Nefarmakologická HOT LINES

GLOBAL LEADERS

“stačí po PCI monoterapie ticagrelorem?”

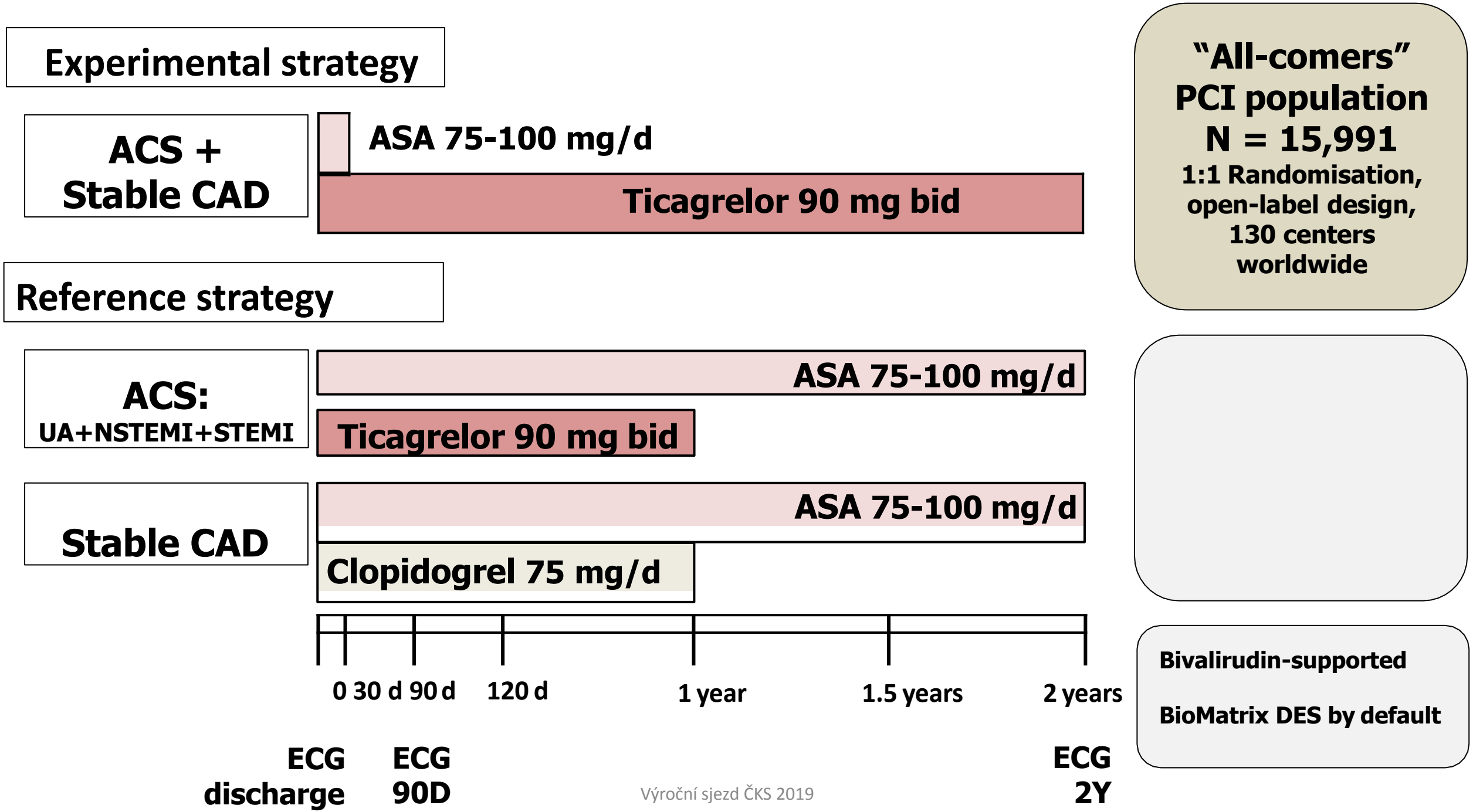
Viktor Kočka
Kardiocentrum FNKV a 3.LF UK
Praha

Myšlenka a design studie

Ticagrelor jako potentní a konsistentní protidestičkový lék může být účinnější než ASA v monoterapii

Monoterapie ticagrelorem může mít méně krvácivých komplikací než duální léčba

Monoterapie ticagrelorem mezi rokem 1 a 2 může být podobně účinná jako duální terapie


Experimental strategy
ACS + Stable CAD
ASA 75-100 mg/d
Ticagrelor 90 mg bid
Reference strategy
ACS: UA+NSTEMI+STEMI
ASA 75-100 mg/d
Ticagrelor 90 mg bid
Stable CAD
ASA 75-100 mg/d
Clopidogrel 75 mg/d
0
30 d
90 d
120 d
1 year
1.5 years
2 years
ECG discharge
ECG 90D
ECG 2Y
"All-comers" PCI population N = 15,991
1:1 Randomisation, open-label design, 130 centers worldwide
Bivalirudin-supported
BioMatrix DES by default

