Supra Family Clinical Journey

Randomized Controlled Trials

Elderly MI+ Multivessel	Three-vessel Disease	Diabetic Multi Vessel	HBR PCI Population
FIRE TRIAL	Multivessel Talent	TUXEDO 2	COMPARE 60 80
1445 patients	1550 patients	1800 patients	732 patients

Registries

All-comers	All-comers	All-comers	Octo- and Nonagenerian All-comers
Cruz HBR	SFlex Netherlands Registry	S Flex UK Registry 2	Cruz Senior
1203 patients	7000 patients	1835 patients	2500 patients

Diameter (mm)	Length (mm)										
	8	12	16	20	24	28	32	36	40	44	48
2.00	FGTZ 200008	FGTZ 200012	FGTZ 200016	FGTZ 200020	FGTZ 200024	FGTZ 200028	FGTZ 200032	FGTZ 200036	FGTZ 200040	FGTZ 200044	FGTZ 200048
2.25	FGTZ 225008	FGTZ 225012	FGTZ 225016	FGTZ 225020	FGTZ 225024	FGTZ 225028	FGTZ 225032	FGTZ 225036	FGTZ 225040	FGTZ 225044	FGTZ 225048
2.50	FGTZ 250008	FGTZ 250012	FGTZ 250016	FGTZ 250020	FGTZ 250024	FGTZ 250028	FGTZ 250032	FGTZ 250036	FGTZ 250040	FGTZ 250044	FGTZ 250048
2.75	FGTZ 275008	FGTZ 275012	FGTZ 275016	FGTZ 275020	FGTZ 275024	FGTZ 275028	FGTZ 275032	FGTZ 275036	FGTZ 275040	FGTZ 275044	FGTZ 275048
3.00	FGTZ 300008	FGTZ 300012	FGTZ 300016	FGTZ 300020	FGTZ 300024	FGTZ 300028	FGTZ 300032	FGTZ 300036	FGTZ 300040	FGTZ 300044	FGTZ 300048
3.50	FGTZ 350008	FGTZ 350012	FGTZ 350016	FGTZ 350020	FGTZ 350024	FGTZ 350028	FGTZ 350032	FGTZ 350036	FGTZ 350040	FGTZ 350044	FGTZ 350048
4.00	FGTZ 400008	FGTZ 400012	FGTZ 400016	FGTZ 400020	FGTZ 400024	FGTZ 400028	FGTZ 400032	FGTZ 400036	FGTZ 400040	FGTZ 400044	FGTZ 400048
4.50	FGTZ 450008	FGTZ 450012	FGTZ 450016	FGTZ 450020	FGTZ 450024	FGTZ 450028	FGTZ 450032	FGTZ 450036	FGTZ 450040	FGTZ 450044	FGTZ 450048

Caution: This product is intended for use by or under the direction of a physician. Prior to use, refer to the "Instructions for use" supplied with these devices for indications, contraindications, side effects, suggested procedure warnings and precautions. As part of our continuous product development policy we reserve the right to change product specifications without prior notification. Information contained herein for distribution outside the USA, Japan & France only. Check the regulatory status of the device before distribution in areas where CE marking is not the regulation in force. Tests performed by and data on file at Sahajanand Medical Technologies Limited. Illustrations are artist's representations only and should not be considered as engineering drawings or photographs. Photos on file at Sahajanand Medical Technologies Limited.

Specifications are subject to modification, revision and improvement.

Registered Office: Sahajanand Medical Technologies Limited
'Sahajanand Estate', Wakharia Wadi, Near Dabholi Char Rasta, Ved Road, Surat 395004, Gujarat, INDIA Tel.: +91 261 6112800
Fax: +91 261 6112801 • CIN: U33119GJ2001PLC040121 • www.smtpl.com

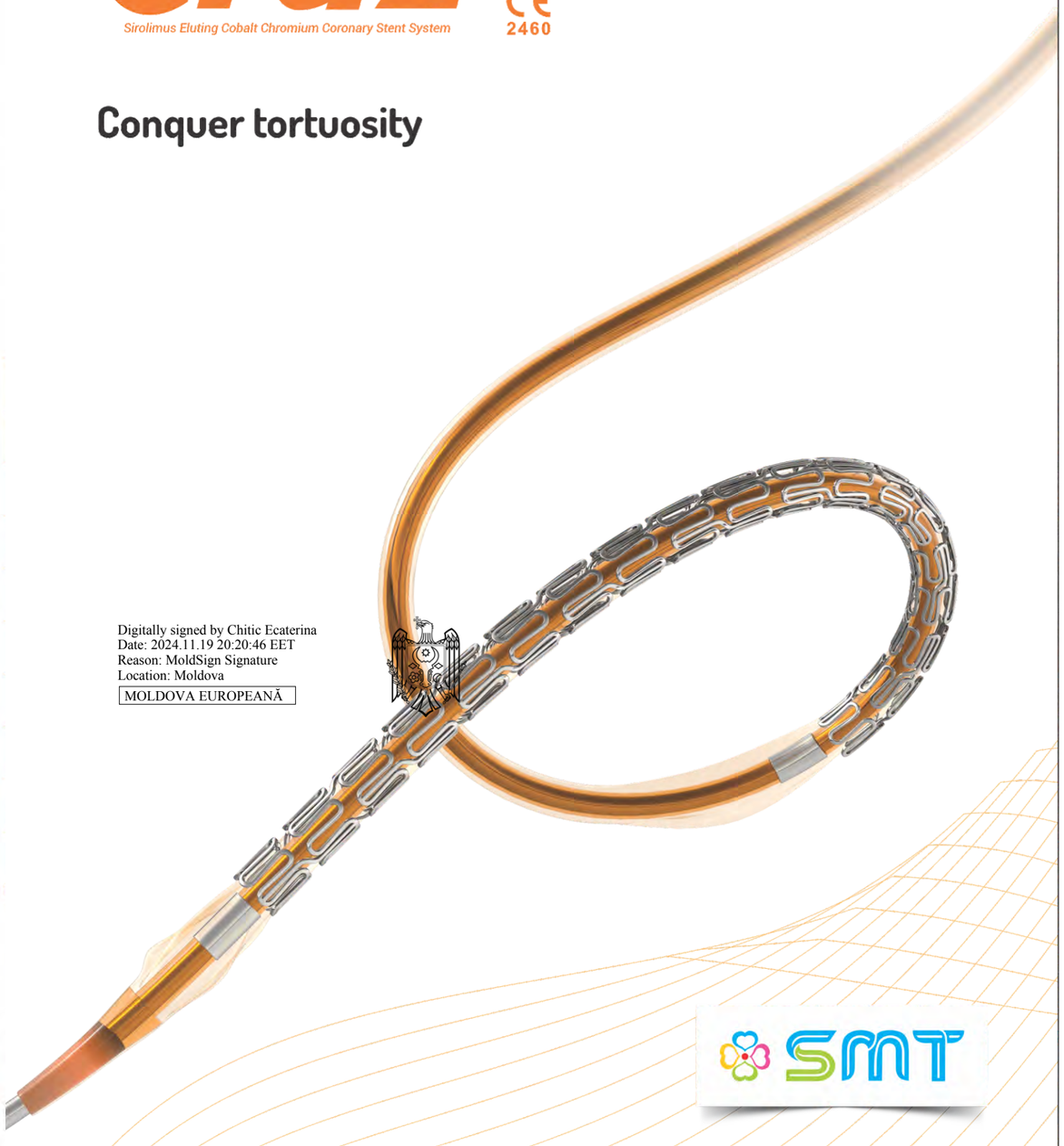
TZ/BRO/EN02 REV 09

Supraflex™ Cruz

CE 2460

Sirolimus Eluting Cobalt Chromium Coronary Stent System

Conquer tortuosity

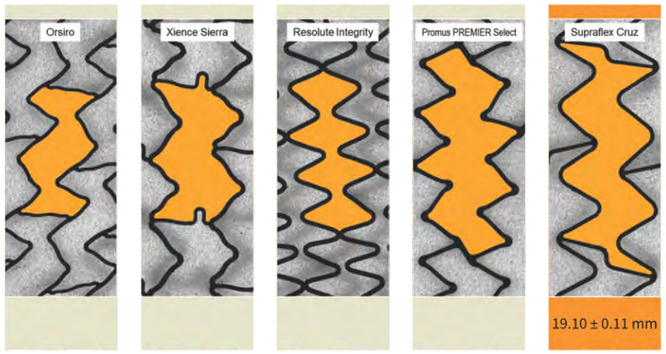


Conquer tortuosity

Supraflex™ Cruz

Sirolimus Eluting Cobalt Chromium Coronary Stent System

Cell Perimeter[1] (mm)
(For 3.00 mm stent diameter)



Comprehensive Overexpansion Limits*

Hydrophilic Coating
For reducing friction

Alternate **LDZ link** to navigate through tortuosity

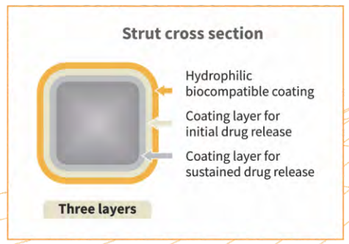
Low Tip Entry Profile[2] (mm)

0.56	0.52	0.45	0.41
Xience Sierra	Synergy	Resolute Onyx	**Supraflex Cruz**

Profile in the Crimped State[2] (mm)

0.97	1.00	1.00	1.01
Supraflex Cruz	Resolute Onyx	Synergy	Xience Sierra

Unique Blend of Biodegradable Polymers



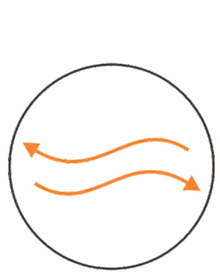
*Reference: 1. Eur J Med Res. 2021 Oct 12;26(1):121. http://doi.org/10.1186/s40001-021-00595-7. 2. Data from independent Research: Tests performed by Institute for Implant Technology and Biomaterials-IIB E.V, Associated Institute of the University of Rostock, Warnemuende, Rostock, Germany (June 29th, 2021). *As per IFU*

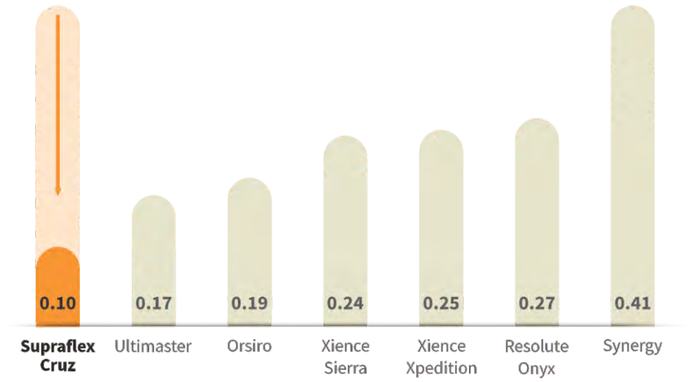
Conquer tortuosity

Supraflex™ Cruz
Sirolimus Eluting Cobalt Chromium Coronary Stent System

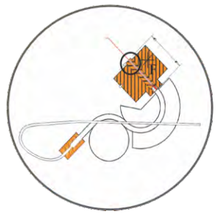
Deliverability[3,4]

