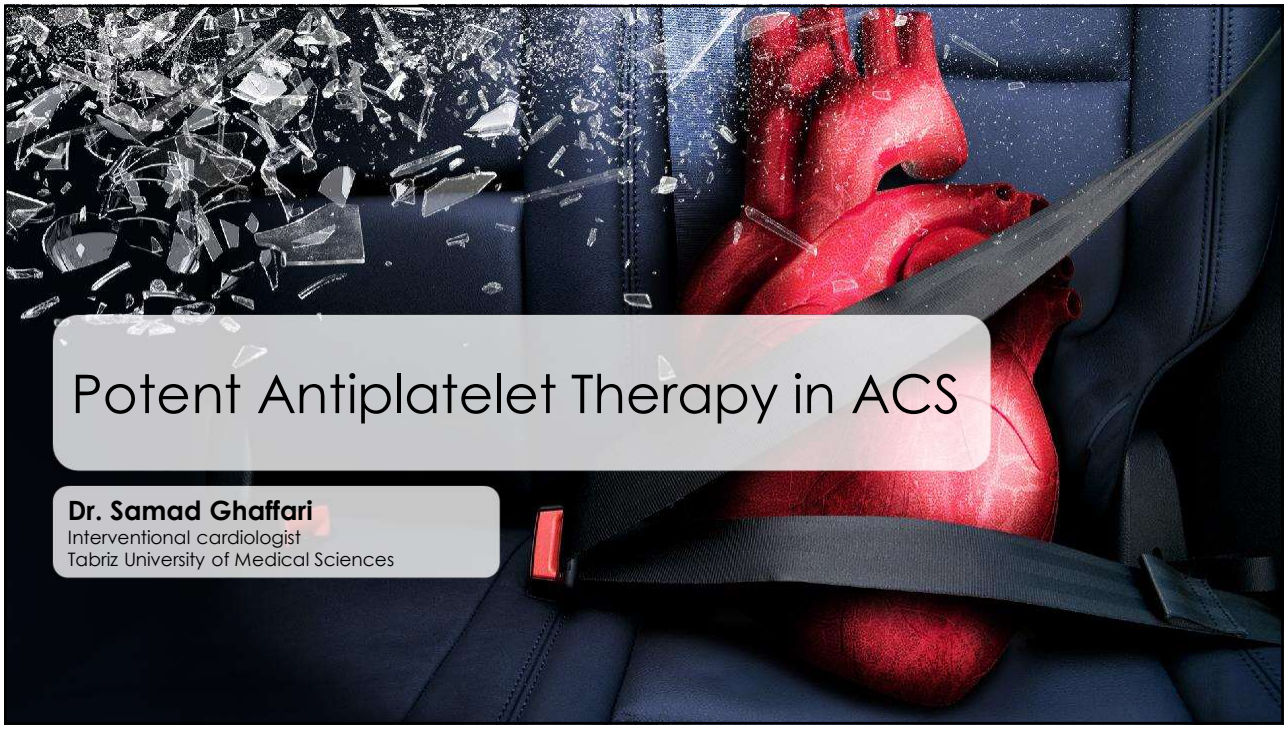
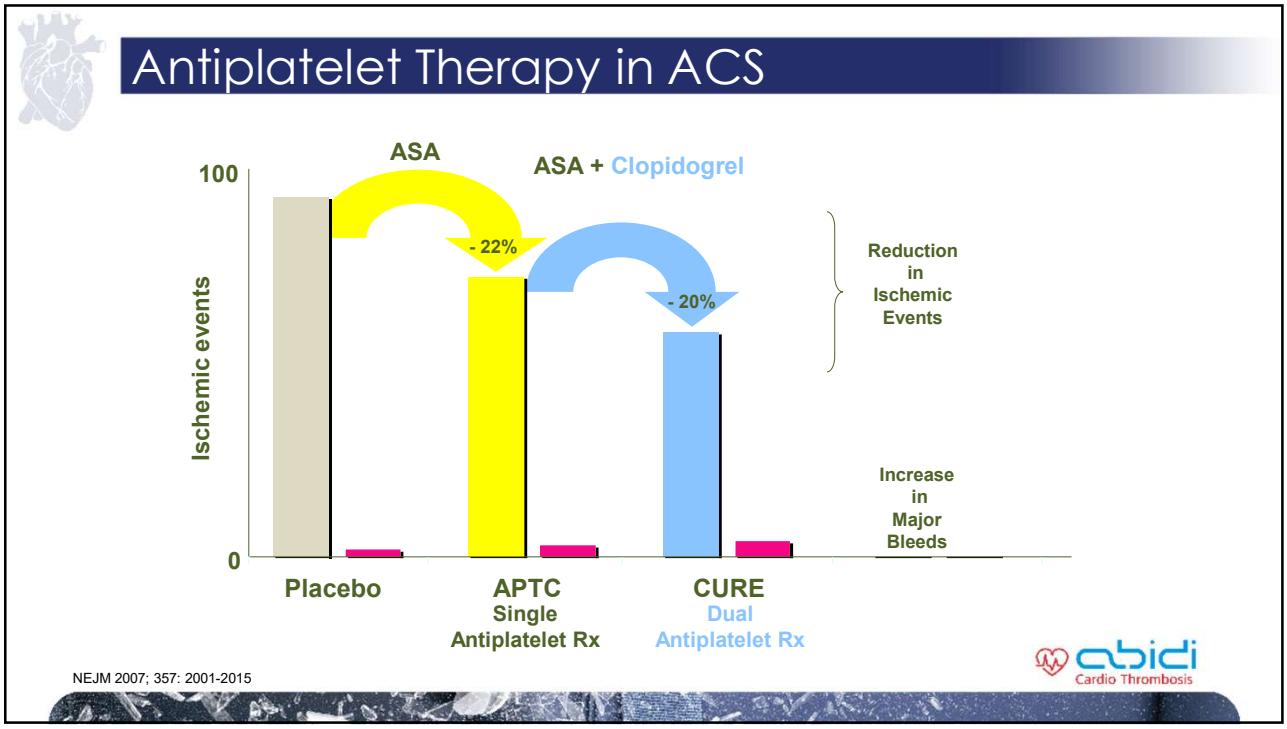

Potent Antiplatelet Therapy in ACS
Dr. Samad Ghaffari
Interventional cardiologist
Tabriz University of Medical Sciences


Antiplatelet Therapy in ACS
ASA
ASA + Clopidogrel
100
0
Ischemic events
- 22%
- 20%
Reduction in Ischemic Events
Increase in Major Bleeds
Placebo
APTC
Single Antiplatelet Rx
CURE
Dual Antiplatelet Rx
NEJM 2007; 357: 2001-2015
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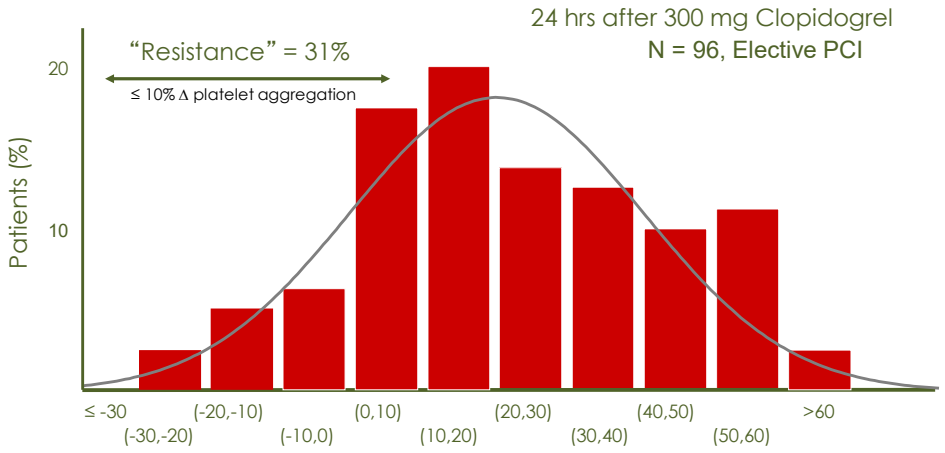
Cardio Thrombosis

