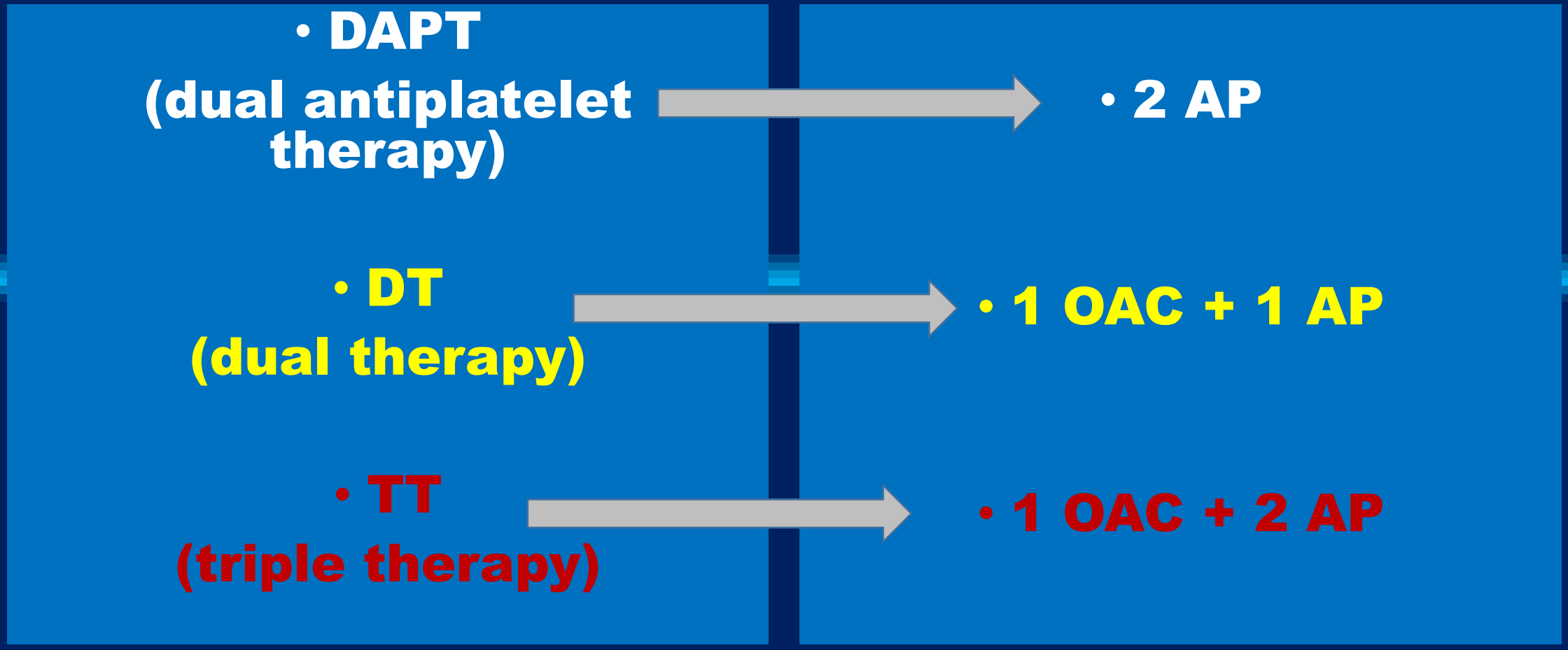
„DUAL“ NEBO „TRIPLE“ THERAPY? WARFARIN, RIVAROXABAN, DABIGATRAN

Varvařovský Ivo

KCA Pardubice

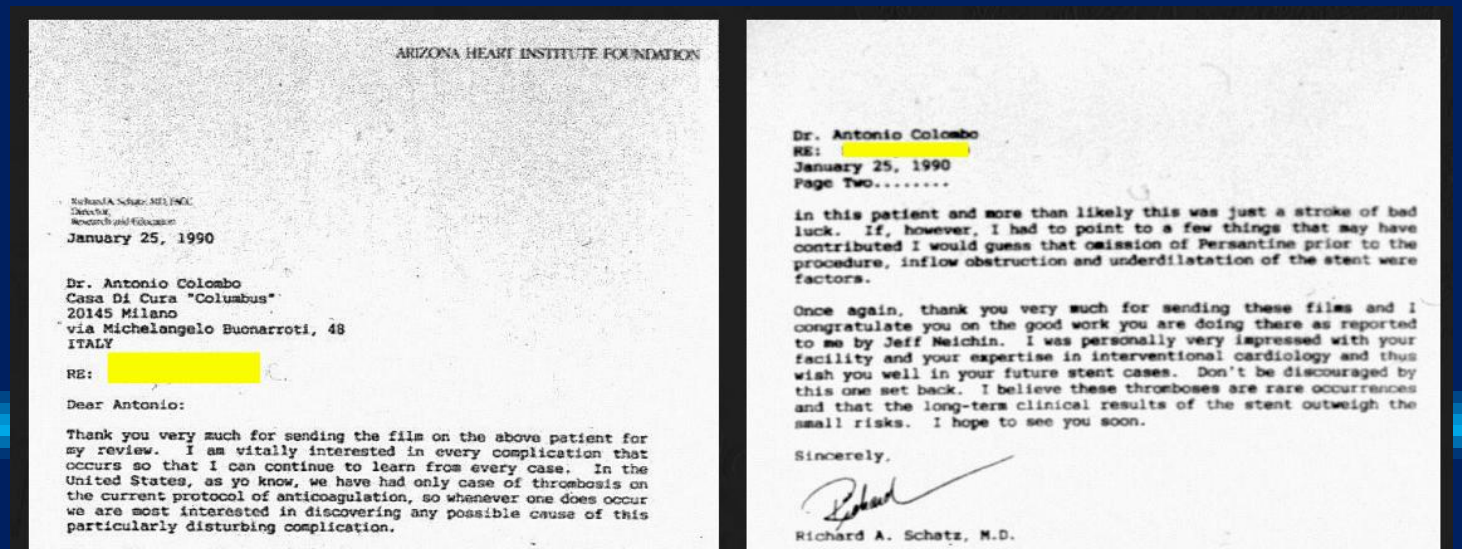
27.sjezd ČKS, Brno 12.-15.5.2019

„Dual (DT)“ nebo „triple (TT)“ therapy
pro PCI při fibrilaci síní



OAC = antikoagulační lék AP = protidestičkový lék

Trombóza koronárního stentu nebude problém: 1990



ARIZONA HEART INSTITUTE FOUNDATION

Richard A. Schatz, M.D., FACC
Director
Research and Education

January 25, 1990

Dr. Antonio Colombo
Casa Di Cura "Columbus"
20145 Milano
via Michelangelo Buonarroti, 48
ITALY

RE: [redacted]

Dear Antonio:

Thank you very much for sending the film on the above patient for my review. I am vitally interested in every complication that occurs so that I can continue to learn from every case. In the United States, as yo know, we have had only case of thrombosis on the current protocol of anticoagulation, so whenever one does occur we are most interested in discovering any possible cause of this particularly disturbing complication.

Dr. Antonio Colombo
RE: [redacted]
January 25, 1990
Page Two.....

in this patient and more than likely this was just a stroke of bad luck. If, however, I had to point to a few things that may have contributed I would guess that omission of Persantine prior to the procedure, inflow obstruction and underdilatation of the stent were factors.

Once again, thank you very much for sending these films and I congratulate you on the good work you are doing there as reported to me by Jeff Neichin. I was personally very impressed with your facility and your expertise in interventional cardiology and thus wish you well in your future stent cases. Don't be discouraged by this one set back. I believe these thromboses are rare occurrences and that the long-term clinical results of the stent outweigh the small risks. I hope to see you soon.

Sincerely,

Richard A. Schatz, M.D.

Don't be discouraged by this one set back. I believe these thrombosis are rare occurances.....

Richard A. Schatz, M.D.

Trombóza koronárního stentu – asi máme problém : 1991

NEJM 1991

ANGIOGRAPHIC FOLLOW-UP AFTER PLACEMENT OF A SELF-EXPANDING CORONARY-ARTERY STENT

PATRICK W. SERRUYS, M.D., BRADLEY H. STRAUSS, M.D., KEVIN J. BEATT, M.B., B.S., MICHEL E. BERTRAND, M.D., JACQUES PUEL, M.D., ANTHONY F. RICKARDS, M.B., B.S., BERNHARD MEIER, M.D., JEAN-JACQUES GOY, M.D., PIERRE VOGT, M.D., LUKAS KAPPENBERGER, M.D., AND ULRICH SIGWART, M.D.