- **Primary endpoint**:
  - All-cause death and non-fatal new Q wave MI
  - at 2 years
- **Design**:
  Superiority of the experimental arm vs. reference arm.
- **Expected event rate**
  5% for primary endpoint
  - Death 4.5%
  - New Q wave MI 0.5%
  - Based on 2-year outcome of LEADERS trial*

- **Expected risk reduction**
  - Based on PLATO trial
- **Sample size**
  2 x 8000 patients
- **Power**
  - 92% to detect a 22.5% relative risk reduction (RRR)
  - 84% to detect a 20% RRR
- Attrition rate: 4%

*Klauss V, Serruys PW, Pilgrim T, Buszman P, Linke A, Ischinger T, et al. 2-year clinical follow-up from the randomized comparison of biolimus-eluting stents with biodegradable polymer and sirolimus-eluting stents with durable polymer in routine clinical practice. JACC Cardiovascular interventions. 2011;4(8):887-95

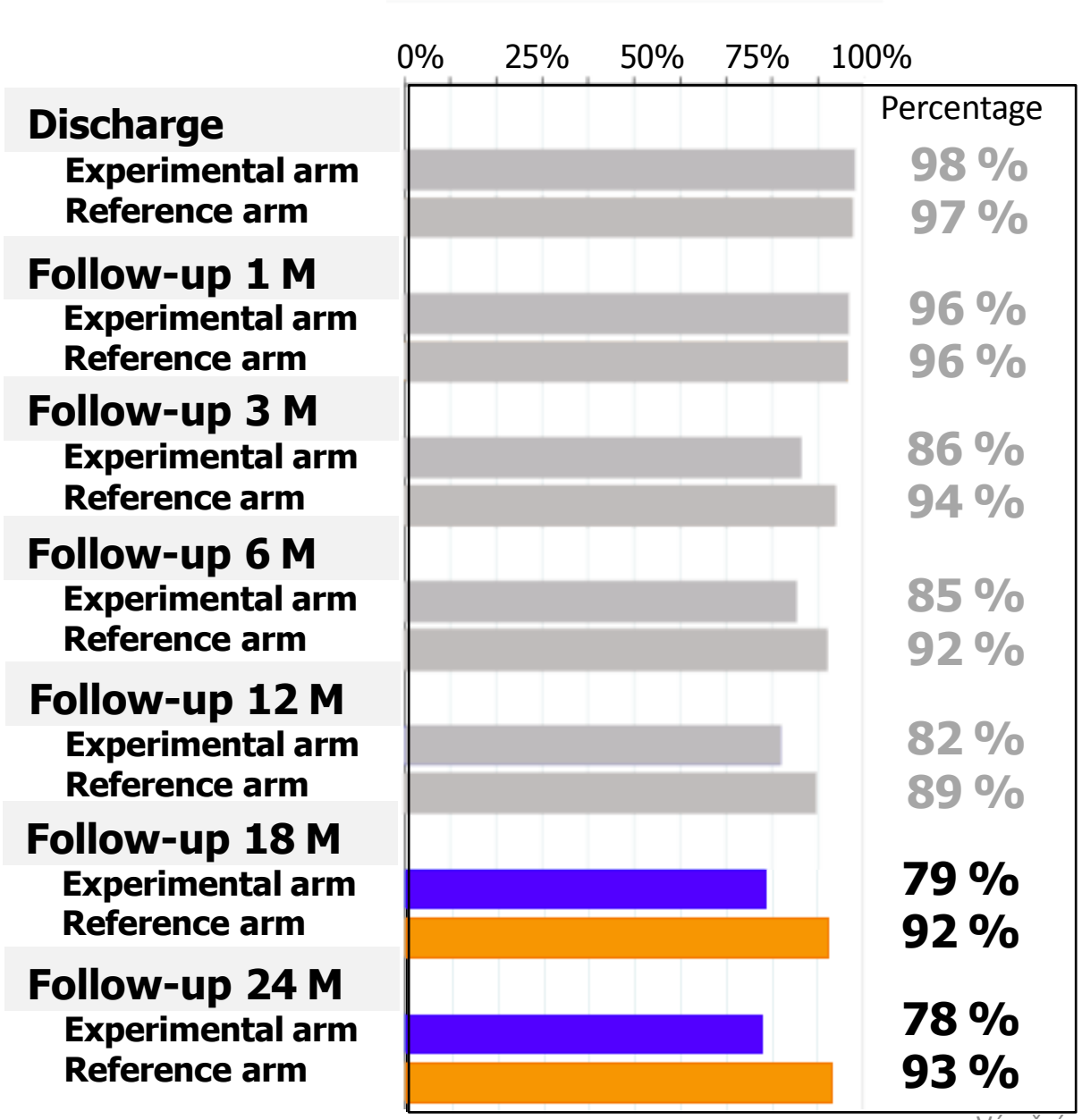
Baseline characteristics

Total number of patients	Experimental Treatment Strategy N = 7980	Reference Treatment Strategy N = 7988
Age (years)	64.5 ± 10.3	64.6 ± 10.3
Females	23.4 %	23.1 %
Body Mass Index (kg/m²)	28.2 ± 4.6	28.2 ± 4.6
Medical history/comorbidities		
Diabetes mellitus	25.7 %	24.9 %
Insulin-dependent diabetes mellitus	7.6 %	7.7 %
Hypertension	74.0 %	73.3 %
Hypercholesterolemia	69.3 %	70.0 %
Current smoker	25.9 %	26.3 %
Peripheral Vascular Disease	6.0 %	6.7 %
Chronic obstructive pulmonary disease	5.1 %	5.2 %
