DEESKALACE PROTIDESTIČKOVÉ LÉČBY: ANO ČI NE?

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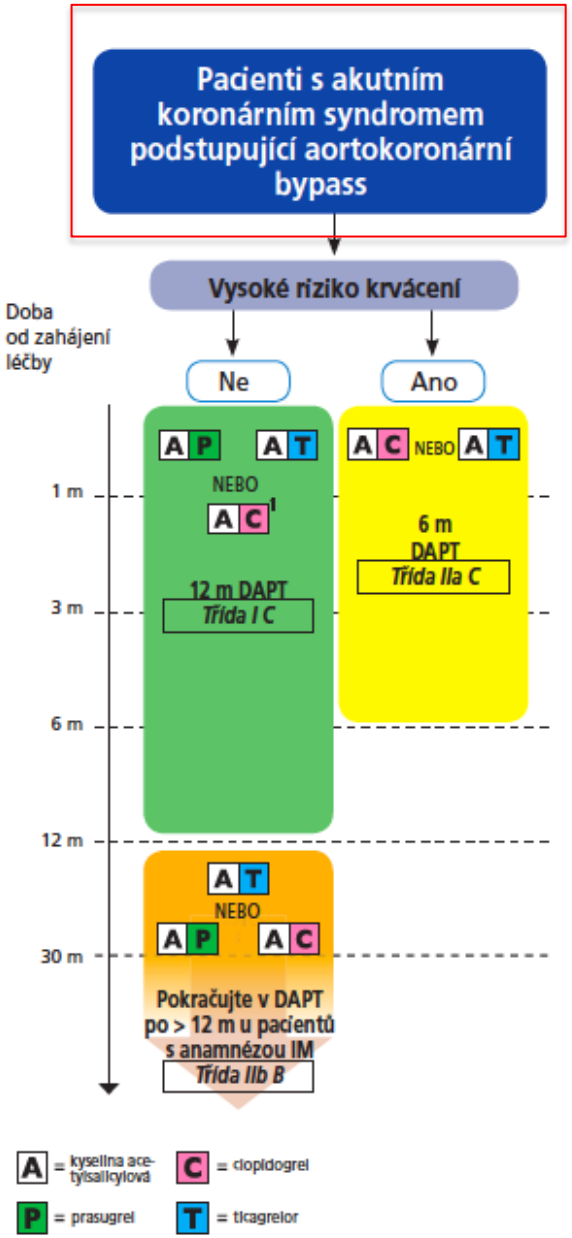
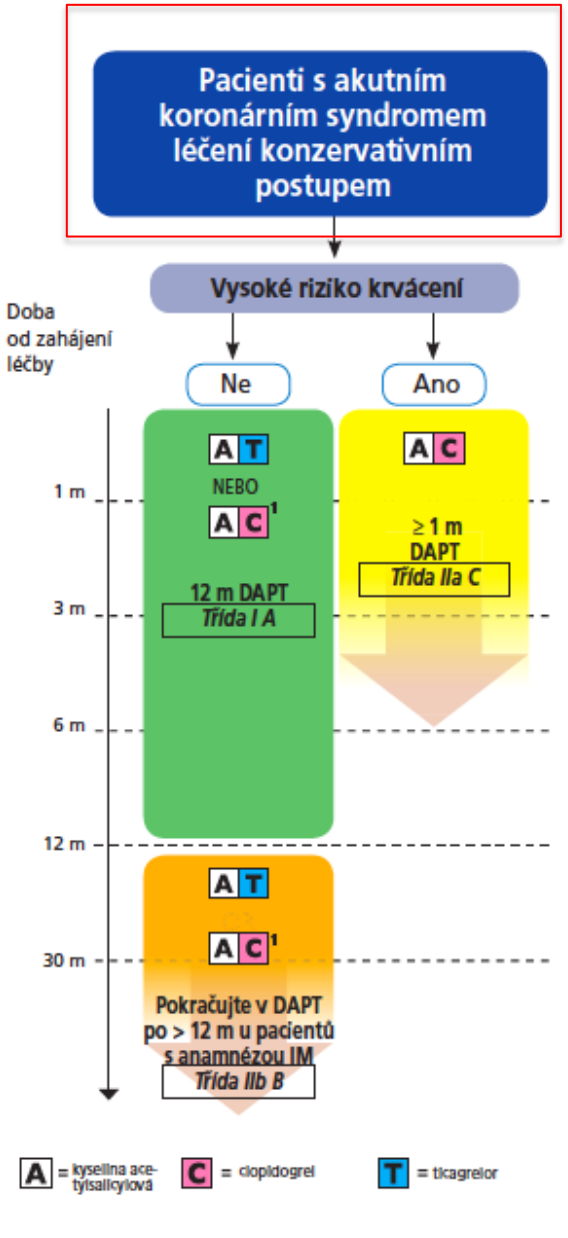
Současná doporučení pro AKS

Doporučení	Třída[a]	Úroveň[b]
U pacientů s AKS je vedle kyseliny acetylsalicylové doporučován ticagrelor (nasycovací dávka 180 mg, tedy 90 mg dvakrát denně),[c] a to nezávisle na vstupní léčebné strategii, což se týká i pacientů předléčených clopidogrelem (ten by měl být po nasazení ticagreloru vysazen), nemají-li kontraindikace.	I	B
U pacientů s AKS podstupujících PCI je vedle kyseliny acetylsalicylové doporučován prasugrel (nasycovací dávka 60 mg, denní dávka 10 mg), což se týká pacientů dosud neléčených inhibitory $P2Y_{12}$ s non-STE AKS nebo se zpočátku konzervativně léčenými STEMI, je-li potvrzena indikace PCI, případně u pacientů se STEMI podstupujících neodkladnou koronární katetrizaci,[c] není-li přítomno vysoké riziko život ohrožujícího krvácení nebo jiná kontraindikace.	I	B
Clopidogrel (nasycovací dávka 300 mg u pacientů ve věku ≤ 75 let, denní dávka 75 mg) přidaný ke kyselině acetylsalicylové je doporučován u pacientů se STEMI podstupujících trombolýzu.	I	A

U pacientů s AKS podstupujících implantaci koronárního stentu je doporučována DAPT kombinací inhibitoru $P2Y_{12}$ a kyseliny acetylsalicylové po dobu 12 měsíců, nejsou-li přítomny kontraindikace jako zvýšené riziko krvácení (např. PRECISE-DAPT ≥ 25).	I
U pacientů s AKS a implantací stentu vykazujících vysoké riziko krvácení (např. PRECISE-DAPT ≥ 25) je vhodné zvážit vysazení inhibitoru $P2Y_{12}$ po šesti měsících.	IIa
U pacientů s AKS léčených vstřebatelnými stenty by měla být zvážena DAPT trvající nejméně 12 měsíců.	IIa
U pacientů s AKS, kteří tolerovali DAPT bez krvácivých komplikací, lze zvážit pokračování v DAPT po dobu delší než 12 měsíců.	IIb
U pacientů s IM a vysokým ischemickým rizikem,[c] kteří tolerovali DAPT bez krvácivých komplikací, lze upřednostnit ticagrelor v dávce 60 mg 2× denně přidaný na dobu delší než 12 měsíců ke kyselině acetylsalicylové před clopidogrelem či prasugrelem.	IIb

ESC focused update on DAPT, 2017





ESC focused update on DAPT, 2017

DEESKALACE = ↓ Intensity DAPT

→ Iniciální tp: ASA + Clopidogrel

→ ASA + Ticagrelor/Prasugrel po dobu < 12 měsíců
(u pp bez kontraindikací a bez vysokého rizika krvácení)

