Evolving Antithrombotic Strategies for Patients with DM and CAD

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Presenter Disclosure Information

Name: Dominick J Angiolillo

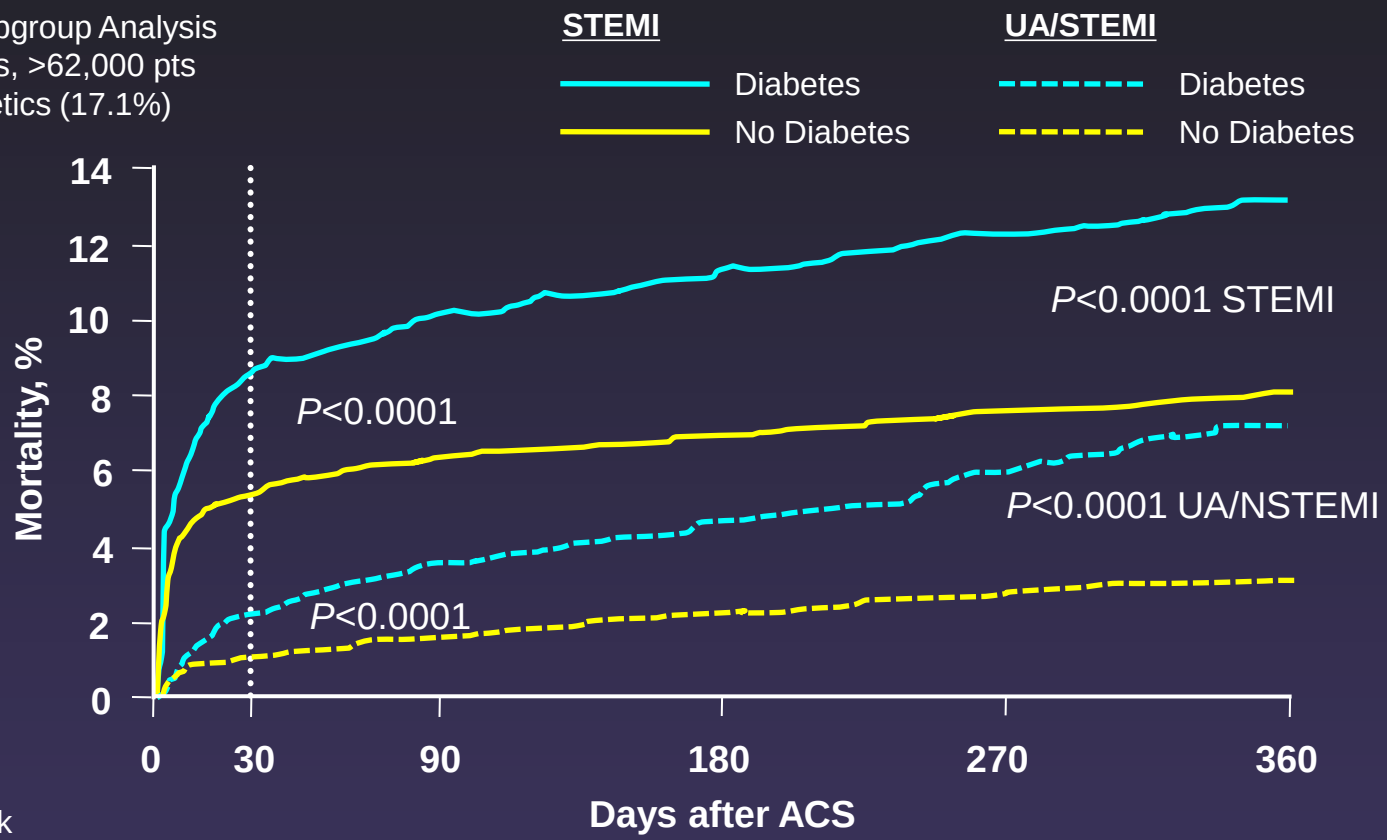
Within the past 12 months, the presenter or their spouse/partner have had a financial interest/arrangement or affiliation with the organization listed below.

Received payment as an individual for:
a) Consulting fee or honorarium from Amgen, Bayer, Chiesi, Sanofi, Eli Lilly, Daiichi-Sankyo, The Medicines Company, AstraZeneca, Merck, Abbott Vascular, Pfizer, and PLx Pharma;
b) Honorarium for participation in review activities (DSMB member) from CeloNova, Johnson & Johnson, St. Jude, and Sunovion.
c) Honorarium from the American Board of Internal Medicine (Interventional Cardiology Subspecialty Exam Writing Committee Member)

Institutional payments for:
a) Grant support industry: from Amgen, Glaxo-Smith-Kline, Eli Lilly, Daiichi-Sankyo, The Medicines Company, AstraZeneca, Janssen Pharmaceuticals, Inc., Osprey Medical, Inc., Novartis, CSL Behring, and Gilead.
b) Grant in gift: Spartan; Scott R. MacKenzie Foundation
c) Federal agency: NIH

Cumulative Incidence of All-Cause Mortality Through 1 Year After ACS

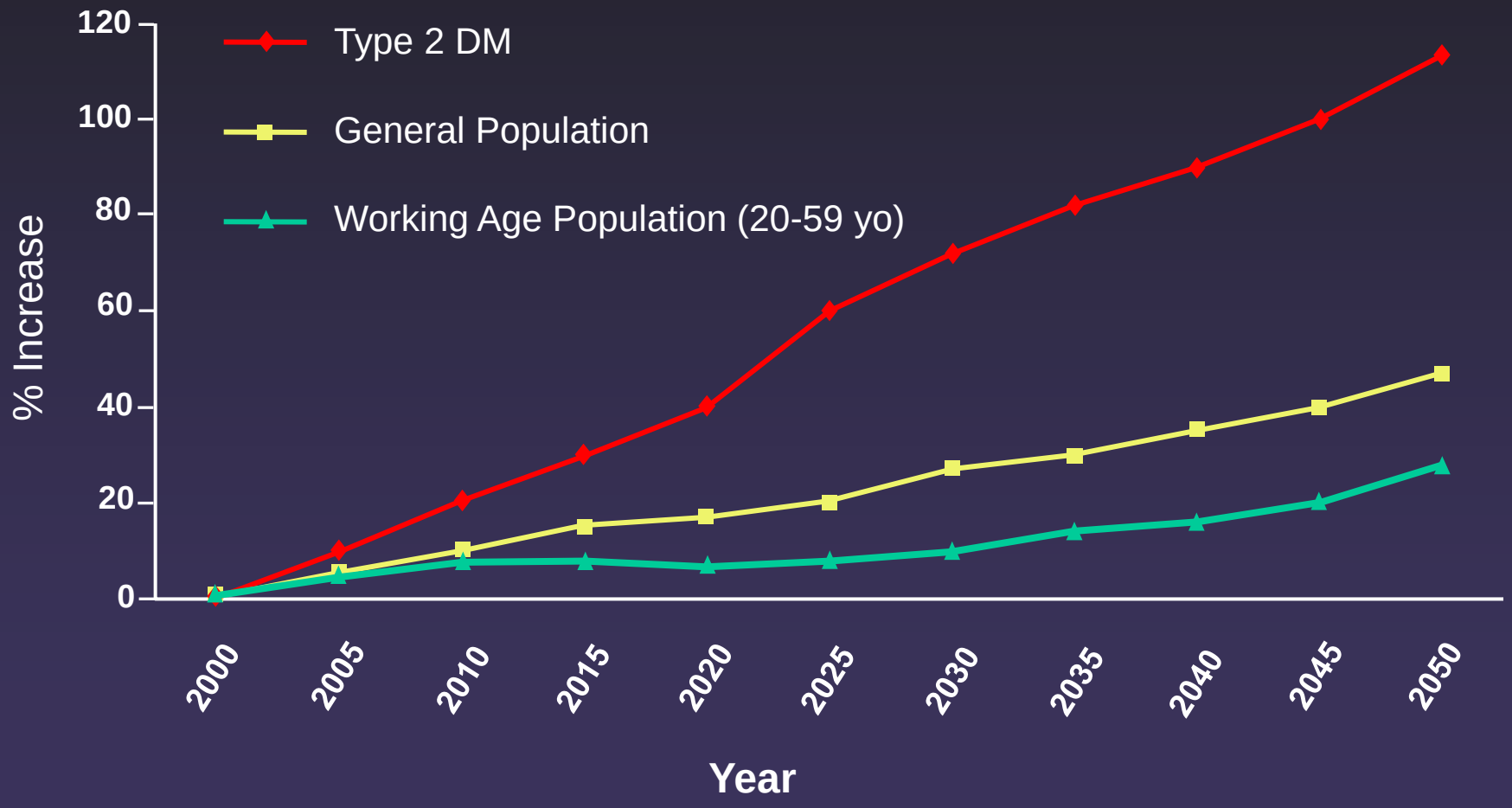
Diabetes Subgroup Analysis
11 TIMI Trials, >62,000 pts
10,613 diabetics (17.1%)



