PLACE

PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

ROMA
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della Tecnica

9ª Edizione

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2022

Il paziente ad alto rischio di sanguinamento

DEFINIZIONE, EVIDENZE CLINICHE E MANAGEMENT DEL PAZIENTE AD ALTO RISCHIO DI SANGUINAMENTO

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HBR patients:

- Up to 40% of subjects undergoing PCI in routine clinical practice.
- Under-represented in randomized clinical trials.
- Paucity of randomized clinical evidence to guide their optimal management
- Historically, large heterogeneity in the definition of HBR (similarly to definition of bleeding events)
- Need for standardized definition of HBR patients and trial design/end-points

Heterogeneity of inclusion criteria in current HBR trials

	LEADERS-FREE	LEADERS-FREE 2	ZEUS-HBR	SENIOR	ONYX ONE	MASTER DAPT	COBRA REDUCE	EVOLVE SHORT DAPT	XIENCE 28-90	POEM
Age ≥75	✓	✓	✓	✓	✓	✓		✓	✓	✓
OAC	✓	✓	✓		✓	✓	✓	✓	✓	✓
Renal failure	✓	✓			✓			✓	✓	✓
Liver disease	✓	✓			✓	✓				✓
Recent cancer	✓	✓			✓	✓				✓
Anemia or transfusion	✓	✓	✓		✓	✓			✓	✓
Trombocytopenia	✓	✓	✓		✓	✓		✓	✓	✓
Stroke or ICH	✓	✓			✓	✓		✓	✓	✓
Actionable bleed						✓		✓	✓	
Hospitalization for bleeding	✓	✓	✓		✓	✓				✓
NSAIDs or steroids	✓	✓	✓		✓	✓				✓

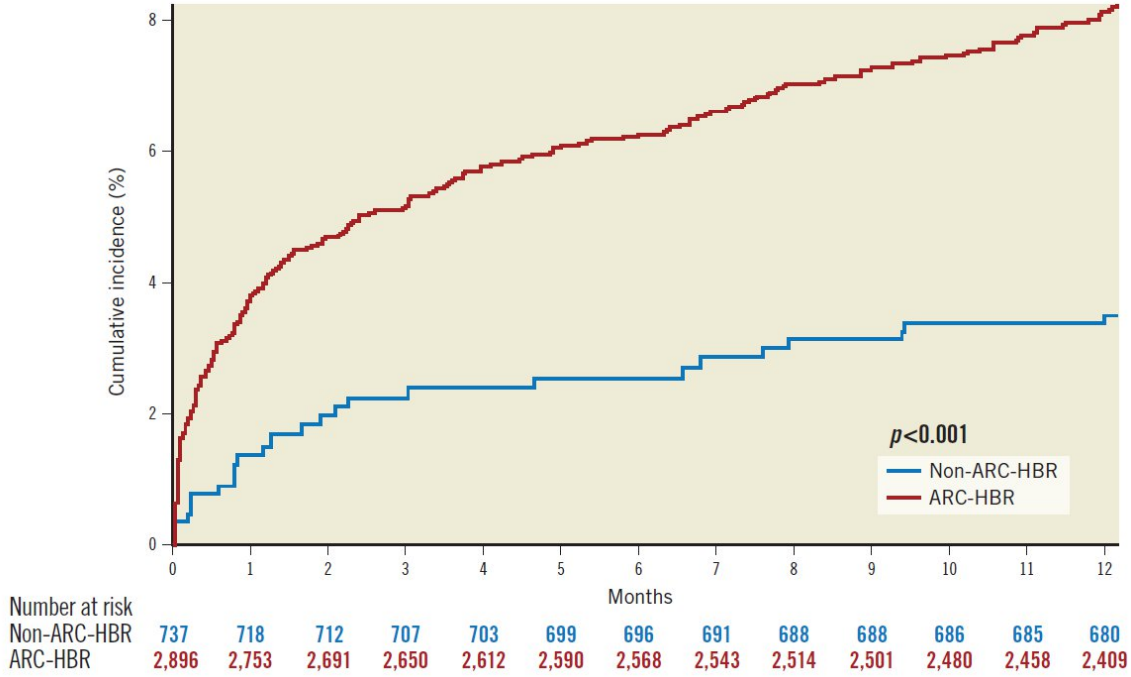
ARC-high bleeding risk criteria

Table 3 Major and minor criteria for hbr at the time of PCI

Major	Minor
	Age ≥75 y
Anticipated use of long-term oral anticoagulation*	
Severe or end-stage CKD (eGFR <30 mL/min)	Moderate CKD (eGFR 30–59 mL/min)
Hemoglobin <11 g/dL	Hemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women
Spontaneous bleeding requiring hospitalization or transfusion in the past 6 mo or at any time, if recurrent	Spontaneous bleeding requiring hospitalization or transfusion within the past 12 mo not meeting the major criterion
Moderate or severe baseline thrombocytopenia† (platelet count <100 × 109/L)	
Chronic bleeding diathesis	
Liver cirrhosis with portal hypertension	
	Long-term use of oral NSAIDs or steroids
Active malignancy‡ (excluding nonmelanoma skin cancer) within the past 12 mo	
Previous spontaneous ICH (at any time)Previous traumatic ICH within the past 12 moPresence of a bAVMModerate or severe ischemic stroke§ within the past 6 mo	Any ischemic stroke at any time not meeting the major criterion
Nondeferrable major surgery on DAPT	
Recent major surgery or major trauma within 30 d before PCI	

Urban et al. Eur Heart J 2019

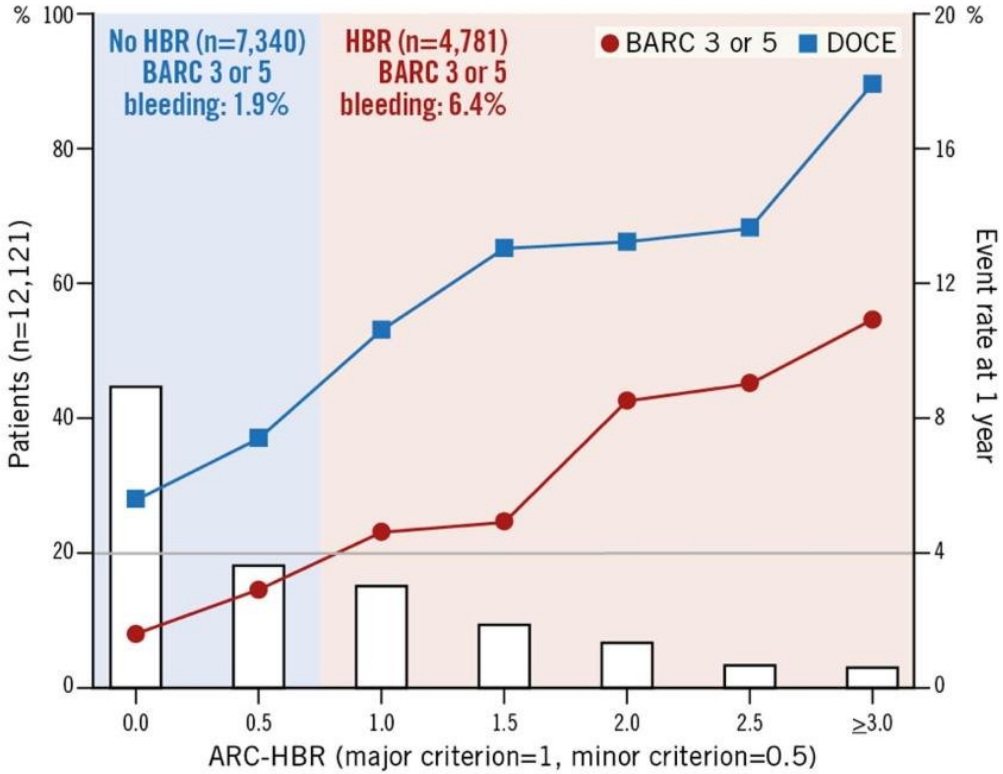
LEADERS FREE and LEADERS FREE II Post-hoc analysis