Previous Major bleeding	0.6 %	0.7 %
Impaired renal function (eGFR < 60 ml/min/1.73m²)	13.9 %	13.5 %
Previous stroke	2.6 %	2.6 %
Previous myocardial infarction	23.0 %	23.6 %
Previous PCI	32.7 %	32.7 %
Previous CABG	5.6 %	6.2 %

Baseline characteristics

Total number of patients	**Exp. Strategy** N = 7980	**Ref. Strategy** N = 7988
Clinical presentation		
• **Stable Coronary Artery Disease**	**53.0** %	**53.2** %
• **Acute Coronary Syndrome (ACS)**	**47.0** %	**46.8** %
Unstable Angina	**12.6 %**	**12.7 %**
Non-STEMI	**21.1 %**	**21.1 %**
STEMI	**13.3 %**	**12.9 %**
Procedural characteristics		
PCI performed	**99.5 %**	**99.4 %**
Radial artery access	**73.9 %**	**74.2 %**
BioMatrix DES	**94.8 %**	**94.4 %**
Bivalirudin-assisted PCI	**87.4 %**	**87.2 %**
Number of lesions treated per patient		
One lesion	**74.6 %**	**74.7 %**
Two lesions	**20.5 %**	**19.8 %**
Three or more lesions	**5.0 %**	**5.5 %**

Adherence



Primary and secondary outcomes at 24 months (Intention to treat)

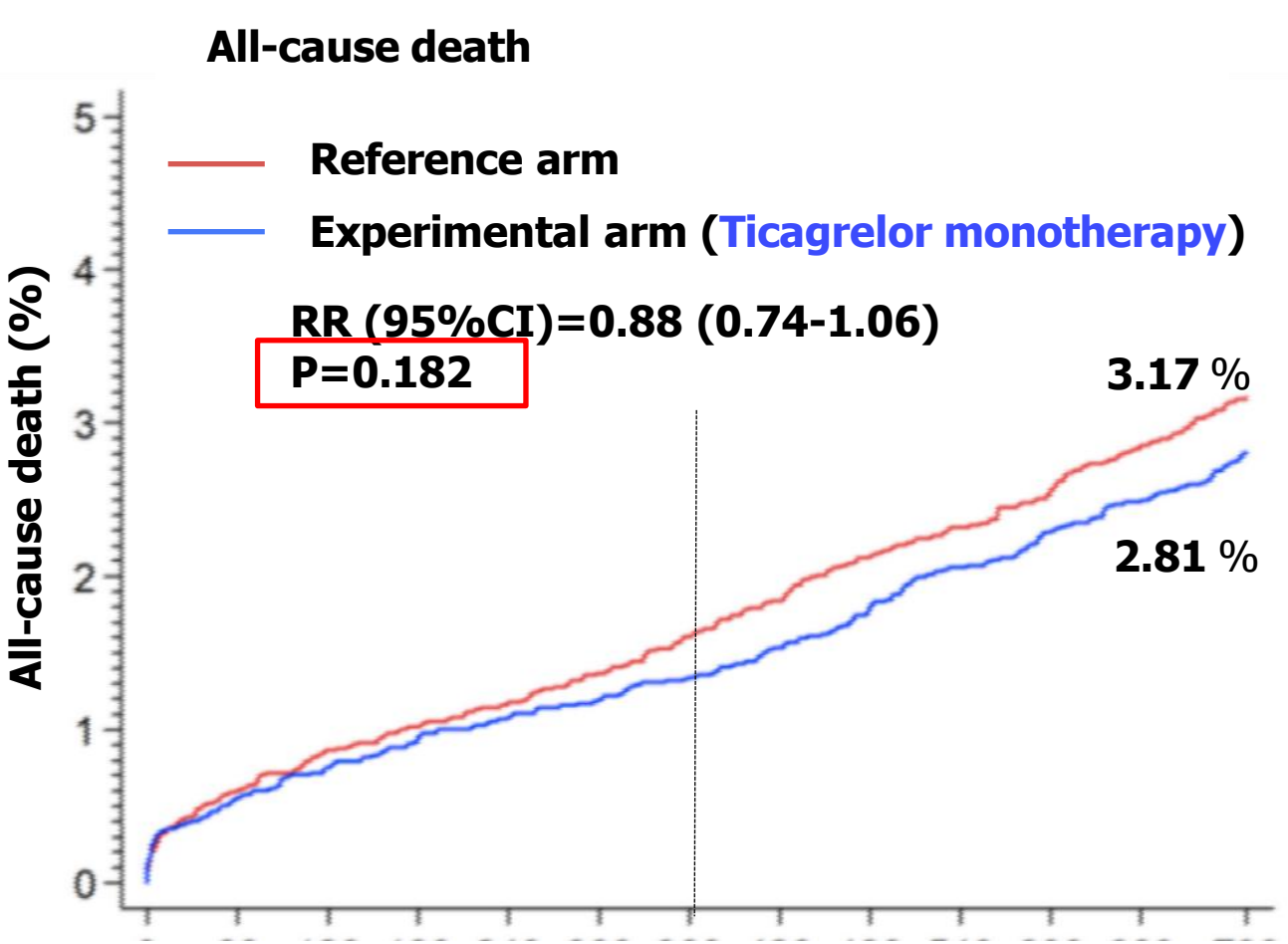
	Experimental group	Reference group	Risk Ratio (95% CI)	p-value
Number of pts.	N=7980	N=7988		
All-cause mortality or new Q-wave MI	**3.81** %, (304)	**4.37** %, (349)	**0.87** (0.75-1.01)	**0.073**
All-cause mortality	**2.81** % (224)	**3.17** % (253)	**0.88** (0.74-1.06)	0.18
New Q-wave MI	**1.04** % (83)	**1.29** % (103)	**0.80** (0.60-1.07)	0.14

