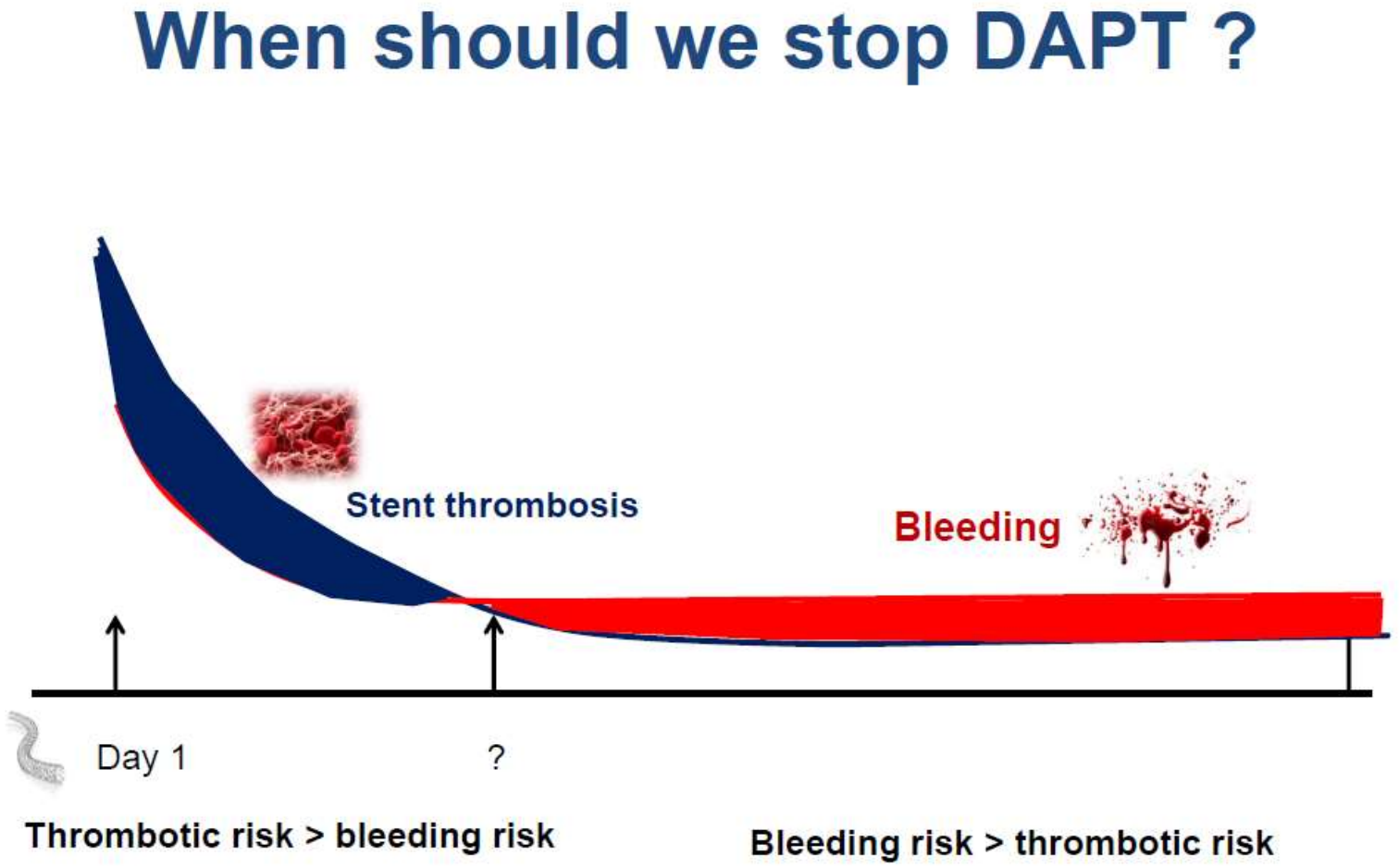
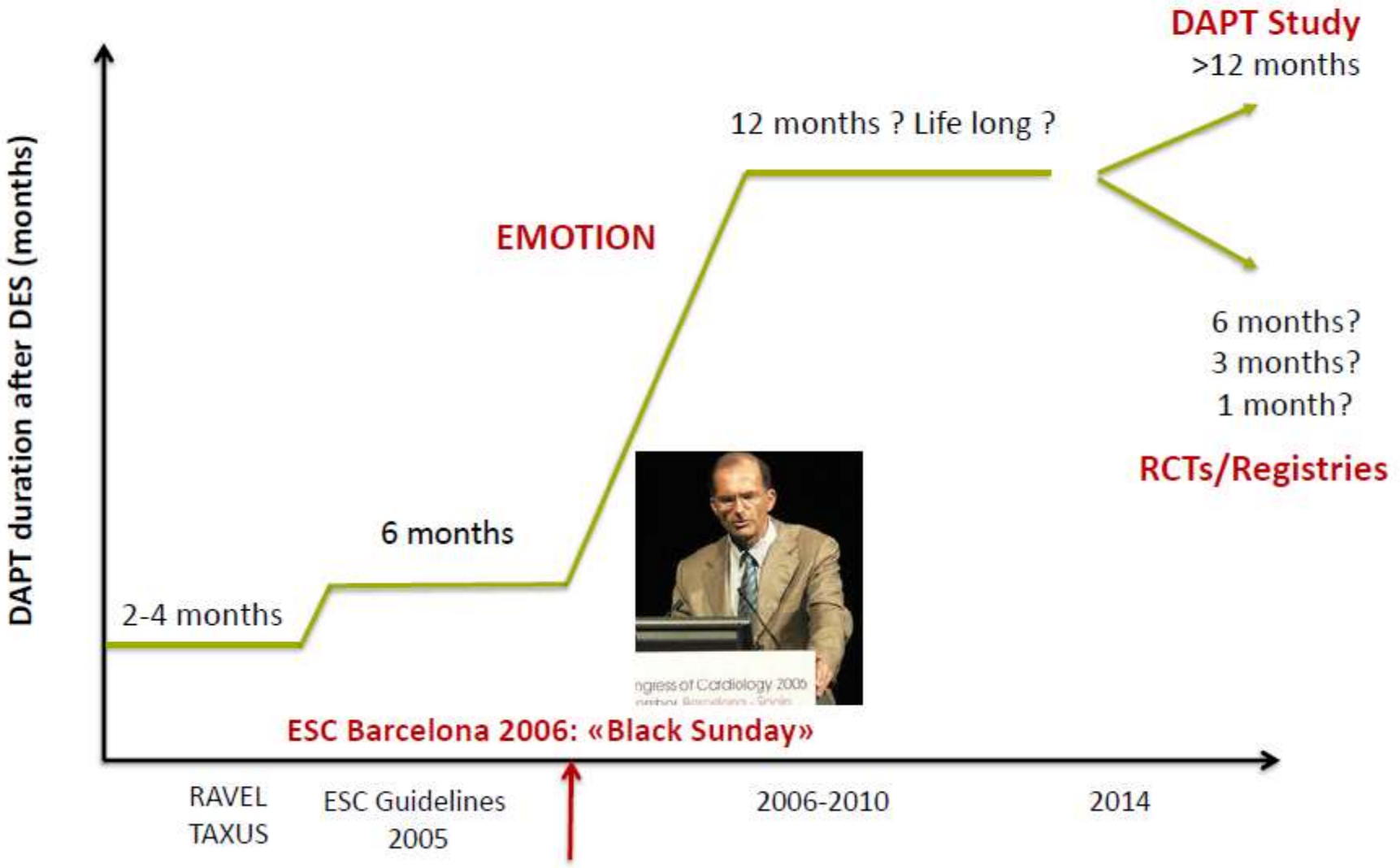
Duální antiagregace u lékových stentů kratší než 3 měsíce? PROTI (kritický pohled na dostupná data)

Petr Neugebauer
Kardiocentrum Nitra
XXVIII. Workshop ČAIK

Kdy je bezpečné ukončit léčbu?



DAPT duration after DES: Optimal duration remains unclear?



Zdroje doporučení a informací

- 1. Guidelines
- 2. Randomizované klinické studie (RCT)
- 3. Metaanalýzy
- 4. Registry
- 5. Informace a doporučení od výrobce (CE approval, SPC - ***s****ummary of* ***p****roduct* ***c****haracteristics*)

Guidelines ESC pro revaskularizaci - 2014

Recommendations for PCI	Class[a]	Level[b]	Ref[c]
Pretreatment with antiplatelet therapy			
Treatment with 600 mg clopidogrel is recommended in elective PCI patients once anatomy is known and decision to proceed with PCI preferably 2 hours or more before the procedure.	I	A	789–792
Pretreatment with clopidogrel may be considered in patients with high probability for significant CAD.	IIb	C	
In patients on a maintenance dose of 75 mg clopidogrel, a new loading dose of 600 mg or more may be considered once the indication for PCI is confirmed.	IIb	C	
Antiplatelet therapy during PCI			
ASA is indicated before elective stenting.	I	B	776,793,794
ASA oral loading dose of 150–300 mg (or 80-150 mg i.v.) is recommended if not pre-treated.	I	C	
Clopidogrel (600 mg loading dose or more, 75 mg daily maintenance dose) is recommended for elective stenting.	I	A	795–798
GP IIb/IIIa antagonists should be considered only for bail-out.	IIa	C	
Antiplatelet therapy after stenting			
DAPT is indicated for at least 1 month after BMS implantation.	I	A	791,799–801
DAPT is indicated for 6 months after DES implantation.	I	B	799,802,803
Shorter DAPT duration (<6 months) may be considered after DES implantation in patients at high bleeding risk.	IIb	A	804,805
Life-long single antiplatelet therapy, usually ASA, is recommended.	I	A	776,794
Instruction of patients about the importance of complying with antiplatelet therapy is recommended.	I	C	-
DAPT may be used for more than 6 months in patients at high ischaemic risk and low bleeding risk.	IIb	C	-

