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GIORNATE
CARDIOLOGICHE
TORINESI

UNIVERSITÀ DEGLI STUDI DI TORINO

AZIENDA OSPEDALIERO-UNIVERSITARIA
Città della Salute e della Scienza di Torino

HIGH BLEEDING RISK PATIENS

Maurizio D'Amico

Responsabile Lab. Emodinamica
Divisione di Cardiologia Universitaria
AOU Città della Salute e della Scienza di Torino

Saturday, October 27th 2018

Who are HBR PATIENTS ?

Definition:

- Clinical indications for treatment with oral anti-coagulant agents

- Recent bleeding episodes requiring medical attention or previous hospitalization for bleeding

- Older than 80 years

- Systemic conditions associated with increased bleeding (e.g. hematlogical disorders)

- Known anemia

- Long term treatment with steroids of NSAIDs


Zotarolimus-Eluting Versus Bare-Metal Stents in Uncertain Drug-Eluting Stent Candidates

- Clinical indications for treatment with oral anti-coagulant agents

- Recent bleeding episodes requiring medical attention or previous hospitalization for bleeding

- Older than 75 years

- Systemic conditions associated with increased bleeding (e.g. hematological disorders)

-Known anemia

- Long term treatment with steroids of NSAIDs

- Cancer in previous three years

- CKD or Chronic LIVER disease

- Planned surgery


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Philip Urban, M.D., Ian T. Meredith, M.B., B.S., Ph.D., Alexandre Abizaid, M.D., Ph.D., Stuart J. Pocock, Ph.D., Didier Carrié, M.D., Ph.D., Christoph Naber, M.D., Ph.D., Janusz Lipiecki, M.D., Ph.D., Gert Richardt, M.D., Andres Iñiguez, M.D., Ph.D., Philippe Brunel, M.D., Mariano Valdes-Chavarri, M.D., Ph.D., Philippe Garot, M.D., Suneel Talwar, M.B., B.S., M.D., Jacques Berland, M.D., Mohamed Abdellaoui, M.D., Franz Eberli, M.D., Keith Oldroyd, M.B., Ch.B., M.D., Robaayah Zambahari, M.B., B.S., M.D., John Gregson, Ph.D., Samantha Greene, B.A., Hans-Peter Stoll, M.D., and Marie-Claude Morice, M.D., for the LEADERS FREE Investigators*

Table 2 Long-term risk factors for bleeding after percutaneous coronary intervention

Procedural factors	Patient characteristics	Pharmacological factors
Short-term risk factors:	Age	Prolonged dual antiplatelet therapy
Femoral access,	History of bleeding	Concomitant use of oral anticoagulation
Large sheath size	Low body weight	
No vascular closure device	Acute coronary syndrome	
Long-term risk factors:	Thrombocytopenia	
Unknown	Gastro-intestinal disease	
	Impaired kidney function	
	Liver disease	
	Cerebrovascular accident	
	Malignancy	

European Heart Journal (2015) 36, 1207–1211
doi:10.1093/eurheartj/ehv103

EDITORS PAGE

Duration of dual antiplatelet therapy after coronary artery stenting: where is the sweet spot between ischaemia and bleeding?

Ronald K. Binder and Thomas F. Lüscher*

CRUSADE Bleeding Score Calculator

- INTRODUCTION
- CALCULATOR
- ABOUT
- REFERENCES
- LINKS
- DISCLAIMER
- DOWNLOADS

Last Updated: March 2008

Enter values in drop-down boxes below:

Baseline Hematocrit	HCT (%)	Prior Vascular Disease	-Select-
GFR: Cockcroft-Gault	mL/min (Calculate GFR)	Diabetes Mellitus	-Select-
Heart rate on admission	bpm	Signs of CHF on admission	-Select-
Systolic blood pressure on admission	mmHg	Sex	-Select-

Clear Selections

CRUSADE Bleeding Score	Risk of In-Hospital Major Bleeding
--	--
Enter all fields above	Enter all fields above

Mehran R et al., J Am Coll Cardiol. 2010.

UNIVERSITÀ DEGLI STUDI DI TORINO

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Città della Salute e della Scienza di Torino

DAPT Risk Calculator

Reset

Patient Characteristics

Age *

Years

Must be between 18-100

Select all that apply

- Diabetes Mellitus
- Prior Myocardial Infarction or Percutaneous Coronary Intervention
- Hypertension
- Peripheral Arterial Disease
- Cigarette Smoking Within Last Two Years
- History of Congestive Heart Failure or Left Ventricular Ejection Fraction < 30%
- Renal Insufficiency

Procedure Characteristics

Select all that apply

- Myocardial Infarction at Presentation
- Stent Diameter < 3mm
- Stenting of Vein of Graft

Yeh, JAMA 2016

PRECISEDAPT

Home | WebCalculator | Disclaimer | About | Contact Us

Haemoglobin unit: g/dl / mmol/L

Age (years)

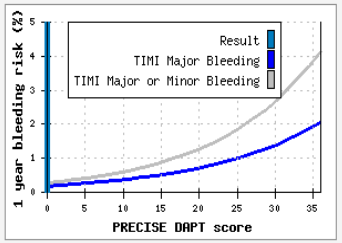
White blood cells unit: u/mcL / 10⁹/L

Creatinine Clearance (ml/min)

Prior Bleeding

CALCULATE

RESET



RESULT:

Cluster of risk:

Score Calculated

---

12 months risk of TIMI major or minor Bleeding

---

12 months risk of TIMI Major Bleeding

Copy to clipboard

Costa P. et al., PRECISE-DAPT Study Investigators, Lancet 2017

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 72, NO. 10, 2018

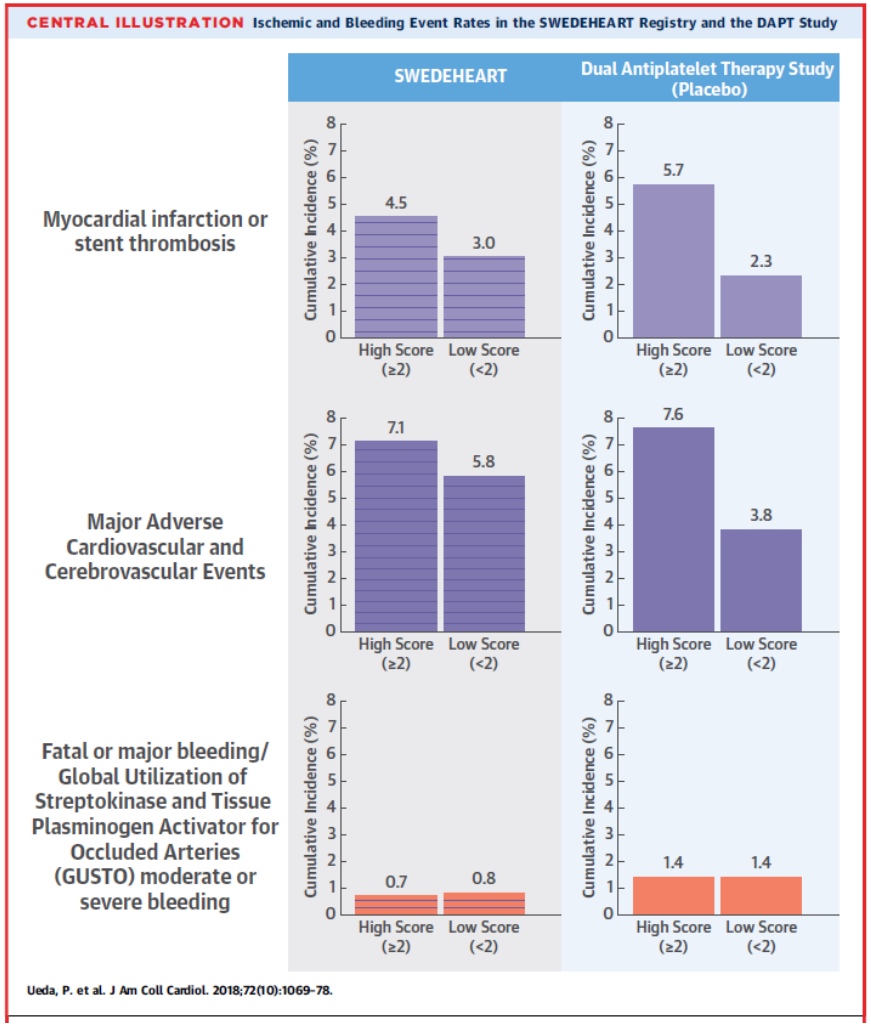
PUBLISHED BY ELSEVIER

ORIGINAL INVESTIGATIONS

External Validation of the DAPT Score in a Nationwide Population

Peter Ueda, MD, PhD,[a] Tomas Jernberg, MD, PhD,[b] Stefan James, MD, PhD,[c,d] Joakim Alfredsson, MD, PhD,[e,f] David Erlinge, MD, PhD,[g] Elmir Omerovic, MD, PhD,[h,i] Jonas Persson, MD, PhD,[b] Annica Ravn-Fischer, MD, PhD,[i] Per Tornvall, MD, PhD,[j] Bodil Svennblad, PhD,[d] Christoph Varenhorst, MD, PhD[c,k]

41101 pts followed beyond
12-months of event free
DAPT



TURIN, October 25th-27th 2018 Starhotels Majestic

GIORNATE CARDIOLOGICHE TORINESI 30

UNIVERSITÀ DEGLI STUDI DI TORINO

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ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.11.028

CLINICAL RESEARCH — Interventional Cardiology

Stent Thrombosis and Bleeding Complications After Implantation of Sirolimus-Eluting Coronary Stents in an Unselected Worldwide Population

A Report From the e-SELECT (Multi-Center Post-Market Surveillance) Registry

Philip Urban, MD,* Alexandre Abizaid, MD,† Adrian Banning, MD,‡ Antonio L. Bartorelli, MD,§ Ana Cebrian Baux, PHD,‖ Vladimír Džavík, MD,¶ Stephen Ellis, MD,# Runlin Gao, MD,** David Holmes, MD,†† Myung Ho Jeong, MD,‡‡ Victor Legrand, MD,§§ Franz-Josef Neumann, MD,‖‖ Maria Nyakern, PHD,‖ Christian Spaulding, MD,¶¶ Stephen Worthley, MD,## for the e-SELECT Investigators

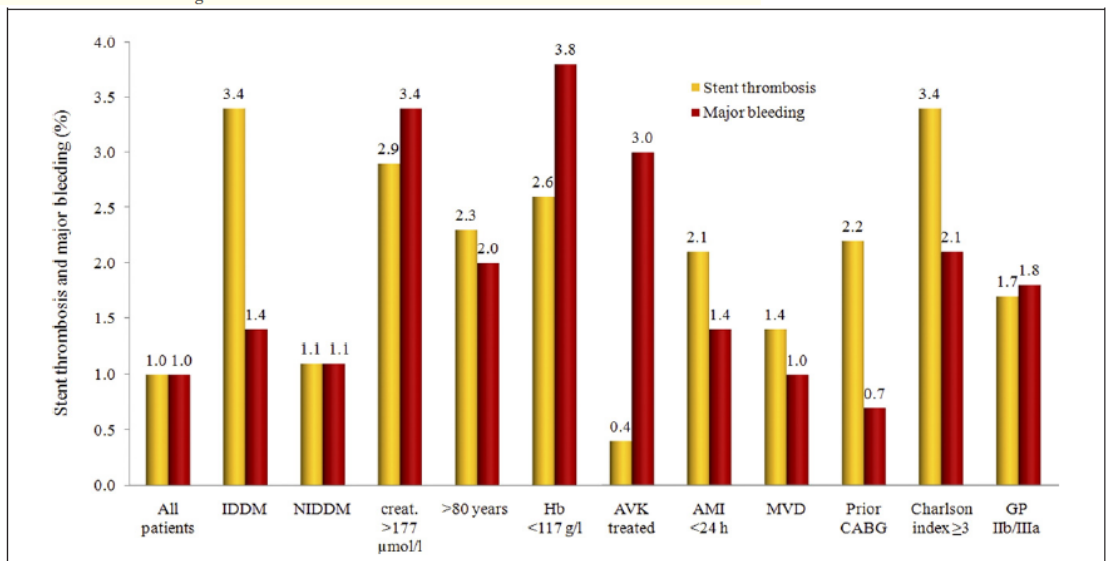
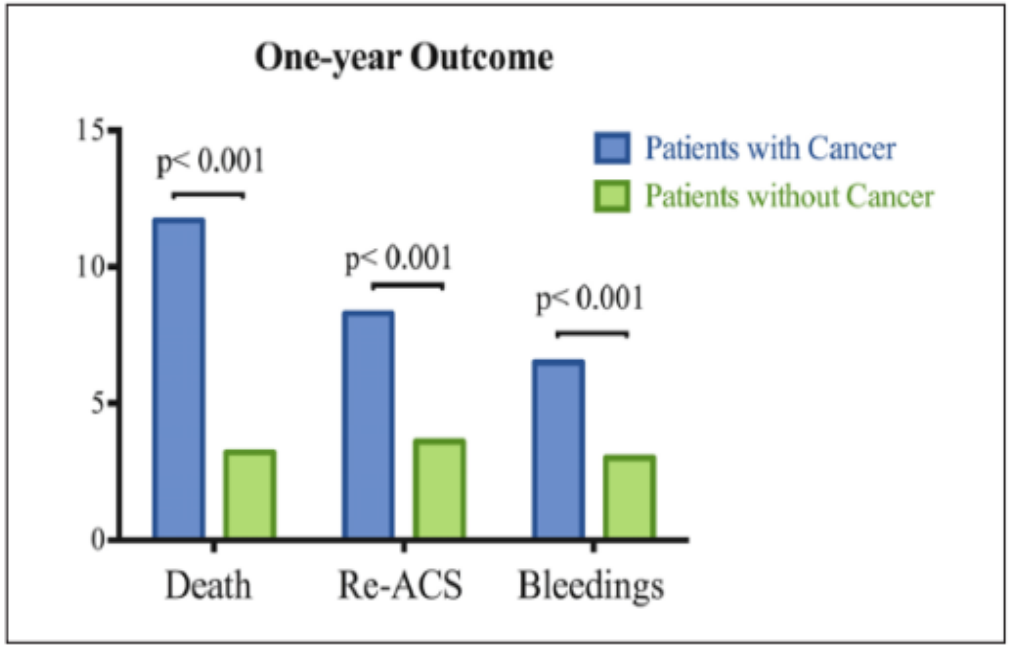


Figure 2 Stent Thrombosis and Major Bleeding in Selected Patient Subgroups



Prevalence and outcome of patients with cancer and acute coronary syndrome undergoing percutaneous coronary intervention: a BleeMACS substudy

Mario Iannaccone[1,2], Fabrizio D'Ascenzo[2], Paolo Vadalà[2],

WHY IS HBR SUCH A MEDICAL CONCERN ?

