DAPT Duration after PCI

: Criteria and Scoring Systems in Clinical Decision Making

Seoul National University Hospital

Kyung Woo Park, MD, PhD, MBA

No potential conflict of interest

Basics of DAPT

1. Whenever you intensify or prolong the duration of DAPT to reduce the risk of ischemia, there is a bleeding tax to pay.

ACC/AHA FOCUSED UPDATE

2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease

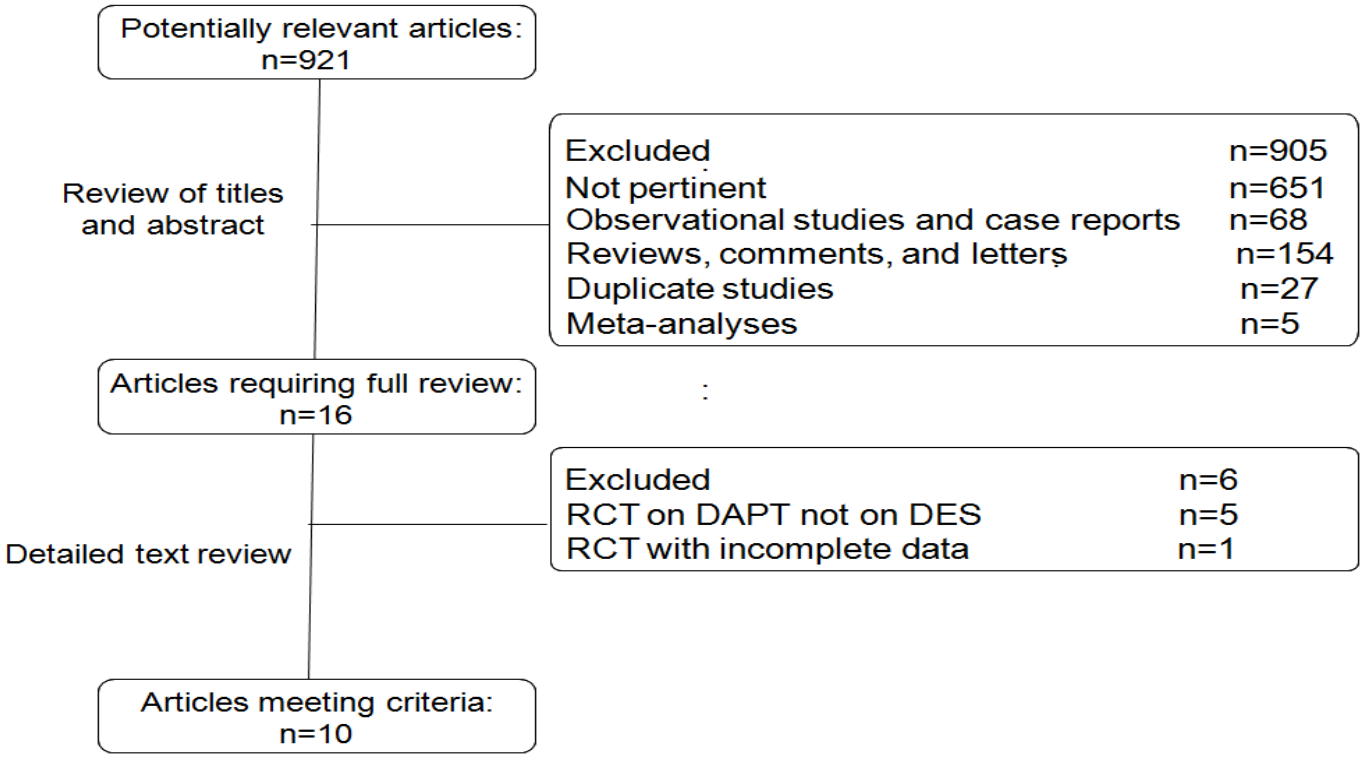
A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

TABLE 3 Overriding Concepts and Updated Recommendations for DAPT and Duration

Intensification of antiplatelet therapy, with the addition of a $P2Y_{12}$ inhibitor to aspirin monotherapy, as well as prolongation of DAPT, necessitates a fundamental tradeoff between decreasing ischemic risk and increasing bleeding risk. Decisions about treatment with and duration of DAPT require a thoughtful assessment of the benefit/risk ratio, integration of study data, and consideration of patient preference.
In general, shorter-duration DAPT can be considered for patients at lower ischemic risk with high bleeding risk, whereas longer-duration DAPT may be reasonable for patients at higher ischemic risk with lower bleeding risk.
Prior recommendations for duration of DAPT for patients treated with DES were based on data from "first-generation" DES, which are rarely if ever used in current clinical practice. Compared with first-generation stents, newer-generation stents have an improved safety profile and lower risk of stent thrombosis. Recommendations in this focused update apply to newer-generation stents.
Updated recommendations for duration of DAPT are now similar for patients with NSTE-ACS and STEMI, as both are part of the spectrum of acute coronary syndrome.

Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials

Tullio Palmerini, Umberto Benedetto, Letizia Bacchi-Reggiani, Diego Della Riva, Giuseppe Biondi-Zoccai, Fausto Feres, Alexandre Abizaid, Myeong-Ki Hong, Byeong-Keuk Kim, Yangsoo Jang, Hyo-Soo Kim, Kyung Woo Park, Philippe Genereux, Deepak L Bhatt, Carlotta Orlandi, Stefano De Servi, Mario Petrou, Claudio Rapezzi, Gregg W Stone