Therapy: aspirin+dypiridamole +subcute heparin for 6 weeks

117 patients:

21 stent occlusions within 14 days, 8 deaths in the first year

Trombóza koronárního stentu – DAPT : 1995

Intracoronary Stenting Without Anticoagulation Accomplished With Intravascular Ultrasound Guidance

Antonio Colombo, MD; Patrick Hall, MD; Shigeru Nakamura, MD; Yaron Almagor, MD; Luigi Maiello, MD; Giovanni Martini, CCP; Antonio Gaglione, MD; Steven L. Goldberg, MD; Jonathan M. Tobis, MD

(*Circulation*. 1995;91:1676-1688.)

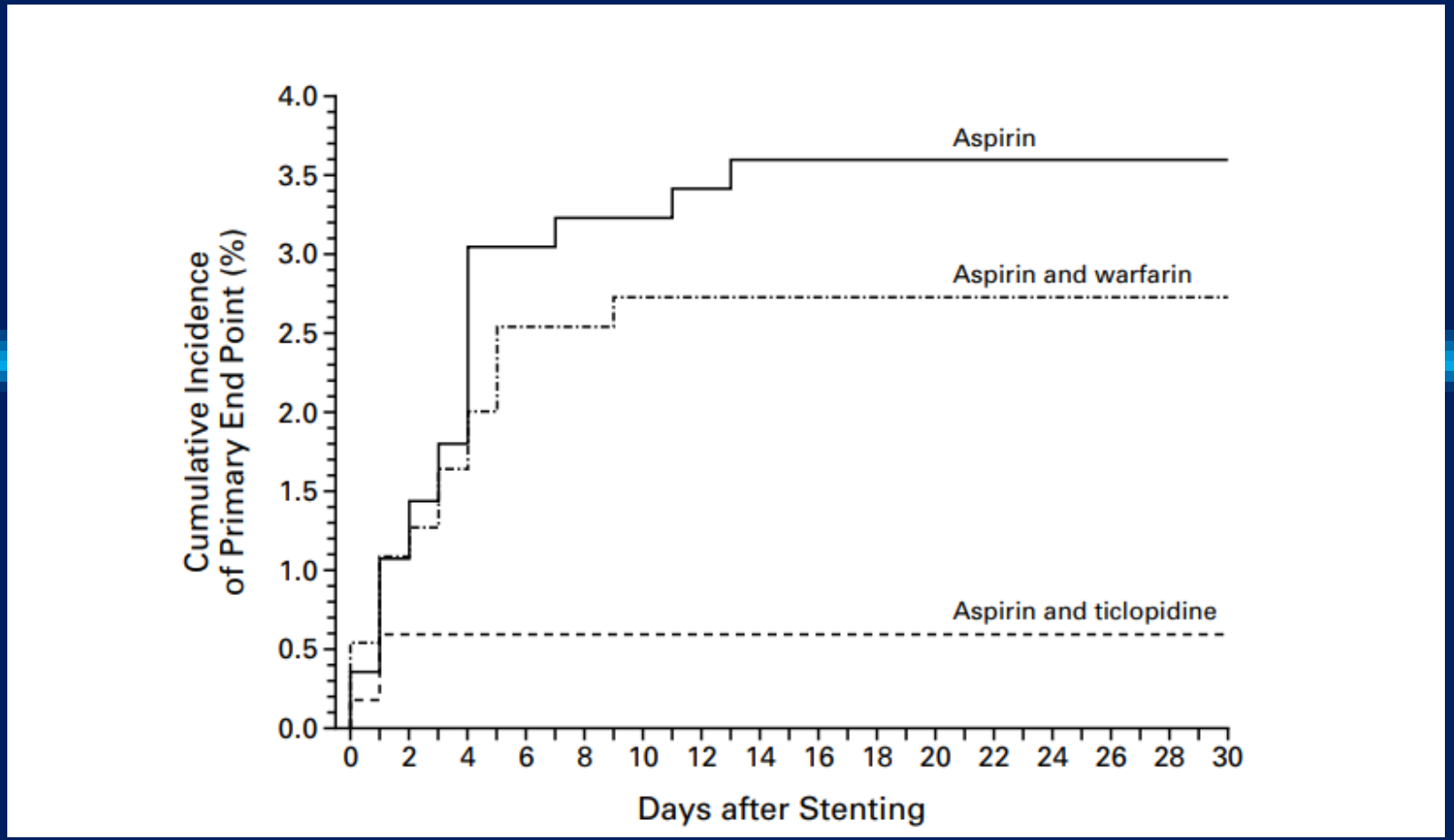
Coronary stenting without anticoagulation

359 patients on Aspirin + Ticlopidine+ IVUS evaluation

- Aspirin + Ticlopidine in most pts
- Average balloon pressure 14.9 atm
- Balloon artery ratio 1.17
- Thrombosis 0.9%