→ Pacienti > 75 let, Pacienti s hmotností < 60kg

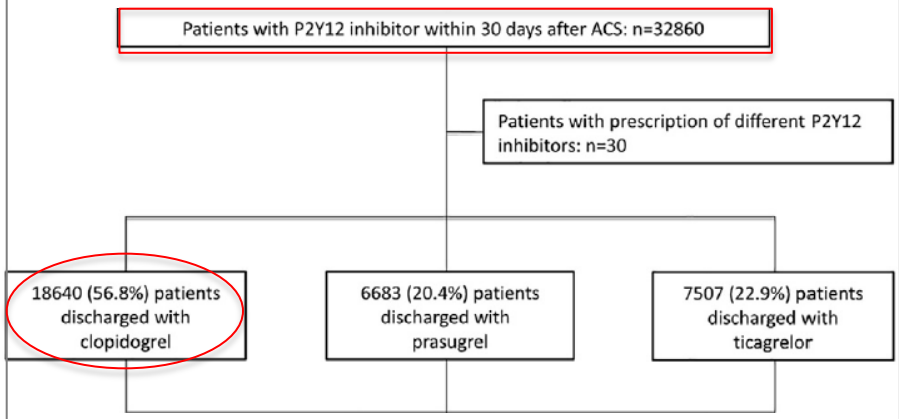
Iniciální DAPT v reálné praxi

Use of prasugrel vs clopidogrel and outcomes in patients with acute coronary syndrome undergoing percutaneous coronary

	Prasugrel (n = 4058)	Clopidogrel (n = 15,856)	P
Age, y	58.7 ± 10.3	65.8 ± 12.3	<.0001
Female sex, n (%)	989 (24.4)	5315 (33.5)	<.0001
African American, n (%)	253 (6.2)	1872 (11.8)	<.0001
BMI (kg/m^2)	30.7 ± 6.2	29.7 ± 6.2	<.0001
Diabetes, n (%)	1382 (34.1)	6198 (39.1)	<.0001
Diabetes on insulin, n (%)	394 (9.7)	2140 (13.5)	<.0001
Hypertension, n (%)	2915 (71.8)	13,466 (84.9)	<.0001
Dyslipidemia, n (%)	3220 (79.3)	13,469 (84.9)	<.0001
Smoking, n (%)	1175 (29.0)	3831 (24.2)	<.0001
Prior MI, n (%)	833 (20.5)	5130 (32.4)	<.0001
Prior PCI, n (%)	788 (19.4)	4250 (26.8)	<.0001
Prior CABG, n (%)	359 (8.8)	3074 (19.4)	<.0001
Prior CVD	188 (4.6)	2197 (13.9)	<.0001
Prior CHF, n (%)	567 (14.0)	3684 (23.2)	<.0001
Prior PAD, n (%)	291 (7.2)	2140 (13.5)	<.0001
CKD, n (%)	619 (15.3)	4994 (31.5)	<.0001
Anemia, n (%)	339 (8.4)	2553 (16.1)	<.0001
CAD presentation, n (%)			
STEMI	773 (19.0)	2512 (15.8)	<.0001
NSTEMI	1159 (28.6)	4253 (26.8)	.03
Unstable angina	2126 (52.4)	9090 (57.3)	<.0001

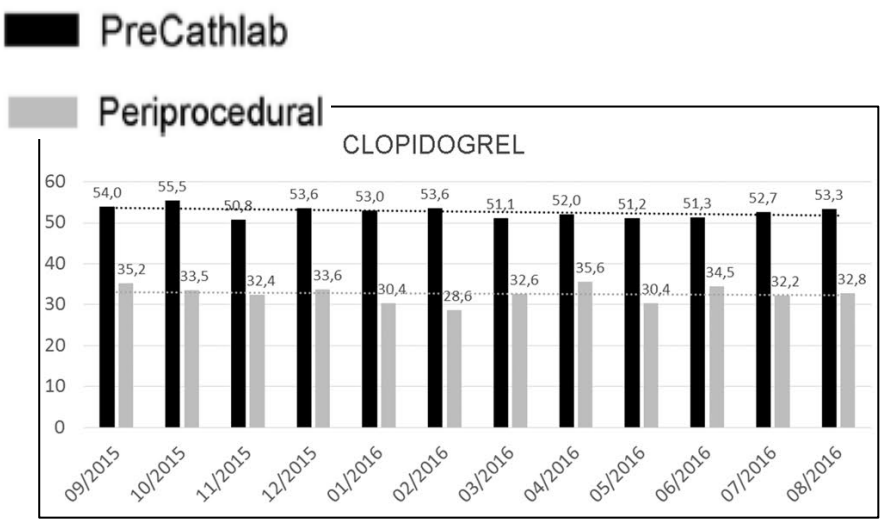
Barber U, Mehran R et al. Am Heart J 2017;188:73-81.

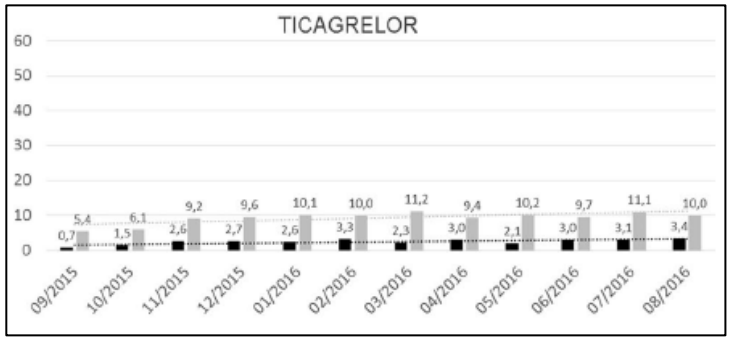
Clopidogrel, prasugrel, or ticagrelor use and clinical outcome in patients with acute coronary syndrome: A nationwide long-termregistry analysis from 2009 to 2014

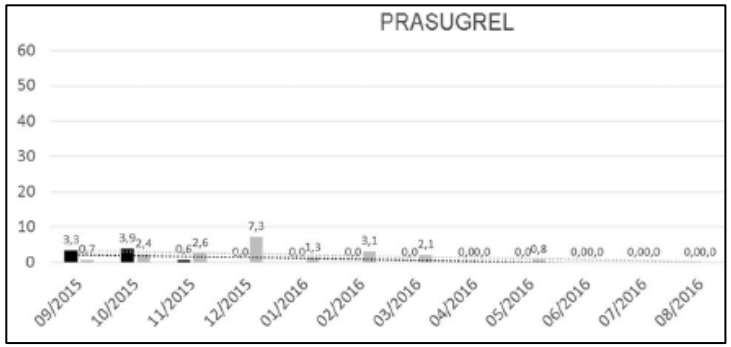


Rezaei S, Molzt M et al. Int J Card 2017; 235: 61–66.

