FAKULTNÍ NEMOCNICE BRNO

Intervenční kardiologie
IKK FN Brno

Jak na to?

Protidestičková a antikoagulační léčba pacientů po implantací koronárních stentů

Petr Kala

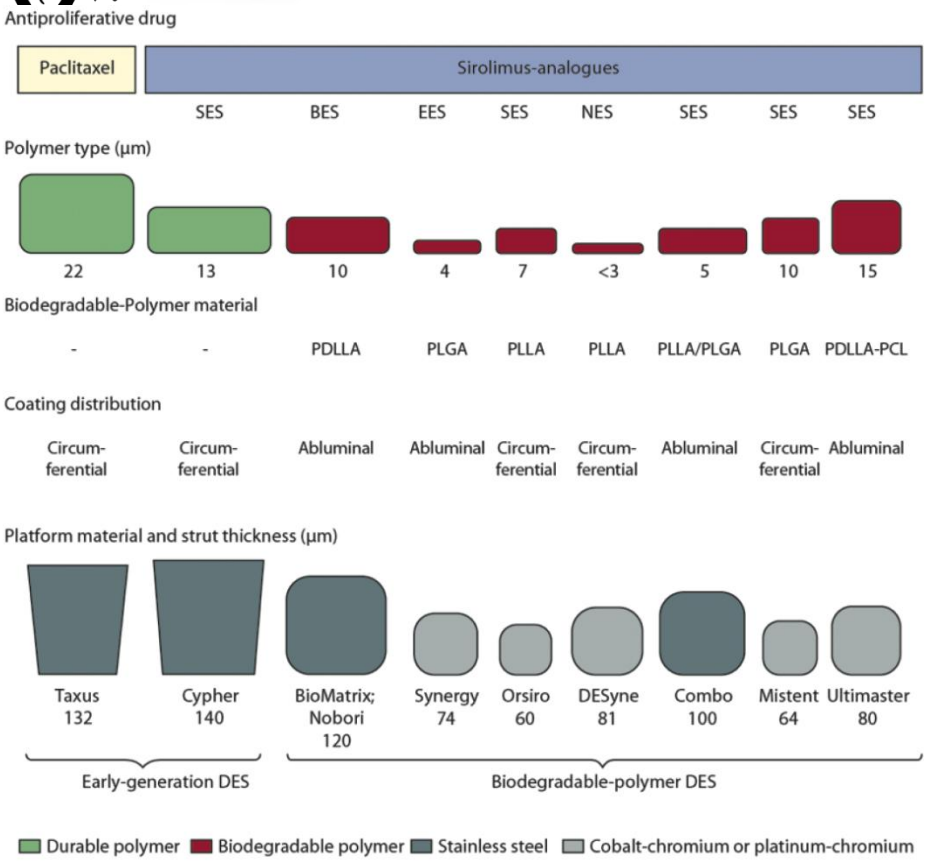
Brno

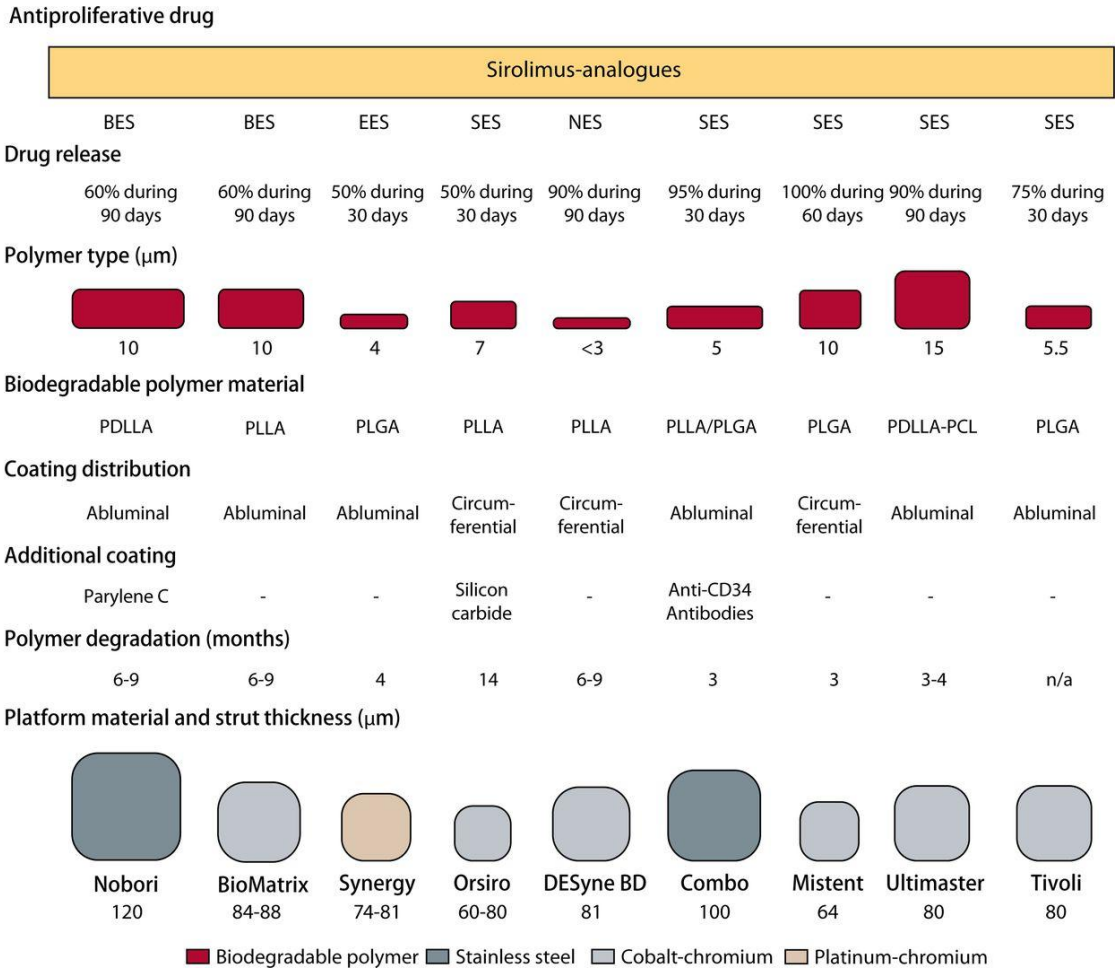
21.11. 2017

Obsah prezentace

- **Stenty**
- Protidestičková léčba
- Antikoagulační léčba
- Guidelines
- Kazuistika

Typy DES



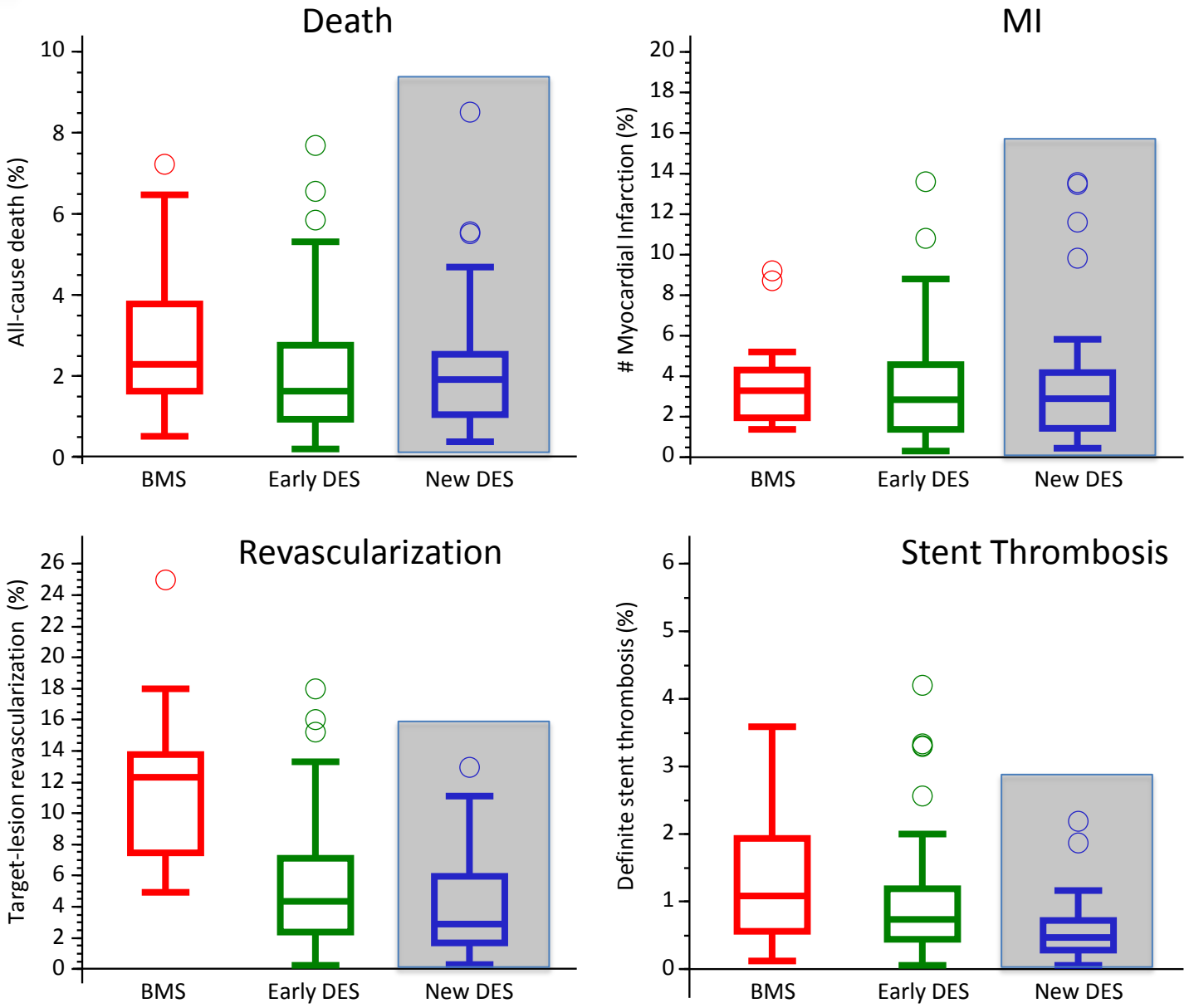


Cardiac Interventions Today

\+ navíc jsou bezpolymerové DES
– tzv. DCS (drug-coated stent)

Piccolo R. et al. Heart BMJ

SYSTEMATIC REVIEW OF 158 RCTs

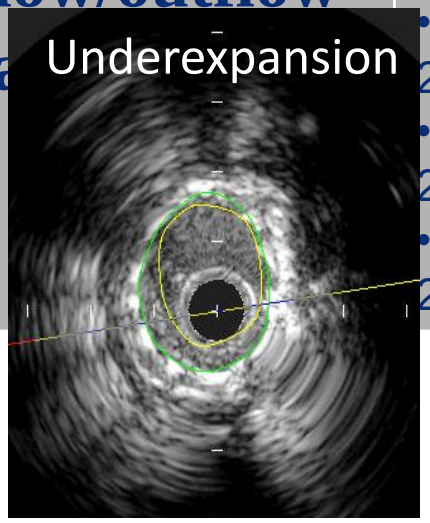


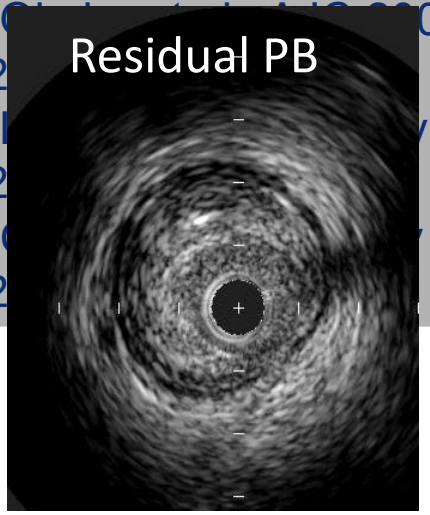
BYRNE ET AL., ESC-EAPCI STENT TASK FORCE | EUR HEART J 2015

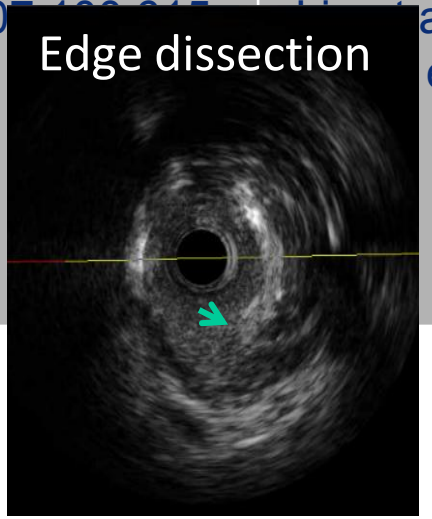
IVUS Mechanisms of DES Failure

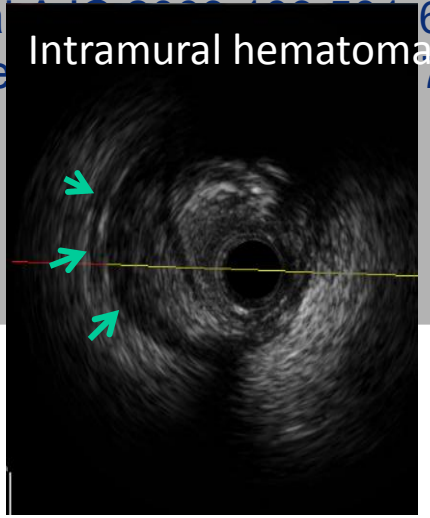
Patient, Device and Procedure–related Multi-factors within 1 year

