24th CARDIOVASCULAR SUMMIT
TCTAP2019

Which stent and which DAPT regimen for High Bleeding Risk patients?

MC Morice,MD, FESC, FACC
CERC, Massy
France

24th CARDIOVASCULAR SUMMIT
TCTAP2019

MC Morice am CEO and share holder of CERC a CRO that conducted the Leaders free and SENIOR Trial

DES: 6 published trials of short DAPT (≤ 3 months)

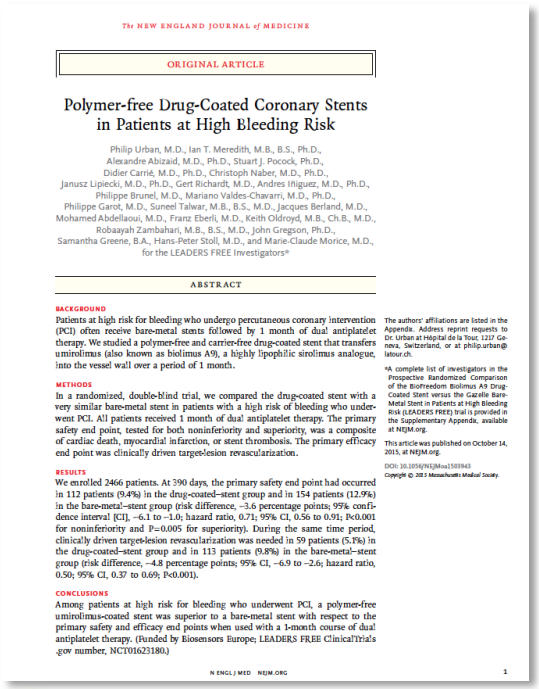
trial	stent	type	limus kinetics	patients	experimental arm DAPT	control arm	primary endpoint
RESET (1)	Endeavor ZES	1st G permanent polymer	fast	2117 low/med risk	3 months	R-ZES, SES or EES & 12 months DAPT	Non-inferiority for NACCE
OPTIMIZE (2)	Endeavor ZES	1st G permanent polymer	fast	3119 low/med risk	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
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 biodegradable polymer	slow	1200 age ≥75	1 month or 6 months (operator discretion)	BMS & same DAPT	Superiority for MACE

3 trials of HBR patients

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. JACC2015;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

3 published trials of short DAPT (≤ 3 months) for HBR patients

LEADERS FREE



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*

ABSTRACT

BACKGROUND

Patients at high risk for bleeding who undergo percutaneous coronary intervention (PCI) often receive bare-metal stents followed by 1 month of dual antiplatelet therapy. We studied a polymer-free and carrier-free drug-coated stent that transfers umirolimus (also known as biolimus A9), a highly lipophilic sirolimus analogue, into the vessel wall over a period of 1 month.

METHODS

In a randomized, double-blind trial, we compared the drug-coated stent with a very similar bare-metal stent in patients with a high risk of bleeding who underwent PCI. All patients received 1 month of dual antiplatelet therapy. The primary safety end point, tested for both noninferiority and superiority, was a composite of cardiac death, myocardial infarction, or stent thrombosis. The primary efficacy end point was clinically driven target-lesion revascularization.

RESULTS

We enrolled 2466 patients. At 390 days, the primary safety end point had occurred in 112 patients (9.4%) in the drug-coated–stent group and in 154 patients (12.9%) in the bare-metal–stent group (risk difference, −3.6 percentage points; 95% confidence interval [CI], −6.1 to −1.0; hazard ratio, 0.71; 95% CI, 0.56 to 0.91; P<0.001 for noninferiority and P=0.005 for superiority). During the same time period, clinically driven target-lesion revascularization was needed in 59 patients (5.1%) in the drug-coated–stent group and in 113 patients (9.8%) in the bare-metal–stent group (risk difference, −4.8 percentage points; 95% CI, −6.9 to −2.6; hazard ratio, 0.50; 95% CI, 0.37 to 0.69; P<0.001).

CONCLUSIONS

Among patients at high risk for bleeding who underwent PCI, a polymer-free umirolimus-coated stent was superior to a bare-metal stent with respect to the primary safety and efficacy end points when used with a 1-month course of dual antiplatelet therapy. (Funded by Biosensors Europe; LEADERS FREE ClinicalTrials.gov number, NCT01623180.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Urban at Hôpital de la Tour, 1217 Geneva, Switzerland, or at philip.urban@latour.ch.

*A complete list of investigators in the Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk (LEADERS FREE) trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on October 14, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1508943

ZEUS HBR

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 9, NO. 5, 2016
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER http://dx.doi.org/10.1016/j.jcin.2015.11.015

CLINICAL RESEARCH

CORONARY

Is Bare-Metal Stent Implantation Still Justifiable in High Bleeding Risk Patients Undergoing Percutaneous Coronary Intervention?

A Pre-Specified Analysis From the ZEUS Trial

Sara Aziotti, MD,[a,b] Marianna Adamo, MD,[b] Francesco Costa, MD,[b] Athanasios Patialiakas, MD,[c] Carlo Briguori, MD, PhD,[d] Attila Thury, MD, PhD,[e] Salvatore Colangelo, MD,[f] Gianluca Campo, MD,[g] Matteo Tebaldi, MD,[g] Imre Ungi, MD, PhD,[e] Stefano Tondi, MD,[h] Marco Roffi, MD,[i] Alberto Menozzi, MD, PhD,[j] Nicoletta de Cesare, MD,[k] Roberto Garbo, MD,[l] Emanuele Meliga, MD,[i] Luca Testa, MD, PhD,[m] Henrique Mesquita Gabriel, MD,[n] Marco Ferlini, MD,[o] Pascal Vranckx, MD, PhD,[p] Marco Valgimigli, MD, PhD,[a,b] for the ZEUS Investigators

ABSTRACT

OBJECTIVES This study sought to investigate the ischemic and bleeding outcomes of patients fulfilling high bleeding risk (HBR) criteria who were randomized to zotarolimus-eluting Endeavor Sprint stent (E-ZES) or bare-metal stent (BMS) implantation followed by an abbreviated dual antiplatelet therapy (DAPT) duration for stable or unstable coronary artery disease.

BACKGROUND DES instead of BMS use remains controversial in HBR patients, in whom long-term DAPT poses safety concerns.

METHODS The ZEUS (Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES Candidates) is a multinational, randomized single-blinded trial that randomized among others, in a stratified manner, 828 patients fulfilling pre-defined clinical or biochemical HBR criteria—including advanced age, indication to oral anticoagulants or other pro-hemorrhagic medications, history of bleeding and known anemia—to receive E-ZES or BMS followed by a protocol-mandated 30-day DAPT regimen. The primary endpoint of the study was the 12-month major adverse cardiovascular event rate, consisting of death, myocardial infarction, or target vessel revascularization.

RESULTS Compared with patients without, those with 1 or more HBR criteria had worse outcomes, owing to higher ischemic and bleeding risks. Among HBR patients, major adverse cardiovascular events occurred in 22.6% of the E-ZES and 29% of the BMS patients (hazard ratio: 0.75; 95% confidence interval: 0.57 to 0.98; p = 0.033), driven by lower myocardial infarction (3.5% vs. 10.4%; p < 0.001) and target vessel revascularization (5.9% vs. 11.4%; p = 0.005) rates in the E-ZES arm. The composite of definite or probable stent thrombosis was significantly reduced in E-ZES recipients, whereas bleeding events did not differ between stent groups.

CONCLUSIONS Among HBR patients with stable or unstable coronary artery disease, E-ZES implantation provides superior efficacy and safety as compared with conventional BMS. (Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES Candidates [ZEUS]; NCT01385319) (J Am Coll Cardiol Intv 2016;9:426–36) © 2016 by the American College of Cardiology Foundation.

SENIOR

Articles

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. Díaz Fernández, Salvatore Brugaletta, Eduardo Pinar-Bermudez, Josepa Mauri Ferre, Philippe Commeau, Emmanouil Tsiger, Kris Bogaerts, Manel Sabaté, Marie-Claude Morice, Peter R Stinnenaar, for the SENIOR investigators

Summary

Background Elderly patients regularly receive bare-metal stents (BMS) instead of drug-eluting stents (DES) to shorten the duration of double antiplatelet therapy (DAPT). The aim of this study was to compare outcomes between these two types of stents with a short duration of DAPT in such patients.

Methods In this randomised single-blind trial, we recruited patients from 44 centres in nine countries. Patients were eligible if they were aged 75 years or older; had stable angina, silent ischaemia, or an acute coronary syndrome; and had at least one coronary artery with a stenosis of at least 70% (≥50% for the left main stem) deemed eligible for percutaneous coronary intervention (PCI). Exclusion criteria were indication for myocardial revascularisation by coronary artery bypass grafting; inability to tolerate, obtain, or comply with DAPT; requirement for additional surgery; non-cardiac comorbidities with a life expectancy of less than 1 year; previous haemorrhagic stroke; allergy to aspirin or $P2Y_{12}$ inhibitors; contraindication to $P2Y_{12}$ inhibitors; and silent ischaemia of less than 10% of the left myocardium with a fractional flow reserve of 0·80 or higher. After the intended duration of DAPT was recorded (1 month for patients with stable presentation and 6 months for those with unstable presentation), patients were randomly allocated (1:1) by a central computer system (blocking used with randomly selected block sizes [two, four, eight, or 16]; stratified by site and antiplatelet agent) to either a DES or similar BMS in a single-blind fashion (ie, patients were masked), but those assessing outcomes were masked. The primary outcome was to compare major adverse cardiac and cerebrovascular events (ie, a composite of all-cause mortality, myocardial infarction, stroke, or ischaemia-driven target lesion revascularisation) between groups at 1 year in the intention-to-treat population, assessed at 30 days, 180 days, and 1 year. This trial is registered with ClinicalTrials.gov, number NCT02099617.