'Supraflex Cruz exhibited the low mean push force required to pass the device compared with other widely used DES' - **Published Data**[3]





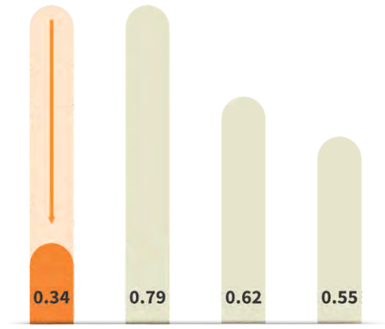
Mean push force in Newton (N) for stents with 38 to 40 mm length

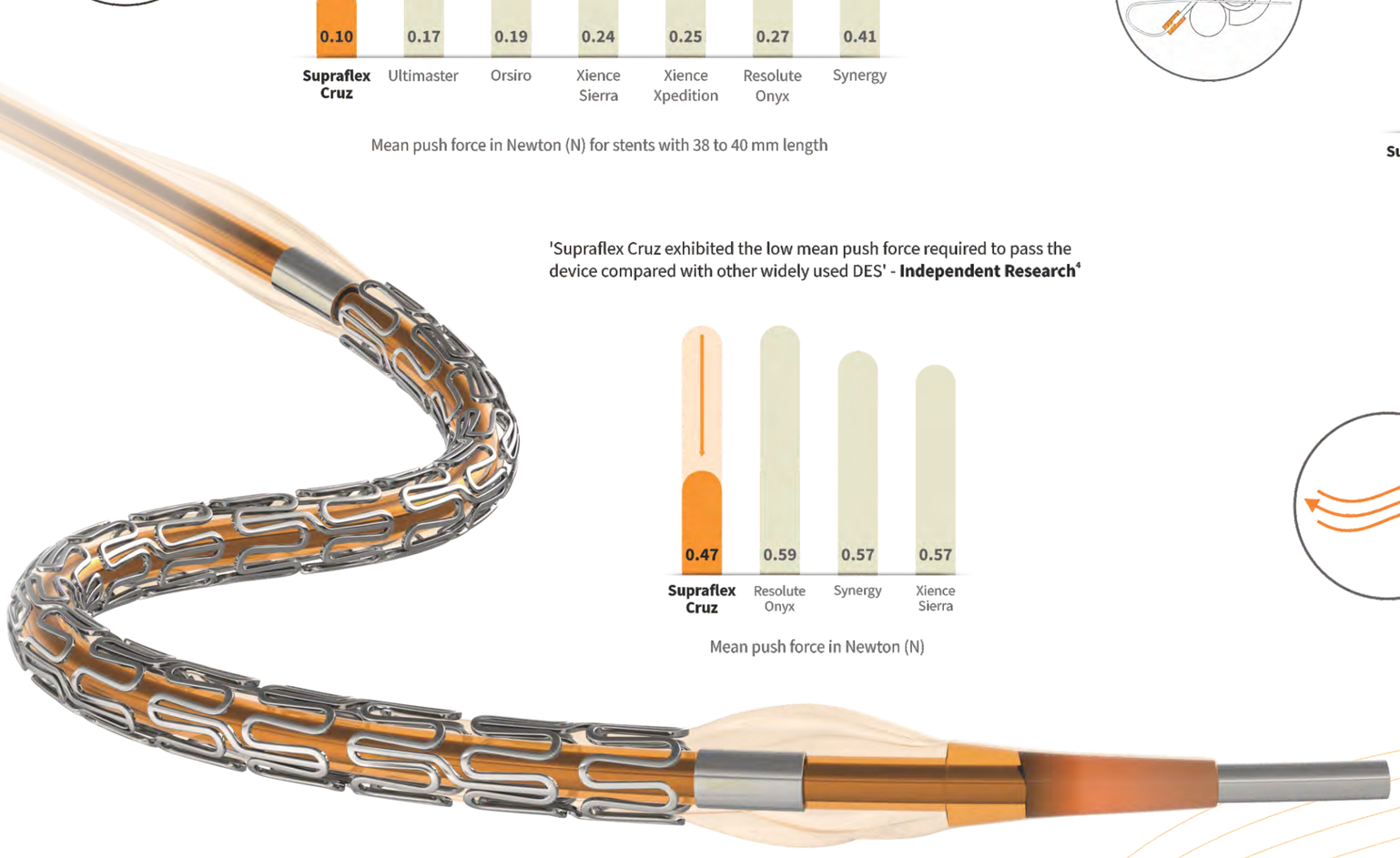


Crossability (N)

(Data from Independent Research[4])

Supraflex Cruz crosses the lesion model with the low force at hub level





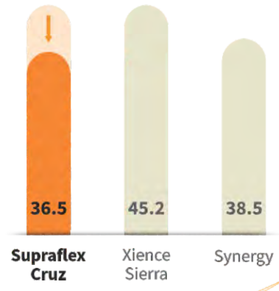
'Supraflex Cruz exhibited the low mean push force required to pass the device compared with other widely used DES' - **Independent Research**[4]

Mean push force in Newton (N)

Pushability (%)

(Data from Independent Research[4])

Supraflex Cruz requires low push force (%)



Reference: 3. Future Cardiol. 2021 Mar;17(2):227-237. doi: 10.2217/fca-2019-0083.
4. Data from independent Research: Tests performed by Institute for Implant Technology and Biomaterials-IIB E.V, Associated Institute of the University of Rostock, Warnemuende, Rostock, Germany. (June 29th, 2021)

Conquer tortuosity

Supra Family Clinical Journey

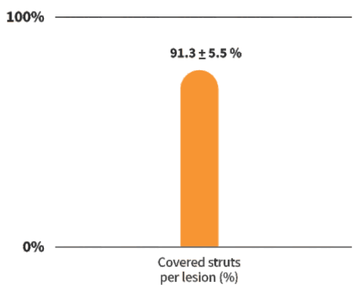
Supraflex™ Cruz
Sirolimus Eluting Cobalt Chromium Coronary Stent System

OCT Data @ 35 days & 6 months

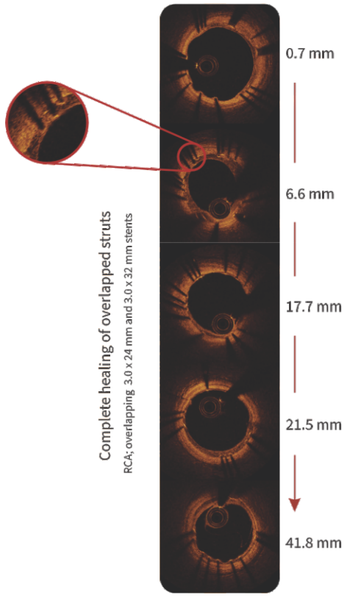
SiBi Study[5]

35.3 ± 5 days

Patients n = 29
Struts n = 14,024



'91.3% endothelialisation in Supraflex Cruz at 4–6 weeks as per the SiBi study.'[5]



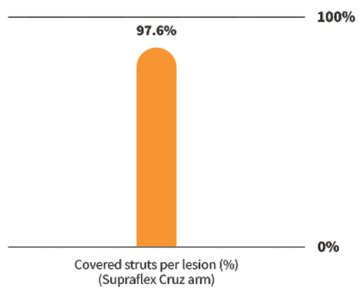
OCT images acquired at 34 days after stent implantation;
880 struts analysed; 97.4% covered struts; 0.22% malapposed struts;
NIH thickness: 105.5 µm

'The result of **SiBi study** provides reasonable justification for early termination of **DAPT** in **HBR** patients, if warranted.'

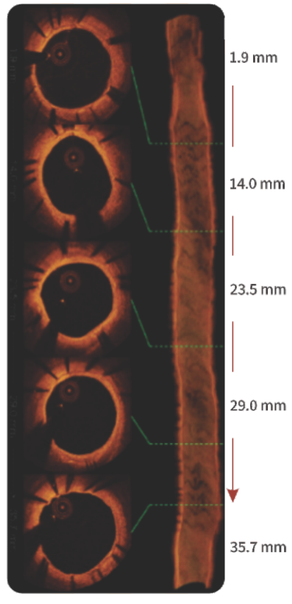
TAXCO Study[6]

6 months

Patients n = 21
Struts n = 9,968



'97.6% endothelialisation in the Supraflex Cruz at 6 months as per the TAXCO study.'[6]



6 months optical coherence tomography
follow-up from the TAXCO study

References : 5. Catheter Cardiovasc Interv. 2021 Dec 1:98(7):1335-1342. doi: 10.1002/ccd.29371. 6. Catheter Cardiovasc Interv. 2021 Feb 15:97(3):423-430. doi: 10.1002/ccd.28833.
OCT: Optical coherence tomography; DAPT: Dual antiplatelet therapy; HBR: High bleeding risk; NIH: Neointimal hyperplasia.

Supraflex Cruz in FIRE TRIAL

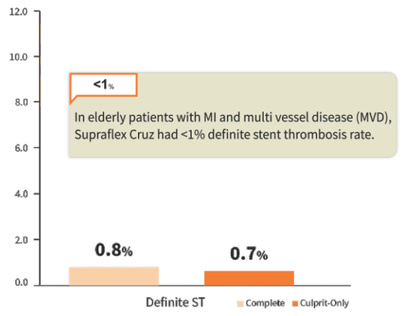
<2% in-stent restenosis rate in complex patients.

Complex patients in FIRE Trial[7]

80 years Age	**35%** STEMI	**65%** NSTEMI	**32%** Diabetes
82% Hypertension	**46%** GFR rate <60 ml/min	**15%** Previous MI	**36%** Female patients

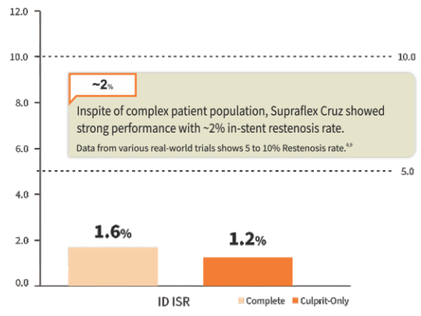
Performance of Supraflex Cruz in FIRE Trial

Definite Stent Thrombosis[7]



<1%
In elderly patients with MI and multi vessel disease (MVD), Supraflex Cruz had <1% definite stent thrombosis rate.

