Current Evidence for Novel Antiplatelet

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16.6.24

Outline:

1. Role of Platelets in Thrombosis
2. Mechanisms of Platelet Inhibition
3. Clinical Evidence for Ticagrelor

Theory of Immature Platelets (Reticulated Platelets)

Platelet Physiology

Newly formed unbound immature platelets more likely to participate in thrombosis

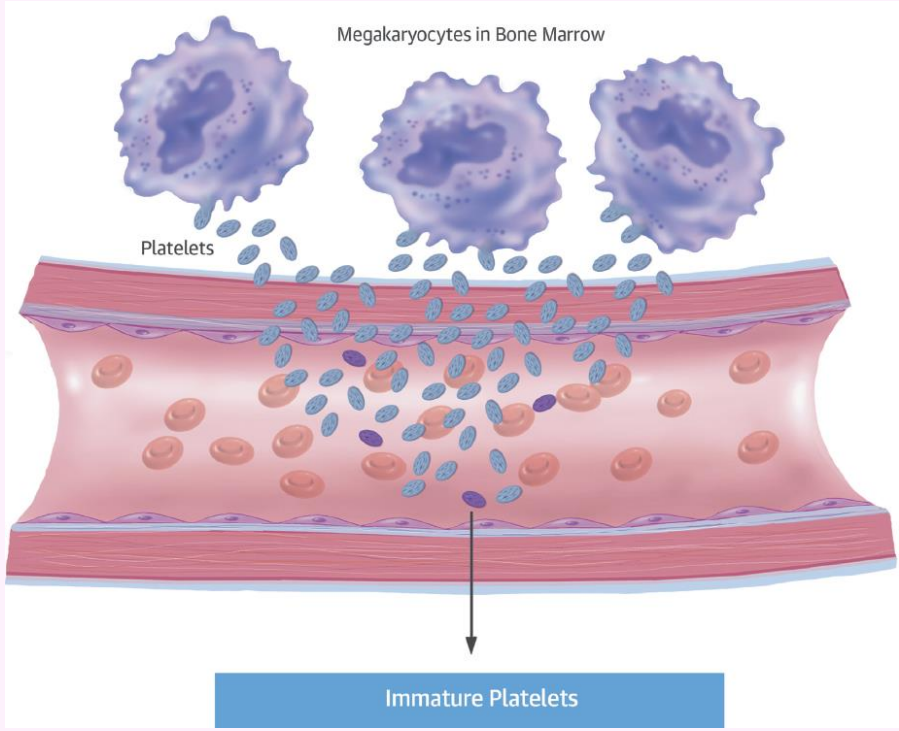
High platelet turnover and reactivity in patients with CAD in the setting of ACS and with other high-risk factors such as DM

-Have a greater number of dense granules vs older, circulating platelets

-Have the capacity for ongoing protein synthesis by residual mRNA

-Have greater reactivity than older platelets

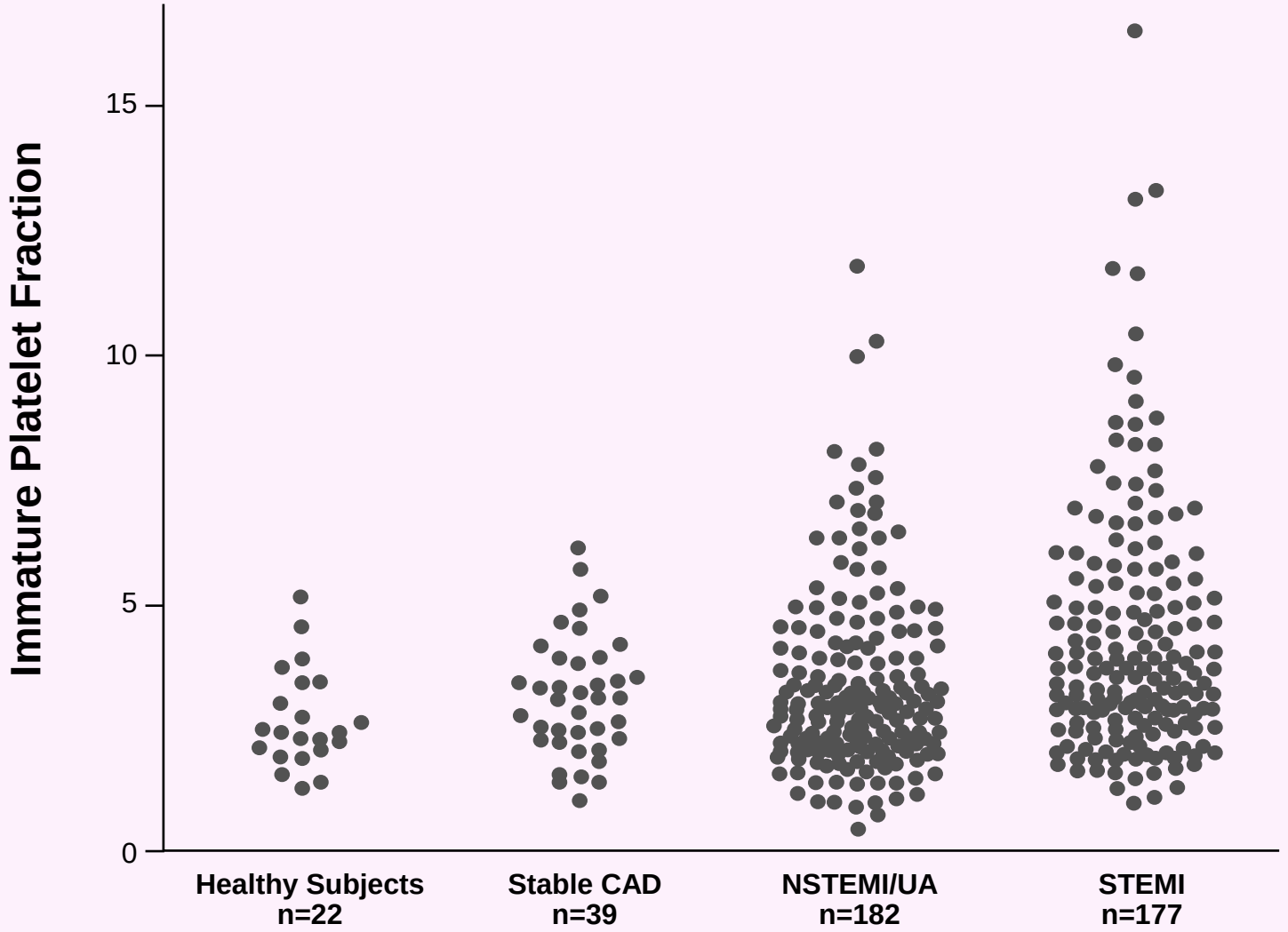
-Are associated with cardiovascular disease



ACS = acute coronary syndrome; BID = twice daily; CAD = coronary artery; DM = diabetes mellitus.

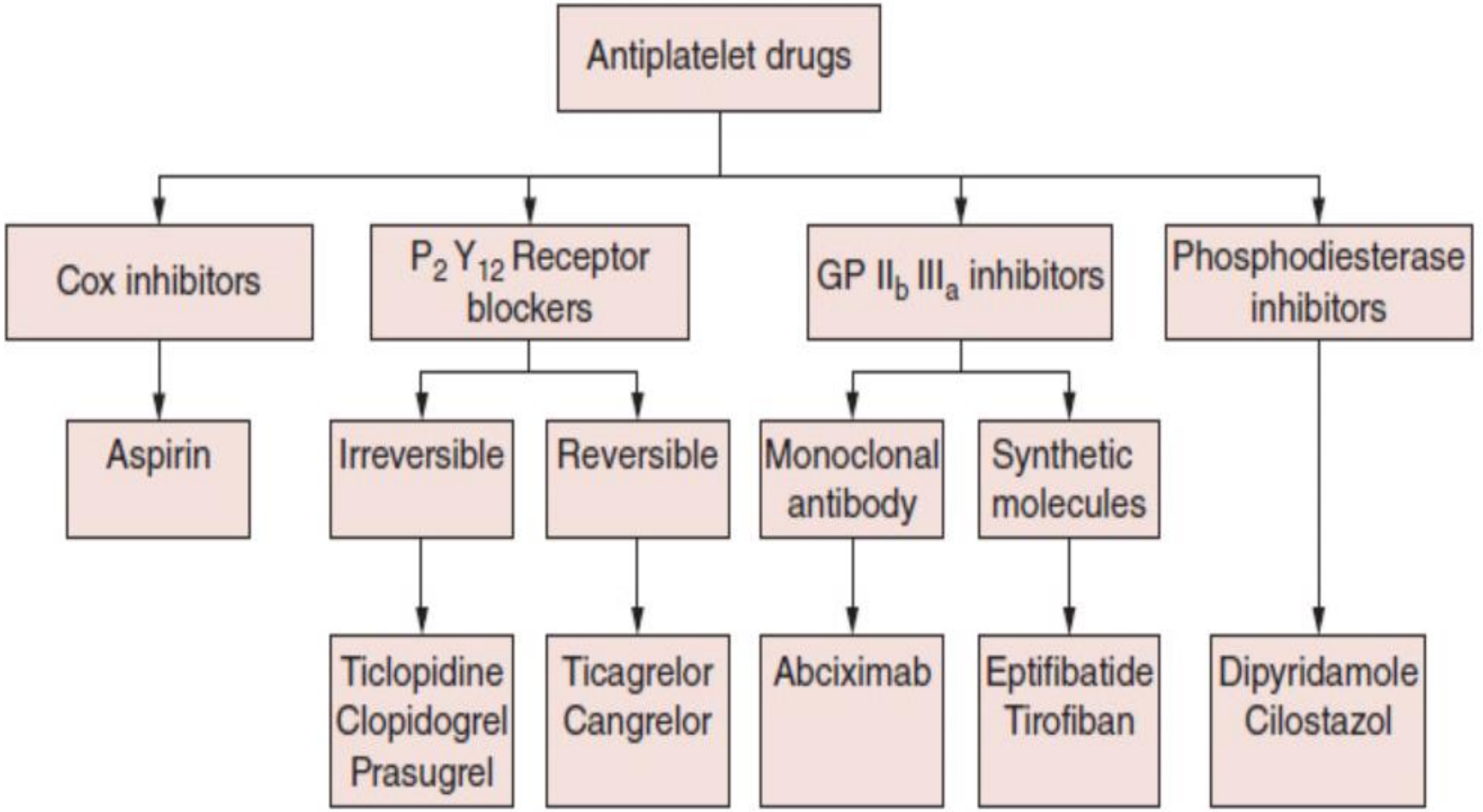
1. Kleiman NS. *J Am Coll Cardiol*. 2016;68(3):294-296; 2. Bernlochner I et al. *Eur Heart J*. 2015;36(45):3202-3210; 3. Grove EL et al. *Thromb Haemost*. 2009;101(1):151-156; 4. Ferreiro et al. *Circulation*. 2011;123:798-813.

Newly Released or Immature Platelets Are More Likely to Participate in Thrombosis Than Older Platelets



CAD = coronary artery disease; NSTEMI = non ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.
Grove EL et al. *Thromb Haemost.* 2009;101(1):151-156.

Classification of Antiplatelet drugs



Classification of antiplatelet drugs based on mechanism of action.

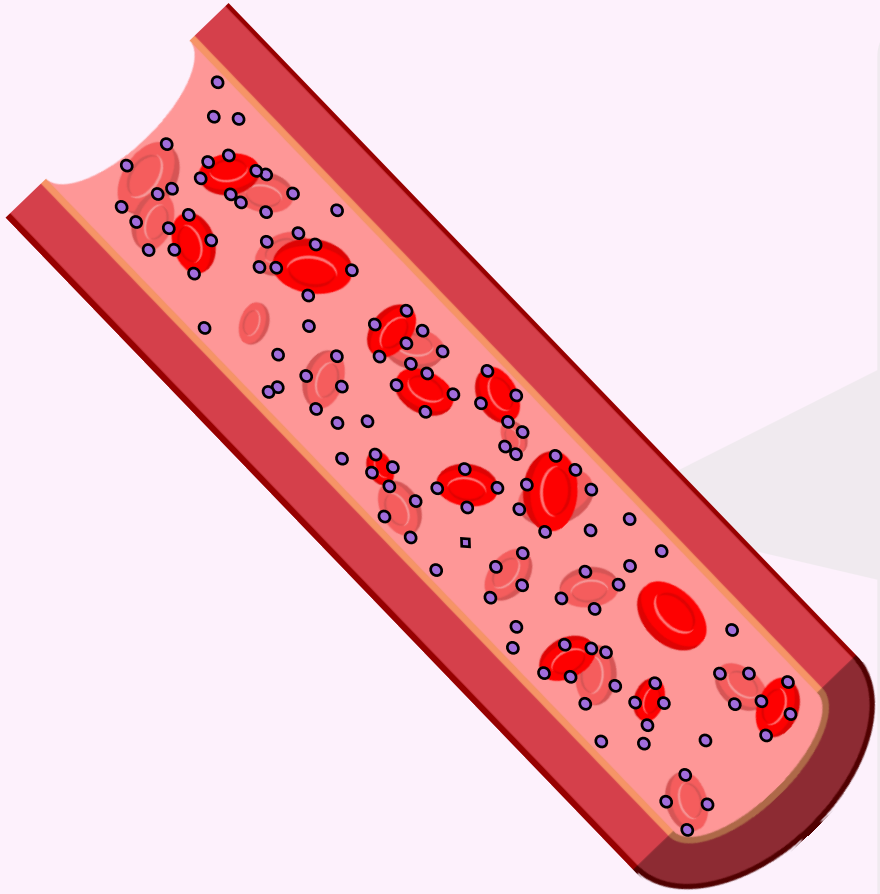
P2Y12 inhibitors

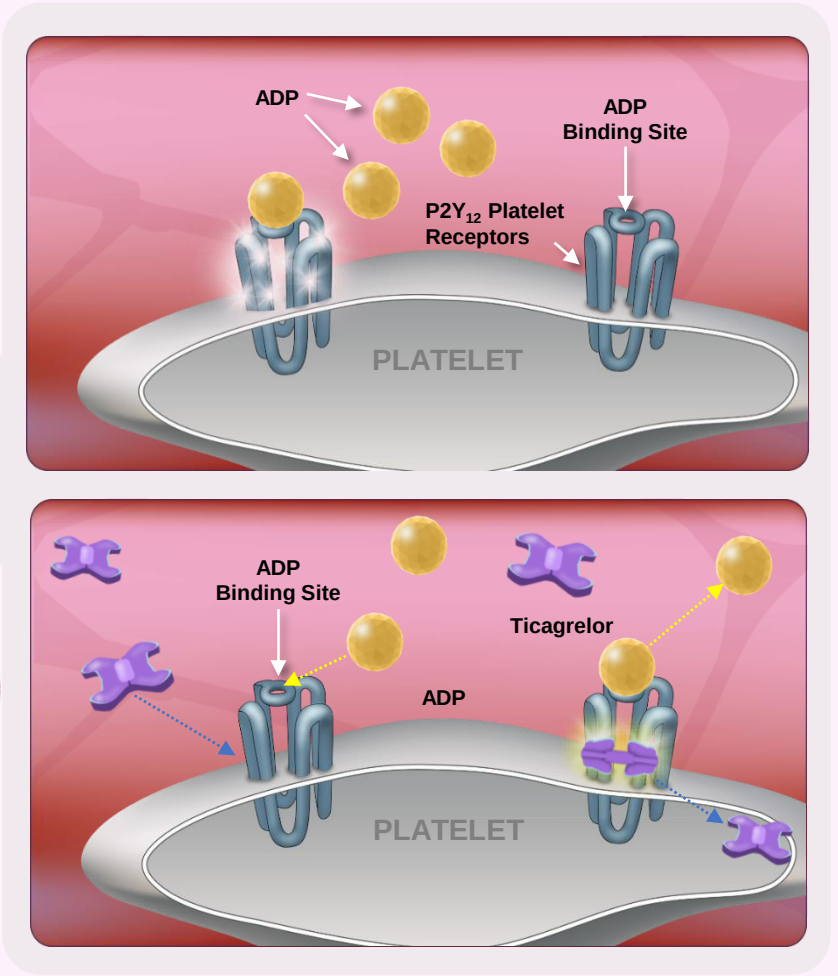
Table I Pharmacodynamics and pharmacokinetics of oral P2Y12 inhibitors

	Clopidogrel	Prasugrel	Ticagrelor
Chemical group	Thienopyridine	Thienopyridine	Cyclopentyltriazolopyrimidine
Dosage (loading; maintenance), mg	300; 75	60; 10	180; 90
Metabolic activation required	Yes	Yes	No
CYP responsible for metabolism*	CYP2C19	CYP3A4/5, CYP2B6	CYP3A4
Metabolism dependent on CYP phenotype	Yes	No	No
IPA, %	50–70	90	90
Time to reach IPA, h	2–4 (depends on phenotype)	1	0.5
Time to reach C_{max}, h	0.5–1	0.5	1.3–2
Reversible binding to ADP receptor	No	No	Yes
Pleiotropism	Yes	Yes	Yes
Adenosine-related pleiotropism**	No	No	Yes

Mean Elimination $T_{1/2}$	6 hours – parent drug 30 min – active metabolite	7 hours for active metabolite	7 hours – parent drug 9 hours – active metabolite

Mechanism of Action of Ticagrelor





Platelets

$P2Y_{12}$ receptor

ADP binds to platelet $P2Y_{12}$ ADP receptors, causing intracellular signal transduction, which initiates platelet aggregation[1]

Ticagrelor

Ticagrelor **reversibly** interacts with platelet $P2Y_{12}$ ADP receptors, preventing ADP-initiated signal transduction and platelet activation[2,3]

- CPTP-selective ADP-receptor antagonist
- Not interact with ADP binding site
- Non-competitive inhibition
- Direct acting inhibitor

Images are for illustrative purposes only.

It is not known how pharmacology or chemical class correlate to clinical efficacy or safety results.

ADP = adenosine diphosphate.

1. Meadows TA et al. *Circ Res*. 2007;100(9):1261-1275; 2. BRILINTA Prescribing Information; 3. Husted S et al. *Cardiovasc Ther*. 2009;27:259-274.