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

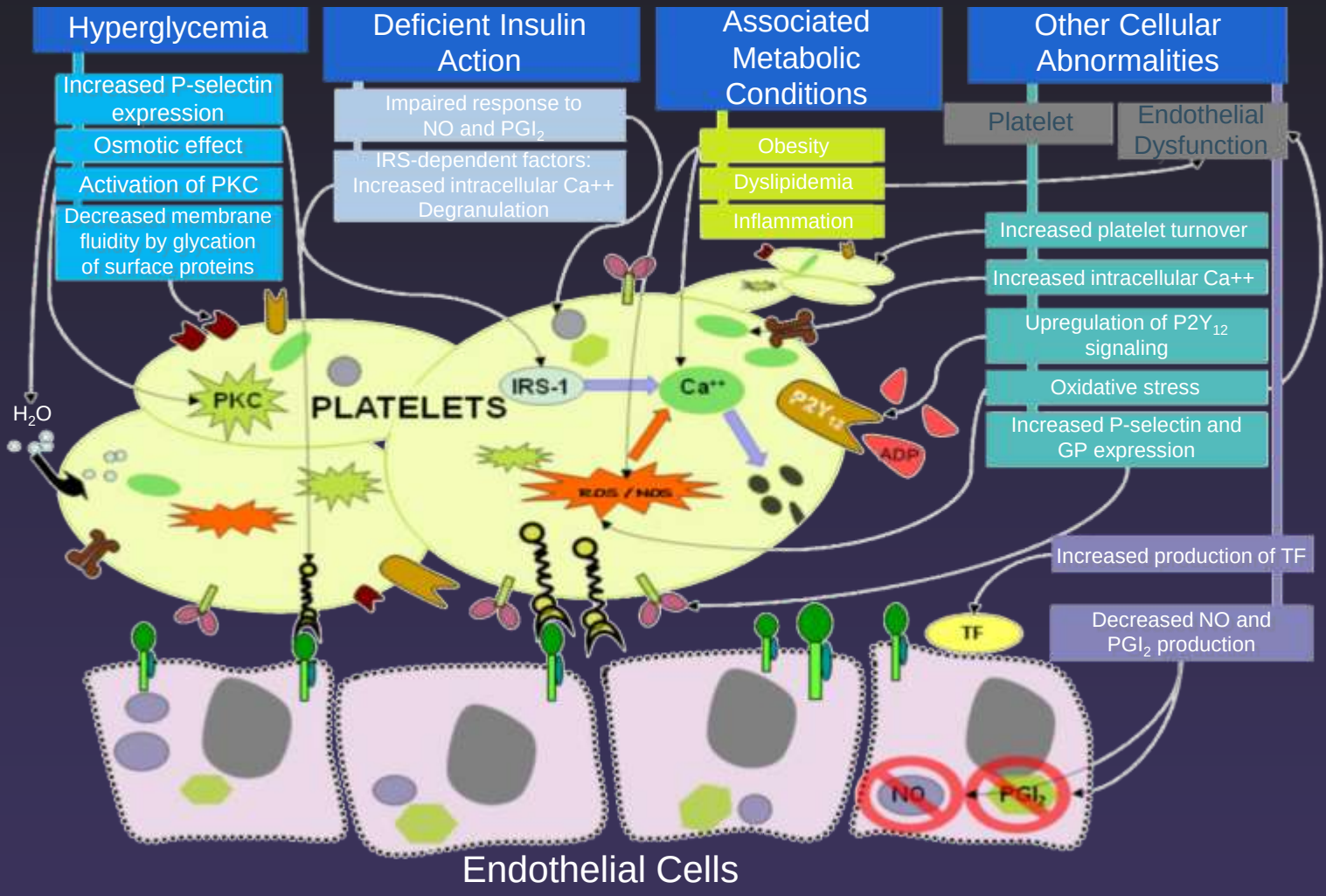
Donahoe SM et al. *JAMA.* 2007;298:765-75.

Estimated Growth in Type 2 Diabetes and US Population From 2000-2050



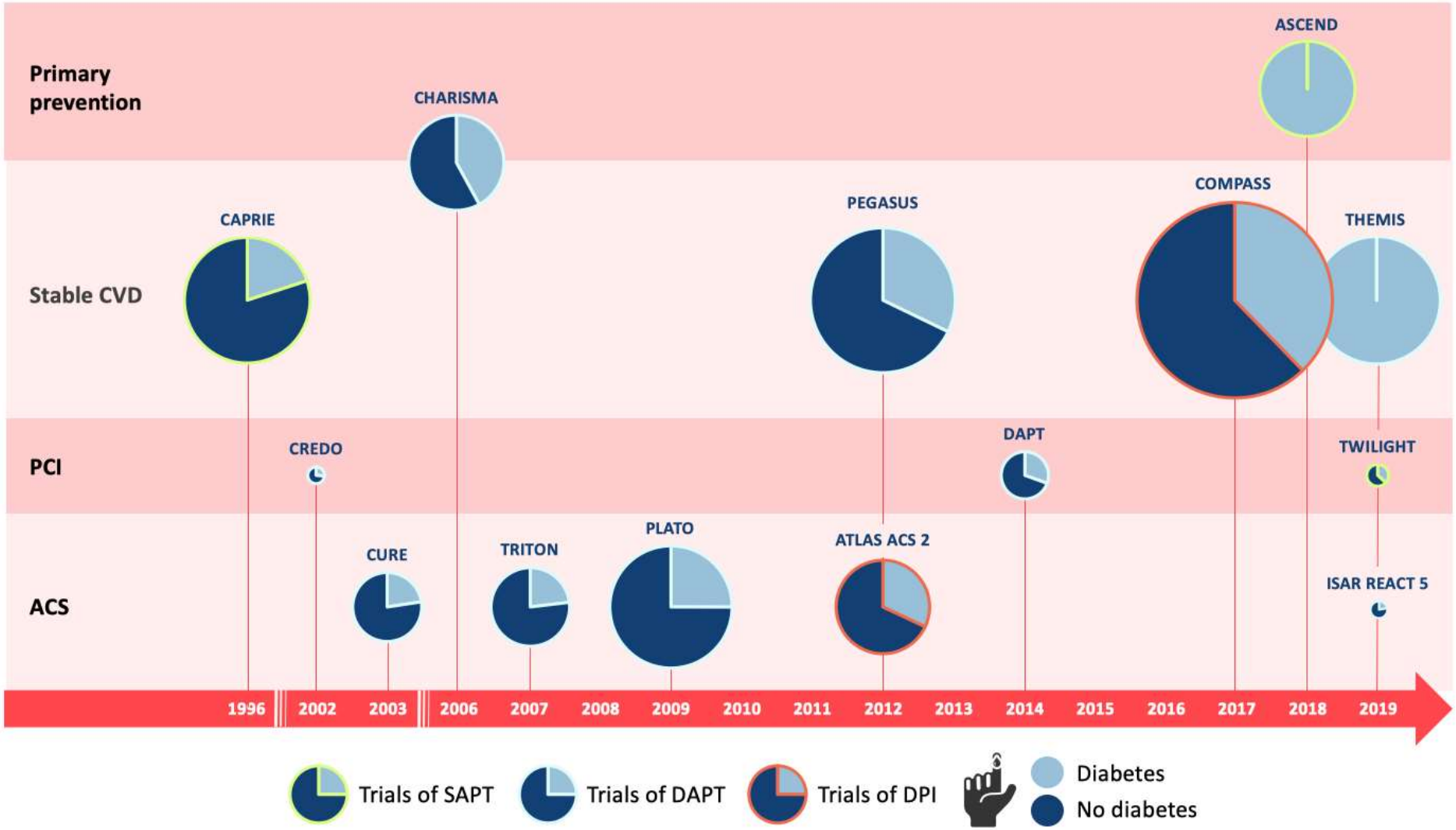
Bagust A et al. *Diabetes.* 2001;50:A205.

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.

Timeline of landmark studies of antithrombotic therapy and proportion of patients with diabetes mellitus.



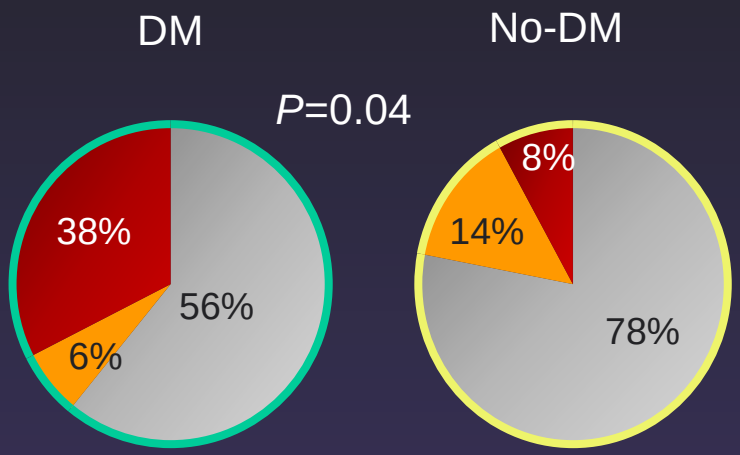
Capodanno D, Angiolillo DJ. *Circulation.* 2020; 142:2172-2188.