In-Stent Restenosis[8]



~2%
Inspite of complex patient population, Supraflex Cruz showed strong performance with ~2% in-stent restenosis rate.
Data from various real-world trials shows 5 to 10% Restenosis rate.[8,9]

The FIRE Trial confirms Supraflex Cruz stent's strong performance in treating extremely complex patient population.[7]

TLF @ 1 year in various **Indications**

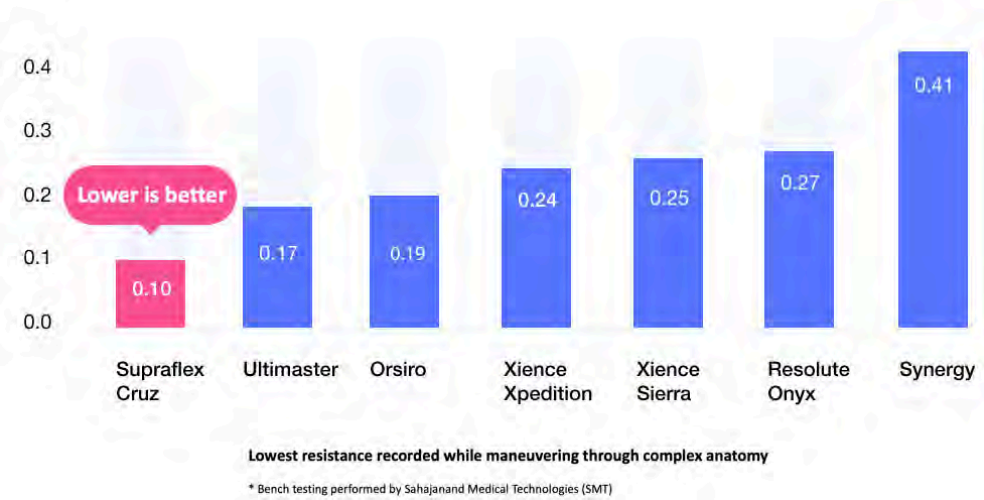
Diabetes[10] 6.9%	**Long lesion (≥28 mm)**[11] 6.6%	**Multi-vessel disease**[12] 6.4%
Small vessel (≤2.5 mm)[13] 6.1%	**ACS**[14] 5.3%	**Total occlusion**[15] 5.2%
STEMI[16] 6.2%	**Female**[17] 4.9%	**Young (≤45 years)**[18] 4.4%

References:
7. N Engl J Med 2023; 389:889-898. DOI: 10.1056/NEJMoa2300468. 8. J Am Coll Cardiol 2020; 76:1521-1531. DOI: 10.1016/j.jacc.2020.08.002. 9. EuroIntervention 2021; 17:355-357. DOI: 10.4244/EIJV17I5A60.
10. Abstracts of PCR e-Course 2020, Vol. 16, Suppl. AC, June 2020 (EuroZOA-POS624). 11. Abstracts of PCR e-Course 2020, Vol. 16, Suppl. AC, June 2020 (EuroZOA-POS703). 12. Abstracts of PCR e-Course 2020, Vol. 16, Suppl. AC, June 2020 (EuroZOA-POS646). 13. Abstracts of PCR e-Course 2020, Vol. 16, Suppl. AC, June 2020 (EuroZOA-POS651). 14. Abstracts of PCR e-Course 2020, Vol. 16, Suppl. AC, June 2020 (EuroZOA-POS650). 15. Abstracts of PCR e Course 2020, Vol. 16, Suppl. AC, June 2020 (EuroZOA-OP124). 16. Abstracts of PCR e-Course 2020, Vol. 16, Suppl. AC, June 2020 (EuroZOA-POS623). 17. Abstracts of PCR e-Course 2020, Vol. 16, Suppl. AC, June 2020 (EuroZOA-POS702). 18. Abstracts of PCR e-Course 2020, Vol. 16, Suppl. AC, June 2020 (EuroZOA-POS899). # Analysis from the FIRE Trial database.

STEMI - ST-Elevation Myocardial Infarction, NSTEMI - Non-ST-Elevation Myocardial Infarction, GFR- Glomerular Filtration Rate, ID ISR - Ischemia Driven In-Stent Restenosis, ST - Stent Thrombosis, MI - Myocardial Infarction, ACS: Acute coronary syndrome.


Supraflex™
Cruz
Sirolimus Eluting Cobalt Chromium Coronary Stent System
CE
2460
Conquer tortuosity

Mean push force in Newton (N) for stents with 38 to 40mm length



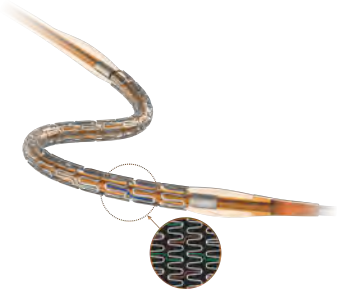
Bench test results may not necessarily be indicative of clinical performance. Test performed by and data on file at Sahajanand Medical Technologies Ltd. Testing performed on Supraflex Cruz Stent System (2.50 x 40 mm) n=5, Ultimaster Stent System (2.5 x 38 mm) n=4, Orsiro Stent System (2.50 x 40 mm) n=5, Xience Sierra Stent System (2.5 x 38 mm) n=4, Xience Xpedition Stent System (2.5 x 38 mm) n=5, Resolute Onyx Stent System (2.5 x 38 mm) n=4, Synergy Stent System (2.5 x 38 mm) n=5. Catheter performance test measures average force to cross a challenging path model

Proprietary 'LDZ' link

Improves flexibility of the stent

Transmits 'Push force' with higher efficiency

Improves overall radial strength



Resists longitudinal compression

Open-Cell Design

Better flexibility

Better side-branch access

Unique blend of hydrophilic-hydrophobic biodegradable polymers from the pioneers in the biodegradable polymer technologies.

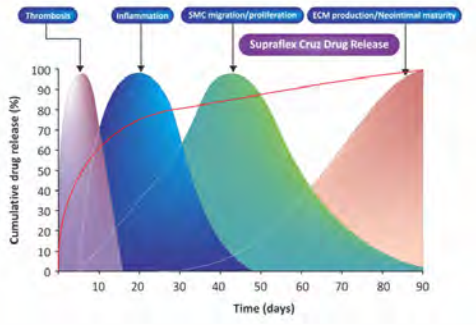
Blend of biodegradable polymers

PLLA: Poly-L-lactide
Hydrophobic

PLCL: Poly L-Lactide-co-Caprolactone
Hydrophobic

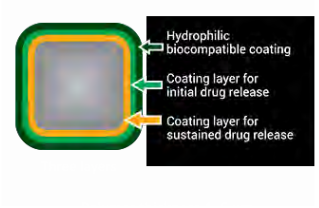
PVP: Polyvinyl Pyrrolidone
Hydrophilic

Drug: Sirolimus
Drug dose: 1.4 μg/mm^2

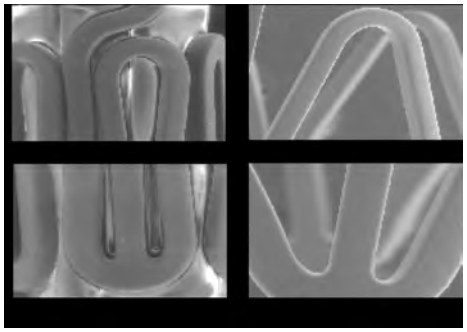


Nearly 80% of drug is released within one month (initial burst). Remaining drug is programmed to get released for 3 months. Designed to cover the entire period of arterial wound healing in real-world patients.

Strut Cross section

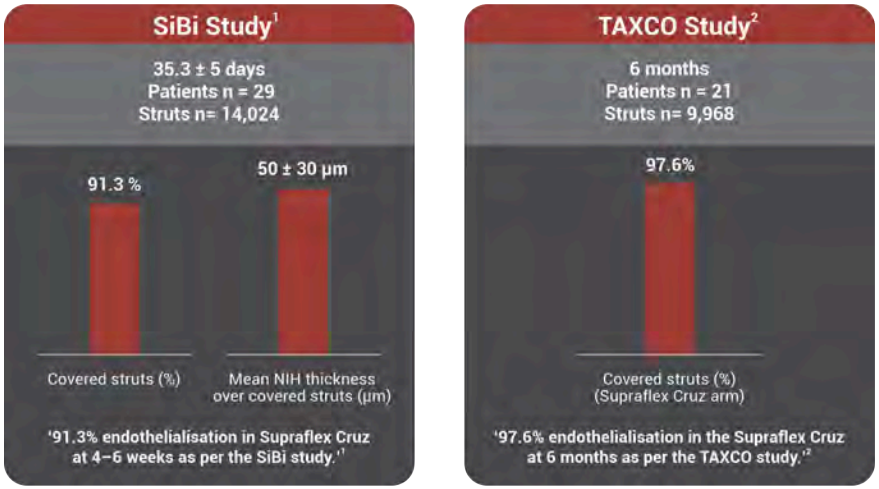


Scanning Electron Microscopy (SEM)



Polymer coating is elastomeric which does not tear off while expansion of stent
No peeling, flaking, cracking of polymer
No webbing formation of polymer during the shelf life of the stent
Proprietary technology ensures complete coating at the outer and inner curves

OCT healing pattern of Supraflex Cruz



NIH: Neointimal hyperplasia

1.Abhyankar, A, Abizaid, A, Chamié, D, Patel, G. SiBi optical coherence tomography study. Catheter Cardiovasc Interv. 2020; 1– 8. https://doi.org/10.1002/ccd.29371 (https://doi.org/10.1002/ccd.29371)

2. Presented at EuroPCR 2019, 22 May 2019 12:15 - 13:15 Room 243 / Level 2

Extensive size range so that there is no compromise

Diameter \ Length	8 mm	12 mm	16 mm	20 mm	24 mm	28 mm	32 mm	36 mm	40 mm	44 mm	48 mm
2.00 mm	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2.25 mm	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2.50 mm	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2.75 mm	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3.00 mm	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3.50 mm	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
4.00 mm	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
4.50 mm	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Long lengths (44mm & 48mm) available.

Overexpansion limits

	Nominal diameter (mm)	Post-Dilatation limit (mm)
Small vessel (4 Crown)	2.00 2.25	3.25
Medium vessel (6 Crown)	2.50 2.75 3.00 3.50	4.25
Large vessel (8 Crown)	4.00 4.50	5.50

Instructions for use **Gebrauchsanweisung** **Instrucciones de uso** **Instructions d'utilisation**

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Supraflex Cruz

Sirolimus Eluting Cobalt Chromium Coronary Stent System

Instructions for use

STERILE EO

CE 2460

SMT

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1.0. Product Description

The **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent system is a combination product comprised of two regulated components: a device (Tetrinium™ coronary stent system as platform) and a drug product (a formulation of Sirolimus drug with the blend of biodegradable polymers).

