2018 euro PCR

TNT session

"Amphilimus™ Eluting Stent: leveraging on innovative technology to go beyond current PCI clinical boundaries in diabetic and HBR patients"

PCI efficacy vs bleeding – An interconnected equation

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EAPCI European Society of Cardiology PCR

Speaker's name: **Pieter Stella**

☑ I have the following potential conflicts of interest to report:

Receipt of honoraria or consultation fees: DEKRA CE

Efficacy *versus* Safety

Balancing Act

Ischemic Events
Stent trombosis

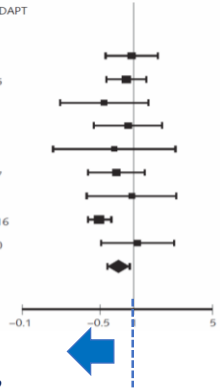
Bleeding Events
Prolonged DAPT

Long vs Short DAPT duration after DES

9 RCTs including 29,531 patients comparing Short vs Long DAPT

Myocardial Infarction

Study, Year (Reference)	Events, *n/N* Longer DAPT	Events, *n/N* Shorter DAPT
Myocardial infarction		
Valgimigli et al, 2013 (16 [PRODIGY])	25/739	26/734
Feres et al, 2013 (12 [OPTIMIZE])	42/1518	49/1525
Gwon et al, 2012 (13 [EXCELLENT])	7/712	13/716
Colombo et al, 2014 (27 [SECURITY])	15/646	16/614
Gilard et al, 2015 (28 [ITALIC])	4/910	6/912
Lee et al, 2014 (14 [DES LATE])	19/2365	27/2337
Collet et al, 2014 (11 [ARCTIC-Interruption])	9/592	9/568
Mauri et al, 2014 (17 [DAPT])	99/4783	198/4716
Schulz-Schüpke, 2015 (29 [ISAR-SAFE])	14/1868	13/1870
Random effects: Heterogeneity: $P = 0.13$; $I^2 = 36\%$ Overall effect: $P = 0.01$		



Long DAPT better

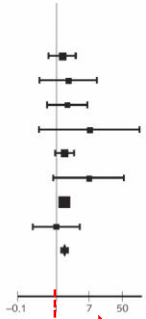
RR =0.73, 95% CI 0.58-0.92

↓8 MI per 1,000 Pts

"Saving Mis" means higher SAFETY!

Major Bleeding

Study, Year (Reference)	Events, *n/N* Longer DAPT	Events, *n/N* Shorter DAPT
Major bleeding		
Feres et al, 2013 (12 [OPTIMIZE])	14/1518	10/1525
Gwon et al, 2012 (13 [EXCELLENT])	4/712	2/716
Colombo et al, 2014 (27 [SECURITY])	8/646	4/614
Gilard et al, 2015 (28 [ITALIC])	3/910	0/912
Lee et al, 2014 (14 [DES LATE])	33/2365	20/2337
Collet et al, 2014 (11 [ARCTIC-Interruption])	7/592	1/568
Mauri et al, 2014 (17 [DAPT])	112/4710	69/4649
Schulz-Schüpke, 2015 (29 [ISAR-SAFE])	4/1868	4/1870
Random effects: Heterogeneity: $P = 0.84$; $I^2 = 0\%$ Overall effect: $P = 0.001$		



Short DAPT better

RR =1.63, 95% CI 1.34-1.99

↑6 Major Bleeds per 1,000 Pts

"Saving Major bleedings" how to?

Spencer FA et al. *Ann Intern Med* 2015;163(2):118-26

Risk scores as guidance for DAPT duration: DAPT Score

DAPT Score: A Decision Tool For DAPT Duration

Predictors of ischemic events

Predictors of bleeding events

Predictors of Events[a]	Predictors of Myocardial Infarction or Stent Thrombosis[b] HR (95% CI)	P Value	Predictors of Moderate or Severe Bleeding[c] HR (95% CI)	P Value
Continued thienopyridine vs placebo	0.52 (0.42-0.65)	<.001	1.66 (1.26-2.19)	<.001
Myocardial infarction at presentation	1.65 (1.31-2.07)	<.001		
Prior PCI or prior myocardial infarction	1.79 (1.43-2.23)	<.001		
History of CHF or LVEF <30%	1.88 (1.35-2.62)	<.001		
Vein graft stent	1.75 (1.13-2.73)	.01		
Stent diameter <3 mm	1.61 (1.30-1.99)	<.001		
Paclitaxel-eluting stent	1.57 (1.26-1.97)	<.001		
Cigarette smoking	1.40 (1.11-1.76)	.01		
Diabetes mellitus	1.38 (1.10-1.72)	.01		
Age, per 10 y			1.54 (1.34-1.78)	<.001
Peripheral arterial disease	1.49 (1.05-2.13)	.03	2.16 (1.46-3.20)	<.001
Hypertension	1.37 (1.03-1.82)	.03	1.45 (1.00-2.11)	.05
Renal insufficiency/failure	1.55 (1.03-2.32)	.04	1.66 (1.04-2.66)	.03

Predictors of ischemic and bleeding events (excluded)

DAPT Score

Clinical Prediction Score

Variable	Points
Age, y	
≥75	-2
65-<75	-1
<65	0
Cigarette smoking	1
Diabetes mellitus	1
MI at presentation	1
Prior PCI or prior MI	1
Paclitaxel-eluting stent	1
Stent diameter <3 mm	1
CHF or LVEF <30%	2
Vein graft stent	2