Findings Between May 21, 2014, and April 16, 2016, we randomly assigned 1200 patients (596 [50%] to the DES group and 604 [50%] to the BMS group). The primary endpoint occurred in 68 (12%) patients in the DES group and 98 (16%) in the BMS group (relative risk [RR] 0·71 [95% CI 0·52–0·94]; p=0·02). Bleeding complications (26 [5%] in the DES group vs 29 [5%] in the BMS group; RR 0·90 [0·51–1·54]; p=0·68) and stent thrombosis (three [1%] vs eight [1%]; RR 0·38 [0·08–1·48]; p=0·13) at 1 year were infrequent in both groups.

Interpretation 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 mortality, myocardial infarction, stroke, and ischaemia-driven target lesion revascularisation. A strategy of combination of a DES to reduce the risk of subsequent repeat revascularisations with a short BMS-like DAPT regimen to reduce the risk of bleeding event is an attractive option for elderly patients who have PCI.

Funding Boston Scientific.

Introduction

Elderly people represent a fast-growing segment of the population, and because of their increased risk of coronary artery disease, they are also more likely to have percutaneous coronary interventions (PCI) than are younger people.[1,2] Management of coronary artery disease in elderly patients can be challenging as they often have more extensive and complex disease and are also more prone to bleeding complications when receiving antiplatelet agents than younger patients.[3]

The optimal PCI strategy for elderly patients remains ill defined, for both the type of stent and duration of dual antiplatelet therapy (DAPT) after intervention. A Scientific Statement[4] from the American Heart Association, American College of Cardiology, and American Geriatrics Society called for closure of the gap of evidence in cardiovascular care between elderly and younger patients, recognising that current guidelines were unable to provide evidence-based recommendations for treatment of older patients.

Current drug-eluting stents (DES) limit the risk of repeat revascularisations compared with bare-metal stents (BMS) in elderly patients.[5–7] Contemporary DES are also safer than are BMS in terms of stent thrombosis.[8–10] In view of the high incidence of complex lesions in elderly patients, these DES are therefore becoming an increasingly attractive option in this population. However, elderly patients regularly receive

LEADERS FREE Trial Design

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

BioFreedom™
DCS

VS.

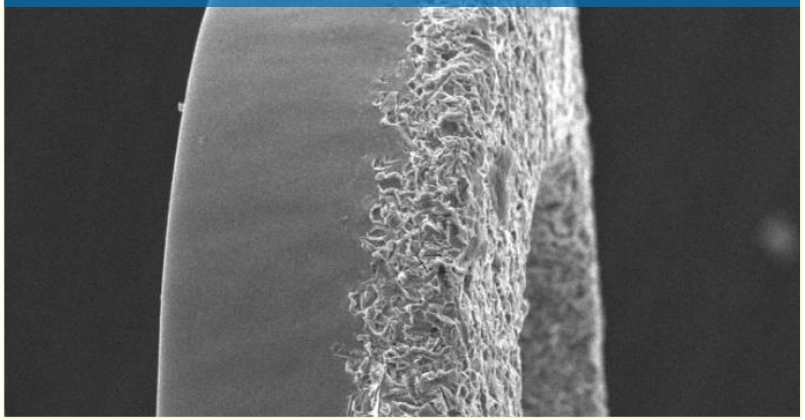
Gazelle™
BMS

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

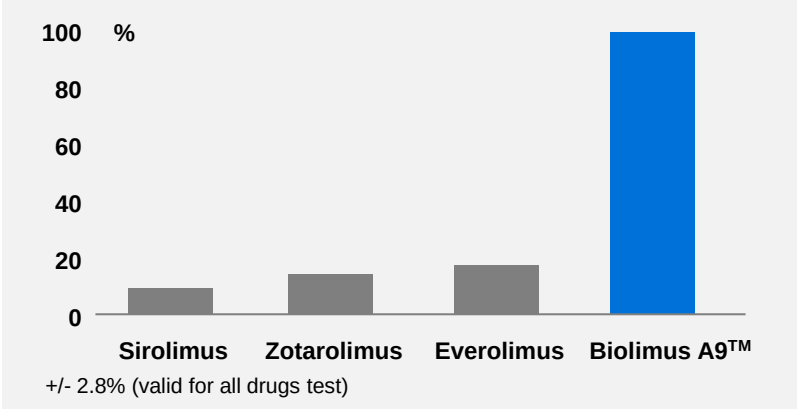
- Primary safety endpoint:
  Composite of cardiac death, MI, definite / probable stent thrombosis at 1 year (non-inferiority then superiority)
- Primary efficacy endpoint:
  Clinically-driven TLR at 1 year (superiority)

BioFreedom™ Drug Coated Stent (DCS)

Selectively Micro-Structured Surface Holds Drug in Abluminal Surface Structures



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

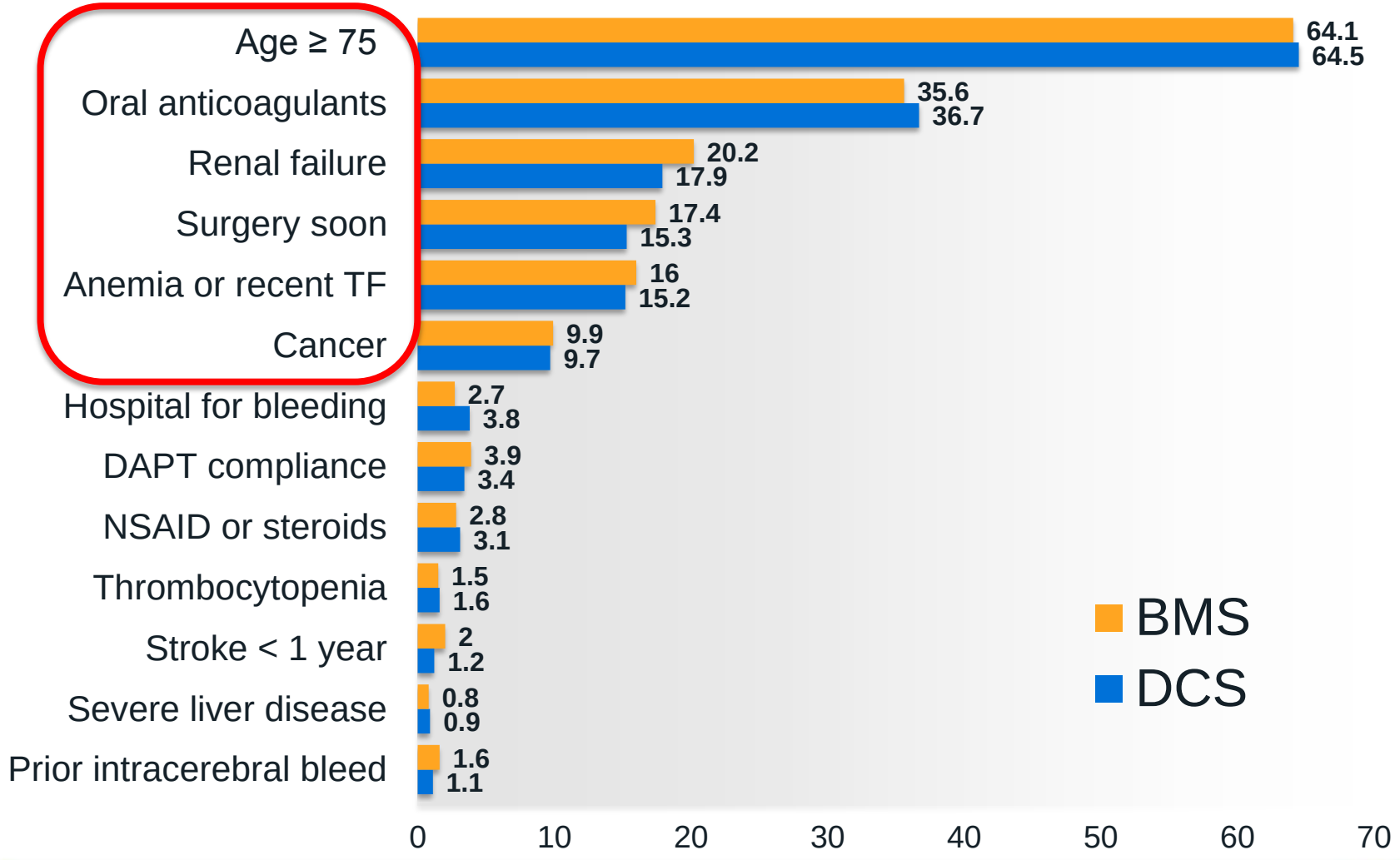


+/- 2.8% (valid for all drugs test)

Advantages:

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

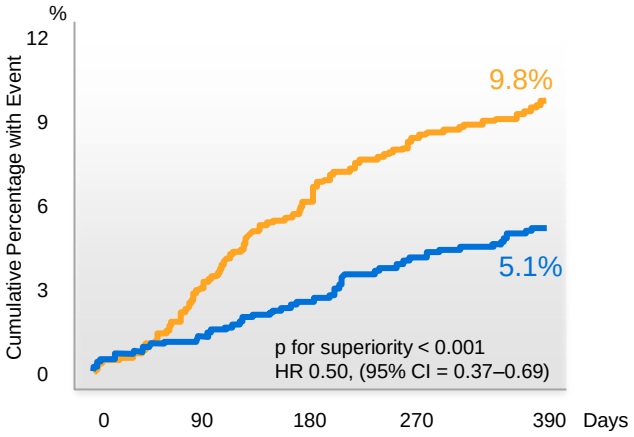
Inclusion Criteria Applied (1.7 criteria / patient)



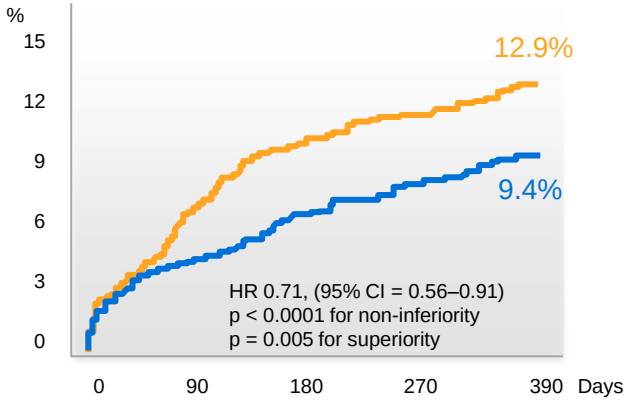
Primary Endpoints and Major Bleeding at 1 Year