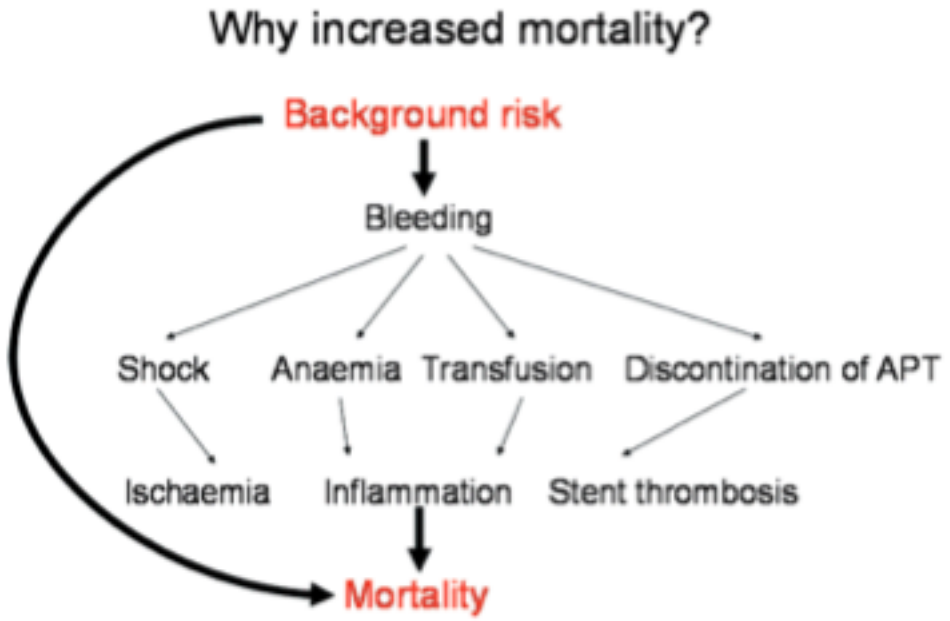
" Bleedings events after succesful PCI are indipendently associated with increased mortality and morbidity...".

2017, ESC focused update on DAPT

"Compared with patients without bleeding, patients who experience bleeding are more likely to die not only early in-hospital but also late after discharge..."

2011, ESC position paper on bleeding in ACS and PCI

WHY IS HBR SUCH A MEDICAL CONCERN ?



European Heart Journal (2009) 30, 655–661
doi:10.1093/eurheartj/ehn358
CLINICAL RESEARCH
Coronary heart disease

Improving clinical outcomes by reducing bleeding in patients with non-ST-elevation acute coronary syndromes

Andrzej Budaj[†1], John W. Eikelboom[2,3*†], Shamir R. Mehta[2,3], Rizwan Afzal[3], Susan Chrolavicius[3], Jean-Pierre Bassand[4], Keith A.A. Fox[5], Lars Wallentin[6], Ron J.G. Peters[7], Christopher B. Granger[8], Campbell D. Joyner[3], and Salim Yusuf[2,3] on behalf of OASIS 5 Investigators

	Major bleeding, *n* (%)	No bleeding, *n* (%)	HR (95% CI)	*p*-value
30 days	*n* = 771	*n* = 18851		
Death/MI/Stroke	168 (21.8%)	1160 (6.2%)	3.99 (3.30–4.82)	<0.0001
180 days	*n* = 937	*n* = 18665		
Death/MI/Stroke	276 (29.7%)	1940 (10.6%)	2.97 (2.55–3.45)	<0.0001
MI	79 (9.2%)	1022 (5.7%)	2.63 (2.13–3.25)	<0.0001
Stroke	42 (4.9%)	212 (1.2%)	4.25 (2.93–6.15)	<0.0001
Death	132 (14.3%)	985 (5.4%)	3.11 (2.55–3.79)	<0.0001

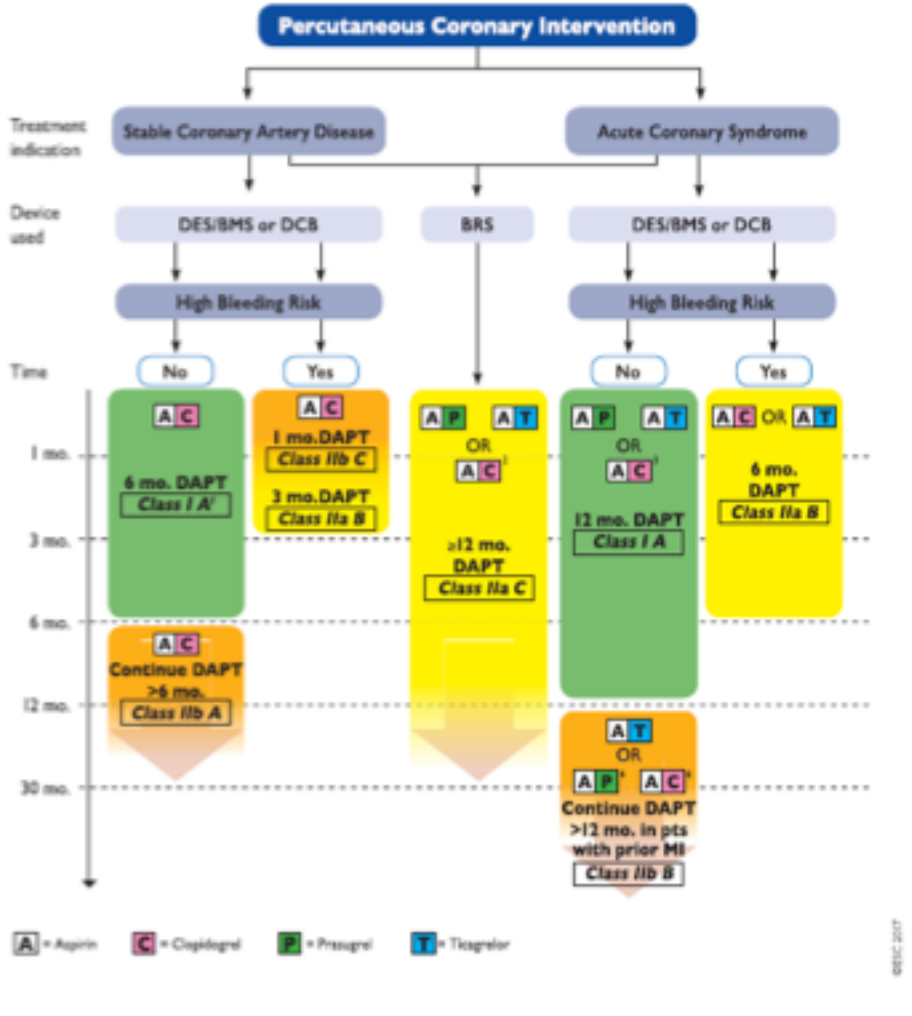
HOW TO MINIMIZE THE RISK OF BLEEDING?

1. The Patient and peri-PCI
2. The DAPT and its duration
3. The Stent

Measures to minimize bleeding while on dual antiplatelet therapy

Recommendations	Class[a]	Level[b]
Radial over femoral access is recommended for coronary angiography and PCI if performed by an expert radial operator.[43,44]	I	A
In patients treated with DAPT, a daily aspirin dose of 75-100 mg is recommended.[45–47,51,52]	I	A
A PPI in combination with DAPT[c] is recommended.[70,79,80,86,87]	I	B
Routine platelet function testing to adjust antiplatelet therapy before or after elective stenting is not recommended.[58–60]	III	A

2. The DAPT and its duration



Dual antiplatelet therapy duration and related stent choices in patients with stable coronary artery disease treated with percutaneous coronary intervention

Recommendations	Class[a]	Level[b]
In patients with stable CAD treated with coronary stent implantation, DAPT consisting of clopidogrel in addition to aspirin is generally recommended[c] for 6 months, irrespective of the stent type.[100,101,104,126–130]	I	A
Irrespective of the intended DAPT duration, DES[c] is the preferred treatment option.[129–132]	I	A
In patients with stable CAD considered at high bleeding risk (e.g. PRECISE-DAPT ≥25), DAPT for 3 months[d] should be considered.[105,106]	IIa	B

Dual antiplatelet therapy duration in patients with acute coronary syndrome treated with percutaneous coronary intervention

Recommendations	Class[a]	Level[b]
In patients with ACS treated with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding (e.g. PRECISE-DAPT ≥25).[102,140]	I	A
In patients with ACS and stent implantation who are at high risk of bleeding (e.g. PRECISE-DAPT ≥25), discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months should be considered.[133,138,143]	IIa	B

2. The DAPT and its duration

In patients with stable CAD considered at high bleeding risk (e.g. PRECISE-DAPT ≥25), DAPT for 3 months[d] should be considered.[105,106]	IIa	B

- RESET TRIAL (RCT) , Byeong-KeukKim et al. JACC 2012 : "E-ZES+3-month DAPT was noninferior to the standard therapy (12 months) with respect to the occurrence of the primary endpoint (CV death, MI, TVR, ST and bleeding).