Contemporary use of $P2Y_{12}$ inhibitors in patients with ST-segment elevation myocardial infarction referred to primary percutaneous coronary interventions in Poland: Data from ORPKI national registry







- **23,139 STEMI patients/ 153 PCI centers**
- September 2015 - **August 2016**.
- Finally 19,437 patients/122 centers
  (lack of ticagrelor or prasugrel usage reported in 31 centers)

J Thromb Thrombolysis. 2018 ;45:151-157

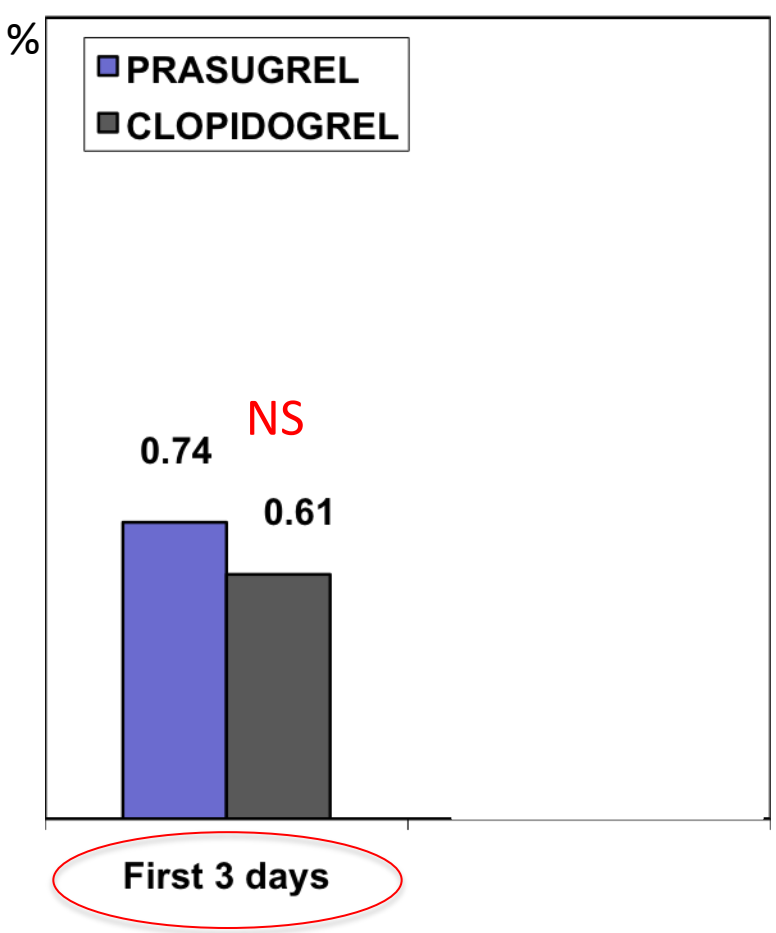
15 months	Prasugrel	Clopidogrel	HR for Prasugrel	p-value
TIMI Major Bleeding				
Non-CABG related	2.4	1.8	1.32	0.03
CABG-related	13.4	3.2	4.76	<0.001
Fatal	0.4	0.1	4.19	0.002

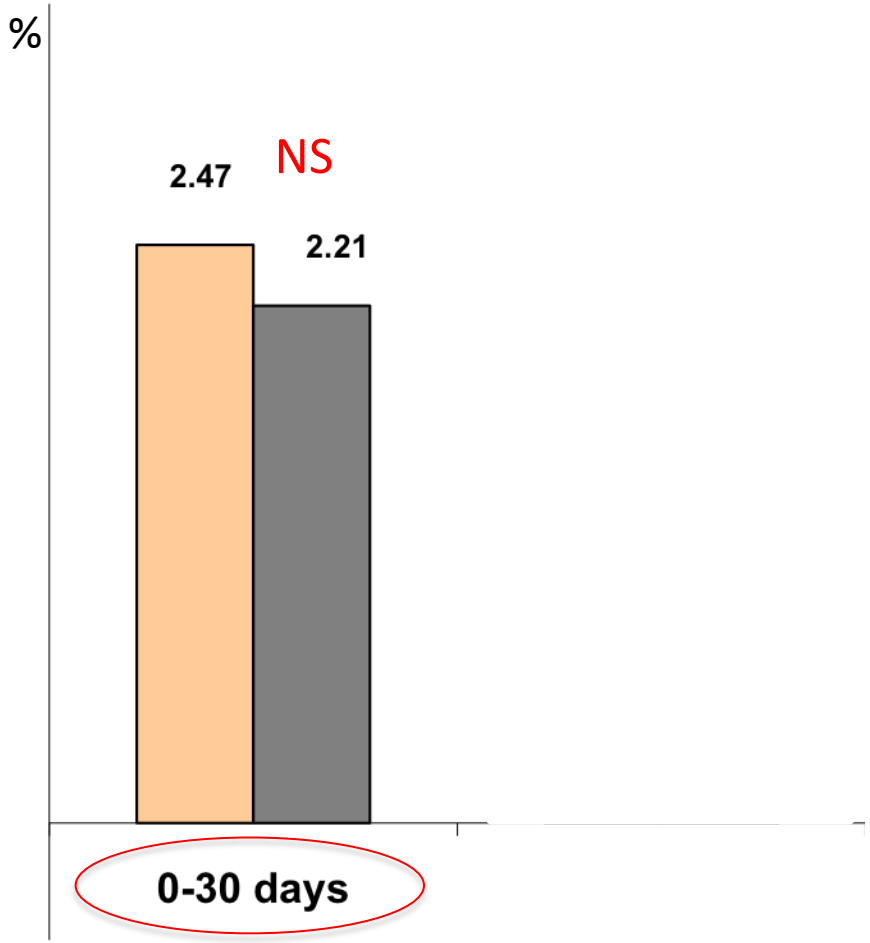
TRITON study; N Engl J Med 2007;357:2001

12 months	Ticagrelor	Clopidogrel	HR for Ticagrelor	p-value
TIMI Major Bleeding				
Non-CABG related	2.8	2.2	1.25	0.03
CABG-related	5.3	5.8	0.94	0.32
Fatal	0.3	0.3	0.87	0.66