Mechanism of Action of Ticagrelor

1) blocks the P2Y12 receptor reversibly

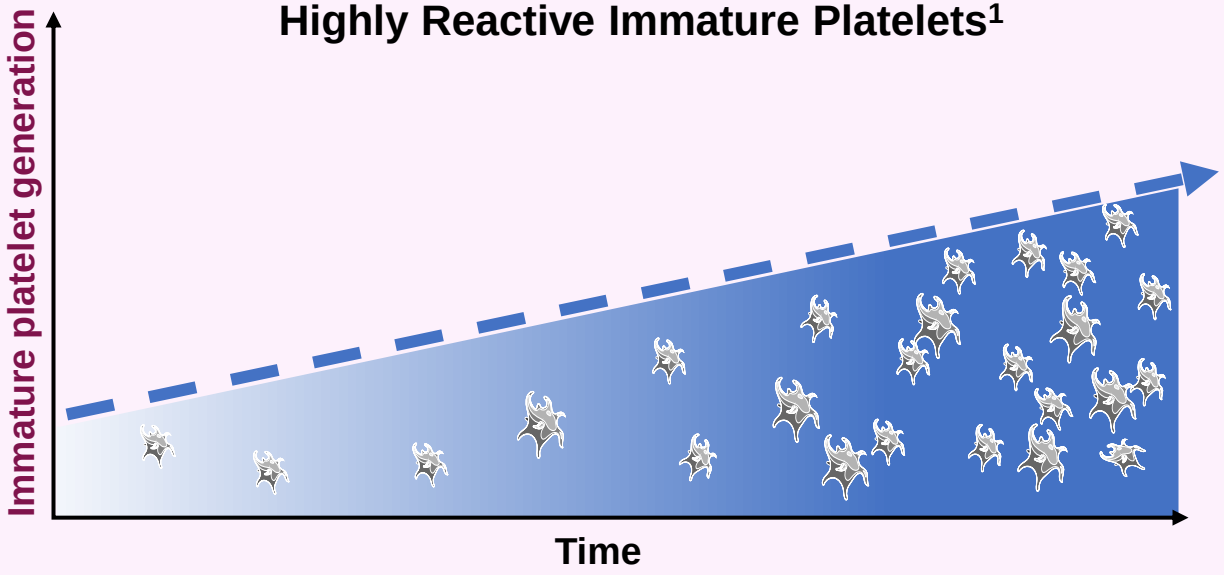
2) increases the concentration of adenosine

3) is metabolized independently of the interindividual genetic variability

- Unique non-thienopyridine P2Y12 antagonist
- Not require metabolic activation
- Reaches IPA within 30 minutes after administration, greater IPA, more rapid onset and offset of inhibition with ticagrelor than clopidogrel (ONSET-OFFSET Result)
- Pleiotropic effects probably by increasing adenosine concentration and unknown mechanisms

Ticagrelor is Available to Inhibit Immature Platelets Over 24 Hours

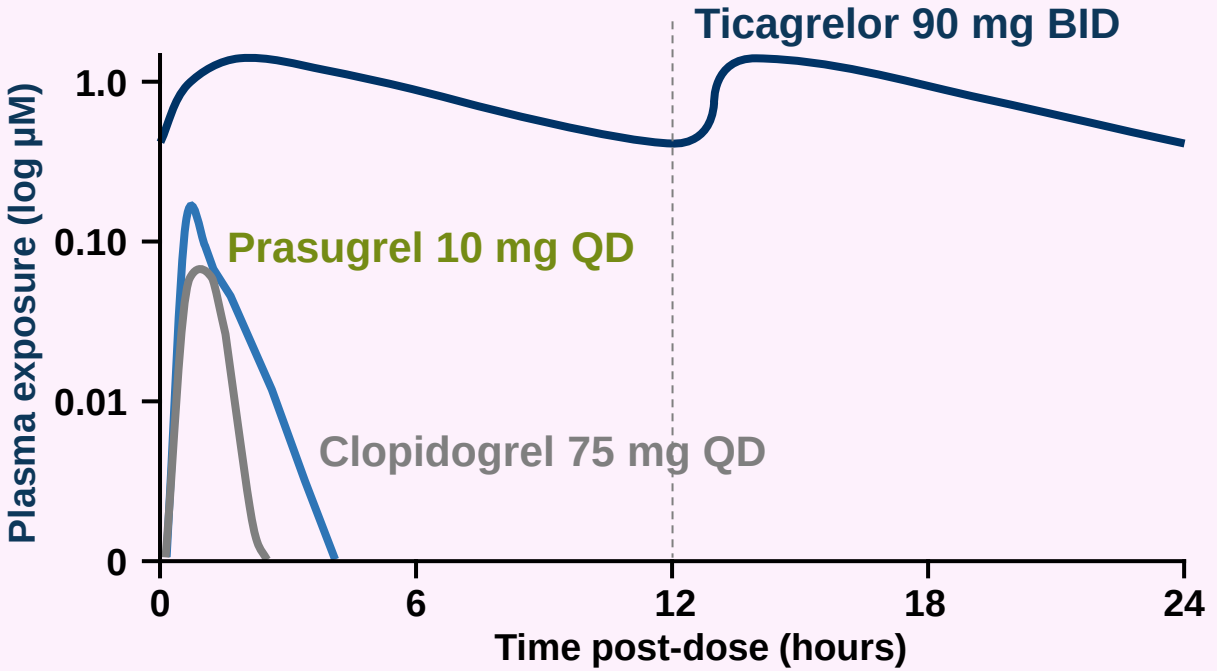
Accelerated Platelet Turnover is Associated with Increased Generation of Highly Reactive Immature Platelets[1]



(For illustrative purposes only)

- Approximately 13% of platelets are replenished daily[3,4]
- Accelerated platelet turnover and increased generation of immature platelets occurs in patients with CAD in the setting of ACS and with other high-risk factors such as DM[5,6]

Plasma Exposure of Ticagrelor Over Time[2,a]

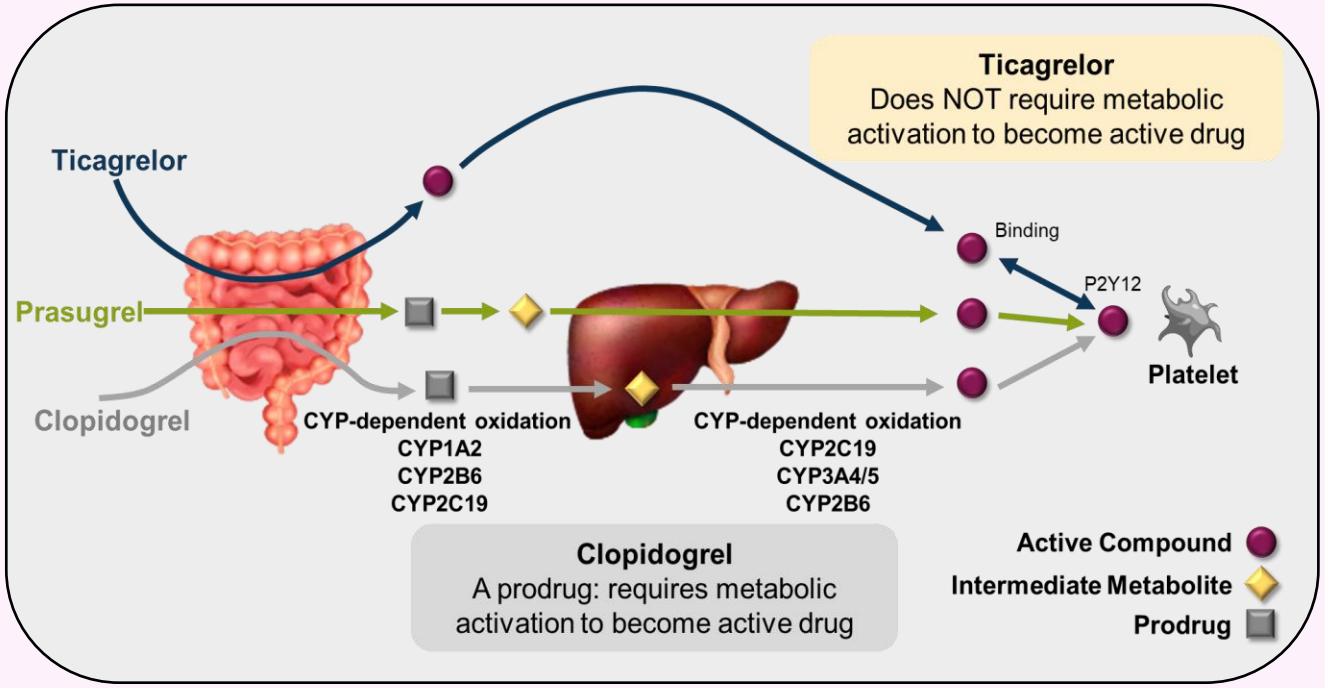


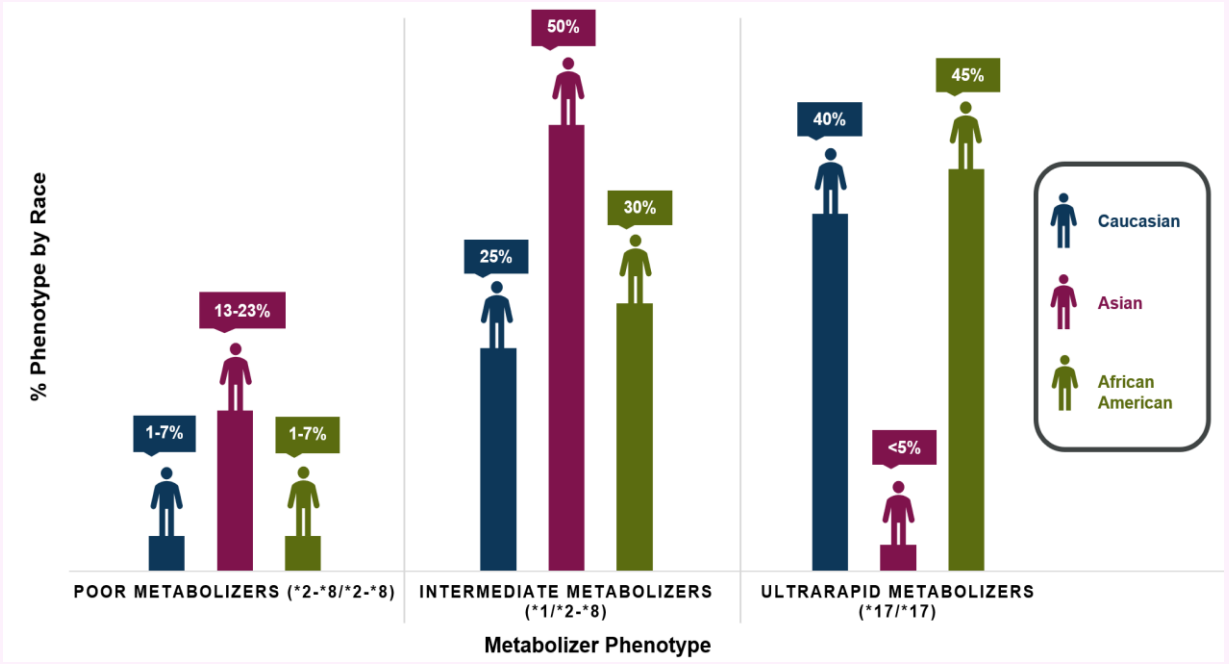
- Ticagrelor's reversible binding, long half-life, and twice daily dosing result in prolonged availability to inhibit immature platelet function[2]

It is not known how pharmacology or chemical class correlate to clinical efficacy or safety results.
[a]Based on ticagrelor 90 mg BID dosing.[2]
ACS = acute coronary syndrome; BID = twice daily; CAD = coronary artery disease; DM = diabetes mellitus; QD = daily.

1. Armstrong et al. *Arterioscler Thromb Vasc Biol.* 2017;37:949-956; 2. Nylander S et al. *Br J Pharmacol.* 2016;173:1163-1178; 3. Grozovsky R et al. *Blood.* 2015;126(16):1877-1884; 4. Gutierrez G et al. *Crit Care.* 2004;8:373-381; 5. Grove et al. *Thromb Haemost.* 2009;101:151–156; 6. Ferreiro et al. *Circulation.* 2011;123:798-813.

Comparison of $P2Y_{12}$ Pharmacology and Frequency of CYP2C19 Phenotypes by Race





- Clopidogrel is a prodrug and must be metabolized by CYP450 enzymes, primarily ***CYP2C19***, to produce the active metabolite that inhibits platelet aggregation[4,5]
- ***CYP2C19*** gene is highly polymorphic leading to gene variants that cause LOF and GOF[3,6]
- Highest frequency of poor and intermediate metabolizer phenotype is seen in Asians and highest frequency of the ultrarapid metabolizer phenotype is seen in Caucasians and African Americans[3]
- By comparison, ticagrelor is not a pro-drug and therefore does not require metabolic activation for pharmacodynamic activity[2]

LOF = loss of function; GOF = gain of function.
Note: Patients without the poor, intermediate, or ultrarapid metabolizer phenotype are presumably extensive (normal) metabolizers.
1. Schomig A. *N Engl J Med.* 2009;361:1108-1111; 2. Wallentin L et al. *Lancet.* 2010;376:1320-1328; 3. Cavallari LH et al. *Pharmgenomics Pers Med.* 2011;4:123-136; 4. Mega JL et al. *N Engl J Med.* 2009;360:354-362; 5. Plavix Prescribing Information, Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, May 2019; 6. **Pereira NL et al. Online ahead of print. *Circ Cardiovasc Interv*. 2019.**

Differences in Platelet Binding Between Thienopyridines and CPTPs

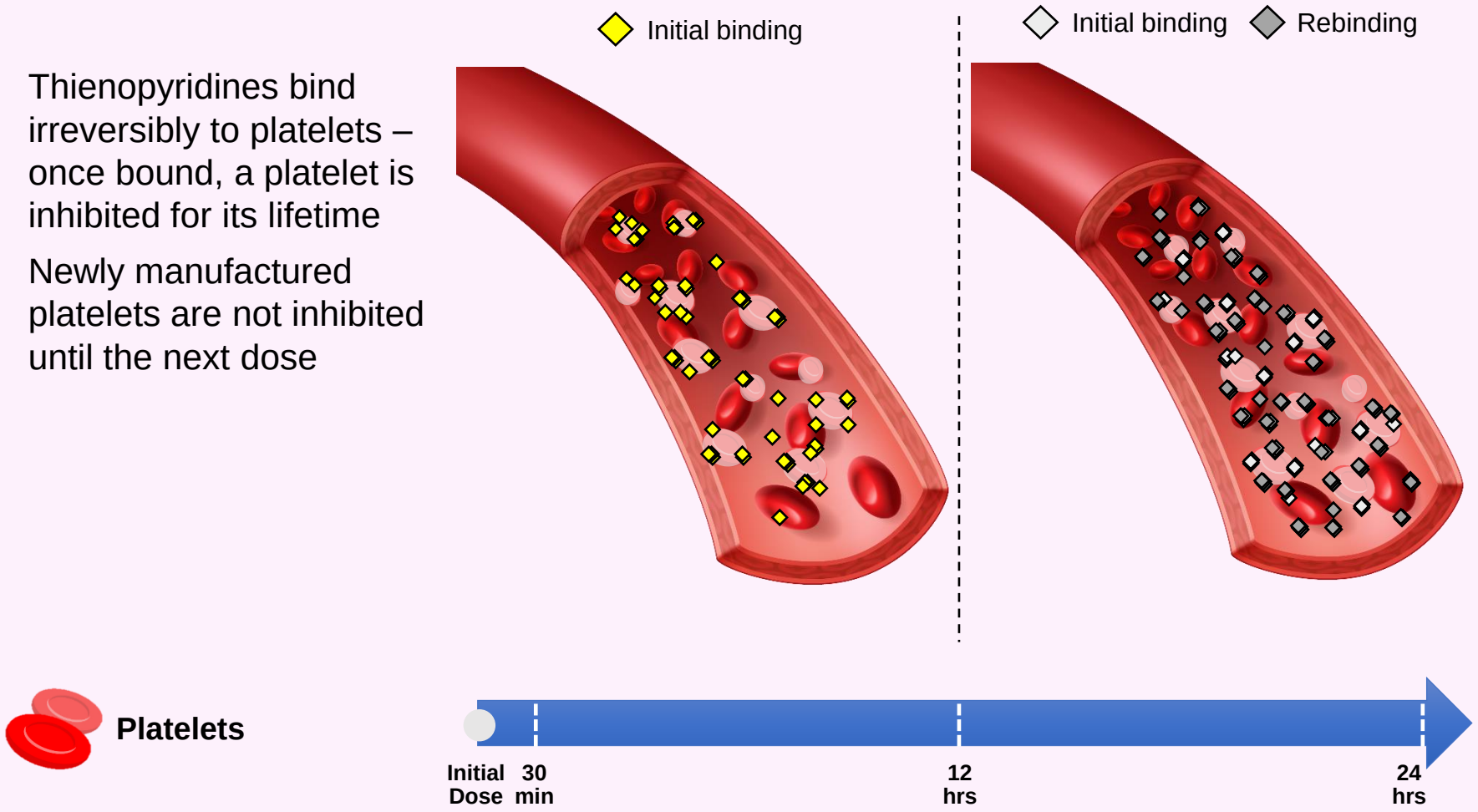
QD Dosing Thienopyridines

- Thienopyridines bind irreversibly to platelets – once bound, a platelet is inhibited for its lifetime
- Newly manufactured platelets are not inhibited until the next dose

BID Dosing CPTPs

- CPTPs bind reversibly to platelets and can redistribute and bind to new platelets before the next dose

- Young immature platelets are less inhibited by prasugrel when compared with ticagrelor especially during the last hours of the dosing interval



BID = twice daily; CPTP = cyclopentyltriazolopyrimidine; QD = once daily.
Porto I et al. *Expert Opin Investig Drugs*. 2009;18(9):1317-1332.

Pleiotropic effects of Ticagrelor

- Comprises :
  - Cardio protection
  - Restoration of the myocardium after an ischemic event
  - Promotion of the release of anticoagulative factors
  - Anti-inflammatory effects

  - Increased concentration of adenosine caused by
  1) inhibition of adenosine reuptake by blocking human equilibrative nucleoside transporter
  2) increased release of ATP, subsequently transformed into adenosine

- Beyond the advantageous effects, the increased concentration of adenosine is responsible for some of ticagrelor's adverse effects, including dyspnea and bradycardia

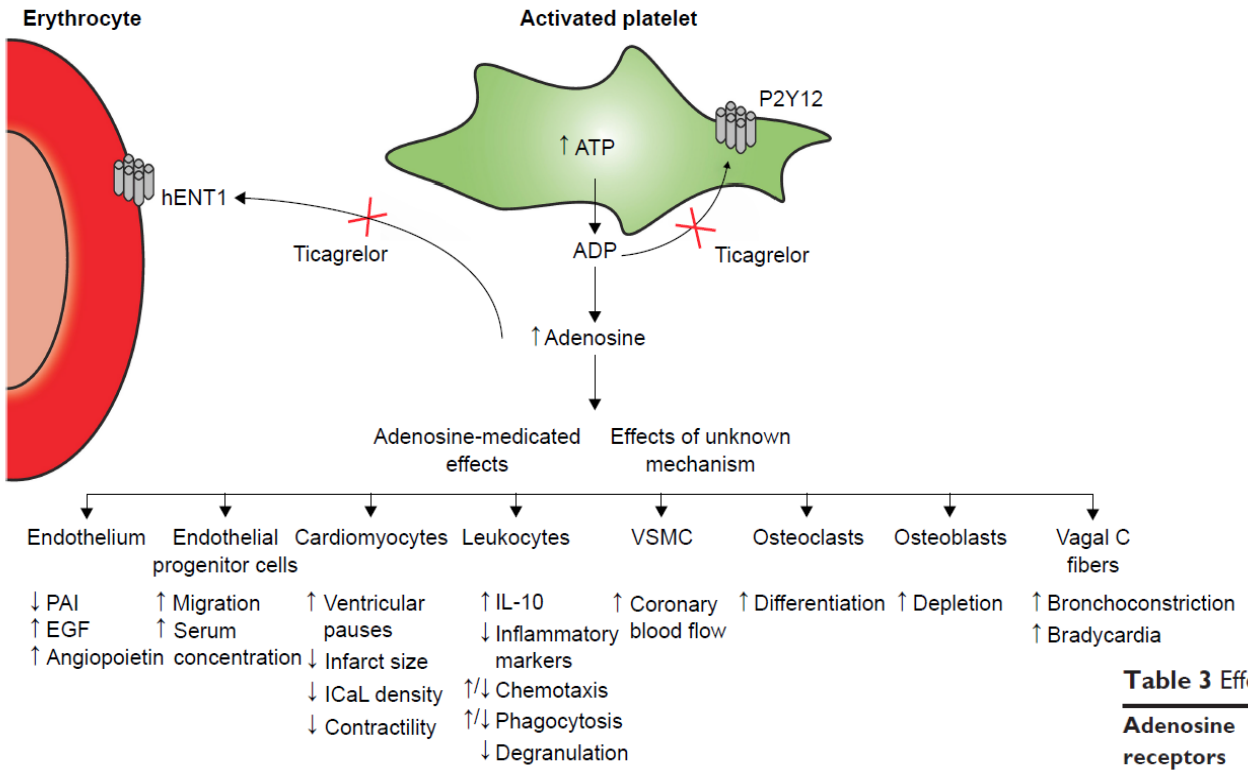


Table 3 Effects induced by stimulation of membrane-bound adenosine receptors (A1–A3)

Adenosine receptors	Ticagrelor-relevant role	Impact on cell cAMP	Concentration of adenosine required for activation
A1	• Coronary vessel spasm • Promotion of neutrophil chemotaxis and phagocytosis • Negative chronotropic effect • Dyspnea • GFR decrease	Decrease	Low
A2a	• Coronary vessel dilation • EPC migration • Inhibition of platelet activation • Dyspnea • Inhibition of neutrophil trafficking, granule release, and production of inflammatory mediators	Increase	Low
A2b	• Coronary vessel dilation • Inhibition of platelet activation • Inhibition of neutrophil trafficking, granule release • Inhibition of production of inflammatory mediators	Increase	High
A3	• Coronary vessel spasm • EPC migration • Promotion of neutrophil chemotaxis and phagocytosis	Decrease	Low

Abbreviations: cAMP, cyclic adenosine monophosphate; GFR, glomerular filtration rate; EPC, endothelial progenitor cell.

