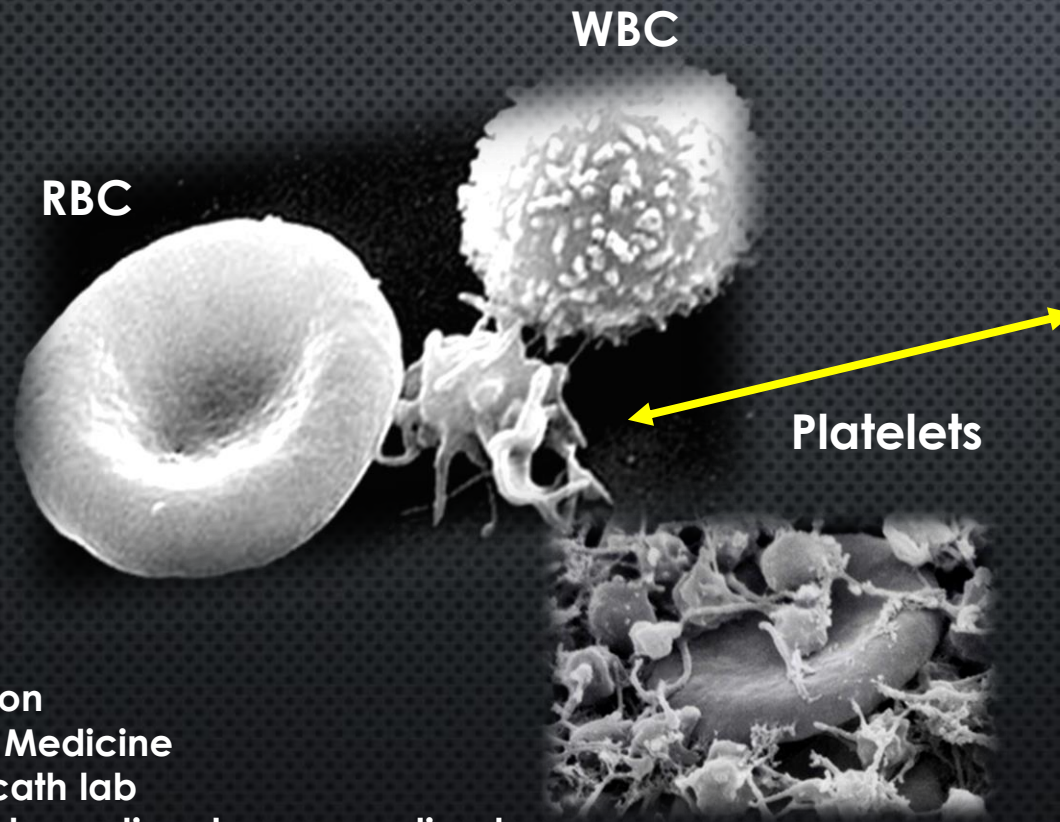


Conflicts of interest: research / companies / my boss



ANTIPLATELET IN THE PREVENTION AND MANAGEMENT OF ASCVD IN DIABETES



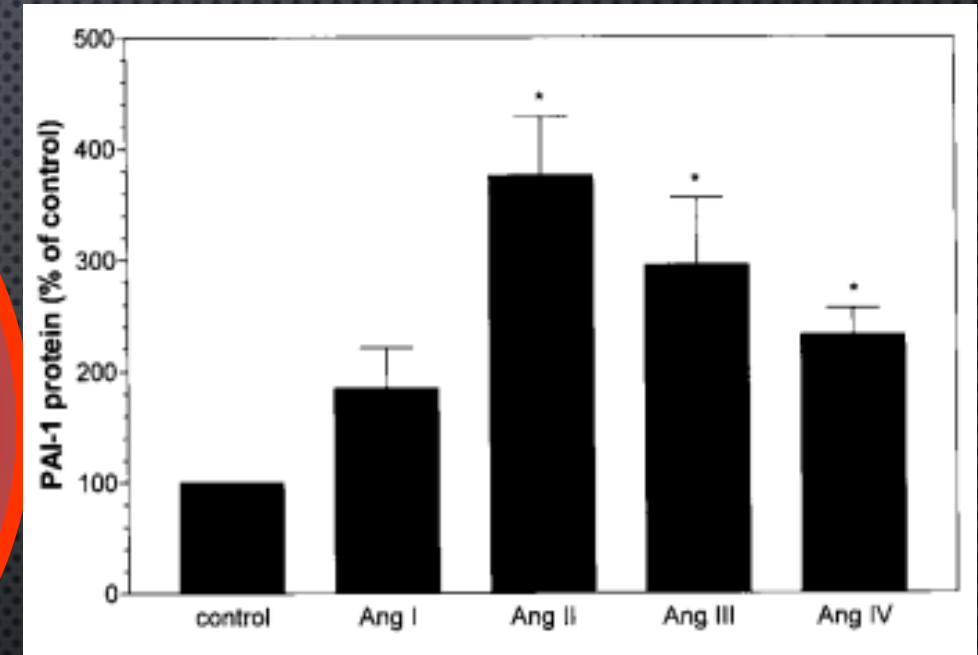
Robert Chilton
Professor of Medicine
Director of cath lab
Associate interventional program director
Director of clinical proteomics UTHSCSA/NIH
University of Texas Health Science Center



Angiotensin III/IV: changes in PAI-1 levels- **adipocyte release**
(Hypertension. 2001;37:1336–1340)

Plaque rupture

Mechanisms of increase in platelet reactivity in ACUTE CORONARY SYNDROME in insulin resistance?



Elevated epinephrine levels

Platelet hyperaggregability as well as platelet hypersensitivity

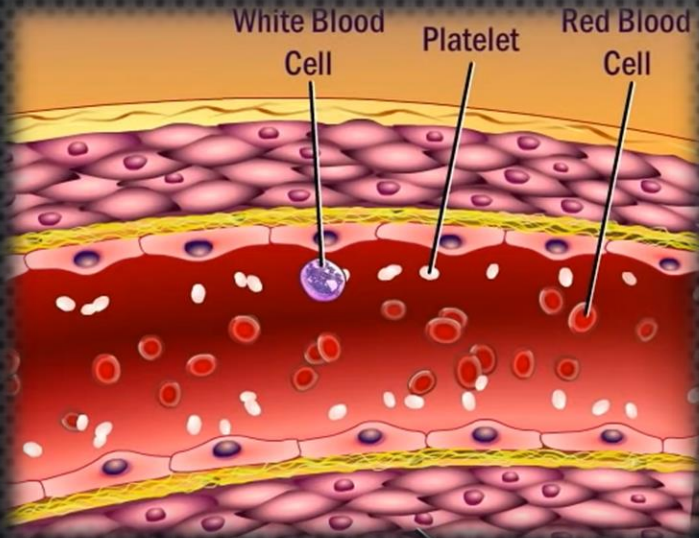


Plasminogen activator inhibitor (PAI)-1 is the main inhibitor of the fibrinolytic system

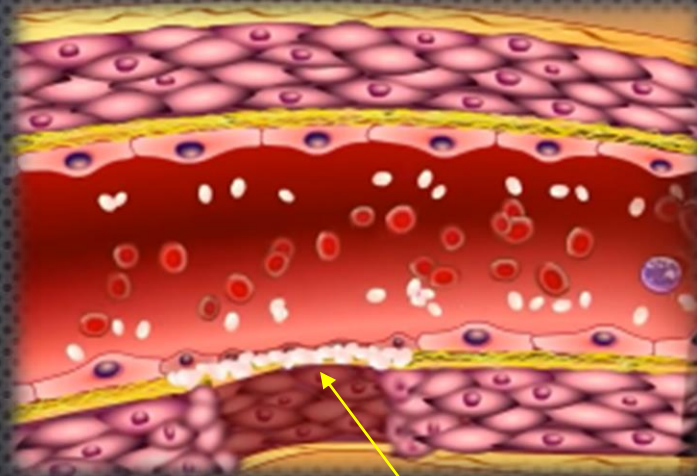
N Engl J Med 1987; 316:1543-1544



Endothelial injury-platelet activation in **prothrombotic** insulin resistant patient

