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## ONE-YEAR OUTCOMES

PRASUGREL VS. TICAGRELOR IN AMI TREATED WITH PPCI

PRAGUE-18 STUDY

Zuzana Motovska, Petr Widimsky on behalf  
of the PRAGUE-18 study investigators

## Slide 1

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**1**

Zuzana Motovska, 11/10/2017

# 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%

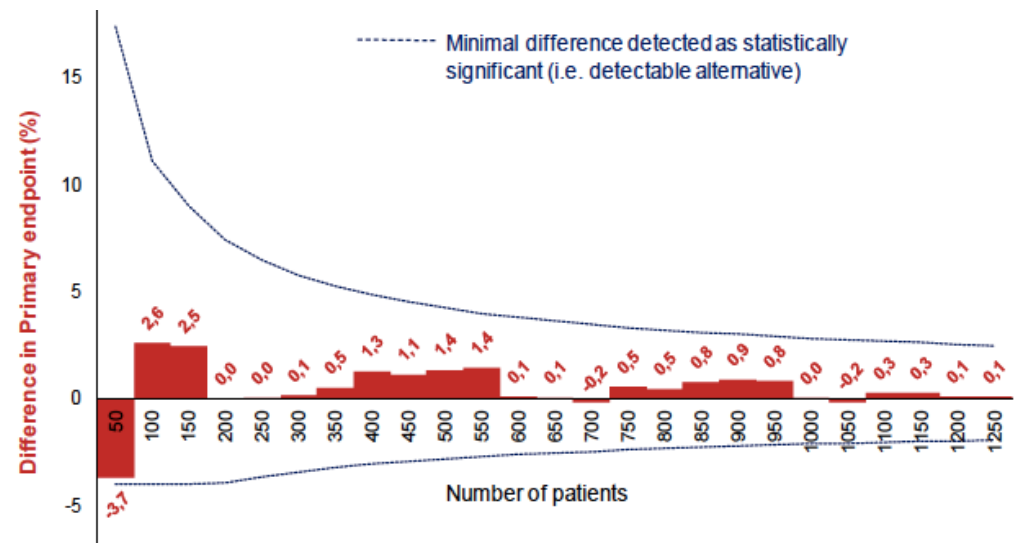
