

SOUTHWEST CARDIOVASCULAR SUMMIT 2008

James de Lemos, MD - Controversies in Antiplatelet Therapy

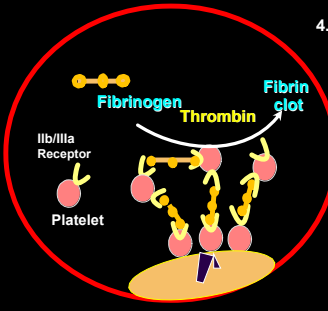
Controversies in Antiplatelet Therapy

James de Lemos, MD

UT Southwestern Medical Center
Dallas, TX

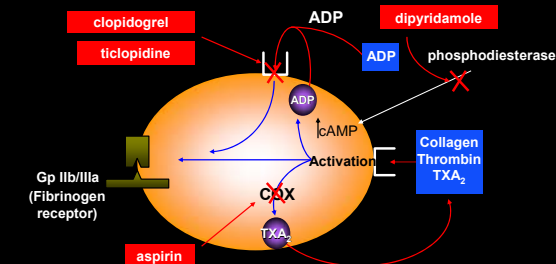


Pathophysiology of Acute Coronary Syndromes and Potential Pharmacologic Interventions



1. Plaque rupture, Cholesterol content, Inflammation (hs-CRP) Infection (Statins)
2. Platelet adhesion/ activation/ aggregation (ASA, IIb/IIIa inhibitors/ Thienopyridines)
3. Activation of clotting cascade - Thrombin (Heparin/LMWH/Bivalirudin)
4. Downstream from thrombus myocardial ischemia/necrosis (Beta-blockers, Nitrates etc)

Mechanisms of Action of Available Oral Antiplatelet Therapies



ADP = adenosine diphosphate, TXA₂ = thromboxane A₂, COX = cyclooxygenase.
Adapted from Schafer Al. *Am J Med.* 1996;101:199-209.

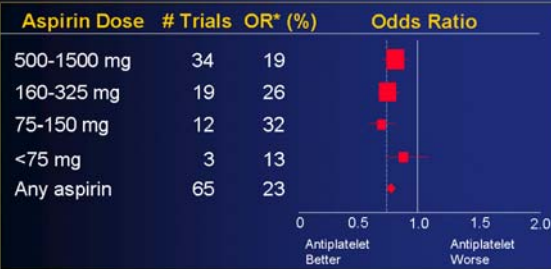
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- Stents+ surgery+ clopidogrel?
- Is there still a role for GP IIb/IIIa inhibitors? Upstream or cath lab?

Antithrombotic Trialists' Collaboration Efficacy of Aspirin Doses on Vascular Events in High-Risk Patients



* Odds reduction.
Treatment effect $P < 0.0001$.
Adapted with permission from the BMJ Publishing Group. Antithrombotic Trialists' Collaboration.
BMJ. 2002;324:71-86.

CURE Study

Major Bleeding by ASA Dose

ASA Dose	Clopidogrel + ASA*	Placebo + ASA*
<100 mg	2.6%	2.0%
100-200 mg	3.5%	2.3%
>200 mg	4.9%	4.0%

*Other standard therapies were used as appropriate.

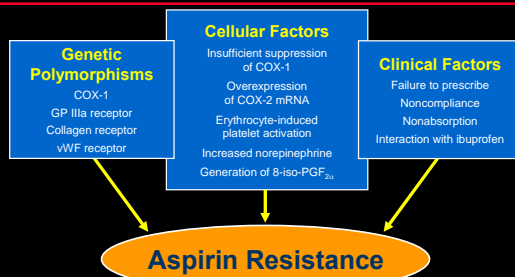
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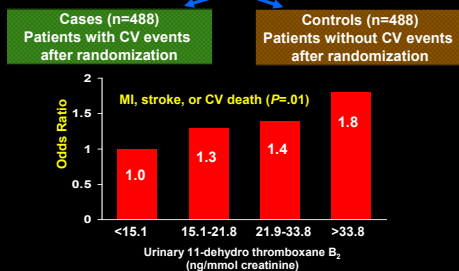
Aspirin Resistance: More Than Just a Laboratory Curiosity?



Adapted with permission from Bhatt DL. *J Am Coll Cardiol*. 2004;43:1127-1129.

