# Optimizing the approach to High Bleeding Risk (HBR) PCI patients

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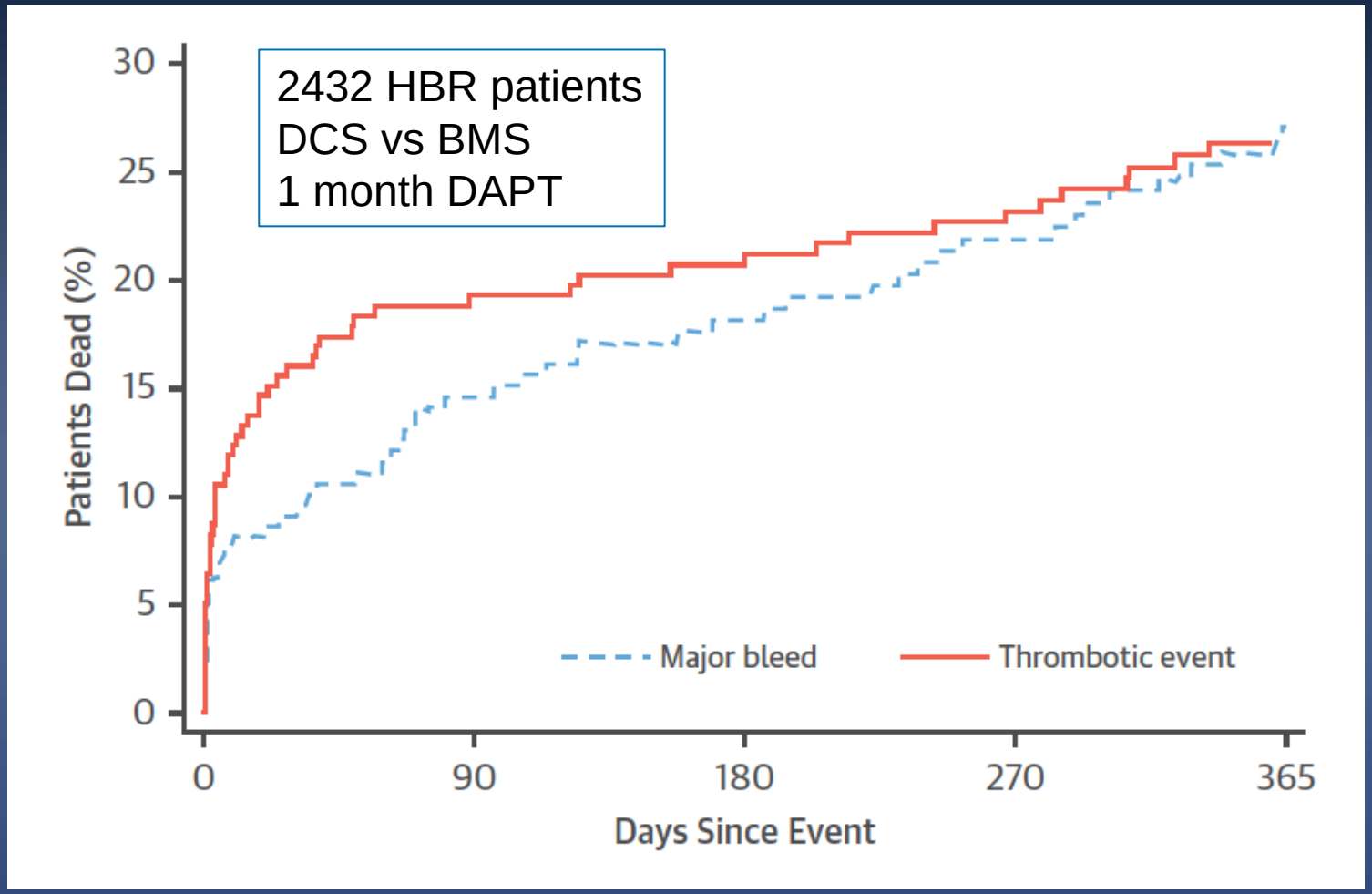
# Conflicts of Interest

- I am a consultant for Biosensors
- I have received honoraria as a speaker, and/or for DSMB or CEC activities from: Edwards Life Sciences, Abbott Vascular and Terumo
- I am medical co-director and shareholder of CERC, a CRO based in Massy, France

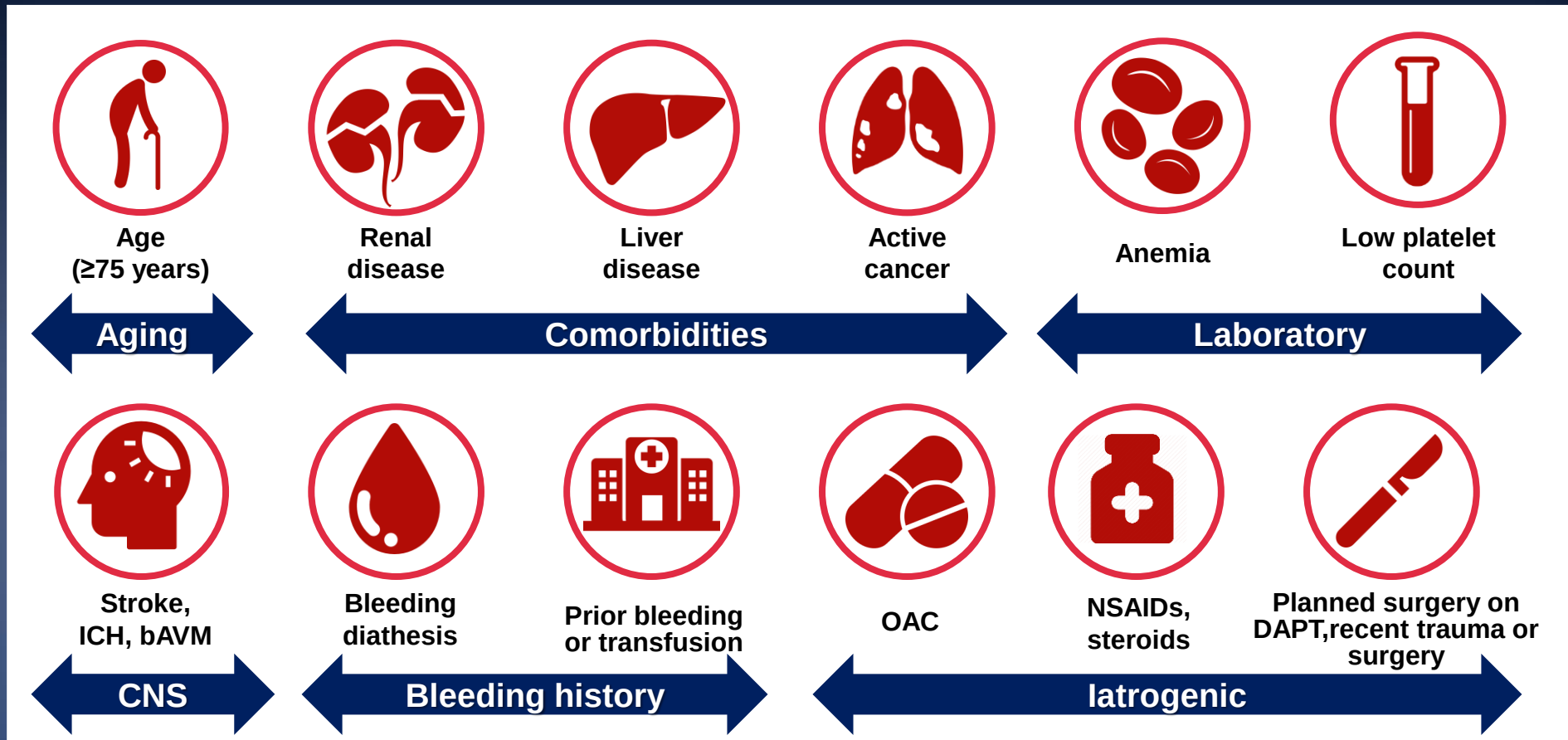
# Does bleeding matter?

