THE "DIABETIC PLATELET":
Tackling the thrombotic burden in patients with DM and ACS

ALPIC 2012. Metsovo, Ioannina-Greece. January 27th-29th, 2012.

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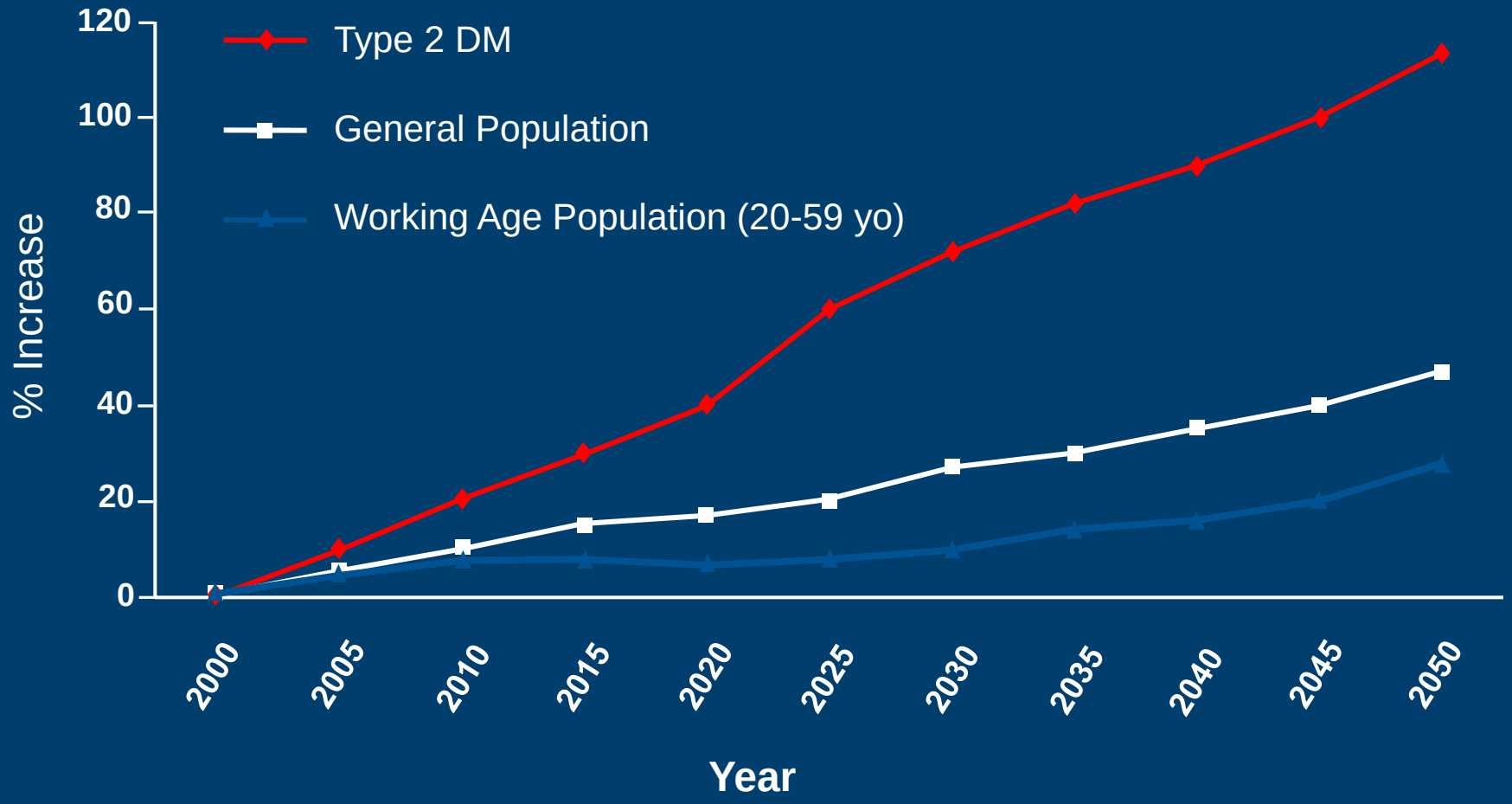
- Introduction: Diabetes Mellitus and CV disease
- Platelet Abnormalities in DM
- Antiplatelet Therapies: Limitations
- Novel and Future Options
- Conclusions

INTRODUCTION:

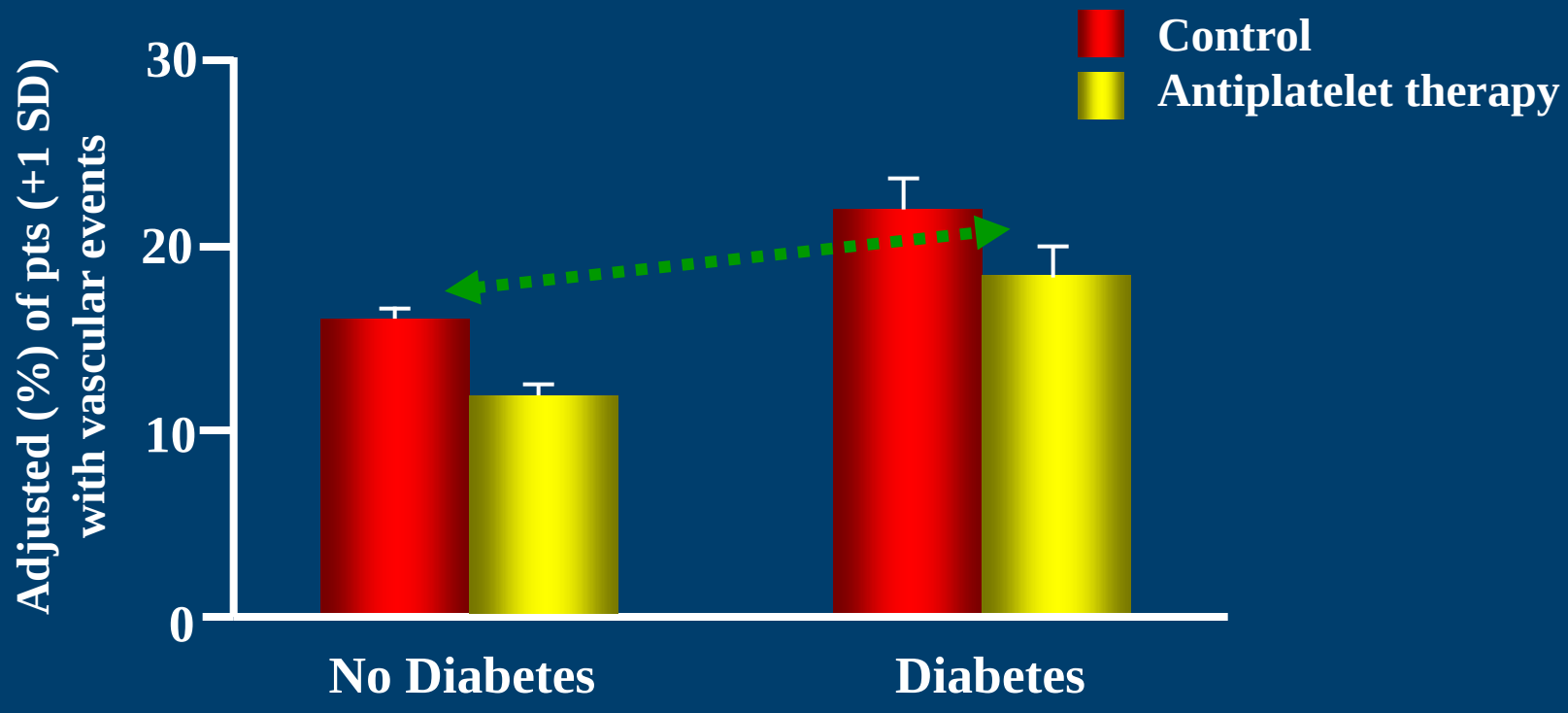
DM AND CV DISEASE

ESTIMATED GROWTH IN TYPE 2 DIABETES AND US POPULATION FROM 2000-2050



Bagust A et al. Diabetes. 2001;50:A205.

EFFECT OF ANTIPLATELET THERAPY IN REDUCING VASCULAR EVENTS IN DIABETIC PATIENTS



	No Diabetes	Diabetes
Benefit/1000 pts (SD):	36 (3)	38 (12)
2P:	<0.00001	<0.002

Antiplatelet Trialists Collaboration. BMJ. 1994; 308:81-106

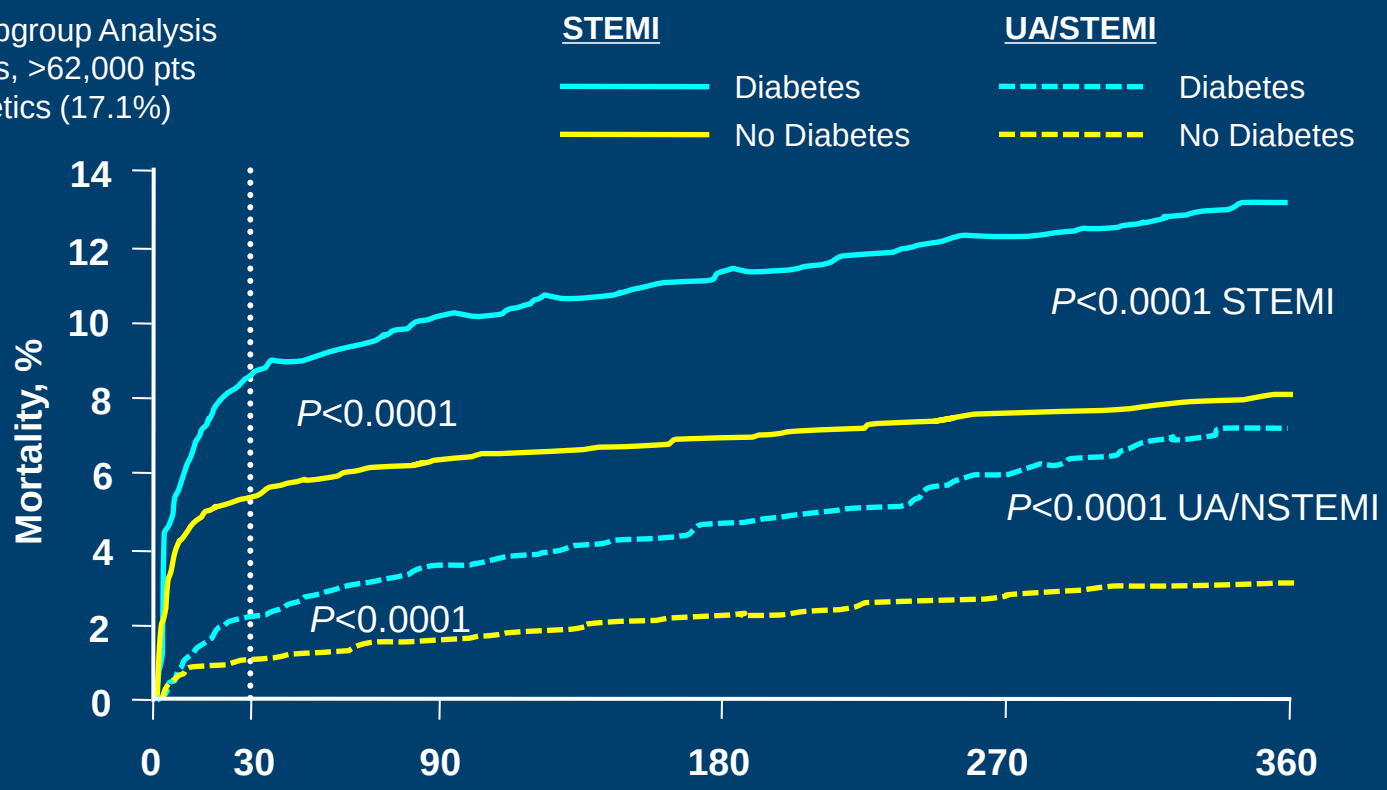
CURE: OUTCOMES IN VARIOUS SUBGROUPS

Characteristic	No. of Patients	Percentage of Patients with Event: Clopidogrel + ASA	Percentage of Patients with Event: Placebo + ASA
Overall	12562	9.3	11.4
Associated MI	3283	11.3	13.7
No associated MI	9279	8.6	10.6
Male sex	7726	9.1	11.9
Female sex	4836	9.5	10.7
≤65 yr old	6354	5.4	7.6
> 65 yr old	6208	13.3	15.3
ST-segment deviation	6275	11.5	14.3
No ST-segment deviation	6287	7.0	8.6
Enzymes elevated at entry	3176	10.7	13.0
Enzymes not elevated at entry	9386	8.8	10.9
Diabetes	2840	14.2	16.7
No diabetes	9722	7.9	9.9
Low risk	4187	5.1	6.7
Intermediate risk	4185	6.5	9.4
High risk	4184	16.3	18.0
History of revascularization	2246	8.4	14.4
No history of revascularization	10316	9.5	10.7
Revascularization after randomization	4577	11.5	13.9
No revascularization after randomization	7985	8.1	10.0

Yusuf S et al. N Engl J Med. 2001;345:494-502.

DM and All-Cause Mortality Through 1 Year After ACS

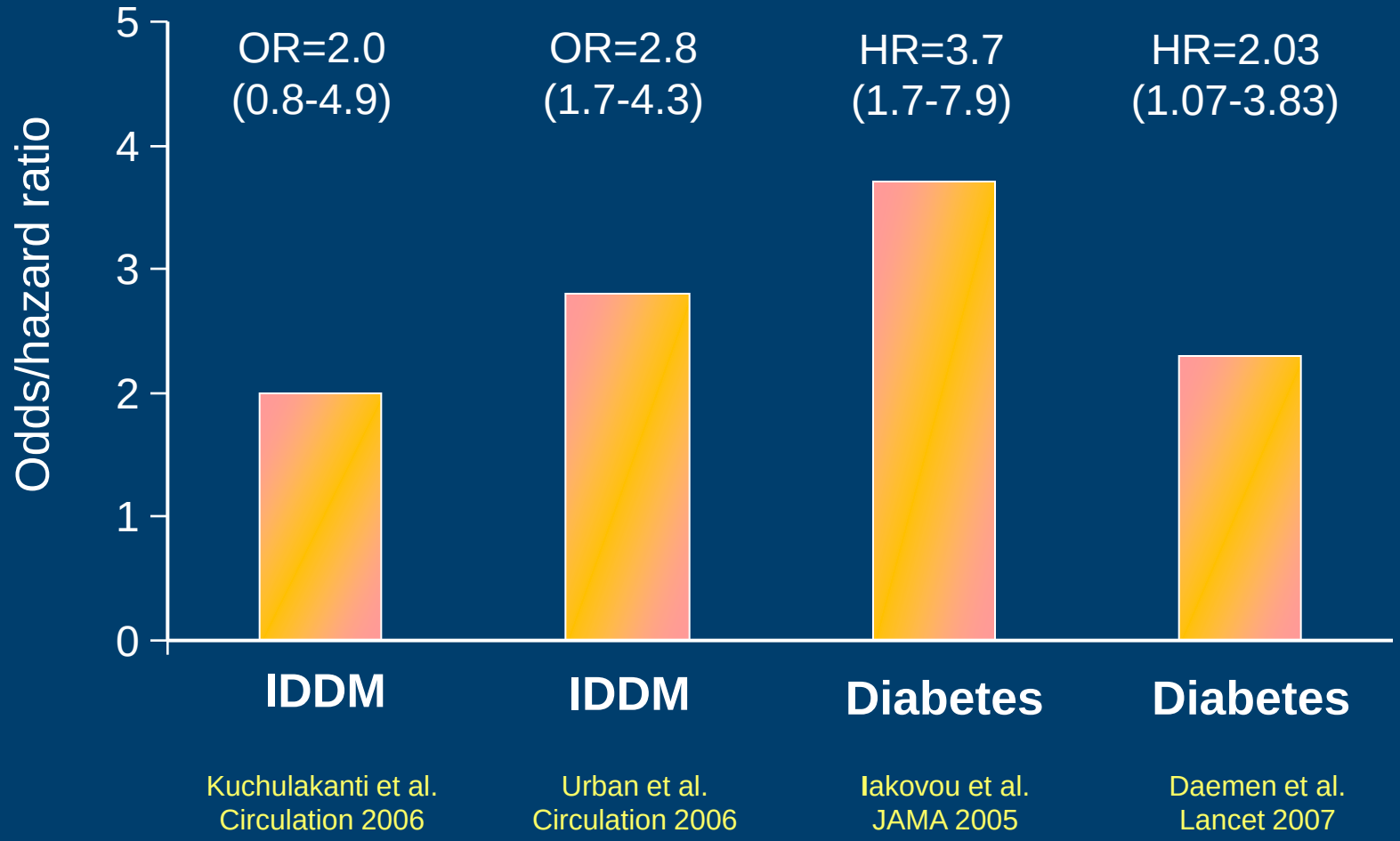
Diabetes Subgroup Analysis
11 TIMI Trials, >62,000 pts
10,613 diabetics (17.1%)



No. at Risk						
STEMI						
Diabetes	7156	6508	2947	2653	2118	1610
No diabetes	39421	37136	16685	15274	12276	9351
UA/NSTEMI						
Diabetes	3457	3313	2923	2339	1317	924
No diabetes	12002	11658	10505	8191	5141	4008

