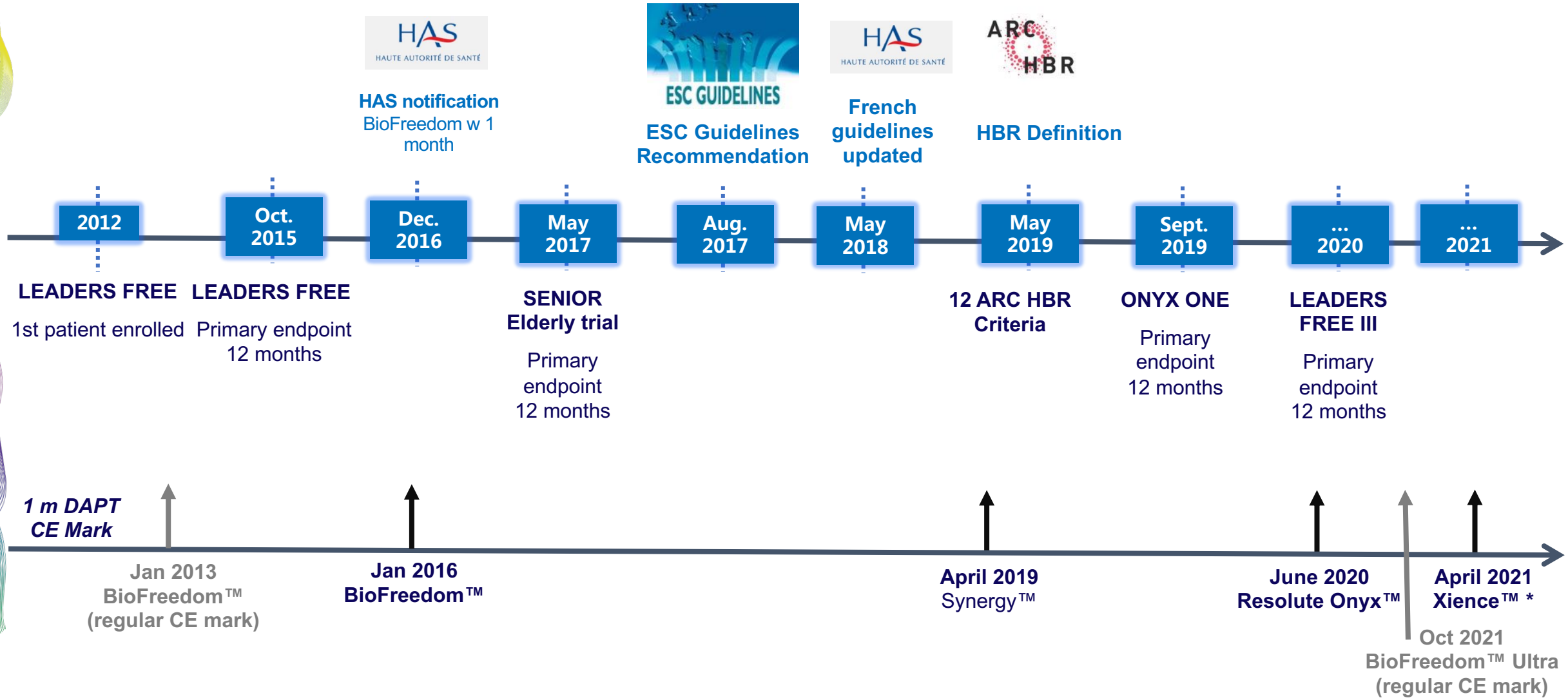
Haut risque hémorragique : tous les stents sont-ils égaux ?

Philippe GAROT

ICPS Massy, France

10 Years History of High Bleeding Risk (HBR)



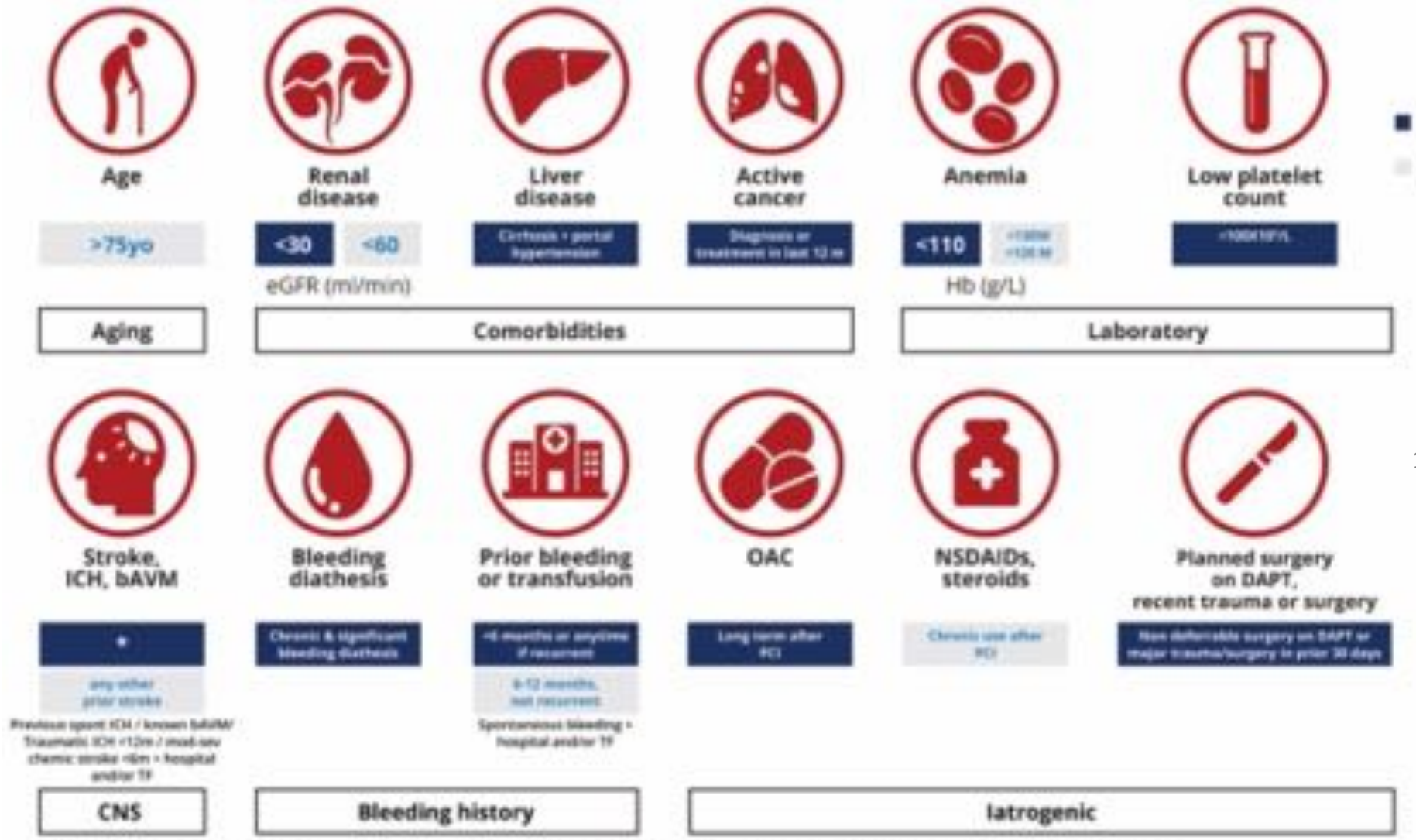
** Xience 28/90 data not yet published*

What are the essential results?

consensus		major criterion		minor criterion
HBR = BARC 3 or 5 bleeding risk of ≥ 4% and/or risk of intracranial hemorrhage (ICH) ≥ 1% within 1 year after PCI	SO…	In isolation, confers: 1) BARC 3 or 5 bleeding risk of ≥ 4% at one year and/ or 2) risk of ICH of ≥ 1% at one year	and	In isolation confers increased bleeding risk, but: risk of BARC 3 or 5 bleeding of <4% at one year and risk of ICH < 1%

HBR status conferred if: 1 major criterion or 2 minor criteria

Who are these High Bleeding Risk Patients (HBR)?



40%[1] of PCI Patients

1. Ueki et al. Validation of Bleeding Risk Criteria (ARC-HBR) in Patients Undergoing Percutaneous Coronary Intervention and Comparison with Contemporary Bleeding Risk Scores. EuroIntervention. 2020 Feb 18. doi: 10.4244/EIJ-D-20-00052

HBR data published

Trial	Design	DAPT	Primary endpoint	Results
LEADERS FREE[1, 2] (1 and 2 years published)	Double-Blind RCT BioFreedom™ vs Gazelle™	30 days	Co-primary endpoints Safety: Composite CD, MI, def/prob ST at 12 months Efficacy: id-TLR at 12 moths	BioFreedom™ significantly safer (MI) and more efficacious (id-TLR) than the Gazelle BMS at 12 and 24 months with one-month ultra-short DAPT
SENIOR[3] (1 and 2 years published)	Single-Blind RCT Synergy™ vs Omega™ / Rebel™	30 days – 6 months	MACCE at 12 months	Synergy™ significantly reduced MACCE at 12 months with a significant reduction in id-TLR *At 2 years: Synergy™ do not reduce MACCE compared to BMS.*
ONYX ONE[4] (2 Years presented[5])	Single-Blind RCT Synergy™ vs ONYX™ / BioFreedom™	30 days	Composite: CD, MI, def/prob ST at 24 months	Resolute Onyx™ was non-inferior for the Composite endpoint of CD, MI def/prob ST vs BioFreedom™ at 12 months *At 2 years: similar outcomes for the primary safety endpoint (CD,MI, ST) and for the key secondary efficacy endpoint (TLF). All death Resolute Onyx™ significantly more frequent Vs. BioFreedom™*