- **OPTIMIZE TRIAL (RCT) ,** Feres F et al. JAMA 2013: "In patients with stable coronary artery disease or low-risk ACS treated with zotarolimus-eluting stents, 3 months of dual antiplatelet therapy was noninferior to 12 months for NACCE, without significantly increasing the risk of stent thrombosis."

BUT……

2. The DAPT and its duration

RESET and OPTIMIZE trial, LIMITATIONS

- LOW EVENTS RATES OBSERVED (Underpowered to detect small differences in ischemic and bleeding events)
- PATIENTS WITH LOW ISCHEMIC RISK (Previous ST **excluded**; Bifurcations with two stents **excluded**; mean stent lenght 22 / 32 mm; mean number of stent per patient 1.3-1.6; total lenght of stents > 60 mm **excluded;** CKD 6%; multivessel 24-26%; CTO excluded)
- PATIENTS WITH LOW BLEEDING RISK (***HBR RISK PATIENTS completely excluded*** from RESET trial)

Table 5 High-risk features of stent-driven recurrent ischaemic events

• Prior stent thrombosis on adequate antiplatelet therapy
• Stenting of the last remaining patent coronary artery
• Diffuse multivessel disease especially in diabetic patients
• Chronic kidney disease (i.e. creatinine clearance <60 mL/min)
• At least three stents implanted
• At least three lesions treated
• Bifurcation with two stents implanted
• Total stent length >60 mm
• Treatment of a chronic total occlusion

©ESC 2017

2. The DAPT and its duration

In patients with ACS and stent implantation who are at high risk of bleeding (e.g. PRECISE-DAPT ≥25), discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months should be considered.[13,18,143]	IIa	B

"By network meta-analysis, 3-month DAPT, but not 6-month DAPT, was associated with higher rates of MI or ST in ACS, whereas no significant differences were apparent in stable patients..."

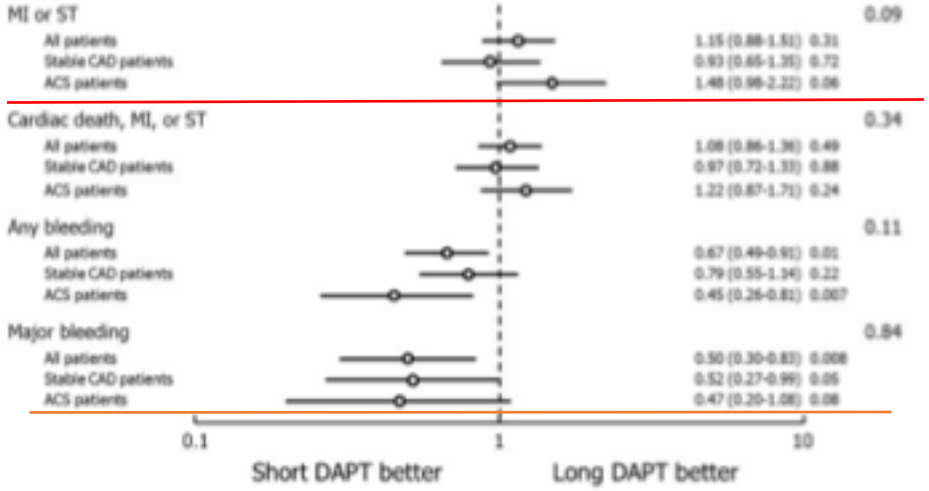
European Heart Journal (2017) 38, 1034–1043
doi:10.1093/eurheartj/ehw627

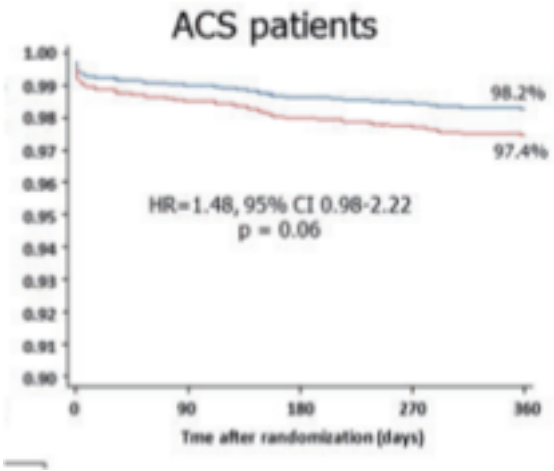
CLINICAL RESEARCH
Interventional cardiology

Three, six, or twelve months of dual antiplatelet therapy after DES implantation in patients with or without acute coronary syndromes: an individual patient data pairwise and network meta-analysis of six randomized trials and 11 473 patients

Tullio Palmerini[1], Diego Della Riva[1], Umberto Benedetto[2], Letizia Bacchi Reggiani[1], Fausto Feres[3], Alexandre Abizaid[3], Martine Gilard[4], Marie-Claude Morice[5], Marco Valgimigli[6], Myeong-Ki Hong[7], Byeong-Keuk Kim[7], Yangsoo Jang[7], Hyo-Soo Kim[8], Kyung Woo Park[8], Antonio Colombo[9], Alaide Chieffo[9], Diego Sangiorgi[1], Giuseppe Biondi-Zoccai[10], Philippe Généreux[11], Gianni D. Angelini[2], Maria Pufulete[2], Jonathon White[11], Deepak L. Bhatt[12], and Gregg W. Stone[11]*

BUT...





2. The DAPT and its duration…

Which DAPT?

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 SEPTEMBER 10, 2009 VOL. 361 NO. 11

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H., Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington, M.D., for the PLATO Investigators*

Secondary safety end points — no./total no. (%)

Non–CABG-related major bleeding, study criteria	362/9235 (4.5)	306/9186 (3.8)	1.19 (1.02–1.38)	0.03
Non–CABG-related major bleeding, TIMI criteria	221/9235 (2.8)	177/9186 (2.2)	1.25 (1.03, 1.53)	0.03
CABG-related major bleeding, study criteria	619/9235 (7.4)	654/9186 (7.9)	0.95 (0.85–1.06)	0.32
CABG-related major bleeding, TIMI criteria	446/9235 (5.3)	476/9186 (5.8)	0.94 (0.82–1.07)	0.32
Major or minor bleeding, study criteria	1339/9235 (16.1)	1215/9186 (14.6)	1.11 (1.03–1.20)	0.008
Major or minor bleeding, TIMI criteria‡	946/9235 (11.4)	906/9186 (10.9)	1.05 (0.96–1.15)	0.33

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 NOVEMBER 15, 2007 VOL. 357 NO. 20

Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

Stephen D. Wiviott, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Gilles Montalescot, M.D., Ph.D., Witold Ruzyllo, M.D., Shmuel Gottlieb, M.D., Franz-Joseph Neumann, M.D., Diego Ardissino, M.D., Stefano De Servi, M.D., Sabina A. Murphy, M.P.H., Jeffrey Riesmeyer, M.D., Govinda Weerakkody, Ph.D., C. Michael Gibson, M.D., and Elliott M. Antman, M.D., for the TRITON–TIMI 38 Investigators*

"Key exclusion criteria included an increased risk of bleeding"

Major or minor TIMI bleeding	303 (5.0)	231 (3.8)	1.31 (1.11–1.56)	0.002
Bleeding requiring transfusion§	244 (4.0)	182 (3.0)	1.34 (1.11–1.63)	<0.001
CABG-related TIMI major bleeding¶	24 (13.4)	6 (3.2)	4.73 (1.90–11.82)	<0.001

CLINICAL RESEARCH
Interventional cardiology

Three, six, or twelve months of dual antiplatelet therapy after DES implantation in patients with or without acute coronary syndromes: an individual patient data pairwise and network meta-analysis of six randomized trials and 11 473 patients