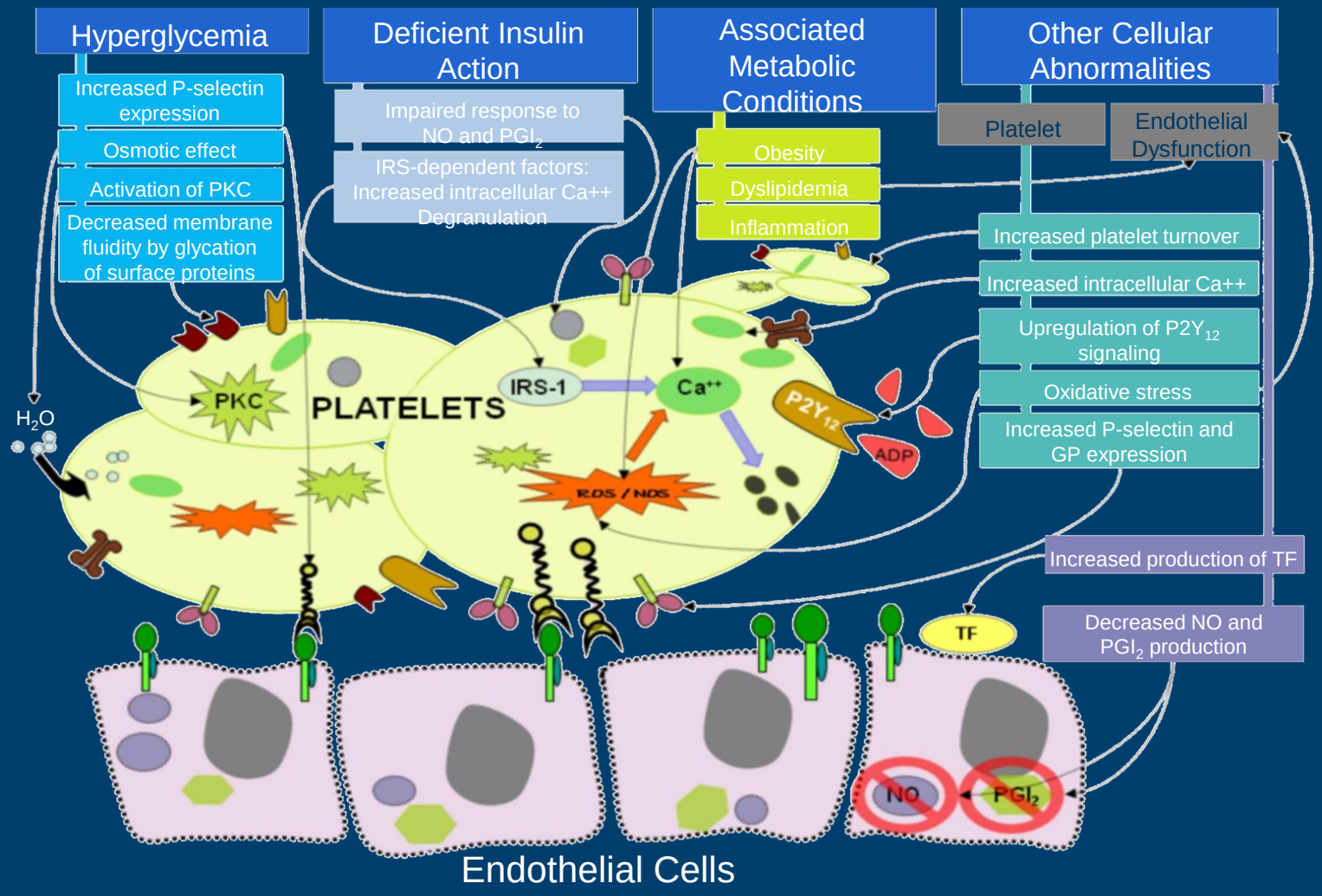
Donahoe SM et al. JAMA. 2007;298:765-75

DM in DES Era: Predictor of Stent Thrombosis at 1 Year



Platelet Abnormalities in Diabetes Mellitus

MECHANISMS INVOLVED IN PLATELET DYSFUNCTION IN DIABETES MELLITUS

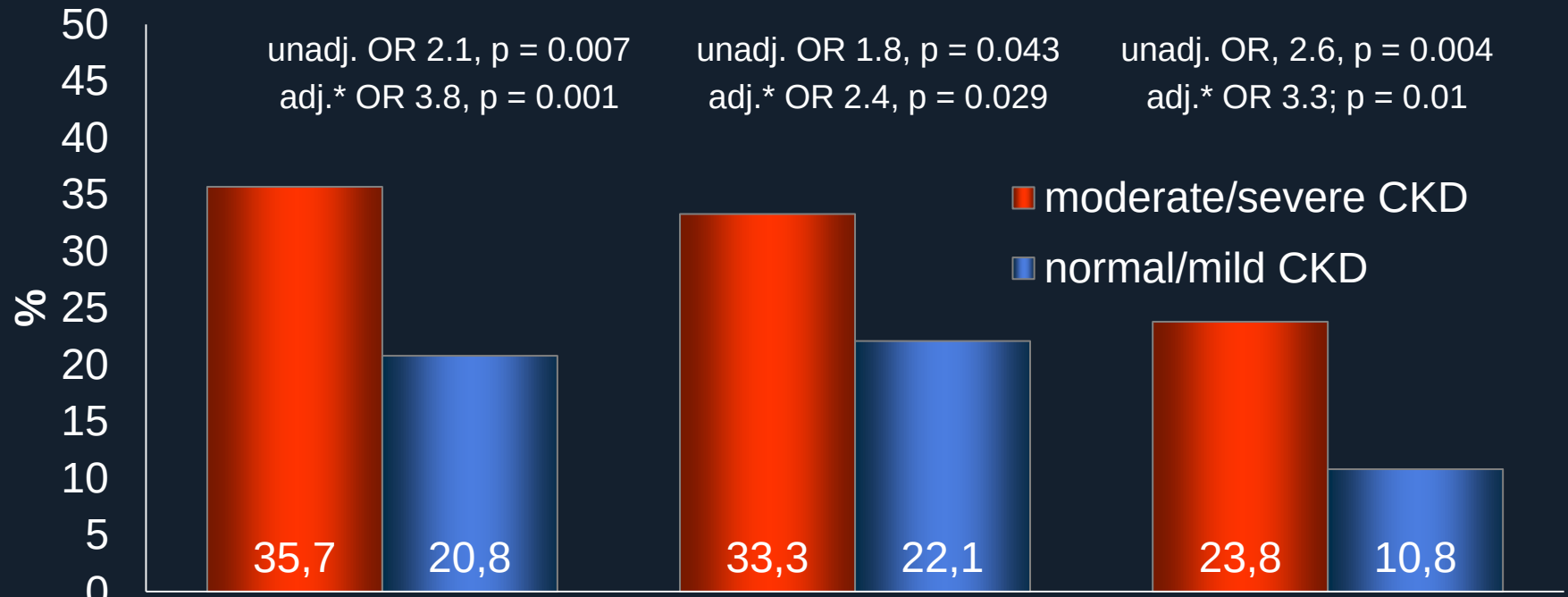


ACP=adenosine disphosphate; GP=glycoprotein; IRS-1=insulin receptor substrate-1; NO=nitric oxide; PGI_2=prostacyclin; PKC= protein kinase C; TF=tissue factor.

Ferreiro JL et al. Circulation. 2011; 123:798-813

Diabetes and Coronary Artery Disease: Do all patients carry the same risk?

HPPR According to Renal Function in DM Patients on Aspirin + Clopidogrel Therapy



	HPPR-ADP			HPPR-COLL			HPPR-ADP+COLL		
	Yes	No	p	Yes	No	p	Yes	No	p
Antifibrinogen	37±20	27±19	< 0.001	37±20	28±20	0.001	40±19	28±20	< 0.001
PAC-1	49±19	34±20	< 0.001	44±19	36±21	0.004	48±19	36±20	< 0.001
P-selectin	44±18	31±18	< 0.001	37±19	33±19	0.19	43±19	33±19	0.001

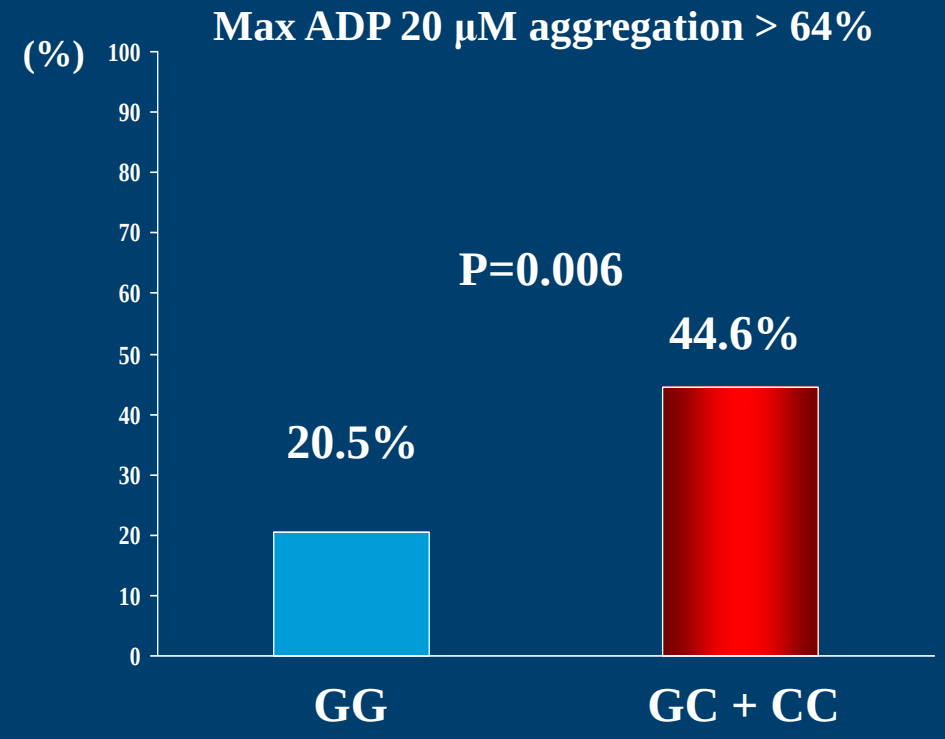
Angiolillo DJ et al. J Am Coll Cardiol. 2010;55:1139-46

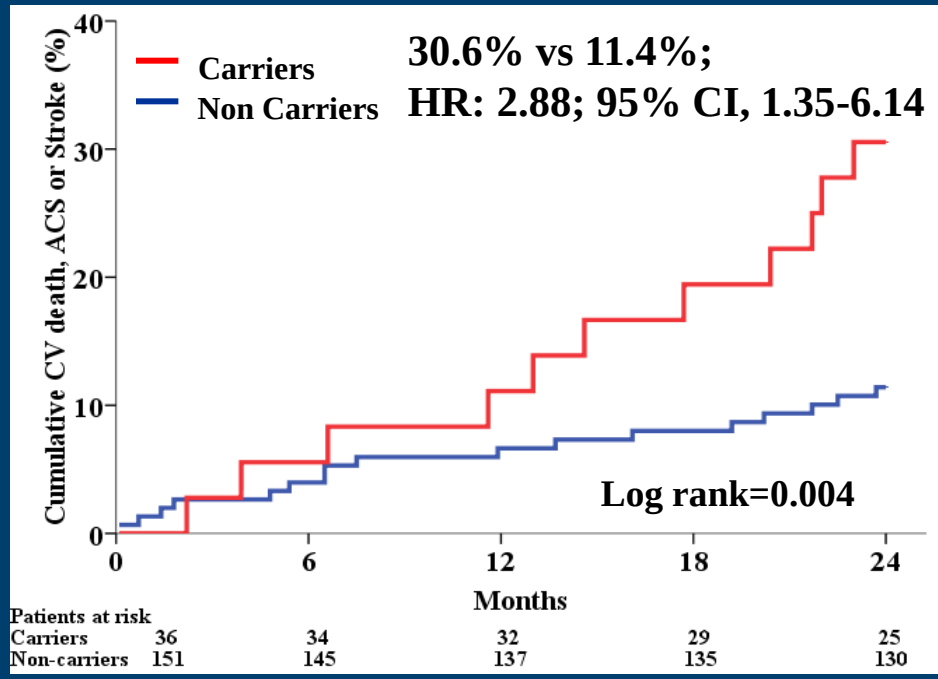
GENETIC DETERMINANTS OF HPR IN DM

Genetic profiling for the insulin receptor substrate (IRS-1)

97% of genetic variance

rs1801278	rs11683087	rs1896832	rs956115	rs2251692	rs1801123	rs6725330



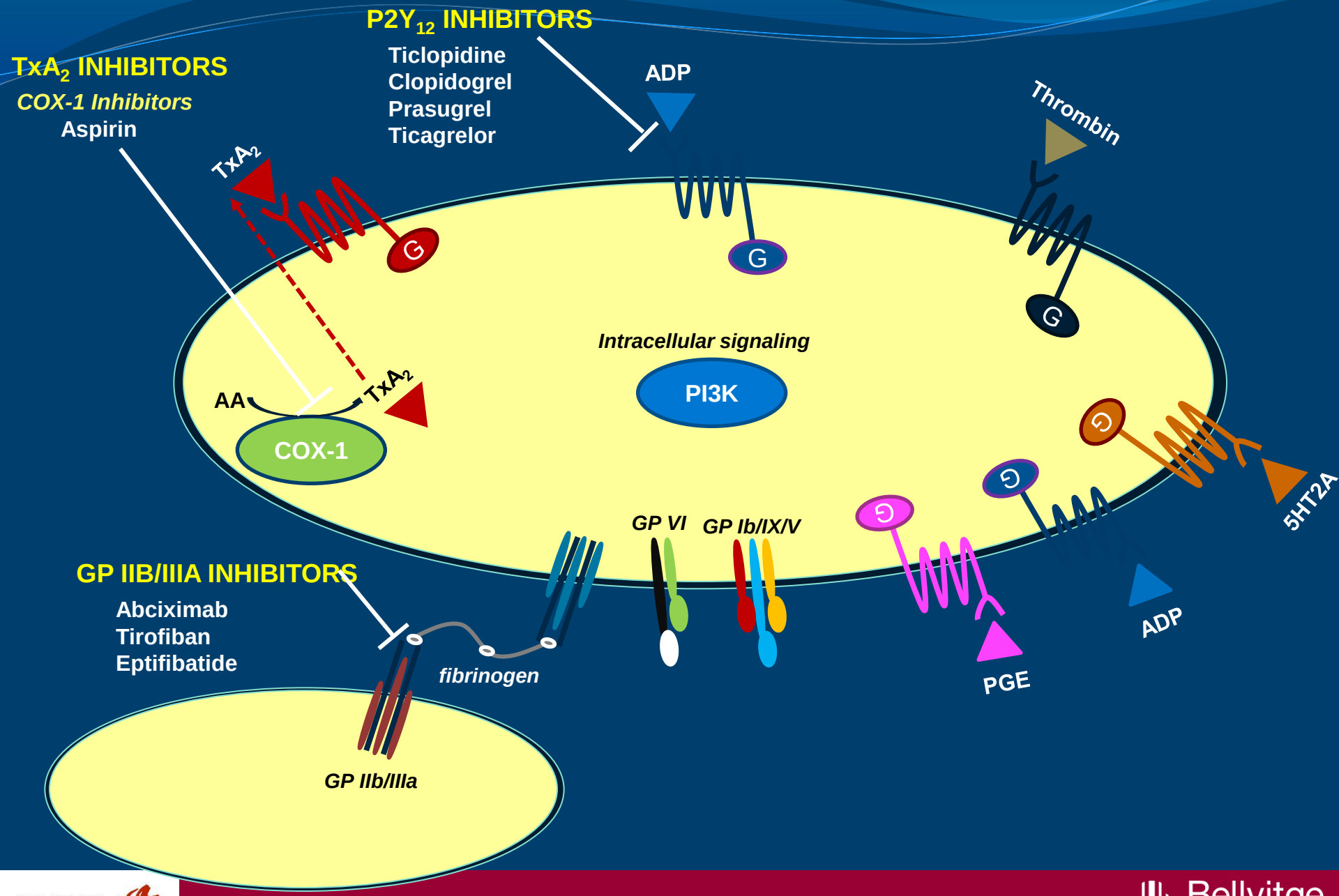


Angiolillo DJ et al. J Am Coll Cardiol. 2011;58:30-9

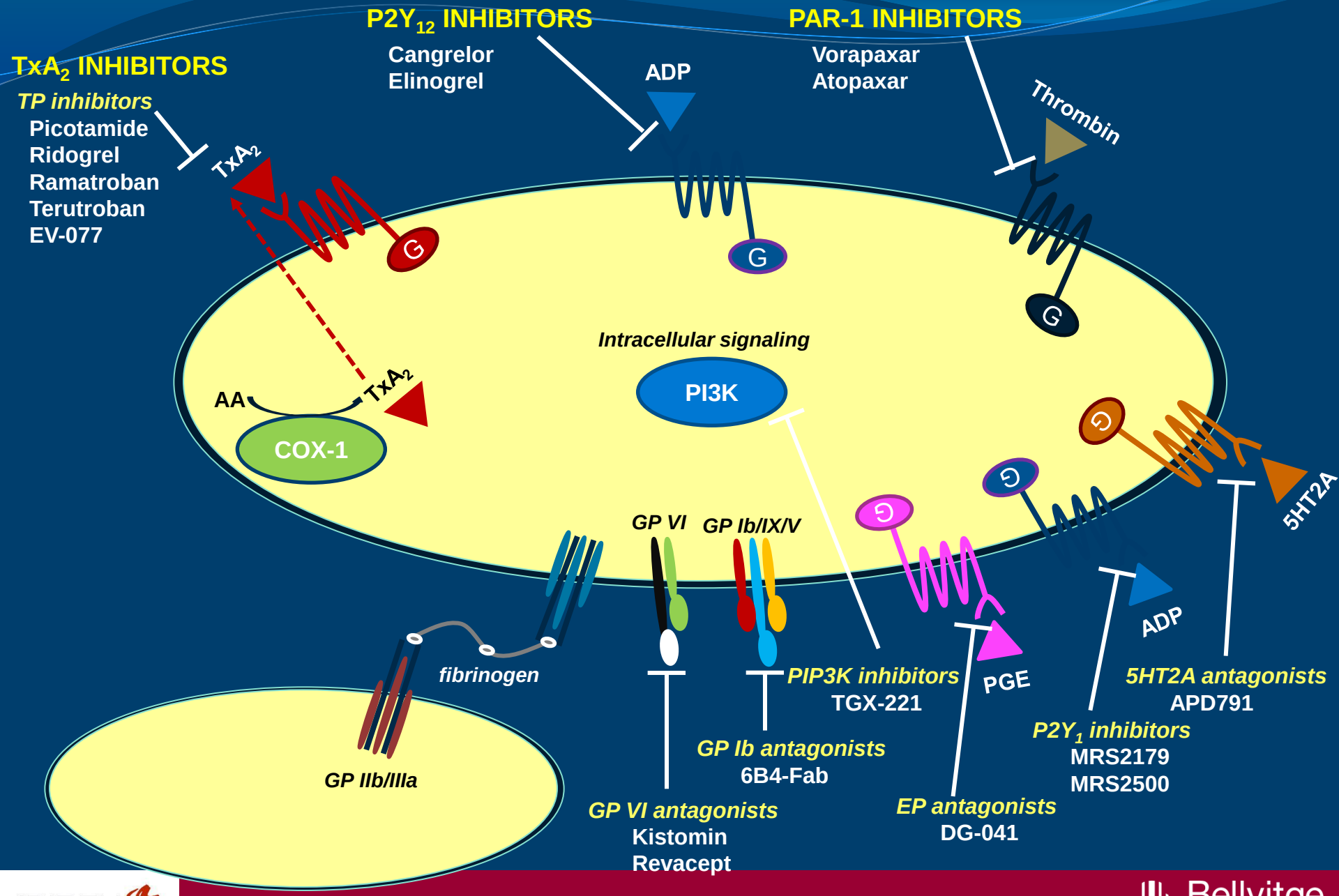
Antiplatelet Therapies:

Limitations

CURRENTLY AVAILABLE ANTIPLATELET AGENTS



NOVEL AGENTS UNDER DEVELOPMENT



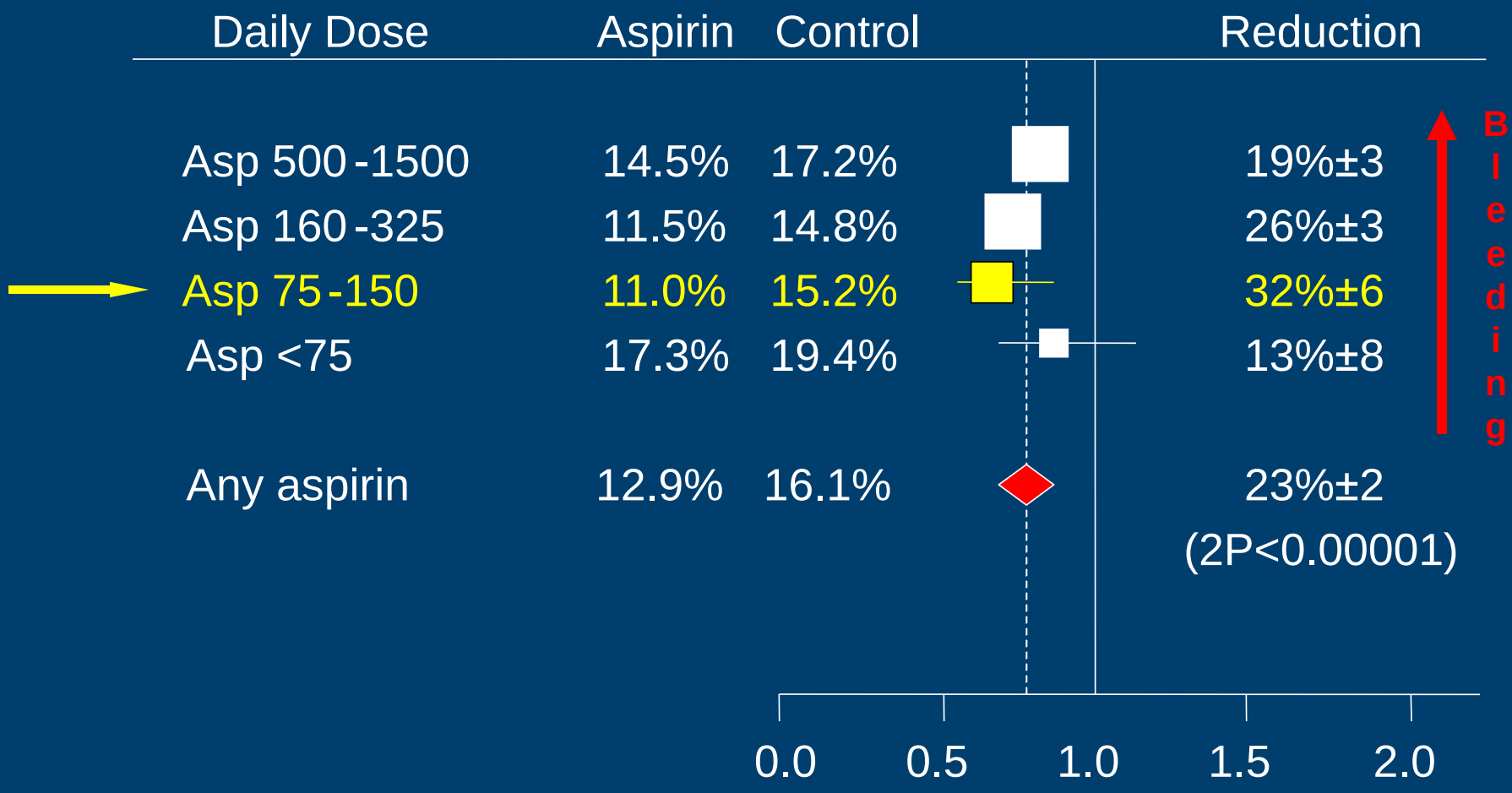
Ferreiro JL et al. 2012 [in press]

AVAILABLE ANTIPLATELET AGENTS

- Oral agents: Acute and Chronic treatment
  - Aspirin
  - $P2Y_{12}$ Inhibitors: Clopidogrel, Prasugrel, Ticagrelor

- Intravenous agents: Acute phase of treatment
  - GP IIb/IIIa Inhibitors

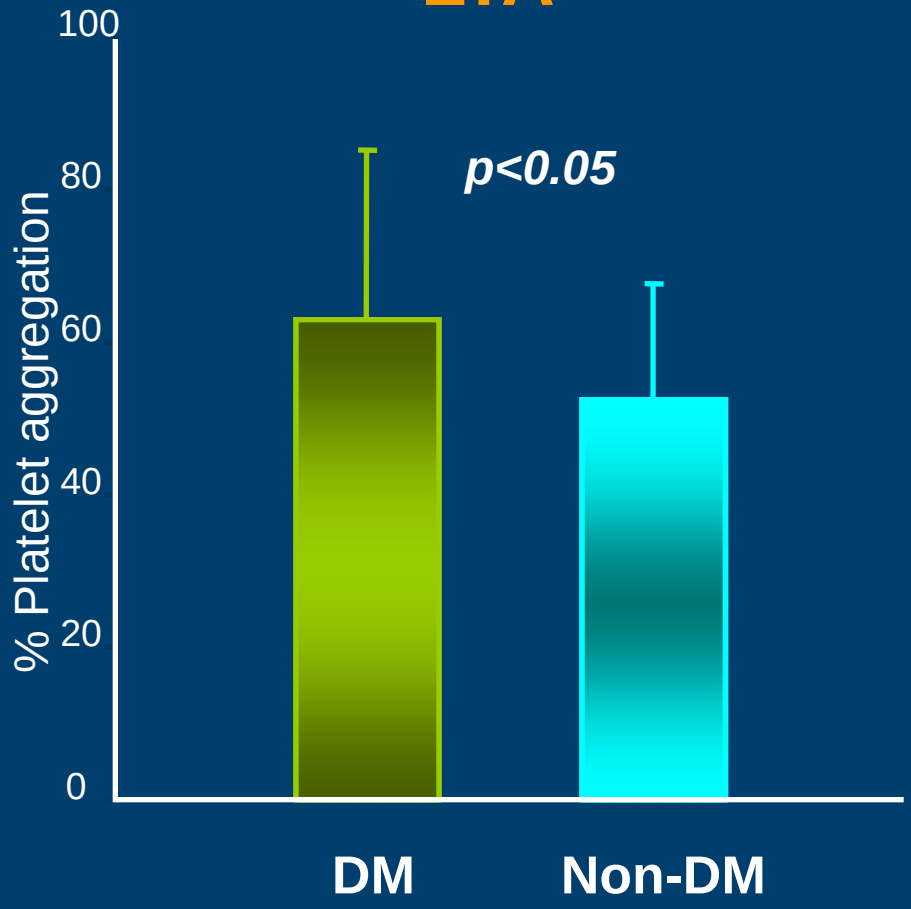
DIFFERENT DOSES OF ASPIRIN VS CONTROL



Antiplatelet Trialists Collaboration. BMJ. 2002;324:71-86

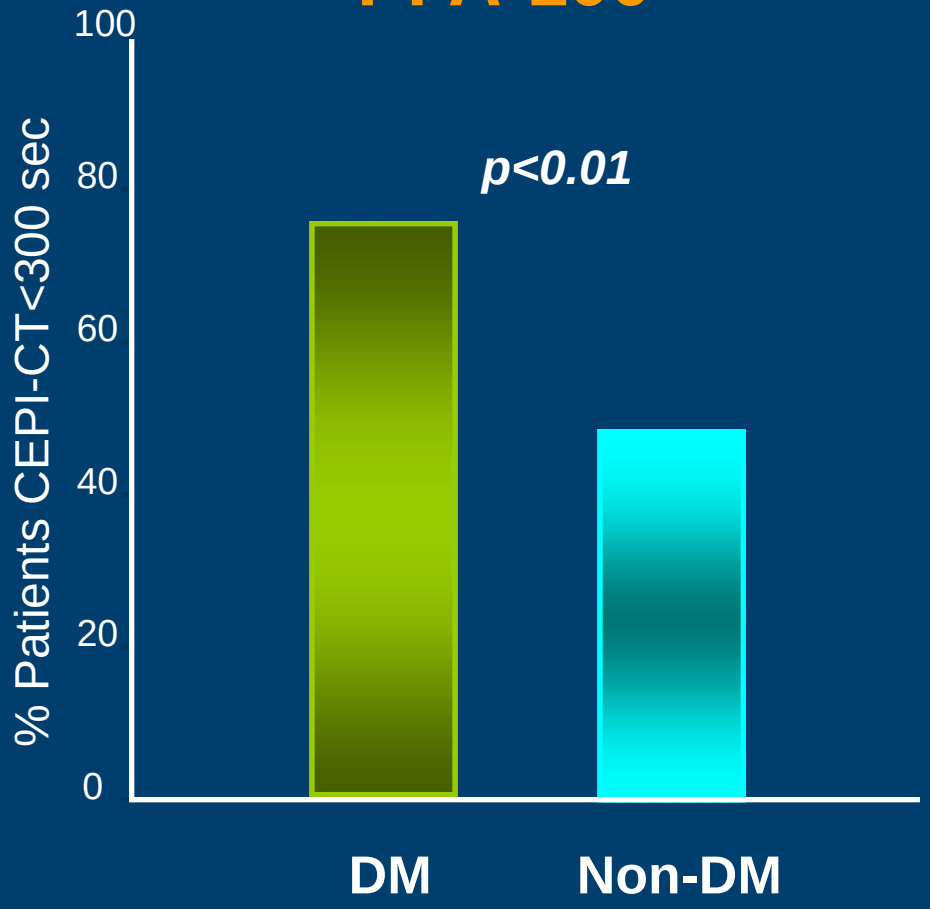
ASPIRIN EFFICACY IN DM VS NON-DM PATIENTS

LTA



Angiolillo DJ et al. Diabetes. 2005; 54:2430-5

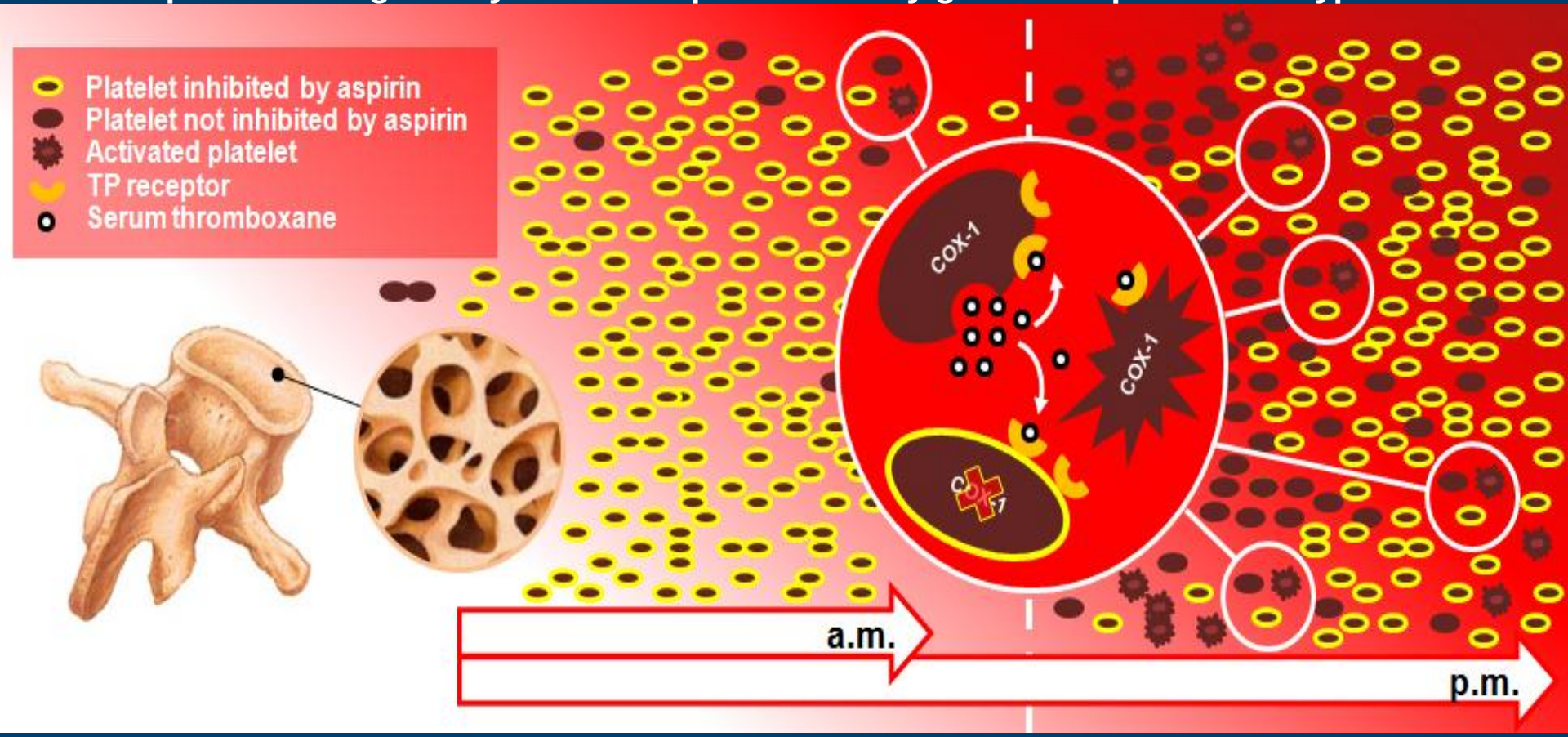
PFA-100



Angiolillo DJ et al. Am J Cardiol. 2006; 97:38-43

CIRCADIAN RELEASE OF PLATELETS INTO BLOODSTREAM FROM BONE MARROW

Impact of a single daily dose of aspirin on newly generated platelets in type 2 DM



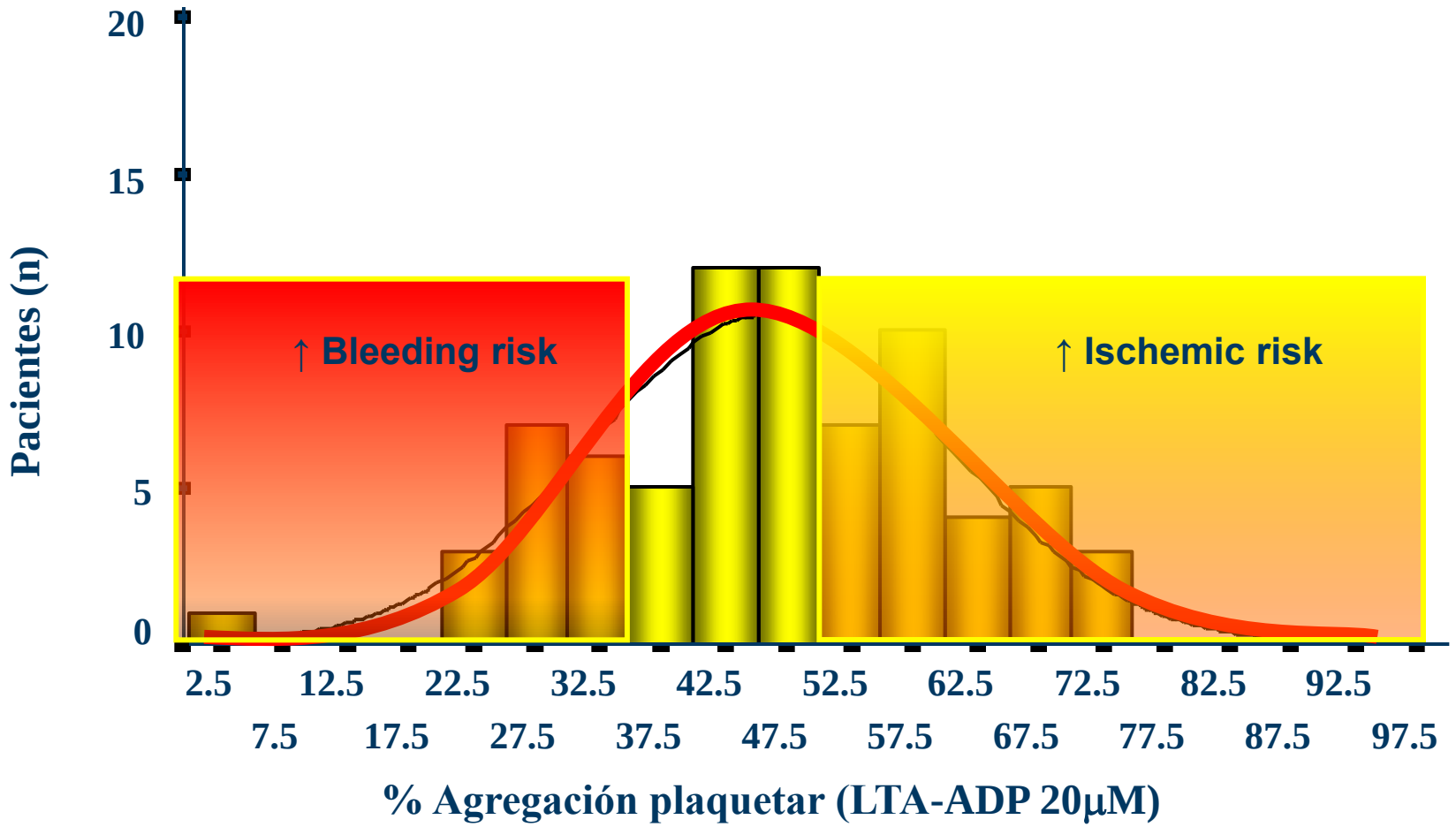
Increased platelet turnover in type 2 DM: Benefit of twice daily dosing?