Marquis-Gravel, EuroIntervention 2021

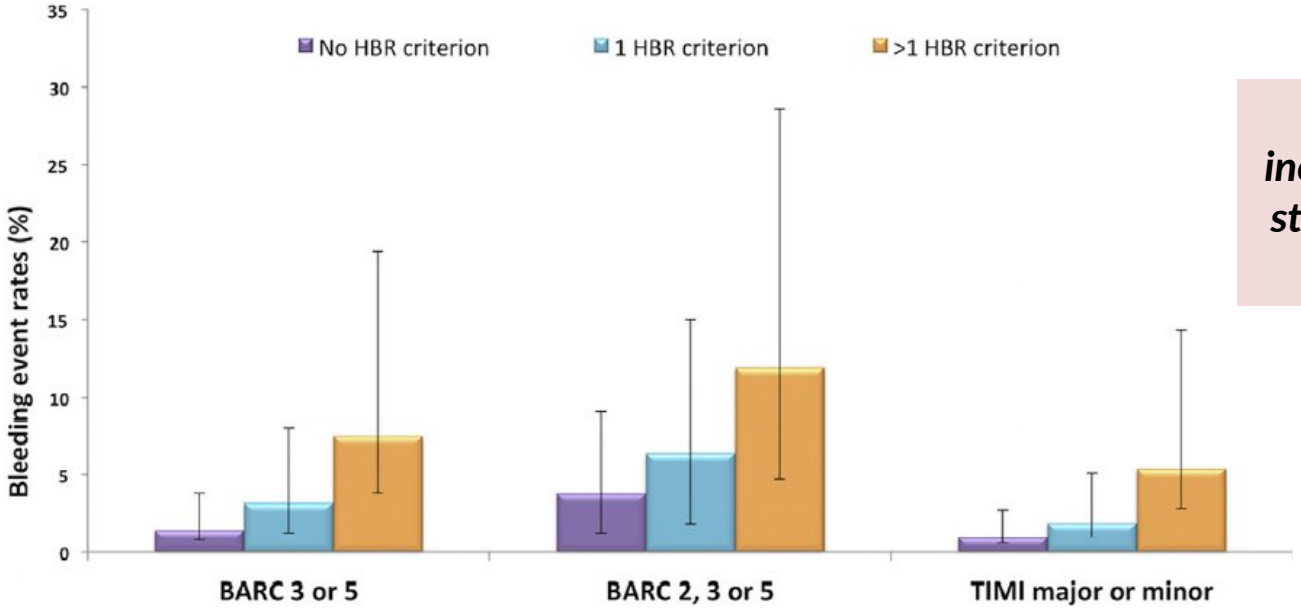
EuroIntervention

Validation of ARC-HBR criteria



Ueki Y, et al. EuroIntervention 2020;16:371-37

ZEUS: Bleeding event rates according to the presence and number of HBR criteria



HBR patients were also at increased risk of death, MI and stent thrombosis as compared to non-HBR patients

Valgimigli et al. JACC Intv 2016

UNIVERSITÀ degli STUDI di CATANIA

Trials of coronary devices in HBR patients

Design principles for HBR trials of PCI devices

P	I	C	O	T
Population	**Intervention**	**Control**	**Outcome**	**Time**
≥1 major or ≥2 minor ARC-HBR criteria, or report proportion of ARC-HBR criteria	Drug-eluting stent with specific design features that allow for short DAPT	Current-generation drug-eluting stent or performance benchmarks	Ischemic or thrombotic: CV death, TV-MI, CD-TLR; Bleeding: BARC type 3-5 ± 2	Typically 1 year. Considering long-term follow-up

Superiority > noninferiority, 1:1 > single-arm, adequately powered, assessor-blinded

Capodanno D, et al. J Am Coll Cardiol. 2020 [In press]

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ONYX-ONE

- **Resolute** Onyx noninferior to Biofreedom DES at 12 months

COBRA-REDUCE

- **Cobra PzF** with 2-week DAPT not noninferior to DES with 3- or 6-month DAPT at 6 months

Randomized trials using drug-eluting stents as a control

DEBUT

- **SeQuent Please DCB** + 1-month DAPT noninferior to BMS + 1-month DAPT ay 9 months

SENIOR

- **Synergy DES** + 1- or 6-month DAPT superior to BMS + 1- or 6-month DAPT at 12 months

LEADERS-FREE

- **BioFreedom DCS** + 1-month DAPT noninferior and superior to BMS + 1-month DAPT at 390 days

Randomized trials using bare metal stents as a control

XIENCE 28

- **Xience DES** + 1-month DAPT noninferior to DES + 6-month DAPT and not superior on bleeding between 1 and 6 months

XIENCE 90

- **Xience DES** + 3-month DAPT noninferior to DES + 1-year DAPT and superior to an OPG between 3 months and 1 year

Onyx ONE Clear

- **Resolute Onyx** DES + 1-month DAPT noninferior to an OPG between 1 month and 1 year

EVOLVE Short DAPT

- **Synergy DES** + 3-month DAPT noninferior to DES + 12-month DAPT and to an OPG between 3 and 15 months