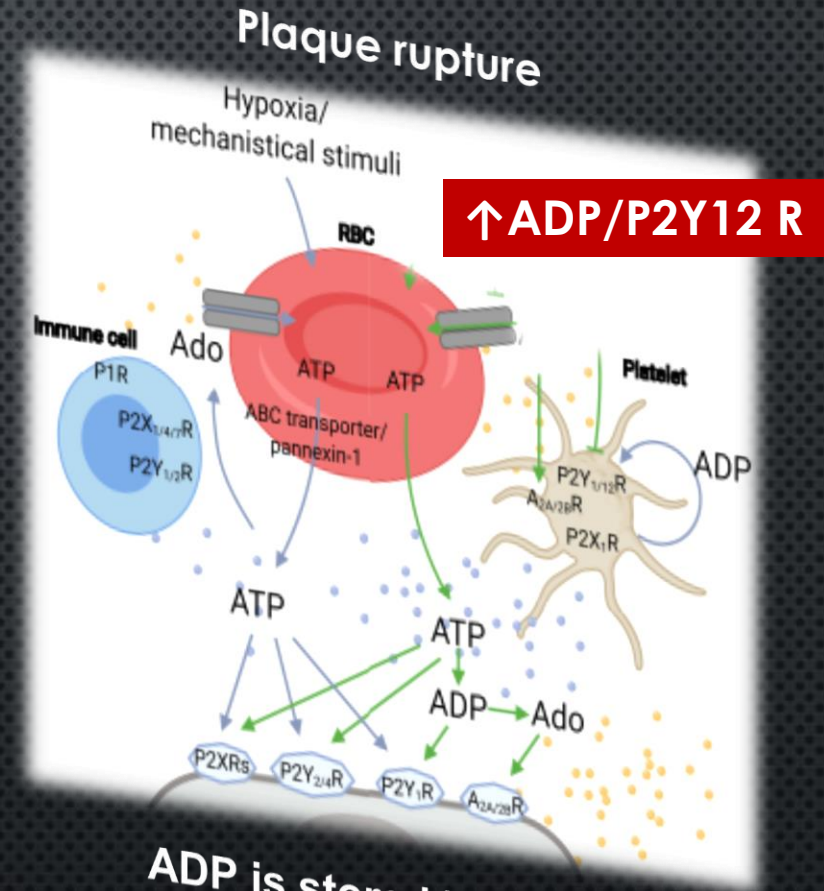


Normal endothelium-"Teflon" like surface



Vessel wall injury
Collagen in
subendothelium
activates platelet
adhesion

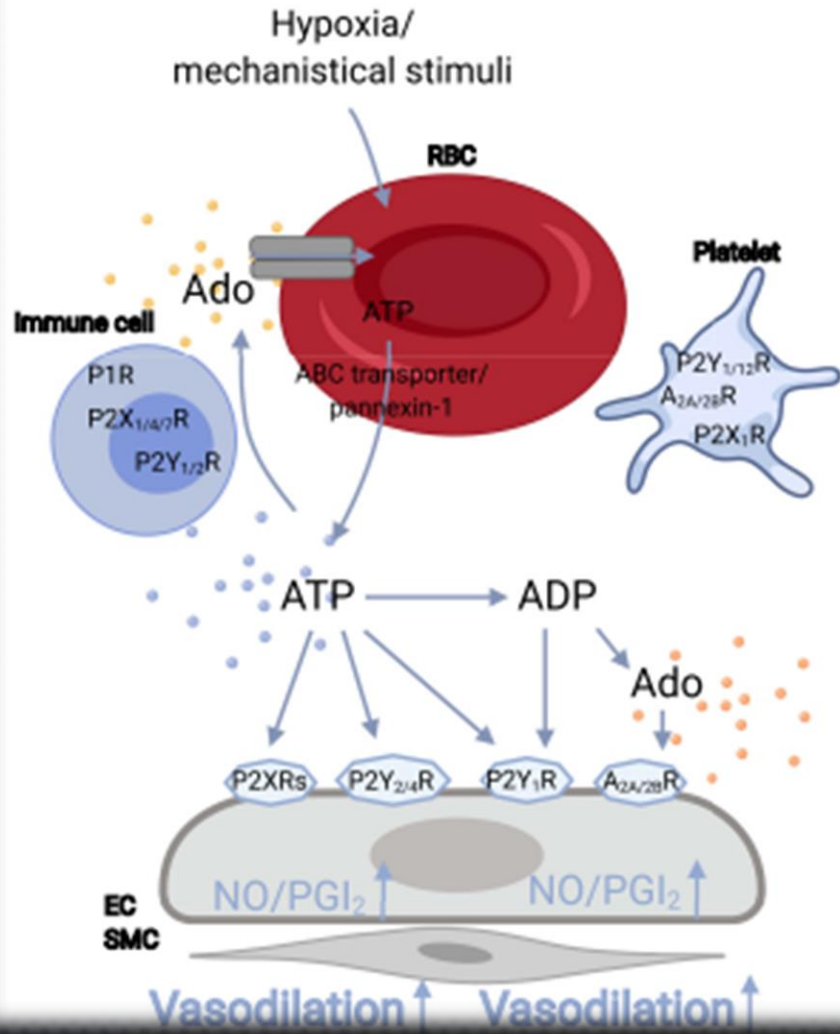
**Dysfunctional RBC (diabetes)
mediates the development of
endothelial cell dysfunction**