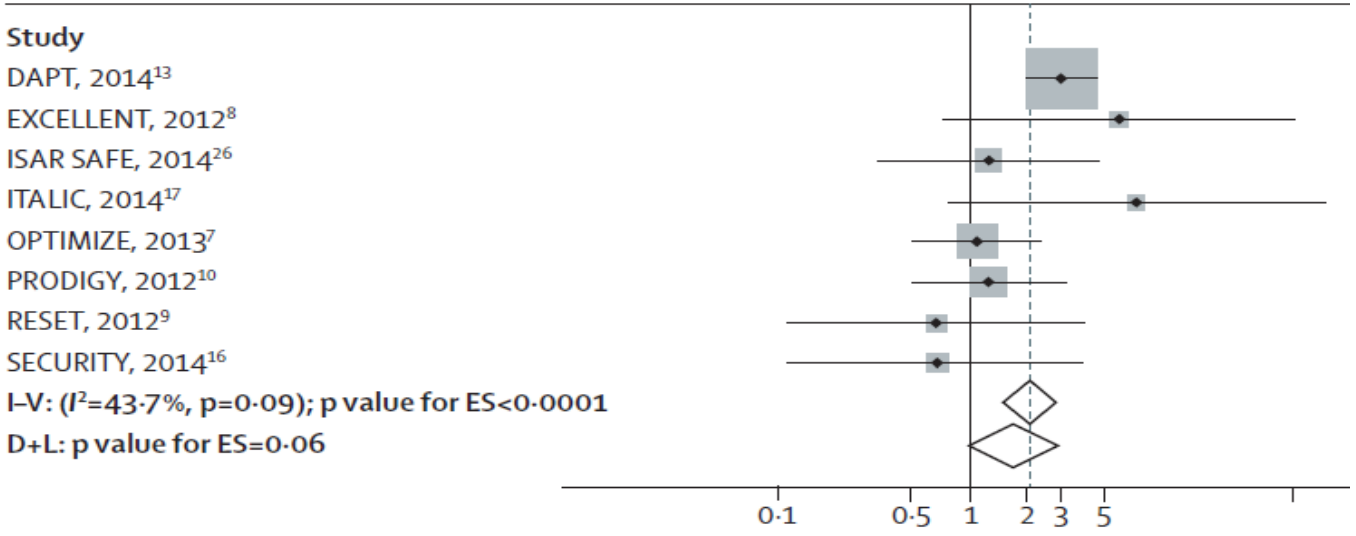


10 RCT
31,666 pts

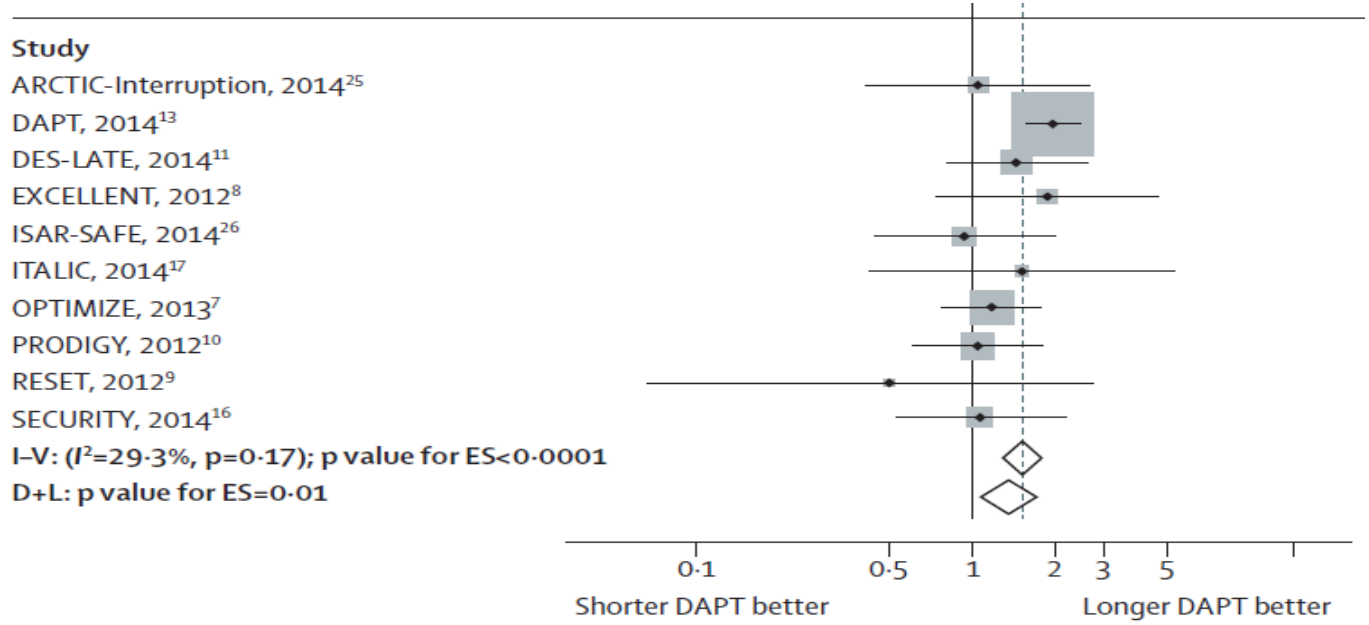
Lancet 2015

Prolonged DAPT: MI and ST

ST

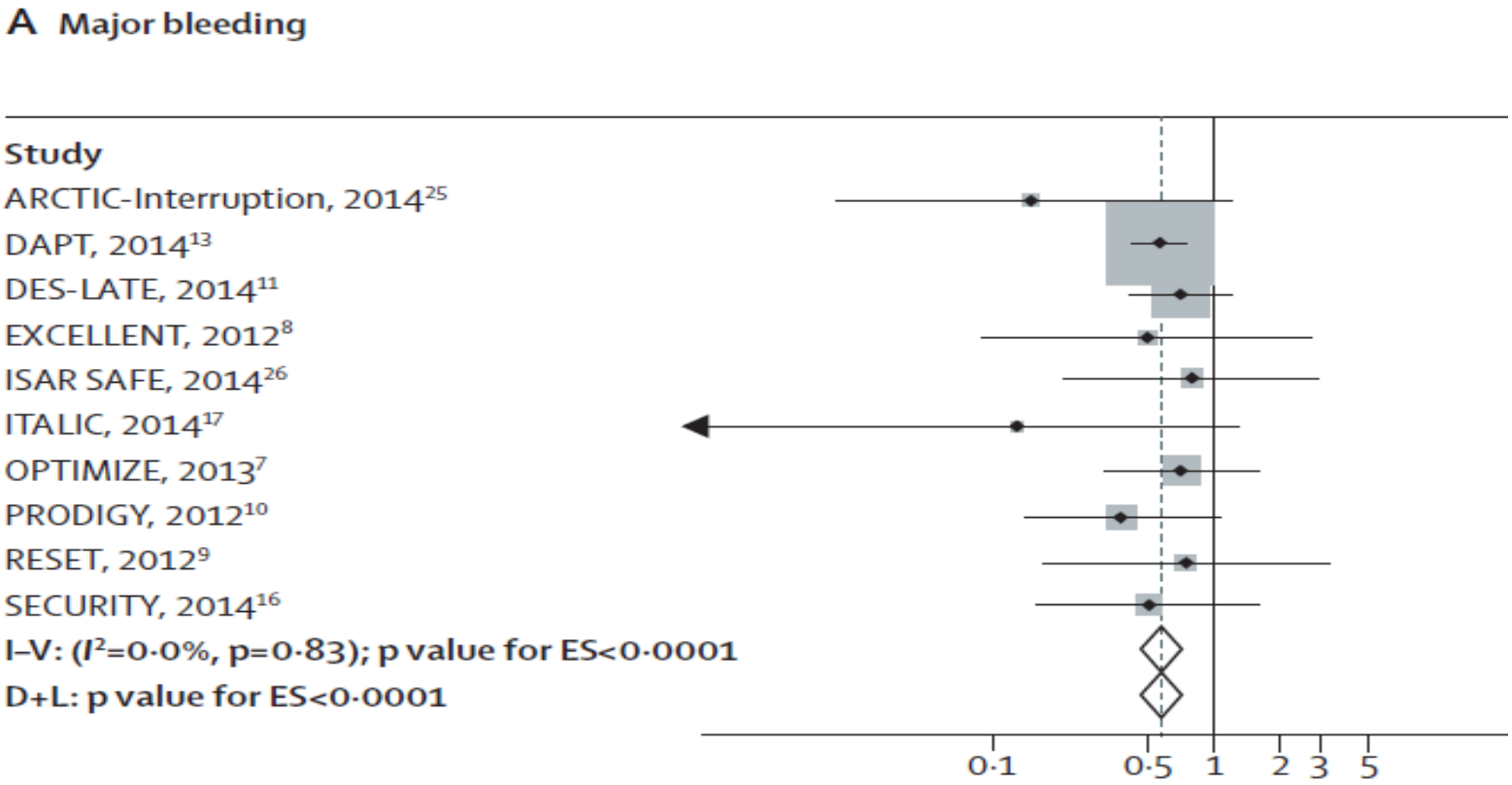


MI



Palmerini et al; Lancet 2015

DAPT and bleeding

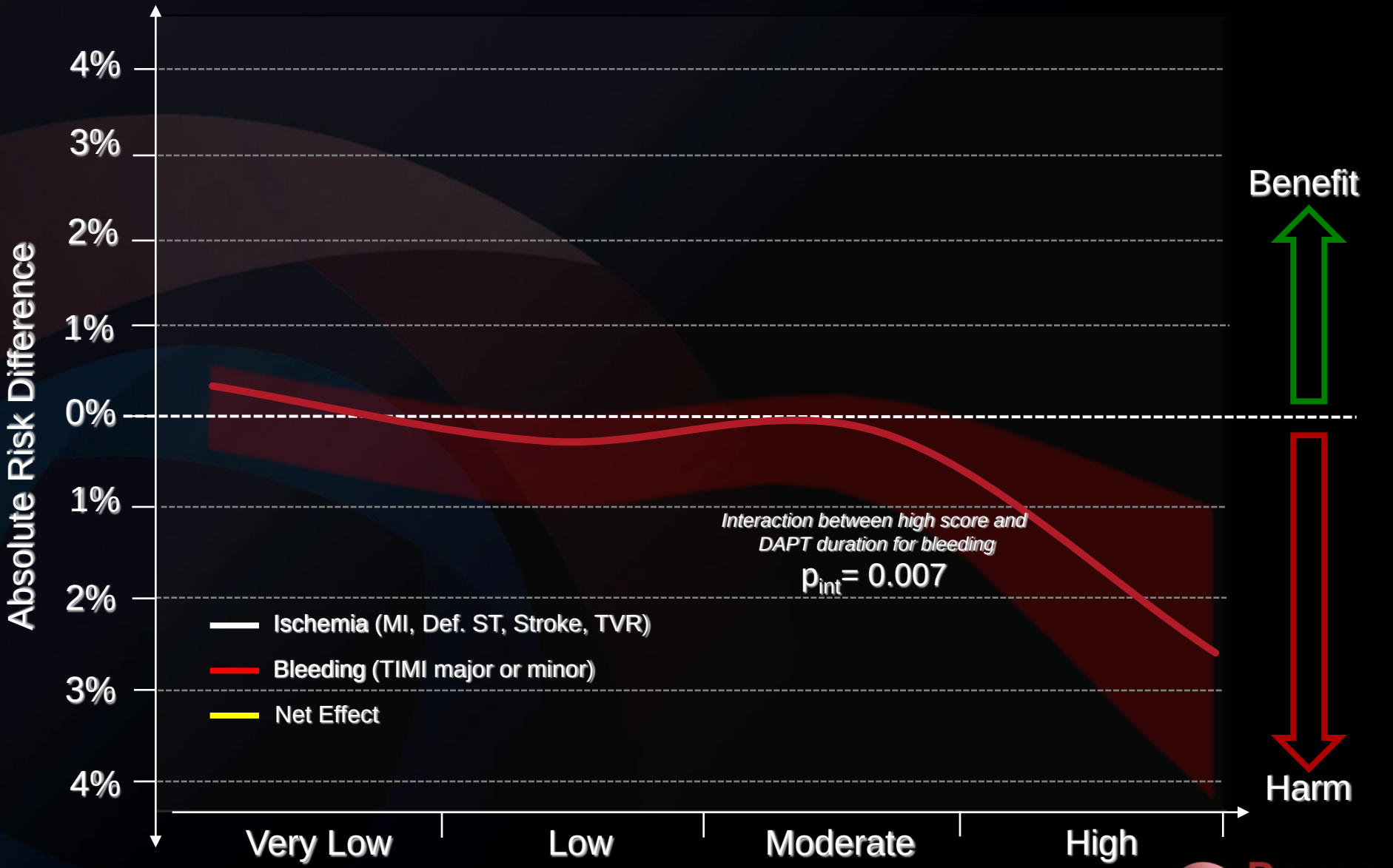


Palmerini et al; Lancet 2015

Basics of DAPT

1. Whenever you intensify or prolong the duration of DAPT to reduce the risk of ischemia, there is a bleeding tax to pay.
2. **Each individual's risk of ischemia and bleeding is different**

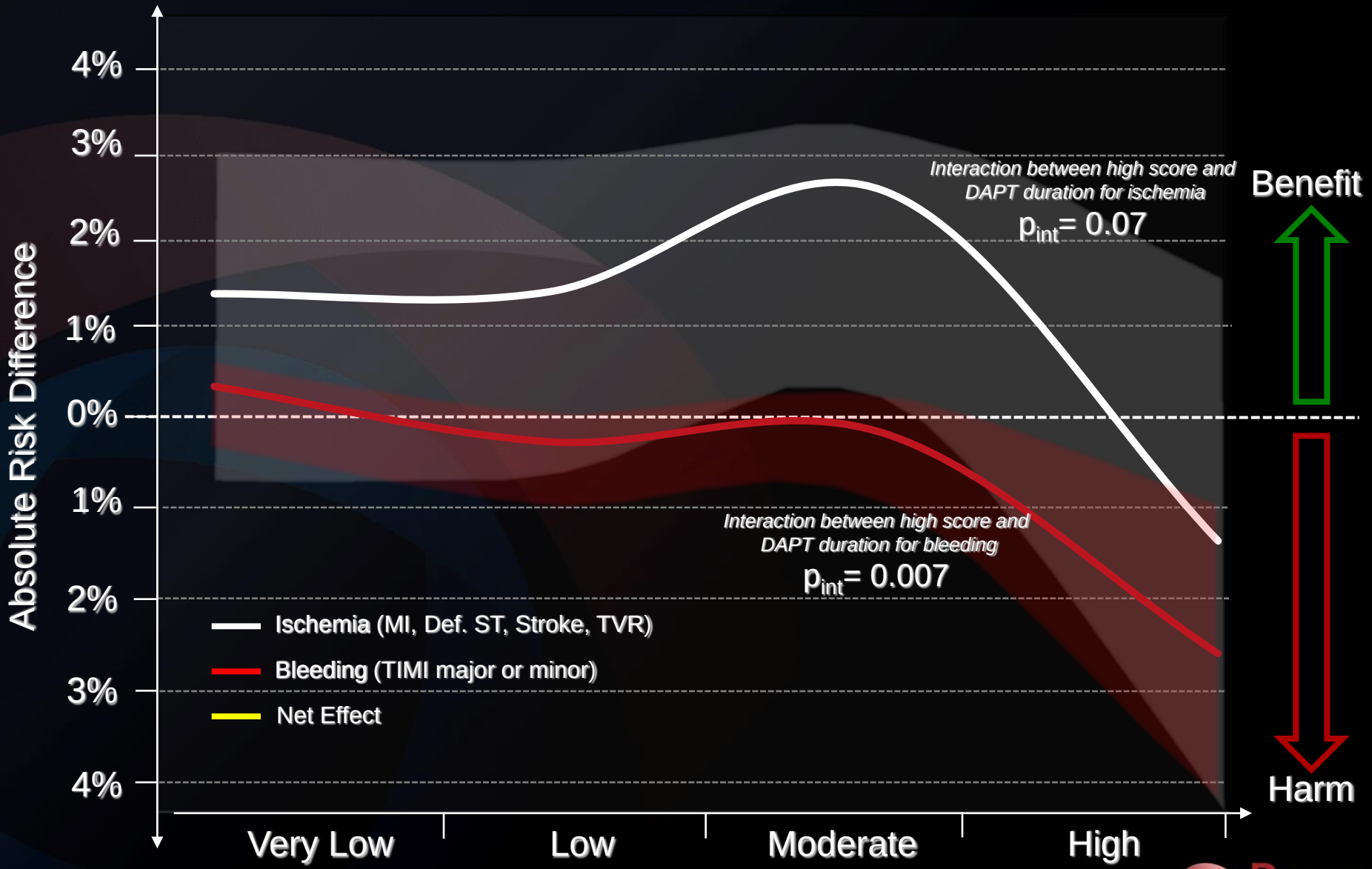
Effect of *Long (12-24 mo.)* vs. short (3-6 mo.) DAPT



PRECISE DAPT

Lancet 2017 Mar 11;389(10073):1025-1034

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



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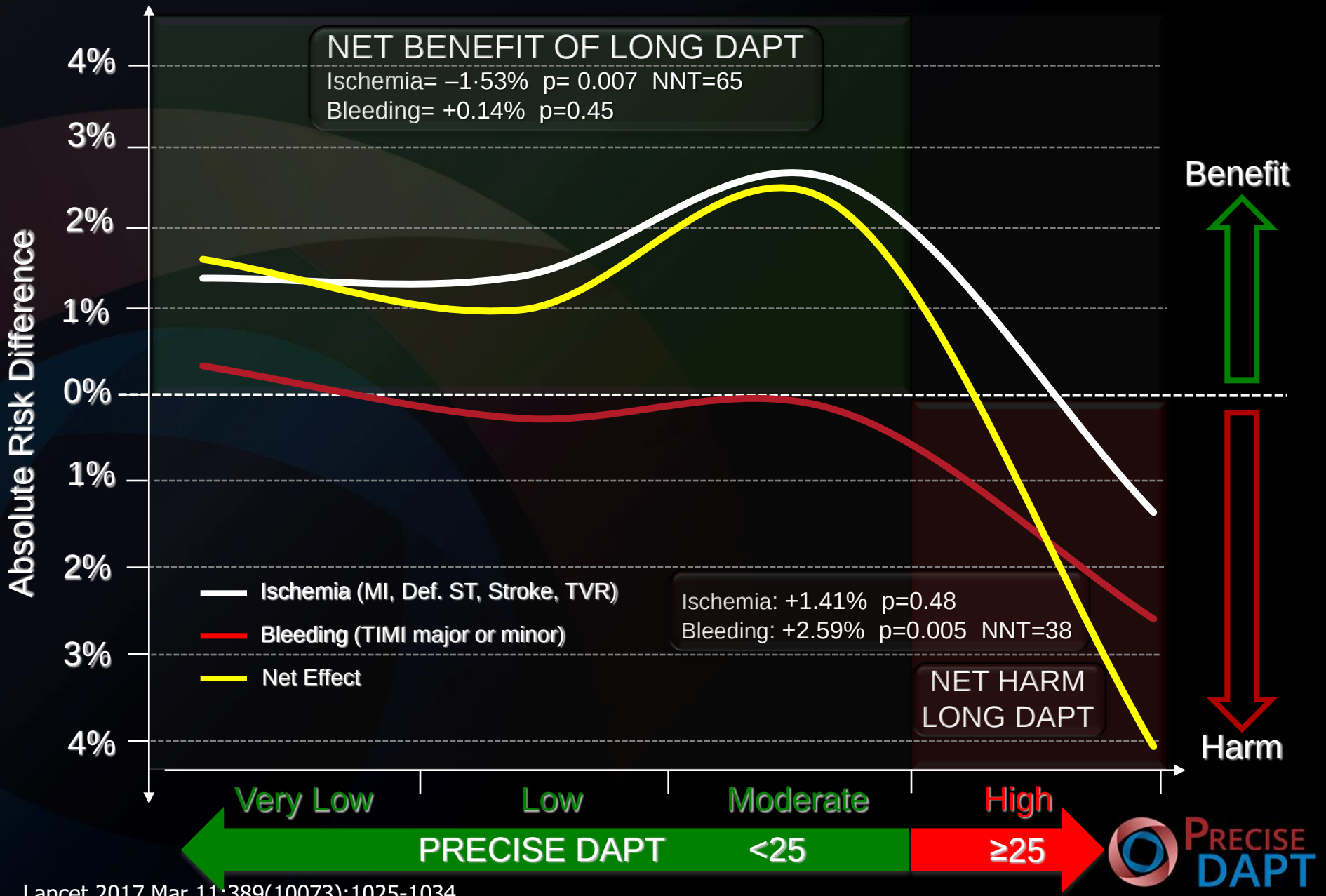
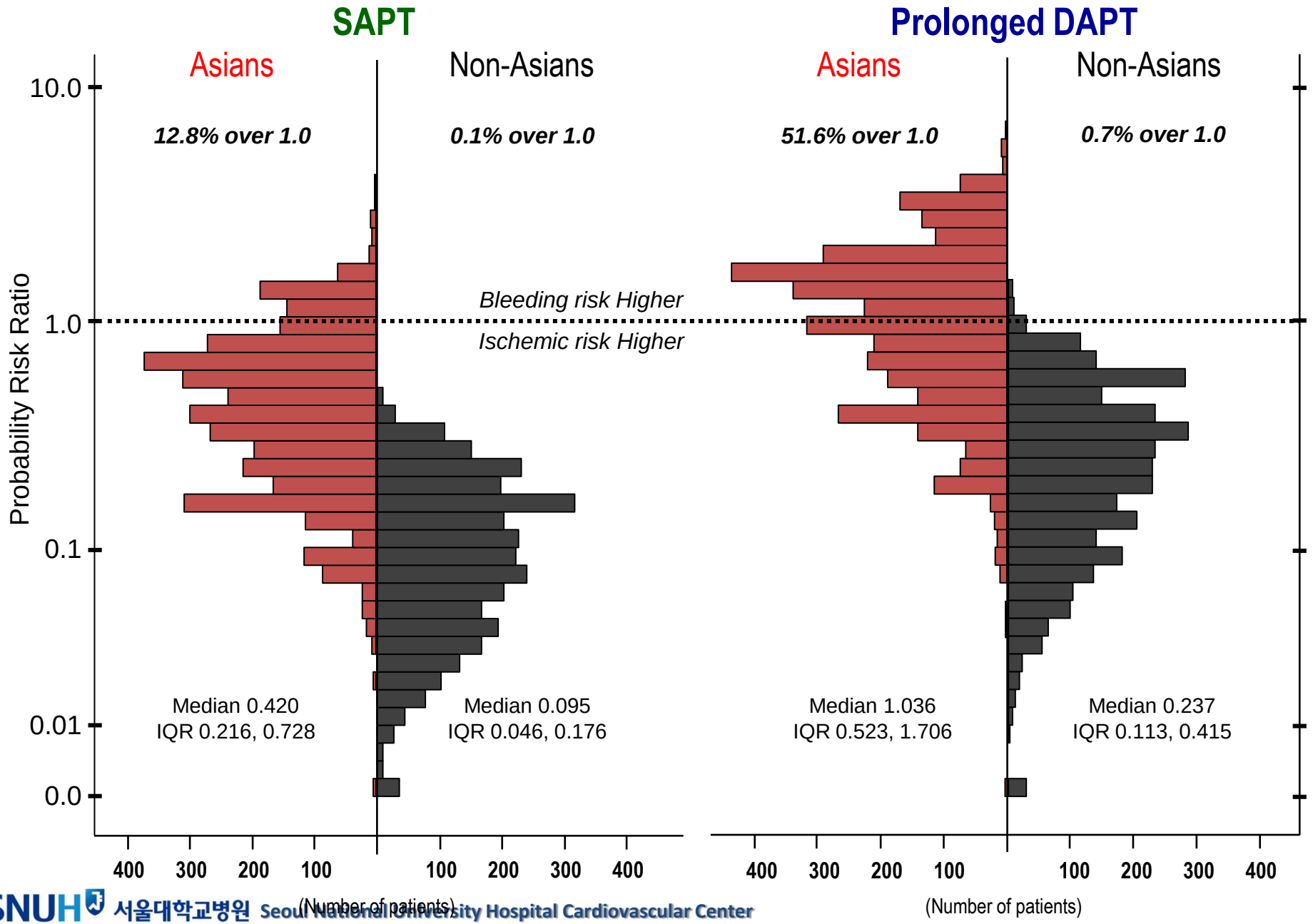


Lancet 2017 Mar 11;389(10073):1025-1034

Probability Risk Ratio of Bleeding to Ischemia

Kang JH, Park KW et al.
Thrombosis and Hemostasis 2018



Basics of DAPT

1. Whenever you intensify or prolong the duration of DAPT to reduce the risk of ischemia, there is a bleeding tax to pay.
2. Each individual's risk of ischemia and bleeding is different
3. **The optimal duration of DAPT cannot be the same for all patients receiving DES. (One size does not fit all).**

Basics of DAPT

Therefore, the *objective is to find the right balance where risk of ischemia is minimized without a marked increase in the risk of major bleeding*.