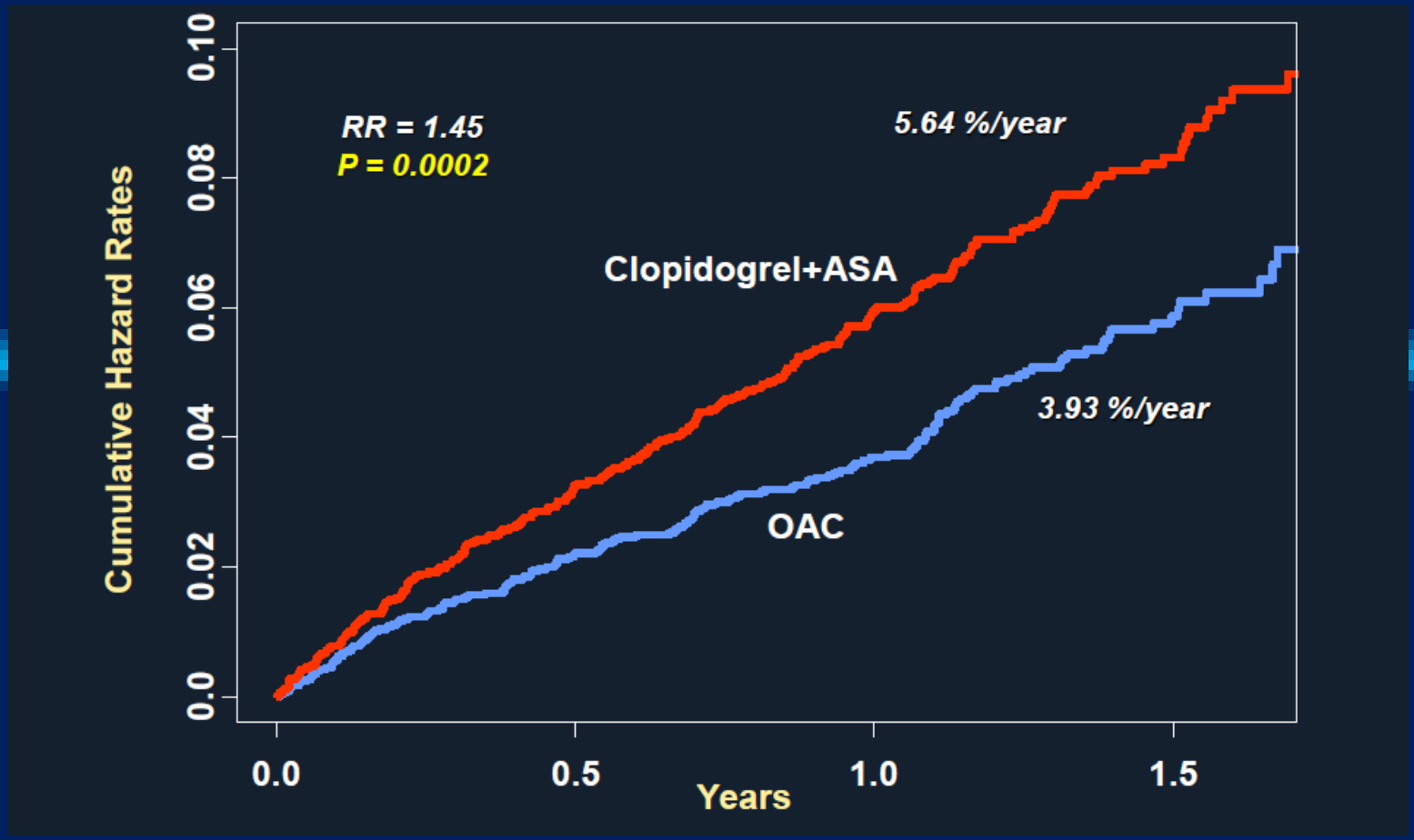
Colombo et al Circulation 1995

DT (s aspirinem!) vs **DAPT** pro prevenci trombózy stentu: 1998



N Engl J Med 1998;339:1665-71

OAC vs DAPT pro prevenci embolizace při fibrilaci síní : 2006



THE LANCET

Jun 10, 2006
Volume 367, Number 9526, p1875-1952

Retrospektivní studie PCI při trvalé OAC : 2007

Table 4 Summary of outcome events during follow-up in stented patients

	Warfarin patients ($n = 219$)	Control patients ($n = 227$)	OR (95% CI)[a]	*P*-value
At 12 months[c]				
Primary endpoint				
Death,[d] *n* (%)	19 (8.7)	4 (1.8)	5.3 (1.8–16.0)	0.003
MI, *n* (%)	22 (10.0)	11 (4.8)	2.2 (1.0–4.7)	0.041
TVR, *n* (%)	24 (11.0)	17 (7.5)	1.5 (0.8–2.9)	0.21
Stent thrombosis, (%)	9 (4.1)	3 (1.3)	3.2 (0.8–12.1)	0.09
Overall, *n* (%)	48 (21.9)	25 (11.0)	2.3 (1.3–3.8)	0.003
Secondary endpoint				
Major bleeding, *n* (%)	18 (8.2)	6 (2.6)	3.3 (1.3–8.6)	0.014
Stroke,[b] *n* (%)	7 (3.2)	5 (2.2)	1.5 (0.5–4.7)	0.52
Overall, *n* (%)	25 (11.4)	11 (4.8)	2.5 (1.2–5.3)	0.014

Pasi P. Karjalainen

European Heart Journal (2007) **28**, 726–732

Retrospektivní studie PCI při trvalé OAC : 2007

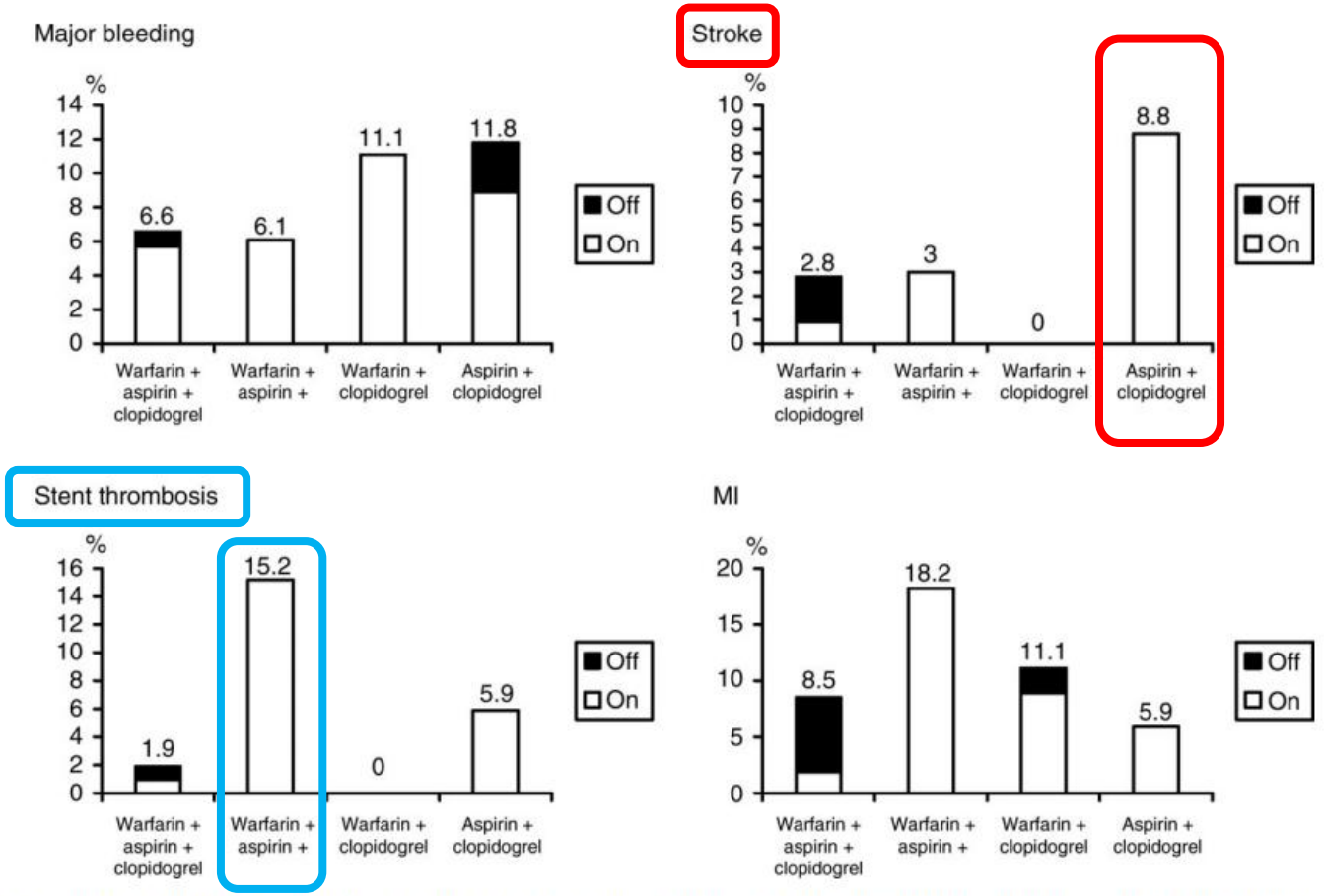


Figure 2 Complications during 12-month follow-up with various drug regimens adopted after stenting in warfarin group (prescribed drug combinations either On or Off at the time of the event).