Total score range: -2 to 10

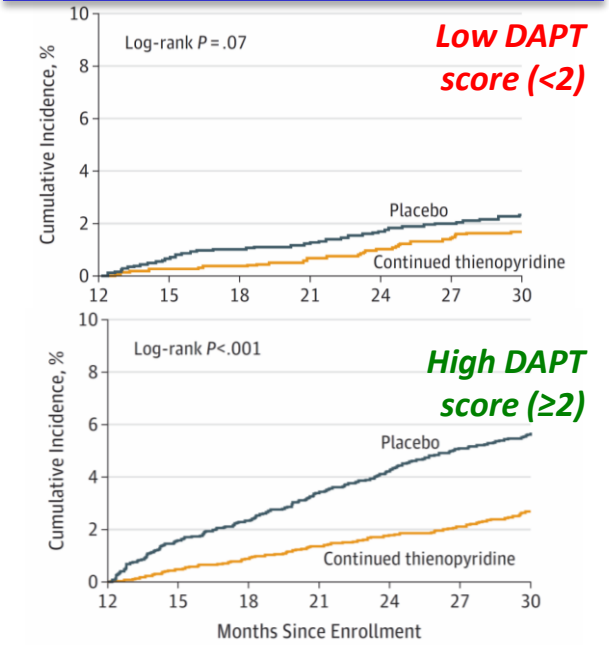
Yeh et al. *JAMA* 2016; 315:1735-49

Risk scores as guidance for DAPT duration: DAPT Score

11,648 Patients enrolled in the DAPT trial

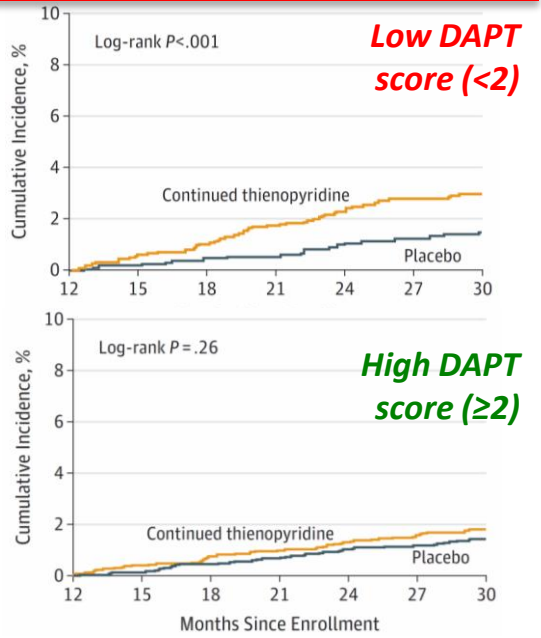
Yeh et al. *JAMA* 2016; 315:1735-49

MI or Stent Thrombosis



P-interaction <0.001, overall cohort
P-interaction =0.18, EES cohort

Gusto Mod/Sev Bleeding

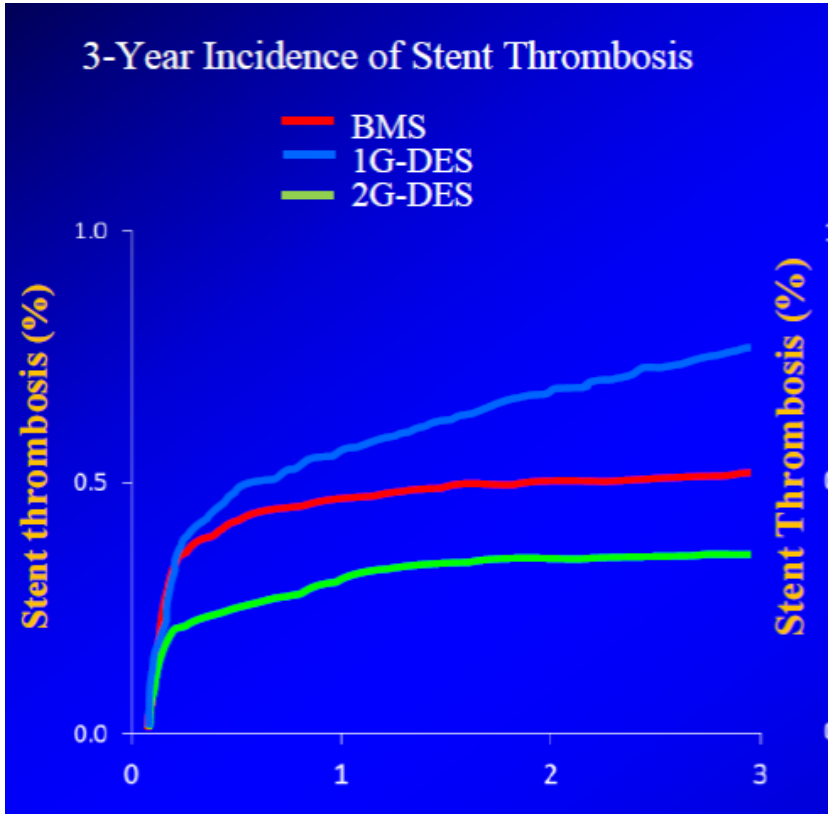


P-interaction =0.02, overall cohort
P-interaction =0.15, EES cohort

New Technologies not included

- Thin Strut stents, CoCr/PtCr
- New polymer formulations
- Non durable polymers
- No polymers

3 years, 18334pts. Kastrati et al



Short versus long duration of dual antiplatelet therapy following drug-eluting stents: a meta-analysis of randomised trials

R. Rozemeijer, M. Voskuil, J. P. Greving, M. L. Bots, P. A. Doevendans & P. R. Stella

Netherlands Heart Journal

ISSN 1568-5888

Neth Heart J
DOI 10.1007/s12471-018-1104-6

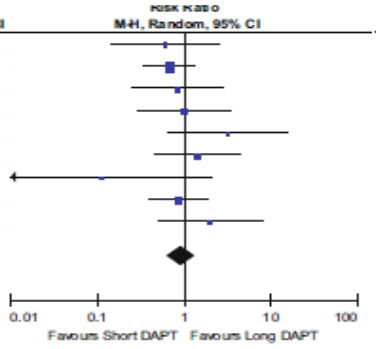
2nd gen stents
6 vs 12months
Same endpoints
>9.500 pts