Tullio Palmerini[1], Diego Della Riva[1], Umberto Benedetto[2], Letizia Bacchi Reggiani[1], Fausto Feres[3], Alexandre Abizaid[3], Martine Gilard[4], Marie-Claude Morice[5], Marco Valgimigli[6], Myeong-Ki Hong[7], Byeong-Keuk Kim[7], Yangsoo Jang[8], Hyo-Soo Kim[9], Kyung Woo Park[9], Antonio Colombo[10], Alaide Chieffo[10], Diego Sangiorgi[11], Giuseppe Biondi-Zoccai[12], Philippe Généreux[13], Gianni D. Angelini[2], Maria Pufulete[2], Jonathon White[14], Deepak L. Bhatt[15], and Gregg W. Stone[13]*

6 trials included with DAPT consisting of Aspirin and **Clopidogrel**

2. The DAPT and its duration…

Dual antiplatelet therapy duration and related stent choices in patients with stable coronary artery disease treated with percutaneous coronary intervention

Recommendations	Class	Level
In patients with stable CAD treated with bioresorbable vascular scaffolds, DAPT for at least 12 months should be considered.	IIa	C
In patients with stable CAD who have tolerated DAPT without a bleeding complication and who are at low bleeding but high thrombotic risk, continuation of DAPT with clopidogrel for >6 months and ≤30 months may be considered.	IIb	A
In patients with stable CAD in whom 3-month DAPT poses safety concerns, DAPT for 1 month may be considered*.	IIb	C

*;1-month DAPT after implantation of zotarolimus-eluting Endeavour sprint stent or drug coated BioFreedom stent reduced risks of adverse events compared to BMS under similar DAPT duration.
It is unclear if this evidence applies to other contemporary DES.

Guidelines, Revascularization, ESC 2018

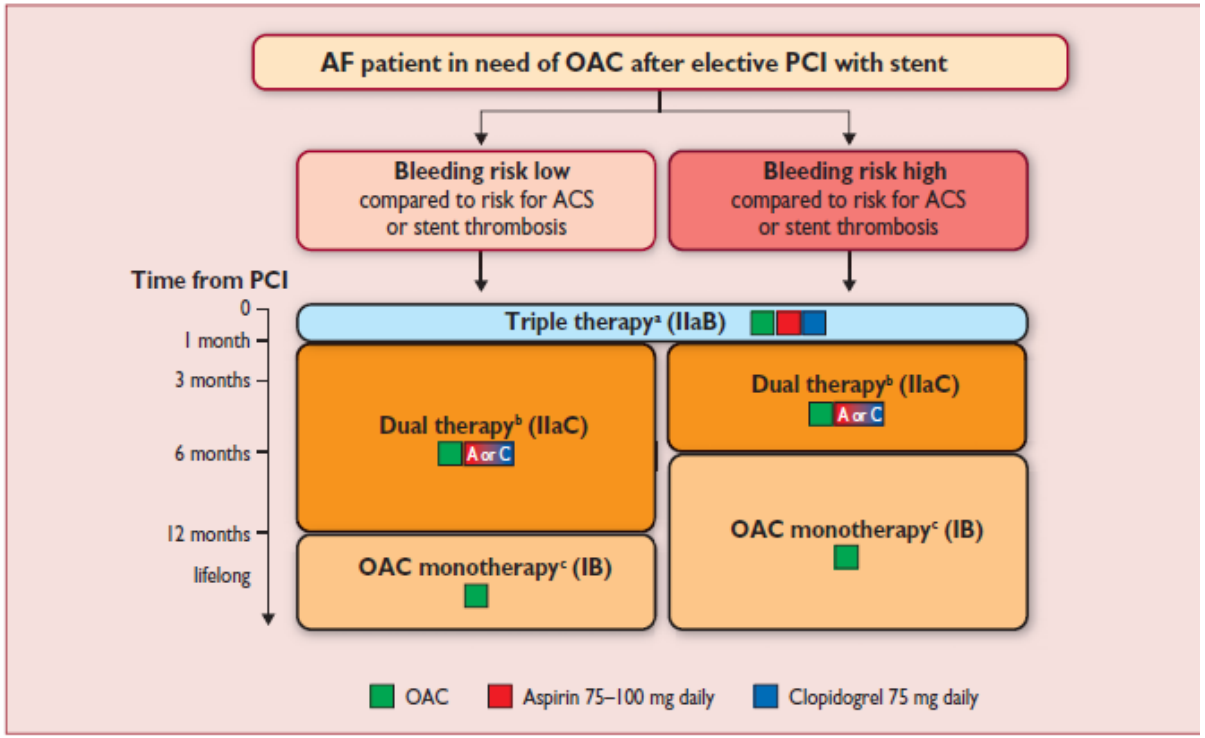
2. DAPT, focus on (N)OAC

Guidelines ESC 2014

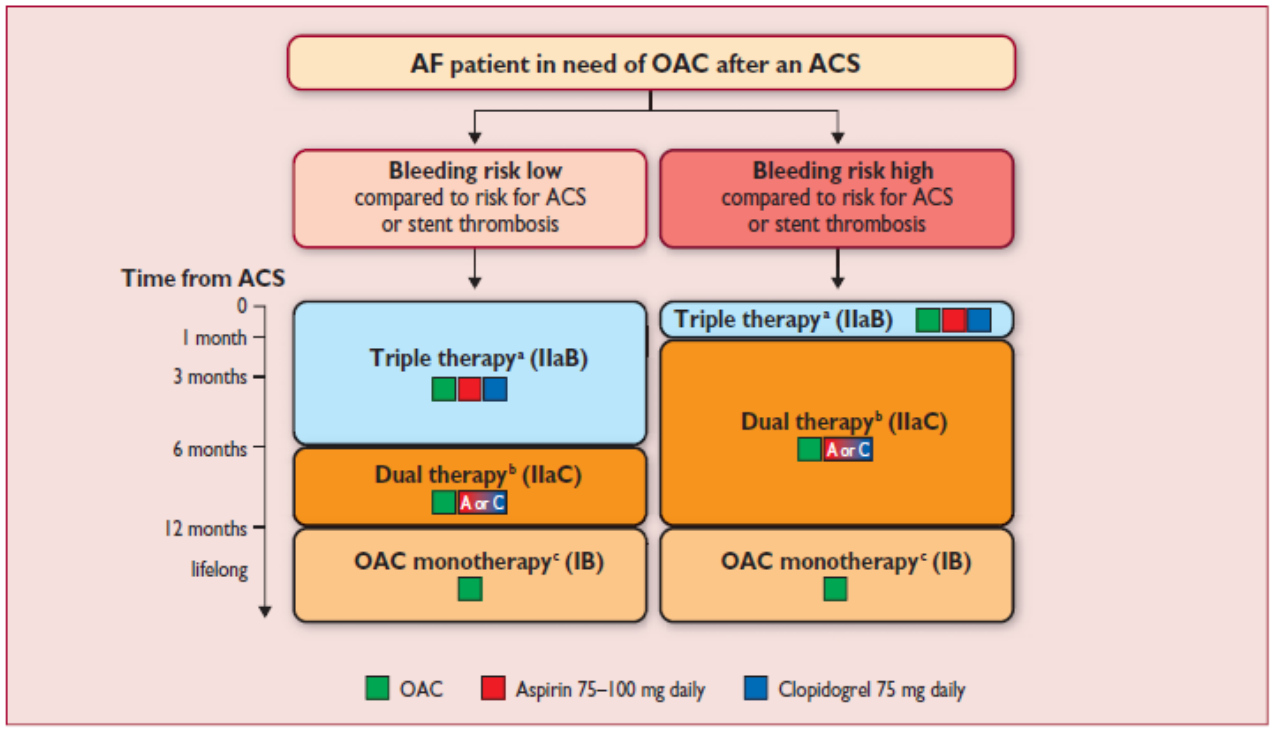
Recommendations	Class[a]	Level[b]	Ref[c]
In patients with a firm indication for oral anticoagulation (e.g. atrial fibrillation with CHA_2DS_2-VASc score ≥2, venous thromboembolism, LV thrombus, or mechanical valve prosthesis), oral anticoagulation is recommended in addition to antiplatelet therapy.	I	C	
New-generation DES are preferred over BMS among patients requiring oral anticoagulation if bleeding risk is low (HAS-BLED ≤2).	IIa	C	
In patients with SCAD and atrial fibrillation with CHA_2DS_2-VASc score ≥2 at low bleeding risk (HAS-BLED ≤2), initial triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of at least 1 month after BMS or new-generation DES followed by dual therapy with (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months.	IIa	C	
DAPT should be considered as alternative to initial triple therapy for patients with SCAD and atrial fibrillation with a CHA_2DS_2-VASc score ≤1.	IIa	C	
In patients with ACS and atrial fibrillation at low bleeding risk (HAS-BLED≤2), initial triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of 6 months irrespective of stent type followed by (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months.	IIa	C	
In patients requiring oral anticoagulation at high bleeding risk (HAS BLED ≥3), triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of 1 month followed by (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) irrespective of clinical setting (SCAD or ACS) and stent type (BMS or new-generation DES).	IIa	C	
Dual therapy of (N)OAC and clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy in selected patients.	IIb	B	865,870
The use of ticagrelor and prasugrel as part of initial triple therapy is not recommended.	III	C	

