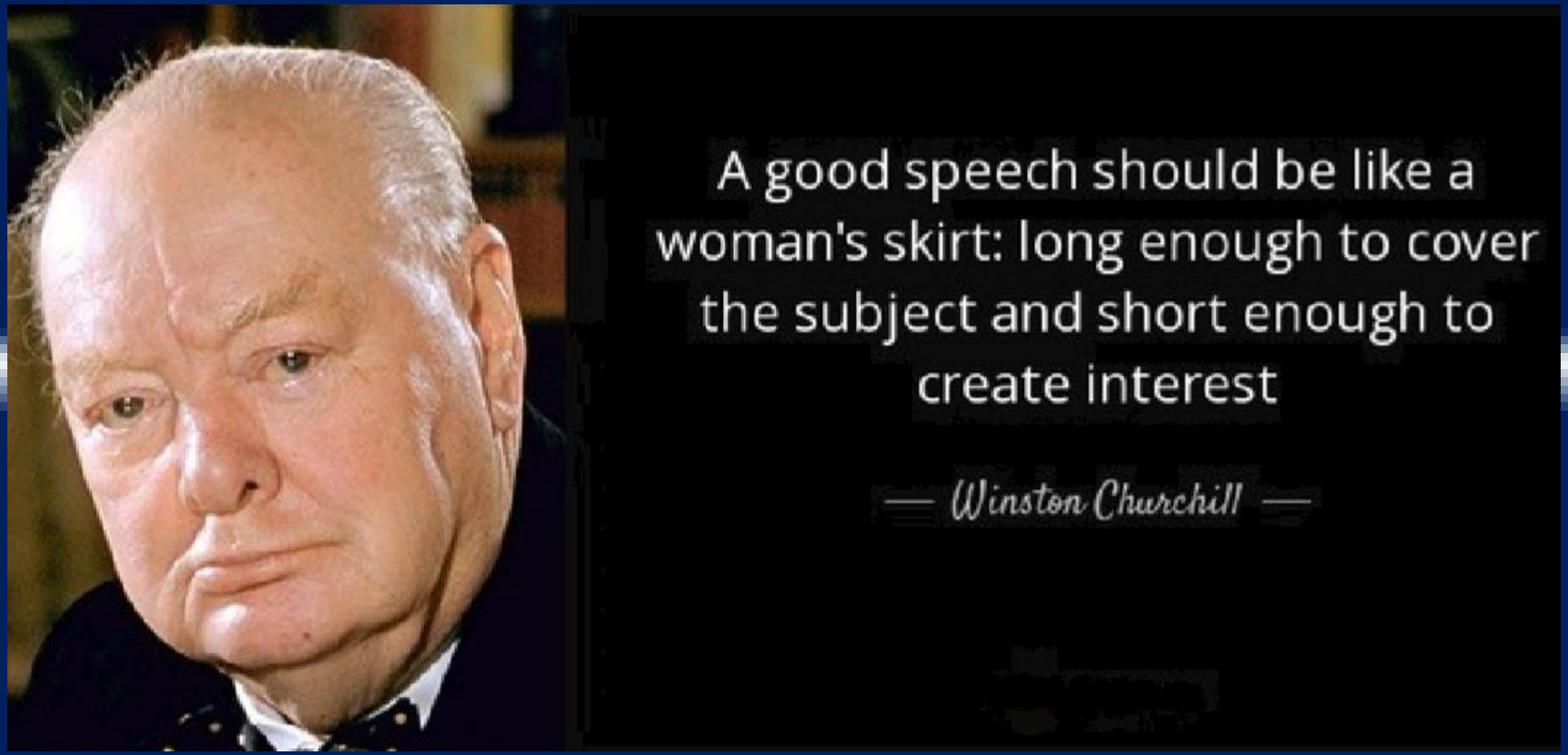
Dlouhodobá antitrombotická léčba po ACS: individuální přístup

Varvařovský Ivo

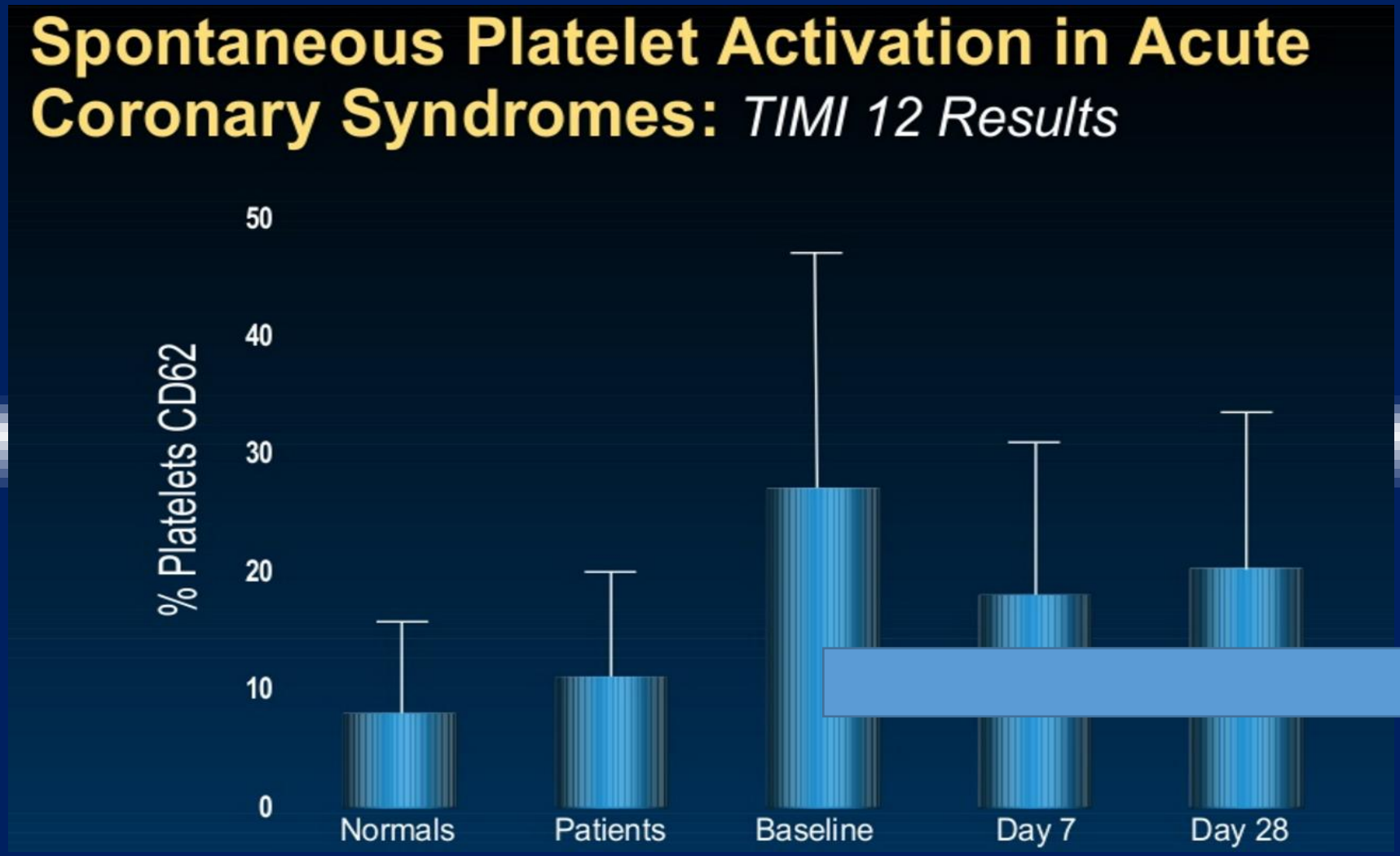
KCA Pardubice

27.sjezd ČKS, Brno 12.-15.5.2019

Dlouhodobá antitrombotická léčba po ACS : individuální přístup



Akutní koronární syndrom: dlouhodobá aktivace trombocytů

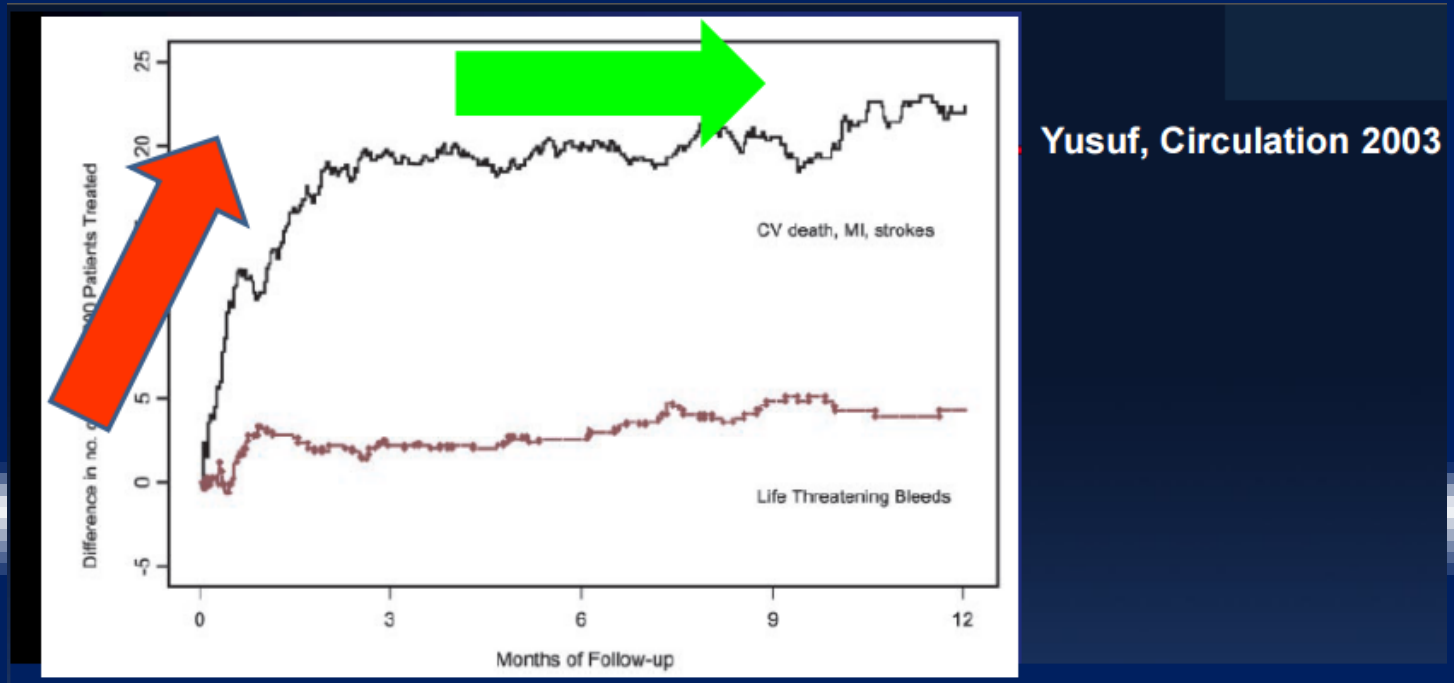


J Am Coll Cardiol. 1999 Mar;33(3):634-9.

Platelet activation in patients after an acute coronary syndrome: results from the TIMI-12 trial. Thrombolysis in Myocardial Infarction.

Ault KA[1], Cannon CP, Mitchell J, McCahan J, Tracy RP, Novotny WF, Reimann JD, Braunwald E.