Variable and Unpredictable Response to Clopidogrel



Circulation 2003; 107: 2908-2913

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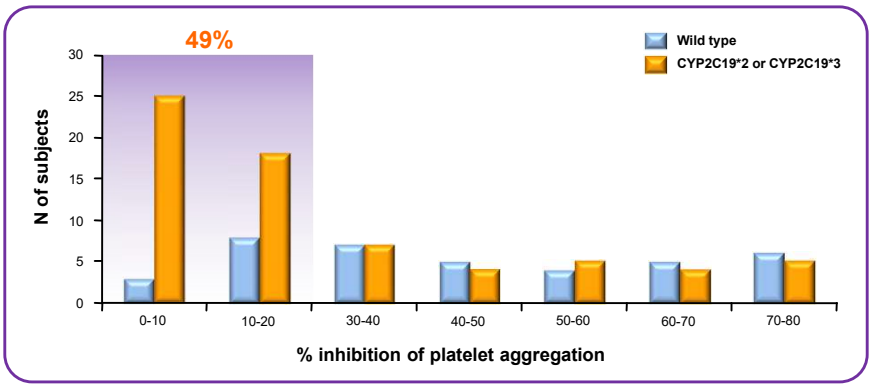
About half of the Korean patients with clopidogrel were reported as non-responders

≤ 20% inhibition of platelets were defined as non-responders to Clopidogrel treatment.



Korean J Lab Med. 2011 Apr;31(2):91-94.

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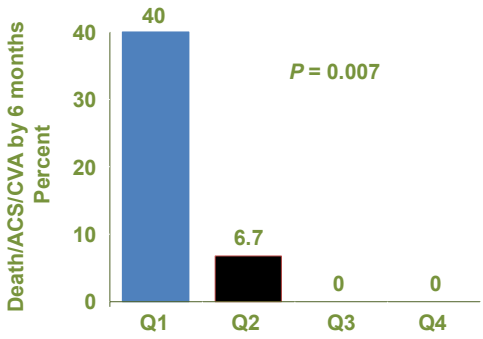
Clopidogrel Response Variability and Increased Risk of Ischemic Events



- STEMI patients were stratified into 4 quartiles according to the percentage reduction of ADP-induced platelet aggregation.
- Patients in the first quartile were resistant to the effects of clopidogrel.

Up to 25% of STEMI patients undergoing primary PCI are resistant to clopidogrel and therefore may be at increased risk for recurrent cardiovascular events.

Circulation. 2004;109:3171–3175

3116.01

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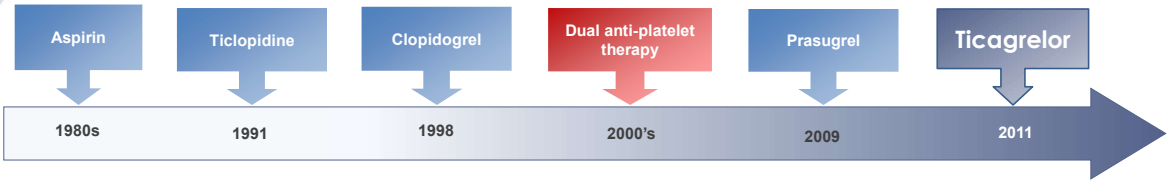
History of Antiplatelet in patients with CAD



DAPT Trial	Population	Comparison	CV Death (RRR)	MI (RRR)	Stent Thrombosis (RRR)	Major Bleeding (%)
Cure (2001)	12,562 NSTE-ACS	Clopidogrel	7.3% (*P* = NS)	22.4% (*P* not given)	Not given	3.7 vs 2.7 (*P* = 0.001)
		Placebo				
TRITON (2007)	13,608 STEMI\NSTEMI (undergoing PCI)	Prasugrel	12.5% (*P* = NS)	23.1% (*P* < 0.001)	47.6% (P < 0.001)	1.4 vs 0.9 (*P* = 0.01)
		Clopidogrel				
PLATO (2009)	18,624 UA\STEMI\NSTEMI (invasive, conservative)	Ticagrelor	21% (*P* = 0.025)	16% (*P* = 0.005)	26.7% (P = 0.014)	11.6 vs 11.2 (*P* = NS)
		Clopidogrel				

European Heart Journal (2011) 32, 2999–3054

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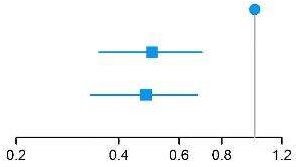
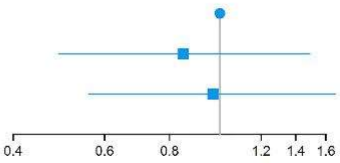
A composite of all-cause mortality, recurrent MI, and ischemic stroke at 1 year:

Treatment	Events (Patients)	IR/100 PY	HR (95% CI)
Clopidogrel	133 (1245)	11.4	Reference
Ticagrelor	114 (1976)	6.0	0.50 (0.35-0.70)
Prasugrel	88 (1902)	4.8	0.48 (0.33-0.68)



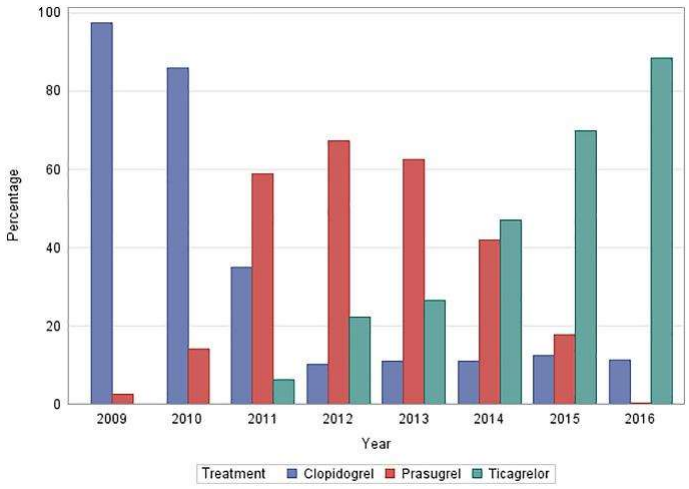
A composite of bleedings leading to hospitalization at 1 year:

Treatment	Events (Patients)	IR/100 PY	HR (95% CI)
Clopidogrel	44 (1245)	3.7	Reference
Ticagrelor	61 (1976)	3.2	0.85 (0.49-1.49)
Prasugrel	53 (1902)	2.9	0.97 (0.56-1.67)



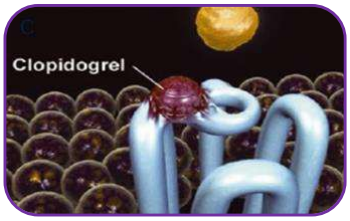
https://doi.org/10.1016/j.ijcard.2021.07.047

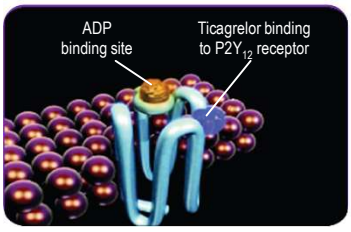
Yearly distribution of treatment with P_2Y_{12} inhibitors among patients with STEMI



https://doi.org/10.1016/j.ijcard.2021.07.047

Ticagrelor directly & reversibly binds to P_2Y_{12} receptors





Cardiovasc Ther. 2009; 27(4): 259-74.