Net clinical benefit with Ticagrelor in Randomized clinical trials

Indications	
ACS/MI	PLATO, PHILO, TICAKOREA, TREAT, POPULAR AGE PRAGUE-18, ISAR-REACT 5, ATLANTIC, DUBIUS
CVA/TIA	SOCRATES, THALES
PAD	EUCLID
Elective PCI	ALPHEUS
CABG	DACAB, TICAB, POPular CABG
Secondary Prevention	PEGASUS, THEMIS

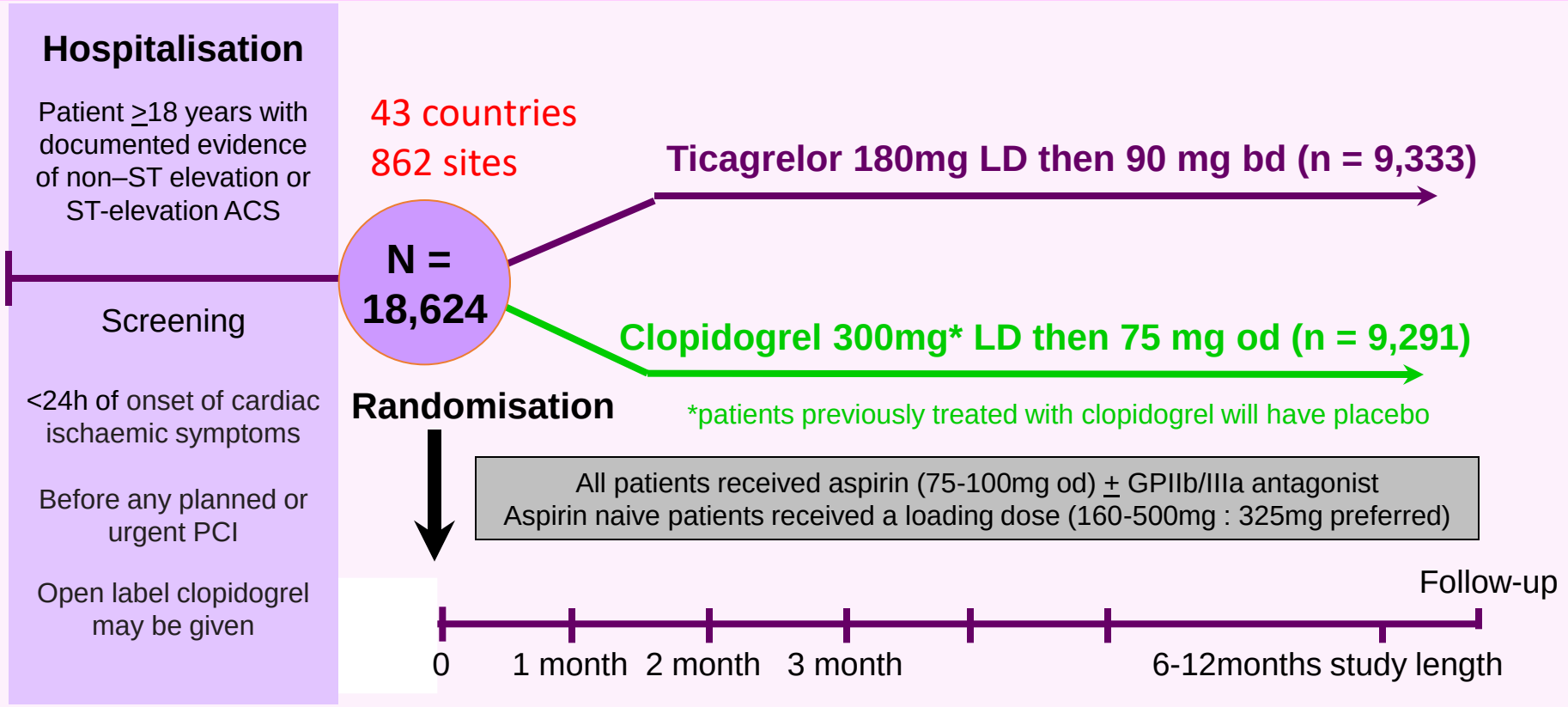
Bleeding Avoidance Strategies	
DAPT De-escalation	TALOS-AMI
Aspirin Withdrawal	GLOBAL LEADERS, TWILIGHT, TICO

↑ Increased Net Clinical Benefit
PLATO
THALES
DACAB
TWILIGHT
TICO

⟺ Neutral Net Clinical Benefit	
PHILO	ALPHEUS
TICAKOREA	TICAB
TREAT	POPular CABG
PRAGUE-18	PEGASUS
ATLANTIC	THEMIS
DUBIUS	GLOBAL LEADERS
SOCRATES	
EUCLID	

↓ Decreased Net Clinical Benefit
POPular Age
ISAR REACT 5
TALOS-AMI

PLATO : Study Design



PLATO study tested the hypothesis that…
ticagrelor will result in a lower risk of recurrent thrombotic events in a broad patient population with ACS as compared to clopidogrel and this would be achieved with a clinically acceptable bleeding rate and overall safety profile

Wallentin *et al*. *New Eng J Med* 2009; 361(11): 1045-1057

PLATO

NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
All receiving ASA; clopidogrel-treated or -naive;
randomised within 24 hours of index event
(N=18,624)

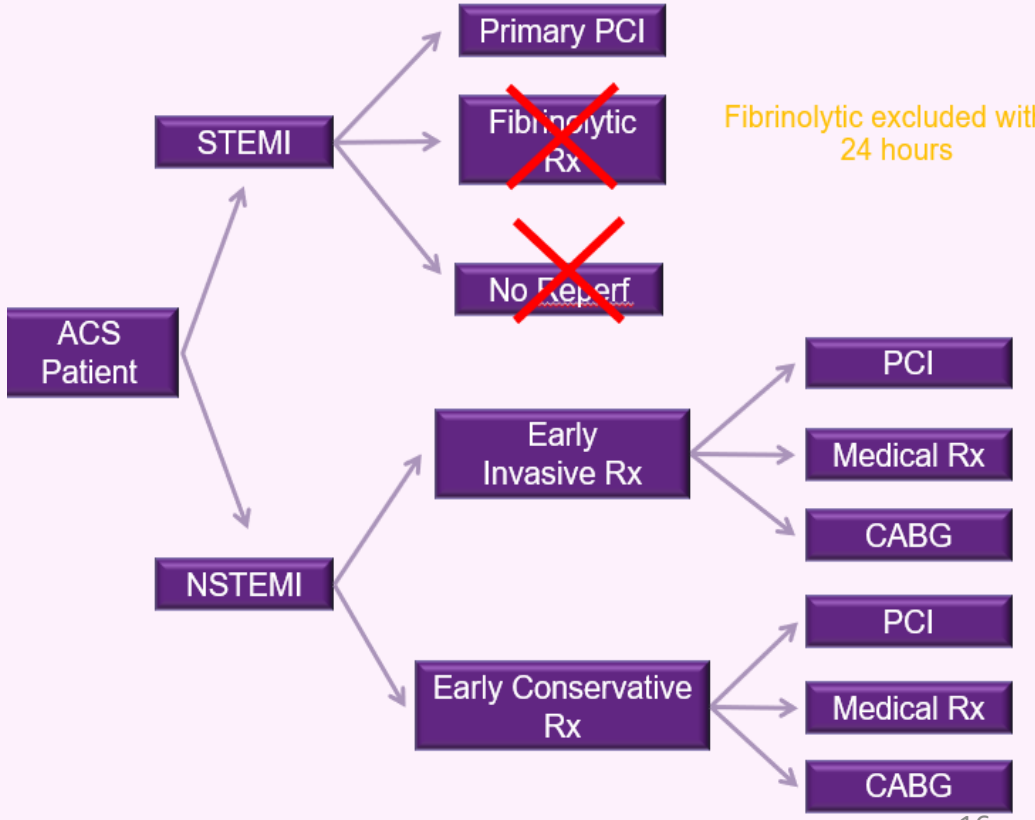
Clopidogrel
If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)

Ticagrelor
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

6–12-month exposure

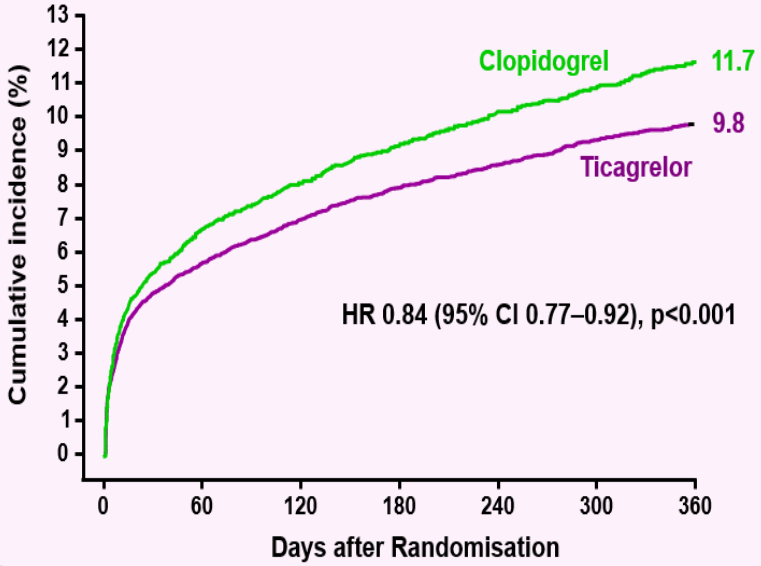
Primary endpoint: CV death + MI + Stroke
Primary safety endpint: Total major bleeding

Broad ACS Patient Population



A significant 16% risk reduction in MACE

Time to first primary efficacy event (composite of CV death, MI or stroke)

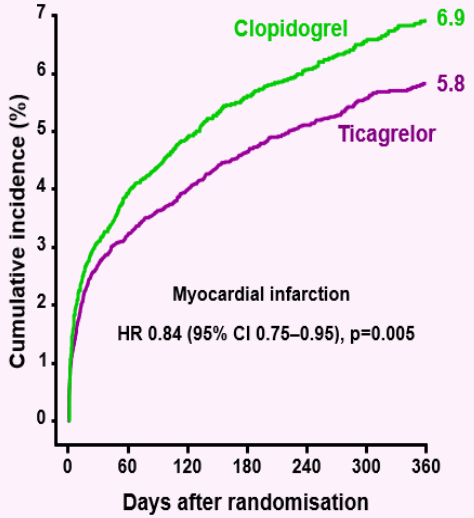


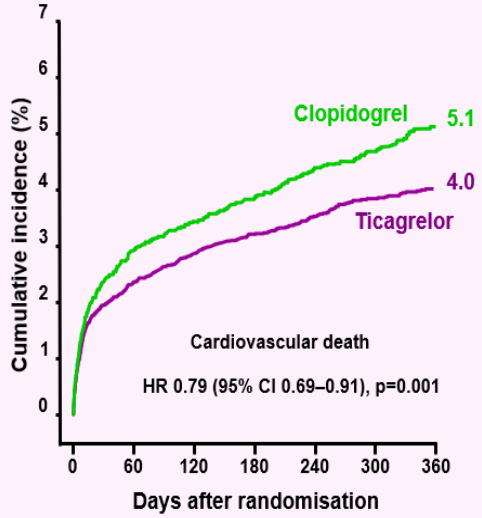
1.9% ARR

16% RRR

No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6, 650	5,096	4,047

Secondary Endpoints: A significant 16% reduction in subsequent MI & 21% reduction in CV death



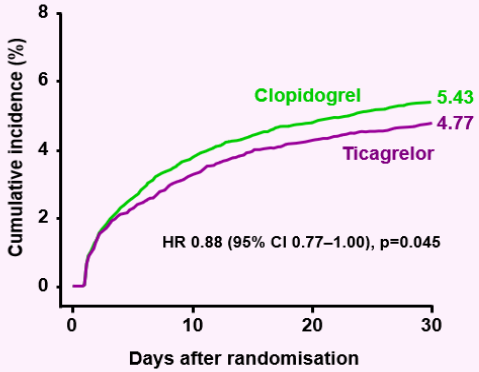


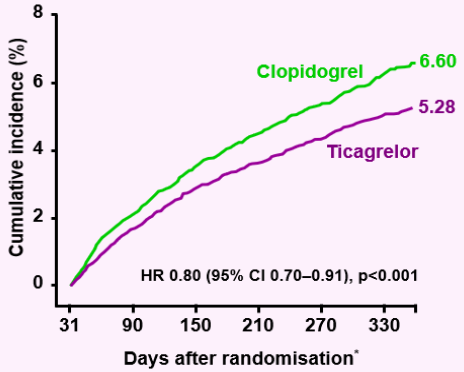
No. at risk							
Ticagrelor	9,333	8,678	8,520	8,279	6,796	5,210	4,191
Clopidogrel	9,291	8,560	8,405	8,177	6,703	5,136	4,109

9,333	8,294	8,822	8,626	7119	5,482	4,419
9,291	8,865	8,780	8,589	7079	5,441	4,364

Benefit Seen as early as day 30 with significant 12% reduction that increased with time

Time to first primary efficacy event (composite of CV death, MI or stroke)



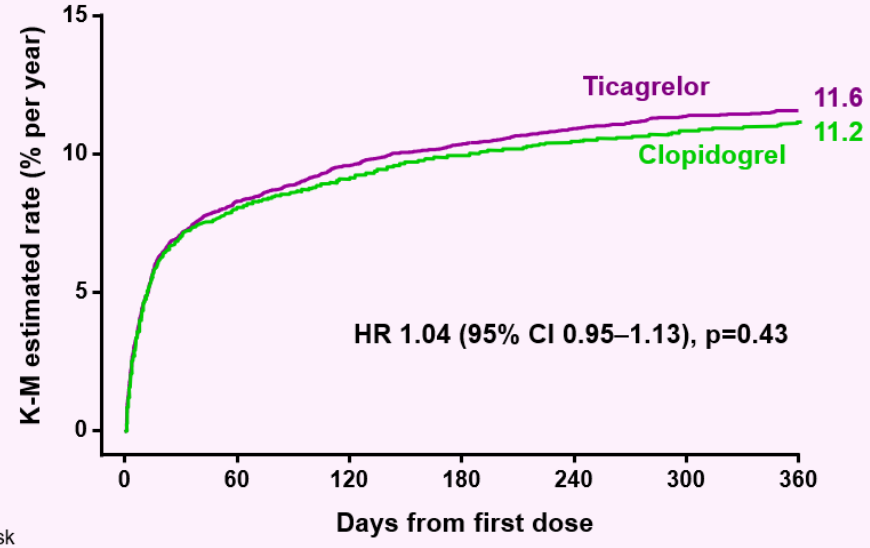


No. at risk				
Ticagrelor	9,333	8,942	8,827	8,763
Clopidogrel	9,291	8,875	8,763	8,688

8,763	8,543	8,397	7,028	6,480	4,822
8,688	8,437	8,286	6,945	6,379	4,751

*Excludes patients with any primary event during the first 30 days

Primary Safety Endpoint: No significant difference in Time to first major bleeding event



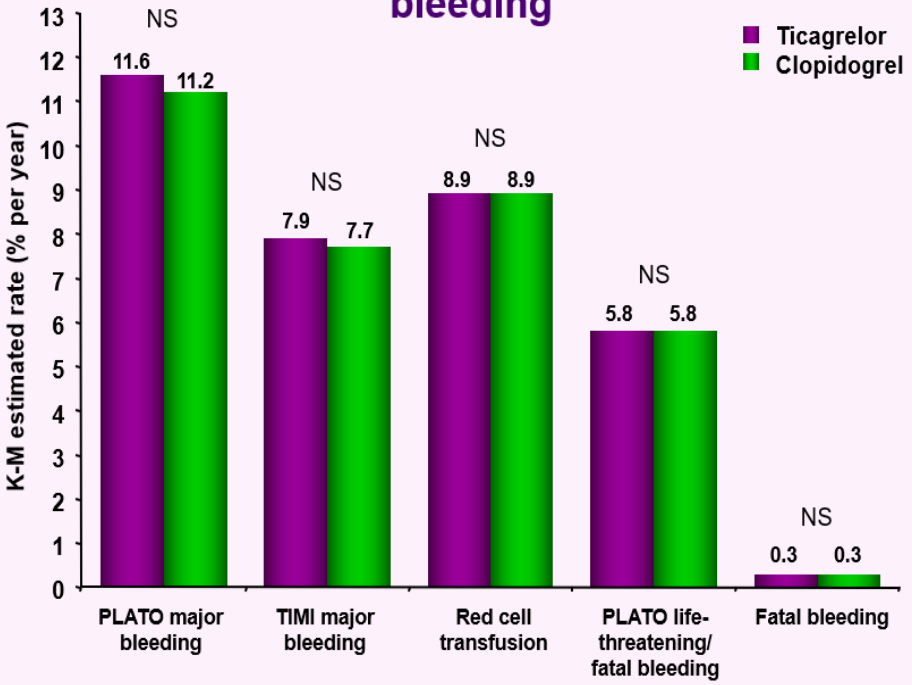
Wallentin *et al. New Eng J Med* 2009; 361(11): 1045-1057

No difference in total major bleeding

No difference in fatal or life-threatening bleeding

More fatal ICH but fewer extracranial fatal bleeds

No significant difference in rates of major bleeding (both PLATO & TIMI), Red Cell Transfusions, life threatening & Fatal bleeding



Wallentin *et al. New Eng J Med* 2009; 361(11): 1045-1057

PLATO: CONCLUSIONS

- In patients with an acute coronary syndrome with or without ST-segment elevation, treatment with ticagrelor compared with clopidogrel
  - reduced the primary endpoint of death form vascular causes, myocardial infarction or stroke
  - reduced the rate of all cause mortality
  - without an increase in the rate of overall major bleeding

