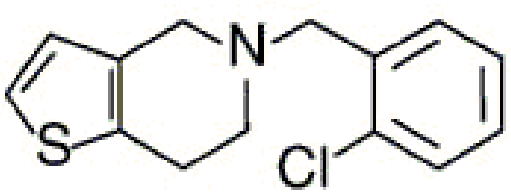
AKS – prasugrel všem?

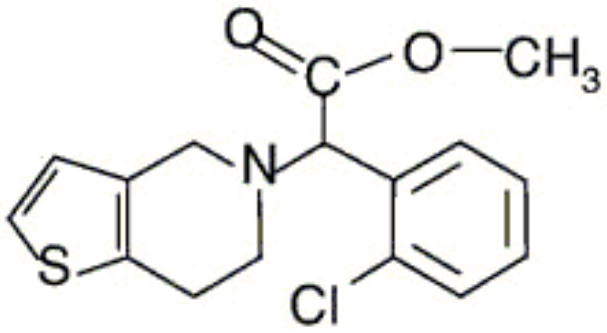
O. Hlinomaz

IKAK, ICRC, FN u sv. Anny, Brno
UNIVMED s.r.o.
CINRE, Bratislava

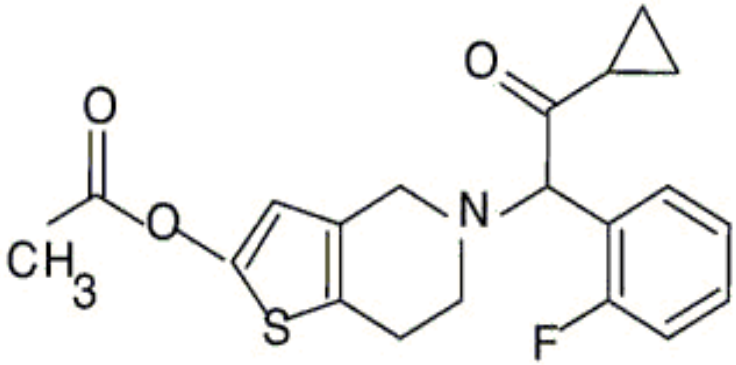
Thienopyridiny