**1-Year Mortality Following a Major Bleed or a Coronary Thrombotic Event**




Garot P et al J Am Coll Cardiol 2017;69:162–71

# Who is at risk?




Courtesy of Davide Capodanno & the ARC-HBR group

# The ARC Focus Group on HBR

ARC HBR Focused Group, Washington April 13,14 2018

- Compliant with the ARC Charter, organized by CERC Europe
- Non-profit initiative, sponsored by 22 pharma and device companies
- 31 experts from Europe, USA, Japan and South Korea
- Two meetings in 2018 - Washington (US), April 13-14 and Paris (FR), October 19-20

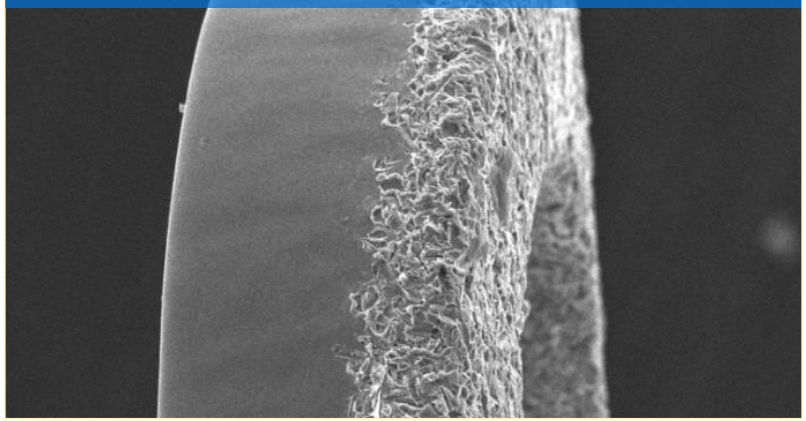
ARC HBR definition to be presented at Euro-PCR, Paris, May 22

# Bleeding Risk after PCI: stents, drugs and others choices

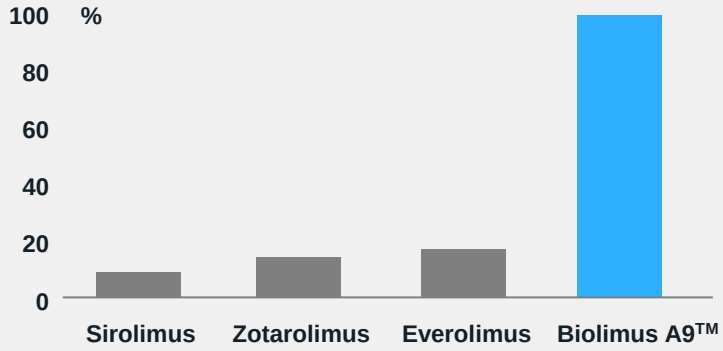
- **Stents**
- Drugs
- Other options

# BioFreedom™ Drug Coated Stent (DCS)

**Selectively Micro-Structured Surface Holds Drug in Abluminal Surface Structures**



**BA9™ Drug 10 Times More Lipophilic than Sirolimus[1]**




+/- 2.8% (valid for all drugs test)

## Potential Advantages:

- ✓ Avoid any possible polymer-related adverse effects
- ✓ Rapid drug transfer to vessel wall (98% within one month[2])
- ✓ Good match with short DAPT

1. Data on file at Biosensors Intl; 2. Tada et al., Circ Cardiovasc Interv 2010;3;174-183

# LEADERS FREE Trial Design

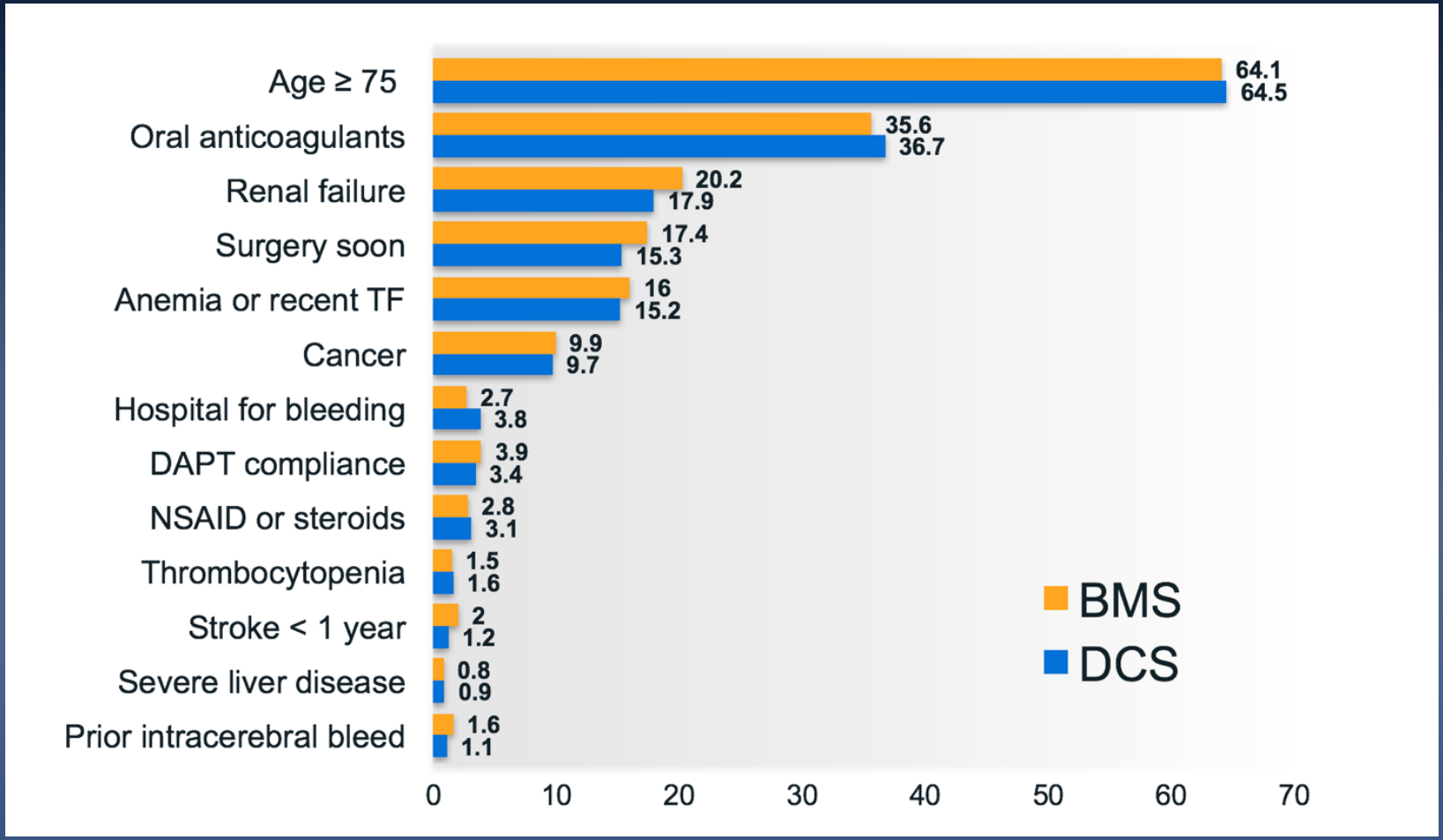
**Prospective, double-blind randomized (1:1) trial**
**2466 High bleeding risk (HBR) PCI patients**