Riziko ischemické příhody klesá v čase



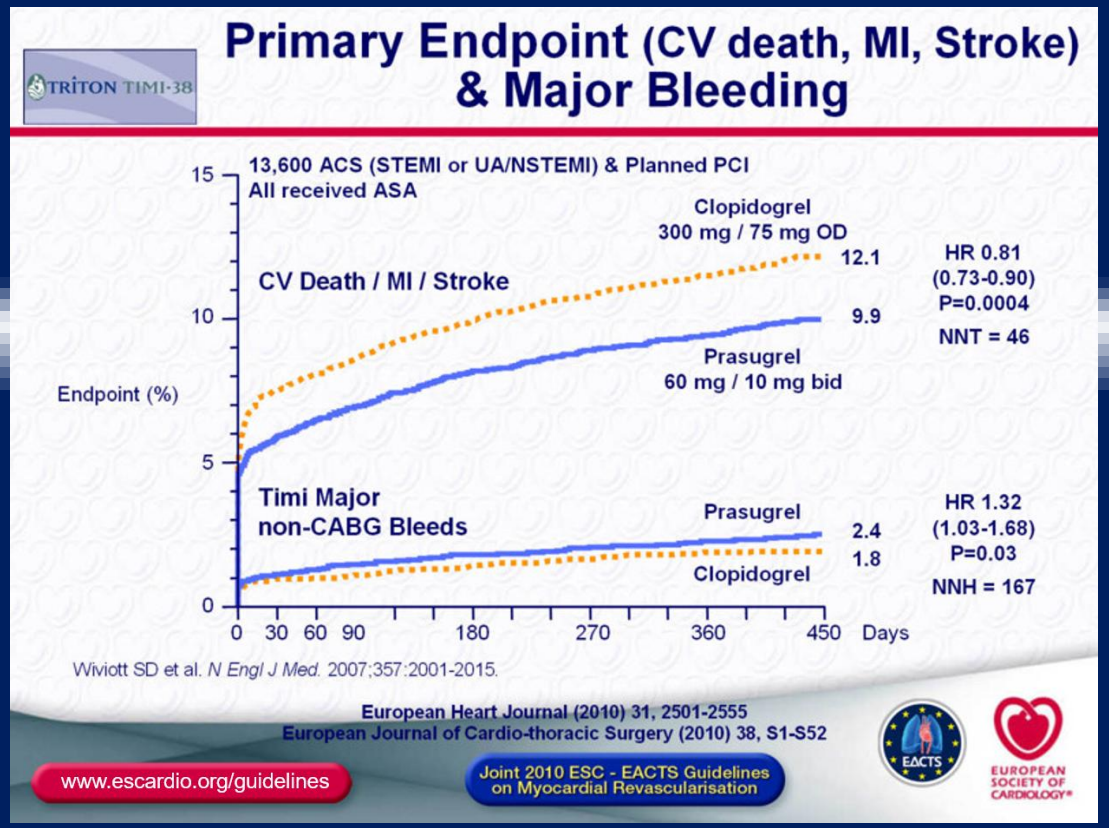
Yusuf, Circulation 2003

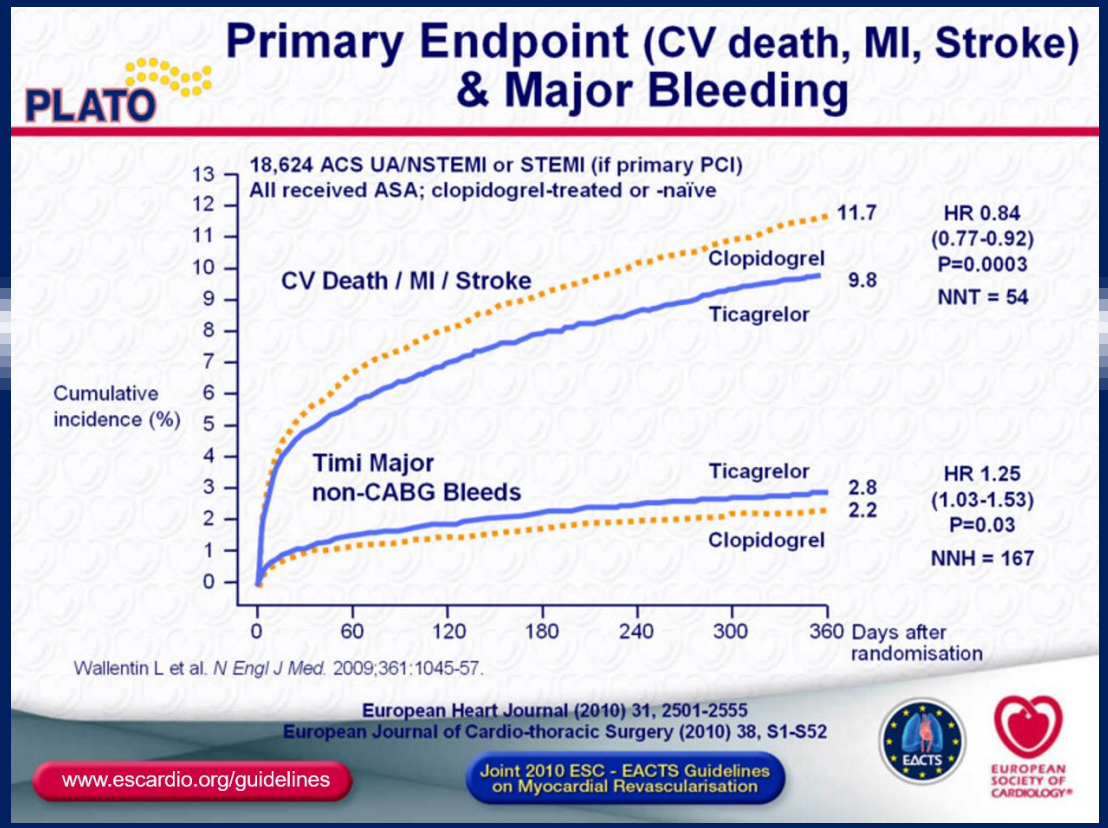
- *DAPT prevented 22CV events/1000 Pts during the 12 months*
- 50% (11CV events/1000) in the first 30 days
- *50% of the benefit ocurred from 1 month to 12 months*
- 9 of the 11 prevented CV events ocurred between 1 & 3 months
- *Only 2 CV events/1000 pts were prevented between 3 & 12 months*

Akutní koronární syndrom : **nové inhibitory $P2Y_{12}$ po dobu 12 měsíců**

TRITON TIMI-38

PLATO

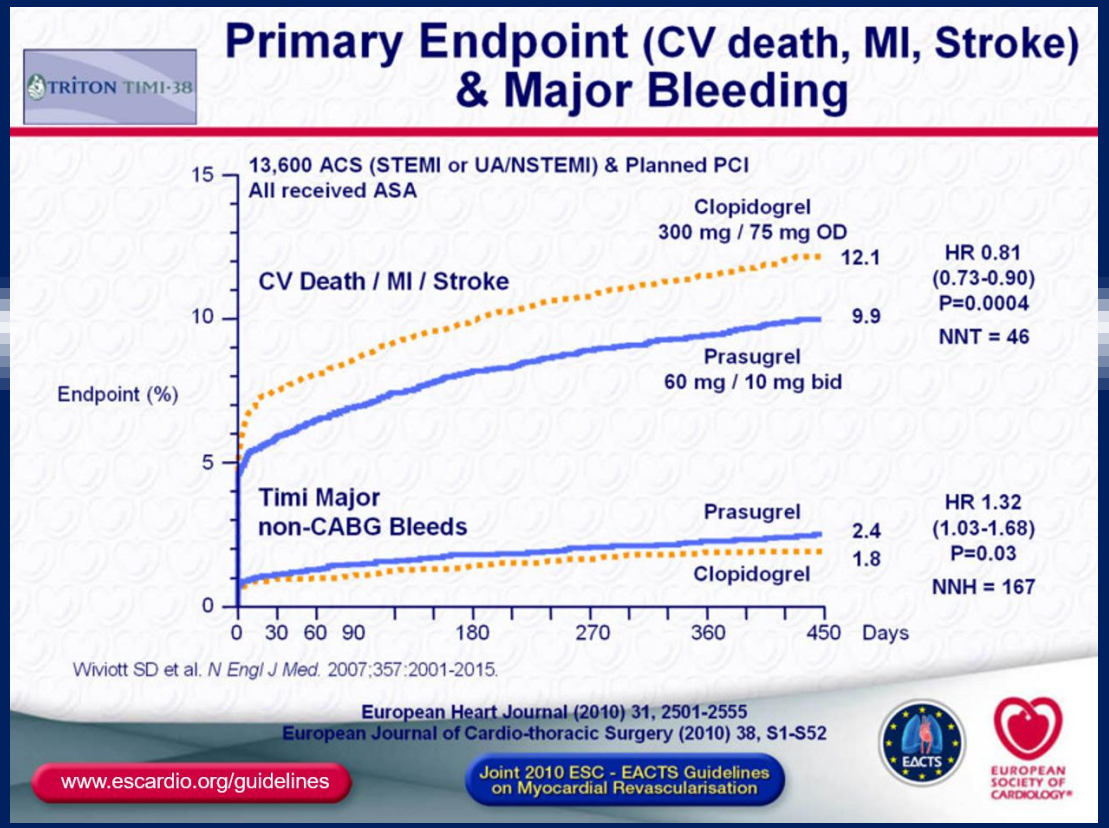




Wiviott SD et al. NEJM 2007;357:2001-15

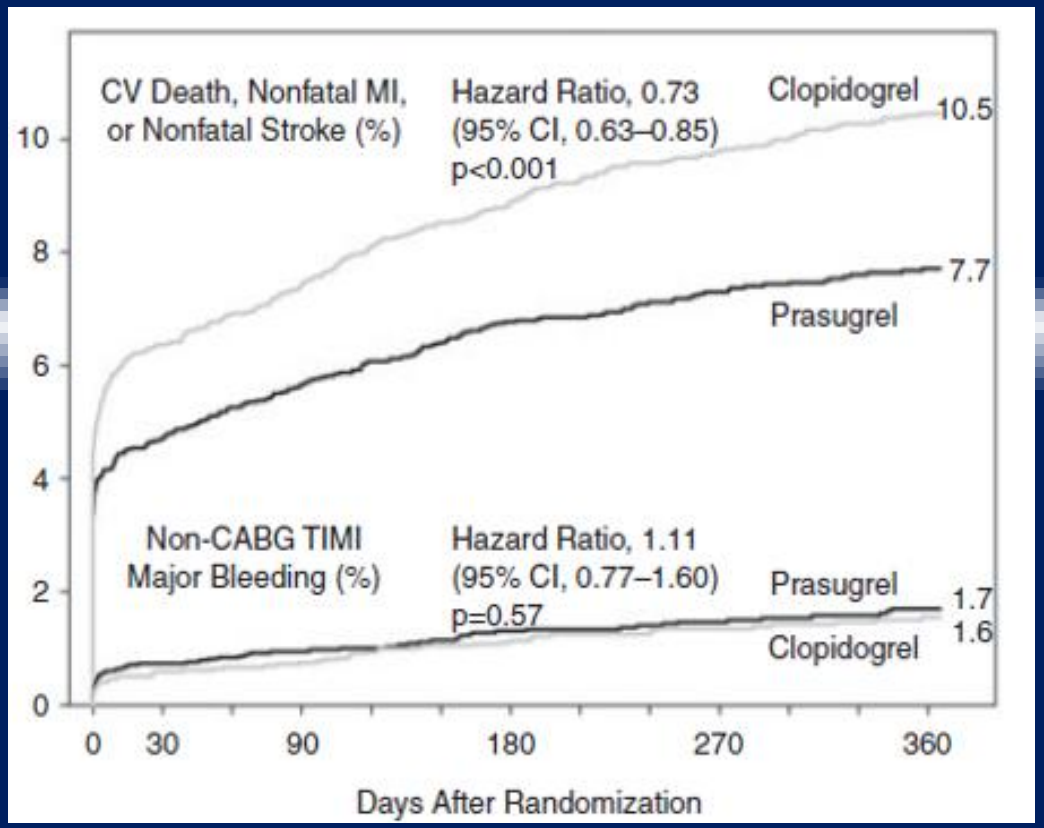
Wallentin L et al. *NEJM* 2009;361:1045-57

Akutní koronární syndrom : **INDIVIDUALIZACE LÉČBY**



Wiviott SD et al. NEJM 2007;357:2001-15

An analysis of TRITON-TIMI 38, based on the 12 month recommended length of therapy in the European label for prasugrel