*Mehran R et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. Lancet, 2103

2. DAPT, focus on (N)OAC



ACS = acute coronary syndrome; AF = atrial fibrillation; OAC = oral anticoagulation (using vitamin K antagonists or non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention.
[a]Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients.
[b]OAC plus single antiplatelet.
[c]Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high risk of coronary events.



ACS = acute coronary syndrome; AF = atrial fibrillation; OAC = oral anticoagulation (using vitamin K antagonists or non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention.
[a]Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients, especially those not receiving a stent or patients at a longer time from the index event.
[b]OAC plus single antiplatelet.
[c]Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high risk of coronary events.

Guidelines AF, ESC 2016

3. The stent

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Zotarolimus-Eluting Versus Bare-Metal Stents in Uncertain Drug-Eluting Stent Candidates

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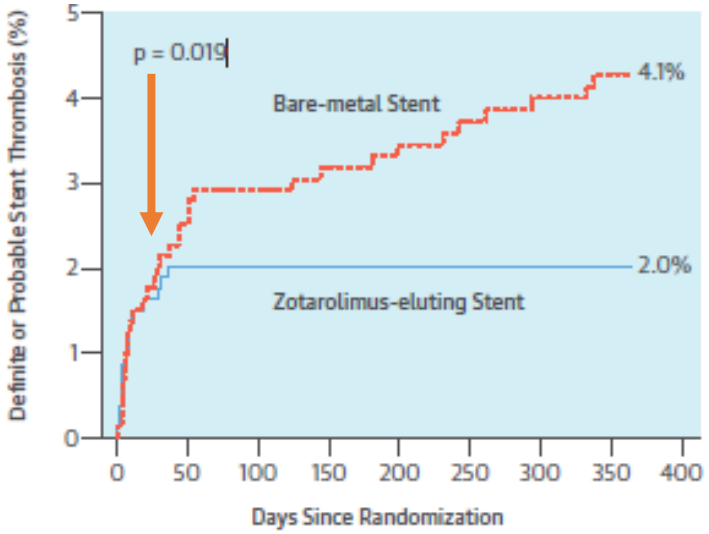
ZES drug fast-release profile (15 days) vs BMS in **HBR patients**

MEAN DAPT DURATION : **1 months**



3. The stent

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

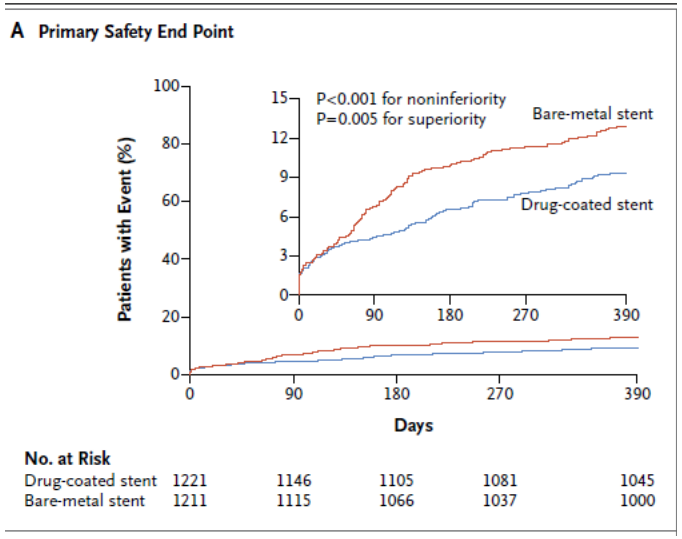
Philip Urban, M.D., Ian T. Meredith, M.B., B.S., Ph.D., Alexandre Abizaid, M.D., Ph.D., Stuart J. Pocock, Ph.D., Didier Carrié, M.D., Ph.D., Christoph Naber, M.D., Ph.D., Janusz Lipiecki, M.D., Ph.D., Gert Richardt, M.D., Andres Iñiguez, M.D., Ph.D., Philippe Brunel, M.D., Mariano Valdes-Chavarri, M.D., Ph.D., Philippe Garot, M.D., Suneel Talwar, M.B., B.S., M.D., Jacques Berland, M.D., Mohamed Abdellaoui, M.D., Franz Eberli, M.D., Keith Oldroyd, M.B., Ch.B., M.D., Robaayah Zambahari, M.B., B.S., M.D., John Gregson, Ph.D., Samantha Greene, B.A., Hans-Peter Stoll, M.D., and Marie-Claude Morice, M.D., for the LEADERS FREE Investigators*

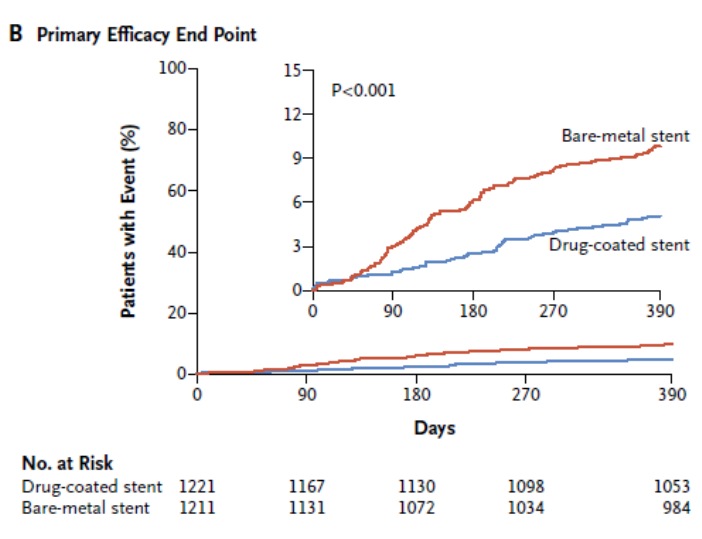
N Engl J Med 2015;

RCT , 2466 pts HBR →

polymer-free biolimus-9 stent vs BMS

Inclusion criteria — no. (%)§		
Age ≥75 yr	788 (64.5)	776 (64.1)
Oral anticoagulation planned to continue after PCI	448 (36.7)	431 (35.6)
Hemoglobin <11 g/liter or transfusion within 4 wk before randomization	185 (15.2)	194 (16.0)
Platelet count <100,000/mm^3	20 (1.6)	18 (1.5)
Hospital admission for bleeding in previous 12 mo	46 (3.8)	33 (2.7)
Stroke in previous 12 mo	15 (1.2)	24 (2.0)
Previous intracerebral hemorrhage	14 (1.1)	19 (1.6)
Severe chronic liver disease	11 (0.9)	10 (0.8)
Creatinine clearance <40 ml/min	219 (17.9)	245 (20.2)
Cancer in previous 3 yr¶	119 (9.7)	120 (9.9)
Planned major surgery in next 12 mo	187 (15.3)	211 (17.4)
Glucocorticoids or NSAID planned for >30 days after PCI	38 (3.1)	34 (2.8)
Expected nonadherence to >30 days of dual antiplatelet therapy	41 (3.4)	47 (3.9)