Capodanno D et al. Circ Cardiovasc Interv. 2011;4:180-7.

ASPIRIN + CLOPIDOGREL IN DM PATIENTS

Study	N (Overall)	Scenario	Results in overall population	N (DM)	Results in DM
CURE	12,562	UA/NSTEMI	9.3% vs. 11.4% RR = 0.80 [0.72-0.90]	2,840	14.2% vs. 16.7% RR = 0.84 [0.70-1.02]
PCI-CURE	2,658	CURE patients undergoing PCI	4.5% vs. 6.4% RR = 0.70 [0.50-0.97]	504	12.9% vs. 16.5% RR = 0.77 [0.48-1.22]
CREDO	2,116	Elective PCI	8.5% vs. 11.5% RRR = 26.9% [3.9%-44.4%]	560	% NR RRR = 11.2 [(-46.8)-46.2]
COMMIT	45,852	Acute MI (93% STEMI)	9.2% vs. 10.1% OR = 0.91 [0.86-0.97]	NR	NR
CLARITY	3,491	STEMI with fibrinolysis	15.0% vs. 21.7% OR = 0.64 [0.53-0.76]	575	NR
PCI-CLARITY	1,863	CLARITY patients undergoing PCI	3.6% vs. 6.2% OR = 0.54 [0.35-0.85]	282	6.0% vs. 10.1% OR = 0.61 {0.24-1.53]

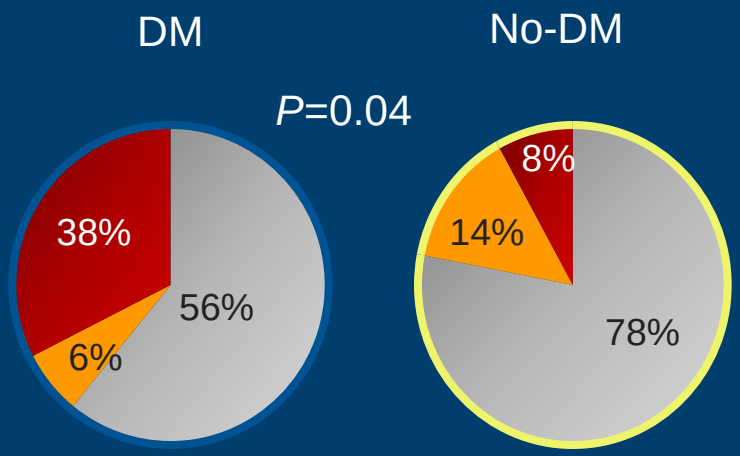
CLOPIDOGREL: VARIABILITY IN RESPONSE



Angiolillo DJ et al. Am J Cardiol 2006;97:38-43.

INFLUENCE OF DM ON CLOPIDOGREL EFFECTS

Acute Phase of Treatment

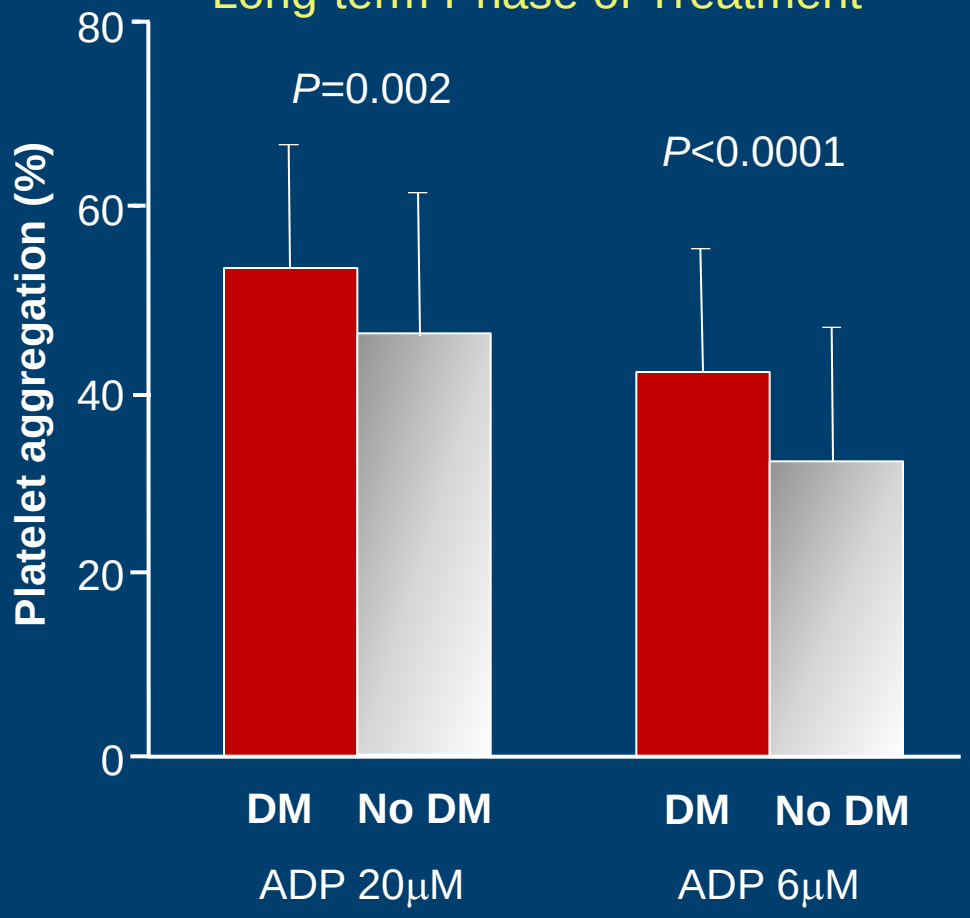


24 hrs post 300 mg LD

- Non-responders (Platelet inhibition <10%)
- Low responders (Platelet inhibition 10-29%)
- Responders (Platelet inhibition >30%)

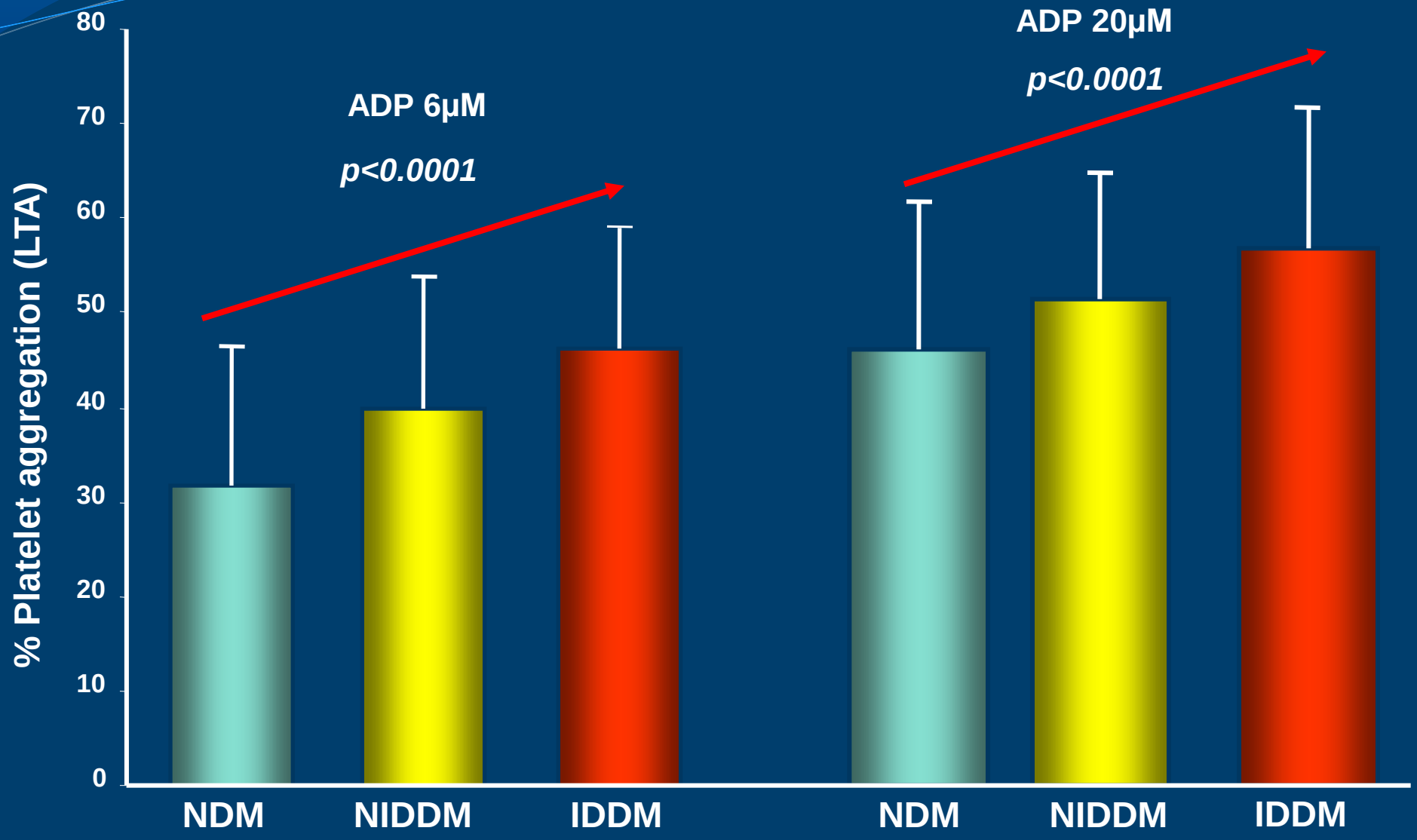
Angiolillo DJ et al. Diabetes. 2005;54:2430-5.

Long-term Phase of Treatment



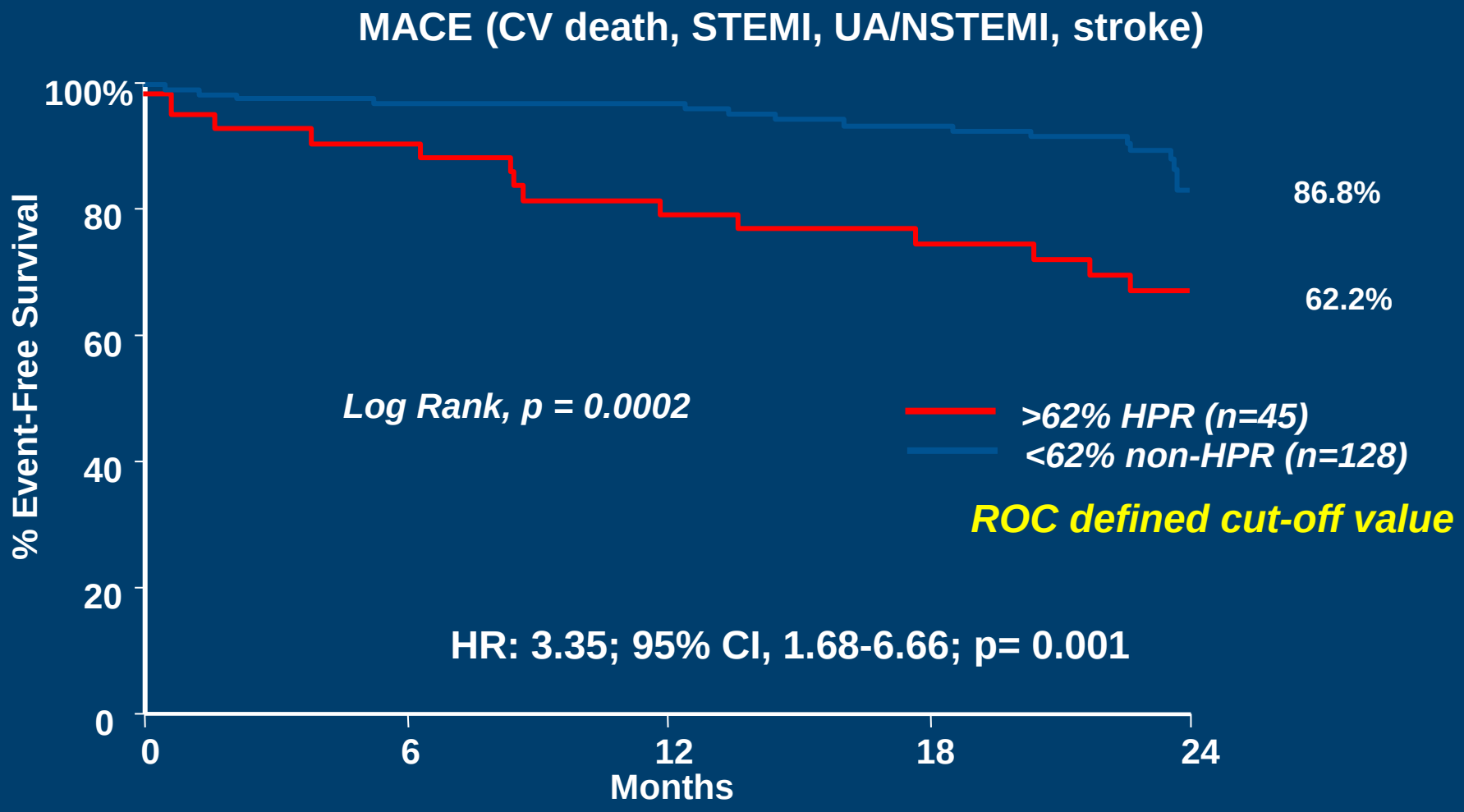
Angiolillo DJ et al. J Am Coll Cardiol. 2006;48:298-304.

PLATELET FUNCTION ACCORDING TO TREATMENT



Angiolillo DJ et al. J Am Coll Cardiol. 2006;48:298-304

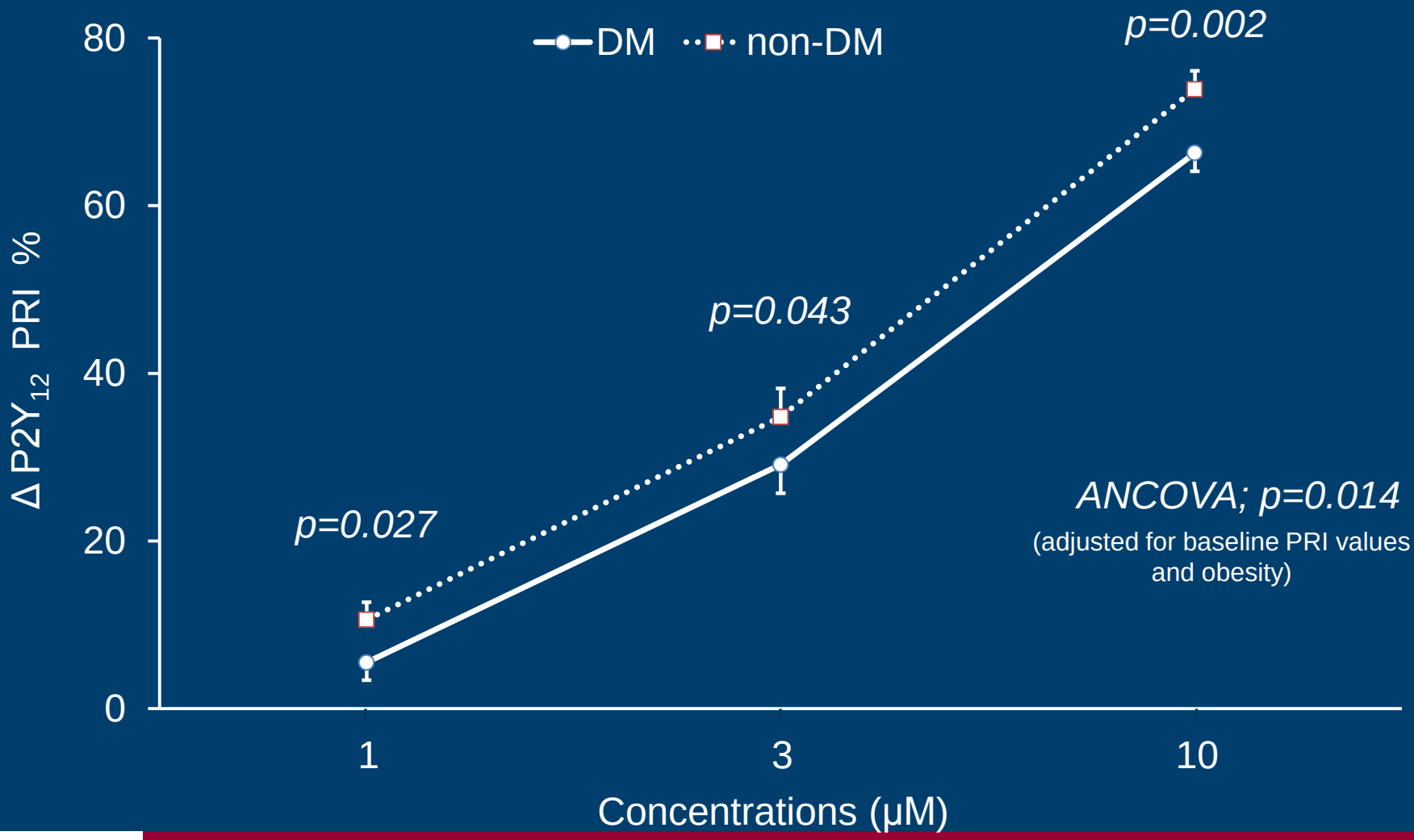
HIGH PLATELET REACTIVITY AND MACE IN DM



Angiolillo DJ et al. J Am Coll Cardiol. 2007;50:1541-7

UPREGULATION OF $P2Y_{12}$ SIGNALING IN DM

Absolute differences in PRI before and after incubation of clopidogrel active metabolite