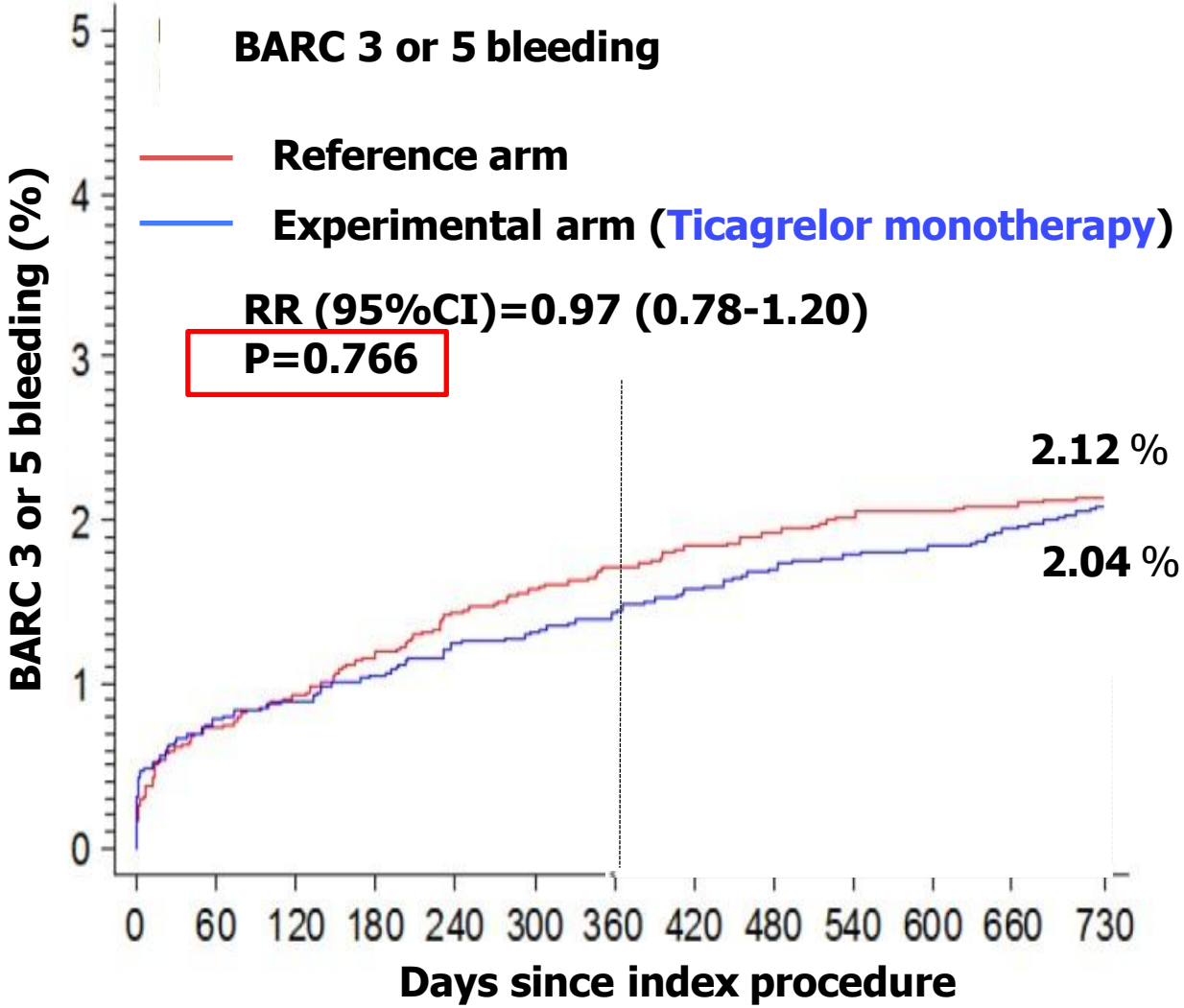
0.87

Ticagrelor monotherapy in ACS and SA

ASA monotherapy in ACS and SA

Kaplan Meier estimate of mortality and safety outcome at 2 years





Ref. DAPT (Tica/Clop) ASA mono

DAPT

Exp. Tica Mono

Ref. DAPT (Tica/Clop) ASA mono

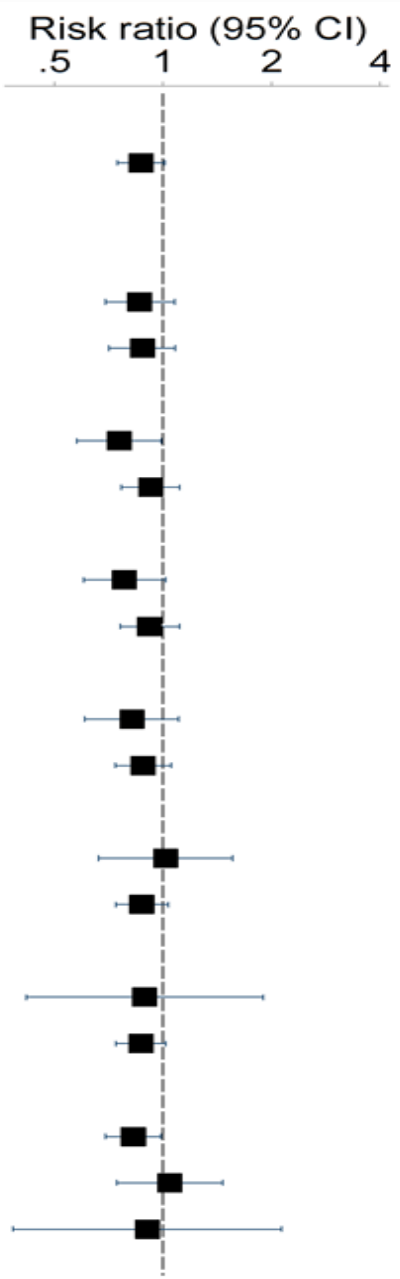
DAPT

Exp. Tica Mono

Primary endpoint at 2 years

Pre-specified subgroups

	Experimental Treatment Exp. Strategy	Reference Treatment Ref. Strategy	Risk Ratio [Exp/Reference]	p-value for interaction
Overall	304/7980	349/7988	(0.75-1.01) 0.87	
Indication				0.926
ACS	147/3750	169/3737	(0.69-1.08) 0.86	
Stable CAD	157/4230	180/4251	(0.71-1.08) 0.87	
Age				0.231
>75 years	**93/1292**	**120/1273**	**(0.58-0.99) 0.75**	
≤75 years	211/6688	229/6715	(0.77-1.11) 0.92	
Diabetes mellitus				0.326
diabetics	102/2049	126/1989	(0.60-1.01) 0.78	
non-diabetics	202/5925	222/5994	(0.76-1.11) 0.92	
Renal failure				0.680
Yes	79/1099	93/1072	(0.61-1.11) 0.82	
No	225/6881	256/6916	(0.74-1.05) 0.88	
PVD				0.521
Yes	40/476	44/529	(0.66-1.56) 1.02	
No	260/7428	295/7389	(0.74-1.03) 0.87	
Left main treated				0.950
Yes	13/197	14/190	(0.42-1.90) 0.89	
No	291/7783	335/7798	(0.74-1.02) 0.87	
Geographic area				0.488
Western Europe	**226/6156**	**273/6167**	**(0.69-0.99) 0.83**	
Eastern Europe*	68/1502	65/1500	(0.74-1.47) 1.04	
Rest of the world	10/322	11/321	(0.38-2.14) 0.91	