« Non significant »

Study or Subgroup	Short DAPT Events	Short DAPT Total	Long DAPT Events	Long DAPT Total	Weight	Risk Ratio M-H, Random, 95% CI
EXCELLENT 2012	3	722	5	721	6.6%	0.60 [0.14, 2.50]
PRODIGY 2012	14	983	21	987	29.9%	0.67 [0.34, 1.31]
RESET 2012	5	1059	6	1058	9.6%	0.83 [0.25, 2.72]
OPTIMIZE 2013	5	1563	5	1556	8.8%	1.00 [0.29, 3.43]
SECURITY 2014	6	682	2	717	5.3%	3.15 [0.64, 15.57]
ISAR-SAFE 2015	7	1997	5	2003	10.2%	1.40 [0.45, 4.42]
ITALIC 2015	0	912	4	910	1.6%	0.11 [0.01, 2.06]
I-LOVE-IT 2 2016	11	909	13	920	21.1%	0.86 [0.39, 1.90]
IVUS-XPL 2016	6	699	3	701	7.0%	2.01 [0.50, 7.99]
Total (95% CI)		**9526**		**9573**	**100.0%**	**0.91 [0.63, 1.31]**
Total events	57		64			

Heterogeneity: Tau² = 0.00; Chi² = 7.33, df = 8 (P = 0.50); I² = 0%

Test for overall effect: Z = 0.51 (P = 0.61)



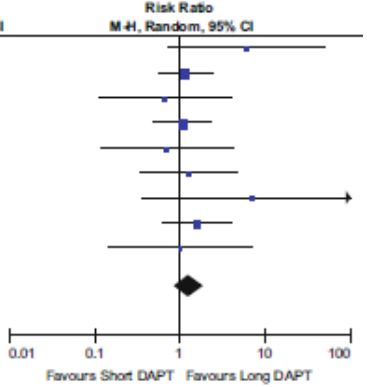
Stroke

c

Study or Subgroup	Short DAPT Events	Short DAPT Total	Long DAPT Events	Long DAPT Total	Weight	Risk Ratio M-H, Random, 95% CI
EXCELLENT 2012	6	722	1	721	3.5%	5.99 [0.72, 49.64]
PRODIGY 2012	15	983	13	987	28.7%	1.16 [0.55, 2.42]
RESET 2012	2	1059	3	1058	4.9%	0.67 [0.11, 3.98]
OPTIMIZE 2013	13	1563	12	1556	25.6%	1.08 [0.49, 2.36]
SECURITY 2014	2	682	3	717	4.9%	0.70 [0.12, 4.18]
ISAR-SAFE 2015	5	1997	4	2003	9.1%	1.25 [0.34, 4.66]
ITALIC 2015	3	912	0	910	1.8%	6.98 [0.36, 135.03]
I-LOVE-IT 2 2016	11	909	7	920	17.5%	1.59 [0.62, 4.08]
IVUS-XPL 2016	2	699	2	701	4.1%	1.00 [0.14, 7.10]
Total (95% CI)		**9526**		**9573**	**100.0%**	**1.25 [0.84, 1.86]**
Total events	59		45			

Heterogeneity: Tau² = 0.00; Chi² = 4.82, df = 8 (P = 0.78); I² = 0%

Test for overall effect: Z = 1.11 (P = 0.27)

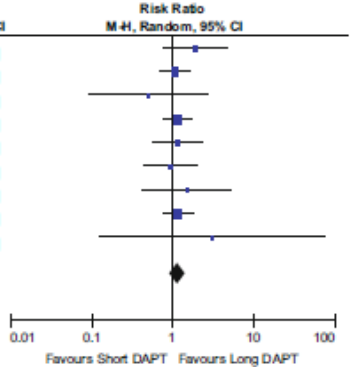


Stent tr.

Study or Subgroup	Short DAPT Events	Short DAPT Total	Long DAPT Events	Long DAPT Total	Weight	Risk Ratio M-H, Random, 95% CI
EXCELLENT 2012	13	722	7	721	5.3%	1.85 [0.74, 4.62]
PRODIGY 2012	41	983	39	987	23.8%	1.06 [0.69, 1.62]
RESET 2012	2	1059	4	1058	1.5%	0.50 [0.09, 2.72]
OPTIMIZE 2013	49	1563	42	1556	26.6%	1.16 [0.77, 1.74]
SECURITY 2014	16	682	15	717	9.0%	1.12 [0.56, 2.25]
ISAR-SAFE 2015	13	1997	14	2003	7.7%	0.93 [0.44, 1.98]
ITALIC 2015	6	912	4	910	2.8%	1.50 [0.42, 5.29]
I-LOVE-IT 2 2016	41	909	36	920	22.8%	1.15 [0.74, 1.79]
IVUS-XPL 2016	1	699	0	701	0.4%	3.01 [0.12, 73.73]
Total (95% CI)		**9526**		**9573**	**100.0%**	**1.14 [0.92, 1.40]**
Total events	182		161			

Heterogeneity: Tau² = 0.00; Chi² = 2.95, df = 8 (P = 0.94); I² = 0%

Test for overall effect: Z = 1.20 (P = 0.23)