DCS BMS

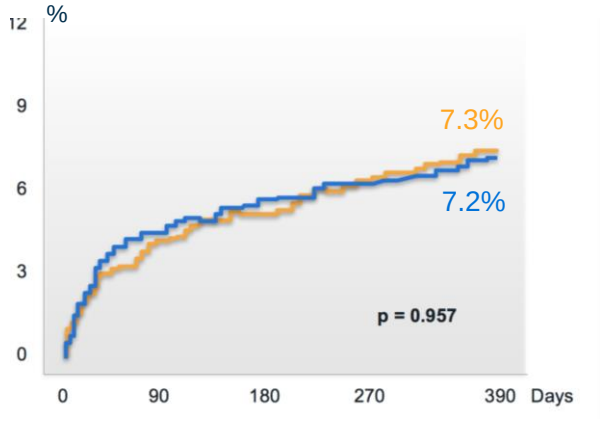
Efficacy (cd-TLR)



Safety (cardiac death, MI, ST)



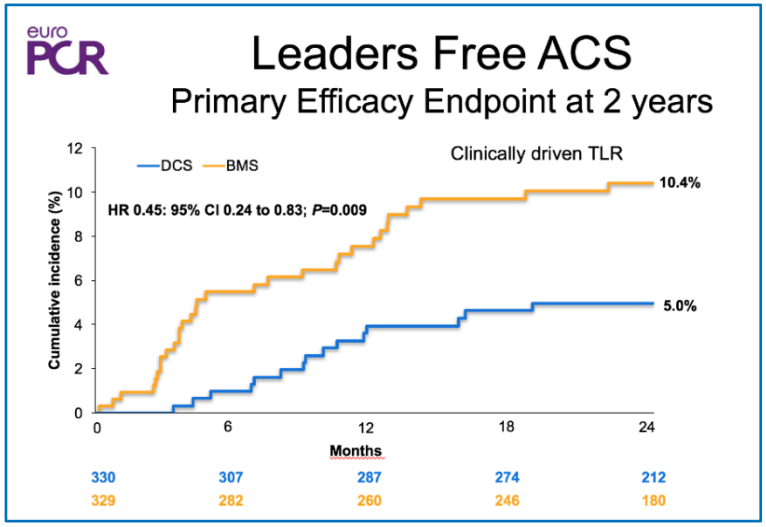
Bleeding (BARC 3-5)

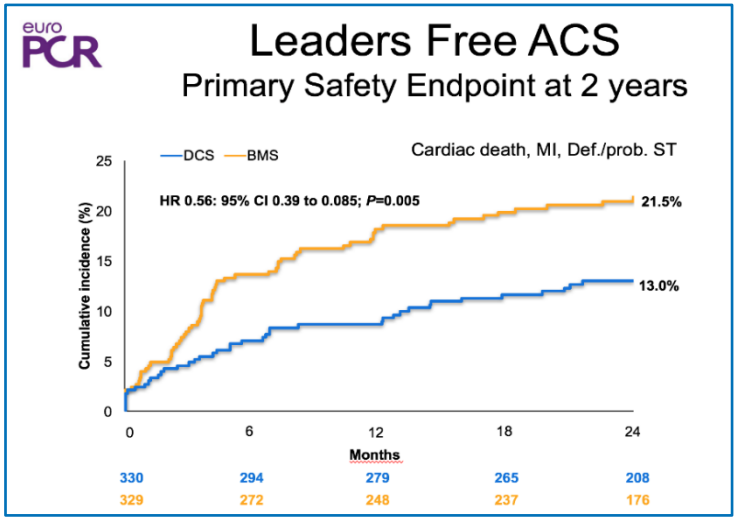


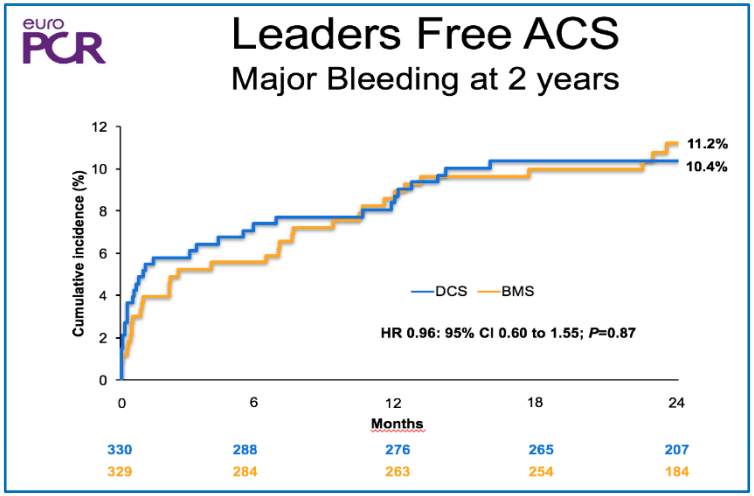
Acute Coronary Syndrome

662 ACS patients enrolled in LEADERS FREE

554 (84%) NSTEMI & 105 (16%) STEMI



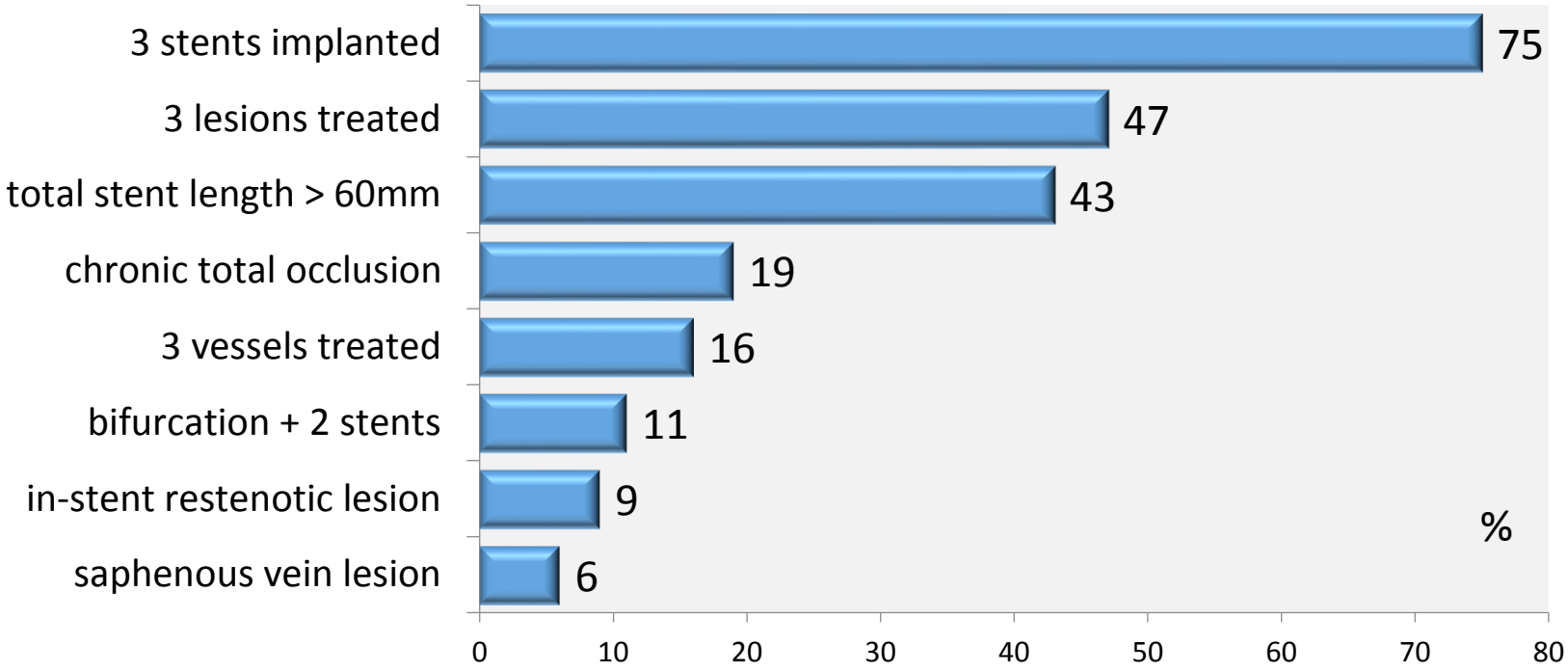




LEADERS FREE

Diagnostic criteria for 667 patients (28%) with complex PCI

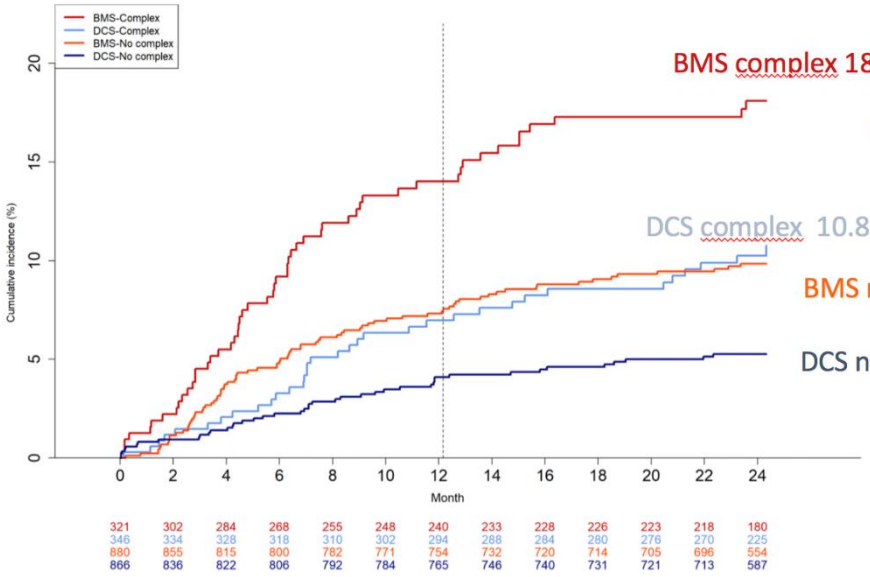
(1 or more)