DON'T BRING A KNIFE

TO A GUNFIGHT

Influence of Diabetes Mellitus on Clopidogrel-induced Antiplatelet Effects

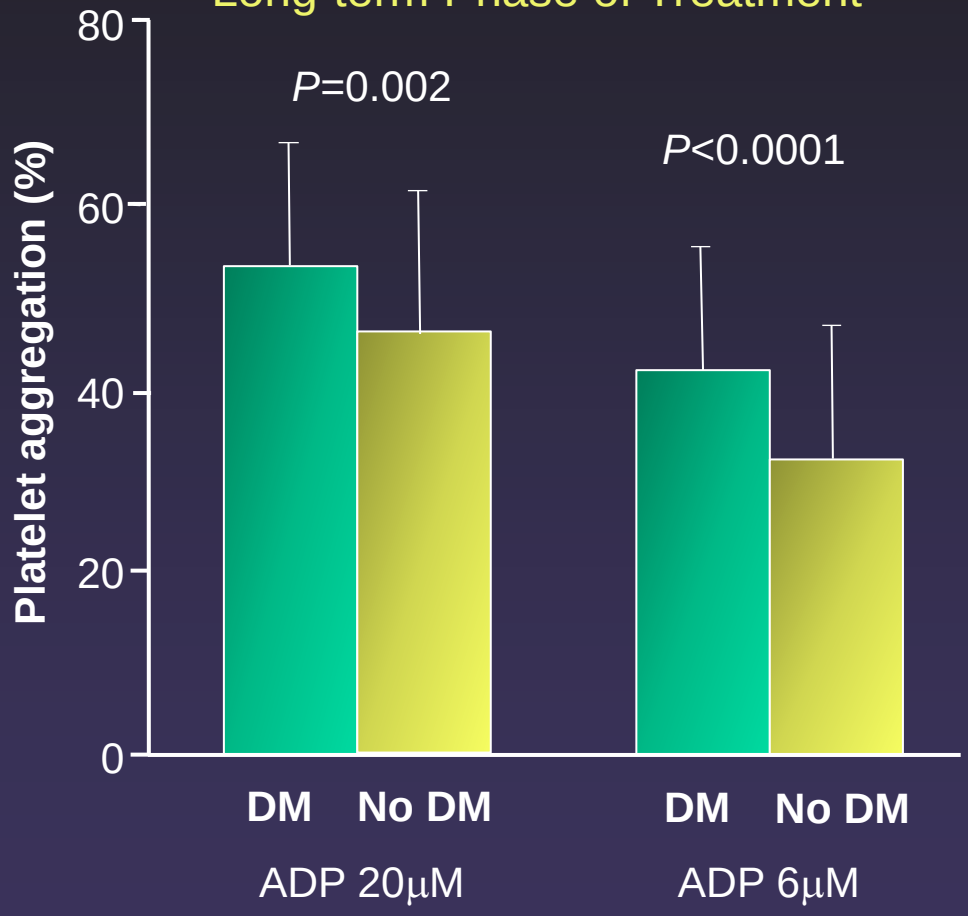
Acute Phase of Treatment



24 hrs post 300 mg LD

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

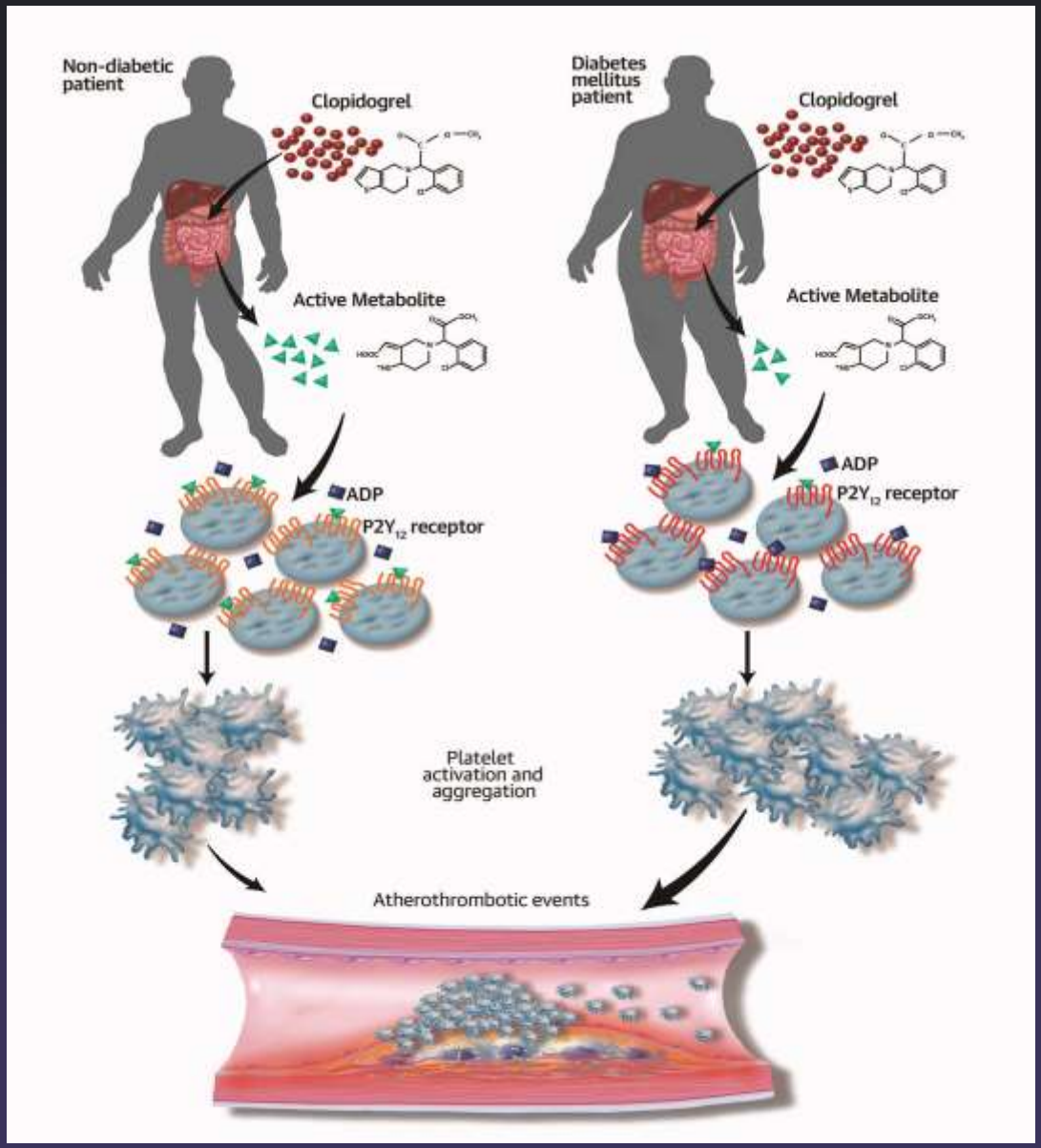
Long-term Phase of Treatment



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

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

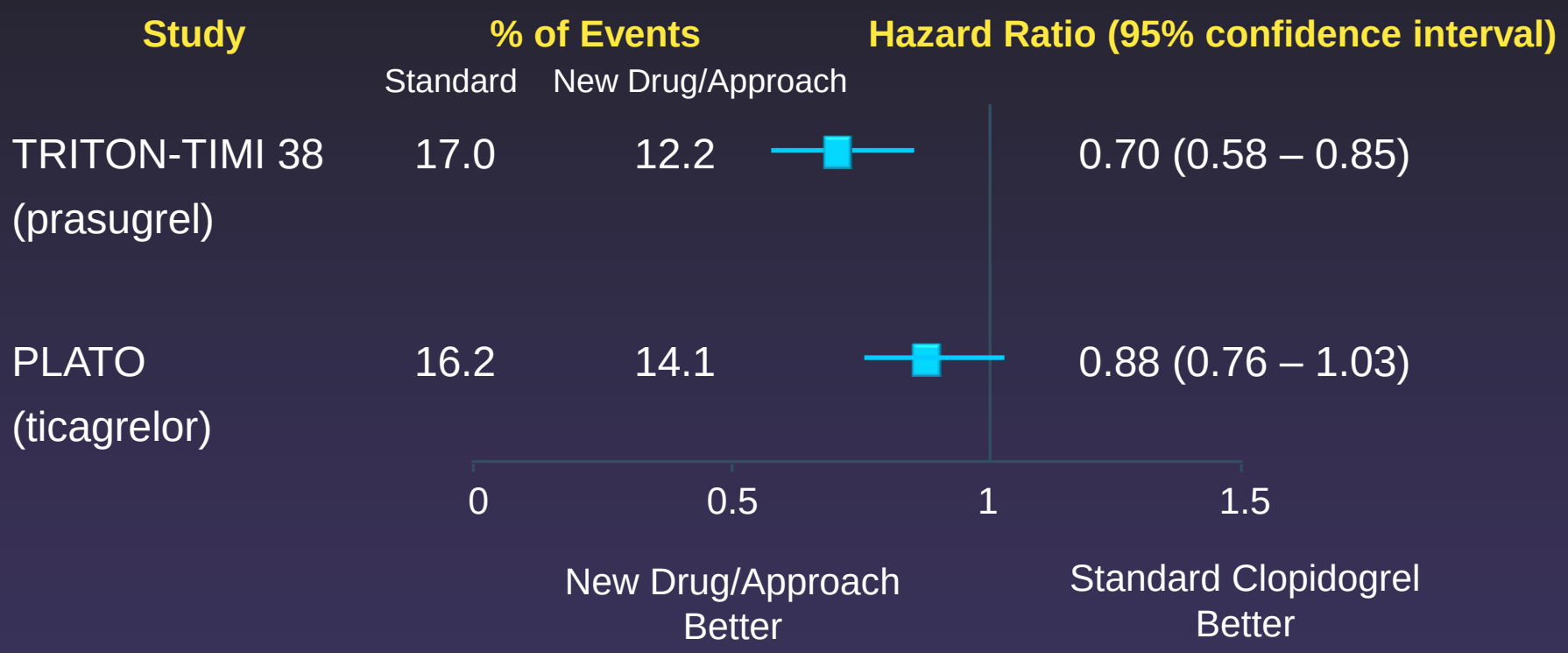
Mechanistic Insights on Impaired Clopidogrel-Induced Antiplatelet Effects in Diabetes Mellitus: Results of an In Vitro and Ex Vivo PD/ PK Investigations



Among DM patients, impaired P2Y12 inhibition mediated by clopidogrel is largely attributable to attenuation of clopidogrel's PK profile, characterized by lower plasma levels of active metabolite compared with non-DM patients and only modestly attributed to upregulation of the P2Y12 signaling pathway.

Angiolillo DJ et al. J Am Coll Cardiol. 2014;64:1005-14.

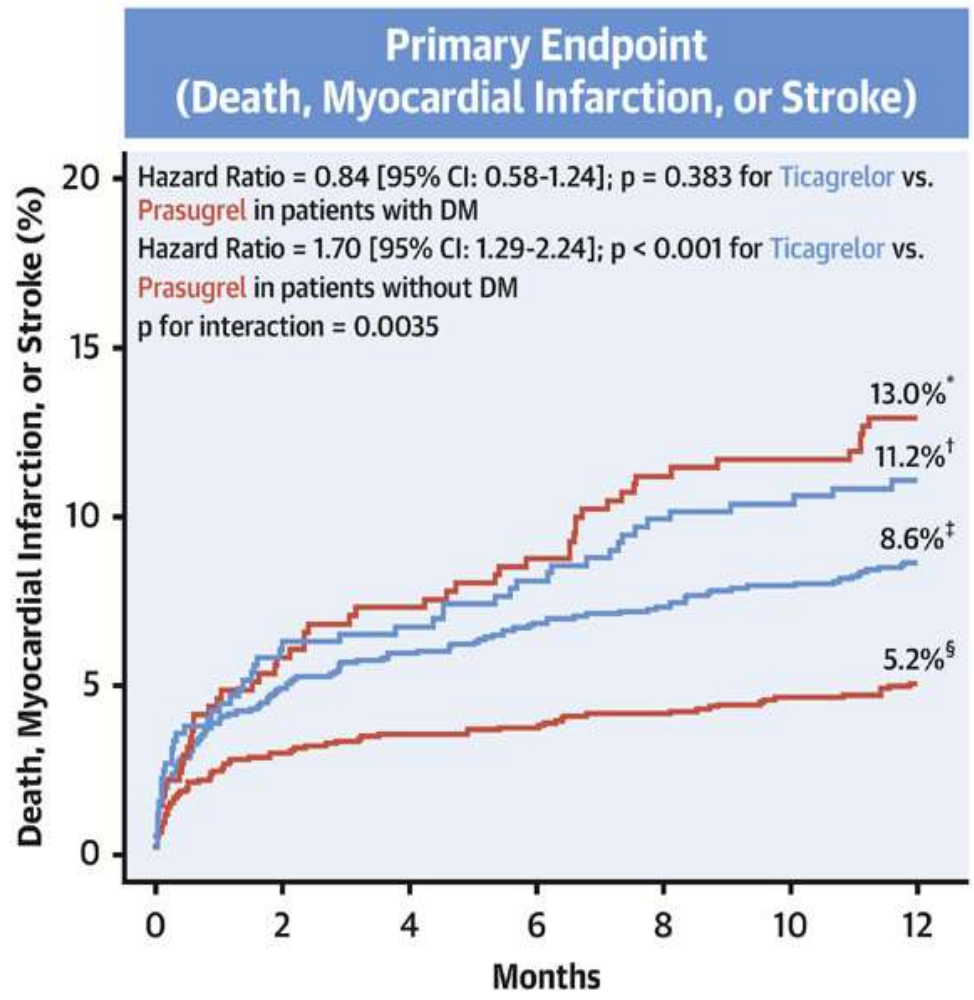
Efficacy of Potent P2Y12 inhibitiorsin Reducing Adverse Outcomes in Diabetes Mellitus From Large-Scale Clinical Trials