	Early Thrombosis	Restenosis
Small MSA (Underexpansion)	•Fujii et al. JACC 2005;45:995-8 •Okabe et al., AJC 2007;100:615-20 •Liu et al. JACC Interv 2009;2:428-34 •Choi et al. Circ Interv 2011;4:239-47	•Sonoda et al. JACC 2004;43:1959-63 •Hong et al. EHJ 2006;27:1305-10 •Doi et al. JACC Interv. 2009;2:1269-75 •Fujii et al. Circulation 2004;109:1085-8 •Kang et al. Circ Interv 2011;4:9-14 •Song et al. CCI in press
Inflow/outflow tra	•Fujii et al. JACC 2005;45:995-8	•Sakurai et al. AJC 2005;96:1251-3









Guagliumi G, TCT 2017

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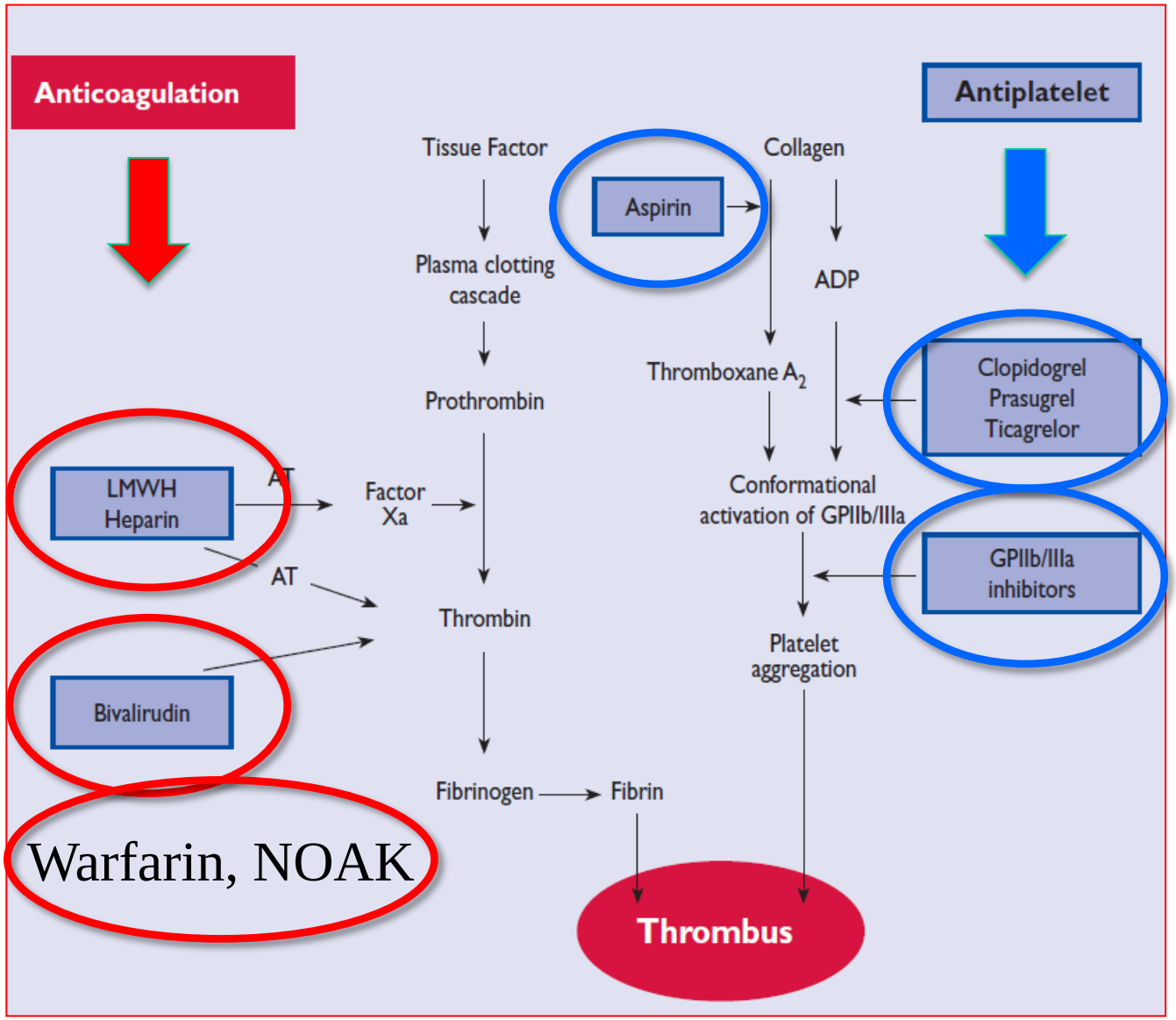
Antitrombotická medikace

Přednemocniční | Peri-procedurální | Nemocniční | Dlouhodobá



Cangrelor

Abciximab

Eptifibatide

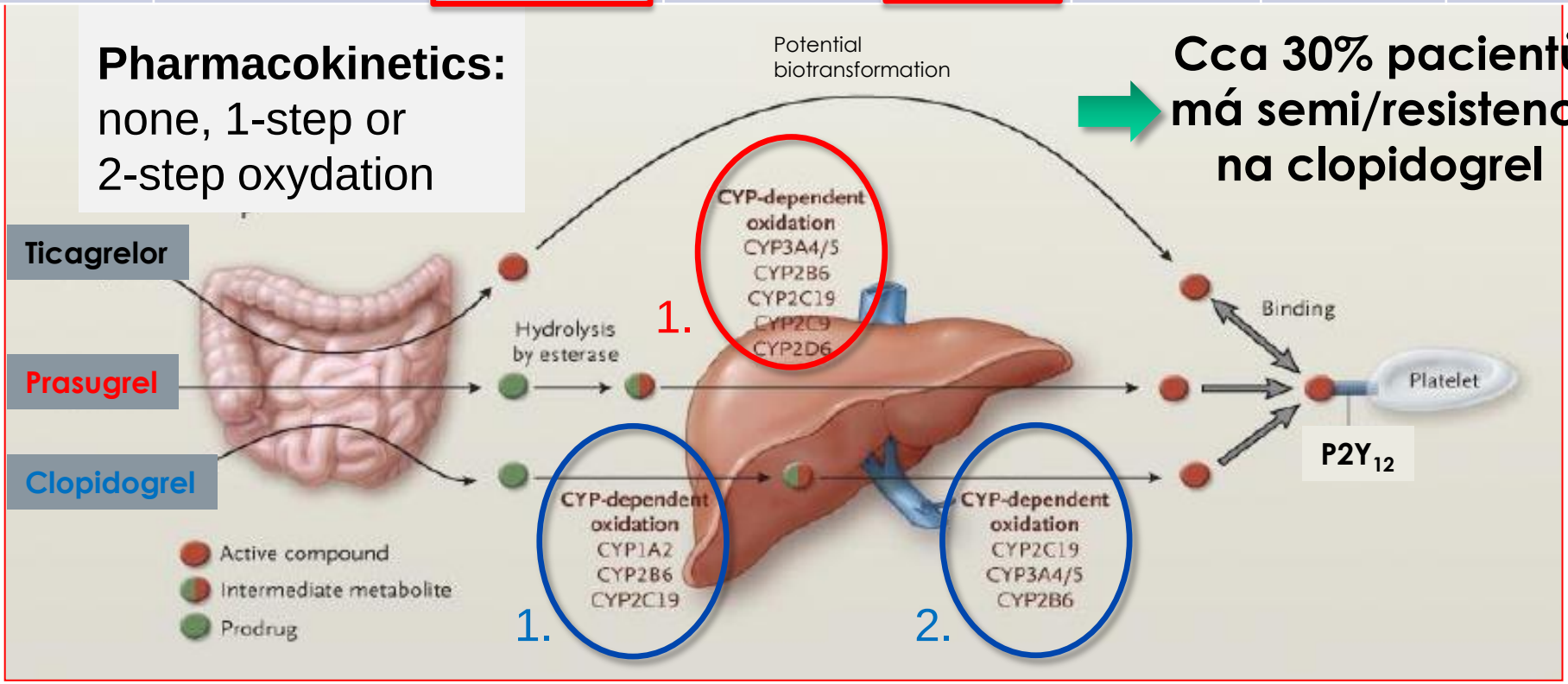
Tirofiban

P2Y12 inhibitory:
Farmakokinetika a farmakodynamika

Drug	Administration	Activation (CYP dependant)	Receptor binding	Onset of action	Offset of action	Loading dose	Maintenance dose
Clopidogrel	oral	sensitive to inhibition	irreversible	2-8 hrs	7-10 days	600mg	1x75mg
Prasugrel	oral	**resistant to inhibition**	irreversible	**0,5-4 hrs**	7-10 days	60mg	1x10mg (5mg)
Ticagrelor	oral	**not needed**	reversible	**0,5-2 hrs**	3-5 days	180mg	2x90mg