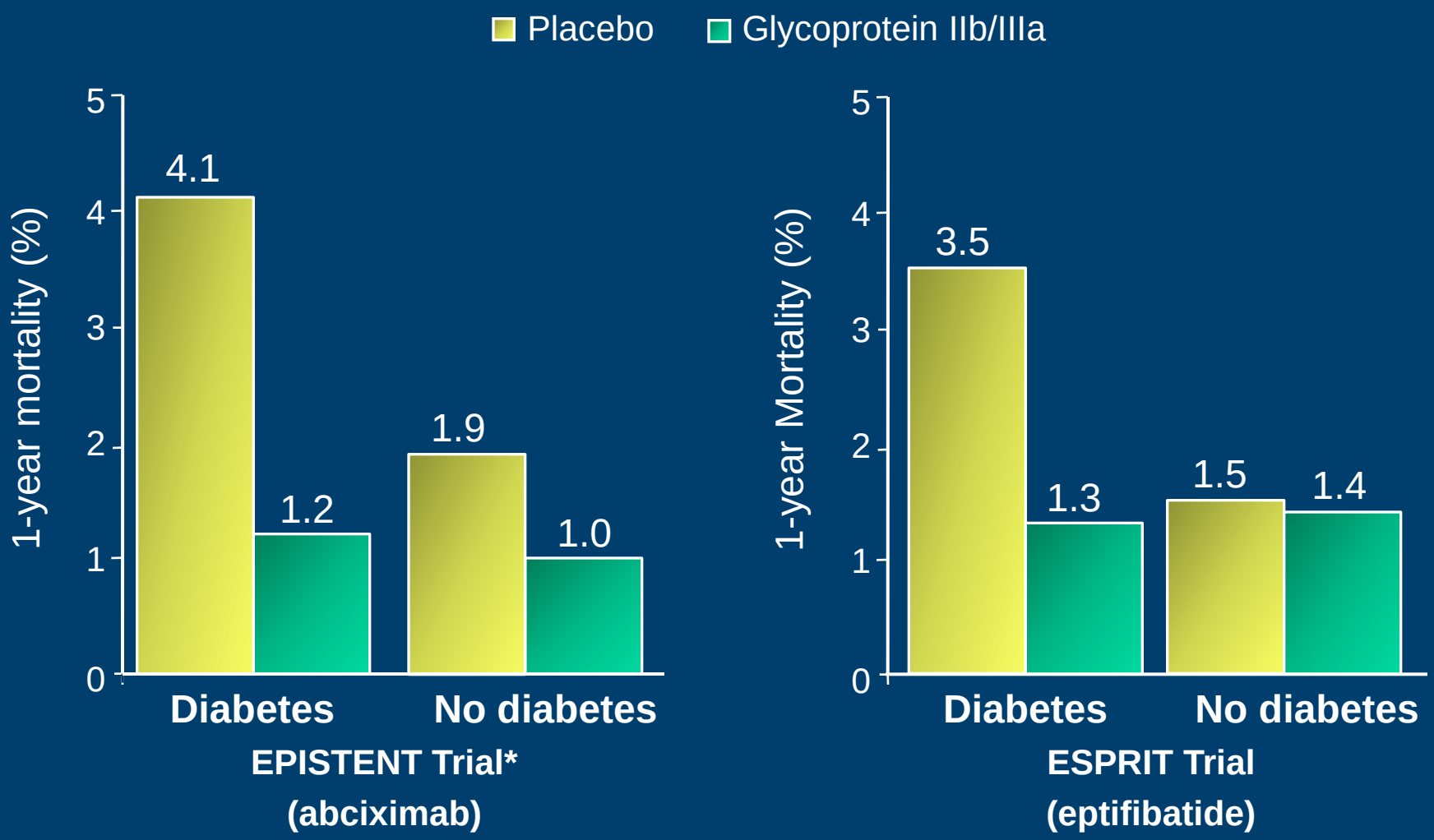


APPROVED ANTIPLATELET AGENTS

- Oral agents: Acute and Chronic treatment
  - Aspirin
  - $P2Y_{12}$ Inhibitors: Clopidogrel, Prasugrel, Ticagrelor

- Intravenous agents: Acute phase of treatment
  - GP IIb/IIIa Inhibitors

GP IIb/IIIa Blockade and Diabetes



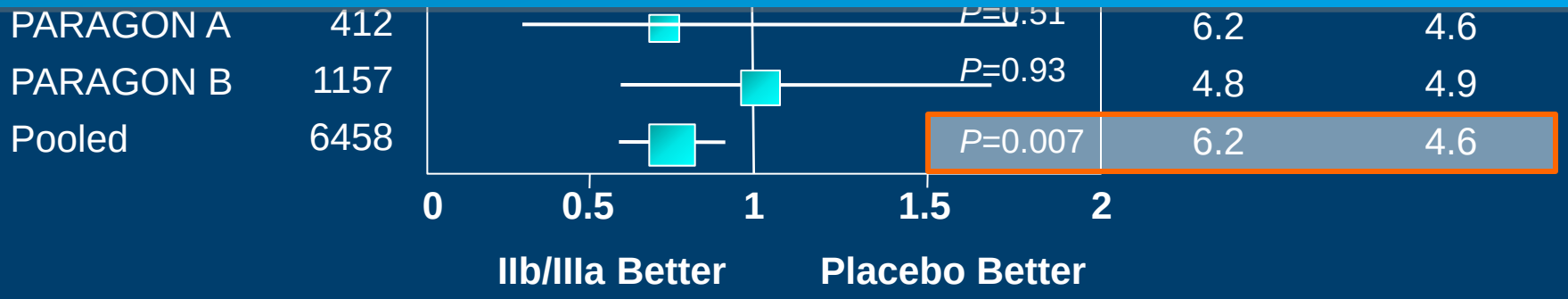
*Stent arms only

Lincoff AM. Circulation. 2003;107:1556-9.

META-ANALYSIS GP IIB/IIIA INHIBITORS: DM PATIENTS WITH NSTEACS

OR with 95% CIs and corresponding P values for treatment effect on 30-day mortality among diabetic patients with ACS (n=6548)

In diabetic patients (n=1279) undergoing PCI during index hospitalization, the GPI use was associated with a mortality reduction at 30 days from 4.0% to 1.2% (OR 0.30; 95% CI 0.14 to 0.69; *P*=0.002; NNT=36).

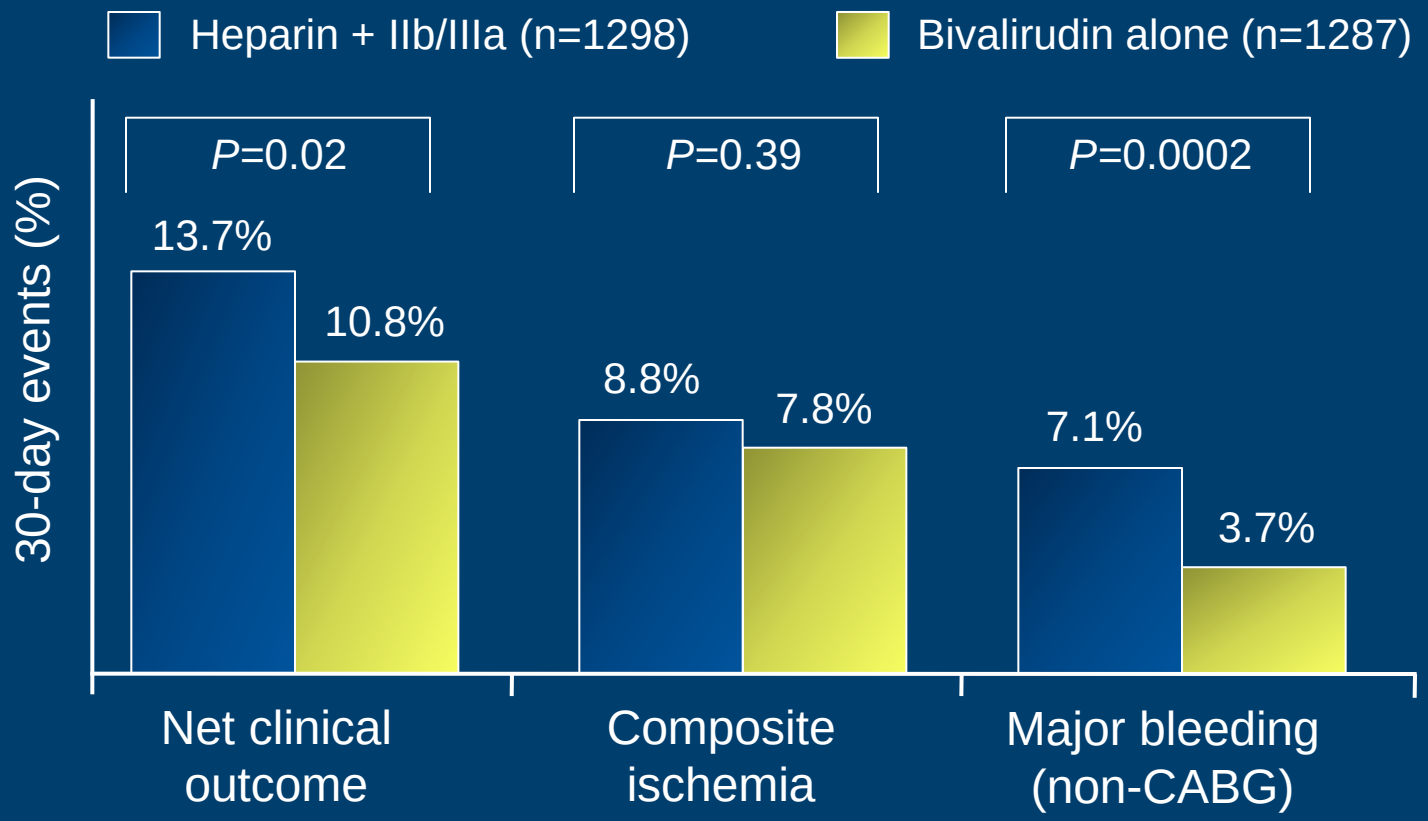


Breslow-Day: *P*=0.50

Roffi M et al. Circulation. 2001;104:2767-71.

ACUITY DIABETIC SUBSTUDY

Heparin* + GP IIb/IIIa vs Bivalirudin alone



* Heparin = unfractionated or enoxaparin

Feit F et al. J Am Coll Cardiol. 2008;51:1645-52.

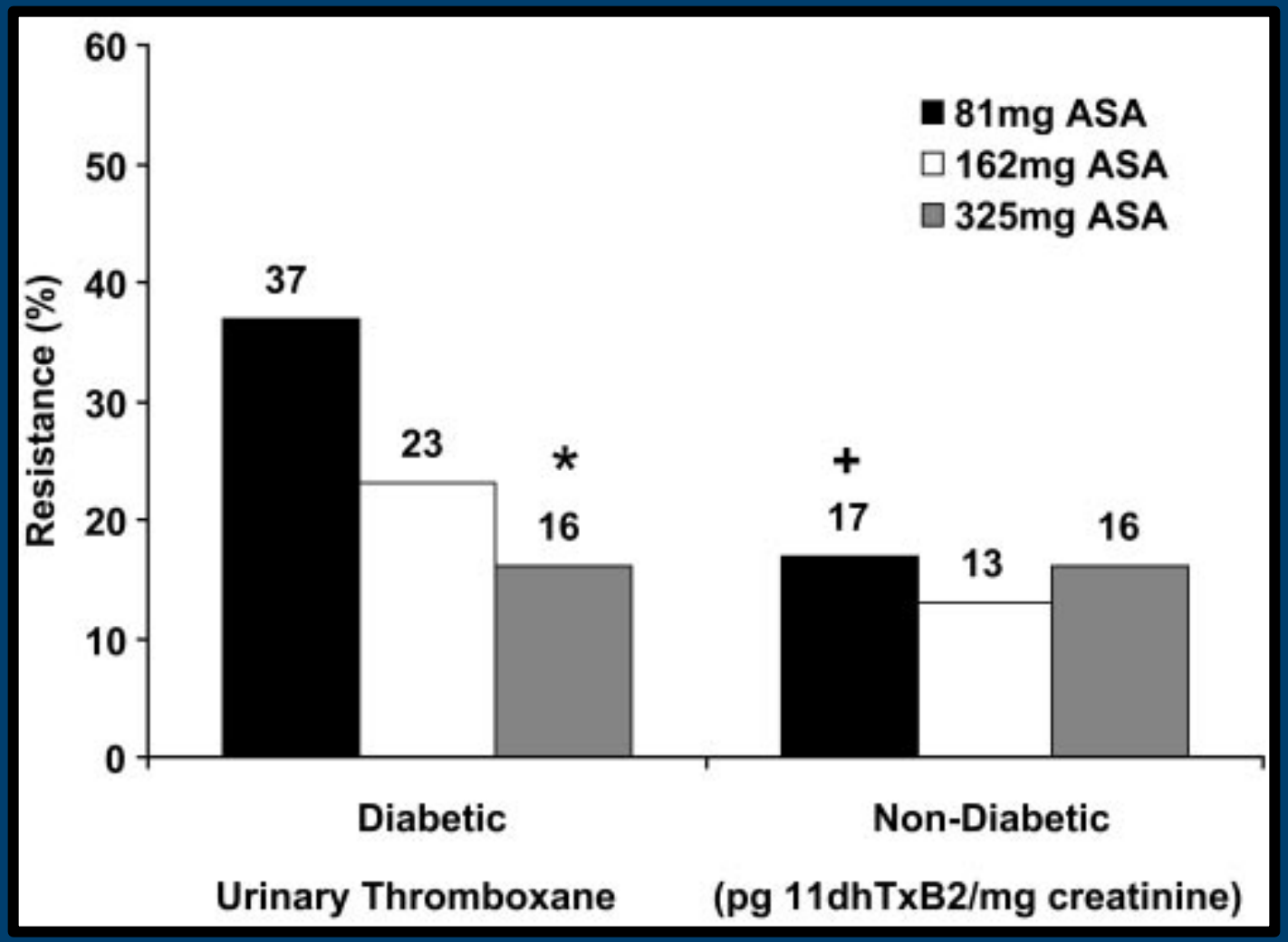
Novel and Future

Options

STRATEGIES TO OPTIMIZE ASPIRIN INHIBITION IN PATIENTS WITH DM

- Increase aspirin dosing
- Modifying dosing regimen
  (e.g. twice daily dosing)
- Using new agents
  (not yet available)

INCREASING ASPIRIN DOSAGE IN DM



DiChiara J et al. Diabetes. 2007;56:3014-9.