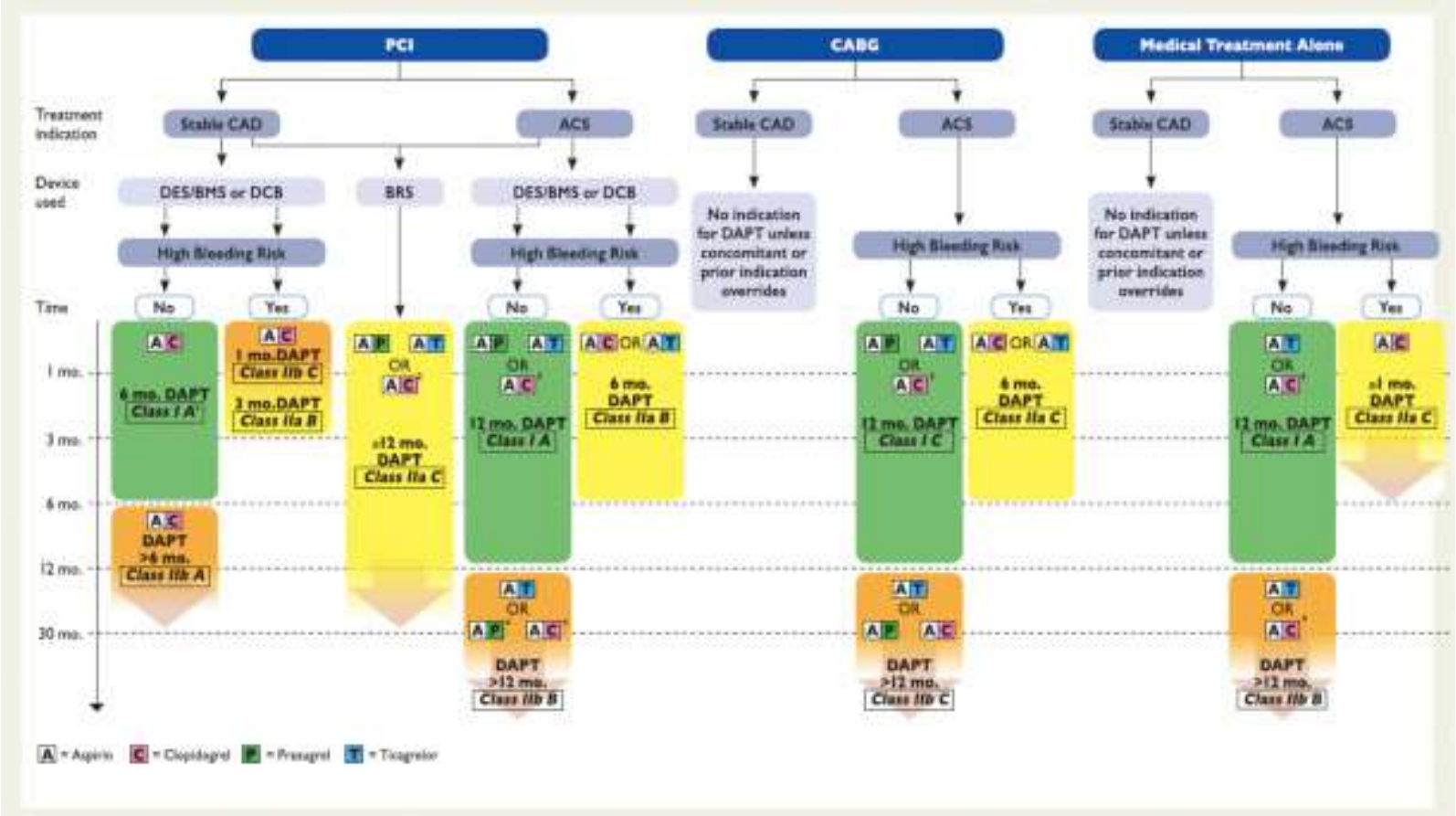
Windecker et al. Eur Heart J 2014

Guidelines AHA/ACC pro revaskularizaci 2016

COR	LOE	RECOMMENDATIONS
I	A	In patients with SIHD treated with DAPT after BMS implantation, $P2Y_{12}$ inhibitor therapy (clopidogrel) should be given for a minimum of 1 month (94,95).
I	B-R SR	In patients with SIHD treated with DAPT after DES implantation, $P2Y_{12}$ inhibitor therapy (clopidogrel) should be given for at least 6 months (17,18,21,30,96,97).
I	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended (56-60,75-78).
IIb	A SR	In patients with SIHD treated with DAPT after BMS or DES implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT with clopidogrel for longer than 1 month in patients treated with BMS or longer than 6 months in patients treated with DES may be reasonable (16,22,24-26,30,50).
IIb	C-LD	In patients with SIHD treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after 3 months may be reasonable (19,20,34,36,37).

Levine et al. J Am Coll Card 2016

2017 ESC focused update on dual antiplatelet therapy



RCT

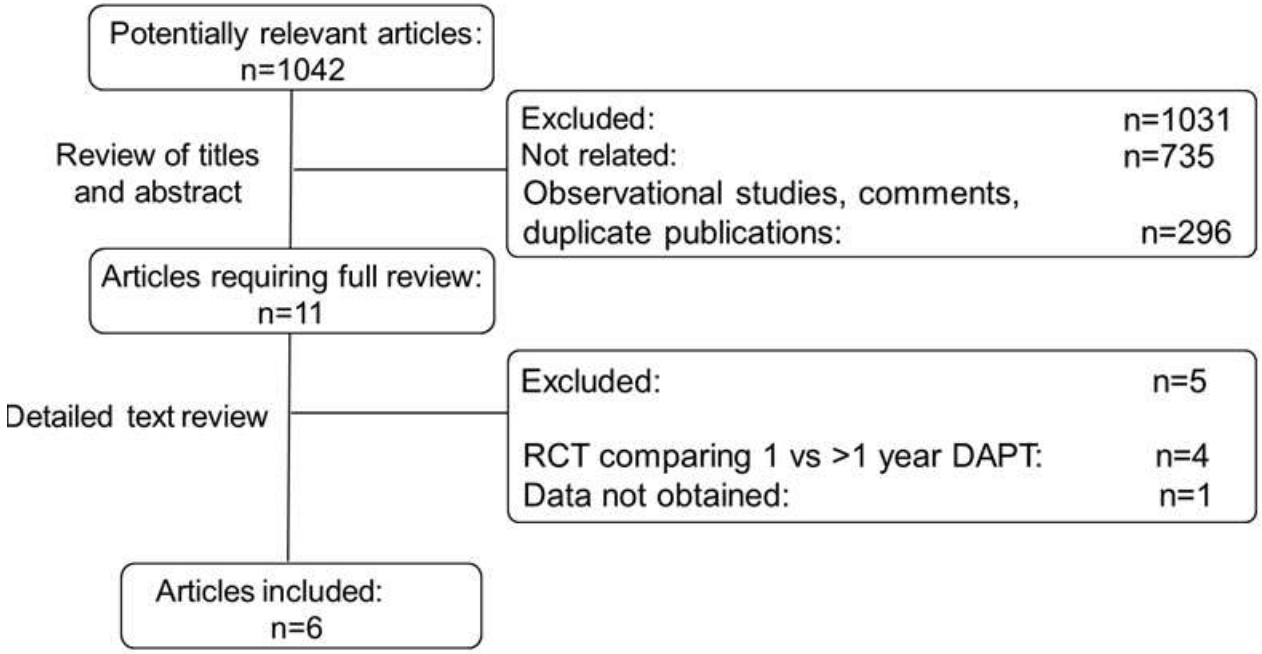
- Odlišná délka DAPT – 3 vs.12, 6 vs.12, 6 vs. 24 m.
- Odlišné populace a typy DES . 1 DES vs. různé DES
- Odlišné endpointy v různých studiích

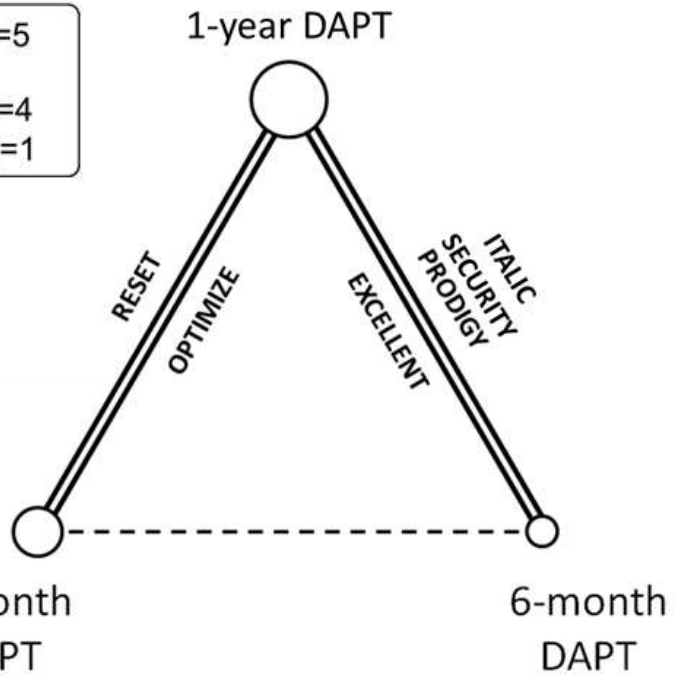
Table 1. Major adverse cardiovascular events and stent thrombosis in clinical trials evaluating short duration of dual antiplatelet therapy (DAPT).

Trial	Short DAPT (months)	Long DAPT (months)	MACCE short vs. long	Hazard ratio/risk difference (%) (95% CI)	*p*-value	Stent thrombosis	Hazard ratio/ risk difference (%) (95% CI)	*p*-value
PRODIGY [17]	6	24	10.0% vs. 10.1%*	0.98 (0.74 to 1.29)	0.91	1.3% vs. 1.5% [Δ]	1.15 (0.55 to 2.41)	0.70
RESET [22]	3	12	4.7% vs. 4.7% [‡]	0.0 (–2.5 to 2.5)	0.84	0.2% vs. 0.3% [§]	–0.1% (-0.5 to 0.3)	0.65
EXCELLENT [23]	6	12	8.0% vs. 8.5% [◊]	0.94 (0.65 to 1.35)	0.72	0.6% vs. 0.1%	6.02 (0.72 to 49.96)	0.10
OPTIMIZE [25]	3	12	8.3% vs. 7.4% [¶]	1.12 (0.87 to 1.45)	0.36	0.8% vs. 0.8% [§]	1.08 (0.49 to 2.36)	0.86
SECURITY [26]	6	12	4.5% vs. 3.7%**	1.22 (–2.4 to 1.7)	0.47	0.3% vs. 0.4% [§]	0.75 (–0.7 to 0.4)	0.70
ISAR-SAFE [27]	6	12	1.5% vs 1.6% [ΔΔ]	0.91 (0.55 to 1.50)	<0.001 [‡‡]	0.3% vs. 0.2%	1.66 (0.4 to 6.96)	0.49
ITALIC [28]	6	24	1.6% vs 1.5% [ΔΔ]	1.07 (0.52 to 2.22)	0.85	0.3% vs. 0%	N/A	0.49

* Death from any cause, myocardial infarction (MI) or cerebrovascular accident at two years. [Δ] Definite stent thrombosis (ST) at two years. [‡] Death from cardiovascular cause, MI, stent thrombosis, ischaemia-driven target vessel revascularisation, or bleeding at one year post procedure. [§] Definite or probable stent thrombosis at one year. [◊] Death, myocardial infarction, stroke, or any revascularisation. [¶] Death from all causes, MI, urgent coronary artery bypass graft surgery, or target lesion revascularisation at one year. ** Cardiac death, MI, stroke, definite or probable stent thrombosis or BARC type 3 or 5 bleeding. [ΔΔ] Death, MI, stroke, stent thrombosis, major bleeding. [‡‡] *p* for non-inferiority.