PLATO study; N Engl J Med 2009;361:1045

TIMI Major Non-CABG related Bleeding





J Am Coll Cardiol 2008;51:2028

Eur Heart J 2011, 32: 2933

DEESKALACE = ↓ Intensity DAPT

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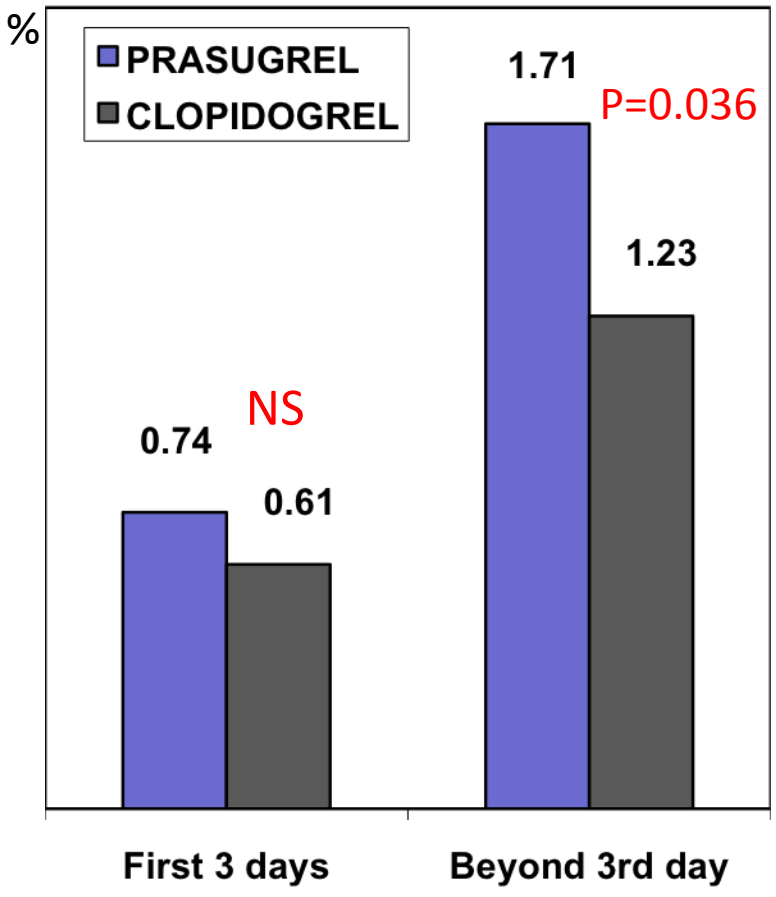
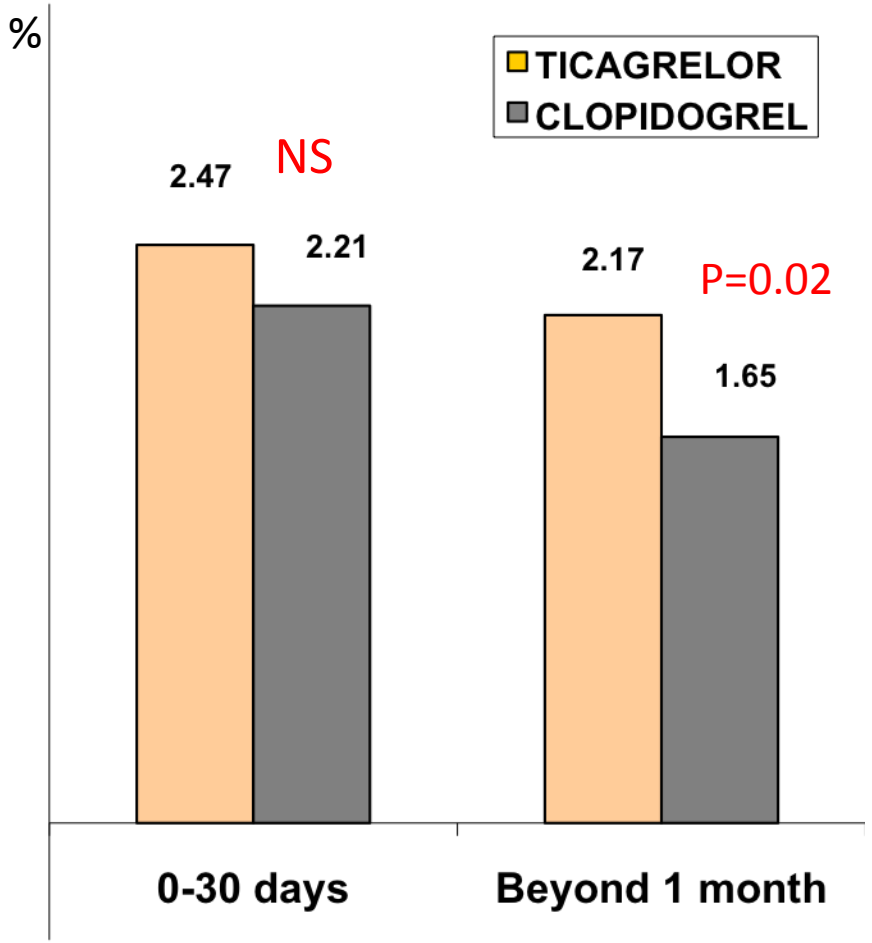
→ Pacienti > 75 let, Pacienti s hmotností < 60kg

TIMI Major Non-CABG related Bleeding





J Am Coll Cardiol 2008;51:2028

Eur Heart J 2011, 32: 2933

Rationale for (“optional”) **De-escalation of DAPT**

The net clinical benefit of Prasugrel/Ticagrelor over Clopidogrel decreases with the time from event

➔ De-escalation of DAPT in **bleeding risk patient** during the maintenance phase

Patient **cost-sharing** (out-of-pocket cost) declines drug adherence

➔ De-escalation to generic formulation of clopidogrel

Z. Motovska, Medscape, 8th February 2018

Studie TOPIC
(timing of platelet inhibition after ACS)

Pacienti (**N 646**) s PCI pro AKS

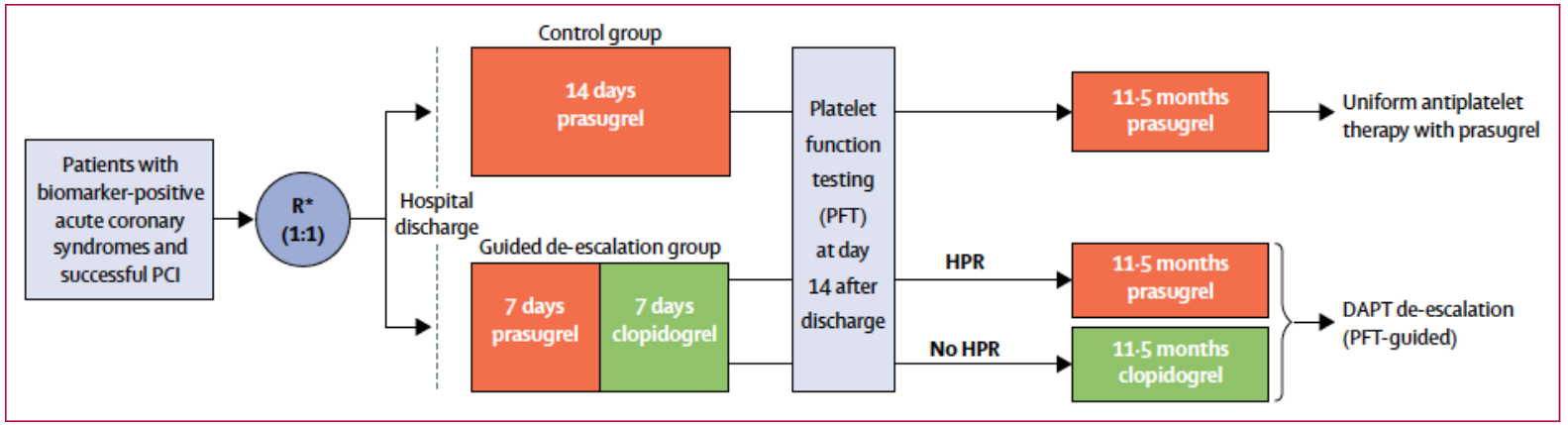
1 měsíc po PCI bez MACE randomizace P/T vs přechod na clopidogrel

Endpoints at 1 year

	Switched DAPT	Unchanged DAPT	HR (95%IC)	P-value
Net clinical benefit	43 (13.4%)	85 (26.3%)	0.48 (0.34–0.68)	<0.01
Any ischaemic event	30 (9.3%)	37 (11.5%)	0.48 (0.34–0.68)	0.36
Cardiovascular death	1 (0.3%)	4 (1.2%)	0.30 (0.05–1.73)	0.18
Unplanned revascularization	28 (8.7%)	30 (9.3%)	0.93 (0.56–1.55)	0.78
Stroke	1 (0.3%)	3 (0.9%)	0.37 (0.05–2.60)	0.32
All bleedings	30 (9.3%)	76 (23.5%)	0.39 (0.27–0.57)	<0.01
Bleeding BARC ≥ 2	13 (4.0%)	48 (14.9%)	0.30 (0.18–0.50)	<0.01
TIMI major	1 (0.3%)	4 (1.2%)	0.30 (0.05–1.73)	0.18
TIMI minor	9 (2.8%)	26 (8.0%)	0.37 (0.19–0.71)	<0.01
TIMI minimal	20 (6.2%)	46 (14.2%)	0.44 (0.27–0.71)	<0.01

Eur Heart J 2017; 38, 3070–3078

Studie TROPICAL-ACS



	Control group (n=1306)	Guided de-escalation group (n=1304)	Hazard ratio (95% CI)	p value
Net clinical benefit				
Primary endpoint (cardiovascular death, myocardial infarction, stroke, bleeding BARC ≥2)	118 (9%)	95 (7%)	0·81 (0·62–1·06)	$p_{non\text{-}inf}$ =0·0004; p_{sup} =0·12
Combined ischaemic events (cardiovascular death, myocardial infarction, stroke) and all bleeds (BARC bleeding 1–5)	175 (13%)	143 (11%)	0·81 (0·65–1·01)	0·06

Interpretation Guided de-escalation of antiplatelet treatment was non-inferior to standard treatment with prasugrel at 1 year after PCI in terms of net clinical benefit. Our trial shows that early de-escalation of antiplatelet treatment can be considered as an alternative approach in patients with acute coronary syndrome managed with PCI.