Pharmacokinetics:
none, 1-step or
2-step oxydation

Cca 30% pacientů má semi/resistenci na clopidogrel

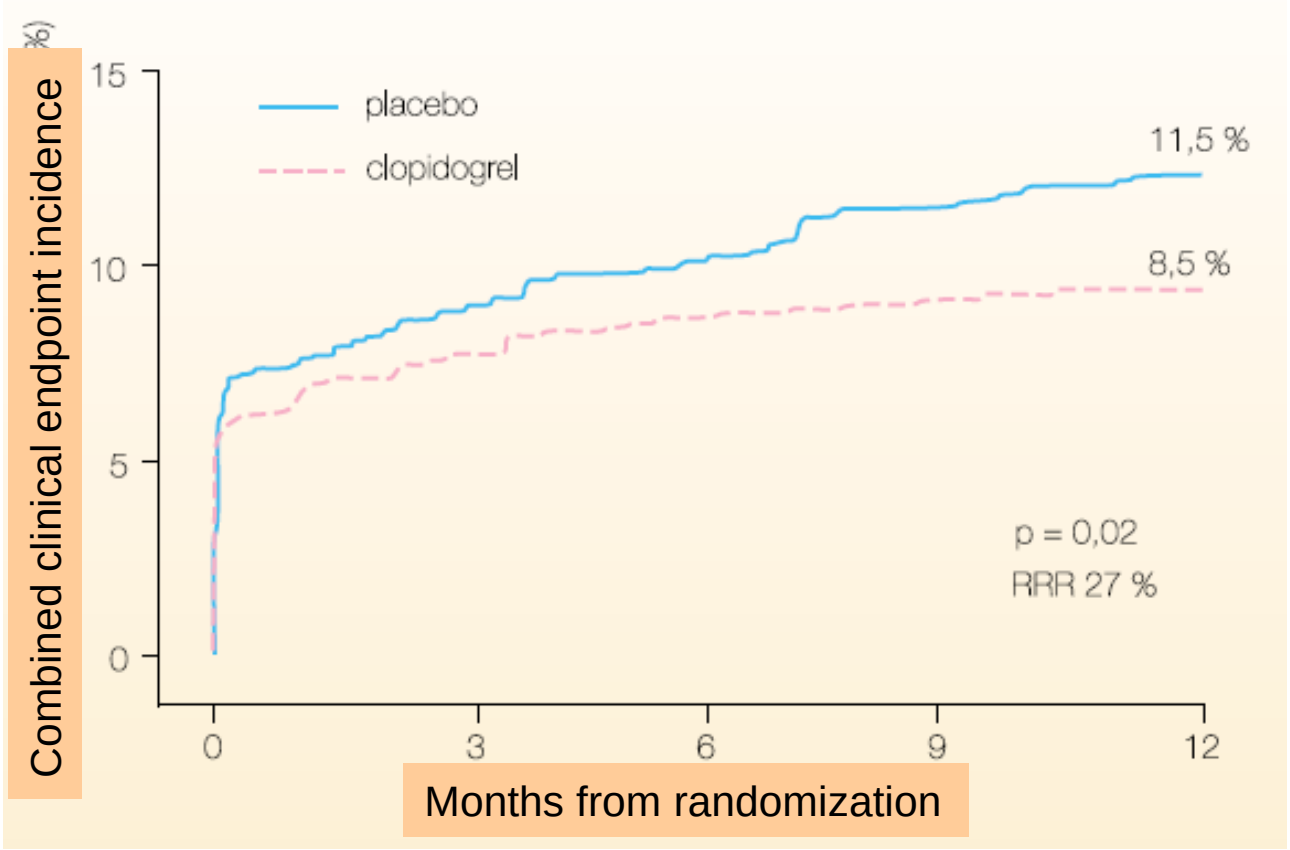


Ferreiro JL, Circ Cardiovasc Interv 2012;5:433-445

Clopidogrel – stabilní ICHS: PCI+stent

CREDO (n=2116): clopidogrel 28 dnů vs 1 rok společně s ASA

- Clopidogrel 1rok: RRR 27% ↓
- s LD 300mg: RRR 38,6% ↓



RES:

- po PCI – DAPT 12m
- LD 300mg > 6hod

Steinhubl SR: JAMA 2002; 288: 2411–2420.

Prasugrel/Ticagrelor vs Clopidogrel trials

Ticagrelor vs clopidogrel – Plato

NSTE-ACS (moderate-to-high risk) **59%**, STEMI (if primary PCI) **38%**
Clopidogrel-treated or -naïve; All patients received ASA
randomized within 24 hours
(N = 18,624)

Clopidogrel
300-mg loading dose unless pre-treated
then 75-mg once-daily maintenance;
(additional 300 mg allowed pre-PCI)
(N = 9,291)

6-12 month expos
Median 9.2 mont

Primary End Point: CV Deat
Primary Safety End Point: Tota

Wallentin L, et al. N Engl J Med 2009;361:1045-1057

Prasugrel vs clopidogrel – Triton TIMI 38

NSTE-ACS (TIMI score ≥3) **74%**
STEMI (primary PCI ≤12 hours or delayed PCI>12 hours – 14 days) **26%**
Clopidogrel-naive; All patients received ASA
randomized within 72 hours of index event
(N = 13,608)

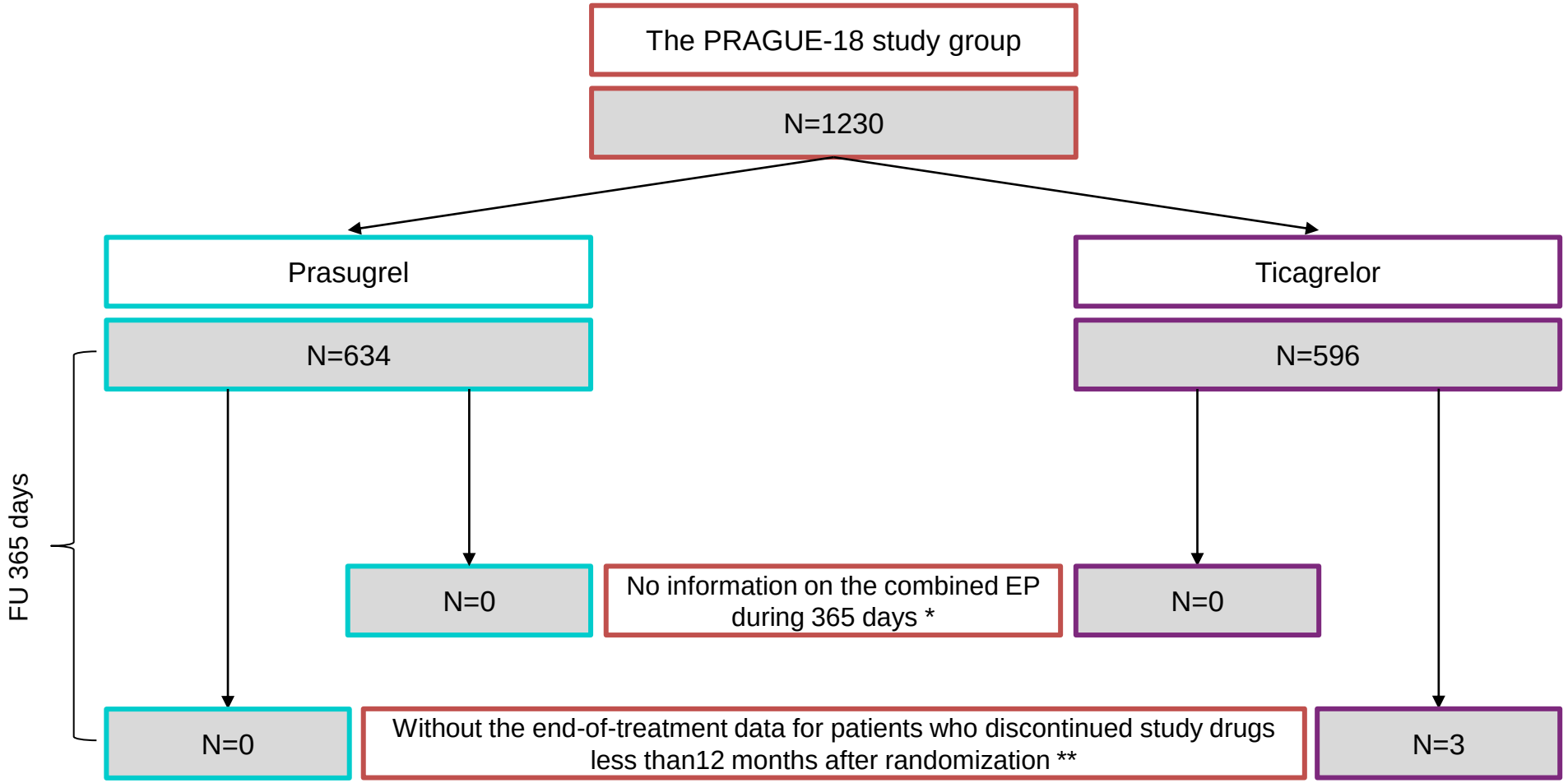
Clopidogrel
300-mg loading dose
then 75-mg once-daily maintenance;
(N = 6,795)

Prasugrel
60-mg loading dose
then 10-mg once-daily maintenance
(N = 6,813)

6-15 month exposure
Median 14.5 months

Primary End Point: CV Death, MI, or Stroke
Primary Safety End Point: TIMI Major Bleeding

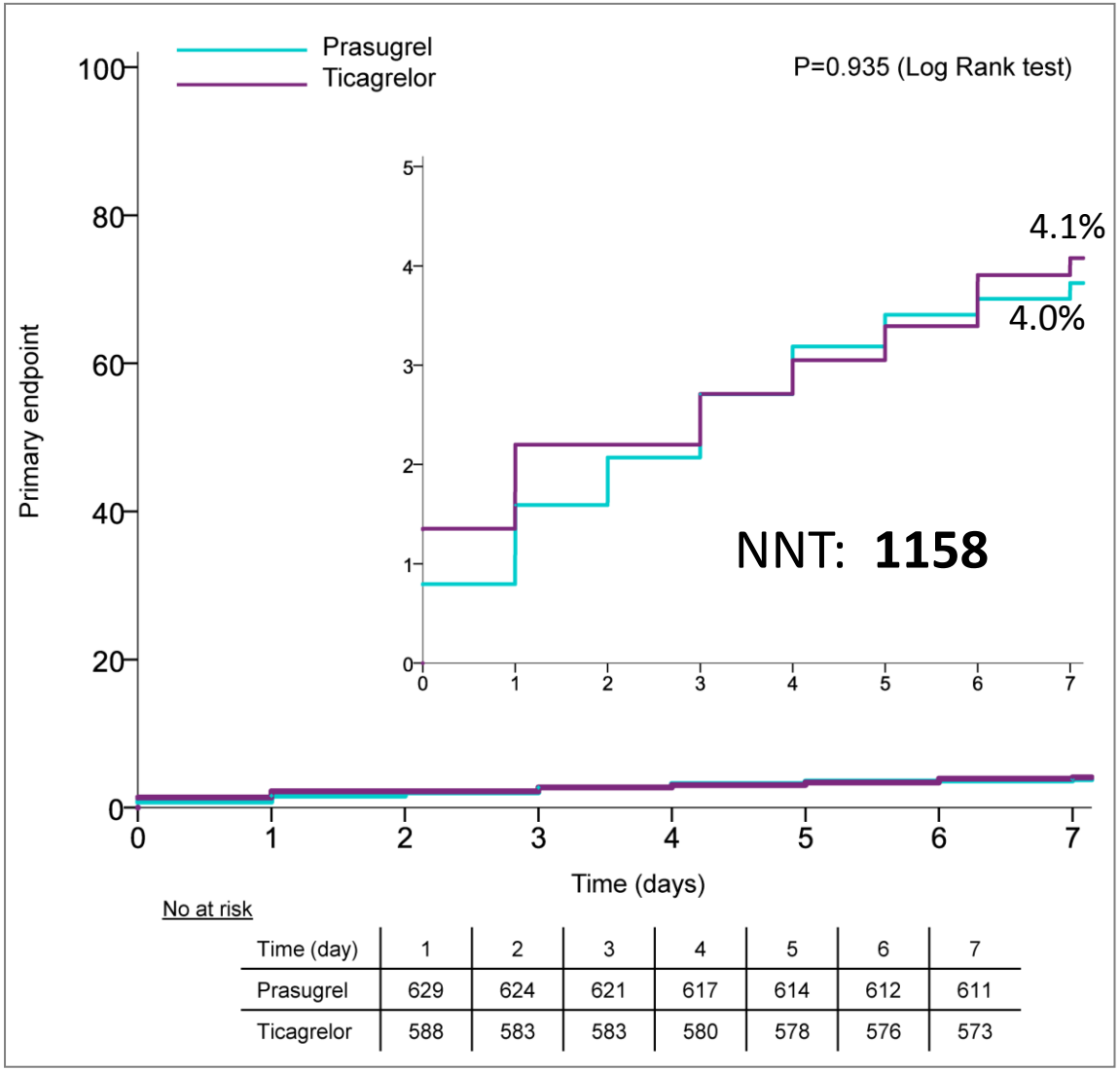
Wiviott SD, et al. *N Engl J* Med 2007;357:2001-2015



* 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.