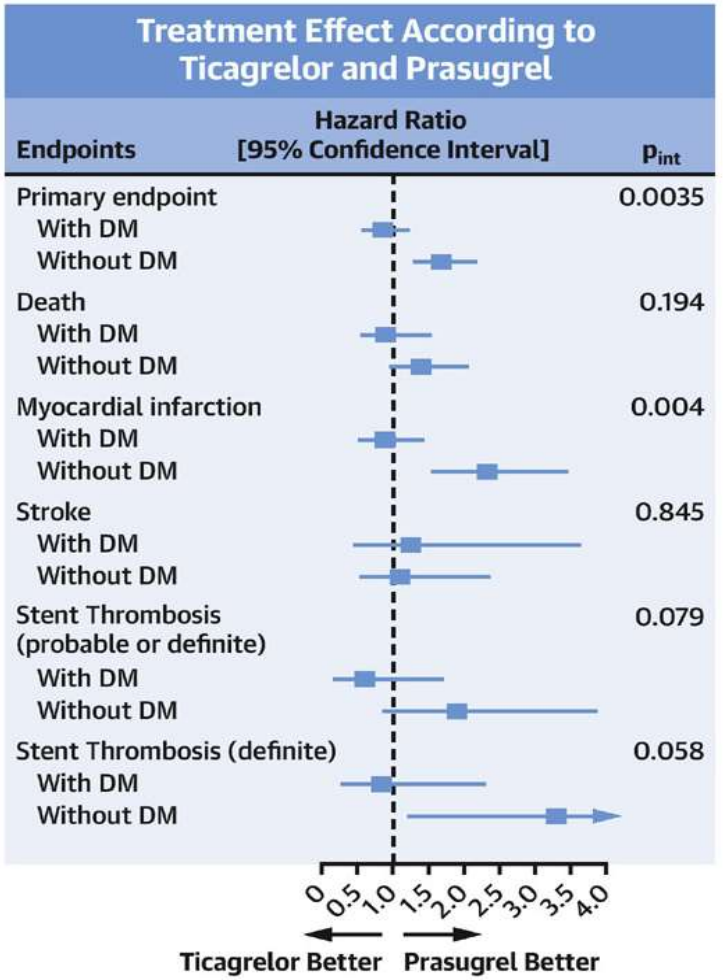


CURRENT-OASIS= Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events Optimal Antiplatelet Strategy for Interventions; PCI=percutaneous intervention; PLATO= A Study of Platelet Inhibition and Patient Outcomes; TRITON-TIMI= Trial To Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel Thrombolysis in Myocardial Infarction.

Adapted from Ferreiro JL, Angiolillo DJ. *Circulation 2011*. 123:798-813.

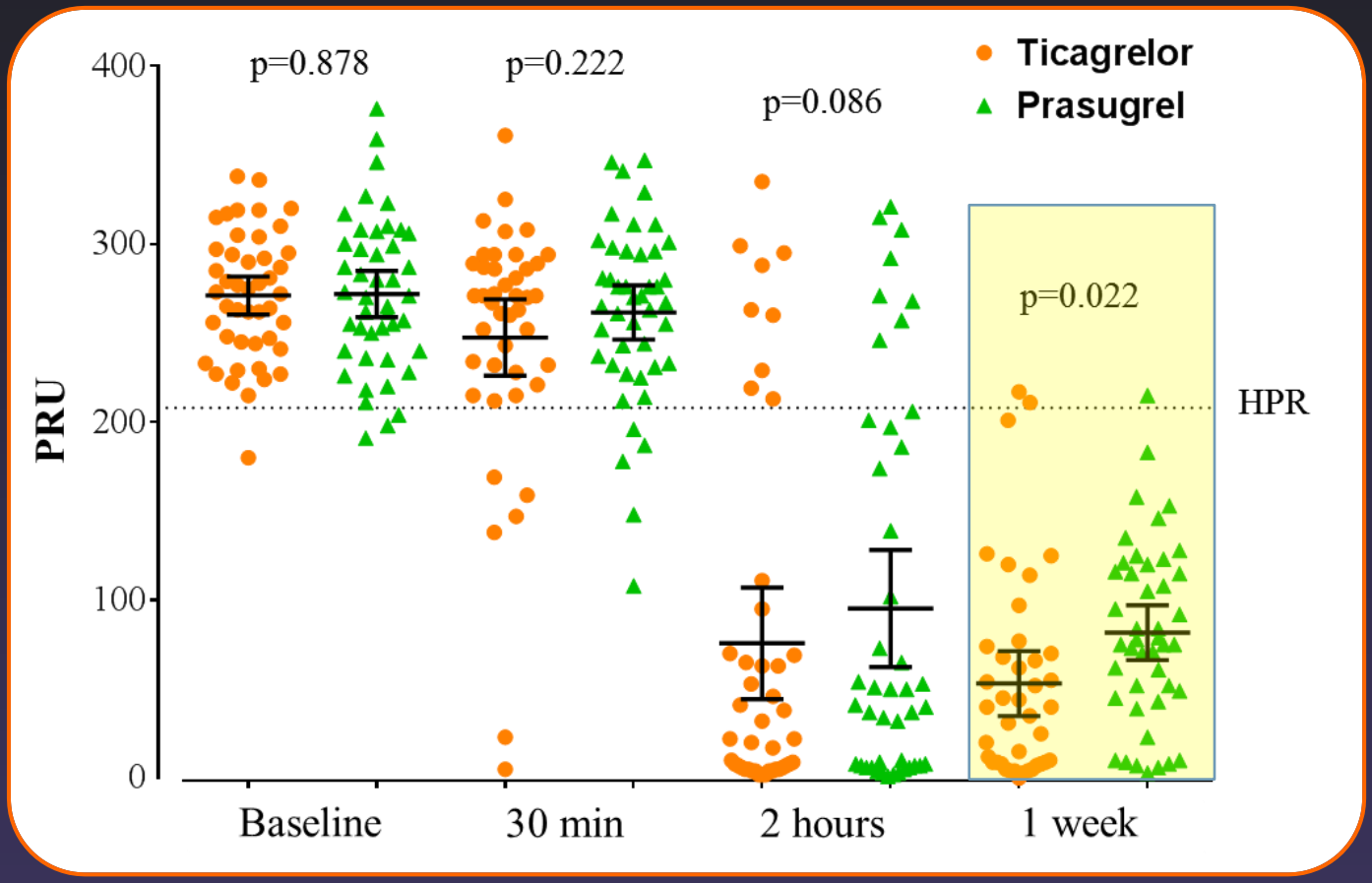
Efficacy of Prasugrel vs Ticagrelor in ACS patients according to DM status: Insights from ISAR-REACT 5





Ndrepepa G. et al. JACC Cardiovasc Interv. 2020;13:2238-47

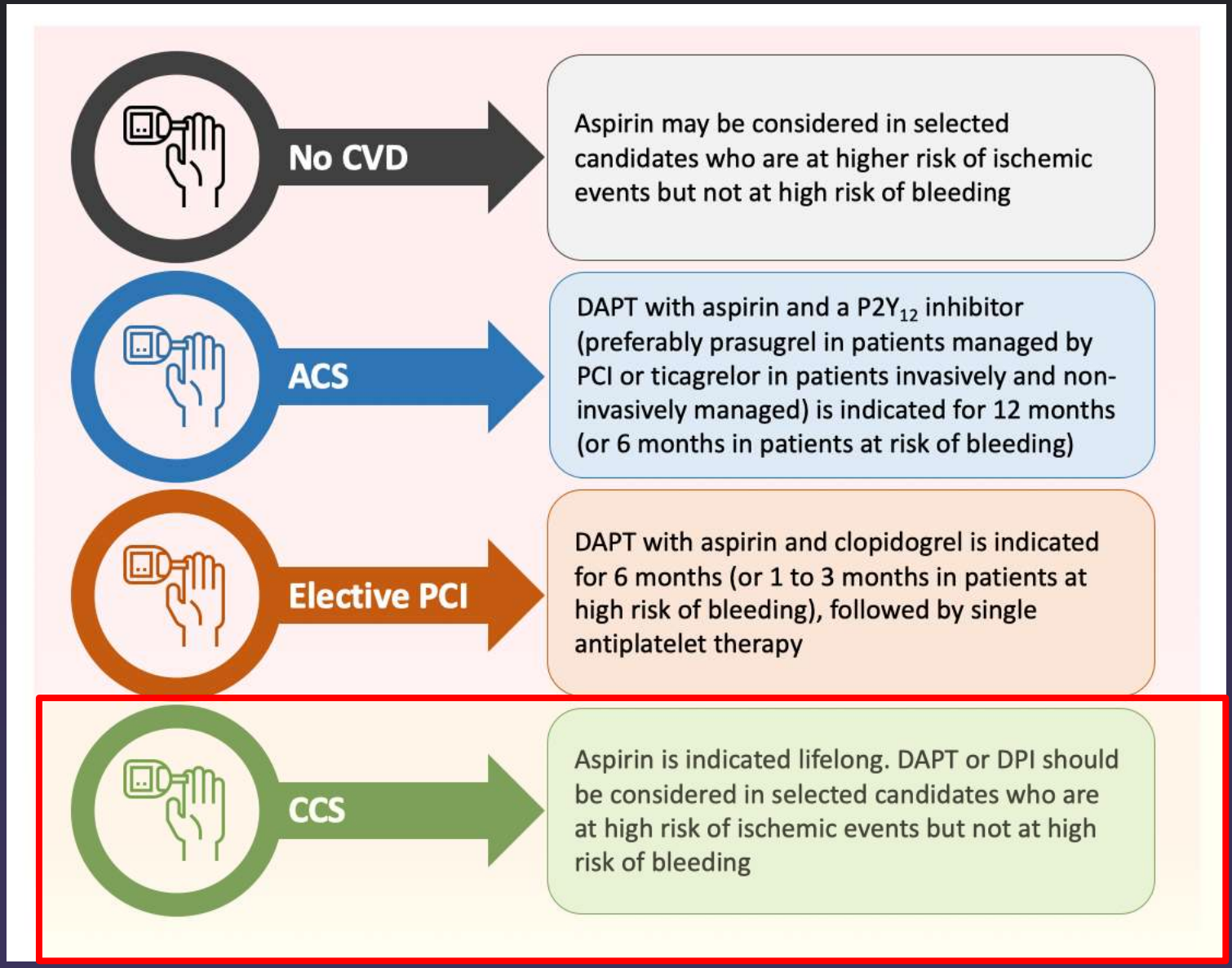
PD Effects of Prasugrel vs Ticagrelor in patients with DM and CAD: the OPTIMUS-4 study



The primary endpoint of PRU defined by VN-P2Y12 after 1 week of MD treatment was significantly lower levels with ticagrelor 90 mg bid compared with prasugrel 10 mg qd (52 [32-72] vs 83 [63-103]; LSM difference: -31; 95% CI: -57 to -4; p=0.022).