If none of the above, PCI was considered «non-complex»

Complex PCI

Primary efficacy endpoint (clinically indicated TLR)



BMS complex 18.1%

DCS complex 10.8%

HR 0.54 (95% CI 0.35-0.83) P < 0.005

BMS non-complex 9.9%

DCS non-complex 5.3%

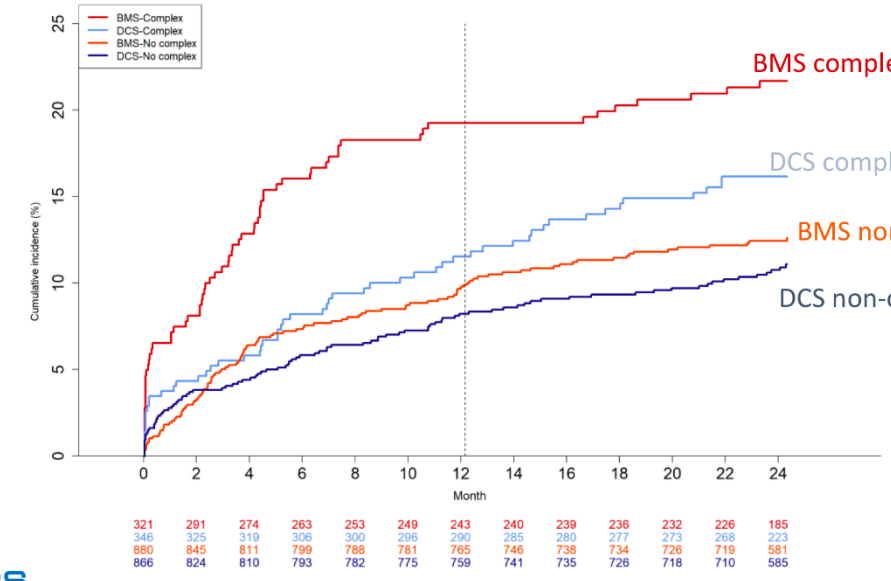
HR 0.52 (95% CI 0.36-0.75), p<0.001

NNT
Complex 14
Non-complex 22

P for interaction = NS

Complex PCI

Primary safety endpoint (cardiac death/MI/ST)



BMS complex, 21.7%

HR 0.70 (95% CI 0.49-0.99) P < 0.05

DCS complex, 16.2%

BMS non-complex, 12.6%

NS

DCS non-complex, 11.1%

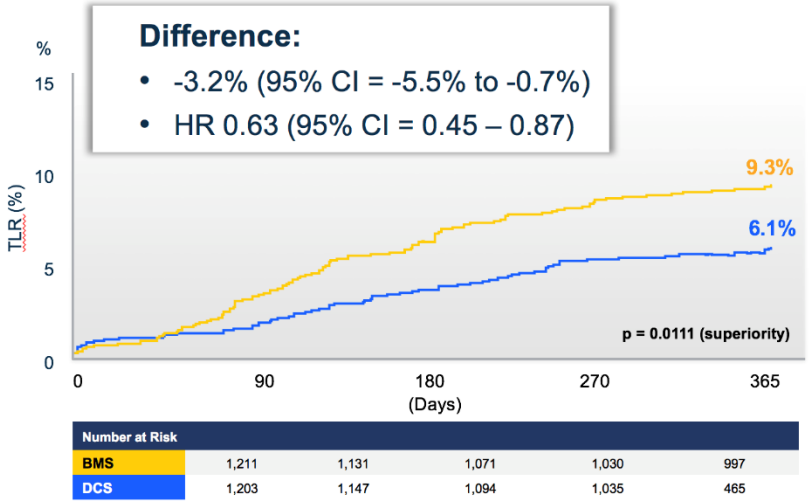
NNT
Complex 18
Non-complex 67

P for interaction = NS

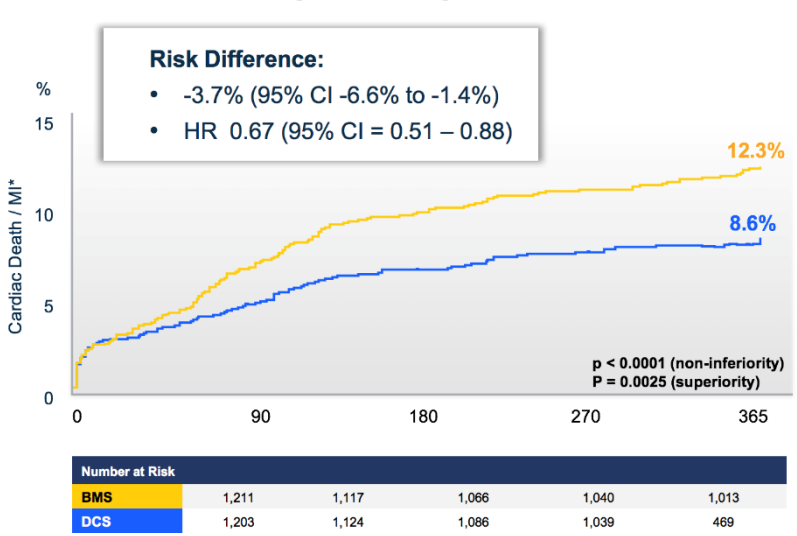
LEADERS FREE II

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

Efficacy (cd-TLR)

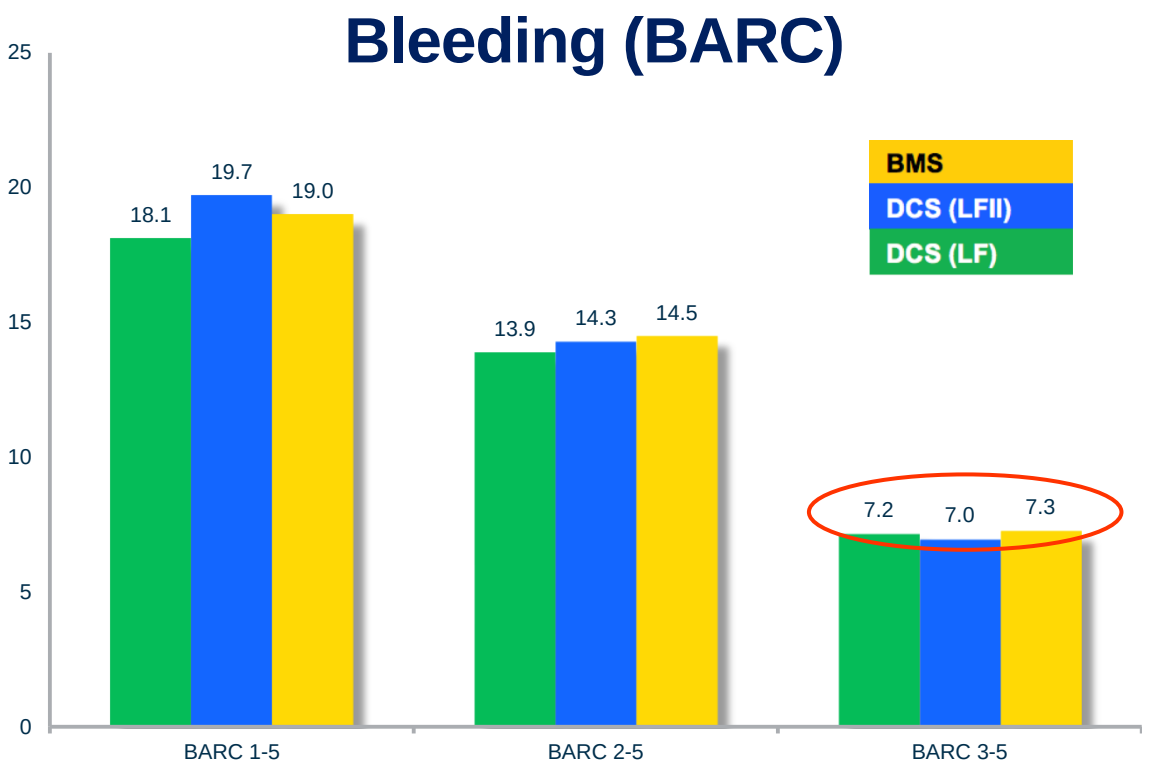


Safety (cardiac death/MI)



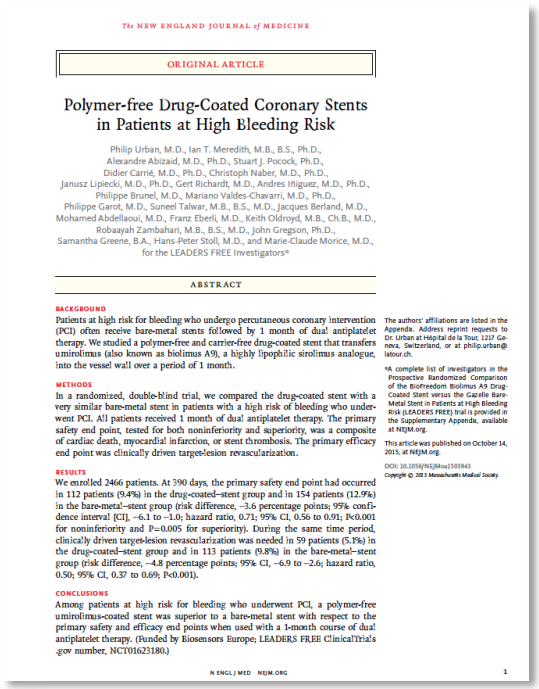
Mitch Krucoff - Late breaking trials - TCT 2018