Pasi P. Karjalainen

European Heart Journal (2007) **28**, 726–732

Retrospektivní studie PCI při trvalé OAC : 2007

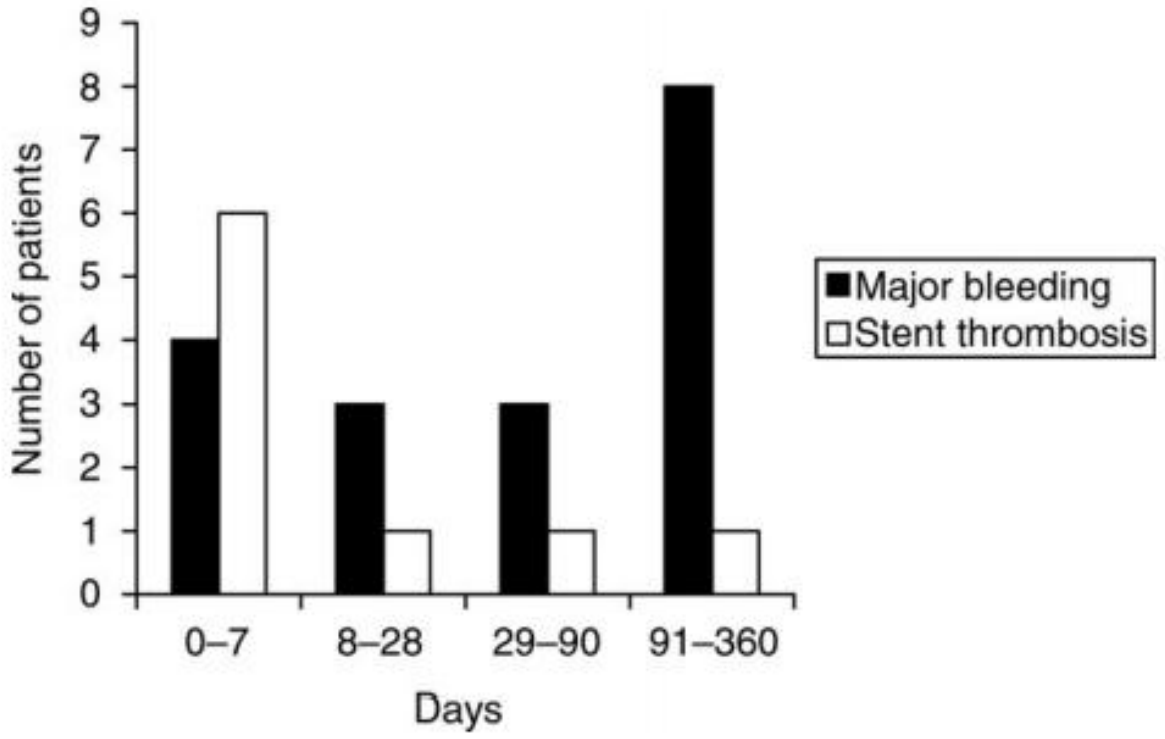
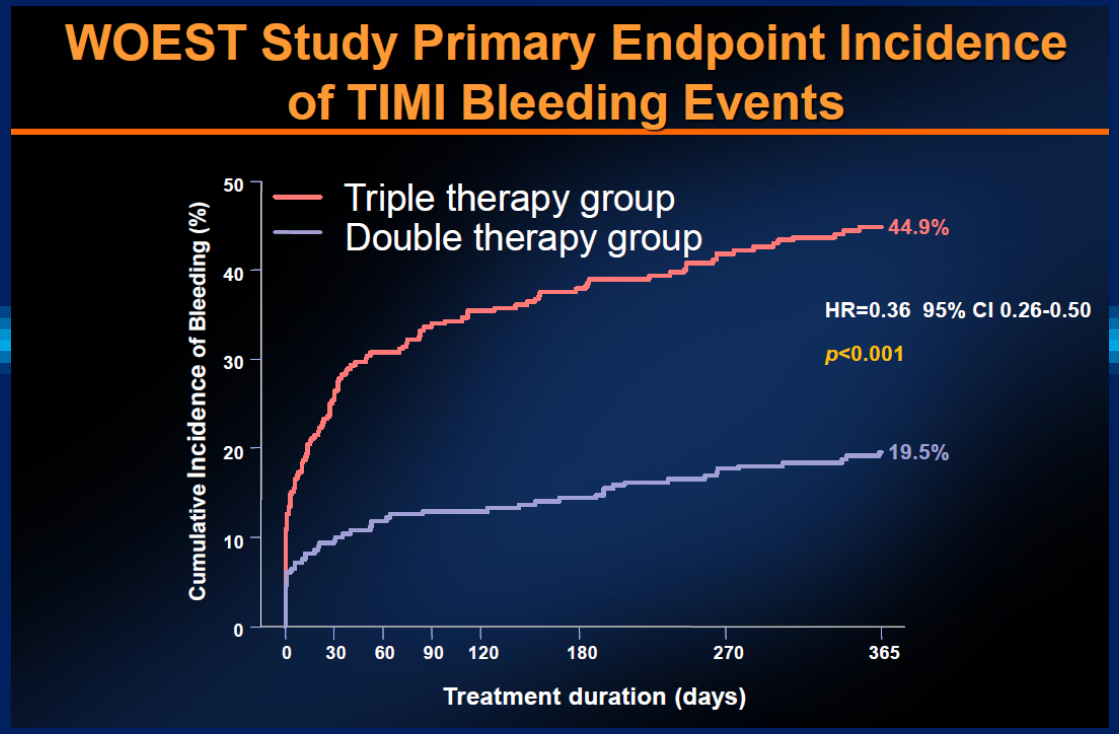
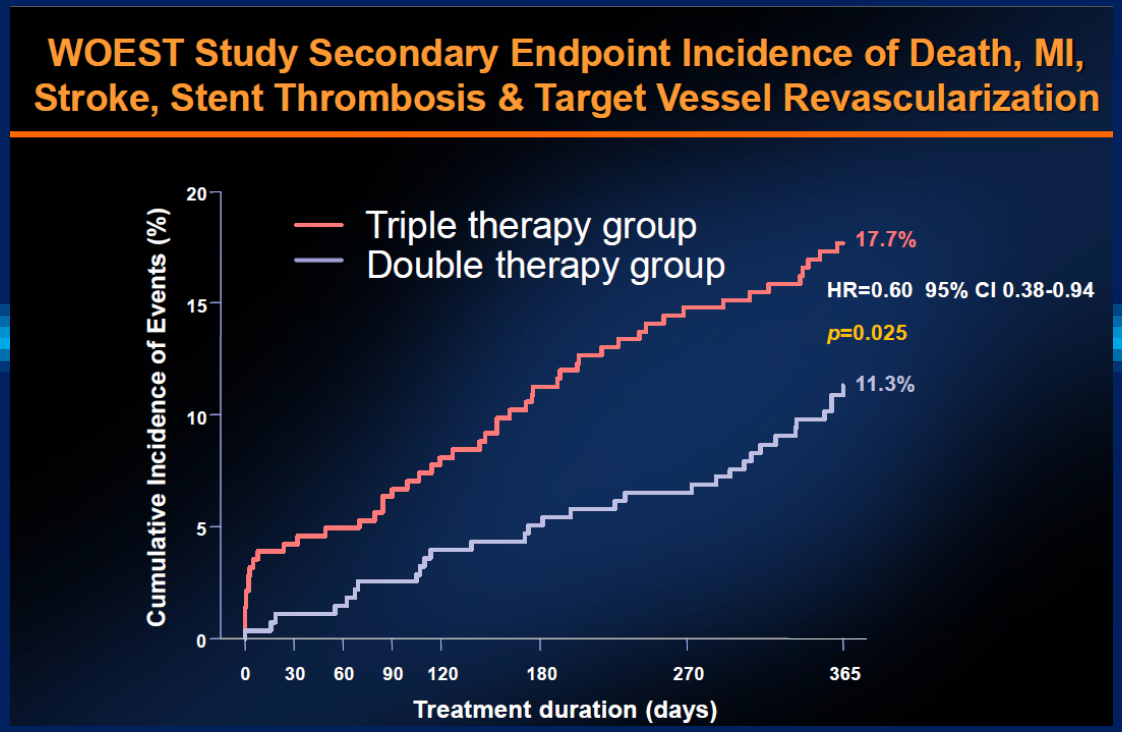


Figure 3 Timing of major bleeding events and stent thrombosis during follow-up. The bleeding risk remained high throughout the treatment period, whereas most of the definite stent thrombosis occurred early after PCI.