Now is this possible in a systemic way?

Risk factors for Ischemia vs Bleeding
(2016 ACC/AHA Guidelines)

ISCHEMIC RISK

- Old age
- Co-Morbidities
  - Prior MI
  - Diabetes
  - PAD
  - CKD
- Clinical Presentation: ACS
- Procedure or lesion related
  - 1° gen DES
  - Small stent diameter
  - Long stent
  - Underexpansion
  - Bifurcation
  - ISR
- Recurrent ST

BLEEDING RISK

- Old age
- Female gender
- Low BMI
- Co-Morbidities
  - Prior bleeding
  - CKD
  - Diabetes
  - Anemia
- Medications
  - NSAID
  - Anticoagulation
  - Steroid use

Levine GN et al. J Am Coll Cardiol 2106

10 centers in Korea

Successful DES implantation

May 2003 ~ May 2007

⇩

Cases: 123 ST Pts

(124 ST cases, 128 ST lesions)

in Korea Stent Thrombosis registry (KoST)

⇕

Controls: 2,192 control pts without ST for at least 6mo

in SNUH DES registry

Park KW, Kim HS et al. Circulation J 2011

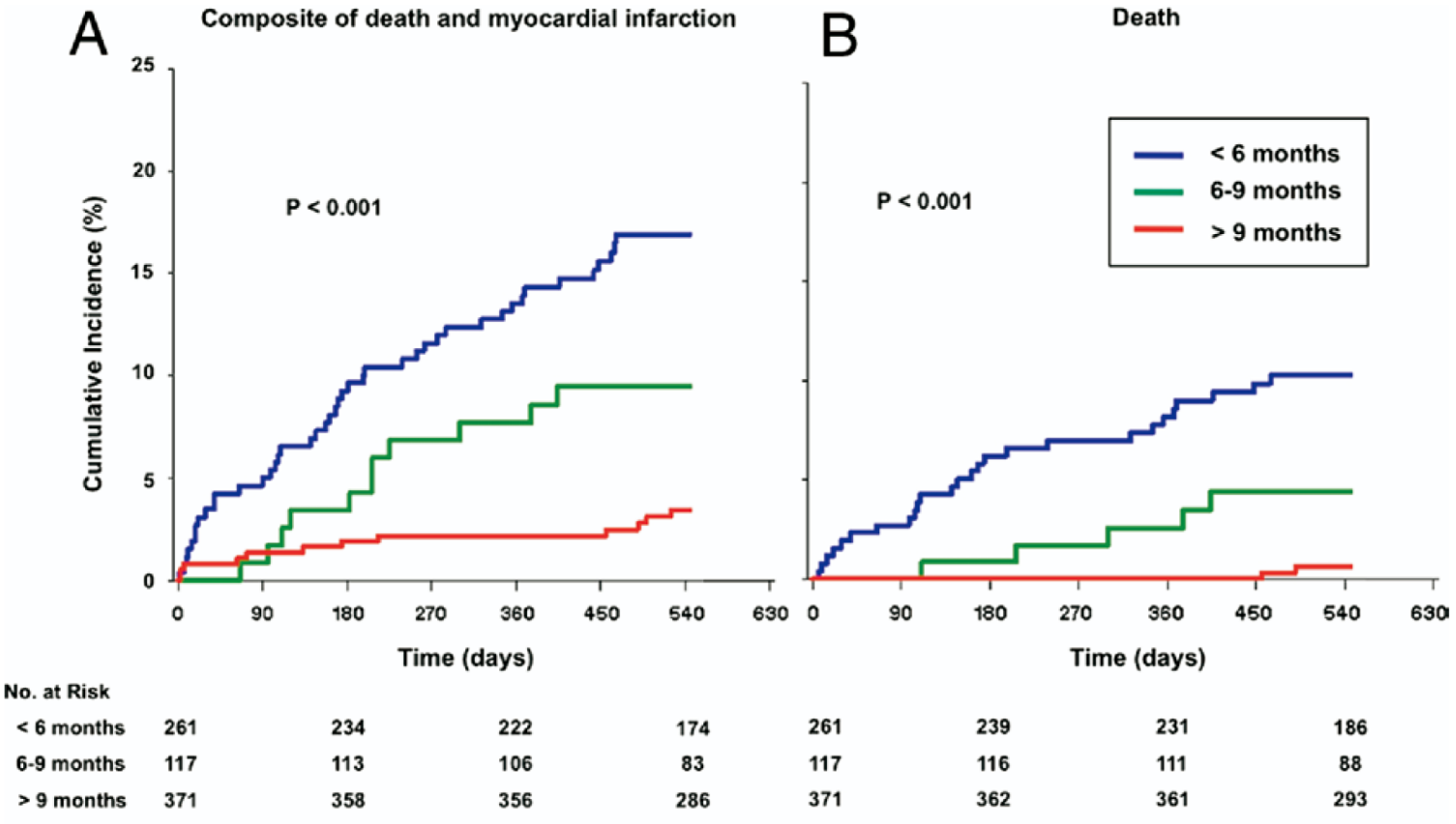
Independent Predictors of ST

	Hazard ratio (95% confidence interval)	p value
Both early and delayed ST		
AMI	3.91(2.66-5.74)	<0.001
Low EF	3.51(2.01-6.13)	<0.001
Stent diameter (per 1mm decrease)	2.71(1.45-5.05)	0.002
DES ISR	4.75(2.32-9.75)	<0.001
Only Early ST		
Bifurcation stenting	2.39 (1.27-4.52)	0.007
Only Delayed ST (Late + VL)		
Younger Age (per decade decrease)	1.8 (1.5-2.1)	<0.001
Hypertension / Anti-HT Med	0.50 (0.27-0.92)	0.025
Renal insufficiency	2.16(1.05-6.31)	0.031
LAD PCI	2.47(1.36-4.51)	0.003

Park KW, Kim HS et al. Circulation J 2011

Co-Morbidity Matters

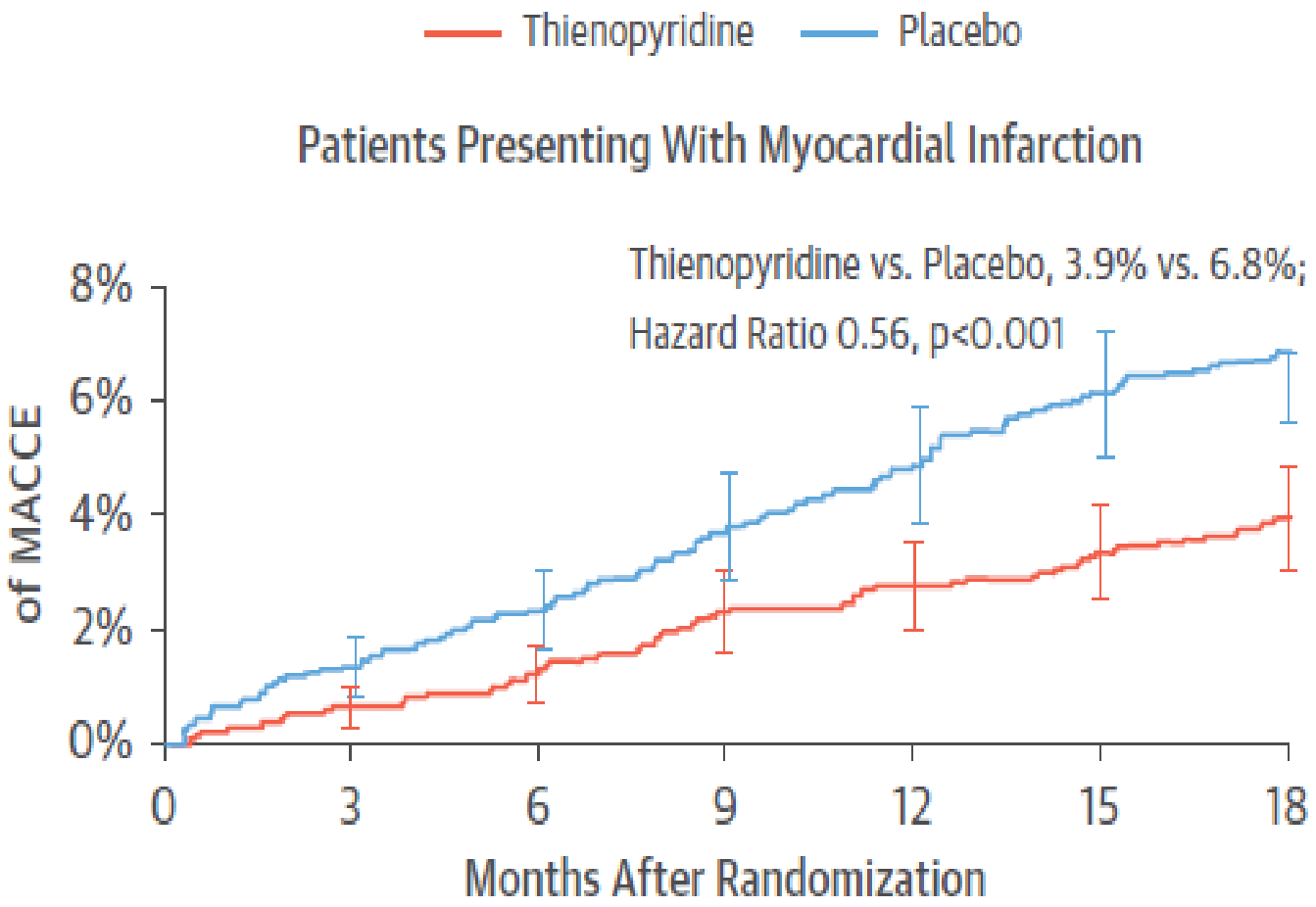
(Duration of DAPT in DM patients and Outcome)



All Patient Analysis

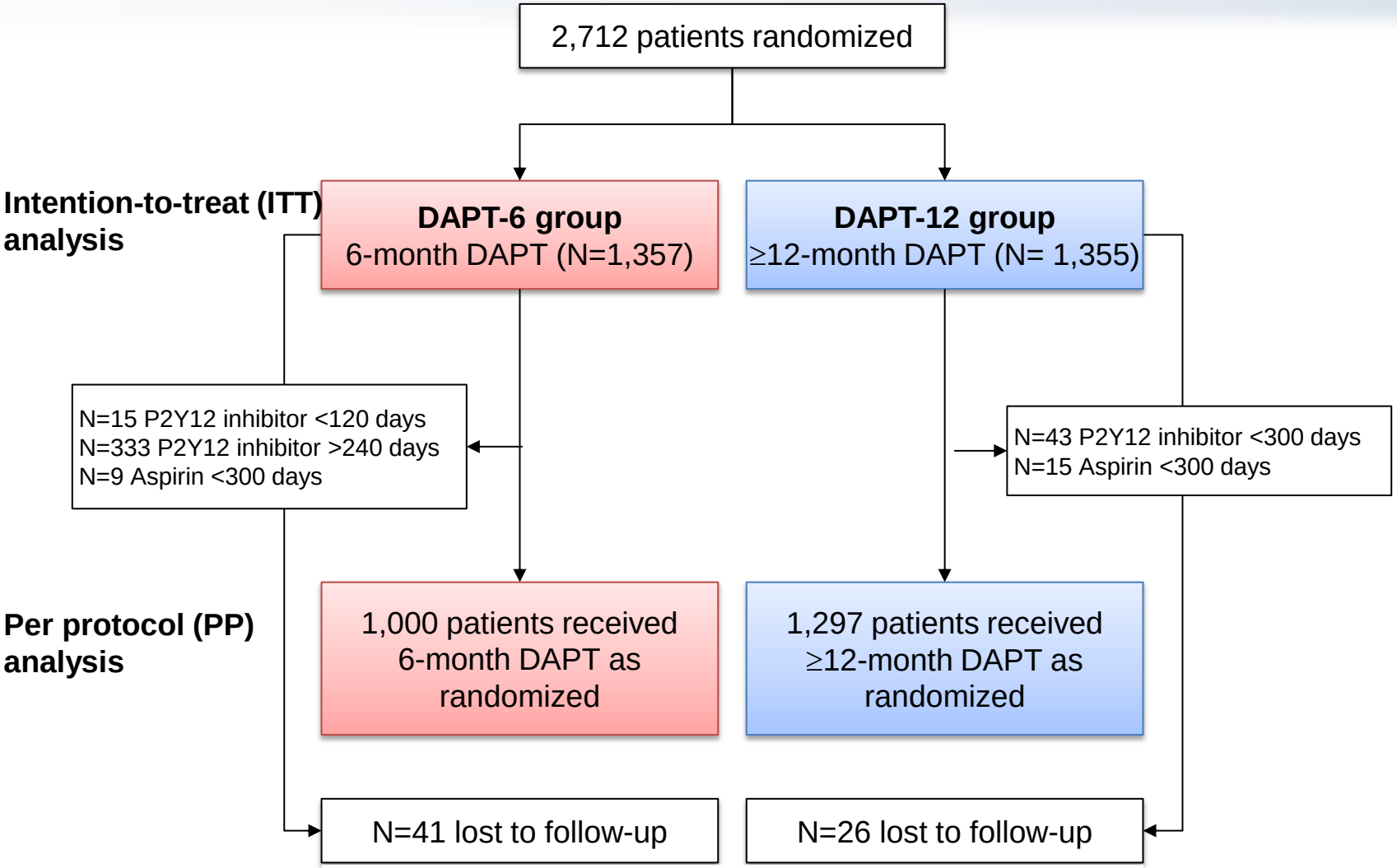
Brar et al. J Am Coll Cardiol 2008; 51:2220-7