1.1. Device Component Description

The **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent system consists of a balloon expandable Sirolimus-eluting stent, premounted on a stent delivery system. The physical characteristics of the device component are shown in Table 1.

Table 1- Device Component Description

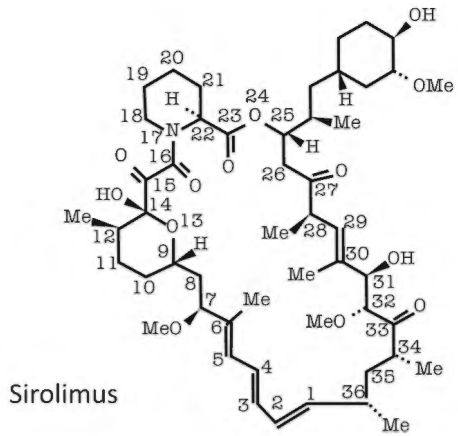
SUPRAFLEX CRUZ™ Sirolimus-eluting Coronary Stent System	
Available Stent Lengths, (mm)	8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48
Available Stent Diameters (mm)	2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 4.50
Stent Material	L-605 Co-Cr Alloy
Stent Design	Laser cut from seamless tubing in a serpentine pattern
Stent Platform	Tetrinium™
Drug	Sirolimus
Polymers Type	Biodegradable Polymers
Delivery System Usable Length	1400 mm (140 cm)
Delivery System Y - Adapter Ports	Single access port to inflation/deflation lumen. A guidewire exit port is located 25 cm away from the tip. Designed for guidewire of Ø 0.014 inch.
Stent Delivery Balloon	Polyamide balloon, nominally 1 mm longer than the stent. Mounted stent length and location is defined by two radio opaque markers at proximal and distal ends of the stent.
Catheter Shaft Outer Diameter	Proximal : 0.72 mm Distal : 0.95 mm
Balloon Inflation Pressure	*NP: 8 atm for 2.00 & 2.25 mm,10 atm for 2.50 to 3.00 mm, 11 atm for 3.50 to 4.50 mm RBP: 16 atm
Guiding Catheter	5 F compatible (min.)
Guidewire Diameter	0.014 inch

*Assure full deployment of the stent (See section 11.5 Deployment Procedure). Deployment pressures should be based on lesion characteristics.
Note: 1F is equivalent to 0.33 mm. NP: Nominal Pressure, RBP: Rated Burst Pressure. 1 atm =1.01 bar

1.2. Drug Component Description

The active pharmaceutical ingredient in the **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent is Sirolimus (also known as Rapamycin).

Sirolimus is a macrocyclic lactone produced by Streptomyces hygroscopicus. The chemical name (IUPAC) of Sirolimus is [3S [3R* [S* (1R*, 3S*, 4S*)), 6S*, 7E, 9S*, 10S*, 12S*, 14R*, 15E, 17E, 19E, 21R*, 23R*, 26S*, 27S*, 34aR*]] - 9, 10, 12, 13, 14, 21, 22, 23, 24, 25, 26, 27, 32, 33, 34, 34 a - Hexadecahydro – 9, 27-dihydroxy - 3 - [2 - (4 - hydroxy - 3 methoxycyclohexyl) -1 methylethyl] - 10, 21 - dimethoxy - 6, 8, 12, 14, 20, 26 - hexamethyl - 23, 27 - epoxy 3H pyrido [2, 1 - c] [1, 4] oxaazacyclohentriacontine - 1, 5, 11, 28, 29 (4H, 6H, 31H) - pentone. Its molecular formula is $C_{51}H_{79}NO_{13}$ and its molecular weight is 914.19 g/mol. The structural formula of Sirolimus is shown below:



Sirolimus is white or off-white powder and soluble in methanol, ethanol, acetone, ethyl acetate, dichloromethane and chloroform. It is sparingly soluble in ethyl ether, hexane and petroleum ether and insoluble in water.

The inactive ingredient in the **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent is a combination of biocompatible, biodegradable polymers formulated to provide programmed release of the drug. The polymeric chains are cleaved by hydrolysis to form monomeric acids and are eliminated from the body through Kreb's cycle, primarily as carbon dioxide (CO_2) and water (H_2O) which are excreted through urine.

The active ingredient, Sirolimus nominal content per stent ranges from 33 to 309 µg as per stent length

2.0. Indications

The **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent system is indicated for improving coronary luminal diameter in patients with symptomatic ischemic heart disease due to discrete de-novo stenotic lesions and in-stent restenotic lesions in native coronary arteries with a reference vessel diameter from 2.00 mm to 4.50 mm.

3.0. Contraindications

Use of the **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent system is contraindicated in the following patient types:

- Patients with contraindication for antiplatelet/anticoagulant therapy.
- Patients judged to have lesion that prevents complete inflation of an angioplasty balloon.
- Known hypersensitivity to Sirolimus or its derivatives.
- Known allergy to Cobalt Chromium.
- Known allergy to biodegradable polymers
- Polymers might enhance inflammatory reactions and prothrombotic response.

4.0. Warnings

- Please ensure that the inner package has not been opened or damaged as this may indicate the sterile barrier has been breached.
- The use of this product carries the risks associated with coronary artery stenting, including subacute thrombosis, vascular complications, and/or bleeding events.

- Persons allergic to L-605 cobalt chromium alloy or Sirolimus or the polymers may suffer an allergic reaction to this implant.
- For single patient use only. Do not reuse, reprocess or resterilize. Reuse, reprocessing or resterilization may compromise the structural integrity of the device and/or lead to device failure which, in turn, may result in patient injury, illness or death. Reuse, reprocessing or resterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient.

5.0. Precautions

5.1. General Precautions

5.1.1 General Precautions

- Only physicians who have received adequate training should perform implantation of the stent.
- Stent placement should only be performed at hospitals where emergency coronary artery bypass graft surgery can be readily performed.
- Subsequent stent blockage may require repeat dilatation of the arterial segment containing the stent. The long-term outcome following repeat dilatation of endothelialized stents is not well characterized.
- Consideration should be given to the risks and benefit of use in patients with history of severe reaction to contrast agents.
- Do not expose the delivery system to organic solvents such as alcohol or detergents.
- Care should be taken to control the position of the guide catheter tip during stent delivery, deployment and balloon withdrawal.
- The use of **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stents in patients and lesions like more tortuous anatomy, may have an increased risk of adverse event including stent thrombosis, stent embolization, myocardial infarction or death.

Overexpansion -Post-Deployment Dilatation

The stents should not be expanded to a diameter beyond the maximum labelled diameter listed on the label per IFU. Do not dilate the stent beyond the following limits:

Nominal Stent Diameter	Dilation Limit
2.00-2.25 mm	3.25 mm
2.50-3.50 mm	4.25 mm
4.00-4.50 mm	5.50 mm

5.1.2 Oral Antiplatelet Therapy

Antiplatelet drugs should be used in combination with the **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent system, per the latest guidelines [the American College of Cardiology, and the American Heart Association (ACC/AHA) or the European Society of Cardiology (ESC)].

It is very important that the patient is compliant with the post-procedural antiplatelet recommendations given by their physician. Premature discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, myocardial infarction or death. Prior to PCI, if a surgical or dental procedure is anticipated that requires early discontinuation of antiplatelet therapy, the interventional cardiologist and patient should carefully consider whether a drug-eluting stent and its associated recommended antiplatelet therapy is the appropriate PCI choice. Following PCI should a surgical or dental procedure be recommended that requires suspension of antiplatelet therapy, the risks and benefits of the procedure should be weighed against the possible risk associated with premature discontinuation of antiplatelet therapy.

In selected higher risk patients where the physician determines that the risks outweigh the benefits of continued DAPT, it may be reasonable to interrupt or discontinue therapy earlier, but not before one month. Early optical coherence tomography study of **SUPRAFLEX CRUZ™** showed adequate healing at 4–6 weeks which supports the safe discontinuation of DAPT in high bleeding risk patients if considered necessary.[1] The decision to interrupt or discontinue DAPT is the responsibility of the treating physician, taking into consideration the individual patient's condition.

Patients who require premature discontinuation of antiplatelet therapy secondary to significant active bleeding should be monitored carefully for cardiac events and, once stabilized, have their antiplatelet therapy restarted as soon as possible per the discretion of their treating physicians.

Reference:

[1]Abhyankar A, Abizaid A, Chamié D, Patel G. Healing and early stent coverage after ultrathin strut biodegradable polymer-coated sirolimus-eluting stent implantation: SiBi optical coherence tomography study. Catheter Cardiovasc Interv. 2020 Nov 28. doi: 10.1002/ccd.29371.

5.2. Use of Multiple Stents

A patient's exposure to drug and polymer is proportional to the number and total length of implanted stents. When multiple stents are required, resulting in stent-to-stent contact, stents should be of similar composition. Placing multiple stents of different materials in contact with each other may increase potential for corrosion. Potential interactions of the **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent with other drug-eluting or coated stents have not been evaluated and should be avoided whenever possible.

5.3. Brachytherapy

The safety and effectiveness of the **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent in patients with prior brachytherapy of the target lesion have not been established. The safety and effectiveness of use of brachytherapy to treat in-stent restenosis in an **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent have not been established. Both vascular brachytherapy and the **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent alter arterial remodeling, the synergy between these two treatments has not been determined.

5.4. Use in Conjunction with Other Procedures

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters in conjunction with **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent implantation have not been established.

5.5. Use in Special Populations

5.5.1 Pregnancy

See Drug Information section 6.4. There are no adequate and well-controlled studies in pregnant women or men intending to father children. Systemic levels of Sirolimus have not been demonstrated in any pre-clinical or clinical trials with the **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent. Effective contraception should be initiated before implanting an **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent and for 12 weeks after implantation. The **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo or fetus.

5.5.2 Use during Lactation

See Drug Information section 6.5. A decision should be made whether to discontinue nursing or to implant the stent, taking into account the importance of the stent to the mother.

5.5.3 Pediatric Use

The safety and efficacy of the **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent in pediatric patients have not been established.

5.5.4 Geriatric Use

Clinical studies of the Sirolimus-eluting Co-Cr coronary stent did not find that patients age 65 years and over differed with regard to safety and efficacy compared to younger patients.

5.5.5 Clinical Experience in Various Indications

The primary clinical safety and performance of **SUPRAFLEX CRUZ™** stent has been established by comprehensive clinical studies.[1-4] The clinical experience of **SUPRAFLEX CRUZ™** stent from two multicenter real-world registries[3,4] demonstrated favourable clinical outcomes with low incidence of target lesion revascularization and stent thrombosis. Baseline patient characteristics, lesion characteristics, and clinical outcomes are summarized in the following table 2, 3, and 4, respectively.

