ONE-YEAR OUTCOMES

PRASUGREL VS. TICAGRELOR IN AMI TREATED WITH PPCI

PRAGUE-18 STUDY

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PRAGUE-18 Study Group

PRAGUE-18 study

Head-to-head randomized comparison of Prasugrel and Ticagrelor in patients with AMI undergoing pPCI

Prasugrel and Ticagrelor dose regimens according to the guidelines, intended treatment duration 12 months

Purely academic project, no industrial support

INCLUSION CRITERIA

- STEMI /very high-risk NSTEMI
- Primary PCI strategy:

  Immediate (<2 hs) CAG ± pPCI
- Signed informed consent

EXCLUSION CRITERIA

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

SAMPLE SIZE

Difference in primary EP 2.5%, a two-sided overall alpha level of 0.05, and a statistical power of 80%

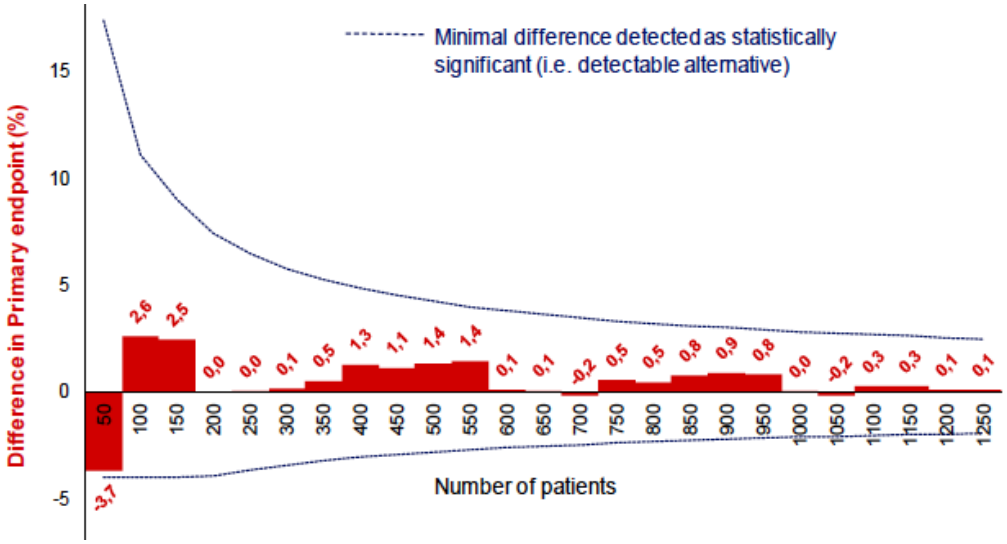
Needed sample size: 1250 each arm

Enrollment terminated prematurely because of futility

Randomized 1230 patients; 634 Prasugrel / 596 Ticagrelor

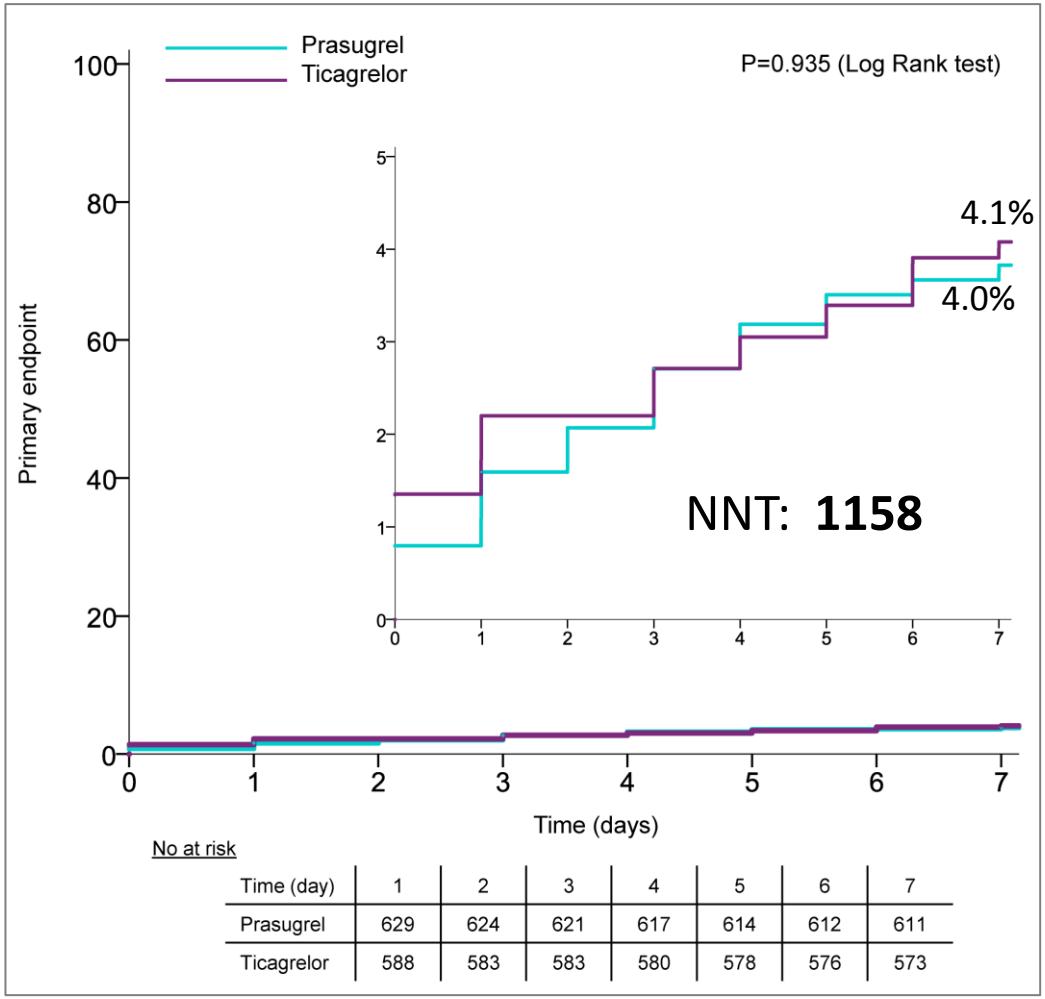
FUTILITY ANALYSIS

COMPARISON OF REAL DIFFERENCES IN 1° EP AND THE MINIMAL DIFFERENCE DETECTED AS STATISTICALLY SIGNIFICANT BASED ON POWER ANALYSIS