Needed sample size: 1250 each arm

Enrollment terminated prematurely because of futility

Randomized 1230 patients; 634 Prasugrel / 596 Ticagrelor

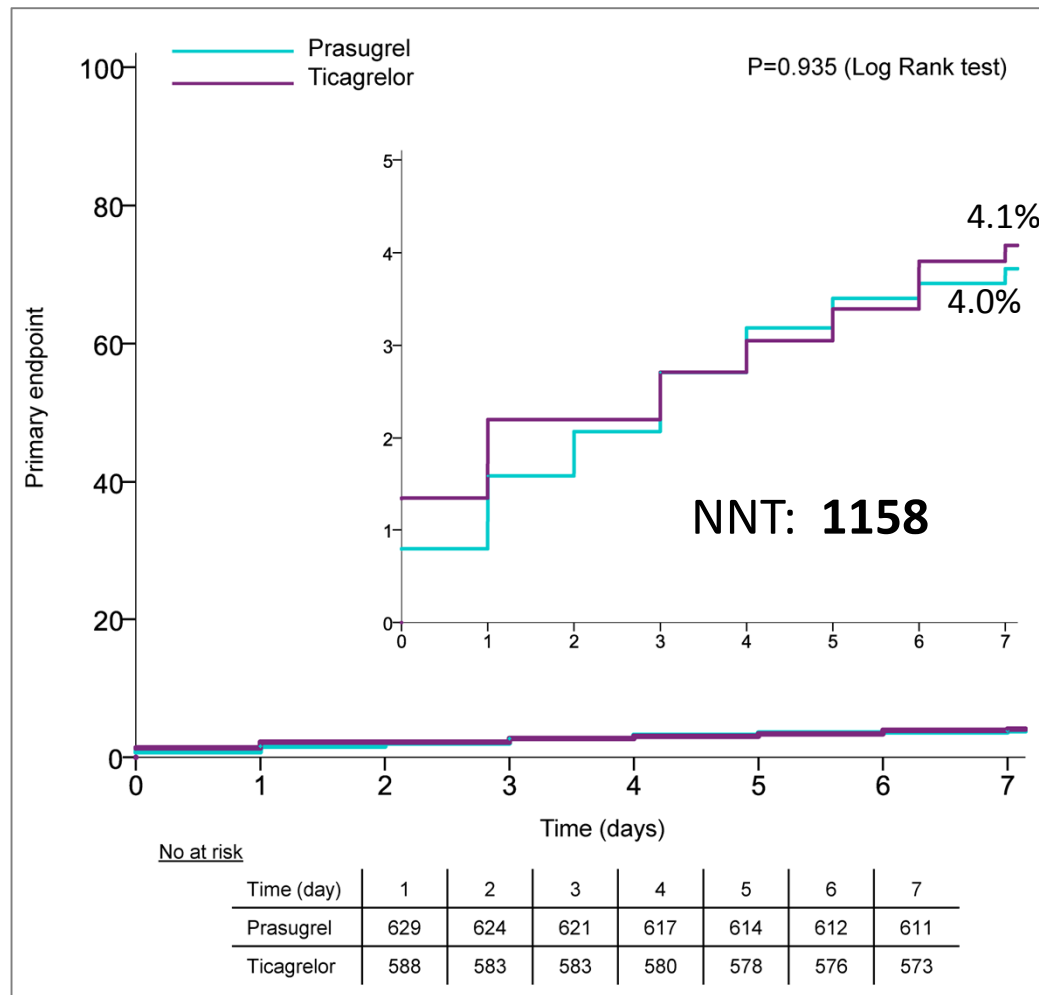
## FUTILITY ANALYSIS

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



## SWITCH TO CLOPIDOGREL AFTER DISCHARGE

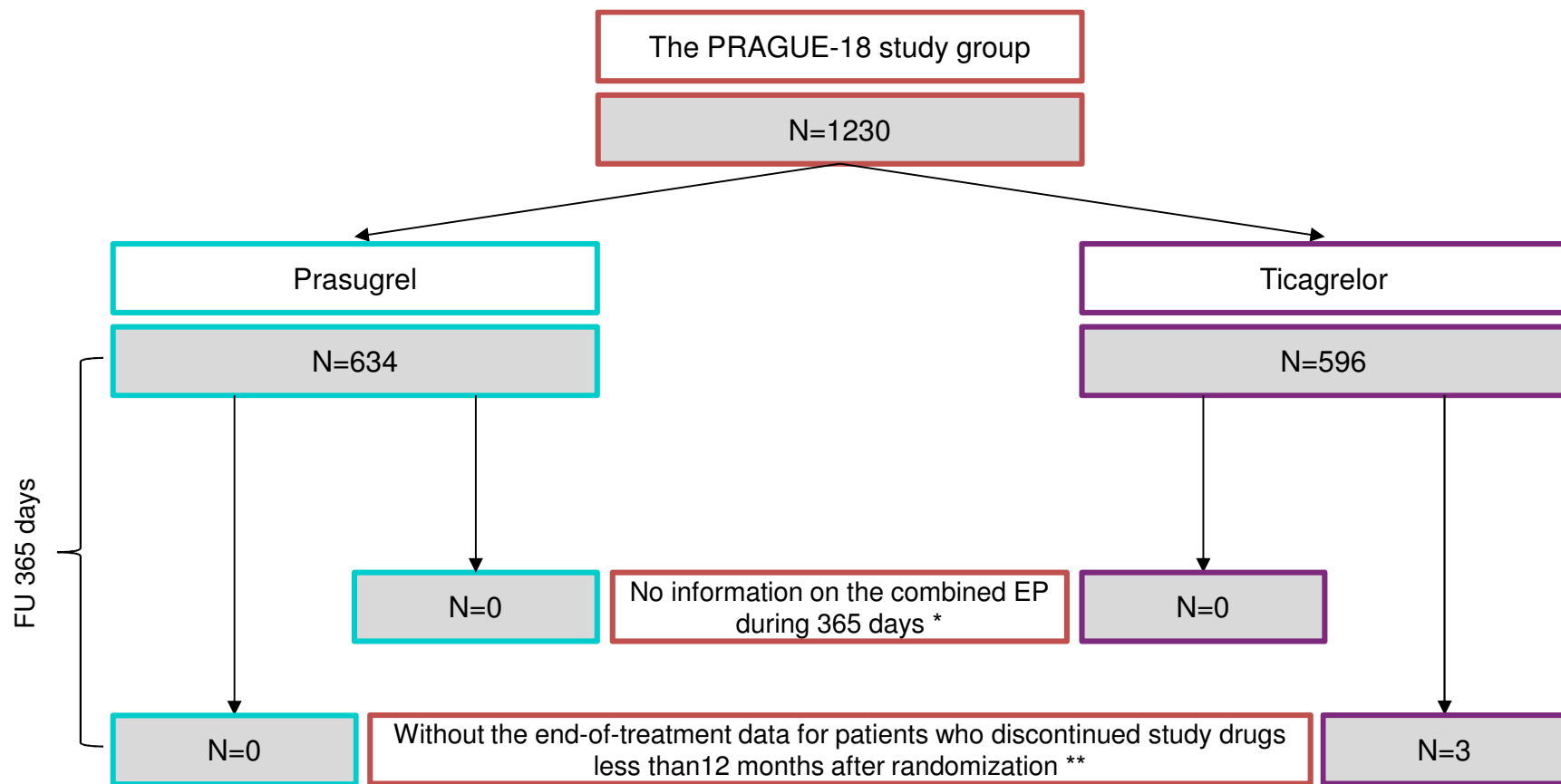
**Prior the end of their hospitalization, every patient was informed**