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

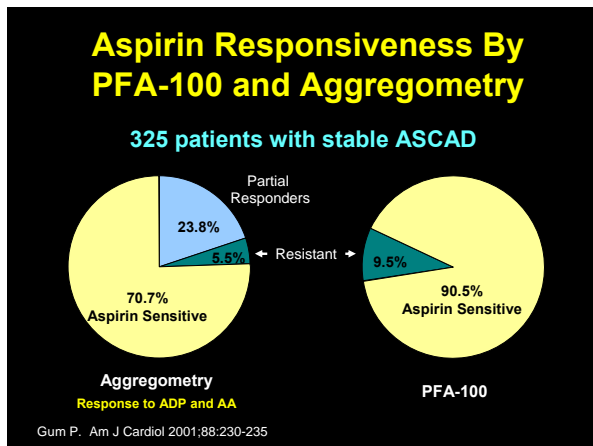
5529 patients from HOPE study with baseline urine samples

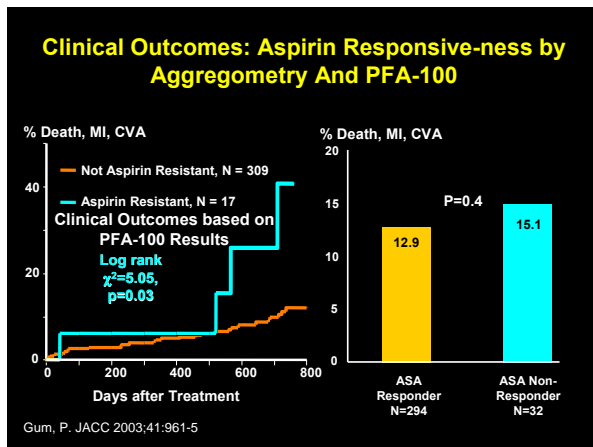


Adapted with permission from Eikelboom JW, et al. *Circulation*. 2002;105:1650-1655.

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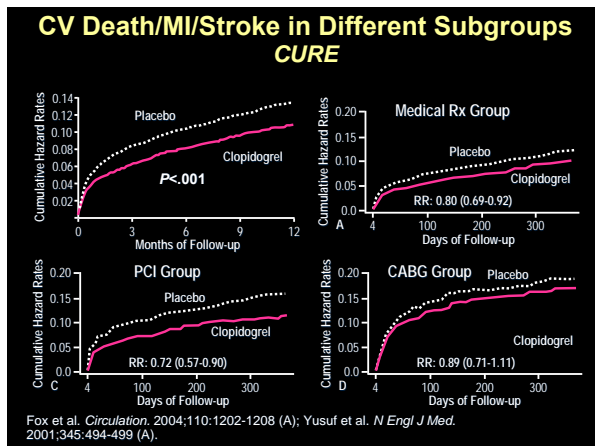


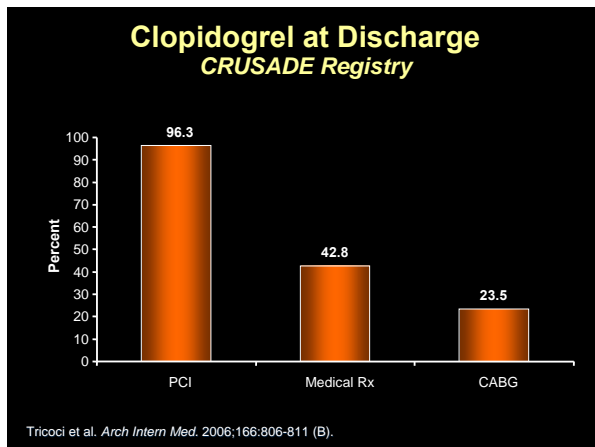
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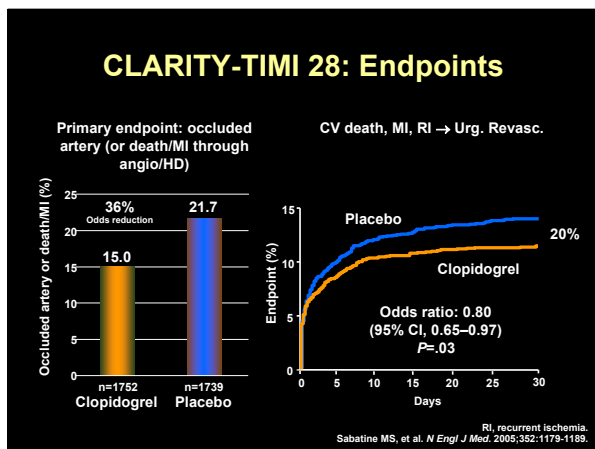
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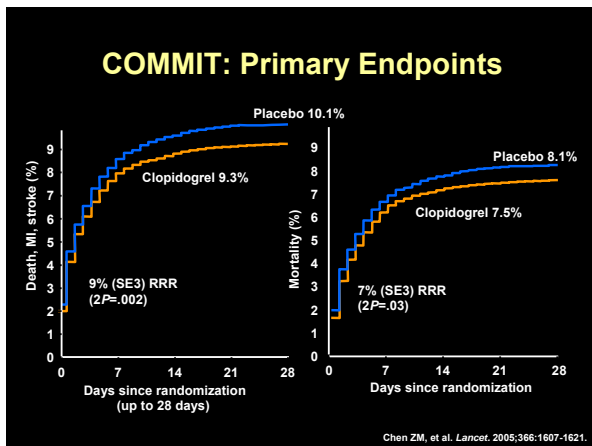