**ADP is stored in dense
granules of platelets**



Healthy

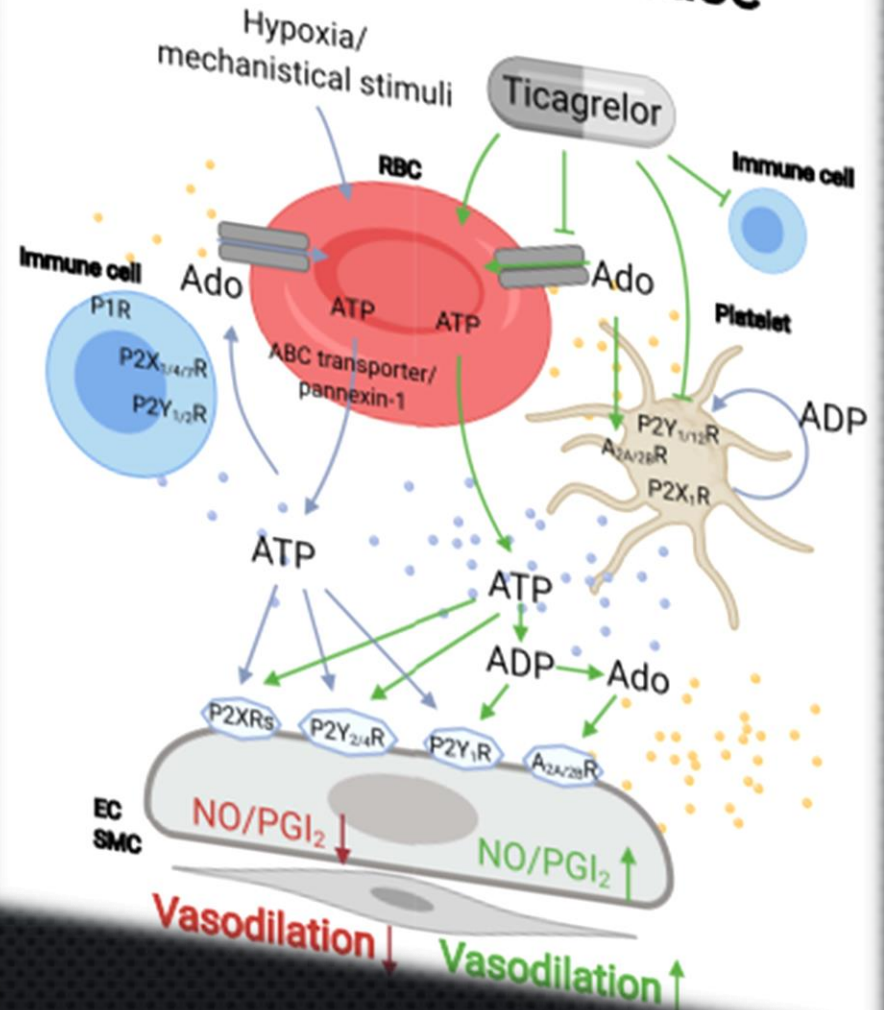


Ticagrelor inhibits adenosine uptake in red blood cells & ↑ ATP

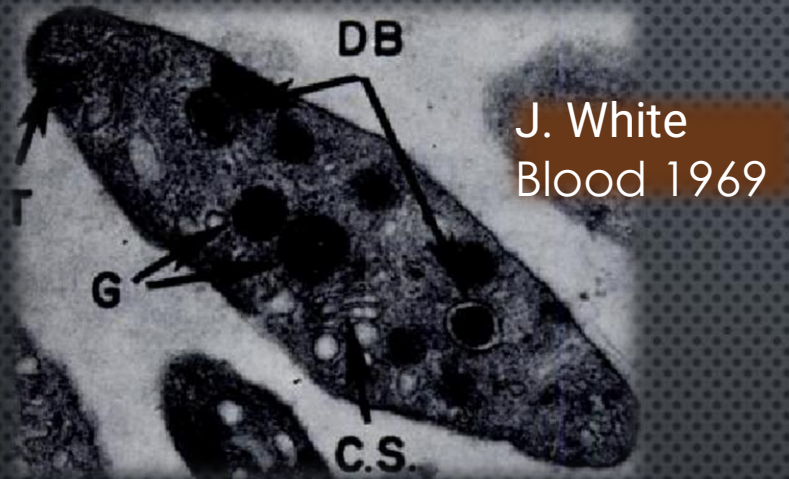
ATP (↓ DM) can activate P2Y R on the endothelium, ↑ nitric oxide (NO) and prostacycline

Diabetes
ADP-mediated P2Y 12 R activation

Cardiometabolic disease



Key molecular translational importance



ADP (*adenosine diphosphate*)



ADP is stored in **dense bodies** inside blood platelets and is released upon platelet activation

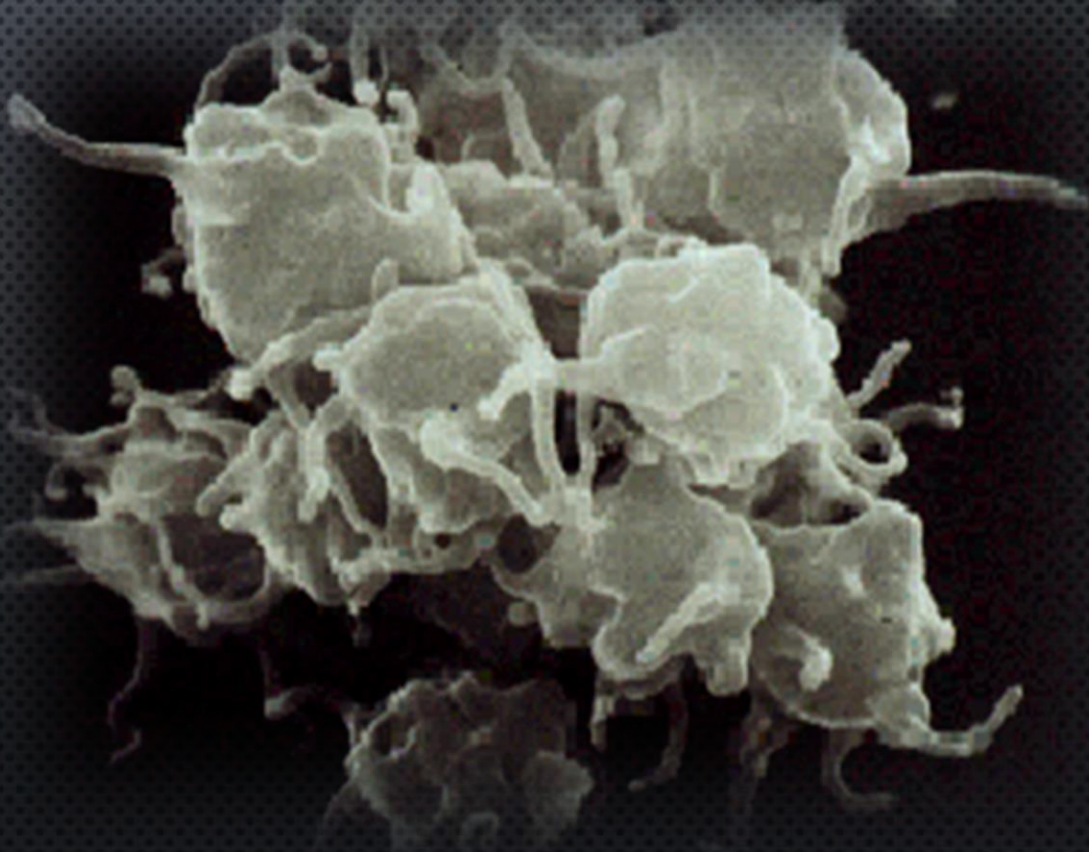
ADP interacts with a **family of ADP receptors** found on platelets (P2Y1, P2Y12, and P2X1), which **leads to platelet activation**



Non activated platelets



Activated platelets



Increased atheroprothrombotic state in diabetes

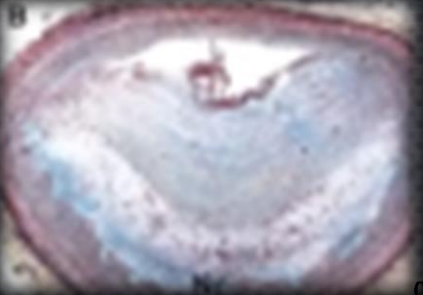
Platelet rich thrombus

Thin fibrous cap <65u

Erosion



No endothelial cells



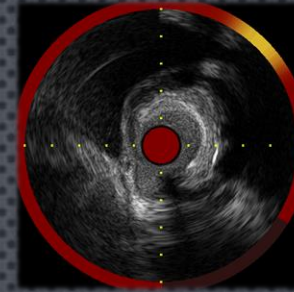
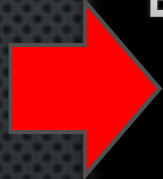
Fibrous cap rupture