MODEL U-SES

- **Ultimaster DES** + 3-month DAPT noninferior to DES + 1-year DAPT at 1 year

LEADERS-FREE 2

- **BioFreedom DCS** + 1-month DAPT superior to BMS + 1-month DAPT at 1 year

Nonrandomized trials using historical cohorts or an OPG as a control

Capodanno, Circ Cardiovasc Interv 2021

RCT in HBR patients - Devices

Study	Year	Device	Polymer	Drug	Comparator	DAPT	results
LEADERS-FREE	2015	Biofreedom	Polymer-free	Biolimus A9	BMS	1 month	D/MI/ST/TLR better with DES
ZEUS-HBR*	2016	Endeavor Sprint	Durable polymer	Zotarolimus	BMS	1 month	D/MI/ST/TLR better with DES
SENIOR	2018	Synergy	Biodegradable polymer	Everolimus	BMS	1 month (SA) 3 months (UA)	D/MI/S/TLR better with DES
DEBUT	2019	SeQuent Please	-	Paclitaxel	BMS	1 month	D/MI/TLR better with DEB
ONYX ONE	2020	Resolute Onyx	Durable polymer	Zotarolimus	Biofreedom	1 month	D/MI/ST non inferiority met
COBRA-REDUCE **	2022	Cobra Polyzene-F	Polyzene-F fluoropolymer	none	FDA-approved DES	14 days (Cobra) vs 3-6 months DAPT	Same MB; non-inferiority for D/MI/ST/Stroke not met
BASKET-SMALL 2* *pre-specified analysis; ** OAC	2022	SeQuent Please	-	Paclitaxel	2° gen-DES	Stable pts: • 4 wks (DCB) • 6 months (DES) ACS: 12 months	No diff. In MACE, trend for less MB with DCB

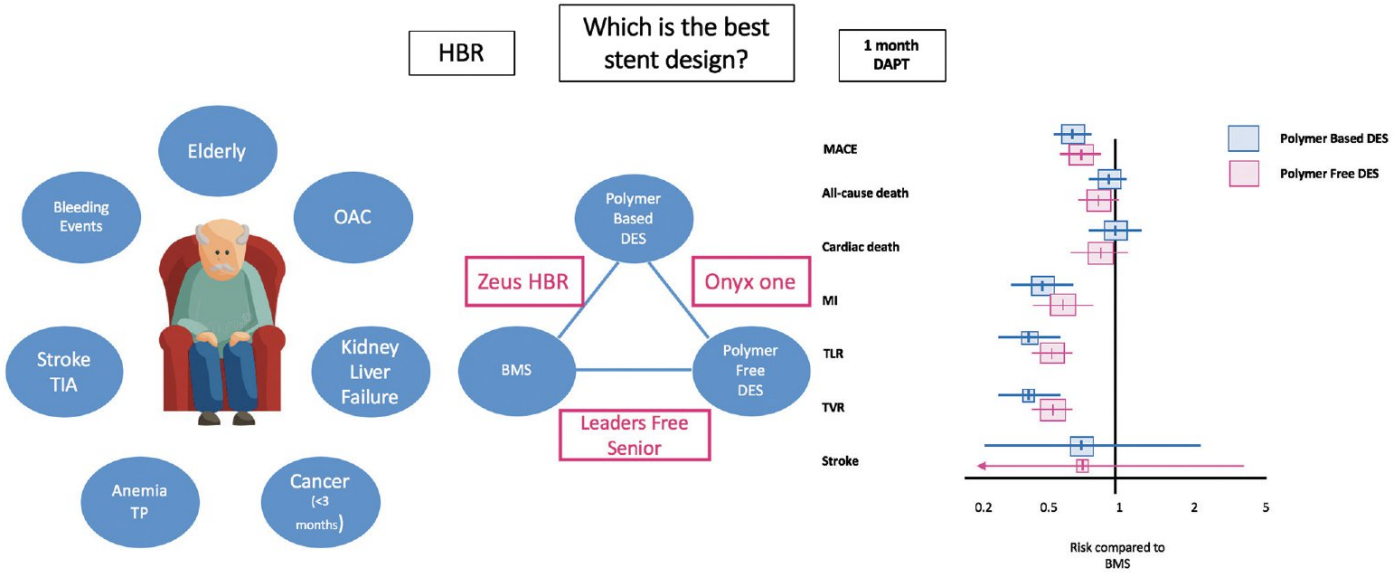

FIGURE 4. We highlight the design and results in efficacy endpoints from the network meta-analysis. BMS = bare-metal stent; DAPT = dual-antiplatelet therapy; DES = drug-eluting stent; HBR = high bleeding risk, MACE = major adverse cardiovascular events; MI = myocardial infarction; OAC = oral anti-coagulation; PB = polymer based; PF = polymer free; TIA = transient ischemic attack; TLR = target-lesion revascularization; TP = thrombocytopenia; TVR = target-vessel revascularization.

Chiabrando et al. J Invasive Cardiol 2021

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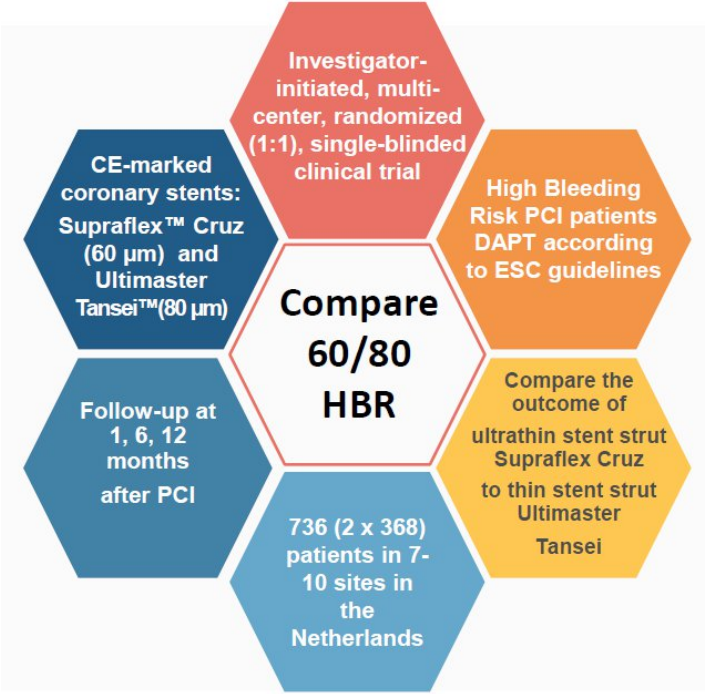
STUDY DESIGN



	Supraflex™ Cruz (SMT)	Ultimaster™ Tansei™ (Terumo)
Stent strut thickness	60 µm (ultrathin)	80 µm (thin)
Drug and dose	Sirolimus 1.4 µg/mm²	Sirolimus 3.9 µg/mm stent length
Stent material	L-605 Co-Cr Alloy	L-605 Co-Cr Alloy
Polymer type	Biodegradable polymer	Biodegradable polymer

Study Hypothesis:

The Supraflex Cruz stent is non-inferior to Ultimaster Tansei stent in terms of Net Adverse Clinical Endpoint (NACE) at 12 months follow-up.