Ticlopidine

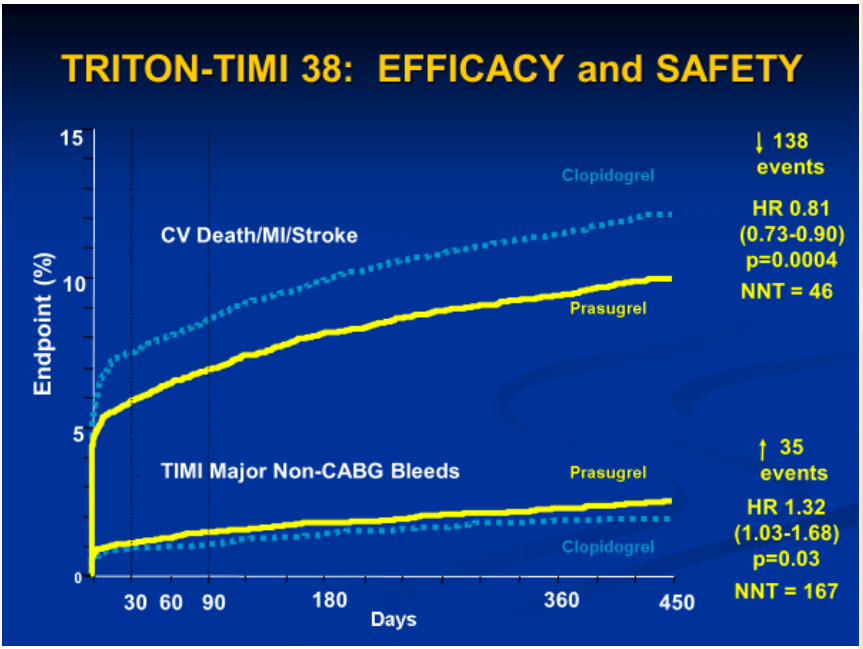


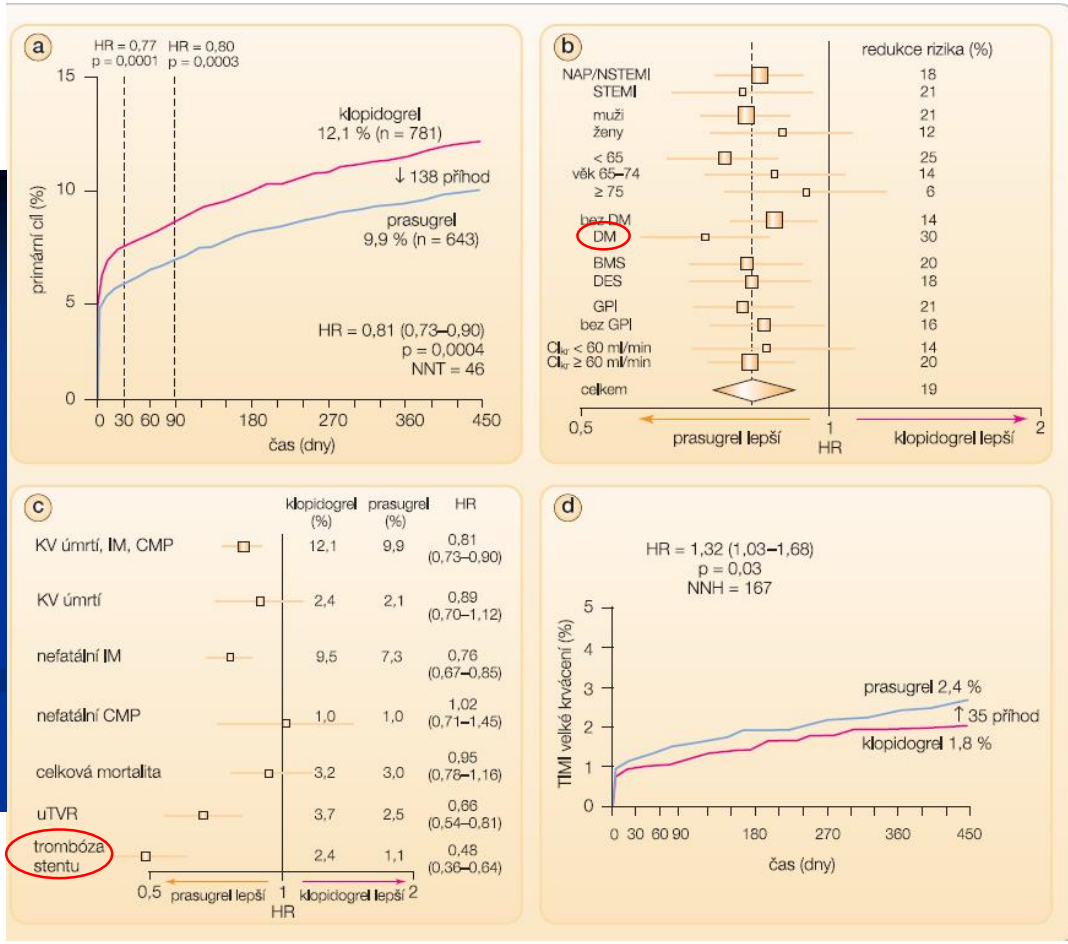
Clopidogrel



Prasugrel

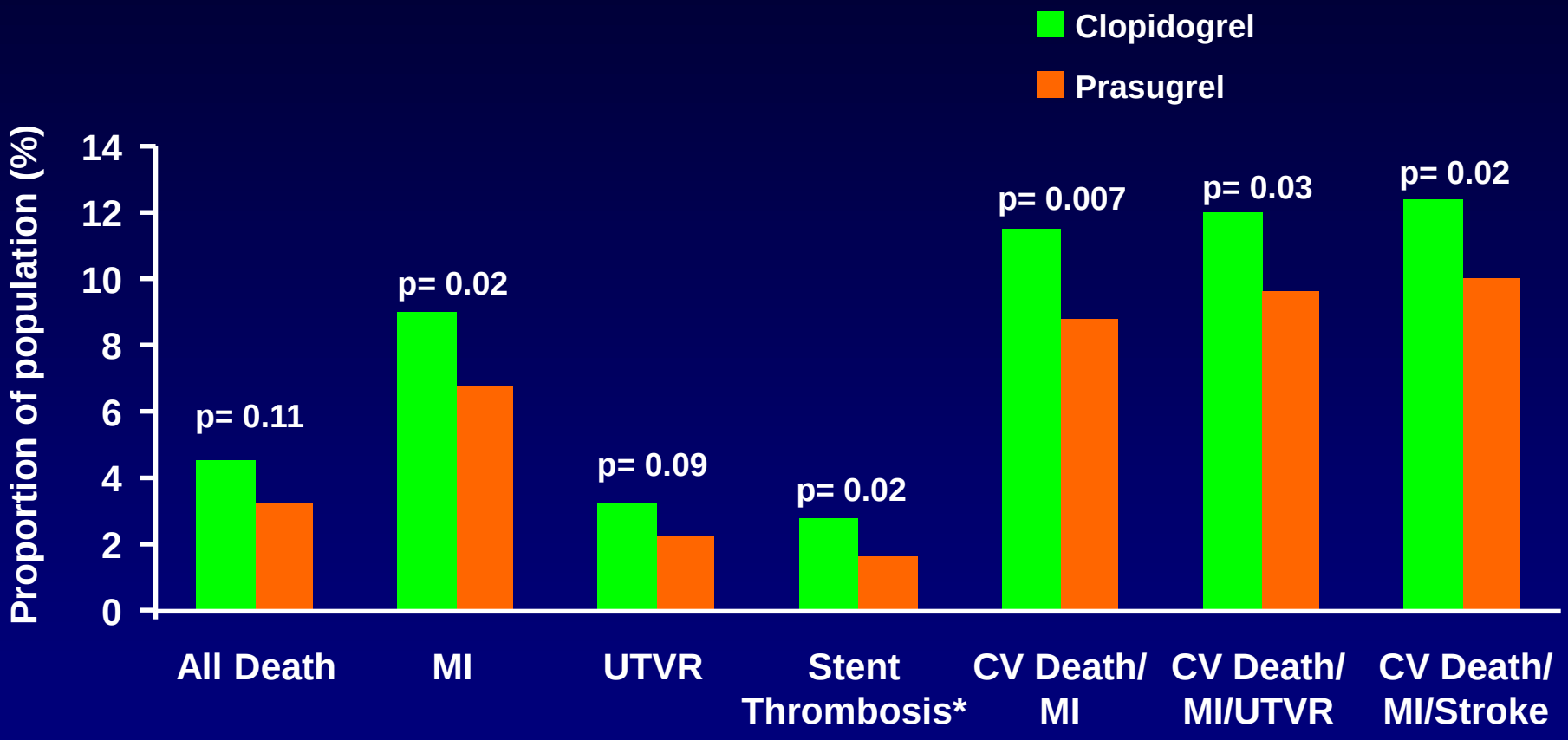
Triton-TIMI 38
prasugrel vs. clopidogrel





Wiviott S et al. NEJM 2007;357:2001.