Clincal Presentation Matters



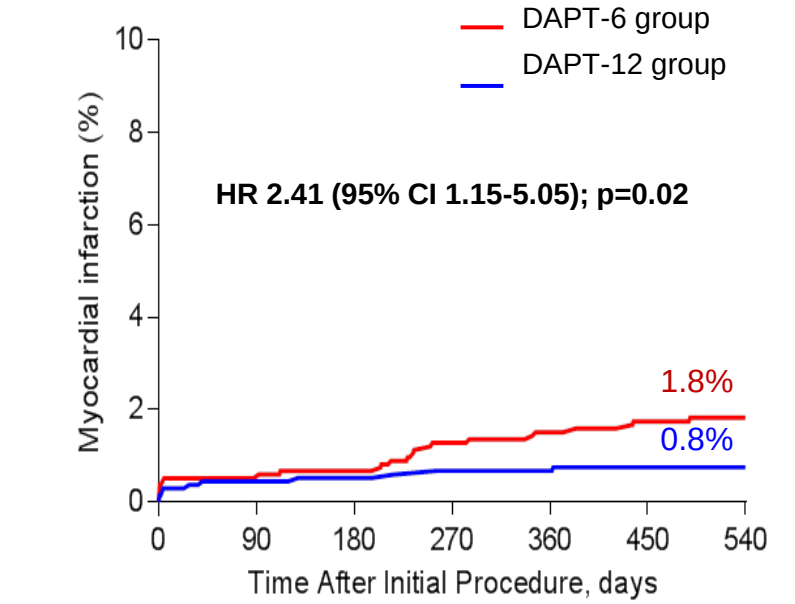
Yeh et al; JACC 2015

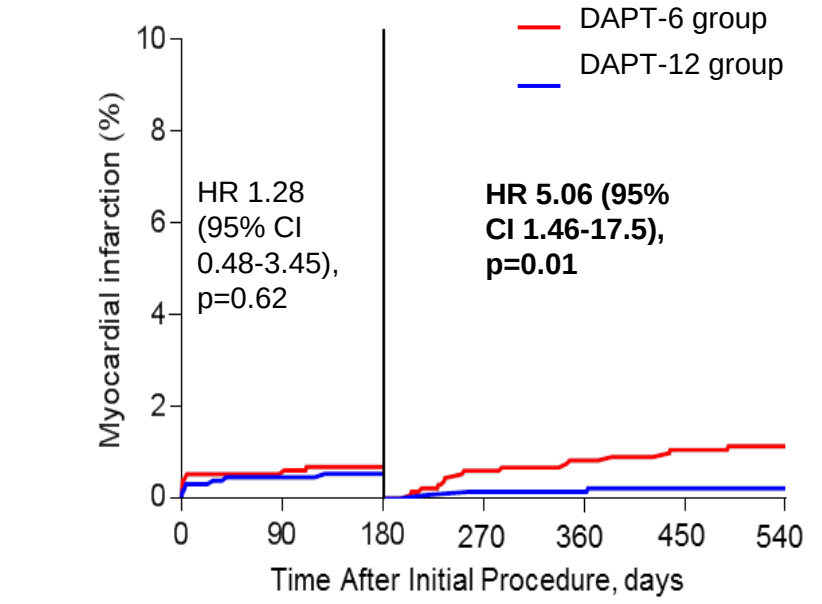
SMART-DATE study: ACS with PCI



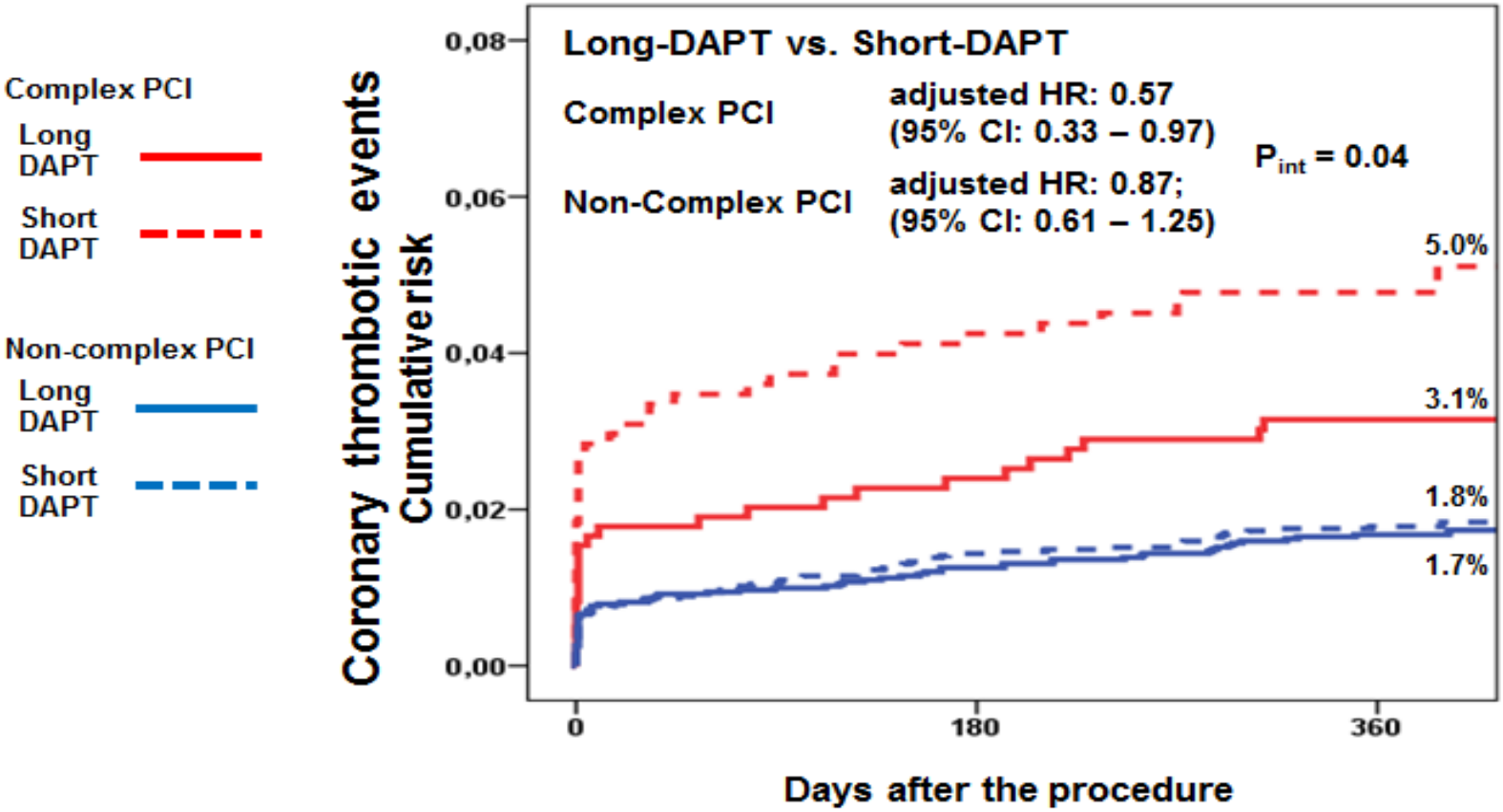
Primary endpoint: 18-month MACCE
a composite of all-cause mortality, MI, and cerebrovascular events

Overall PEP Neutral but….
Myocardial infarction (ITT)





Lesion Complexity Matters



Complex PCI - Long DAPT	854	806	689
Non-complex PCI - Long DAPT	3946	3828	3503
Complex PCI - Short DAPT	826	767	668
Non-complex PCI - Short DAPT	3951	3816	3500

Giustino et al; JACC 2016

Way too many factors, factors, and factors……

Can we please use a risk scoring system to simplify?

DAPT score

Original Investigation

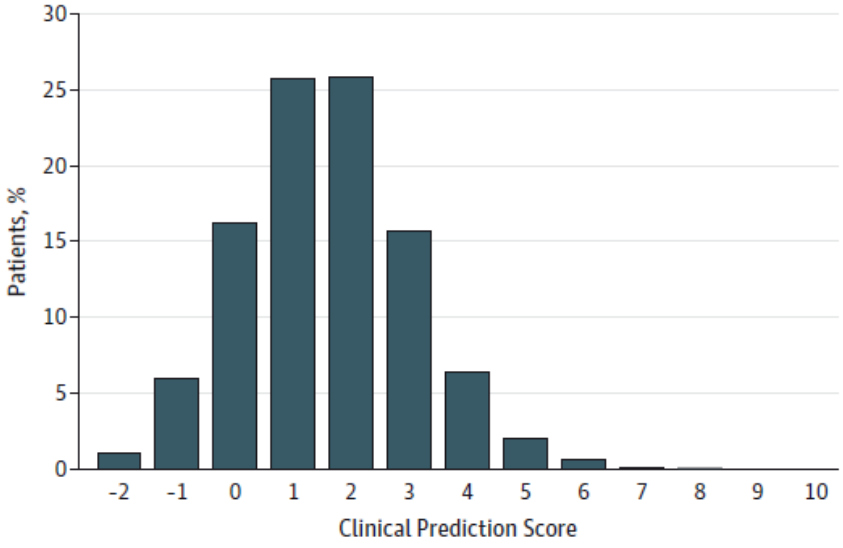
Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention

Robert W. Yeh, MD, MSc; Eric A. Secemsky, MD, MSc; Dean J. Kereiakes, MD; Sharon-Lise T. Normand, PhD; Anthony H. Gershlick, MBBS; David J. Cohen, MD, MSc; John A. Spertus, MD, MPH; Philippe Gabriel Steg, MD; Donald E. Cutlip, MD; Michael J. Rinaldi, MD; Edoardo Camenzind, MD; William Wijns, MD, PhD; Patricia K. Apruzzese, MA; Yang Song, MS; Joseph M. Massaro, PhD; Laura Mauri, MD, MSc; for the DAPT Study Investigators

- ✓ A total of 11,648 patients undergoing PCI with coronary stents
  - ✓ (EES: 40.3%; PES: 22.9%; ZES: 10.9%;SES: 9.6%; BMS: 14.4%)
- ✓ Validation: PROTECT trial, PCI with SES vs. ZES and followed up for 5 years

Figure 2. Elements of Clinical Prediction Score and Distribution of Score Among Randomized DAPT Study Patients (Derivation Cohort, 11 648 Patients)

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	



JAMA. 2016;315(16):1735-1749.

DAPT score

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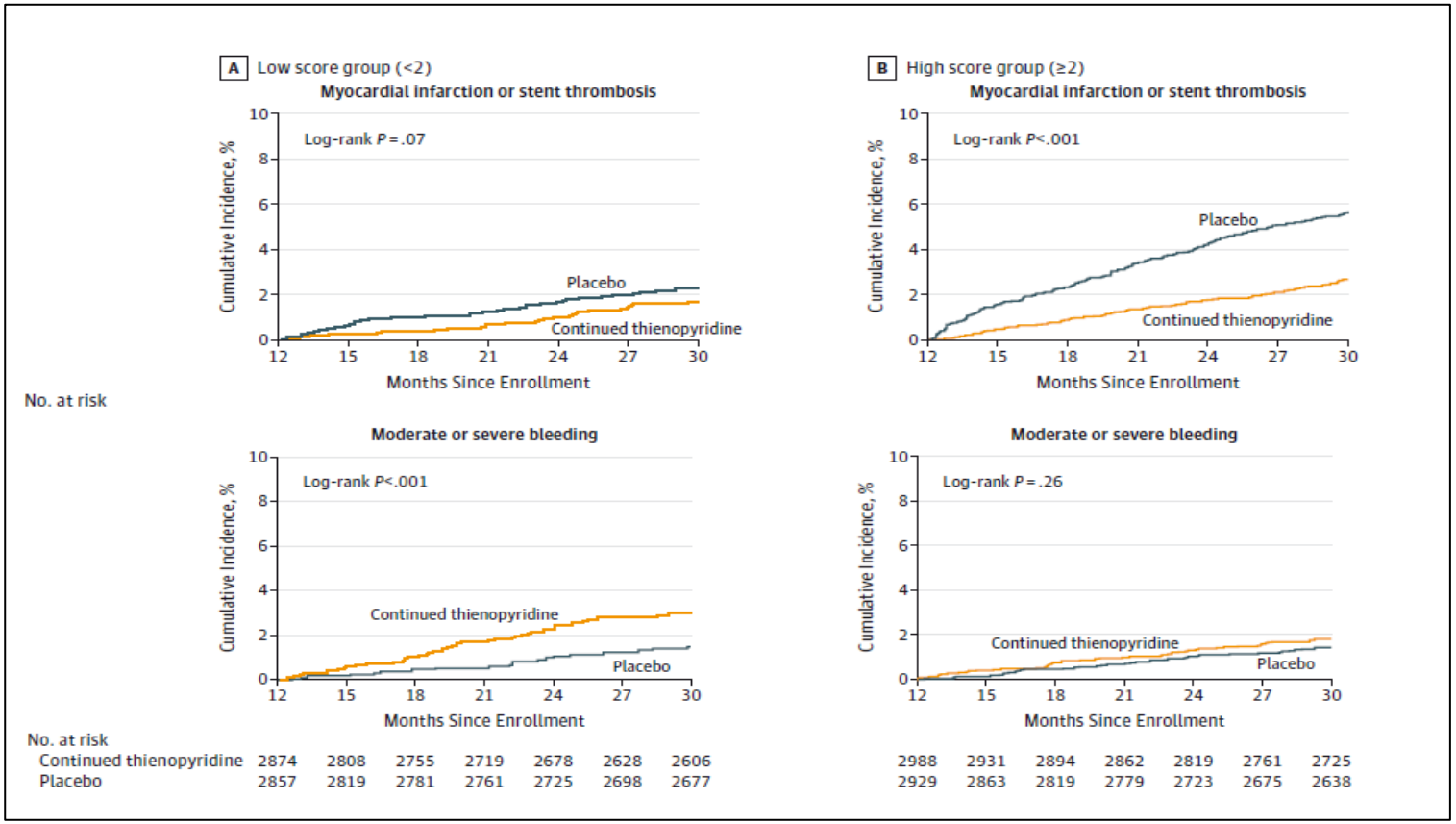
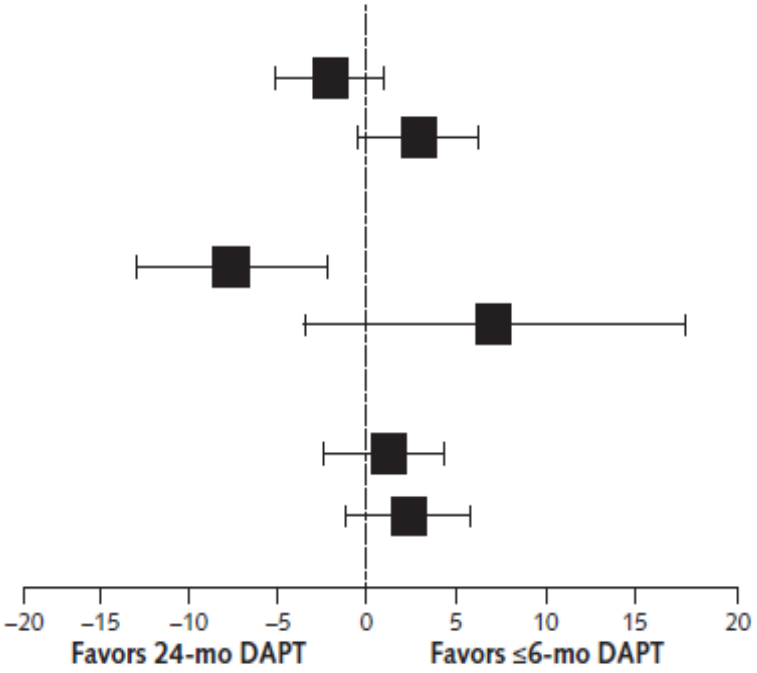
- ✓ Limitations
  - ✓ 60% were 1st gen DES or BMS (obsolete stents)
  - ✓ Validation in PROTECT study (1st gen DES)
  - ✓ Vein graft stent?
  - ✓ How should be decide whether to use <12 months?