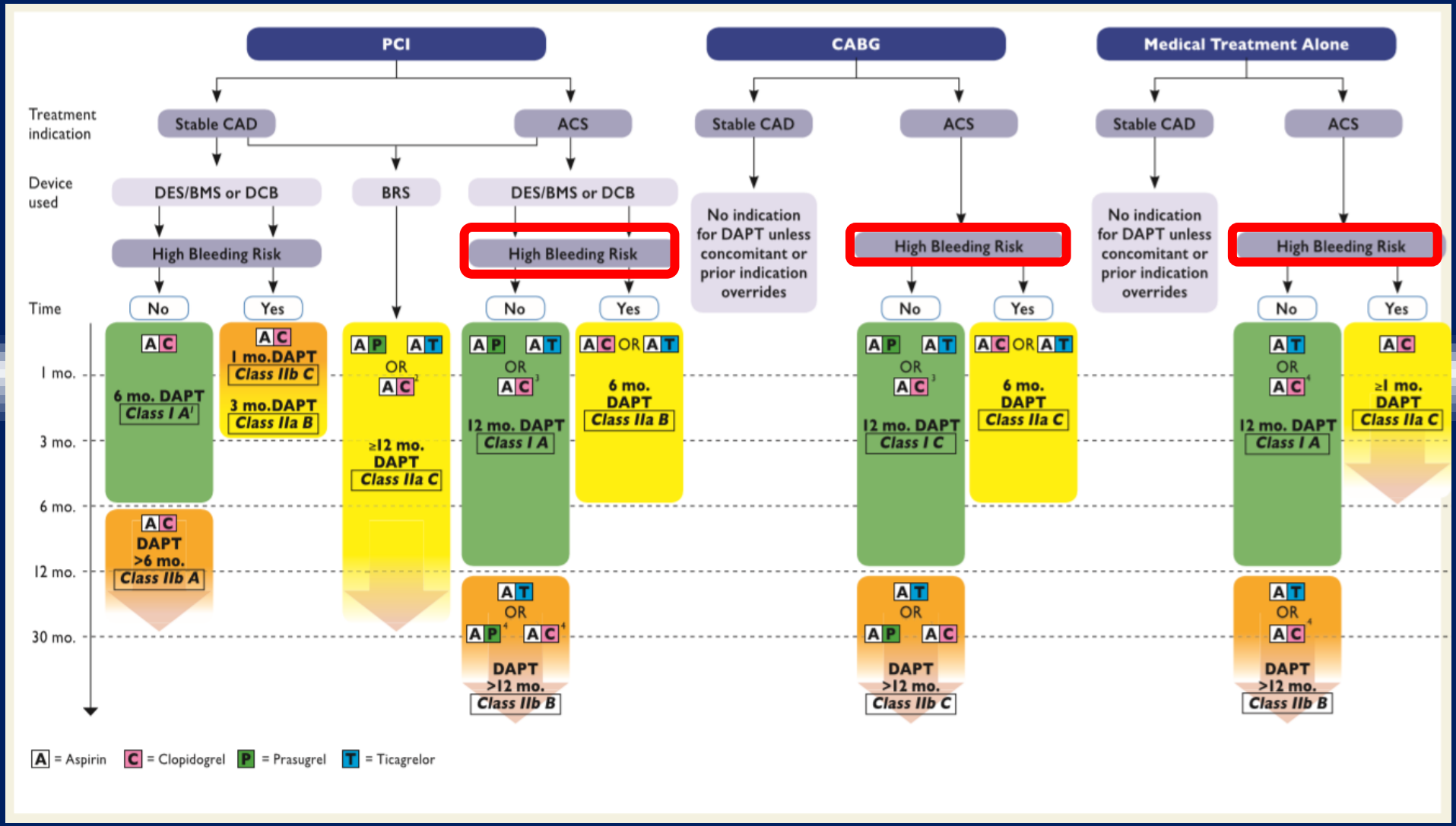


Curr Med Res Opin. 2014 Nov;30(11):2193-205. doi: 10.1185/03007995.2014.944638. Epub 2014 Aug 6.

An analysis of TRITON-TIMI 38, based on the 12 month recommended length of therapy in the European label for prasugrel.

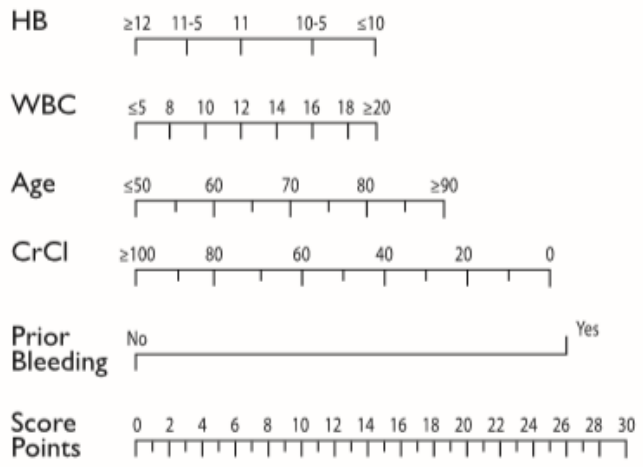
Wilcox R[1], Iqbal K, Costigan T, Lopez-Sendon J, Ramos Y, Widimsky P.

Smysl individualizace antitrombotické léčby po ACS :
ZVÝŠIT PROSPĚCH, SNÍŽIT RIZIKO



Inhibitory P2Y12 u akutního koronárního syndromu : URČENÍ ÚVODNÍ INTENZITY DAPT

Table 3 **Risk scores validated for dual antiplatelet therapy duration decision-making**

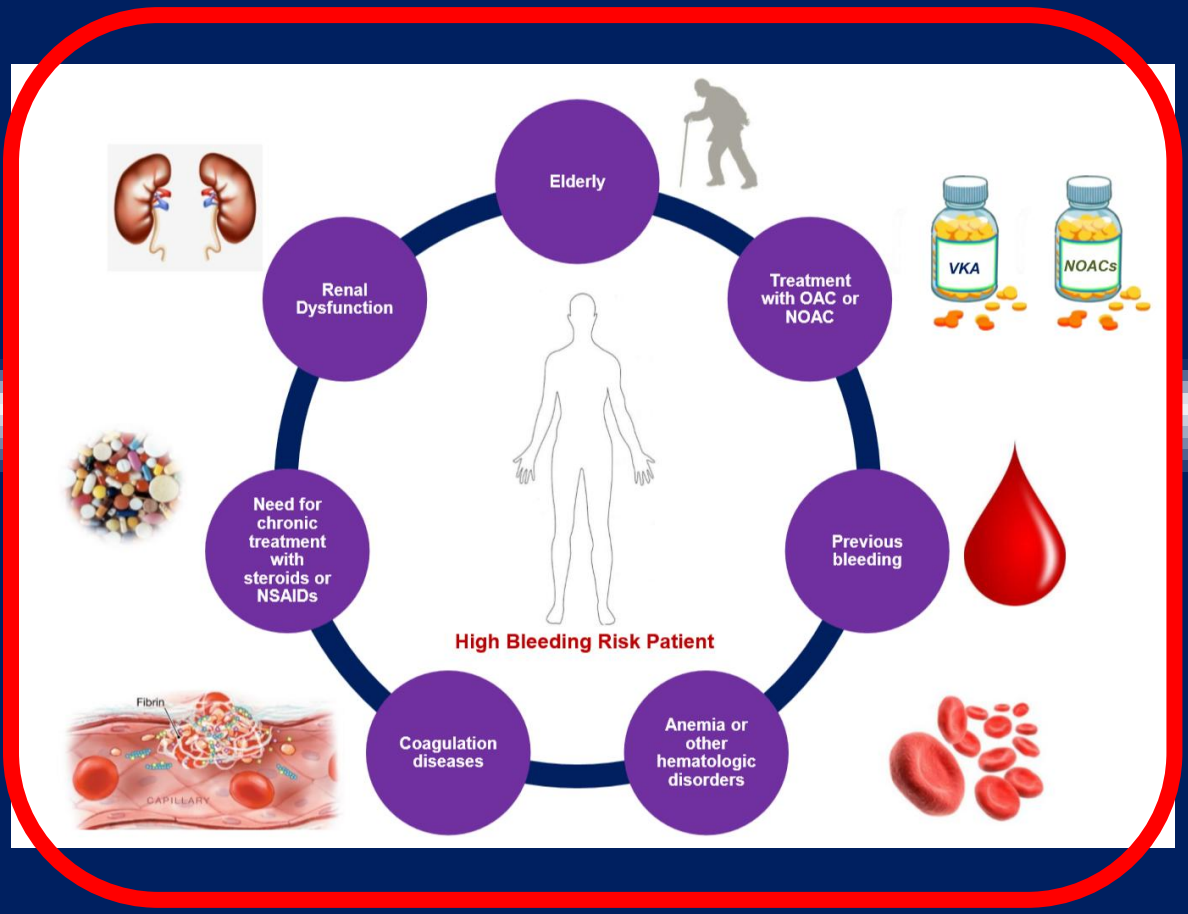
	PRECISE-DAPT score[18]	DAPT score[15]	
Time of use	At the time of coronary stenting	After 12 months of uneventful DAPT	
DAPT duration strategies assessed	Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)	Standard DAPT (12 months) vs. Long DAPT (30 months)	
Score calculation[a]		Age ≥75 65 to <75 <65 Cigarette smoking Diabetes mellitus MI at presentation Prior PCI or prior MI Paclitaxel-eluting stent Stent diameter <3 mm CHF or LVEF <30% Vein graft stent	 –2 pt –1 pt 0 pt +1 pt +1 pt +1 pt +1 pt +1 pt +1 pt +2 pt +2 pt
Score range	0 to 100 points	–2 to 10 points	
Decision making cut-off suggested	Score ≥25 → Short DAPT Score <25 → Standard/long DAPT	Score ≥2 → Long DAPT Score <2 → Standard DAPT	
Calculator	www.precisedaptscore.com	www.daptstudy.org	

Inhibitory P2Y12 u akutního koronárního syndromu :
URČENÍ ÚVODNÍ INTENZITY DAPT

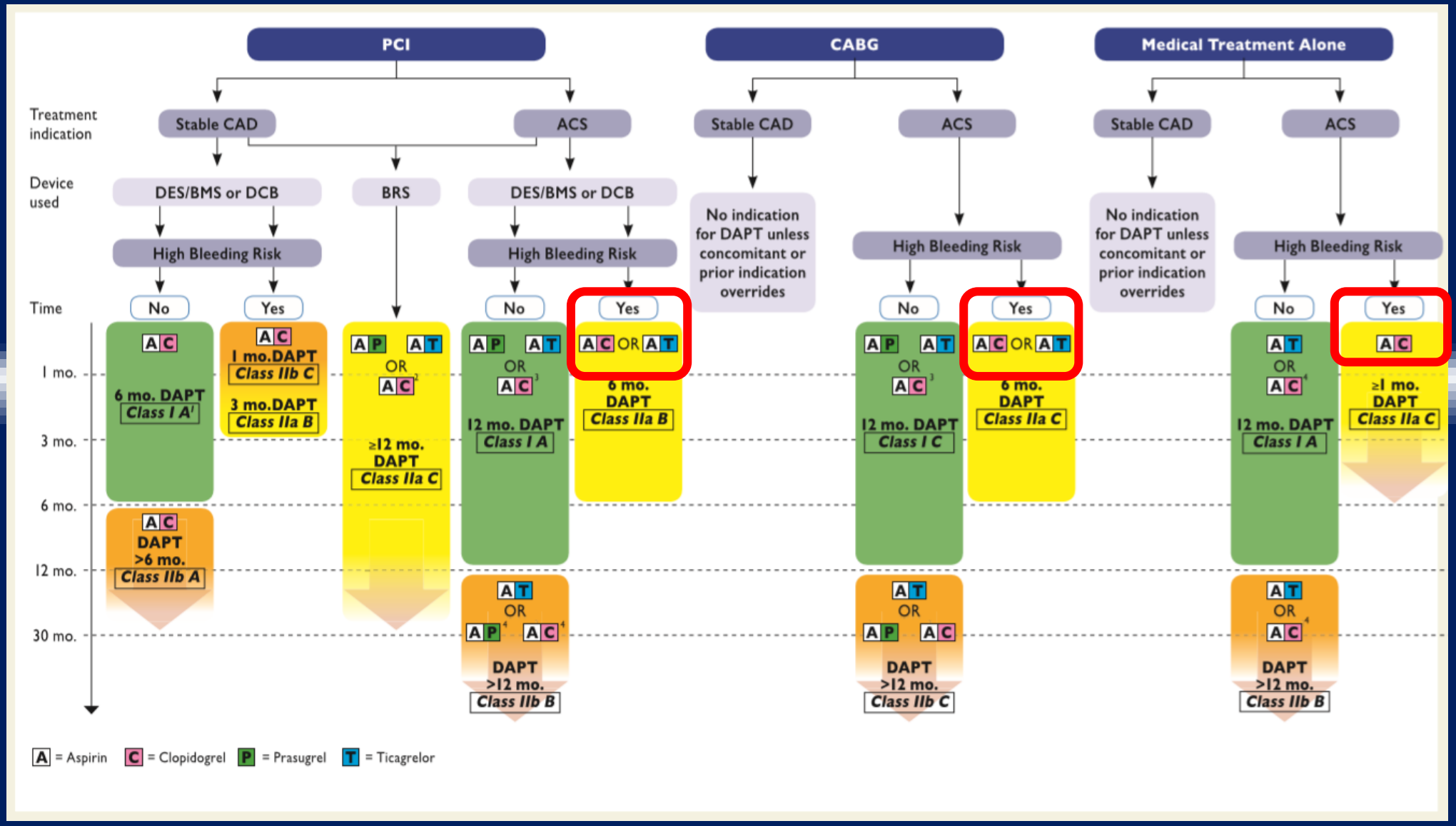
Use of risk scores as guidance for the duration of dual antiplatelet therapy

Recommendations	Class[a]	Level[b]
The use of risk scores designed to evaluate the benefits and risks of different DAPT durations[c] may be considered.[15,18]	IIb	A

DAPT = dual antiplatelet therapy.
[a]Class of recommendation.
[b]Level of evidence.
[c]The DAPT and PRECISE-DAPT scores are those currently fulfilling these requirements.