Dyspnea associated with Ticagrelor

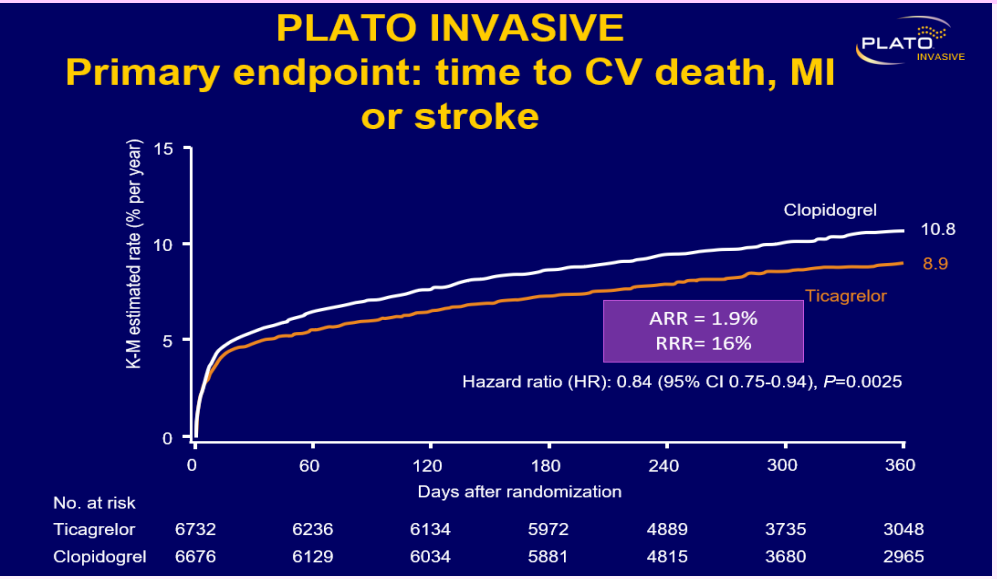
Dyspnea in PLATO

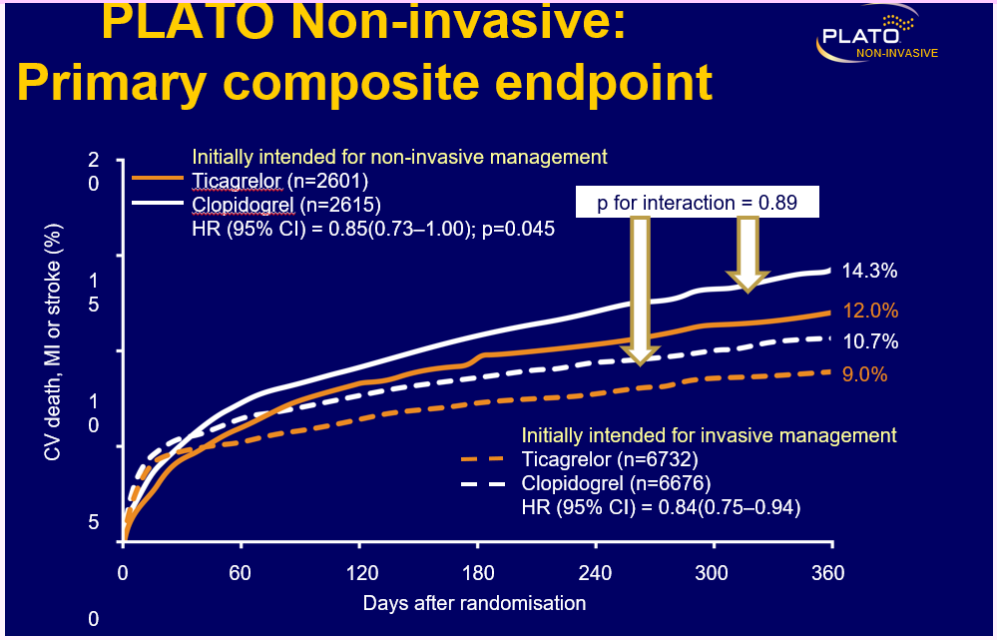
	Ticagrelor (n=9235)	Clopidogrel (n=9186)	*P* value
Dyspnea, %			
Any	13.8	7.8	<0.001
With discontinuation of study treatment	0.9	0.1	<0.001

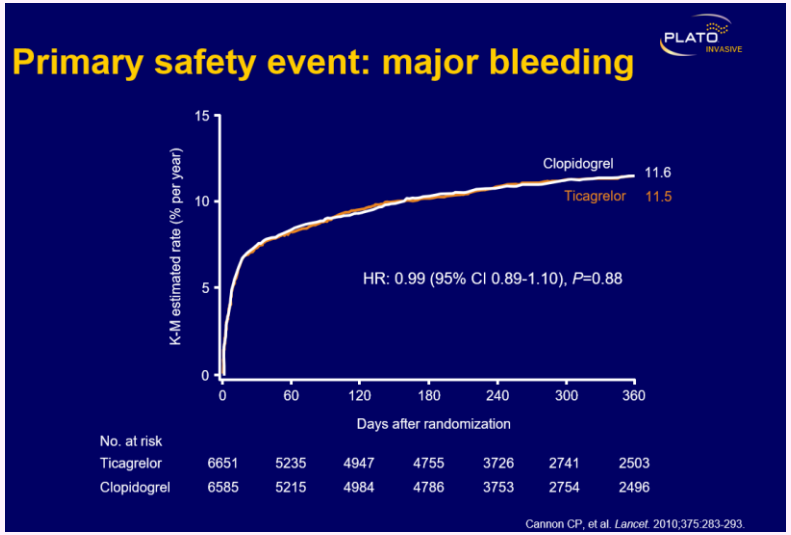
P values were calculated using Fisher's exact test

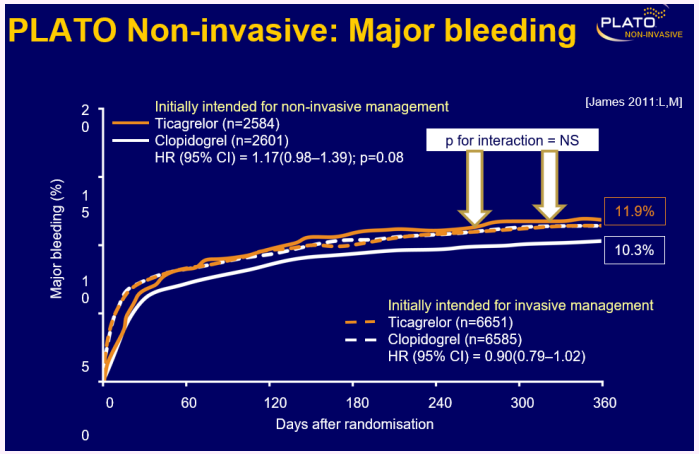
- Usually mild to moderate
- Observed within 1st 7 days, median time 23 days
- Mostly resolves spontaneously
- Patients with baseline cardiopulmonary disease were not at an increased relative risk of dyspnea
  - No measured changes in pulmonary function/ BNP levels
- Benefit of ticagrelor is maintained in patients at risk for dyspnea and those who experience dyspnea
- Patient with mild to moderate dyspnea should be encouraged to continue with Ticagrelor considering consistency of benefit

PLATO: Invasive and Non-invasive









Timing of Stent Thrombosis : Findings from PLATO

Ticagrelor Significantly reduced Stent Thrombosis: Early and Late

ST Reduction within 30 Days

(4 hours–30 days; HR, 0.60; 95% CI, 0.39–0.93)

ST Reduction from 30 – 360 Days

(>30 days; HR, 0.48; 95% CI, 0.24–0.96)

Steg PG et al, Circulation. 2013;128:1055–1065

- A higher proportion of patients with definite stent thrombosis compared with patients with no definite stent thrombosis were: men, habitual smokers, diabetes mellitus, a history of prior cardiovascular disease, non-haemorrhagic stroke, PAD, STEMI at randomization, along with a final diagnosis of STEMI

•Patients with previous stent or underwent stenting during the course is 11289 (60.6%)

- Patients in **Ticagrelor arm is 5640** and **Clopidogrel arm is 5649**

PLATO INVASIVE - Stent thrombosis reduced by 36%

	Ticagrelor (n=6,732)	Clopidogrel (n=6,676)	HR for ticagrelor (95% CI)	p value*
Stent thrombosis, %				
Definite	1.3	2.0	0.64 (0.46–0.88)	0.0054

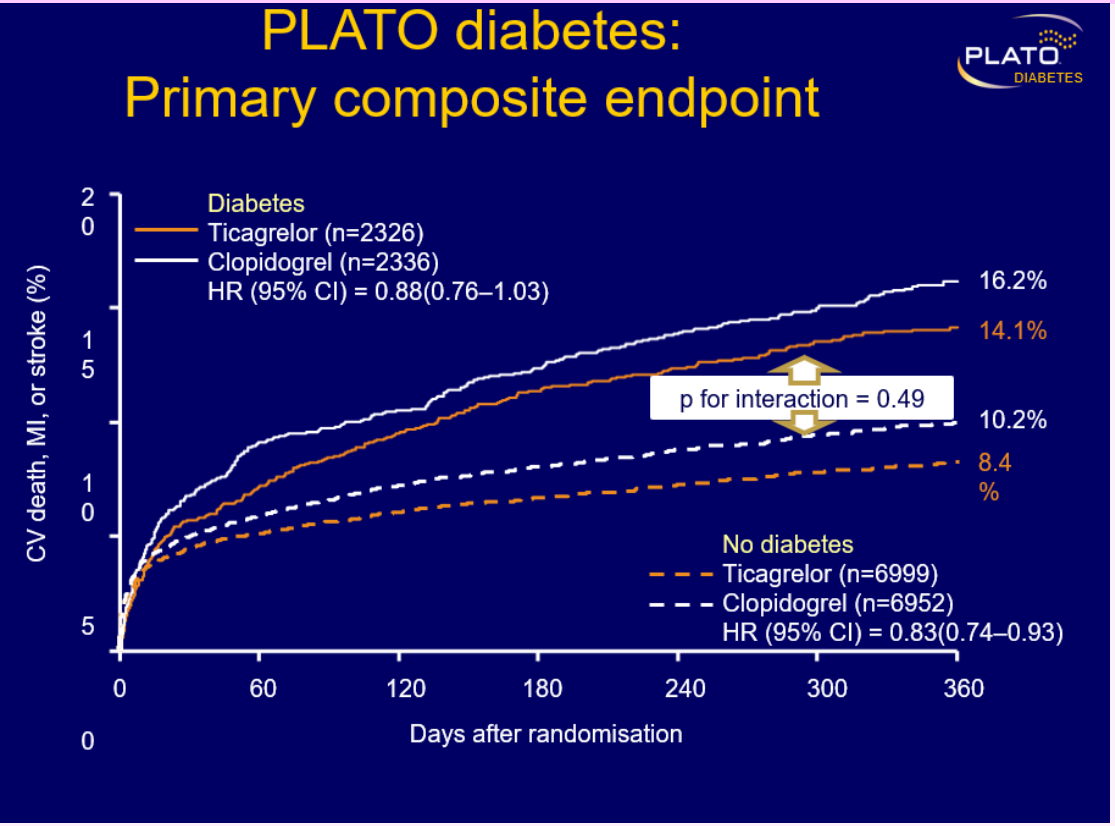
¶ Evaluated in patients with any stent during the study

Time-at-risk is calculated from the date of first stent insertion in the study or date of randomization

* By univariate Cox model

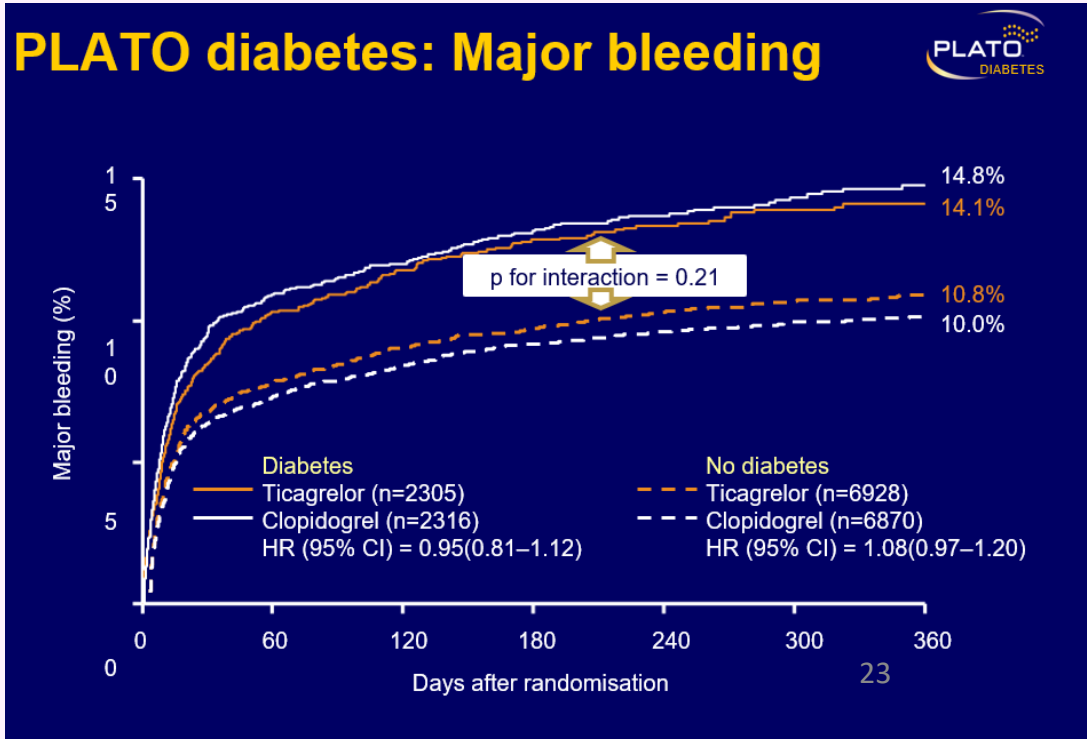
Cannon CP, et al. *Lancet*. 2010;375:283-293.

PLATO: Diabetes

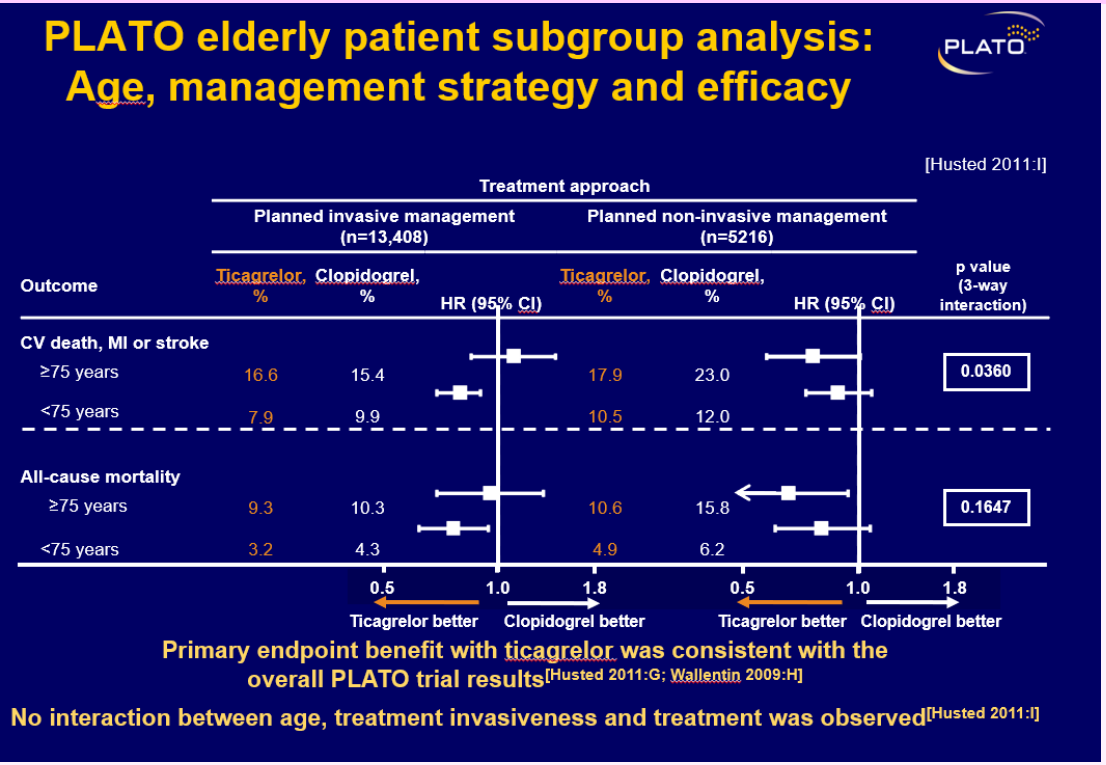


- No significant increase in major bleeding was observed in diabetic patients treated with ticagrelor compared with clopidogrel
  - –However, it should be noted that in the PLATO main analysis, there were higher rates of non-CABG major bleeding.

- Efficacy of ticagrelor in the diabetic patient subgroup is consistent with that observed in the overall PLATO study population
  - Incidence of CV death, MI or stroke and all-cause mortality in diabetic patients with ACS was numerically lower in patients treated with ticagrelor compared with clopidogrel
  - No definitive efficacy conclusion between the treatment groups can be drawn due to the small sample size

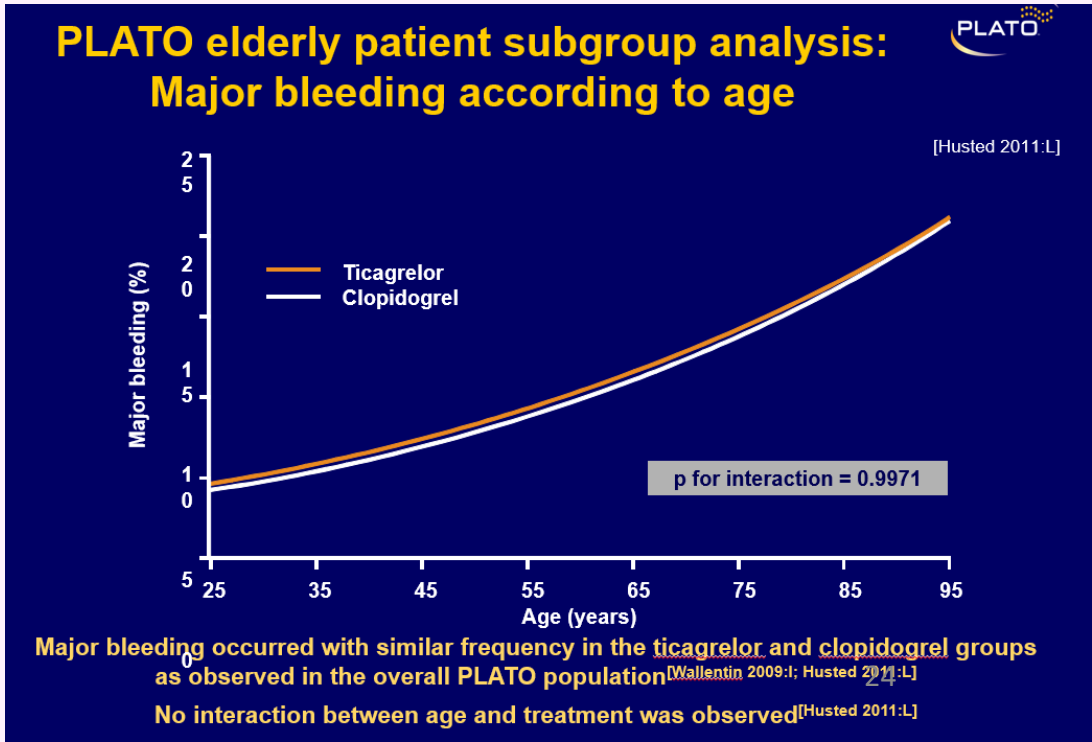


PLATO: Elderly

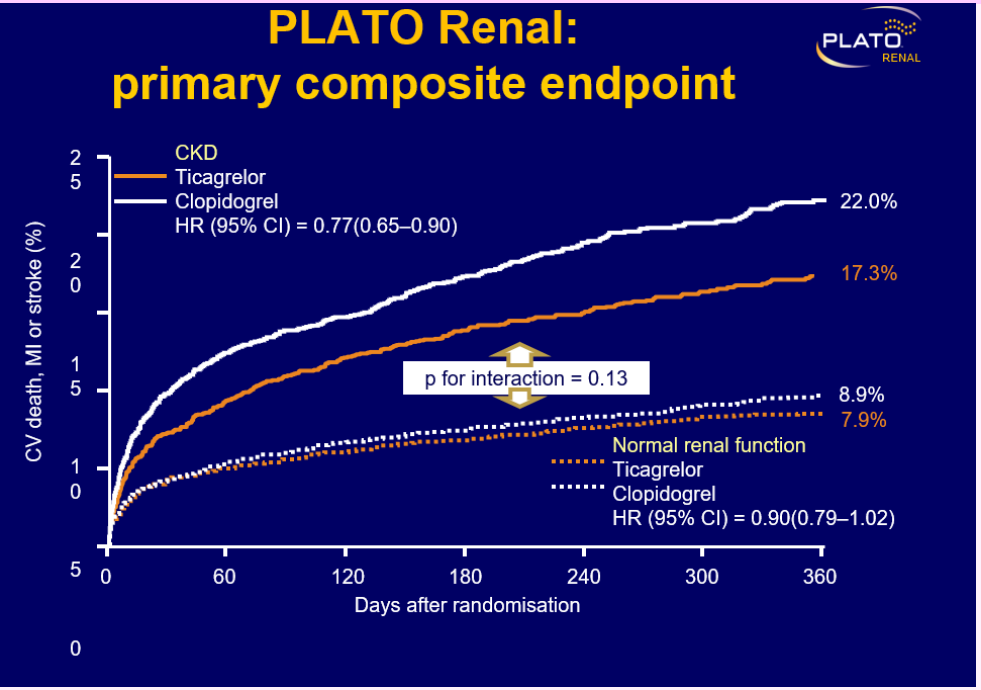


- In elderly ACS patients, the benefits of ticagrelor over clopidogrel were consistent with the overall PLATO study
- The efficacy of ticagrelor compared with clopidogrel was independent of age