**BioFreedom™ DCS** **vs.** **Gazelle™ BMS**

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

- **Primary safety endpoint:**
  Composite of cardiac death, MI, definite / probable stent thrombosis at 1 year (non-inferiority then superiority)
- **Primary efficacy endpoint:**
  Clinically-driven TLR at 1 year (superiority)

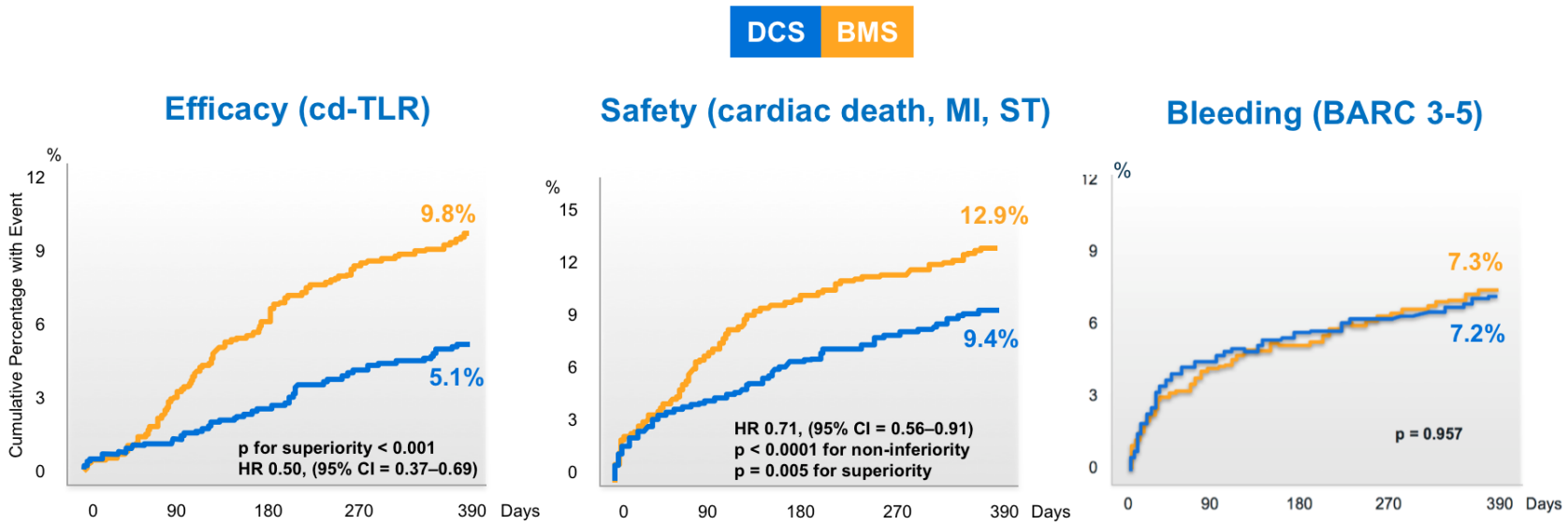
# Inclusion Criteria Applied (1.7 criteria / patient)



LEADERS FREE

# 2466 HBR patients randomised to BA-9 DCS or BMS
# One month DAPT only for all

## Primary Endpoints and Major Bleeding at 1 Year

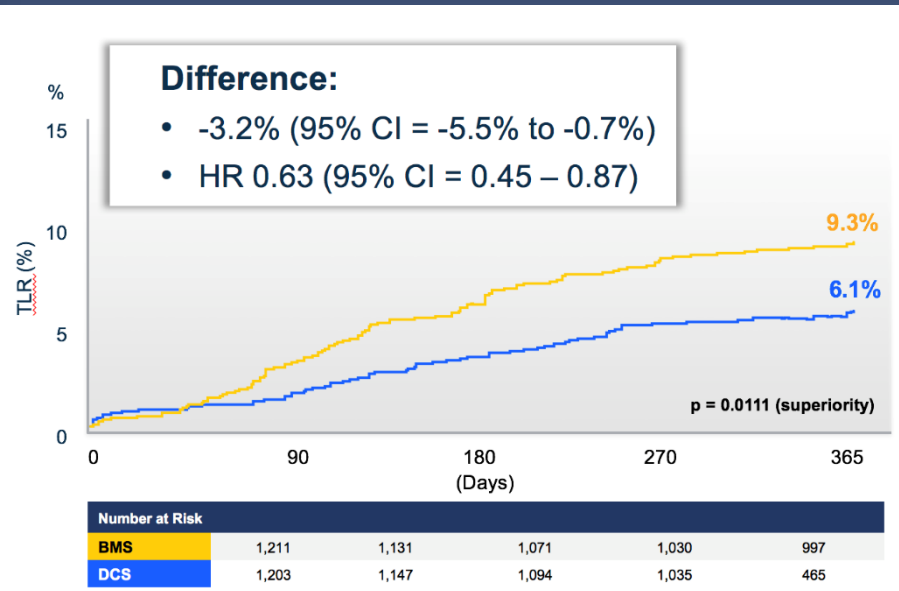



Urban P et al. N Engl J Med 2015;373:2038-47

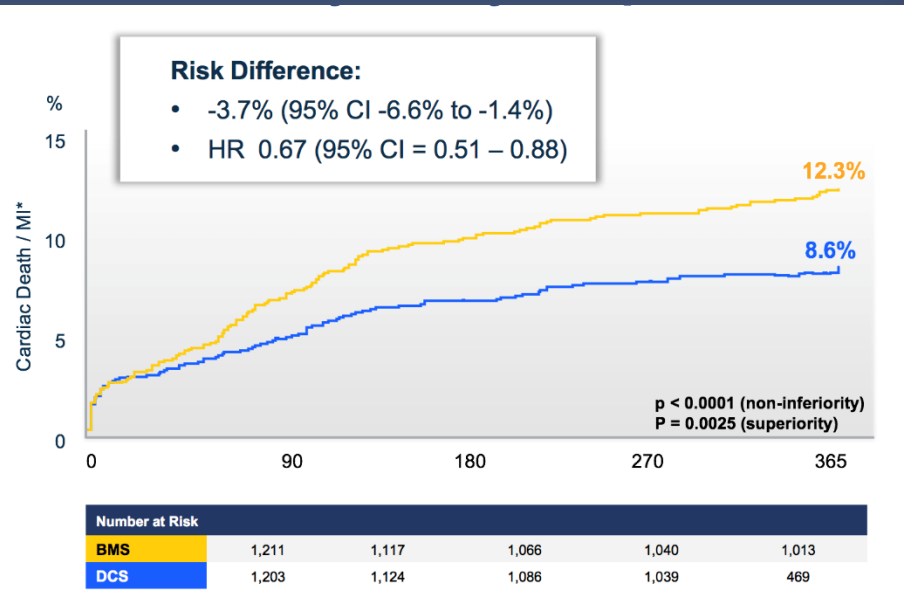
# LEADERS FREE II

DCS single arm, 1200 patients in US, Canada and Europe
Propensity-adjusted vs. BMS arm of LEADERS FREE