Lancet 2017; 390: 1747–57

1-Year Outcomes of Patients Undergoing Primary Angioplasty for Myocardial Infarction Treated With Prasugrel Versus Ticagrelor

Zuzana Motovska, MD, PhD,[a] Ota Hlinomaz, MD, CSc,[b] Petr Kala, MD, PhD,[c] Milan Hromadka, MD, PhD,[d] Jiri Knot, MD, PhD,[a] Ivo Varvarovsky, MD, PhD,[e] Jaroslav Dusek, MD, PhD,[f] Jiri Jarkovsky, MSc, PhD,[g] Roman Miklik, MD, PhD,[c] Richard Rokyta, MD, PhD,[d] Frantisek Tousek, MD,[h] Petra Kramarikova, Mgr,[b] Michal Svoboda, MSc,[g] Bohumil Majtan, MD,[i,j] Stanislav Simek, MD, CSc,[k] Marian Branny, MD, PhD,[l] Jan Mrozek, MD,[m] Pavel Cervinka, MD, PhD,[n] Jiri Ostransky, MD,[o] Petr Widimsky, MD, DrSc,[a] PRAGUE-18 Study Group

J AmColl Cardiol 2018;71:371–81

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

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.

PRAGUE 18, JACC 2018

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

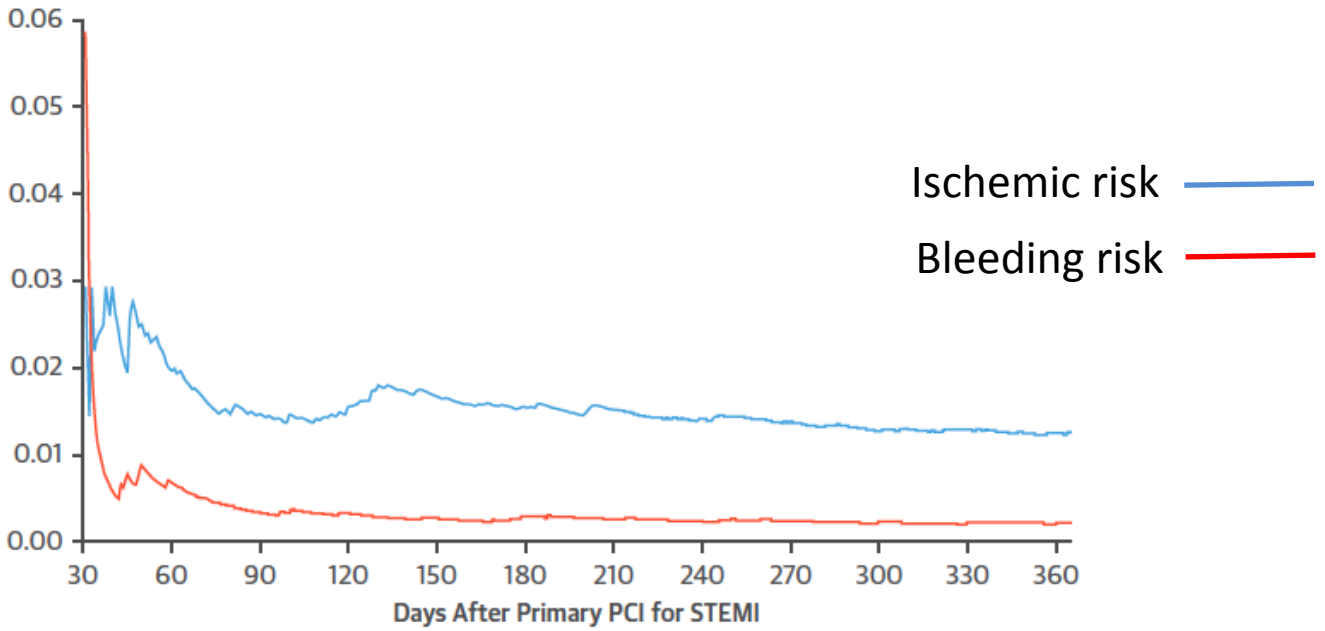
	SWITCH TO CLOPIDOGREL		P-value
	No	Yes	
BMI > 30	223 (29.8%)	172 (35.8%)	0.029
ECG			
Left bundle branch block	17 (2.3%)	1 (0.2%)	0.002
Bundle branch block	33 (4.4%)	7 (1.5%)	0.005
Killip classification			
I	642 (85.7%)	443 (92.1%)	0.004
II	59 (7.9%)	23 (4.8%)	
III	11 (1.5%)	6 (1.2%)	
IV	37 (4.9%)	9 (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

The observed consequences of switching or not switching to clopidogrel were not the results of a randomized comparison. Benefit and harm of a transition from recommended potent $P2Y_{12}$ inhibitors to clopidogrel in AMI shortly after discharge, based on patient-related risk and procedural results, must be validated in a proof-of-concept randomized trial.

PRAGUE 18, JACC 2018

Characterization of the Average Daily Ischemic and Bleeding Risk After Primary PCI for STEMI

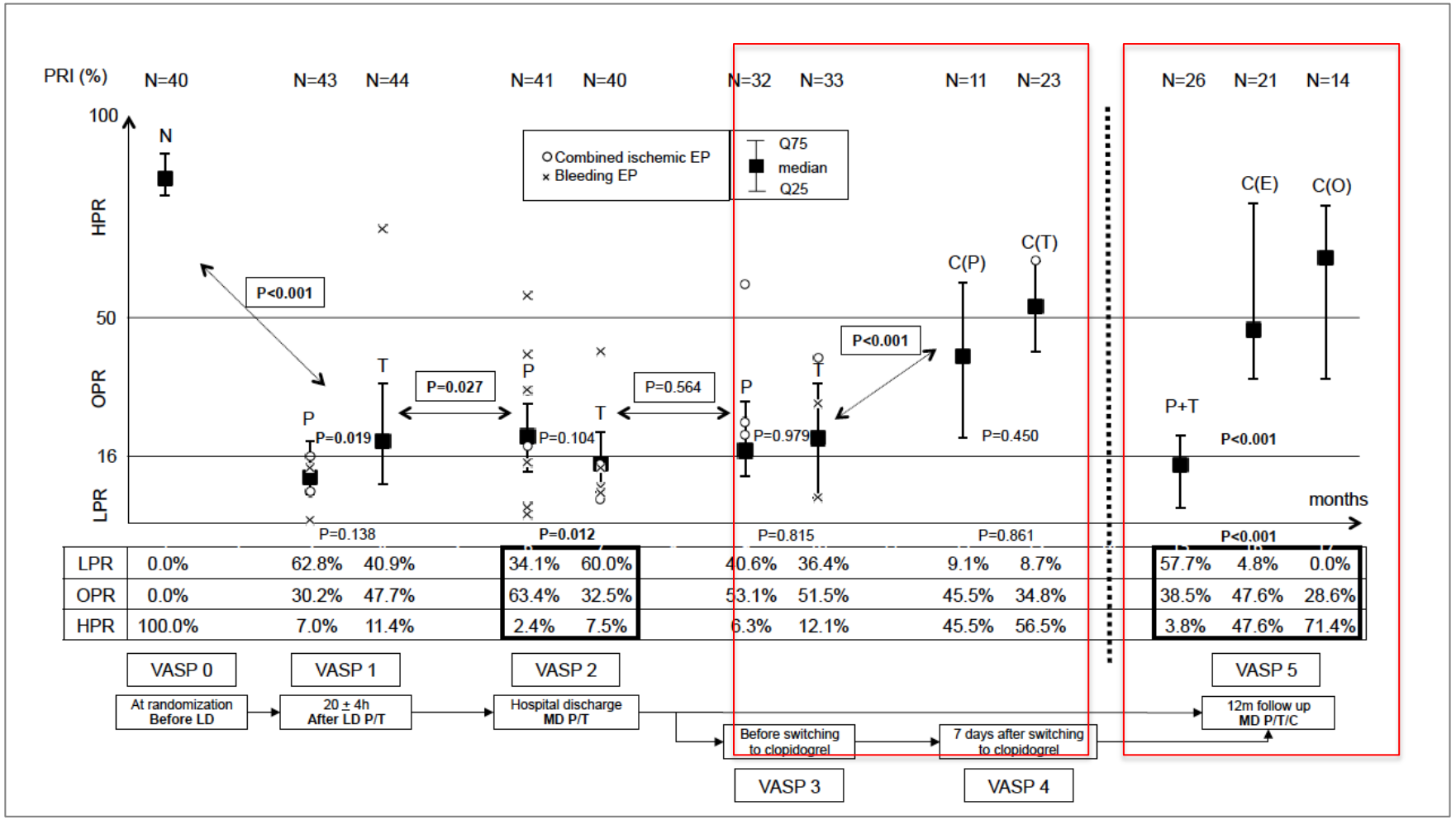
3602 patients, **DAPT: ASA + Clopidogrel**