Dlouhodobá antitrombotická léčba po ACS :
URČENÍ ÚVODNÍ INTENZITY DAPT



Dlouhodobá antitrombotická léčba po ACS :
URČENÍ ÚVODNÍ INTENZITY DAPT

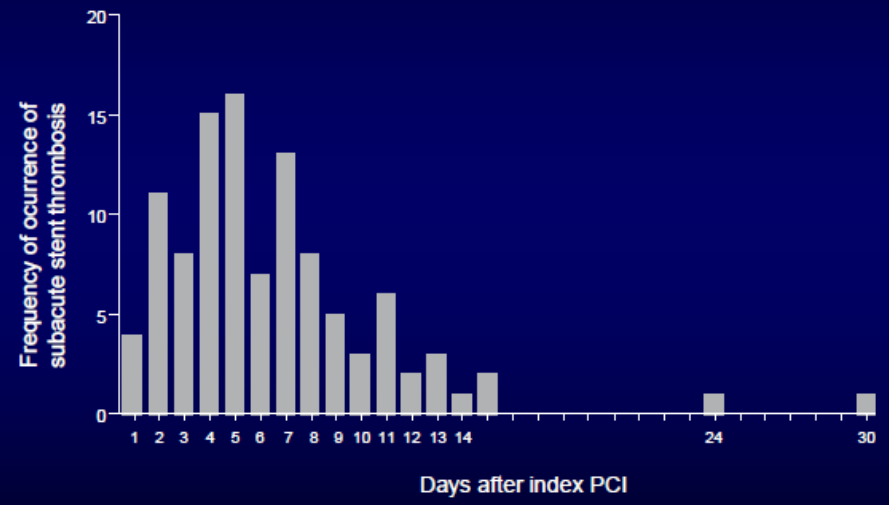
Table 9 **High-risk features for ischaemic events**

Prior stent thrombosis on adequate antiplatelet therapy
Stenting of the last remaining patent coronary artery
Diffuse multivessel disease, especially in diabetic patients
Chronic kidney disease (i.e. creatinine clearance <60 mL/min)
At least three stents implanted
At least three lesions treated
Bifurcation with two stents implanted
Total stented length >60 mm
Treatment of a chronic total occlusion
History of STEMI

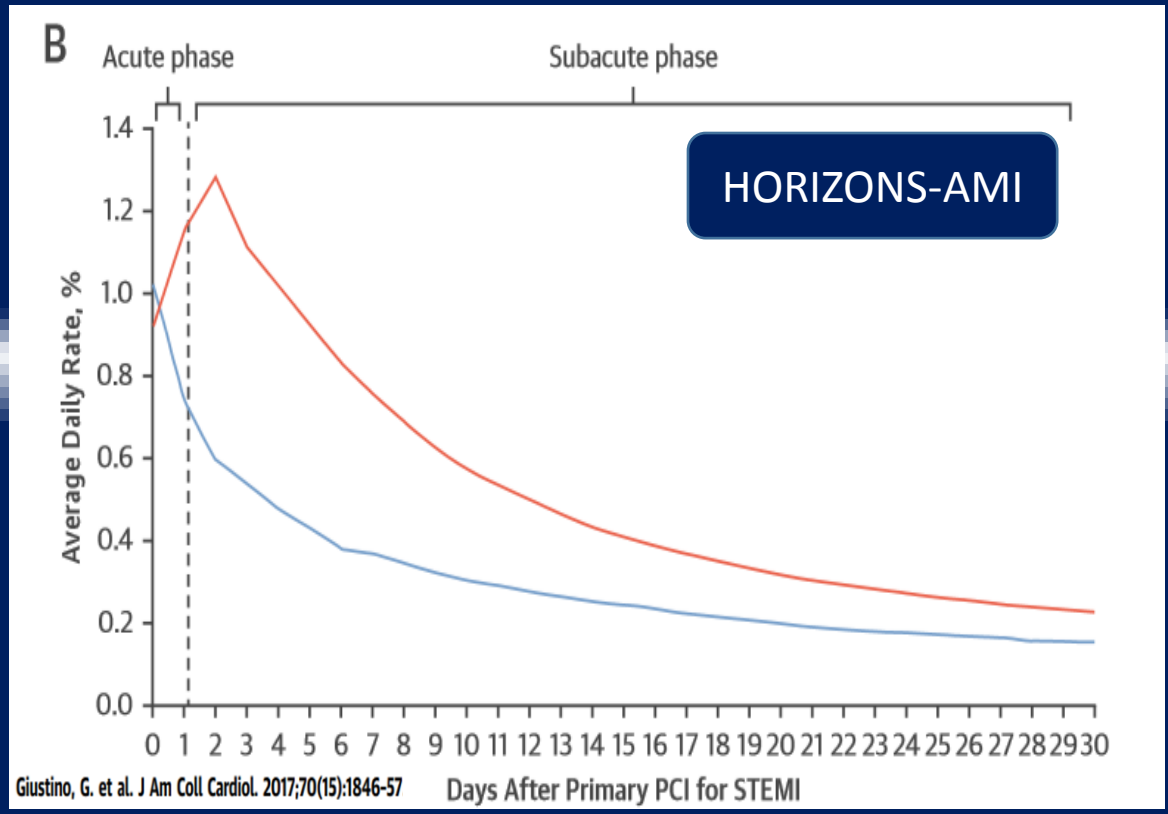
Jak dlouho trvá ischemické riziko po direktní PCI ?

Subacute ST after primary PCI

- Time distribution of subacute stent thrombosis after primary PCI for STEMI
- Among 5842 patients, 1.8% had subacute ST (n=104), mean time to ST was 6.9 ± 4.6 days



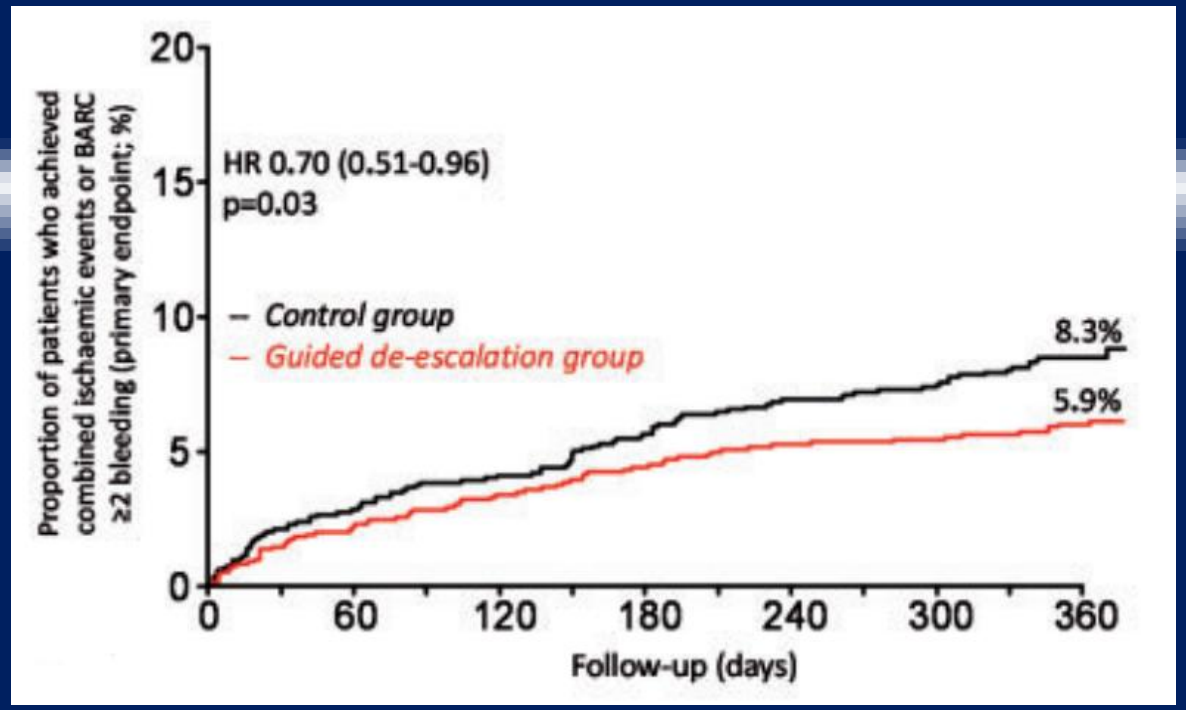
Heestermans A et al *J Thromb Haem* 2010; 8: 2385–93

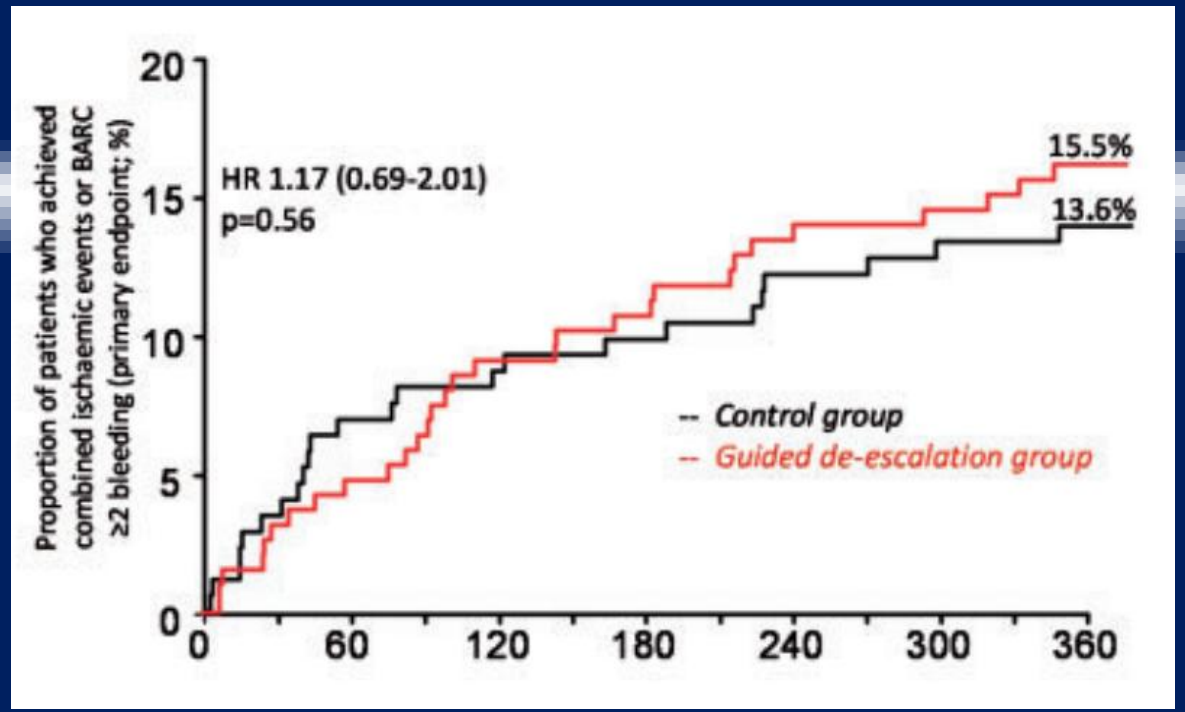


Giustino, G. et al. J Am Coll Cardiol. 2017;70(15):1846-57

Plánovaná deeskalace DAPT : TROPICAL - ACS

De-escalation of $P2Y_{12}$ inhibitor treatment (e.g. with a switch from prasugrel or ticagrelor to clopidogrel) guided by platelet function testing may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for 12-month potent platelet inhibition.[717]	IIb	B