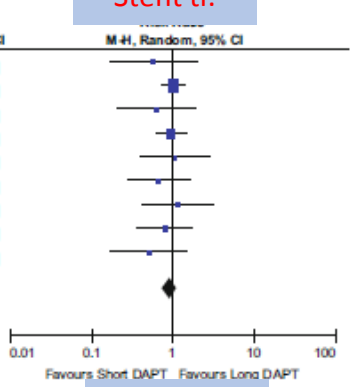
MI

a

Study or Subgroup	Short DAPT Events	Short DAPT Total	Long DAPT Events	Long DAPT Total	Weight	Risk Ratio M-H, Random, 95% CI
EXCELLENT 2012	4	722	7	721	3.0%	0.57 [0.17, 1.94]
PRODIGY 2012	65	983	65	987	40.8%	1.00 [0.72, 1.40]
RESET 2012	5	1059	8	1058	3.6%	0.62 [0.20, 1.90]
OPTIMIZE 2013	43	1563	45	1556	26.5%	0.95 [0.63, 1.44]
SECURITY 2014	8	682	8	717	4.7%	1.05 [0.40, 2.79]
ISAR-SAFE 2015	8	1997	12	2003	5.7%	0.67 [0.27, 1.63]
ITALIC 2015	8	912	7	910	4.4%	1.14 [0.42, 3.13]
I-LOVE-IT 2 2016	11	909	14	920	7.3%	0.80 [0.36, 1.74]
IVUS-XPL 2016	5	699	10	701	3.9%	0.50 [0.17, 1.46]
Total (95% CI)		**9526**		**9573**	**100.0%**	**0.90 [0.73, 1.11]**
Total events	157		176			

Heterogeneity: Tau² = 0.00; Chi² = 3.42, df = 8 (P = 0.91); I² = 0%

Test for overall effect: Z = 0.96 (P = 0.34)



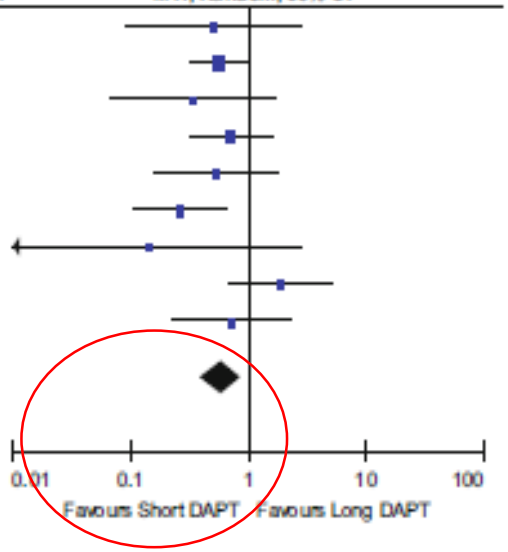
Mortality

BARC bleed >3

Study or Subgroup	Short DAPT Events	Short DAPT Total	Long DAPT Events	Long DAPT Total	Weight	Risk Ratio M-H, Random, 95% CI
EXCELLENT 2012	2	722	4	721	4.9%	0.50 [0.09, 2.72]
PRODIGY 2012	19	983	34	987	26.2%	0.56 [0.32, 0.98]
RESET 2012	2	1059	6	1058	5.4%	0.33 [0.07, 1.65]
OPTIMIZE 2013	10	1563	14	1556	16.5%	0.71 [0.32, 1.60]
SECURITY 2014	4	682	8	717	9.0%	0.53 [0.16, 1.74]
ISAR-SAFE 2015	6	1997	23	2003	14.2%	0.26 [0.11, 0.64]
ITALIC 2015	0	912	3	910	1.7%	0.14 [0.01, 2.76]
I-LOVE-IT 2 2016	11	909	6	920	12.2%	1.86 [0.69, 5.00]
IVUS-XPL 2016	5	699	7	701	9.7%	0.72 [0.23, 2.25]
Total (95% CI)		**9526**		**9573**	**100.0%**	**0.58 [0.39, 0.86]**
Total events	59		105			

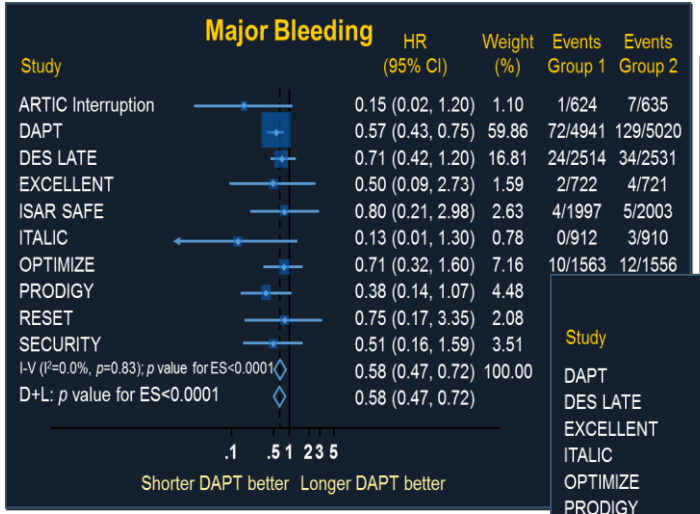
Heterogeneity: Tau² = 0.07; Chi² = 10.12, df = 8 (P = 0.26); I² = 21%

Test for overall effect: Z = 2.70 (P = 0.007)



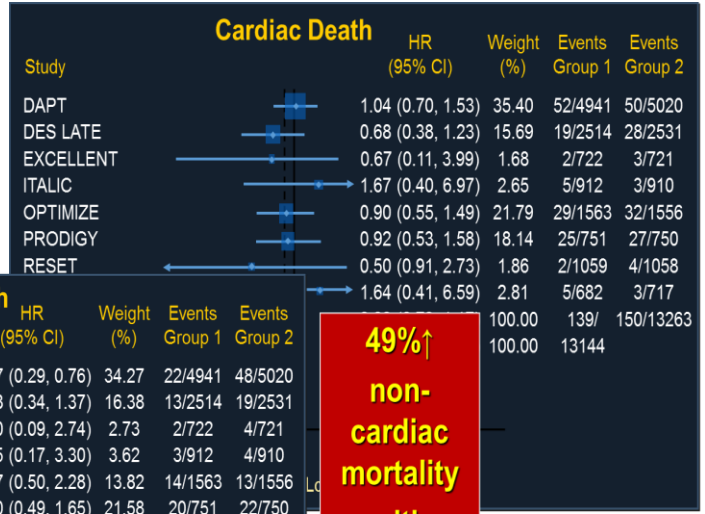
Long DAPT Duration vs. Death

Mortality with Extended DAPT Duration After DES: A Pairwise and Bayesian Network Meta-Analysis of 10 RCTs and 31,666 Pts