Study Population:

High Bleeding Risk Population (according to HBR ARC criteria) eligible for PCI with stents for treatment of native coronary artery lesions (no stent thrombosis)

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	Abbott/Boston Xience/Promus	Medtronic Resolute Onyx	Biosensors BioMatrix	Terumo Nobori	Terumo Ultimaster	Boston Synergy	Biotronik Orsiro
STENT PLATFORM	CoCr/PtCr	CoNi	316L SS	316L SS	CoCr	PtCr	CoCr
STRUT THICKNESS	81 µm	81 µm	120 µm	120 µm	80 µm	74 µm	60 µm
POLYMER COATING	DURABLE POLYMER	DURABLE POLYMER	BIOABSORBABLE POLYMER	BIOABSORBABLE POLYMER	BIOABSORBABLE POLYMER	BIOABSORBABLE POLYMER	BIOABSORBABLE POLYMER
	PVDF-HFP	BioLinx	PLA	PLA	PDLLA-PCL copolymer	PLGA	PLLA
POLYMER DEGRADATION	n/a	n/a	6-9 mo	6-9 mo	3-4 mo	4 mo	> 12 mo
POLYMER DISTRIBUTION	Circumferential	Circumferential	Abluminal	Abluminal	Abluminal	Abluminal	Circumferential
	7-8 µm/side	6 µm/side	10 µm	20 µm	15 µm	4 µm	4-7 µm/side
DRUG TYPE/DOSAGE	Everolimus	Zotarolimus	Biolimus A9	Biolimus A9	Sirolimus	Everolimus	Sirolimus
	1.0 µg/mm²	1.6 µg/mm²	15.6 µg/mm	15.6 µg/mm	3.9 µg/mm	113 µg / 20 mm	1.4 µg/mm²

Expected in 2023

BIOFLOW DAPT
N=1,948

BP-SES
Orsiro™

vs

DP-ZES
Resolute Onyx™

Primary endpoint
Death, MI or ST
12 months

A total of 1.948 subjects will be randomized 1:1 to receive either Orsiro or Resolute Onyx. After index procedure, all patients will receive DAPT (ASA + P2Y12 inhibitor) for 30 days, followed by monotherapy with either P2Y12 inhibitor or ASA only until the end of the study.

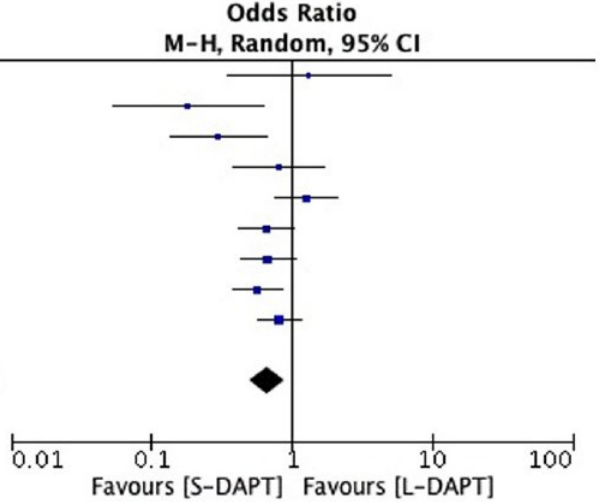
Short (≤3 months) versus long (6-12 months) DAPT followed by aspirin or P2Y12 inhibitor monotherapy in high bleeding risk patients

BARC 3-5

Study or Subgroup	S-DAPT Events	S-DAPT Total	L-DAPT Events	L-DAPT Total	Weight	Odds Ratio M-H, Random, 95% CI
SAFE-A	5	102	4	106	3.7%	1.31 [0.34, 5.04]
STOPDAPT 2	3	496	18	558	4.3%	0.18 [0.05, 0.62]
TWILIGHT	8	521	27	543	8.1%	0.30 [0.13, 0.66]
ISAR TRIPLE	13	307	16	307	8.8%	0.80 [0.38, 1.70]
EVOLVE Short DAPT	30	1032	31	1333	13.3%	1.26 [0.76, 2.09]
TICO	31	682	47	694	14.3%	0.66 [0.41, 1.05]
XIENCE 28	33	1362	49	1380	14.8%	0.67 [0.43, 1.06]
XIENCE 90	41	1629	53	1217	15.6%	0.57 [0.37, 0.86]
MASTER DAPT	55	2295	67	2284	17.0%	0.81 [0.57, 1.17]
Total (95% CI)		**8426**		**8422**	**100.0%**	**0.68 [0.51, 0.89]**
Total events	219		312			

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 16.87$, df = 8 (P = 0.03); $I^2 = 53\%$

Test for overall effect: Z = 2.73 (P = 0.006)