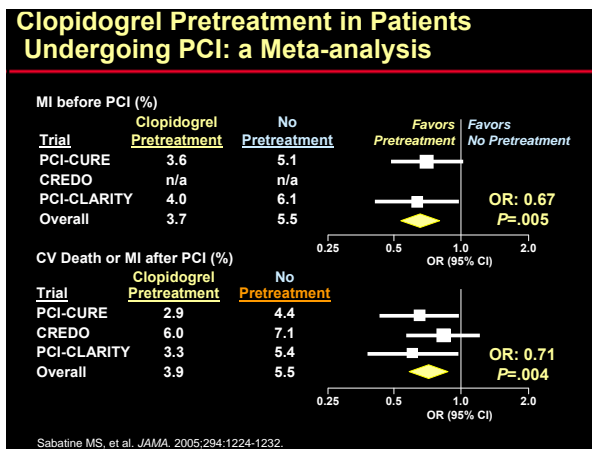


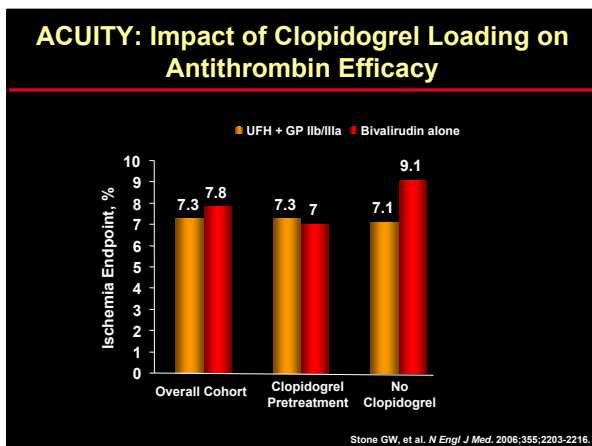


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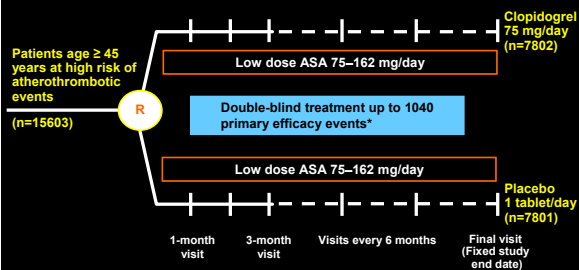
Major/Life-Threatening Bleeds within 7 Days of CABG Surgery

	Plac	Clop	RR	p
Stopped \leq 5 days prior to CABG	N = 476	N = 436		
Pts with Maj/LT Bleeds	6.3%	9.6%	1.53	0.06
Stopped > 5 days prior to CABG	N = 454	N = 456		
Pts with Maj/LT Bleeds	5.3%	4.4%	0.83	0.53

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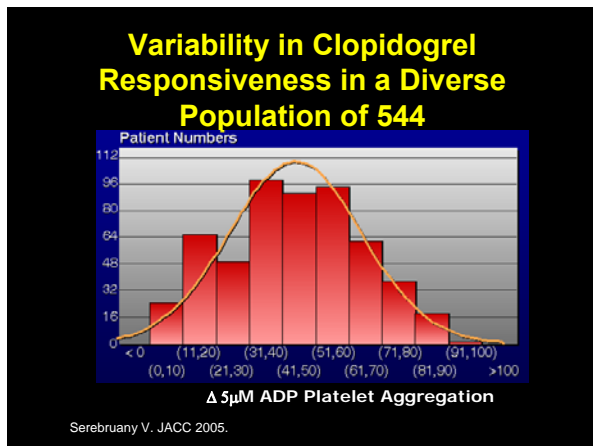
CHARISMA Trial Design