Efficacy endpoints at 15 months



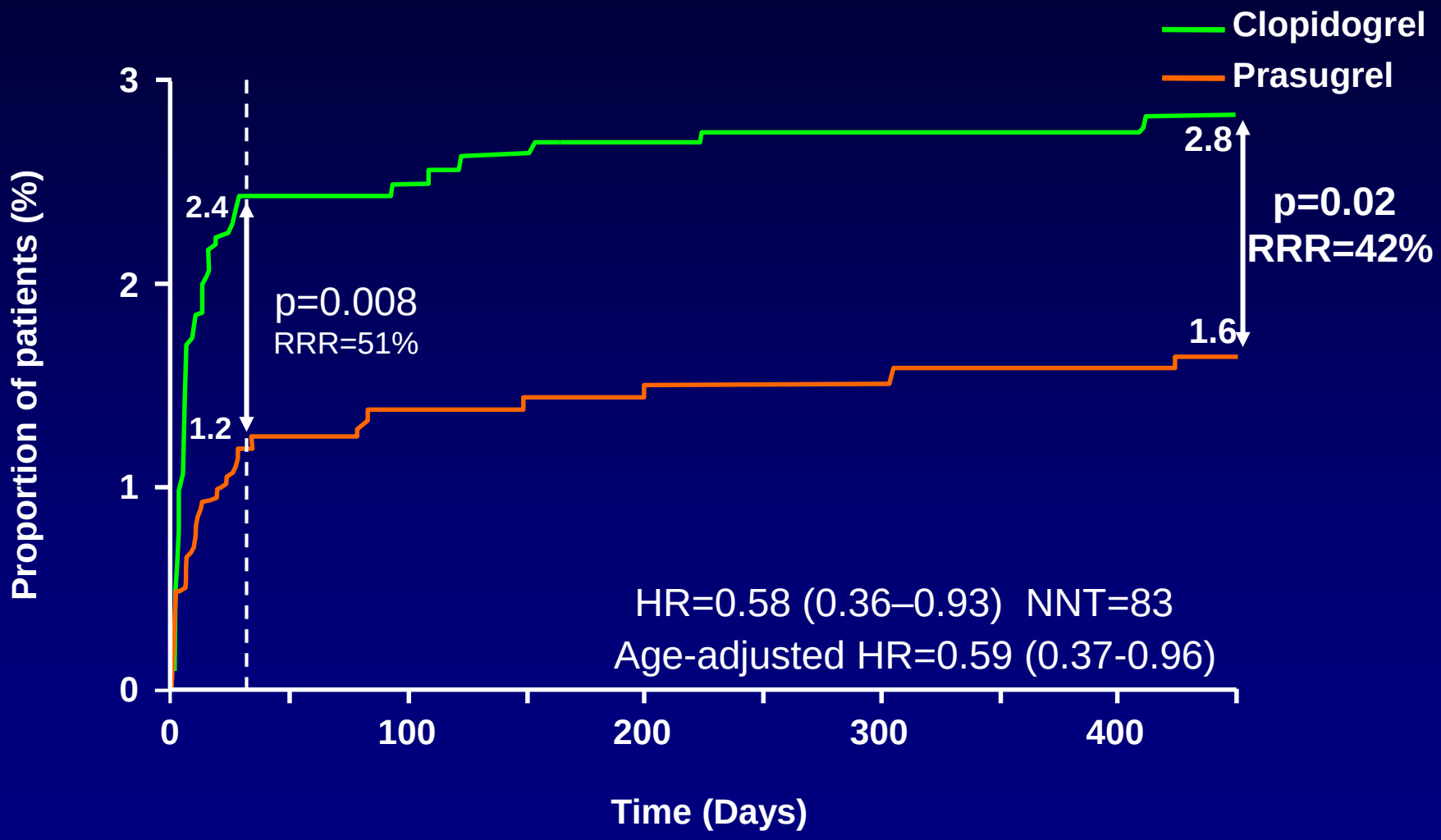
* ARC def/probable

Montalescot et al. ESC 2008

TRITON TIMI-38 STEMI cohort

Stent thrombosis

ARC Definite/probable

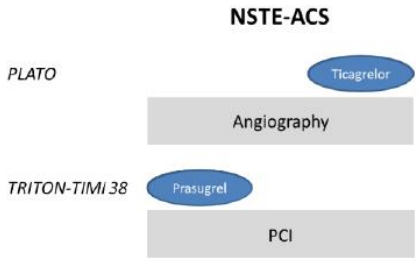


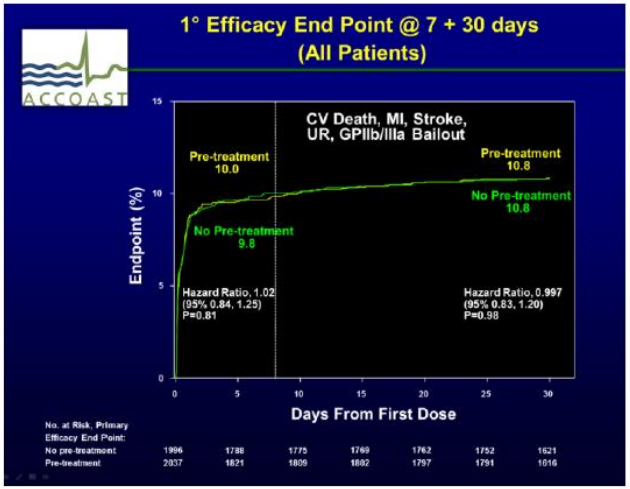
Montalescot et al. ESC 2008

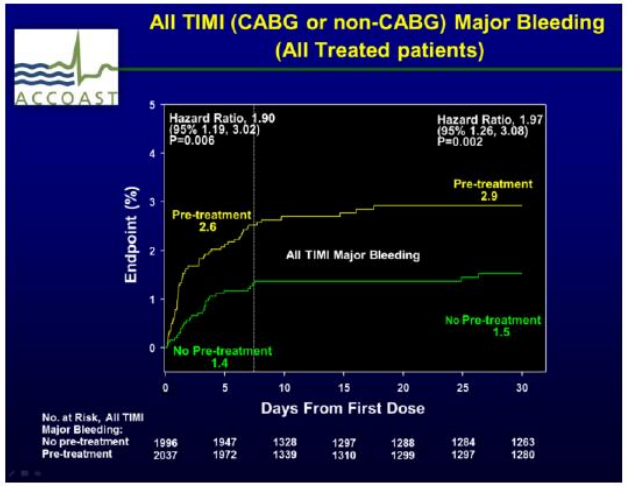

Height
+8
FD
48
X-ray disabled
Exp
15
Fluo
Low
Time
06:59
0.09
366

ACCOAST

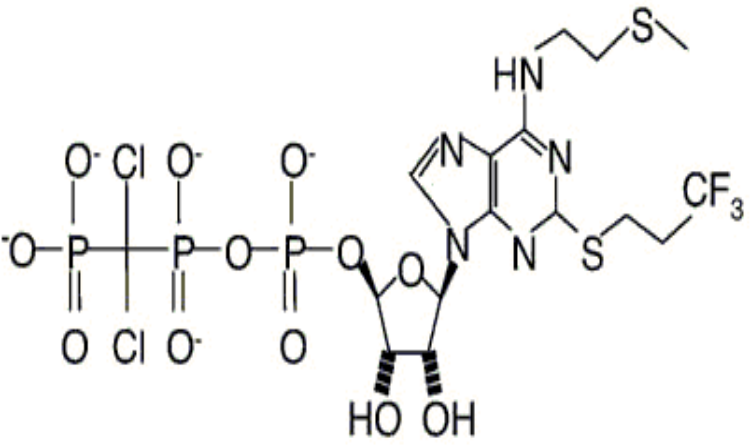
A Comparison of prasugrel at the time of PCI Or as pretreatment At the time of diagnosis in patients with NSTEMI



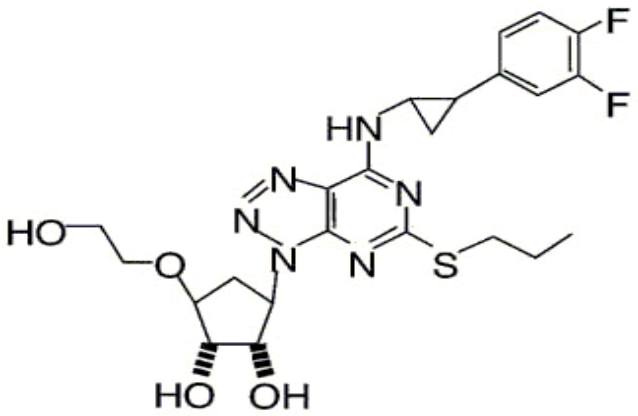




Cyclopentyltriazolopyrimidiny
Ticagrelor and Cangrelor



Cangrelor



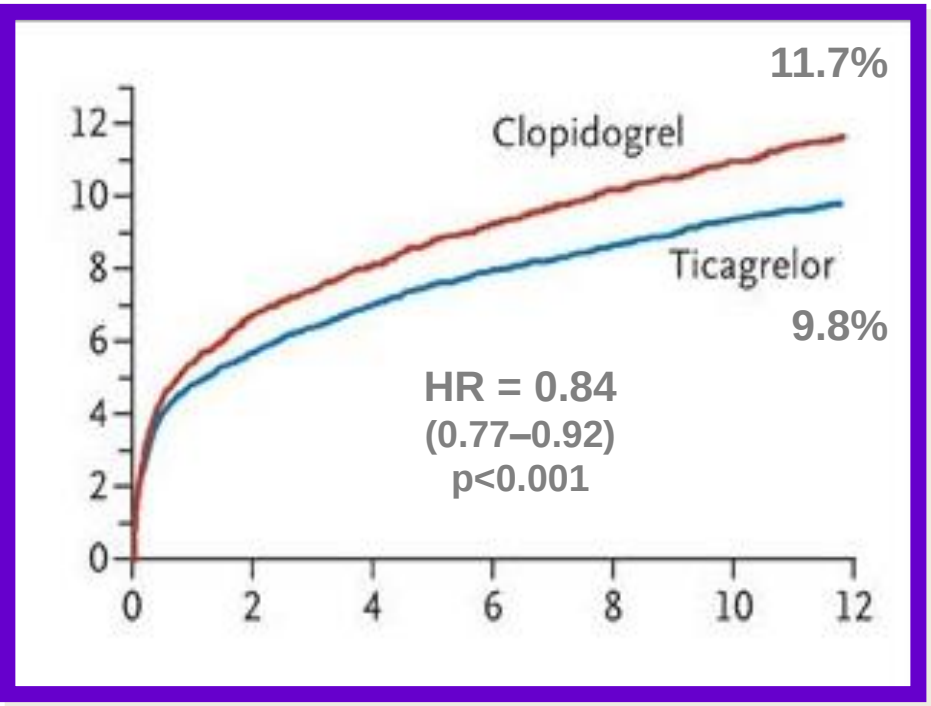
Ticagrelor

- **Reversibilně inhibují P2Y12 ADP-receptor.**
- **Nepotřebují metabolickou aktivaci.**
- **Cangrelor pouze i.v.**

