of platelet aggregation induced by ADP 20 μM

Suppression of residual platelet aggregation response by AZD6140 in clopidogrel-pretreated ACS patients



Platelet aggregation induced by ADP 20 μM

PLATO



- Estimated number of countries: 40
- Estimated number of sites: 1,000
- Estimated trial size: 16,000 patients
- Patient recruitment to start late 2006

Cangrelor

- Stabilised ATP analogue
- Reversible platelet $P2Y_{12}$ receptor antagonist
- Intravenous use only
- Onset of action within minutes
- Acts directly (no metabolic activation required)
- Plasma $t_{½}$ < 9 minutes
- Phase 3 studies - CHAMPION

Stent coatings

- Higher incidence of late stent thrombosis seen with DES in BASKET-LATE study and in follow up studies of Taxus and Cypher stents
- Heparin coated stents – no convincing evidence of clinical benefit
- Stem cells – under investigation to assess whether they can be used to promote endothelialisation
- Need for new agents, either systemic or stent coated, that reduce neointima formation without impairing endothelialisation

CONCLUSIONS (1)

- True aspirin resistance is rare
- Compliance is important – patients should be advised of the reasons for antiplatelet therapy, intended duration of treatment and risks of poor compliance

CONCLUSIONS (2)

- Inadequate $P2Y_{12}$ receptor blockade by clopidogrel in some patients is probably a major risk factor for stent thrombosis and 3 new $P2Y_{12}$ antagonists are in phase 3 development to address this:
  - Prasugrel (oral thienopyridine)
  - AZD6140 (oral reversible antagonist)
  - Cangrelor (short-acting iv antagonist)

CONCLUSIONS (3)

- DES appear to increase the risk of late stent thrombosis and further work is required to establish whether novel stent coatings or systemic agents can reduce subacute and late thrombosis risk