- **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

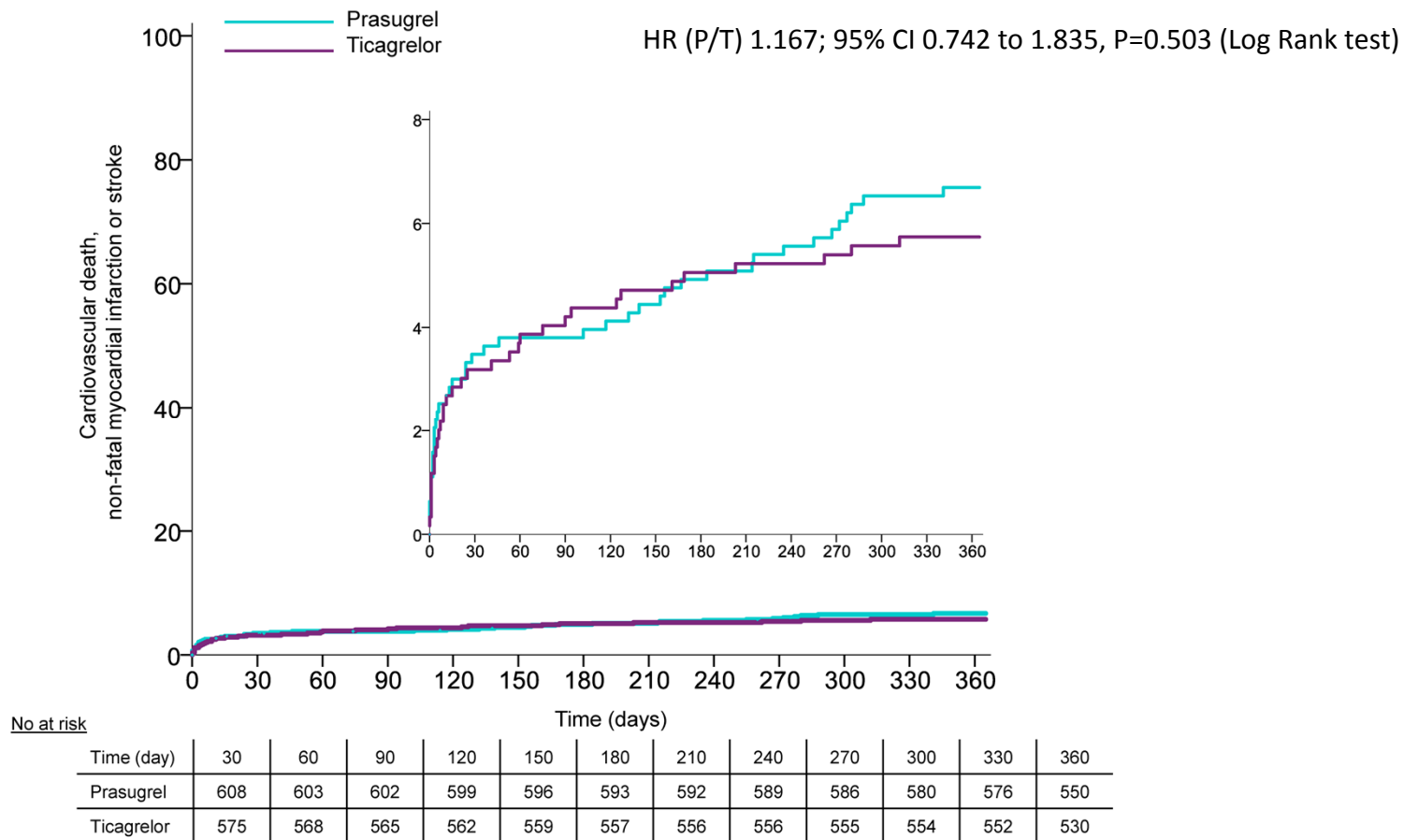
- 1) Comparison of efficacy and safety between Prasugrel and Ticagrelor during the whole 12-months study period
- 1) Risk of major ischemic events related to an economically motivated post-discharge switch to clopidogrel



\* 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.