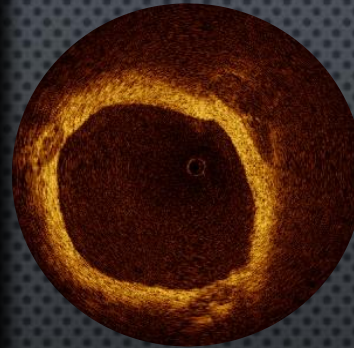
RISK FACTORS OF ACUTE CORONARY SYNDROME

- INDEPENDENT RISK FOR CV EVENTS-CLINICAL

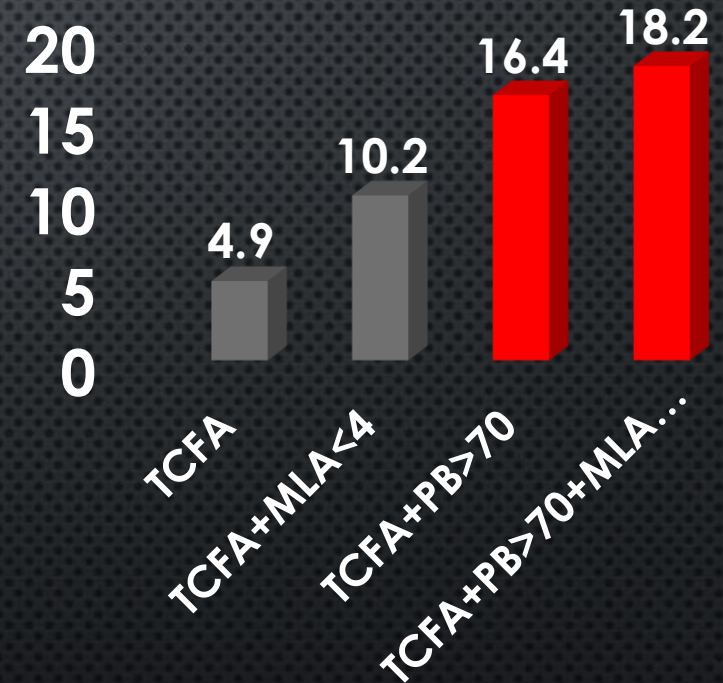
- DIABETES-INSULIN $P < 0.005$
- PRIOR CABG $P < 0.02$
- IVUS LESIONS ($P < 0.001$)
 - PLAQUE BURDEN $> 70\%$
 - THIN CAP
 - MIN LUMEN AREA < 4.0



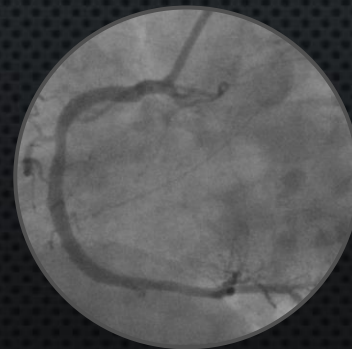
Mild disease at **baseline** by IVUS but represents major CV risk by 3 years



% CV events by 3 years



A Prospective Natural-History Study of Coronary Atherosclerosis



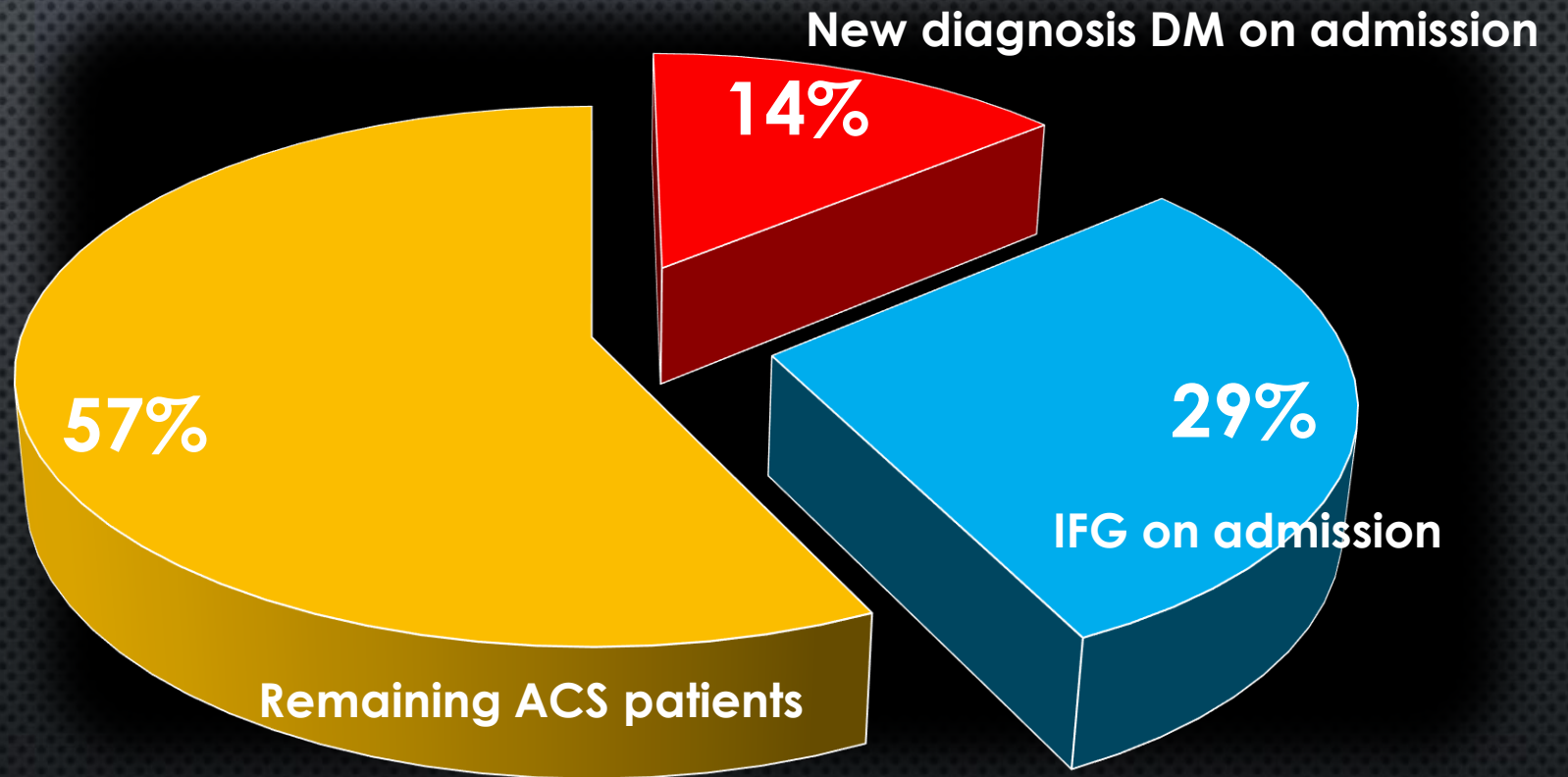
Stone et al N Engl J Med 2011;364:226-35



Patients With **Acute Coronary Syndrome**: high percentage have **undiagnosed diabetes**