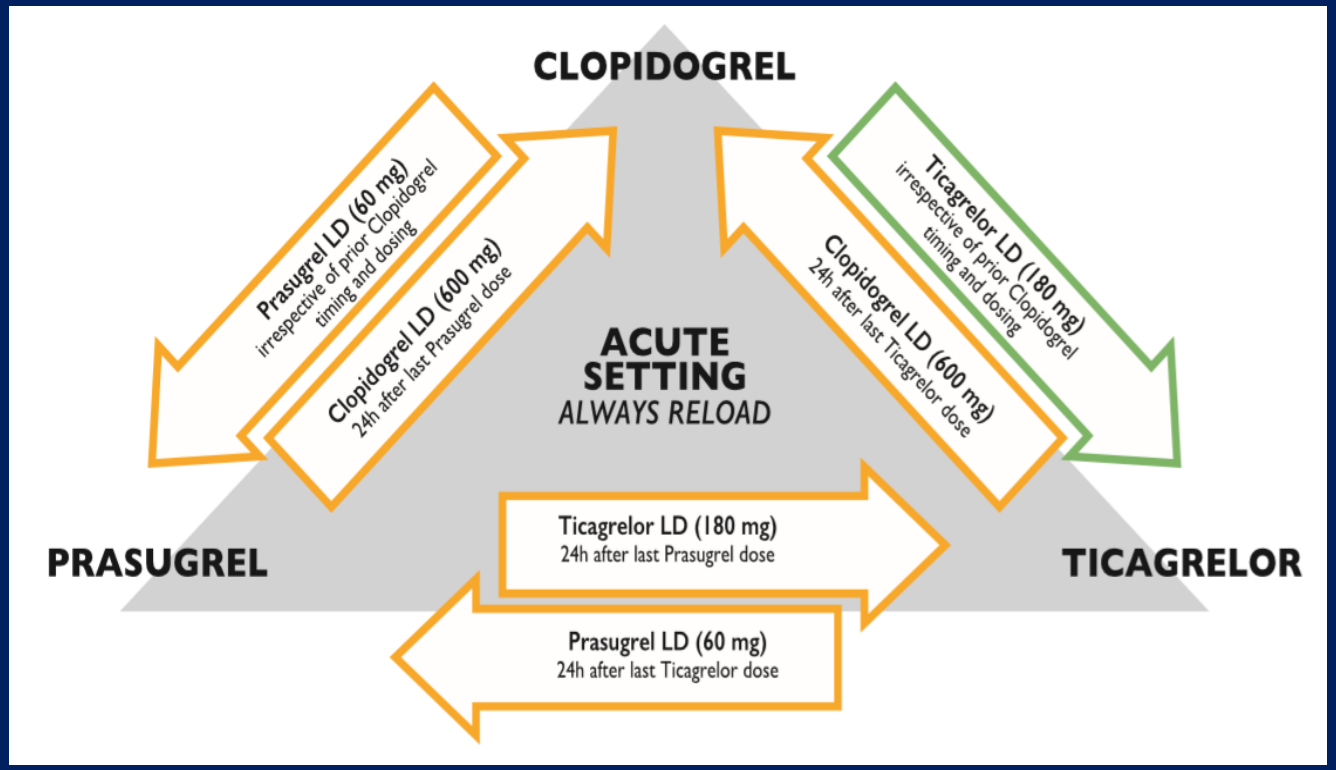
European Heart Journal (2018) **39**, 2749–2758

Vynucená deeskalace DAPT : akutní fáze

Vysoké riziko krvácení

Prodělané krvácení při DAPT

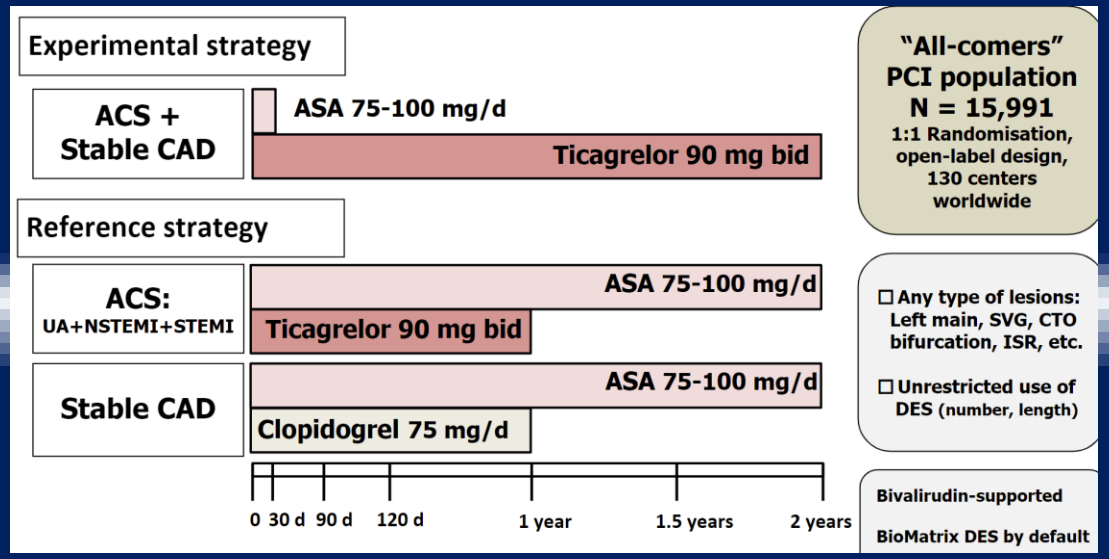
Ekonomické důvody



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

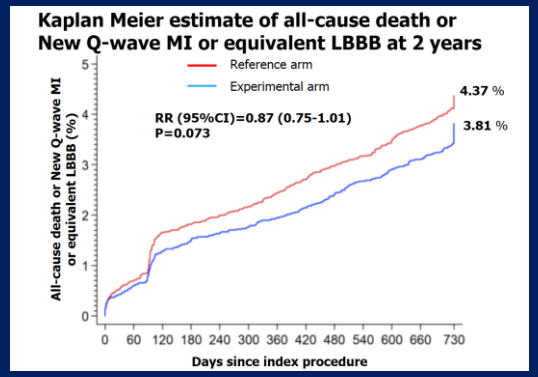
Circulation 2017;136:1955–1975

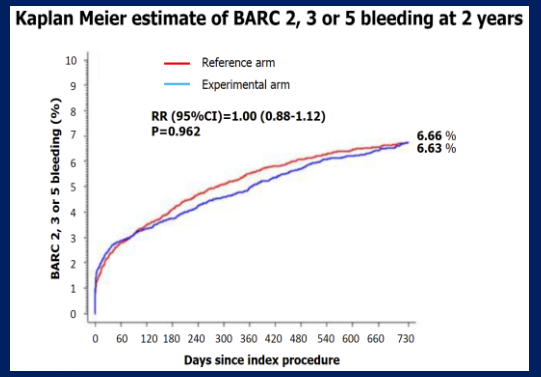
Akutní koronární syndrom : monoterapie $P2Y_{12}$



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





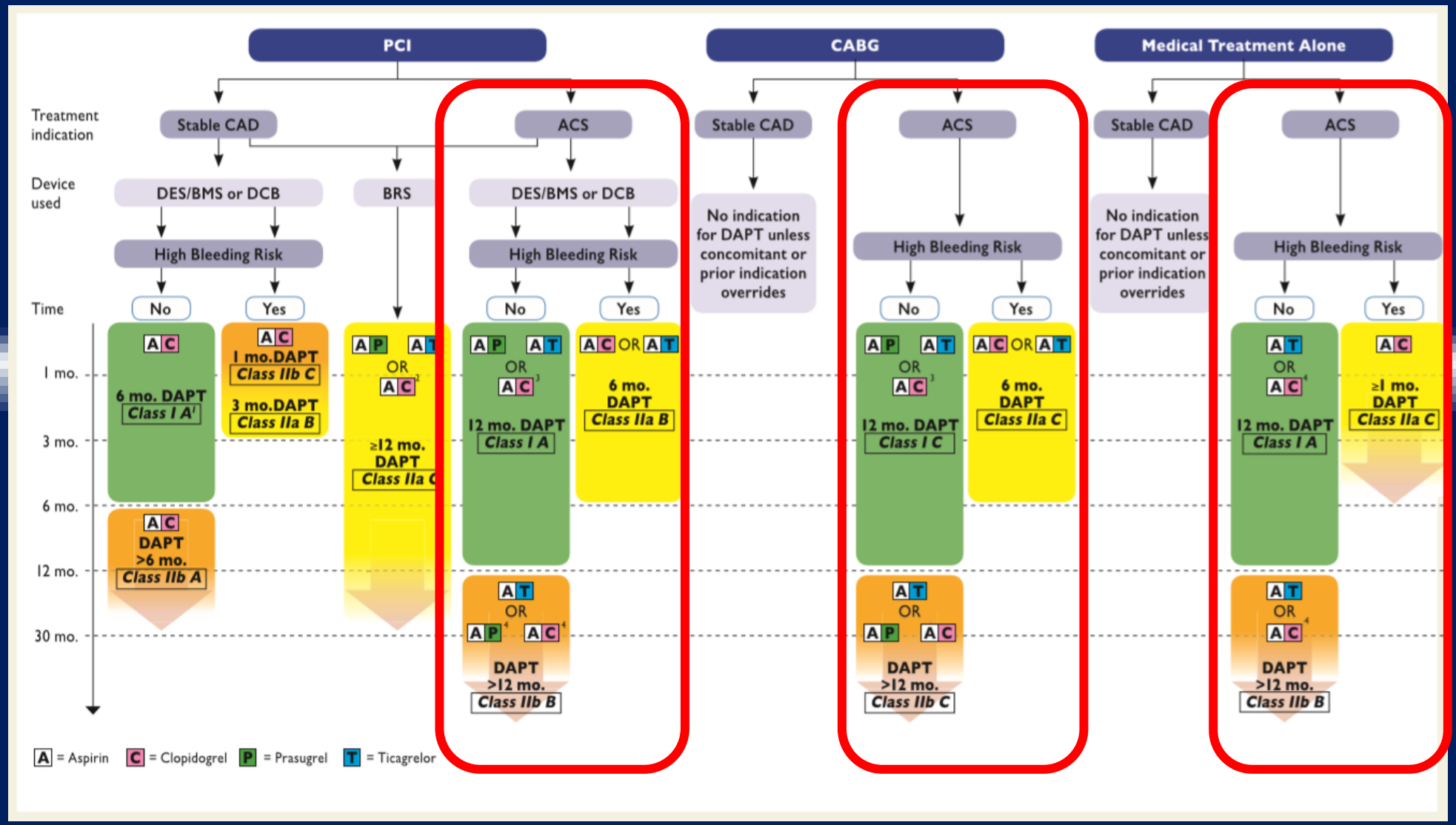
Lancet. 2018 Sep 15;392(10151):940-949

MONOTERAPIE P2Y12 po ACS : DAPT pouze 1 měsíc ?

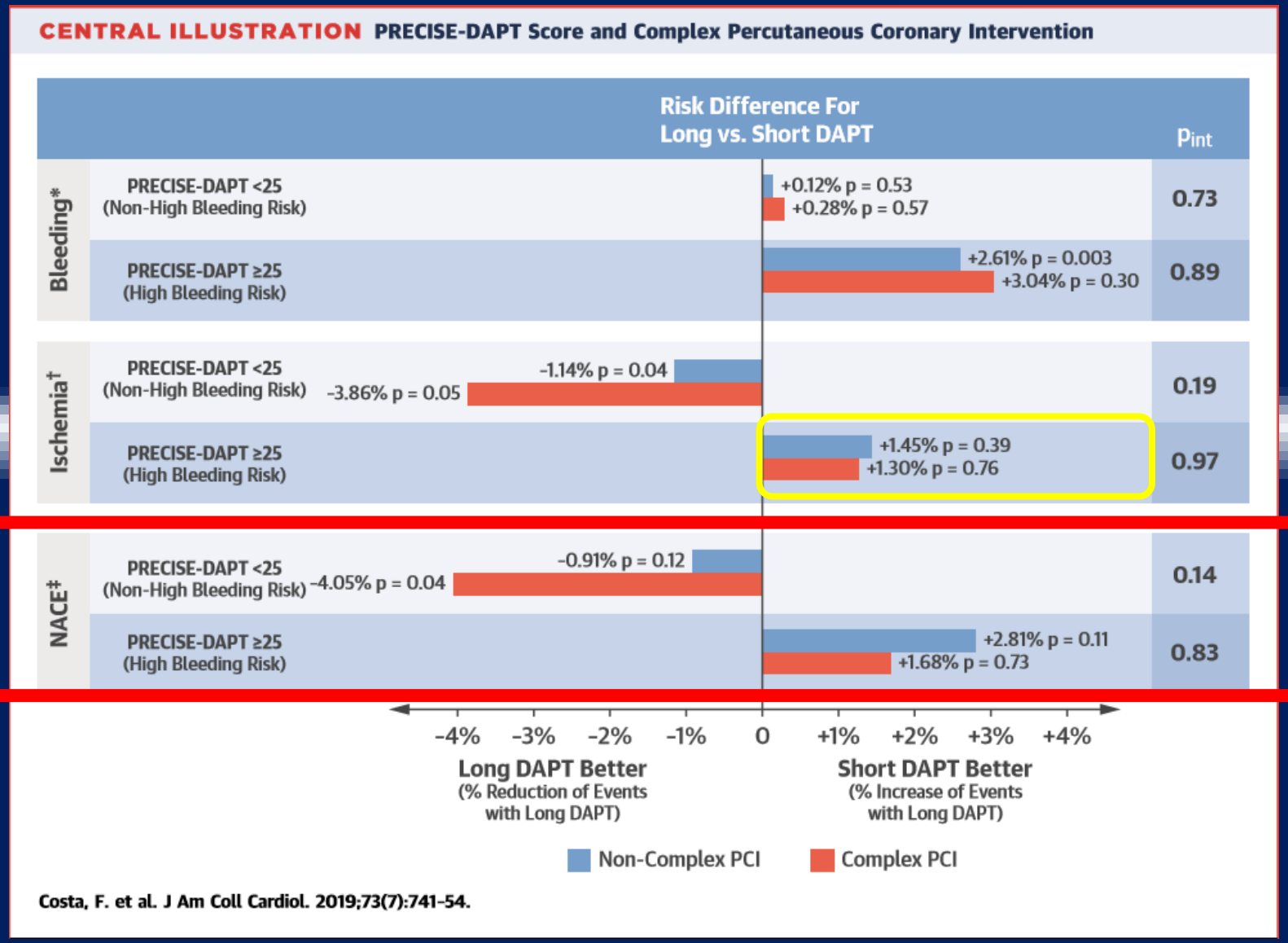
ACS	ASA+ticagrelor do 1m Ticagrelor 2-24m	ASA+ ticagrelor do 12m ASA 13-24 m	RR (95% CI)
Úmrtí + infarkt myokardu	147	169	0,86 (0,69-1,08)
Krvácení BARC 3,5	73	100	0,73 (0,54-0,98)