European Heart Journal (2007) **28**, 726–732

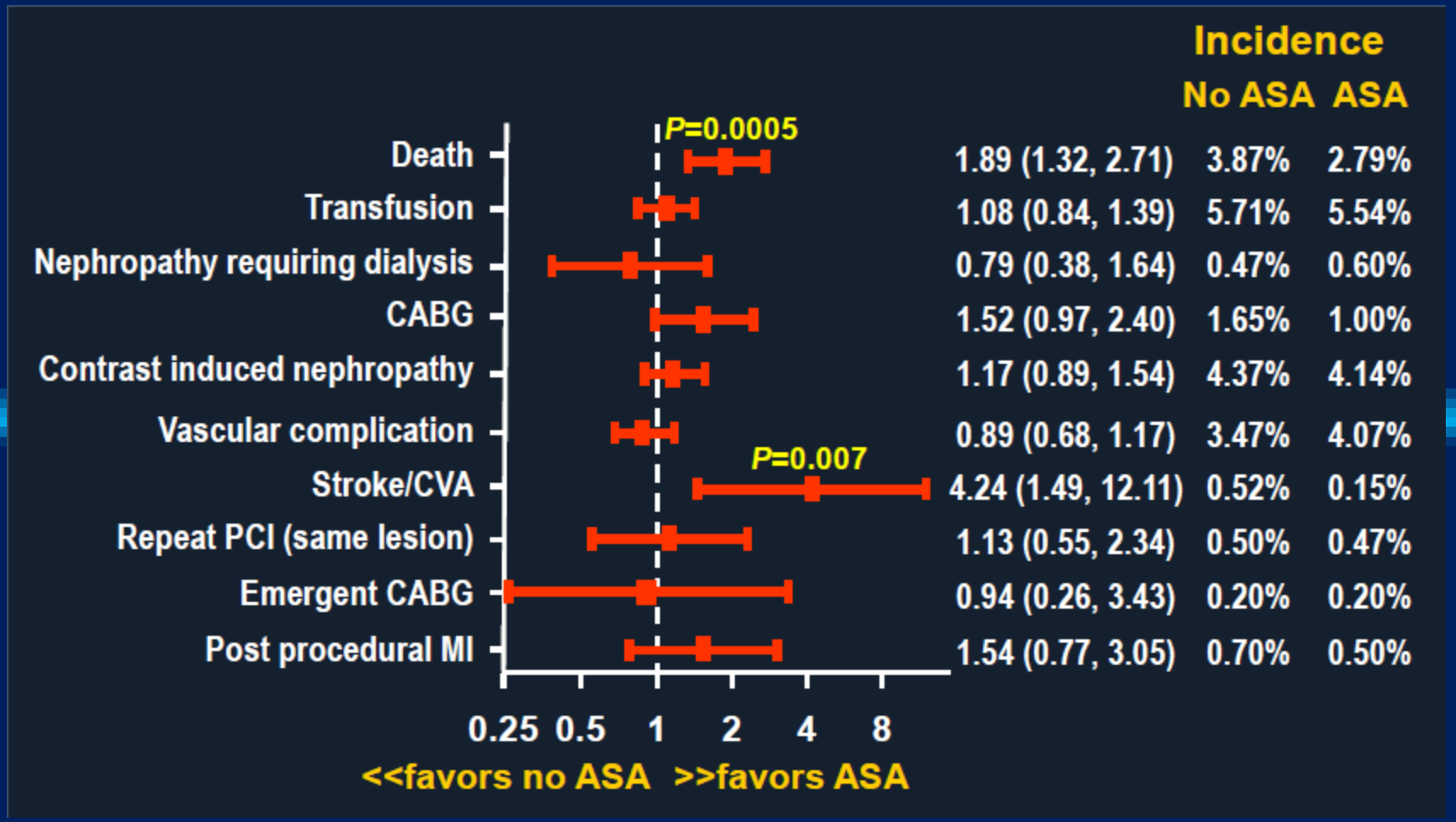
WOEST : DT s vynecháním aspirinu 2012





DeWilde W, et al. ESC Munich, August 28, 2012

PCI bez aspirinu ?

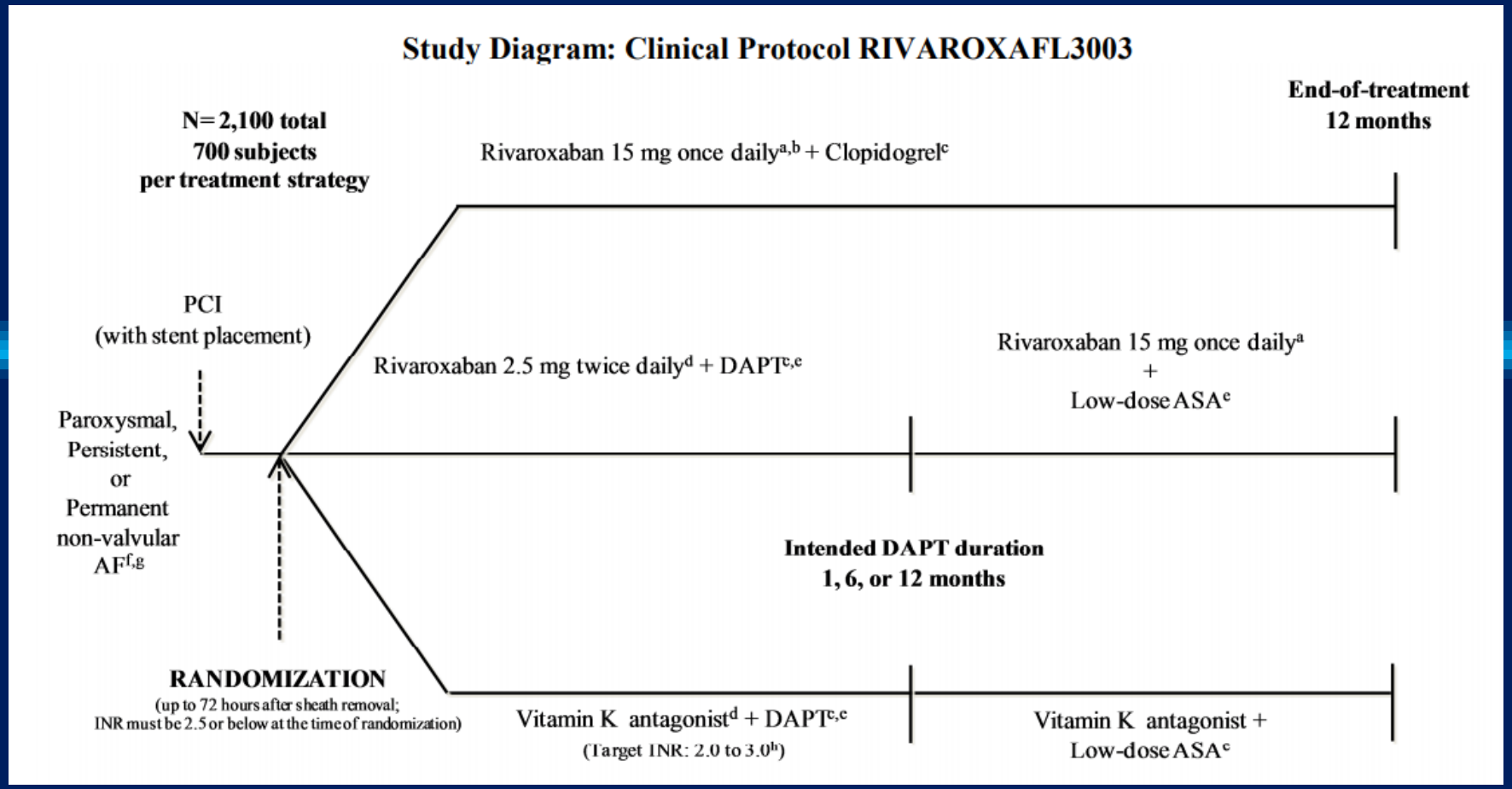


J Am Coll Cardiol 2013;62:2083–9

Aspirin během PCI ve studiích s DT

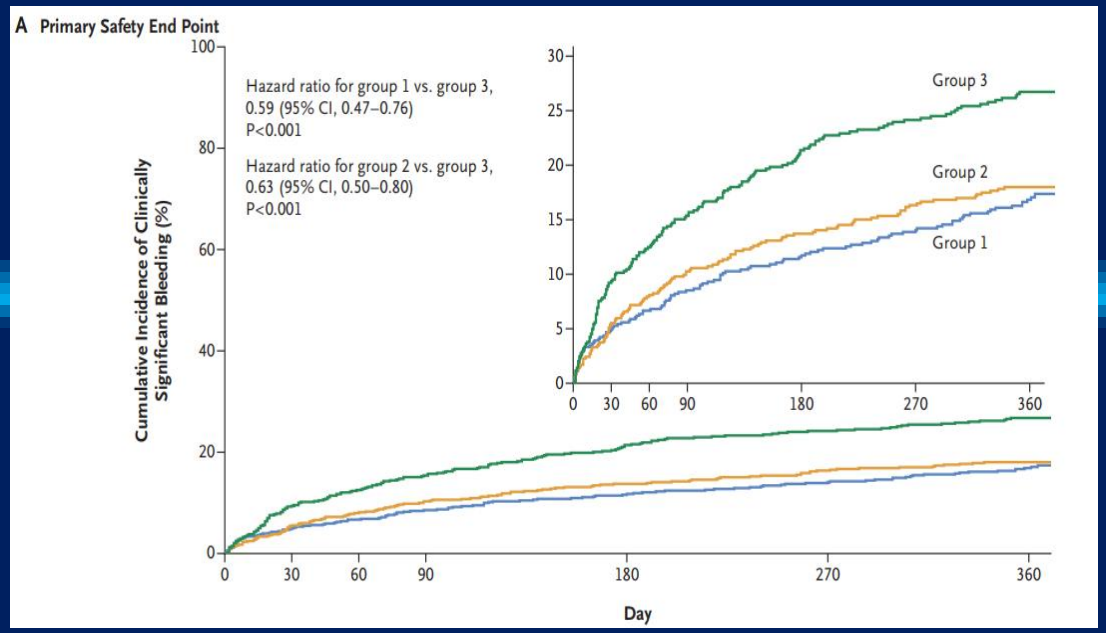
Studie	Aspirin během PCI u pacientů léčených DT	Doba randomizace
WOEST	ne	do 4 hodin po PCI
PIONEER AF - PCI	ano	72 hodin po PCI
RE-DUAL PCI	ano	120 hodin po PCI
AUGUSTUS	ano	6,6 dne po PCI