Metaanalýza 4/2017 – Palmerini et al,, 11 473 pts. European Heart Journal (2017) 38, 1034–1043





RCT – klinická relevance

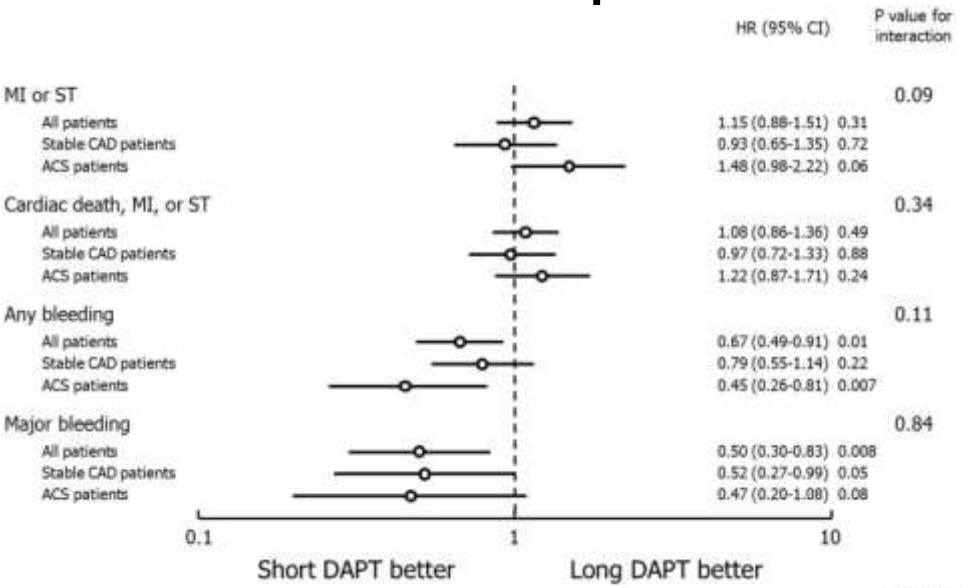
Study	Randomization	Major inclusion criteria	Major exclusion criteria	Concealment of allocation treatment	Intention-to-treat analysis	Blinded adjudication of events
EXCELLENT	Index procedure	Clinical or instrumental evidence of myocardial ischemia with at least 1 lesion in native coronary vessel with vessel diameter 2.25 mm to 4.25 mm.	MI within 72 hours, LVEF<25%, cardiogenic shock, serum Creatinine>265.2 μmol/L, CTO, left main disease, true bifurcation requiring 2 stents.	Yes	Yes	Yes
ITALICS	Index procedure	Stable/unstable angina, treated with at least 1 everolimus-eluting stent.	In-stent restenosis, left main disease, SVG, STEMI within 48 h, NSTEMI within 6 months; LVEF < 30%; CKD; BMS implanted in the 3 months before the target procedure.	Yes	Yes	Yes
OPTIMIZE	Index procedure	Stable angina or low risk unstable angina with at least 1 lesion in native coronary vessel ≥2.5 mm in diameter.	STEMI, scheduled elective surgery within 12 months, in stent restenosis of DES, BMS in non target vessel in the last 6 months.	Yes	Yes	Yes
PRODIGY	30 days after PCI	Stable angina or acute coronary syndrome including STEMI with at least 1 lesion in native coronary vessel ≥2.25 mm in diameter.	Planned surgery within 24 months, history of bleeding, concomitant need of oral anticoagulant therapy.	Yes	Yes	Yes
RESET	Index procedure	Stable angina or acute MI with more than 50% diameter stenosis in a coronary artery.	Cardiogenic shock, STEMI within 48 hours, LVEF<40%, previous stent thrombosis, CTO, restenotic lesion.	Yes	Yes	Yes
SECURITY	Index procedure	All comers.	STEMI, left main disease.	Yes	Yes	Yes

RCT – výsledky a endpointy

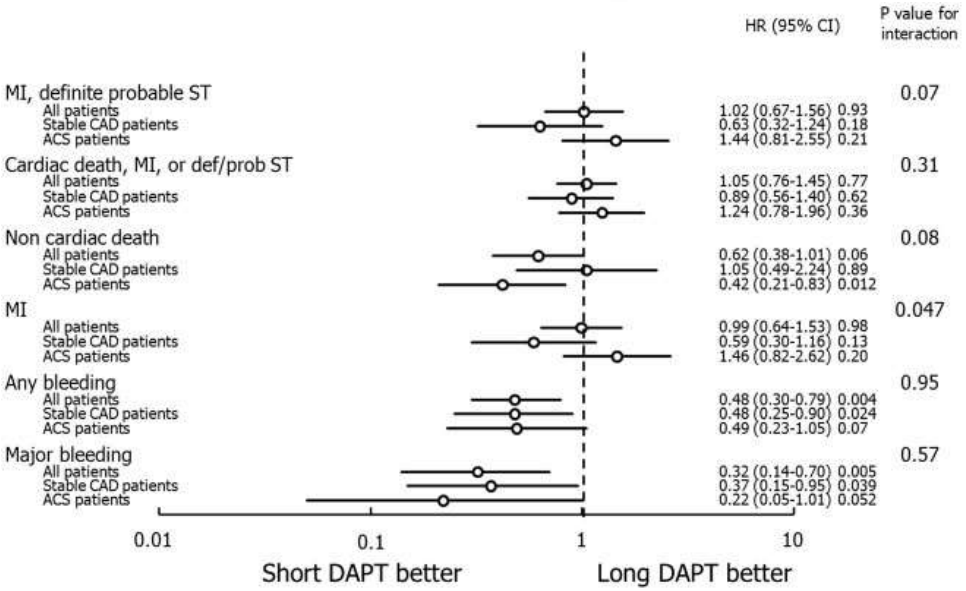
Study	N patients	Primary endpoint	Design	Follow-up	DAPT duration (months)	Results of the primary endpoint
EXCELLENT	6 months (n=722) 12 months (n=721)	Cardiac death/MI/ ischemia-driven TVR	Non-inferiority	1 year	6 versus 12	Non-inferiority demonstrated
ITALIC	6 months (n=953) 24 months (n=941)	Death/MI/ TVR/Stroke/Major bleeding	Non-inferiority	36 months	6 versus 24	Non-inferiority demonstrated
OPTIMIZE	3 months (n=1,563) 12 months (n=1,556)	Death/MI/CVA/major bleeding	Non-inferiority	1 year	3 versus 12	Non-inferiority demonstrated
PRODIGY	6 months (n=751) 12 months (n=750)	Death/MI/CVA	Superiority	2 years	6 versus 24	Superiority of 24-month DAPT not demonstrated
RESET	3 months (n=1,059) 12 months (n=1,058)	Cardiac death/MI/ST/TVR/ major bleeding	Non-inferiority	1 year	3 versus 12	Non-inferiority demonstrated
SECURITY	6 months (n=682) 12 months (n=717)	Cardiac death/MI/Stroke/ST/Major Bleeding	Non-inferiority	1 year	6 versus 12	Non-inferiority demonstrated

Metaanalýza 4/2017 – Palmerini et al, EHJ, 11 473 pts.

intention-to-treat:



per protocol:



In patients with ACS, 3-month DAPT was associated with increased ischaemic risk, whereas 3-month DAPT appeared safe in stable CAD. Prolonged DAPT increases bleeding regarding of clinical presentation.

Metanalýza Xiang – 15870 pts

"Short-term DAPT is associated with lower bleeding risk compared with long-term DAPT. Number of ST and MI was higher with short-term DAPT without reaching statistical significance."

Table 1. Characteristics of included randomized studies

	Gwon et al., 2012 (EXCELLENT) (22)		Valgimigli et al., 2012 (PRODIGY) (24)		Kim et al., 2012 (RESET) (23)		Feres et al., 2013 (OPTIMIZE) (25)		Giland et al., 2015 (ITALIC) (9)		Colombo et al., 2014 (SECURITY) (26)		Schulz-Schüpke et al., 2015 (ISAR-SAFE) (8)	
	S-DAPT	L-DAPT	S-DAPT	L-DAPT	S-DAPT	L-DAPT	S-DAPT	L-DAPT	S-DAPT	L-DAPT	S-DAPT	L-DAPT	S-DAPT	L-DAPT
Duration, months	6	12	6	24	3	12	3	12	6	12	6	12	6	12
Patients, n	722	721	983	987	1059	1058	1563	1556	912	910	682	717	1997	2003
Age, years mean*	63.0±9.6	62.4±10.4	67.9±11	67.8±11	62.4±9.4	62.4±9.8	61.3±10.4	61.9±10.6	61.7±10.9	61.5±11.1	64.9±10.2	65.5±10.1	67.2 (59.3–73.3)	67.2 (59.1–73.7)
Male gender	65%	64%	76%	77%	64%	63%	64%	63%	81%	79%	78%	77%	81%	81%
Diabetes	38%	39%	24%	25%	30%	29%	35%	35%	36%	38%	30%	31%	25%	24%
Hypertension	73%	74%	70%	73%	62%	61%	86%	88%	65%	65%	75%	71%	90%	92%
Dyslipidemia	75%	76%	53%	56%	58%	60%	63%	64%	67%	67%	65%	61%	88%	87%
Stent type														
BMS	0%	0%	25%	25%	0%	0%	0%	0%	0%	0%	0%	0%	0.4%	0.3%
1st-gen. DES	25%	25%	25%	25%	0%	28%	0%	0%	0%	0%	0%	0%	11%	10%
2nd-gen. DES	75%	75%	50%	50%	100%	72%	100%	100%	100%	100%	100%	100%	88%	89%
Follow-up (months)	12	12	24	24	12	12	12	12	36	36	24	24	15	15
MB criteria	TIMI	TIMI	TIMI	TIMI	TIMI	TIMI	REPLACE-2, GUSTO	REPLACE-2, GUSTO	TIMI	TIMI	BARC	BARC	TIMI	TIMI
Primary Endpoint	Composite of cardiac death, MI, or TVR during 1-year period after randomization.		Incidence of death from any cause, nonfatal MI, or cerebrovascular accident at 2 years		Composite of cardiovascular death, MI, ST, TVR, or bleeding at 1 year		Composite of death from any cause MI, stroke, or MB at 1 year		Composite of death, MI, emergency TVR, stroke, or MB within 12 months after stenting		Composite of cardiac death, MI, stroke, ST, or type 3 or 5 bleeding at 12 months		Composite of death MI, ST, stroke, or MB at 9 months after randomization	

*Age data of ISAR-SAFE are shown as median (interquartile range). BARC - Bleeding Academic Research Consortium; BMS - bare metal stent; DAPT - dual antiplatelet therapy; DES - drug-eluting stent; GUSTO - Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; L-DAPT - long-term (>6 months) duration of DAPT after drug-eluting stent; MB - major bleeding; MI - myocardial infarction; PCI - percutaneous coronary intervention; REPLACE-2 - Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events; S-DAPT - short-term (≤6 months) duration of DAPT after drug-eluting stent; ST - stent thrombosis; TIMI - thrombolysis in myocardial infarction; TVR - target vessel revascularization

Lin Xiang et al.Anatol J Cardiol 2017; 17: 168-75

DCS BioFreedom – LEADERS FREE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk

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ABSTRACT

BACKGROUND

Patients at high risk for bleeding who undergo percutaneous coronary intervention (PCI) often receive bare-metal stents followed by 1 month of dual antiplatelet therapy. We studied a polymer-free and carrier-free drug-coated stent that transfers umirolimus (also known as biolimus A9), a highly lipophilic sirolimus analogue, into the vessel wall over a period of 1 month.

METHODS

In a randomized, double-blind trial, we compared the drug-coated stent with a very similar bare-metal stent in patients with a high risk of bleeding who underwent PCI. All patients received 1 month of dual antiplatelet therapy. The primary safety end point, tested for both noninferiority and superiority, was a composite of cardiac death, myocardial infarction, or stent thrombosis. The primary efficacy end point was clinically driven target-lesion revascularization.

RESULTS

We enrolled 2466 patients. At 390 days, the primary safety end point had occurred in 112 patients (9.4%) in the drug-coated–stent group and in 154 patients (12.9%) in the bare-metal–stent group (risk difference, −3.6 percentage points; 95% confidence interval [CI], −6.1 to −1.0; hazard ratio, 0.71; 95% CI, 0.56 to 0.91; P<0.001 for noninferiority and P=0.005 for superiority). During the same time period, clinically driven target-lesion revascularization was needed in 59 patients (5.1%) in the drug-coated–stent group and in 113 patients (9.8%) in the bare-metal–stent group (risk difference, −4.8 percentage points; 95% CI, −6.9 to −2.6; hazard ratio, 0.50; 95% CI, 0.37 to 0.69; P<0.001).

CONCLUSIONS

Among patients at high risk for bleeding who underwent PCI, a polymer-free umirolimus-coated stent was superior to a bare-metal stent with respect to the primary safety and efficacy end points when used with a 1-month course of dual antiplatelet therapy. (Funded by Biosensors Europe; LEADERS FREE ClinicalTrials.gov number, NCT01623180.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Urban at Hôpital de la Tour, 1217 Geneva, Switzerland, or at philip.urban@latour.ch.