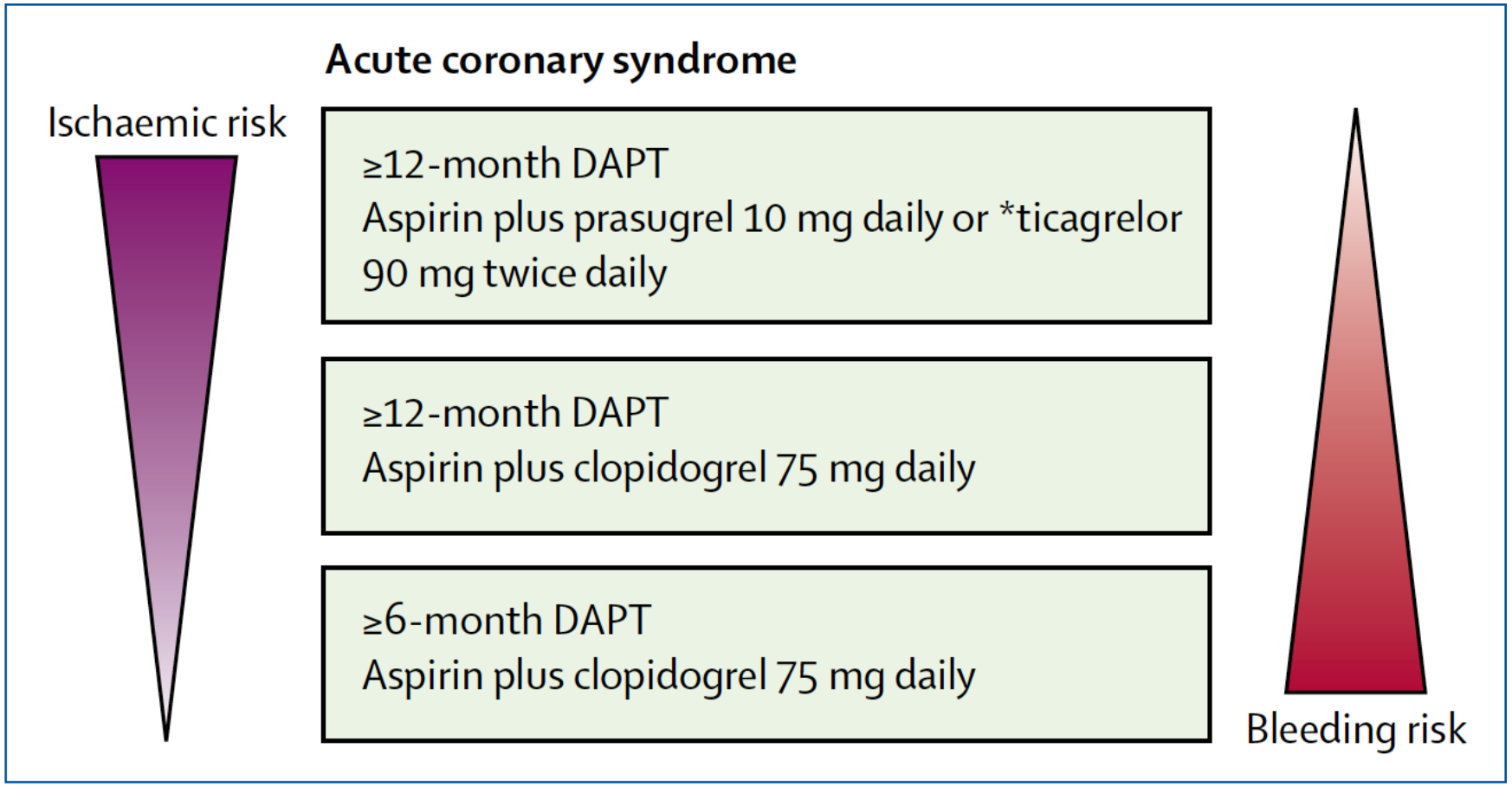
The daily risk of ischemia significantly exceeded the daily risk of bleeding beyond 30 days, supporting the use of intensified platelet inhibition during the first year after STEMI

JACC 2017;70:1846–57

PLATELET REACTIVITY SUB-STUDY OF THE RANDOMIZED COMPARISON OF PRASUGREL AND TICAGRELOR IN ACUTE MYOCARDIAL INFARCTION TREATED WITH PRIMARY ANGIOPLASTY. VASP PRAGUE-18 STUDY



Miklik R et all PRAGUE 18 investigators, AHA, Orlando 2018 (published in JACC)



DAPT=dual antiplatelet therapy.
*Ticagrelor 90 mg twice daily for 12 months and 60 mg twice daily after 12 months.

Z. Motovska, DL Bhatt, Lancet 2018

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→ ASA + Ticagrelor/Prasugrel po dobu < 12 měsíců
(u pp bez kontraindikací a bez vysokého rizika krvácení)

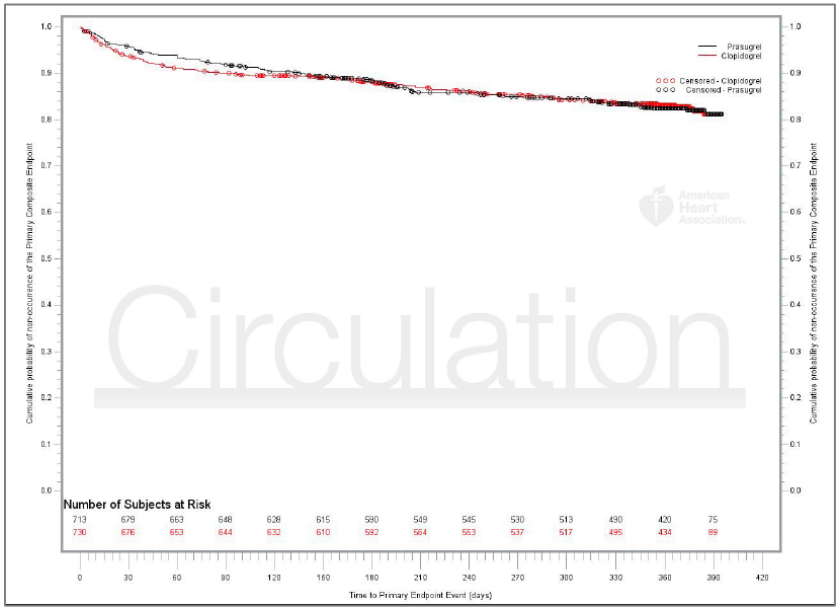
→ Pacienti > 75 let, Pacienti s hmotností < 60kg