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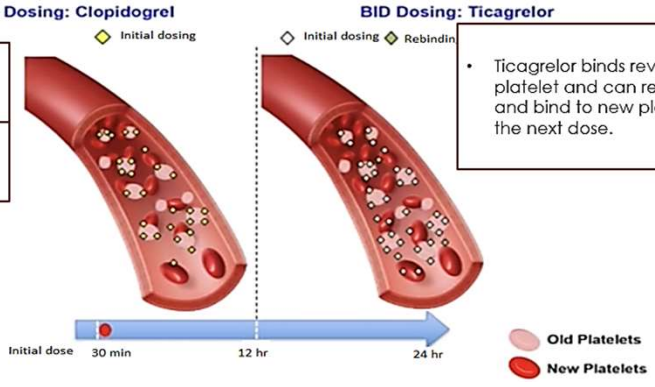
Differences in platelet binding between Clopidogrel and Ticagrelor

- Clopidogrel binds Irreversibly to platelets-once bound, a platelet is inhibited for its lifetime.
- Newly manufactured platelets are not inhibited until the next dose.



- Ticagrelor binds reversibly to platelet and can redistribute and bind to new platelets before the next dose.

Cardiovasc Ther. 2009; 27(4): 259–274.

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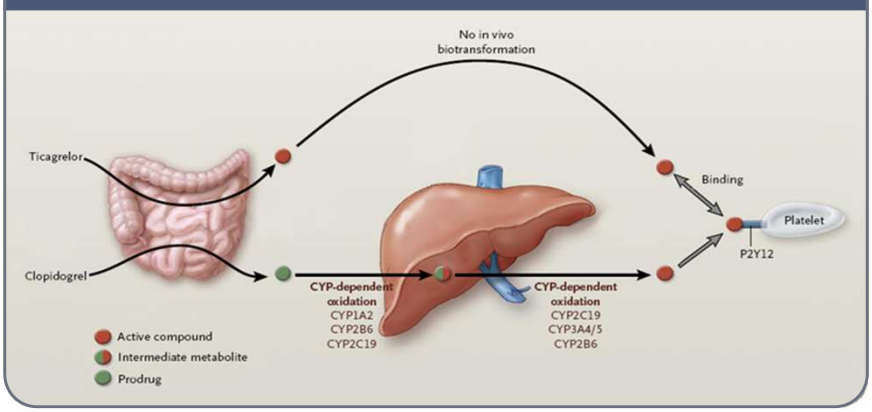
Ticagrelor does not require hepatic metabolism for activation

Ticagrelor is orally active and does not require hepatic metabolism for activity[1,2]



Cardio Ther. 2009;27:259-274.
Adapted from *New Eng J Med* 2009; 361(11): 1108-1111

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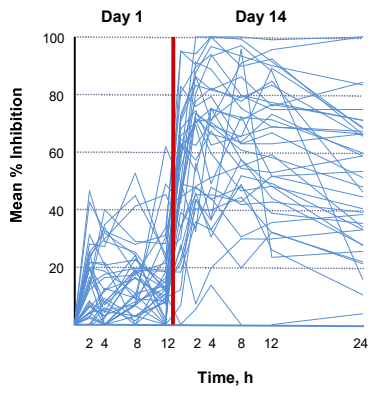
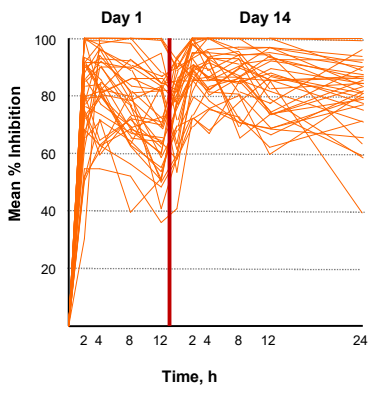
More consistent and greater IPA with Ticagrelor vs. Clopidogrel

Clopidogrel 75 mg od



Ticagrelor 100 mg bd



Eur Heart J. Supp (2007) 9 (Supp D):D20-D27.

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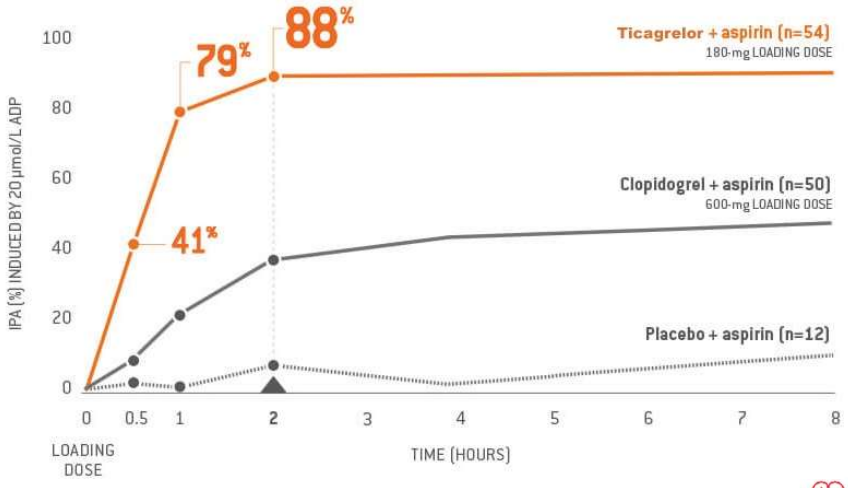
The faster and greater IPA with Ticagrelor vs. Clopidogrel

- **Ticagrelor** 90 mg bid for 6 weeks with **180 mg** loading dose
- **Clopidogrel** 75 mg qd for 6 weeks with **600 mg** loading dose



Circulation. 2009;120:2577–2585.

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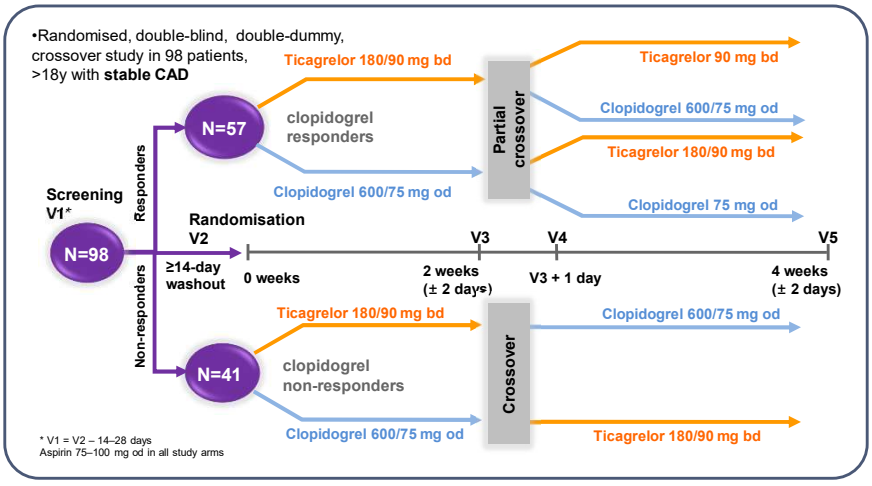
RESPOND: Study Design