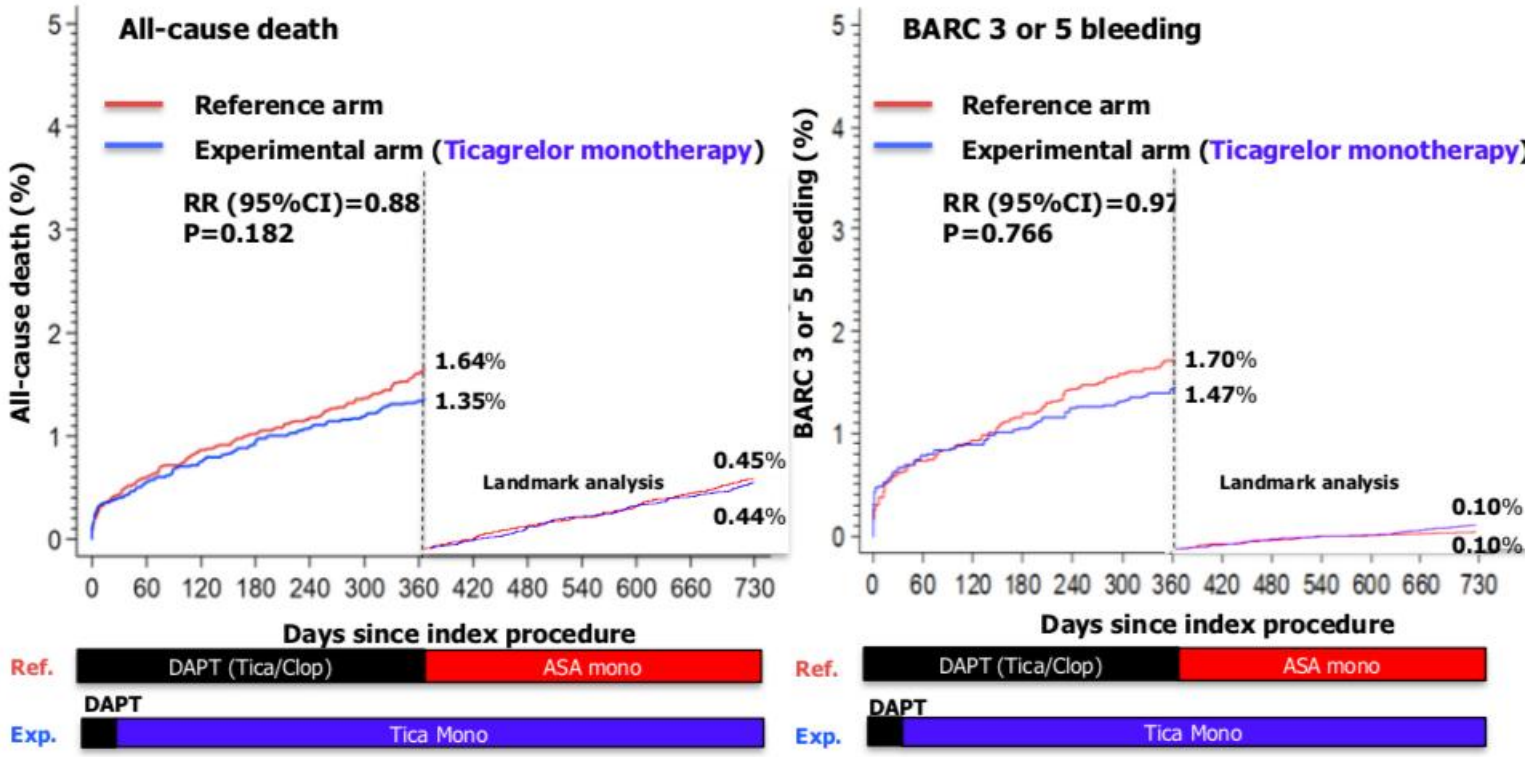
*Eastern Europe included Poland, Bulgaria, Hungary

Hypotéza 1 – kéž by studie skončila po 1. roce

Primary and secondary outcomes at 12 months (Intention to treat)

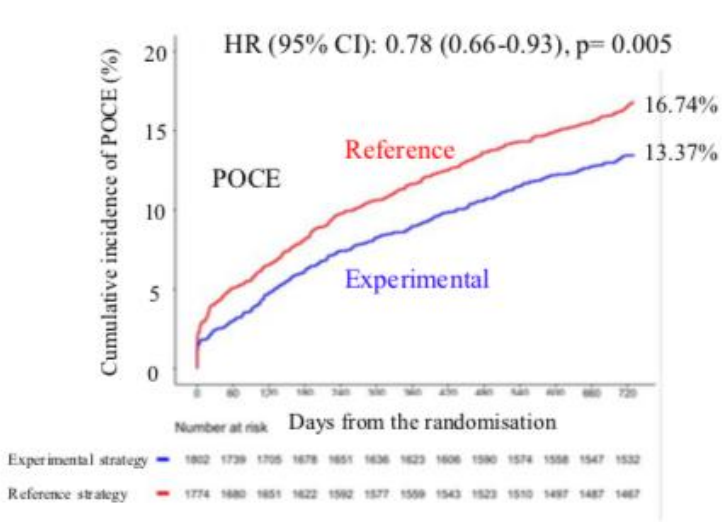
	Experimental group	Reference group	Risk Ratio (95% CI)	p-value
Number of pts.	N=7980	N=7988		
All-cause mortality or new Q-wave MI*	**1.95** %, (156)	**2.47** %, (197)	**0.79** (0.64-0.98)	**0.028**
All-cause mortality	**1.35** % (108)	**1.64** % (131)	**0.82** (0.64-1.06)	0.138
New Q-wave MI	**0.60** % (48)	**0.86** % (69)	**0.70** (0.48-1.00)	0.052
BARC 3 or 5 Bleeding**	**1.47** %	**1.70** %	**0.86** (0.67-1.11)	0.243
BARC 5 Bleeding	**0.18** %	**0.20** %	**0.88** (0.43-1.80)	0.722
BARC 3 Bleeding	**1.34** %	**1.60** %	**0.84** (0.65-1.08)	0.179