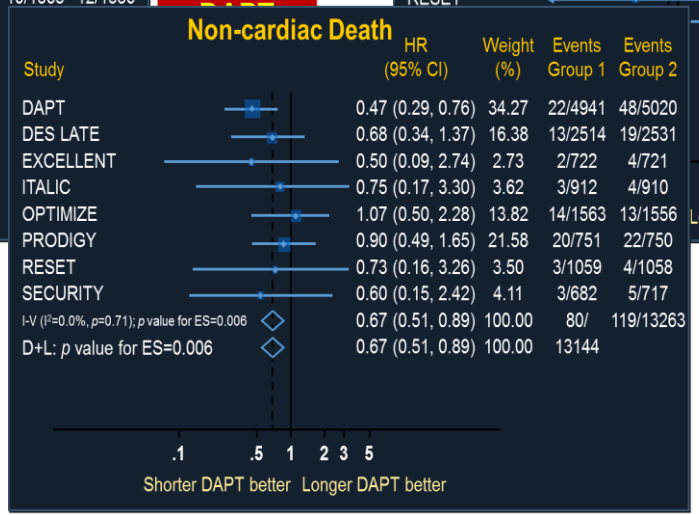


ES=effect size

72%↑ bleeding with prolonged DAPT



8% ↑ cardiac mortality with prolonged DAPT (p=NS)



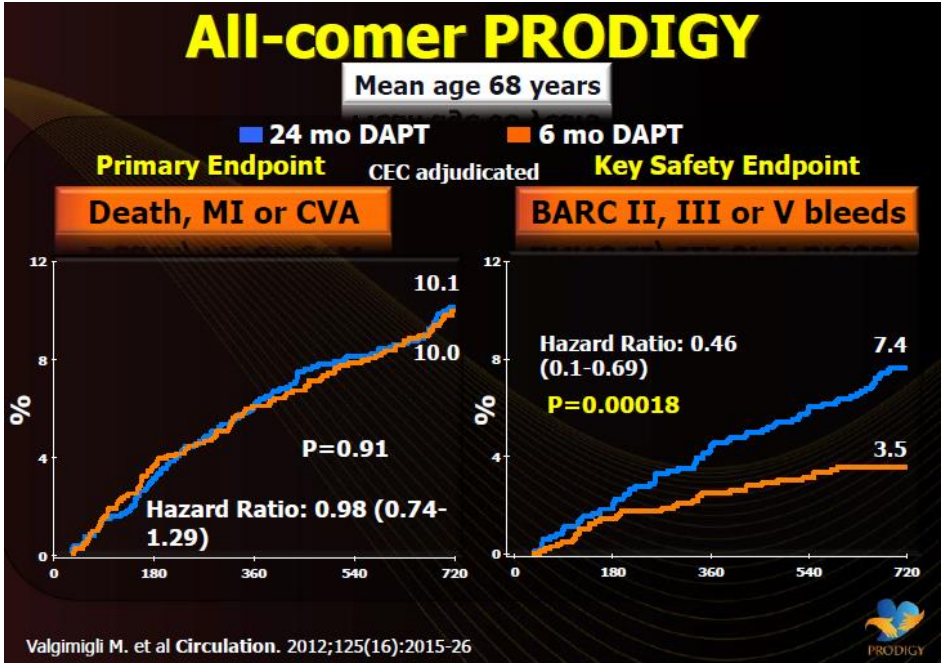
ES=effect size

49%↑ non-cardiac mortality with prolonged DAPT (p=0.006)

"Saving Major Bleedings" means higher SAFETY!