## Efficacy (cd-TLR)




## Safety (cardiac death/MI)




Krucoff M. TCT 2018

# DES: 12 completed trials of short DAPT (≤ 3 months)

| trial | stent | type | limus kinetics | patients | experimental arm DAPT | control arm | primary endpoint |
|---|---|---|---|---|---|---|---|
| RESET (1) | Endeavor ZES | 1st G permanent polymer | fast | 2117 low/med risk | 3 months | Other DES & 12 months DAPT | Non-inferiority for NACCE |
| OPTIMIZE (2) | Endeavor ZES | 1st G permanent polymer | fast | 3119 low/med risk | 3 months | E-ZES & 12 months DAPT | Non-inferiority for NACCE |
| ZEUS (3) | Endeavor ZES | 1st G permanent polymer | fast | 1606 doubtful DES candidates | 30-180 days (IQR) median 32 days | BMS & same DAPT | Superiority for MACE |
| REDUCE (4) | Combo | DES + CD34 AB | slow | 1500 ACS | 3 months | 12 months DAPT | Non-inferiority for NACCE |
| STOPDAPT-2 (9) | Xience EES | 2nd G permanent polymer | slow | 3000 low/med risk successful PCI | 1 month | 1 year DAPT | Superiority for NACE (driven by lower bleeding rate) |
| SMART CHOICE (10) | 2ndG DES (EES, SES) | any | na | 3000 all-comers successful PCI | 3 months (then P2Y12 SAPT) | 1 year DAPT | Non-inferiority for MACE (superior for BARC2-5) |
| GLOBAL LEADERS (11) | BioMatrix BES | BD polymer | slow | 16000 all-comers | 1 mth ASA + tica. Then 23 mths tica. SAPT | Same stent, 1 year DAPT then SAPT | Not superior to guideline-based DAPT (Lancet 2018) |
| ReCre8 (12) | Cre8 Amphilimus-SES | polymer-free | slow | 1532 all-comers | SCAD 1 month ACS 12 months | R-ZES same DAPT | Non-inferior (not powered for DAPT) |
| LEADERS FREE (5) | BioFreedom BA9 DCS | polymer-free | fast | 2400 HBR | 1 month | BMS & 1 month DAPT | Superiority for safety Superiority for efficacy |
| ZEUS HBR (6) | Endeavor ZES | 1st G permanent polymer | fast | 828 HBR | 30 days | BMS & same DAPT | Superiority for MACE |
| SENIOR (7) | Synergy EES | 2nd G biodeg. polymer | slow | 1200 age ≥75 | 1 month (SCAD) or 6 months (ACS) | BMS & same DAPT | Superiority for MACE |
| LEADERS FREE II (8) | BioFreedom BA9 DCS | polymer-free | fast | 1200 HBR | 1 month | BMS arm of LEADERS FREE | Superiority for safety Superiority for efficacy |

HBR


1) Kim B-K et al. JACC 2012; 60: 1340-8
2) Feres F et al. JAMA 2013; 310: 2510-22
3) Valgimigli M et al. JACC 2015;65:805-15
4) Suryanapranata H et al, presented TCT 2017
5) Urban P et al. NEJM 2015; 373: 2038-47
6) Ariotti S et al. JACC interv 2016; 9: 426-36
7) Varenne O et al. Lancet 2017; 391: 41-50
8) Krucoff M. et al TCT 2018
9) Watanabe H et al. ACC 2019
10) Hahn JH et al. ACC2019
11) Vranckx P et al, Lancet 2018
12) Recre8, Stella P et al,

# 10 ongoing trials of ≤ 3 months DAPT for HBR patients

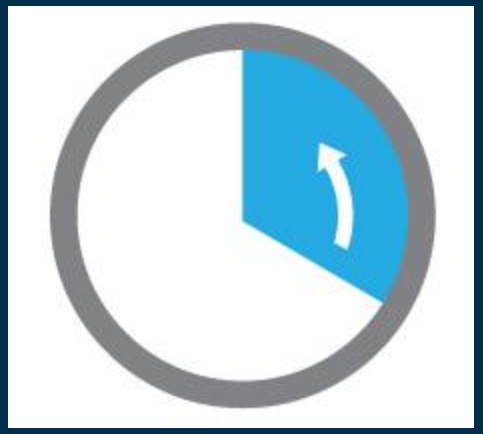
| | Trial | stent | type | limus kinetics | patients | experimental arm DAPT | control arm | Status September 2018 |
|---|---|---|---|---|---|---|---|---|
| randomized | ONYX ONE | Resolute Onyx DES vs. BioFreedom DCS | Permanent polymer vs. polymer-free | slow vs. fast | 2000 HBR | 1 month | 1 month | follow-up |
| | COBRA-REDUCE | Cobra PzF | Polyzene-F nanocoating | na | 840 on AVK or NOAC | 2 weeks | EES or R-ZES & 6 months DAPT | enrolling |
| | MASTER DAPT | Ultimaster SES | 2nd G BD polymer | slow | 4300 HBR | 1 month | guidelines | enrolling |
| | TARGET SAFE | Firehawk | Biodegradable polymer | slow | 1700 HBR | 1 months DAPT | 6 months DAPT | planned |
| single arm | EVOLVE SHORT DAPT | Synergy EES | 2nd G BD polymer | slow | 2000 HBR | 3 months | single arm trial | follow-up |
| | POEM | Synergy EES | 2nd G BD polymer | slow | 1023 HBR | 1 month | single arm trial | enrolling |
| | XIENCE 90 (Xience Short DAPT) | Xience EES | Permanent polymer | slow | 2000 HBR | 3 months | single arm trial | enrolling |
| | XIENCE Global 28 | Xience EES | Permanent polymer | slow | 800 HBR | 1 month | single arm trial | enrolling |
| | ONYX ONE CLEAR | Resolute Onyx DES | Permanent polymer | slow | 800 HBR | 1 month | Single arm trial | enrolling |
| | LEADERS FREE III | CoCr BioFreedom | Polymer-free | fast | 1200 HBR | 1 month | DCS arm of LEADERS FREE | enrolling |