The Elderly ACS-2 Randomised Trial

Prasugrel 5 mg vs. Clopidogrel 75 mg MD

>74 years old patients with ACS undergoing PCI

	Prasugrel (N=713)	Clopidogrel (N=730)	HR (95% CI)	P value
Primary endpoint*	121 (17.0%)	121 (16.6%)	1.01 (0.78-1.30)	0.96
All-cause death†	36 (5.0%)	28 (3.8%)		
Myocardial infarction†	14 (2.0%)	19 (2.6%)		
Disabling stroke†	1 (0.1%)	6 (0.8%)		
Rehospitalization CV causes†	55 (7.7%)	57 (7.8%)		
Rehospitalization for bleeding†	15 (2.1%)	11 (1.5%)		
Key secondary endpoints:				
All-cause death and MI	60 (8.4%)	60 (8.2%)	1.02 (0.71-1.45)	0.93
CV death	26 (3.6%)	31 (4.2%)	0.85 (0.51-1.4)	0.55
Strokes	7 (1.0%)	13 (1.8%)	0.55 (0.22-1.37)	0.20
Definite/probable stent thrombosis	5 (0.7%)	14 (1.9%)	0.36 (0.13-1.00) ‡	0.06‖
Acute	1	1		
Subacute	4	12		
Late	-	1		
Bleeding leading to new hospitalization BARC 2	8 (1.1%)	7 (0.9%)		
BARC 3	9 (1.2%)	9 (1.2%)		
BARC 2,3	17 (2.3%)	16 (2.1%)		
All bleedings BARC 2	16 (2.2%)	8 (1.1%)		
BARC 3	12 (1.6%)	12 (1.6%)		
BARC 5	1 (0.1%)	0		
BARC 2,3,5	29 (4.1%)	20 (2.7%)	1.52 (0.85-3.16) ‡	0.18‖



Conclusions—The present study in elderly ACS patients showed no difference in the primary endpoint between reduced-dose prasugrel and standard-dose clopidogrel. However, the study should be interpreted in the light of premature termination of the trial. .

Circulation. 2018 [Epub ahead of print]

Závěry

1. Deeskalace antiagregační léčby t.j. nenasazení nebo zkrácení doporučené DAPT (ASA + T/P) u pacientů s AKS (bez ohledu na léčebnou strategii) bez kontraindikací a/nebo bez vysokého rizika krvácení = NEADHERENCE K DOPORUČENÍM

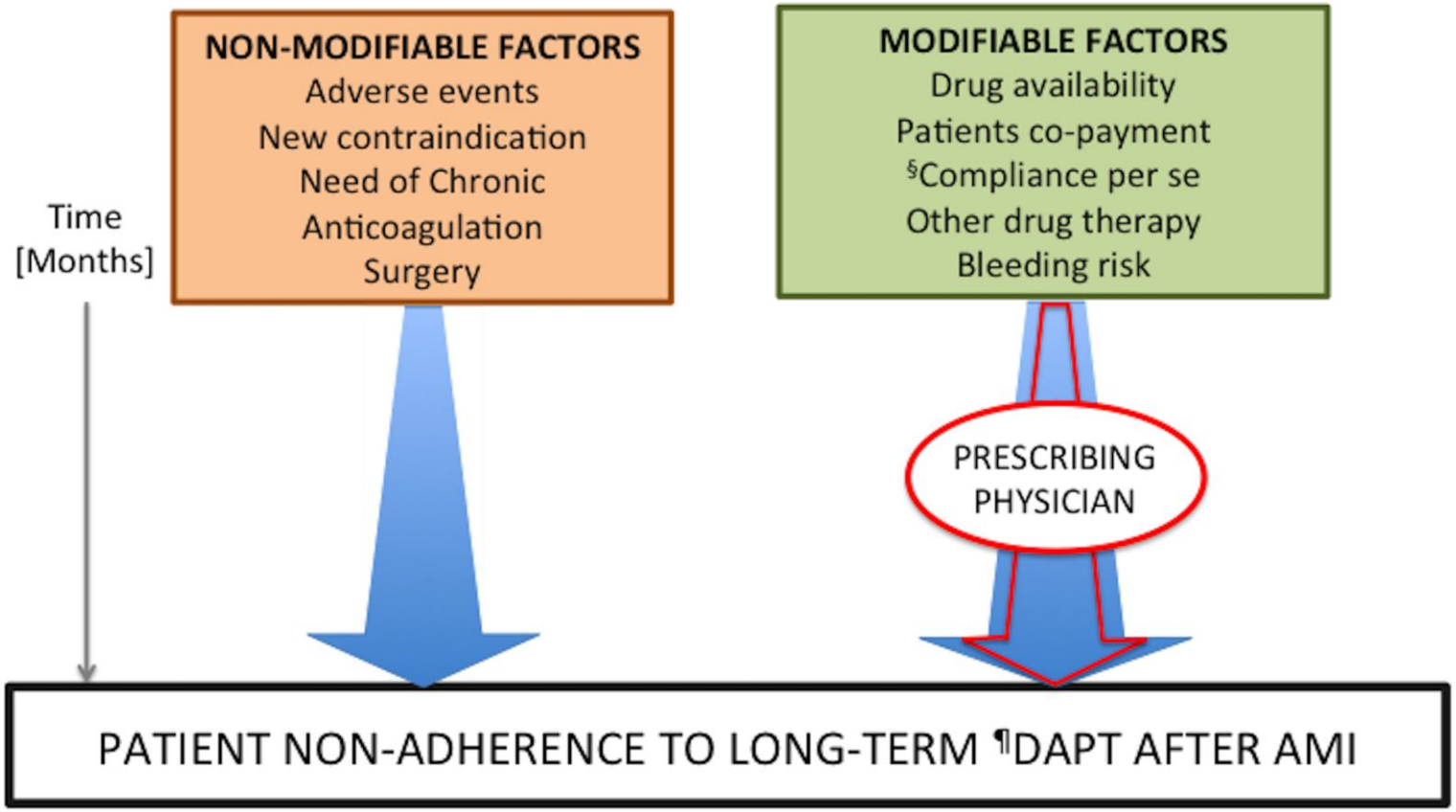
2. Neadherence k doporučené DAPT zhoršuje prognózu pacientů s AKS

International Expert Consensus on Switching Platelet $P2Y_{12}$ Receptor–Inhibiting Therapies