1° NET-CLINICAL ENDPOINT AT DAY 7

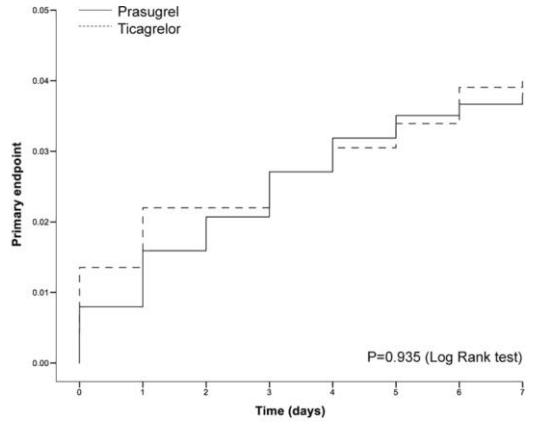
All-cause Death/reMI/urgent TVR/Stroke/Serious bleeding



No at risk

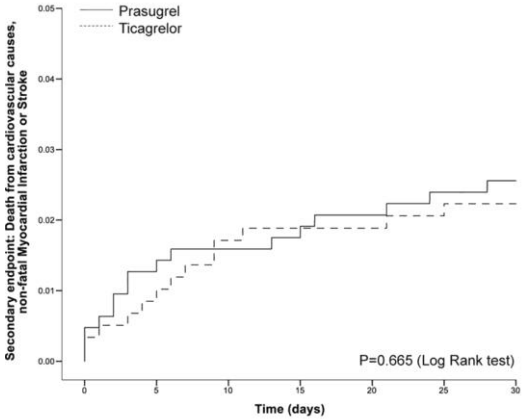
Time (day)	1	2	3	4	5	6	7
Prasugrel	629	624	621	617	614	612	611
Ticagrelor	588	583	583	580	578	576	573

Cumulative Kaplan-Meier estimates of the percentages of the primary and key secondary end points.



No at risk

Time (day)	1	2	3	4	5	6	7
Prasugrel (N=634)	629	624	621	617	614	612	611
Ticarelor (N=596)	588	583	583	580	578	576	573



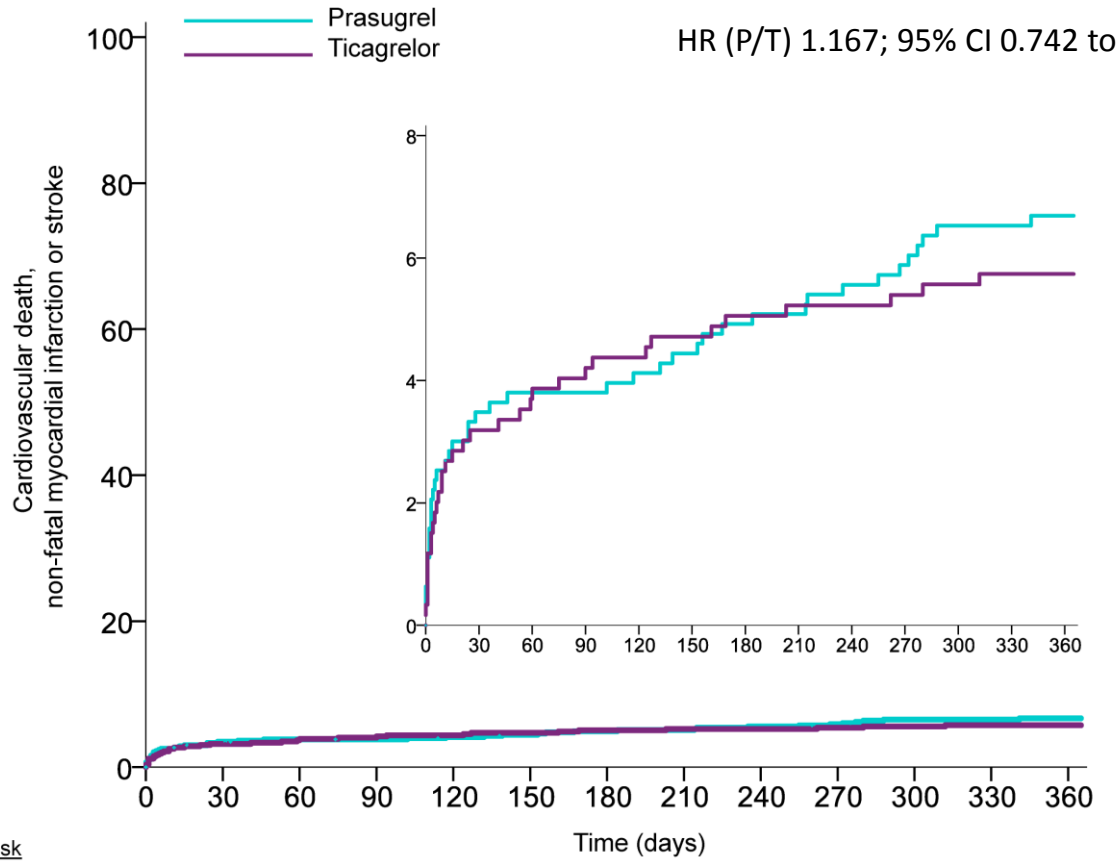
No at risk

Time (day)	5	10	15	20	25	30
Prasugrel (N=634)	626	623	622	619	617	616
Ticarelor (N=596)	591	585	583	583	582	580

Zuzana Motovska et al. Circulation. 2016;134:1603-1612

American Heart Association.

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



HR (P/T) 1.167; 95% CI 0.742 to 1.835, P=0.503 (Log Rank test)

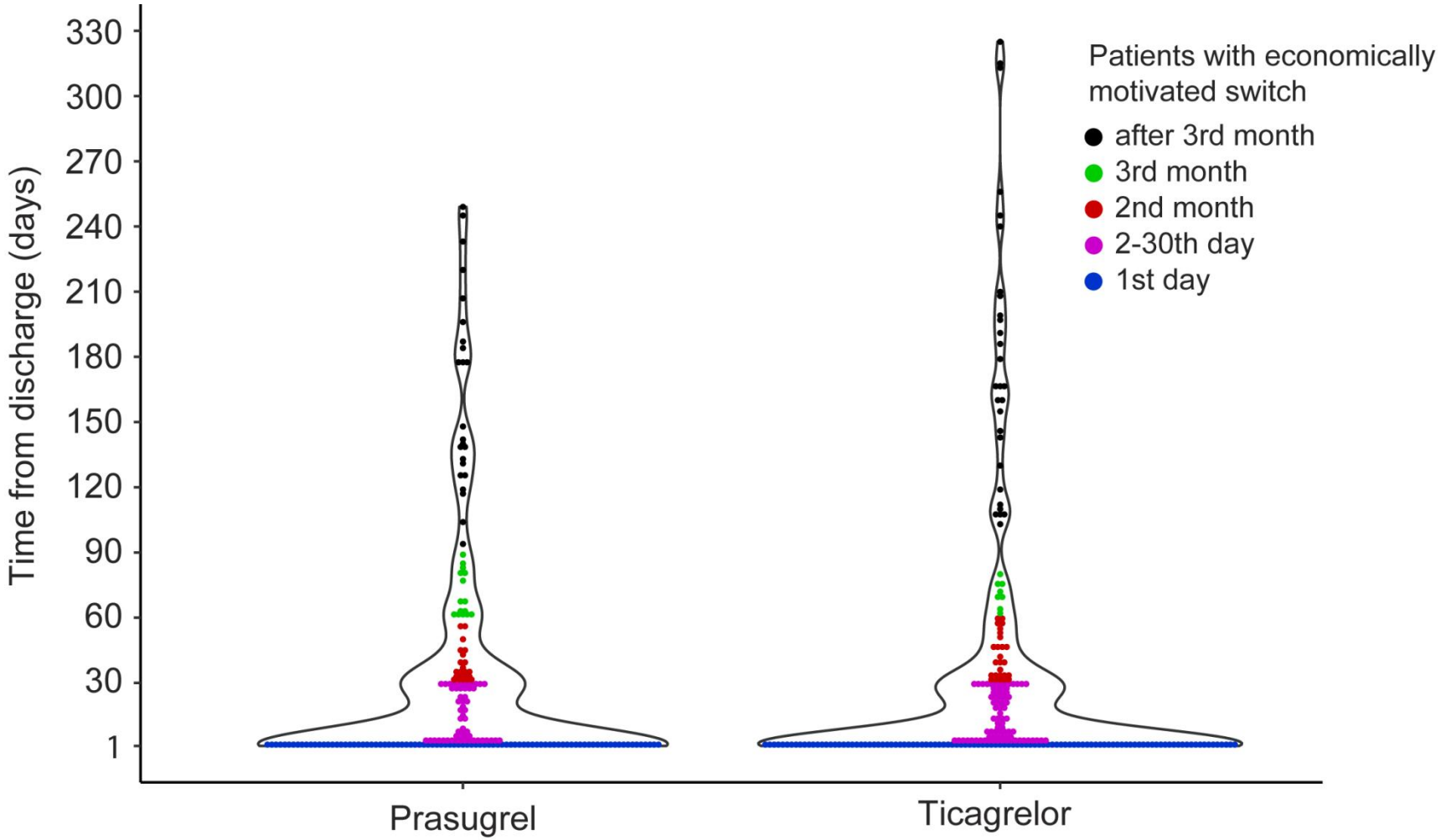
No at risk

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

SWITCH 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

Time distribution of economically motivated switches to clopidogrel after discharge



		HR (95% CI)	P-value
Risk of ischemic endpoint *	**Economically motivated switch** (N=481)	**0.433 (0.210–0.894)**	**0.024**
	Switch from 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**

* Cardiovascular death, non-fatal myocardial infarction or stroke.

The hazard ratio was based on the Cox proportional hazard model with time dependent covariates

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

Reference: JAC 24432

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WOEST Study Design

Inclusion criteria
- Indication for OAC for ≥1 year
- PCI of a single coronary lesion

1:1 Randomization:

Double therapy group:	Triple therapy group
OAC + 75mg Clopidogrel qd	OAC + 75mg Clopidogrel qd + 80mg Aspirin qd
1 month minimum after BMS	1 month minimum after BMS
1 year after DES	1 year after DES

Follow up: 1 year

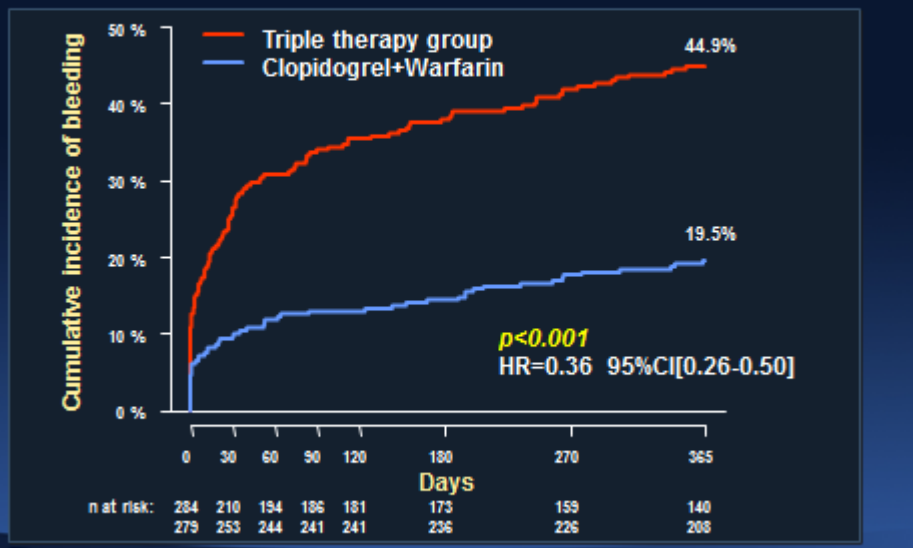
Primary Endpoint: The occurence of all bleeding events (TIMI criteria) (powered for a reduction from 12% to 5%)

Secondary Endpoints:
- Combination of stroke, death, myocardial infarction, stent thrombosis and target vessel revascularisation
- All individual components of primary and secondary endpoints

Mount Sinai Heart

WOEST 1o Endpoint: TIMI Major-Minor-Minimal Bleed

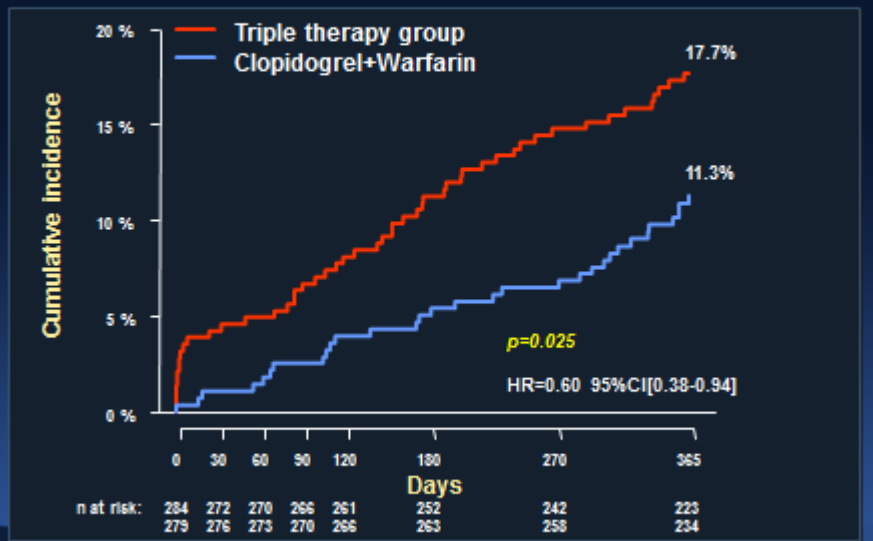
The Curves start diverging within days!