Lancet. 2018 Sep 15;392(10151):940-949

Dlouhodobá antitrombotická léčba po ACS :
URČENÍ DÉLKY LÉČBY



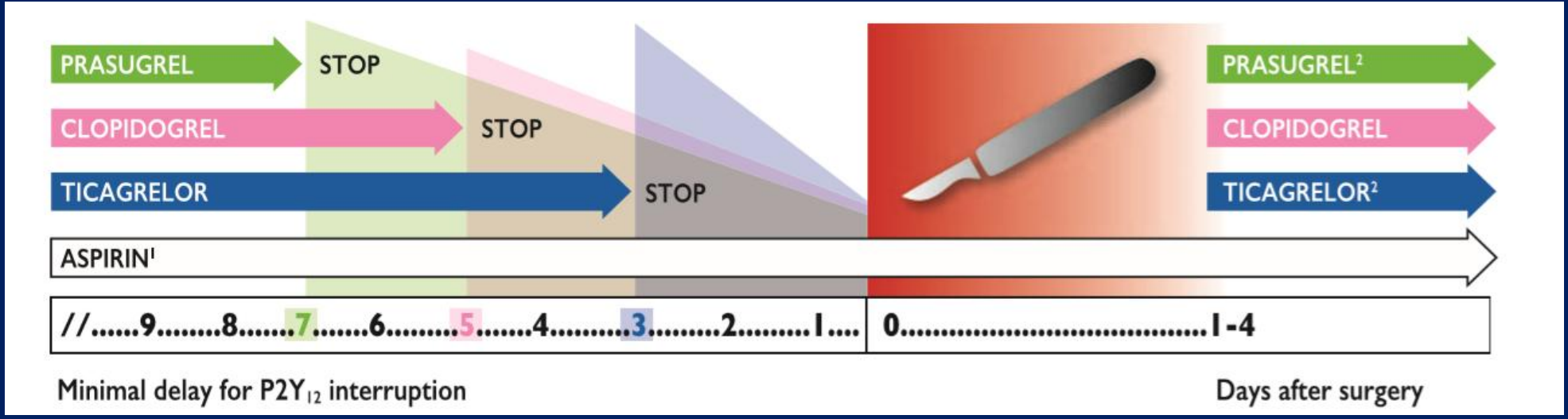
RIZIKO KRVÁCENÍ JE PRO URČENÍ DÉLKY LÉČBY ROZHODUJÍCÍ



Costa, F. et al. J Am Coll Cardiol. 2019;73(7):741-54.

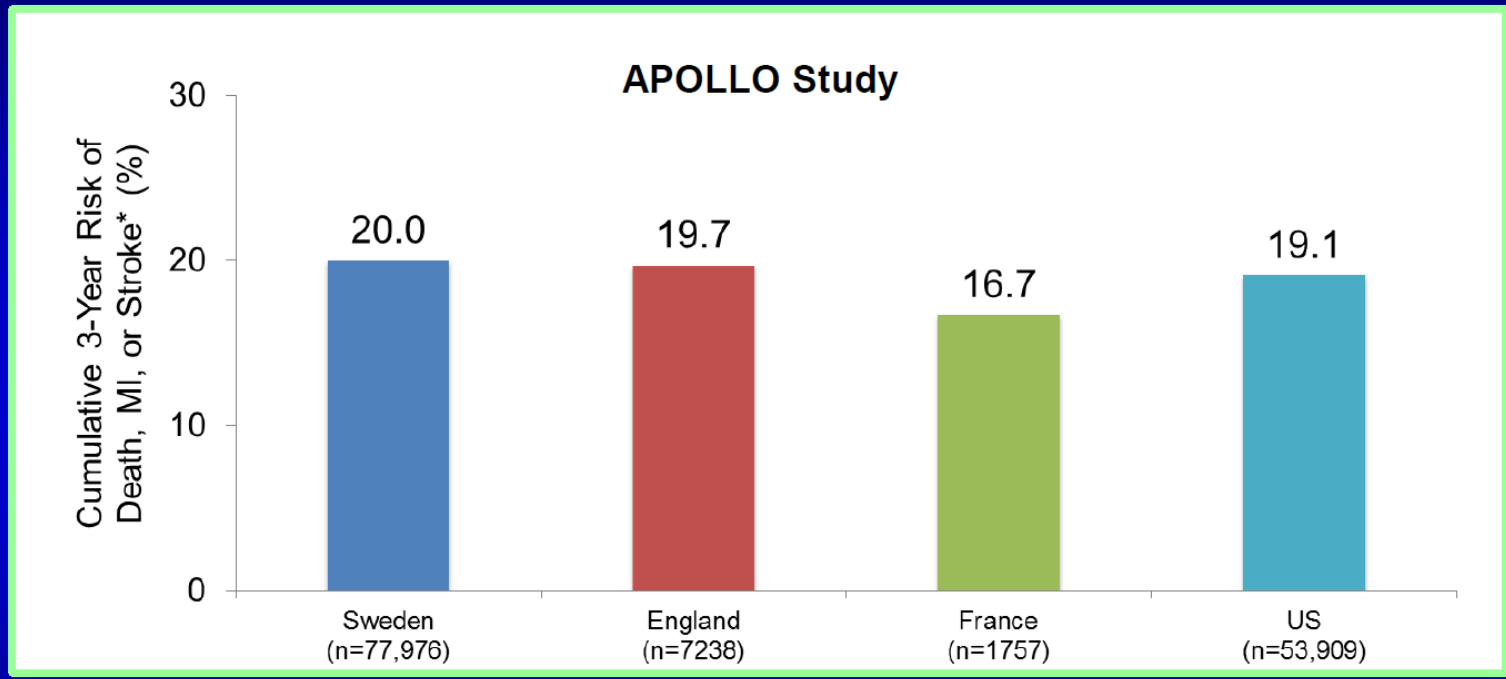
Přerušení DAPT

Dual antiplatelet therapy in patients undergoing elective cardiac and non-cardiac surgery		
It is recommended to continue aspirin perioperatively if the bleeding risk allows, and to resume the recommended antiplatelet therapy as soon as possible post-operatively.	I	B
It is not recommended to discontinue DAPT within the first month of treatment in patients undergoing elective non-cardiac surgery.	III	B



Akutní koronární syndrom : postačuje 12-měsíční léčba?

Patients Free of MI for 1 Year Continued to Be at Risk for CV Events Over the Next 3 Years

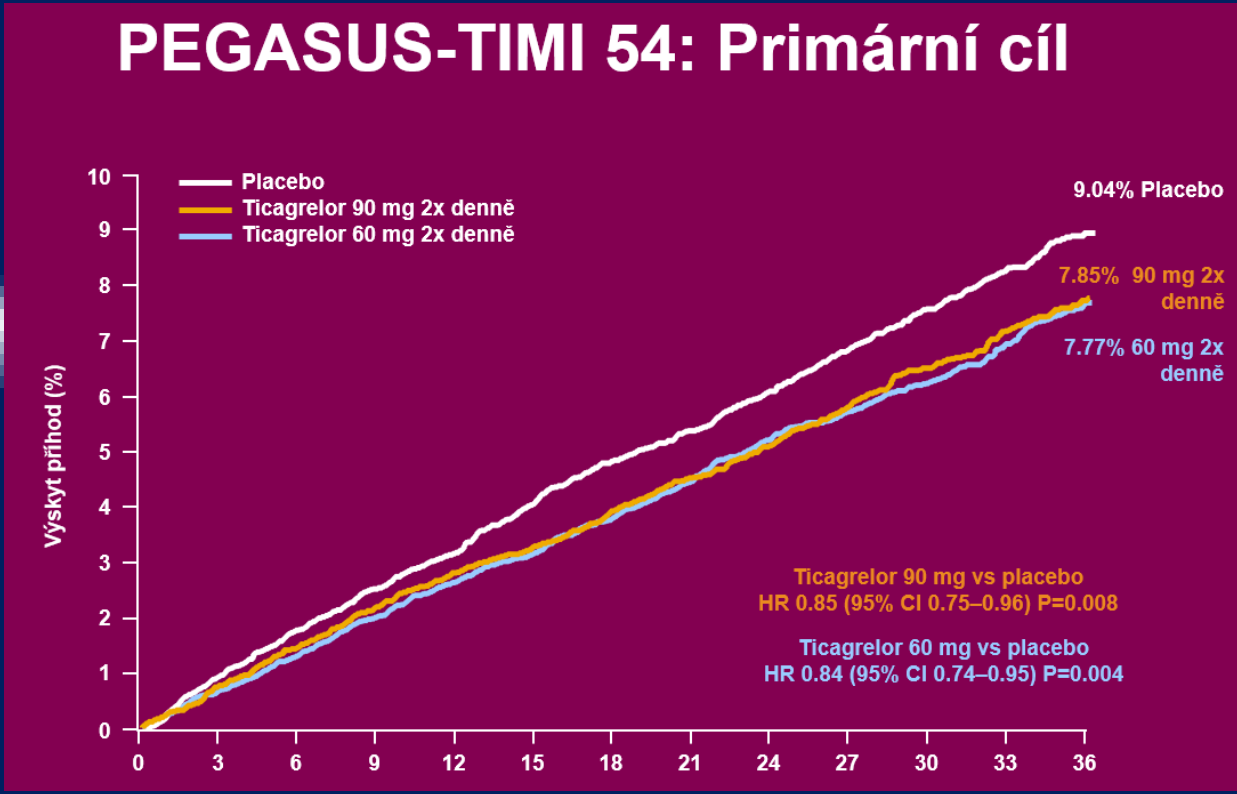


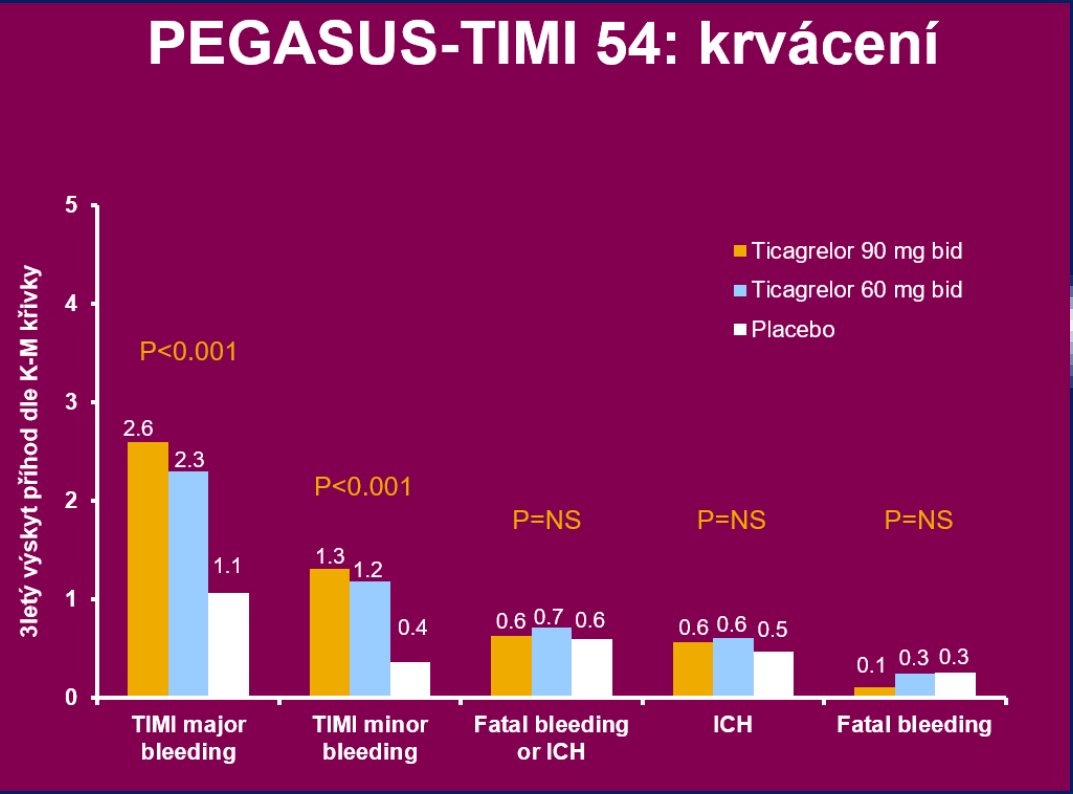
Retrospective 4-country analysis of patients who survived without a further MI for 1 year following hospitalization for MI in 2002 to 2011. Results are based on data from national linked electronic health records and disease registries as well as administrative data

*Adjusted for differences in study populations.