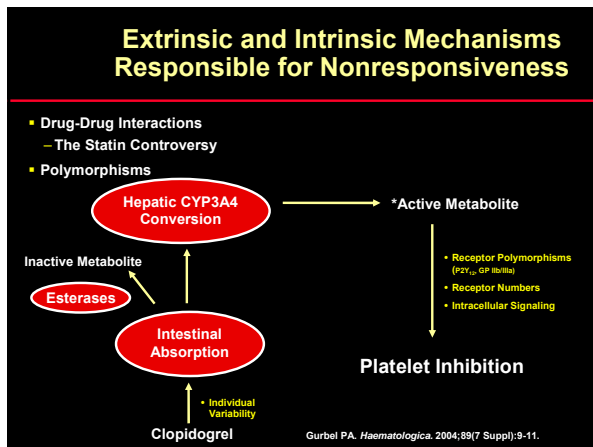


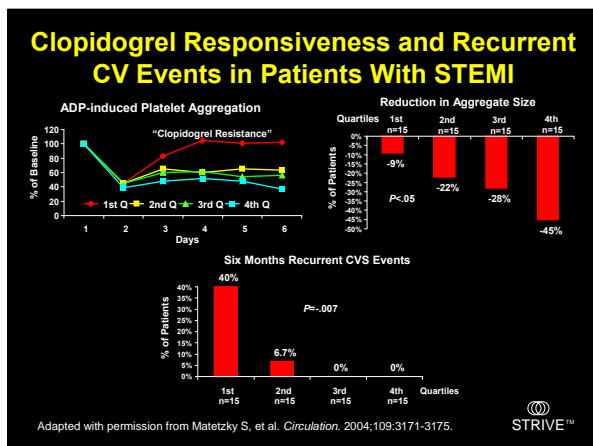
* MI (fatal or non-fatal), stroke (fatal or non-fatal), or cardiovascular death; event-driven trial
Bhatt DL et al. Am Heart J 2004; 148: 263-268.

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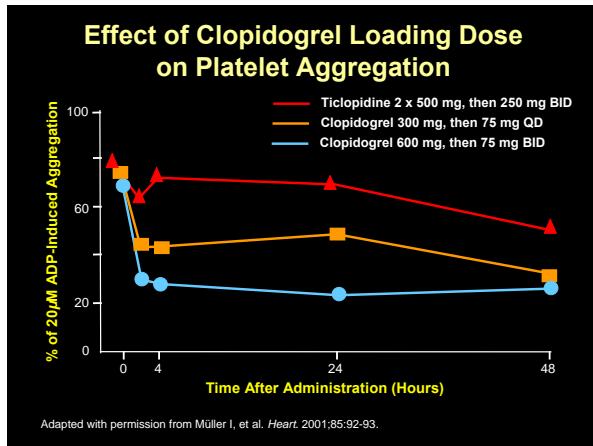


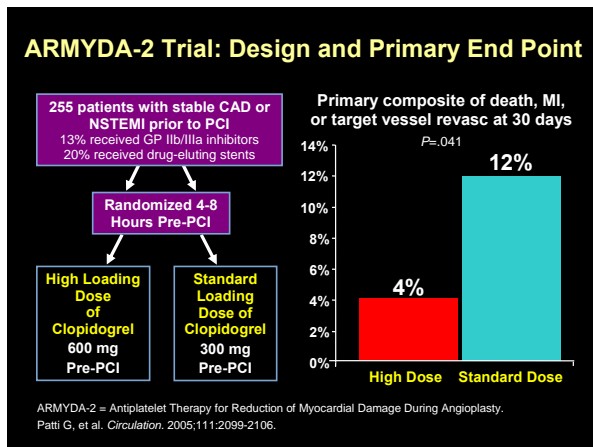


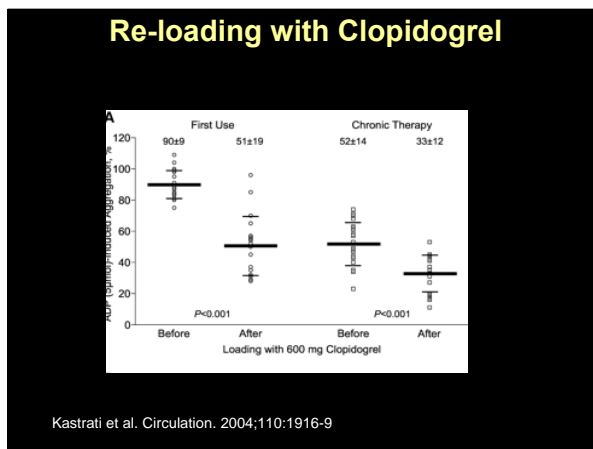


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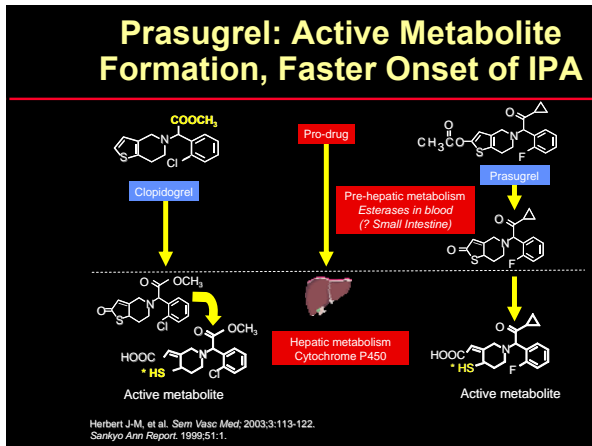