STRATEGIES TO OPTIMIZE ASPIRIN INHIBITION IN PATIENTS WITH DM

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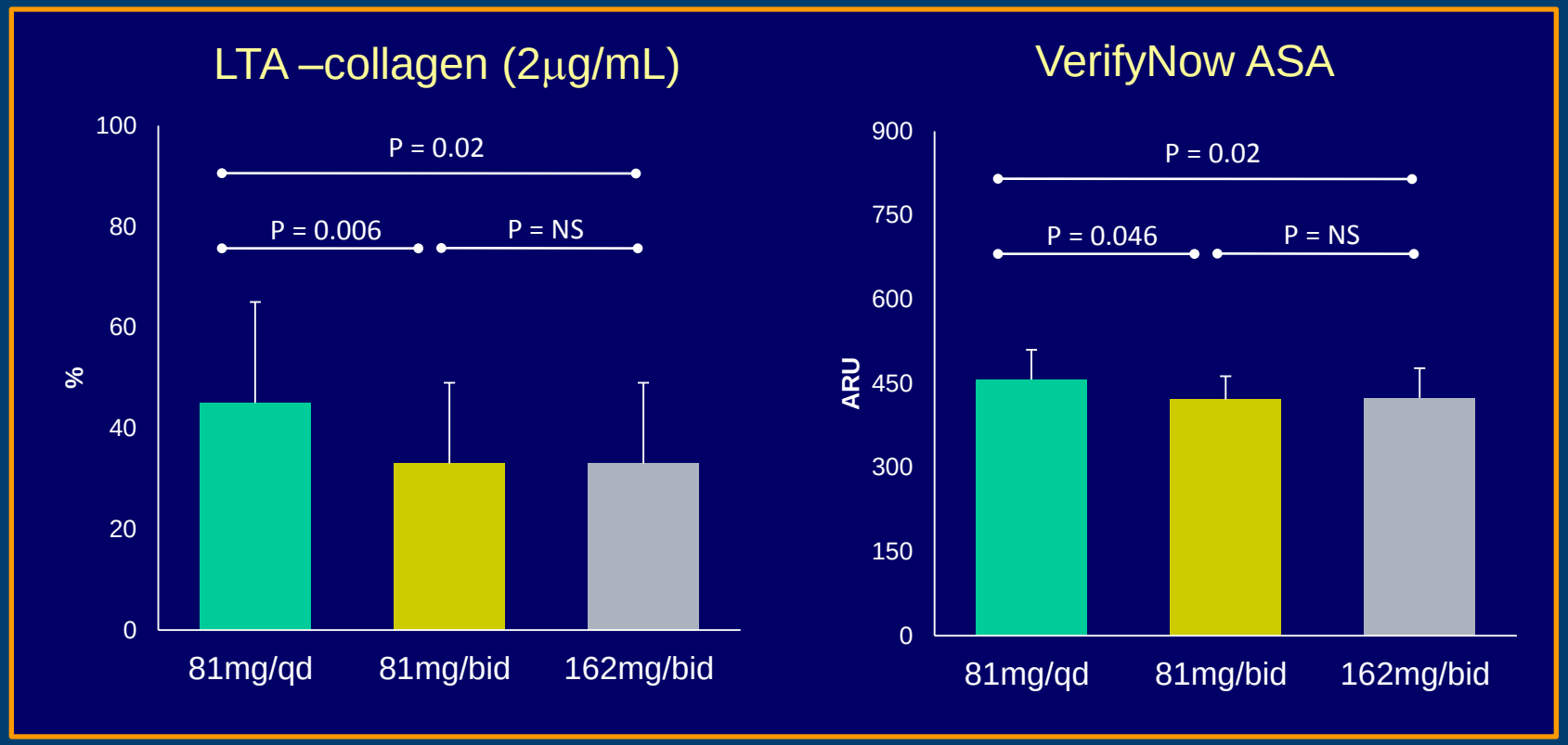
IMPACT OF ONCE Vs. TWICE DAILY ASPIRIN DOSING ON PLATELET REACTIVITY



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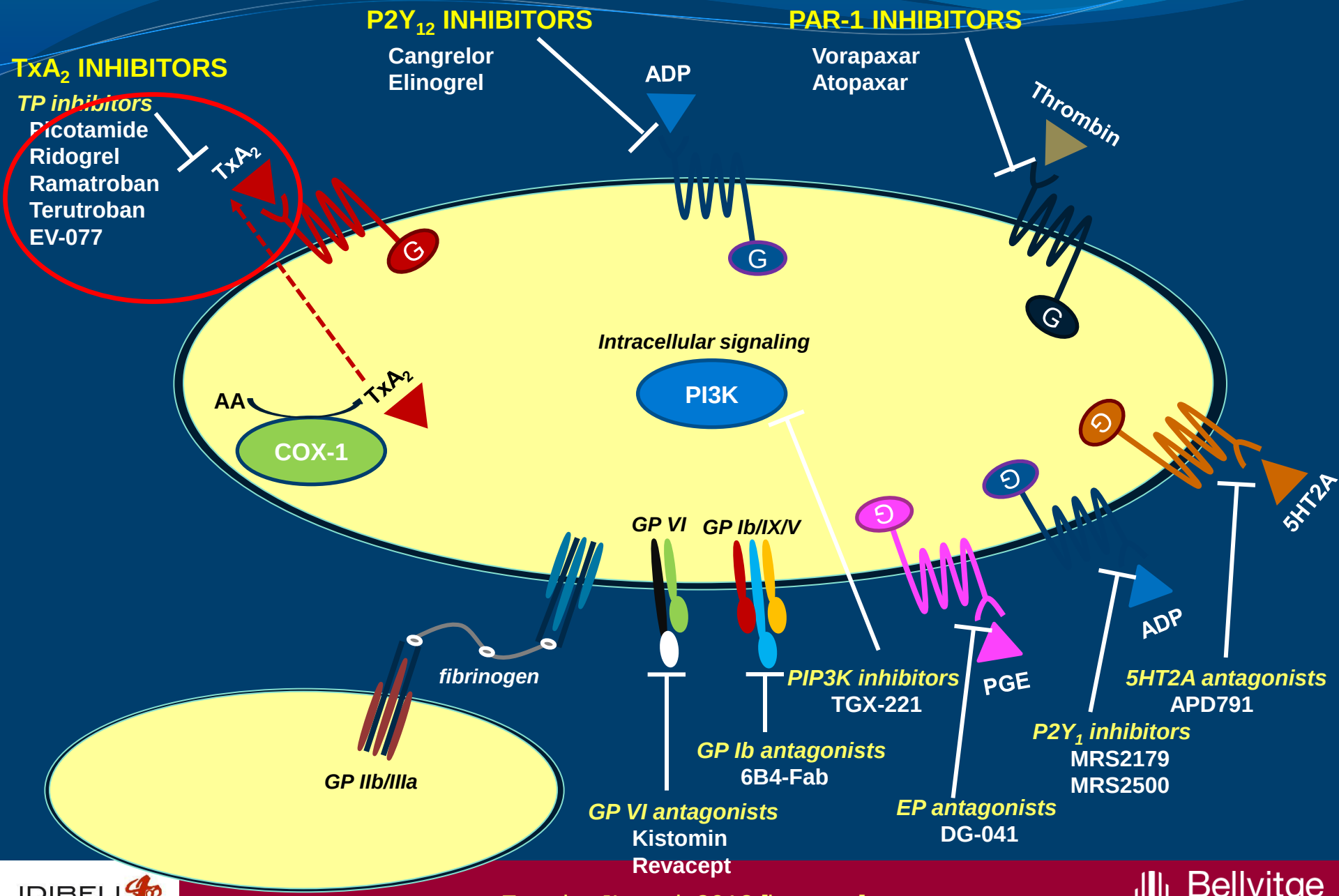


Ferreiro JL et al. 2012 [in press]

IDIBELL Institut d'Investigació Biomèdica de Bellvitge

Bellvitge Hospital

STRATEGIES TO ENHANCE $P2Y_{12}$ INHIBITION IN PATIENTS WITH DM

- Increase clopidogrel dosing
  (e.g. 150 mg maintenance dosing)

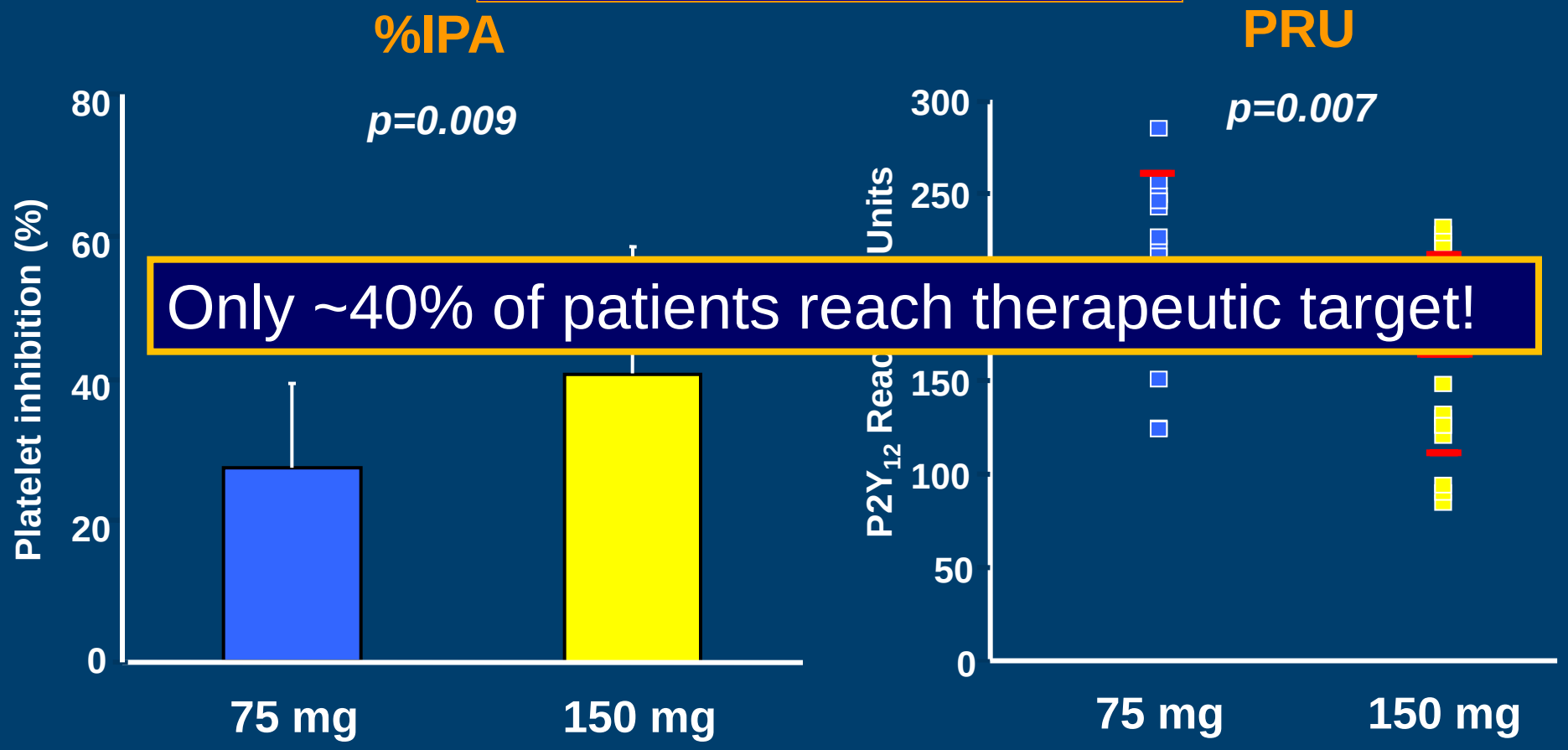
- Adding agents that modulate intraplatelet cAMP
  (e.g. triple therapy: ASA + clopidogrel + cilostazol)

- Using more potent $P2Y_{12}$ inhibitors
  (e.g. prasugrel, ticagrelor, cangrelor, elinogrel)

HIGH CLOPIDOGREL MAINTENANCE DOSING IN POOR-RESPONDERS DM

PATIENTS WITH SUBOPTIMAL CLOPIDOGREL RESPONSE

VerifyNow $P2Y_{12}$ substudy



Only ~40% of patients reach therapeutic target!

Angiolillo DJ et al. Circulation. 2007;115:708-16.

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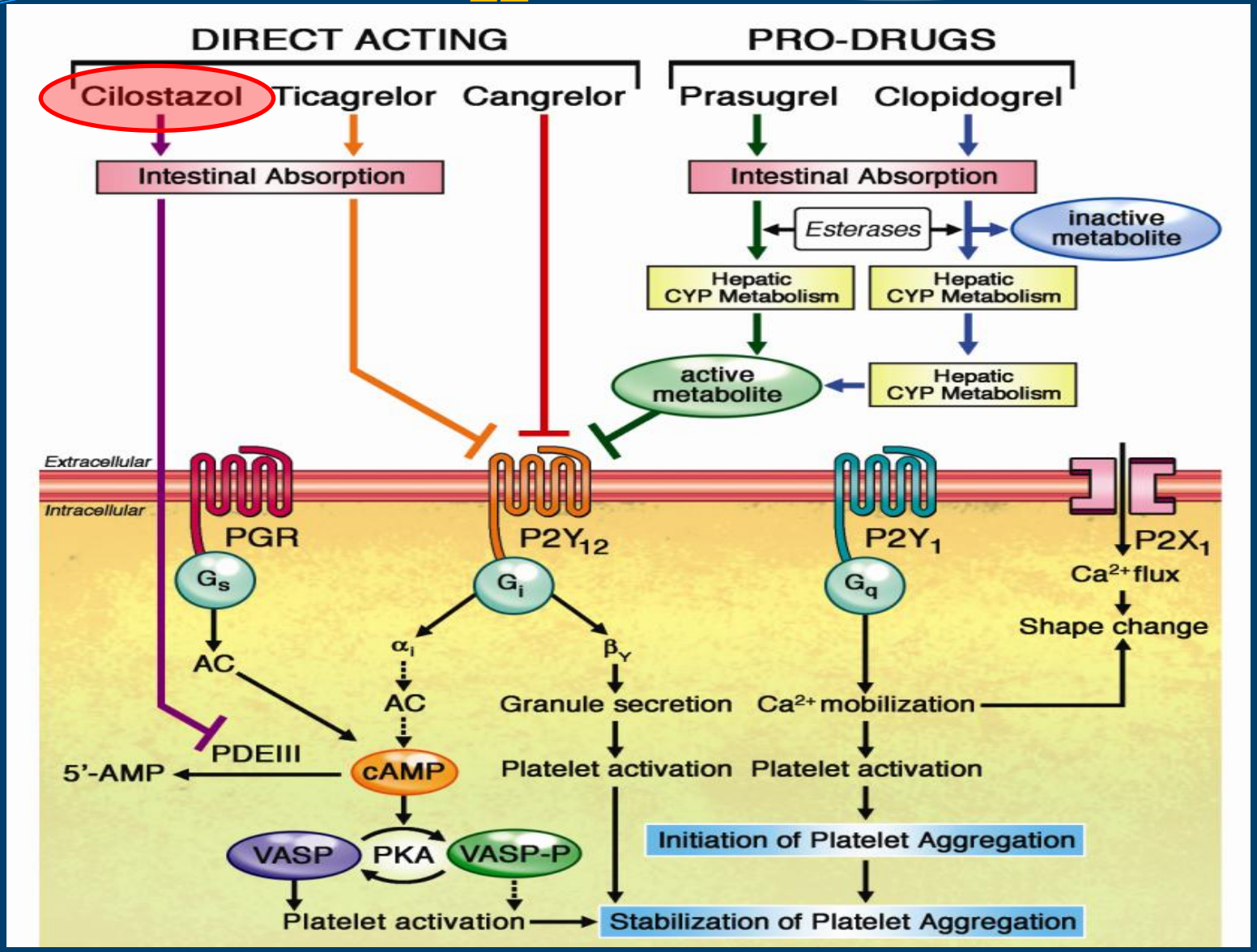
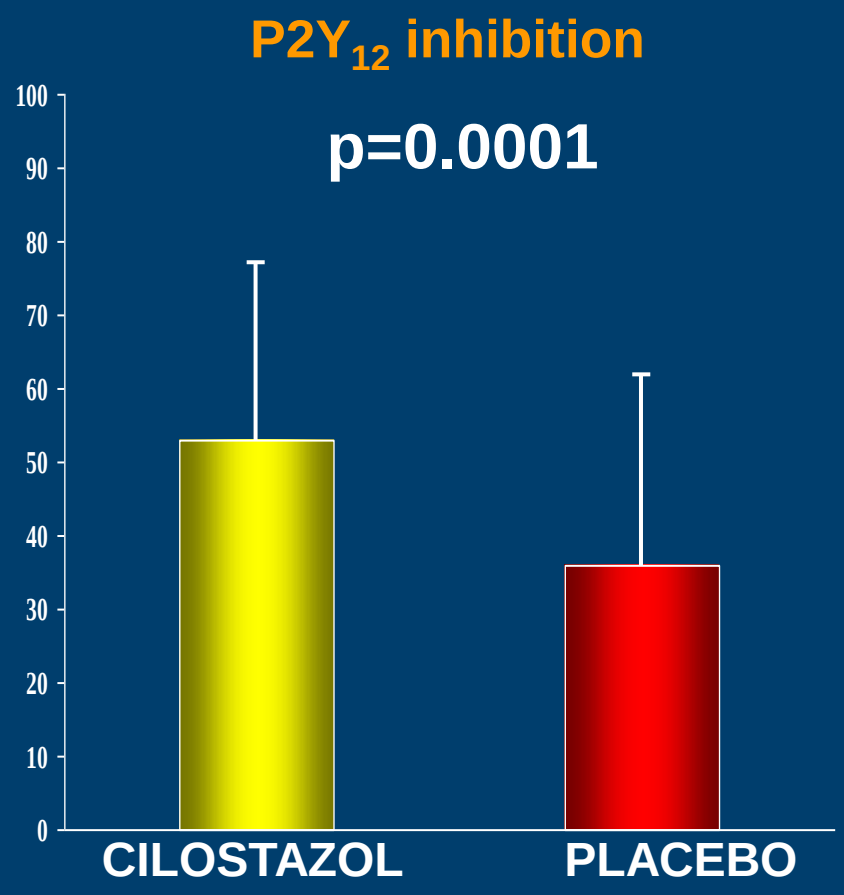
$P2Y_{12}$ INHIBITORS