*A complete list of investigators in the Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk (LEADERS FREE) trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on October 14, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1503943

- DES Biofreedom vs. BMS Gazelle
- Prokázána lepší účinnost i bezpečnost DES
- POZOR! – studie nesrovnávala dvě odlišné délky DAPT u DES, ale 1měsíční DAPT u obou stentů

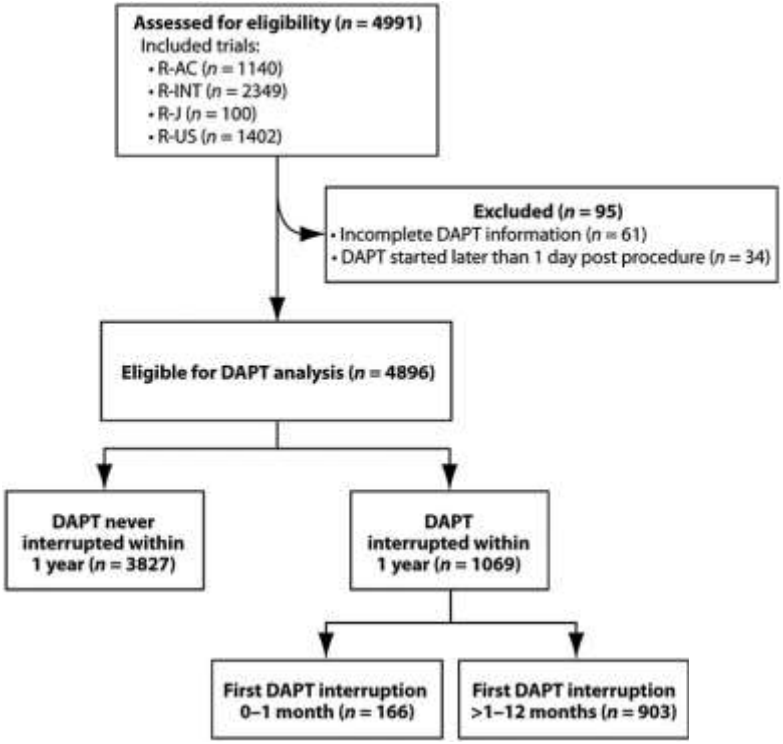
Registry

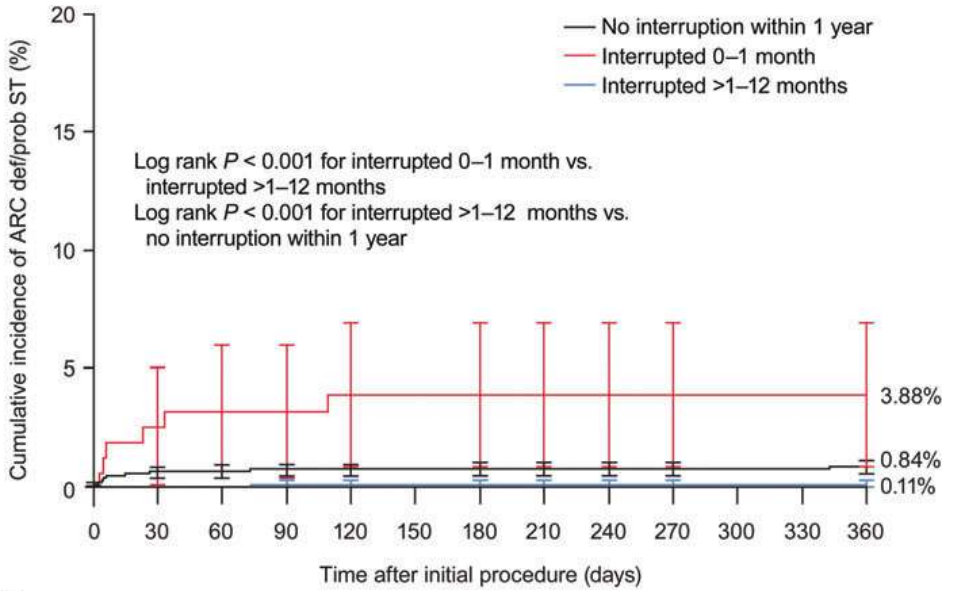
- SCAAR registry (Synergy, N = 7886; BioMatrix, N = 1,953; Orsiro, N = 4,946; Promus Element Plus, N= 2,543; Promus Premier, N= 20,414; Xience Xpedition, N= 7,971, Resolute/Resolute Integrity, N = 19,021; Ultimaster, N = 1,156; Resolute Onyx, N = 6,425)
- Resolute Global Clinical Trial Program – N = 7618
- Promus Element – P-Plus-PAS US registry – (N = 2683)
- XienceV/Promus in Japan – N = 2010
- Cre8 – Astute registr – N = 1218
- BioFreedom – RUDI Free Registr – N = 1103
- e-Ultimaster – N = 20 000
- a mnoho dalších..

Výhody a nevýhody registrů

- Poskytují reálná data z neselektovaných populací, a to i v off-label indikacích.
- Byla potvrzena dlouhodobá bezpečnost i účinnost u DES 2. a 3. generace.
- Většina poskytuje žádné nebo jen minimální informace o zkrácené DAPT.
- Pokud data jsou, jde o retrospektivní analýzu.

Resolute clinical programme

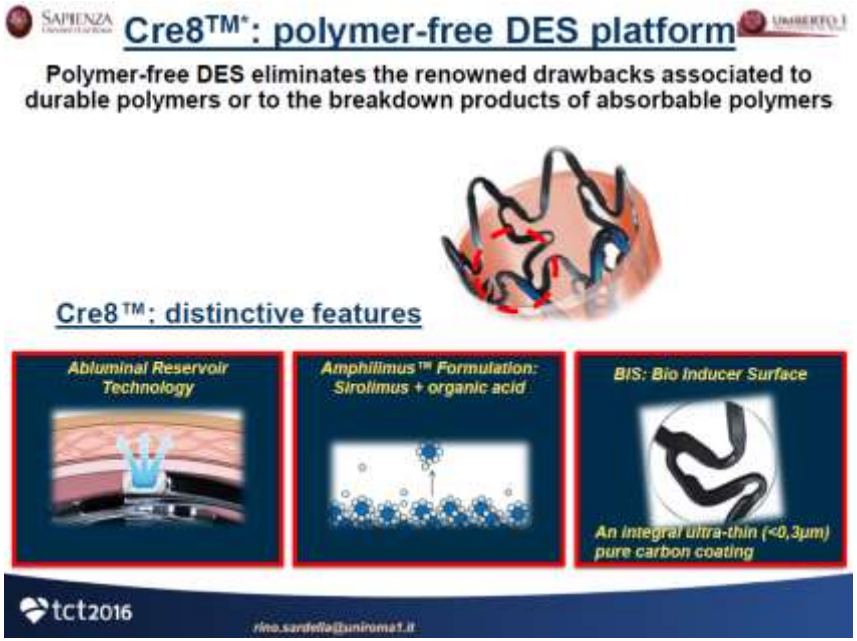




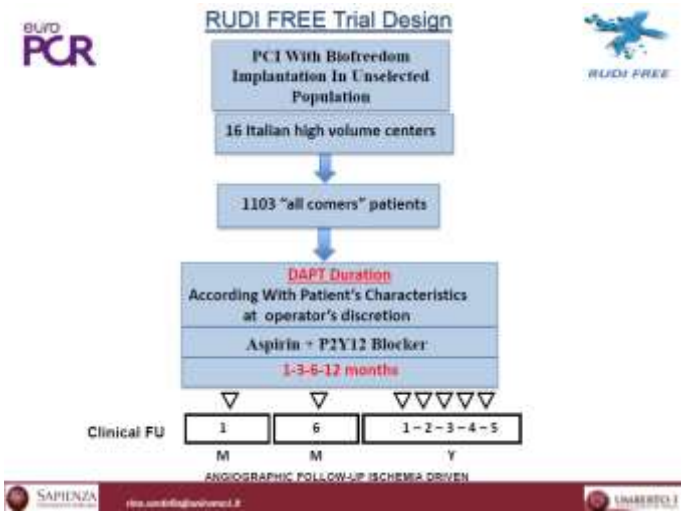
Number at risk											
No interruption within 1 year	3827	3822	3795	3791	3788	3787	3784	3783	3780		3780
Interrupted 0–1 month	166	164	149	147	144	142	141	139	138		137
Interrupted >1–12 months	903	903	902	892	883	877	855	844	841		837

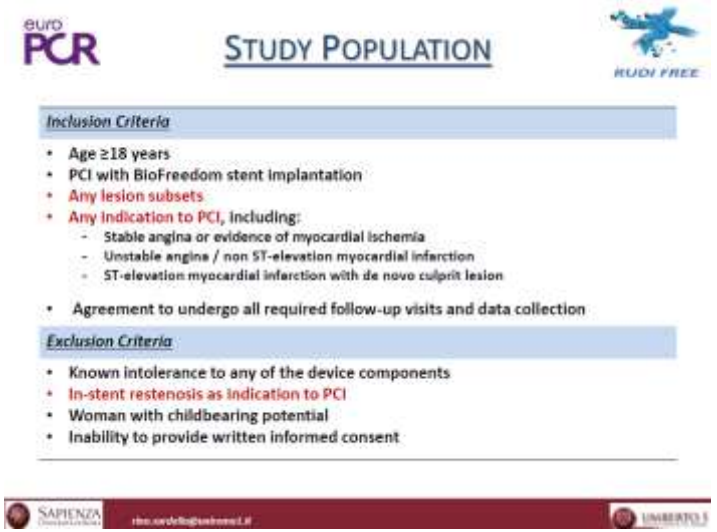
DCS Cre 8 - ASTUTE registr

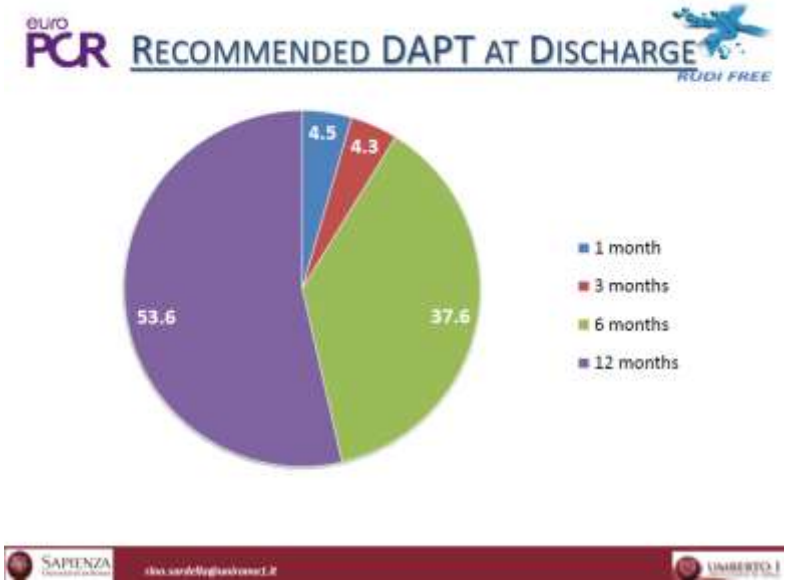
- 1218 pacientů - 106 pac. ≤3-měsíční DAPT (83 ± 19 dnů; S-DAPT group) vs. 1102 pac. (90.6%) s ≥6-měsíční DAPT (342 ± 6 dnů; L-DAPT group)
- **Results:** between S-DAPT and L-DAPT groups **no significant differences were observed in TVF** at 1-year (5.7% vs 5.1%); **1-year BARC major bleeding rate was higher in S-DAPT group** (3.4% vs 0.2%, *p* = 0.007) with all bleeding events occurred within 3 months. The landmark analysis (started at 90 days, ended at 1 year) showed no differences in BARC major bleedings between groups (0% vs. 0.3%).