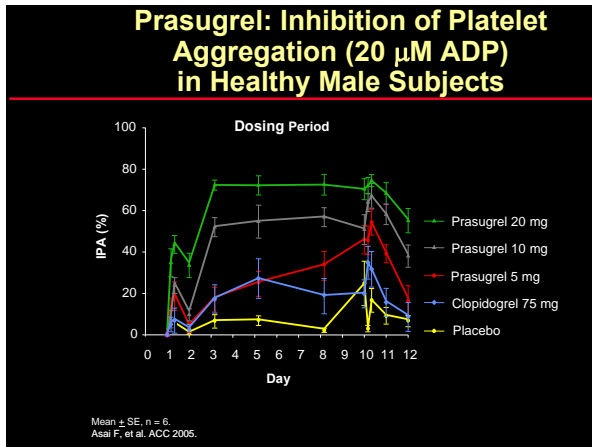


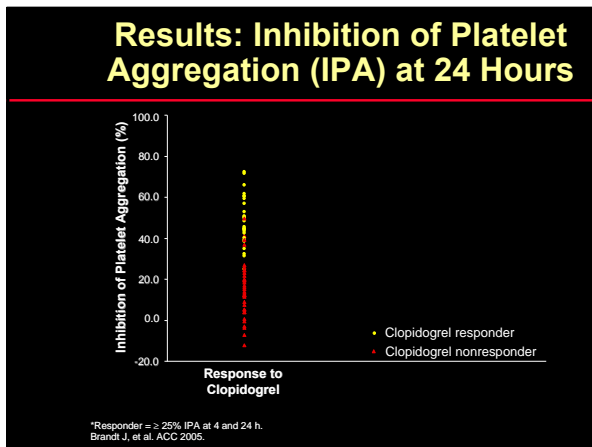


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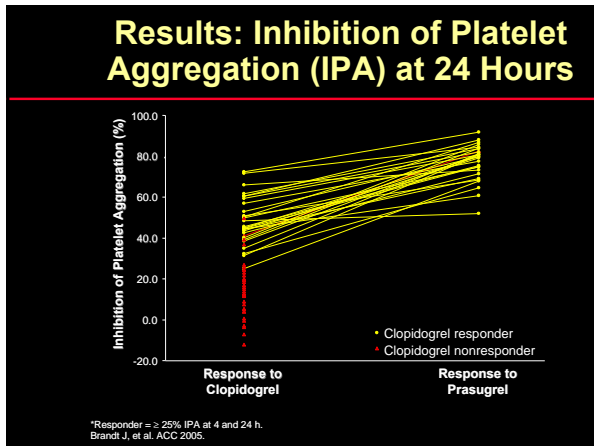


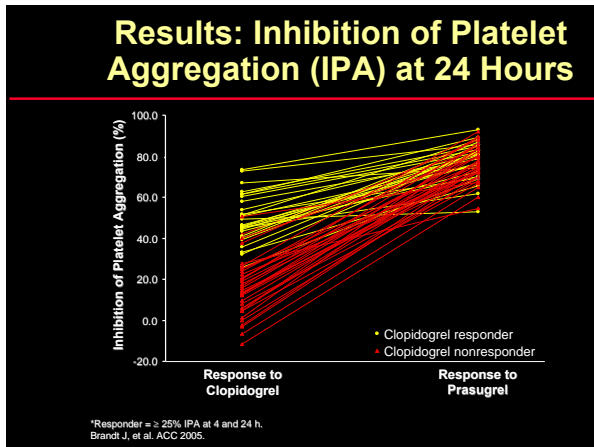


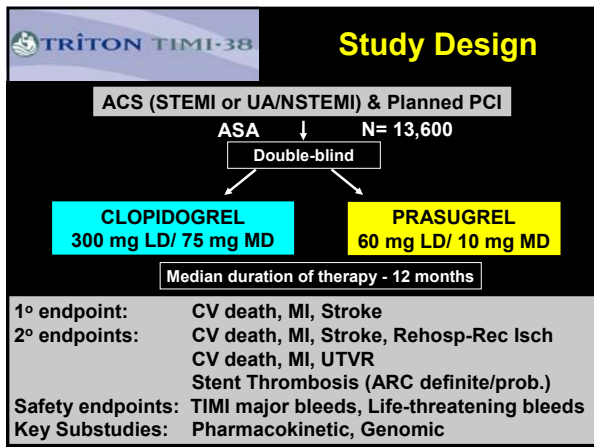


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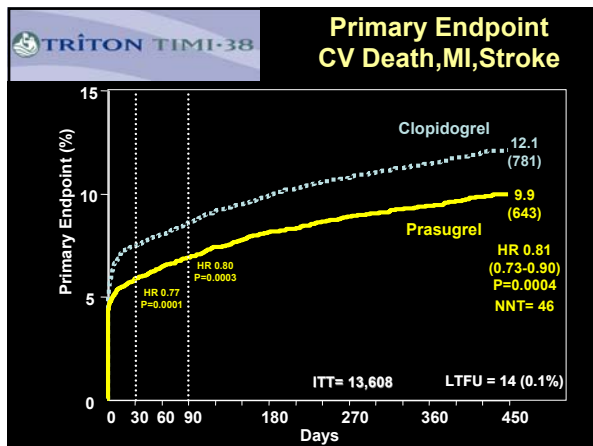