Table 2 – Baseline patient characteristics

Parameter	T-FLEX Registry[3]	Supraflex Cruz Real-world Registry[4]
No. of patients	1203	1269
Age (years), mean ± SD	56.6±10.7	54.99±10.80
Male, n (%)	884 (73.5%)	910 (71.7%)
Cardiovascular Risk		
Diabetes mellitus, n (%)	387 (32.2%)	465 (36.6%)
Hypertension, n (%)	516 (42.9%)	622 (49.0%)
Smoking, n (%)	236 (19.6%)	218 (17.2%)
Hypercholesterolemia, n (%)	402 (33.4%)	370 (29.2%)
Family history of CAD, n (%)	38 (3.2%)	32 (2.5%)
Previous MI, n (%)	70 (5.8%)	136 (10.7%)
Previous CABG, n (%)	14 (1.2%)	23 (1.8%)
Previous PCI, n (%)	92 (7.6%)	89 (7.0%)
Previous stroke, n (%)	26 (2.2%)	26 (2.0%)
Renal insufficiency, n (%)	14 (1.2%)	17 (1.3%)
Cardiogenic shock, n (%)	33 (2.7%)	40 (3.2%)

Coronary Artery Disease (CAD), Myocardial Infarction (MI), Coronary Artery Bypass Graft (CABG), Percutaneous Coronary Intervention (PCI)

Table 3 – Lesion and Procedural Characteristics

Parameter	T-FLEX Registry[3]	Supraflex Cruz Real-world Registry[4]
No. of patients	1203	1269
No. of lesions	1430	1515
Target-vessel location		
LM, n (%)	4 (0.3%)	5 (0.3%)
LAD, n (%)	721 (50.4%)	723 (47.7%)
LCX, n (%)	270 (18.9%)	311 (20.5%)
RCA, n (%)	431 (30.1%)	470 (31.0%)
SVG, n (%)	4 (0.3%)	6 (0.4%)

Stent details		
Total no. of stents	1624	1682
No. of stents deployed per patient, mean ± SD	1.35±0.53	1.23±0.45
No. of stents deployed per lesion, mean ± SD	1.13±0.36	1.11±0.33
Stent length (mm), mean ± SD	25.95±8.77	25.15±8.83
Stent diameter (mm), mean ± SD	2.87±0.31	2.89±0.32

Left Main (LM), Left Anterior Descending (LAD), Left Circumflex (LCX), Right Coronary Artery (RCA), Saphenous Vein Graft (SVG)

Table 4 – Clinical Outcomes

Parameter	T-FLEX Registry[3]	Supraflex Cruz Real-world Registry[4]
Follow-up	2-year	1-year
No. of patients at follow-up	1103	1218
Death from any cause, n (%)	21 (1.9%)	17 (1.39%)
Cardiac death, n (%)	9 (0.8%)	10 (0.82%)
Non-cardiac death, n (%)	12 (1.1%)	7 (0.57%)
Target vessel MI, n (%)	24 (2.2%)	39 (3.20%)
TLR, n (%)	32 (2.9%)	21 (1.72%)
Non-TL-TVR, n (%)	15 (1.4%)	13 (1.07%)
Overall ST, n (%)	10 (1.0%)	8 (0.65%)
Target lesion failure, n (%)	65 (5.9%)	70 (5.75%)

Myocardial Infarction (MI), Target Lesion Revascularization (TLR), Target Vessel Revascularization (TVR), Stent Thrombosis (ST)

The discrete clinical experience of **SUPRAFLEX CRUZ™** stent from two multicenter real-world registries[3,4] includes total 2472 patients, demonstrates favourable safety and performance outcomes of **SUPRAFLEX CRUZ™** stent among various patient and lesion subsets such as diabetes mellitus, multivessel disease, long lesions, small vessels, acute coronary syndrome (ACS), ST-elevation myocardial infarction (STEMI), total occlusion, left main disease and female patients. Baseline patient characteristics, lesion characteristics, and clinical outcomes of **SUPRAFLEX CRUZ™** stent at 1-year in various indicated subgroups are summarized in the following table 5, 6, and 7, respectively.

Table 5 - Baseline patient characteristics

Group of Patients	Diabetic Mellitus	Multivessel Disease	Long Lesion[#]	Small Vessels[®]	ACS	STEMI	Total Occlusion	Left Main	Female Patients
No. of patients	852	406	1241	726	1824	689	420	9	678
Age (years), mean ± SD	55.6±9.8	58.01±10.30	56.0±10.8	57.6±10.0	56.0±10.8	55.3±11.5	55.3±10.8	53.1±9.4	57.7±10.6
Male, n (%)	575 (67.5%)	288 (70.9%)	929 (74.9%)	491 (67.6%)	1329 (72.9%)	509 (73.9%)	302 (71.9%)	8 (88.9%)	-
Cardiovascular risk									
Diabetes mellitus, n (%)	852 (100%)	155 (38.2%)	417 (33.6%)	291 (40.1%)	583 (32%)	194 (28.2%)	131 (31.2%)	2 (22.2%)	277 (40.9%)
Hypertension, n (%)	566 (66.4%)	193 (47.5%)	578 (46.6%)	340 (46.8%)	842 (46.2%)	276 (40.1%)	189 (45.0%)	4 (44.4%)	362 (53.4%)
Smoking, n (%)	123 (14.4%)	55 (13.5%)	232 (18.7%)	107 (14.7%)	331 (18.1%)	144 (20.9%)	79 (18.8%)	4 (44.4%)	86 (12.7%)
Hypercholesterolemia, n (%)	308 (36.2%)	129 (31.8%)	396 (31.9%)	217 (29.9%)	555 (30.4%)	193 (28.0%)	147 (35.0%)	4 (44.4%)	229 (33.8%)
Family history of CAD, n (%)	31 (3.6%)	6 (1.5%)	198 (16.0%)	24 (3.3%)	35 (1.9%)	9 (1.3%)	14 (3.3%)	1 (11.1%)	15 (2.2%)
Previous MI, n (%)	75 (8.8%)	28 (6.9%)	102 (8.2%)	60 (8.3%)	157 (8.6%)	51 (7.4%)	36 (8.6%)	3 (33.3%)	54 (8.0%)
Previous CABG, n (%)	19 (2.2%)	6 (1.5%)	18 (1.5%)	15 (2.1%)	31 (1.7%)	10 (1.5%)	5 (1.2%)	-	9 (1.3%)
Previous PCI, n (%)	74 (8.7%)	21 (5.2%)	91 (7.3%)	66 (9.1%)	150 (8.2%)	37 (5.4%)	30 (7.1%)	1 (11.1%)	43 (6.3%)
Previous stroke, n (%)	26 (3.1%)	9 (2.2%)	27 (2.2%)	20 (2.8%)	36 (2.0%)	14 (2.0%)	6 (1.4%)	-	16 (2.4%)
Renal insufficiency, n (%)	13 (1.5%)	5 (1.2%)	18 (1.5%)	16 (2.2%)	25 (1.4%)	9 (1.3%)	7 (1.7%)	-	5 (0.5%)
Cardiogenic shock, n (%)	21 (2.5%)	10 (2.5%)	32 (2.6%)	22 (3.0%)	50 (2.7%)	18 (2.6%)	8 (1.9%)	-	19 (2.8%)

[#]≥28 mm, [®]≤2.5 mm,
Acute Coronary Syndrome (ACS), ST-elevation Myocardial Infarction (STEMI), Coronary Artery Disease (CAD), Myocardial Infarction (MI), Coronary Artery Bypass Graft (CABG), Percutaneous Coronary Intervention (PCI)

Table 6 - Lesion and Procedural Characteristics

Group of Patients	Diabetic Mellitus	Multivessel Disease	Long Lesion[#]	Small Vessels[®]	ACS	STEMI	Total Occlusion	Left Main	Female Patients
No. of patients	852	406	1241	726	1824	689	420	9	678
No. of lesions	1024	824	1360	771	2128	784	436	9	802
Target-vessel location									
LM, n (%)	2 (0.2%)	4 (0.5%)	-	1 (0.1%)	8 (0.4%)	2 (0.3%)	2 (0.5%)	9 (100.0%)	1 (0.1%)
LAD, n (%)	487 (47.6%)	326 (39.6%)	684 (50.3%)	397 (51.5%)	1040 (48.9%)	396 (50.5%)	192 (44.0%)	-	391 (48.8%)
LCX, n (%)	215 (21.0%)	229 (27.8%)	205 (15.1%)	224 (29.1%)	419 (19.7%)	138 (17.6%)	67 (15.4%)	-	142 (17.7%)
RCA, n (%)	313 (30.6%)	265 (32.2%)	470 (34.6%)	145 (18.8%)	652 (30.6%)	245 (31.3%)	175 (40.1%)	-	266 (33.2%)
SVG, n (%)	7 (0.7%)	-	1 (0.1%)	4 (0.5%)	9 (0.4%)	3 (0.4%)	-	-	2 (0.2%)
Stent details									
Total no. of stents	1158	855	1441	807	2395	893	524	9	891
No. of stents deployed per patient, mean ± SD	1.29±0.50	1.96±0.45	1.2±0.4	1.1±0.3	1.31±0.52	1.30±0.49	1.3±0.5	1.0±0.0	1.31±0.53
No. of stents deployed per lesion, mean ± SD	1.12±0.34	1.04±0.20	1.1±0.2	1.1±0.4	1.13±0.34	1.14±0.4	1.2±0.4	1.0±0.0	1.11±0.34
Stent length (mm), mean ± SD	25.53±8.70	25.94±9.20	33.9±5.8	25.6±9.2	25.3±9.0	25.5±8.9	27.3±9.1	17.8±10.4	25.1±8.9
Stent diameter (mm), mean ± SD	2.84±0.30	2.84±0.30	2.9±0.3	2.5±0.02	2.87±0.3	2.9±0.3	2.9±0.3	3.3±0.4	2.83±0.3

[#]≥28 mm, [®]≤2.5 mm,
Left Main (LM), Left Anterior Descending (LAD), Left Circumflex (LCX), Right Coronary Artery (RCA), Saphenous Vein Graft (SVG), Acute Coronary Syndrome (ACS), ST-elevation Myocardial Infarction (STEMI)