Mount Sinai Heart

WOEST 2ary Endpoint: Death, MI, TVR, Stroke, ST

Concordant Results With the 1o Bleeding Events!



Mount Sinai Heart

WOEST Key Investigators: JW Dewilde, JM ten Berg Lancet. 2013 Mar 30;381(9872):1107-15
EuroIntervention 2015 Aug;11(4):381-90

Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation (ISAR-TRIPLE Trial)

Katrin A. Fiedler, Michael Maeng, Julinda Mehilli, Stefanie Schulz, Robert A. Byrne, Dirk Sibbing, Petra Hoppmann, Simon Schneider, Massimiliano Fusaro, Ilka Ott, Steen D. Kristensen, Tareq Ibrahim, Steffen Massberg, Heribert Schunkert, Karl-Ludwig Laugwitz, Adnan Kastrati and Nikolaus Sarafoff

Deutsches Herzzentrum, Technische Universität, Munich, Germany; Aarhus University Hospital, Aarhus, Denmark; Klinikum der Ludwig Maximilians Universität, Munich, Germany; Klinikum rechts der Isar, Technische Universität, Munich, Germany

Mount Sinai Heart

ISAR-TRIPLE: Stud

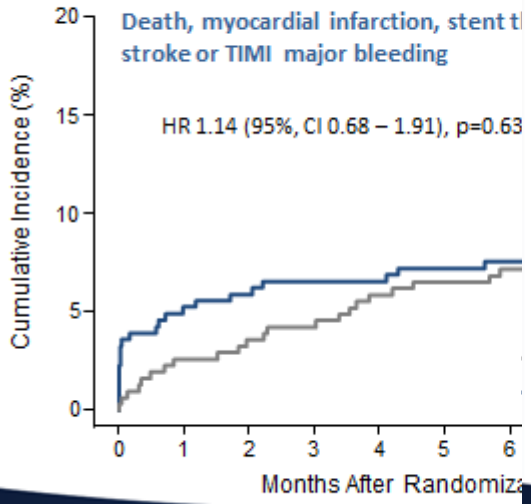
TEST HYPOTHESES:
6-week superior to 6-month therapy; Primary Endpoint 10%, Risk reduction 60% with 6-week therapy; Power = 80%, alpha = 0.05; 283 patients per group

PRIMARY ENDPOINT:
- Death, myocardial infarction, definite stent thrombosis, stroke or TIMI major bleeding at 9 months

SECONDARY ENDPOINTS:
- Ischemic complications: Cardiac death, myocardial infarction, definite stent thrombosis or ischemic stroke
- Bleeding complications (TIMI major)

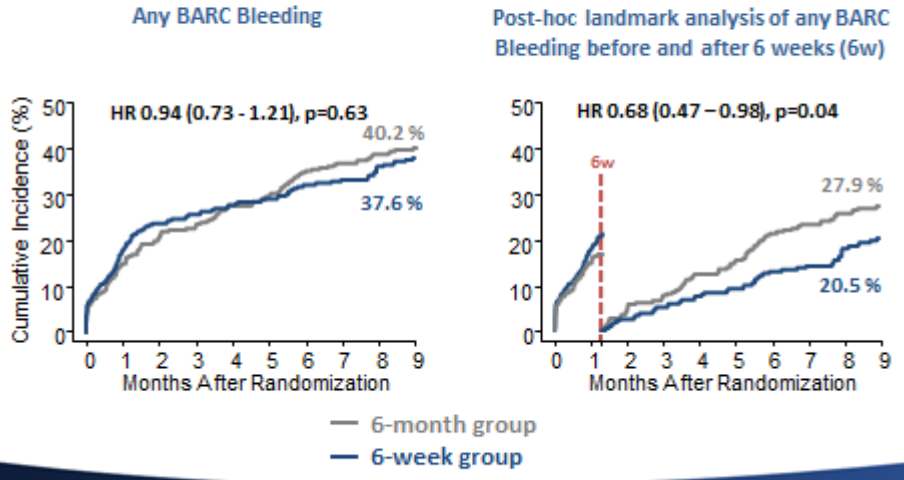
tct2014 VKA: Vitamin K Antagonist

Primary Endpoint



tct2014

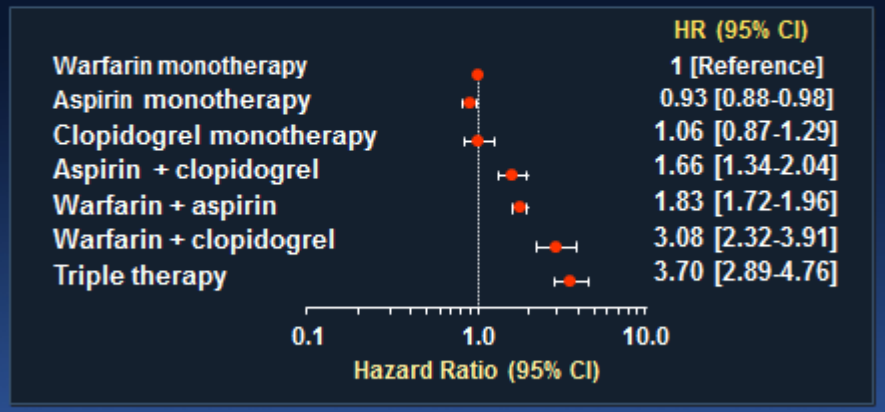
Any BARC Bleeding (type 1-5)



tct2014 CRF

Riziko krvácení u pacientů s FISI

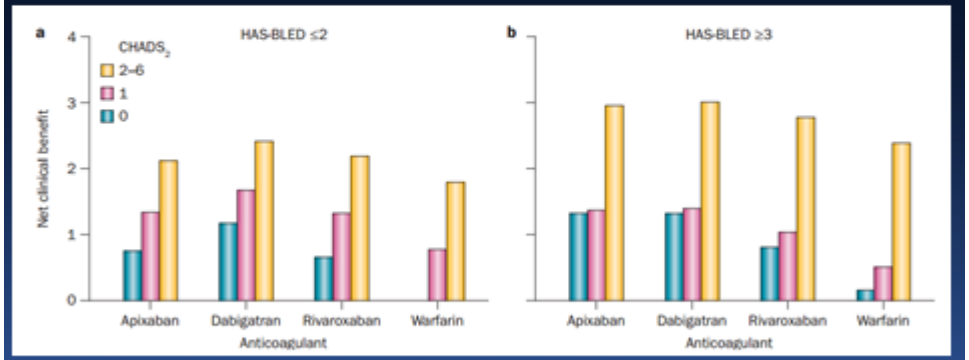
Bleeding Associated with Warfarin, Aspirin, Clopidogrel in Patients with AF n=82,854



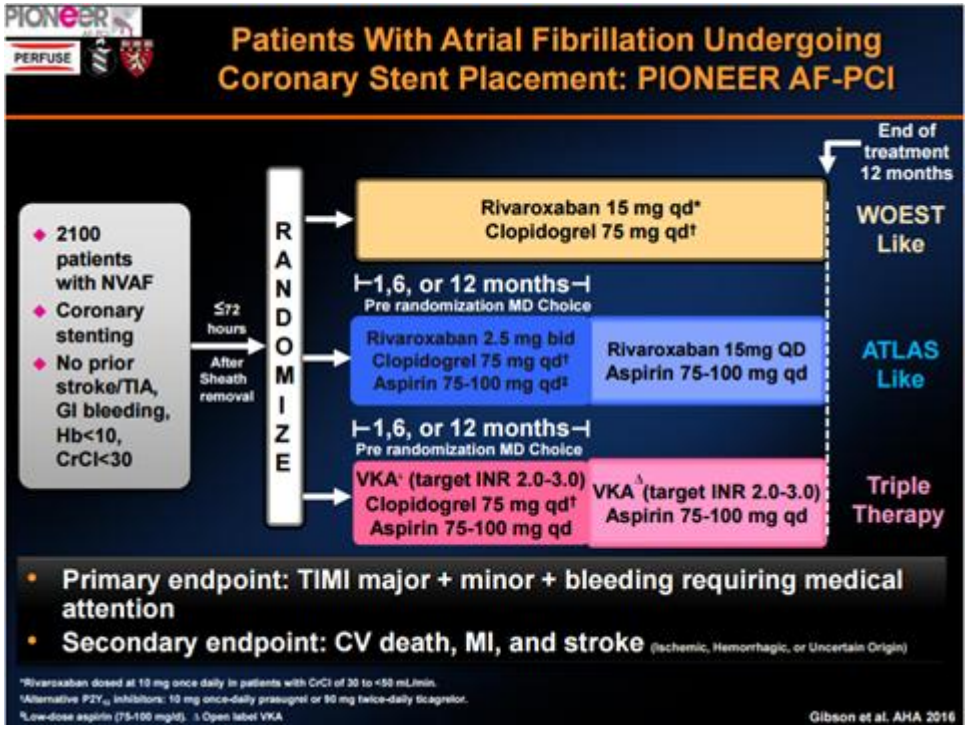
Hansen et al, *Arch Intern Med*, 2010;170:1433-1441

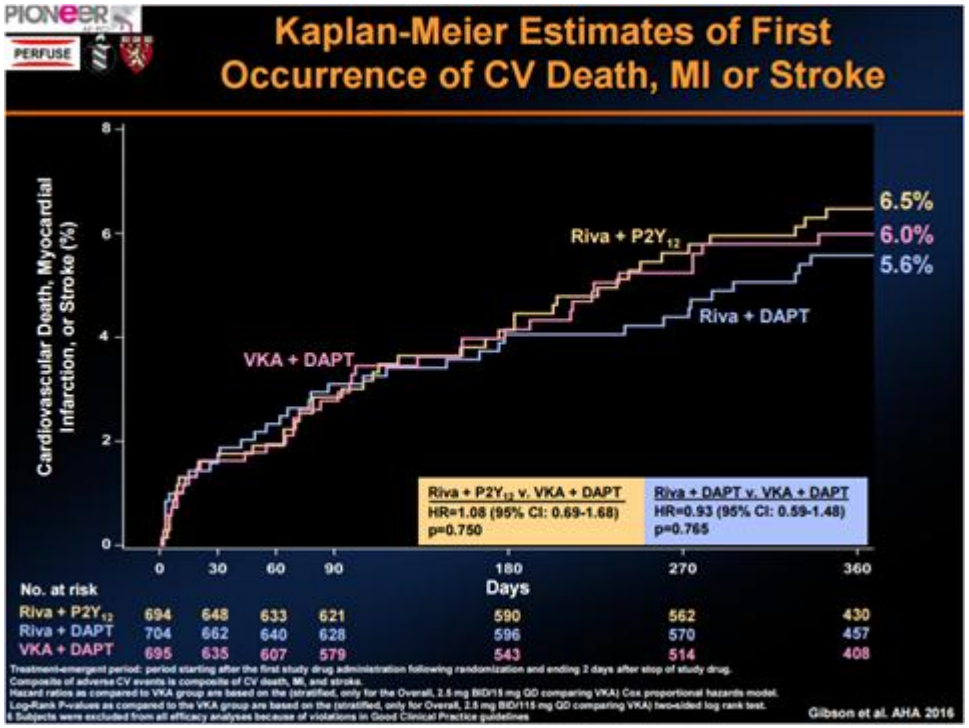
BLEEDING RISK IS A MATTER OF CONCERN!!