# Bleeding Risk after PCI: stents, drugs and others choices

- Stents
- **Drugs**
- Other options

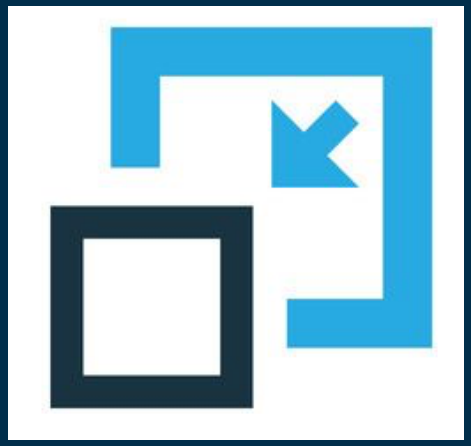
# ONGOING DIRECTIONS IN TAILORING ANTITHROMBOTIC PHARMACOTHERAPY FOR HBR PATIENTS

## STRATEGIES TO REDUCE THE RISK OF BLEEDING AFTER PCI



### Shortening DAPT

11 TRIALS OF SHORT
VS. STANDARD DAPT



### De-escalation

TOPIC
TROPICAL ACS

AF + PCI
WOEST
PIONEER- AF-PCI
RE-DUAL PCI
AUGUSTUS ACC 2019
ENTRUST ESC 2019

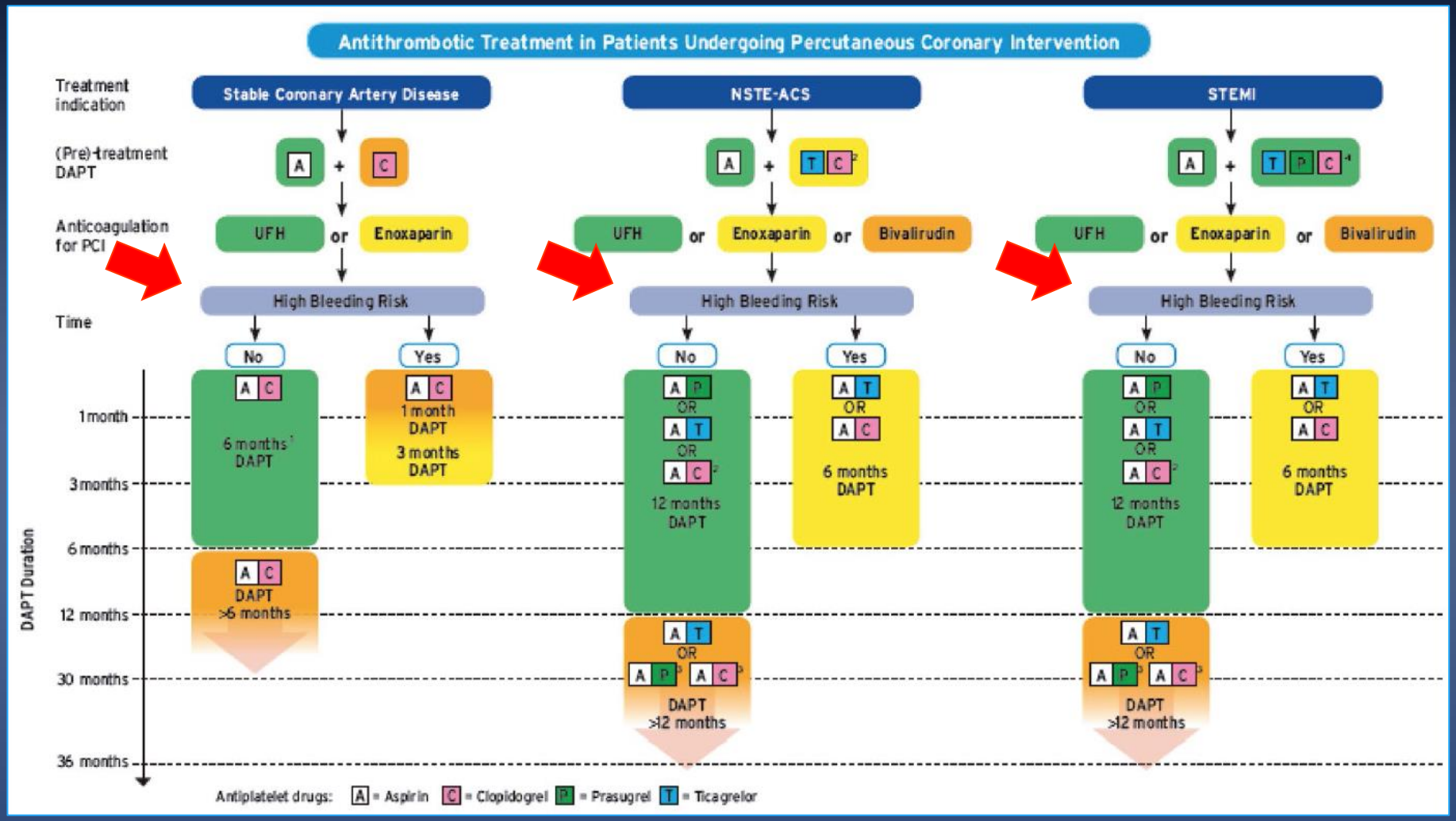
### Aspirin withdrawal

GLOBAL LEADERS
GLASSY ACC 2019
SMART-CHOICE ACC 2019
STOPDAPT-2 ACC 2019
TWILIGHT

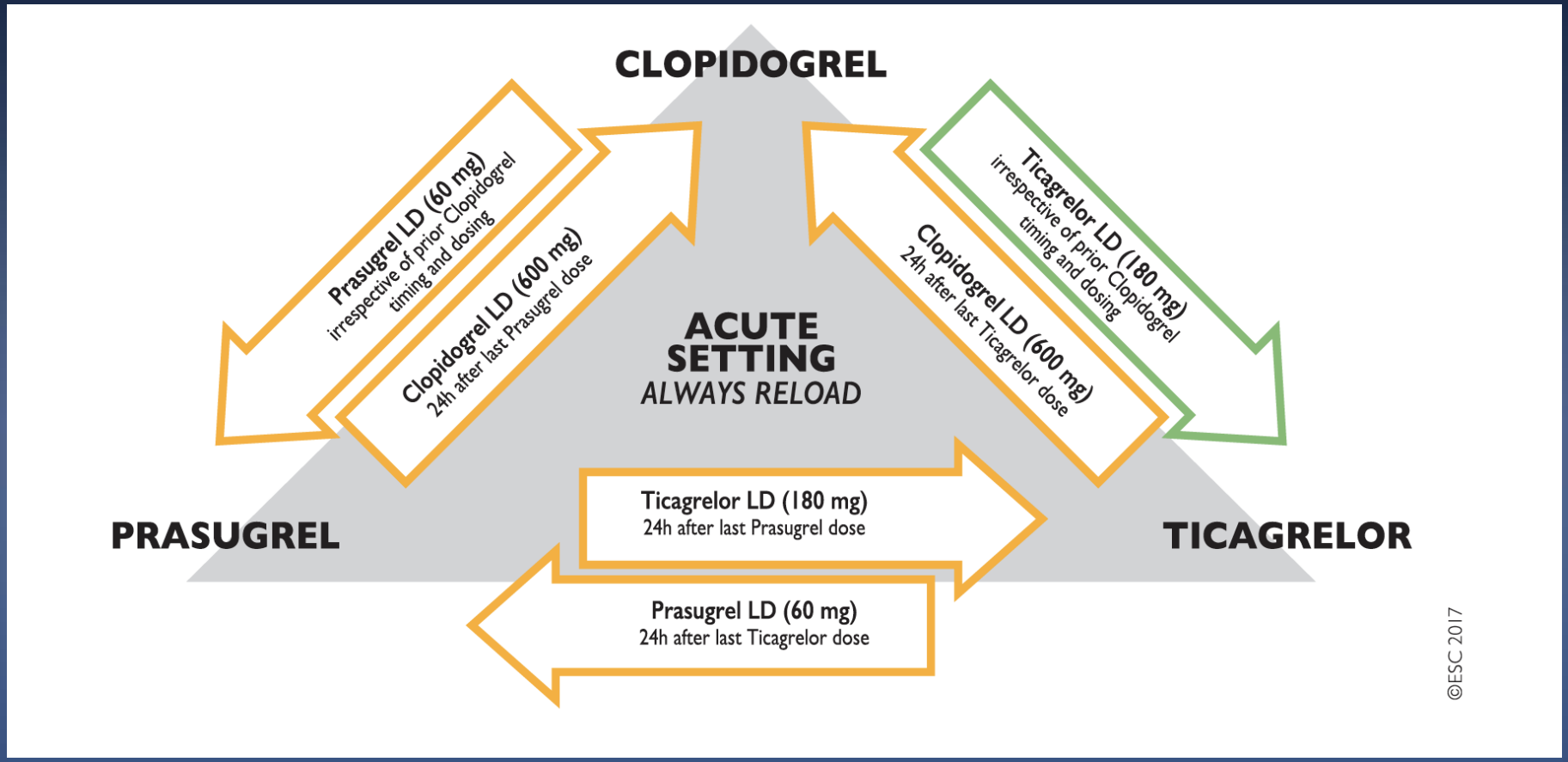
Courtesy of D. Angiolillo

# 2018 ESC/EACTS Guidelines on myocardial revascularization

(Neuman F-J et al. European Heart Journal 2018 doi:10.1093/eurheartj/ehy394)