*all-cause death, MI, stroke, Bleeding 3-5. **all-causedeath, MI, stroke. ***composite of type 2, 3 and 5 BARC bleeding events CD= Cardiac Death, MI= Myocardial Infarction, ST= Stent Thrombosis id-TLR=ischemia driven Target Lesion Revascularization 1. Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. Urban p. et al. N Engl J Med. 2015;373(21):2038-47 2. 2-Year Outcomes of High Bleeding Risk Patients After Polymer-Free Drug-Coated Stents. Garot P et al. JACC VOL.6 9, NO.2, 2017 3. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. Varenne O et al. LANCET 2018 Jan 6;391(10115):41-50 4. Polymer-based or Polymer-free Stents in Patients at High Bleeding Risk Windecker S, et al. N Engl J Med. 12th February 2020; 1-11 5. Final Two-year Results From the Randomized Onyx ONE Trial in High Bleeding Risk Patients Treated With 1-month DAPT , presented at ACC 2021 S.Windecker

LEADERS FREE

Primary Endpoints at 1 Year

Prospective, double-blind randomized (1:1) trial
2466 High bleeding risk (HBR) PCI patients

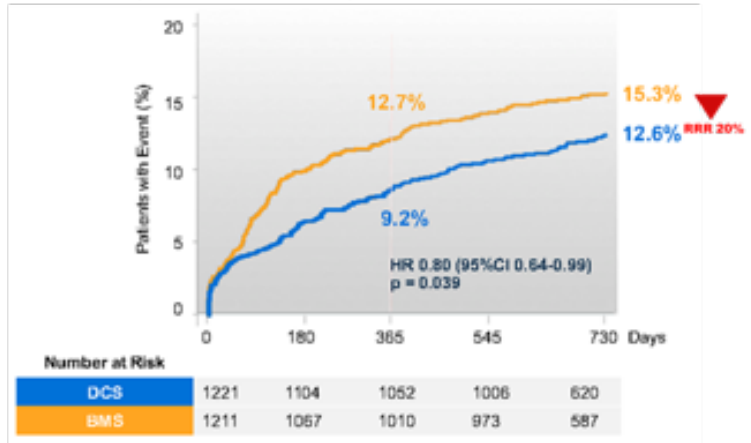
BioFreedom™ DCS vs. **Gazelle™ BMS**

DAPT mandated for 1 month only, followed by long-term SAPT

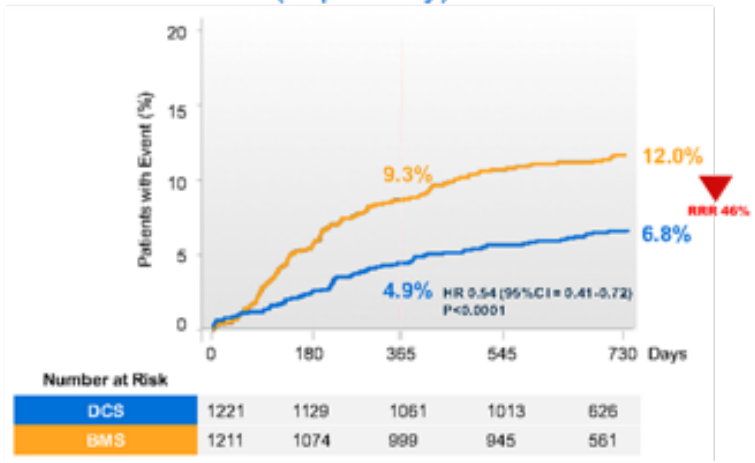
BioFreedom™ maintains a significantly improvement in safety and efficacy in HBR patient's vs BMS with 1-month ultra-short DAPT in the long term

*Cardiac Death, Myocardial Infarction, Definite Probable Stent Thrombosis

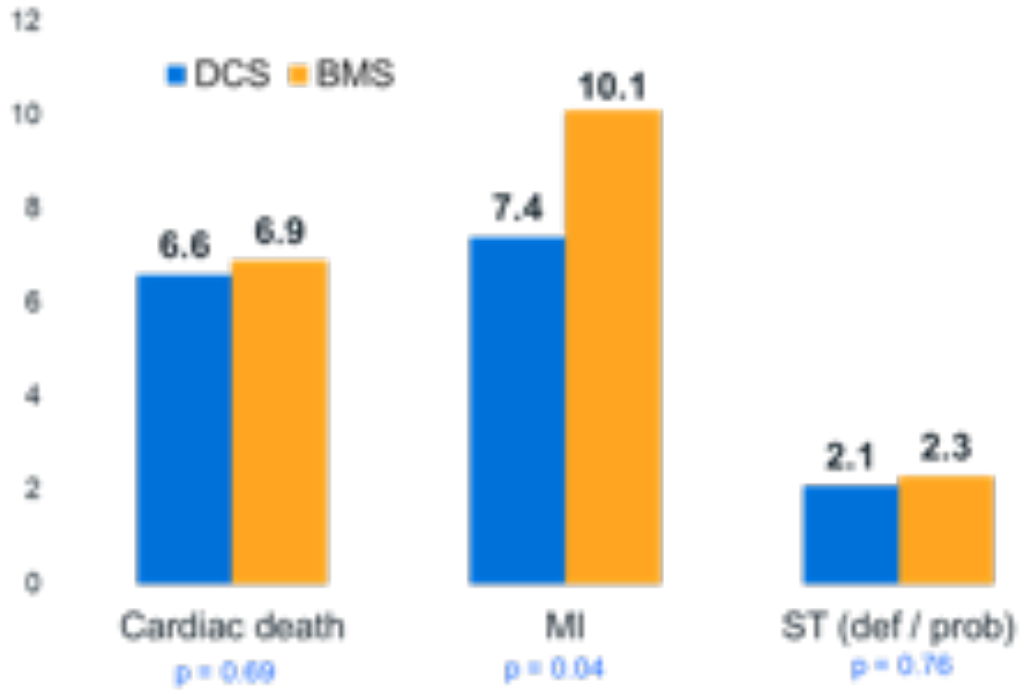
Primary safety endpoint: Composite* at 1 year (non-inferiority then superiority)

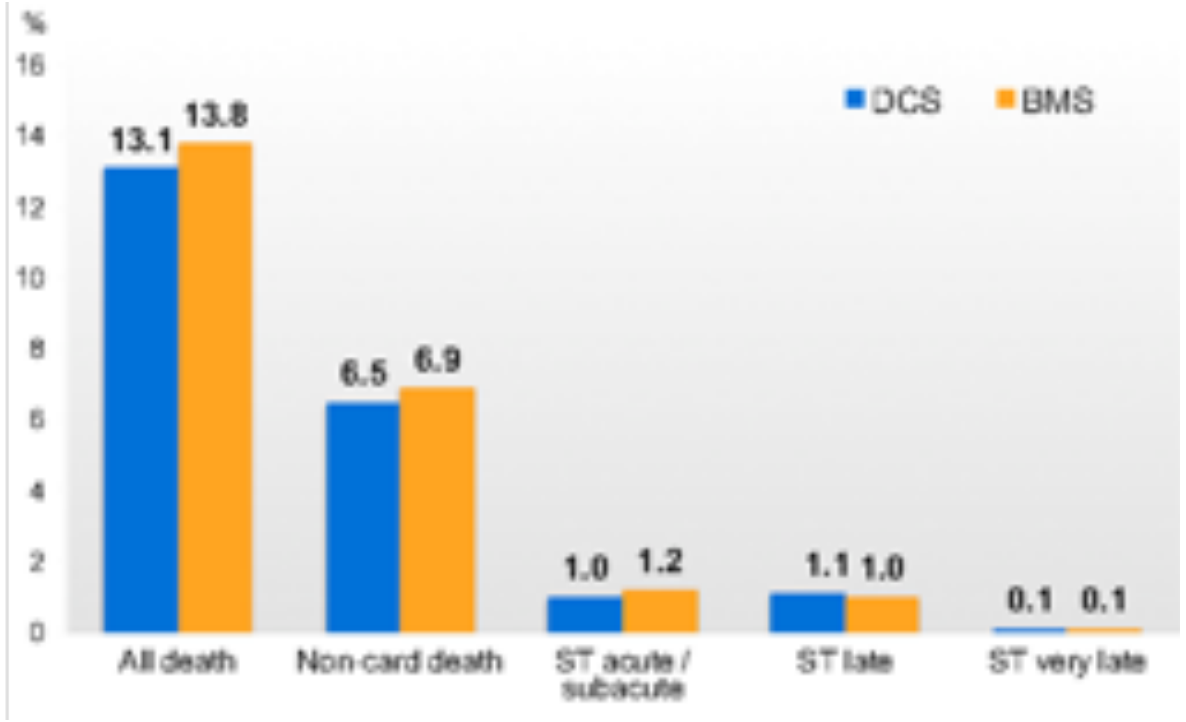


Primary efficacy endpoint: Cd TLR at 1 year (superiority)