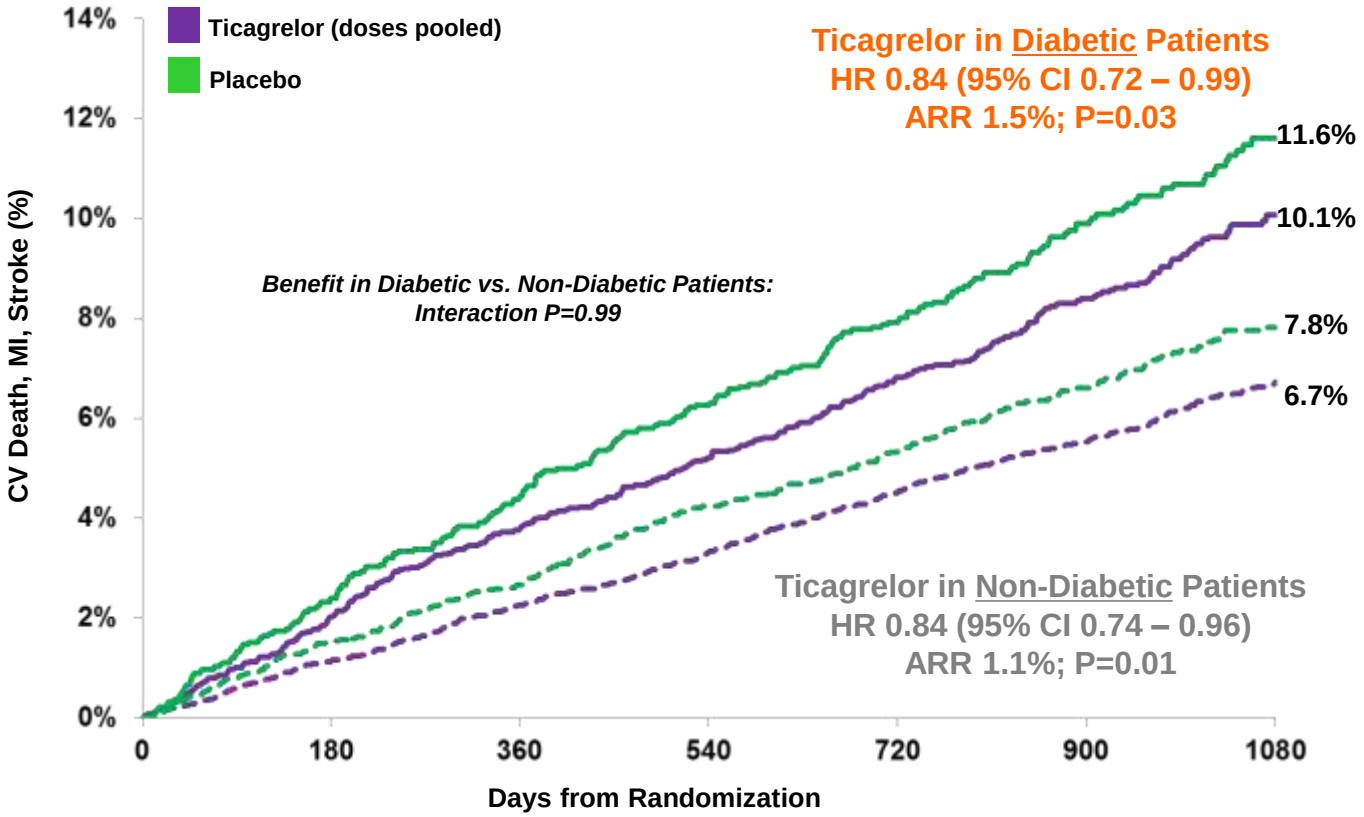
Franchi F & Angiolillo DJ. Circulation. 2016;134:780–792

Antithrombotic strategies for patients with diabetes mellitus



Capodanno D, Angiolillo DJ. *Circulation.* 2020; 142:2172-2188.

PEGASUS TIMI 54: Primary Endpoint – MACE
Impact of DM status with prior MI (1-3 yrs post-MI)

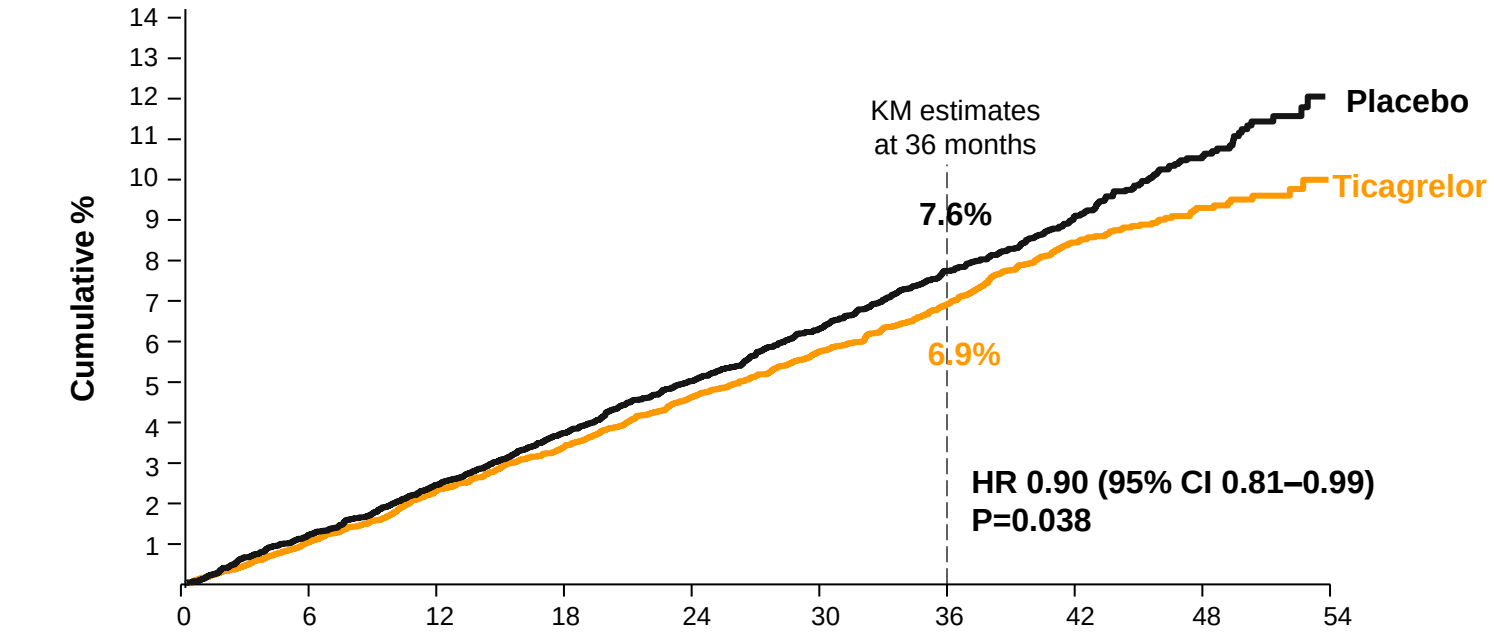


Bhatt DL, Bonaca MP, Bansilal S, et al. *J Am Coll Cardiol*. 2016;67:2732-2740.

THEMIS: Patients with DM and CAD but no prior acute cardiovascular event (MI/CVA)