- Primary composite endpoint of CV death, MI or stroke was lower with ticagrelor compared with clopidogrel, irrespective of age
- All-cause mortality, CV death, MI and definite stent thrombosis were reduced by ticagrelor compared with clopidogrel, irrespective of age



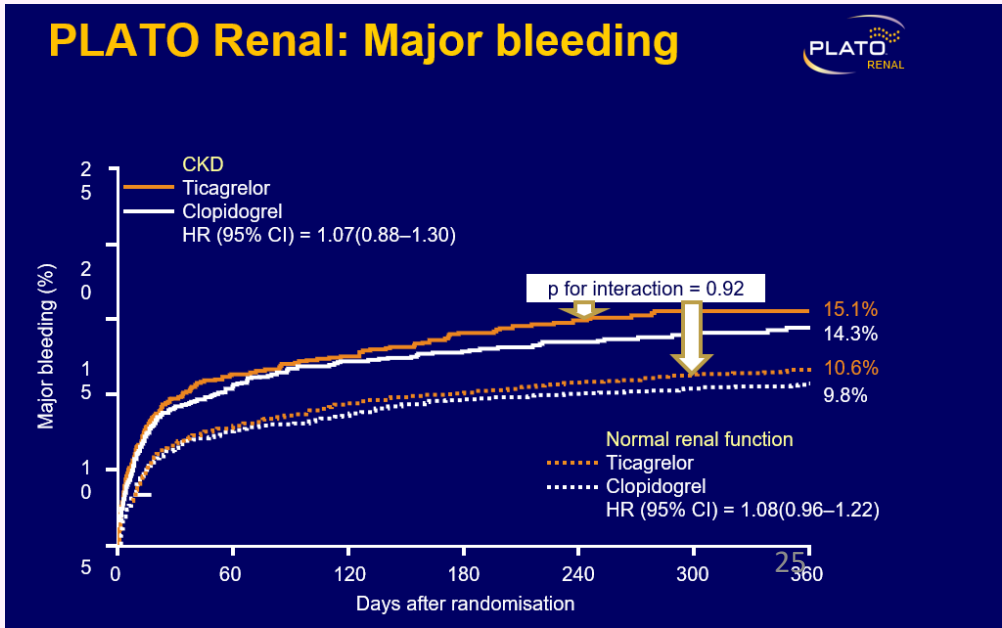
PLATO: Renal



- Independent of renal function, ticagrelor was associated with a lowered risk of CV death, MI and stroke compared with clopidogrel
  - Result is consistent with the overall results in the PLATO trial
  - Effect appears to be more pronounced in patients with CKD

- Composite endpoint of CV death, MI and stroke was lower in patients with ACS and CKD treated with ticagrelor compared with clopidogrel

- No difference in the risk of bleeding was observed in patients with renal dysfunction treated with ticagrelor or clopidogrel



- No dose adjustment is necessary for patients with renal impairment
  - No information is available for patients with end-stage renal failure, therefore ticagrelor is not recommended for these patients

- Ticagrelor is associated with a mild increase in serum creatinine, but remains efficacious in those with non dialysis-dependent CKD and is therefore recommended in this population

SWEDEHEART REGISTRY - PRACTICAL

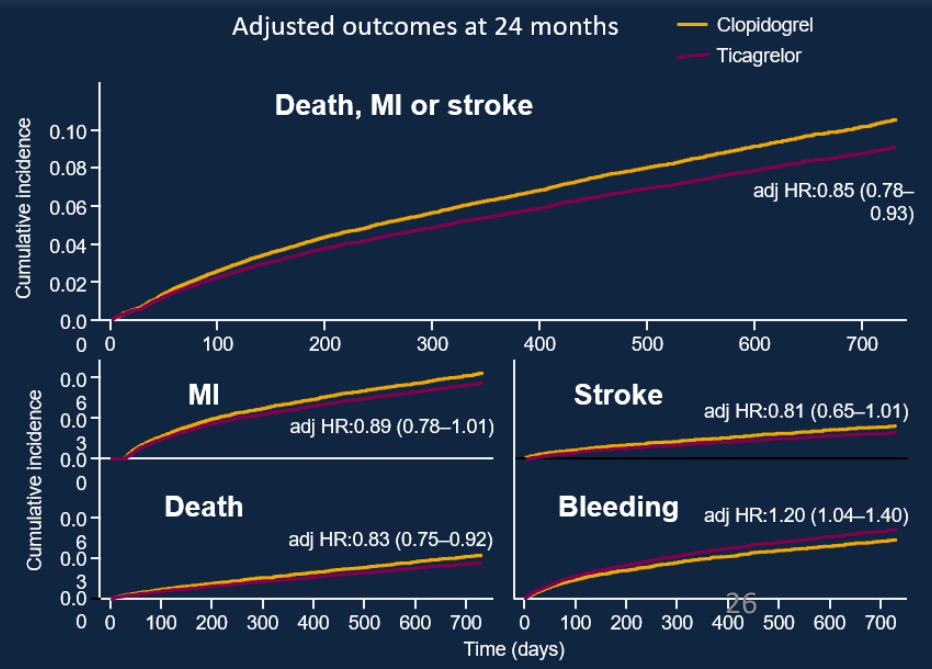
Benefits of ticagrelor 90 mg in PRACTICAL versus clopidogrel showed consistency with a PLATO secondary endpoint in a real-world setting at 12 months*

- PRACTICAL was derived from the world-renowned SWEDEHEART registry
- PRACTICAL evaluated treatment outcomes in a large population of real-world ACS patients treated with ticagrelor or clopidogrel
- Total of 45,073 consecutive patients who survived an acute MI‡ were prospectively enrolled between 2010 and 2013
- Primary outcome: Composite of death, readmission for MI or stroke within two years*
- Bleeding outcomes: Readmission with bleeding; PCI-related in-hospital bleeding†

Sahlén A et al. Article and supplementary online content. *Eur Heart J*. 2016;37:3335-3342; 2. Wallentin L et al. *N Engl J Med*. 2009;361:1045-1057

SWEDEHEART REGISTRY - PRACTICAL

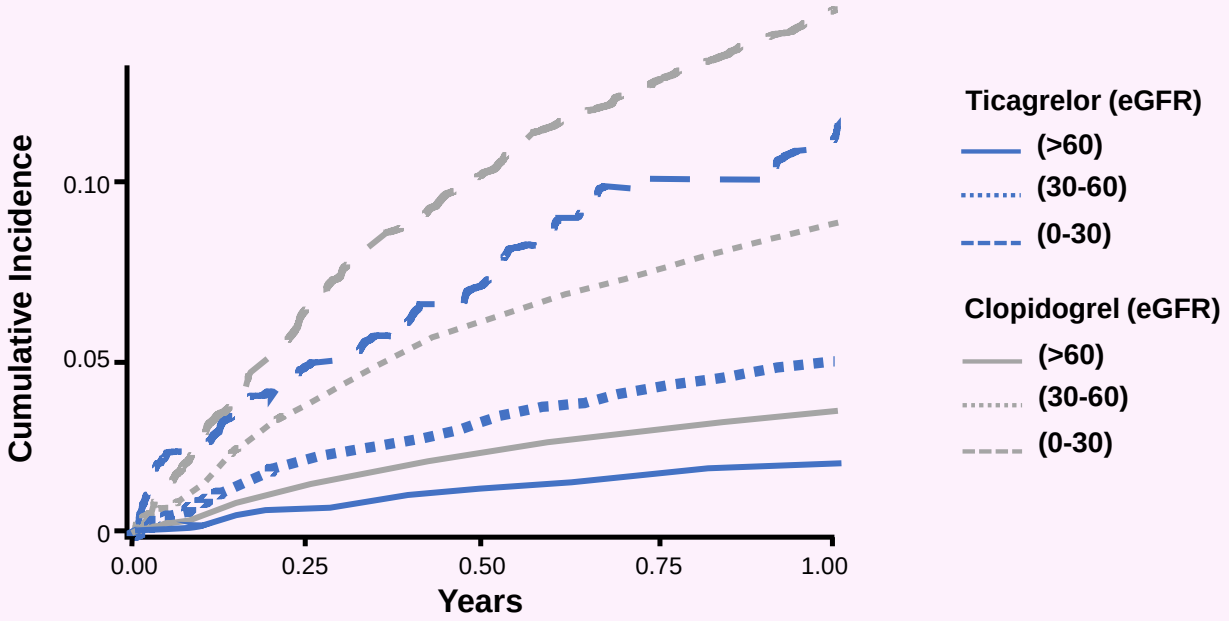
- Ticagrelor was associated with a lower risk of death, MI or stroke, as well as death alone
- The efficacy benefit with ticagrelor occurred early and continued to accrue over the planned treatment period
- Ticagrelor was associated with an increased risk of bleeding



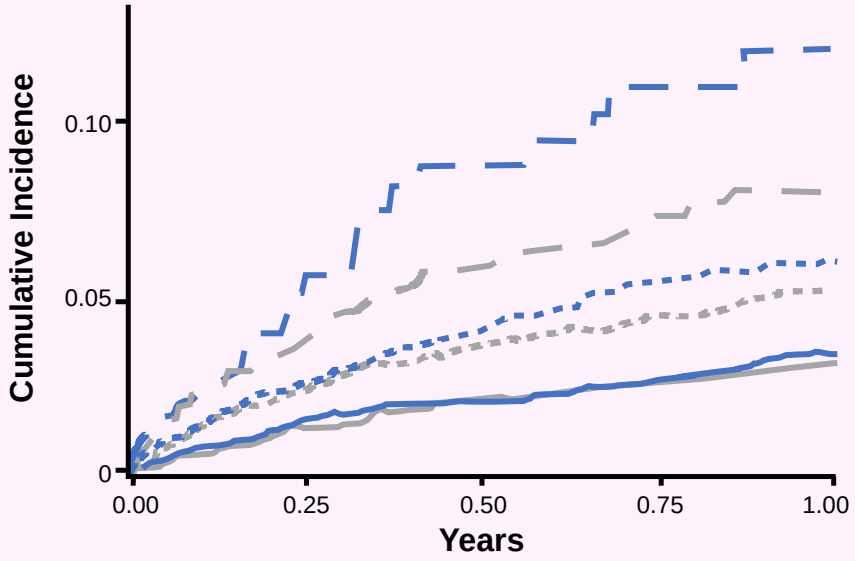
SWEDEHEART Renal Function Substudy: Ticagrelor vs Clopidogrel by Renal Function in the Real World

- Large RWE, observational study from the SWEDEHEART registry (January 2010 - December 2013), 45,206 patients with NSTEMI or STEMI discharged with DAPT were stratified by eGFR levels

Primary Endpoint: Composite of Death, Stroke, or MI at 1 Year



Secondary Endpoint: Bleeding



Treatment with ticagrelor as compared with clopidogrel was consistently associated with a lower risk of the composite of death, MI, or stroke without a significant interaction for subgroups based on eGFR (*P*-interaction: 0.55)

- Ticagrelor as compared to clopidogrel was associated with a higher risk of readmission with bleeding across the eGFR strata
  - Bleeding: eGFR >60, HR 1.10 (95% CI: 0.90-1.35); eGFR 30-60, HR 1.13 (95% CI: 0.84-1.51); eGFR <30, HR 1.79 (95% CI: 1.00-3.21)
  - Note that bleeding was higher in patients with eGFR <30; however, the *P* for interaction=0.30 for subgroups based on eGFR

CI = confidence interval; DAPT = dual antiplatelet therapy; eGFR = estimated glomerular filtration rate; HR = hazard ratio; MI = myocardial infarction; NSTEMI = non-ST elevation myocardial infarction; RWE = real-world evidence; STEMI = ST elevation myocardial infarction; SWEDEHEART=Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies.
Edfors R et al. *Heart*. 2018;104(19):1575-1582.

ACUTE CORONARY SYNDROME RCTS

Trial Acronym	PLATO (14)	PHILO (17)	TICAKOREA (18)	TREAT (19)	POPular AGE (21)
Total patients	18624	801	800	3799	1002
Study design	Double-blind	Double-blind	Open-label	Open-label	Open-label
Location	Multinational	Japan, Taiwan, South Korea	South Korea	Multinational	Netherlands
Indication	ACS with or without ST elevation	ACS with or without ST elevation, PCI	ACS with or without ST elevation, PCI	STEMI, fibrinolysis	ACS without ST elevation, age >70 y
Experimental group	Ticagrelor/aspirin	Ticagrelor/aspirin	Ticagrelor/aspirin	Ticagrelor/aspirin	Clopidogrel/aspirin
Comparison group	Clopidogrel/aspirin	Clopidogrel/aspirin	Clopidogrel/aspirin	Clopidogrel/aspirin	Ticagrelor/aspirin (5% prasugrel/aspirin)
Duration of follow-up	12 mo	12 mo	12 mo	30 d	12 mo
Primary end point	Cardiovascular death, MI, stroke: 9.8% vs 11.7%; HR, 0.84 [95% CI, 0.77–0.92; *P*<0.001]	Co-primary ischemia and bleeding end points	PLATO major or minor bleeding: 11.7% vs 5.3%; HR, 2.26 [95% CI, 1.34–3.79; *P*=0.002]	TIMI major bleeding: 0.73% vs 0.69%; absolute difference 0.04%; 95% CI 0.49–0.58; *P*<0.001 for noninferiority	PLATO major or minor bleeding: 18% vs 24%; HR, 0.71 [95% CI 0.54–0.94; *P*=0.02] Net clinical benefit of all-cause death, MI, stroke, PLATO major and minor bleeding: 28% vs 32%; HR, 0.82 [95% CI, 0.66–1.03; *P*=0.11]
Ischemic end point	Cardiovascular death: 4.0% vs 5.1%; HR, 0.79 [95% CI, 0.69–0.91; *P*=0.001] MI: 5.8% vs 6.9%; HR, 0.84 [95% CI 0.75–0.95; *P*=0.005] Stroke: 1.5% vs 1.3%; HR, 1.17 [95% CI, 0.91–1.52; *P*=0.22]	Cardiovascular death, MI, or stroke: 9.0% vs 6.3%; HR, 1.47 [95% CI, 0.88–2.44]	Cardiovascular death, MI, or stroke: 9.2% vs 5.8%; HR, 1.62 [95% CI, 0.96–2.74; *P*=0.07]	Cardiovascular death, MI, or stroke: 4.0% vs 4.3%; HR, 0.91 [95% CI, 0.67–1.25; *P*=0.57]	Cardiovascular death, MI, stroke: 11% vs 12%; HR, 0.92 [95% CI, 0.64–1.34; *P*=0.71]

Non inferior to Clopidogrel

Clopidogrel-significantly lower mj/minor bleeding with similar efficacy

ACUTE CORONARY SYNDROME RCTS

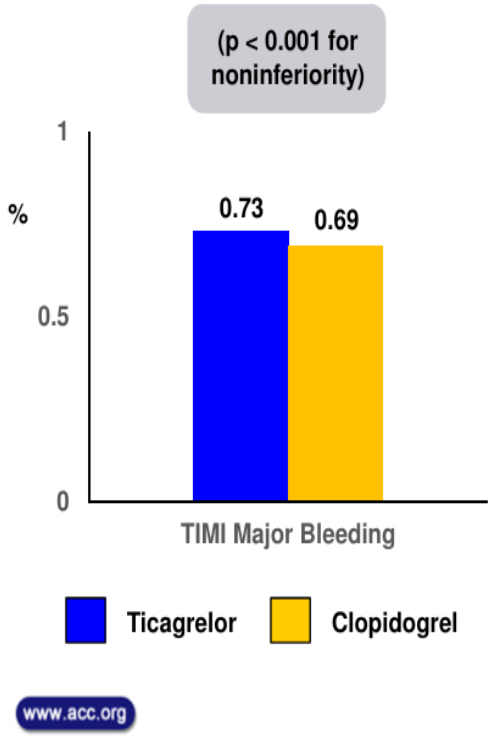
Trial Acronym	PLATO (14)	PHILO (17)	TICAKOREA (18)	TREAT (19)	POPular AGE (21)
Total patients	18624	801	800	3799	1002
Study design	Double-blind	Double-blind	Open-label	Open-label	Open-label
Ischemic end point	Cardiovascular death: 4.0% vs 5.1%; HR, 0.79 [95% CI, 0.69–0.91; *P*=0.001] MI: 5.8% vs 6.9%; HR, 0.84 [95% CI 0.75–0.95; *P*=0.005] Stroke: 1.5% vs 1.3%; HR, 1.17 [95% CI, 0.91–1.52; *P*=0.22]	Cardiovascular death, MI, or stroke: 9.0% vs 6.3%; HR, 1.47 [95% CI, 0.88–2.44]	Cardiovascular death, MI, or stroke: 9.2% vs 5.8%; HR, 1.62 [95% CI, 0.96–2.74; *P*=0.07]	Cardiovascular death, MI, or stroke: 4.0% vs 4.3%; HR, 0.91 [95% CI, 0.67–1.25; *P*=0.57]	Cardiovascular death, MI, stroke: 11% vs 12%; HR, 0.92 [95% CI, 0.64–1.34; *P*=0.71]
Bleeding end point	PLATO major bleeding: 11.6% vs 11.2%; HR, 1.04 [95% CI, 0.95–1.13; *P*=0.43] Non-CABG PLATO major bleeding: 4.5% vs 3.8%; HR 1.19; 95% CI 1.02–1.38; *P*=0.03	PLATO major bleeding: 10.3% vs 6.8%; HR, 1.54 [95% CI, 0.94–2.53]	PLATO major or minor bleeding: 11.7% vs 5.3%; HR 2.26; 95% CI 1.34–3.79; *P*=0.002]	TIMI major bleeding: 0.73% vs 0.69%; absolute difference 0.04%; 95% CI, 0.49–0.58; *P*<0.001 for noninferiority	PLATO major or minor bleeding: 18% vs 24%; HR 0.71 [95% CI, 0.54–0.94; *P*=0.02]

Both PLATO Mj Bleed and composite of CV death, MI, stroke higher with Tica but trial was underpowered to show statistically differences

PLATO Mj Bleed significantly higher and MACE insignificantly higher with Tica

TREAT

Trial design: Patients who received fibrinolytic therapy for STEMI were randomized to delayed ticagrelor (n = 1,913) versus clopidogrel (n = 1,886). Patients were randomized a median of 11 hours after fibrinolysis and 90% had been pretreated with clopidogrel.



www.acc.org

Results

- TIMI major bleeding: 0.73% of the ticagrelor group vs. 0.69% of the clopidogrel group (p < 0.001 for noninferiority)
- Fatal bleeding: 0.16% with ticagrelor vs. 0.11% with clopidogrel (p = 0.67)
- Intracranial bleeding: 0.42% with ticagrelor vs. 0.37% with clopidogrel (p = 0.82)
- Major adverse cardiovascular events: 4.0% with ticagrelor vs. 4.3% with clopidogrel (p = 0.57)

Conclusions

- Among patients <75 years of age who were treated with fibrinolysis for STEMI, delayed administration of ticagrelor was noninferior to clopidogrel
- There was no excess of major bleeding, fatal bleeding, or intracranial bleeding with ticagrelor vs. clopidogrel

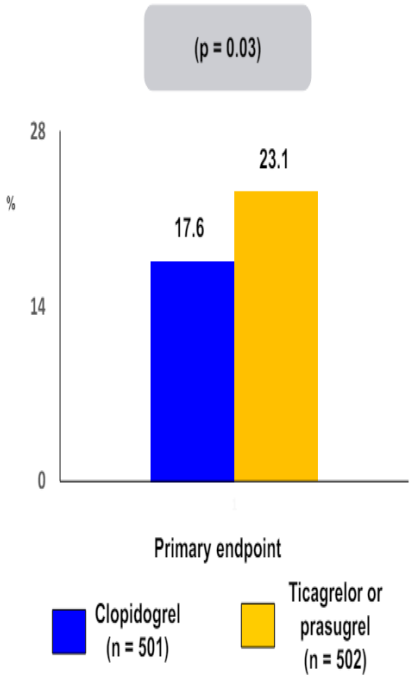
TREAT Study Group. JAMA Cardiol 2018;Mar 11:[Epub]

POPular AGE

#ESCCongress

AMERICAN COLLEGE of CARDIOLOGY

Trial Description: Patients ≥70 years of age with a non-ST-segment elevation acute coronary syndrome were randomized to clopidogrel vs. ticagrelor or prasugrel for 12 months.



