PRAGUE-18 trial: Prasugrel or Ticagrelor in AMI PCI, which is better?

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According to the latest European Guidelines for ACS management , what are the differences between both Ticagrelor and Prasugrel ?

	Prasugrel	Ticagrelor
Chemical class	Thienopyridine	Cyclopentyl-triazolopyrimidine
Administration	Oral	Oral
Dose	60 mg orally then 10 mg a day	180 mg orally then 90 mg twice a day
Dosing in CKD		
• Stage 3 (eGFR 30–59 mL/min/1.73m²)	No dose adjustment	No dose adjustment
• Stage 4 (eGFR 15–29 mL/min/1.73m²)	No dose adjustment	No dose adjustment
• Stage 5 (eGFR <15 mL/min/1.73m²)	Not recommended	Not recommended
Binding reversibility	Irreversible	Reversible
Activation	Prodrug, with predictable liver metabolism	Active drug, with additional active metabolite
Onset of loading dose effect[a]	30 min[b]	30 min[b]
Duration of effect	7–10 days	3–5 days
Withdrawal before surgery	7 days[c]	5 days[c]
Plasma half-life of active $P2Y_{12}$ inhibitor[d]	30–60 min[e]	6–12 hours
Inhibition of adenosine reuptake	No	Yes

2014 ESC/EACTS Guidelines on myocardial revascularization

Recommendations for antithrombotic treatment in patients with STEMI undergoing primary PCI

Recommendations	Class[a]	Level[b]
Antiplatelet therapy		
ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg i.v.) and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A
A $P2Y_{12}$ inhibitor is recommended in addition to ASA and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:	I	A
• Prasugrel (60 mg loading dose, 10 mg daily dose) if no contraindication	I	B
• Ticagrelor (180 mg loading dose, 90 mg twice daily) if no contraindication	I	B
• Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated.	I	B
It is recommended to give $P2Y_{12}$ inhibitors at the time of first medical contact.	I	B

2014 ESC/EACTS Guidelines on myocardial revascularisation. *European Heart Journal*. 2014

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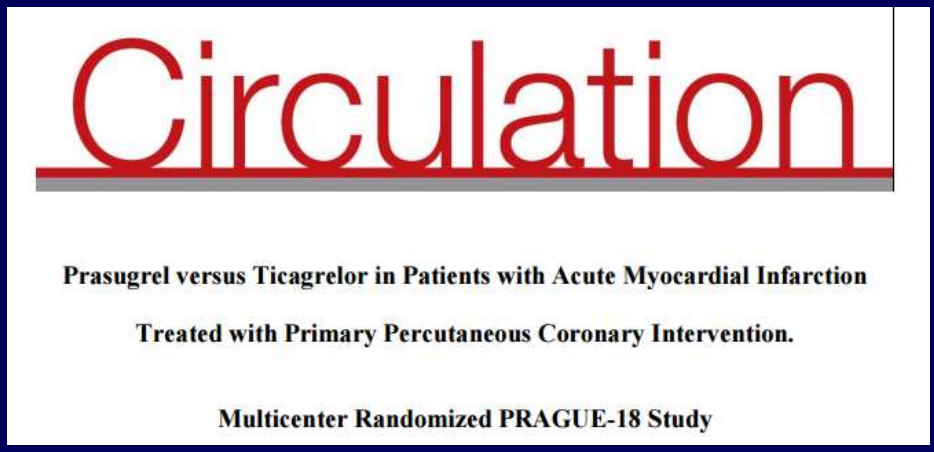
Are there any head to head trials comparing Ticagrelor to Prasugrel in ACS ?

Which P2Y12 inhibitor is more beneficial in our ACS management?

PRAGUE-18 study
Prasugrel vs Ticagrelor in patients with AMI treated with primary PCI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Prasugrel versus Ticagrelor in Patients with Acute Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention.

Multicenter Randomized PRAGUE-18 Study

The main objective of PRAGUE-18 study

- To compare the efficacy and safety of prasugrel and ticagrelor in acute myocardial infarction (AMI) treated with primary or immediate percutaneous coronary intervention (PCI).
- A total of 1230 patients were randomly assigned, across 14 sites, to either prasugrel or ticagrelor, which was initiated before PCI.

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Entry criteria

Inclusion:

- STEMI (or non-STEMI with ongoing ischemia)
- Emergent CABG / pPCI
- Signed informed consent.