Primary Composite Endpoint

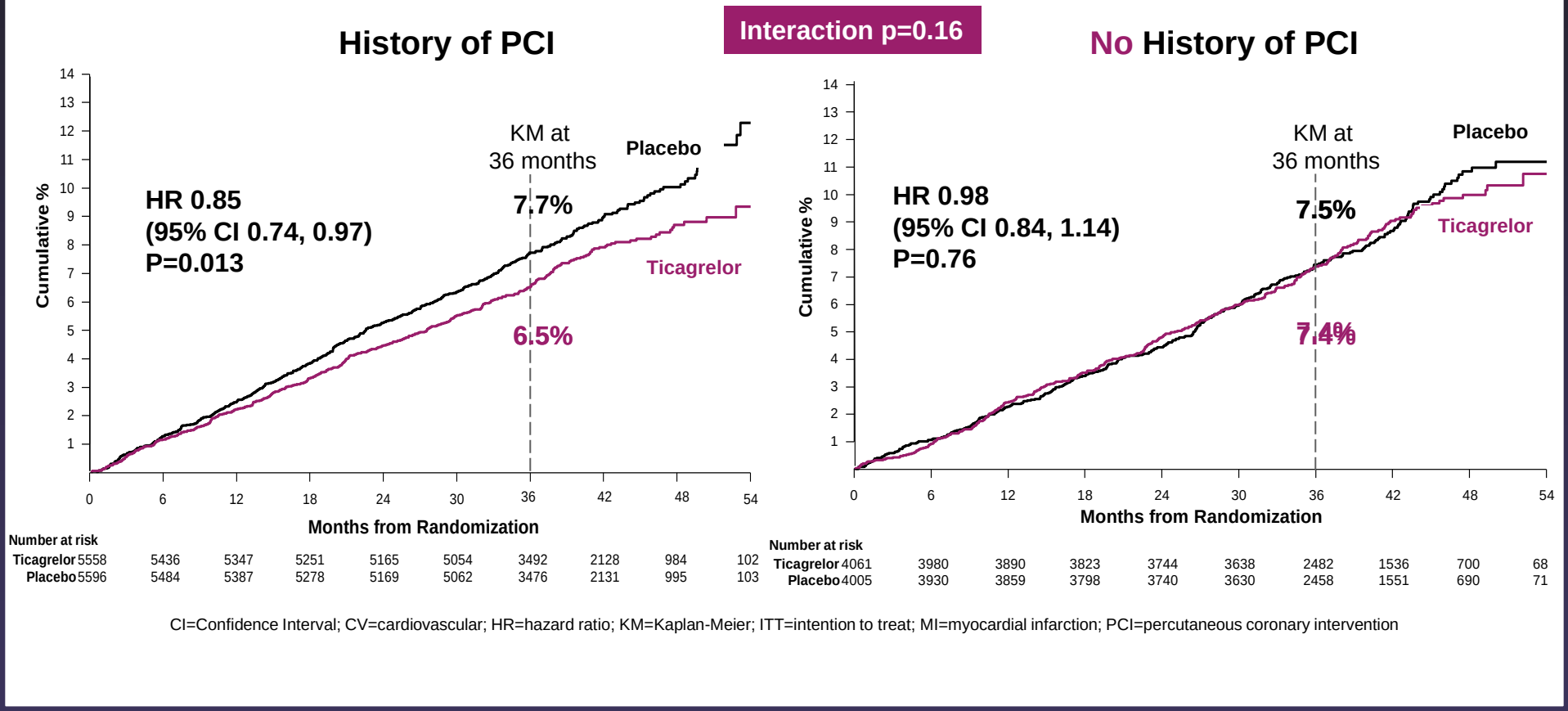
Cardiovascular Death/MI/Stroke



N at Risk										
Ticagrelor	9619	9416	9237	9074	8909	8692	5974	3664	1684	170
Placebo	9601	9414	9246	9076	8909	8692	5934	3682	1685	174

Steg PG, Bhatt DL, et al. *N Engl J Med*. 2019;381:1309-1320.

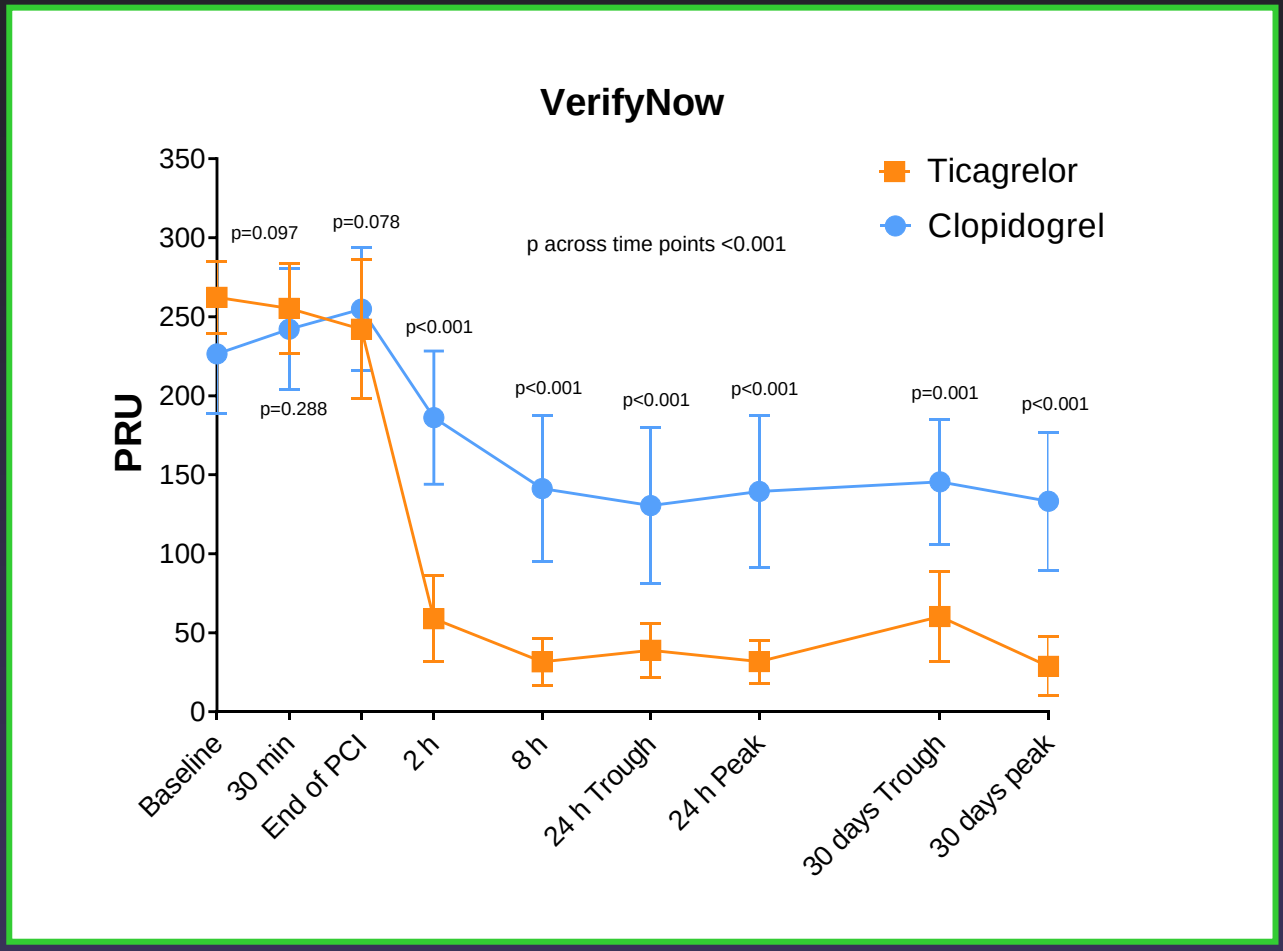
THEMIS-PCI: Primary Composite Endpoint
Cardiovascular Death/MI/Stroke



CI=Confidence Interval; CV=cardiovascular; HR=hazard ratio; KM=Kaplan-Meier; ITT=intention to treat; MI=myocardial infarction; PCI=percutaneous coronary intervention

Bhatt DL, Steg PG, et al. *Lancet* 2019 http://dx.doi.org/10.1016/ S0140-6736(19)31887-2.

PD effects of low-dose ticagrelor vs standard dose clopidogrel in THEMIS-like patients undergoing PCI: the OPTIMUS-6 study

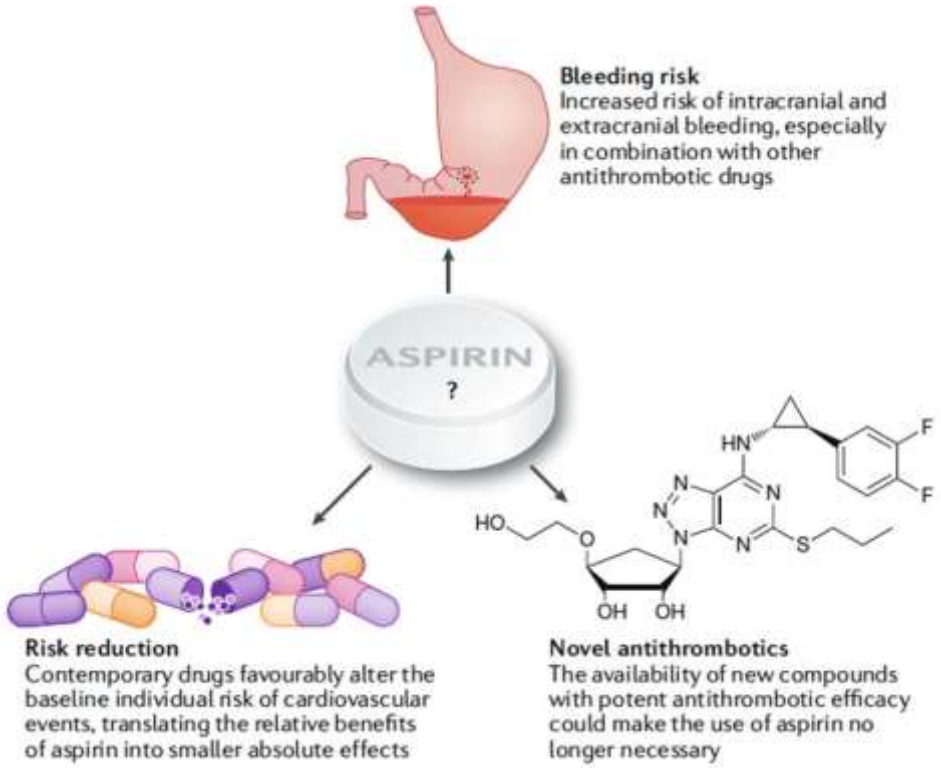


Primary endpoint measure of trough levels of PRU at 30 days (ticagrelor 60mg bid vs clopidogrel 75mg qd): 146 (106 to 185) vs. 60 (32 to 89); least square mean difference 91; 95% CI 42-140; p=0.001

Franchi F & Angiolillo DJ. Circulation. 2020; 142:1500-1502

Patients with DM are not only at increased risk for recurrent thrombotic/ischemic events, but also at increased risk for bleeding.