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



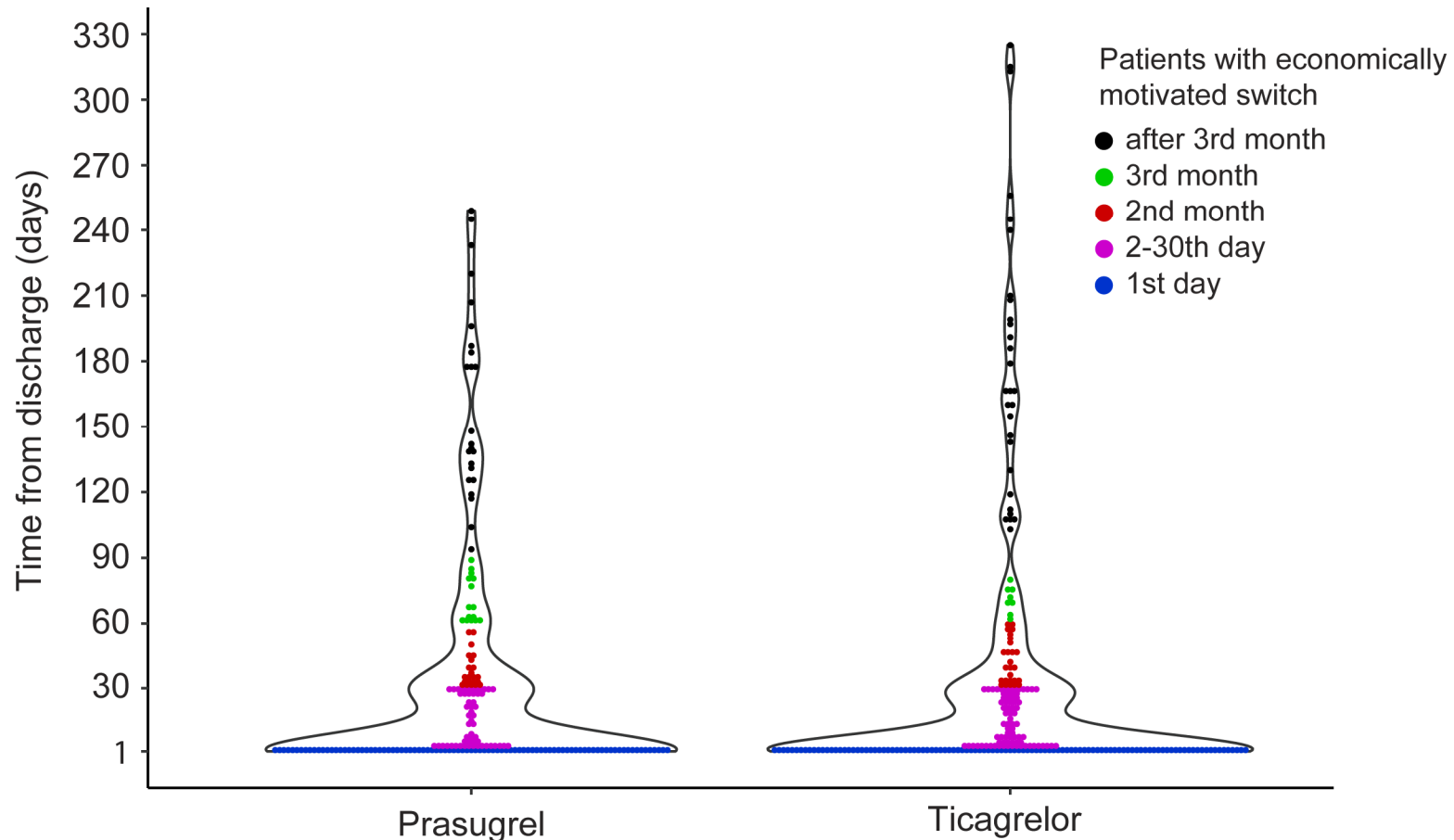
# END POINTS

	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 $\geq 3$	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%)	<b>0.003</b>
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

# Time distribution of economically motivated switches to clopidogrel after discharge



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

\* 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 ≥ II	642 (85.7%) 107 (14.3%)	443 (92.1%) 38 (7.9%)	<0.001
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

Zuzana Motovska, MD, PhD, Ota Hlinomaz, MD, CSc, Petr Kala, MD, PhD, Milan Hromadka, MD, PhD, Jiri Knot, MD, PhD, Ivo Varvarovsky, MD, PhD, Jaroslav Dusek, MD, PhD, Jiri Jarkovsky, MSc, PhD, Roman Miklik, MD, PhD, Richard Rokyta, MD, PhD, Frantisek Tousek, MD, Petra Kramarikova, Mgr, Michal Svoboda, MSc, Bohumil Majtan, MD, Stanislav Simek, MD, CSc, Marian Branny, MD, PhD, Jan Mrozek, MD, Pavel Cervinka, MD, PhD, Jiri Ostransky, MD, Petr Widimsky, MD, DrSc, PRAGUE-18 Study Group

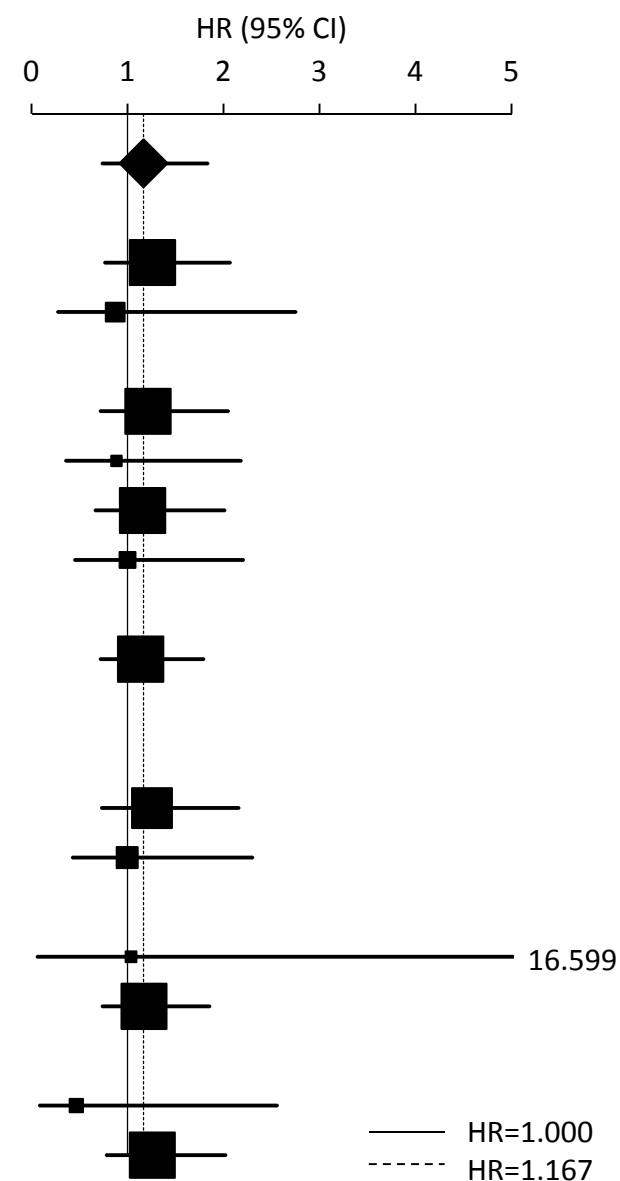
PII: S0735-1097(17)41524-5

DOI: [10.1016/j.jacc.2017.11.008](https://doi.org/10.1016/j.jacc.2017.11.008)