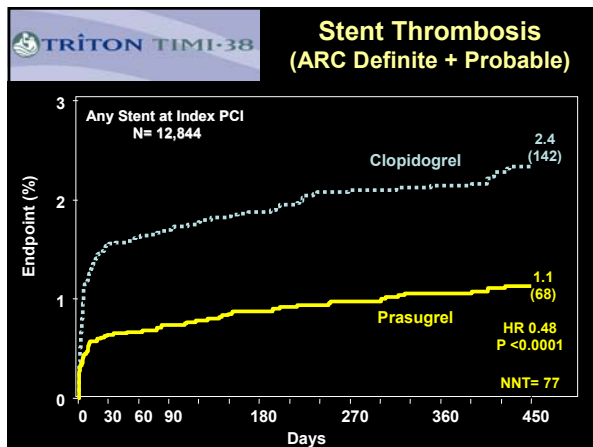


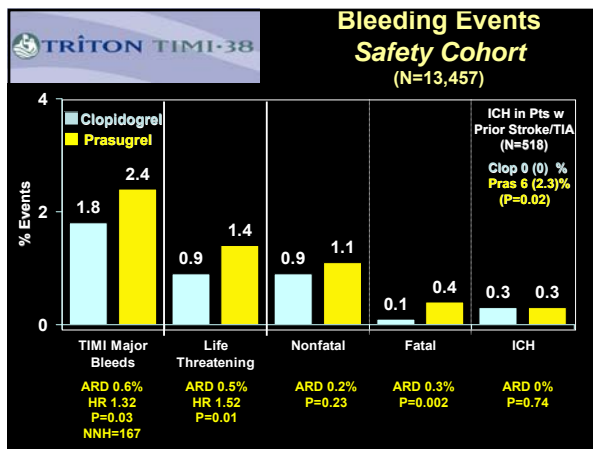


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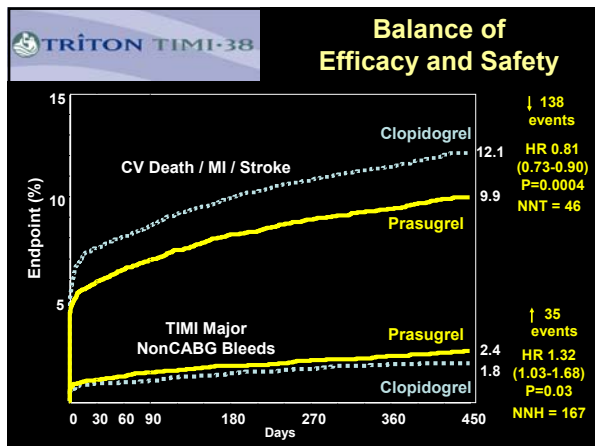