Circulation 2010; 121: 1188-1199

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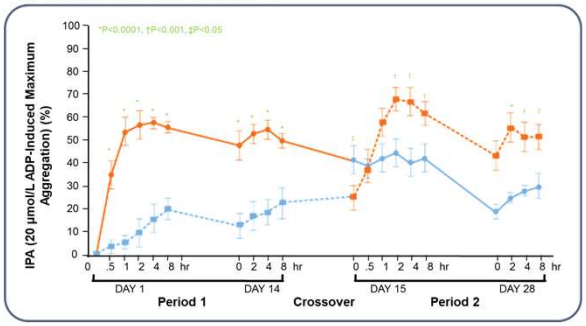
RESPOND

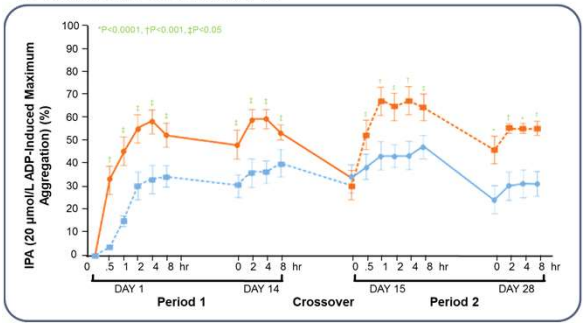
Non-responder

IPA in Response to 20 mmol/L ADP



Responder

IPA in Response to 20 mmol/L ADP



Clopidogrel → Ticagrelor
Ticagrelor → Clpidopgrel

Circulation 2010; 121: 1188-1199

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The unique pharmacology: CPTP vs. Thienopyridine

Type	Ticagrelor CPTP	Clopidogrel Thienopyridine	Prasugrel Thienopyridine
Prodrug	No	Yes	Yes
CYP-450 activation	No	Yes (twice)	Yes
Onset of action	Rapid	Delayd	Rapid
Time to peak inhibition (h)	2	~12*	2
Individual variability	Small	Large	Small
Reversible P_2Y_{12} inhibition	Yes	No	No
Half-life	7-12 h	Life of platelet	Life of platelet
Mean platelet inhibition	~95%	~50%	~70%
Relative potency	High	Low	High
Frequency of administration	Twice daily	Once daily	Once daily

*With 300 mg loading dose

Heart. 2010;96:656-61

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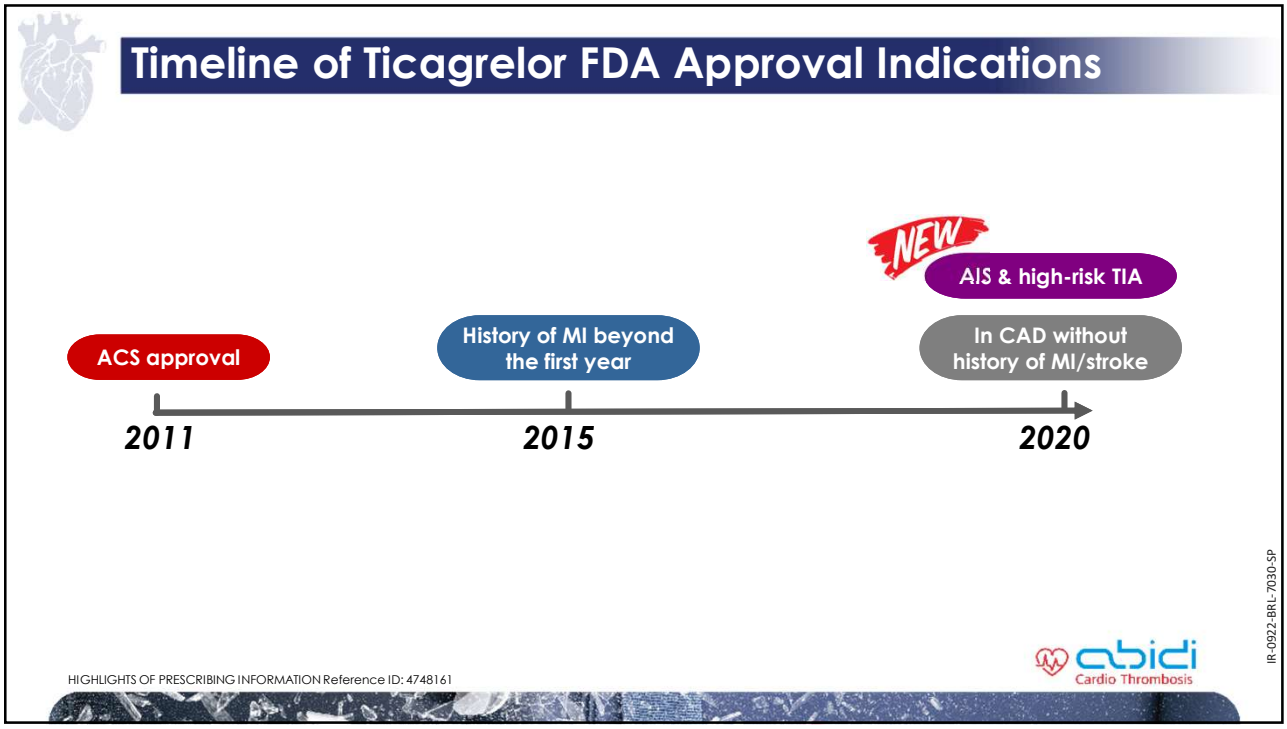
Ticagrelor
Prescribing Information
IR-0922-BRL-7030-SP


Timeline of Ticagrelor FDA Approval Indications
NEW
AIS & high-risk TIA
ACS approval
History of MI beyond the first year
In CAD without history of MI/stroke
2011
2015
2020
HIGHLIGHTS OF PRESCRIBING INFORMATION Reference ID: 4748161
abidi Cardio Thrombosis
IR-0922-BRL-7030-SP

Indications

Acute Coronary Syndrome or a History of Myocardial Infarction

✓ **To reduce the risk of cardiovascular (CV) death, myocardial infarction (MI), and stroke in patients with ACS or a history of MI for at least the first 12 months following ACS, it is superior to clopidogrel**

LOADING

Ticagrelor 180mg oral (2*90 mg)

Aspirin 300-325mg

MAINTENANCE First year

Ticagrelor 90mg bd oral

Aspirin 75-100mg qd

MAINTENANCE After 1 year

Ticagrelor 60mg bd oral

Aspirin 75-100mg qd

HIGHLIGHTS OF PRESCRIBING INFORMATION Reference ID: 4748161

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IR-0922-BRL-7030-SP

Indications

Coronary Artery Disease but No Prior Stroke or Myocardial Infarction

✓ **To reduce the risk of a first MI or stroke in patients with CAD at high risk for such events**

Ticagrelor 60mg bd oral

Aspirin 75-100mg qd

HIGHLIGHTS OF PRESCRIBING INFORMATION Reference ID: 4748161

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IR-0922-BRL-7030-SP

Indications

Acute Ischemic Stroke or Transient Ischemic Attack (TIA)

✓ **To reduce the risk of stroke in patients with AIS (NIHSS score ≤5) or high-risk TIA**

LOADING

Ticagrelor 180mg oral (2*90 mg)

Aspirin 300-325mg

MAINTENANCE 30 Days

Ticagrelor 90mg bd oral

Aspirin 75-100mg qd

HIGHLIGHTS OF PRESCRIBING INFORMATION Reference ID: 4748161

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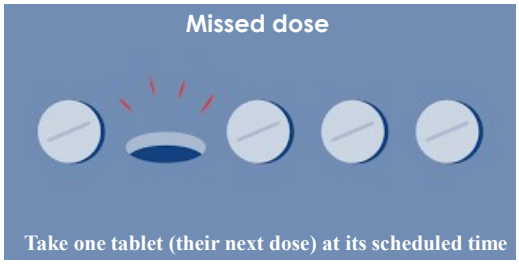
Administration