Reference: JAC 24432

# Back-up slides

	Patients	Ischemic endpoint		HR (95% CI)	P-value for interaction
		Prasugrel	Ticagrelor	Prasugrel : Ticagrelor	
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**

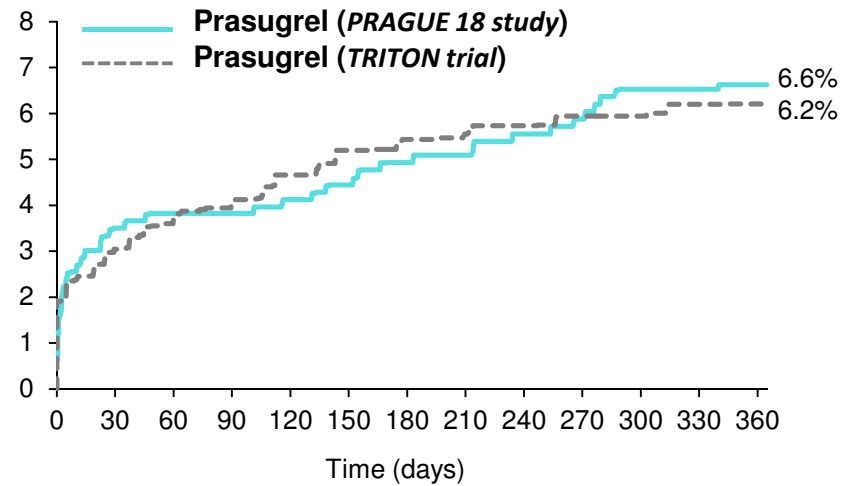
### Non-preference between Prasugrel/Ticagrelor

PRAGUE-18

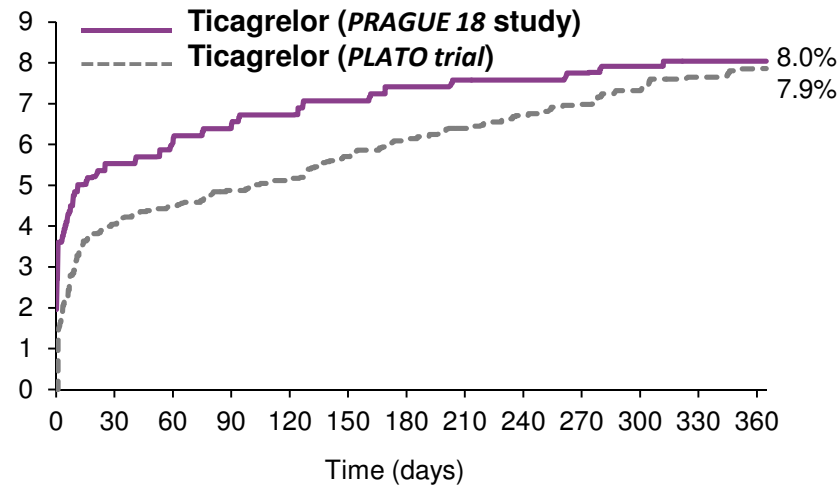
Primary Net-clinical EP difference: **0.1%** NNT: **1158**