1° NET-CLINICAL ENDPOINT AT DAY 7

All-cause Death/reMI/urgent TVR/Stroke/Serious bleeding



No at risk

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

SWITCH TO CLOPIDOGREL AFTER DISCHARGE

Prior the end of their hospitalization, every patient was informed

- **about the out-of-pocket costs for study drugs**
- **about the clinical benefit of long-term prasugrel/ticagrelor compared to clopidogrel**

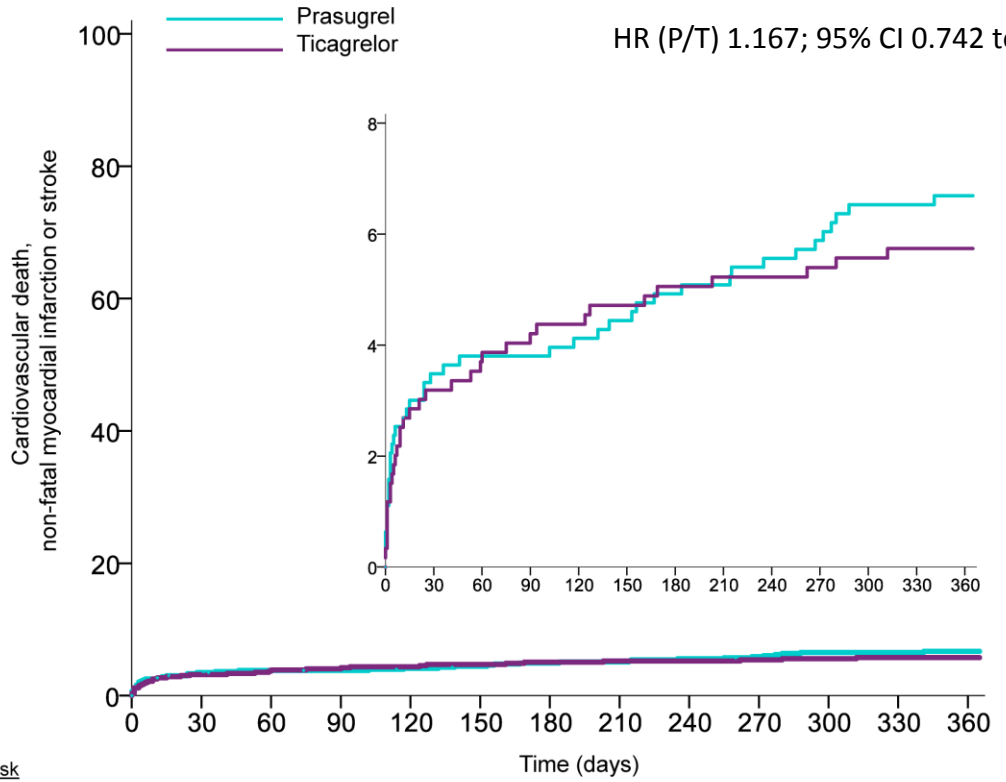
The study protocol allowed patients, who were not willing to accept the costs associated with a study medication, to switch to clopidogrel

OBJECTIVE

1) Comparison of efficacy and safety between Prasugrel and Ticagrelor during the whole 12-months study period

1) Risk of major ischemic events related to an economically motivated post-discharge switch to clopidogrel

KEY EFFICACY ENDPOINT: CV Death/Non-fatal MI/Stroke



HR (P/T) 1.167; 95% CI 0.742 to 1.835, P=0.503 (Log Rank test)

No at risk

Time (day)	30	60	90	120	150	180	210	240	270	300	330	360
Prasugrel	608	603	602	599	596	593	592	589	586	580	576	550
Ticagrelor	575	568	565	562	559	557	556	556	555	554	552	530

END POINTS

	Prasugrel	Ticagrelor	P-value
CV Death, Non-fatal MI or Stroke	42 (6.6%)	34 (5.7%)	0.503
Death from cardiovascular causes	21 (3.3%)	18 (3.0%)	0.769
Non-fatal myocardial infarction	19 (3.0%)	15 (2.5%)	0.611
Stroke	7 (1.1%)	4 (0.7%)	0.423
Definite stent thrombosis	7 (1.1%)	9 (1.5%)	0.535
Death from any cause	30 (4.7%)	25 (4.2%)	0.654
Bleeding	69 (10.9%)	66 (11.1%)	0.930
TIMI major	6 (0.9%)	4 (0.7%)	0.754
BARC ≥ 3	15 (2.4%)	9 (1.5%)	0.308

SWITCH TO CLOPIDOGREL

	Prasugrel	Ticagrelor	P-value
Economic reasons (Patient cost sharing)	216 (34.1%)	265 (44.4%)	**0.003**
Chronic anticoagulation therapy	19 (3.0%)	21 (3.5%)	0.999
Adverse effects	31 (4.9%)	24 (4.0%)	0.999
Other	44 (7.0%)	39 (6.5%)	0.999

		HR (95% CI)	P-value
Risk of ischemic endpoint *	**Economically motivated switch** (N=481)	**0.433 (0.210–0.894)**	**0.024**
	Switch from other reasons (N=178)	**3.420 (1.823–6.415)**	**<0.001**
Risk of bleeding	**Economically motivated switch** (N=481)	**0.416 (0.246–0.701)**	**0.001**

* Cardiovascular death, non-fatal myocardial infarction or stroke.