- ❑ Oral (with or without Food)
- ❑ If unable to swallow tablet, crush and mix with water.
- ❑ May also administer the crushed tablet and water mixture via an NG tube (CH8 or greater).
- ❑ Overdosage:
  - Ticagrelor is not dialyzable
  - ~~Platelet transfusion~~
  - Bleeding: appropriate supportive measures should be taken



HIGHLIGHTS OF PRESCRIBING INFORMATION Reference ID: 4748161

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Contraindications

- **History of intracranial hemorrhage**
- **Active pathological bleeding**
- **Hypersensitivity to Ticagrelor or any component of the product**
- **Severe hepatic impairment**

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HIGHLIGHTS OF PRESCRIBING INFORMATION Reference ID: 4748161

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Warning and Precautions

- **Discontinuation of ticagrelor:**
  Will increase the risk of myocardial infarction, stroke, and death in patients being treated for coronary artery disease
- **Bradyarrhythmias**
- **Severe Hepatic Impairment:**
  Avoid use of BRILINTA in patients with severe hepatic impairment
- **Laboratory Test Interferences:**
  False negative functional tests for Heparin Induced Thrombocytopenia (HIT)
- **Concomitant Aspirin Maintenance Dose:**
  Maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor and **should be avoided**

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HIGHLIGHTS OF PRESCRIBING INFORMATION Reference ID: 4748161

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Adverse Reactions

Bleeding

- Ticagrelor, like other antiplatelet agents, can cause significant, sometimes fatal bleeding.
- If possible, manage bleeding without discontinuing ticagrelor, stopping ticagrelor increases the risk of subsequent cardiovascular events

Dyspnea

- Usually mild to moderate in intensity
- Often resolved during continued treatment

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HIGHLIGHTS OF PRESCRIBING INFORMATION Reference ID: 4748161

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Drug Interactions

- **Avoid use** with strong **CYP3A inhibitors** (ketoconazole,…) or **CYP3A inducers** (rifampin, phenytoin, carbamazepine,…).
- Patients receiving more than 40 mg per day of **Simvastatin or Lovastatin** may be at increased risk of statin-related adverse effects.
- **Digoxin**: Monitor digoxin levels with initiation of or any change in ticagrelor.
- **Opioids** (Morphine): Co-administration of opioid agonists delay and reduce the absorption of ticagrelor and its active metabolite.
- **Aspirin**: Concomitant use of ticagrelor with aspirin maintenance doses above 100 mg reduced the effectiveness of ticagrelor

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HIGHLIGHTS OF PRESCRIBING INFORMATION Reference ID: 4748161

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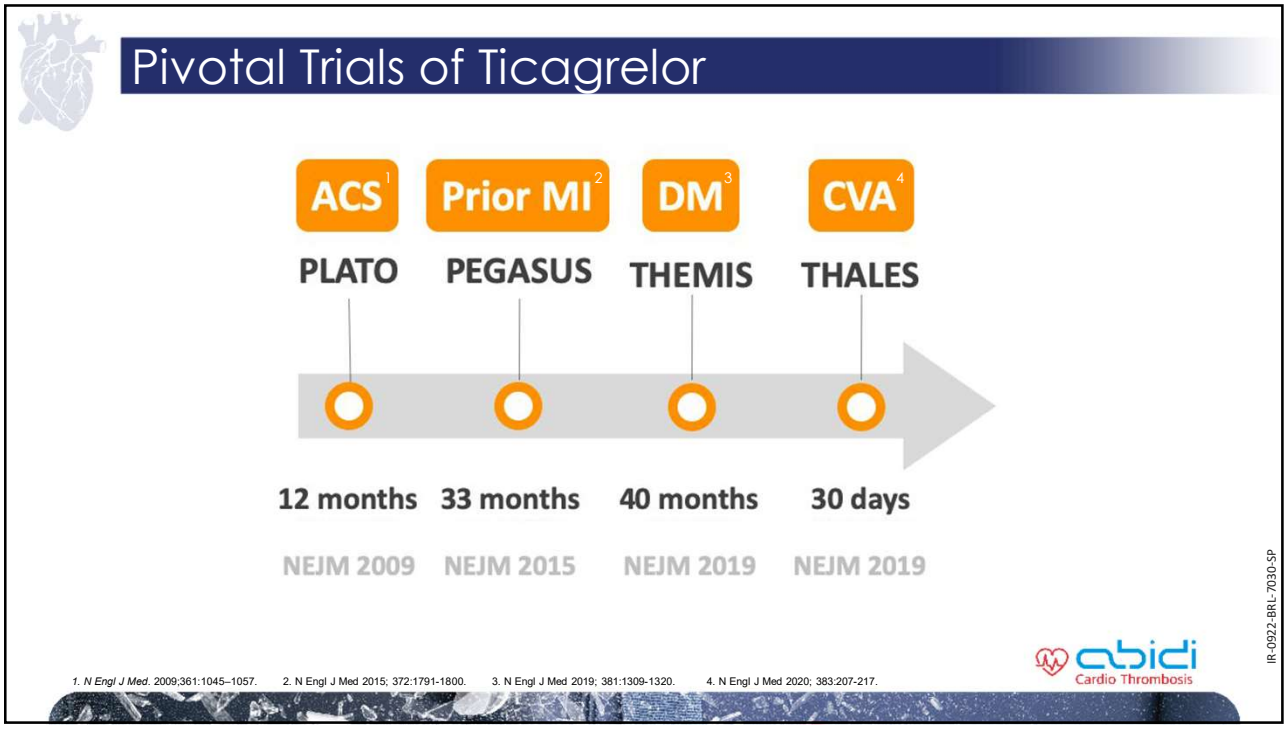
Ticagrelor in ACS
Clinical Studies
IR-0922-BRL-7030-SP


Pivotal Trials of Ticagrelor
ACS 1
Prior MI 2
DM 3
CVA 4
PLATO
PEGASUS
THEMIS
THALES
12 months
33 months
40 months
30 days
NEJM 2009
NEJM 2015
NEJM 2019
NEJM 2019
1. N Engl J Med. 2009;361:1045–1057. 2. N Engl J Med 2015; 372:1791-1800. 3. N Engl J Med 2019; 381:1309-1320. 4. N Engl J Med 2020; 383:207-217.
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IR-0922-BRL-7030-SP

Ticagrelor vs Clopidogrel in Patients with ACS

PLATO Study

Randomized, placebo-controlled, double-blind

To determine whether ticagrelor is superior to clopidogrel for the prevention of vascular events and death in a broad population of patients presenting with an acute coronary syndrome.

18,624 Patients
43 countries
862 sites

Eligible patients
- Hospitalized patients for an ACS, with or without ST-segment elevation
- An onset of symptoms during the previous 24 h

Major exclusion criteria
- Any contraindication against the use of clopidogrel
- Fibrinolytic therapy within 24 h before randomization
- A need for OAC, an increased risk of bradycardia
- Concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer

N Engl J Med 2009; 361:1045-1057

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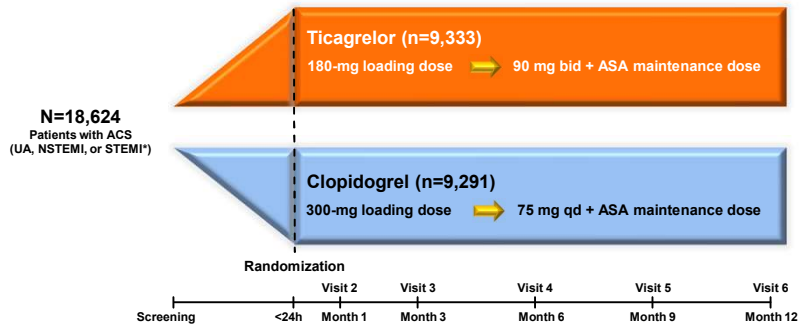
Ticagrelor vs Clopidogrel in Patients with ACS

PLATO Study



Initial Treatment approaches
- **Medically managed (n=5,216 — 28.0%)**
- **Invasively managed (n=13,408 — 72.0%)**

*STEMI patients scheduled for primary PCI were randomized; however, they may not have received PCI.