Like PLATO/TRITON Primary EP Difference: **0.3%** NNT: **333**

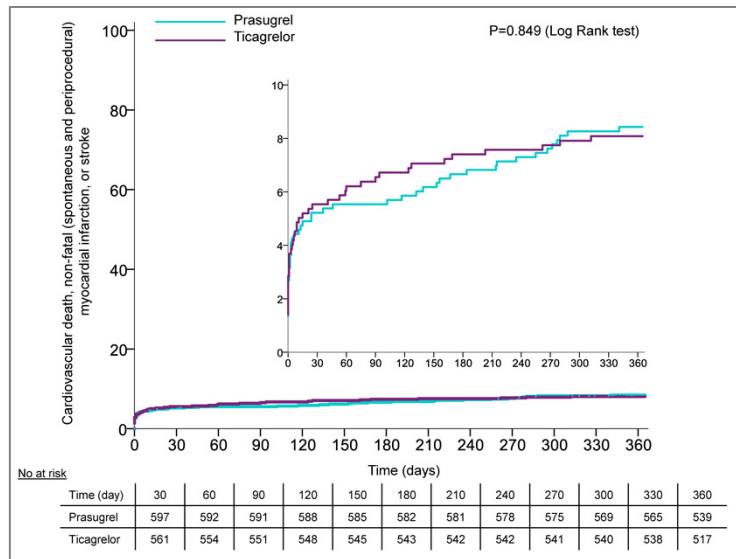
## CV Death/Spontaneous MI/Stroke



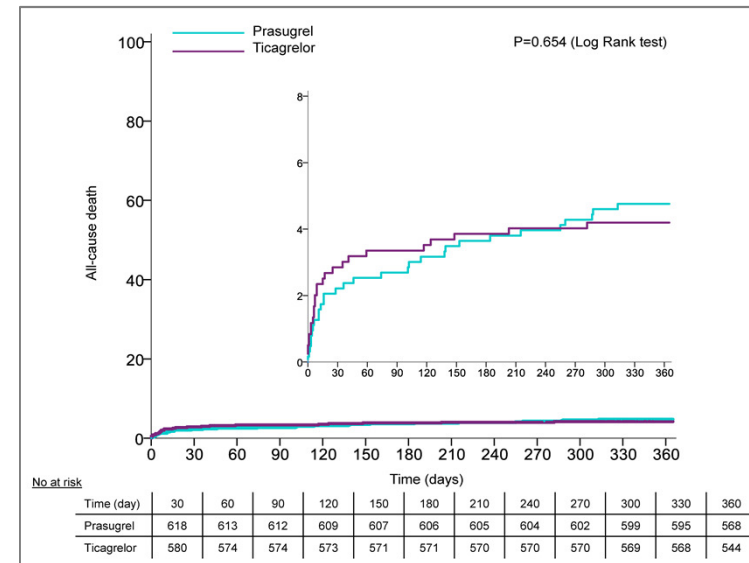
## CV Death/Spont. + Peri-PCI MI/Stroke



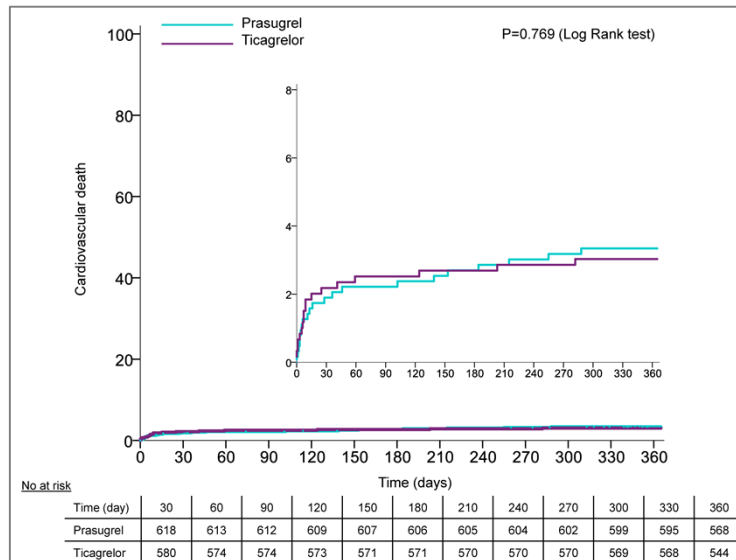
## CV DEATH/SPONT. + PERI-PCI MI/STROKE



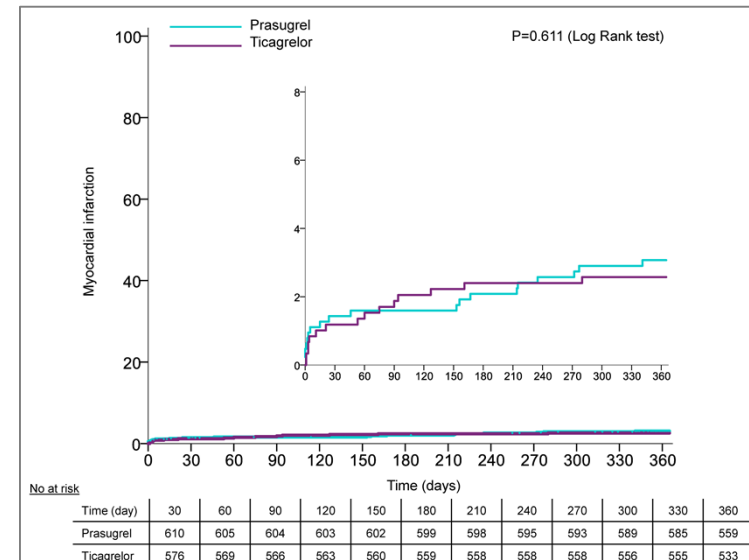
## ALL-CAUSE DEATH



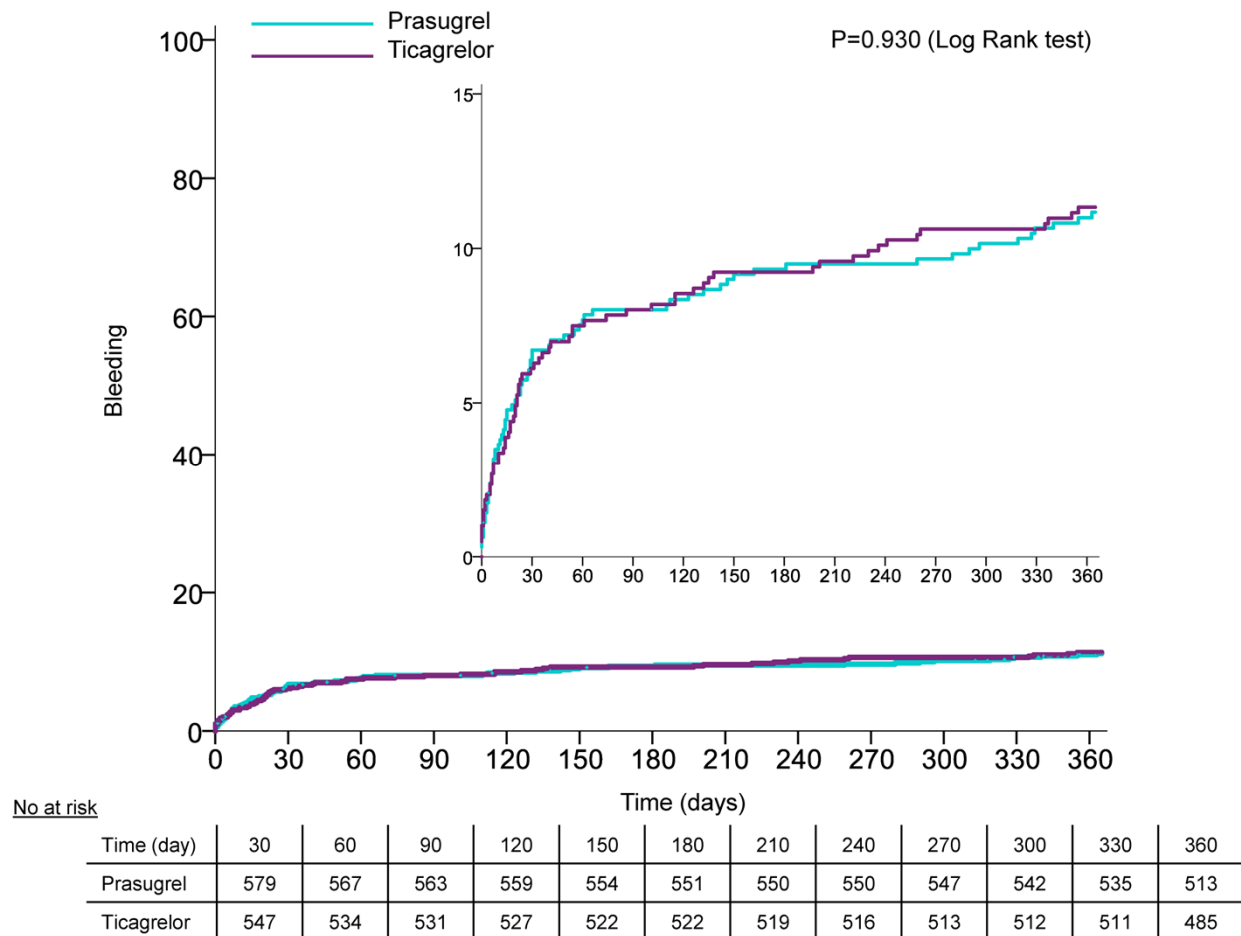