The hazard ratio was based on the Cox proportional hazard model with time dependent covariates

Significant differences in patient- and procedure related characteristics and economically motivated switch to clopidogrel

	SWITCH TO CLOPIDOGREL		P-value
	No	Yes	
BMI > 30	223 (29.8%)	172 (35.8%)	0.029
ECG			
Left bundle branch block	17 (2.3%)	1 (0.2%)	0.002
Bundle branch block	33 (4.4%)	7 (1.5%)	0.005
Killip classification			
I	642 (85.7%)	443 (92.1%)	0.004
II	59 (7.9%)	23 (4.8%)	
III	11 (1.5%)	6 (1.2%)	
IV	37 (4.9%)	9 (1.9%)	
I	642 (85.7%)	443 (92.1%)	<0.001
≥ II	107 (14.3%)	38 (7.9%)	
History			
Hypertension	359 (47.9%)	271 (56.3%)	0.004
Smoker	467 (62.3%)	331 (68.8%)	0.023
Left main disease	36 (4.8%)	5 (1.0%)	<0.001
Postprocedural result – suboptimal + failure	44 (5.9%)	15 (3.1%)	0.028

CONCLUSIONS

1) Prasugrel and Ticagrelor are similarly effective and safe during the first year after MI treated with pPCI

1) Economically motivated, early post-discharge switch to clopidogrel, when approved by treating physicians, was not associated with increased risk of ischemic events

Accepted Manuscript

One-year Outcomes of Prasugrel Versus Ticagrelor In Acute Myocardial Infarction Treated With Primary Angioplasty: The PRAGUE-18 Study

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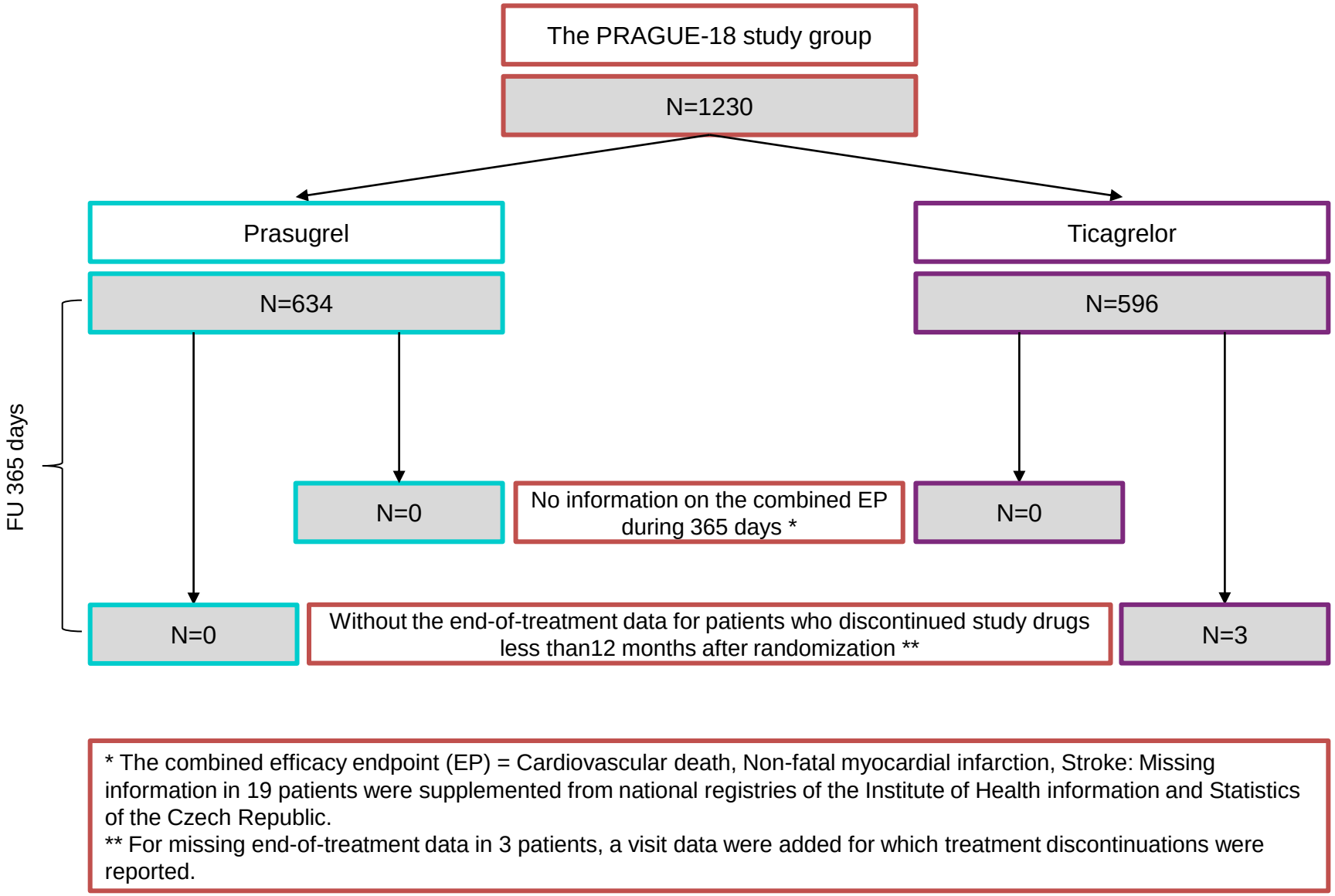
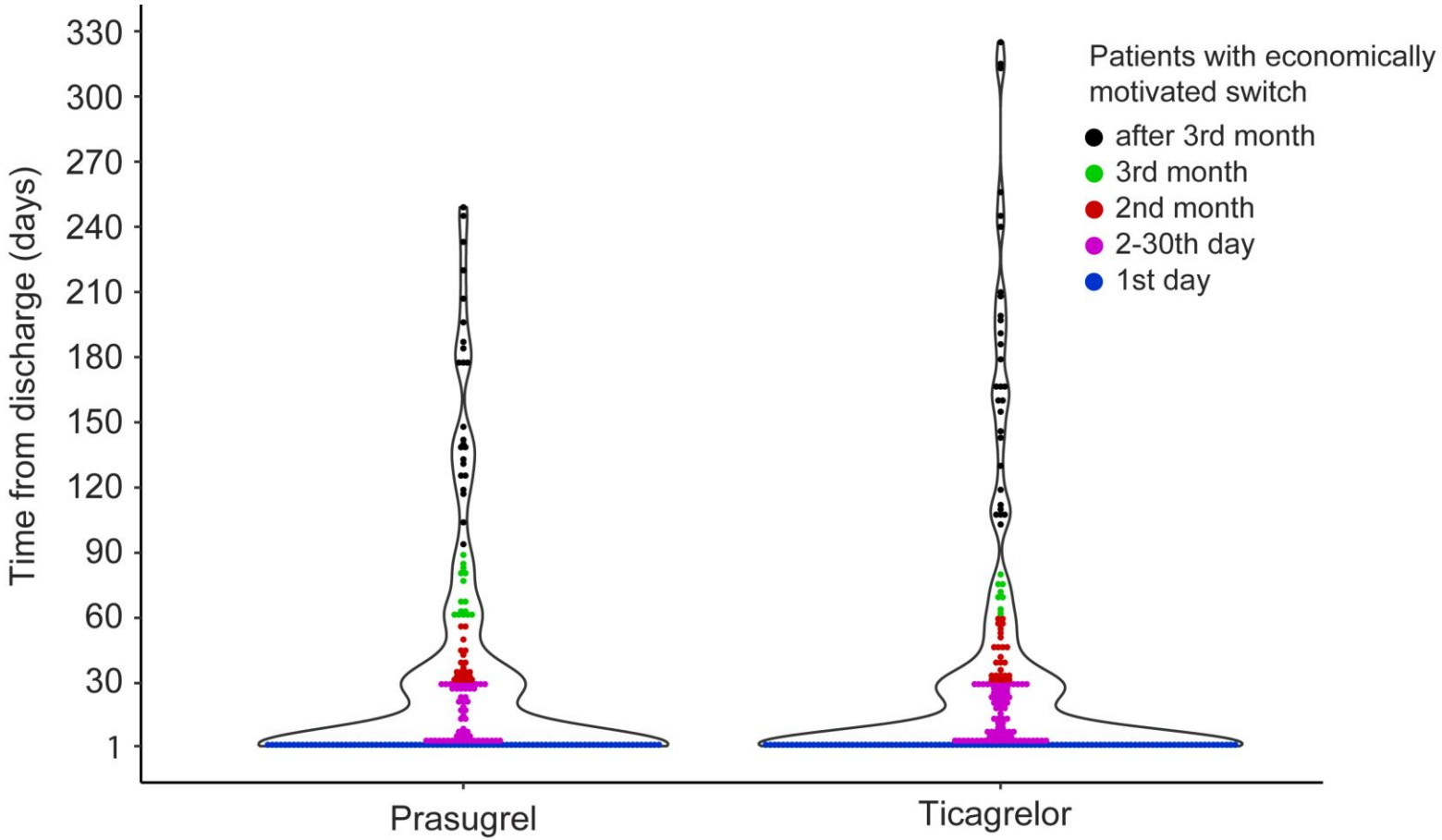
Back-up slides