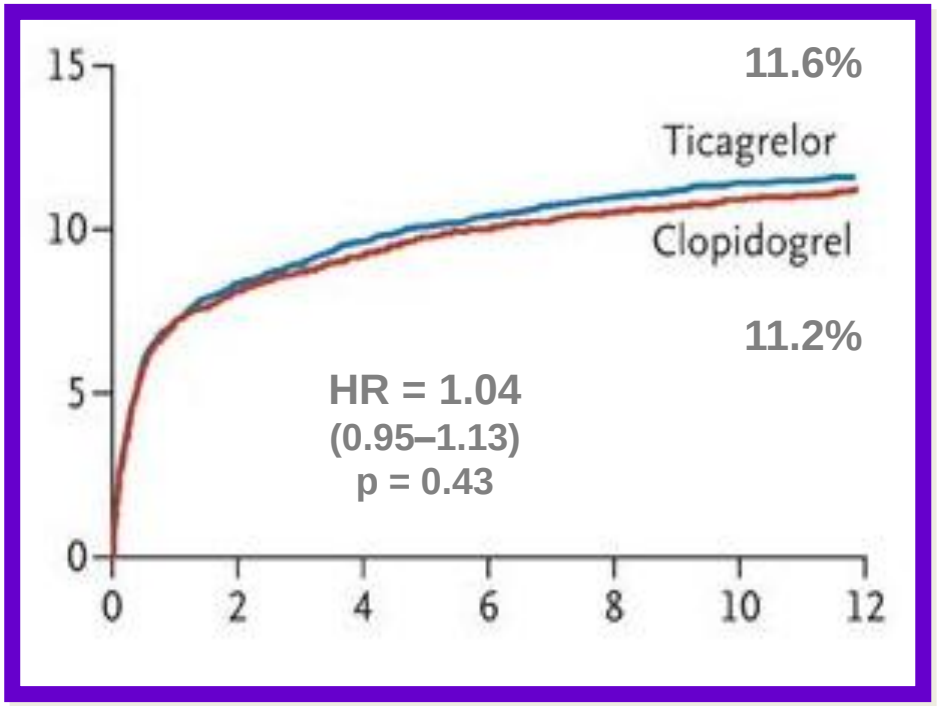
PLATO studie

Ticagrelor vs Clopidogrel u AKS

Ischemický endpoint



Krvácení



Wallentin L et al. NEJM 2009;361:1045

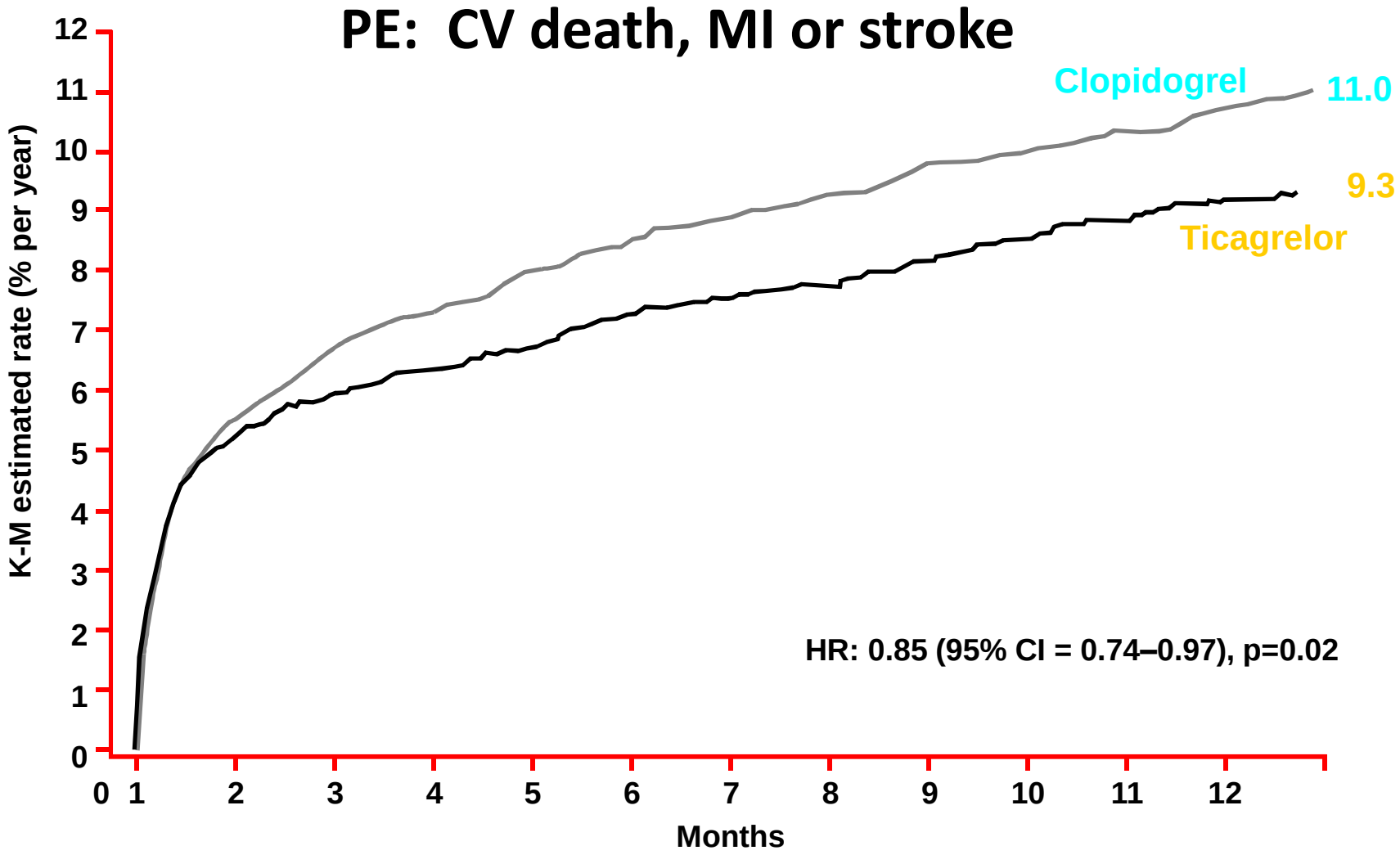
PLATO studie

Ticagrelor vs Clopidogrel u AKS

Endpoint (% of patients)	Ticagrelor (n = 9333)	Clopidogrel (n = 9291)	HR	P-value
Primary composite	9.8	11.7	0.84	<0.001
Vascular death	4.0	5.1	0.79	0.001
MI	5.8	6.9	0.84	0.005
Stroke	1.5	1.3	1.17	0.22
Any death	4.5	5.9	0.78	<0.001
Severe recurrent ischemia	3.5	4.0	0.87	0.08
Stent thrombosis	2.2	2.9	0.75	0.01