3. The stent

End Point	Drug-Coated Stent (N=1221)	Bare-Metal Stent (N=1211)	Hazard Ratio (95% CI)	P Value
	no. of events (% of patients)			
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

→ After DAPT discontinuation

Leaders Free, N Engl J Med 2015

3. The stent

LEADERS FREE II

Pivotal Study of the Biolimus A9™ Drug-Coated Stent in High Bleeding Risk Patients: Primary Report

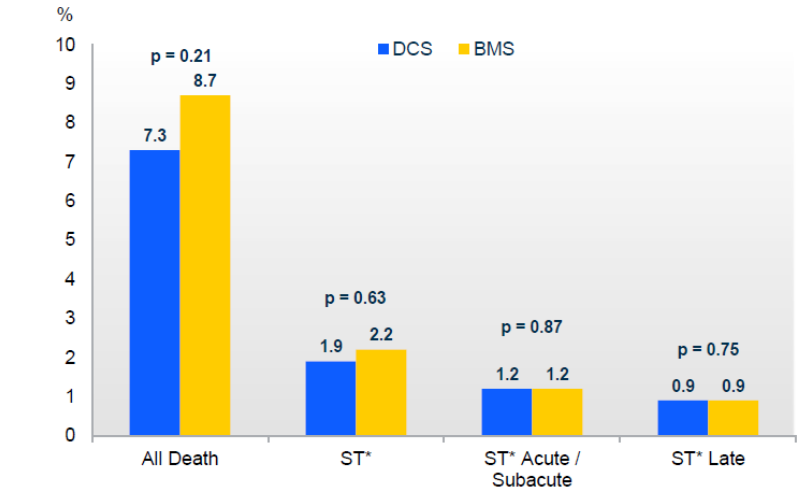
Mitchell W. Krucoff on behalf of Philip Urban (EU-PI), Study Leadership and the LEADERS FREE II Investigators

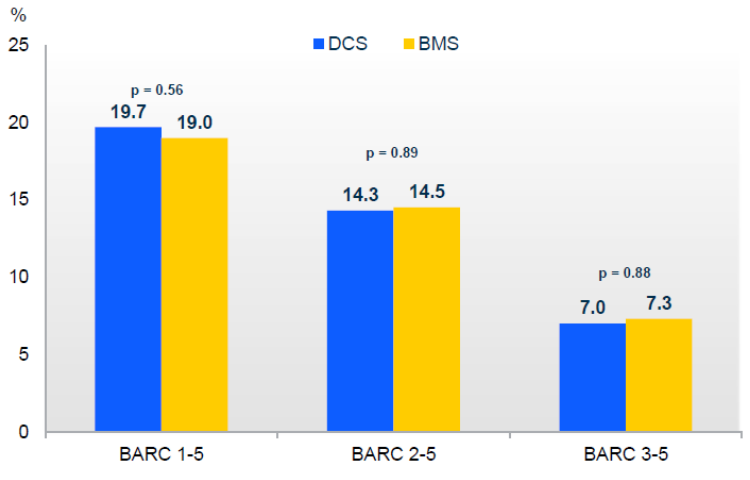
Confronto indiretto con popolazione BMS Europea, 2424 pts HBR →

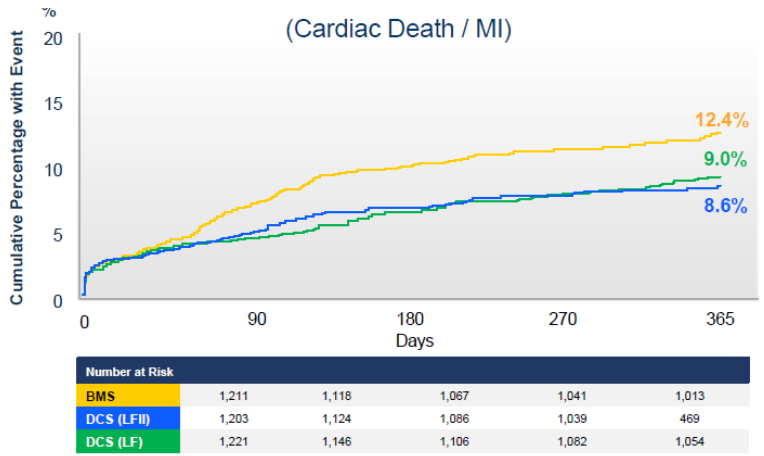
polymer-free biolimus-9 stent vs BMS

	DCS	BMS	p-value
Mean age (years)	74.6 ± 9.7	75.7 ± 9.3	0.0086
Female gender (%)	31.3	30.9	0.8093
BMI (kg/m²)	28.7 ± 5.8	27.2 ± 4.6	<0.0001
Diabetes (%)	34.5	32.3	0.2614
All ACS (%)	45.2	43.1	0.2953
STEMI presentation (%)	2.3	4.0	0.0213
Prior MI (%)	24.1	21.4	0.1166
Prior PCI (%)	38.1	21.9	<0.0001
Prior CABG (%)	15.5	10.1	<0.0001
Congestive heart failure (%)	19.7	12.4	<0.0001
Atrial fibrillation (%)	35.0	34.6	0.8379
Peripheral vascular disease (%)	17.4	15.8	0.2850
Chronic obstructive lung disease (%)	14.0	11.7	0.0983

Pivotal results







3. The stent

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

Olivier Varenne, Stéphane Cook, Georgios Sideris, Sasko Kedev, Thomas Cuisset, Didier Carrié, Thomas Hovasse, Philippe Garot, Rami El Mahmoud, Christian Spaulding, Gérard Helft, José F Diaz Fernandez, Salvatore Brugaletta, Eduardo Pinar-Bermudez, Josepa Mauri Ferre, Philippe Commeau, Emmanuel Teiger, Kris Bogaerts, Manel Sabate, Marie-Claude Morice, Peter R Sinnaeve, for the SENIOR investigators

Lancet,2018

RCT 1:1 Synergy stent vs BMS

Age > 75 yo
Diabetes 26%
CKD 17%
Anaemia 15%

ACS 45%
MVD 32%
Bifurcation 15%
Total stent length 31 mm

DAPT:
6 months in ACS
1 month in Stable CAD

	Drug-eluting stent (n=596)	Bare-metal stent (n=604)	Relative risk	p value
Primary endpoint				
All-cause mortality, myocardial infarction, stroke, or ischaemia-driven target lesion revascularisation				
1 year	68 (12%)	98 (16%)	0·71 (0·52–0·94)	0·02
BARC 3–5				
30 days	10 (2%)	8 (1%)	1·26 (0·43–4·37)	0·62
180 days	15 (3%)	14 (2%)	1·08 (0·48–2·47)	0·83
1 year	20 (3%)	21 (4%)	0·95 (0·49–1·81)	0·86
Definite and probable stent thrombosis				
30 days	2 (<1%)	7 (1%)	0·28 (0·00–1·36)	0·09
180 days	3 (1%)	8 (1%)	0·38 (0·00–1·48)	0·13
1 year	3 (1%)	8 (1%)	0·38 (0·00–1·48)	0·13

" A strategy of combination of a DES to reduce the risk of subsequent repeat revascularizations with a short BMS-like DAPT regimen to reduce the risk of bleeding event is an attractive option for elderly patients who have PCI. "