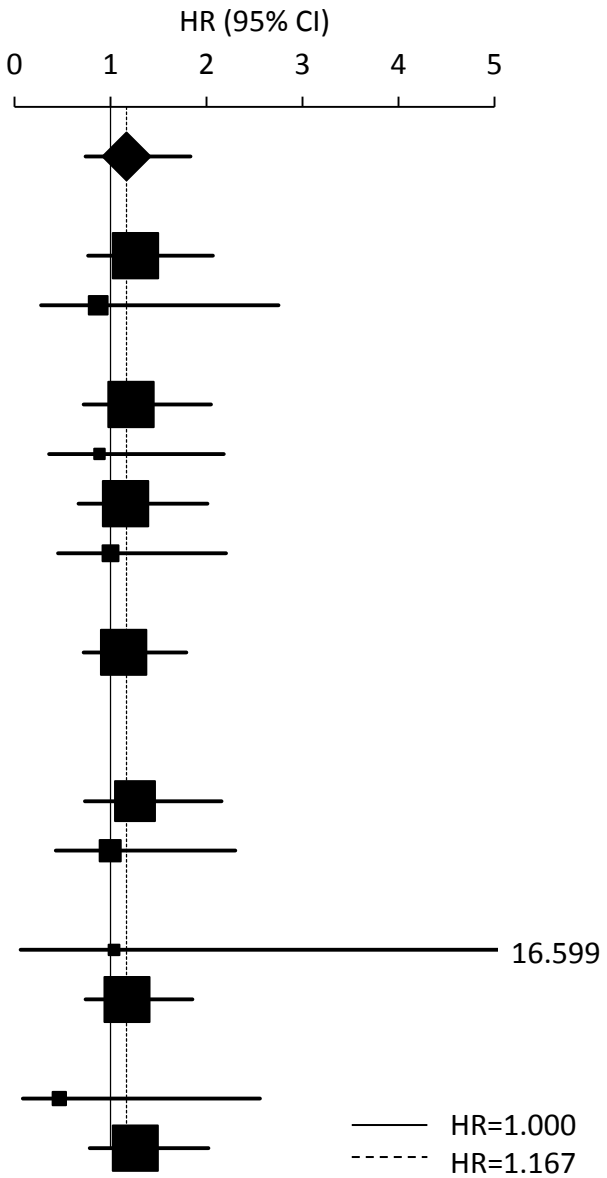


* The combined efficacy endpoint (EP) = Cardiovascular death, Non-fatal myocardial infarction, Stroke: Missing information in 19 patients were supplemented from national registries of the Institute of Health information and Statistics of the Czech Republic.
** For missing end-of-treatment data in 3 patients, a visit data were added for which treatment discontinuations were reported.