Wallentin L et al. NEJM 2009;361:1045

PLATO – STEMI



Ticagrelor	4,201	3,887	3,834	3,732	3,011	2,297	1,891
Clopidogrel	4,229	3,892	3,823	3,730	3,022	2,333	1,868

Steg G et al.: 2007

Hierarchical testing of major efficacy endpoints

PLATO STEMI

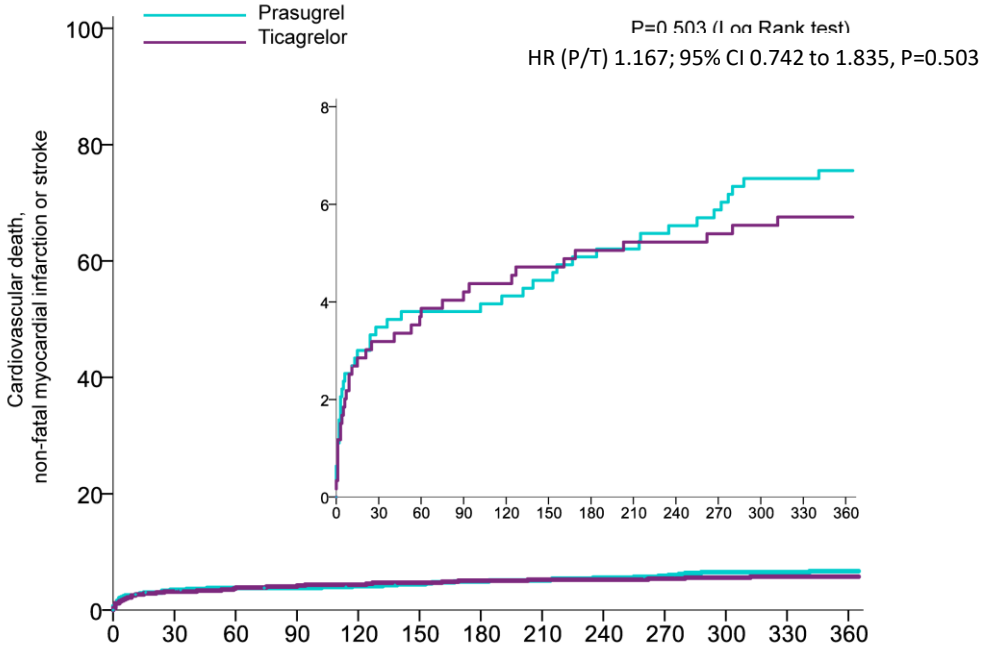
Endpoint*	Ticagrelor (n=4,201)	Clopidogrel (n=4,229)	HR for ticagrelor (95% CI)	p-value†
Primary endpoint, %				
CV death + MI + stroke	9.3	11.0	0.85 (0.74–0.97)	0.02
Secondary endpoints, %				
Total death + MI + stroke	9.7	11.5	0.84 (0.73–0.96)	0.01
CV death + MI + stroke + ischaemia + TIA + arterial thrombotic events	13.4	15.4	0.86 (0.76–0.96)	0.01
MI	4.7	6.1	0.77 (0.63–0.93)	0.01
CV death	4.5	5.4	0.84 (0.69–1.03)	0.09
Stroke	1.6	1.0	1.45 (0.98–2.17)	0.07
All-cause mortality	4.9	6.0	0.82 (0.68–0.99)	0.04

The percentages are K-M estimates of the rate of the endpoint at 12 months. Patients could have had more than one type of endpoint.

†By univariate Cox model

PRAGUE-18 trial

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



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

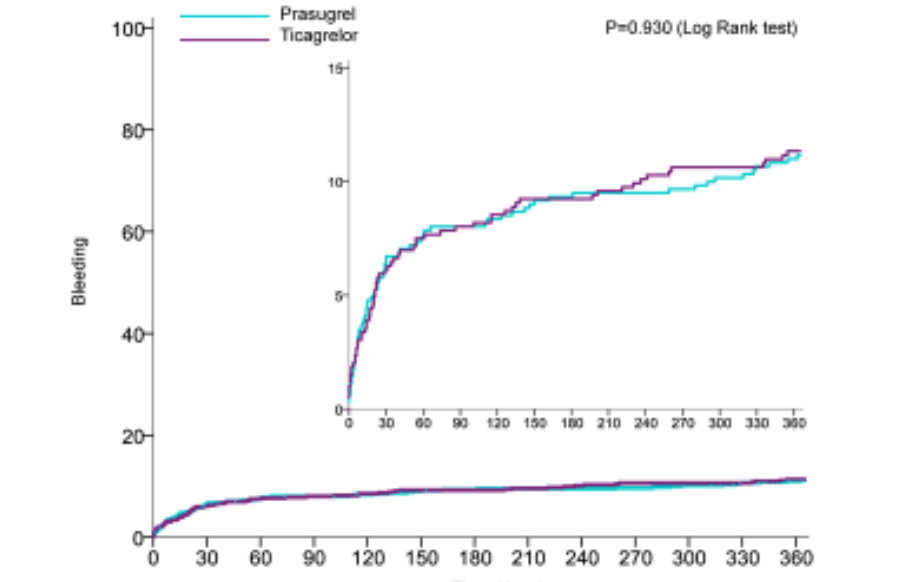
AHA SCIENTIFIC SESSIONS
Anaheim 2017

PRAGUE – 18 STUDY

Motovska Z, Hlinomaz O, Kala P et al.: J Am Coll Cardiol. 2018 Jan 30;71(4):371-381

PRAGUE-18 trial

SAFETY ENDPOINT: Bleeding



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

AHA SCIENTIFIC SESSIONS
Anaheim 2017

PRAGUE – 18 STUDY

Motovska Z, Hlinomaz O, Kala P et al.: J Am Coll Cardiol. 2018 Jan 30;71(4):371-381

PRAGUE-18 trial

TABLE 2 Switch to Clopidogrel and Resulting Ischemic and Bleeding Risks

		HR (95% CI)	p Value
Risk of ischemic endpoint*	Economically motivated switch (n = 481)	0.433 (0.210-0.894)	**0.024**
	Switch for 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**

The hazard ratio was based on the Cox proportional hazard model with time-dependent covariates. **Bold** values are statistically significant. *Cardiovascular death, nonfatal myocardial infarction, or stroke.

Abbreviations as in Table 1.

Switch 659/1230 = 53,6%

Motovska Z, Hlinomaz O, Kala P et al.: J Am Coll Cardiol. 2018 Jan 30;71(4):371-381

PRAGUE-18 trial

Online Table 4 Reasons for switching 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

Absolute and relative frequencies were used for categorical variables; statistical significance of differences between patient groups were tested using the Fisher exact test (Bonferroni correction was used).