Rapsomaniki E et al. Presented at: European Society of Cardiology Meeting; August 30-September 3, 2014; Barcelona, Spain.

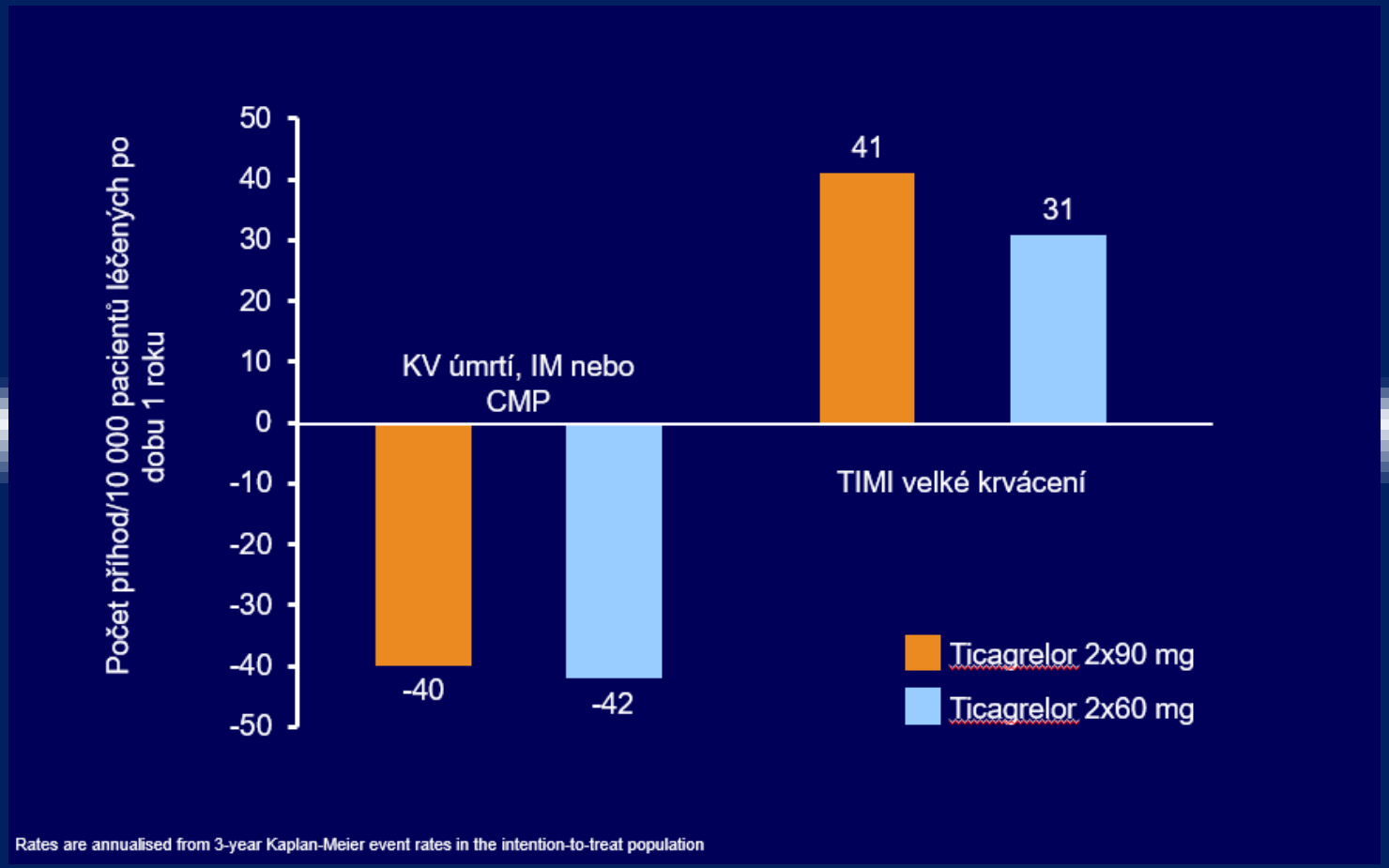
Akutní koronární syndrom : postačuje 12-měsíční léčba?
Prodloužení DAPT : PEGASUS-TIMI 54





N Engl J Med 2015; 372:1791-1800

Akutní koronární syndrom : postačuje 12-měsíční léčba?
Prodloužení DAPT : PEGASUS-TIMI 54



N Engl J Med 2015; 372:1791-1800

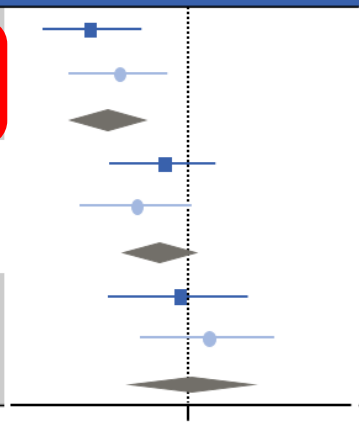
Pokračování v DAPT po 12 měsících : kdy se rozhodnout?

Time from $P2Y_{12}$ Inhibitor Withdrawal to Ticagrelor Initiation Has a Significant Effect on the Efficacy of Ticagrelor

PEGASUS: ticagrelor (90 mg bid or 60 mg bid) plus aspirin versus placebo plus aspirin

- Ticagrelor was most efficacious in patients with the shortest gap from $P2Y_{12}$ inhibitor withdrawal to ticagrelor initiation[1]
  - In COMPASS, there was no association between time from MI to rivaroxaban inhibition and rivaroxaban efficacy[2]

Study population	Time from $P2Y_{12}$ inhibitor withdrawal to randomization	3-year Kaplan–Meier rate (%)		HR (95% CI)	*p*-value
		Ticagrelor	Placebo		
90 mg	≤30 days (n=7181)	7.4		0.70 (0.57–0.87)	
60 mg		8.0		0.75 (0.61–0.92)	
Pooled		7.7	9.9	073 (0.61–0.87)	<0.001
90 mg	>30 days–1 year (n=6501)	8.1		0.90 (0.72–1.12)	
60 mg		7.2		0.82 (0.65–1.02)	
Pooled		7.6	8.7	0.86 (0.71–1.04)	0.11
90 mg	>1 year (n=5079)	6.3		0.96 (0.73–1.26)	
60 mg		6.9		1.06 (0.81–1.38)	
Pooled		6.6	6.9	1.01 (0.80–1.27)	0.96
				p_{trend} <0.001	



1. Bonaca MP *et al*, *Eur Heart J* 2016;37:1133–1142; 2. Connolly SJ *et al*, *Lancet* 2017;391:205–218

Akutní koronární syndrom : postačuje 12-měsíční léčba?
Prodloužení DAPT : PEGASUS-TIMI 54

PEGASUS-TIMI 54 EU label populace:
Pacienti ≤2 roky od IM nebo ≤1 rok od vysazení léčby inhibitorem $P2Y_{12}$

Výsledky	Tikagrelor 60 mg 2xdenně N=5388		Placebo N=5391		Hazard ratio (95% CI)	*P*
	n	3 roky KM%	n	3 roky KM%		
KV úmrtí, IM či CMP	373	7,9	463	9,6	0,80 (0,70–0,91)	0,001
KV úmrtí	119	2,6	167	3,6	0,71 (0,56–0,90)	0,0041
IM	230	4,8	274	5,6	0,83 (0,70–0,99)	0,041
CMP	71	1,5	95	2,0	0,74 (0,55–1,01)	0,058
Celková mortalita	206	4,4	256	5,4	0,80 (0,67–0,96)	0,018

Dellborg M *et al*. *Eur Heart J* 2017;38(suppl):794–795

Prodloužení DAPT nad 12 měsíců : doporučení ESC

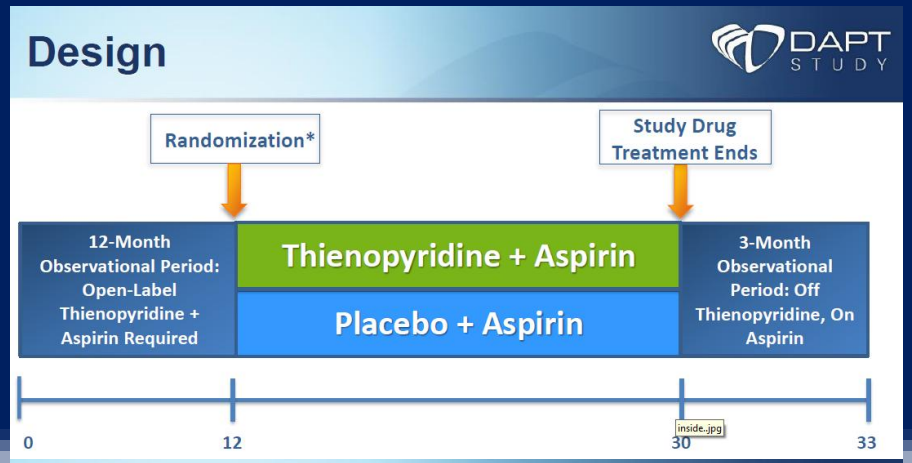
DAPT 2017

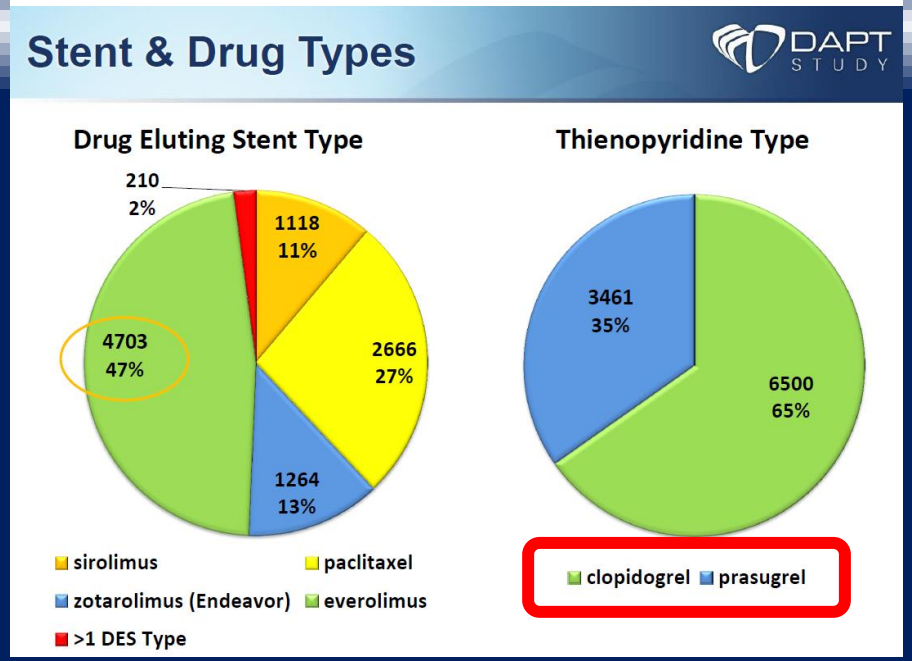
In patients with prior MI at high ischaemic risk who are managed with medical therapy alone and have tolerated DAPT without a bleeding complication, treatment with DAPT in the form of ticagrelor 60 mg *b.i.d.* on top of aspirin for longer than 12 months and up to 36 months may be considered.[139]	IIb	B
In patients with prior MI not treated with coronary stent implantation, who have tolerated DAPT without a bleeding complication and who are not eligible for treatment with ticagrelor, continuation of clopidogrel on top of aspirin for longer than 12 months may be considered.	IIb	C