RATIONALE FOR ASPIRIN-FREE STRATEGIES AFTER PCI



Three major uncertainties surround the use of aspirin for secondary prevention:

- Major bleeding (e.g. GI and intracranial)
- Actual risk reduction on top of – for example - statins
- Role of newer antiplatelet drugs (e.g. ticagrelor)

Capodanno D, Angiolillo DJ. Nat Rev Cardiol. 2018;15:480-496

Landmark Trials and Ongoing Directions

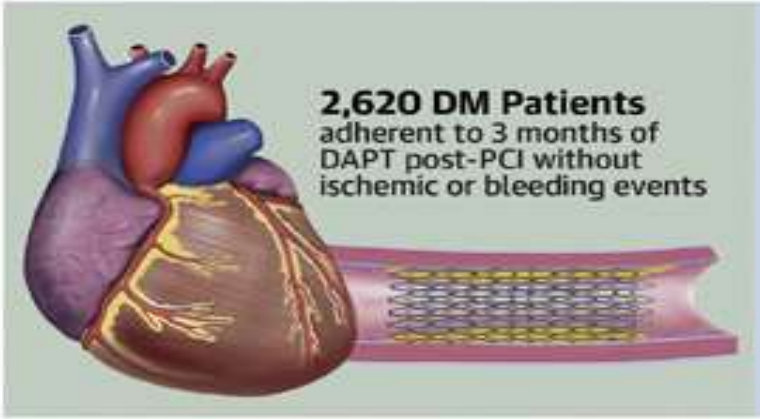
Trials of Very Short DAPT (Dropping Aspirin)

	Trial (N)	DAPT duration	Pts	Design	Objective	Result
PCI	GLOBAL LEADERS (N=15,968)	1 vs. 12 mo	PCI	Superiority	Death or MI	✗
	GLASSY (7,585)	1 vs 12 mo	PCI	Noninferiority	MACE	✓
	STOP-DAPT 2 (N=3,045)	1 vs. 12 mo	PCI	Noninferiority	NACE	✓
	SMART-CHOICE (N=3,000)	3 vs. 12 mo	PCI	Noninferiority	MACE	✓
	TWILIGHT (N=9,000)	3 vs. 12 mo	PCI	Superiority	Bleeding	✓
	TICO (N=3,000)	3 vs. 12 mo	ACS-PCI	Superiority	NACE	✓
	STOPDAPT-2 ACS (N=3,000)	1 vs. 12 mo	ACS-PCI	Noninferiority	NACE	Ongoing
AF-PCI	WOEST (N=573)	0 vs. 12 mo	PCI (HBR)	Superiority	Bleeding	✓
	PIONEER-AF PCI (N=2,124)	0 vs. 1-12 mo	PCI (HBR)	Superiority	Bleeding	✓
	RE-DUAL PCI (N=2,725)	0 vs. 1-3 mo	PCI (HBR)	NI -> Superiority	Bleeding	✓
	AUGUSTUS (N=4,614)	0 vs. 6 mo	PCI (HBR)	Superiority	Bleeding	✓
	ENTRUST-AF PCI (N=1,506)	0 vs. 1-12 mo	PCI (HBR)	NI -> Superiority	Bleeding	✓

Capodanno D. *EuroIntervention*. 2019;15:e475-e478.

Ticagrelor With or Without Aspirin After Percutaneous Coronary Intervention in High-Risk Patients With Diabetes Mellitus

Pre-defined cohort analysis from the multicenter, double-blind, randomized TWILIGHT Trial



2,620 DM Patients
adherent to 3 months of DAPT post-PCI without ischemic or bleeding events

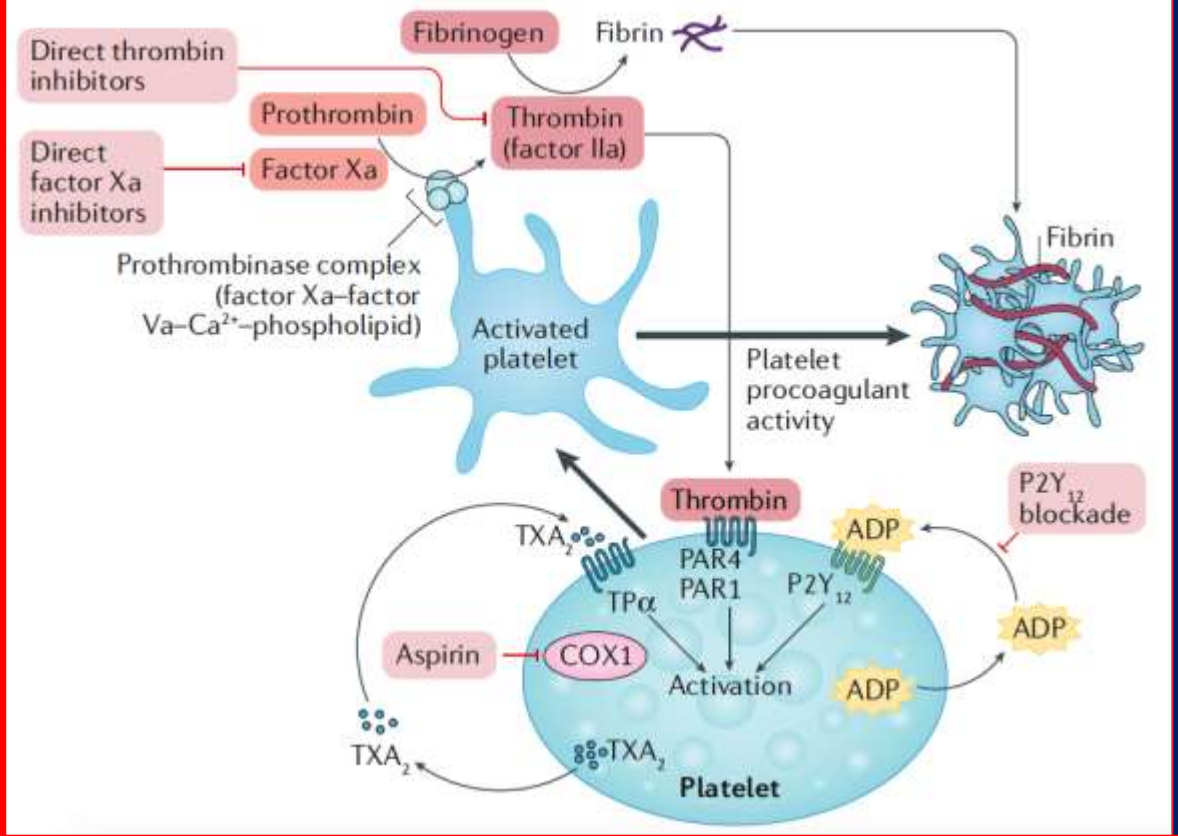
	Ticagrelor + Placebo (90 mg twice daily)	Ticagrelor + Aspirin (90 mg twice daily) (81-100 mg daily)
	N = 1,319	N = 1,301
BARC 2, 3, or 5 Bleeding 12 Months After Randomization	4.5%	6.7%
	HR: 0.65; 95% CI: 0.47-0.91; p = 0.012	
BARC 3 or 5 Bleeding 12 Months After Randomization	1.1%	3.1%
	HR: 0.34; 95% CI: 0.19-0.63; p = 0.001	

Ticagrelor monotherapy was not associated with an increase in ischemic events (all-cause death, MI or stroke) compared to ticagrelor plus aspirin
4.6% vs. 5.9%; HR: 0.77; 95 CI: 0.55 to 1.09; p = 0.14

Net adverse clinical events (composite of BARC 3 or 5 bleeding, death, MI, or stroke) favored ticagrelor monotherapy with a NNT of 30
5.4% vs. 8.7%; HR: 0.61; 95% CI: 0.45 to 0.82; p = 0.001

Angiolillo DJ & Mehran R. *JACC* 2020; 75:2403-2413

Emerging Concepts: Dual-Pathway Inhibition (DPI)

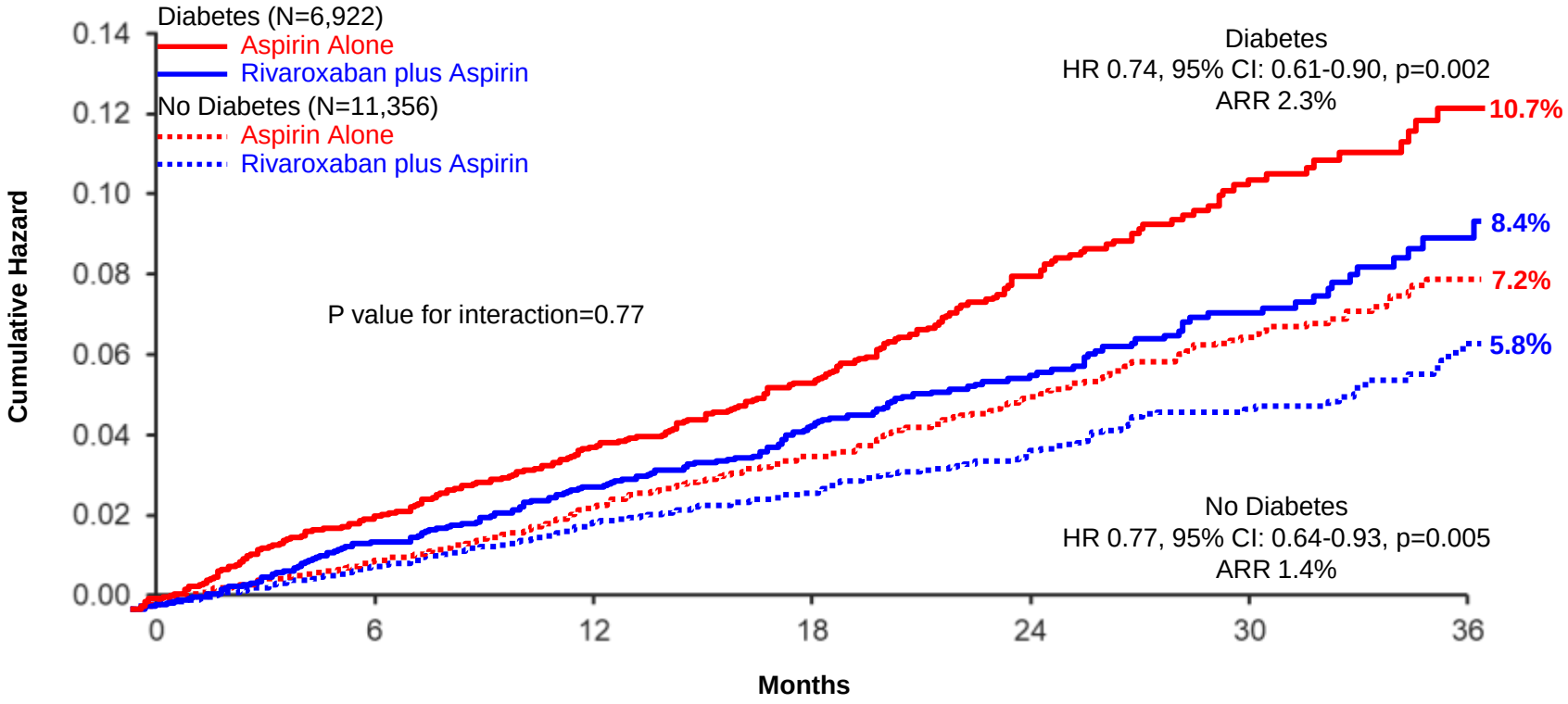


Synergy of oral anticoagulant and antiplatelet therapy

Oral anticoagulant therapy, including direct inhibitors of factor IIa and Xa, and antiplatelet agents, such as acetylsalicylic acid and $P2Y_{12}$ inhibitors, synergistically target two essential components of thrombosis: coagulation and platelet activation.