Motovska Z, Hlinomaz O, Kala P et al.: J Am Coll Cardiol. 2018 Jan 30;71(4):371-381

NSTEMI PCI

Doporučení antitrombotické léčby u pacientů s non-STE akutními koronárními syndromy, kteří podstupují perkutánní koronární intervenci		
Inhibitor $P2Y_{12}$ je doporučen spolu s ASA po dobu 12 měsíců, pokud nejsou kontraindikace v podobě výrazného rizika krvácení. Možnosti jsou:	I	A
• Prasugrel u inhibitor $P2Y_{12}$-naivních pacientů, kteří podstupují PCI (60 mg nasycovací dávka, 10 mg denně).	I	B
• Ticagrelor bez ohledu na předchozí podané inhibitory $P2Y_{12}$ (180 mg nasycovací dávka, 90 mg 2× denně).	I	B
• Clopidogrel (600 mg nasycovací dávka, 75 mg denně) pouze u pacientů s kontraindikacemi k prasugrelu nebo ticagreloru nebo v případě jejich nedostupnosti.	I	B
K předléčení pacientů s non-STE AKS, kteří jsou léčeni invazivně, by mělo být zváženo podání ticagreloru (180 mg nasycovací dávka, 90 mg 2× denně) nebo clopidogrelu (600 mg nasycovací dávka, 75 mg denně), pokud není možné podat ticagrelor, ihned po určení diagnózy.	IIa	C
Cangrelor může být zvážen u pacientů doposud neléčených inhibitorem $P2Y_{12}$, kteří podstupují PCI.	IIb	A
Podání prasugrelu u pacientů s neznámou koronární anatomií není doporučeno.	III	B

Mates M et al.: CorVasa 2018

STEMI pPCI

Doporučení pro antitrombotickou léčbu u pacientů s infarktem myokardu s elevacemi úseků ST, kteří podstupují perkutánní koronární intervenci		
Účinný inhibitor $P2Y_{12}$ (prasugrel nebo ticagrelor) nebo clopidogrel, pokud tyto nejsou dostupné nebo jsou kontraindikovány, je doporučen před (nebo alespoň během) PCI a po dobu 12 měsíců, pokud neexistují kontraindikace jako vysoké riziko krvácení.	I	A
Cangrelor může být zvážen u pacientů doposud neléčených inhibitorem $P2Y_{12}$, kteří podstupují PCI.	IIb	A

Mates M et al.: CorVasa 2018

ISAR – REACT 5

DZHK
DEUTSCHES ZENTRUM FÜR
HERZ-KREISLAUF-FORSCHUNG E.V.

Technische Universität München
Deutsches Herzzentrum München

ISAR-REACT 5:

Ticagrelor vs. Prasugrel in Acute Coronary Syndromes

S. Schüpke, F.-J. Neumann, M. Menichelli, K. Mayer, I. Bernlochner, J. Wöhrle, G. Richardt, C. Liebetrau, B. Witzenbichler, D. Antoniucci, I. Akin, L. Bott-Flügel, M. Fischer, U. Landmesser, H. A. Katus, D. Sibbing, M. Seyfarth, M. Janisch, D. Boncompagni, R. Hilz, W. Rottbauer, R. Okrojek, H. Möllmann, W. Hochholzer, A. Migliorini, S. Cassese, P. Mollo, E. Xhepa, S. Kufner, A. Strehle, S. Leggewie, A. Allali, G. Ndrepepa, H. Schühlen, D. J. Angiolillo, C. W. Hamm, A. Hapfelmeier, R. Tölg, D. Trenk, H. Schunkert, K.-L. Laugwitz, A. Kastrati, for the ISAR-REACT 5 Investigators

ESC Congress Paris 2019 Together with World Congress of Cardiology

Schüpke S, Neumann FJ, Menichelli M et al.: N Engl J Med. 2019 Oct 17;381(16):1524-1534.

ISAR – REACT 5

Study Schedule

DZHK
DEUTSCHES ZENTRUM FÜR
HERZ-KREISLAUF-FORSCHUNG E.V.

STEMI

Randomization

Ticagrelor	Prasugrel
180 mg loading	60 mg loading

Angiography + PCI

Ticagrelor	Prasugrel
90 mg 1-0-1	10 mg 1-0-0*

Unstable Angina, NSTEMI

Randomization

Ticagrelor	Prasugrel#
180 mg loading	60 mg loading

Angiography

Prasugrel
60 mg loading

PCI

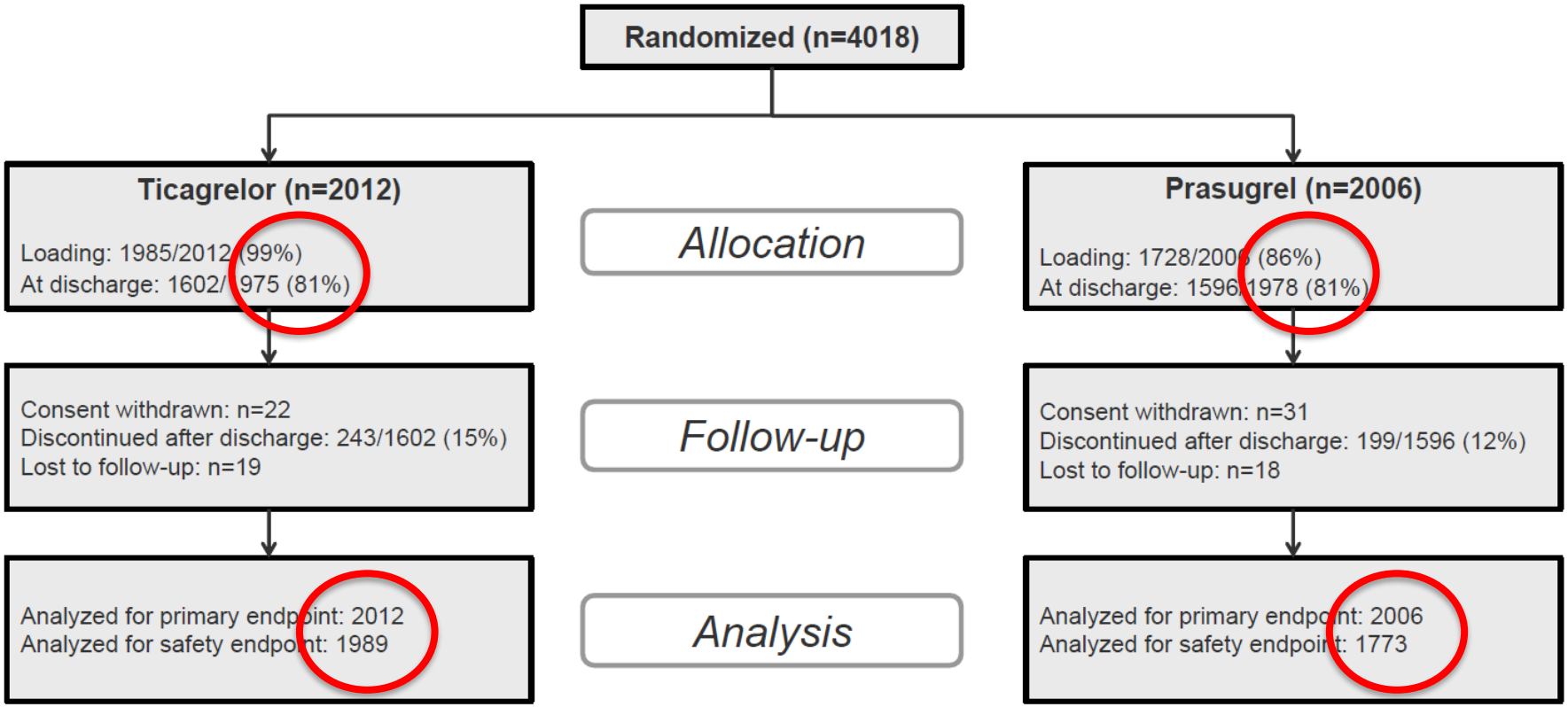
Ticagrelor	Prasugrel
90 mg 1-0-1	10 mg 1-0-0*

Duration of ADP receptor therapy: 12 months
Concomitant ASA: 75-150 mg/d
In patients with known coronary anatomy
* Prasugrel 5 mg in patients ≥ 75 years of age or weight < 60 kg

Schüpke S, Neumann FJ, Menichelli M et al.: N Engl J Med. 2019 Oct 17;381(16):1524-1534.