RUDI FREE - BioFreedom







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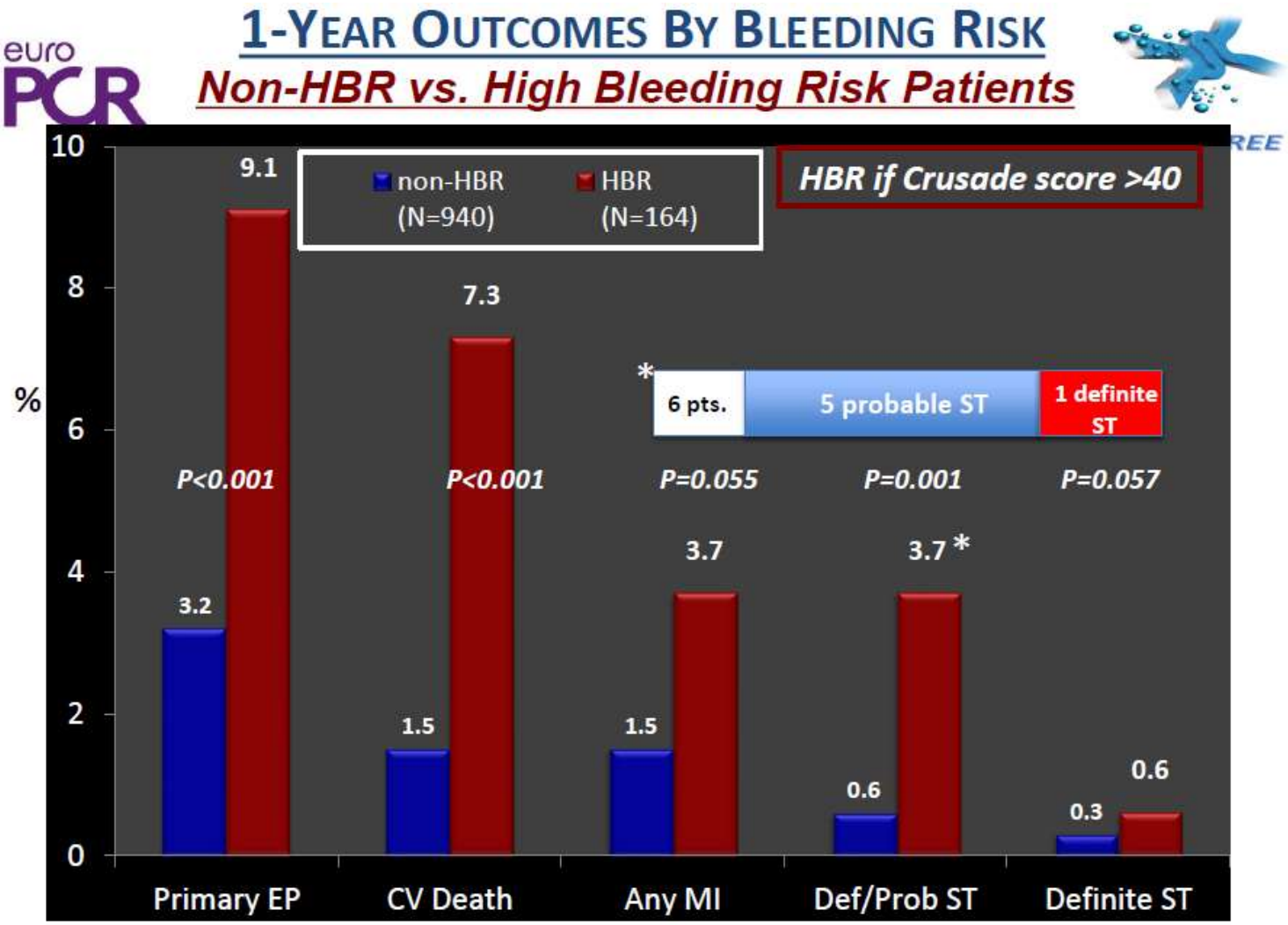
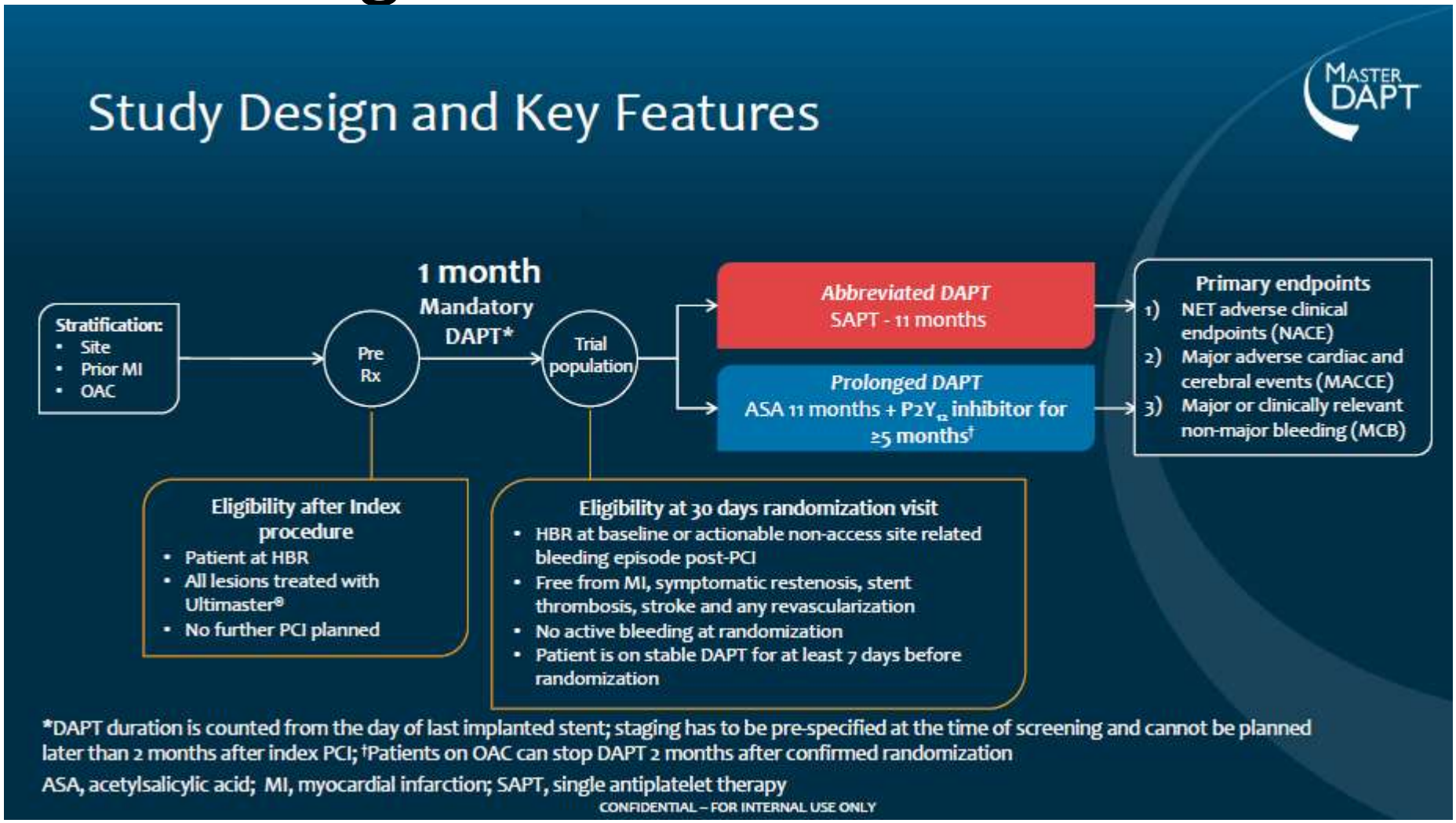
RUDI FREE - výsledky



Běžící nebo nedávno ukončené studie na zkrácenou dobu DAPT

- MASTER DAPT – Ultimaster 1 vs. 11m DAPT
- RECRE8 – Cre8 stent vs. Resolute
- ***SENIOR*** – DES Synergy vs. BMS (Omega+Rebel)
- ***REDUCE*** – Combo stent 3 vs. 12m DAPT
- ***SMART-DATE*** – AKS, 6 vs. 12m DAPT – ^riziko IM
- ***NIPPON*** – Nobori 6 vs. 18m DAPT
- ***DAPT-STEMI*** – Resolute Integrity 6 vs. 12m DAPT

Design studie MASTER DAPT



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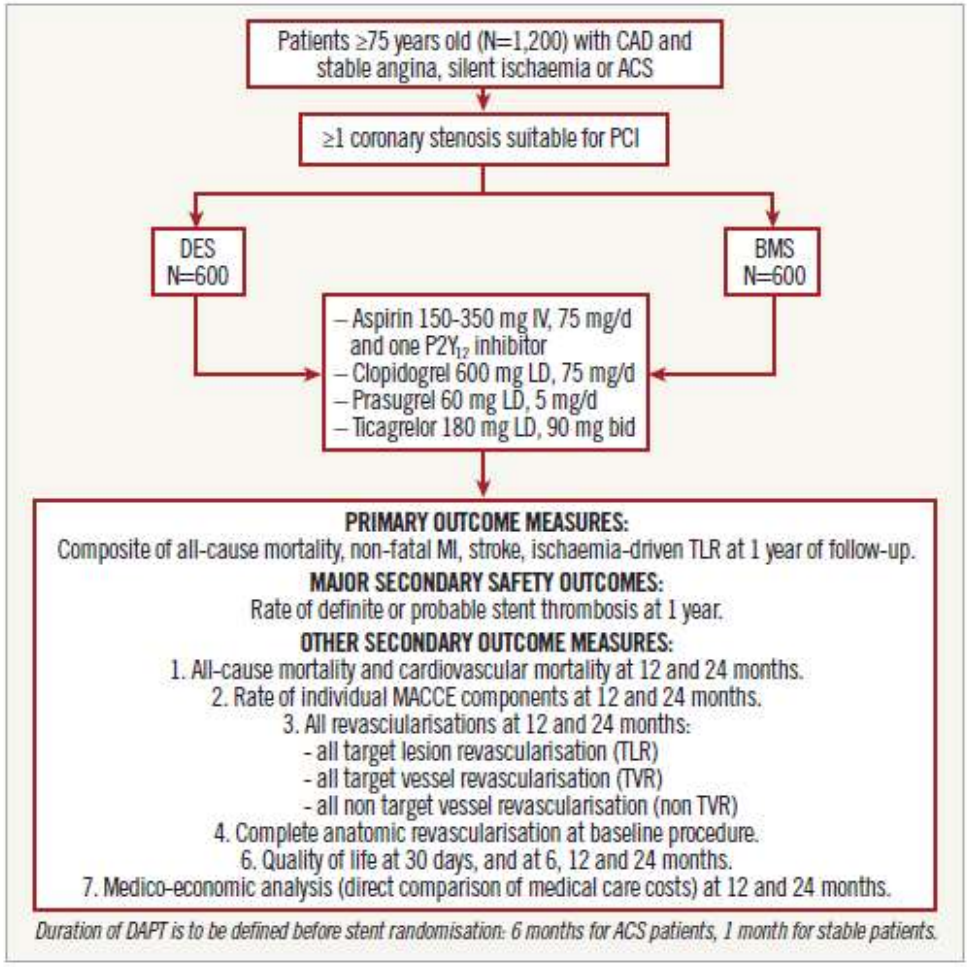
Design studie Senior