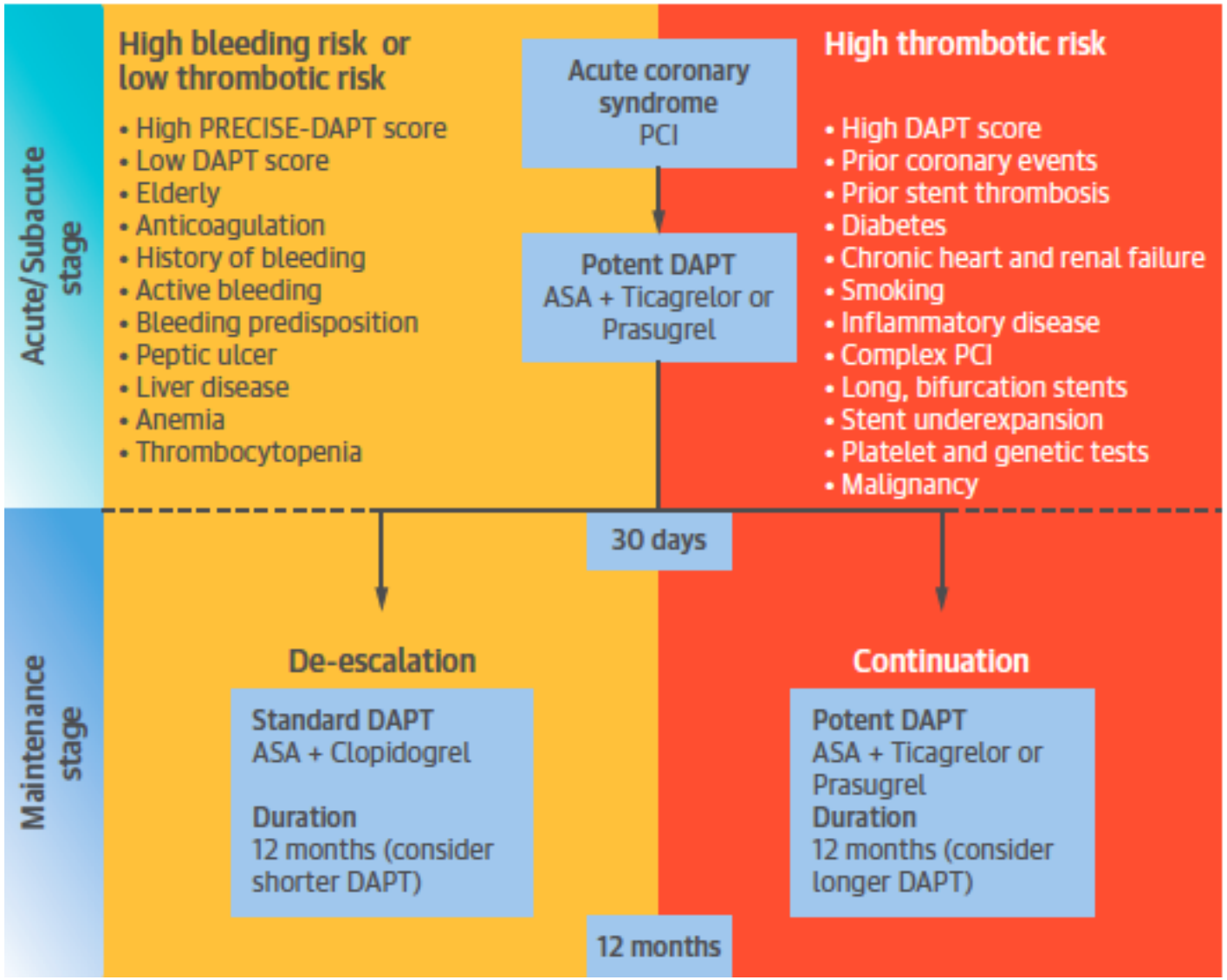
De-escalation (Switching From Prasugrel or Ticagrelor to Clopidogrel)

Despite the evidence for the sustained efficacy and safety of prasugrel and ticagrelor with long-term treatment, many physicians limit treatment duration with these agents to the early weeks or months after the index event.[36–41] Reduced costs associated with a generic formulation of clopidogrel and concerns about increased risk of bleeding with prasugrel and ticagrelor remain the most important reasons for de-escalation.

Circulation. 2017;136:1955–1975.

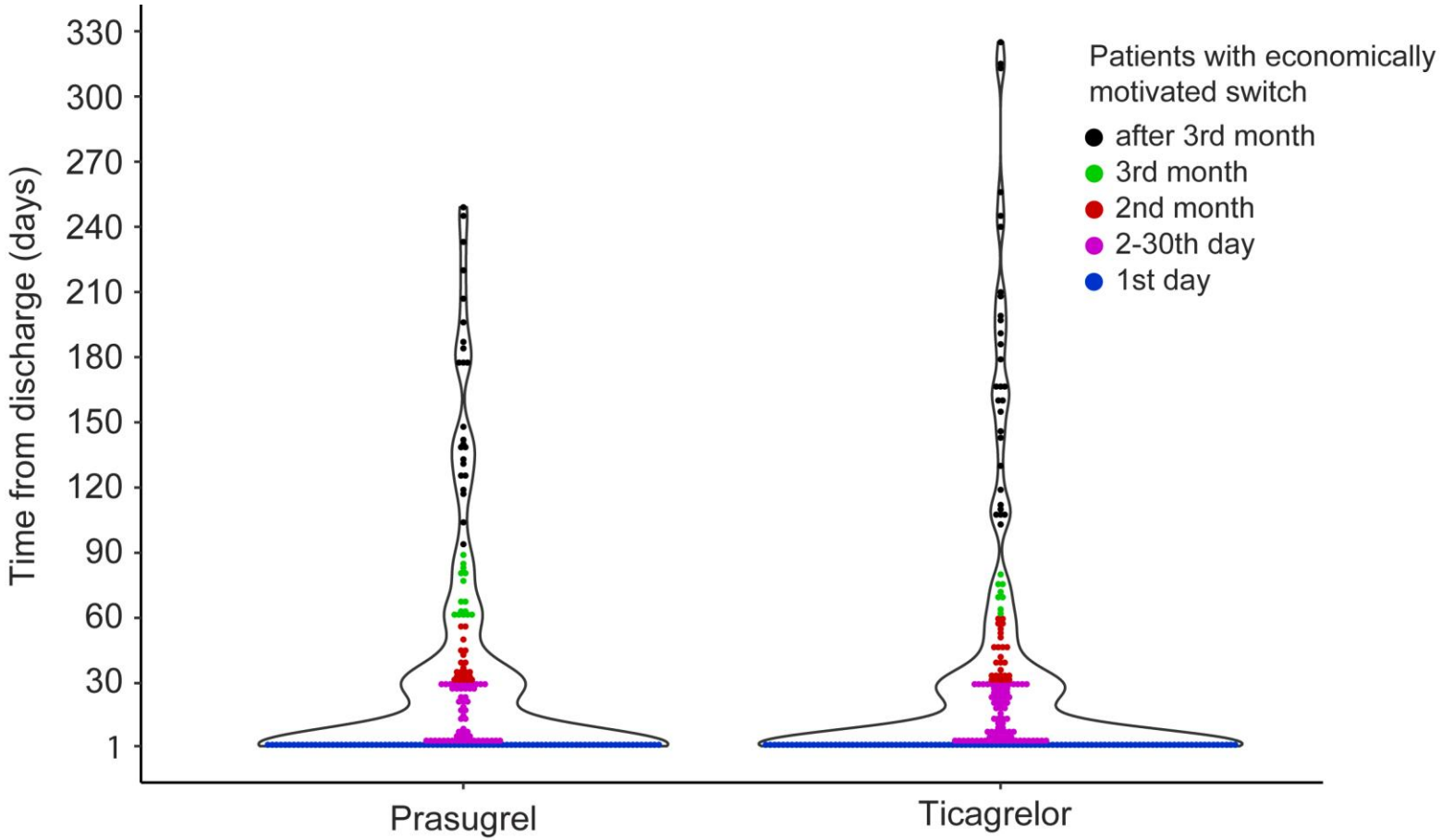


Z. Motovska, O. Hlinomaz, P. Kala, JACC 2018 (in press)



Chatzizisis Y,Stefanadis S, JACC 2018

Time distribution of economically motivated switches to clopidogrel after discharge



De-escalation of DAPT after AMI treated with PCI with new generation DES

I. During the maintenance phase

II. Selective according to risk stratification

"Yes" in High Bleeding risk patients

"No" in High Thrombotic risk patients

Z. Motovska, Medscape, 8th February 2018