Exclusion criteria:

- History of stroke
- Serious bleeding during previous 6 months
- Indication for OAC
- Pre-randomization clopidogrel ≥300 mg
- Body weight <60 kg in a patient>75 years
- Moderate-to-severe liver disease
- Concomitant treatment with potent CYP3A4 inhibitors
- Known hypersensitivity to prasugrel or ticagrelor.

The primary composite endpoint

- Consisted of all-cause death, re-infarction, stroke, serious bleeding requiring transfusion or prolonging hospitalization, or urgent target vessel revascularization within 7 days after randomization or at discharge if prior to the 7th day.

The secondary endpoint

- Composite of cardiovascular death, nonfatal myocardial infarction, or stroke during the follow-up period.
- definite stent thrombosis within 30 days from enrollment in the study

The safety endpoint

- Bleeding occurrences defined according to the TIMI and BARC criteria during the follow-up was a secondary safety endpoint

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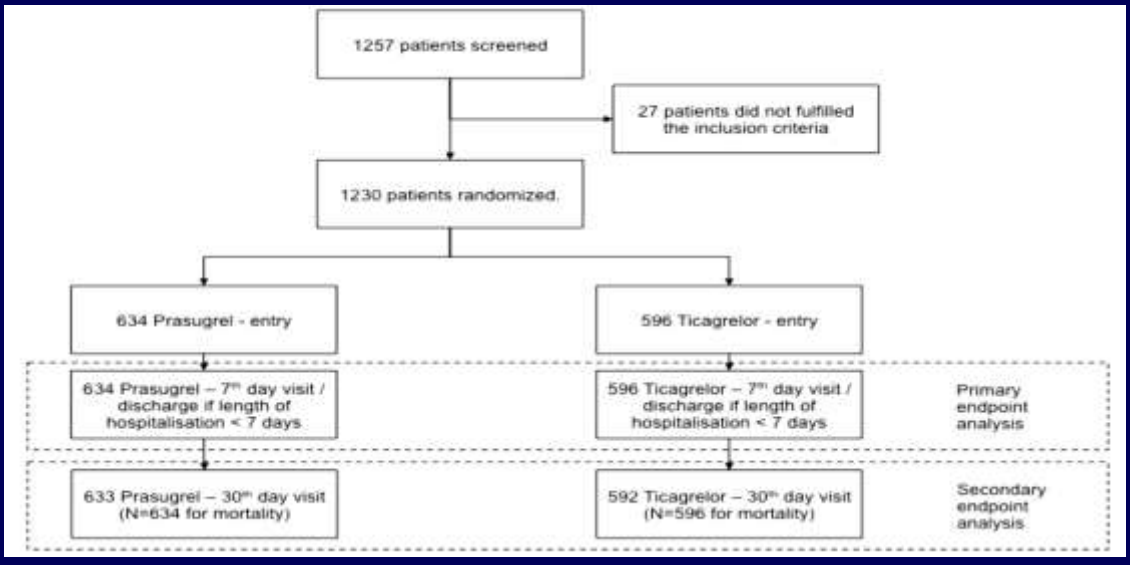
PRAGUE-18 study design



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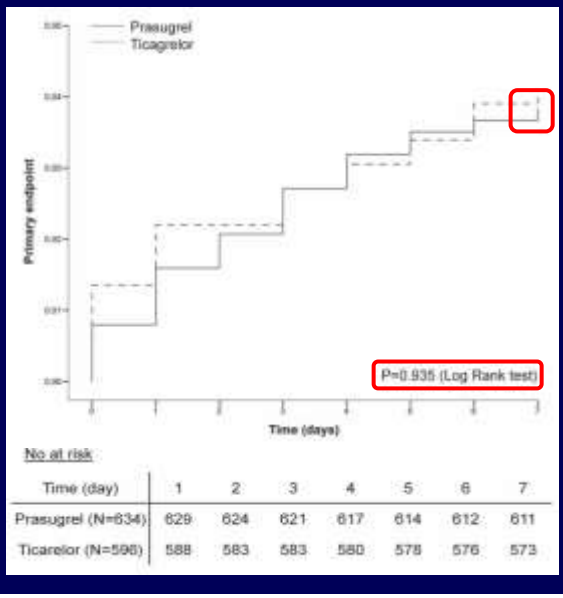
No significance difference of Primary end point occurrence at 7 days



No at risk

Time (day)	1	2	3	4	5	6	7
Prasugrel (N=634)	629	624	621	617	614	612	611
Ticarelor (N=596)	588	583	583	580	578	576	573