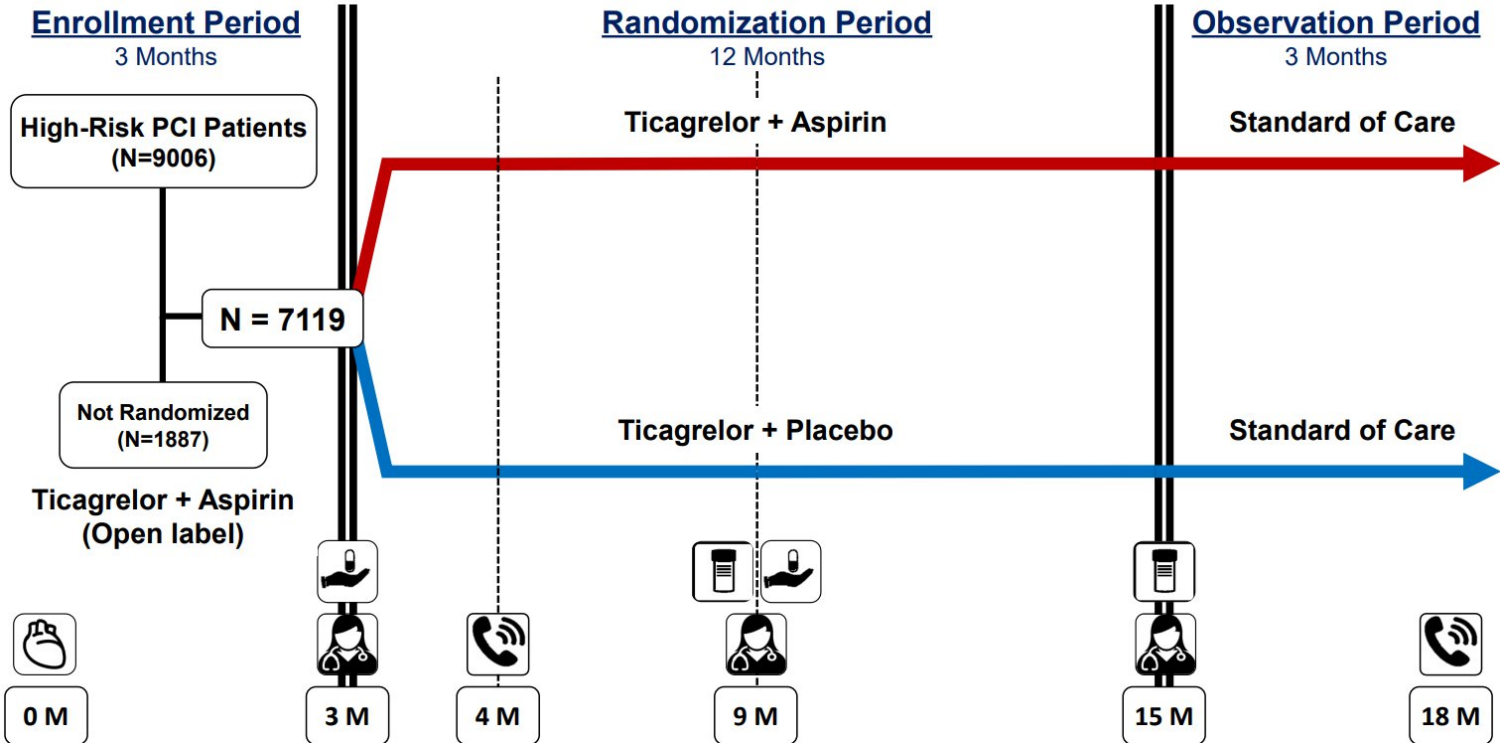
Garg et al. Am Heart J 2022

RCT in HBR patients – Drugs/strategy

Study	Year	Population	Exp.arm	Comparator	Primary EP	Results--
MASTER DAPT	2021	4434 pts treated by PCI with Ultimaster sirolimus-eluting stent	1 month DAPT	≥ 3 month DAPT	• NACE (non-inferiority) • MACCE (non inferiority) • BARC 2-3-5 (superiority)	• NACE: non-inferiority met • MACCE: non-inferiority met • BARC 2-3-5 (superiority met)
TWILIGHT-HBR*	2021	1064 HBR, 5114 non-HBR pts undergoing PCI with high-risk clinical/angio criteria	3 month DAPT with ASA-ticagrelor followed by ticagrelor monotherapy	12 month DAPT with ASA-ticagrelor	• BARC 2-3-5	• 3 month DAPT superior

*pre-specified analysis

Study Design



Mehran et al. NEJM 2019

twilight

Clinical criteria

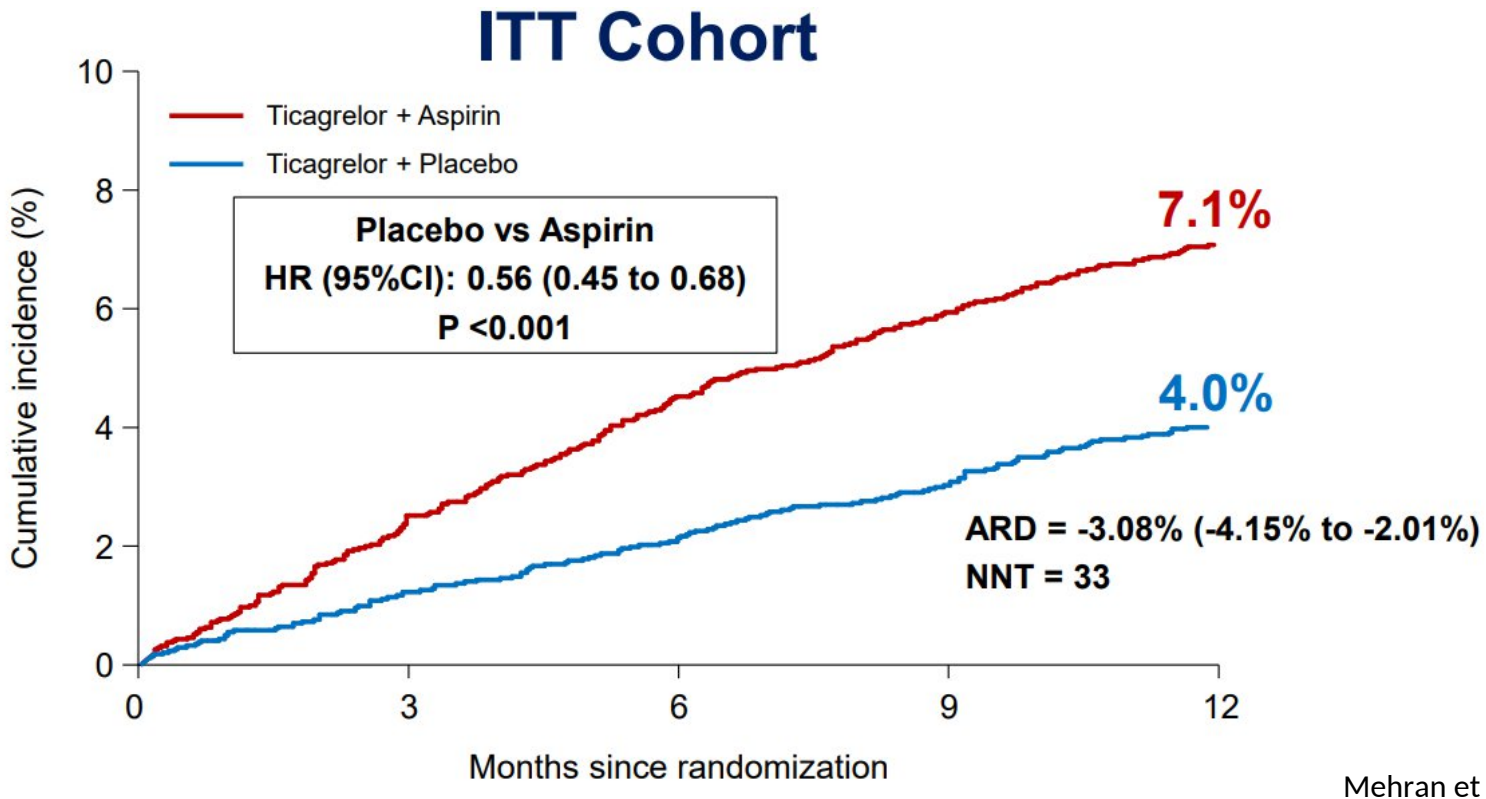
- Age ≥65 years
- Female gender
- Troponin positive ACS
- Established vascular disease (previous MI, documented PAD or CAD/PAD revasc)
- DM treated with medications or insulin
- CKD (eGFR <60ml/min/1.73m^2 or CrCl <60ml/min)