JAMA. 2016;315(16):1735-1749.

Limitation of the DAPT score

Subgroup	Risk Difference (95% CI), %	*P* Value for Interaction
Primary efficacy outcome		
Overall (*n* = 1970)		
High DAPT score	−2.05 (−5.04 to 0.95)	0.030
Low DAPT score	2.91 (−0.43 to 6.25)	
Paclitaxel-eluting stents (*n* = 490)		
High DAPT score	−7.55 (−12.85 to −2.25)	0.015
Low DAPT score	7.15 (−3.43 to 17.73)	
Other coronary stents (*n* = 1480)		
High DAPT score	1.23 (−2.41 to 4.86)	0.65
Low DAPT score	2.38 (−1.12 to 5.87)	



Piccolo Ann Int Med 2017

PARIS score

- The PARIS (Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients) registry
  - a prospective, multicenter, observational study of patients undergoing PCI with stent implantation in the United States and Europe between July 2009 and Dec ember 2010
  - 15% 1st G DES, 85% 2nd G DES
- Endpoints
  - Coronary thrombotic events (CTE)
    - definite or probable ST, spontaneous myocardial infarction (MI)
  - Major bleeding events: Bleeding Academic Research Consortium type 3 or 5
- External validation
  - ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) registry

Drug-eluting stent type*	
Everolimus-eluting	5538 (64·5%)
Paclitaxel-eluting	1415 (16·5%)
Sirolimus-eluting	1155 (13·5%)
Zotarolimus-eluting fast release	535 (6·2%)
Zotarolimus-eluting slow release	187 (2·2%)
Other	21 (0·2%)

PARIS score

Coronary Thrombosis and Major Bleeding After PCI With Drug-Eluting Stents

Risk Scores From PARIS

TABLE 2 Procedural Characteristics in Patients With Versus Without 2-Year Coronary Thrombotic Events or Major Bleeding Events

	CTE (n = 151)	No CTE (n = 4,039)	p Value	MB (n = 133)	No MB (n = 4,057)	p Value
Target vessel						
LAD	75 (47.8)	1,947 (48.1)	0.94	62 (42.8)	1,960 (48.3)	0.19
LM	5 (3.2)	137 (3.4)	0.89	8 (5.5)	134 (3.3)	0.15
LCx	42 (26.8)	1,281 (31.6)	0.19	45 (31.0)	1,278 (31.5)	0.91
RCA	56 (35.7)	1,362 (33.6)	0.59	58 (40.0)	1,360 (33.5)	0.10
Type of stent implanted			0.79			0.61
First-generation DES	24 (15.3)	650 (16.1)		21 (14.5)	653 (16.1)	
Second-generation DES	133 (84.7)	3,400 (84.0)		124 (85.5)	3,409 (83.9)	
Multivessel PCI	20 (13.3)	632 (15.7)	0.42	25 (18.8)	627 (15.4)	0.30
Total stent length, mm						
<20	43 (28.5)	1,355 (33.6)	0.19	33 (24.8)	1,365 (33.7)	0.03
20–40	61 (40.4)	1,434 (35.5)	0.22	54 (40.6)	1,441 (35.5)	0.23
>40	47 (31.1)	1,250 (30.9)	0.96	46 (34.6)	1,251 (30.8)	0.36
Baseline TIMI flow grade 0/1	13 (8.7)	376 (9.7)	0.69	373 (10.0)	16 (11.7)	0.41
Final TIMI flow grade 3	150 (99.3)	3,929 (99.7)	0.49	0 (0.0)	14 (0.4)	0.48
Stent diameter	3.0 ± 0.5	3.1 ± 0.5	0.03	3.1 ± 0.5	3.1 ± 0.5	0.84
Complex procedure*	49 (32.5)	1,352 (33.5)	0.48	54 (40.6)	1,347 (33.2)	0.08

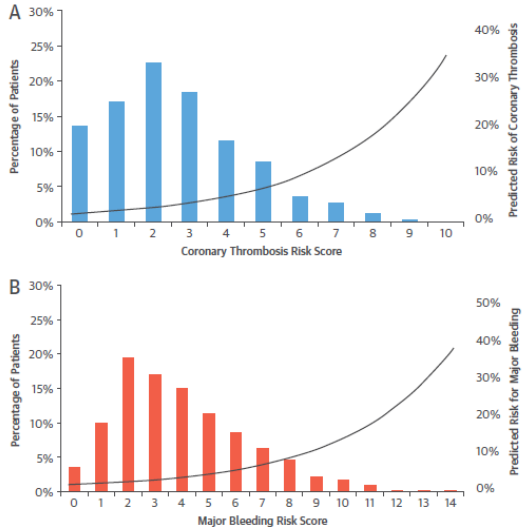
TABLE 4 Integer Risk Score for Major Bleeding

Parameter	Score
Age, yrs	
<50	0
50–59	+1
60–69	+2
70–79	+3
≥80	+4
BMI, kg/m^2	
<25	+2
25–34.9	0
≥35	+2
Current smoking	
Yes	+2
No	0
Anemia	
Present	+3
Absent	0
CrCl <60 ml/min	
Present	+2
Absent	0
Triple therapy on discharge	
Yes	+2
No	0

TABLE 5 Integer Risk Score for Coronary Thrombotic Events

Parameter	Score
Diabetes mellitus	
None	0
Non-insulin-dependent	+1
Insulin-dependent	+3
Acute coronary syndrome	
No	0
Yes, Tn-negative	+1
Yes, Tn-positive	+2
Current smoking	
Yes	+1
No	0
CrCl <60 ml/min	
Present	+2
Absent	0
Prior PCI	
Yes	+2
No	0
Prior CABG	
Yes	+2
No	0

FIGURE 2 Histograms Displaying the Frequency of Thrombotic and Bleeding Risk Scores

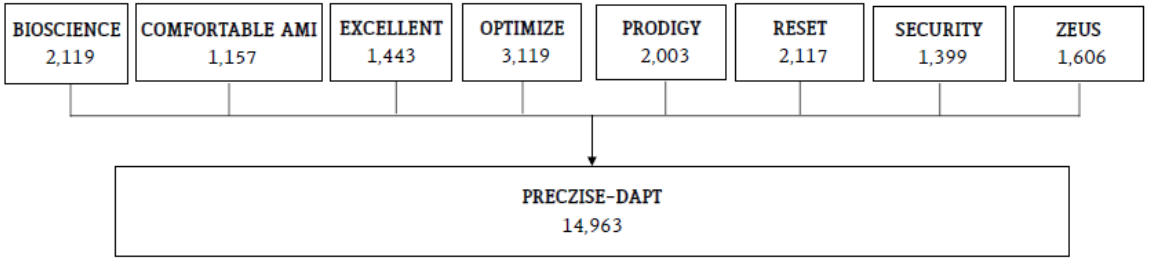


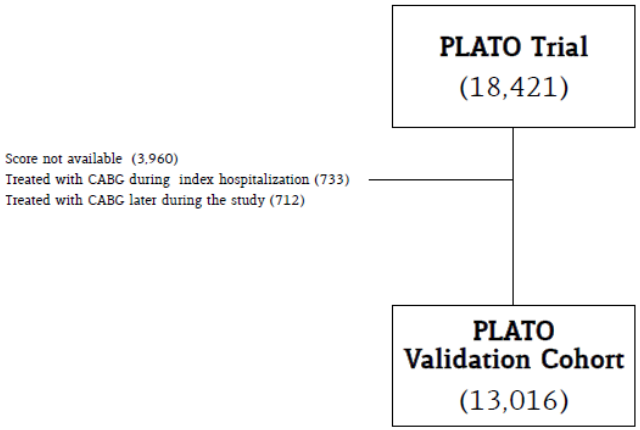
Solid line shows the mean predicted probability of coronary thrombotic and major bleeding events by thrombotic **(A)** and bleeding **(B)** integer scores.

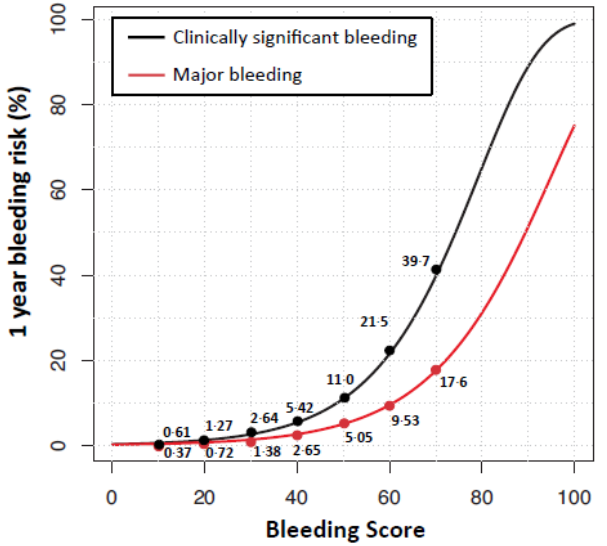
Validation cohort: C statistics of 0.65 and 0.64 for the thrombotic and bleeding risk scores.

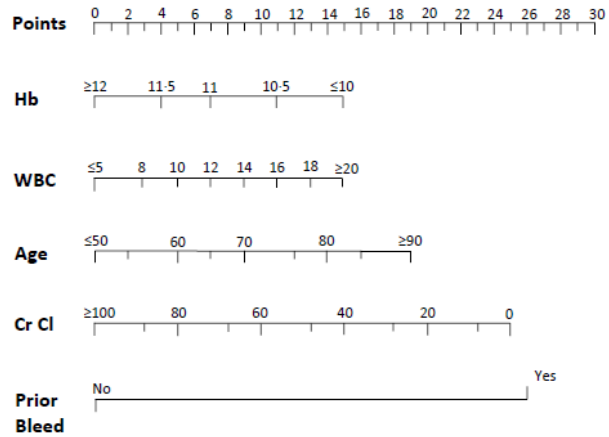
PRECISE-DAPT score

- ✓ A total of 14,963 patients with CAD who underwent PCI subsequent DAPT therapy
- ✓ Validation: PLATelet inhibition and patient Outcomes (PLATO) trial







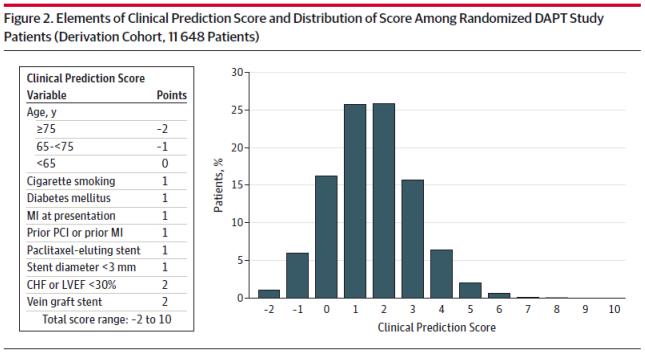


PRECISE-DAPT score

- ✓ Limitations of the PRECISE-DAPT score
  - ✓ 'Prior bleeding' events were recorded only in 4300 cases within the derivation cohort (14000 patients)
  - ✓ 'DAPT duration' is not a predictor of bleeding events. Then, is longer DAPT the better?
  - ✓ Factors such as 'old age', 'low Cr Cl', 'low Hb", seem to wrap up to CRF.
  - ✓ The validation cohort was the PLATO trial cohort (derivation cohort almost exclusively clopidogrel use)
    - ✓ which used ticagrelor with a 'suspected' high bleeding risk per se.

DAPT, PARIS, PRECISE DAPT scores

	Setting	Predicted Outcome	Development cohort	Validation cohort	Number of variables
DAPT	PCI patients in DAPT event free for 12 mo	Ischemic/Bleeding endpoints between 12-30 months	DAPT RCT (11648 pts)	PROTECT Trial: C Index: 0.64 for isc hemic and bleeding	5 clinical 3 procedural
PARIS	PCI patients on DAPT	Ischemic/Bleeding endpoints at 24 months after PCI	4190 multicenter registry	ADAPT-DES Registry 0.65 for ischemia / 0.64 for bleeding	Thrombotic: 6 clinical Bleeding: 6 clinical
PRECISE-DAPT	PCI patients on DAPT	Bleeding events at 12 months after PCI	14963 patients of pooled RCTs	PLATO Trial 0.66	5 clinical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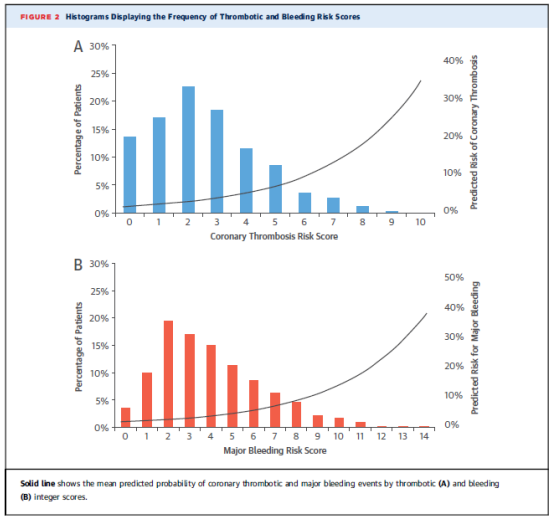
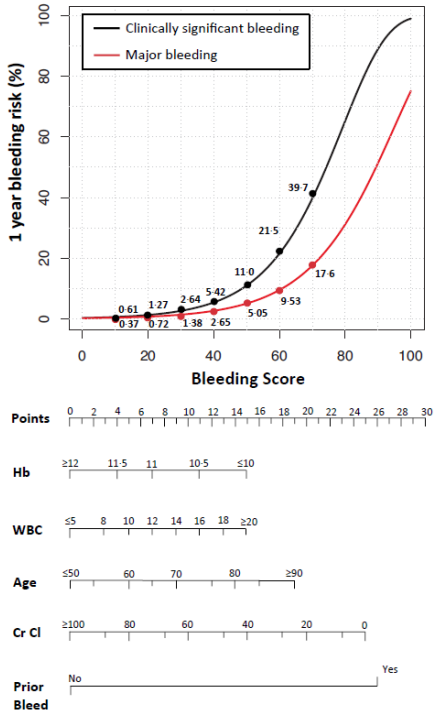
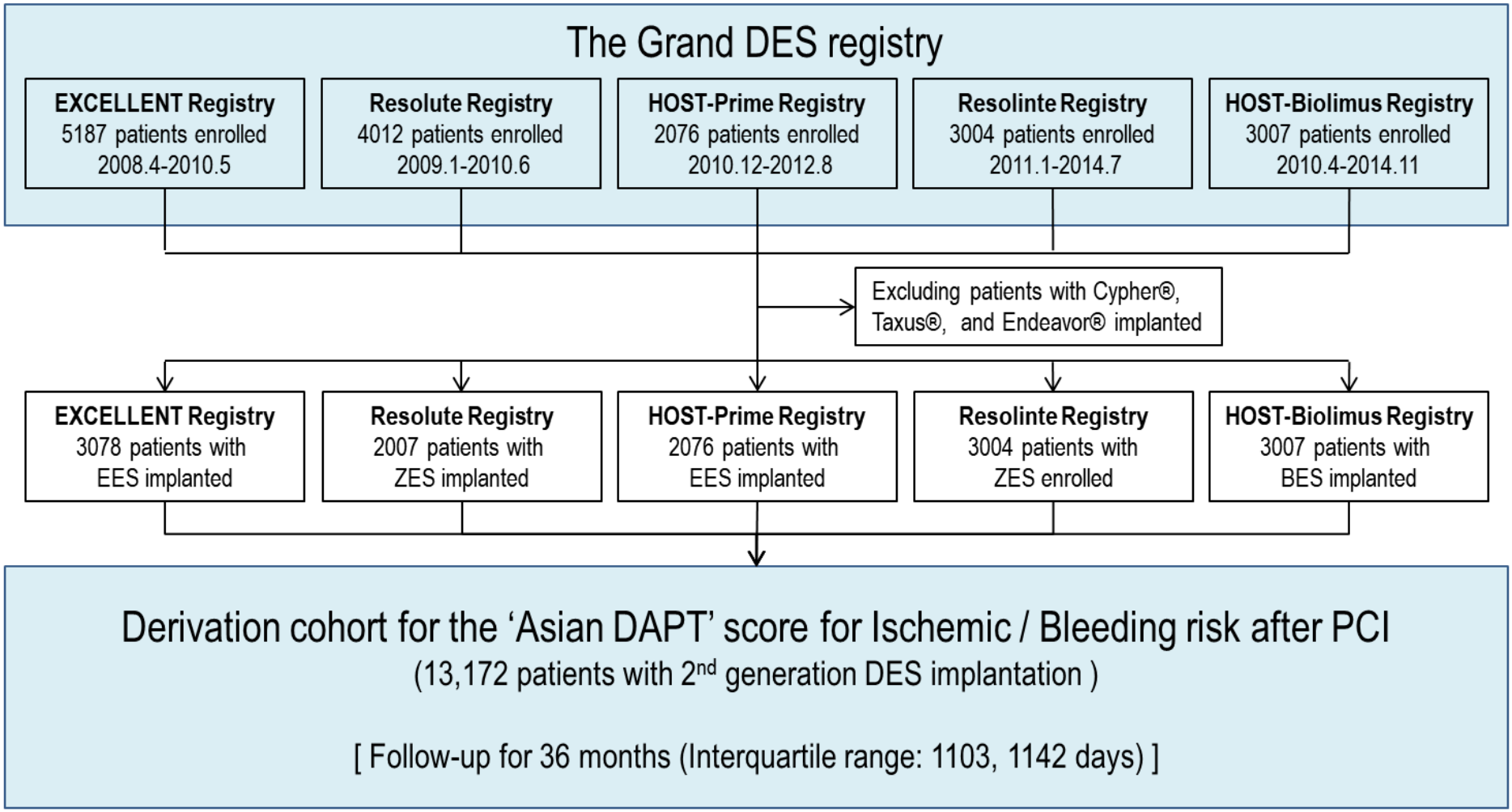