LEADERS FREE vs. LEADERS FREE II (unadjusted)



3 completed trials of short DAPT (≤ 3 months) for HBR patients

LEADERS FREE



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CONCLUSIONS

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This article was published on October 14, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1508943

ZEUS HBR

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 9, NO. 5, 2016
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION ISSN 1936-8798/$36.00
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Sara Aziotti, MD,[a,b] Marianna Adamo, MD,[b] Francesco Costa, MD,[b] Athanasios Pataliakas, MD,[c] Carlo Briguori, MD, PhD,[d] Attila Thury, MD, PhD,[e] Salvatore Colangelo, MD,[f] Gianluca Campo, MD,[g] Matteo Tebaldi, MD,[g] Imre Ungi, MD, PhD,[e] Stefano Tondi, MD,[h] Marco Roffi, MD,[c] Alberto Menozzi, MD, PhD,[i] Nicoletta de Cesare, MD,[b] Roberto Garbo, MD,[f] Emanuele Meliga, MD,[i] Luca Testa, MD, PhD,[g] Henrique Mesquita Gabriel, MD,[c] Marco Ferlini, MD,[c] Pascal Vranckx, MD, PhD,[c] Marco Valgimigli, MD, PhD,[a,b] for the ZEUS Investigators

ABSTRACT

OBJECTIVES This study sought to investigate the ischemic and bleeding outcomes of patients fulfilling high bleeding risk (HBR) criteria who were randomized to zotarolimus-eluting Endeavor Sprint stent (E-ZES) or bare-metal stent (BMS) implantation followed by an abbreviated dual antiplatelet therapy (DAPT) duration for stable or unstable coronary artery disease.

BACKGROUND DES instead of BMS use remains controversial in HBR patients, in whom long-term DAPT poses safety concerns.

METHODS The ZEUS (Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES Candidates) is a multinational, randomized single-blinded trial that randomized among others, in a stratified manner, 828 patients fulfilling pre-defined clinical or biochemical HBR criteria—including advanced age, indication to oral anticoagulants or other pro-hemorrhagic medications, history of bleeding and known anemia—to receive E-ZES or BMS followed by a protocol-mandated 30-day DAPT regimen. The primary endpoint of the study was the 12-month major adverse cardiovascular event rate, consisting of death, myocardial infarction, or target vessel revascularization.

RESULTS Compared with patients without, those with 1 or more HBR criteria had worse outcomes, owing to higher ischemic and bleeding risks. Among HBR patients, major adverse cardiovascular events occurred in 22.6% of the E-ZES and 29% of the BMS patients (hazard ratio: 0.75; 95% confidence interval: 0.57 to 0.98; p = 0.033), driven by lower myocardial infarction (3.5% vs. 10.4%; p < 0.001) and target vessel revascularization (5.9% vs. 11.4%; p = 0.005) rates in the E-ZES arm. The composite of definite or probable stent thrombosis was significantly reduced in E-ZES recipients, whereas bleeding events did not differ between stent groups.

CONCLUSIONS Among HBR patients with stable or unstable coronary artery disease, E-ZES implantation provides superior efficacy and safety as compared with conventional BMS. (Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES Candidates [ZEUS]; NCT01385319) (J Am Coll Cardiol Intv 2016;9:426–36) © 2016 by the American College of Cardiology Foundation.

SENIOR

Articles

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, Emmanouil Tsiger, Kris Bogaerts, Manel Sabaté, Marie-Claude Morice, Peter R Stinnenare, for the SENIOR investigators

Summary

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Methods In this randomised single-blind trial, we recruited patients from 44 centres in nine countries. Patients were eligible if they were aged 75 years or older; had stable angina, silent ischaemia, or an acute coronary syndrome; and had at least one coronary artery with a stenosis of at least 70% (≥50% for the left main stem) deemed eligible for percutaneous coronary intervention (PCI). Exclusion criteria were indication for myocardial revascularisation by coronary artery bypass grafting; inability to tolerate, obtain, or comply with DAPT; requirement for additional surgery; non-cardiac comorbidities with a life expectancy of less than 1 year; previous haemorrhagic stroke; allergy to aspirin or $P2Y_{12}$ inhibitors; contraindication to $P2Y_{12}$ inhibitors; and silent ischaemia of less than 10% of the left myocardium with a fractional flow reserve of 0·80 or higher. After the intended duration of DAPT was recorded (1 month for patients with stable presentation and 6 months for those with unstable presentation), patients were randomly allocated (1:1) by a central computer system (blocking used with randomly selected block sizes [two, four, eight, or 16]; stratified by site and antiplatelet agent) to either a DES or similar BMS in a single-blind fashion (ie, patients were masked), but those assessing outcomes were masked. The primary outcome was to compare major adverse cardiac and cerebrovascular events (ie, a composite of all-cause mortality, myocardial infarction, stroke, or ischaemia-driven target lesion revascularisation) between groups at 1 year in the intention-to-treat population, assessed at 30 days, 180 days, and 1 year. This trial is registered with ClinicalTrials.gov, number NCT02099617.

Findings Between May 21, 2014, and April 16, 2016, we randomly assigned 1200 patients (596 [50%] to the DES group and 604 [50%] to the BMS group). The primary endpoint occurred in 68 (12%) patients in the DES group and 98 (16%) in the BMS group (relative risk [RR] 0·71 [95% CI 0·52–0·94]; p=0·02). Bleeding complications (26 [5%] in the DES group vs 29 [5%] in the BMS group; RR 0·90 [0·51–1·54]; p=0·68) and stent thrombosis (three [1%] vs eight [1%]; RR 0·38 [0·08–1·48]; p=0·13) at 1 year were infrequent in both groups.

Interpretation 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 mortality, myocardial infarction, stroke, and ischaemia-driven target lesion revascularisation. A strategy of combination of a DES to reduce the risk of subsequent repeat revascularisations with a short BMS-like DAPT regimen to reduce the risk of bleeding event is an attractive option for elderly patients who have PCI.

Funding Boston Scientific.

Introduction

Elderly people represent a fast-growing segment of the population, and because of their increased risk of coronary artery disease, they are also more likely to have percutaneous coronary interventions (PCI) than are younger people.[1,2] Management of coronary artery disease in elderly patients can be challenging as they often have more extensive and complex disease and are also more prone to bleeding complications when receiving antiplatelet agents than younger patients.[3]

The optimal PCI strategy for elderly patients remains ill defined, for both the type of stent and duration of dual antiplatelet therapy (DAPT) after intervention. A Scientific Statement[4] from the American Heart Association, American College of Cardiology, and American Geriatrics Society called for closure of the gap of evidence in cardiovascular care between elderly and younger patients, recognising that current guidelines were unable to provide evidence-based recommendations for treatment of older patients.

Current drug-eluting stents (DES) limit the risk of repeat revascularisations compared with bare-metal stents (BMS) in elderly patients.[5–7] Contemporary DES are also safer than are BMS in terms of stent thrombosis.[8–10] In view of the high incidence of complex lesions in elderly patients, these DES are therefore becoming an increasingly attractive option in this population. However, elderly patients regularly receive

Lancet 2018; 391: 41–50
Published Online November 1, 2017
http://dx.doi.org/10.1016/S0140-6736(17)32713-7

See Comment page 4

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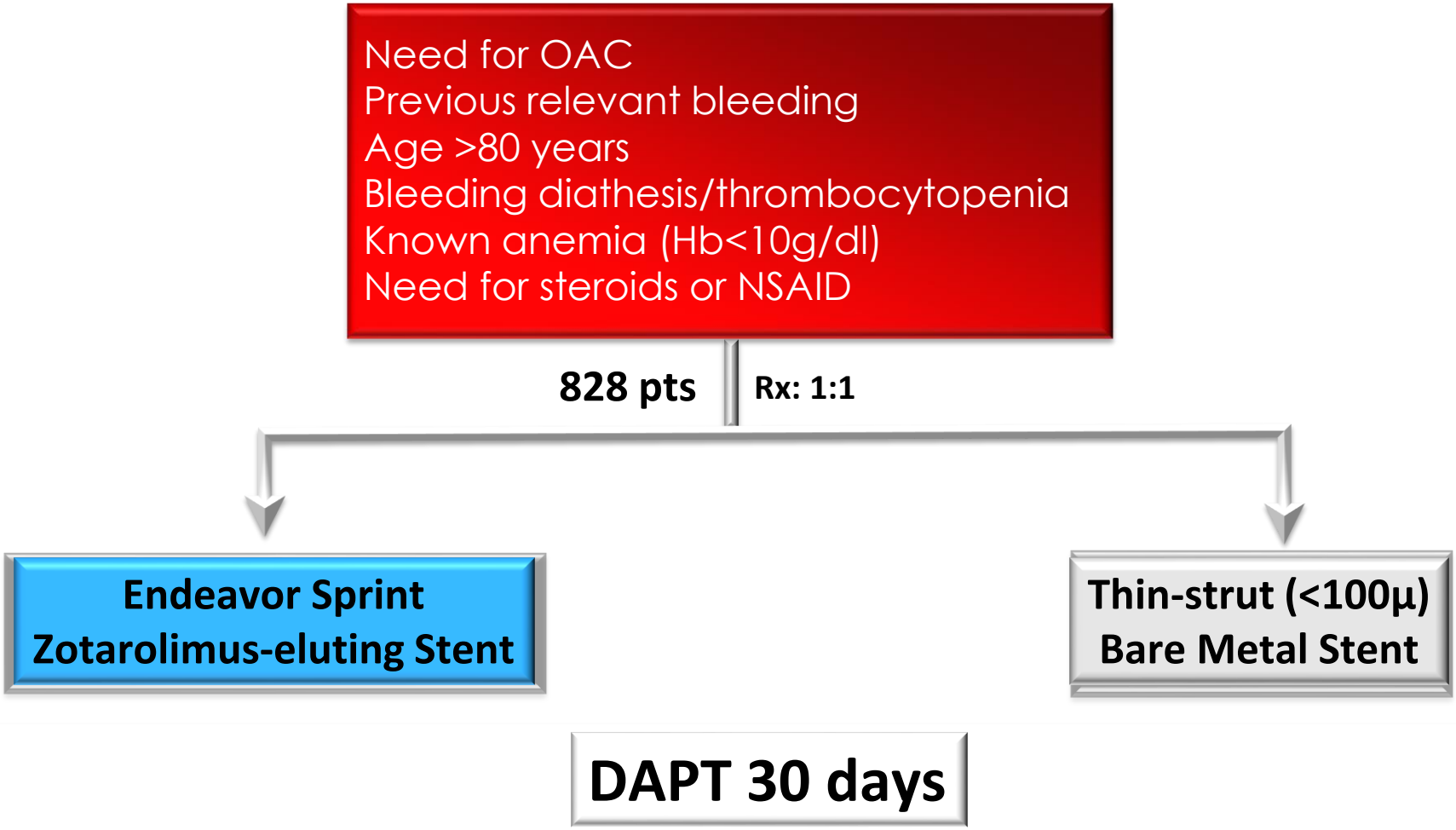
ZEUS-HBR study design