RESULTS

- Co-primary safety endpoint: PLATO major and minor bleeding occurred in 17.6% of the clopidogrel group compared with 23.1% of ticagrelor/prasugrel group (p = 0.03)
- Co-primary net clinical benefit endpoint: death, MI, stroke, or PLATO major and minor bleeding occurred in 27.3% of the clopidogrel group compared with 30.7% of ticagrelor/prasugrel group (p for noninferiority = 0.06)

CONCLUSIONS

- Among elderly patients (≥70 years of age) being treated for a non-ST-segment elevation acute coronary syndrome, long-term treatment with clopidogrel was associated with less PLATO major/minor bleeding, less fatal bleeding vs. a more potent $P2Y_{12}$ inhibitor (i.e., ticagrelor or prasugrel)

Presented by Dr. Marieke Gimbel at ESC Congress 2019

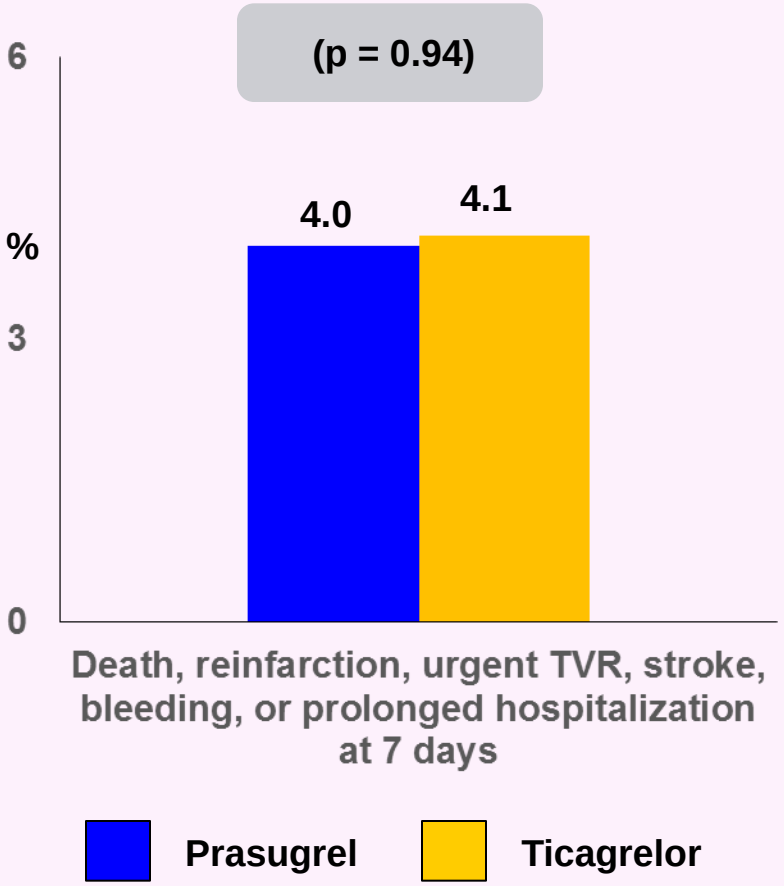
Clopidogrel-significantly lower mj/minor bleeding with similar efficacy

Acute Coronary Syndromes RCTs

Trial Acronym	PRAGUE-18 (29)	ISAR-REACT 5 (30)	ATLANTIC (33)	DUBIUS (34)
Total patients	1230	4018	1862	1449
Study design	Open-label	Open-label	Double-blind	Open-label
Indication	STEMI, primary PCI	ACS with or without ST elevation, PCI	STEMI, primary PCI	ACS without ST elevation, PCI
Experimental group	Prasugrel	Ticagrelor	Prehospital ticagrelor	No ticagrelor treatment
Comparison group	Ticagrelor	Prasugrel	In-hospital ticagrelor	Ticagrelor pretreatment
Duration of follow-up	7 d	1 y	30 d	30 d
Primary end point	Composite of all-cause death, reinfarction, urgent target vessel revascularization, stroke, bleeding requiring transfusion or prolonged hospitalization: 4.0% vs 4.1%; OR, 0.98 [95% CI, 0.55–1.73; *P*=0.94]	Composite of all-cause death, MI, stroke: 9.3% vs 6.9%; HR, 1.36 [95% CI, 1.09–1.70; *P*=0.006]	Absence of ST-segment elevation resolution ≥70% before PCI: 86.8% vs 87.6%; OR, 0.93 [95% CI, 0.69–1.25; *P*=0.63] Absence of TIMI flow grade 3 in infarct-related artery at initial angiography: 82.6% vs 83.1%; OR, 0.97 [95% CI, 0.75–1.25; *P*=0.82]	Composite of cardiovascular death, MI, stroke, BARC type 3–5 bleeding: 2.9% vs 3.3%; ARR −0.46; 95% CI, 2.87–1.89; *P*=0.50
Ischemic end point	Composite of cardiovascular death, MI, or stroke at 30 d: 2.7% vs 2.5%; OR 1.06, 95% CI 0.53–2.15; *P*=0.86	Death: 4.5% vs 3.7% MI: 4.8% vs 3.0% Stroke: 1.1% vs 1.0%	Composite of death, MI, stroke, urgent revascularization, or definite stent thrombosis at 30 d: 4.5% vs 4.4%; OR, 1.03 [95% CI, 0.66–1.60; *P*=0.91]	Cardiovascular death: 0.4% vs 0.2% MI: 0.9% vs 0.9% Stroke: 0.2 vs 0.1%
Bleeding end point	TIMI major bleeding at 30 d; 0.6% vs 0.7%; OR, 0.86 [95% CI, 0.17–4.27; *P*=0.85]	BARC type 3–5 bleeding: 5.4% vs 4.8%; HR, 1.12 [95% CI, 0.83–1.51; *P*=0.46]	PLATO major bleeding within 48 h: 1.8% vs 1.6%; *P*=0.76	BARC type 3–5 bleeding: 1.6% vs 1.9%; ARR −0.3; 95% CI, 2.24–1.57

PRAGUE-18

Trial design: Patients with STEMI undergoing primary PCI were randomized to prasugrel (n = 634) versus ticagrelor (n = 596).



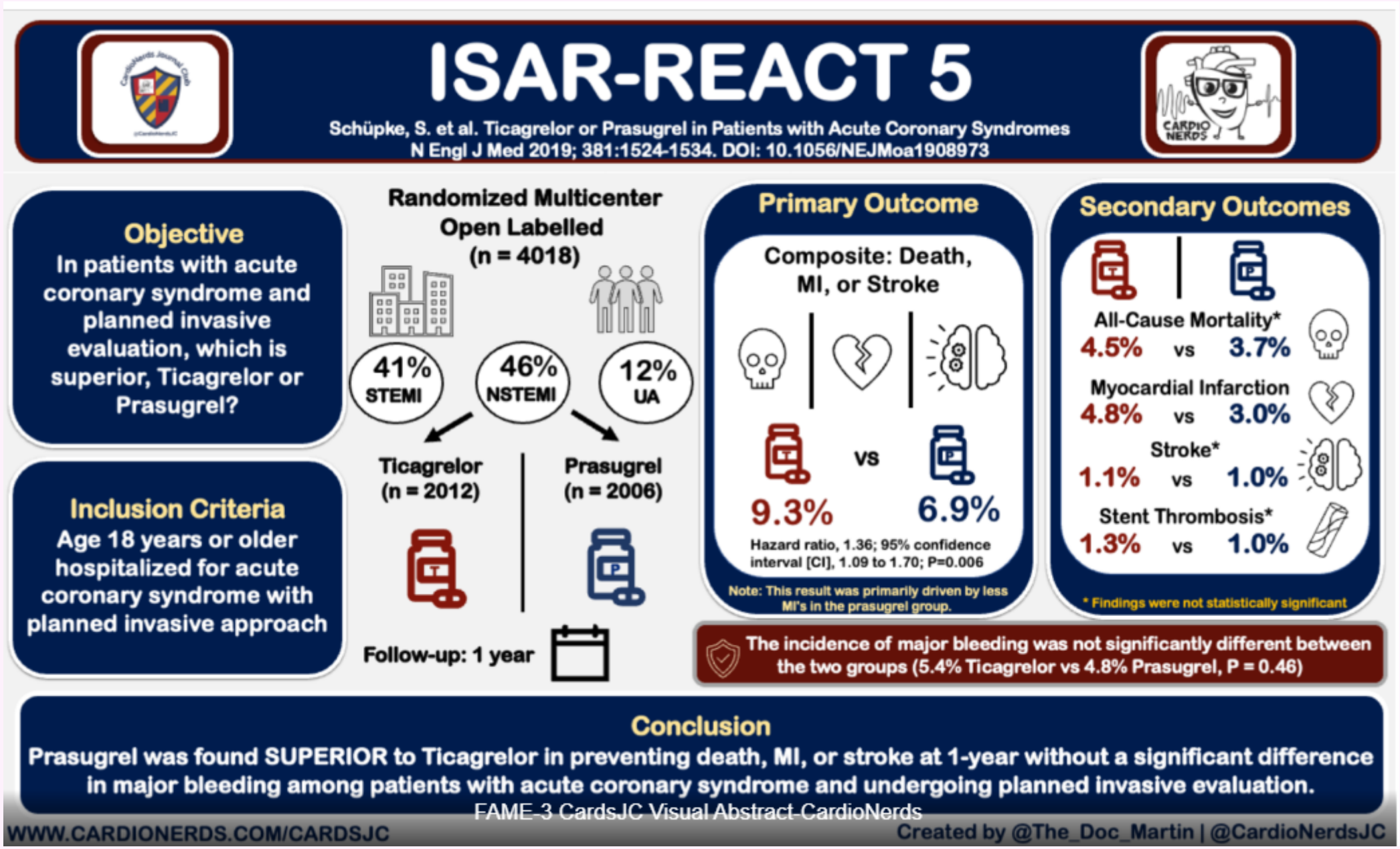
Results

- Death, reinfarction, urgent TVR, stroke, bleeding, or prolonged hospitalization at 7 days: 4.0% of the prasugrel group versus 4.1% of the ticagrelor group (p = 0.94)
- CV death, nonfatal MI, or stroke at 30 days: 2.7% versus 2.5% (p = 0.86), respectively, for prasugrel versus ticagrelor
- TIMI major bleeding at 30 days: 0.6% versus 0.7% (p = 0.85), respectively, for prasugrel versus ticagrelor

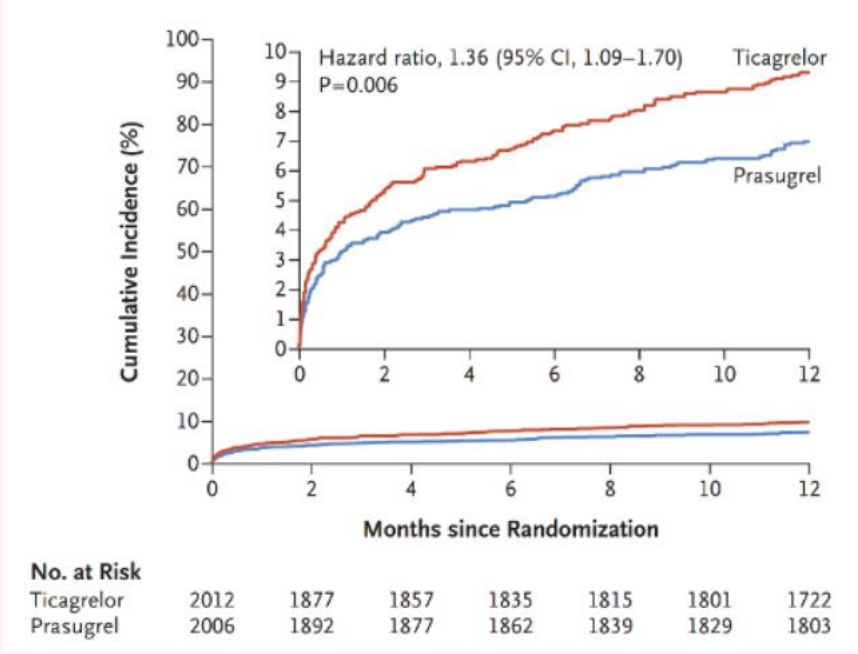
Conclusions

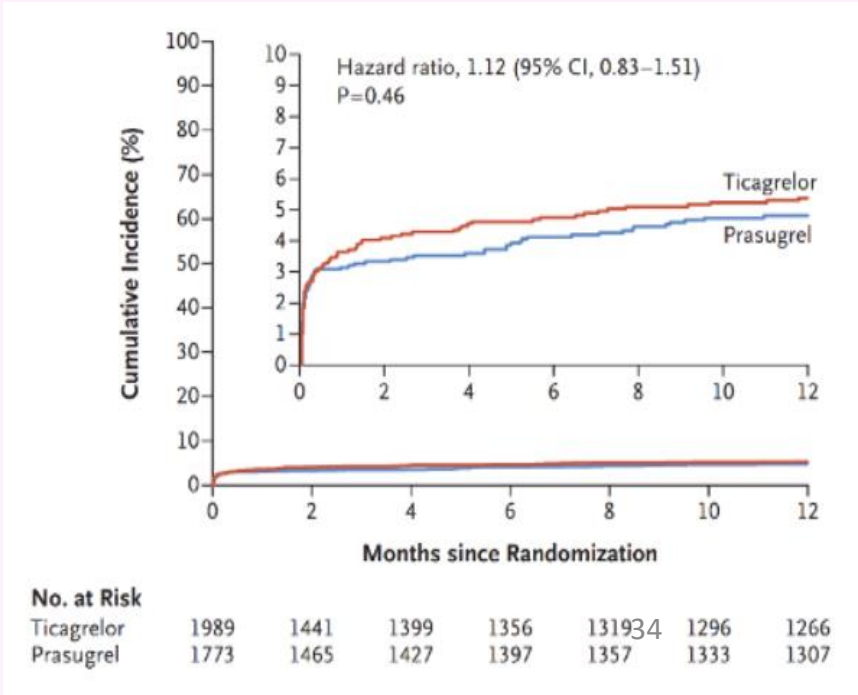
- Among patients with STEMI undergoing primary PCI, similar efficacy and bleeding was observed for either prasugrel or ticagrelor. Among such patients, the use of either agent is acceptable.

Motovska Z, et al. Circulation 2016;Aug 30:[Epub]


ISAR-REACT 5
Schüpke, S. et al. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes
N Engl J Med 2019; 381:1524-1534. DOI: 10.1056/NEJMoa1908973
Objective
In patients with acute coronary syndrome and planned invasive evaluation, which is superior, Ticagrelor or Prasugrel?
Inclusion Criteria
Age 18 years or older hospitalized for acute coronary syndrome with planned invasive approach
Randomized Multicenter
Open Labelled
(n = 4018)
41% STEMI
46% NSTEMI
12% UA
Ticagrelor (n = 2012)
Prasugrel (n = 2006)
Follow-up: 1 year
Primary Outcome
Composite: Death, MI, or Stroke
9.3%
vs
6.9%
Hazard ratio, 1.36; 95% confidence interval [CI], 1.09 to 1.70; P=0.006
Note: This result was primarily driven by less MI's in the prasugrel group.
Secondary Outcomes
All-Cause Mortality*
4.5% vs 3.7%
Myocardial Infarction
4.8% vs 3.0%
Stroke*
1.1% vs 1.0%
Stent Thrombosis*
1.3% vs 1.0%
* Findings were not statistically significant
The incidence of major bleeding was not significantly different between the two groups (5.4% Ticagrelor vs 4.8% Prasugrel, P = 0.46)
Conclusion
Prasugrel was found SUPERIOR to Ticagrelor in preventing death, MI, or stroke at 1-year without a significant difference in major bleeding among patients with acute coronary syndrome and undergoing planned invasive evaluation.
FAME-3 CardsJC Visual Abstract-CardioNerds
WWW.CARDIONERDS.COM/CARDSJC
Created by @The_Doc_Martin | @CardioNerdsJC

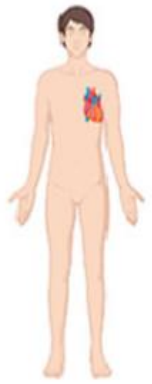
End Point	Ticagrelor (n = 2012)	Prasugrel (n = 2006)	[Hazard Ratio]	P value
Primary: Death from any cause, myocardial infarction or stroke at 1 year – no. (%)	184 (9.1)	137 (6.8)	1.36	0.006
Secondary: Death from any cause at 1 year– no. (%)	90 (4.5)	73 (3.7)	1.23	
Secondary: Myocardial infarction at 1 year– no. (%)	96 (4.8)	60 (3.0)	1.63	
Secondary: Stroke at 1 year– no. (%)	22 (1.1)	19 (1.0)	1.17	
Secondary: Incidence of probably or definite stent thrombosis at 1 year– no. (%)	26 (1.3)	20 (1.0)	1.30	
Secondary: Safety end point (incidence of bleeding at 1 year, type 3,4 ot 5 on BARC scale) – no. (%)	95 (5.4)	80 (4.8)	1.12	0.46





Meta-Analysis Comparing Prasugrel and Ticagrelor

Patients with Acute Coronary Syndrome (STEMI, NSTEMI, Unstable Angina requiring PCI)



Aspirin + Prasugrel

VS.