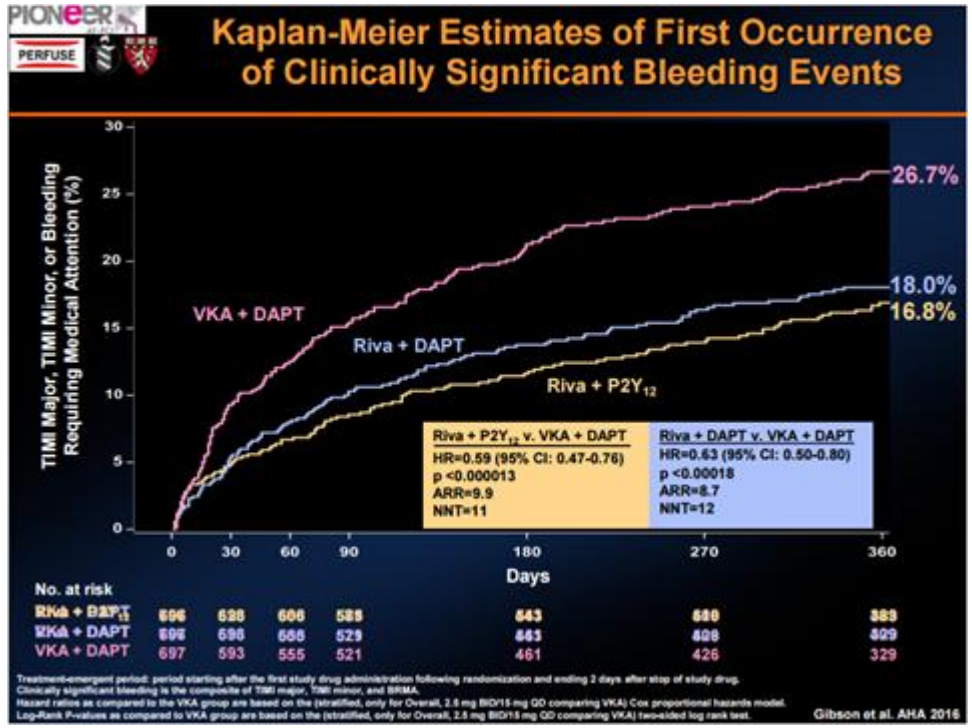
Net clinical benefit of apixaban, dabigatran, rivaroxaban, and warfarin in prevention of ischaemic stroke and intracranial haemorrhage stratified by risk of ischaemic stroke (CHADS2 score) and bleeding (HAS-BLED score).



Baber, et al. Nature Reviews 2014

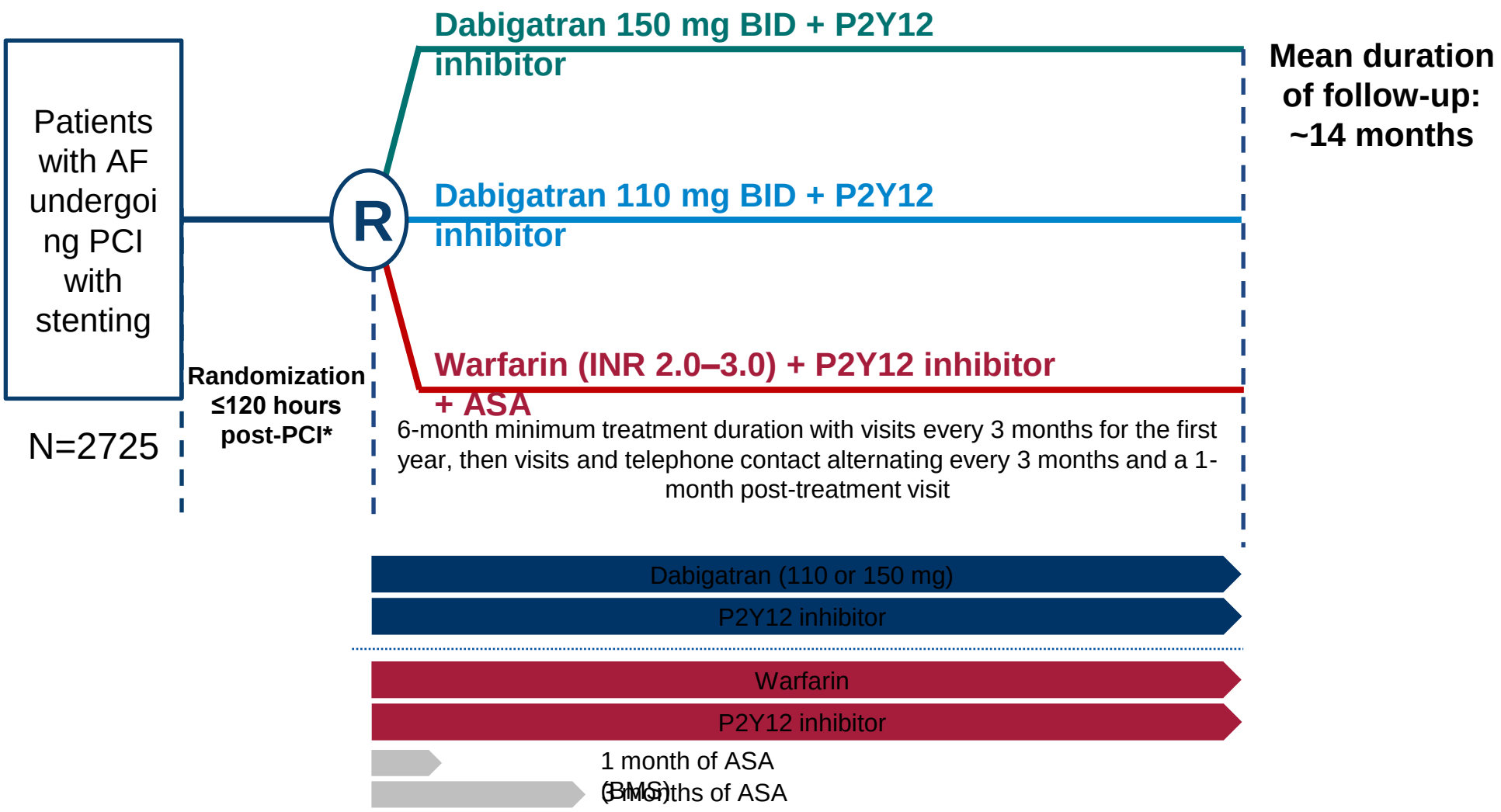

PIONEER AF-PCI
PERFUSE
Patients With Atrial Fibrillation Undergoing Coronary Stent Placement: PIONEER AF-PCI
2100 patients with NVAF
Coronary stenting
No prior stroke/TIA, GI bleeding, Hb<10, CrCl<30
≤72 hours
After Sheath removal
RANDOMIZE
Rivaroxaban 15 mg qd*
Clopidogrel 75 mg qd†
End of treatment 12 months
WOEST Like
1,6, or 12 months
Pre randomization MD Choice
Rivaroxaban 2.5 mg bid
Clopidogrel 75 mg qd†
Aspirin 75-100 mg qd‡
Rivaroxaban 15mg QD
Aspirin 75-100 mg qd
ATLAS Like
1,6, or 12 months
Pre randomization MD Choice
VKA^ (target INR 2.0-3.0)
Clopidogrel 75 mg qd†
Aspirin 75-100 mg qd
VKA Δ (target INR 2.0-3.0)
Aspirin 75-100 mg qd
Triple Therapy
Primary endpoint: TIMI major + minor + bleeding requiring medical attention
Secondary endpoint: CV death, MI, and stroke (Ischemic, Hemorrhagic, or Uncertain Origin)
*Rivaroxaban dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.
†Alternative P2Y12 inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.
‡Low-dose aspirin (75-100 mg/d). Δ Open label VKA
Gibson et al. AHA 2016


PIONEER AF-PCI
PERFUSE
Kaplan-Meier Estimates of First Occurrence of CV Death, MI or Stroke
Cardiovascular Death, Myocardial Infarction, or Stroke (%)
Riva + P2Y12
Riva + DAPT
VKA + DAPT
6.5%
6.0%
5.6%
Riva + P2Y12 v. VKA + DAPT
HR=1.08 (95% CI: 0.69-1.68)
p=0.750
Riva + DAPT v. VKA + DAPT
HR=0.93 (95% CI: 0.59-1.48)
p=0.765
Days
No. at risk
Riva + P2Y12 694 648 633 621 590 562 430
Riva + DAPT 704 662 640 628 596 570 457
VKA + DAPT 695 635 607 579 543 514 408
Gibson et al. AHA 2016


PIONEER AF-PCI
PERFUSE
Kaplan-Meier Estimates of First Occurrence of Clinically Significant Bleeding Events
TIMI Major, TIMI Minor, or Bleeding Requiring Medical Attention (%)
VKA + DAPT
Riva + DAPT
Riva + P2Y12
26.7%
18.0%
16.8%
Riva + P2Y12 v. VKA + DAPT
HR=0.59 (95% CI: 0.47-0.76)
p <0.000013
ARR=9.9
NNT=11
Riva + DAPT v. VKA + DAPT
HR=0.63 (95% CI: 0.50-0.80)
p <0.00018
ARR=8.7
NNT=12
Days
No. at risk
VKA + DAPT 697 593 555 521 461 426 329
Gibson et al. AHA 2016