CLINICAL RESEARCH

The SYNERGY II Everolimus elutiNg stent In patients Older than 75 years undergoing coronary Revascularisation associated with a short dual antiplatelet therapy (SENIOR) trial: rationale and design of a large-scale randomised multicentre study

Olivier Varenne[1,2*], MD, PhD; Thouan Cuisset[3], MD, PhD; Aurès Chaib[1,2], MD; Marie-Claude Morice[4], MD; Mamel Sabaté[5], MD; Tun-Hin Koh[6], MD; Isabelle Durand-Zaleski[7], MD, PhD; Olivier Hanon[2,8], MD, PhD; Kris Bogaerts[9,10], PhD; Peter Sinnaeve[11], MD, PhD



Design studie ReCre8

ReCre8*: Study design

Patients with ischemic myocardial symptoms
All-comer study with the following associated DAPT:

- **1 month DAPT in elective PCI**
- **12 months DAPT in ACS**

1530 patients
2 European Sites
Randomization 1:1

Cre8™

Resolute

PI: P. Stella – The Netherlands

Primary Endpoint: 12 months NACE

Clinical FU

*** Enrollment ongoing**

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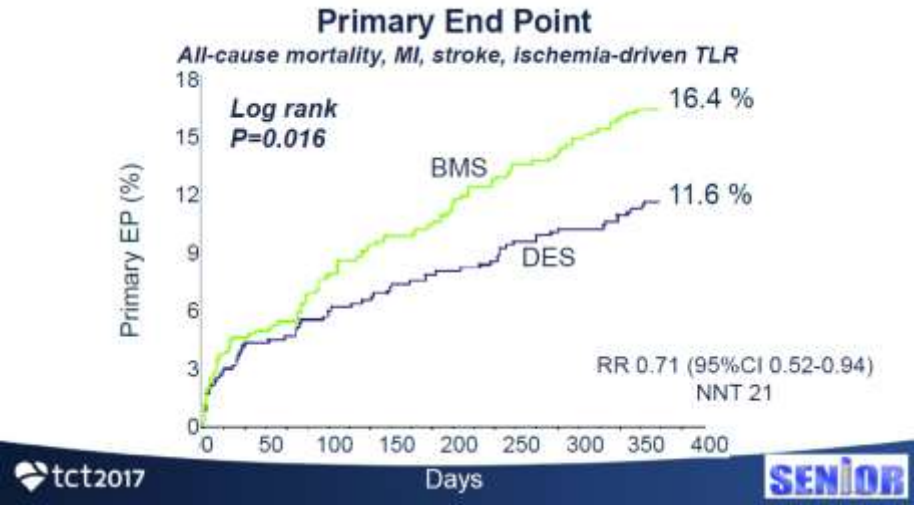
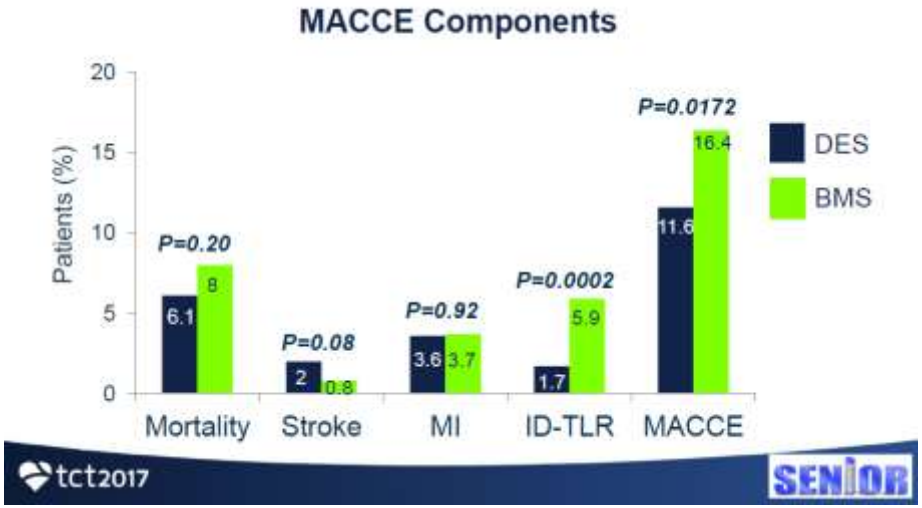
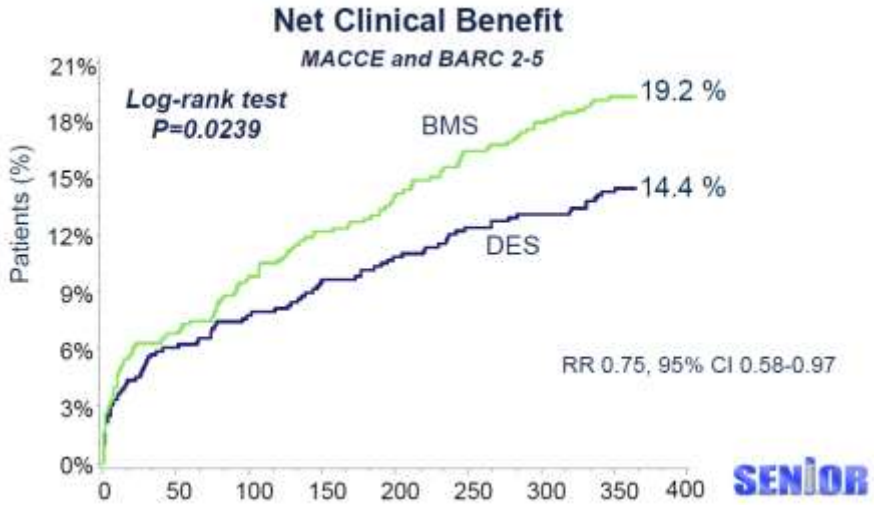
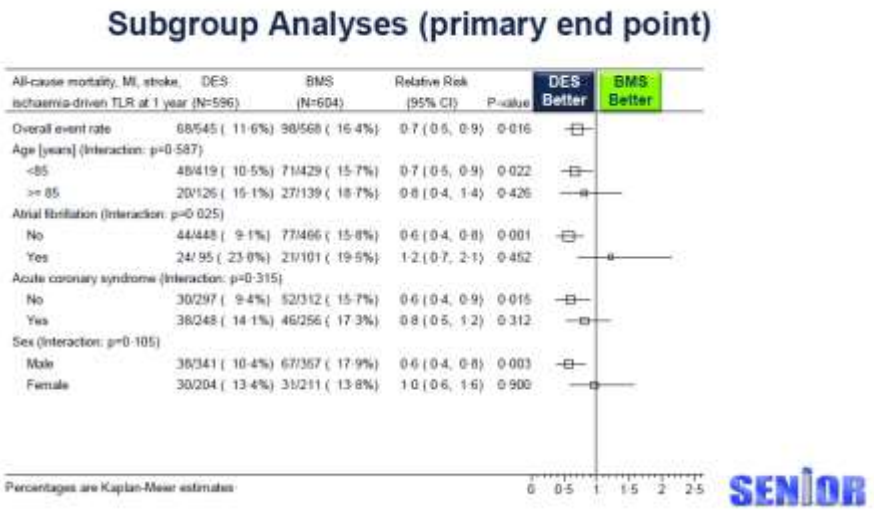
SENIOR trial - výsledky









Firmy – výrobci DES

- EuroPCR 2017 – dle sdělení zástupců firem jsou produkty bezpečné a lze indikovat i DAPT kratší než 6 měsíců (3 měsíce)
- SPC – u žádného z dostupných DES není ani v roce 2017 uvedena zkrácená délka duální antiagregace – odkaz na guidelines, klinická data nebo „routine clinical practice“
- 2016 – CE (Conformité Européenne) mark body udělila schválení pro 3měsíční duální antiagregaci u firem Abbott, Boston Scientific a Medtronic
- Zdrojová data???

Euro Intervention 2016 Apr 20;11(13):1449-50

EuroIntervention
Official journal of EuroPCR and the European Association of Percutaneous Cardiovascular Interventions (EAPCI)
IMPACT FACTOR 3.769

EDITORIAL

DAPT: a historical accident in the pharmacological treatment of post-percutaneous coronary intervention

Pannipa Suwannasom[1], MD; Patrick W. Serruys[2], MD, PhD, FESC

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REFERENCES

the exception of the Mauri et al report[15], we think it is fair to say that we should exert caution when interpreting the studies in general due to some shortcomings in the reports such as underpowering to detect differences in hard endpoints, the slow enrolment, patients lost to follow-up and underreporting.

What is puzzling is that most of the stent manufacturers such as Abbott, Boston Scientific and Medtronic, have obtained an endorsement, a kind of labelling, from the CE mark body for three-month DAPT usage. Yet, it remains unclear for the average physician on which data the CE body took this decision. The EAPCI chairman tried to obtain some information to justify the decision on three months of DAPT, but at the present time there is no transparency in the data used by the CE body in the EU, something which is in stark contrast with what occurs in the USA. It is remarkable that the CE body, a device approval entity assessing not only medical devices but also household appliances such as fridges, hairdryers and curling tongs, is giving a recommendation for a pharmaceutical therapy.

What is the future?

Today, we still see a lot of conventional DES usage picking up this pharmacological debate, generated, as we said, by a historical accident, to promote or create additional trials with various duration times (three versus six months, six months versus 12 months, etc.). Some of us believe that the LEADERS FREE study[16] was, from that point of view, a landmark trial, since it addressed an unmet need in the use of DES in patients at high risk of bleeding, and it now becomes an ethical must to test and provide

follow-up. *Circulation*. 2001;104:2007-11.

9. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnàr F, Falotico R; RAVEL Study Group. Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med*. 2002;346:1773-80.

10. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE; SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med*. 2003;349:1315-23.

Doporučení FDA – TCT 2016

Parting Thoughts

- Studies of shorter DAPT duration must be well-designed and executed to protect patients and support the studied DAPT duration in labeling.
- Pre-Submission discussions with FDA highly recommended to reach consensus on an acceptable study design to establish the safety of shorter DAPT duration in DES patients.

Závěr

- Drtivá většina DES 2. a 3. generace je dlouhodobě účinná a bezpečná pro pacienta.
- V roce 2018 **stále nemáme dostatečná data** k indikaci DAPT u implantace DES na dobu kratší 3 měsíce.
- Výjimky? – BioFreedom? Synergy? - LEADERS FREE ani SENIOR nesrovnávaly různé délky DAPT u identické populace.
- Studie + registry – často velmi heterogenní soubory stran délky terapie, typu stentu a klinické prezentace pacienta
- CAVE **metodika!**
- Je třeba zachovat zdravý rozum, kritické myšlení a nepodléhat tlaku výrobců.
- Není důvod k pesimismu nebo nihilismu – běží další studie.

Děkuji za pozornost!