Aspirin + Ticagrelor

Inclusion criteria

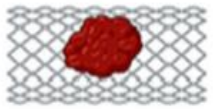
- Age>18
- Patient undergoing PCI
- Studies must include at-least one clinical adverse outcome as their endpoint

No significant difference in outcomes among patients receiving DAPT with Prasugrel compared to Ticagrelor

MI

Non-CV Death

Stroke



Stent Thrombosis

CV Death

Bleeding

All cause Mortality

Low-Moderate Risk Stroke or High-Risk TIA RCTs

Trial Acronym	SOCRATES (35)	THALES (36)
Total patients	13 199	11 016
Study design	Double-blind	Double-blind Placebo controlled
Enrollment period	January 2014–October 2015	January 2018–October 2019
Publication year	2016	2020
Location	Multinational	Multinational
Indication	Mild/Moderate ischemic stroke or high-risk TIA	Mild/Moderate ischemic stroke or high-risk TIA
Experimental group	Ticagrelor	Ticagrelor/aspirin
Comparison group	Aspirin	Aspirin
Duration of follow-up	90 d	30 d
Primary end point	MI, stroke, all-cause death: 6.7% vs 7.5%; HR, 0.89 [95% CI, 0.78–1.01; *P*=0.07]	Stroke or all-cause death: 5.5% vs 6.6%; HR, 0.83 [95% CI, 0.71–0.96; *P*=0.02]
Ischemic end point	Ischemic stroke: 5.8% vs 6.7%; HR, 0.87 [95% CI, 0.76–1.00; *P*=NS]	Ischemic stroke: 5.0% vs 6.3%; HR 0.79 [95% CI, 0.68–0.93; *P*=0.004]
Bleeding end point	PLATO major bleeding: 0.5% vs 0.6%; HR, 0.83 [95% CI, 0.52–1.34; *P*=0.45] Intracranial Hemorrhage: 0.2% vs 0.3%; HR, 0.68 [95% CI, 0.33–1.41; *P*=0.30]	GUSTO major bleeding: 0.5% vs 0.1%; HR, 3.99 [95% CI, 1.74–9.14; *P*=0.001] Intracranial hemorrhage: 0.4% vs 0.1%; HR, 3.33 [95% CI, 1.34–8.28; *P*=0.01]

Atherosclerotic Vascular Disease RCTs

Trial Acronym	EUCLID (41)	ALPHEUS (42)	DACAB (43)	TiCAB (44)	POPular CABG (45)
Total patients	13855	1910	500	1859	499
Study design	Double-blind	Open-label	Open-label	Double-blind Placebo controlled	Double blind Placebo controlled
Enrollment period	December 2012–March 2014	January 2017–May 2020	July 2014–November 2015	April 2013–April 2017	March 2015–January 2019
Publication year	2017	2020	2018	2019	2020
Location	Multinational	France, Czech Republic	China	Germany, Austria, Switzerland	Netherlands
Indication	Symptomatic PAD	Elective high-risk PCI	Elective CABG	Elective CABG	Elective CABG
Experimental group	Ticagrelor	Ticagrelor	Ticagrelor/aspirin or ticagrelor	Ticagrelor	Ticagrelor/aspirin
Comparison group	Clopidogrel	Clopidogrel	Aspirin	Aspirin	Aspirin
Duration of follow-up	30 mo	48 h	1 y	1 y	1 y
Primary end point	Composite of cardiovascular death, MI, ischemic stroke: 10.8% vs 10.6%; HR, 1.02 [95% CI, 0.92–1.13; *P*=0.65]	Composite of Type 4 MI or major myocardial injury: 35% vs 36%; OR, 0.97 [95% CI, 0.80–1.17; *P*=0.75]	SVG patency: DAPT 88.7%, Ticagrelor 82.8%, aspirin 76.5% DAPT vs aspirin: difference 12.2%, [95% CI 5.2%–19.2%; *P*<0.001] Ticagrelor vs aspirin: Difference 6.3%, [95% CI, 1.1% vs 13.7%, *P*=0.10]	Composite of cardiovascular death, MI, repeat revascularization, stroke: 9.7% vs 8.2%; HR, 1.19 [95% CI, 0.87–1.62; *P*=0.28]	SVG occlusion: 9.6% vs 10.1%; OR, 0.87 [95% CI, 0.49–1.55; *P*=0.64]

Atherosclerotic Vascular Disease RCTs

	EUCLID	ALPHEUS	DACAB	TiCAB	POPular CABG
Primary end point	Composite of cardiovascular death, MI, ischemic stroke: 10.8% vs 10.6%; HR, 1.02 [95% CI, 0.92–1.13; *P*=0.65]	Composite of Type 4 MI or major myocardial injury: 35% vs 36%; OR, 0.97 [95% CI, 0.80–1.17; *P*=0.75]	SVG patency: DAPT 88.7%, Ticagrelor 82.8%, aspirin 76.5% DAPT vs aspirin: difference 12.2%, [95% CI 5.2%–19.2%; *P*<0.001] Ticagrelor vs aspirin: Difference 6.3%, [95% CI, 1.1% vs 13.7%, *P*=0.10]	Composite of cardiovascular death, MI, repeat revascularization, stroke: 9.7% vs 8.2%; HR, 1.19 [95% CI, 0.87–1.62; *P*=0.28]	SVG occlusion: 9.6% vs 10.1%; OR, 0.87 [95% CI, 0.49–1.55; *P*=0.64]
Ischemic end point	Acute limb ischemia: 1.7% vs 1.7%: HR, 1.03 [95% CI, 0.79–1.33; *P*=0.85]	MI: 9% vs 8%; OR, 1.03 [95% CI, 0.63–1.68; *P*=0.90]	Composite of death, MI, stroke: DAPT 1.8%, Ticagrelor 2.4%, aspirin 5.4% *P*=NS	Composite of cardiovascular death, MI, stroke: 6.3% vs 6.5%; HR, 0.99, [95% CI, 0.69–1.42; *P*=0.94]	SVG occlusion, SVG revascularization, MI in SVG territory, or sudden death: 12.9% vs 13.0%; HR, 1.04 [95% CI, 0.63–1.69; *P*=0.89]
Bleeding end point	TIMI major bleeding: 1.6% vs 1.6%; HR, 1.10 [95% CI, 0.84–1.43; *P*=0.49]	BARC type 3 or 5 major bleeding: 1 vs 0; *P*=0.5	TIMI major bleeding: DAPT 1.8%, Ticagrelor 1.2%, aspirin 0% *P*=NS	BARC type 3–5 major bleeding: 3.7% vs 3.2%; HR, 1.17 [95% CI, 0.71–1.92; *P*=0.53]	BARC type 3–5 major bleeding: 2.8% vs 3.2%; HR, 0.87 [95% CI, 0.32–2.40; *P*=0.79]

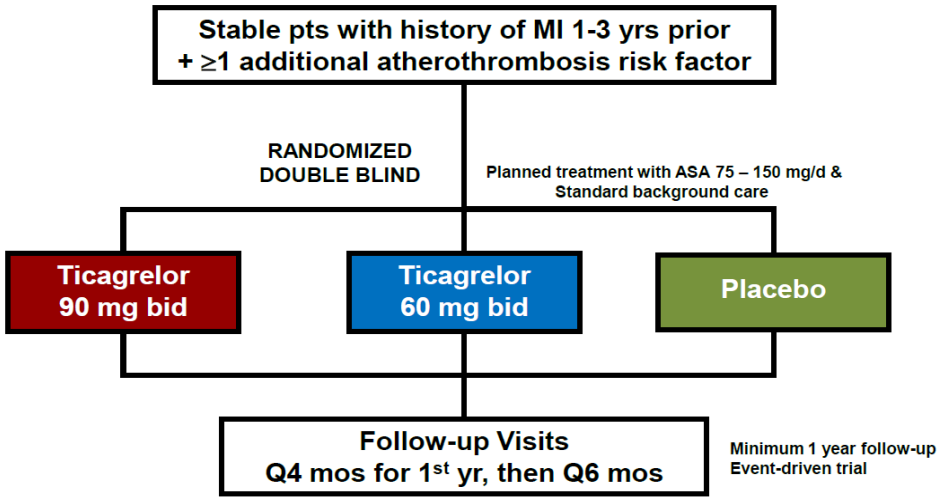
Secondary Prevention RCTs

Trial Acronym	PEGASUS-TIMI 54 (48)	THEMIS (49)
Total patients	21 162	19220
Study design	Double-blind Placebo controlled	Double-blind Placebo controlled
Enrollment period	Oct 2010-May 2013	Feb 2014-May 2016
Publication year	2015	2019
Location	Multinational	Multinational
Indication	MI 1 to 3y earlier	CAD, diabetes, no history of MI or stroke
Experimental group	Ticagrelor 90mg/aspirin Ticagrelor 60mg/aspirin	Ticagrelor/aspirin
Comparison group	Aspirin	Aspirin
Duration of follow-up	33mo	39.9mo
Primary end point	Cardiovascular death, MI, stroke: 90mg: 7.85% vs 9.04%; HR, 0.85 [95% CI, 0.75–0.96; *P*=0.008] 60mg: 7.77% vs 9.04%; HR, 0.84% [95% CI, 0.74–0.95; *P*=0.004]	Cardiovascular death, MI, stroke: 7.7% vs 8.5%; HR, 0.90 [95% CI, 0.81–0.99; *P*=0.04]
Ischemic end point	MI: 90mg: 4.40% vs 5.25%; HR 0.81, 95% CI 0.69–0.95; *P*=0.01 60mg: 4.53% vs 5.25%; HR, 0.84 [95% CI, 0.72–0.98; *P*=0.03]	MI: 2.8% vs 3.4; HR, 0.84 [95% CI, 0.71–0.98]
Bleeding end point	TIMI major bleeding: 90mg: 2.60% vs 1.06%; HR, 2.69 [95% CI, 1.96–3.70; *P*<0.001] 60mg: 2.30% vs 1.06%; HR, 2.32 [95% CI, 1.68–3.21; *P*<0.001]	TIMI major bleeding: 2.2% vs 1.0%; HR 2.32 [95% CI, 1.82–2.94] *P*<0.001 Intracranial hemorrhage: 0.7% vs 0.5%; HR, 1.71 [95% CI, 1.18–2.48; *P*=0.005]

Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin

Marc S. Sabatine, MD, MPH
on behalf of the PEGASUS-TIMI 54
Executive & Steering Committees and Investigators

Trial Design

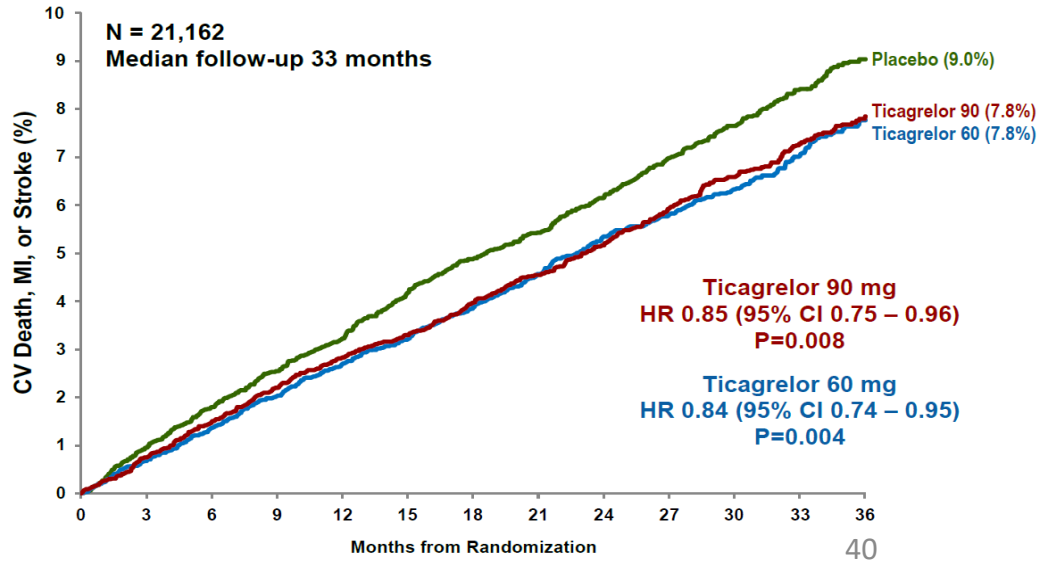


Endpoints

- **Efficacy: hierarchical testing**
  - Primary: cardiovascular (CV) death, MI, or stroke
  - Secondary: CV death; all-cause mortality
  - Prespecified exploratory: substituting coronary for CV death; other individual coronary and cerebrovascular ischemic outcomes; pooling ticagrelor doses
- **Safety**
  - Primary: TIMI Major Bleeding
  - Other: intracranial hemorrhage (ICH), fatal bleeding
  - AEs/SAEs
- **TIMI Clinical Events Committee (CEC)**
  - Adjudicated all efficacy endpoints & bleeding events
  - Members unaware of treatment assignments

Bonaca MP et al. *Am Heart J* 2014;167:437-44

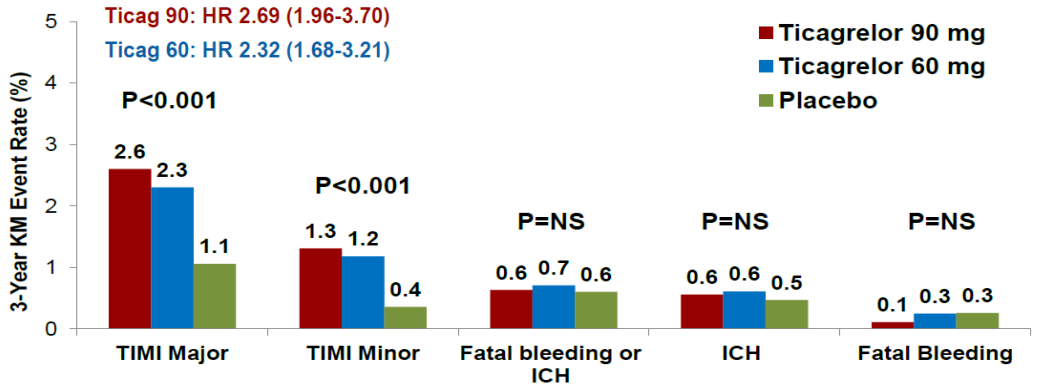
Primary Endpoint



Other Efficacy Outcomes

Outcome	Ticagrelor 90 mg bid (N=7050)	Ticagrelor 60 mg bid (N=7045)	Placebo (N=7067)	Ticagrelor 90 vs Placebo p-value	Ticagrelor 60 vs Placebo p-value
	3-yr KM rate (%)				
Coronary Death, MI, or Stroke	7.0	7.1	8.3	HR 0.82 P=0.002	HR 0.83 P=0.003
Coronary Death or MI	5.6	5.8	6.7	HR 0.81 P=0.004	HR 0.84 P=0.01
Coronary Death	1.5	1.7	2.1	HR 0.73 P=0.02	HR 0.80 P=0.09
Death from any cause	5.2	4.7	5.2	HR 1.00 P=0.99	HR 0.89 P=0.14

Bleeding



Summary

- Adding ticagrelor to low-dose aspirin in stable patients with a history of MI reduced the risk of CV death, MI or stroke
- The benefit of ticagrelor was consistent
  - For both fatal & non-fatal components of primary endpoint
  - Over the duration of treatment
  - Among major clinical subgroups
- Ticagrelor increased the risk of TIMI major bleeding, but not fatal bleeding or ICH
- The two doses of ticagrelor had similar overall efficacy, but bleeding and other side effects tended to be less frequent with 60 mg bid dose

An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

DAPT De-Escalation and Aspirin Withdrawal RCTs

Trial Acronym	TALOS-AMI (55)	GLOBAL LEADERS (51)	TWILIGHT (64)	TICO (65)
Total patients	2697	15 968	7119	3056
Study design	Open-label Non-inferiority	Open-label	Double-blind Placebo controlled	Open label
Enrollment period	Feb 2014-Dec 2018	Jul 2013-Nov 2015	Jul 2015-Dec 2017	Aug 2015-Oct 2018
Publication year	2021	2018	2019	2020
Location	South Korea	Multinational	Multinational	South Korea
Indications	MI with or without ST elevation, Ticagrelor/aspirin for 1 mo	CAD or ACS with or without ST elevation, PCI	PCI, high-risk for bleeding or ischemic event, ticagrelor/aspirin for 3 mo	ACS with or without ST elevation, PCI
Experimental group	Clopidogrel/aspirin	Ticagrelor/aspirin for 1 mo, followed by Ticagrelor for 23 mo	Ticagrelor	Ticagrelor/aspirin for 3 mo, ticagrelor for 9 mo
Comparison group	Ticagrelor/aspirin	CAD: Clopidogrel/aspirin for 12 mo, followed by aspirin for 12 mo ACS: ticagrelor/aspirin for 12 mo, followed by aspirin for 12 mo	Ticagrelor/aspirin	Ticagrelor/aspirin
Duration of follow-up	12 mo	24 mo	12 mo	12 mo
Primary end point	Cardiovascular death, MI, stroke, BARC type 2, 3, 5 bleeding: 4.6% vs 8.2%; HR, 0.55 [95% CI, 0.40–0.76; *P*=0.001]	All-cause death, Q-wave MI: 3.81% vs 4.37%; RR 0.87 [95% CI, 0.75–1.01; *P*=0.73]	BARC 2, 3, 5 type bleeding: 4.0% vs 7.1%; HR, 0.56 [95% CI, 0.45–0.68; *P*<0.001]	TIMI major bleeding, all-cause death, MI, stent thrombosis, stroke, target vessel revascularization; 3.9% vs 5.9%; HR 0.66 [95% CI, 0.48–0.92; *P*=0.01]

DAPT De-Escalation and Aspirin Withdrawal RCTs

	TALOS AMI	GLOBAL LEADERS	TWILIGHT	TICO
Primary end point	Cardiovascular death, MI, stroke, BARC type 2, 3, 5 bleeding: 4.6% vs 8.2%; HR, 0.55 [95% CI, 0.40–0.76; *P*=0.001]	All-cause death, Q-wave MI: 3.81% vs 4.37%; RR 0.87 [95% CI, 0.75–1.01; *P*=0.73]	BARC 2, 3, 5 type bleeding: 4.0% vs 7.1%; HR, 0.56 [95% CI, 0.45–0.68; *P*<0.001]	TIMI major bleeding, all-cause death, MI, stent thrombosis, stroke, target vessel revascularization; 3.9% vs 5.9%; HR 0.66 [95% CI, 0.48–0.92; *P*=0.01]
Ischemic end point	Cardiovascular death, MI, stroke: 2.1% vs 3.1%; HR, 0.69 [95% CI, 0.42–1.14; *P*=0.15]	MI: 3.11% vs 3.13%; RR, 1.00 [95% CI, 0.84–1.19; *P*=0.98] Definite stent thrombosis: 0.80% vs 0.80%; RR, 1.00 [95% CI, 0.71–1.42, *P*=0.98]	All-cause death, MI, stroke: 3.9% vs 3.9%; HR, 0.99 [95% CI, 0.78–1.25]	All-cause death, MI, stent thrombosis, stroke, target vessel revascularization: 2.3% vs 3.4%; HR, 0.69 [95% CI, 0.45–1.06; *P*=0.09]
Bleeding end point	BARC type 2,3,5 bleeding: 3.0% vs 5.6%; HR, 0.52 [95% CI, 0.35–0.77; *P*=0.0012]	BARC type 3 or 5 bleeding: 2.04% vs 2.12%, RR, 0.97 [95% CI, 0.78–1.20; *P*=0.77]	BARC 2, 3, 5 type bleeding: 4.0% vs 7.1%; HR, 0.56 [95% CI, 0.45–0.68; *P*<0.001]	TIMI major bleeding: 1.7% vs 3.0%; HR, 0.56 [95% CI, 0.34–0.91; *P*=0.02]

Ticagrelor With AspIrin or ALone In HiGH-Risk Patients After Coronary InTervention

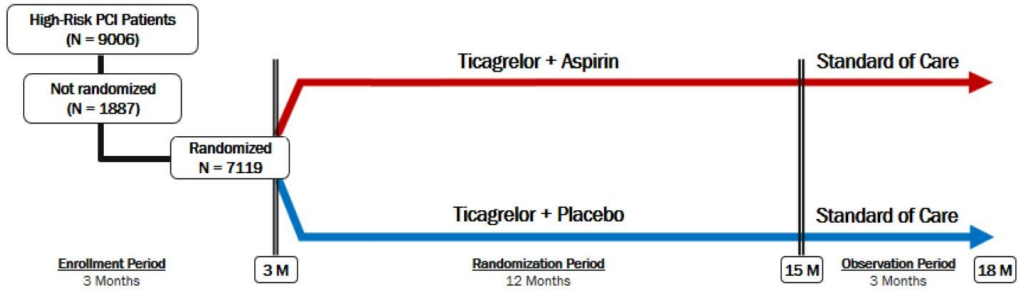
R. Mehran, U. Baber, Samin K. Sharma, D.J. Cohen, D.J. Angiolillo, C. Briguori, J.Y. Cha, T. Collier, G. Dangas, D. Dudek, V. Džavík, J. Escaned, R. Gil, P. Gurbel, C.W. Hamm, T. Henry, K. Huber, A. Kastrati, U. Kaul, R. Kornowski, M. Krucoff, V. Kunadian, S.O. Marx, S.R. Mehta, D. Moliterno, E.M. Ohman, K. Oldroyd, G. Sardella, S. Sartori, R. Shlofmitz, P.G. Steg, G. Weisz, B. Witzenbichler, Y. Han, S. Pocock, and C.M. Gibson.