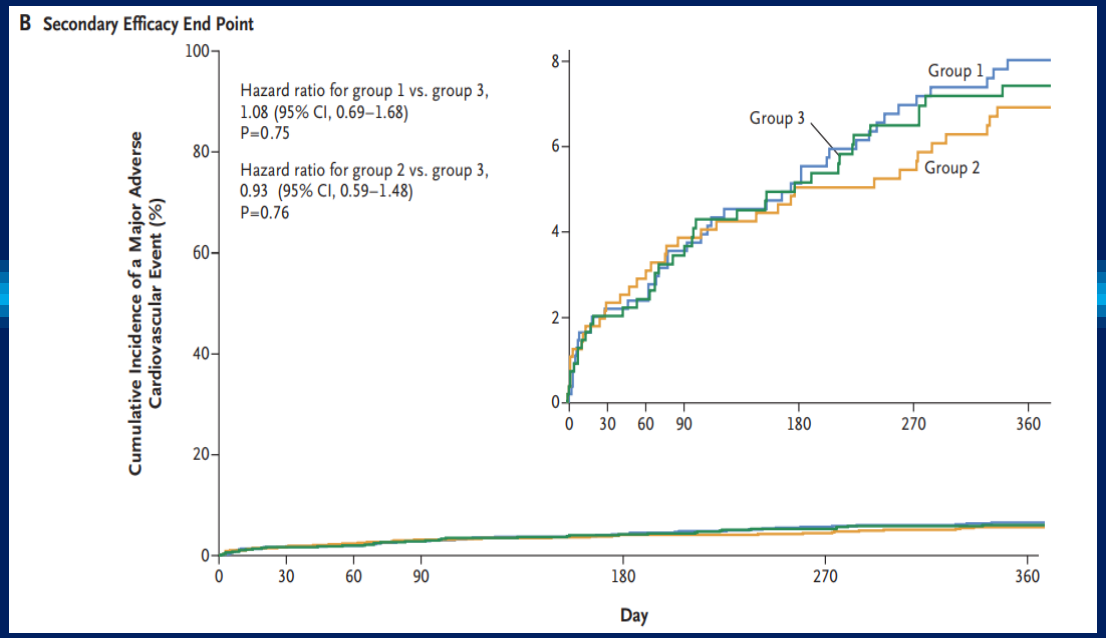
PIONEER-AF PCI (rivaroxaban DT / warfarin TT)



N Engl J Med 2016;375:2423-34

PIONEER-AF PCI (rivaroxaban DT / warfarin TT)





N Engl J Med 2016;375:2423-34

Je nižší dávka rivaroxabanu adekvátní pro prevenci CMP?

Figure S11

Subgroup Analysis of Time to First Ischemic Stroke

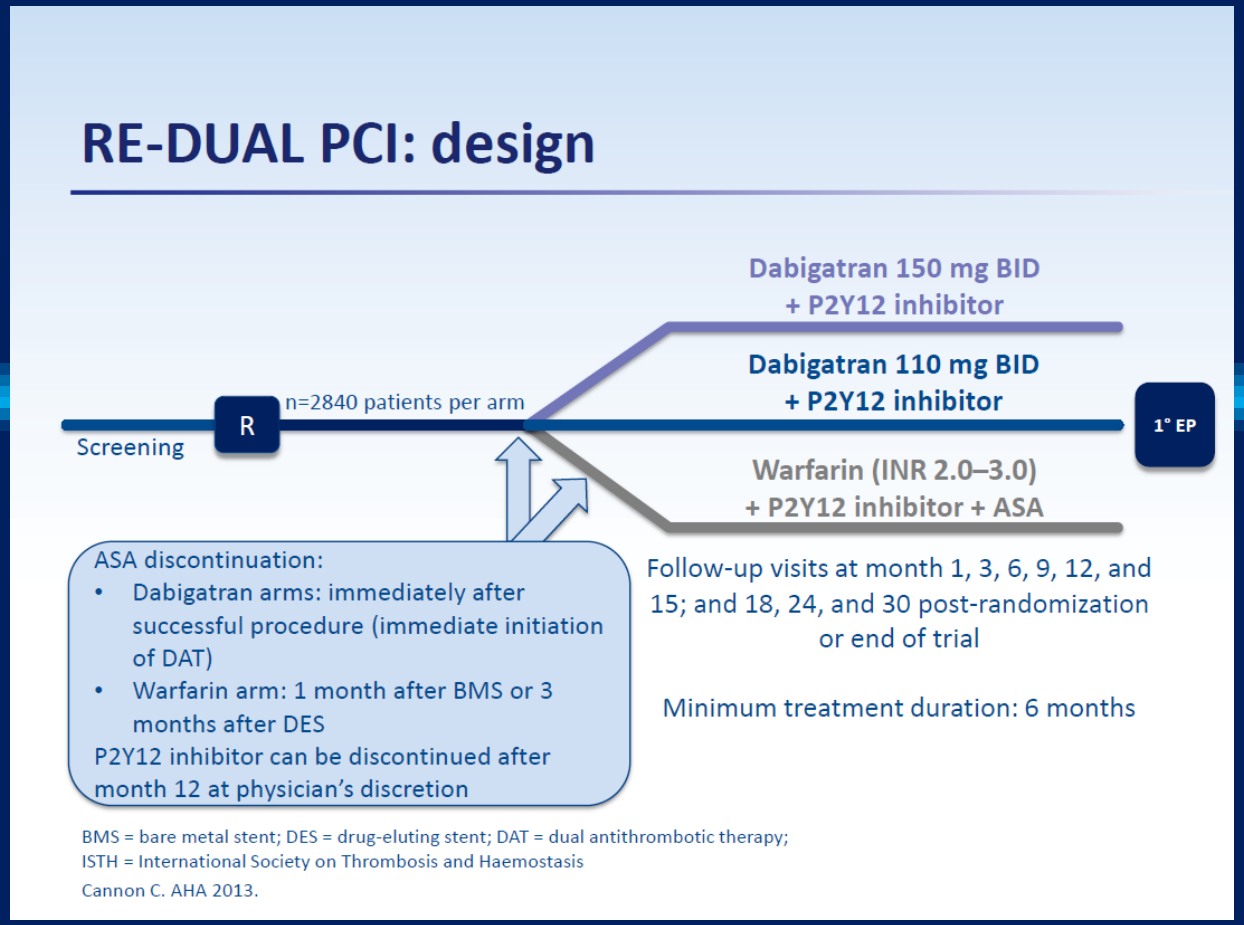
15 mg Rivaroxaban plus $P2Y_{12}$ Inhibitor vs. VKA plus DAPT

Figure S12

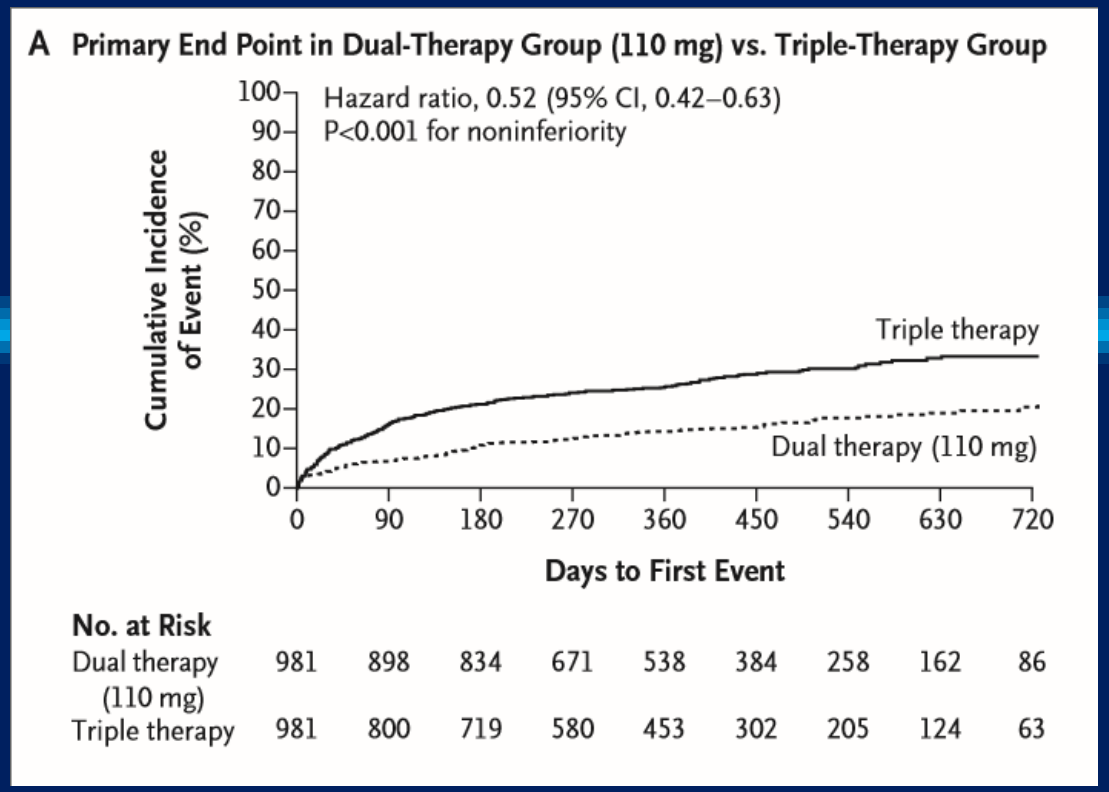
Subgroup Analysis of Time to First Ischemic Stroke