LEADERS FREE
Selected Safety Endpoints at 2 Years





BioFreedom™ maintains a significant reduction in MI at 2 years with VLST of 0.1%

LEADERS FREE-14 published data sets

Repeatability
Reproducibility

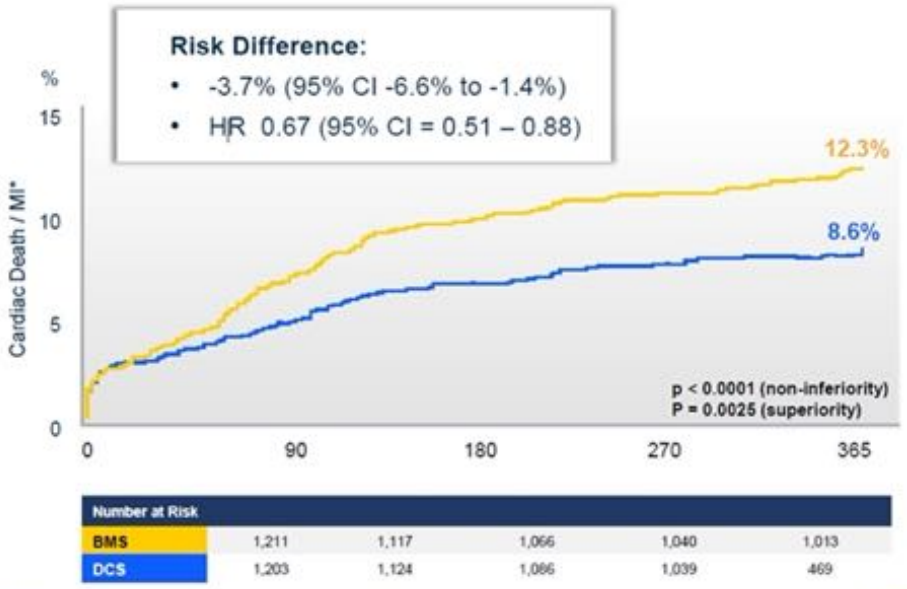
	No. of patients	Superiority* in Efficacy	Superiority* in Safety^	BARC 3-5 bleeding at 1 year
LEADERS FREE[1] 2-year follow-up[2]	2,466	✓	✓	7.2%
ACS subgroup[3] 2-year follow-up[4]	659	✓	✓	9.1%
Elderly subgroup[5]	1564	✓	✓	7.7&
OAC subgroup[6] 2-year follow-up[7]	879	✓	-	8.8%
Diabetics subgroup[8]	805	✓	✓**	10.2%
Vascular Access subgroup[9]	40% Radial Access	Two year benefits of the BioFreedom™ over the BMS remain and were broadly similar whether radial or femoral access were chosen		
Japanese population[10]	140	✓	-	5.0%
Complex PCI subgroup[11]	667	✓	✓	9.8%
non-Cardiac Surgery subgroup[12]	278	✓	-	8.8%
Health Economics[13]	The LEADERS FREE Economic Evaluation found that using BioFreedom in patients at increased risk of bleeding was consistently cost-saving and event-reducing in all 6 countries studies			
LEADERS FREE II[14]	1203	✓	✓	7.2%

p<0.05 or less ^(Composite endpoint) Cardiac Death, Myocardial Infarction, Stent Thrombosis - non-inferiority was met study was powered for non inferiority ** IDDM

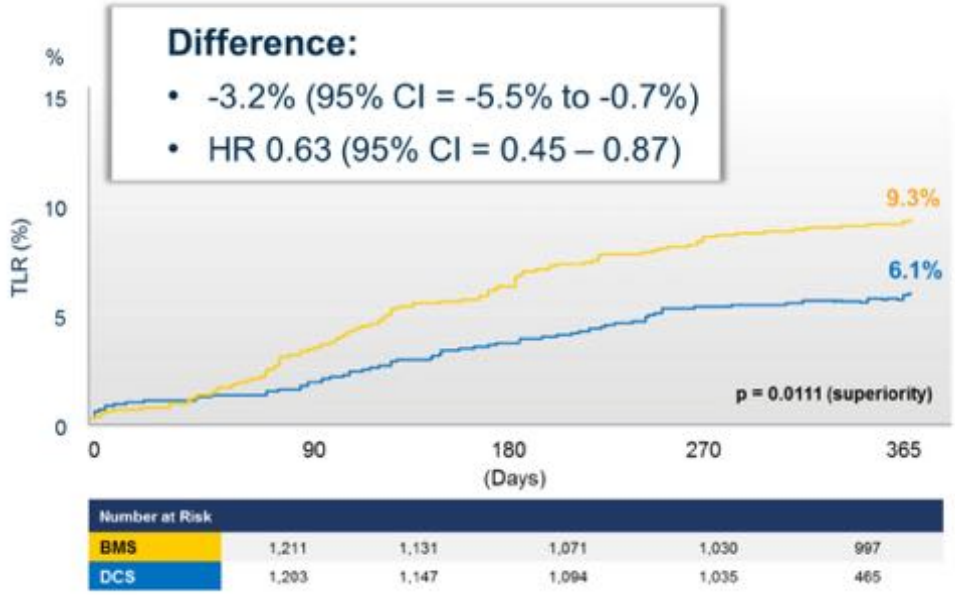
Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. Urban p. et al. N Engl J Med. 2015;373(21):2038-47 2-Year Outcomes of High Bleeding Risk Patients After Polymer-Free Drug-Coated Stents. Garot P et al. JACC VOL.6 9, NO.2 , 2017 3. Biolimus-A9 polymer-free coated stent in high bleeding risk patients with acute coronary syndrome: a Leaders Free ACS sub-study. Naber C et al. Eur Heart J 2016;38:961-969 4. Two-year outcomes of high bleeding risk patients with acute coronary syndrome after Biolimus A9 polymer-free drug-coated stents: a LEADERS FREE substudy. Jensen C. EuroIntervention 2018;13:1946-194 5. Drug-coated versus bare-metal stents for elderly patients: A predefined sub-study of the LEADERS FREE trial Morice M-C. et al. Int. J. Cardiol. 243 (2017) 110–115 6. Biolimus A9 coated versus bare metal stents in patients requiring oral anticoagulation. A pre-specified subgroup analysis of the LEADERS FREE trial. Carrié D. et al. JACC Volume 68, Issue 18 Supplement, November 2016. 7. Safety and Efficacy of Polymer-Free Biolimus A9-Coated Versus Bare-Metal Stents in Orally Anticoagulated Patients: 2-Year Results of the LEADERS FREE Oral Anticoagulation Substudy. Carrie D. et al. JACC Cardiovasc Interv. 2017 Aug 28;10(16):1633-1642 8. Polymer-free drug-coated coronary stents in diabetic patients at high bleeding risk: a pre-specified sub-study of the LEADERS FREE trial. Richardt G. et al. Clinical Research in Cardiology volume 108, pages31–38(2019) 9 Impact of vascular access on outcome after PCI in patients at high bleeding risk: a pre-specified sub-analysis of the LEADERS FREE trial. Diaz V. Revista Espanola de Cardiologia Available online 10 March 2020 10. S.Saito. LEADERS FREE Japan study (single BioFreedom DCS arm with 1-month DAPT, compared to BMS arm of LEADERS FREE). ePoster EuroPCR 2017. 11. Biolimus A9 polymer-free coated stents in high bleeding risk patients undergoing complex PCI: evidence from the LEADERS FREE randomised clinical trial. Lipiecki1 J. EuroIntervention 2018;14th May 2018) 12. Polymer-free drug-coated vs. bare-metal coronary stents in patients undergoing non-cardiac surgery: a subgroup analysis of the LEADERS FREE trial. Richardt G. et al. Clinical Research in Cardiology · May 2020 13. Polymer-free drug-coated coronary stents are cost-effective in patients at high bleeding risk: economic evaluation of the LEADERS FREE trial. Filipovic-Pierucci A. EuroIntervention 2018;14:1688-1695 Global Approach to High Bleeding Risk Patients With Polymer-Free Drug-Coated Coronary Stents: The LF II Study. M.W. Krucoff. Circ Cardiovasc Interv. 2020 Apr;13

LEADERS FREE II
Primary Endpoints at 1 Year

Primary Safety Endpoint: Composite of cardiac death and MI at 1 year (non-inferiority then superiority)



Primary Efficacy Endpoint: Clinically-driven TLR at 1 year (superiority)



BioFreedom again safer and more efficacious than BMS in HBR patients treated with 1-month DAPT

*Cardiac Death, Myocardial Infarction, Definite Probable Stent Thrombosis

Global Approach to High Bleeding Risk Patients With Polymer-Free Drug-Coated Coronary Stents: The LF II Study. M.W. Krucoff. Circ Cardiovasc Interv. 2020 Apr;13

LEADERS FREE III

Main outcomes at 1 Year

	DCS CoCr LF III (N=401)	DCS StS LF I (N=1221)	BMS LF I (N=1211)
Primary safety endpoint*	31 (8.0%)	110 (9.2%)	151 (12.7%)
Cardiac Death	14 (3.7%)	49 (4.1%)	61 (5.1%)
Myocardial Infarction	17 (4.4%)	70 (5.9%)	103 (8.7%)
Def/Prob. Stent thrombosis	4 (1.0%)	24 (2.0%)	26(2.2%)
Clinically-driven TLR**	16 (4.2%)	57 (4.9%)	107 (9.3%)
BARC 3-5	21 (5.4%)	85 (7.2%)	85 (7.2%)
All Death	25 (6.4%)	91 (7.5%)	105 (8.7%)

** p-value for superiority versus BMS LF I: < 0.0001
* p-value for non-inferiority versus DCS LF I: 0.0006 (non-inferiority margin: 3.9%)

The new thin-strut drug coated **CoCr stent was noninferior** to the stainless steel DCS stent **in safety** and **superior to the BMS in efficacy**.

The results confirm the **good outcome of HBR patients** treated with a CoCr DCS followed by a **1-month DAPT regime**.

- Single Arm Trial, **400 all-comers HBR patients, 1-month DAPT for all patients**
- **Double primary endpoint with historical comparison to the BMS / StS DCS arms of LEADERS FREE:**
  - **Safety**: Composite of Cardiac Death – MI – ST (non-inferiority)
  - **Efficacy**: cd-TLR (superiority)

BioLimus-A9™ coated thin strut stents in High Bleeding Risk patients Oral abstract presentation Eberli R PCR e-course 2020

SENIOR[1] trial.
Study design

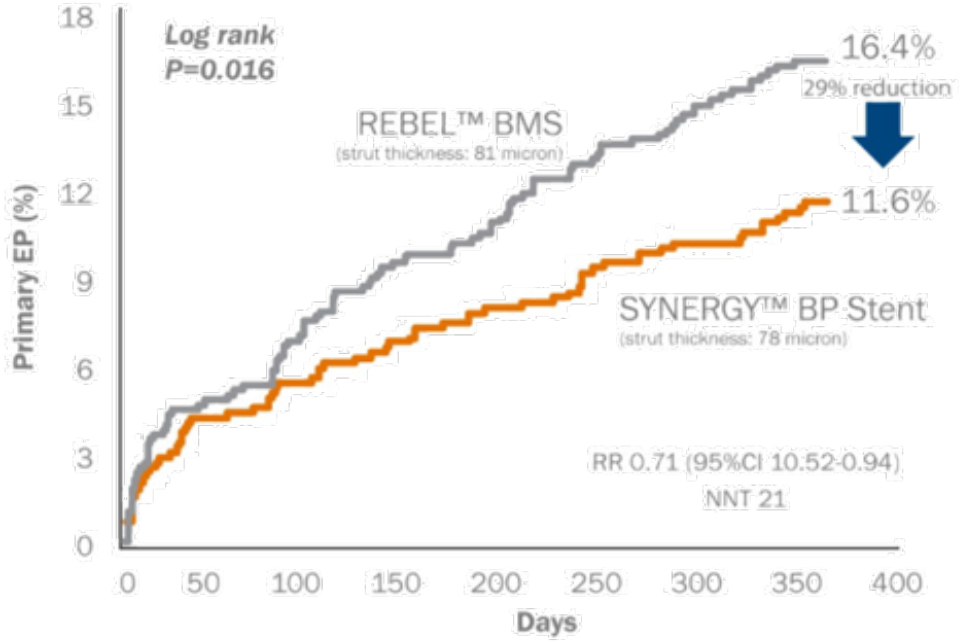
Inclusion criteria: patients aged ≥ 75 years old and presence of ≥1 stenosis (≥70%) in any coronary (or LM ≥50%) and stable angina or silent ischemia or ACS.