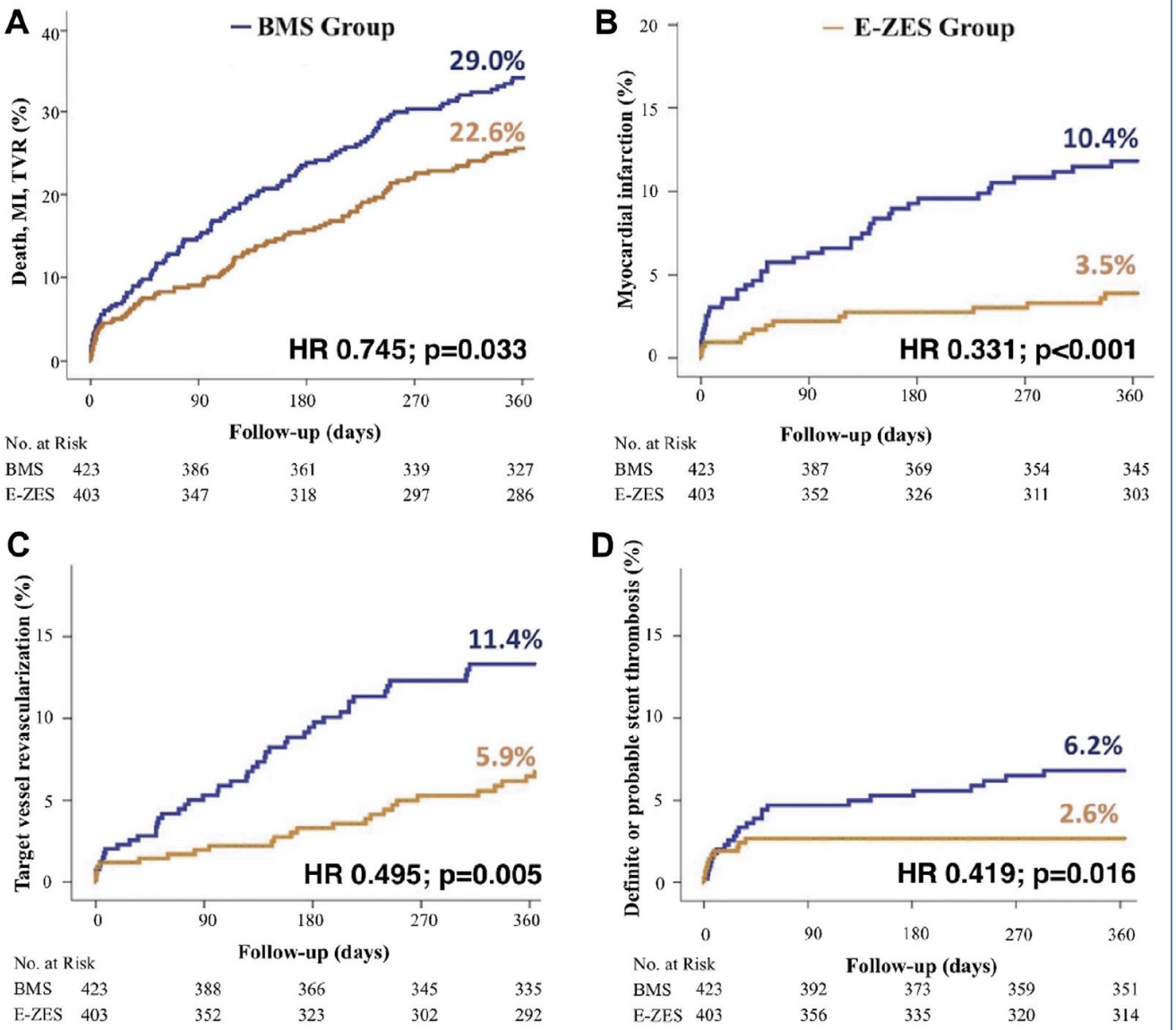
Urgent or emergent coronary stenting in patients fulfilling ≥1 of the below:



ZEUS

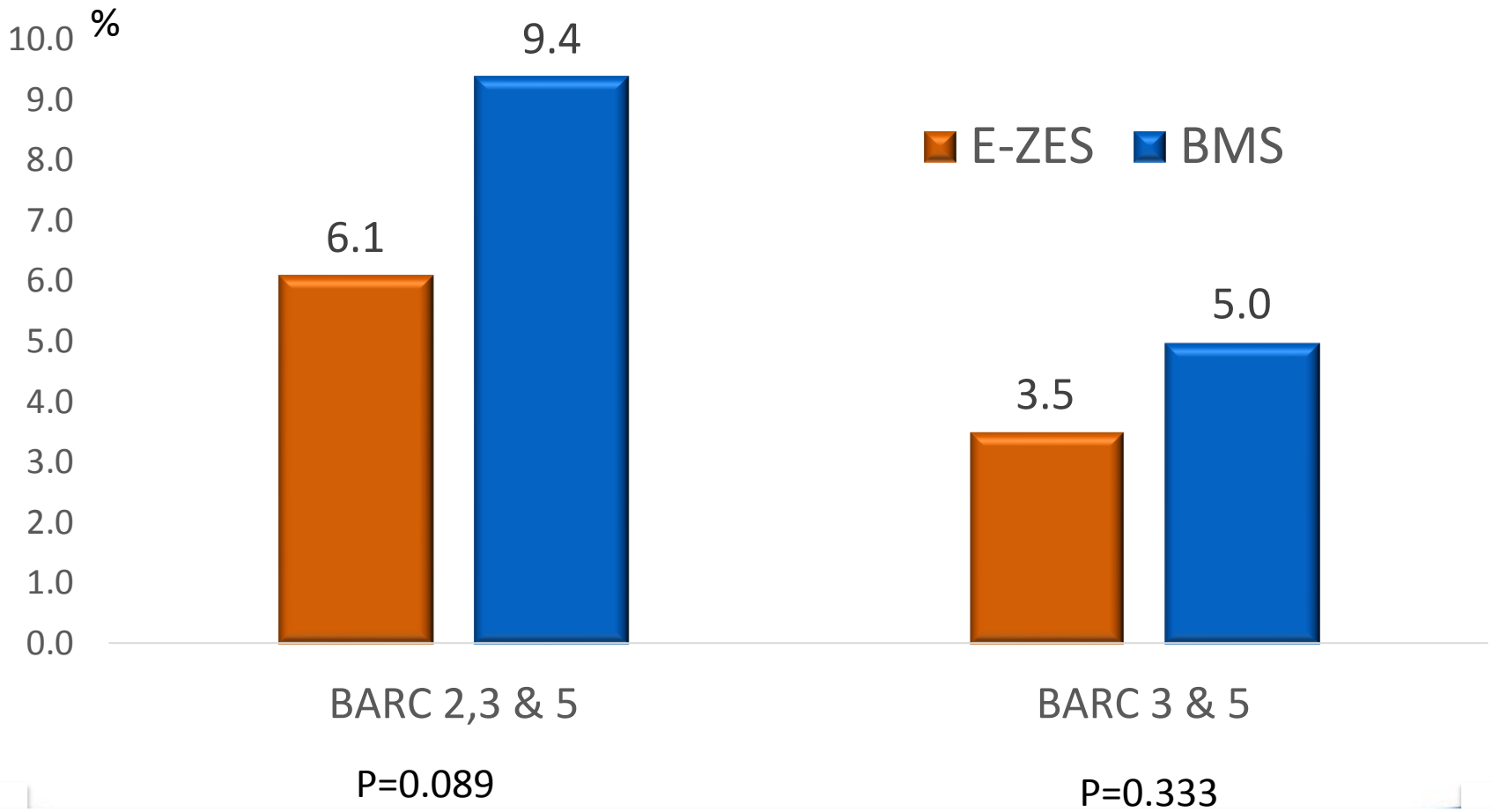
Primary EP

FIGURE 3 Clinical Outcomes in the HBR Population Treated With Zotarolimus-Eluting Stents Versus BMS



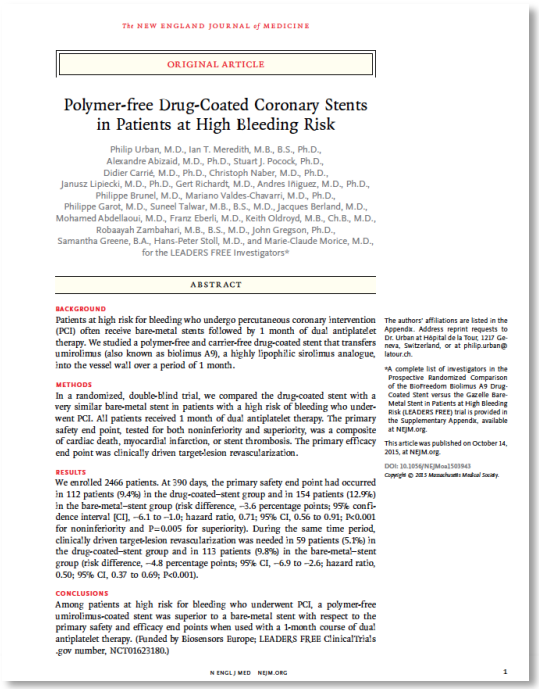
Ariotti S et al. JACC interv 2016; 9: 426-36

Bleeding for 828 HBR patients



3 completed trials of short DAPT (≤ 3 months) for HBR patients

LEADERS FREE



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*

ABSTRACT

BACKGROUND

Patients at high risk for bleeding who undergo percutaneous coronary intervention (PCI) often receive bare-metal stents followed by 1 month of dual antiplatelet therapy. We studied a polymer-free and carrier-free drug-coated stent that transfers umirolimus (also known as biolimus A9), a highly lipophilic sirolimus analogue, into the vessel wall over a period of 1 month.