Angiographic criteria

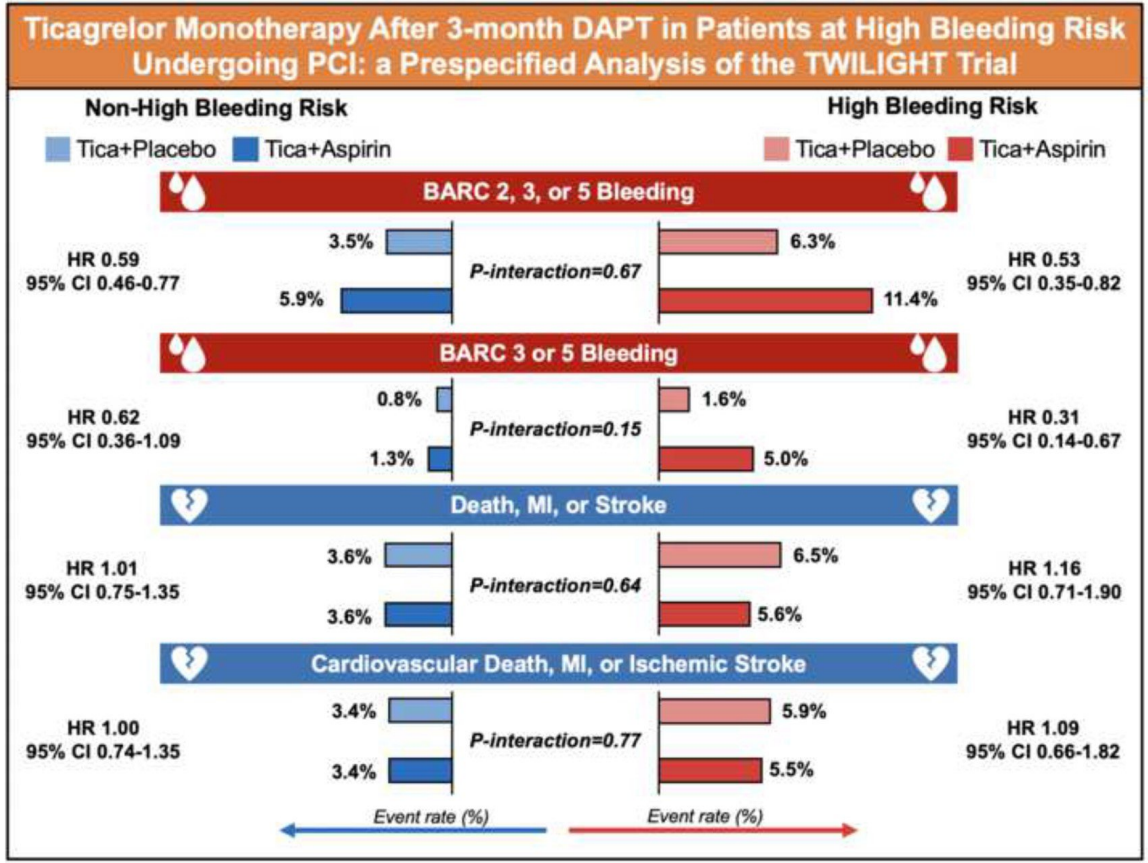
- Multivessel CAD
- Target lesion requiring total stent length >30mm
- Thrombotic target lesion
- Bifurcation lesion(s) with Medina X,1,1 classification requiring ≥2 stents
- Left main (≥50%) or proximal LAD (≥70%) lesions
- Calcified target lesion(s) requiring atherectomy