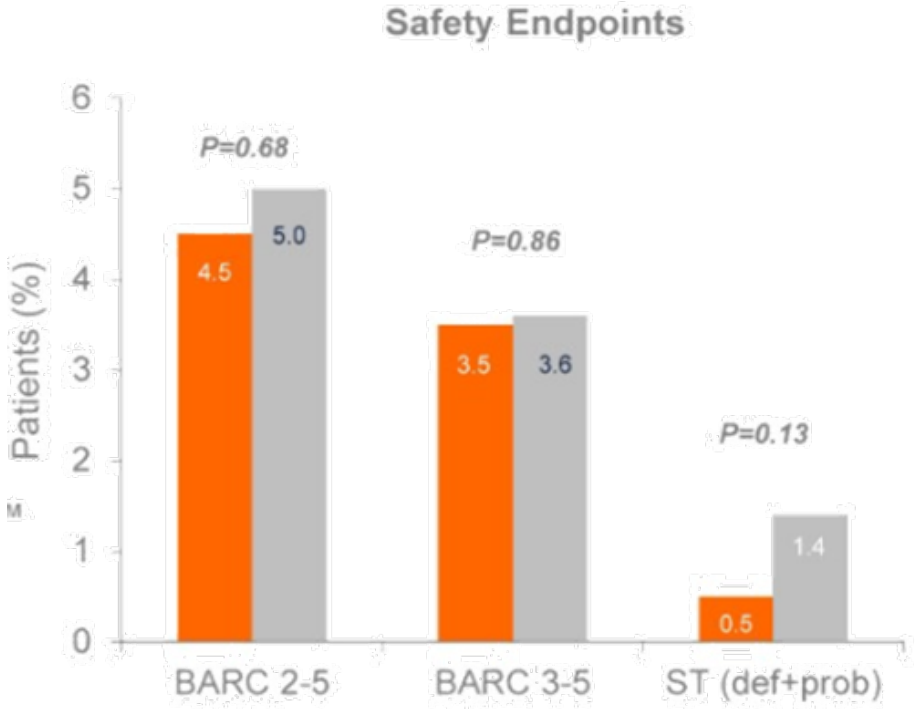
Exclusion criteria: unable to comply with DAPT for: at least 1 month (stable angina or silent ischemia) or at least 6 months (ACS); planned surgery within one month; prior hemorrhagic stroke*; indication for surgical myocardial revascularization; known allergy

1. Varenne O. et al. EuroIntervention. 2017;12(13):1614-22

*These patients were included in LEADERS FREE

SENIOR[1] trial.
Main results at 1 Year





Among elderly patients who have PCI, a DES and a short duration of DAPT are better than BMS and a similar duration of DAPT with respect to the occurrence of all cause of mortality, MI, stroke and ischemia-driven TLR.

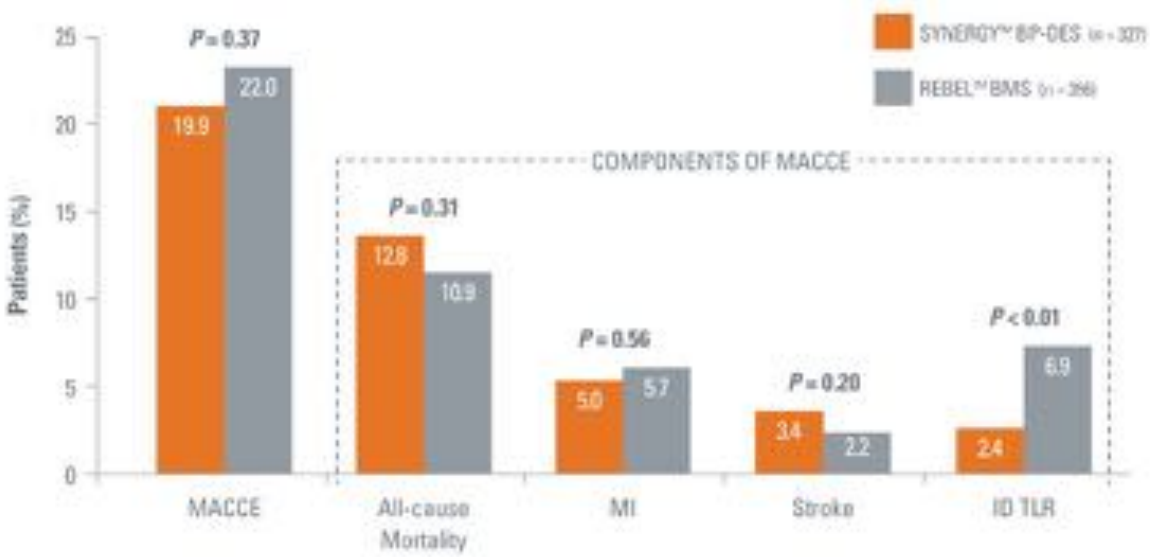
The secondary safety endpoints were numerically better for the DES but no statistically significant.

Based on the ARC-HBR definition, the SENIOR trial shouldn't be considered as a HBR patient study.

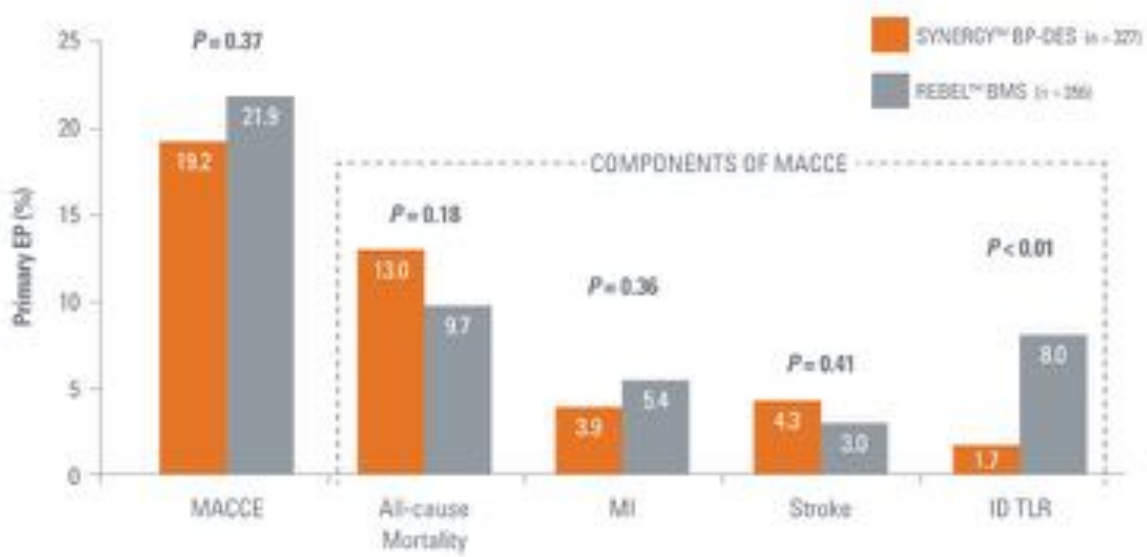
1. Varenne O. et al. EuroIntervention. 2017;12(13):1614-22