N Engl J Med. 2009;361:1045–1057.
Am Heart J. 2009;157:599–605.

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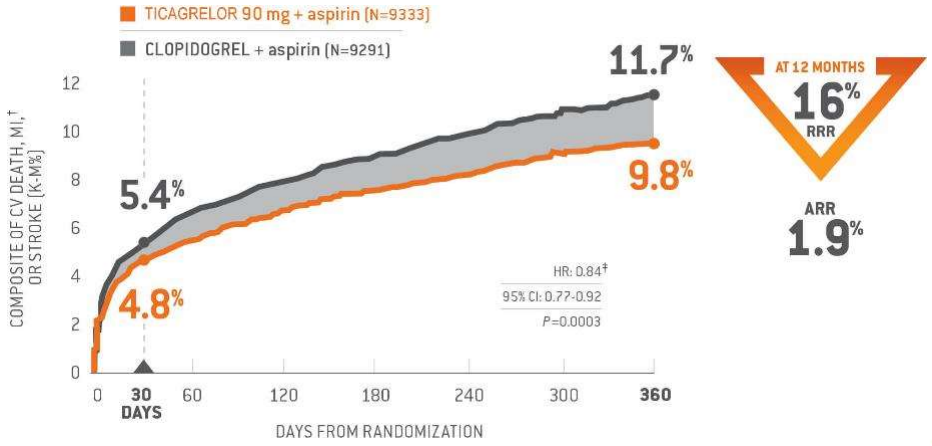
Ticagrelor reduced the combined risk of CV death, MI, or stroke by 16% vs. Clopidogrel

PLATO Study



N Engl J Med. 2009;361:1045–1057.

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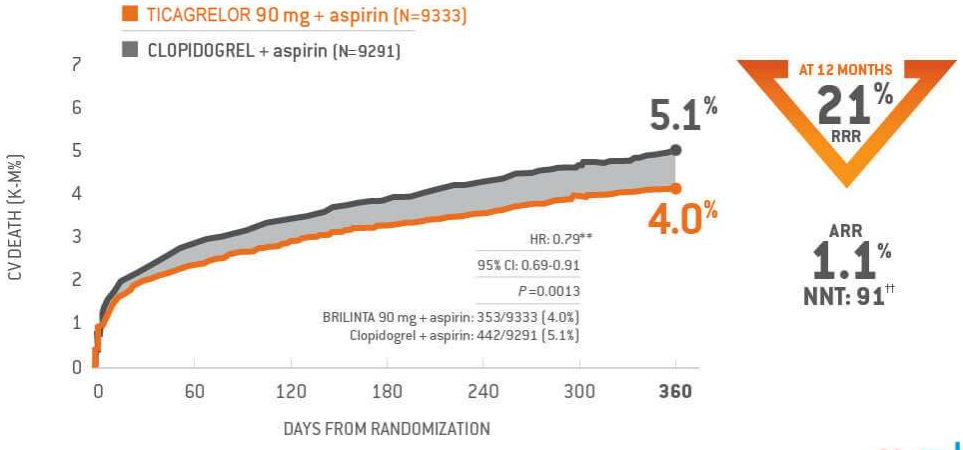
Ticagrelor saves more lives than Clopidogrel by reducing **CV death** at 12 months

PLATO Study



N Engl J Med. 2009;361:1045–1057.

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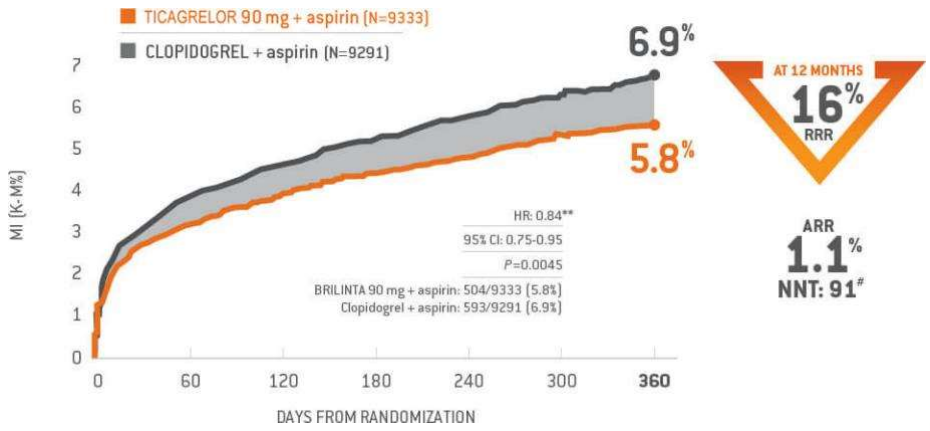
More patients taking clopidogrel suffered **MI** at 12 months than those taking Ticagrelor

PLATO Study

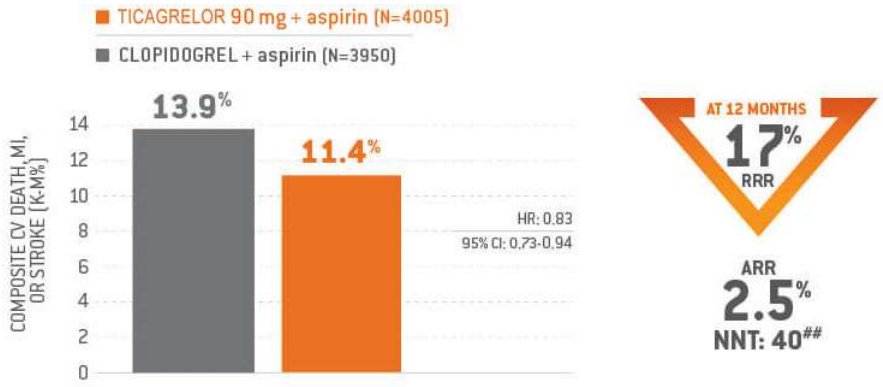


N Engl J Med. 2009;361:1045–1057.

IR-0922-BRL-7030-SP

NSTEMI subgroup composite end point at 12 months

PLATO Study



N Engl J Med. 2009;361:1045–1057.

IR-0922-BRL-7030-SP

PLATO Study

In 1,000 ACS patients, replacing clopidogrel with ticagrelor for 12 months:

- 14 fewer deaths (absolute risk reduction 1.4%)
- 11 fewer MI
- 6-8 fewer cases of stent thrombosis
- No increase in bleeding requiring transfusion
- 9 patients may switch to thienopyridine treatment because of reversible symptoms of dyspnea

Treating 54 patients with ticagrelor instead of with clopidogrel for one year will prevent one event of CV death, MI or stroke

N Engl J Med. 2009;361:1045–1057.

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IR-0922-BRL-7030-SP

Ticagrelor-associated **dyspnea** was mostly mild to moderate in severity and did not reduce efficacy

PLATO Study

Dyspnoea in the PLATO trial	Ticagrelor	Clopidogrel	*P* Value
Incidence of dyspnoea adverse events (%)	13.8	7.8	<0.001
Patients who discontinued treatment due to dyspnoea (%)	0.9	0.1	<0.001

- Ticagrelor-associated dyspnea was mostly **mild** to **moderate** in severity and did not reduce efficacy.
- Most events were reported as **single episode** occurring early after starting treatment.
- **Not associated with new or worsening heart or lung disease.**

Dyspnea from ticagrelor is self-limiting

Label precautions and warnings: use with caution in patients with history of asthma and COPD.