LEADERS FREE – pozdní trombóza stentu

The NEW ENGLAND JOURNAL of MEDICINE

Table 2. Primary and Secondary End Points.*

End Point	Drug-Coated Stent (N=1221)	Bare-Metal Stent (N=1211)	Hazard Ratio (95% CI)	P Value
	no. of events (% of patients)			
Primary safety end point: cardiac death, myocardial infarction, or stent thrombosis	112 (9.4)	154 (12.9)	0.71 (0.56–0.91)	0.005†
Primary efficacy end point: clinically driven TLR	59 (5.1)	113 (9.8)	0.50 (0.37–0.69)	<0.001
Death				
From any cause	97 (8.0)	108 (9.0)	0.89 (0.67–1.17)	0.39
From cardiac causes	50 (4.2)	63 (5.3)	0.78 (0.54–1.14)	0.20
Myocardial infarction‡				
Any	72 (6.1)	104 (8.9)	0.68 (0.50–0.91)	0.01
Q-wave infarction	6 (0.5)	7 (0.6)	0.85 (0.29–2.53)	0.77
Non–Q-wave infarction	57 (4.8)	80 (6.9)	0.70 (0.50–0.98)	0.04
Undetermined type	10 (0.8)	25 (2.1)	0.39 (0.19–0.82)	0.01
Stent thrombosis‡				
Definite or probable	24 (2.0)	26 (2.2)	0.91 (0.53–1.59)	0.75
Definite	16 (1.3)	17 (1.4)	0.93 (0.47–1.84)	0.84
Probable	8 (0.7)	9 (0.8)	0.88 (0.34–2.28)	0.80
Possible	25 (2.2)	27 (2.3)	0.91 (0.53–1.57)	0.74
Acute	5 (0.4)	5 (0.4)	0.99 (0.29–3.43)	0.99
Subacute	7 (0.6)	10 (0.8)	0.69 (0.26–1.82)	0.45
Early: acute + subacute	12 (1.0)	15 (1.2)	0.79 (0.37–1.70)	0.55
Late	13 (1.1)	11 (1.0)	1.17 (0.52–2.61)	0.70
Revascularization				
Urgent TLR	39 (3.3)	67 (5.8)	0.57 (0.38–0.84)	0.004
Any TLR	60 (5.1)	115 (10.0)	0.50 (0.37–0.68)	<0.001
Clinically driven TVR	66 (5.7)	121 (10.5)	0.52 (0.39–0.71)	<0.001
Any TVR	67 (5.8)	125 (10.9)	0.51 (0.38–0.69)	<0.001
TVR by CABG	4 (0.3)	11 (1.0)	0.36 (0.11–1.12)	0.06
Any revascularization	97 (8.4)	141 (12.2)	0.67 (0.51–0.86)	0.002
Bleeding‡§				
BARC 1–5	215 (18.1)	225 (19.1)	0.95 (0.78–1.14)	0.56
BARC 2–5	166 (13.9)	172 (14.7)	0.96 (0.77–1.18)	0.68
BARC 3–5	85 (7.2)	85 (7.3)	0.99 (0.73–1.34)	0.96

* Percentages are Kaplan–Meier estimates at 390 days. TLR denotes target-lesion revascularization, and TVR target-vessel revascularization.

† P<0.001 for noninferiority comparison (primary analysis).

‡ Subcategories of myocardial infarction, stent thrombosis, or bleeding are not mutually exclusive, because patients could have more than one subtype of these events during follow-up.

§ Bleeding was defined according to the Bleeding Academic Research Consortium (BARC) definitions. BARC type 0 indicates no bleeding, and BARC type 5 indicates fatal bleeding.[11]

SENIOR trial - Lancet. 2018 Jan 6;391(10115):41-50.

Articles

Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial

Olivier Varenne, Stéphane Cook, Georgios Sideris, Saskia Kedev, Thomas Cuisset, Didier Carrié, Thomas Hovasse, Philippe Garot, Remi El Mahmoud, Christian Spaulding, Eduard Reffit, José F Díaz Fernández, Salvatore Brugaletta, Eduardo Pinar Bermudez, Josepa Mauri Ferre, Philippe Commeau, Emmanuel Teiger, Kim Huguett, Muriel Sabbane, Marie-Claude Morice, Peter B Simonsen, for the SENIOR Investigators

Summary

Background Elderly patients regularly receive bare-metal stents (BMS) instead of drug-eluting stents (DES) to shorten the duration of dual antiplatelet therapy (DAPT). The aim of this study was to compare outcomes between these two types of stents with a short duration of DAPT in such patients.

Methods In this randomised single-blind trial, we recruited patients from 44 centres in nine countries. Patients were eligible if they were aged 75 years or older, had stable angina, silent ischaemia, or an acute coronary syndrome, and had at least one coronary artery with a stenosis of at least 70% (≥50% for the left main stem) deemed eligible for percutaneous coronary intervention (PCI). Exclusion criteria were indication for myocardial revascularisation by coronary artery bypass grafting; inability to tolerate, obtain, or comply with DAPT; requirement for additional surgery; non-cardiac comorbidities with a life expectancy of less than 1 year; previous haemorrhagic stroke; allergy to aspirin or $P2Y_{12}$ inhibitors; contraindication to $P2Y_{12}$ inhibitors; and silent ischaemia of less than 10% of the left myocardium with a fractional flow reserve of 0·80 or higher. After the intended duration of DAPT was recorded (1 month for patients with stable presentation and 6 months for those with unstable presentation), patients were randomly allocated (1:1) by a central computer system (blocking used with randomly selected block sizes [two, four, eight, or 16]; stratified by site and antiplatelet agent) to either a DES or similar BMS in a single-blind fashion (ie, patients were masked), but those assessing outcomes were masked. The primary outcome was to compare major adverse cardiac and cerebrovascular events (ie, a composite of all-cause mortality, myocardial infarction, stroke, or ischaemia-driven target lesion revascularisation) between groups at 1 year in the intention-to-treat population, assessed at 30 days, 180 days, and 1 year. This trial is registered with ClinicalTrials.gov, number NCT02099617.

Findings Between May 21, 2014, and April 16, 2016, we randomly assigned 1200 patients (596 [50%] to the DES group and 604 [50%] to the BMS group). The primary endpoint occurred in 68 (12%) patients in the DES group and 98 (16%) in the BMS group (relative risk [RR] 0·71 [95% CI 0·52–0·94]; p=0·02). Bleeding complications (26 [5%] in the DES group vs 29 [5%] in the BMS group; RR 0·90 [0·51–1·54]; p=0·68) and stent thrombosis (three [1%] vs eight [1%]; RR 0·38 [0·09–1·48]; p=0·13) at 1 year were infrequent in both groups.

Interpretation Among elderly patients who have PCI, a DES and a short duration of DAPT are better than BMS and a similar duration of DAPT with respect to the occurrence of all-cause mortality, myocardial infarction, stroke, and ischaemia-driven target lesion revascularisation. A strategy of continuation of a DES to reduce the risk of subsequent repeat revascularisations with a short BMS-like DAPT regimen to reduce the risk of bleeding event is an attractive option for elderly patients who have PCI.

Funding Boston Scientific.

Introduction

Elderly people represent a fast-growing segment of the population, and because of their increased risk of coronary artery disease, they are also more likely to have percutaneous coronary interventions (PCI) than are younger people.[1,2] Management of coronary artery disease in elderly patients can be challenging as they often have more extensive and complex disease and are also more prone to bleeding complications when receiving antiplatelet agents than younger patients.[3]

The optimal PCI strategy for elderly patients remains ill defined, for both the type of stent and duration of dual antiplatelet therapy (DAPT) after intervention. A Scientific Statement[4] from the American Heart Association, American College of Cardiology, and American Geriatrics Society called for closure of the gap of evidence in cardiovascular care between elderly and younger patients, recognising that current guidelines were unable to provide evidence-based recommendations for treatment of older patients.

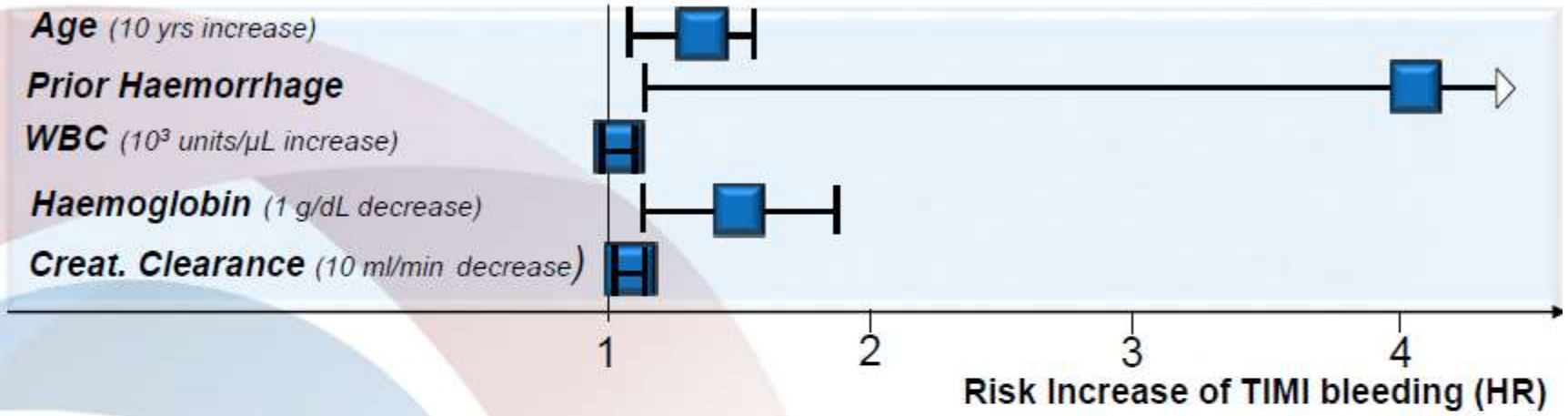
Current drug-eluting stents (DES) limit the risk of repeat revascularisations compared with bare-metal stents (BMS) in elderly patients.[5–7] Contemporary DES are also safer than are BMS in terms of stent thrombosis.[8–10] In view of the high incidence of complex lesions in elderly patients, these DES are therefore becoming an increasingly attractive option in this population. However, elderly patients regularly receive

„The duration of DAPT was intended to be uniform, reflecting the shortest duration recommended by guidelines per baseline presentation. The intended DAPT duration was recommended to be 1 month for stable patients and 6 months for unstable patients and required to be specified by the investigator before randomisation.
The study was not designed to evaluate the optimal duration of DAPT. The safety profile of a short DAPT regimen after DES implantation therefore needs to be interpreted cautiously and might not necessarily apply to other patient populations.“

The PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual AntiPlatelet Therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials

Francesco Costa, David van Klaveren, Stefan James, Dik Heg, Lorenz Räber, Fausto Feres, Thomas Pilgrim, Myeong-Ki Hong, Hyo-Soo Kim, Antonio Colombo, Philippe Gabriel Steg, Thomas Zanchin, Tullio Palmerini, Lars Wallentin, Deepak L Bhatt, Gregg W Stone, Stephan Windecker, Ewout W Steyerberg and Marco Valgimigli for the PRECISE-DAPT Study Investigators