Palmerini T and Stone GW. Lancet 2015

Bleeding following PCI: Long DAPT vs. Short DAPT

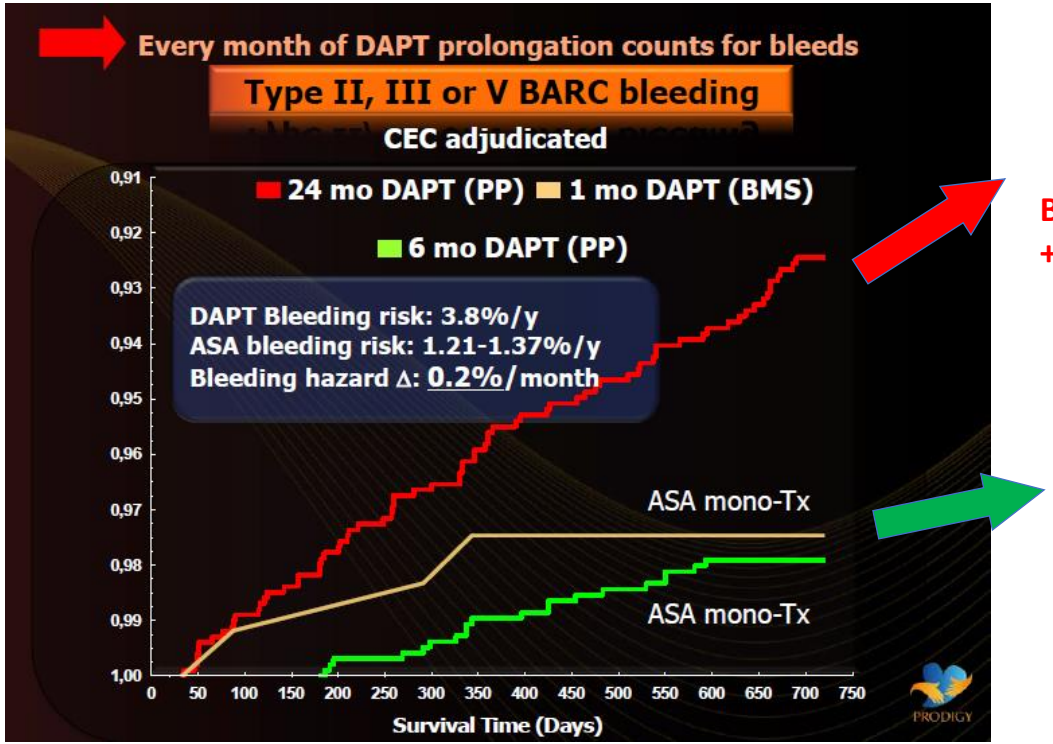


The type of medical therapy prescribed after PCI impacts on bleeding.

Prolonged DAPT (24 months) results in more bleeding events than Reduced DAPT (6 months) without any difference in Death, MI or CVA.

Bleeding following PCI: DAPT vs ASA

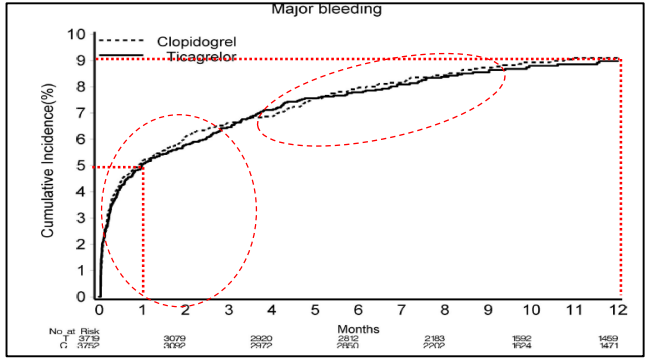
The Bleeding hazard difference between DAPT and ASA alone has been calculated in ~0,2%/month*



Bleeding: +0,2%/month

* Data estracted from Prodigy (Valgimigli – presentation @ EuroPCR)

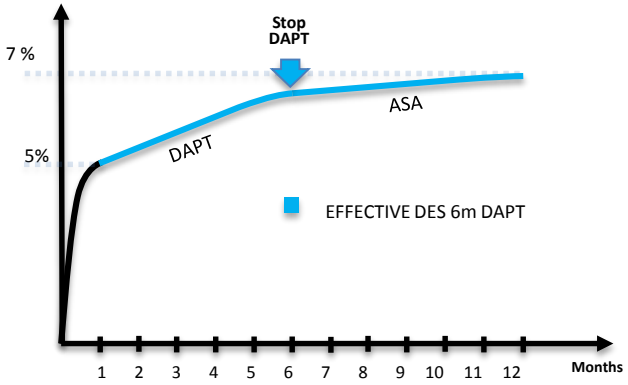
PCI Efficacy vs Bleeding: An interconnected equation



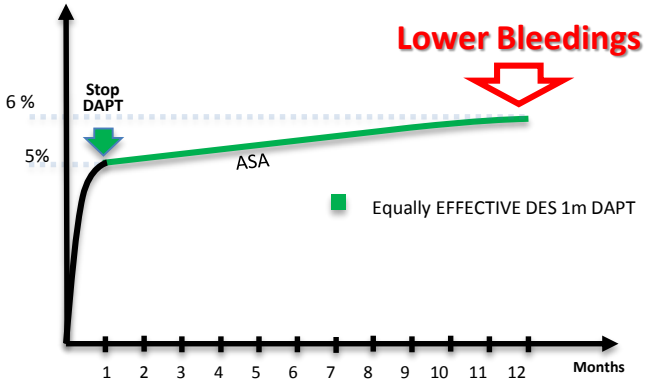
Bleeding events occur:

- 50%, or even more, in the first month after PCI
- The remaining 50% in the following 11 months

EFFECTIVE DES* - 6m DAPT

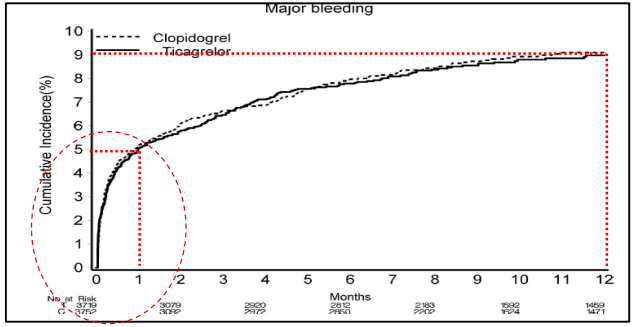


Equally EFFECTIVE DES* - 1m DAPT

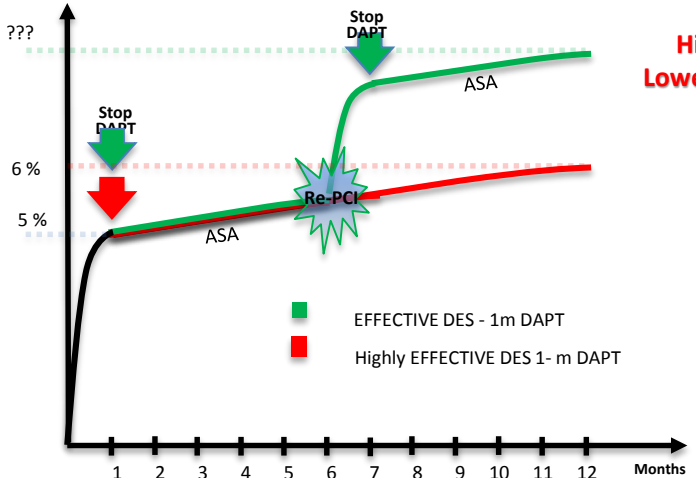


* Simulation based on Plato study results (above) and Prodigy bleeding rate per month for DAPT or ASA alone