ISAR – REACT 5

Study Flow



Schüpke S, Neumann FJ, Menichelli M et al.: N Engl J Med. 2019 Oct 17;381(16):1524-1534.

ISAR – REACT 5

Baseline Characteristics (2/2)

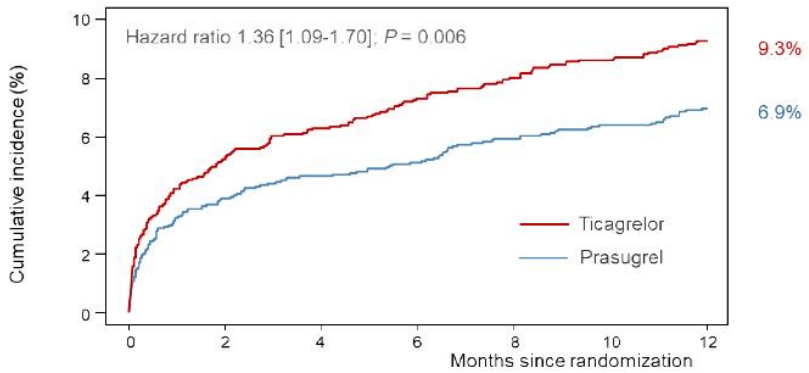
	Ticagrelor	Prasugrel
Blood pressure		
– Systolic – mmHg	144 ± 25	143 ± 24
– Diastolic – mmHg	82 ± 15	82 ± 14
Heart rate – beats/min	77 ± 16	76 ± 16
Diagnosis at admission – %		
– Unstable angina	12.4	13.0
– NSTEMI	46.2	46.1
– STEMI	41.4	40.9
Coronary angiography – %	99.6	99.8
Treatment strategy – %		
– PCI	83.5	84.8
– CABG	2.3	1.8
– Conservative	14.2	13.4
– Other	<0.1	0

Schüpke S, Neumann FJ, Menichelli M et al.: N Engl J Med. 2019 Oct 17;381(16):1524-1534.

ISAR – REACT 5

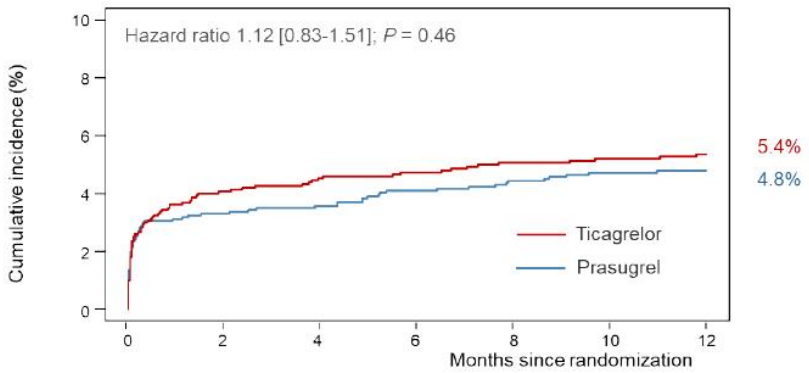
Clinical End Points

Primary End point
(Composite of Death, MI, or Stroke)



No. at Risk							
Ticagrelor	2012	1877	1857	1835	1815	1801	1772
Prasugrel	2006	1892	1877	1862	1839	1829	1803

BARC Type 3-5 Bleeding
(Safety End point)



No. at Risk							
Ticagrelor	1989	1441	1399	1356	1319	1296	1266
Prasugrel	1773	1465	1427	1397	1357	1333	1307

Schüpke S, Neumann FJ, Menichelli M et al.: N Engl J Med. 2019 Oct 17;381(16):1524-1534.

ISAR – REACT 5

Clinical End Points

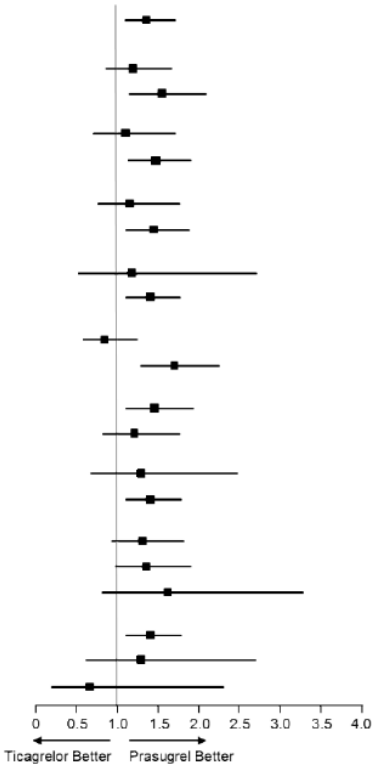
	Ticagrelor (n=2012)	Prasugrel (n=2006)	HR [95% CI]
Death	90 (4.5)	73 (3.7)	**1.23 [0.91-1.68]**
– Cardiovascular	63 (3.2)	59 (3.0)	
– Non-cardiovascular	27 (1.4)	14 (0.7)	
Myocardial infarction	96 (4.8)	60 (3.0)	**1.63 [1.18-2.25]**
– STEMI	31	14	
Stroke	22 (1.1)	19 (1.0)	**1.17 [0.63-2.15]**
– Ischemic	16	17	
– Hemorrhagic	6	2	
Definite or probable stent thrombosis	26 (1.3)	20 (1.0)	**1.30 [0.72-2.33]**
Definite stent thrombosis	22 (1.1)	12 (0.6)	

Schüpke S, Neumann FJ, Menichelli M et al.: N Engl J Med. 2019 Oct 17;381(16):1524-1534.

ISAR – REACT 5

Subgroup Analysis

Subgroup	Ticagrelor	Prasugrel	Hazard Ratio (95% CI)
	no. of patients with event/total no. of patients (%)		
Overall	184/2012 (9.3)	137/2006 (6.9)	1.36 (1.09-1.70)
Age			
≥75 years	74/490 (15.3)	66/492 (13.7)	1.19 (0.85-1.66)
<75 years	110/1522 (7.3)	71/1514 (4.8)	1.55 (1.15-2.09)
Sex			
Female	42/478 (8.9)	39/478 (8.3)	1.10 (0.71-1.70)
Male	142/1534 (9.4)	98/1528 (6.5)	1.47 (1.13-1.90)
Smoking status			
Active	47/682 (7)	41/667 (6.2)	1.15 (0.76-1.75)
Non-active	133/1320 (10.2)	94/1332 (7.2)	1.44 (1.10-1.87)
Weight			
<60 kg	13/108 (12.2)	10/94 (10.7)	1.18 (0.52-2.71)
≥60 kg	171/1895 (9.1)	124/1894 (6.4)	1.40 (1.11-1.77)
Diabetes mellitus			
Yes	51/463 (11.2)	55/429 (13)	0.84 (0.58-1.24)
No	132/1548 (8.6)	81/1576 (5.2)	1.70 (1.29-2.24)
Creatinine			
≥83.1 µmol/L	125/1005 (12.6)	88/1009 (8.8)	1.46 (1.11-1.92)
<83.1 µmol/L	59/1002 (6)	49/996 (5)	1.21 (0.83-1.76)
Cardiogenic Shock			
Yes	19/31 (62.6)	18/34 (52.9)	1.29 (0.67-2.47)
No	165/1981 (8.4)	119/1972 (6.1)	1.40 (1.11-1.78)
Clinical Presentation			
STEMI	83/833 (10.1)	64/820 (7.9)	1.31 (0.94-1.81)
NSTEMI	81/930 (8.8)	60/925 (6.6)	1.36 (0.97-1.90)
Unstable Angina	20/249 (8.2)	13/261 (5.1)	1.62 (0.81-3.26)
Treatment Strategy			
PCI	162/1676 (9.8)	120/1701 (7.1)	1.41 (1.11-1.78)
conservative	17/285 (6.1)	12/268 (4.6)	1.29 (0.62-2.70)
CABG	5/47 (10.6)	5/36 (13.9)	0.66 (0.19-2.30)