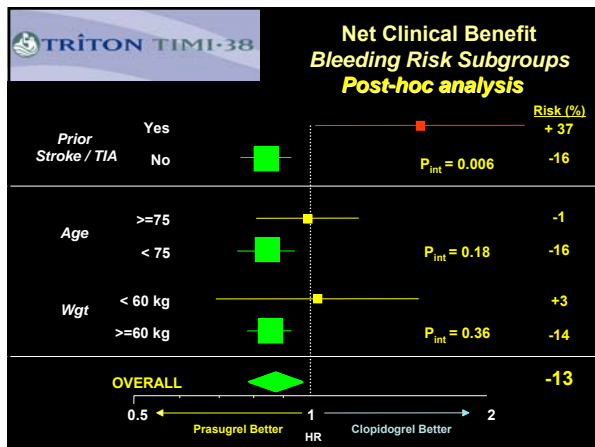


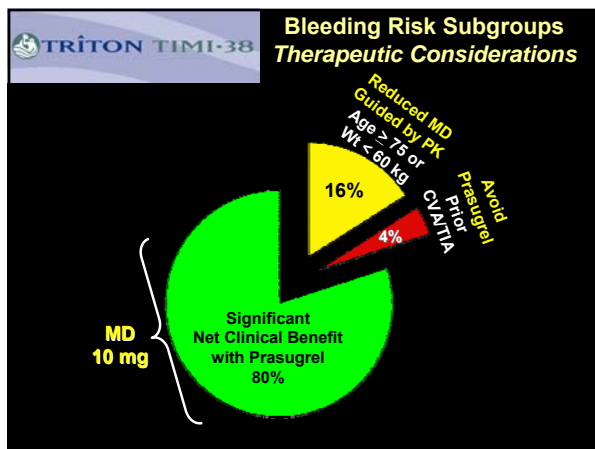


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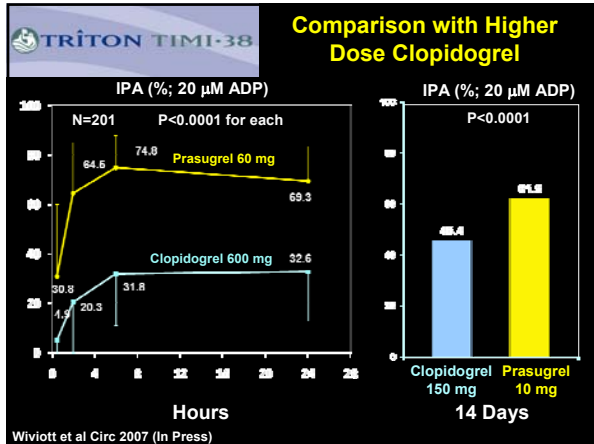






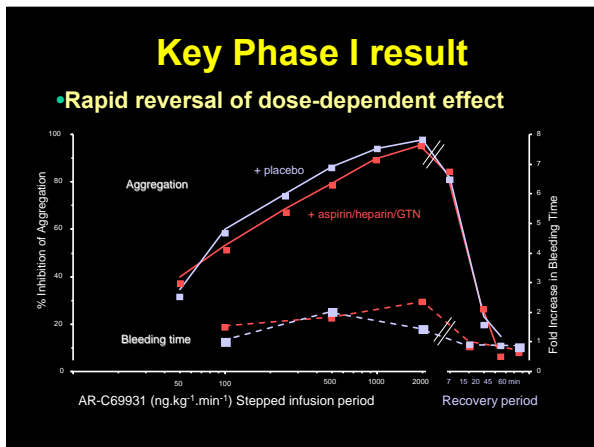
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Cangrelor (AR-C69931MX)

- Parenteral ADP-P2Y12 receptor antagonist
- ATP analogue
- Molecular weight 800 Daltons
- Plasma half-life of 5-9 minutes
- 20 minutes for return to normal platelet function



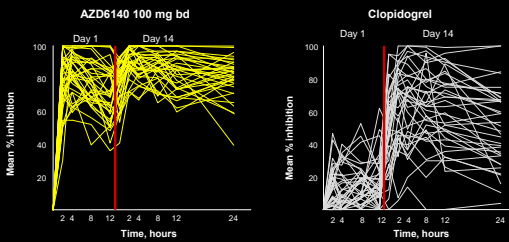
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AZD6140

- First oral reversible ADP receptor antagonist
- A non-thienopyridine, in the chemical class CPTP (CycloPentylTriazoloPyrimidine)
- Direct acting via the P2Y₁₂ receptor
- Blocks platelet activation and aggregation more consistently and completely than clopidogrel
- Metabolism not required for activity

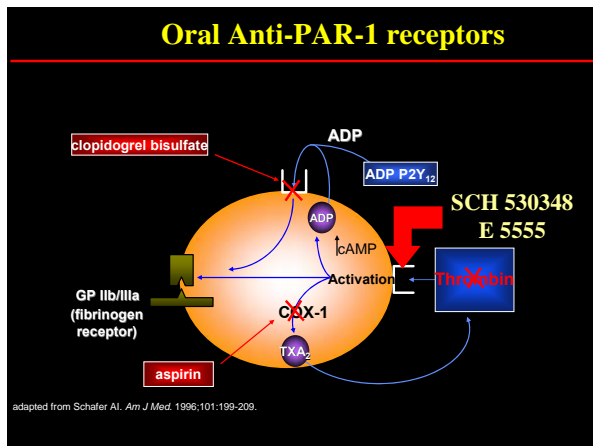
DISPERSE 2

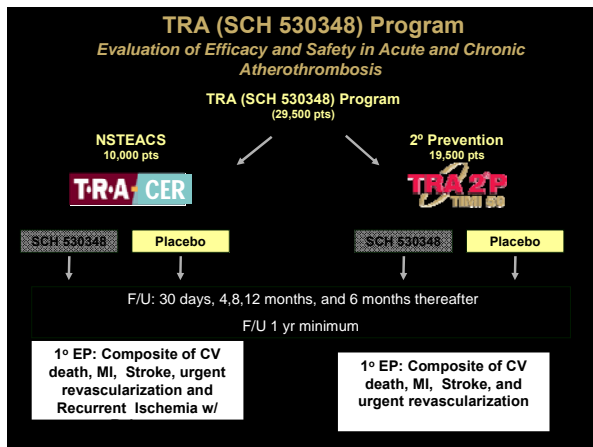




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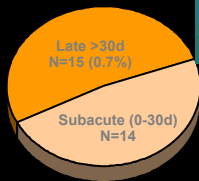
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Stent Thrombosis and DES