SENIOR² trial.
Main results at 2 years

All patients



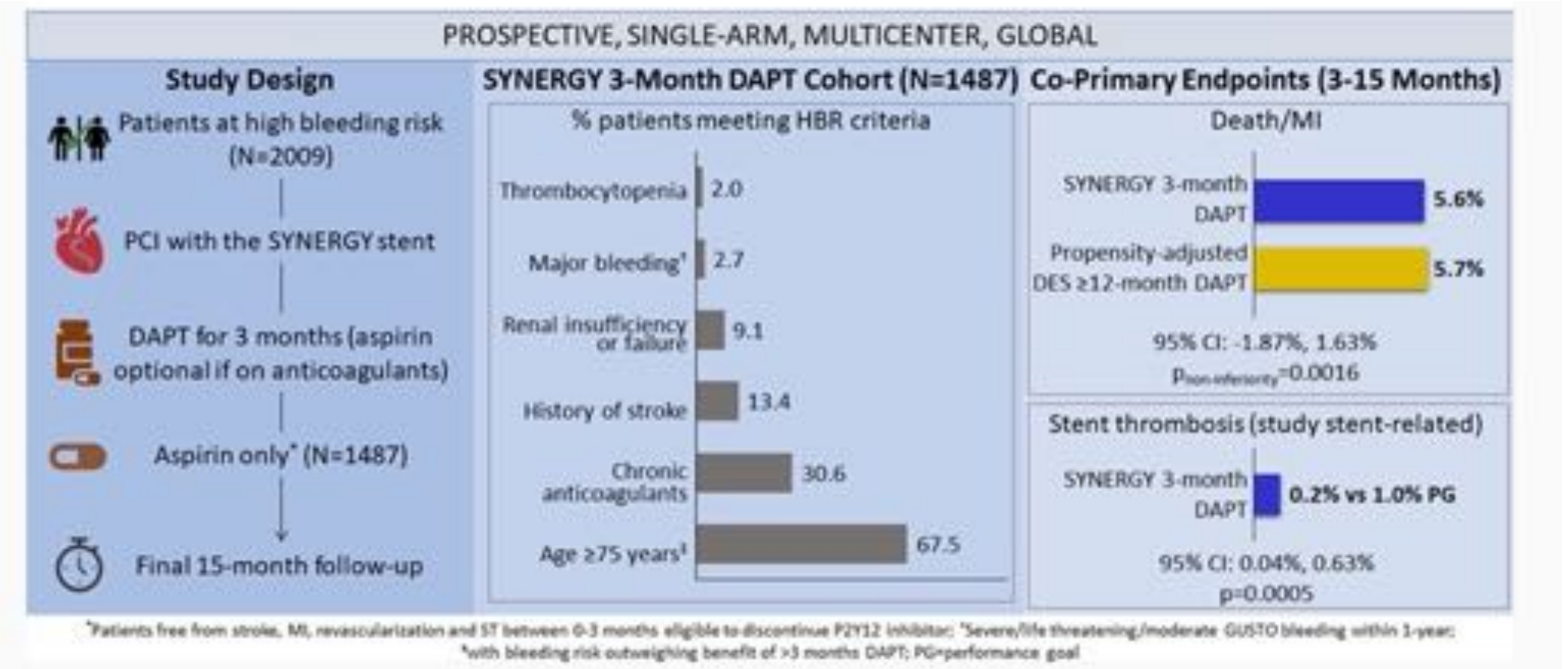
1month DAPT discontinuation cohort



Among elderly patients who have PCI, a DES and a short duration of DAPT is associated with a reduction in revascularization up to 2 years compared with BMS.

2. Lafont A, Sinnaeve PR, Cuisset T,et al. Two-year outcomes after percutaneous coronary intervention with drug-eluting stents or bare-metal stents in elderly patients with coronary artery disease. Catheter Cardiovasc Interv. 2021;97:E607–E613. https://doi.org/10.1002/ccd.29159
https://www.bostonscientific.com/en-US/products/stents--coronary/bioabsorbable-polymer-stent/studying-dapt/senior-trial.html

EVOLVE SHORT DAPT[1] trial.
Study design & main outcomes



Favorable rates of ischemic outcomes were observed among **selected HBR** patients undergoing PCI with the Synergy™ stent who tolerated **3 months of DAPT** and then discontinued it, supporting the safety of abbreviated DAPT with this stent platform.

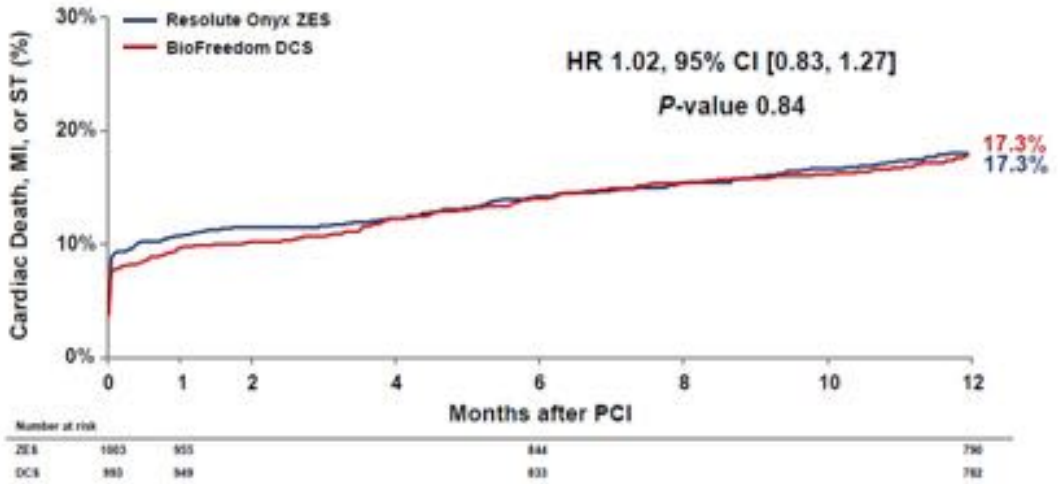
1. Kirtane AJ. et al. Circulation: Cardiovascular Interventions. 2021;14:e010144

ONYX ONE[1] trial.
Study design

1. Windecker S, Latib A, Kedhi E, et al. Polymer-based or Polymer-free Stents in Patients at High Bleeding Risk. *N Engl J Med*. March 26, 2020;382(13):1208-1218.

ONYX ONE[1] trial.
Main results at 1 Year

Primary Safety Endpoint: Cardiac Death, MI, or ST



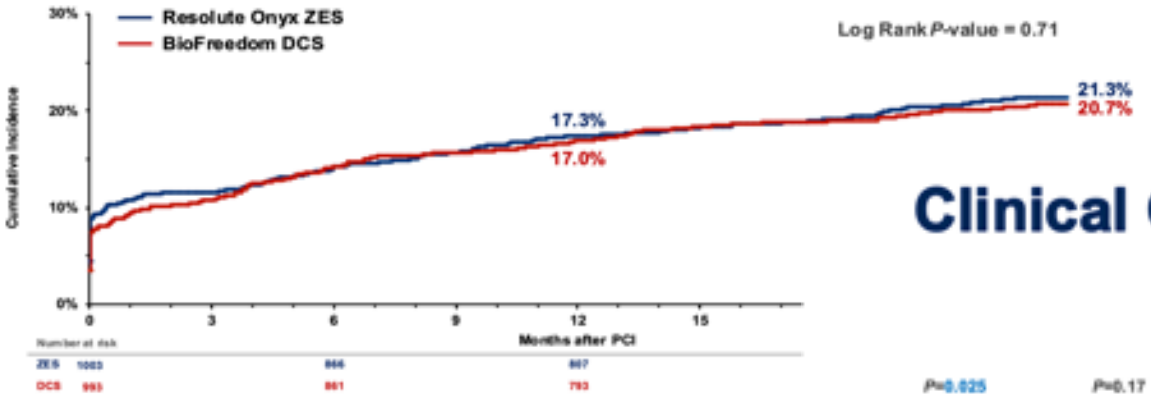
Powered Secondary Effectiveness Endpoint: TLF

Among complex HBR patients treated with 1-month DAPT after PCI, the CoCr Resolute Onyx™ was non inferior to the StS BioFreedom™

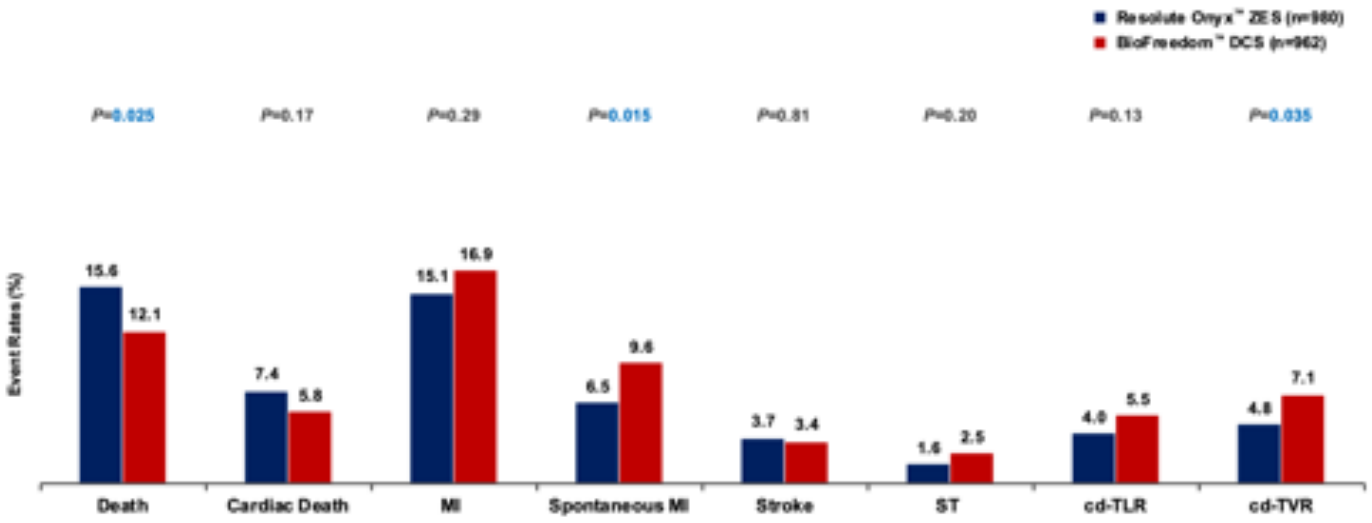
1. Windecker S, Latib A, Kedhi E, et al. Polymer-based or Polymer-free Stents in Patients at High Bleeding Risk. *N Engl J Med*. March 26, 2020;382(13):1208-1218.