Schüpke S, Neumann FJ, Menichelli M et al.: N Engl J Med. 2019 Oct 17;381(16):1524-1534.

ISAR – REACT 5

- Nezaslepená, otevřená
- Telefonický follow up (83%)
- Ischem. PE překvapivě 6,9% v Pra (10,7% Triton)
- ↓ ischem. EP, bez vlivu na krvácení po Pra
- 2x více periproc. IM na Tic
- 2x vyšší nekardiovask. mortalita na Tic
- 19% nem. nebylo propuštěno na přidělené th.
- 34% nem. v Tic nebralo lék, 31,8% v Pra ve 12M
- Z analýzy bezpečnosti vyloučeno 233 pac. (11,6%) Pra vs 23 pac. (1,1%) Tic
- STEMI 41% vs 89% v Prague 18

Schüpke S, Neumann FJ, Menichelli M et al.: N Engl J Med. 2019 Oct 17;381(16):1524-1534.

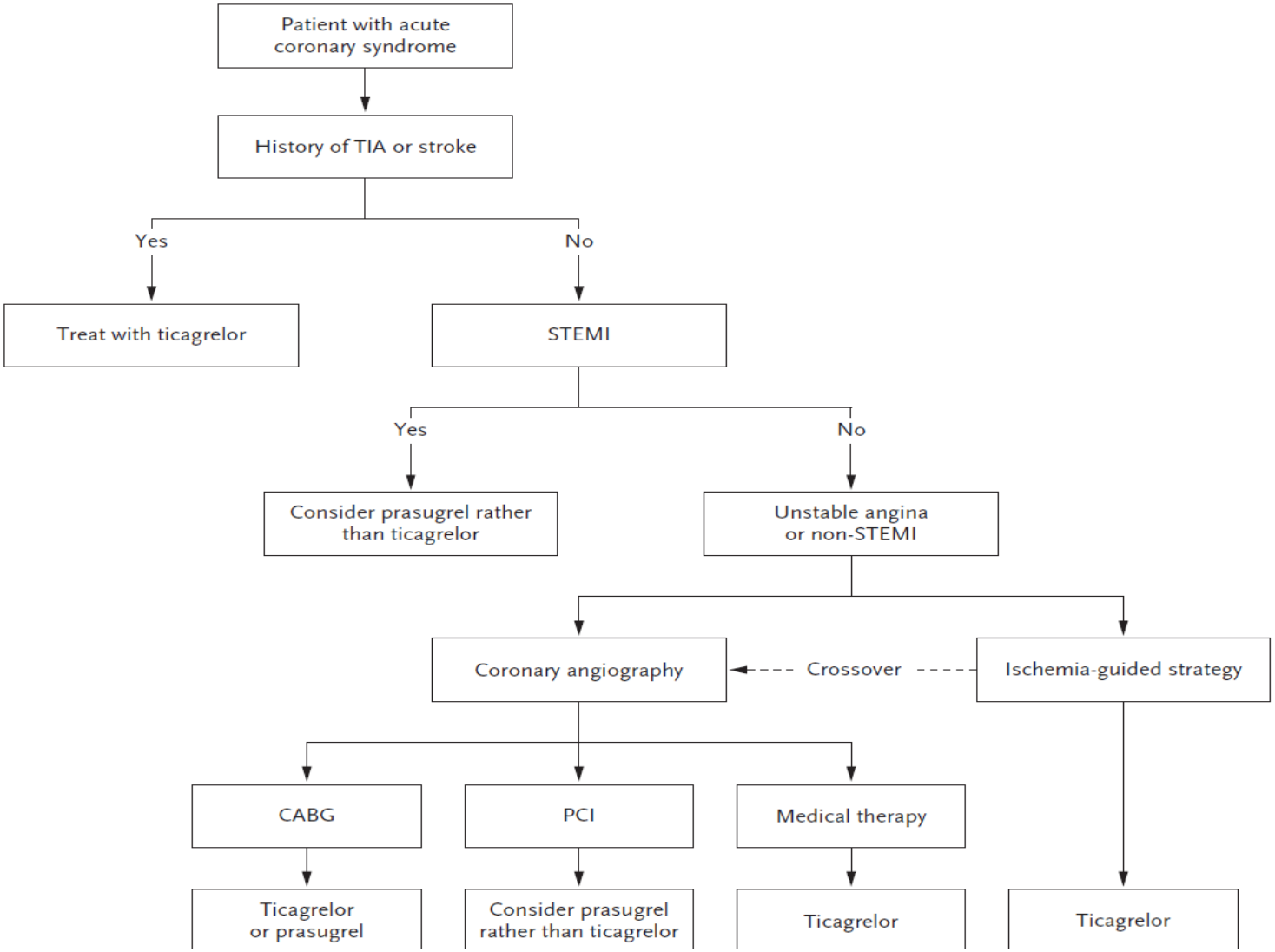
ISAR – REACT 5

- Ticagrelor vysazen dříve a častěji než prasugrel (15.2% a 12.5%; P = 0.03) – více NÚ

- ISAR-REACT 5 studie podporuje strategii založenou na prasugrelu u nem. s AKS
  (bez rutinního předléčení u NSTE AKS)

Schüpke S, Neumann FJ, Menichelli M et al.: N Engl J Med. 2019 Oct 17;381(16):1524-1534.

Algorithm for the Choice of an Oral P2Y12 Receptor Inhibitor in ACS Patients



Jneid H: NEJM 2019,381;16

AKS – prasugrel všem?

NE

Prasugrel

- AKS léč. PCI
  - Stenóza kmene ACS
  - Stenóza prox. RIA
  - MVD
  - Trombóza stentu
  - Suboptimálny výsledek PCI

  - Ostatní AKS léč. PCI Pra - Tic

Ticagrelor

- AKS léč. konzervativně
- AKS léč. CABG (3-5 vs 7 dní)
- V anamnéze TIA, CMP
- CHRI
- Předpoklad léčby >12 měsíců

- Ostatní AKS léč. PCI Tic – Pra

Clopidogrel

- Vysoké riziko krvácení
- Ekonomické důvody
- Fibrilace síní (NOAK)

Cangrelor

- AKS s rizikovou PCI, nelze p.o. příjem