N=10911 evaluated with
1199 ACS patients

Prospective cohort of patients who had acute coronary syndrome



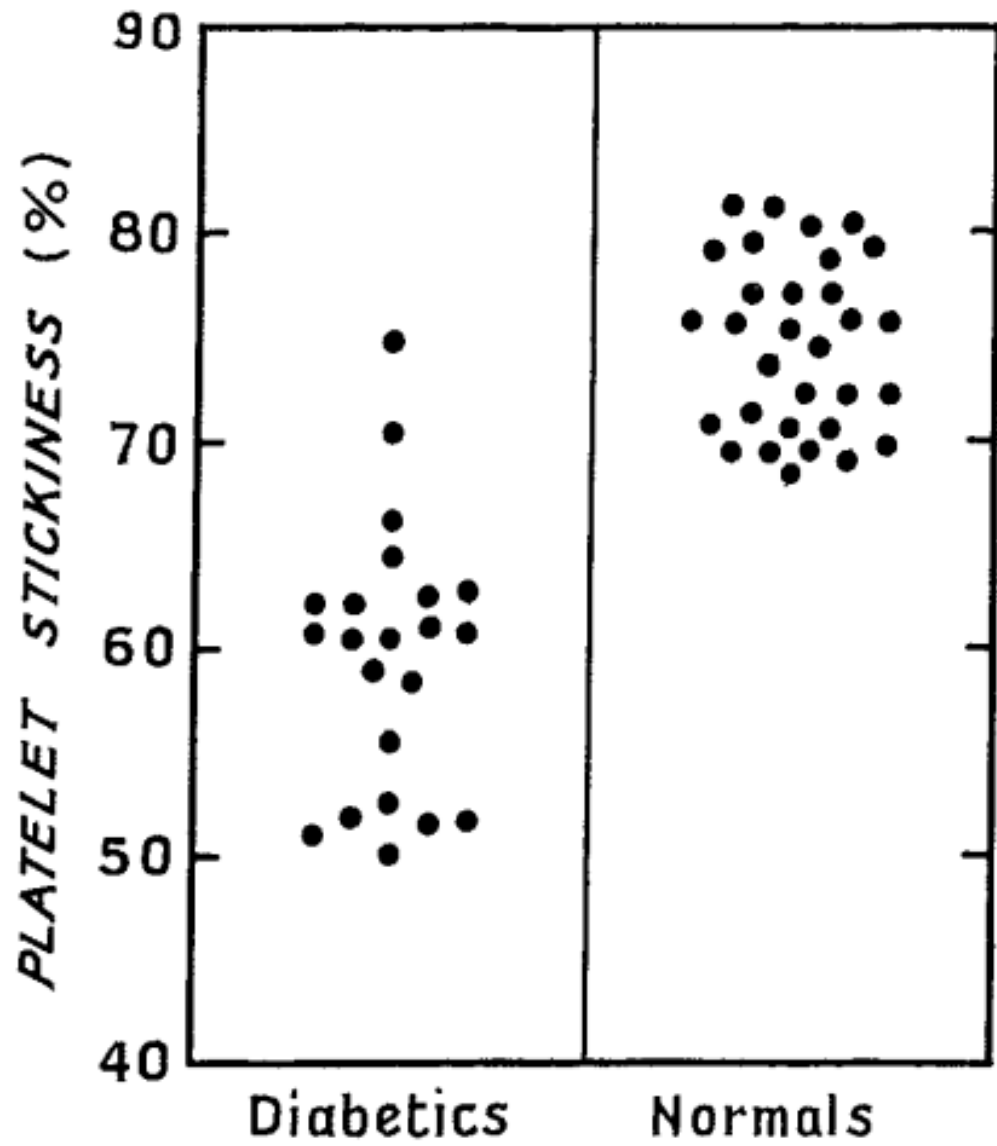


Fig. 1—Platelet stickiness in diabetic and normal subjects.

AN EFFECT OF D-GLUCOSE ON PLATELET STICKINESS

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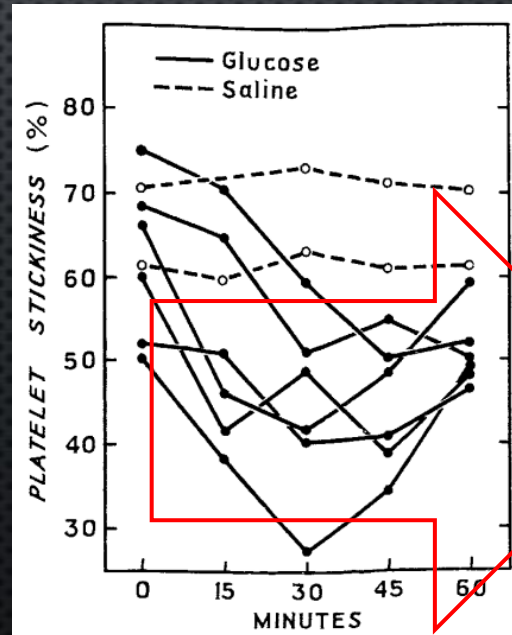


Fig. 4—The change in platelet stickiness after intravenous glucose administration (0.33 g. per kg.).

Increased platelet activation

Lancet 1 (1965) 75-77



THEMIS trial

Ticagrelor in
stable CAD with
DM

Focus: P2Y12 inhibitors

PEGASUS TIMI 54

Ticagrelor in prior MI
patients (DM subset)

Clinical trials of importance in diabetes



The **NEW ENGLAND**
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OCTOBER 3, 2019

VOL. 381 NO. 14

**Ticagrelor in Patients with Stable Coronary Disease
and Diabetes**

P.G. Steg, D.L. Bhatt, T. Simon, K. Fox, S.R. Mehta, R.A. Harrington, C. Held, M. Andersson, A. Himmelmann, W. Ridderstråle, M. Leonsson-Zachrisson, Y. Liu, G. Opolski, D. Zateyshchikov, J. Ge, J.C. Nicolau, R. Corbalán, J.H. Cornel, P. Widimský, and L.A. Leiter, for the THEMIS Steering Committee and Investigators*

ABSTRACT

**N=19220 randomized double blind
Stable CAD and diabetes**

Median follow up 39.9 months

THEMIS trial



ASA 75-150 mg

**Ticagrelor 90 bid
ASA 75-150 mg**

Primary endpoint:

**composite of cardiovascular
death, myocardial infarction, or
stroke**

N Engl J Med 2019;381:1309-20



THEMIS trial: stable CAD with diabetes

Table 1. Characteristics of the Patients at Baseline.*

Race — no. (%)‡

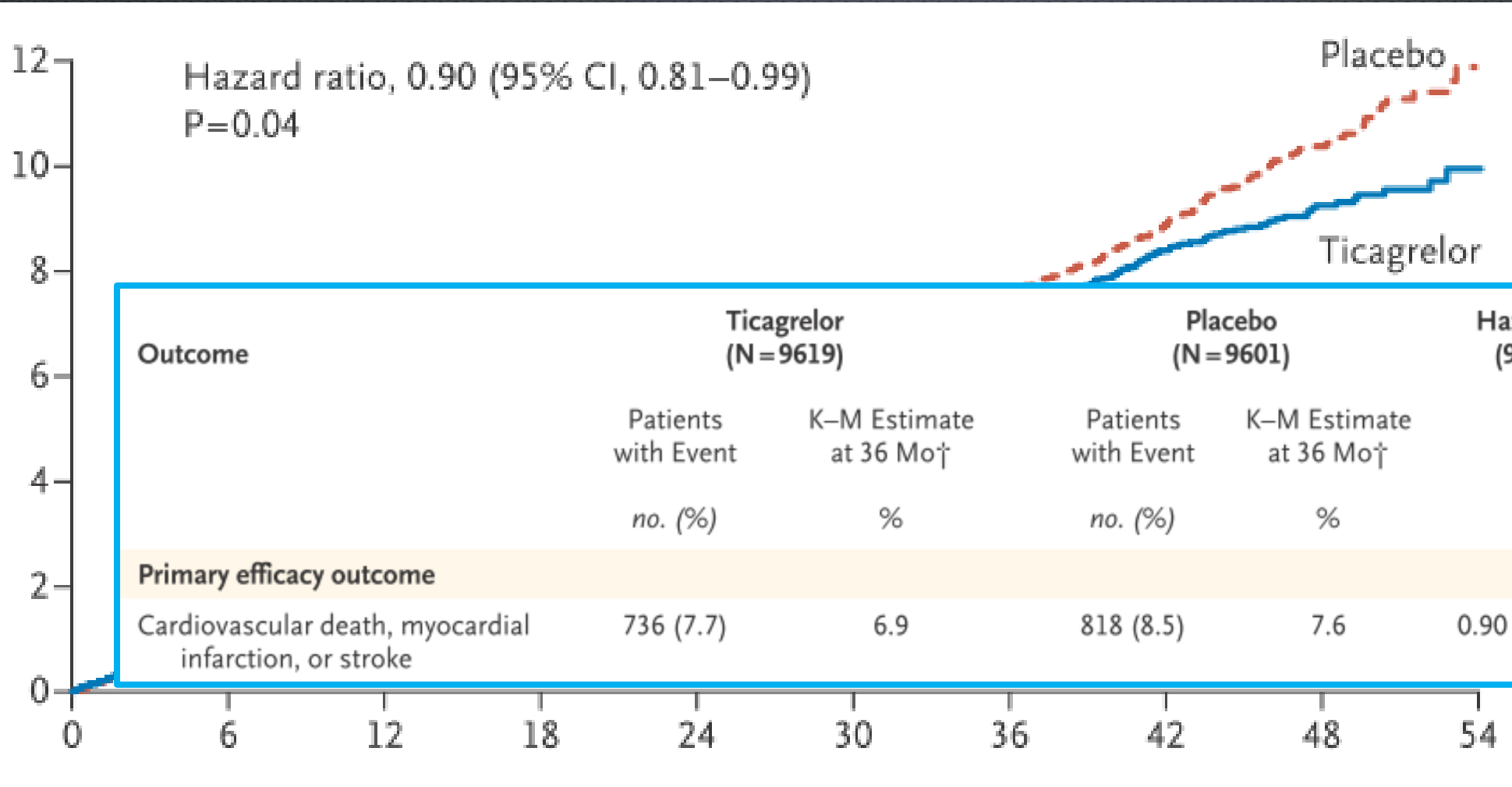
Asian	2211 (23.0)	2195 (22.9)
Black	205 (2.1)	198 (2.1)
White	6838 (71.1)	6858 (71.4)
Other	365 (3.8)	350 (3.6)

Geographic region — no. (%)

Asia and Australia	2145 (22.3)	2143 (22.3)
Central and South America	1100 (11.4)	1078 (11.2)
Europe and South Africa	4884 (50.8)	4875 (50.8)
North America	1490 (15.5)	1505 (15.7)



THEMIS trial: primary endpoint



NNT 142.5

Outcome	Ticagrelor (N=9619)		Placebo (N=9601)		Hazard Ratio (95% CI)*	P Value
	Patients with Event no. (%)	K–M Estimate at 36 Mo† %	Patients with Event no. (%)	K–M Estimate at 36 Mo† %		
Primary efficacy outcome						
Cardiovascular death, myocardial infarction, or stroke	736 (7.7)	6.9	818 (8.5)	7.6	0.90 (0.81–0.99)	0.04

N Engl J Med 2019;381:1309-20



THEMIS trial: secondary endpoint

Secondary efficacy outcomes

Cardiovascular death	364 (3.8)	3.3	357 (3.7)	3.0	1.02 (0.88–1.18)	0.79
Myocardial infarction	274 (2.8)	2.6	328 (3.4)	3.3	0.84 (0.71–0.98)	
Ischemic stroke	152 (1.6)	1.5	191 (2.0)	1.8	0.80 (0.64–0.99)	
Death from any cause‡	579 (6.0)	5.1	592 (6.2)	4.9	0.98 (0.87–1.10)	

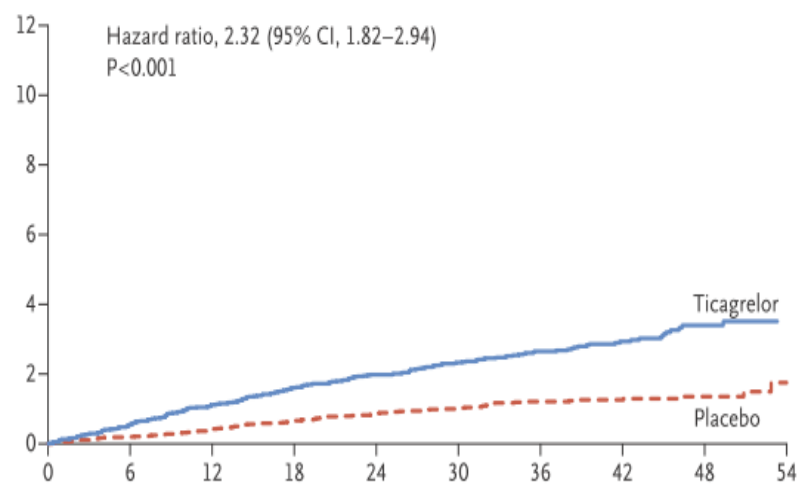
N Engl J Med 2019;381:1309-20



THEMIS trial: safety

NNH 83

Table 3. Safety Outcomes (Safety Population, On-Treatment Analysis).*



	Ticagrelor (N = 9562)		Placebo (N = 9531)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no. (%)	no./100 patient-yr	no. %	no./100 patient-yr		
Adjudicated adverse events†						
TIMI major bleeding	206 (2.2)	0.89	100 (1.0)	0.38	2.32 (1.82–2.94)	<0.001
TIMI major or minor bleeding	285 (3.0)	1.23	129 (1.4)	0.49	2.49 (2.02–3.07)	<0.001

N Engl J Med 2019;381:1309-20



THEMIS trial: safety

Using **lower dose appears much safer** (60mg bid)

TIMI major bleeding	Estimate	Ticagrelor			Placebo			Hazard Ratio (95% CI)
		N	Patients with events (%)	KM at 24 months	N	Patients with events (%)	KM at 24 months	
Using treatment as only explanatory variable, including patients randomized to ticagrelor 60 mg or matching placebo*	Ticagrelor 60 mg bid vs matching placebo	2482	33 (1.3%)	1.3%	2516	21 (0.8%)	0.7%	1.74 (1.00–3.00)

Intracranial hemorrhage was more frequent with ticagrelor than with placebo, with 70 events and 46 events, respectively (0.7% vs. 0.5%; hazard ratio, 1.71; 95% CI, 1.18 to 2.48; P=0.005)

N Engl J Med 2019;381:1309-20



Supplement

THEMIS trial: conclusion

STABLE CAD and diabetes **without** a history of myocardial infarction or stroke, those who received ticagrelor plus aspirin had a **lower incidence of ischemic cardiovascular events** but a **higher incidence of major bleeding**

N Engl J Med 2019;381:1309-20



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MAY 7, 2015

VOL. 372 NO. 19

**Long-Term Use of Ticagrelor in Patients with Prior
Myocardial Infarction**

Marc P. Bonaca, M.D., M.P.H., Deepak L. Bhatt, M.D., M.P.H., Marc Cohen, M.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., Eva C. Jensen, M.D., Ph.D., Giulia Magnani, M.D., Sameer Bansilal, M.D., M. Polly Fish, B.A., Kyungah Im, Ph.D., Olof Bengtsson, Ph.Lic., Ton Oude Ophuis, M.D., Ph.D., Andrzej Budaj, M.D., Ph.D., Pierre Theroux, M.D., Mikhail Ruda, M.D., Christian Hamm, M.D., Shinya Goto, M.D., Jindrich Spinar, M.D., José Carlos Nicolau, M.D., Ph.D., Robert G. Kiss, M.D., Ph.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Peter Held, M.D., Ph.D., Eugene Braunwald, M.D., and Marc S. Sabatine, M.D., M.P.H., for the PEGASUS-TIMI 54 Steering Committee and Investigators*