Table 7 - Clinical Outcomes at 1-year

Group of Patients	Diabetic Mellitus	Multivessel Disease	Long Lesion[#]	Small Vessels[®]	ACS	STEMI	Total Occlusion	Left Main	Female Patients
No. of patients at follow-up	807	391	1185	701	1753	660	407	9	655
Death from any cause, n (%)	14 (1.7%)	5 (1.3%)	19 (1.6%)	11 (1.6%)	24 (1.4%)	11 (1.7%)	9 (2.2%)	0 (0%)	9 (1.4%)
Cardiac death, n (%)	6 (0.7%)	3 (0.8%)	11 (0.9%)	5 (0.7%)	15 (0.9%)	9 (1.4%)	5 (1.2%)	0 (0%)	5 (0.8%)
Non-cardiac death, n (%)	8 (1.0%)	2 (0.5%)	8 (0.7%)	6 (0.9%)	9 (0.5%)	2 (0.3%)	4 (1.0%)	0 (0%)	4 (0.6%)
Target vessel MI, n (%)	19 (2.4%)	9 (2.3%)	36 (3.0%)	20 (2.9%)	43 (2.5%)	14 (2.1%)	7 (1.7%)	0 (0%)	15 (2.3%)
TLR, n (%)	31 (3.8%)	13 (3.3%)	31 (2.6%)	18 (2.6%)	34 (1.9%)	18 (2.7%)	9 (2.2%)	0 (0%)	12 (1.8%)
Non-TL TVR, n (%)	11 (1.4%)	9 (2.3%)	8 (0.7%)	7 (1.0%)	12 (0.7%)	8 (1.2%)	5 (1.2%)	0 (0%)	6 (0.9%)
Overall ST, n (%)	8 (1.0%)	3 (0.8%)	10 (0.8%)	9 (1.3%)	11 (0.6%)	8 (1.2%)	2 (0.5%)	0 (0%)	4 (0.6%)
Target lesion failure, n (%)	56 (6.9%)	25 (6.4%)	78 (6.6%)	43 (6.1%)	92 (5.3%)	41 (6.2%)	21 (5.2%)	0 (0%)	32 (4.9%)

[#]≥28 mm, [®]≤2.5 mm,
Myocardial Infarction (MI), Target Lesion Revascularization (TLR), Non-Target Lesion Target Vessel Revascularization (Non-TL TVR), Stent Thrombosis (ST), Acute Coronary Syndrome (ACS), ST-elevation Myocardial Infarction (STEMI), Target lesion failure includes cardiac death, target vessel myocardial infarction and target lesion revascularization

SUPRAFLEX CRUZ™ stent shares significant similarities with SMT's state-of-the-art CE approved Supraflex™ stent. Therefore, clinical data of Supraflex™ stent are summarized in this section as a supportive clinical evidence for **SUPRAFLEX CRUZ™** stent. The discrete analysis of patients, including diabetes mellitus, multivessel disease, long lesions, small vessels, acute coronary syndrome (ACS), ST-elevation myocardial infarction (STEMI), total occlusion, left main disease and female patients, from TALENT randomized controlled trial and FLEX registry (table 8 and 9) confirmed the safety and performance of Supraflex™ stent.

Table 8 - Discreate analysis from TALENT randomized controlled trial (total patients=1435)[5]

Group of Patients	% of patients from TALENT trial	Supraflex DOCE%	Xience DOCE%	HR (95%CI)	p value
Diabetic Mellitus	23.3%	5.8%	8.5%	0.66 (0.29–1.52)	0.331
Multivessel Disease	21.7%	10.0%	5.7%	1.81 (0.79–4.14)	0.159
Long Lesion#	56.4%	5.7%	7.0%	0.81 (0.47–1.41)	0.465
Small Vessels@	44.9%	8.0%	5.8%	1.41 (0.77–2.57)	0.266
STEMI	16.4%	2.5%	3.4%	0.73 (0.16–3.25)	0.678
Left Main	2.1%	13.3%	26.7%	0.49 (0.09–2.67)	0.408

#>18 mm, @≤ 2.75 mm
Device Oriented Composite Endpoints (DOCE), ST-elevation Myocardial Infarction (STEMI), DOCE includes cardiac death, target-vessel myocardial infarction, or clinically indicated target lesion revascularization

Table 9 - Discreate analysis from FLEX Registry (total patients=995)[6]

Group of Patients	% of patients from FLEX registry	MACE%	Cardiac death (%)	MI (%)	TLR (%)	ST (%)
Multivessel Disease	22.7%	5.5%	2.7%	2.7%	1.4%	1.8%
Long Lesion#	58.0%	4.4%	1.6%	1.9%	0.9%	0.9%
Small Vessels@	18.7%	5.9%	1.1%	2.7%	2.2%	0.5%
ACS	40.0%	5.9%	2.3%	2.3%	1.3%	1.0%
STEMI	19.9%	6.6%	2.5%	2.5%	1.5%	1.5%
Total Occlusion	18.6%	6.6%	1.6%	2.7%	2.2%	1.6%
Left Main	1.1%	9.1%	9.1%	0.0%	0.0%	0.0%
Female Patients	20%	6.2%	2.1%	2.6%	1.5%	1.5%

#≥28 mm, @≤2.5 mm
Major Adverse Cardiac Events (MACE), Myocardial Infarction (MI), Target Lesion Revascularization (TLR), Stent Thrombosis (ST), Acute Coronary Syndrome (ACS), ST-elevation Myocardial Infarction (STEMI), MACE includes cardiac death, myocardial infarction, target lesion revascularization and non-target lesion target vessel revascularization
Reference:[1]Abhyankar A et al. Catheter Cardiovasc Interv. 2020 Nov 28. doi: 10.1002/ccd.29371. [2]Abhyankar A et al. Catheter Cardiovasc Interv. 2021 Feb 15;97(3):423-430. [3]Pothineni R et al. J Am Coll Cardiol. 2019 Oct, 74 (13 Supplement) B300. [4]Data on file [5]Zaman A et al. Lancet. 2019 Mar 9;393(10175):987-997. [6]Lemos PA et al. BMJ Open. 2016 Feb 17;6(2):e010028.

5.6. Lesion/Vessel Characteristics

The safety and effectiveness of the **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent have not been established in patients with coronary artery reference vessel diameter < 2.00 mm and > 4.50 mm

5.7. Drug Interactions

Several drugs are known to affect the metabolism of Sirolimus, and other drug interactions may be inferred from known metabolic effects. Sirolimus is known to be a substrate for both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein (P-gp).

Consideration should be given to the potential for drug interaction when deciding to place a **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent in a patient who is taking a drug that could interact with Sirolimus, or when deciding to initiate therapy with such a drug in a patient who had recently received a **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent. The effect of drug interactions on the safety or efficacy of the **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent has not been determined.

5.8. Magnetic Resonance Imaging (MRI) – Safety Information

Non-clinical testing and MRI simulations were performed to evaluate the entire family, including single and two-overlapped versions of the **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent. Non-clinical testing demonstrated that the entire family of this product (i.e., including all single and two or more overlapped versions up to 120 mm in length) is MR Conditional. The **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent has been shown in non-clinical testing to be MRI safe immediately following implantation. A patient with an implant from this family can be scanned safely in an MR system under the following conditions:

- Static magnetic field of 1.5-Tesla or 3-Tesla
- Maximum spatial gradient magnetic field of 1,500-gauss/cm (15-T/m)
- Maximum MR System reported, whole body averaged specific absorption rate (SAR) of 2-W/kg for 15 minutes of scanning (i.e. per pulse sequence) in normal operating mode

Under the scan condition defined, an implant from the **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent is expected to produce a maximum temperature rise of 3.5°C after 15 minutes of continuous scanning (i.e. per pulse sequence).

In non-clinical testing, the image artifact caused by an implant from the **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent extends approximately 4 mm from this device when imaged with a gradient echo pulse sequence and a 3-Tesla MR system.

5.9. Stent Handling Precautions

- For single use only. Do not resterilize or reuse this device. Note the "Use By" date on the product label.
- Do not remove the stent from the delivery balloon – removal may damage the stent and/or lead to stent embolization. The stent system is intended to perform as a system.
- Do not induce a vacuum on the delivery system prior to reaching the target lesion.
- Special care must be taken not to handle or in any way disrupt the stent on the balloon. This is most important while removing the catheter from the packaging, placing it over the guidewire, and advancing it through the large- bore rotating hemostatic valve and guiding catheter hub.
- Stent manipulation (e.g., rolling the mounted stent with your fingers) may loosen the stent from the delivery system balloon and cause dislodgment as well as it may damage the coating.
- Use only the appropriate balloon inflation media. Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in deployment of the stent.

5.10. Stent Placement Precautions

- Do not prepare or pre-inflate balloon prior to stent deployment other than as directed. Use balloon purging technique described in Section 11.0. Operator's Manual.
- When treating multiple lesions, the distal lesion should be initially stented, followed by stenting of the proximal lesion. Stenting in this order obviates the need to cross the proximal stent in placement of the distal stent and reduces the chances for dislodging the proximal stent.
- Implanting a stent may lead to dissection of the vessel distal and/or proximal to the stent and may cause acute closure of the vessel requiring additional intervention (CABG, further dilatation, placement of additional stents, or other).
- Do not expand the stent if it is not properly positioned in the vessel. See Precautions – 5.11. Stent/System Removal Precautions.
- Placement of a stent has the potential to compromise side branch patency.
- The vessel should be pre-dilated with an appropriate sized balloon.
- Balloon pressures should be monitored during inflation. Do not exceed rated burst pressure as indicated on the product label. (See Inflation Pressure Recommendations in 11.7.) Use of pressures higher than those specified on the product label may result in a ruptured balloon with possible intimal damage and dissection.
- Do not attempt to pull an unexpanded stent back through the guiding catheter, as dislodgement of the stent from the balloon may occur. Remove as a single unit as per instructions in Precautions 5.11. Stent/System Removal Precautions.
- If an unexpanded stent is to be retracted back into the guiding catheter, it is recommended to be done extremely carefully with no or minimal forward movement of the stent delivery system. Once the unexpanded stent is retrieved in the guiding catheter, then the entire system along with the guiding catheter should be withdrawn as a single unit. No attempts should be made to remove the unexpanded stent from the guiding system or the body by itself.
- Stent retrieval methods (use of additional wires, snares and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include bleeding, hematoma or pseudoaneurysm.
- Do not induce a negative pressure on the delivery catheter prior to placement of the stent across the lesion. This may cause premature dislodgment of the stent from the balloon.
- Although the stent delivery balloon catheter is strong enough to expand the stent without rupture, a circumferential tear of the carrier balloon distal to the stent and prior to complete expansion of the stent could cause the balloon to become tethered to the stent, requiring surgical removal. In case of rupture of the balloon, it should be withdrawn and, if necessary, a new balloon catheter exchanged over the guidewire to complete the expansion of the stent.
- Ensure full coverage of the entire lesion/dissection site so that there are no gaps between stents.