Study Design: Multicenter, randomized, open-label trial following a PROBE design

RE-DUAL PCI
Study in NVAF patients undergoing PCI

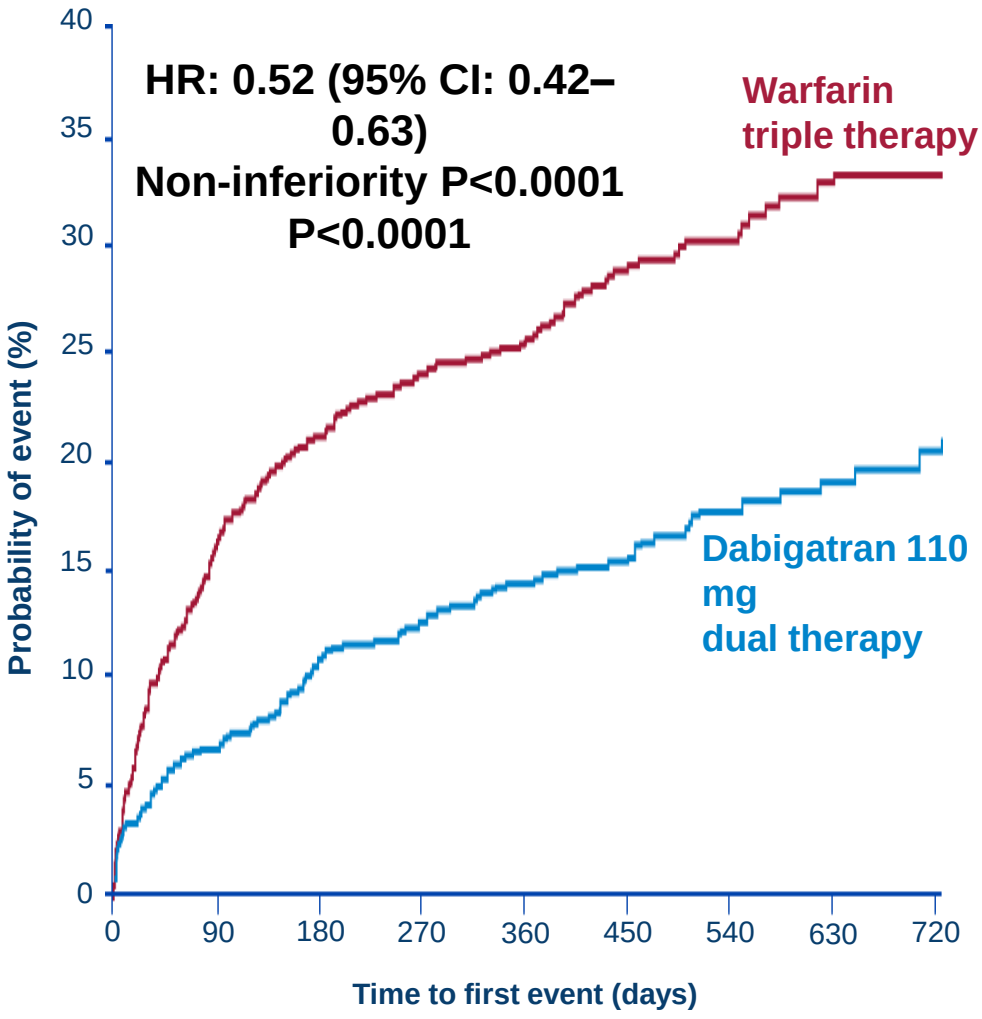


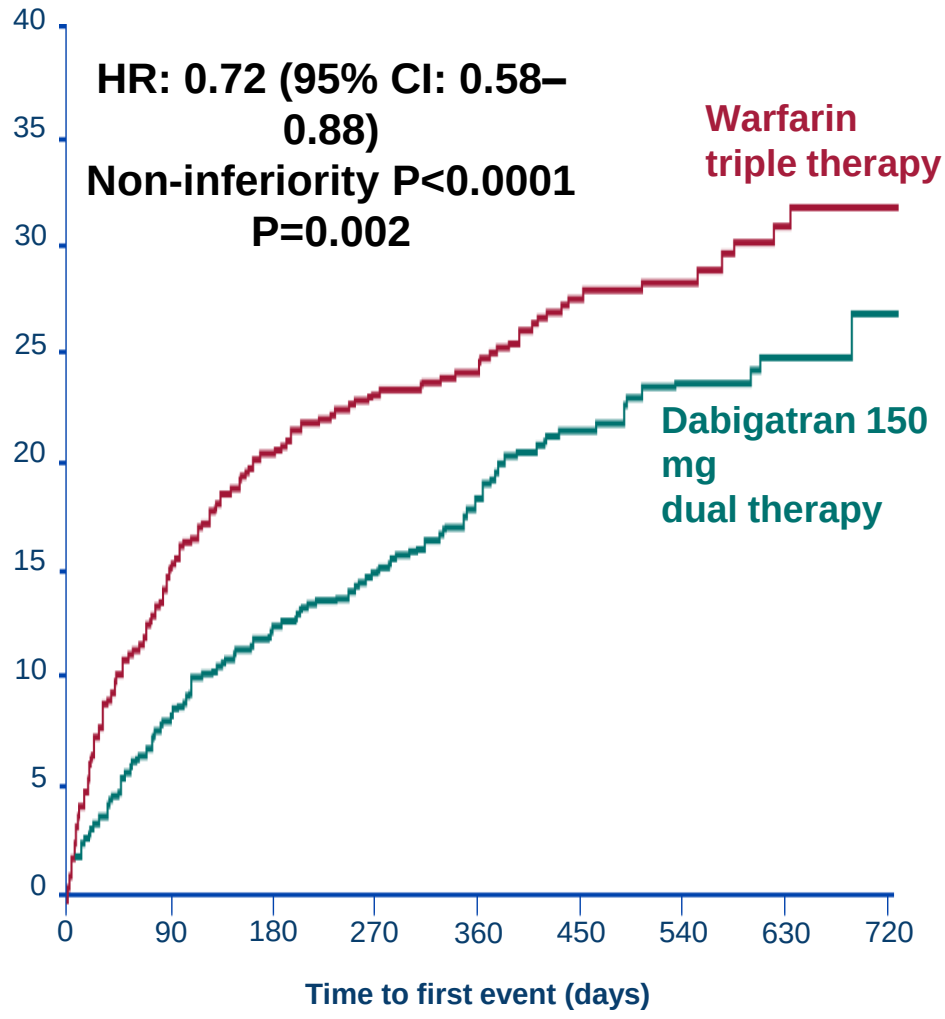
***Study drug should be administered 6 hours after sheath removal and no later than ≤120 hrs post-PCI (≤72 hrs is preferable).** PROBE, prospective, randomized, open, blinded end-point; R, randomization; BMS, bare metal stent; DES, drug-eluting stent. ClinicalTrials.gov: NCT02164864; Cannon et al. Clin Cardiol 2016

Cannon et al. NEJM 2017

Primary Endpoint: Time to first ISTH major or clinically relevant non-major bleeding event

RE-DUAL PCI
Study in NVAF patients undergoing PCI





Full analysis set presented. HRs and Wald CIs from Cox proportional-hazard model. For the dabigatran 110 mg vs warfarin comparison, the model is stratified by age, non-elderly vs elderly
(<70 or ≥70 in Japan and <80 or ≥80 years old elsewhere). For the dabigatran 150 mg vs warfarin comparison, an unstratified model is used, elderly patients outside the USA are excluded. Non-inferiority P value is one sided (alpha=0.025). Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05)

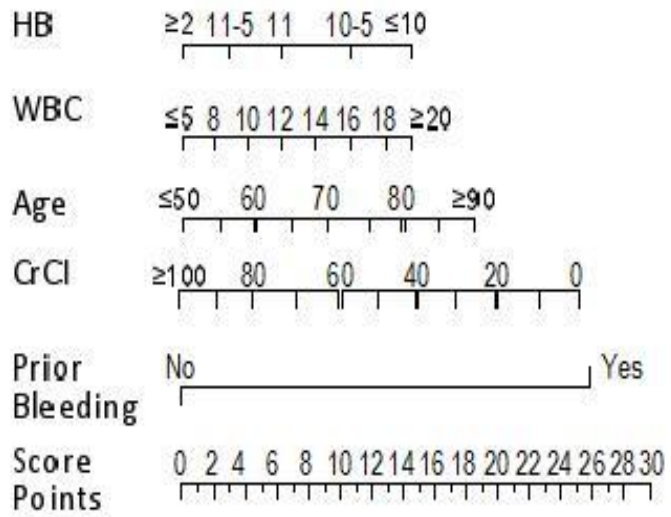
Cannon et al. NEJM 2017

Obsah prezentace

- Stenty
- Protidestičková léčba
- Antikoagulační léčba
- **Guidelines**
- Kazuistika

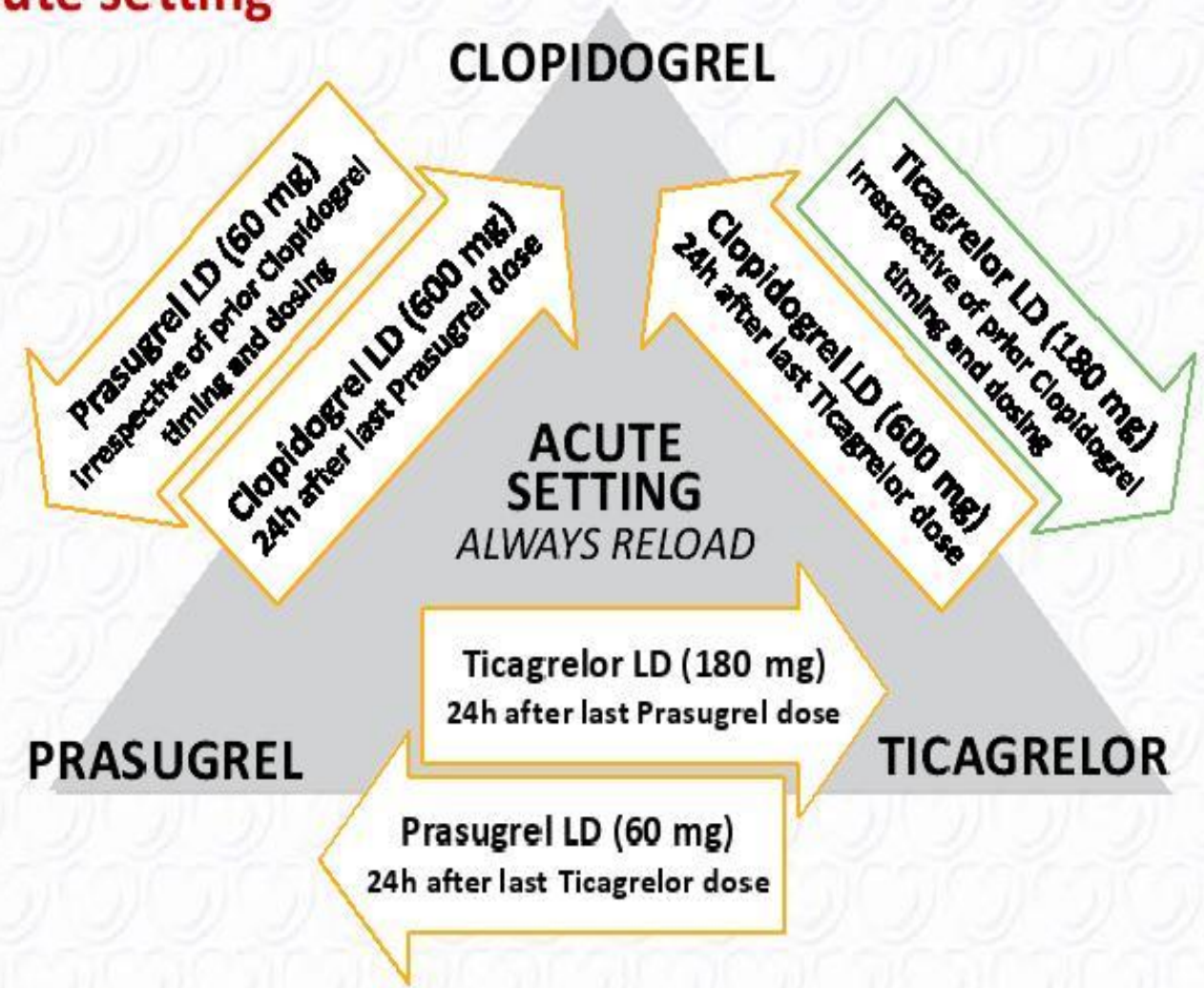
Risk scores validated for dual antiplatelet therapy duration decision-making

ESC European Society of Cardiology

	PRECISE-DAPT score	DAPT score	
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		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	

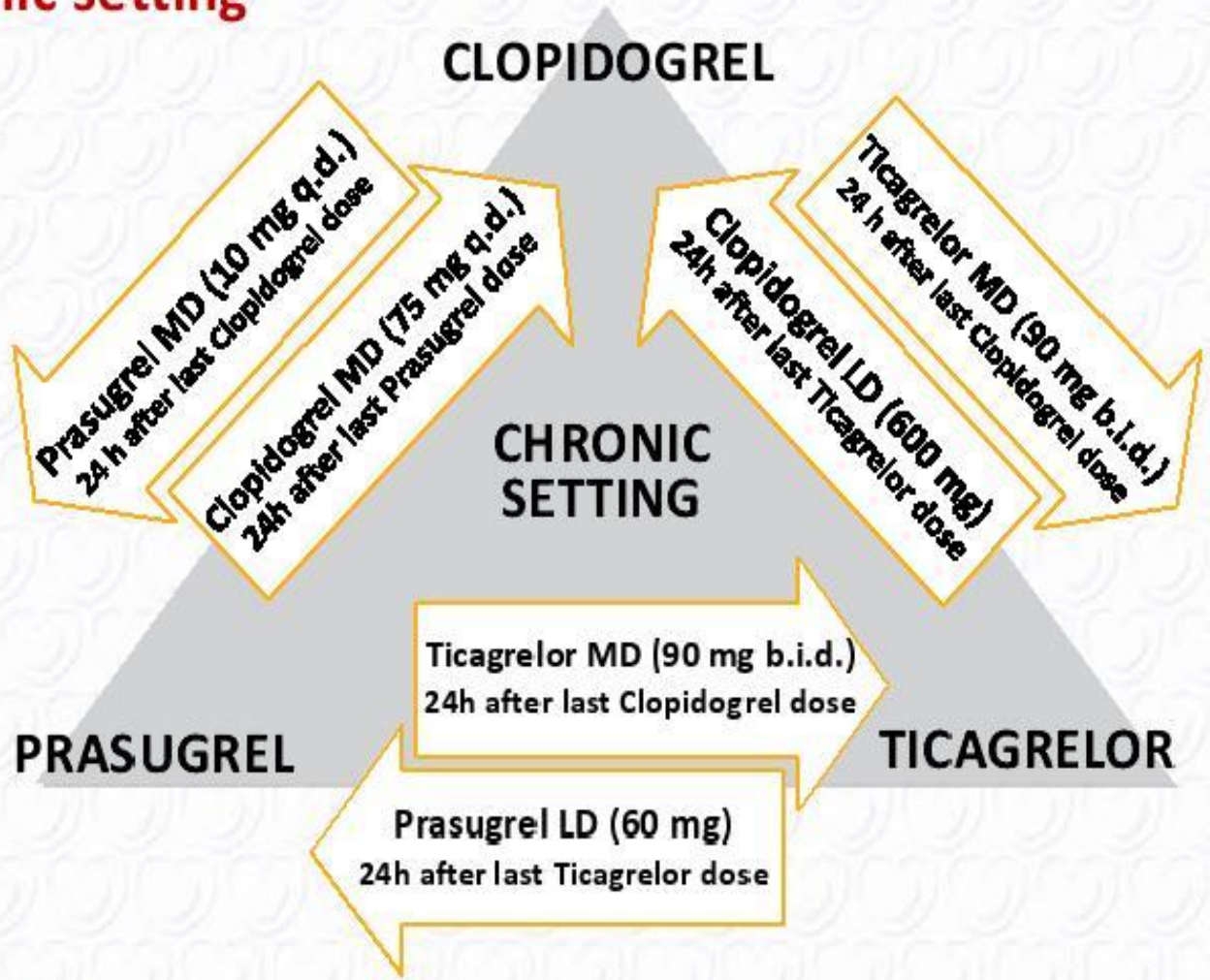
2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Algorithm for switching between oral $P2Y_{12}$ inhibitors in the acute setting