ONYX ONE^2 trial.
Main results at 2 Years

Primary Safety Endpoint Continued to 2 Years
Cardiac Death, MI, ST



Clinical Outcomes at 2 Years

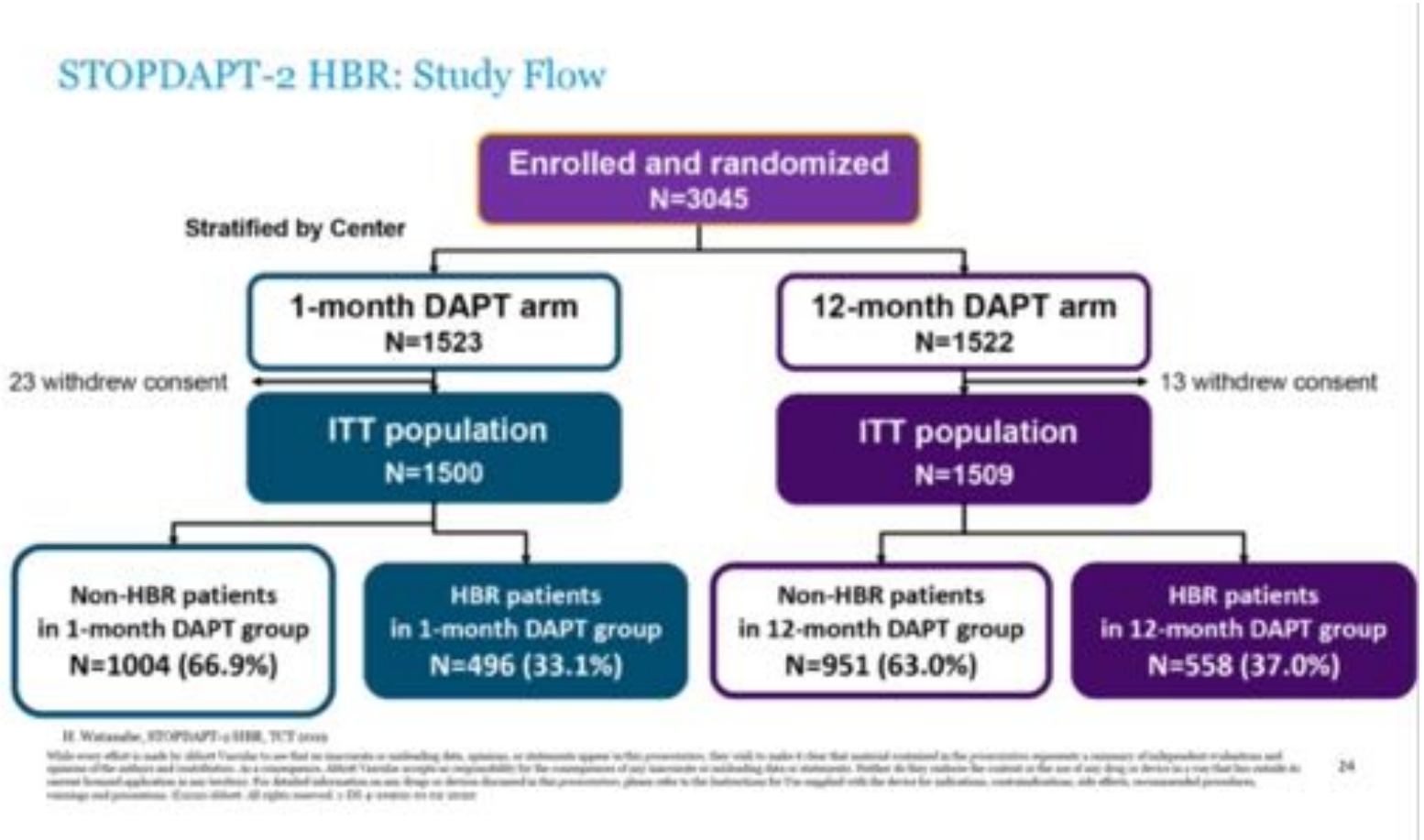


Final Two-year Results From the Randomized Onyx ONE Trial in High Bleeding Risk Patients Treated With 1-month DAPT , presented at ACC 2021 S.Windecker

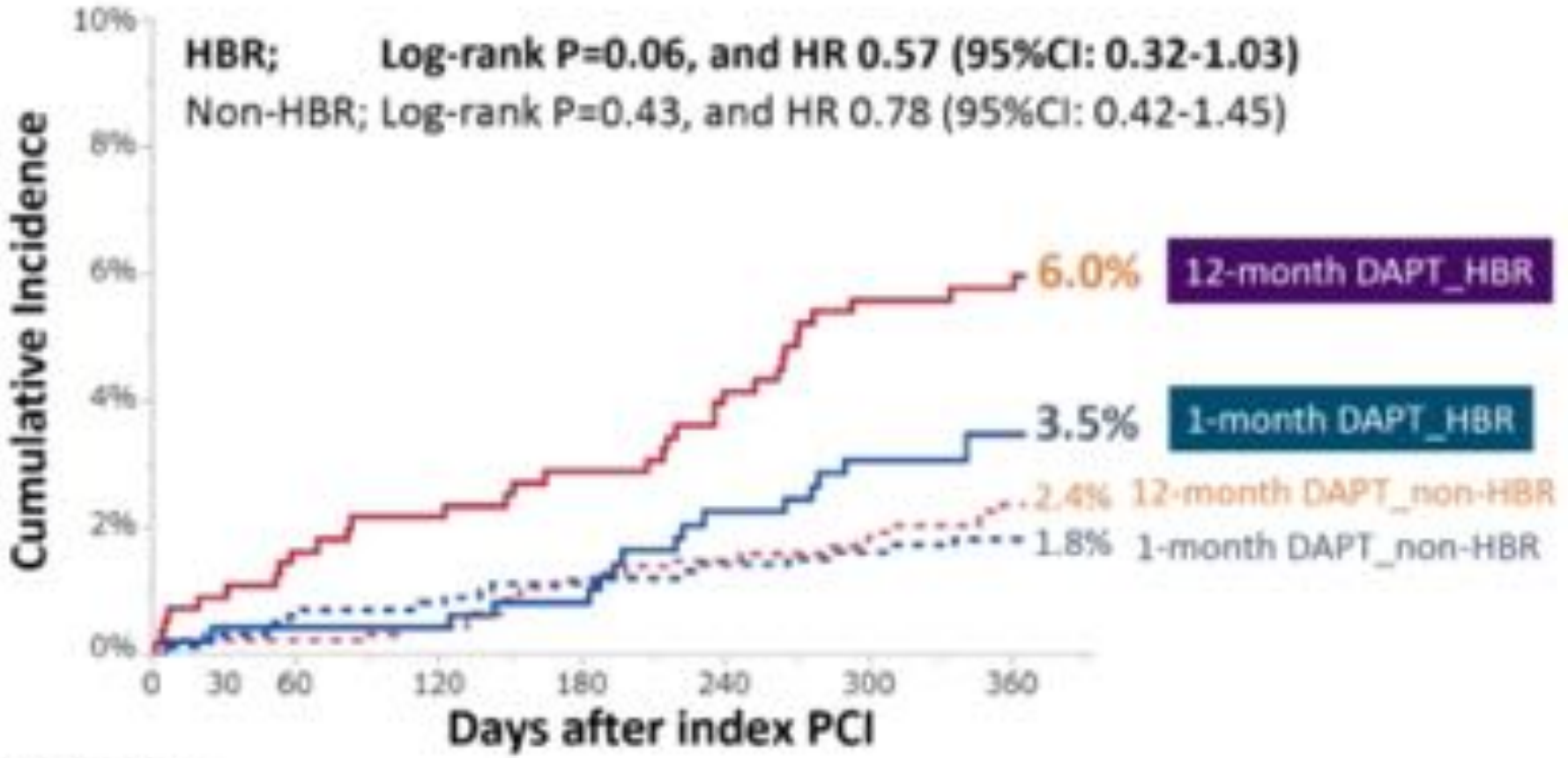
MI assessed by the 3rd Universal Definition of Myocardial Infarction
ST is defined as ARC definite or probable stent thrombosis

Onyx ONE

STOPDAPT-2 XIENCE



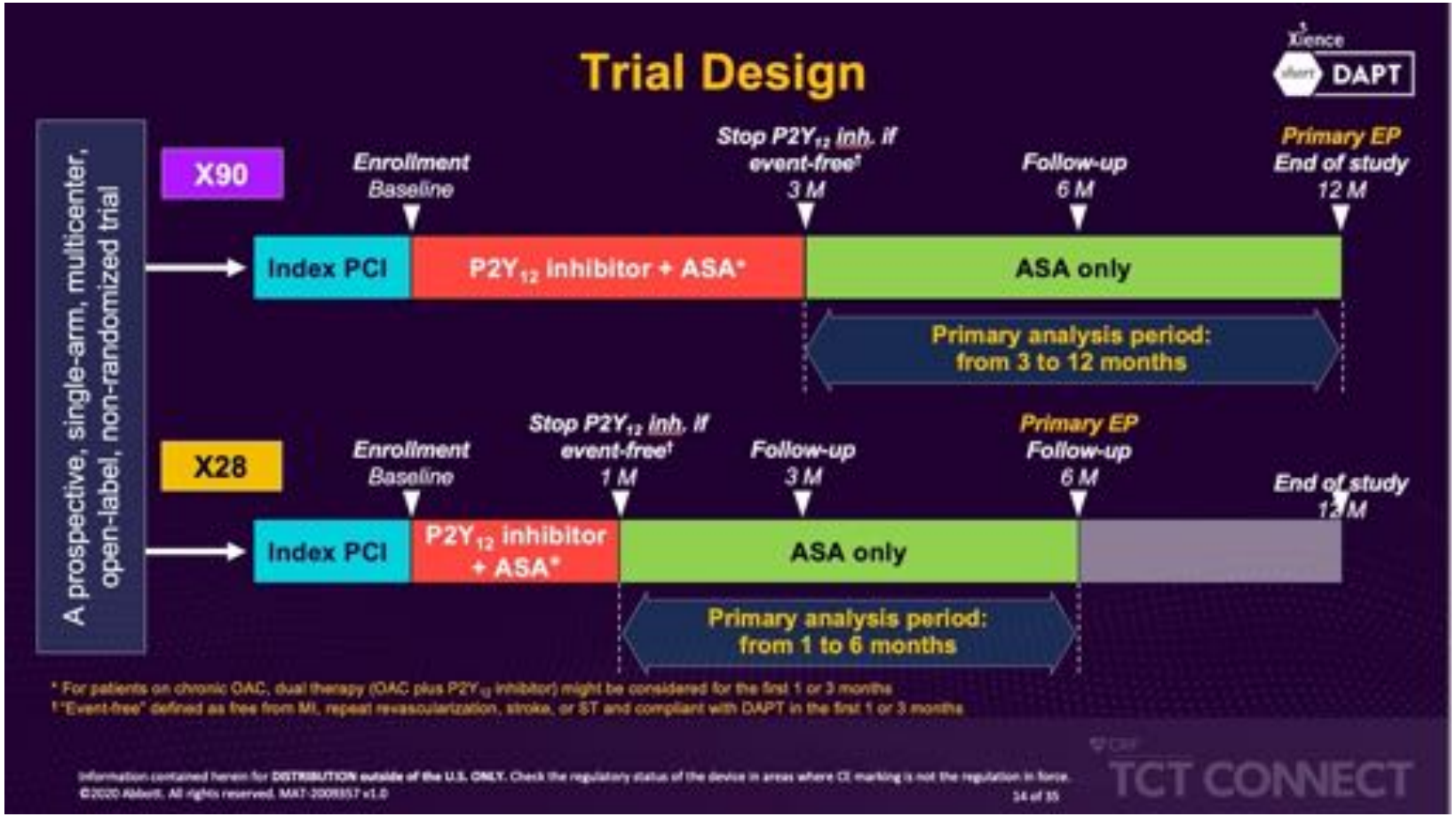
Primary outcome:
CV death/MI/ST/Stroke/TIMI major/minor bleeding