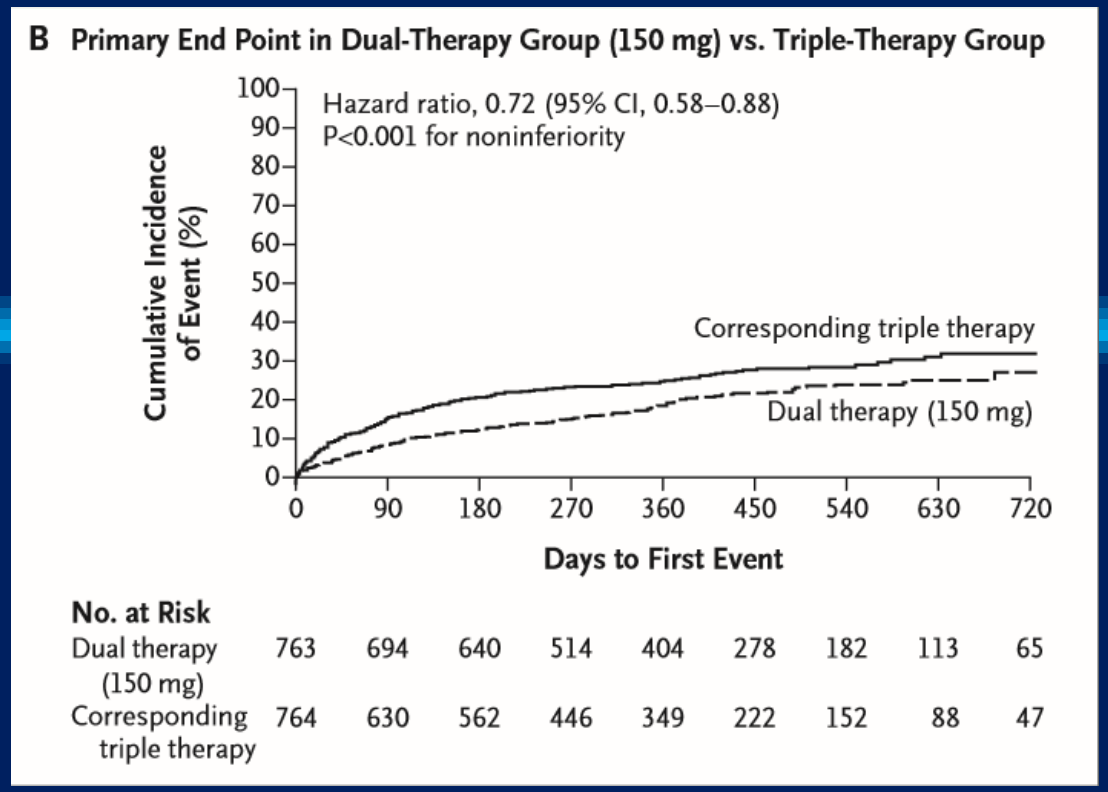
2.5 mg Rivaroxaban plus DAPT vs. VKA plus DAPT

RE-DUAL PCI (dabigatran DT / warfarin TT)



RE-DUAL PCI (dabigatran DT / warfarin TT)





N Engl J Med 2017; 377:1513-1524

RE-DUAL PCI (dabigatran DT / warfarin TT)

Table 2. Safety End Points.*

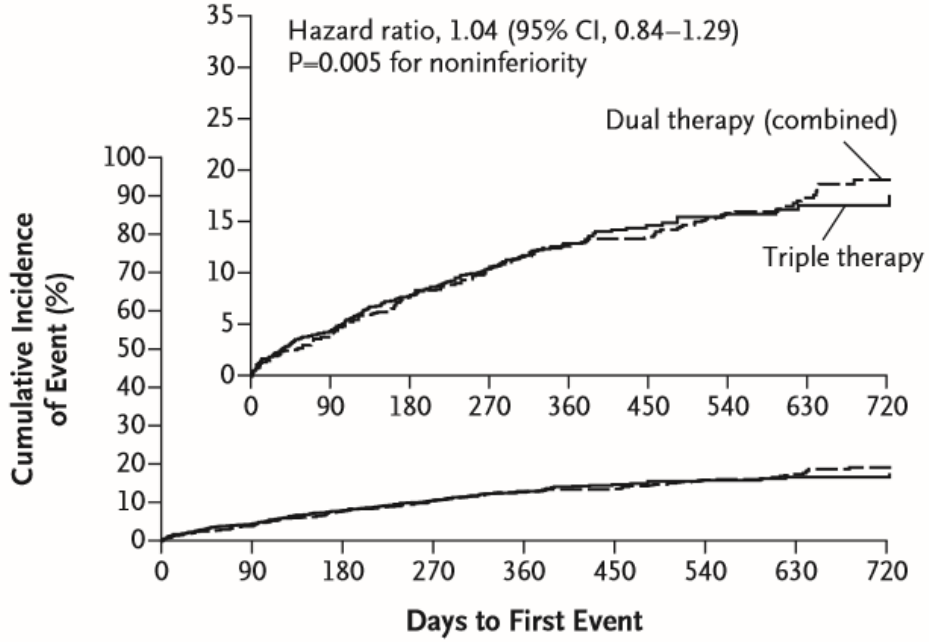
End Point	Dual Therapy with Dabigatran, 110 mg (N=981)	Triple Therapy with Warfarin (N=981)	Hazard Ratio (95% CI)	P Value†	Dual Therapy with Dabigatran, 150 mg (N=763)	Corresponding Triple Therapy with Warfarin (N=764)	Hazard Ratio (95% CI)	P Value†
	no. (%)				*no. (%)*			
Primary end point: ISTH major or clinically relevant nonmajor bleeding	151 (15.4)	264 (26.9)	0.52 (0.42–0.63)	<0.001 (<0.001 for noninferiority)	154 (20.2)	196 (25.7)	0.72 (0.58–0.88)	0.002 (<0.001 for noninferiority)
ISTH major bleeding	49 (5.0)	90 (9.2)	0.52 (0.37–0.74)	<0.001	43 (5.6)	64 (8.4)	0.64 (0.43–0.94)	0.02
Total bleeding	266 (27.1)	421 (42.9)	0.54 (0.46–0.63)	<0.001	254 (33.3)	316 (41.4)	0.72 (0.61–0.84)	<0.001
Intracranial hemorrhage	3 (0.3)	10 (1.0)	0.30 (0.08–1.07)	0.06	1 (0.1)	8 (1.0)	0.12 (0.02–0.98)	0.047
TIMI major bleeding	14 (1.4)	37 (3.8)	0.37 (0.20–0.68)	0.002	16 (2.1)	30 (3.9)	0.51 (0.28–0.93)	0.03
TIMI major or minor bleeding	29 (3.0)	69 (7.0)	0.41 (0.26–0.63)	<0.001	27 (3.5)	48 (6.3)	0.53 (0.33–0.85)	0.009