N=21162 (1-3 years before had MI)
Randomized double blind

F/U 33 months

N Engl J Med 2015;372:1791-800



Pegasus.pdf



nejmca1500857_appendix.pdf

PEGASUS-TIMI 54

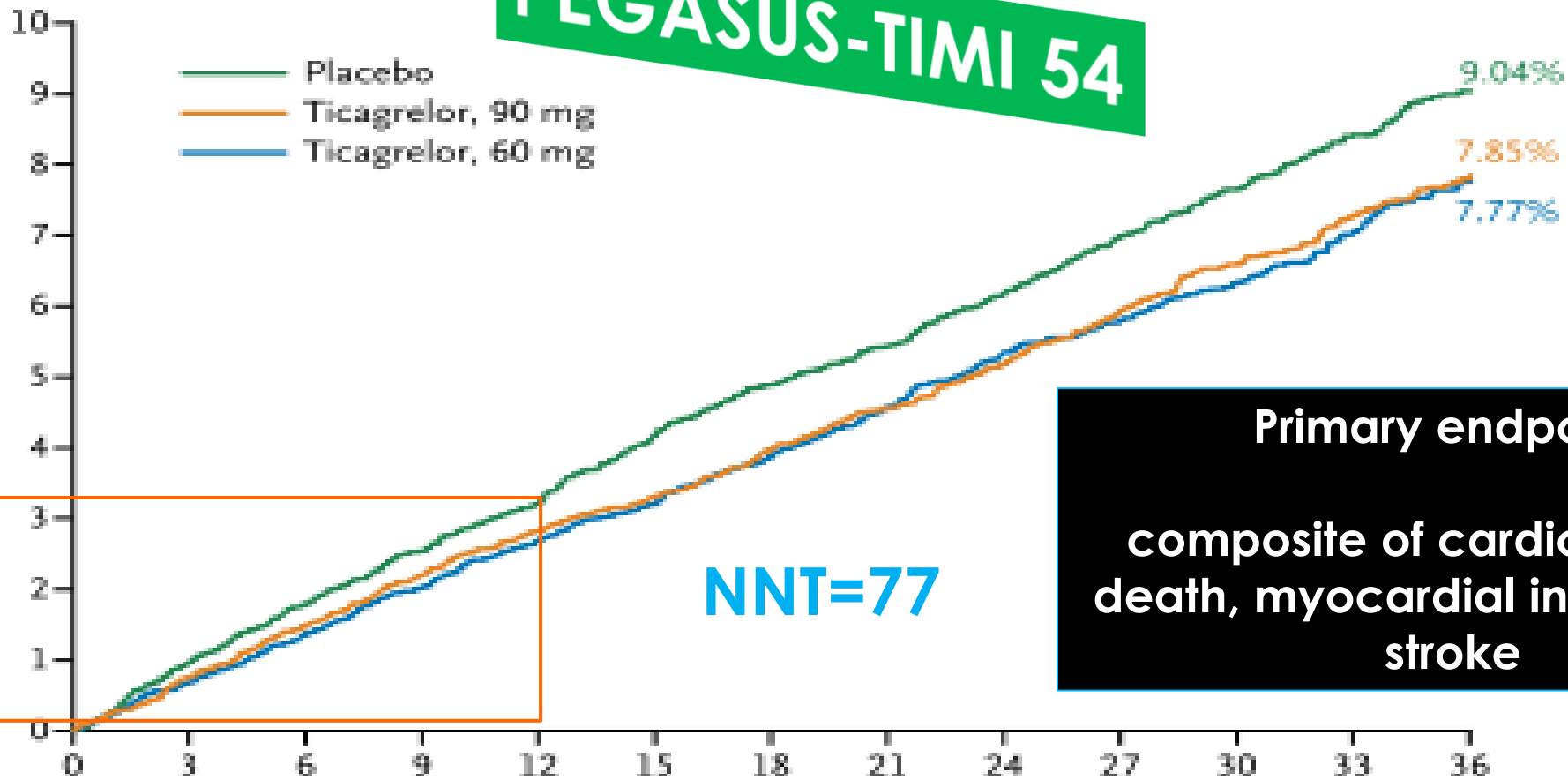
FOCUS: diabetes subgroup

Primary endpoint:

**composite of cardiovascular
death, myocardial infarction, or
stroke**



PEGASUS-TIMI 54



Primary endpoint:
composite of cardiovascular death, myocardial infarction, or stroke

NNT=77

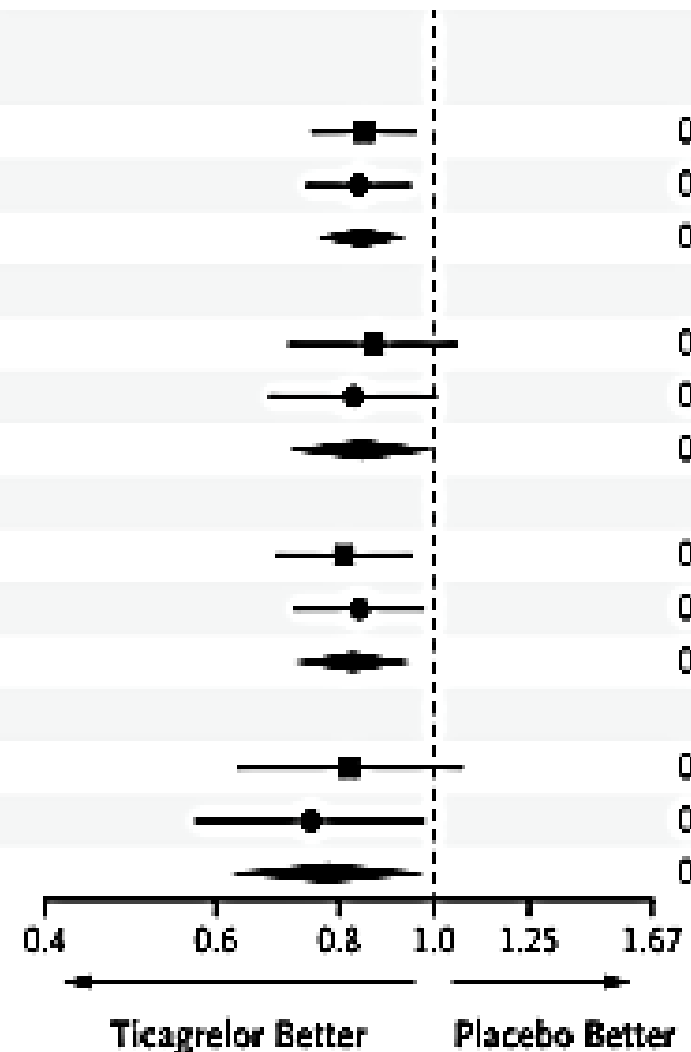
Ticagrelor, 90 mg vs. placebo:
Hazard ratio, 0.85 (95% CI, 0.75–0.96)
P=0.008