Wallentin L, et al. *N Engl J Med.* 2009;361:1045–1057.
Storey R, et al. *J Am Coll Cardio.* 2010;55(Suppl 1):A108.E1007.

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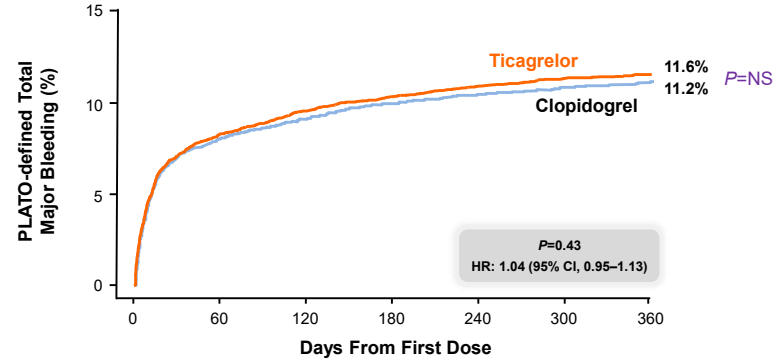
IR-0922-BRL-7030-SP

No significant difference in rate of total major **bleeding** with Ticagrelor vs. Clopidogrel

PLATO Study



No. at risk							
Ticagrelor	9,235	7,246	6,826	6,545	5,129	3,783	3,433
Clopidogrel	9,186	7,305	6,930	6,670	5,209	3,841	3,479

Both groups included aspirin.

N Engl J Med. 2009;361:1045–1057.

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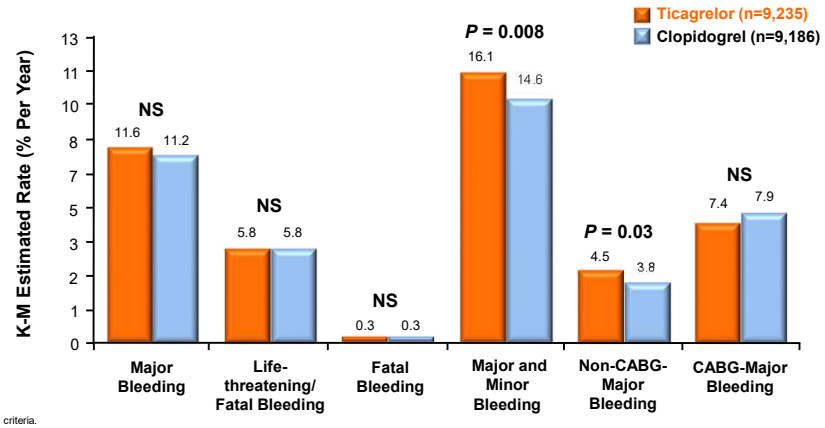
IR-0922-BRL-7030-SP

No significant difference in major fatal/life-threatening **bleeding** with Ticagrelor vs. Clopidogrel

PLATO Study



All values presented by PLATO criteria.
Both groups included aspirin.

N Engl J Med. 2009;361:1045–1057.

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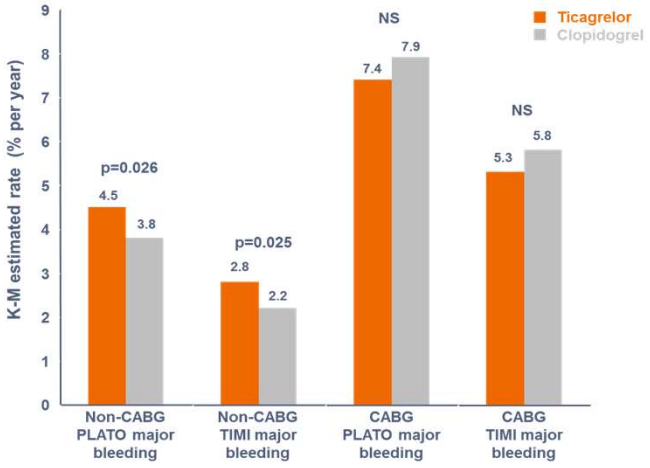
When antiplatelet therapy was stopped 5 days before CABG,
major bleeding occurred 7.4% with ticagrelor vs 7.9% with clopidogrel.

PLATO Study



N Engl J Med. 2009;361:1045–1057.

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	TICAGRELOR REAL-WORLD STUDY	PLATO
TRIAL DESIGN	Observational study using SWEDEHEART registry	Randomized, double-blind, controlled comparative study
PATIENT TYPE	Acute MI patients enrolled in the SWEDEHEART registry discharged on aspirin and either Ticagrelor or clopidogrel from 2010 to 2013	International ACS patients hospitalized with or without ST-segment elevation, with an onset of symptoms within 24 hours
NUMBER OF PATIENTS	45,073	18,624
STUDY PERIOD	24 months	12 months
TICAGRELOR DOSAGE	90 mg twice daily	90 mg twice daily
ASPIRIN DOSAGE	75 mg daily	75-100 mg daily maintenance dose

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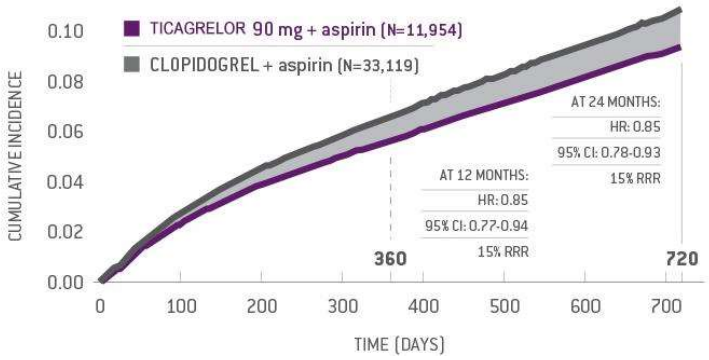
Significant reductions in cv events for ticagrelor vs clopidogrel

Real-world Study

Composite of all-cause death, readmission for MI, or stroke (at 24 months)



Bleeding outcomes from patients studied in a real-world registry were consistent with those seen in PLATO.

Eur Heart J. 2016;37(44):3335-3342.

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Ticagrelor with or without Aspirin in High-Risk Patients after PCI

TWILIGHT study

open label, double-blind, randomized controlled trial

Monotherapy with a P_2Y_{12} inhibitor after a minimum period of dual antiplatelet therapy is an emerging approach to reduce the risk of bleeding after PCI.

7,119

Patients

Eligible patients:

- High ischemia- or bleeding- risk patients who underwent successful PCI with at least one DES and had successfully tolerated DAPT for 3 months post-PCI without an ischemic or bleeding event.