PCI Efficacy vs Bleeding: “hypothesis”



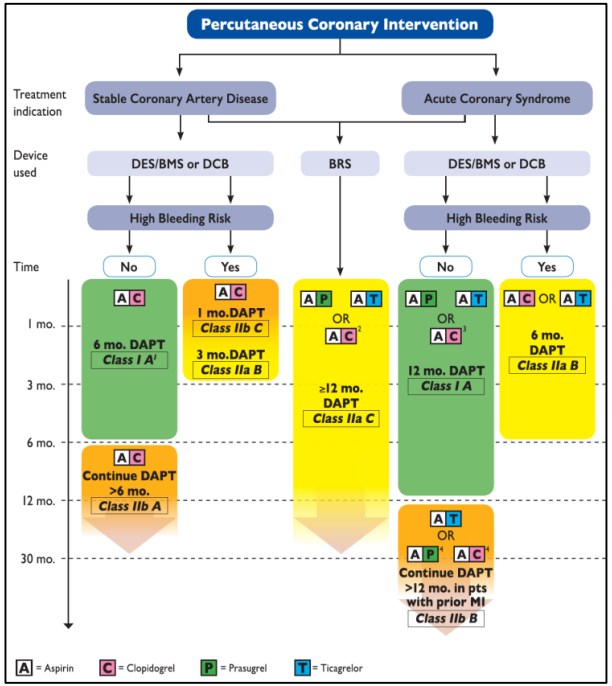
COMPLEX PATIENTS: In-EFFECTIVE DES* - 1m DAPT vs. Highly EFFECTIVE DES* - 1m DAPT



Highly EFFECTIVE DES: Lower Bleedings in complex patients!

* Simulation based on Plato study results (above) and Prodigy bleeding rate per month for DAPT or ASA alone

Comments to the new ESC guidelines



- The extension of DAPT duration is seen as the ONLY way to maximize efficacy (minimize ischemic events) for "treated lesions" and "act" as protection on disease progression. This is based on the assumption that all DES perform the same (except TAXUS).

DAPT score

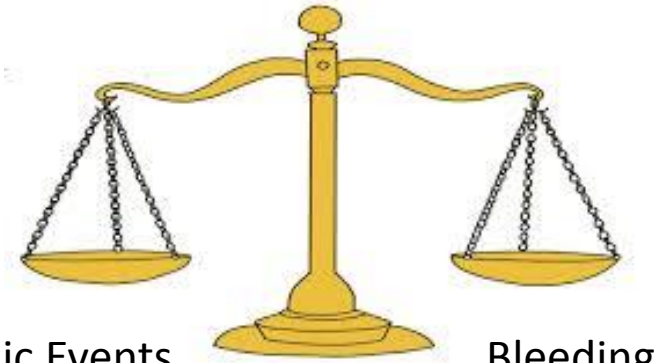
Clinical Prediction Score

	Variable	Points
	Age, y	
Bleeding	≥75	-2
Bleeding	65-<75	-1
	<65	0
Ischemic	Cigarette smoking	1
Ischemic	Diabetes mellitus	1
Ischemic	MI at presentation	1
Ischemic	Prior PCI or prior MI	1
Ischemic	Paclitaxel-eluting stent	1
Ischemic	Stent diameter <3 mm	1
Ischemic	CHF or LVEF <30%	2
Ischemic	Vein graft stent	2

Total score range: -2 to 10

- If a more effective DES is becoming available, specifically for complex lesions in complex patients, it may represent THE NEW ELEMENT able to play a role in the reduction of overall bleeding events.

Efficacy *AND* Safety



Ischemic Events
Stent trombosis

Bleeding Events
Prolonged DAPT

Effective Stent – such as Cre8 Evo:

allows us a ***variable choice*** on DAPT duration based on guidelines, scores *AND* ***patient characteristics***

ReCre8 Trial

- First results of **Re**solute vs **Cre8** @ TCT

Thank you for the attention

UMC Utrecht

ESC guidelines: Risk scores as guidance for DAPT duration

Nowadays there are scores that help deciding which DAPT duration should be given to a patient undergoing PTCA (DAPT score/ Precise/…)

Their use is still limited and their validity (ESC guidelines) needs further data/ evidence

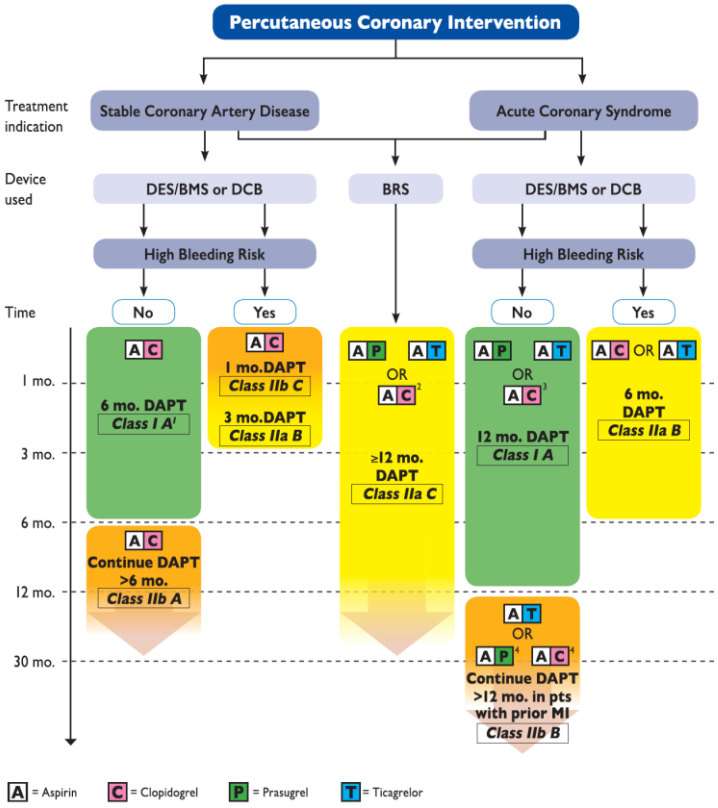
Use of risk scores as guidance for the duration of dual antiplatelet therapy