Multivariable prediction model and derivation of the score

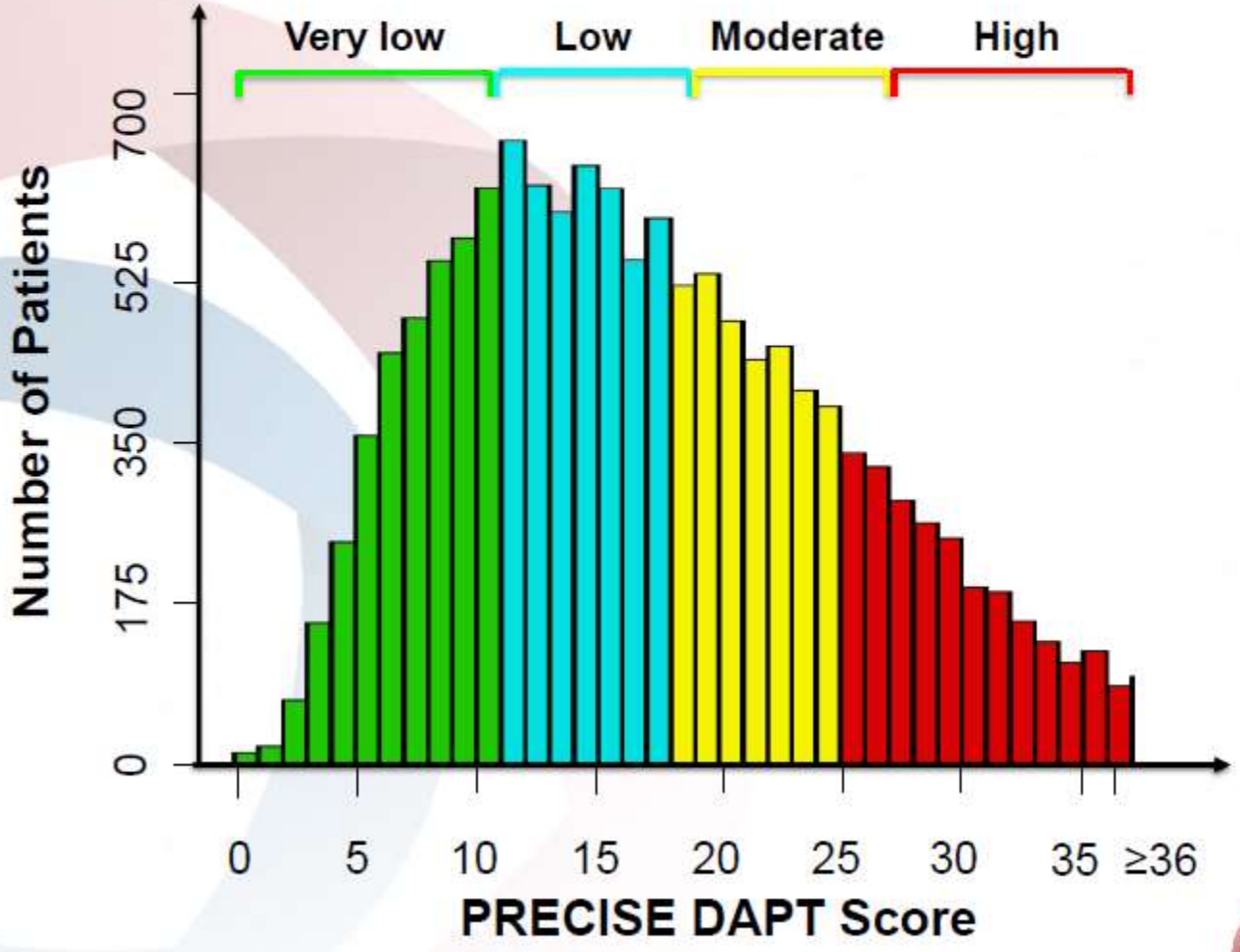


SCORE

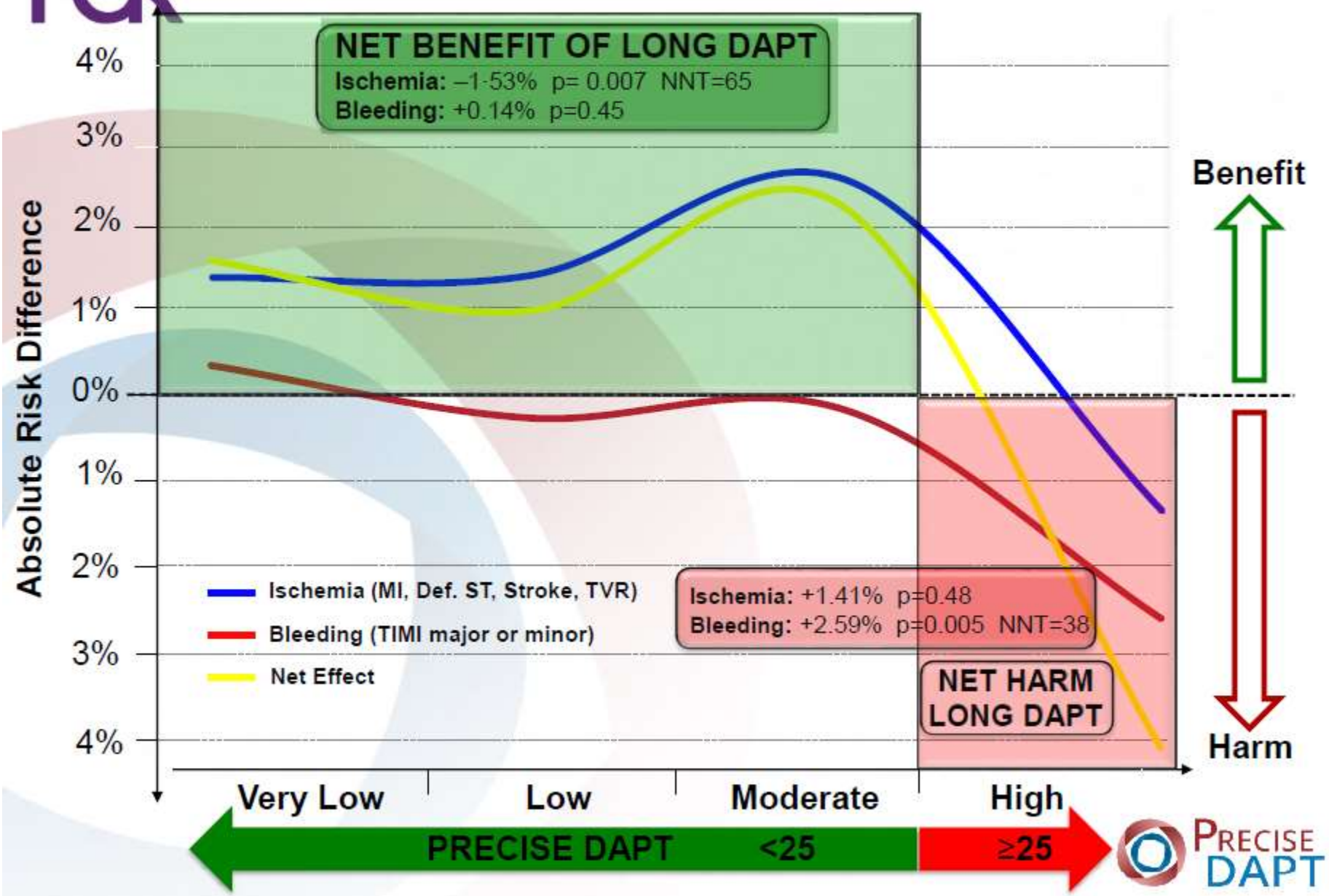
Hb	0 to 15 pts
WBC	0 to 15 pts
Age	0 to 19 pts
Creat. Clear.	0 to 25 pts
Prior Bleed	0 to 26 pts

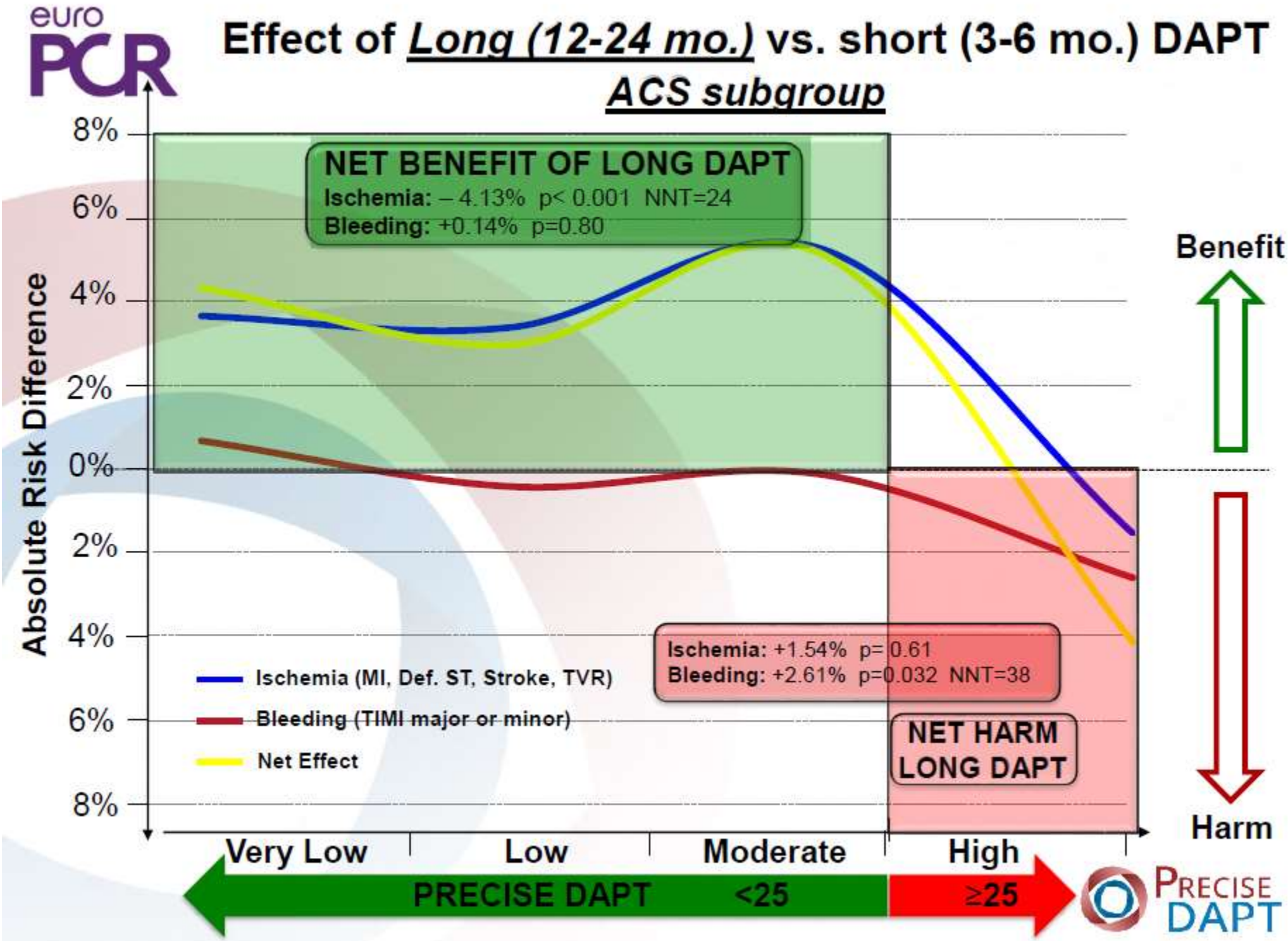
0 PRECISE DAPT SCORE 100

PRECISE-DAPT score distribution derivation cohort



Effect of *Long (12-24 mo.)* vs. short (3-6 mo.) DAPT




Effect of Long (12-24 mo.) vs. short (3-6 mo.) DAPT
ACS subgroup
NET BENEFIT OF LONG DAPT
Ischemia: – 4.13% p< 0.001 NNT=24
Bleeding: +0.14% p=0.80
Ischemia: +1.54% p= 0.61
Bleeding: +2.61% p=0.032 NNT=38
NET HARM LONG DAPT
Ischemia (MI, Def. ST, Stroke, TVR)
Bleeding (TIMI major or minor)
Net Effect
Absolute Risk Difference
8%
6%
4%
2%
0%
2%
4%
6%
8%
Benefit
Harm
Very Low
Low
Moderate
High
PRECISE DAPT
<25
≥25
PRECISE DAPT

Conclusions:

In the context of a comprehensive clinical evaluation PRECISE-DAPT score can support clinical decision making for treatment duration.

Non – high PRECISE DAPT Score (<25)
Ischemic benefit long DAPT (12-24m)
No increase in TIMI bleeding

High PRECISE DAPT Score ≥ 25
No ischemic benefit long DAPT
Increase in TIMI bleeding

LONG DAPT (12-24 months) BETTER

SHORT DAPT (3-6 months) BETTER