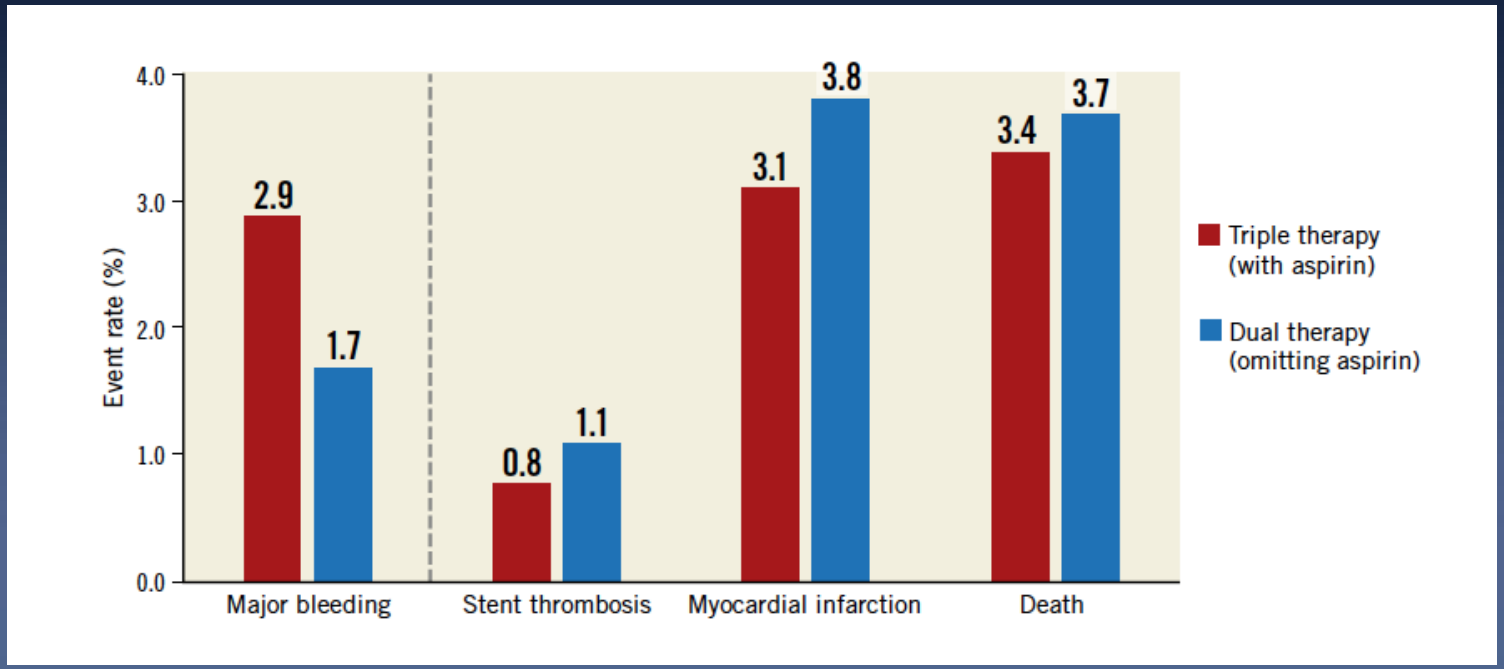
# P2Y12 SWITCHING




2017 ESC focused update on dual antiplatelet therapy in coronary artery disease.

# Omission of aspirin after ACS or stenting in patients with OAC

Robert Byrne, EuroIntervention 2019;14:e1793-e1795



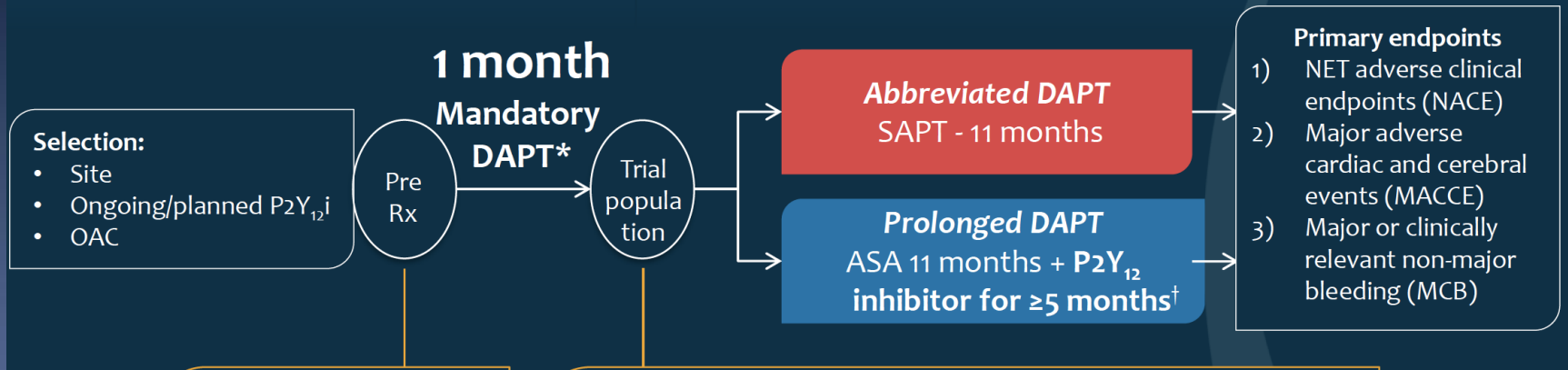

4 trials: WOEST, PIONEER-AF, REDUAL-AF, AUGUSTUS 9924 patients

"systematic adoption of dual therapy for all patients receiving oral anticoagulation with ACS or undergoing coronary intervention would seem ill-advised, as we cannot be sure that omitting aspirin does not cause harm. At a minimum, it would seem pertinent that the period of highest risk for stent thrombosis should be covered by DAPT"