Characteristic	Dabigatran 110 Dual-therapy (n=981)	Warfarin Triple-therapy (n=981)	Dabigatran 150 Dual-therapy (n=763)	Warfarin Triple-therapy (n=764)§
Prior stroke/TIA, n (%)*	108 (11.0)	142 (14.5)	67 (8.8)	108 (14.1)
CHA_2DS_2-VASC score, n (%)				
≤2	230 (23.4)	193 (19.7)	247 (32.4)	184 (24.1)
>2	751 (76.6)	788 (80.3)	516 (67.6)	580 (75.9)
HAS-BLED score, n (%)				
<3	326 (33.2)	288 (29.4)	309 (40.5)	257 (33.6)
≥3	655 (66.8)	693 (70.6)	454 (59.5)	507 (66.4)

N Engl J Med 2017; 377:1513-1524

RE-DUAL PCI (dabigatran DT / warfarin TT)

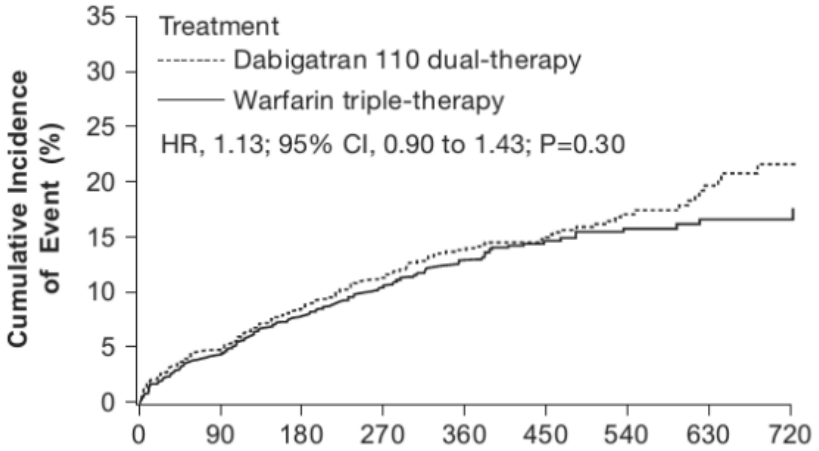
C Secondary Efficacy End Point in Dual-Therapy Groups (Combined) vs. Triple-Therapy Group



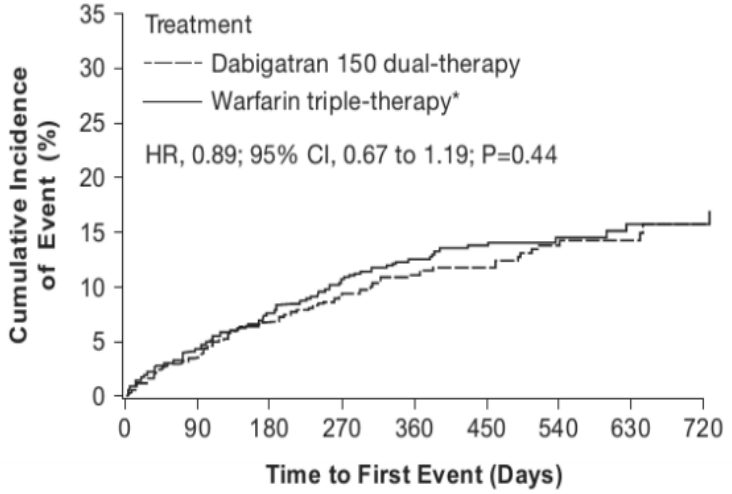
No. at Risk									
Dual therapy (combined)	1744	1660	1561	1257	1003	720	481	295	161
Triple therapy	981	921	854	700	548	383	259	161	81

N Engl J Med 2017; 377:1513-1524

A. Dabigatran 110 Dual-therapy versus Warfarin Triple-therapy



B. Dabigatran 150 Dual-therapy versus Warfarin Triple-therapy



RE-DUAL PCI (dabigatran DT / warfarin TT)

Table 3. Efficacy End Points.*

End Point	Dual Therapy with Dabigatran (Combined) vs. Triple Therapy with Warfarin				Dual Therapy with Dabigatran (110 mg) vs. Triple Therapy with Warfarin				Dual Therapy with Dabigatran (150 mg) vs. Triple Therapy with Warfarin			
	Combined Dual-Therapy Groups (N=1744)	Triple-Therapy Group (N=981)	Hazard Ratio (95% CI)	P Value†	110-mg Dual-Therapy Group (N=981)	Triple-Therapy Group (N=981)	Hazard Ratio (95% CI)	P Value†	150-mg Dual-Therapy Group (N=763)	Corresponding Triple-Therapy Group (N=764)	Hazard Ratio (95% CI)	P Value†
	no. (%)				*no. (%)*				*no. (%)*			
Composite efficacy end point: thromboembolic events, death, or unplanned revascularization	239 (13.7)	131 (13.4)	1.04 (0.84–1.29)	0.74 (0.005 for noninferiority)	149 (15.2)	131 (13.4)	1.13 (0.90–1.43)	0.30	90 (11.8)	98 (12.8)	0.89 (0.67–1.19)	0.44
Thromboembolic events or death	168 (9.6)	83 (8.5)	1.17 (0.90–1.53)	0.25 (0.11 for noninferiority)	108 (11.0)	83 (8.5)	1.30 (0.98–1.73)	0.07	60 (7.9)	60 (7.9)	0.97 (0.68–1.39)	0.88
Death					55 (5.6)	48 (4.9)	1.12 (0.76–1.65)	0.56	30 (3.9)	35 (4.6)	0.83 (0.51–1.34)	0.44
Myocardial infarction					44 (4.5)	29 (3.0)	1.51 (0.94–2.41)	0.09	26 (3.4)	22 (2.9)	1.16 (0.66–2.04)	0.61
Stroke					17 (1.7)	13 (1.3)	1.30 (0.63–2.67)	0.48	9 (1.2)	8 (1.0)	1.09 (0.42–2.83)	0.85
Definite stent thrombosis					15 (1.5)	8 (0.8)	1.86 (0.79–4.40)	0.15	7 (0.9)	7 (0.9)	0.99 (0.35–2.81)	0.98

N Engl J Med 2017; 377:1513-1524

What is new in the 2018 Guidelines?

Calculation of the Syntax Score, if left main or multivessel revascularization is considered	Completeness of revascularization prioritized, when considering CABG vs PCI	Routine non-invasive imaging surveillance in high-risk patients 6 months after revascularization
Radial access as standard approach for coronary angiography and PCI	NOAC preferred over VKA in patients with non-valvular AF requiring anticoagulation and antiplatelet treatment	Double-kissing crush technique preferred over provisional T-stenting in true left main bifurcations.
DES for any PCI	No-touch vein technique, if open vein harvesting for CABG	Cangrelor in $P2Y_{12}$-inhibitor naïve patients undergoing PCI
Systematic re-evaluation of patients after myocardial revascularization	Annual operator volume for left main PCI of at least 25 cases per year	GP IIb/IIIa inhibitors for PCI in $P2Y_{12}$-inhibitor naïve patients with ACS undergoing PCI
Stabilised NSTE-ACS patients: revascularization strategy according to principles for SCAD	Pre- and post-hydration with isotonic saline in patients with moderate or severe CKD if the expected contrast volume is >100 mL	Dabigatran 150-mg dose preferred over 110-mg dose when combined with single antiplatelet therapy after PCI
Use of the radial artery grafts over saphenous vein grafts in patients with high-degree stenosis		De-escalation of $P2Y_{12}$ inhibitor guided by platelet function testing in ACS patients
Myocardial revascularization in patients with CAD, heart failure, and LVEF ≤35% CABG preferred		Routine revascularization of non-IRA lesions in myocardial infarction with cardiogenic shock
PCI as alternative to CABG		Current generation BRS for clinical use outside clinical studies

	Class I		Class IIa
	Class IIb		Class III

European Heart Journal (2019) **40**, 87–165

Trvalá antikoagulační léčba a PCI : stav k 16.3.2019

Víme, že:

1. Po PCI je potřeba antikoagulační i protidestičková léčba
2. „Dual therapy“ je bezpečnější než „triple therapy“

Nevíme, zda:

1. Je aspirin nutnou součástí kombinace ?
2. Je NOAC lepší než warfarin ve srovnatelné kombinaci (DT/TT) ?
3. Jsou nové inhibitory $P2Y_{12}$ bezpečné v kombinaci s (N)OAC (DT/TT) ?