Time distribution of economically motivated switches to clopidogrel after discharge



	Patients	Ischemic endpoint		HR (95% CI)	P-value for
		Prasugrel	Ticagrelor	Prasugrel : Ticagrelor	interaction
Total					
	N=1230	42 (6.6%)	34 (5.7%)	1.167 (0.742–1.835)	-
Age					
<75	N=1108	37 (6.4%)	27 (5.1%)	1.260 (0.767–2.069)	0.565
≥75	N=122	5 (9.3%)	7 (10.3%)	0.873 (0.277–2.751)	
Killip classification					
I–III	N=1184	32 (5.3%)	25 (4.3%)	1.214 (0.720–2.049)	0.564
IV	N=46	10 (40.0%)	9 (42.9%)	0.886 (0.360–2.182)	
I+II	N=1167	28 (4.7%)	23 (4.0%)	1.158 (0.667–2.010)	0.772
III+IV	N=63	14 (40.0%)	11 (39.3%)	1.000 (0.454–2.204)	
Chronic kidney disease					
No	N=1214	41 (6.6%)	34 (5.8%)	1.138 (0.722–1.793)	–
Yes	N=16	1 (12.5%)	0 (0.0%)	–	
Diabetes					
No	N=980	31 (6.1%)	23 (4.9%)	1.257 (0.733–2.156)	0.642
Yes	N=250	11 (8.7%)	11 (8.9%)	0.998 (0.433–2.302)	
Weight					
< 60	N=27	1 (7.7%)	1 (7.1%)	1.038 (0.065–16.599)	0.926
≥ 60	N=1203	41 (6.6%)	33 (5.7%)	1.173 (0.742–1.855)	
STEMI					
No	N=72	2 (5.6%)	4 (11.1%)	0.468 (0.086–2.558)	0.274
Yes	N=1158	40 (6.7%)	30 (5.3%)	1.259 (0.784–2.021)	



CLINICAL SIGNIFICANCE
NUMBER NEEDED TO TREAT

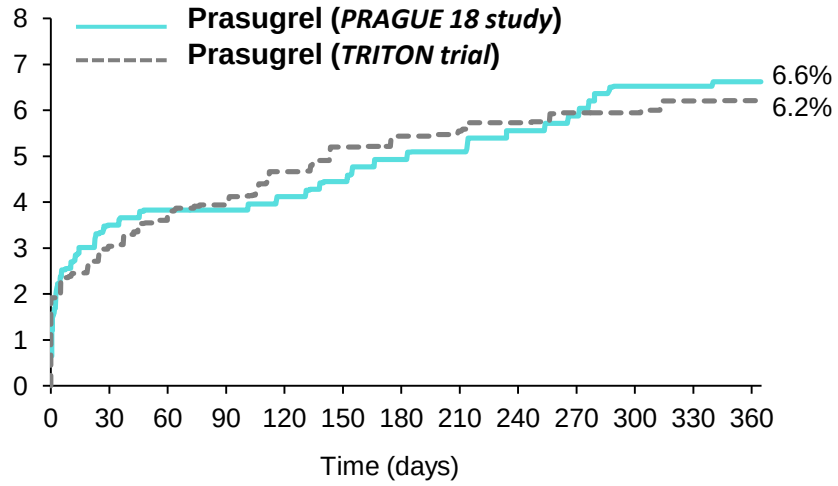
Preference of Prasugrel/Ticagrelor over Clopidogrel

TRITON Primary ischemic EP Difference: **2.2%** NNT: **46**
PLATO Primary ischemic EP Difference: **1.9%** NNT: **53**

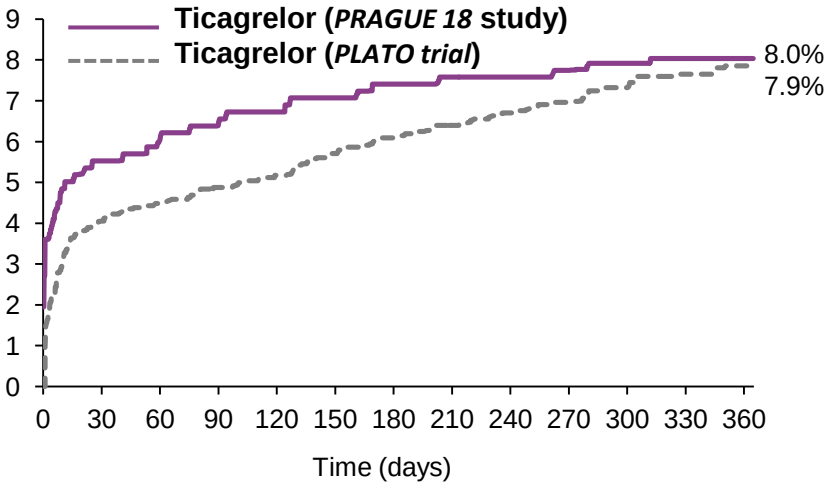
Non-preference between Prasugrel/Ticagrelor

PRAGUE-18
Primary Net-clinical EP difference: **0.1%** NNT: **1158**
Like PLATO/TRITON Primary EP Difference: **0.3%** NNT: **333**