# DAPT: how long & how short?

# Study Design and Key Features

## 4300 patients - >100 international sites




**Eligibility after Index procedure**

- Patient at HBR
- All lesions treated with Ultimaster®
- No further PCI planned

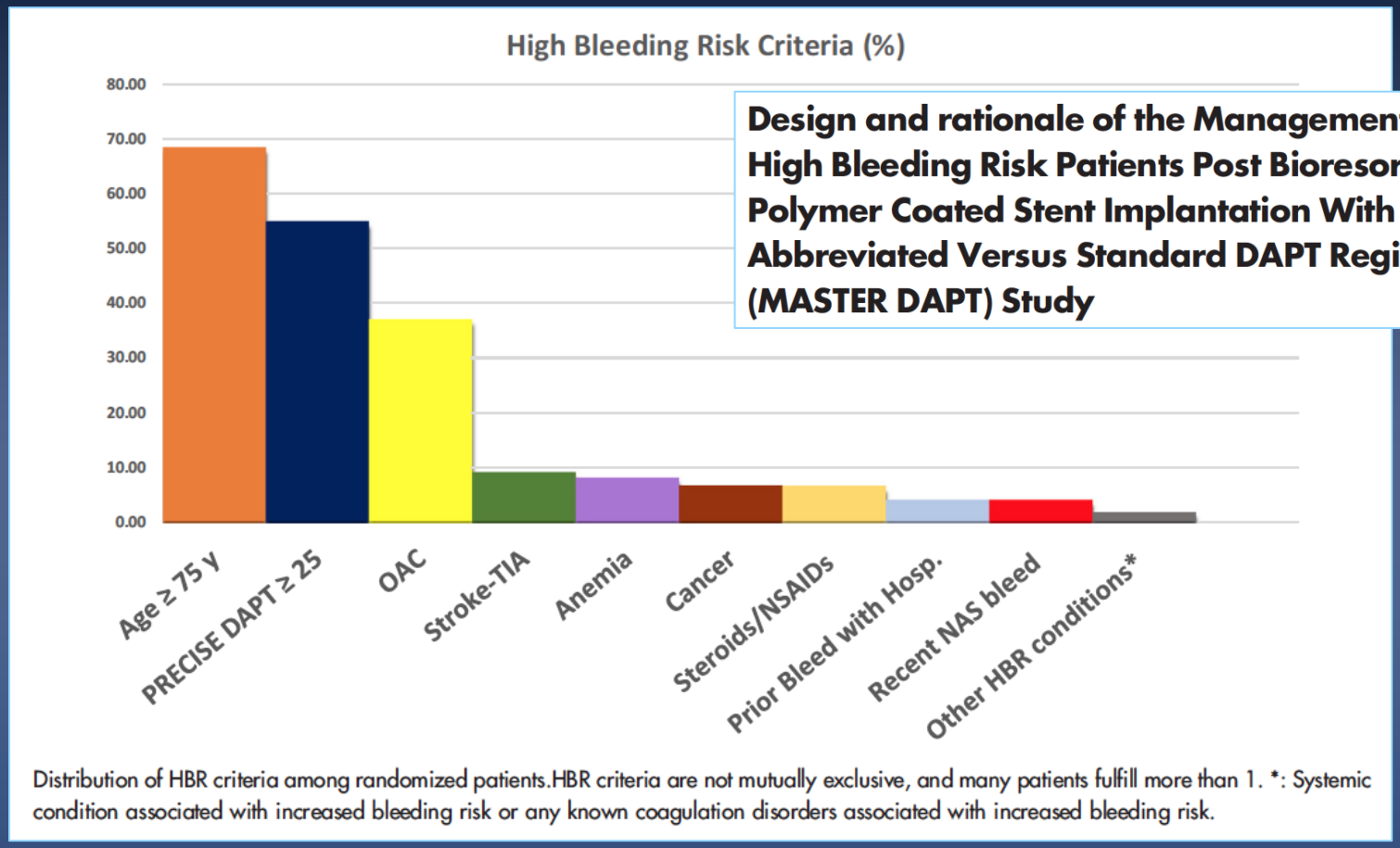
**Eligibility at 30 days randomization visit**

- HBR at baseline or actionable non-access site related bleeding episode post-PCI
- Free from MI, symptomatic restenosis, stent thrombosis, stroke and any revascularization
- No active bleeding within 7 days before randomization
- Patient is on stable DAPT for at least 7 days before randomization

*DAPT duration is counted from the day of last implanted stent; staging has to be pre-specified at the time of screening and cannot be planned later than 2 months after index PCI; †Patients on OAC can stop DAPT 2 months after confirmed randomization

ASA, acetylsalicylic acid; MI, myocardial infarction; SAPT, single antiplatelet therapy

# HBR criteria applied (n=2196)




Distribution of HBR criteria among randomized patients.HBR criteria are not mutually exclusive, and many patients fulfill more than 1. *: Systemic condition associated with increased bleeding risk or any known coagulation disorders associated with increased bleeding risk.