5.11. Stent/System Removal Precautions

- If unusual resistance is felt at any time during lesion access before stent implantation, the Stent System and the guide catheter should be removed as a single unit.
- Do not attempt to pull an unexpanded stent back into the guide catheter, as stent or coating damage or stent dislodgment from the balloon may occur.
- Stent retrieval methods (use of additional wires, snares and/or forceps) may result in additional trauma to the vascular site. Complications can include bleeding, hematoma or pseudoaneurysm.
- Note: When removing the entire stent system and guide catheter as a single unit, the following steps should be executed under direct visualization using fluoroscopy.
- Following stent placement, confirm complete balloon deflation. If greater than usual resistance is felt during delivery system balloon withdrawal, pay particular attention to

guide catheter position. In some cases it may be necessary to pull back slightly on the guide catheter in order to prevent deep seating (unplanned advancement) of the guide catheter and subsequent vessel damage. In cases where unplanned guide catheter movement has occurred, angiographic assessment of the coronary tree should be undertaken to ensure that there is no damage to the coronary vasculature.

- Maintain guidewire placement across the lesion during the entire removal process. Carefully pull back the stent system until the proximal balloon marker of the stent system is just distal to the guide catheter distal tip.
- The stent system and the guide catheter should be pulled back until the tip of the guide catheter is just distal to the arterial sheath, allowing the guide catheter to straighten. Carefully retract the stent system into the guide catheter and remove the stent system and the guide catheter from the patient as a single unit while leaving the guidewire across the lesion. Failure to follow these steps, and/or applying excessive force to the stent system, can potentially result in stent or coating damage, stent dislodgment from the balloon, and/or damage to the delivery system.

5.12. Post Implantation Precautions

- Great care must be exercised when crossing a newly deployed stent with an intravascular ultrasound (IVUS) catheter, a coronary guidewire or balloon catheter to avoid disrupting the stent geometry and stent coating.
- If patient requires MR imaging, refer to Section 5.8 – Magnetic Resonance Imaging (MRI) Safety Information above

6.0. Drug Information

6.1. Mechanism of Action

The mechanism (or mechanisms) by which Sirolimus-eluting Co-Cr coronary stent affects neointima proliferation as seen in clinical studies has not been established. It is known that Sirolimus inhibits T-lymphocyte activation and smooth muscle and endothelial cell proliferation in response to cytokine and growth factor stimulation. In cells, Sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12). The Sirolimus-FKBP-12 complex binds and inhibits the activation of the mammalian Target of Rapamycin (mTOR), leading to inhibition of cell cycle progression from G1 to S phase.

6.2. Drug Interactions Following Oral Administration of Sirolimus

Drug interaction studies have not been conducted with the Sirolimus-eluting Co-Cr coronary stent. Sirolimus is extensively metabolized by cytochrome P450 3A4 (CYP3A4) in the gut wall and liver and undergoes efflux from enterocytes of the small intestine by P-glycoprotein (P-gp). Therefore, absorption and the subsequent elimination of systemically absorbed Sirolimus may be influenced by drugs that affect these protein complexes. Inhibitors of CYP3A4 and P-gp may increase Sirolimus levels, while inducers of CYP3A4 and P-gp may decrease Sirolimus levels. The pharmacokinetic interaction between orally administered Sirolimus and concomitantly administered drugs is discussed below.

6.2.1 Ketoconazole

Multiple-dose Ketoconazole administration significantly affected the rate and extent of absorption and Sirolimus exposure after administration of a Sirolimus oral formulations, as reflected by increases in Sirolimus C_{max}, t_{max}, and AUC of 4.3-fold, 38%, and 10.9-fold, respectively. However, the terminal $t_{1/2}$ of Sirolimus was not changed. Single-dose Sirolimus did not affect steady-state 12-hour plasma Ketoconazole concentrations. It is recommended that Sirolimus oral solution and oral tablets should not be administered with Ketoconazole.

6.2.2 Rifampin

Pretreatment of 14 healthy volunteers with multiple doses of Rifampin, 600 mg daily for 14 days, followed by a single 20 mg dose of Sirolimus, greatly increased Sirolimus oral-dose clearance by 5.5-fold (range = 2.8 to 10), which represents mean decrease in AUC and C_{max} of about 82% and 71%, respectively. In patients where Rifampin is indicated, alternative therapeutic agents with less enzyme induction potential should be considered.

6.2.3 Diltiazem

The simultaneous oral administration of 10 mg of a Sirolimus oral solution and 120 mg of Diltiazem to 18 healthy volunteers significantly affected the bioavailability of Sirolimus. Sirolimus C_{max}, t_{max}, and AUC were increased 1.4-, 1.3-, and 1.6-fold, respectively. Sirolimus did not affect the pharmacokinetics of either Diltiazem or its metabolites desacetyldiltiazem and desmethyldiltiazem.

6.2.4 Cyclosporine

Single-dose pharmacokinetic interactions between Cyclosporine and Sirolimus were investigated for two Sirolimus oral formulations in studies using 24 healthy volunteers. Compared to results obtained when oral Sirolimus was administered alone, the oral administration of 10 mg Sirolimus 4 hours after a single dose of 300 mg Cyclosporine soft gelatin capsules increased mean Sirolimus AUC by 33% to 80% and increased mean Sirolimus C_{max} by 33% to 58%, depending on the Sirolimus formulation. The half-life of Sirolimus was not significantly affected. The Cyclosporine mean AUC and mean C_{max} were not significantly affected.

In a single dose cross-over drug-drug interaction study, 33 healthy volunteers received 5 mg Sirolimus alone, 2 hours before, and 2 hours after a 300 mg dose of cyclosporine soft gelatin capsules. When given 2 hours before the cyclosporine administration, Sirolimus C_{max} and AUC were comparable to those with administration of Sirolimus alone. However, when given 2 hours after, the mean C_{max} and AUC of Sirolimus were increased by 126 % and 141 %, respectively, relative to administration of Sirolimus alone.

6.2.5 Erythromycin

The simultaneous oral administration of 2 mg daily of Sirolimus oral solution and 800 mg q 8 h of erythromycin as erythromycin ethylsuccinate tablets at steady state to 24 healthy volunteers significantly affected the bioavailability of Sirolimus and erythromycin. Sirolimus C_{max} and AUC were increased 4.4- and 4.2- fold, respectively, and t_{max} was increased by 0.4 hr. Erythromycin C_{max} and AUC were increased 1.6- and 1.7- fold, respectively, and t_{max} was increased by 0.3 hr.

6.2.6 Verapamil

The simultaneous oral administration of 2 mg daily of Sirolimus oral solution and 180 mg q 12 h of verapamil at steady state to 26 healthy volunteers significantly affected the bioavailability of Sirolimus and verapamil. Sirolimus C_{max} and AUC were increased 2.3- and 2.2- fold, respectively, without substantial change in t_{max}. The C_{max} and AUC of the pharmacologically active S (-) enantiomer of verapamil were both increased 1.5-fold and t_{max} was decreased by 1.2 hr.

6.2.7 Drugs which may be co administered without dose adjustment

Clinically significant pharmacokinetic drug-drug interactions were not observed in studies of drugs listed below in conjunction with orally administered Sirolimus. Sirolimus and these drugs may be co administered without dose adjustments.

- Acyclovir
- Digoxin
- Glyburide
- Nifedipine
- Norgestrel/ethinyl estradiol

- Prednisolone
- Sulfamethoxazole/Trimethoprim

6.2.8 Other drug interactions

Drugs that may increase Sirolimus blood concentrations include:

- **Calcium channel blockers:** nicardipine, verapamil
- **Antifungal agents:** clotrimazole, fluconazole, itraconazole
- **Macrolide antibiotics:** clarithromycin, erythromycin, troleandomycin
- **Gastrointestinal prokinetic agents:** cisapride, metoclopramide
- **Other drugs:** bromocriptine, cimetidine, danazol, HIV-protease inhibitors (e.g., ritonavir, indinavir)

Drugs that may decrease Sirolimus blood concentration include:

- **Anticonvulsants:** carbamazepine, phenobarbital, phenytoin
- **Antibiotics:** rifabutin, rifapentine

Care should be exercised when drugs or other substances that are metabolized by CYP3A4 are administered concomitantly with Sirolimus-eluting Co-Cr coronary stent.

6.2.9 Grapefruit juice

Grapefruit juice reduces CYP3A4-mediated metabolism of Sirolimus.

6.2.10 Vaccination

Immunosuppressant may affect response to vaccination. Therefore, during treatment with Sirolimus, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid.

6.2.11 Drug-laboratory test interactions

There are no studies on the interactions of Sirolimus in commonly employed clinical laboratory tests.

6.3. Mutagenesis, Carcinogenicity and Reproductive Toxicology

The genotoxicity, carcinogenicity, and reproductive toxicity of Sirolimus-eluting Co-Cr coronary stent have not been evaluated. However, the genotoxicity, carcinogenicity, and reproductive toxicity of Sirolimus have been investigated in bacterial and mammalian cells *in vitro* and in laboratory animals *in vivo*.

Sirolimus was not genotoxic in the *in vitro* bacterial reverse mutation assay, Chinese hamster ovary cell chromosomal aberration assay, mouse lymphoma cell forward mutation assay, or *in vivo* mouse micronucleus assay.

Carcinogenicity studies in mouse showed hepatocellular adenoma and carcinoma at dosages of 1, 3 and 6 mg/kg/day orally. In the 104-week rat study at dosage of 0.2 mg/kg/day, there was a significant increase in the incidence of testicular adenoma.

There was no effect on fertility in female rats following the administration of Sirolimus at dosages up to 0.5 mg/kg/day. In male rats, there was no significant difference in fertility rate compared to controls at a dosage of 2 mg/kg/day. Reductions in testicular weights and/or histological lesions (e.g., tubular atrophy and tubular giant cells) were observed in rats following dosages of ≥0.65 mg/kg/day. These dosages are quite higher than the amount of drug delivered by Sirolimus-eluting Co-Cr coronary stent.

6.4. Pregnancy

There are no adequate data from the use of Sirolimus in pregnant women. Sirolimus was embryo toxic in rats at dosages of ≥ 0.1 mg/kg/day. Embryo toxicity was manifested as mortality and reduced fetal weights (with associated delays in skeletal ossification). No teratogenic effect of Sirolimus was evident. There was no effect of Sirolimus on rabbit development at the maternally toxic dosage of 0.05 mg/kg/day. Effective contraception should be initiated before Sirolimus therapy, during Sirolimus therapy and for 12 weeks after Sirolimus therapy. The Sirolimus should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo or fetus.

6.5. Lactation

Sirolimus is excreted in trace amounts in milk of lactating rats. It is not known whether Sirolimus is excreted in human milk. The pharmacokinetic and safety profiles of Sirolimus in infants are not known. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from Sirolimus, a decision should be made whether to discontinue nursing or to implant the stent, taking into account the importance of the stent to the mother.