N Engl J Med 2019; 381:2032-2042

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TWILIGHT study

Table 1: Clinical and Angiographic Characteristics that Satisfy the High-risk Criteria

High-risk Criteria*	
Clinical Criteria	**Angiographic Criteria**
Age ≥65 years	Multi-vessel coronary artery disease
Female sex	Total stent length of >30 mm
Troponin-positive acute coronary syndrome	Thrombotic target lesion
Established vascular disease	Bifurcation lesion treated with two stents
Diabetes treated with medications	Obstructive left main or proximal left anterior descending lesion
Chronic kidney disease	Calcified target lesion treated with atherectomy

** Patients should have at least one clinical and one angiographic criteria to be considered high risk.*

N Engl J Med 2019; 381:2032-2042

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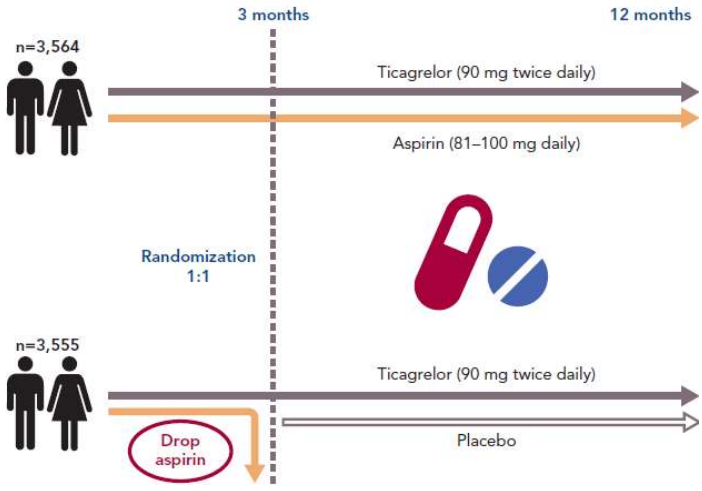
TWILIGHT study



N Engl J Med 2019; 381:2032-2042

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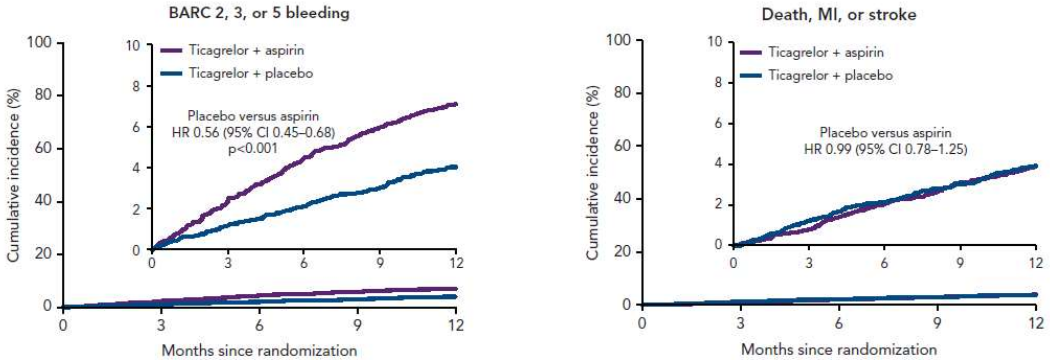
TWILIGHT study



Among high-risk patients who underwent PCI and completed 3 months of DAPT, ticagrelor monotherapy was associated with a lower incidence of clinically relevant bleeding than ticagrelor plus aspirin, with no higher risk of death, myocardial infarction, or stroke.

N Engl J Med 2019; 381:2032-2042

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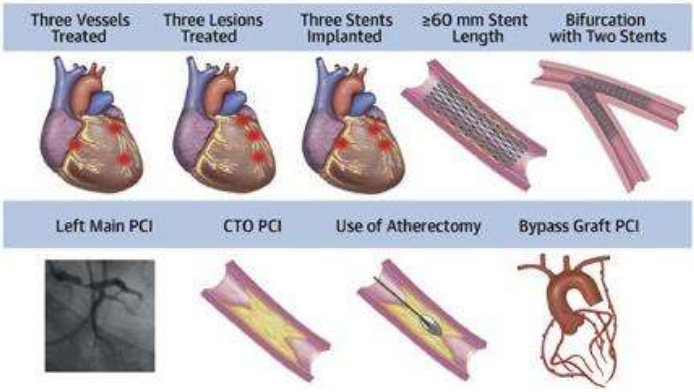
Complex PCI Sub-analysis

TWILIGHT study

Effect of Ticagrelor Monotherapy Versus Ticagrelor Plus Aspirin After 3 Months of DAPT in Patients Who Undergo Complex PCI

Complex PCI Defined as Any of the Following Characteristics:



J Am Coll Cardiol. 2020;75(19):2414–24.

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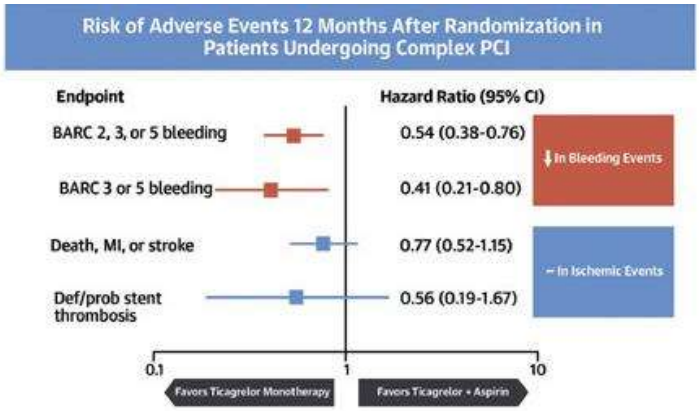
Complex PCI Sub-analysis

TWILIGHT study



J Am Coll Cardiol. 2020;75(19):2414–24.

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Effect of Ticagrelor Monotherapy vs Ticagrelor with Aspirin on Major Bleeding and CV Events in Patients With ACS

TICO Trial

a randomized, unblinded controlled trial

To determine whether switching to ticagrelor monotherapy after 3 months of DAPT reduces net adverse clinical events compared with ticagrelor-based 12-month DAPT in patients with ACS treated with drug-eluting stents.

3,056
Patients

Patients with ACS treated with DES and were randomized to receive ticagrelor monotherapy (90 mg bd) after 3-month DAPT or ticagrelor-based 12-month DAPT.

JAMA. 2020;323(23):2407-2416.

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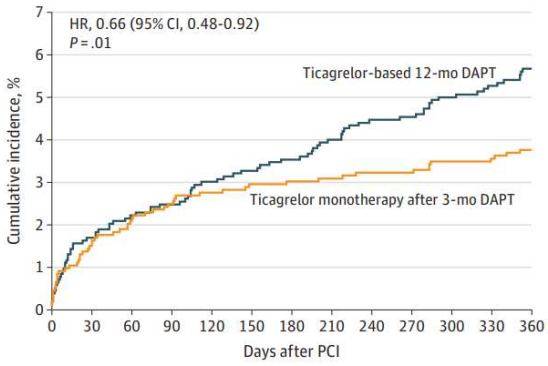
TICO Trial

Net adverse clinical event
(composite of major bleeding and major adverse cardiac and cerebrovascular event)



Among patients with ACS treated with DES, ticagrelor monotherapy after 3 months of DAPT, compared with ticagrelor-based 12-month DAPT, resulted in a modest but statistically significant reduction in a composite outcome of major bleeding and cardiovascular events at 1 year.

JAMA. 2020;323(23):2407-2416.

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Indication for patients with ACS

BY DIAGNOSIS		BY TREATMENT		
Unstable angina/Non–ST-elevation MI (UA/NSTEMI)	ST-elevation MI (STEMI)	Medical management	PCI	CABG
✔	✔	✔	✔	✔

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Summary

- **Ticagrelor is:**
  - Direct and reversible binding, oral ADP receptor antagonist
  - More rapid, consistent and greater inhibition of platelet aggregation vs. clopidogrel
  - First and only OAP reducing CV death by 21% vs. Clopidogrel (NNT=91)
  - No increase in overall major bleeding & fatal/life-threatening bleeding vs. clopidogrel
  - Indicated in a wide spectrum of ACS patients regardless of diagnosis or treatment strategy

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