Frigoli et al. Am Heart J 2019;209:97–105

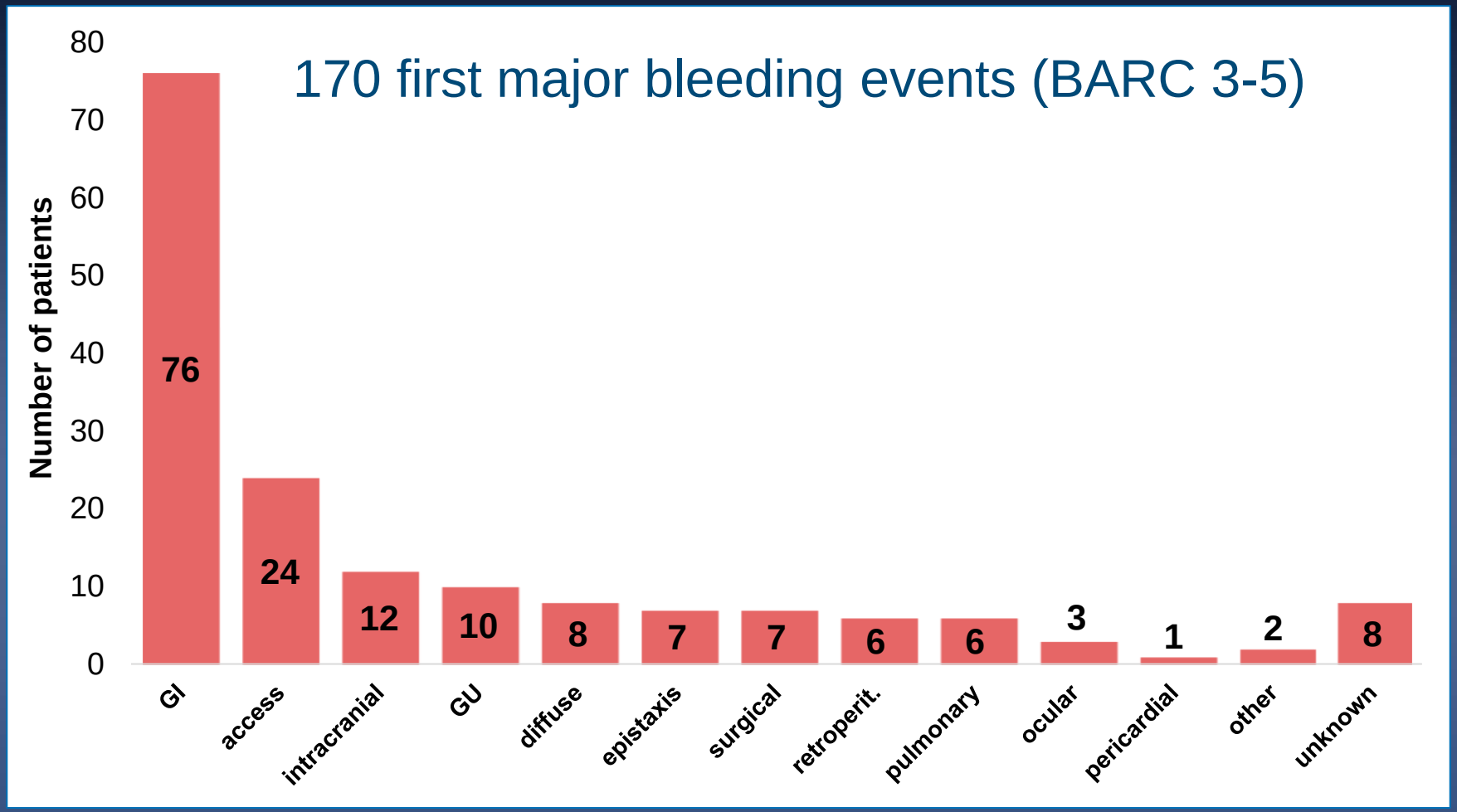
# Bleeding Risk after PCI: stents, drugs and others choices

- Stents
- Drugs
- **Other options**

# Bleeding Risk after PCI: drugs, stents and others choices

- **Radial access** ✓
- **Liberal use of PPI**
- **Also assess thrombotic risk**

# Location of Major Bleeding



# Bleeding Risk after PCI: drugs, stents and others choices

- Radial access
- Liberal use of PPI
- **Also assess thrombotic risk**

# 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

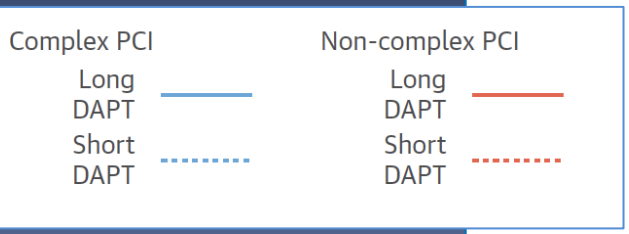
+ SVG

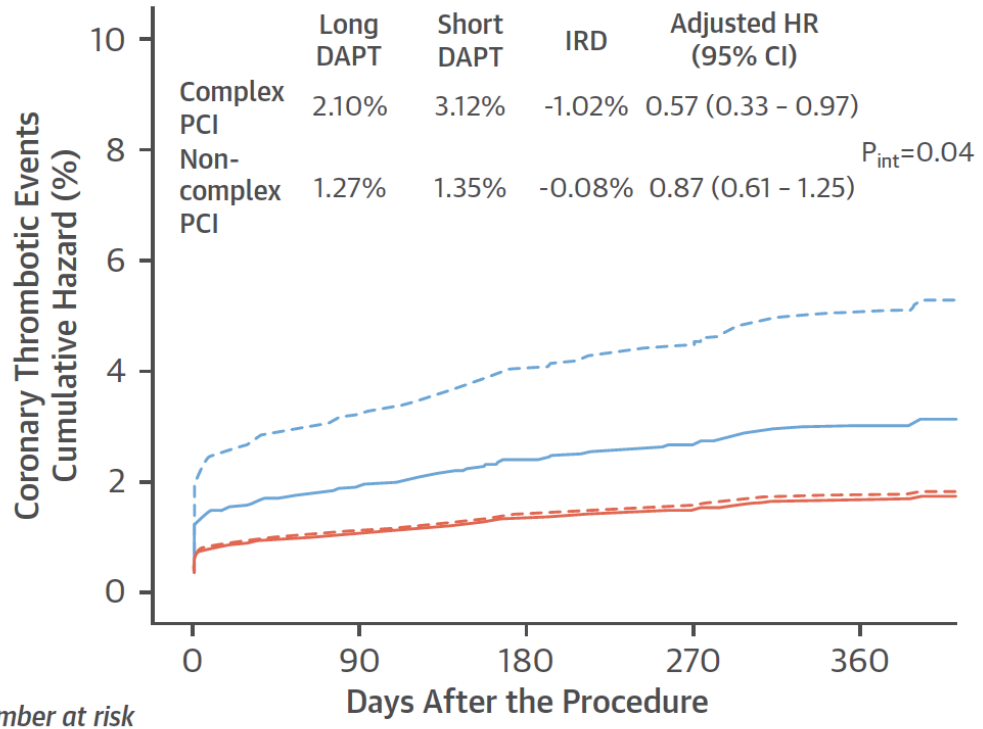
2017 ESC focused update on dual antiplatelet therapy in coronary artery disease

# Complex PCI in DAPT trials after PCI

1680 patients of 9577 (17.5%) underwent complex PCI

Data from PRODIGY, OPTIMIZE, RESET, EXCELLENT, SECURITY, ITALIC.




*Number at risk*

| | | | | | |
|---|---|---|---|---|---|
| Non-complex PCI - Short DAPT | 3938 | 3873 | 3817 | 3784 | 3515 |
| Non-complex PCI - Long DAPT | 3932 | 3875 | 3828 | 3797 | 3524 |
| Complex PCI - Short DAPT | 801 | 776 | 767 | 760 | 671 |
| Complex PCI - Long DAPT | 840 | 817 | 806 | 797 | 694 |

Giustino G et al. JACC 2016; 68: 1851–64

# Conclusions

- For HBR patients considered to require ultra-short (1 month) DAPT today, use of the BA-9 DCS is supported by the most convincing evidence.
- Clopidogrel is generally the preferred P2Y12 blocker for HBR patients, either immediately or following early de-escalation, and there is increasing (but not definitive) evidence that dual rather than triple therapy may often be preferred early after PCI for patients on oral anticoagulation
- The optimal duration and intensity of DAPT for HBR patients is currently not known. The MASTER-DAPT trial will help to better understand the trade-off between bleeding and thrombotic risks

# Thank you

# SORT OUT IX

3151 all-comer patients randomized - DAPT according to guidelines
Orsiro ultra-thin BD-SES vs. BioFreedom PF-DCS