METHODS

In a randomized, double-blind trial, we compared the drug-coated stent with a very similar bare-metal stent in patients with a high risk of bleeding who underwent PCI. All patients received 1 month of dual antiplatelet therapy. The primary safety end point, tested for both noninferiority and superiority, was a composite of cardiac death, myocardial infarction, or stent thrombosis. The primary efficacy end point was clinically driven target-lesion revascularization.

RESULTS

We enrolled 2466 patients. At 390 days, the primary safety end point had occurred in 112 patients (9.4%) in the drug-coated–stent group and in 154 patients (12.9%) in the bare-metal–stent group (risk difference, −3.6 percentage points; 95% confidence interval [CI], −6.1 to −1.0; hazard ratio, 0.71; 95% CI, 0.56 to 0.91; P<0.001 for noninferiority and P=0.005 for superiority). During the same time period, clinically driven target-lesion revascularization was needed in 59 patients (5.1%) in the drug-coated–stent group and in 113 patients (9.8%) in the bare-metal–stent group (risk difference, −4.8 percentage points; 95% CI, −6.9 to −2.6; hazard ratio, 0.50; 95% CI, 0.37 to 0.69; P<0.001).

CONCLUSIONS

Among patients at high risk for bleeding who underwent PCI, a polymer-free umirolimus-coated stent was superior to a bare-metal stent with respect to the primary safety and efficacy end points when used with a 1-month course of dual antiplatelet therapy. (Funded by Biosensors Europe; LEADERS FREE ClinicalTrials.gov number, NCT01623180.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Urban at Hôpital de la Tour, 1217 Geneva, Switzerland, or at philip.urban@latour.ch.

*A complete list of investigators in the Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk (LEADERS FREE) trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on October 14, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1508943

ZEUS HBR

JACC: CARDIOVASCULAR INTERVENTIONS
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 9, NO. 5, 2016
ISSN 1936-8798/$36.00
http://dx.doi.org/10.1016/j.jcin.2015.11.015

CLINICAL RESEARCH

CORONARY

Is Bare-Metal Stent Implantation Still Justifiable in High Bleeding Risk Patients Undergoing Percutaneous Coronary Intervention?

A Pre-Specified Analysis From the ZEUS Trial

Sara Ariotti, MD,[a,b] Marianna Adamo, MD,[b] Francesco Costa, MD,[b] Athanasios Pataliakas, MD,[c] Carlo Briguori, MD, PhD,[d] Attila Thury, MD, PhD,[e] Salvatore Colangelo, MD,[f] Gianluca Campo, MD,[g] Matteo Tebaldi, MD,[g] Imre Ungi, MD, PhD,[e] Stefano Tondi, MD,[h] Marco Roffi, MD,[c] Alberto Menozzi, MD, PhD,[i] Nicoletta de Cesare, MD,[b] Roberto Garbo, MD,[f] Emanuele Meliga, MD,[i] Luca Testa, MD, PhD,[g] Henrique Mesquita Gabriel, MD,[c] Marco Ferlini, MD,[i] Pascal Vranckx, MD, PhD,[c] Marco Valgimigli, MD, PhD,[c,b] for the ZEUS Investigators

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SENIOR

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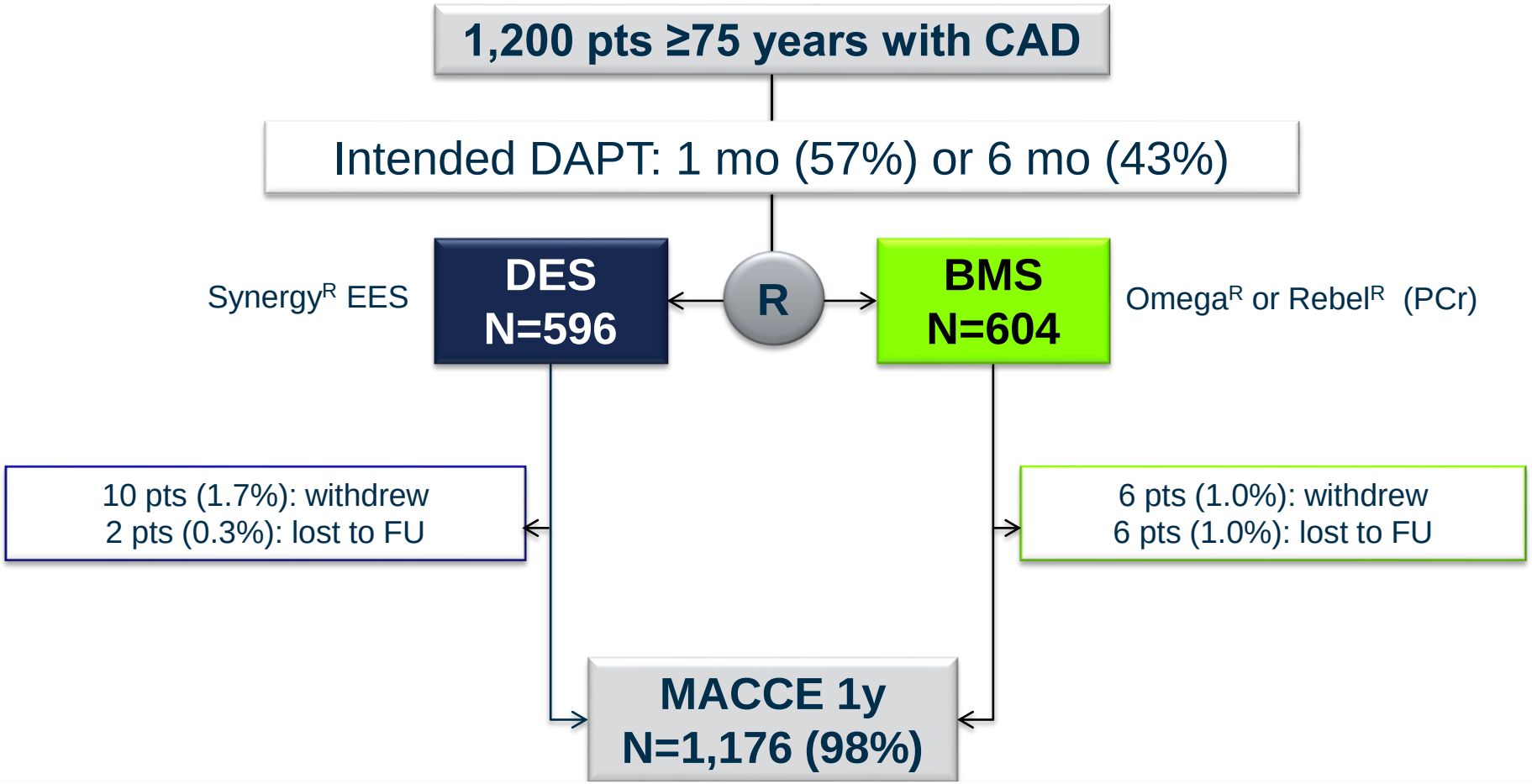
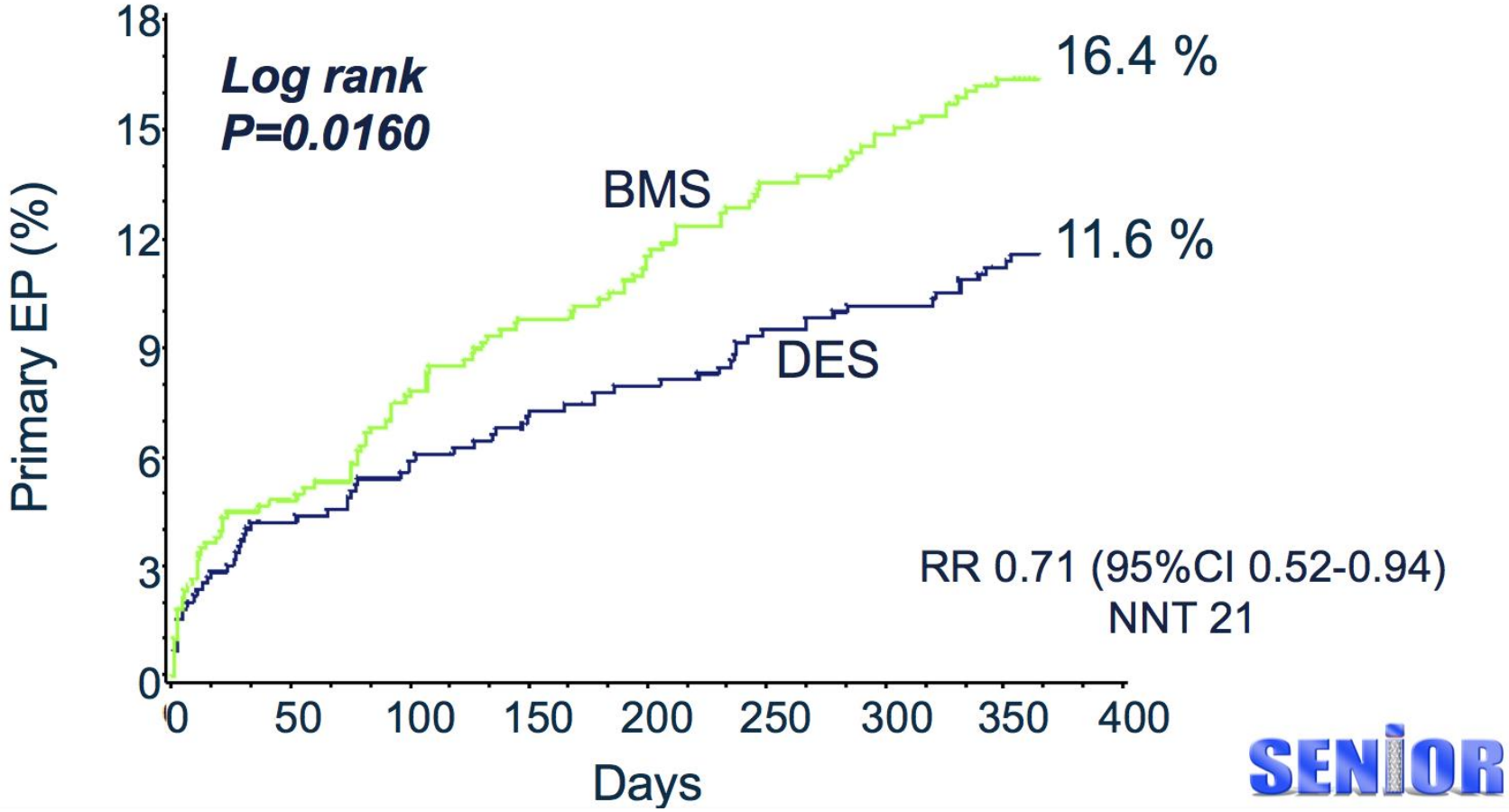
ARC HBR