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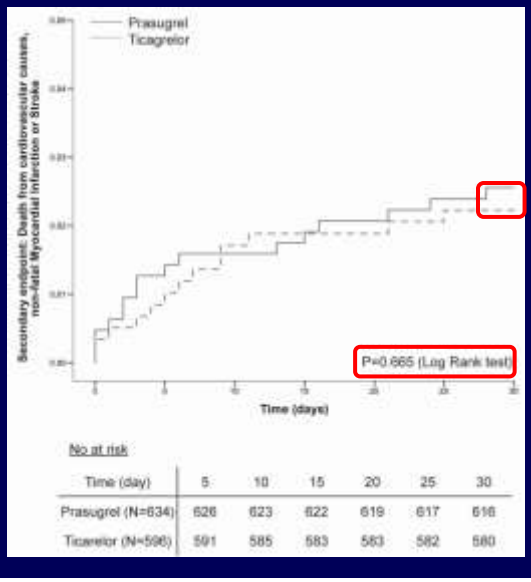
No significance difference as well in secondary end point at 30 days after randomization



No at risk

Time (day)	5	10	15	20	25	30
Prasugrel (N=634)	626	623	622	619	617	616
Ticarelor (N=596)	591	585	583	583	582	580

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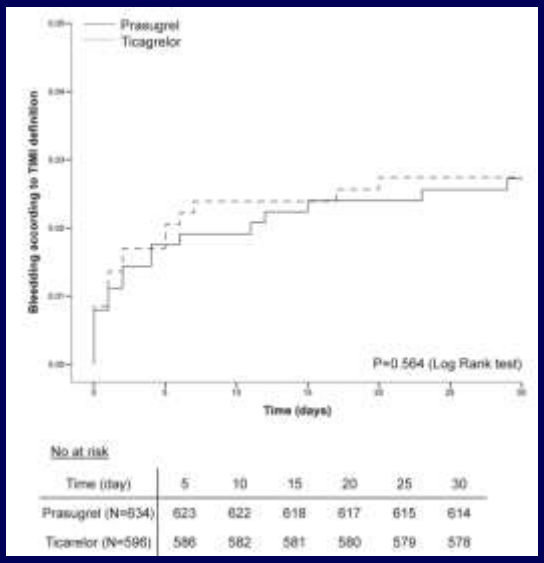
No significant difference in TIMI bleeding at 30 days after randomization



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PRAGUE-18

- The study was prematurely terminated for futility (no differences)
- This head-to-head comparison of prasugrel and ticagrelor does not support the hypothesis that one is more effective or safer than the other in preventing ischemic and bleeding events in the acute phase of myocardial infarction treated with primary PCI strategy.
- The observed rates of major outcomes were similar, although with broad confidence intervals around the estimates.

These interesting observations need to be confirmed in a larger trial

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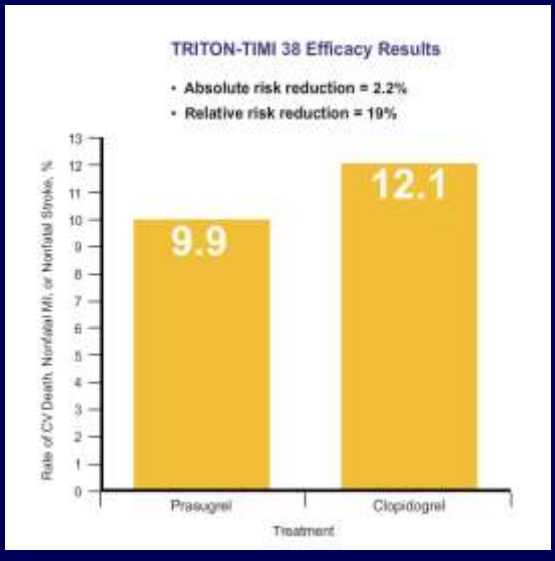
Data from PRAGUE-18 trial needs to be investigated in larger trials

But what are the data we have in hand regarding the new P2Y12 inhibitors vs clopidogrel?

TRITON-TIMI 38 showed strong Efficacy Results

- The primary end point occurred at a significantly lower rate in patients in the prasugrel group compared to patients in the clopidogrel group (9.9% vs 12.1%, **RRR of 19%,** p<0.001).



TRITON-TIMI 38
Efficacy on the expense of Safety Results

- The rate of non–CABG-related TIMI **major or minor bleeding** was significantly higher in the prasugrel group compared with the clopidogrel group (4.5% vs 3.4%, p=0.002).
- The rate of non–CABG-related TIMI **major bleeding** was significantly higher in patients receiving prasugrel. The end point occurred in 2.2% of the prasugrel group and 1.7% of the clopidogrel group, p=0.029.