Pitfalls of current scoring systems

1. Mix of first and second generation DES and even BMS in the derivation and validation cohort.
2. Mostly from studies in Western patients.
3. If ethnic heterogeneity exists, it may result in good discrimination in one ethnic population but not in another population.

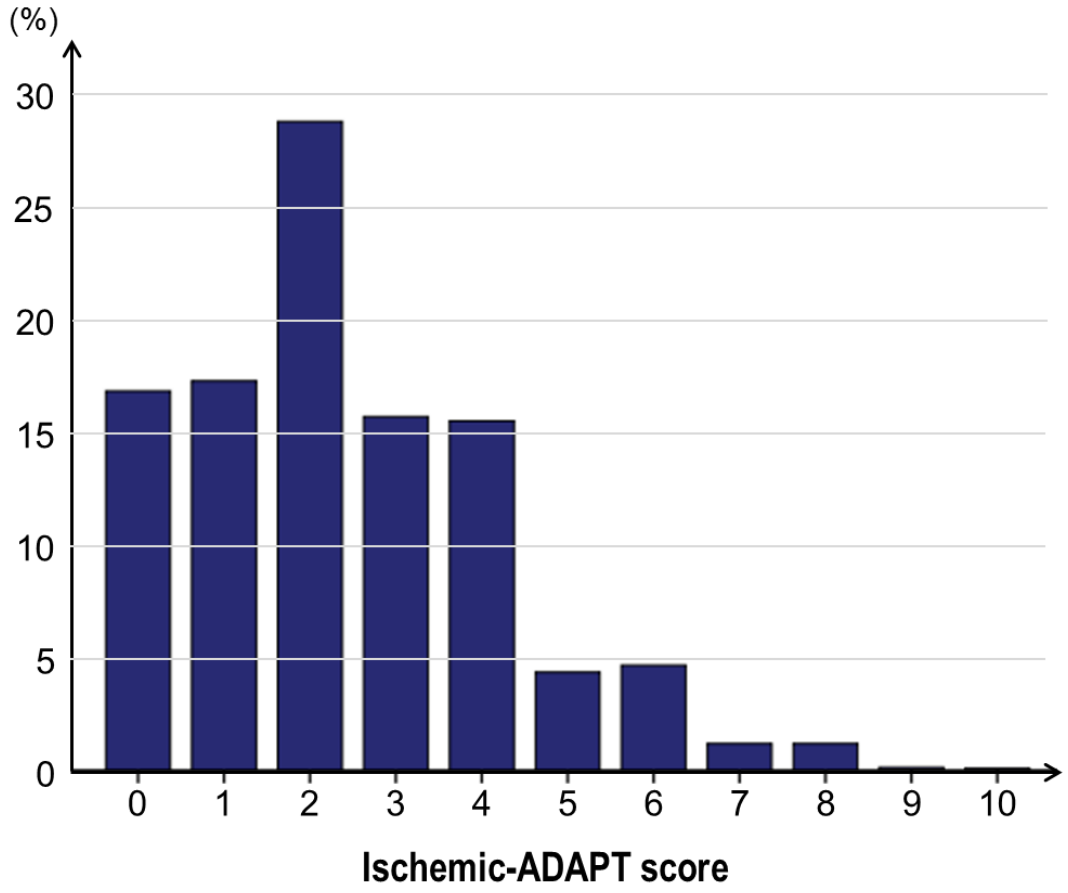
Study Population



Kang JH, Park KW, Kim HS et al. submitted.

Ischemic ADAPT Score

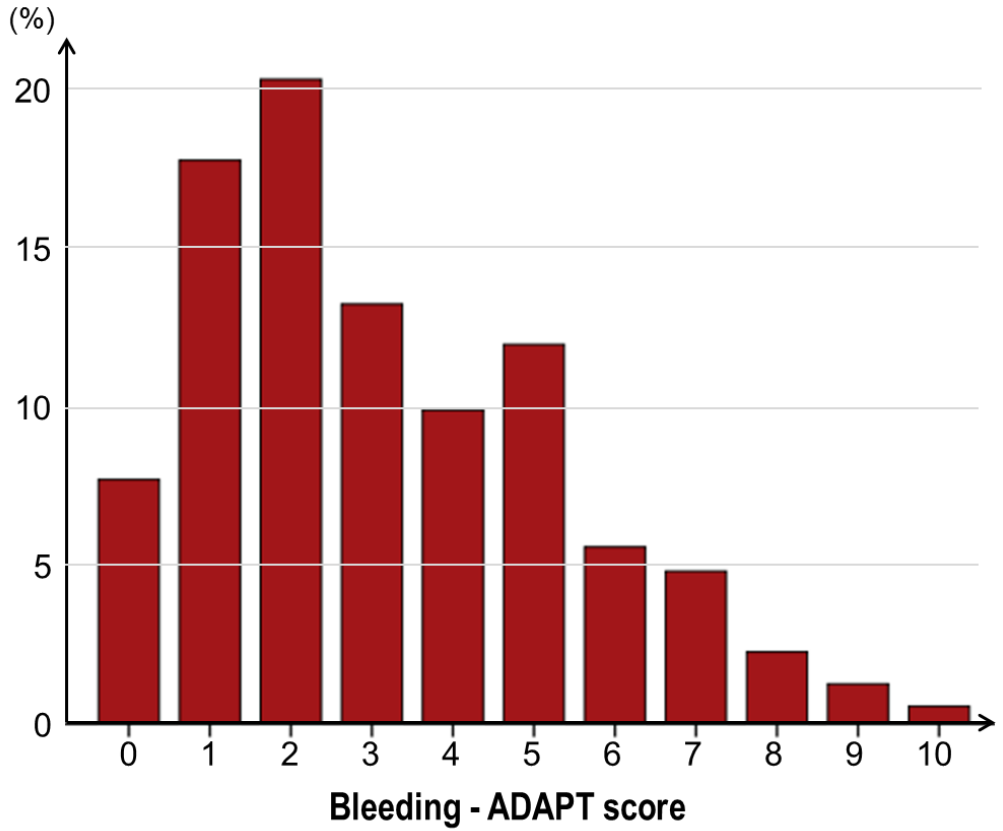
Variable	Score	*Weight*	Weighted score
Previous MI or PCI	1	*2*	2
Presentation as AMI	1	*2*	2
Anemia - Hb ≥ 12mg/dL - 10 mg/dL ≤ Hb < 12mg/dL - Hb < 10mg/Dl	 0 1 2	*2*	 0 2 4
Total Stent Length ≥30mm	1	*1*	1
Minimal stent diameter <3mm	1	*1*	1
Total score			*10*



Kang JH, Park KW, Kim HS et al. submitted.

Bleeding ADAPT Score

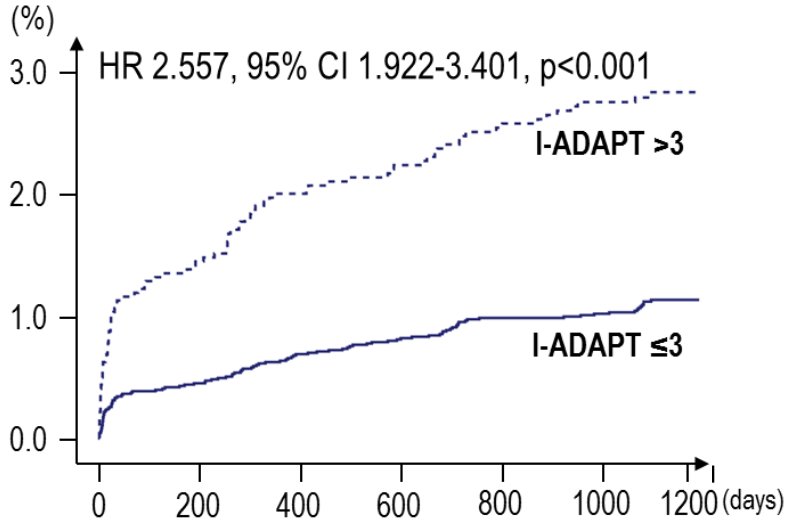
Variable	Score	*Weight*	Weighted score
Old Age			
- Age <50 years old	0	*1*	0
- 50 ≤ Age < 60 years old	1		1
- 60 ≤ Age < 70 years old	2		2
- 70 ≤ Age < 80 years old	3		3
- Age ≥ 80 years old	4		4
Previous CKD or CrCl <60ml/min	1	*2*	2
Anemia			
- Hb ≥ 12mg/dL	0	*2*	0
- 10 mg/dL ≤ Hb < 12mg/dL	1		2
- Hb < 10mg/dL	2		4
Total score			***10***



Kang JH, Park KW, Kim HS et al. submitted.