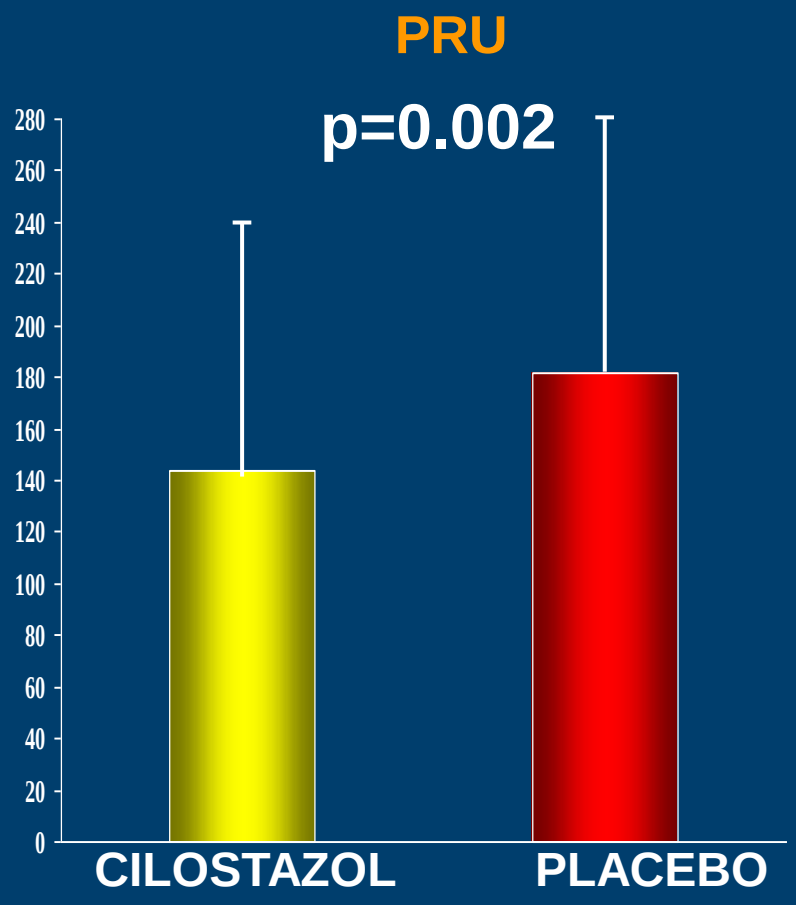


JACC Interv 2011

ADJUNCTIVE CILOSTAZOL THERAPY IN DM PATIENTS ON DAPT

VerifyNow $P2Y_{12}$ assay

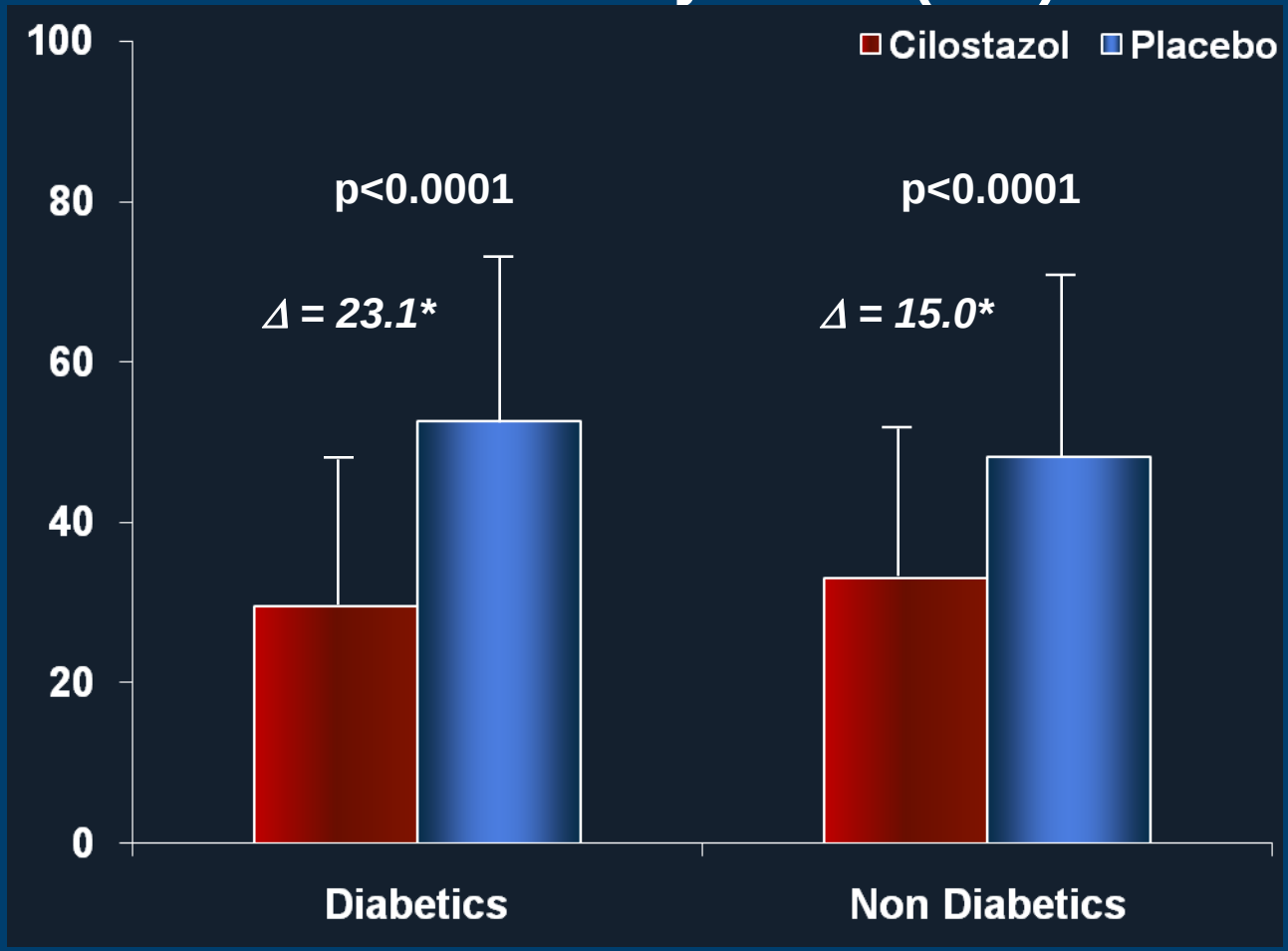




Angiolillo DJ et al. Eur Heart Journal. 2008; 29:2202-11

ADJUNCTIVE CILOSTAZOL IN PATIENTS ON DAPT

P2Y12 Reactivity Index (PRI)



** p between Δ = 0.039*

Angiolillo DJ et al. Thromb Haemost. 2011;106(2)

STRATEGIES TO ENHANCE $P2Y_{12}$ INHIBITION IN PATIENTS WITH DM

- Increase clopidogrel dosing
  (e.g. 150 mg maintenance dosing)

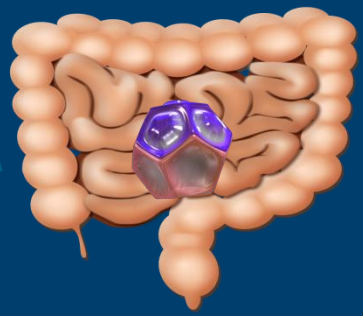
- Adding agents that modulate intraplatelet cAMP
  (e.g. triple therapy: ASA + clopidogrel + cilostazol)

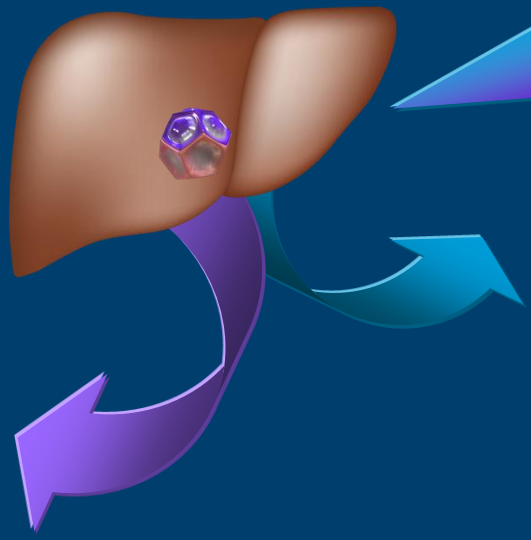
- Using more potent $P2Y_{12}$ inhibitors
  (e.g. prasugrel, ticagrelor, cangrelor, elinogrel)

MECHANISM OF ACTION OF THIENOPYRIDINES

Variable proportion of prodrug metabolized to active drug by cytochrome P450

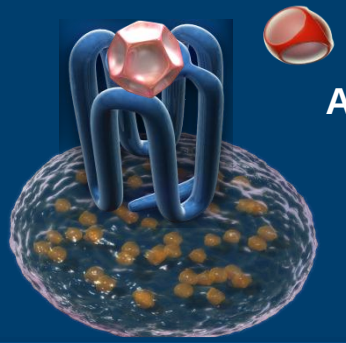
Hydrolysis by esterases





Active drug

Irreversible, covalent binding to $P2Y_{12}$ receptor



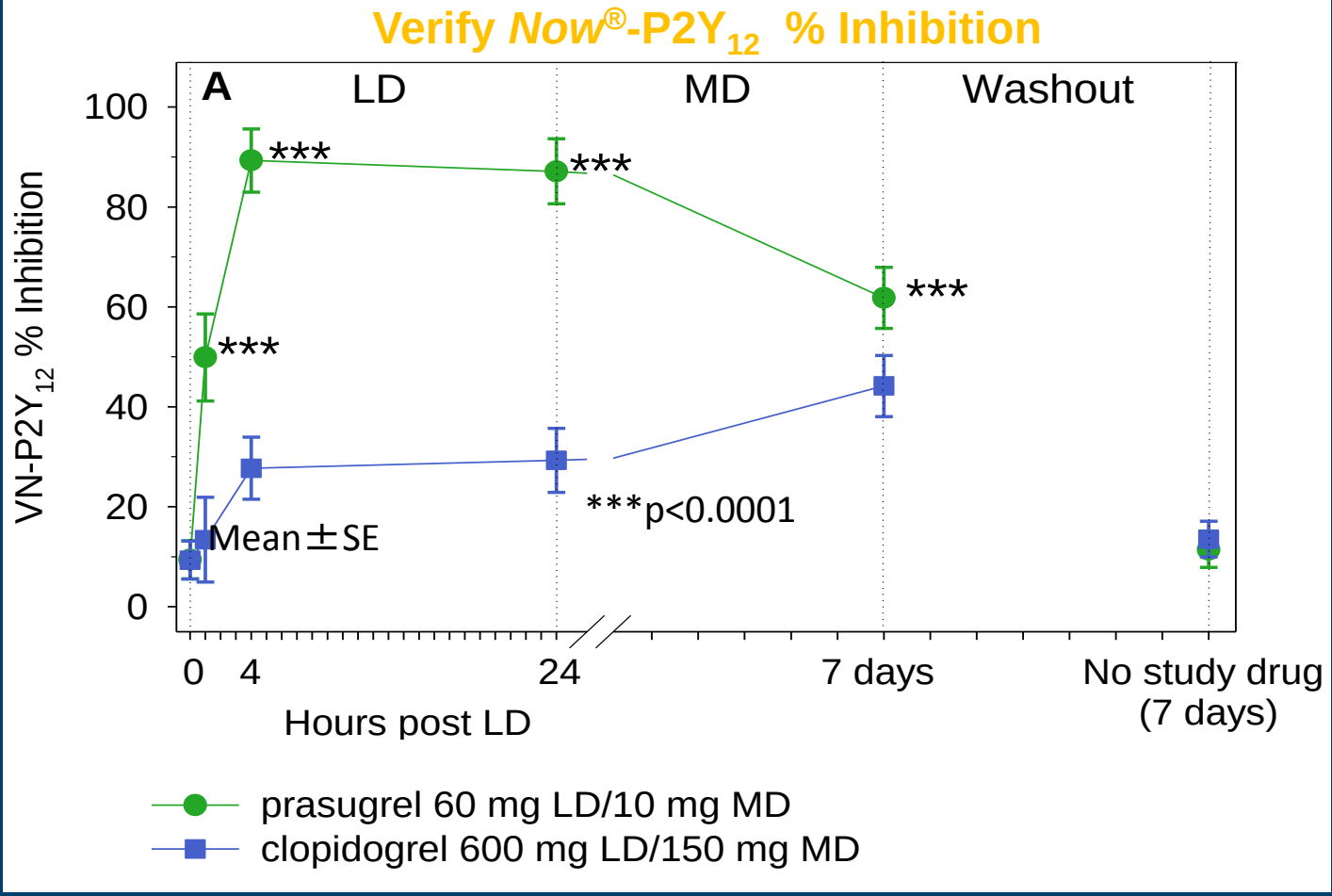
ADP

Inactive metabolites elimination by urine/feces

Platelets require replacement for return to activity

IMPACT OF PRASUGREL IN PLATELET FUNCTION IN DM PATIENTS

Prasugrel (standard dose) vs Clopidogrel (high dose) in DM patients



Similar findings obtained with MPA to 5 and 20 μM ADP, VASP PRI, and Verify *Now*® PRU

Angiolillo DJ et al. Eur Heart J. 2011; 32: 838-46.

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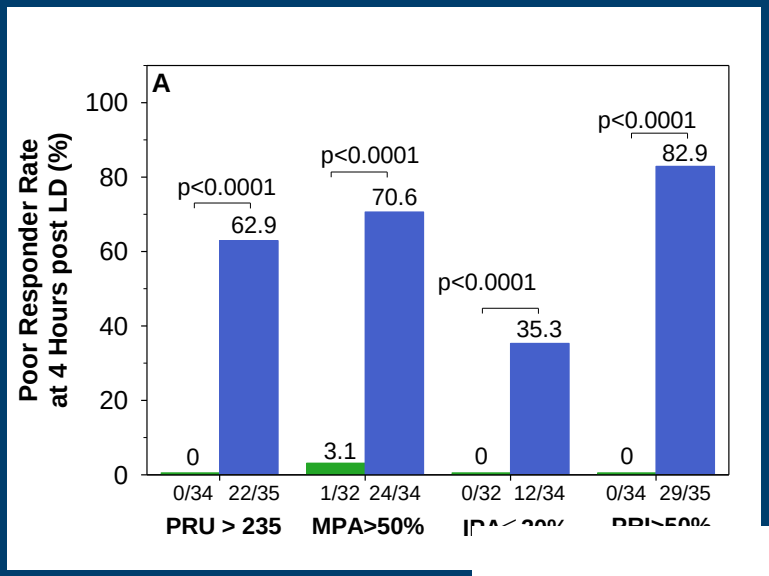
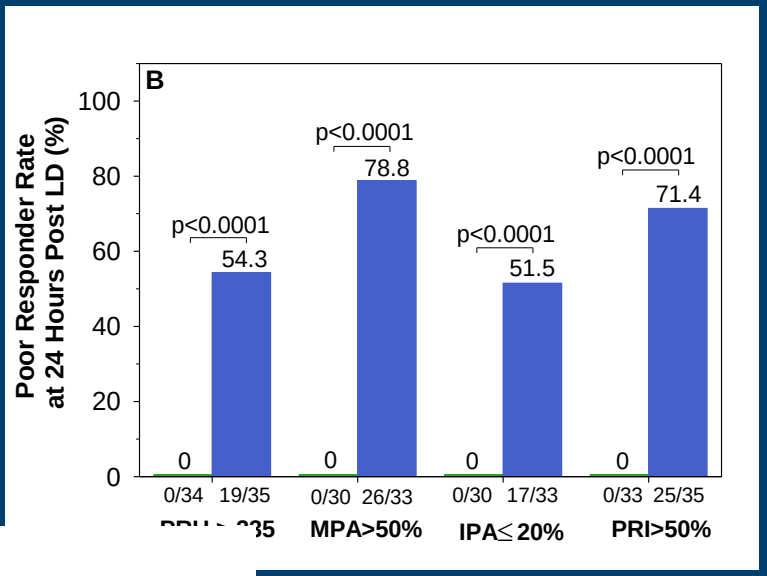
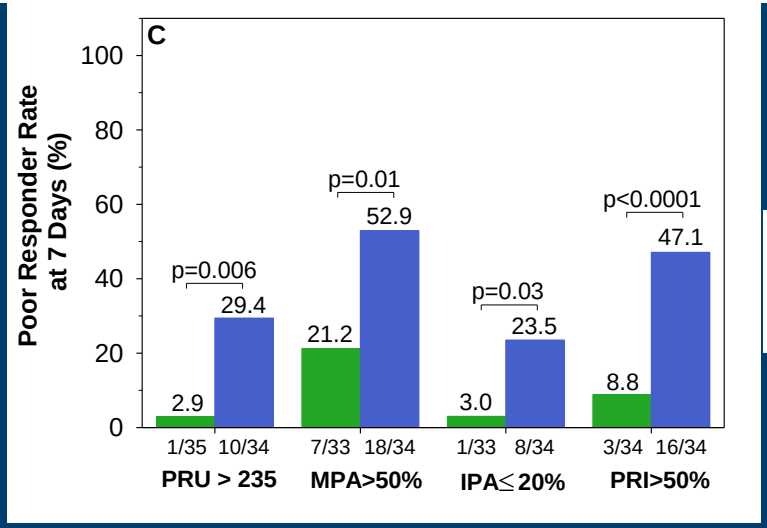
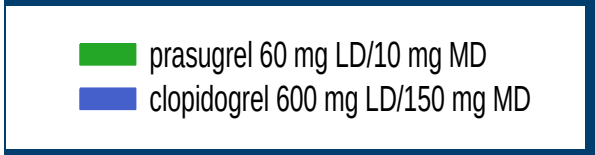
PRASUGREL AND POOR RESPONSIVENESS

Poor responder analyses at: A) 4 h post LD ; B) 24 h post LD; and C) 7 days post MD