SENIOR

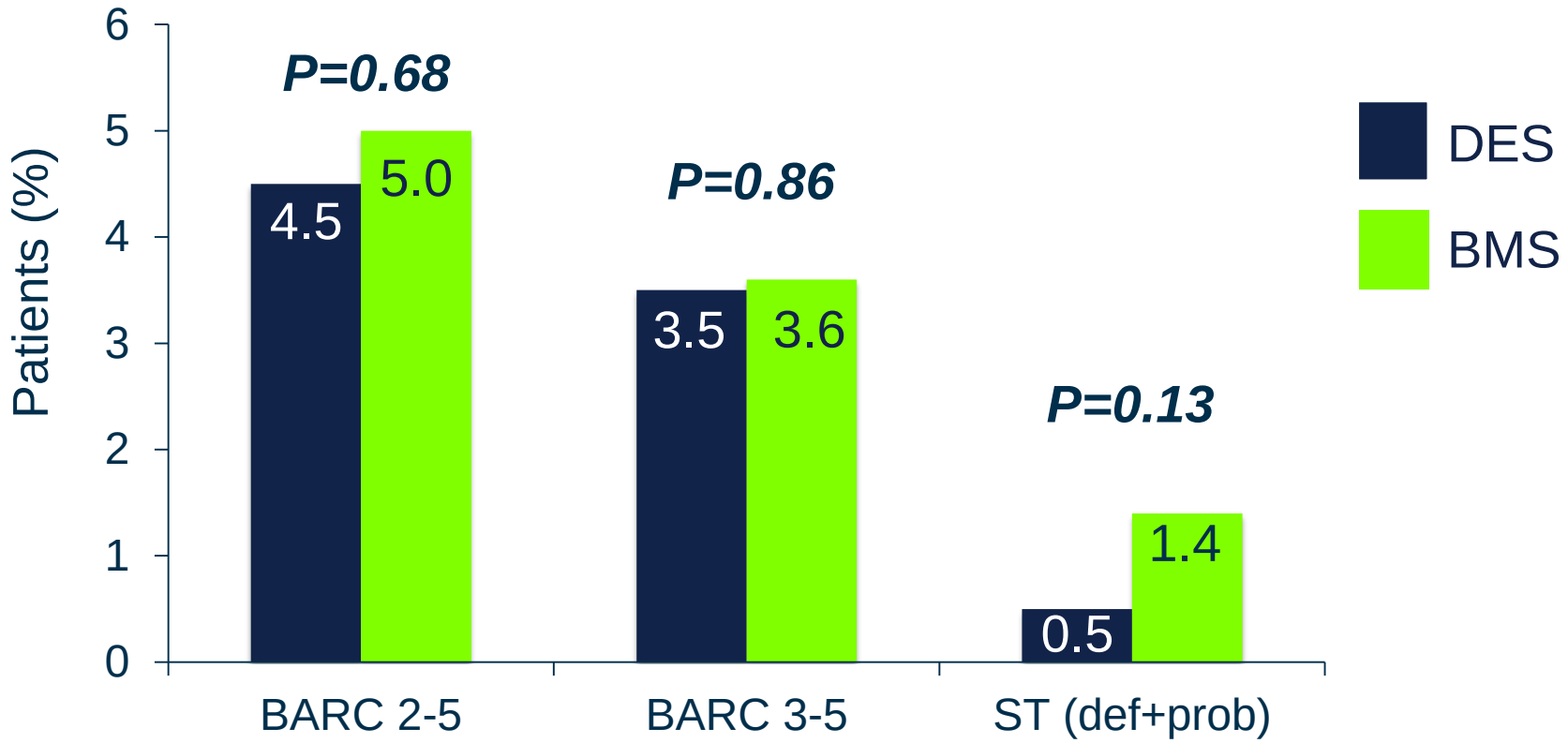


Primary End Point (MACCE)

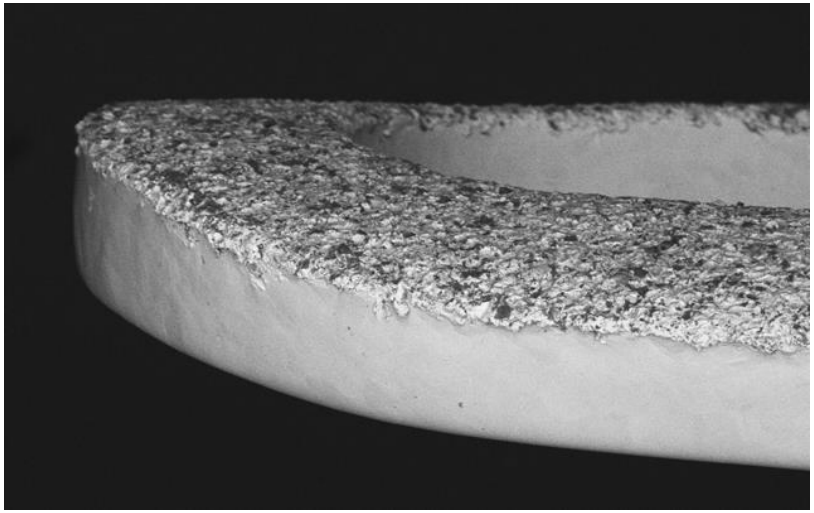
All-cause mortality, MI, stroke, ischemia-driven TLR



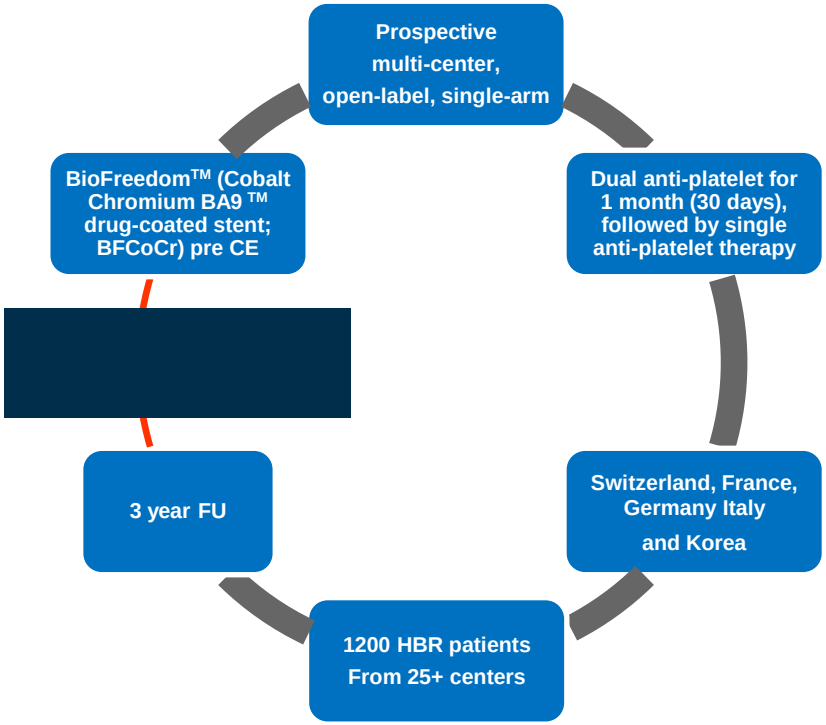
Safety Endpoints



LEADERS FREE III



CoCr thin struts (84-88 µm)



CERC Cardiovascular European Research

Conclusions

WHAT WE NOW KNOW:

- Most second generation DES can be used safely with shorter DAPT regimen but today, only Endeavor, Synergy and Biofreedom proved it in a prospective dedicated trial:
- For HBR patients, a DCS (LEADERS FREE) or a DES (ZEUS HBR and SENIOR) have superior efficacy over a BMS with a short DAPT course
- LEADERS FREE and ZEUS also documented superior safety of DCS/DES (in higher risk patients) results of Leaders free were confirmed in Leaders free 2 (pivotal trial for US) (no more role for BMS)
- Bleeding rates varied between the trials, reflecting the heterogeneous nature of the HBR population, justifying the ARC HBR initiative
- **WHAT WE STILL NEED TO KNOW:**
- Do stent characteristics matter for short DAPT (polymers, limus, kinetics)?
- What is the optimal DAPT duration for different HBR patients?
- Who exactly are the “HBR” patients? ARC HBR initiative