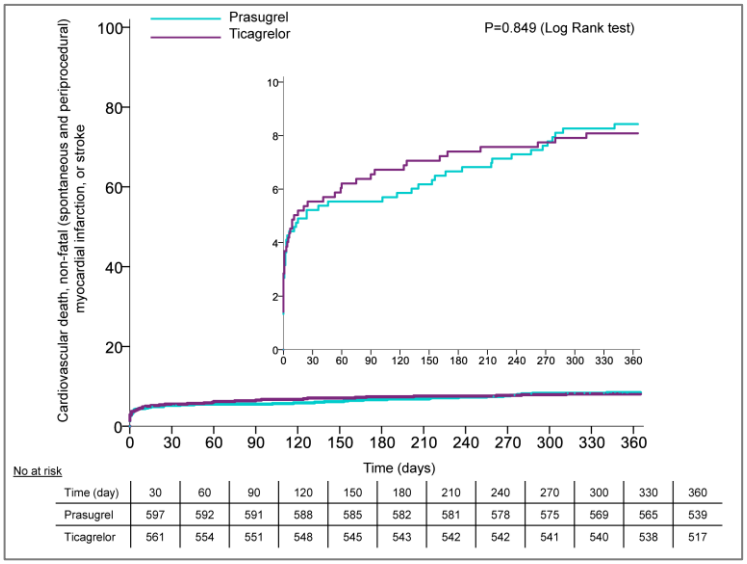
CV Death/Spontanoeus MI/Stroke



CV Death/Spont. + Peri-PCI MI/Stroke



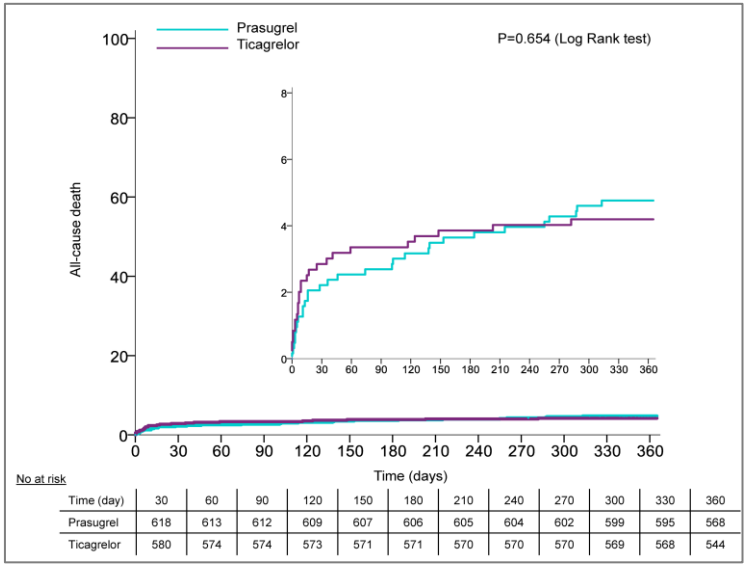
CV DEATH/SPONT. + PERI-PCI MI/STROKE



No at risk

Time (day)	30	60	90	120	150	180	210	240	270	300	330	360
Prasugrel	597	592	591	588	585	582	581	578	575	569	565	539
Ticagrelor	561	554	551	548	545	543	542	542	541	540	538	517

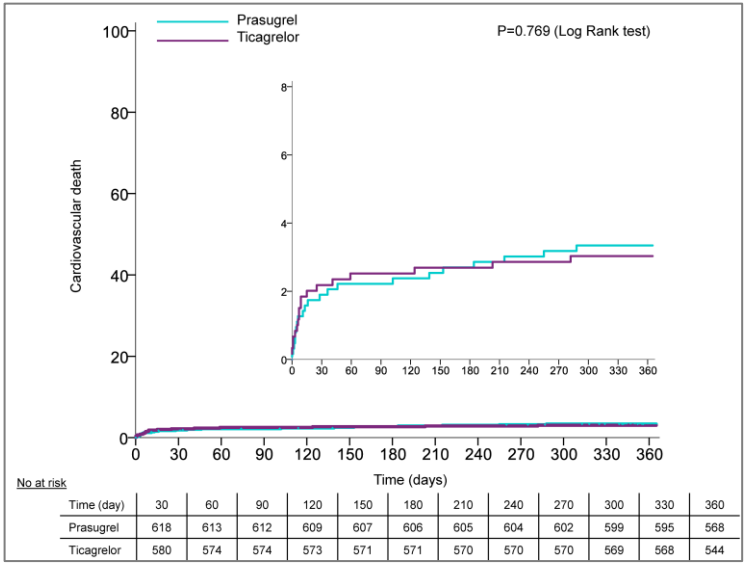
ALL-CAUSE DEATH



No at risk

Time (day)	30	60	90	120	150	180	210	240	270	300	330	360
Prasugrel	618	613	612	609	607	606	605	604	602	599	595	568
Ticagrelor	580	574	574	573	571	571	570	570	570	569	568	544

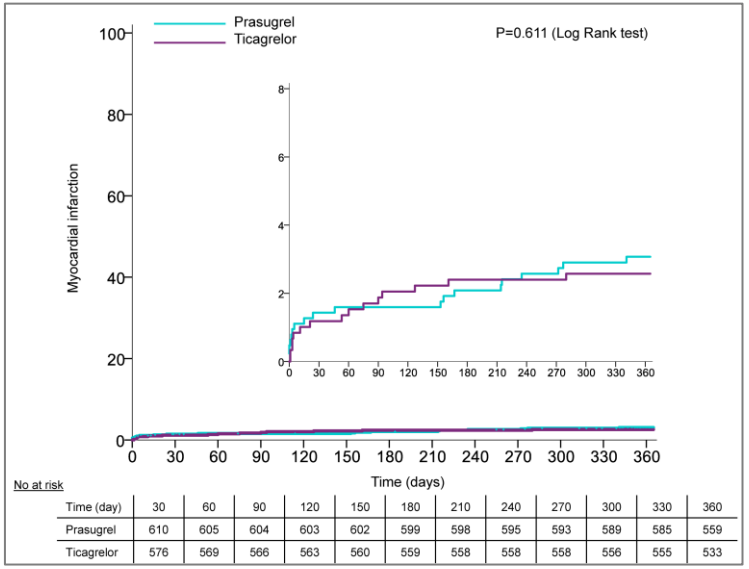
CARDIOVASCULAR DEATH



No at risk

Time (day)	30	60	90	120	150	180	210	240	270	300	330	360
Prasugrel	618	613	612	609	607	606	605	604	602	599	595	568
Ticagrelor	580	574	574	573	571	571	570	570	570	569	568	544