I-ADAPT & B-ADAPT predicts clinical events

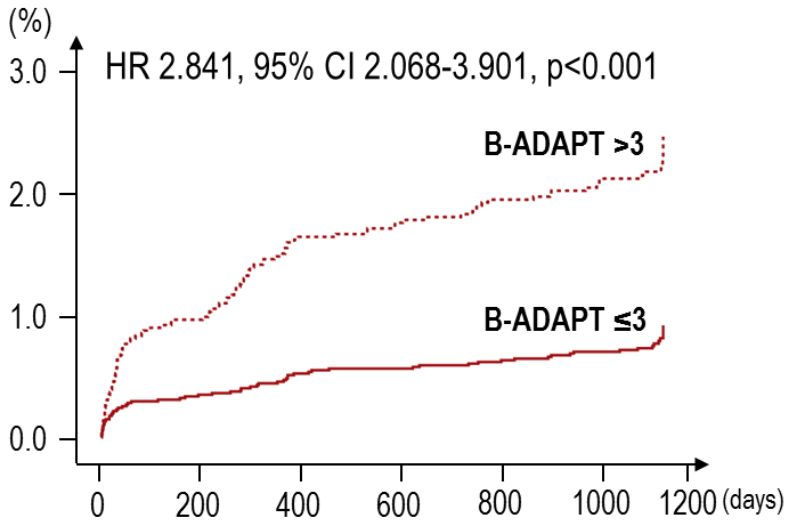
Ischemic events



Num. at risk

I-ADAPT ≤3	8042	7931	7870	7827	7600	7475
I-ADAPT >3	4515	4316	4220	4132	4012	3912

Bleeding events



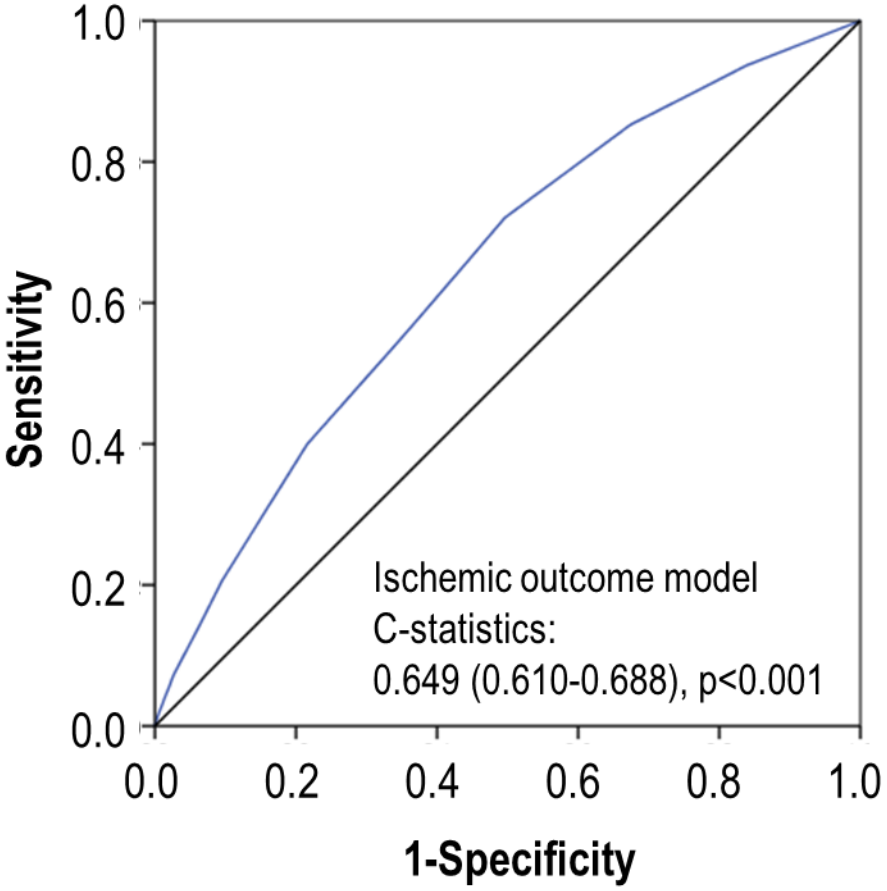
Num. at risk

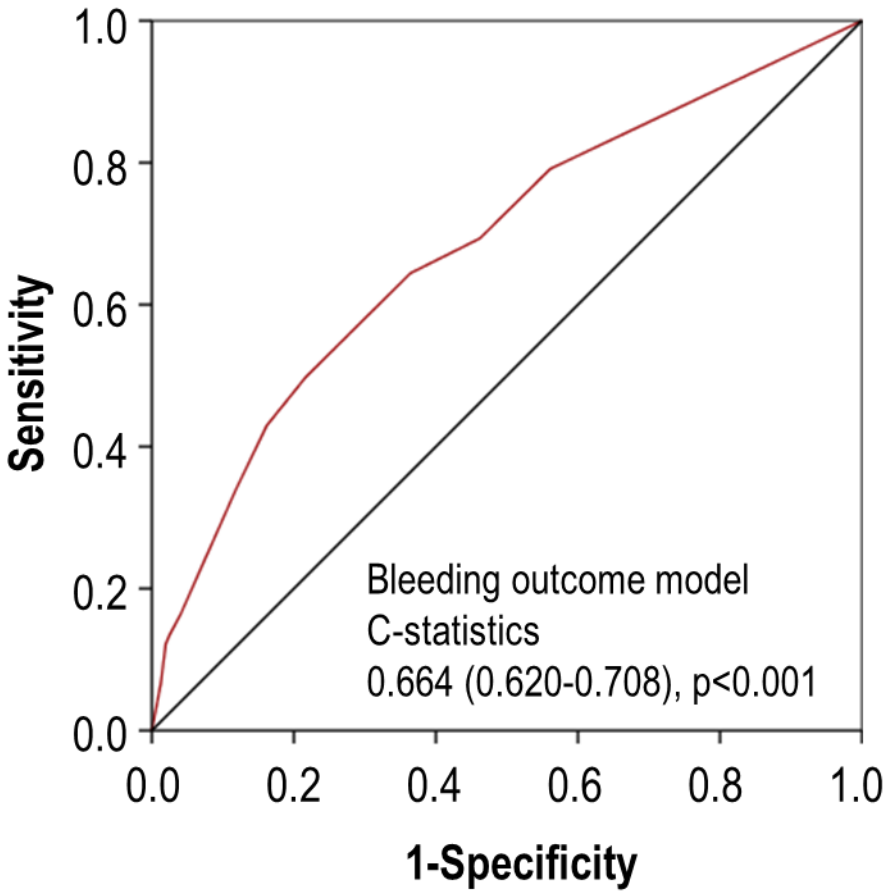
B-ADAPT ≤3	9950	9804	9737	9683	9425	9207
B-ADAPT >3	2797	2605	2512	2447	2348	2250

Kang JH, Park KW, Kim HS et al. submitted.

GRAND DES registry

- Model fit of the ischemia and bleeding score
- Predictive power of the Ischemic and bleeding risks





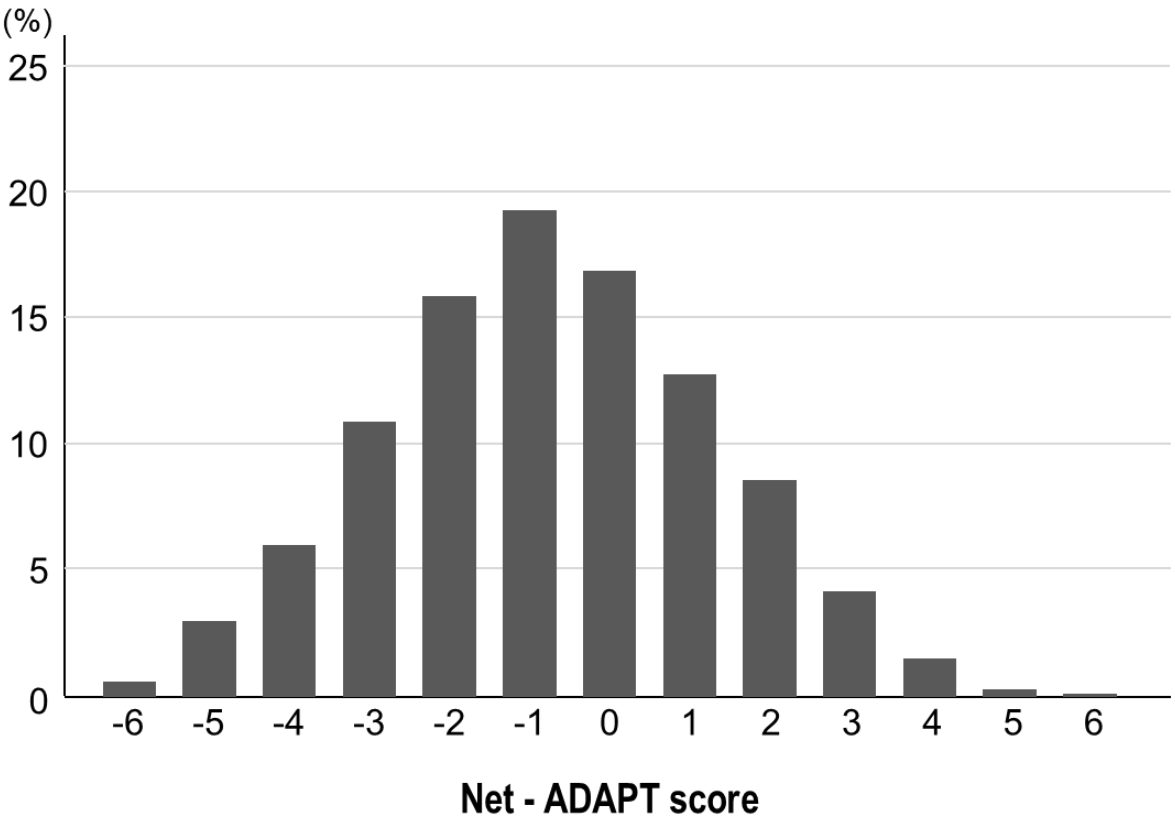
What score to use to determine DAPT Duration?

- Net score (Ischemic score - bleeding score)

- Plot of 'Net score' with 'net clinical events'
  - Net score = as above
  - Net clinical events
    - » 'estimated ischemic event rate' – 'estimated bleeding event rate'

Net-ADAPT Score

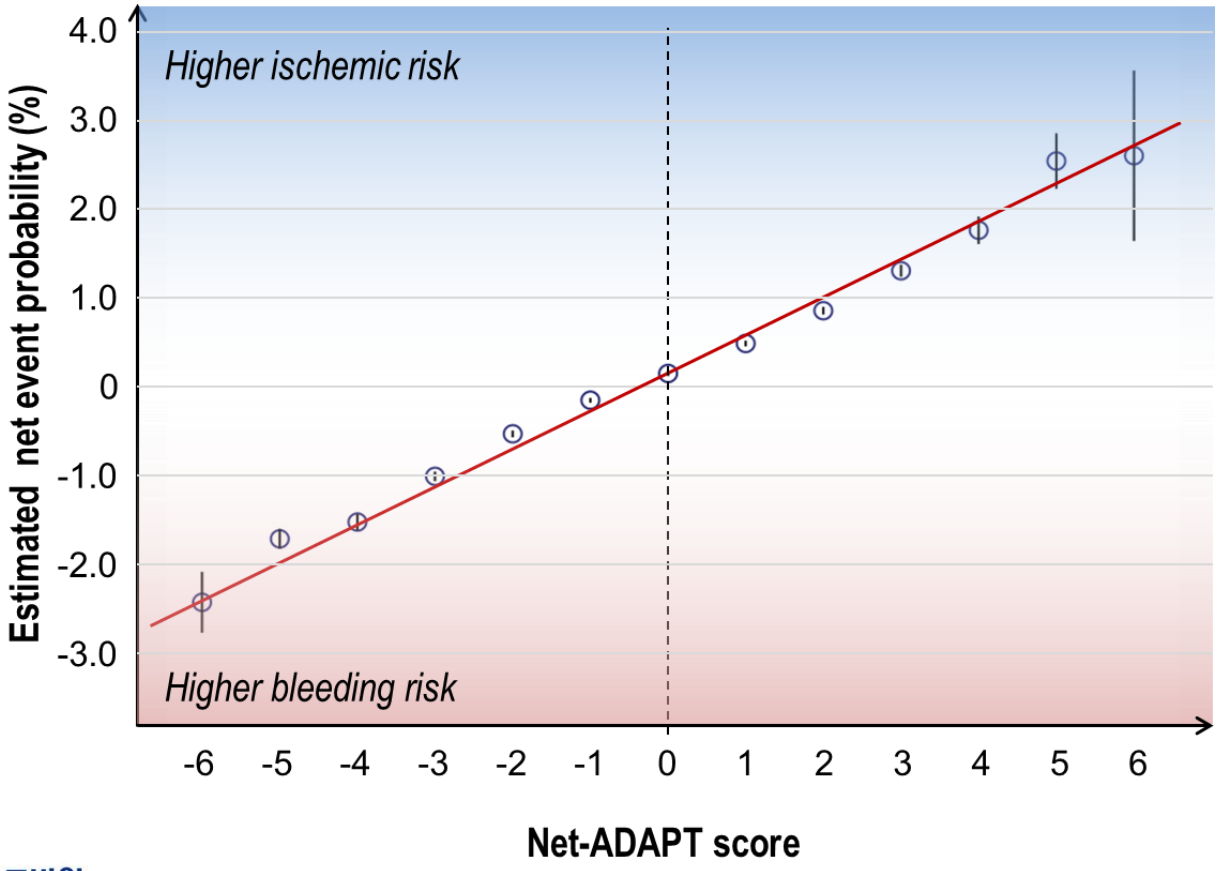
Variable	Score
Previous MI or PCI	2
Presentation as AMI	2
Total Stent Length ≥30mm	1
Minimal stent diameter <3mm	1
Previous CKD or CrCl <60ml/min	-2
Old Age	
- Age <50 years old	0
- 50 ≤ Age < 60 years old	-1
- 60 ≤ Age < 70 years old	-2
- 70 ≤ Age < 80 years old	-3
- Age ≥ 80 years old	-4
Total score range	*-6 to 6*



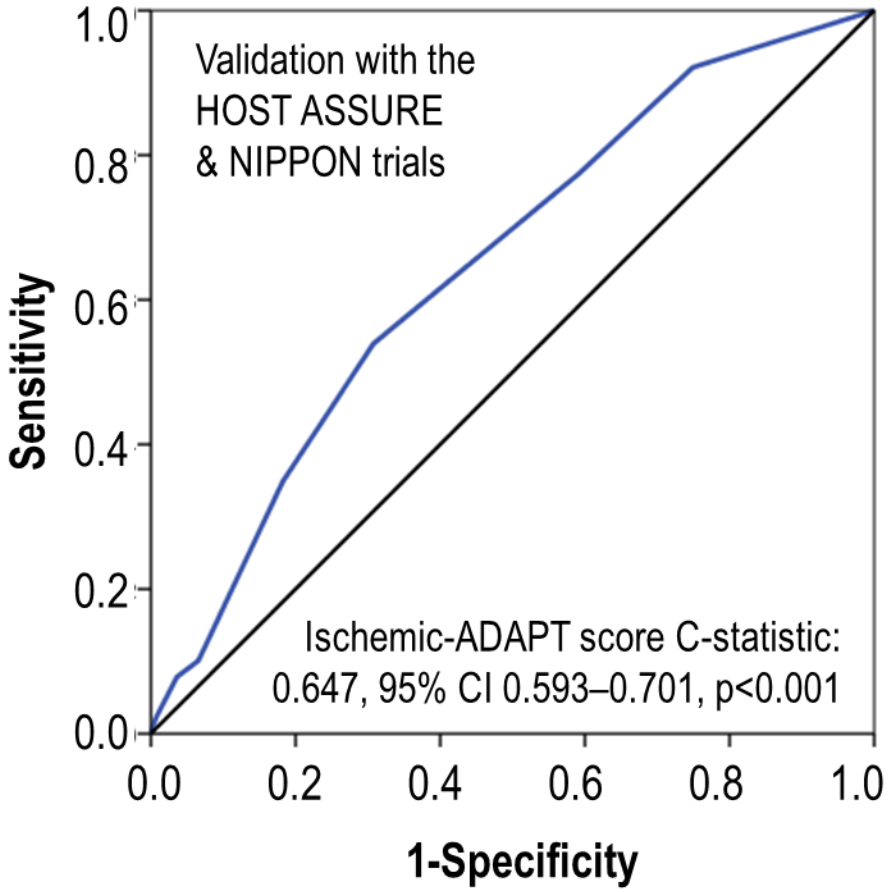
Kang JH, Park KW, Kim HS et al. submitted.