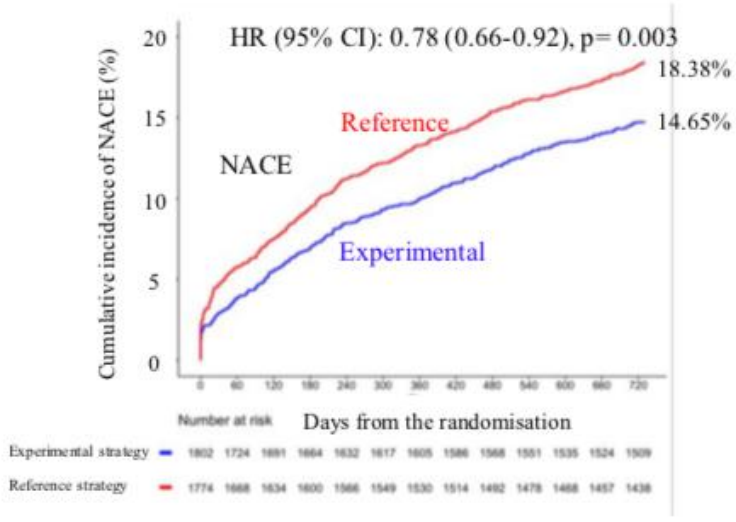
Kaplan Meier estimate of mortality and safety outcome at 2 years

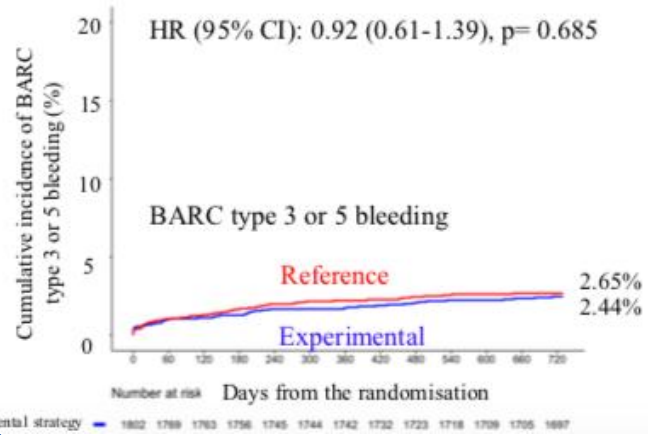


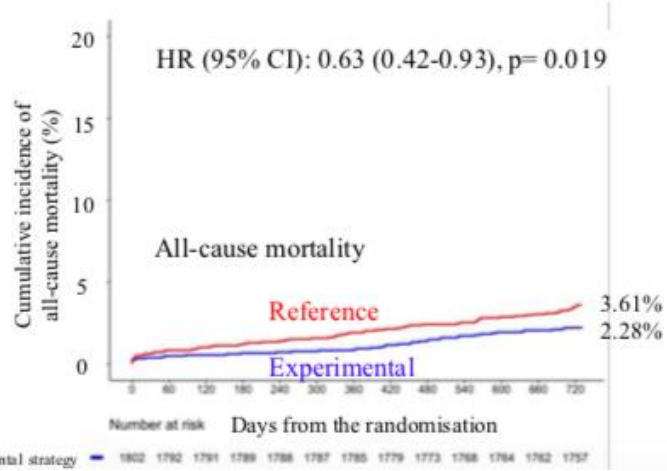
Hypotéza 2 – PCI více tepen, dlouhé stenty…

Clinical outcomes in patients with Multivessel PCI









Reasons of non-adherence to the allocated strategy at 2 years

Cross sectional analysis/mutually exclusive

24 months Follow-up	Experimental strategy N=4254	Reference strategy N=4291	p value
Adherent to treatment strategy	n=4043,	n=4049,	
Yes	(78%) 3145	(93%) 3776	
No	898 (22%)	(7%) 273	
Reason of non-adherence			
Dyspnea	233 (26%)	(3%) 8	0.001
Bleeding	(21%) 191	(16%) 44	0·070
Percutaneous Coronary Intervention	(14%) 128	(18%) 50	0·102
Oral anticoagulation	77)9(%	4) 717(%	0.001
Medical decision	24 (3%)	14 (5%)	
Surgery	35 (4%)	4 (1%)	
Others	94 (10%)	28(11%)	
Reason unclear	(13%) 116	(29%) 78	0.001

* Patients included in the adherence sub-study (n=8545) were those who were assessed using the new version of the eCRF at 1 month Follow-up and later, so reasons for non-adherence could be entered into the system. Percentages and two-sided P-values from Fisher's exact test for reasons of non-adherence refer to the denominator of non-adherent patients at 24 months. Reasons of non-adherence were classified in accordance with the Non-adherence Academic Research Consortium document.

Závěr

Ticagrelor v monoterapii 2 roky po PCI není účinnější ani bezpečnější než zavedená duální terapie na 1 rok a poté monoterapie ASA, není tedy důvod ke změně doporučení.

Hypotéza 1:

Monoterapie ticagrelorem měsíc 2-12 po PCI je účinnější a bezpečnější než DAPT dle doporučení ESC.