Mehran et al. NEJM 2019

Primary end-point: BARC 2,3 or 5 bleeding

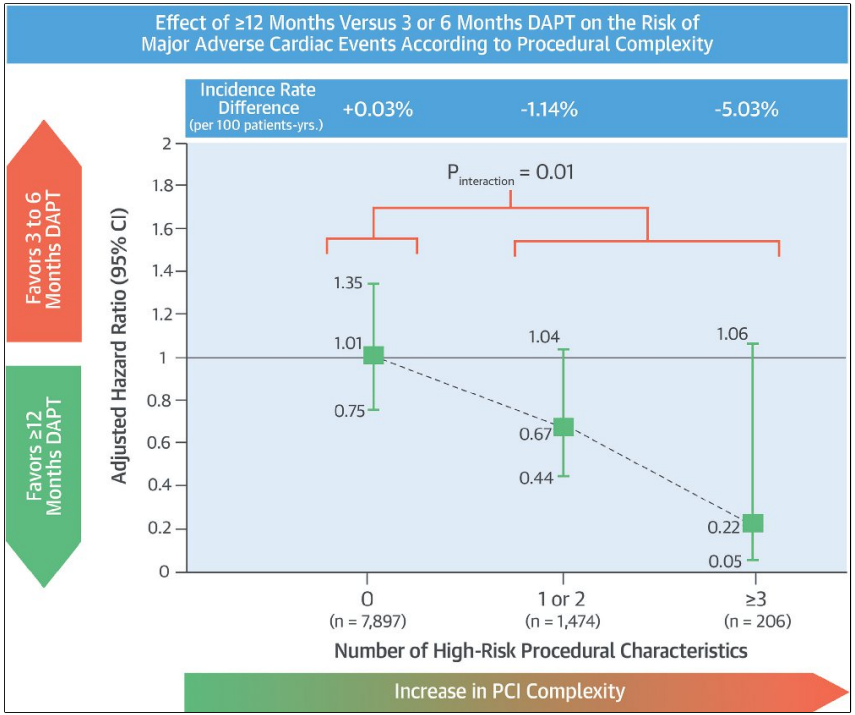


Mehran et al. NEJM 2019

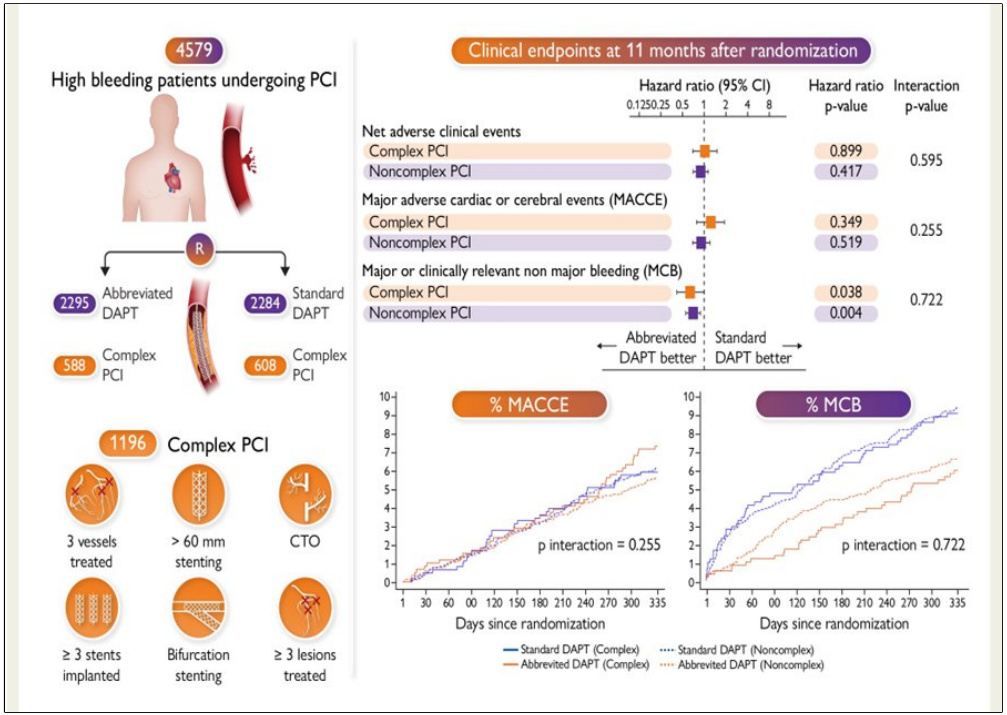


Escaned et al. Eur Heart J 2021

DAPT duration after complex PCI

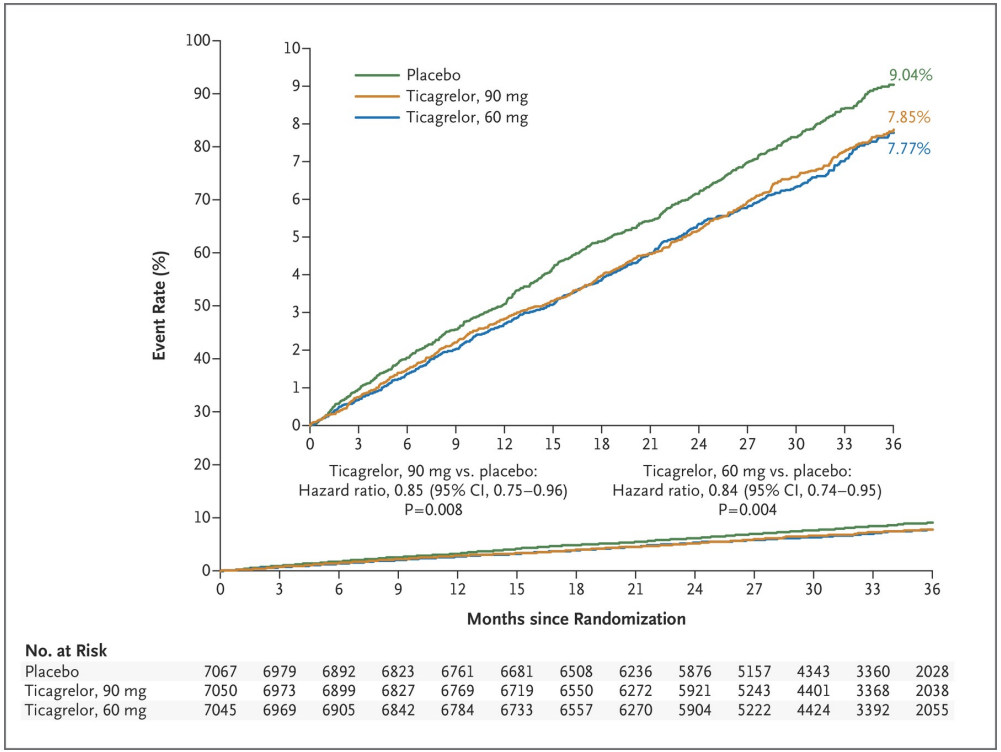


Giustino et al. JACC 2016

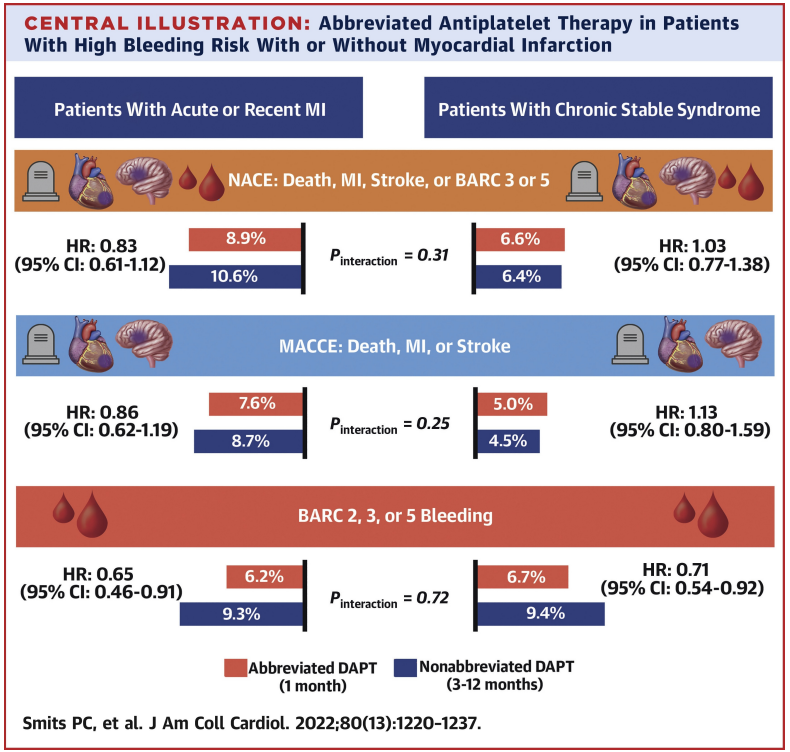


Valgimigli et al. Eur Heart J 2022

DAPT duration in previous MI patients



Bonaca et al. NEJM 2015



Patients with atrial fibrillation undergoing coronary stenting

Default duration of triple antithrombotic therapy should be one week

Pro

Five major trials in this field including almost 12,000 patients showed that 1-week TT followed by OAC plus SAPT reduced bleeding with a similar rate of ischaemic events compared with 6-12 months TT

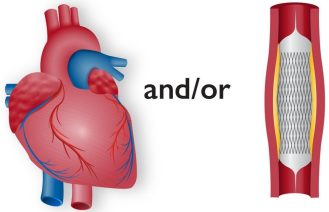
The number of patients enrolled in these 5 trials and the trials' cumulative results exclude an absolute risk increase of ischaemic events > 1.4% for 1-week vs long-term TT and show an absolute risk reduction > 8% for bleeding

No subgroup has been shown to benefit from long-term TT

Reducing bleeding has important benefits for patients' quality of life and ability to avoid hospitalizations

Atrial fibrillation

and



ACS **PCI**

Contra

The abrupt shortening of TT duration by guidelines from 6 months to one week stems from the evidence of RCTs which, however, have important limitations