H. Watanabe, STOPDAPT-2 HBR, TCT 2019

JAMA 2019;321:2414-2427

XIENCE 90/28


Trial Design
Xience short DAPT
A prospective, single-arm, multicenter, open-label, non-randomized trial
X90
Enrollment
Baseline
Stop P2Y12 inh. if event-free†
3 M
Follow-up
6 M
Primary EP
End of study
12 M
Index PCI
P2Y12 inhibitor + ASA*
ASA only
Primary analysis period:
from 3 to 12 months
X28
Enrollment
Baseline
Stop P2Y12 inh. if event-free†
1 M
Follow-up
3 M
Primary EP
Follow-up
6 M
End of study
12 M
Index PCI
P2Y12 inhibitor + ASA*
ASA only
Primary analysis period:
from 1 to 6 months
* For patients on chronic OAC, dual therapy (OAC plus P2Y12 inhibitor) might be considered for the first 1 or 3 months
† "Event-free" defined as free from MI, repeat revascularization, stroke, or ST and compliant with DAPT in the first 1 or 3 months
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©2020 Abbott. All rights reserved. MAT-2009557 v1.0
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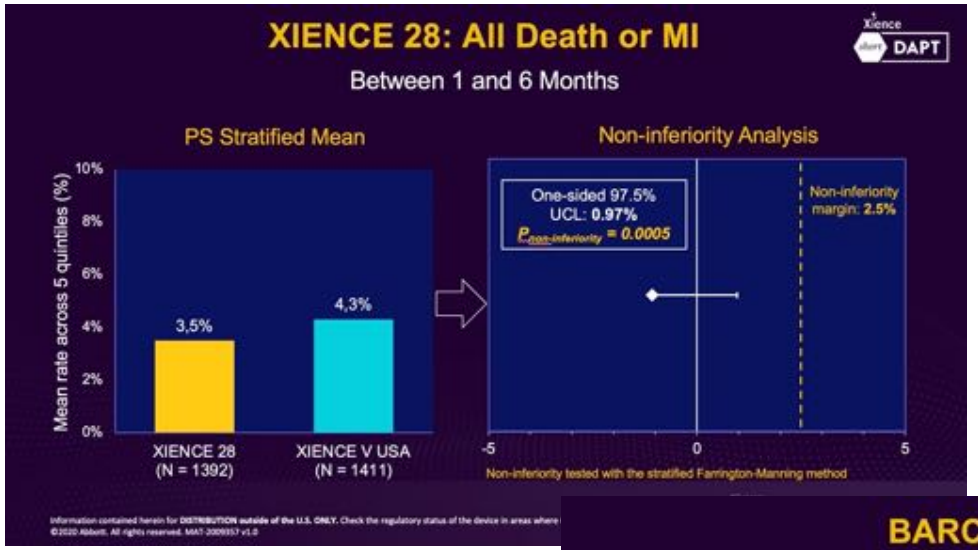
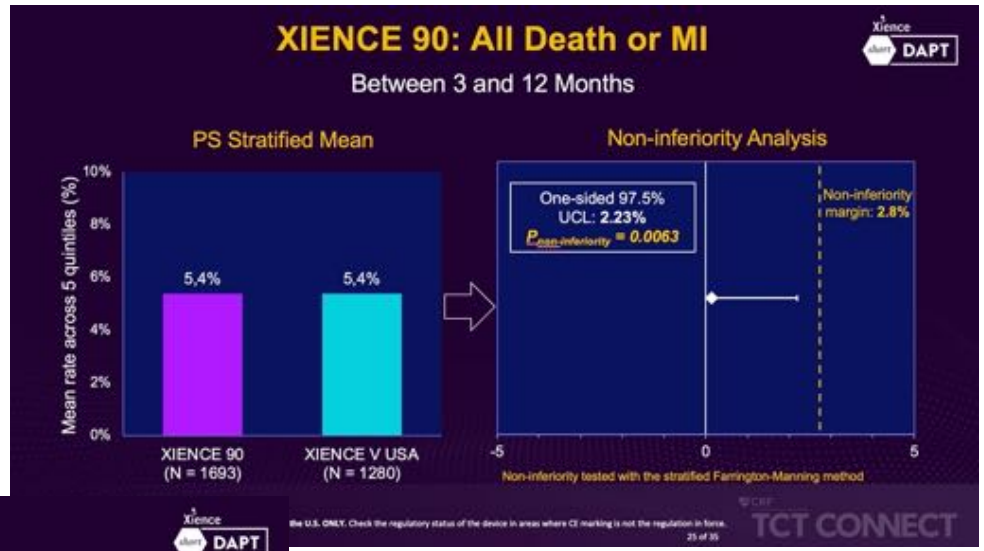
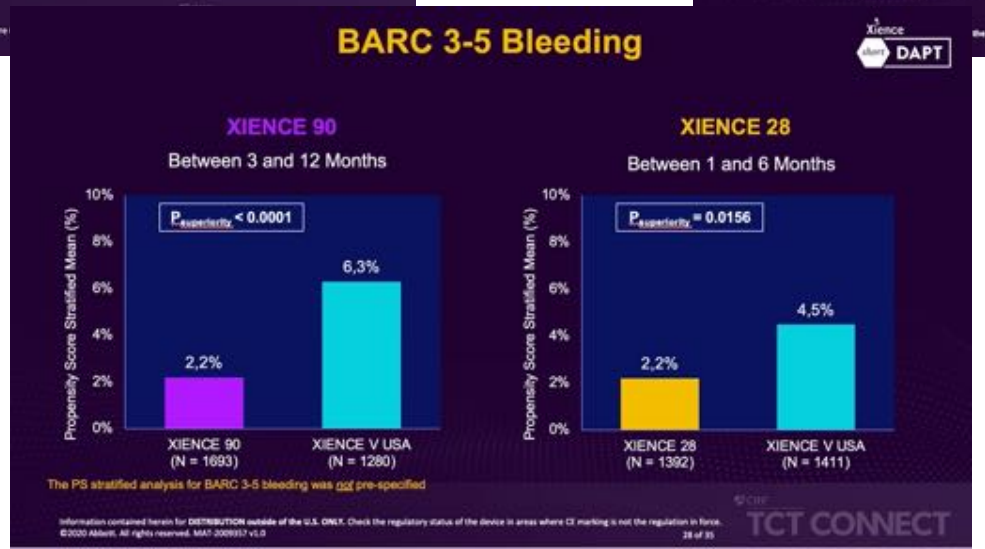
TCT CONNECT

XIENCE 90/28







Presented at TCT, unpublished data.

HBR trials ongoing

Trial	Design	DAPT	Primary endpoint	Status/Preliminary results
BIOFLOW-DPAT *Orsiro*	Orsiro Vs. Onyx	1 month	MACE (cardiac death, MI and definite/probable ST)	Recruitment
POEM[3] *Synergy*	Registry Single arm vs OPC parameters	1 month	MACE (cardiac death, MI and definite/probable ST)	Preliminary results presented @EuroPCR 2018. 1-year results presented @EuroPCR 2021 showed low risk of ischemic/bleeding events.
MASTER DAPT[4] *Ultimaster*	Single arm Open label	1 month vs 6-12 month	Non inferiority: NACE (all-cause death, MI , stroke and bleeding events BARC 3-5) and MACCE (all-cause death, MI and stroke) Superiority: Major or clinically relevant non-major bleeding (MCB) defined as a composite of type 2, 3 and 5 BARC bleeding events	Submitted

1.Valgimigli M, et al. TCT Connect 2020 – XIENCE 28. 2.Mehran R, et al. TCT Connect 2020 – XIENCE 90. 3. https://media.pcronline.com/diapos/EuroPCR2018/218 20180524_1245 4. https://www.clinicaltrials.gov/ct2/show/NCT03023020

BIOFLOW-DAPT

Design, objectif et critère primaire

Design de l'étude

- Etude **randomisée 1:1**, de non-infériorité, prospective, multicentrique, et internationale. 1948 patients HBR à inclure dont 315 en France (35 patients par centre)

Objectif de l'étude

- Evaluer la sécurité du stent Orsiro Mission chez des patients à haut risque hémorragique ayant subi une angioplastie coronaire suivie de 30 jours de DAPT.