DES thrombosis: risk factors

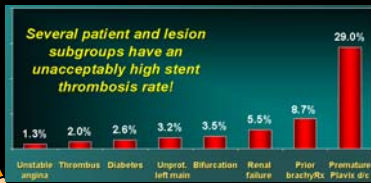
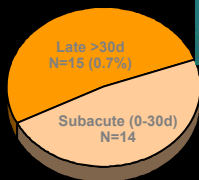
29/2229 pts (1.3%)



Iakovou et al, JAMA 2005

DES thrombosis: risk factors

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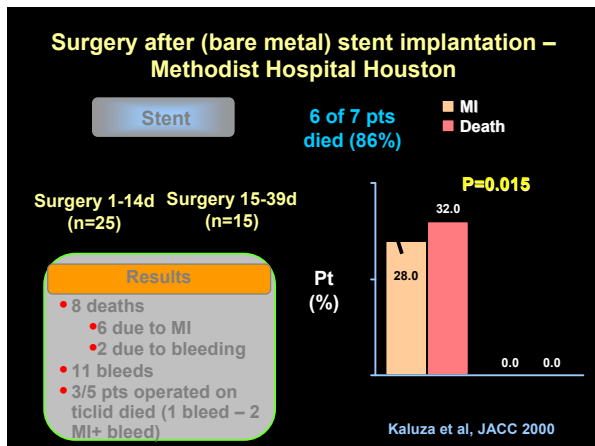


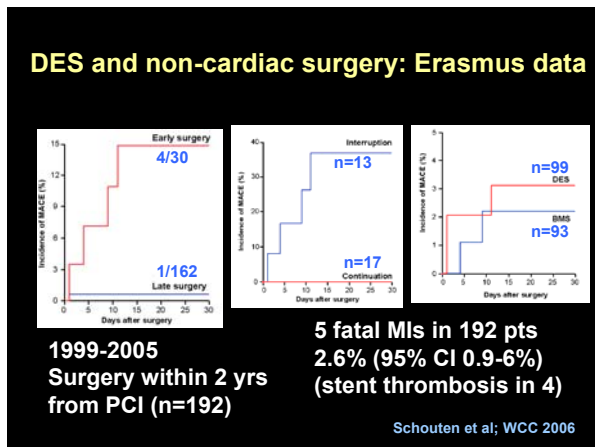
+ SURGERY!

Iakovou et al, JAMA 2005

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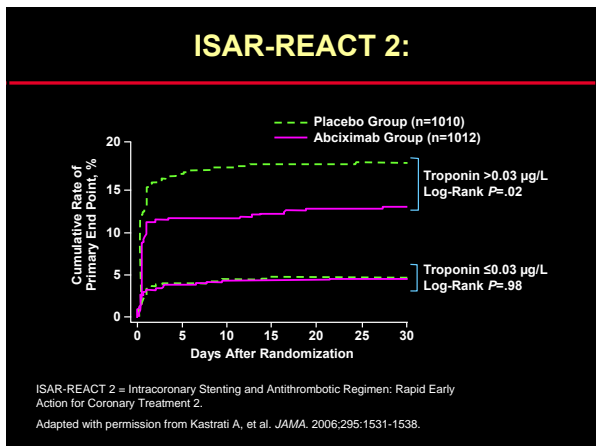


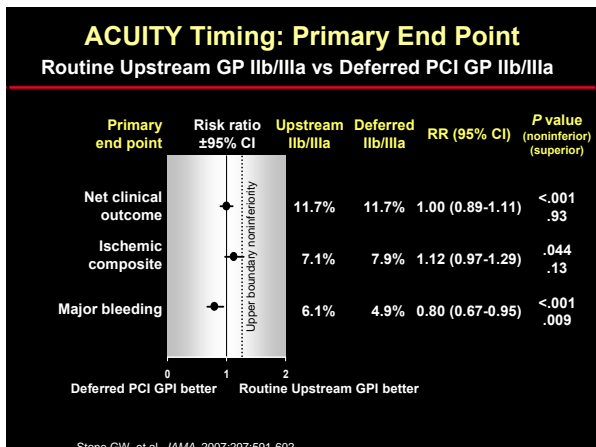
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- ### Conclusions
- Best aspirin dose is 81 mg
 - **Exception: early after stenting**
 - Variability in response to available agents likely an important issue
 - **Not ready for routine testing**
 - Clopidogrel loading
 - Beneficial, but CABG issue a problem
 - Load if bivalirudin is your anticoagulant of choice
 - Clopidogrel maintenance
 - **Remember medically treated patient**
 - 1 year routine, ? Longer with DES
 - **No routine role in stable CVD or AF**
 - New agents require careful safety/efficacy balance
 - DES use needs to be managed with regard to possible clopidogrel discontinuation/noncompliance