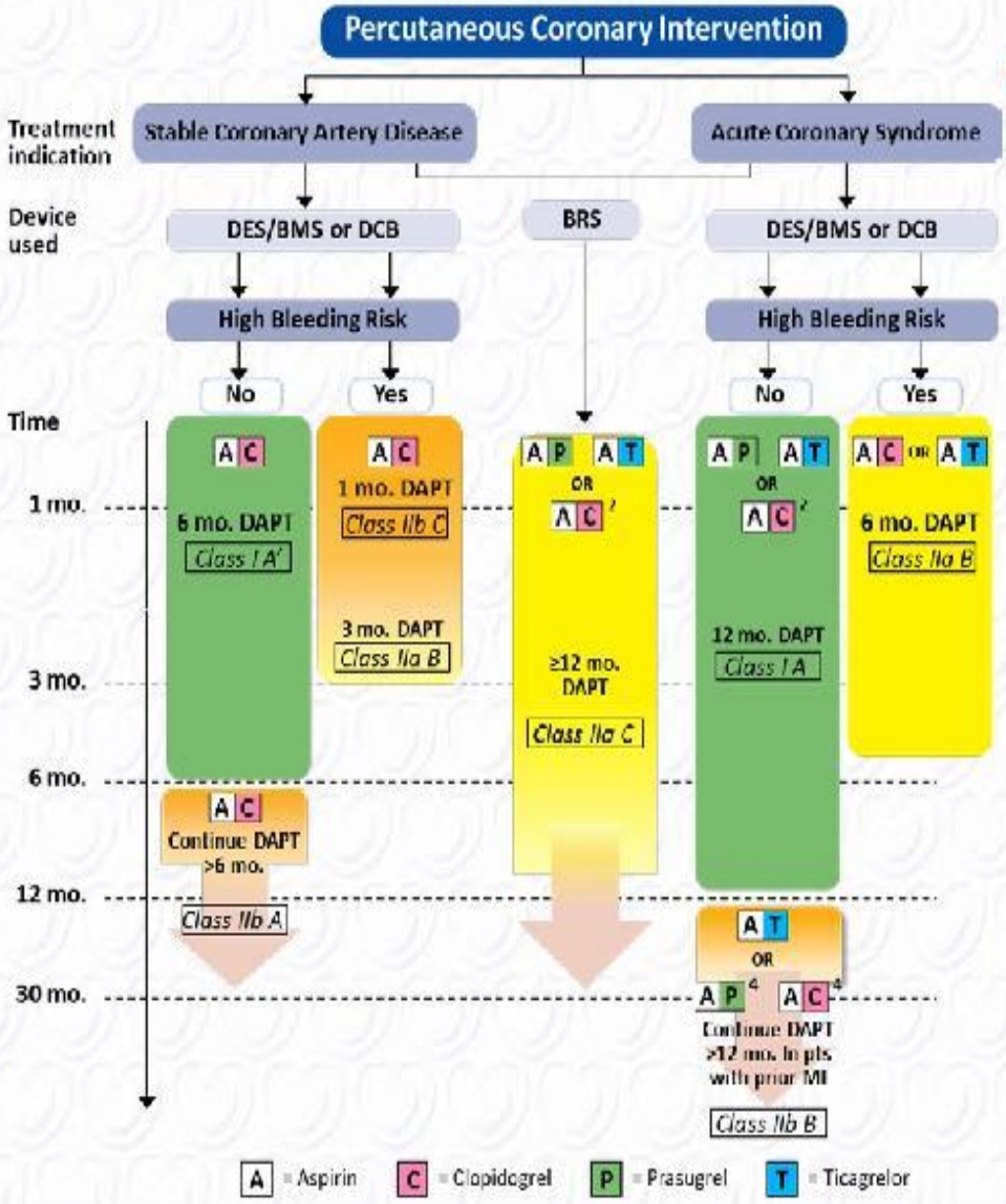
2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Algorithm for switching between oral $P2Y_{12}$ inhibitors in the chronic setting



2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Algorithm for dual antiplatelet therapy (DAPT) in patients treated with percutaneous coronary intervention

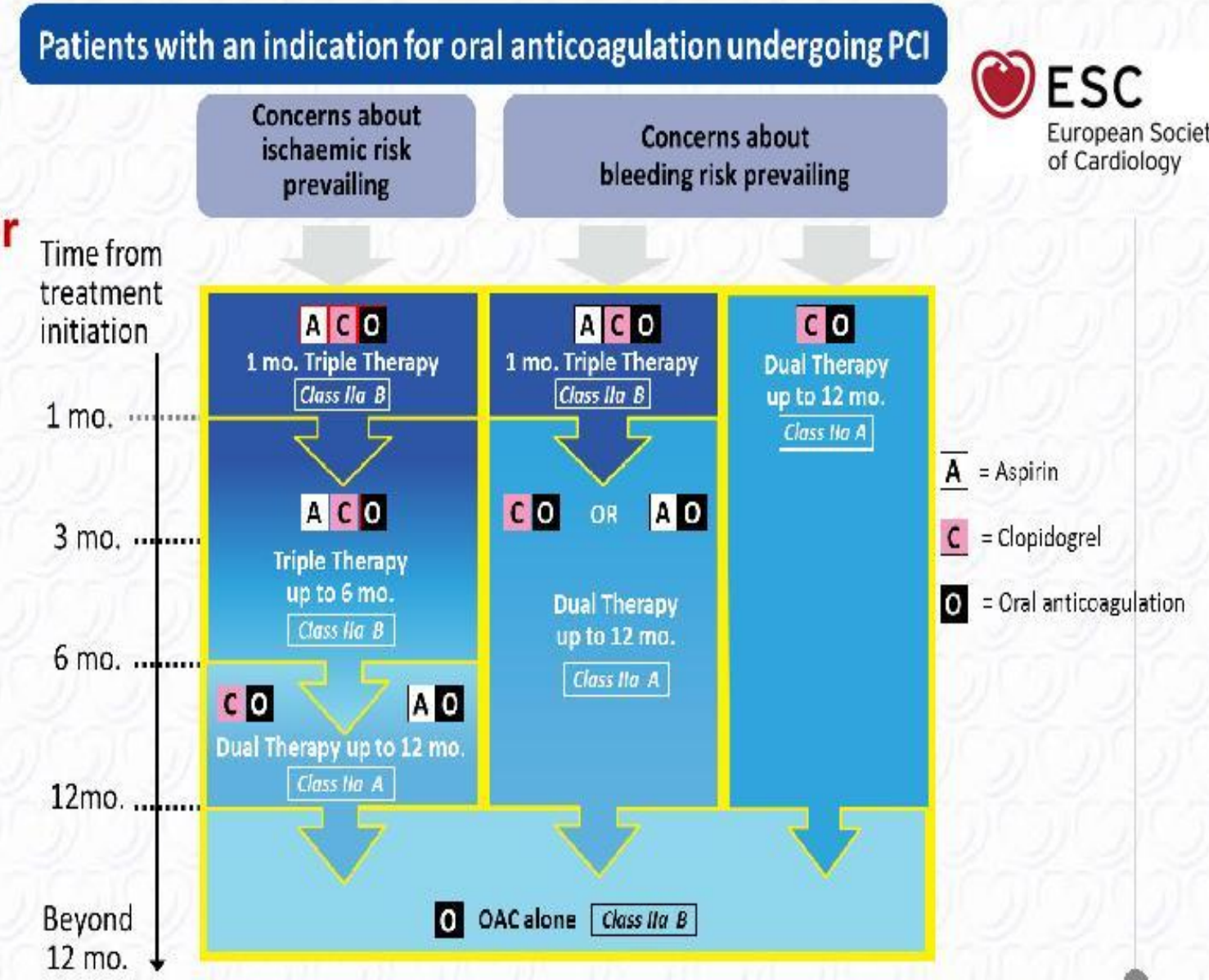


ESC European Society of Cardiology

www.escardio.org/guidelines

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention (PCI)



ESC European Society of Cardiology

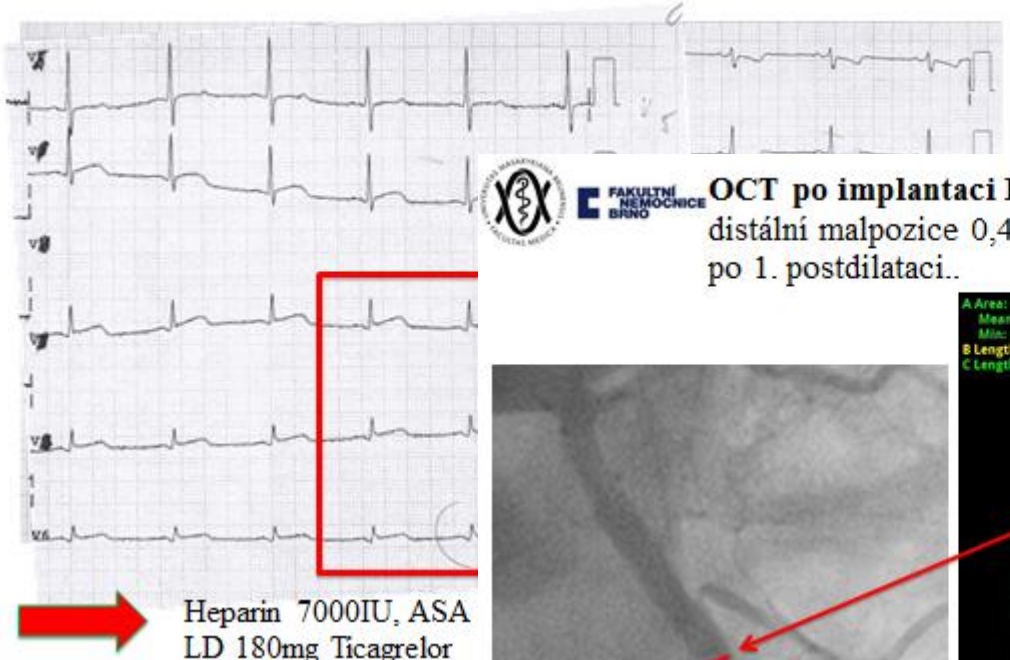
2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Kazuistika

Intervenční kardiologie
IKK FN Brno

M, 61 let, BMI 28kg/m2, kuřák 15cig/den

EKG: **Zadní STEMI**



Heparin 7000IU, ASA
LD 180mg Ticagrelor

OCT po implantaci DES 2. generace vel. 3,0/18
distální malpozice 0,41mm délky 1mm (10 frames)
po 1. postdilataci..

Optimální výsledek
po 2. postdilataci NC balonkem 3,5/15 na 16atm