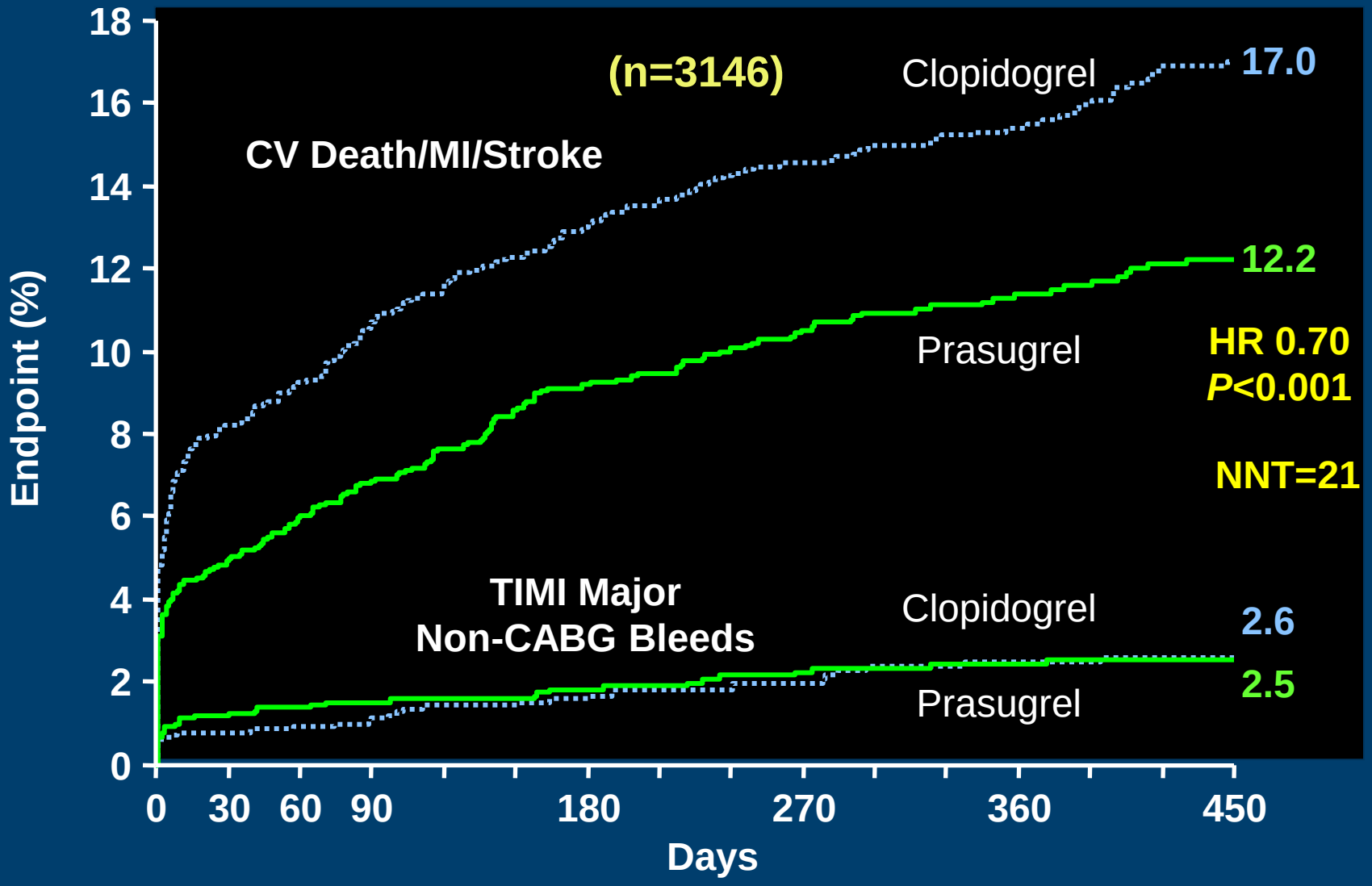






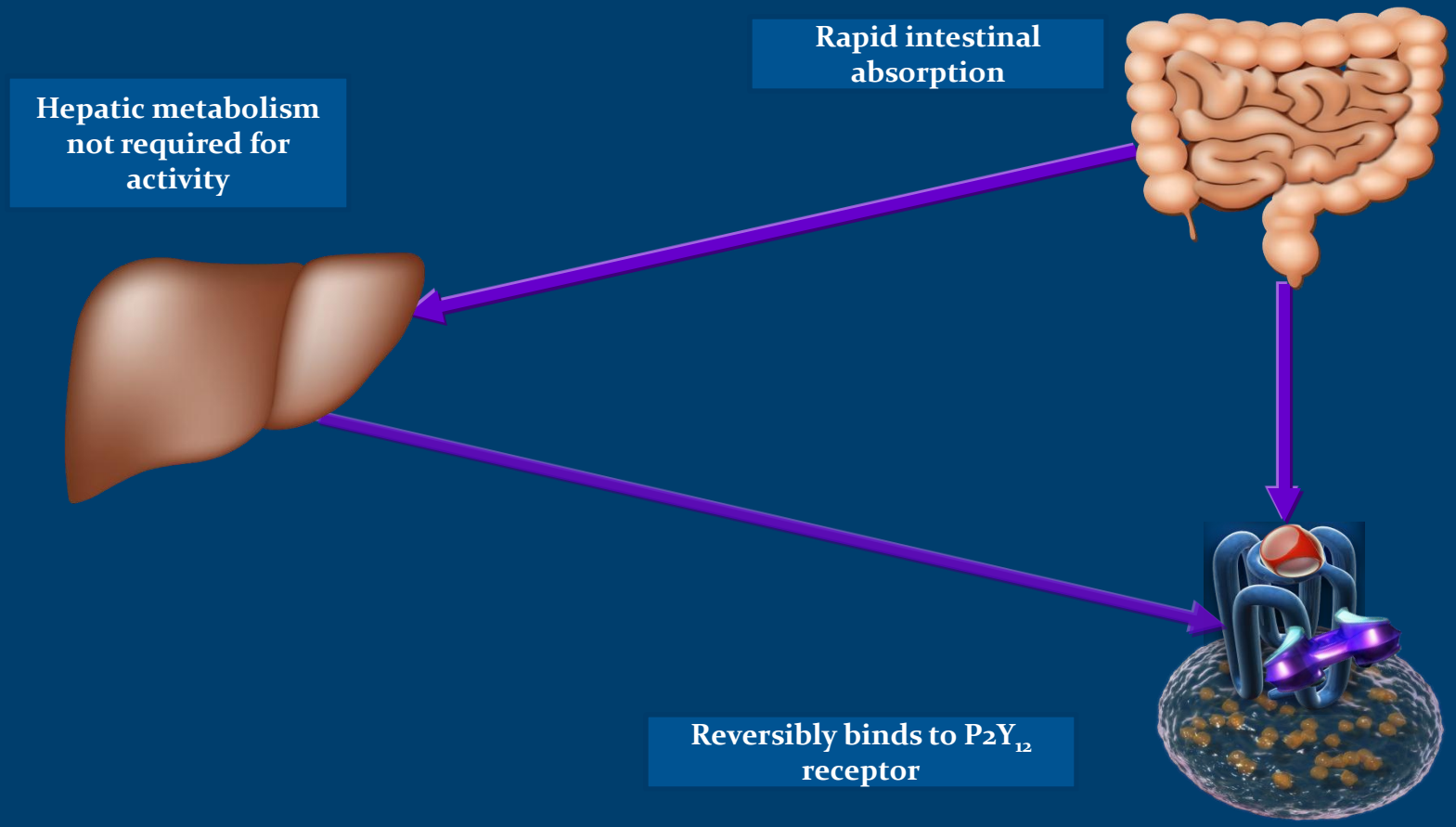
Angiolillo DJ et al. Eur Heart J. 2011; 32: 838-46.

DM AND PRASUGREL



Wiviott SD et al. Circulation 2008;118:1626–36.

TICAGRELOR METABOLISM

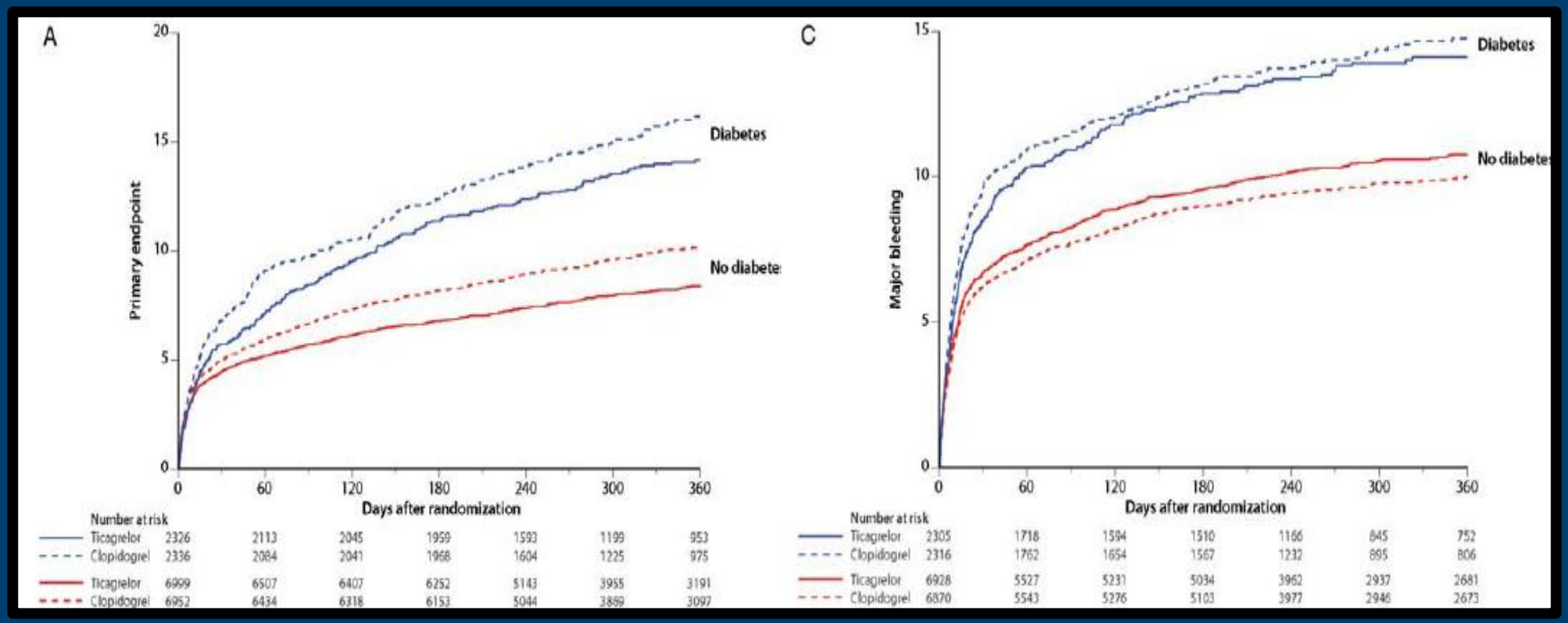


Adapted from Husted S et al. Cardiovasc Ther. 2009;27:259-274.

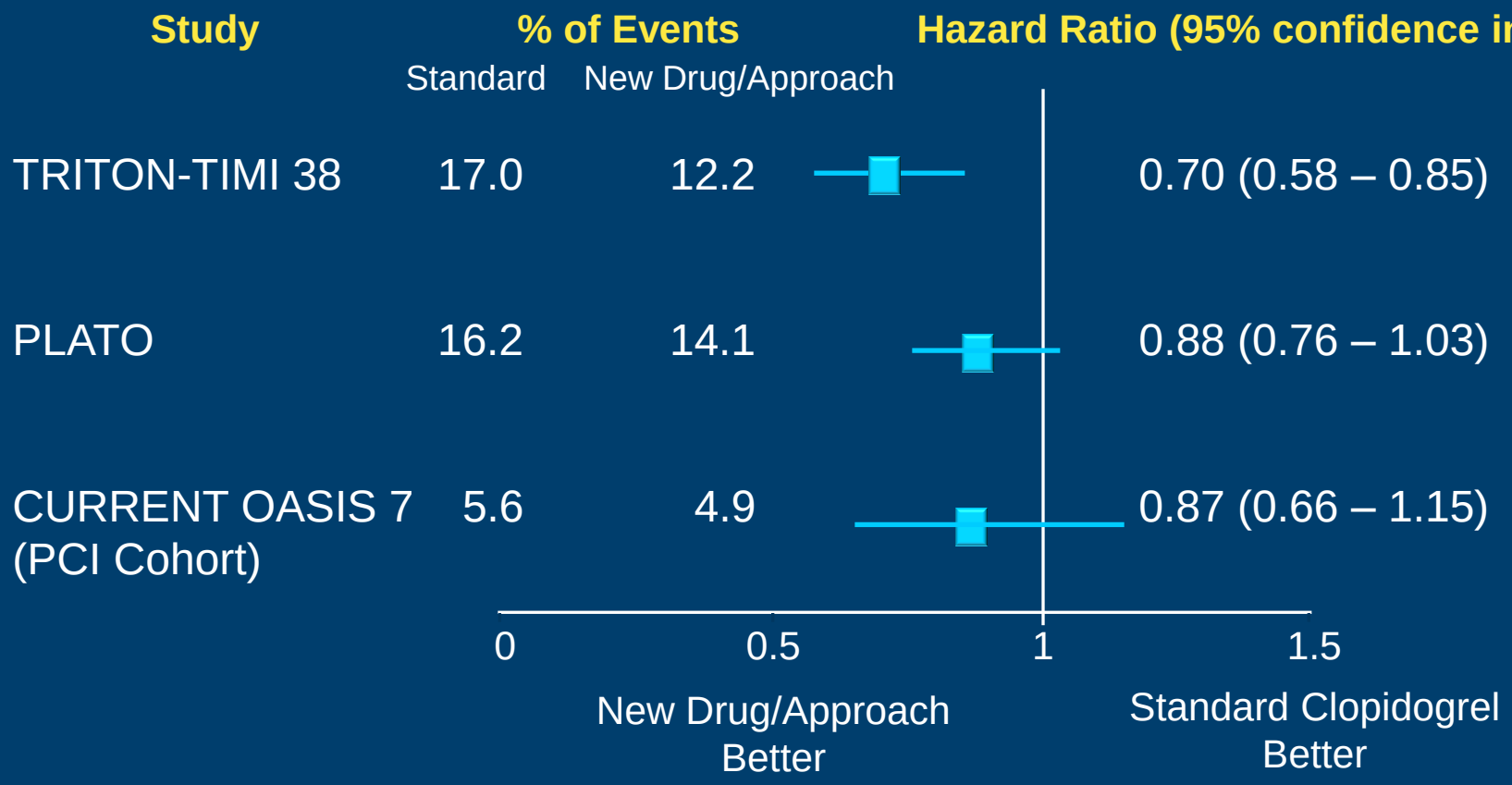
DM AND TICAGRELOR

CV death, MI, stroke

Major Bleeding



NEW DRUGS/APPROACHES IN DM

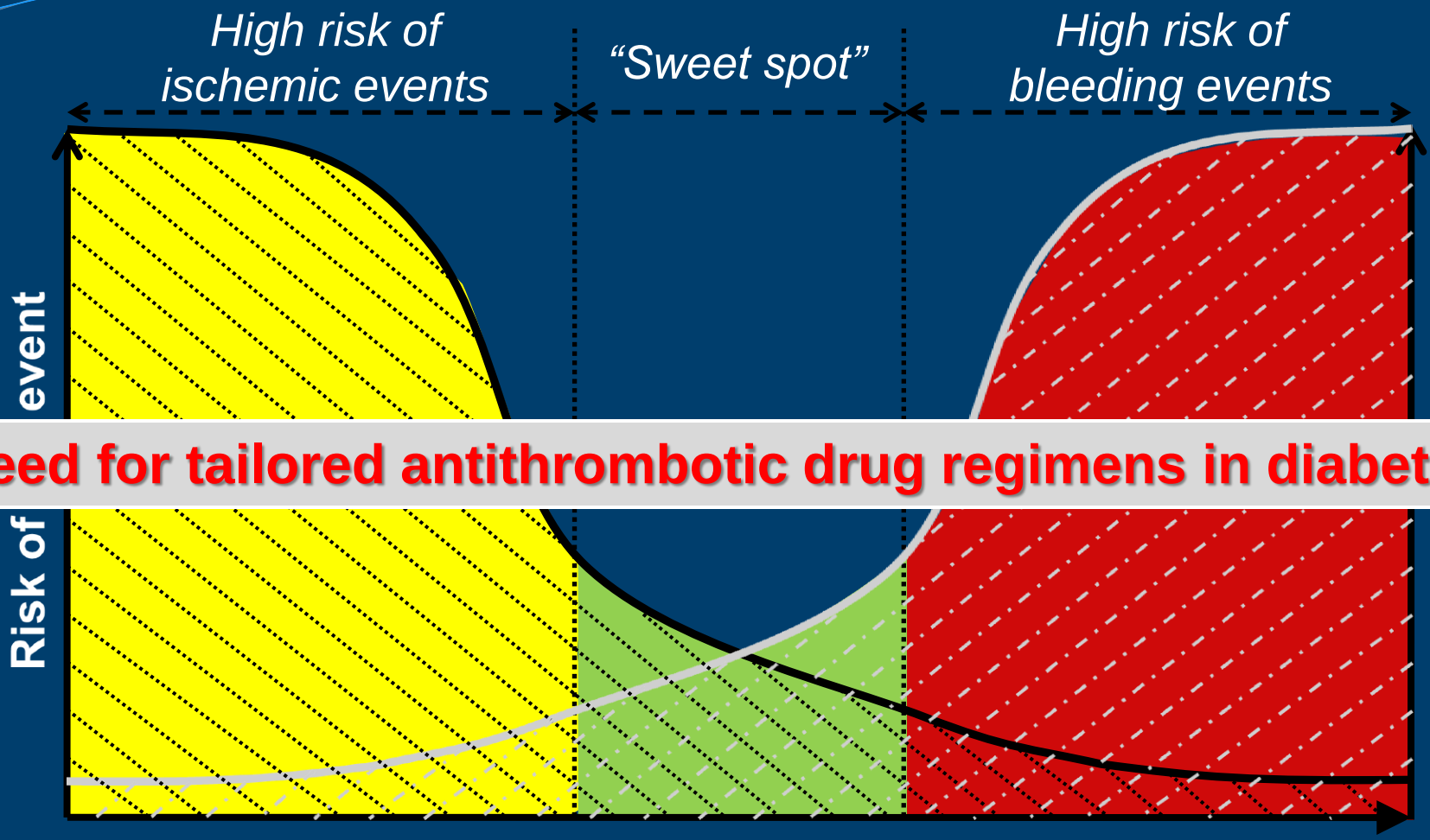


Ferreiro JL et al. *Circulation 2011*. 123:798-813.

CONCLUSIONS

Does one size fit all??

BALANCING ISCHEMIA / BLEEDING



Ferreiro JL et al. Thromb Haemost 2010;103:1128-35.

ABCs OF TREATMENT OF DIABETIC PATIENTS AND IMPACT ON THROMBOSIS

A A1C (blood glucose): <7%

B Blood pressure: <130/80 mm Hg

C Cholesterol-LDL: <70 mg/dl

Platelet Reactivity

CONCLUSIONS

- DM is a predictor of worse outcomes in ACS
- Abnormalities in DM platelets (dysfunctional):
  - increased platelet reactivity
  - reduced responsiveness to antiplatelet agents
- Increased platelet reactivity and reduced responsiveness to standard DAPT (aspirin plus clopidogrel) are associated with atherothrombotic risk
- Control of “ABC” improves platelet function profiles
- Specific (*“tailored”*) drug regimens in DM patients are warranted
- Novel and more potent antiplatelet agents may improve blockade of the diabetic platelet

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Thanks for Your Attention