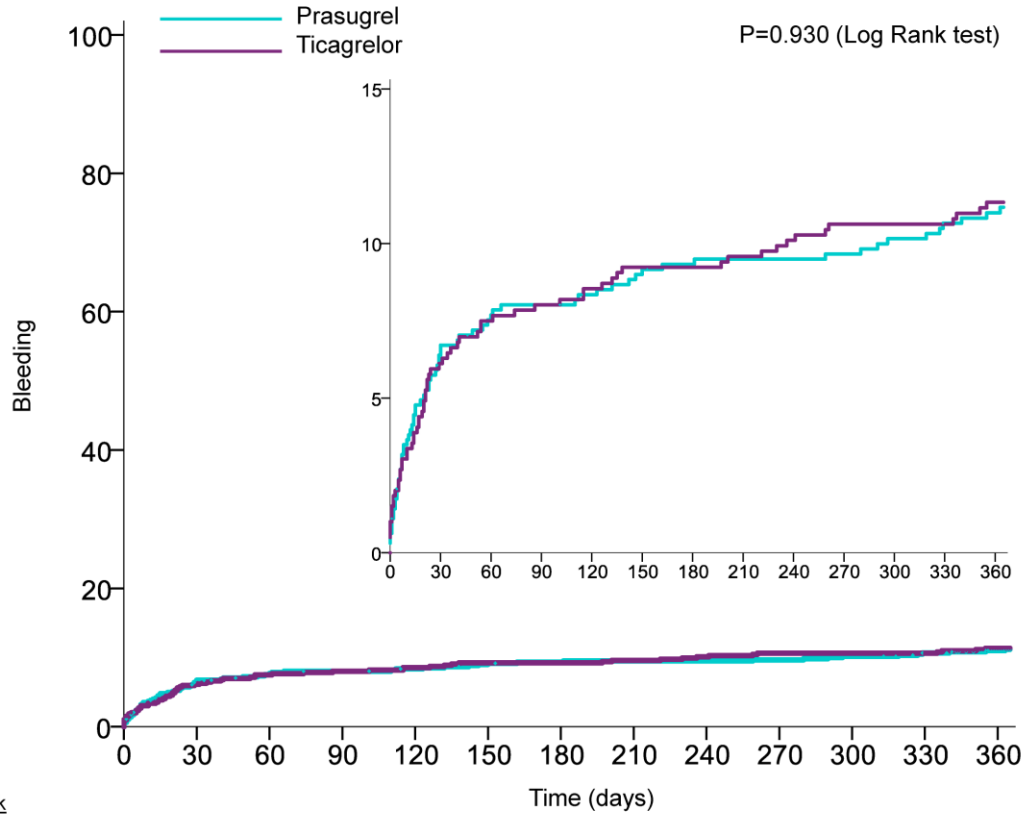
NON-FATAL MYOCARDIAL INFARCTION



No at risk

Time (day)	30	60	90	120	150	180	210	240	270	300	330	360
Prasugrel	610	605	604	603	602	599	598	595	593	589	585	559
Ticagrelor	576	569	566	563	560	559	558	558	558	556	555	533

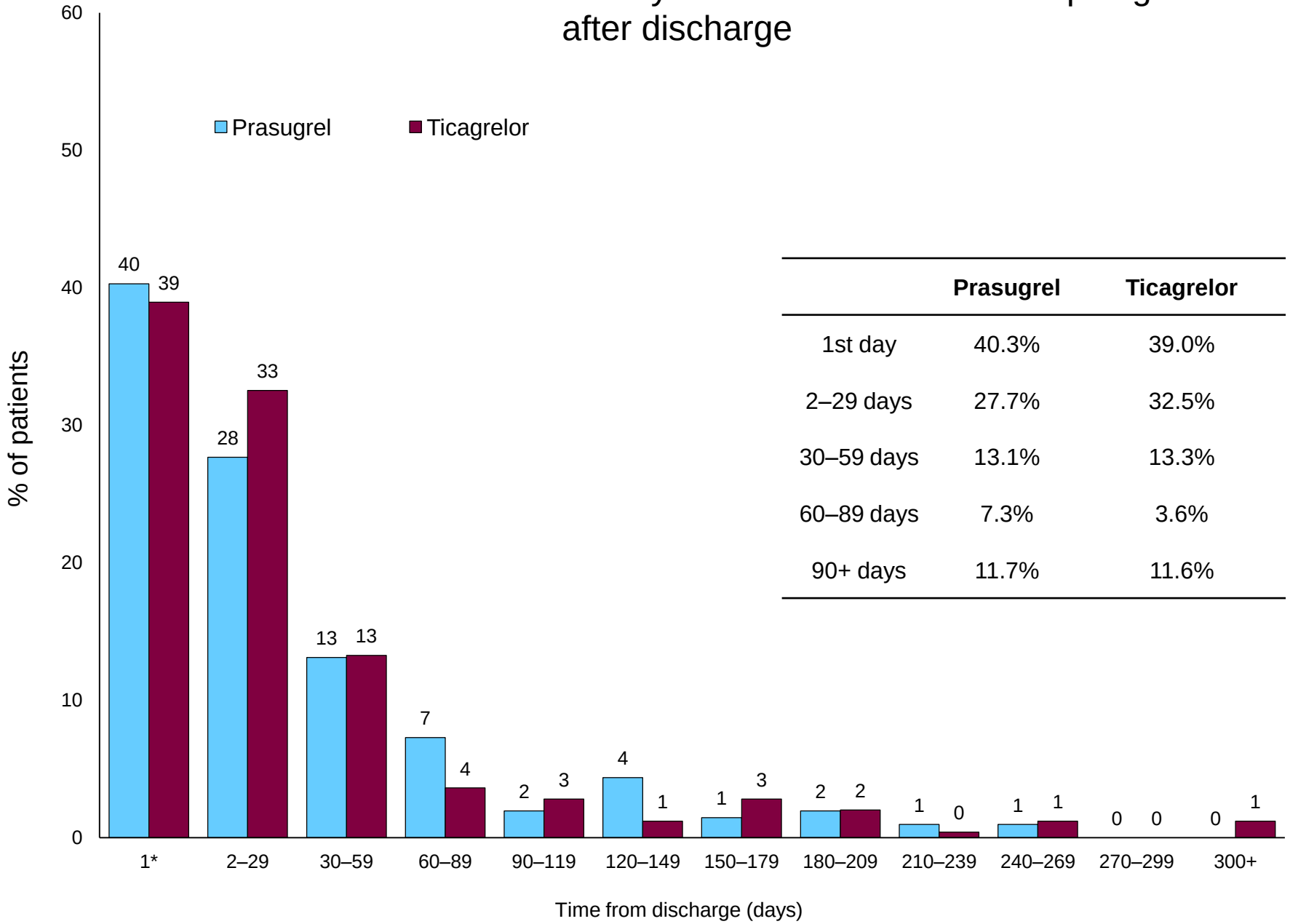
SAFETY



No at risk

Time (day)	30	60	90	120	150	180	210	240	270	300	330	360
Prasugrel	579	567	563	559	554	551	550	550	547	542	535	513
Ticagrelor	547	534	531	527	522	522	519	516	513	512	511	485