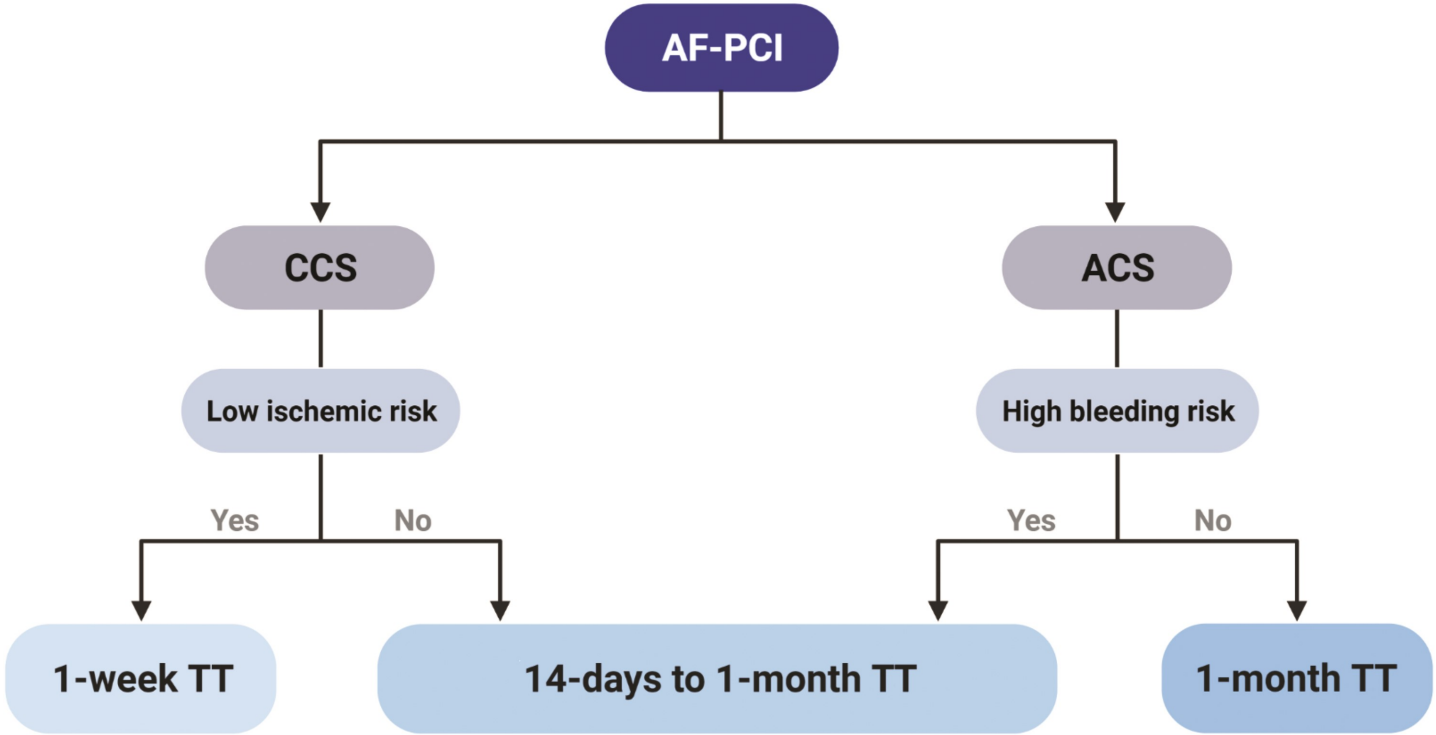
1-week TT is associated with increased risk of ischaemic events, which may be of concern particularly among high-ischaemic risk subgroups of patients such as those with ACS or complex PCI

The increased risk of bleeding conferred by TT is counterbalanced by a reduction of ischaemic events up to 30 days after PCI/ACS

The need for more personalized antithrombotic regimens prevents from recommending a 1-week TT for the majority of patients

De Caterina et al. Eur Heart J 2022

Patients with atrial fibrillation undergoing coronary stenting



Galli et al. Eur Heart J 2022

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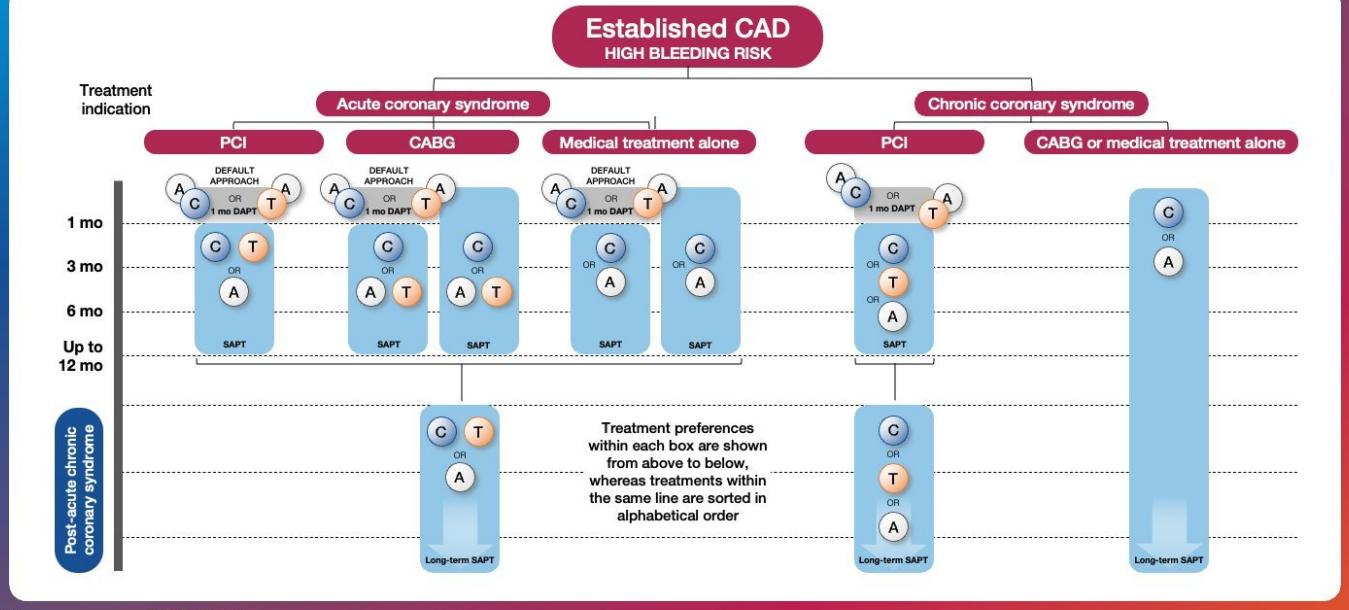
EAPCI/ACVC/EAPC consensus document on antithrombotic treatment strategies for secondary or tertiary prevention in patients with established coronary artery disease

Overview (high bleeding risk)



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by D. Capodanno

CONCLUSIONS

- HBR patients are increasing (mainly because of ageing of the population)
- They present higher risk of both bleeding and ischemic events as compared to non-HBR patients
- Several stent platforms proved to be effective and safe with 30-days DAPT in these patients, without clear advantage of one specific design (polymer-free vs durable polymer vs bioabsorbable polymer) with the possible (negative) exception of nanopolymer-drug free stent
- In the near future data on ultra-thin, bioabsorbable polymer, sirolimus-eluting stent as compared to thin-strut DES will be available
- Prolonged DAPT in these patients is associated with increased bleeding and should be avoided; 1-month DAPT strategy for most.
- A SAPT strategy with a P2Y12 inhibitor, instead of ASA, could be considered