Critère d'évaluation primaire

- Critère composite des décès cardiaques, des infarctus du myocarde et des thromboses de stents certaines ou probables à 12 mois

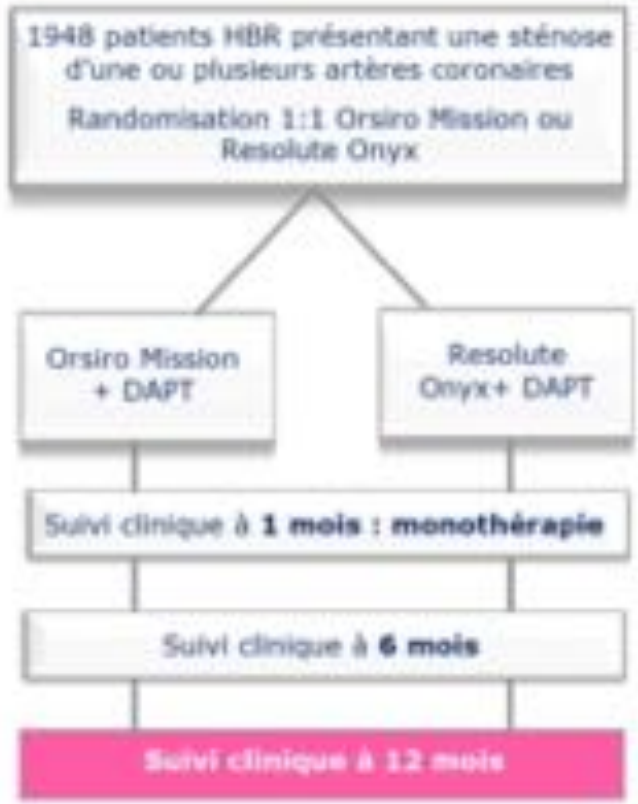
Centres et investigateur coordonnateur France

- **20 pays, 100 centres dont 9 en France**
- Pr Guillaume CAYLA, CHU de Nimes

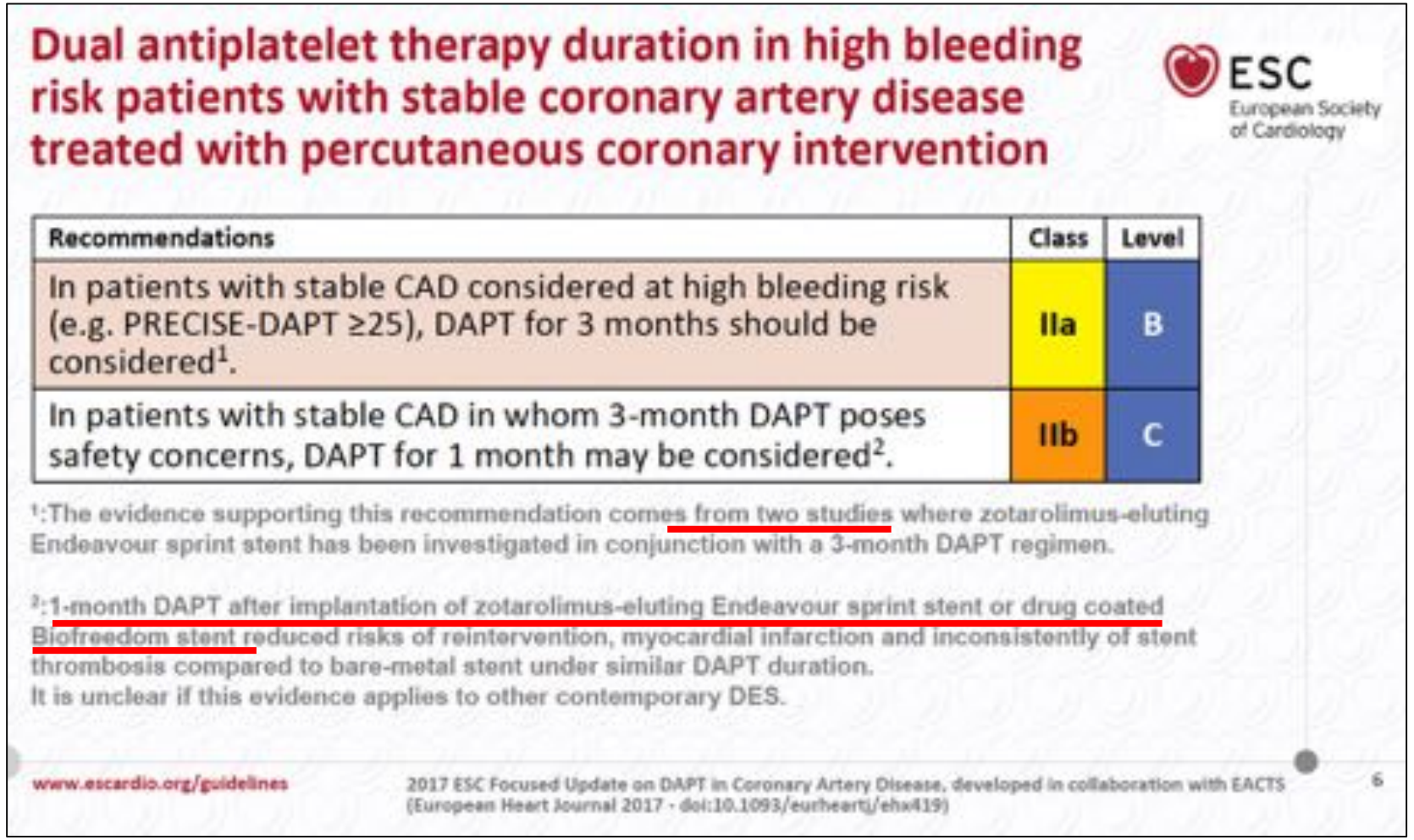
Dates clés

- Démarrage de l'étude : **septembre 2020**
- Durée des inclusions : **2 ans**

BIOFLOW-DAPT



DAPT ESC Guidelines – Last online update 2018



Dual antiplatelet therapy duration in high bleeding risk patients with stable coronary artery disease treated with percutaneous coronary intervention

ESC European Society of Cardiology

Recommendations	Class	Level
In patients with stable CAD considered at high bleeding risk (e.g. PRECISE-DAPT ≥25), DAPT for 3 months should be considered[1].	IIa	B
In patients with stable CAD in whom 3-month DAPT poses safety concerns, DAPT for 1 month may be considered[2].	IIb	C

[1]:The evidence supporting this recommendation comes from two studies where zotarolimus-eluting Endeavour sprint stent has been investigated in conjunction with a 3-month DAPT regimen.

[2]:1-month DAPT after implantation of zotarolimus-eluting Endeavour sprint stent or drug coated Biofreedom stent reduced risks of reintervention, myocardial infarction and inconsistently of stent thrombosis compared to bare-metal stent under similar DAPT duration.
It is unclear if this evidence applies to other contemporary DES.

www.escardio.org/guidelines

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

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« Selon la société européenne de cardiologie, une bithérapie de plus d'un an est envisageable en cas de haut risque ischémique (dont antécédent de thrombose de stent, artériopathie périphérique) avec tolérance aux 2 AAPs (aspirine et ticagrelor) (classe IIb niveau C ou B). Dans tous les cas, l'interruption de la DAPT avant 1 mois n'est pas recommandée même en cas de chirurgie non cardiaque programmée ou de complication hémorragique (classe III niveau B). » [3]

3-Rapport d'évaluation technologique Date de validation par la Commission nationale d'évaluation des dispositifs médicaux et des technologies de santé (CNEDIMTS) : mai 2018
https://www.has-sante.fr/upload/docs/application/pdf/2018-05/rapports_devaluation_endoprotheses_stents_coronaires_2018-05-18_16-37-11_73.pdf

Les recommandations HAS

« En France, la durée actuelle recommandée est plus courte en cas d'implantation de stents nus qu'en cas d'implantation de stents actifs (au maximum 12 mois pour un stent actif vs 1 à 3 mois pour un stent nu dont la ré-endothélialisation est plus rapide que celle d'un actif donc à moindre risque thrombotique. Après un SCA, la durée est d'1 an compte tenu du risque thrombotique élevé, et ce quelle que soit la méthode de revascularisation9 . Ainsi, l'arrêt de la bithérapie est envisageable plus tôt après la pose d'un stent nu qu'après celle d'un stent actif et ce quelle que soit la forme clinique de la maladie coronaire (coronaropathie stable ou SCA). » [1]

+ Modalités de Prescription et d'utilisation propre à chaque stent

MODALITES DE PRESCRIPTION ET D'UTILISATION :
Le nombre maximal d'unités prises en charge est de 1 stent par patient sauf en cas de dissection occlusive aiguë (3 unités par patient peuvent être prises en charge au maximum). Dans les lésions pluritronculaires, la prise en charge est au maximum de 3 stents par patient.
La durée recommandée de la bithérapie antiplaquettaire après pose d'un stent actif est comprise entre 6 et 12 mois. En cas de risque hémorragique élevé, la durée de la bithérapie peut être ramenée à 1 mois après prise en compte du risque de saignement par rapport au risque ischémique.
En raison de la nécessité de la bithérapie antiplaquettaire, l'intérêt thérapeutique des stents actifs est reconnu sous réserve que les conditions suivantes soient respectées :

Biosensors reste la seule société disposant d'une modalité de prescription spécifique où il est indiqué que la durée de DAPT peut être ramenée à 1 mois si patient est HBR. (p1022 https://www.ameli.fr/professionnel-de-la-lpp/exercice-professionnel/facturation/liste-des-produits-et-prestations-lpp/liste-produits-prestations-lpp

1- Rapport d'évaluation technologique Date de validation par la Commission nationale d'évaluation des dispositifs médicaux et des technologies de santé (CNEDIMTS) : mai 2018
https://www.has-sante.fr/upload/docs/application/pdf/2018-05/rapports_devaluation_endoprotheses_stents_coronaires_2018-05-18_16-37-11_73.pdf

Sources 1 month DAPT CE Mark

1) **XIENCE**: **April 6th, 2021**.
   - https://abbott.mediaroom.com/2021-04-06-Abbotts-XIENCE-TM-Stent-Receives-European-Approval-for-One-Month-Dual-Anti-Platelet-Therapy-DAPT-for-High-Bleeding-Risk-Patients.
1) **Resolute ONYX: June 5th, 2020**
   - https://newsroom.medtronic.com/news-releases/news-release-details/medtronic-resolute-onyxtm-des-receives-first-and-only-one-month/.
1) **SYNERGY:** https://endovascular.kz/images/aktau_2019/15_synergy.pdf

Conclusion: Tous les Stents sont ils Egaux?

- Eviter une DAPT>1 mois chez le HBR (identifier, et suivre la DAPT)
- ARC HBR (App)
- Plusieurs stents ont le CE Mark HBR (DAPT 1 mois)
- Les stents ne sont pas tous égaux (études/recommandations)
  - Biofreedom/Onyx
- Onyx (2018) est non inférieur au Biofreedom (2012)
- Données des registres et autres études non comparatives
- DAPT **1 mois** minimum
- Pas de données sur SAPT chez les HBR