Mount Sinai

ClinicalTrials.gov Number: NCT02270242

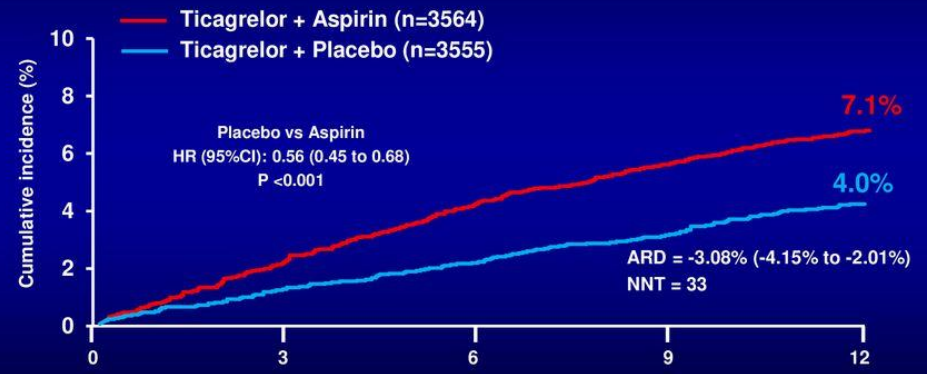
TWILIGHT
Study Design

- Randomized, double-blind, placebo controlled trial in 187 sites and 11 countries
- High-risk PCI patients treated with ticagrelor + aspirin for 3 months
- Event-free and adherent patients were randomized to aspirin vs placebo and continued ticagrelor for an additional 12 months



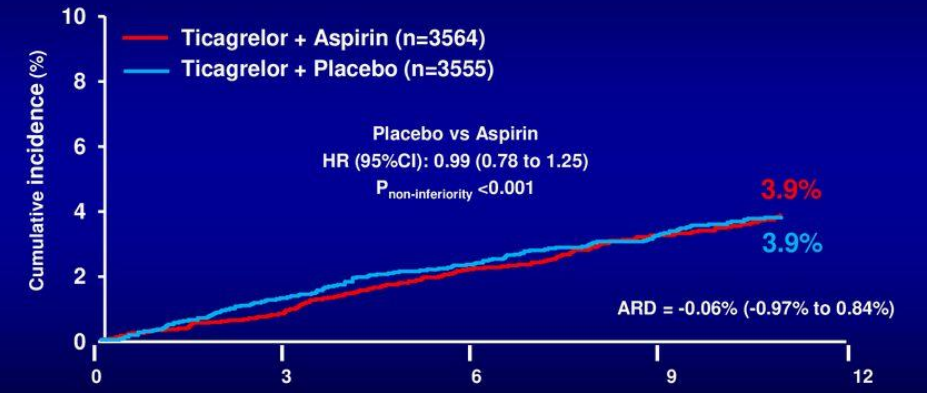
Mehran R, et al. *N Engl J Med*. 2019;381:2032-2042.

TWILIGHT Trial: Primary Endpoint (ITT Cohort)
BARC 2, 3 or 5 Bleeding



Mehran et al., N Engl J Med 2019 Sept 26 [Epub ahead of print]

TWILIGHT Trial: Key Standard Endpoint (PP Cohort)
Death, MI or Stroke



Mehran et al., N Engl J Med 2019 Sept 26 [Epub ahead of print

TICO-STEMI: A Randomized Trial of Ticagrelor Monotherapy vs. Ticagrelor With Aspirin in STEMI

Late-Breaking Clinical Trial at 2020 TCT Connect

Byeong-Keuk Kim, MD, PhD

On the behalf of the TICO trial investigators

TICO-STEMI study

- To assess the safety and feasibility of **ticagrelor monotherapy after 3 months of DAPT in STEMI patients** treated with ultrathin bioresorbable polymer sirolimus-eluting stents, using a prespecified subgroup analyses of the STEMI cohort of the TICO trial

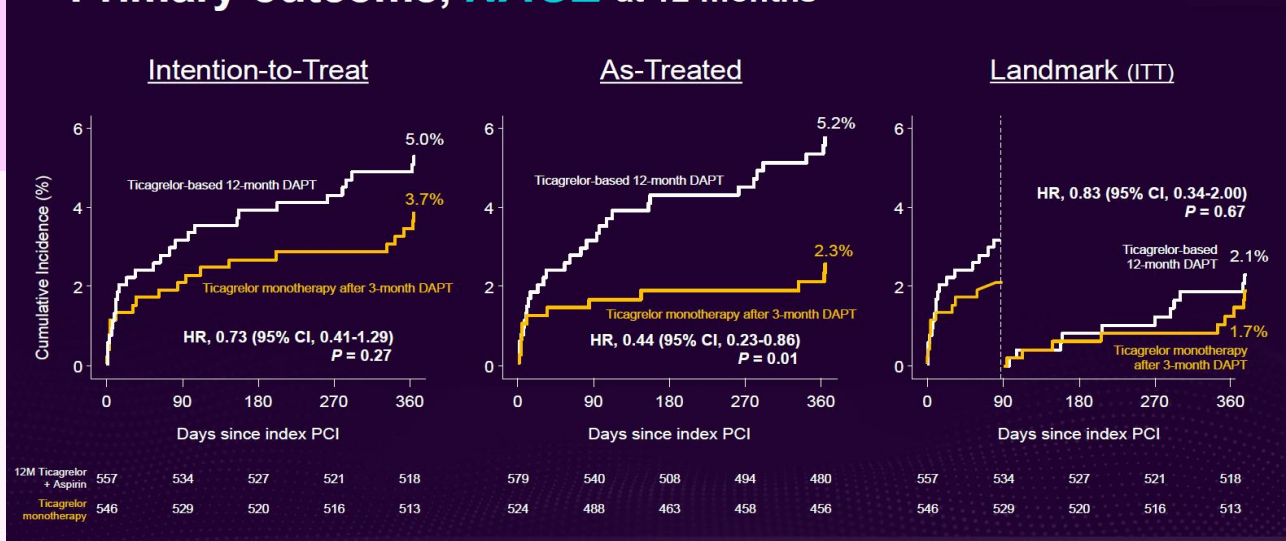
TICO trial …
- A prospective, randomized, multi-center trial conducted at 38 centers in South Korea
- All types of ACS (UA, 30.3%; NSTEMI, 33.6%; and STEMI, 36.1%) were enrolled.
- According to the presence of STEMI, stratified randomization was performed.

- **Primary outcome:**

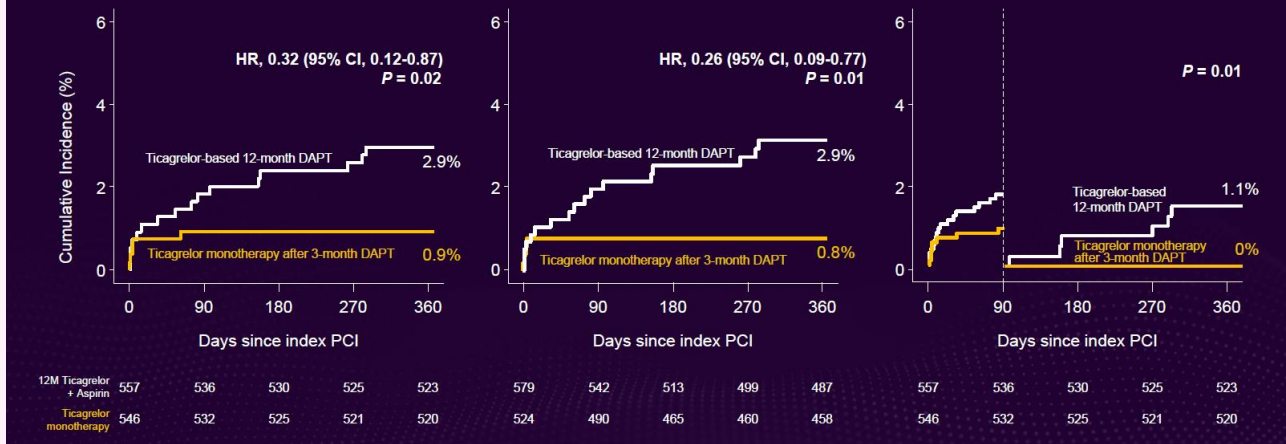
Net adverse clinical event (NACE) including bleeding & ischemic outcomes

- **Bleeding outcomes – TIMI major bleeding**
- **Ischemic outcomes – Major adverse cardiac & cerebrovascular event (MACCE); all-cause death, MI, stent thrombosis, stroke, or TVR**

Primary outcome, *NACE* at 12-months



Bleeding outcome; TIMI Major bleeding at 12 months



TICO Conclusions

Conclusions

This is the first report assessing the feasibility of the ticagrelor monotherapy after short-term DAPT for STEMI patients with DES.

Among patients with *STEMI treated with ultrathin bioresorbable polymer sirolimus-eluting stents*,

- ***Ticagrelor monotherapy after 3-month DAPT*, compared with ticagrelor-based 12-month DAPT, resulted in a reduced risk of major bleeding.**
- **As for MACCE, there were no significant differences between the two treatment groups, without significant interaction with clinical presentation in this study.**
- **However, care should be taken in applying these results to the overall STEMI population, especially those at high risk for ischemia.**

One-month Ticagrelor Monotherapy After PCI in Acute Coronary Syndromes:

Principal Results From the Double-blind, Placebo-controlled ULTIMATE-DAPT Trial

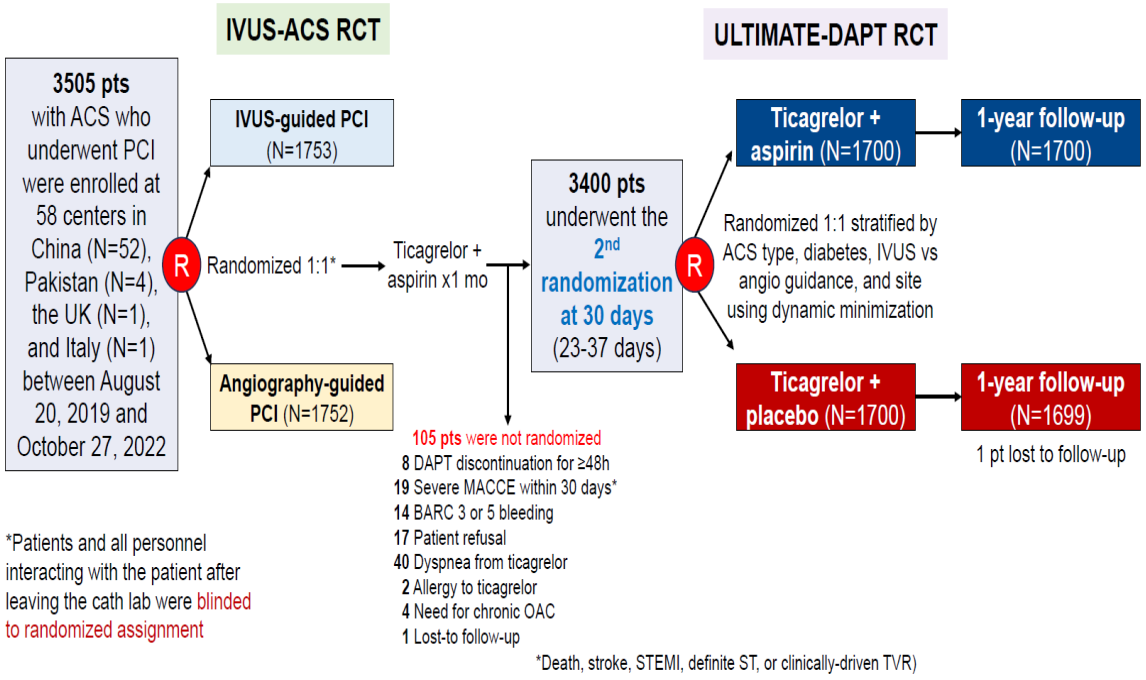
Gregg W Stone MD

Icahn School of Medicine at Mount Sinai

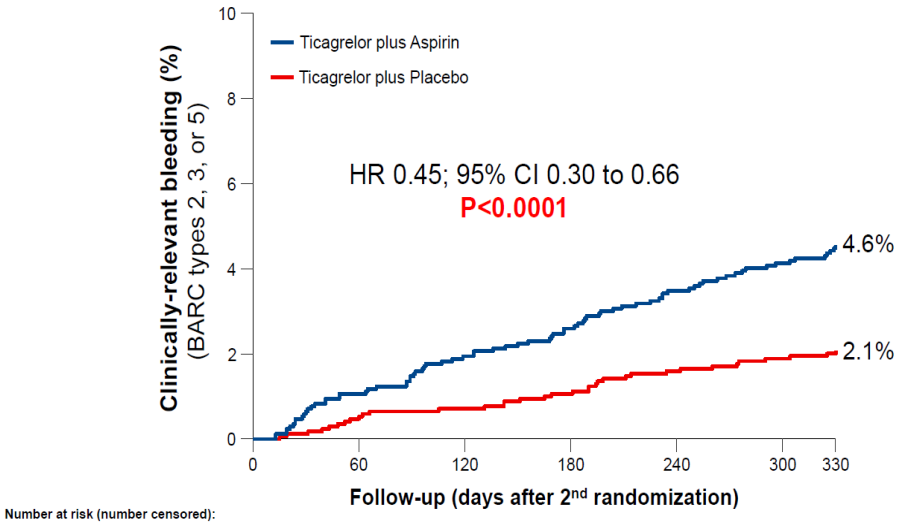
on behalf of Shao-Liang Chen and the ULTIMATE-DAPT Investigators

@GreggWStone

2x2 Randomization and Study Flowchart



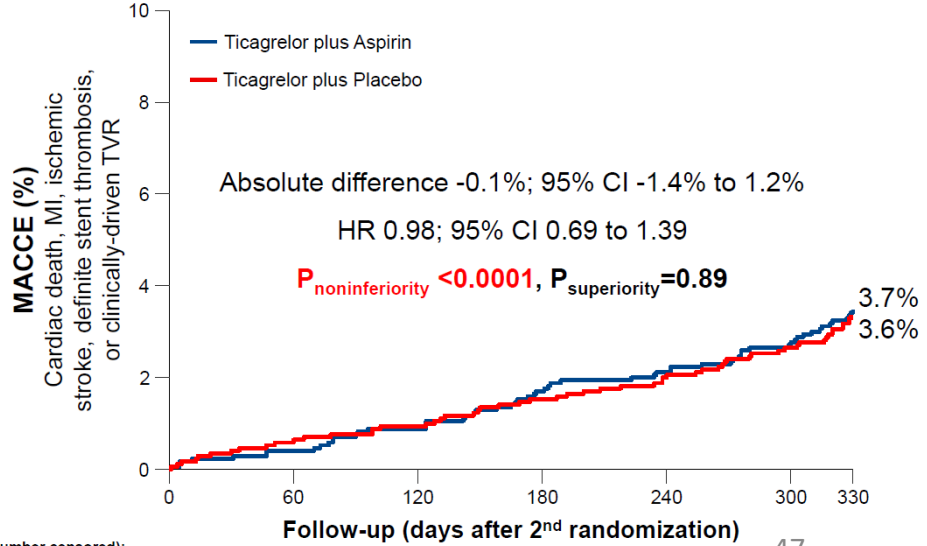
Primary Effectiveness Endpoint: BARC types 2, 3 or 5 bleeding



Number at risk (number censored):

Ticagrelor plus Aspirin	1700 (0)	1681 (1)	1664 (2)	1652 (1)	1634 (3)	1622 (2)	1615 (2)
Ticagrelor plus Placebo	1700 (0)	1688 (2)	1684 (2)	1676 (2)	1665 (2)	1657 (3)	1654 (3)

Primary Safety Endpoint: MACCE



Number at risk (number censored):

Ticagrelor plus Aspirin	1700 (0)	1693 (0)	1684 (1)	1669 (2)	1659 (2)	1648 (2)	1636 (2)
Ticagrelor plus Placebo	1700 (0)	1690 (0)	1684 (0)	1673 (1)	1664 (1)	1652 (2)	1640 (2)

ULTIMATE DAPT Conclusions and Limitations

Conclusions and Clinical Implications

- The present results demonstrate that in pts with ACS treated with PCI with contemporary DES who are free from major adverse ischemic and bleeding events after 1 month on DAPT, treatment with ticagrelor alone between 1 and 12 months will decrease clinically-relevant and major bleeding while providing similar protection from MACCE compared with ticagrelor plus aspirin
- These results, in concert with prior trials, warrant updating the guidelines and change in practice to treat most pts with ACS after PCI with 1-month DAPT only followed by conversion to SAPT with a potent $P2Y_{12}$ inhibitor (with the strongest evidence supporting ticagrelor)

Limitations

1. The primary efficacy endpoint included minor bleeding (BARC type 2)
   - However, major bleeding was also significantly reduced with ticagrelor monotherapy (BARC types 3 or 5, TIMI major or minor, GUSTO and ISTH)
2. Non-inferiority for MACCE was tested with an absolute margin of 2.5%. Given the lower observed ischemic event rate in the control group than anticipated (3.7% vs. 6.2%), this relative margin is wide
   - Given the 95% CI of the observed difference, it is likely that the absolute MACCE rate with ticagrelor monotherapy is <1.2% greater than with ticagrelor + aspirin
3. ~40% of pts had biomarker-negative unstable angina
   - hs-troponin assays were not widely available in China and Pakistan during the enrollment period, and it is likely that many of these pts had NSTEMI
4. 88.1% of pts were from China, possibly affecting the generalizability of the results

Review of Ticagrelor Trials Evidence Base
Randomized Clinical Trials

Indication	Trial	Ischemic Event	Major Non-CABG Bleeding Event	Treatment
ACS/MI	**PLATO** [NCT00391872]			Ticagrelor+ASA vs. clopidogrel+ASA in ACS
	PHILO [NCT01294462]			Ticagrelor+ASA vs. clopidogrel+ASA in ACS in Japanese, South Korean, and Taiwanese patients
	TICAKOREA [NCT02094963]			Ticagrelor+ASA vs. clopidogrel+ASA in ACS in South Korean patients
	TREAT [NCT02298088]		 *	Ticagrelor+ASA vs. clopidogrel+ASA in fibrinolytic -treated STEMI
	POPular AGE [NCT02317198]			Ticagrelor+ASA vs. clopidogrel+ASA in elderly NSTE -ACS
	PRAGUE -18 [NCT02808767]		 *	Ticagrelor+ASA vs. prasugrel+ASA in acute MI treated with primary PCI
	ISAR-REACT 5 [NCT01944800]		 *	Ticagrelor+ASA vs. prasugrel+ASA in ACS with planned invasive management
	ATLANTIC [NCT01347580]			Ticagrelor pre-hospital administration vs. catherization lab administration in STEMI
	DUBIUS [NCT02618837]		 *	Ticagrelor pretreatment before angiography vs. no pretreatment in NSTE-ACS

Key

- Significantly better outcome with ticagrelor
- Not statistically inferior or different
- Numerically worse with ticagrelor (>1% absolute difference); not statistically inferior or different
- Significantly worse outcome with ticagrelor

Review of Ticagrelor Trials Evidence Base
Randomized Clinical Trials

TIA/Stroke	**SOCRATES** [NCT01994720]			Ticagrelor+ASA vs. ASA in mild/moderate risk stroke and high -risk transient ischemic attack
	THALES [NCT03354429]			Ticagrelor+ASA vs. ASA in mild/moderate risk stroke and high -risk transient ischemic attack
PAD	**EUCLID** [NCT01732822]			Ticagrelor vs. clopidogrel in symptomatic PAD
Elective PCI	**ALPHEUS** [NCT02617290]			Ticagrelor+ASA vs. clopidogrel+ASA in high -risk elective PCI
CABG	**DACAB** [NCT02201771]			Ticagrelor+ASA vs. ticagrelor vs. ASA in elective CABG in Chinese patients
	TiCAB [NCT01755520]			Ticagrelor vs. ASA in elective CABG
	POPular-CABG [NCT02352402]			Ticagrelor+ASA vs. ASA in elective CABG

Review of Ticagrelor Trials Evidence Base
Randomized Clinical Trials

Secondary Prevention	**PEGASUS** [NCT01225562]			Ticagrelor+ASA vs. ASA in patients with a history of MI
	THEMIS [NCT01991795]			Ticagrelor+ASA vs. ASA in patients with CAD and diabetes
De-escalation	**TALOS-AMI** [NCT02018055]			Ticagrelor+ASA vs. de-escalation to clopidogrel+ASA in acute MI in South Korean patients
Aspirin Withdrawal	**GLOBAL LEADERS** [NCT02018055]			Ticagrelor+ASA (1 month) followed by ticagrelor (23 months) vs. ticagrelor or clopidogrel+ASA (12 months) followed by ASA (12 months) in ACS and CAD
	TWILIGHT [NCT02270242]			Ticagrelor+ASA for 3 months followed by ticagrelor for 12 months vs. ticagrelor+ASA for 12 months in high-risk PCI
	TICO [NCT02494895]			Ticagrelor+ASA for 3 months followed by ticagrelor monotherapy vs. ticagrelor+ASA for 12 months in ACS in South Korean patients

THANK YOU