Ticagrelor, 60 mg vs. placebo:
Hazard ratio, 0.84 (95% CI, 0.74–0.95)
P=0.004

N Engl J Med 2015;372:1791-800



End Point	Ticagrelor 3-yr Kaplan-Meier event rate (%)	Placebo	Hazard Ratio (95% CI)	P Value
Cardiovascular death, myocardial infarction, or stroke				
Ticagrelor, 90 mg	7.85	9.04	0.85 (0.75–0.96)	0.008
Ticagrelor, 60 mg	7.77	9.04	0.84 (0.74–0.95)	0.004
Ticagrelor pooled	7.81	9.04	0.84 (0.76–0.94)	0.001
Cardiovascular death				
Ticagrelor, 90 mg	2.94	3.39	0.87 (0.71–1.06)	0.15
Ticagrelor, 60 mg	2.86	3.39	0.83 (0.68–1.01)	0.07
Ticagrelor pooled	2.90	3.39	0.85 (0.71–1.00)	0.06
Myocardial infarction				
Ticagrelor, 90 mg	4.40	5.25	0.81 (0.69–0.95)	0.01
Ticagrelor, 60 mg	4.53	5.25	0.84 (0.72–0.98)	0.03
Ticagrelor pooled	4.47	5.25	0.83 (0.72–0.95)	0.005
Stroke				
Ticagrelor, 90 mg	1.61	1.94	0.82 (0.63–1.07)	0.14
Ticagrelor, 60 mg	1.47	1.94	0.75 (0.57–0.98)	0.03
Ticagrelor pooled	1.54	1.94	0.78 (0.62–0.98)	0.03



PEGASUS-TIMI 54

NNH 76

Table 3. Safety End Points as 3-Year Kaplan–Meier Estimates.*

End Point	Ticagrelor, 90 mg (N=6988)	Ticagrelor, 60 mg (N=6958)	Placebo (N=6996)	Ticagrelor, 90 mg vs. Placebo		Ticagrelor, 60 mg vs. Placebo	
	<i>number (percent)</i>			Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Bleeding							
TIMI major bleeding	127 (2.60)	115 (2.30)	54 (1.06)	2.69 (1.96–3.70)	<0.001	2.32 (1.68–3.21)	<0.001
TIMI minor bleeding	66 (1.31)	55 (1.18)	18 (0.36)	4.15 (2.47–7.00)	<0.001	3.31 (1.94–5.63)	<0.001

N Engl J Med 2015;372:1791-800



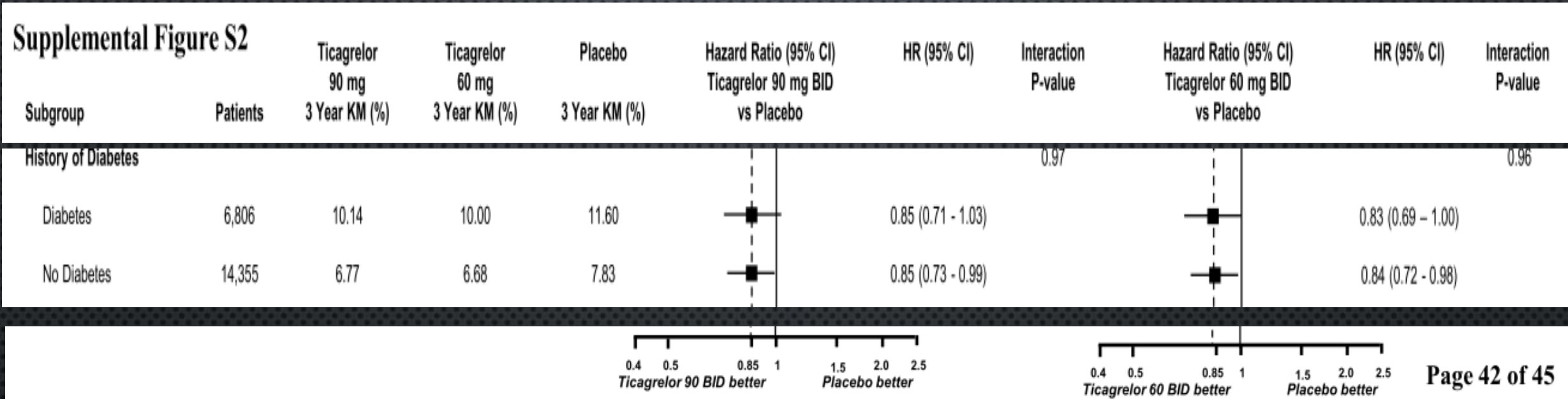
Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Ticagrelor, 90 mg (N = 7050)	Ticagrelor, 60 mg (N = 7045)	Placebo (N = 7067)
Age — yr	65.4±8.4	65.2±8.4	65.4±8.3
Female sex — no. (%)	1682 (23.9)	1661 (23.6)	1717 (24.3)
White race — no. (%)†	6126 (86.9)	6077 (86.3)	6124 (86.7)
Weight — kg	82.0±16.7	82.0±17.0	81.8±16.6
Hypertension — no. (%)	5462 (77.5)	5461 (77.5)	5484 (77.6)
Hypercholesterolemia — no. (%)	5410 (76.7)	5380 (76.4)	5451 (77.1)
Current smoker — no. (%)	1187 (16.8)	1206 (17.1)	1143 (16.2)
Diabetes mellitus — no. (%)	2241 (31.8)	2308 (32.8)	2257 (31.9)

N Engl J Med 2015;372:1791-800



FOCUS: diabetes subgroup



N Engl J Med 2015;372:1791-800



Patients with a myocardial infarction more than 1 year previously, treatment with ticagrelor significantly reduced the risk of cardiovascular death, myocardial infarction, or stroke and increased the risk of major bleeding.

FOCUS: diabetes subgroup: need more studies

N Engl J Med 2015;372:1791-800



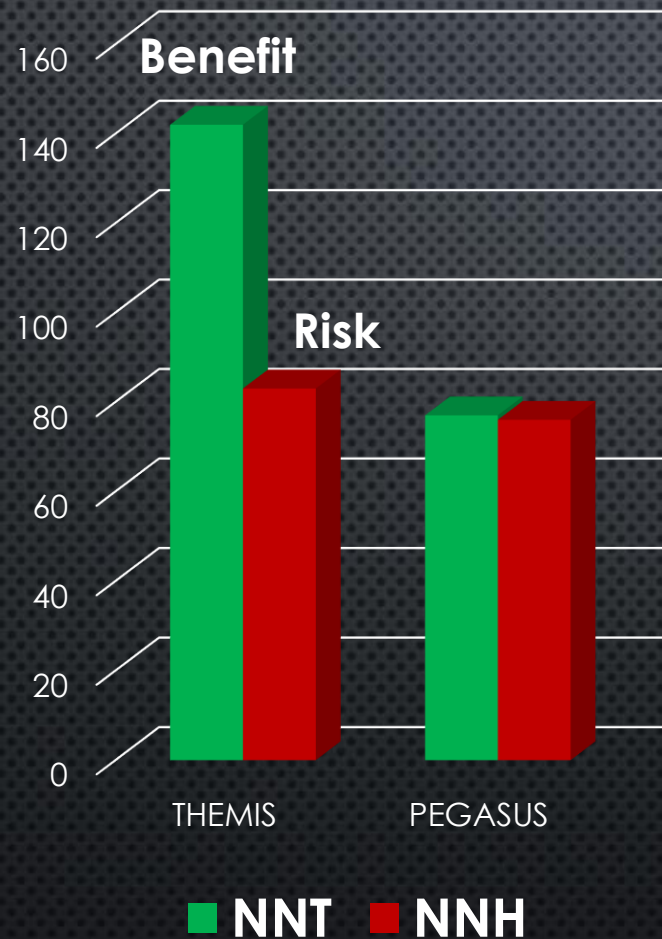
Summary: P2Y12 receptor blockade in diabetes

THEMIS trial

Ticagrelor in
stable CAD
with DM

PEGASUS TIMI 54

Ticagrelor in prior
MI patients (DM
subset)



Benefit

Risk

Diabetes high risk state

Precision medicine is not perfect

Thank you