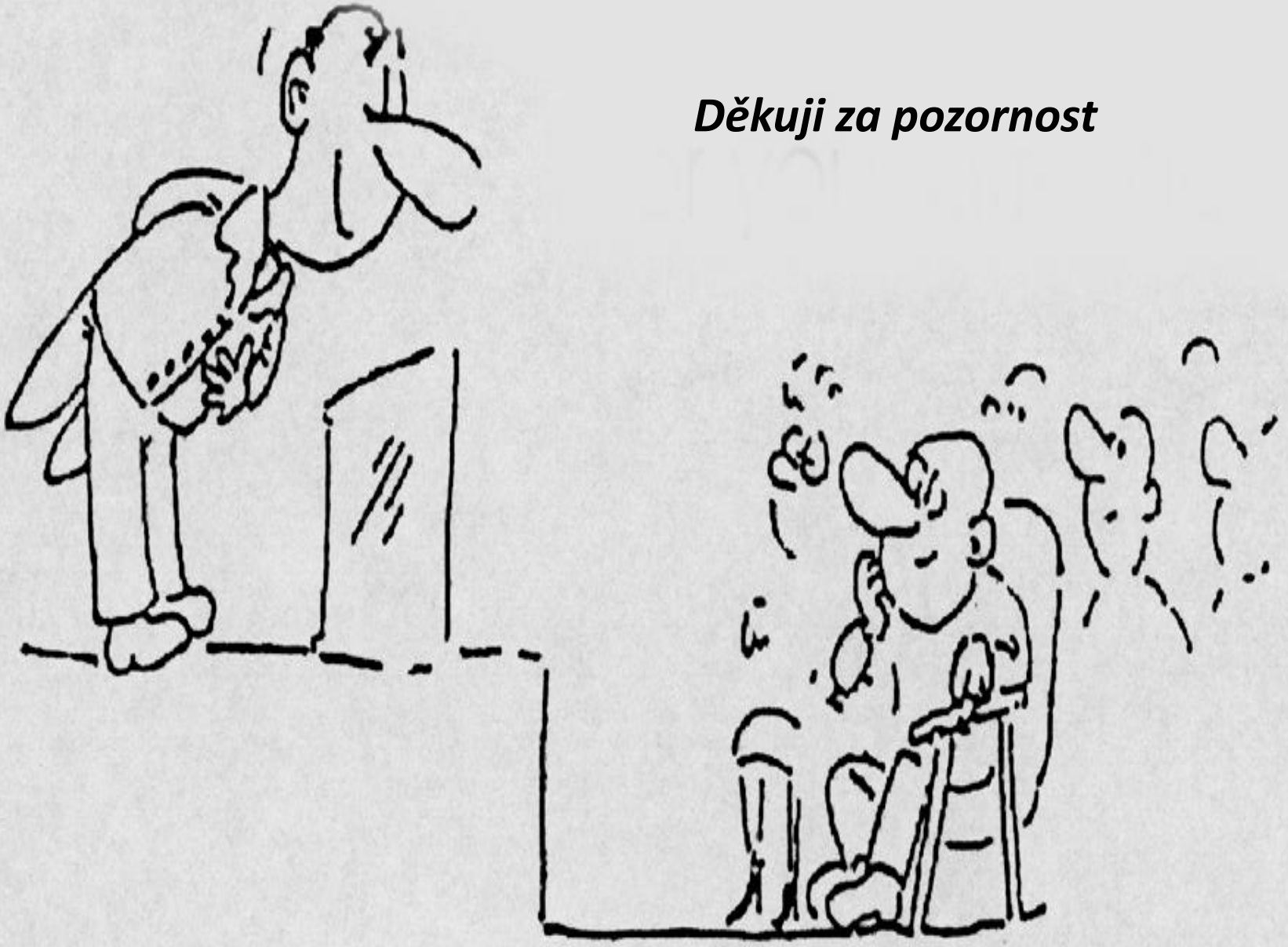
Hypotéza 2:

Monoterapie ticagrelorem měsíc 2-24 může být účinnější a stejně bezpečná než postup dle doporučení ESC u pacientů s PCI více tepen či dlouhými stenty.

Závěr 2

Různí pacienti potřebují různé režimy antiagregační terapie, univerzální řešení neexistuje.

Děkuji za pozornost



Study drug/strategy non-adherence in published ticagrelor trials

Study	Experimental Treatment Group	Reference treatment Group	Follow up
Global Leaders	27.40%	6.90%	2 years
Plato	23.40%	23.10%	1 year
Plato invasive	23.10%	21.80%	1 year
Pegasus	(32.0% (90mg (28.7% (60mg	21.40%	36 months
Socrates	17.50%	14.70%	90 days
Euclid	30.10%	25.90%	30 months

Plato denotes the Study of Platelet Inhibition and Patient Outcomes; Pegasus: the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin trial; Socrates: The Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes trial; Euclid: the Examining Use of Ticagrelor in Peripheral Artery Disease (EUCLID) trial.