Capodanno D & Angiolillo DJ. Nat Rev Cardiol. 2018; 15:480-496

Efficacy of DPI strategy with vascular dose of rivaroxaban (2.5 mg bid) plus aspirin vs aspirin alone according to DM status

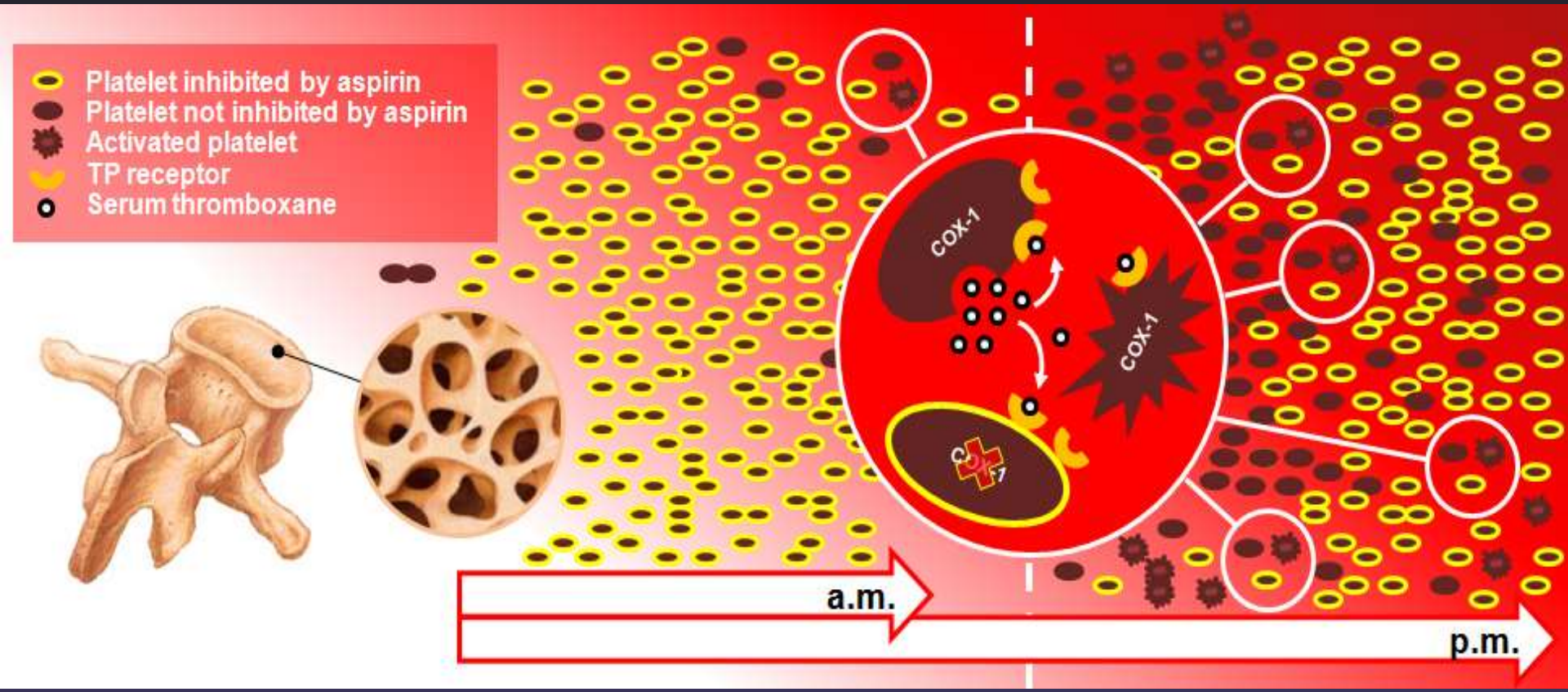


Bhatt DL, Eikelboom JW, Connolly SJ, et al, Yusuf S. *Circulation*. 2020.

Aspirin still remains the mainstay of treatment for long-term secondary prevention in patient with DM and CAD.

Can we be "smarter" about aspirin?

Schematic of circadian release of platelets into bloodstream from bone marrow and impact of a single daily dose of aspirin on newly generated platelets in type 2 DM



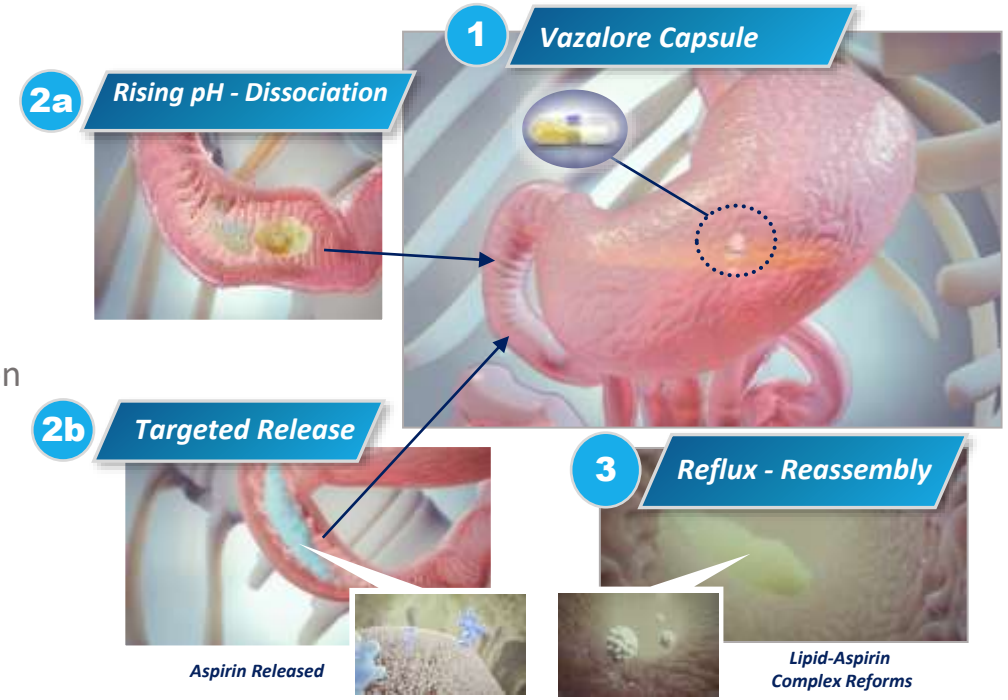
Capodanno D & Angiolillo DJ. Circ Cardiovasc Interv. 2011;4:180-7.

Novel, Pharmaceutical Lipid-Aspirin Complex (PL-ASA; Vazalore): Mechanism of Action

1 **Stomach**
Capsule rapidly dissolves releasing the liquid lipid-aspirin complex

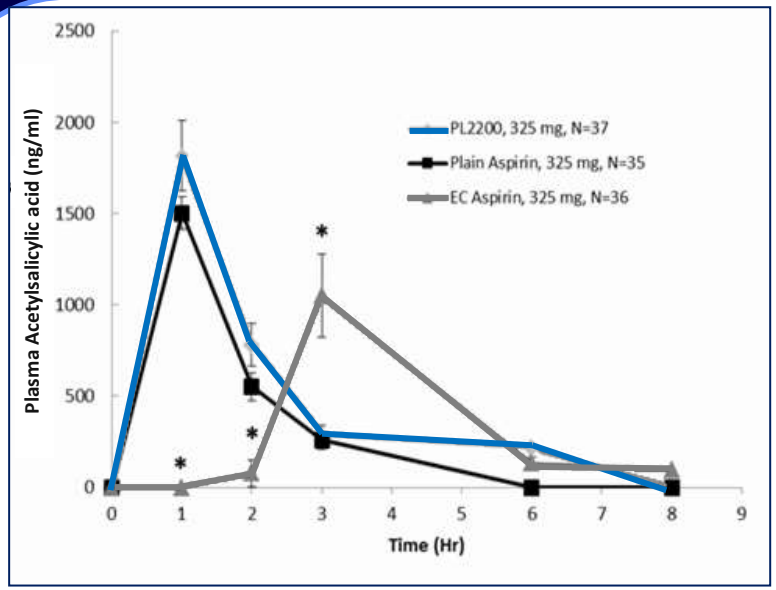
2 **Duodenum**
a)Rising pH leads to dissociation
b)Aspirin is now free for absorption

3 **Bidirectional Protection**
Reassembly of the lipid-aspirin complex at low pH

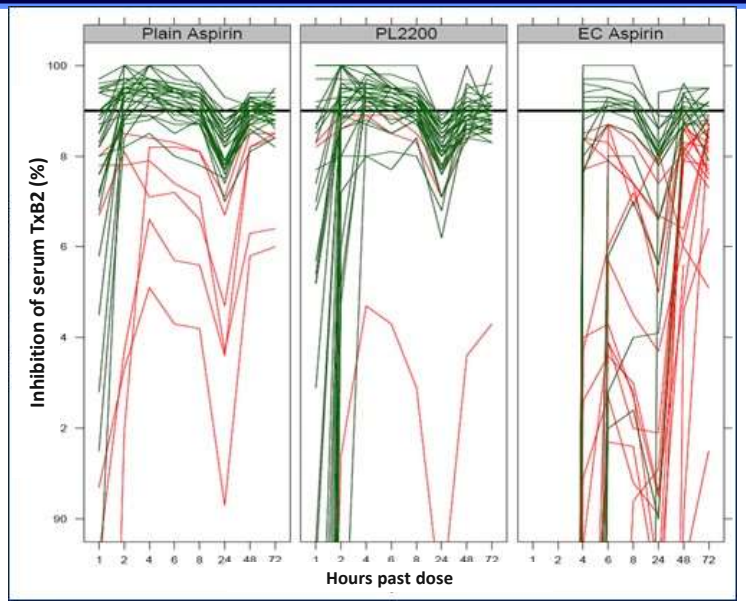


Angiolillo DJ et al. J Thromb Thrombolysis 2019

PK/PD Comparison of ASA, EC-ASA & PL-ASA (i.e., VAZALORE): Implications for Aspirin Efficacy in Patients with Diabetes Mellitus



C_{max} and T_{max} for serum ASA concentrations
Plain Aspirin: 1964 PL2200: 2523 EC: aspirin 456



Patients with complete antiplatelet response
Plain Aspirin: 84% Vazalore: 92% EC aspirin: 47%

Bhatt DL. *JACC* 2017;69(6):603-612

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