## CARDIOVASCULAR DEATH



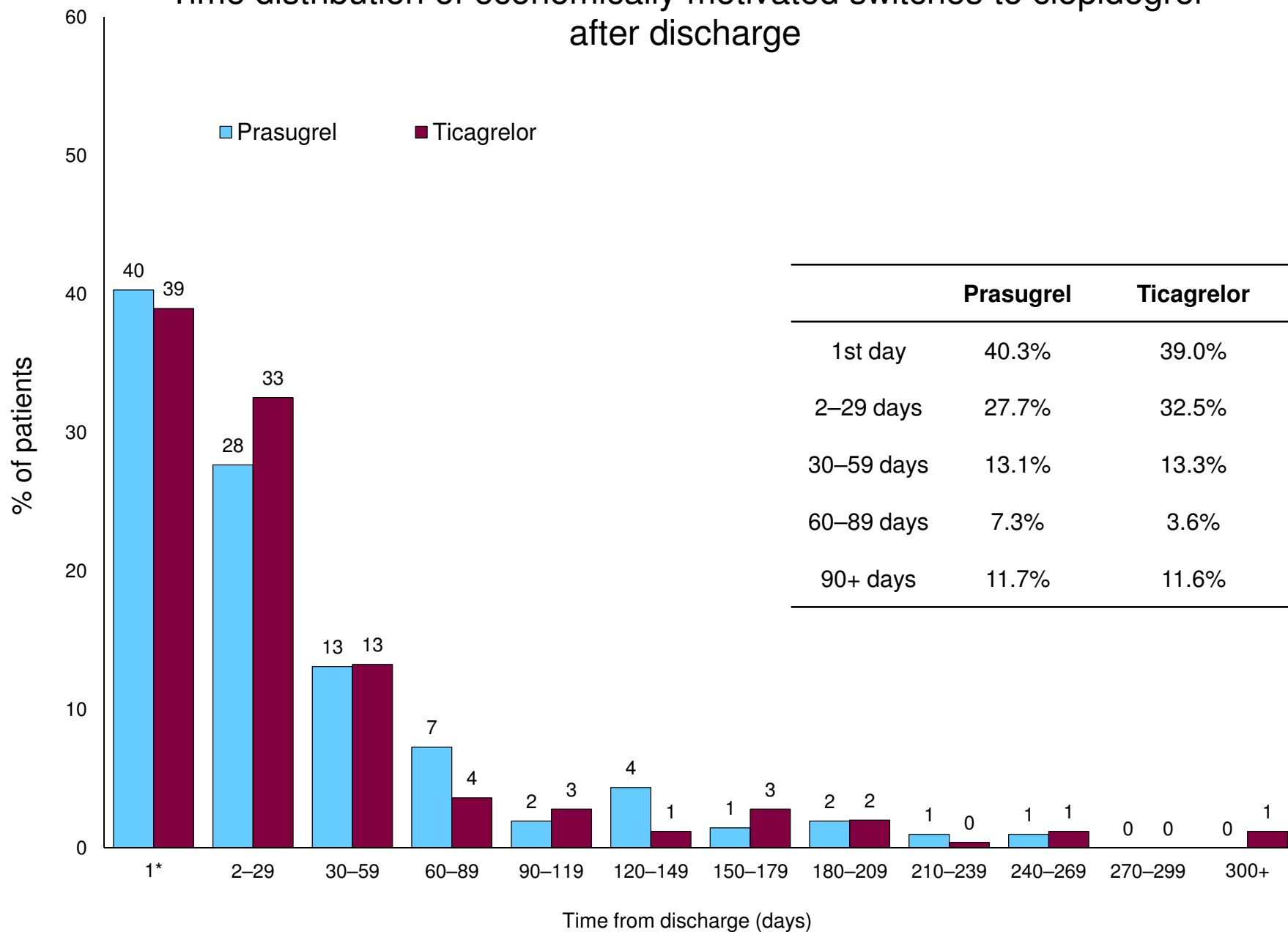
## NON-FATAL MYOCARDIAL INFARCTION



# SAFETY

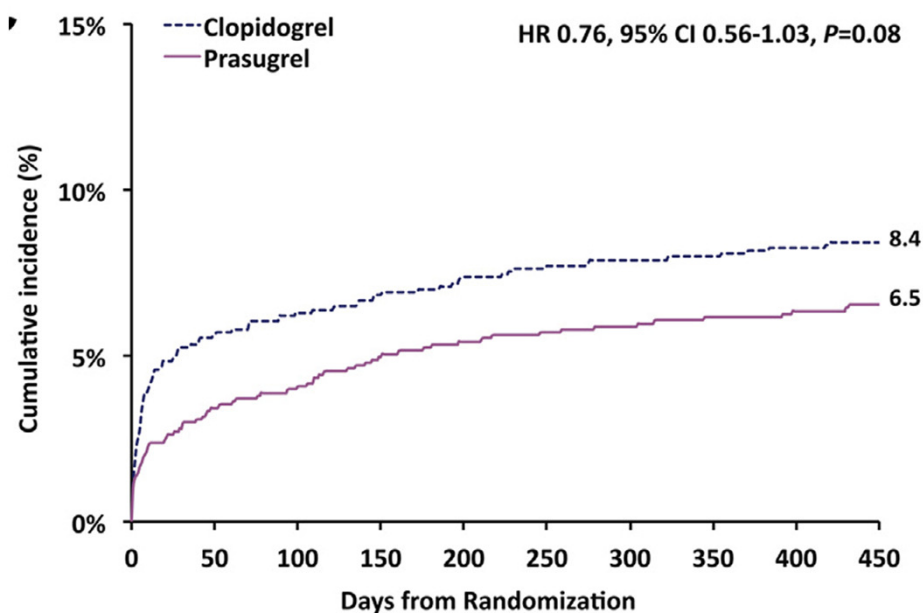


## Time distribution of economically motivated switches to clopidogrel after discharge



# BENEFIT OF DAPT IN STEMI and pPCI

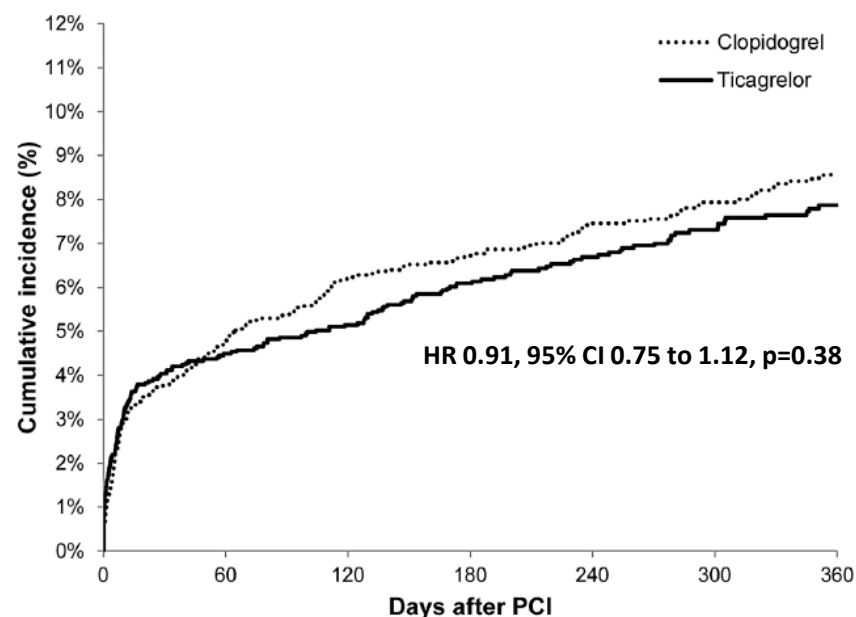
**“Spontaneous” primary endpoint  
(CV death, nonprocedural MI, stroke)  
among primary PCI patients**



*TRITON trial*

J Am Coll Cardiol Interv 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		
			%	
<b>Unstable angina and non-ST-segment-elevation myocardial infarction</b>				
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
<b>ST-segment-elevation myocardial infarction</b>				
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
<b>Overall</b>				
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