Non–CABG-Related Bleeding* in TRITON-TIMI 38†

	Prasugrel (%) (N=6741)	Clopidogrel (%) (N=6716)	p-value
TIMI Major or Minor bleeding	4.5	3.4	p=0.002
TIMI Major bleeding	2.2	1.7	p=0.029
Life-threatening	1.3	0.8	p=0.015
Fatal	0.3	0.1	
Symptomatic intracranial hemorrhage (ICH)	0.3	0.3	
Requiring inotropes	0.3	0.1	
Requiring surgical intervention	0.3	0.3	
Requiring transfusion (≥4 units)	0.7	0.5	
TIMI Minor bleeding	2.4	1.9	p=0.022

*Patients may be counted in more than one row.

In TRITON TIMI 38

Prasugrel didn't differ significantly in terms of Overall Mortality versus Clopidogrel

Table 2. Major Efficacy End Points in the Overall Cohort at 15 Months.*

End Point	Prasugrel (N = 6813)	Clopidogrel (N = 6795)	Hazard Ratio for Prasugrel (95% CI)	P Value†
	no. of patients (%)			
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary end point)	643 (9.9)	781 (12.1)	0.81 (0.73–0.90)	<0.001
Death from cardiovascular causes	133 (2.1)	150 (2.4)	0.89 (0.70–1.12)	0.31
Nonfatal MI	475 (7.3)	620 (9.5)	0.76 (0.67–0.85)	<0.001
Nonfatal stroke	61 (1.0)	60 (1.0)	1.02 (0.71–1.45)	0.93
Death from any cause	188 (3.0)	197 (3.2)	0.95 (0.78–1.16)	0.64
Death from cardiovascular causes, nonfatal MI, or urgent target-vessel revascularization	652 (10.0)	798 (12.3)	0.81 (0.73–0.89)	<0.001
Death from any cause, nonfatal MI, or nonfatal stroke	692 (10.7)	822 (12.7)	0.83 (0.75–0.92)	<0.001
Urgent target-vessel revascularization	156 (2.5)	233 (3.7)	0.66 (0.54–0.81)	<0.001
Death from cardiovascular causes, nonfatal MI, nonfatal stroke, or rehospitalization for ischemia	797 (12.3)	938 (14.6)	0.84 (0.76–0.92)	<0.001
Stent thrombosis‡	68 (1.1)	142 (2.4)	0.48 (0.36–0.64)	<0.001

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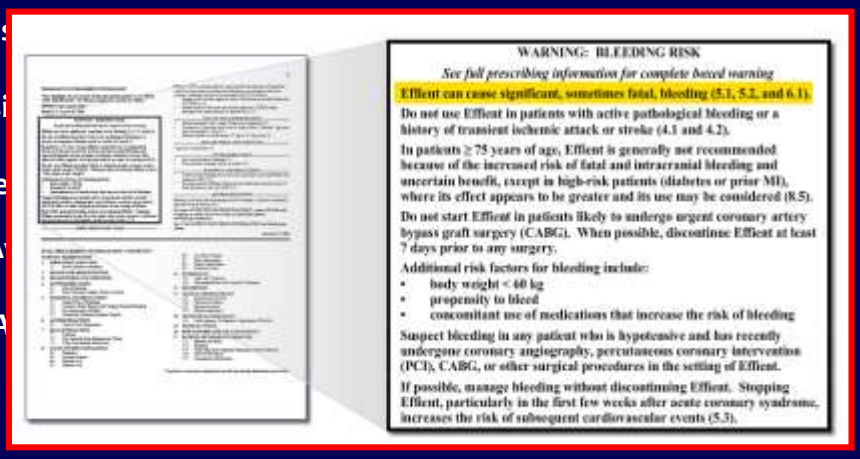
Prasugrel limitations

- Requires
- Irreversi
- Increase
- To be A
- To be A
- Can not



WARNING: BLEEDING RISK

See full prescribing information for complete boxed warning

Effient can cause significant, sometimes fatal, bleeding (5.1, 5.2, and 6.1).

Do not use Effient in patients with active pathological bleeding or a history of transient ischemic attack or stroke (4.1 and 4.2).

In patients ≥ 75 years of age, Effient is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk patients (diabetes or prior MI), where its effect appears to be greater and its use may be considered (8.5).