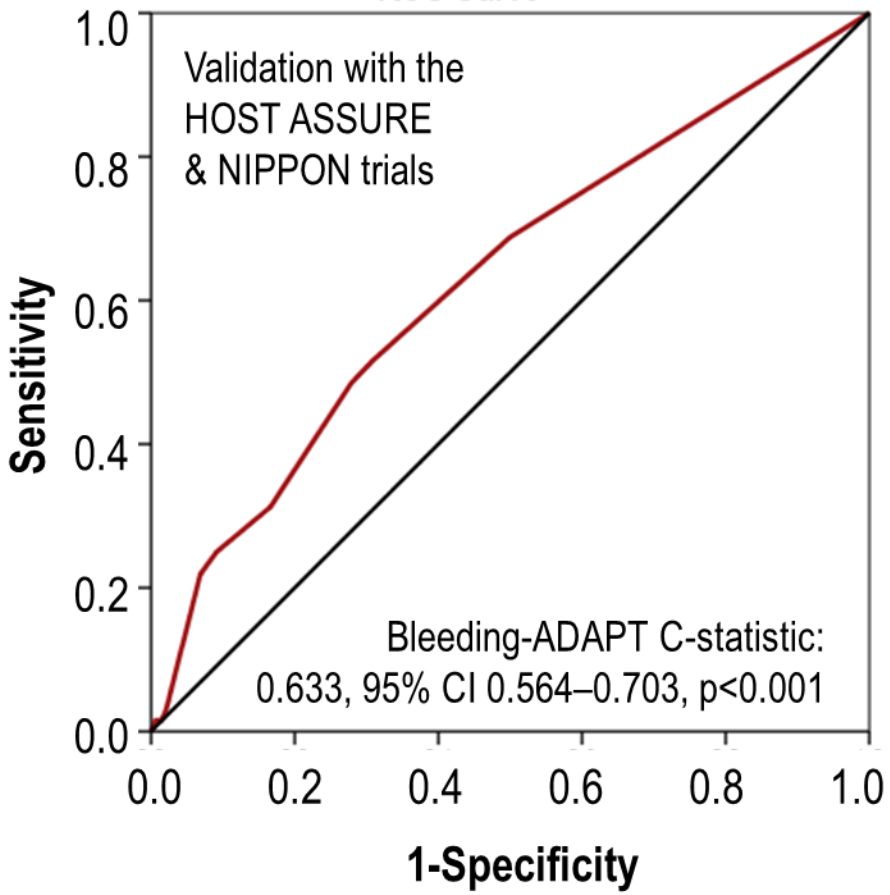
Net-ADAPT Score (Agnostic at 0)

- Plot of 'Net score' with 'net clinical events'
  - Net score >0: **ischemic risk** > bleeding risk → longer DAPT should be considered
  - Net score <0: ischemic risk < **bleeding risk** → shorter DAPT should be considered

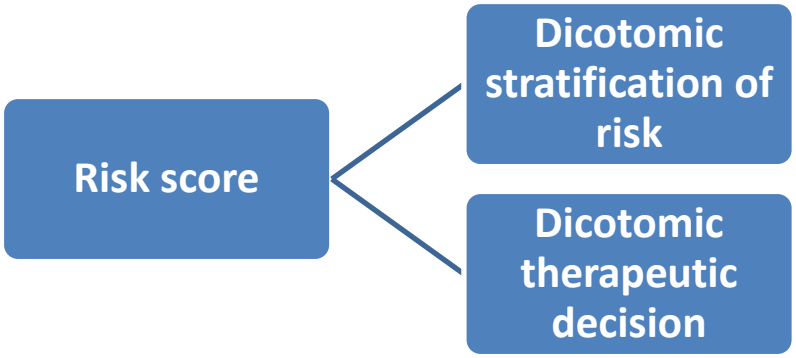


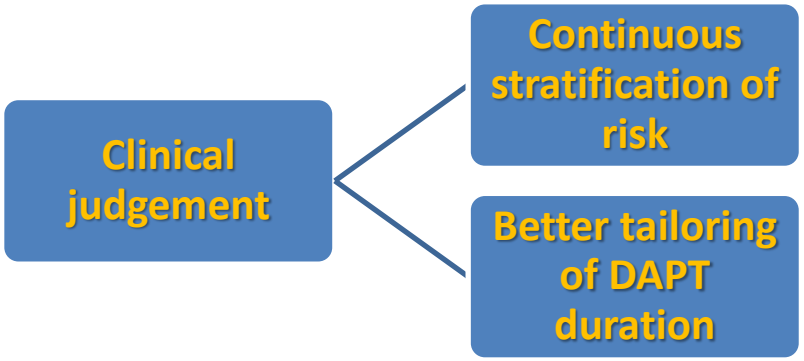
Validation cohort: HOST ASSURE RCT + NIPPON RCT (7,529 patients)





Some thoughts about Risk Scores

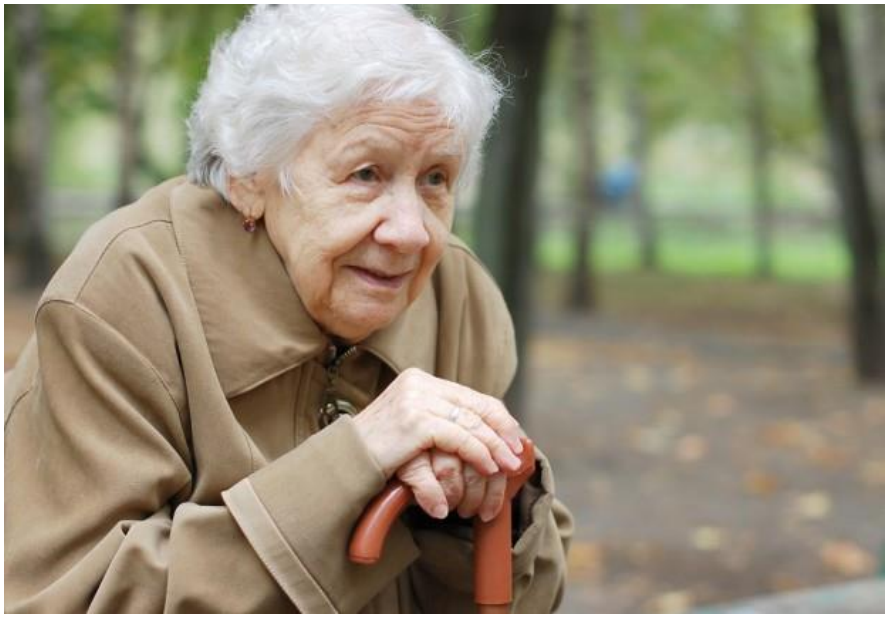




1. How do we incorporate factors that predict both ischemia and bleeding?
2. Is old age or a specific age value a truly good determinant of risk?
3. How do we incorporate anemia? (Anemia from recurrent bleeding episodes vs. Anemia from poor oral intake, multiple risk factors and frailty)
4. At what time point do we incorporate the risk score? At time of procedure? 1 Month? 1 Year?

What does it mean to be old?

80 years young (DAPT -2)

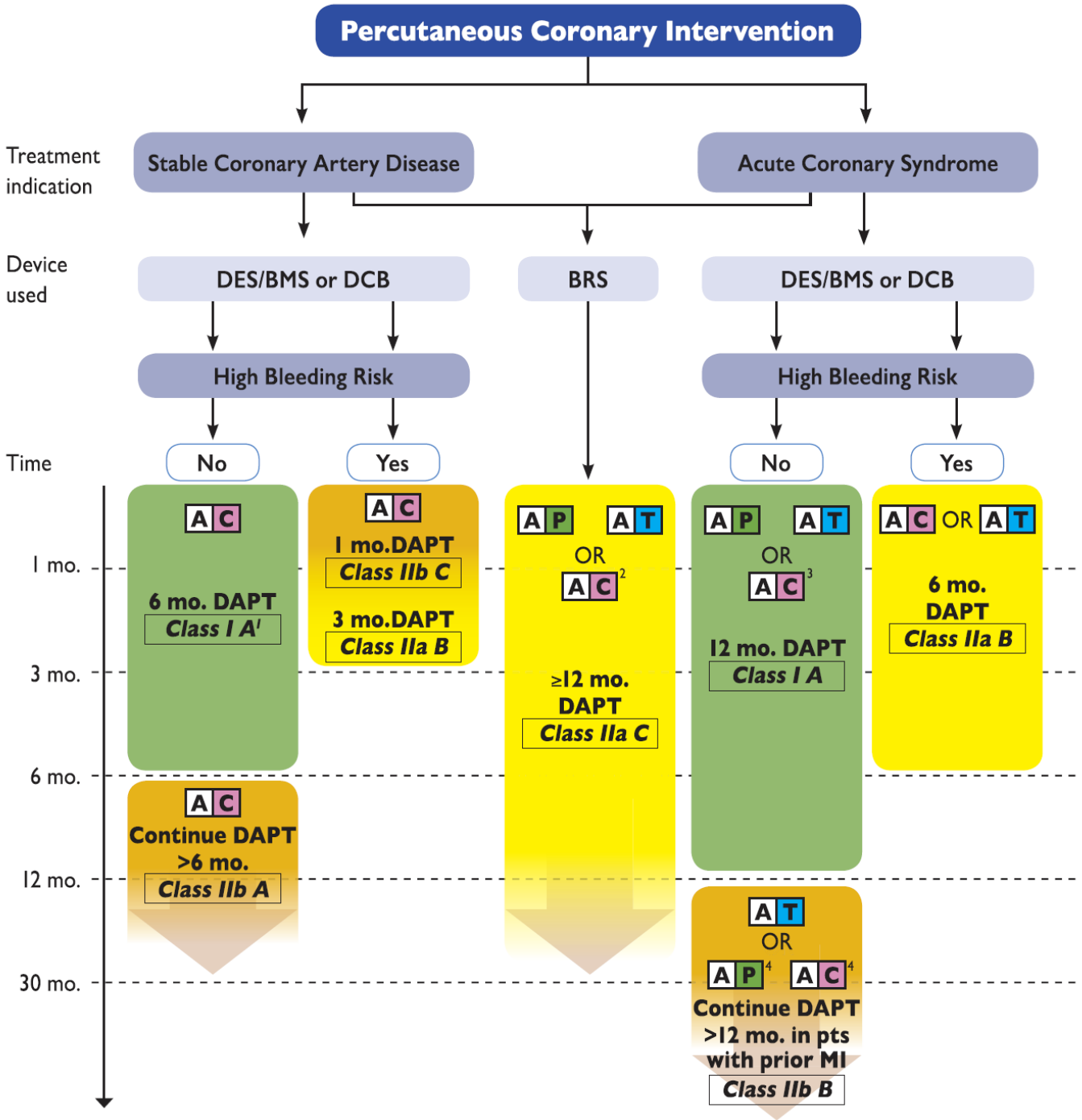


72 years old (DAPT -1)

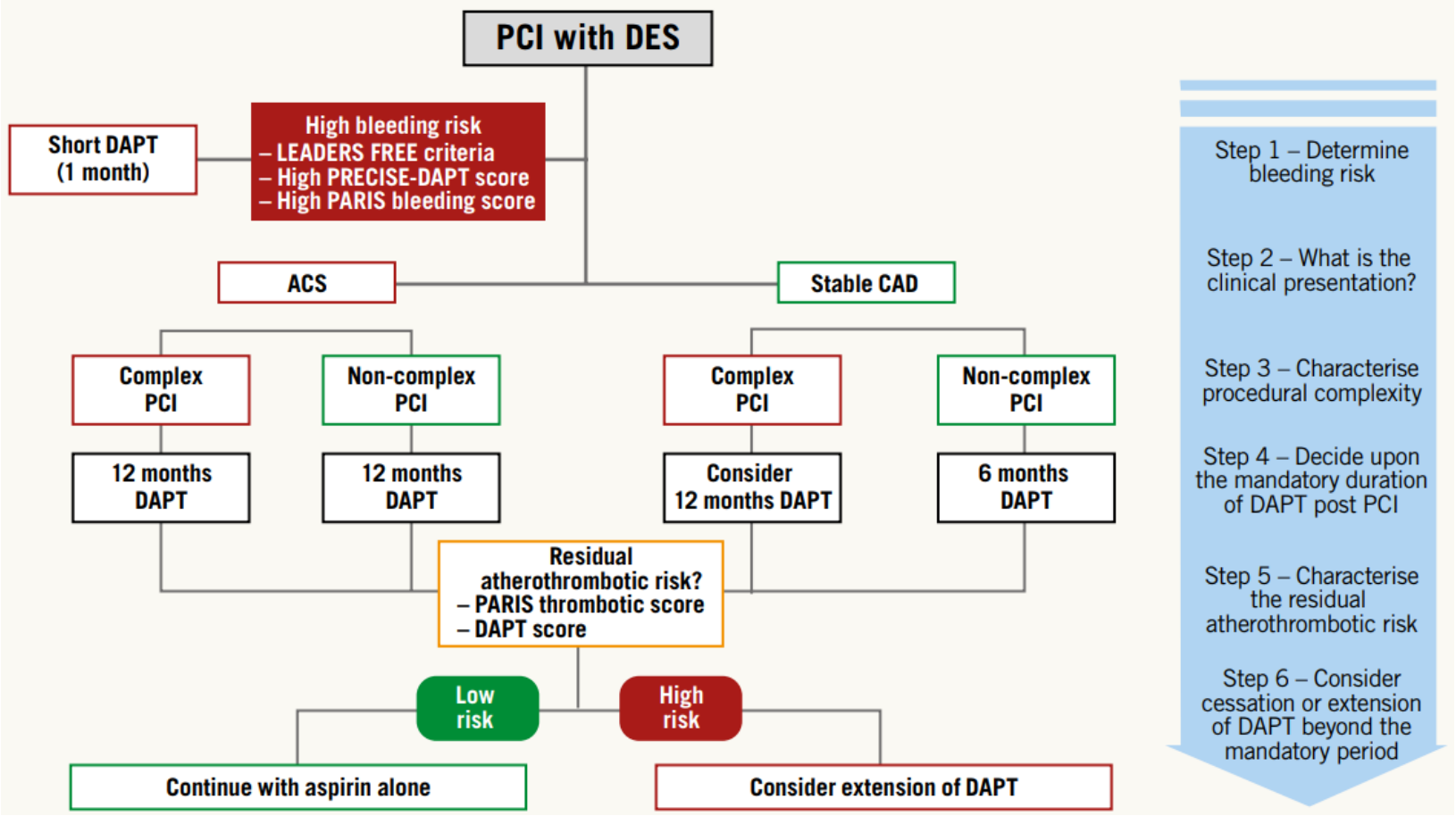
Clinical decision making is a continuous process incorporating not only future risk but also taking into account the past history

1. The DAPT score was derived in patients that were event free at 1 year post PCI.
2. The ischemic and bleeding risk of the patient changes with time (it is not a fixed rate).
3. What if patient presents with ACS, and has a low bleeding score. Yet after 2mo of DAPT, has a major bleeding episode. Will you stick with your original plan? Or Adjust?
4. Even if we knew the exact probability(risk) of an event, it's probability changes at each time due to what we have observed up to that time point. (Gambler's Fallacy)

ex. Probability of 5 heads in a row vs. Probability of 5th heads after you have seen 4 heads in a row.


Percutaneous Coronary Intervention
Treatment indication
Stable Coronary Artery Disease
Acute Coronary Syndrome
Device used
DES/BMS or DCB
BRS
DES/BMS or DCB
High Bleeding Risk
High Bleeding Risk
Time
No
Yes
No
Yes
1 mo.
3 mo.
6 mo.
12 mo.
30 mo.
A C
6 mo. DAPT
Class I A[1]
A C
1 mo.DAPT
Class IIb C
3 mo.DAPT
Class IIa B
A P
A T
OR
A C[2]
≥12 mo. DAPT
Class IIa C
A P
A T
OR
A C[3]
12 mo. DAPT
Class I A
A C OR A T
6 mo. DAPT
Class IIa B
A C
Continue DAPT >6 mo.
Class IIb A
A T
OR
A P[4]
A C[4]
Continue DAPT >12 mo. in pts with prior MI
Class IIb B

Decision-making algorithm for DAPT duration integrating bleeding risk, procedural complexity and the acuteness of clinical presentation



Giustino G, Et al. EuroIntervention. 2018 Jul 20;14(4):e383-e385

Summary

1. The optimal duration of DAPT should take into consideration both the risk of ischemia and risk of bleeding.
2. Risk scores have inherent limitations and all of the currently available risk scores have major pitfalls.
3. In general, patients with ACS, young age, and complex multivessel CAD benefit the most from prolonged DAPT, whereas the elderly and patients with previous bleeding or anemia benefit the most from shorter DAPT
4. There is no magic bullet, so best clinical judgement incorporating patient compliance to drug, clinical presentation, co-morbidity, procedural complexity, and bleeding risk, along with scoring systems when needed seems to be the best we can do.

THANK YOU FOR YOUR ATTENTION!