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

ESC Focused Update on DAPT - Valgimigli et al. Eur Heart J 2017

EUROPEAN SOCIETY OF CARDIOLOGY®

ESC guidelines: Algorithm for DAPT duration after PCI



The TYPE OF DEVICE has NO IMPACT on DAPT duration

"PATIENT CONDITIONS at admission" + "HIGH BLEEDING RISK" impact on DAPT duration

What can we do to facilitate understanding for "LONG vs. SHORT DAPT" to be applied?

Thrombotic/ Bleeding SCORES?

ESC Focused Update on DAPT - Valgimigli et al. Eur Heart J 2017

Risk scores as guidance for DAPT duration: DAPT Score

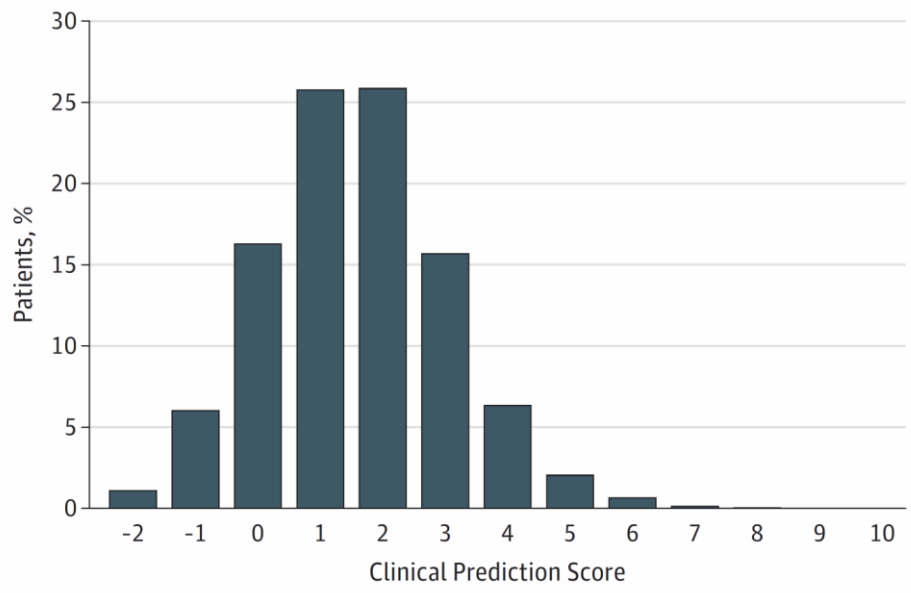
11,648 Patients enrolled in the DAPT trial

Yeh et al. *JAMA* 2016; 315:1735-49

Clinical Prediction Score

Variable	Points
Age, y	
≥75	-2
65-<75	-1
<65	0
Cigarette smoking	1
Diabetes mellitus	1
MI at presentation	1
Prior PCI or prior MI	1
Paclitaxel-eluting stent	1
Stent diameter <3 mm	1
CHF or LVEF <30%	2
Vein graft stent	2
Total score range: -2 to 10	

Predictors of both ischemic and bleeding events (excluded): PAD, Hypert, CKD



Harm | **Benefit**

Low DAPT score (<2)

High DAPT score (≥2)

DAPT and bleeding events post PCI

Bleeding events occur:

- 50%, or even more, in the first month after PCI
- The remaining 50% in the following 11 months

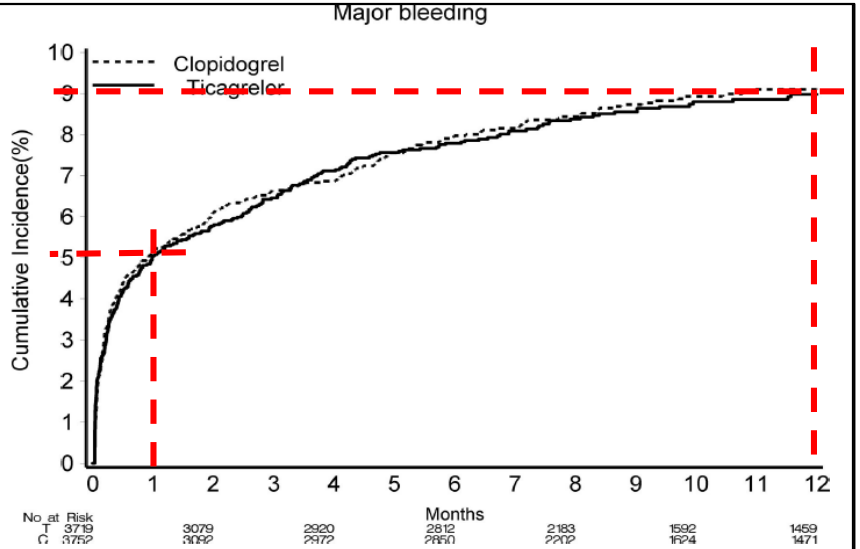


Figure 4. Time-related Kaplan–Meier estimate for major bleeding according to the PLATO definition (HR, 0.98; 95% CI, 0.83 to 1.14; P=0.76).

Time-related Kaplan-Meier estimate for major bleeding according to the PLATO definition