Do not start Effient in patients likely to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue Effient at least 7 days prior to any surgery.

Additional risk factors for bleeding include:

- body weight < 60 kg
- propensity to bleed
- concomitant use of medications that increase the risk of bleeding

Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of Effient.

If possible, manage bleeding without discontinuing Effient. Stopping Effient, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events (5.3).

1. Wallentin L. *Euro Heart J* 2009;30:1964-1977. 2. James S, et al. *Am Heart J* 2009;157:599-605. 3. Plavix. Summary of product characteristics. 2010.
4. Dahl MJ, Gunes A. *Pharmaceuticals* 2010;3:782-794. 5. Wiviott SD, et al. *N Engl J Med* 2007;357:2001-2015.
6. Wiviott SD, et al. (TRITON-TIMI 38). Am Heart J 2006;152:627–635. 7. Montalescot G, et al. N Engl J Med 2013;369:999–1010.
8. Nguyen TA. Et al. J Am Coll Cardiol, 005 Apr 19;45(8):1157-64

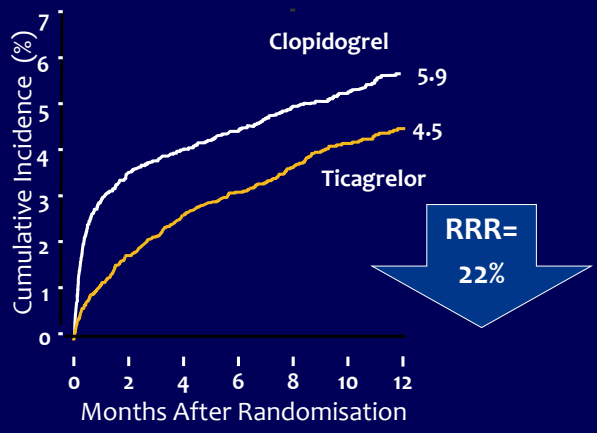
What's different with Ticagrelor?

- **Doesn't** Require metabolic activation
- **Rapid** onset of action within 30 minutes .
- **Reversible** $P2Y_{12}$ receptor binding
- **NO** inter-subject variation in IPA with Ticagrelor

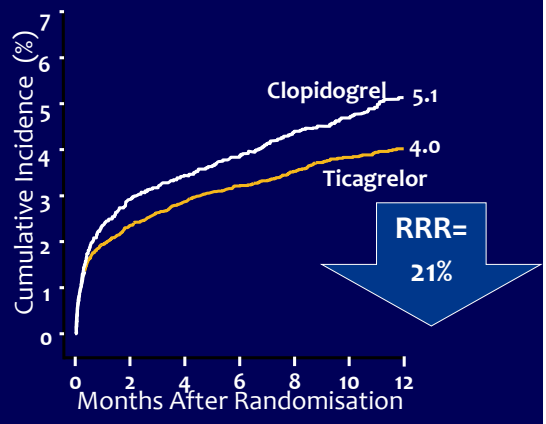
(IPA response **NOT** affected by *CYP2C19* polymorphisms)

In PLATO trial : Ticagrelor is The Only p2y12 Inhibitor Offering mortality benefits starting the 1st month up to a year of treatment

All causes of death



Cardiovascular Death



*** All-cause mortality was a secondary endpoint of the PLATO study and was 4.5% with BRILIQUE vs 5.9% with clopidogrel (1.4% ARR 22% RRR; HR 0.78; 95% CI 0.69-0.89; nominal p<0.001)**

Wallentin L et al. N Engl J Med 2009; 361: 1045-57.

In conclusion

- According to the latest European guidelines of ACS management Ticagrelor and Prasugrel are both indicated for AMI undergoing primary PCI with similar LOE and COR
- PRAGUE-18 study was investigated on only 1230 AMI planned for p PCI with no significant difference between Ticagrelor and Prasugrel in terms of efficacy and safety
- These observations need to be investigated on larger trials

Data in Hand …

- Compared to clopidogrel, Prasugrel showed significant efficacy results BUT
- Prasugrel can't be adminstered in patients of unknown coronary anatomy , patients with previuos history of TIA or stroke, and should be used cautiously in patients older than 75 years , or less than 60 kgs In weight
- Compared to clopidogrel, Ticagrelor showed significant efficacy results without increasing the incidence of major bleeding in all types of patients.
- Ticagrelor can be adminstered in the subset of Patients who can't receive Prasugrel .

Thank you