3. The stent

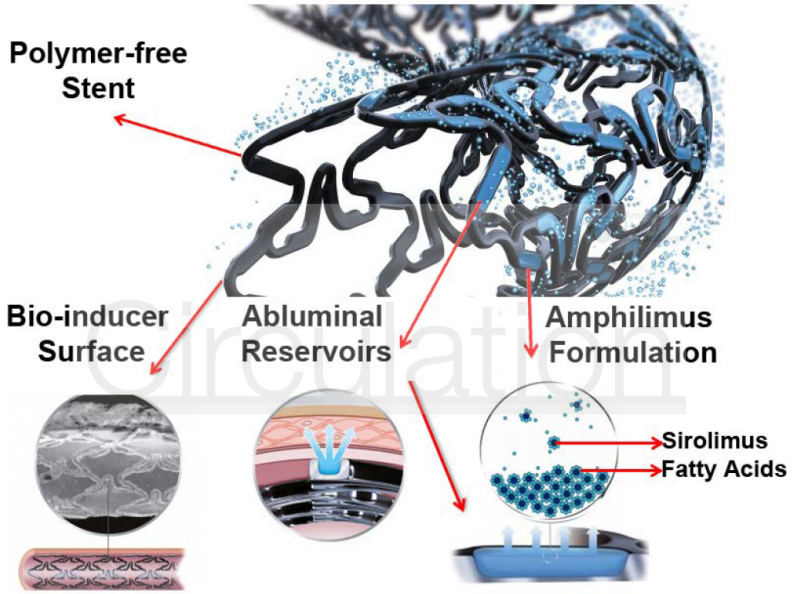
10.1161/CIRCULATIONAHA.118.037707

Randomized All-Comers Evaluation of a Permanent Polymer Zotarolimus-Eluting Stent Versus a Polymer-Free Amphilimus-Eluting Stent: (ReCre8) A Multicenter, Non-Inferiority Trial

Running Title: *Rozemeijer et al.; The ReCre8 Trial*

Rik Rozemeijer, MD, MSc, PharmD[1*]; Mera Stein, MD, PhD[1,2*]; Michiel Voskuil, MD, PhD[1]; Rutger van den Bor, MSc, PhD[3]; Peter Frambach, MD[4]; Bruno Pereira, MD[4]; Stefan Koudstaal MD, PhD[1,5]; Geert E. Leenders, MD, PhD[1]; Leo Timmers, MD, PhD[1]; Saskia Z. Rittersma, MD, PhD[1]; Adriaan O. Kraaijeveld, MD, PhD[1]; Pierfrancesco Agostoni, MD, PhD[1,6]; Kit Roes, MSc, PhD[3]; Pieter A. Doevendans, MD, PhD, FESC[1]; Pieter Stella, MD, PhD[1]; The ReCre8 Study Investigators.

Circulation 2018,
Epub ahead of print



1502 pts, all-comers population, 3 European sites
Mean age 64 yo, 24% female, 16% CKD, 48% ACS, 58% complex lesions
Mean total stent lengh 47 mm

Tnt + → 12 months DAPT
Tnt - → 1 month DAPT

3. The stent

	Overall (n=1491)	PP-ZES (n=744)	PF-AES (n=747)	p-value
Device-oriented primary endpoint*	88 (5·9)	42 (5·6)	46 (6·2)	0·67
Patient-oriented secondary endpoint†	177 (11·9)	86 (11·6)	91 (12·2)	0·69
Any death	35 (2·3)	18 (2·4)	17 (2·3)	0·86
Cardiac death	20 (1·3)	10 (1·3)	10 (1·3)	1·00
Myocardial infarction	53 (3·6)	24 (3·2)	29 (3·8)	0·49
Target-vessel myocardial infarction	35 (2·3)	17 (2·3)	18 (2·4)	0·87
Stent thrombosis (definite, or probable)‡	15 (1·0)	6 (0·8)	9 (1·2)	0·61
Acute (< 24 h)	4 (0·3)	0	4 (0·5)	0·12
Subacute (24 h to 30 days)	5 (0·3)	2 (0·3)	3 (0·4)	1·00
Late (31 days to 12 months)	6 (0·4)	4 (0·5)	2 (0·3)	0·45
Any unplanned revascularization	73 (4·9)	38 (5·1)	35 (4·7)	0·71
Target-lesion revascularization	42 (2·8)	20 (2·6)	22 (2·9)	0·75
Stroke	12 (0·8)	6 (0·8)	6 (0·8)	1·00
Major Bleeding (BARC ≥ 3)	25 (1·7)	13 (1·7)	12 (1·6)	0·84

Circulation 2018,
Epub ahead of print

ONGOING STUDIES LEADERS FREE-LIKE

Study	Device	DAPT Duration	Inclusion	Major Exclusion	Status
COBRA REDUCE	**Cobra PzF** vs Xcience/Resolute	2 weeks	OAC	StagingPCI,DAPT> 2weeks,Major surgery within 1y	recruiting
MASTER-DAPT	**Ultimaster**	1 mos vs 12 mos	HBR criteria	BARC>2	recruiting
POEM	**Synergy** Registry	1 month	HBR criteria	Cardiogenic shock,major active bleeding	recruiting
ONYX ONE-MONTH DAPT	**Resolute** vs Biofreedom	1 month	HBR criteria	Planned surgery within 1 month	recruiting
SHORT DAPT 90	Xcience Registry	3 months	HBR criteria	Planned surgery within 1 month,ACS	recruiting
XIENCE 28	Xience Registry	1 month	HBR criteria	STEMI,LVEF<30	announced
EVOLVE Short DAPT	Synergy Registry	3 months	HBR criteria	ACS	recruiting
STOP-DAPT 2	CoCr-EES	1 mos vs 12 mos	Not only HBR	OAC,Intracranial hemorrage	announced

3. The stent

1. Età ≥75 anni
2. Necessità di terapia anticoagulante orale
3. Emoglobina <11 g/l
4. Emotrasfusione nelle 4 settimane precedenti
5. Piastrinopenia (<100'000/ml)
6. Ricovero per sanguinamento nei 12 mesi precedenti
7. Ictus nei 12 mesi precedenti
8. Storia di sanguinamento intracranico
9. Epatopatia severa
10. Clearance creatinina <40 ml/min
11. Storia di neoplasia nei 3 anni precedenti
12. Programma di chirurgia maggiore nei 12 mesi successivi
13. Terapia con glucocorticoidi o antiinfiammatori non steroidei per >30 giorni dopo l'angioplastica
14. Prevista non adesione a una doppia terapia antiaggregante per oltre 30 giorni

Ongoing…POEM trial

"PERFORMANCE OF BIORESORBABLE POLYMER-COATED EVEROLIMUS-ELUTING **SYNERGY® STENT** IN PATIENTS AT HIGH BLEEDING RISK UNDERGOING PERCUTANEOUS CORONARY REVASCULARIZATION FOLLOWED BY 1-MONTH DUAL ANTIPLATELET THERAPY" – 012017POEM

N of patients 1023

Endpoint primario: composito di mortalità per cause cardiovascolari, infarto del miocardio e trombosi di stent (definita/probabile secondo la definizione ARC) a 1 anno di follow-up.

Endpoint secondary: …Sanguinamenti maggiori (tipo 3-5 secondo la definizione BARC) a 30 giorni e 1 anno

CONCLUSION

- **HBR patients are an increasing medical concern**
  - Identification (clinical judgment vs Scores / Age and OAC = main factors in daily practice)
  - Ischemic risk to be considered and balanced to bleeding risk
- **HBR patients are exposed to an higher risk of death**
  - Even after successful PCI
- **Antithrombotic strategies to be tailored in HBR patients**
  - Less potent drugs and shorter duration
  - GL recommendations often based on low ischemic and bleeding risk patients
- **PCI strategies and device selection specific to HBR patients**
  - New stent generation (current evidences for BIOFREEDOM/SYNERGY)
  - Avoid complex procedures (whenever possible)
- **Future scenarios?**
  - New stents and tailored DAPT models

Thank you