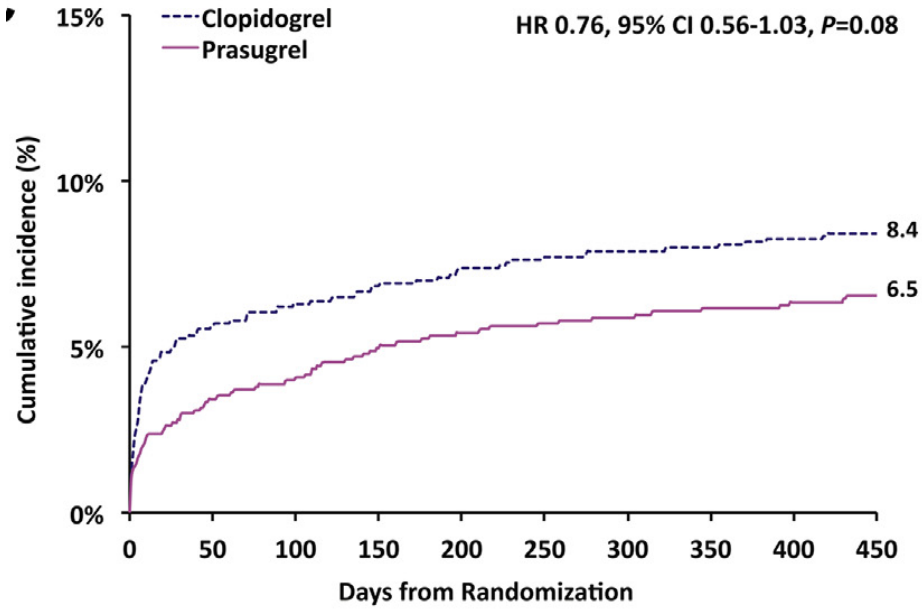
Time distribution of economically motivated switches to clopidogrel after discharge



	Prasugrel	Ticagrelor
1st day	40.3%	39.0%
2–29 days	27.7%	32.5%
30–59 days	13.1%	13.3%
60–89 days	7.3%	3.6%
90+ days	11.7%	11.6%

BENEFIT OF DAPT IN STEMI and pPCI

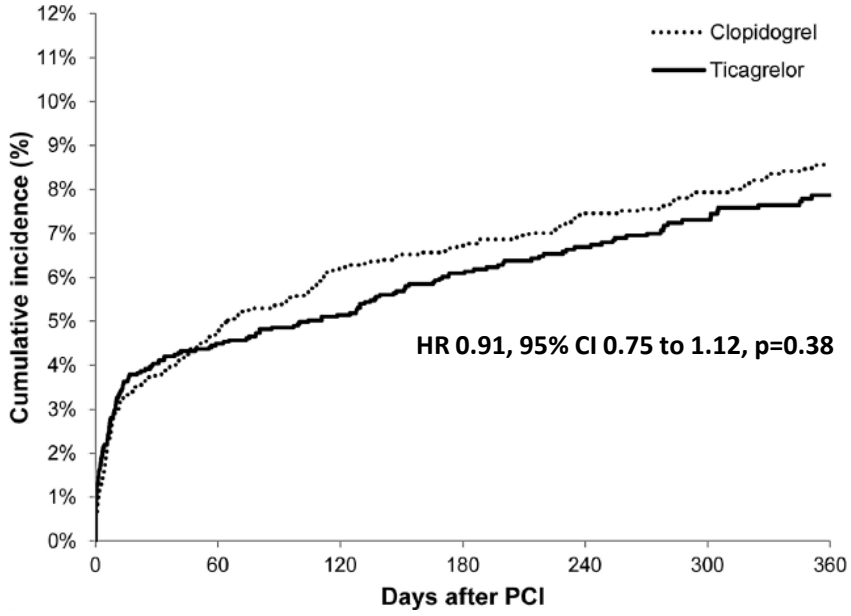
"Spontaneous" primary endpoint (CV death, nonprocedural MI, stroke) among primary PCI patients



TRITON trial

J Am Coll Cardiol Intv 2014;7:604

Primary endpoint (CV death, MI, stroke) among primary PCI patients



PLATO trial

Heart 2016;102:617

Weighing Benefits and Risks — The FDA's Review of Prasugrel

Ellis F. Unger, M.D.

Patients with Outcome Events in TRITON–TIMI 38.*

Patient Group at Presentation	Treatment Group		Relative Risk Reduction (95% CI)†	P Value
	Prasugrel	Clopidogrel	%	
Unstable angina and non–ST-segment-elevation myocardial infarction				
No. of patients	5044	5030		
End-point event (% of patients)				
Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	9.3	11.2	18.0 (7.3 to 27.4)	0.002
Cardiovascular death	1.8	1.8	2.1 (–30.9 to 26.8)	0.89
Nonfatal myocardial infarction	7.1	9.2	23.9 (12.7 to 33.7)	<0.001
Nonfatal stroke	0.8	0.8	2.1 (–51.3 to 36.7)	0.92
ST-segment-elevation myocardial infarction				
No. of patients	1769	1765		
End-point event (% of patients)				
Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	9.8	12.2	20.7 (3.2 to 35.1)	0.02
Cardiovascular death	2.4	3.3	26.2 (–9.4 to 50.3)	0.13
Nonfatal myocardial infarction	6.7	8.8	25.4 (5.2 to 41.2)	0.02
Nonfatal stroke	1.2	1.1	–9.7 (–104 to 41.0)	0.77
Overall				
No. of patients	6813	6795		
End-point event (% of patients)				
Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	9.4	11.5	18.8 (9.8 to 26.8)	<0.001
Cardiovascular death	2.0	2.2	11.4 (–11.8 to 29.9)	0.31
Nonfatal myocardial infarction	7.0	9.1	24.3 (14.7 to 32.8)	<0.001
Nonfatal stroke	0.9	0.9	–1.6 (–45.1 to 28.8)	0.93

ment. The FDA made sure that prasugrel's label clearly articulates the balance between efficacy and risk — a balance that physicians will need to assess carefully when choosing treatment for individual patients.

NEJM 2009