Revaskularizace 2018

In patients with MI and high ischaemic risk[c] who have tolerated DAPT without a bleeding complication, ticagrelor 60 mg b.i.d. for longer than 12 months on top of aspirin may be preferred over clopidogrel or prasugrel.[732–734]	IIb	B

Akutní koronární syndrom : postačuje 12-měsíční léčba?
Prodloužení DAPT : studie DAPT





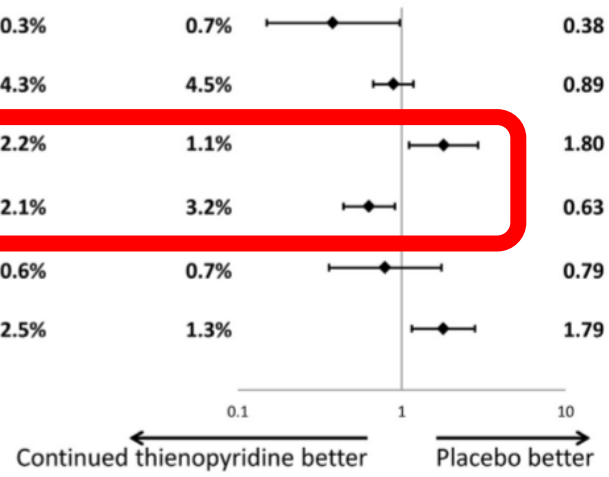
Benefits and Risks of Extended Dual Antiplatelet Therapy After Everolimus-Eluting Stents

James B. Hermiller, MD,* Mitchell W. Krucoff, MD,† Dean J. Kereiakes, MD,‡ Stephan Windecker, MD,§

FIGURE 3 Outcomes (12 to 30 Months) in Randomized Patients According to Treatment Arm

A

Outcome	Continued Thienopyridine N=2345	Placebo N=2358	HR (95% CI)	P Value
Stent Thrombosis	0.3%	0.7%	0.38 (0.15, 0.97)	0.04
MACCE	4.3%	4.5%	0.89 (0.67, 1.18)	0.42
Death	2.2%	1.1%	1.80 (1.11, 2.92)	0.02
Myocardial Infarction	2.1%	3.2%	0.63 (0.44, 0.91)	0.01
Stroke	0.6%	0.7%	0.79 (0.36, 1.75)	0.56
Bleeding	2.5%	1.3%	1.79 (1.15, 2.80)	0.01



J Am Coll Cardiol Intv 2016;9:138–47

Prodloužení DAPT nad 12 měsíců : doporučení ESC nebo studijní data ?

DAPT score[15]	
After 12 months of uneventful DAPT	
Standard DAPT (12 months) vs. Long DAPT (30 months)	
Age	
≥75	−2 pt
65 to <75	−1 pt
<65	0 pt
Cigarette smoking	+1 pt
Diabetes mellitus	+1 pt
MI at presentation	+1 pt
Prior PCI or prior MI	+1 pt
Paclitaxel-eluting stent	+1 pt
Stent diameter <3 mm	+1 pt
CHF or LVEF <30%	+2 pt
Vein graft stent	+2 pt
−2 to 10 points	
Score ≥2 → Long DAPT Score <2 → Standard DAPT	
www.daptstudy.org	

Hlavní zařazující kritéria PEGASUS

- IM (před1-3 roky)
- věk ≥50 let
- a další rizikový faktor:
  - věk ≥ 65 let
  - diabetes mellitus
  - další infarkt myokardu v anamnéze
  - vícečetné postižení koronárních tepen
  - chronická renální insuficience (GF≤60 ml/min)

Současné možnosti prodloužené DAPT v ČR

STÁTNÍ ÚSTAV PRO KONTROLU LÉČIV
Šrobárova 48
100 41 Praha 1
Telefon:+420 272 185 111
Fax: +420 271 732 377
E-mail:posta@sukl.cz
Web: www.sukl.cz

Sp. zn. SUKLS485/2018
Č. j. sukl73241/2019

Vyřizuje/linka Mgr. Eva Forgáčová

Datum: 25. 3. 2019

Vyvěšeno dne: 25. 3. 2019

ROZHODNUTÍ

Podmínky úhrady ze zdravotního pojištění:
V
L/ INT, KAR
P: Ticagrelor 60 mg podávaný v kombinaci s kyselinou acetylsalicylovou je hrazen u pacientů s anamnézou infarktu myokardu a s vysokým rizikem aterotrombotických příhod. Léčbu lze zahájit maximálně dva roky od akutní příhody, léčba trvá nejvýše 3 roky od jejího zahájení. Pacient s vysokým rizikem aterotrombotických příhod je definován věkem 50 let a více a musí splňovat alespoň jedno z následujících dodatečných vysoce rizikových faktorů:

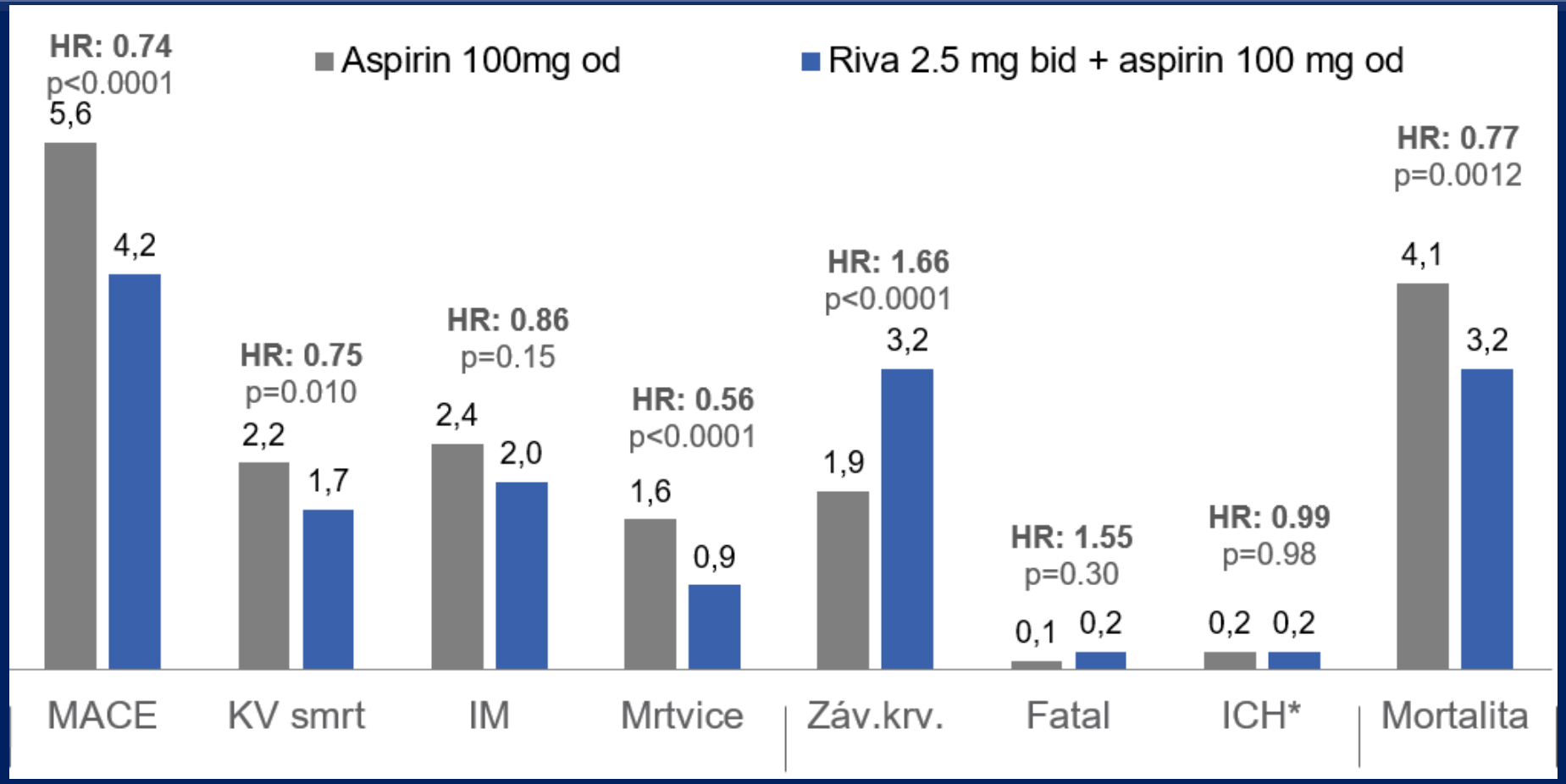
- Věk nad 65 let
- Diabetes mellitus vyžadující farmakoterapii
- Další infarkt myokardu v anamnéze
- Vícečetné postižení koronárních tepen
- Chronická renální dysfunkce definovaná clearance kreatininu pod 60 ml/min.

F-CAU-003-02R/31.8.2018

SÚKL

Rozhodnutí SUKL F-CAU-003-02R/31.8.2018, od 1.6. 2019 také na www.sukl.cz

Dlouhodobá antitrombotická léčba po ACS nad 12 měsíců:
COMPASS : vaskulární dávka rivaroxabanu 2 x 2.5mg + aspirin



Lancet 2018; 391: 205–18

Dlouhodobá antitrombotická léčba po ACS nad 12 měsíců:
vaskulární dávka rivaroxabanu 2 x 2.5mg + aspirin

		COMPASS [1] Riva 2.5 mg + ASA	PEGASUS [2] Ticagrelor 60 mg + ASA
Věk		69	65
Diabetes		37 %	33 %
Postižení více koronárních tepen		63 %	60 %
Medikace	iACE, ARB	72 %	80 %
	Statins	92 %	92 %
PAD		**20 %**	**5 %**
Předchozí IM		**68 %**	**100 %**
Průměrná doba od IM		**7.1 roku**	**1.7 roku**

1. Connolly SJ et al. *Lancet* 2018;391:205–218., 2. Bonaca MP *et al, N Engl J Med* 2015;372:1791–1800

Dlouhodobá antitrombotická léčba po ACS nad 12 měsíců:
vaskulární dávka rivaroxabanu 2 x 2.5mg + aspirin

Subgroup COMPASS: podskupiny podle doby od IM	Rivaroxaban 2.5 mg bid plus aspirin n/N (%)		Aspirin alone n/N (%)		HR (95% CI)	HR (95% CI)	*p*-value
History of MI							0.93
<2 years prior	49/1218	(4)	67/1205	(6)		0.70 (0.48–1.01)	
2–5 years prior	71/1612	(4)	91/1667	(5)		0.81 (0.59–1.10)	
>5 years prior	127/2824	(4)	174/2849	(6)		0.72 (0.57–0.91)	
No MI prior	100/2659	(4)	128/2540	(5)		0.76 (0.58–0.98)	

	Low-dose rivaroxaban plus aspirin (n=8313)	Rivaroxaban alone (n=8250)	Aspirin alone (n= 8261)
Previous myocardial infarction	5654 (68%)	5653 (69%)	5721 (69%)
<1 year	410 (5%)	403 (5%)	425 (5%)

Connolly SJ *et al*, *Lancet* 2018;391:205–218

Dlouhodobá antitrombotická léčba po ACS nad 12 měsíců:
vaskulární dávka rivaroxabanu 2 x 2.5mg + aspirin

Table 3 Comparison of the effects of guideline indicated secondary prevention pharmacological therapies for patients with vascular disease

Outcomes	Lipid lowering[41,42] (1 mmol/L reduction in LDL)	BP lowering[43] (10 mmHg reduction in systolic BP)	ACE inhibitors[44]	Aspirin[40]	COMPASS[1–3] rivaroxaban + aspirin
MACE[a]	-21%	-20%	-18%	-19%	-24%
Mortality	-9%	-13%	-14%	-9% (NS)	-18%
Stroke	-15%	-27%	-23%	-19%	-42%
MI	-24%	-17%	-18%[b]	-20%	-14% (NS)

ACE, angiotensin-converting enzyme; BP, blood pressure; CV, cardiovascular; LDL, low density lipoprotein; MACE, major adverse cardiovascular events; MI, myocardial infarction; NS, non significant.
[a]Major coronary event.
[b]Non-fatal MI.

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Dlouhodobá antitrombotická léčba po ACS : individuální přístup