7.0 Adverse Events

7.1. Potential Adverse Events

Potential adverse events (in alphabetical order) which may be associated with the use of a Coronary Stent in native coronary arteries include but are not limited to:

- Abrupt stent closure
- Acute myocardial infarction
- Allergic reaction to anticoagulants or antithrombotic therapy or contrast medium or stent materials including stent scaffold
- Aneurysm (coronary)
- Angina
- Arrhythmias, including ventricular fibrillation (VF) and ventricular tachycardia (VT)
- Arteriovenous fistula
- Cardiac tamponade
- Cardiogenic shock
- Death
- Dissection
- Emboli, distal (air, tissue, thrombotic, device materials or stent delivery system materials)
- Heart failure
- Hematoma
- Hemorrhage, requiring transfusion
- Infection, local and/or systemic
- Myocardial Ischemia
- Pain at the access site
- Perforation or rupture of one or more coronary arteries
- Pericardial effusion
- Pseudoaneurysm, femoral
- Pulmonary edema
- Renal failure
- Respiratory failure
- Restenosis of stented segment
- Shock
- Stent embolization
- Stent migration
- Stent thrombosis/occlusion
- Stroke/cerebrovascular accident/transient ischemic attack (TIA)
- Total occlusion of coronary artery
- Vessel spasm
- Vessel trauma (dissection, perforation, rupture or injury, including coronary) requiring surgical repair or reintervention

Potential adverse events not captured above, that may be unique to the sirolimus drug coating:

- Abnormal liver function tests
- Anemia
- Arthralgias
- Diarrhea
- Hypercholesterolemia
- Hypersensitivity, including anaphylactic/anaphylactoid type reactions

- Hypertriglyceridemia
- Hypokalemia
- Infections
- Interstitial lung disease
- Leukopenia
- Lymphoma and other malignancies
- Thrombocytopenia

8.0. Individualization of Treatment

See also Precautions section 5.5. Use in Special Populations and Precautions section 5.6 Lesion/Vessel Characteristics.

The risks and benefits described above should be considered for each patient before use of the **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent. Patient selection factors to be assessed should include a judgment regarding risk of antiplatelet therapy. Stenting is generally avoided in those patients at heightened risk of bleeding (e.g., those patients with recently active gastritis or peptic ulcer disease, see section 3 Contraindications).

Premorbid conditions that increase the risk of a poor initial result and the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure, and severe obesity) should be reviewed.

9.0. Patient Counseling Information

Physicians should consider the following in counseling patient about this product:

- Discuss the risks associated with stent placement
- Discuss the risks associated with a Sirolimus-eluting implant
- Discuss the risks/benefits issues for this particular patient
- Discuss alteration to current lifestyle immediately following the procedure and over the long terms.

10.0. How Supplied

Sterile : This product is sterilized with ethylene oxide gas. It is intended for single use only. Do not resterilize. Non-pyrogenic. Do not use if package is opened or damaged.

Contents : One (1) **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent mounted on a rapid exchange stent delivery system.

Storage : Storage temperature: 20° to 30° C

- Avoid exposure to direct sunlight or heaters.
- Keep the product in a cool, dark and dry place.

11.0. Operator's Manual / Clinical Use Information

11.1 Inspection Prior to Use

1. Carefully inspect the sterile package before opening and check for damage to the sterile barrier. Do not use if the integrity of the sterile package has been compromised.
2. Check foil pouch for "Use By" date. Do not use after the "Use By" date.
3. Tear open the foil pouch and remove the inner pouch.
   Note: The outside of the inner pouch is NOT sterile. Open the inner pouch and pass or drop the product into the sterile field using an aseptic technique.
   Note: Special care must be taken not to handle the stent or in any way disrupt its placement on the balloon. This is most important during catheter removal from packaging, placement over guidewire, and advancement through the rotating hemostatic valve and guiding catheter hub.
   Note: Excessive manipulation, e.g., rolling the mounted stent, may cause dislodgement of the stent from the delivery balloon.
4. If sterile package is intact, carefully remove the system from the package and inspect for bends, kinks, and other damage. Do not use if any defects are noted. However, do not manipulate, touch, or handle the stent which may cause coating damage, contamination, or stent dislodgement from the delivery balloon.

Note: At any time during use of device, if the stainless steel proximal shaft has been bent or kinked, do not continue to use the catheter.

5. If the integrity of the foil pouch or the sterile package has been compromised prior to the product "Use By" date (e.g., damage of the package), contact your local **SMT** representative for return information.

11.2 Materials Required (not included in stent system package)

Quantity	Material
N/A	Guiding catheter(s) ≥ 5F [(1.42 mm, 0.056 inch) inner diameter]
2-3	20 cc syringes
1,000 u /500 cc	Heparinized normal saline (HepNS)
1	<0.014 inch (0.36 mm) guidewire
1	Rotating hemostatic valve with 0.096 inch (2.44 mm) minimum inner diameter
N/A	Contrast diluted 1:1 with heparinized normal saline
1	Inflation Device (with luer fitting)
1	Three-way stopcock
1	Torque device (Optional)
1	Guidewire introducer
1	Pre-deployment dilatation catheter
N/A	Appropriate arterial sheath
N/A	Appropriately sized pre-dilatation angioplasty balloon
N/A	Appropriately sized post-dilatation noncompliant angioplasty balloon
N/A	Appropriate anticoagulation and antiplatelet drugs

11.3 Preparation

11.3.1 Packaging Removal

Note: The foil pouch is not a sterile barrier. The inner Tyvek Pouch within the foil pouch is the sterile barrier. Only the contents of the inner pouch should be considered sterile. The outside surface of the inner pouch is NOT sterile.

1. Carefully remove the delivery system from its protective tubing for preparation of the delivery system. When using a rapid exchange (RX) system, do not bend or kink the hypotube during removal.
2. Remove the product mandrel by grasping the catheter just proximal to the stent (at the proximal balloon bond site), and with the other hand, grasp the stent protector and gently remove distally. If unusual resistance is felt during product mandrel removal, do not use this product and replace with another. Follow product returns procedure for the unused device.
3. Examine the device for any damage. If it is suspected that the sterility or performance of the device has been compromised, the device should not be used.

11.3.2 Guidewire Lumen Flush

1. Connect a syringe containing heparinized normal saline to an appropriately sized flushing needle. Carefully apply the needle to the distal tip of the delivery system and flush the guidewire lumen until fluid exits the guidewire exit port.

   Note: Use caution while flushing guidewire lumen with flushing needle to avoid damage to catheter tip.

   Note: Avoid manipulation of the stent while flushing the guidewire lumen, as this may disrupt the placement of the stent on the balloon.

   Note: Stent contact with any fluid is not recommended as there is a possibility of initiating drug release. However, if it is absolutely necessary to flush the stent with saline, contact time should be limited (1 minute maximum).
2. Prepare balloon lumen with 50/50 contrast-saline mixture as follows:

a) Using a 20 cc syringe containing 5 cc of contrast-saline mixture, apply negative pressure for 20-30 seconds, allowing air removal from the balloon. An excessive amount of air released into the syringe or no air released from the balloon may indicate damage to the stent delivery system.

Should there be an indication of damage to the stent delivery system, do not use.

b) Release pressure slowly allowing negative pressure to draw mixture into balloon lumen.

Do not apply negative pressure on inflation device after balloon preparation and prior to delivering the stent.

c) Detach syringe, leaving a meniscus of mixture on the hub of the balloon lumen.

11.3.3 Delivery System Preparation

- Do not attempt pre-inflation technique to purge balloon lumen.
- Do not use air or any gaseous medium to inflate the balloon.

1. Prepare an inflation device/syringe with diluted contrast medium.
2. Attach an inflation device/syringe to the stopcock; attach it to the inflation port of the product. Do not bend the product hypotube when connecting to the inflation device/syringe.
3. With the tip down, orient the delivery system vertically.
4. Open the stopcock to delivery system; pull negative for 30 seconds, release to neutral for contrast fill.
5. Close the stopcock to the delivery system; purge the inflation device/syringe of all air.

   Attach inflation device to balloon lumen directly. Apply the "meniscus to meniscus" technique to ensure that no air bubbles remain at connection.
6. Repeat steps 3 through 5 until all air is expelled. If bubbles persist, do not use the product.
7. If a syringe was used, attach a prepared inflation device to stopcock.
8. Open the stopcock to the delivery system.
9. Leave on neutral.

Do not wipe with gauze sponges as fibers may disrupt the stent.

Note: Do not pull negative pressure on inflation device before beginning the preparation step.

Note: Do not apply positive pressure to the balloon during the delivery system preparation.

Note: Do not apply negative pressure on inflation device after balloon preparation and prior to delivering the stent. This may cause dislodgement of the stent from the balloon.

Note: If air is seen in the shaft, repeat Section 11.3.3 Delivery System Preparation, steps 3 through 5, to prevent uneven stent expansion.

11.4. Delivery Procedure

Step	Action
1	Prepare the vascular access site according to standard practice.
2	Predilate the lesion with PTCA catheter.
3	Maintain neutral pressure on the inflation device. Open the rotating hemostatic valve as widely as possible.
4	Backload the delivery system onto the proximal portion of guidewire while maintaining the guidewire position across target lesion.
5	Advance the stent delivery system over the guidewire to the target lesion. Use the radiopaque balloon markers to position the stent across lesion; perform angiography to confirm the position of the stent. NOTE: If during the process of moving the delivery system into position you notice the stent has moved on the balloon, do not deploy the stent. The entire system should be removed as a single unit. See 5.11 Stent/System Removal Precautions section for specific delivery system removal instructions.
6	Tighten rotating hemostatic valve. Stent is now ready to be deployed.

11.5. Deployment Procedure

Step	Action
1	Inflate the delivery system expanding the stent to a nominal pressure. Higher pressure may be necessary to optimize stent apposition to the arterial wall. Balloon pressure must not exceed RBP.
2	Maintain inflation pressure for 15-30 seconds for full expansion of the stent
3	Deflate balloon by pulling negative pressure on inflation device until balloon is fully deflated.
4	Confirm stent position and deployment using standard angiographic techniques. For optimal results, the entire stenosed arterial segment should be covered by the stent. Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum expanded stent diameter as compared to the proximal and distal coronary artery diameter(s). Optimal expansion requires that the stent be in full contact with the artery wall. Stent wall contact should be verified through routine angiography or intravascular ultrasound (IVUS).
5	If stent sizing/apposition requires optimization, readvance the Stent System balloon, or another high-pressure, non-compliant balloon catheter of the appropriate size, to the stented area using standard angioplasty techniques.

11.6. Removal Procedure

Step	Action
1	Ensure that the balloon is fully deflated.
2	Fully open rotating hemostatic valve.
3	While maintaining guidewire position and negative pressure on inflation device, withdraw delivery system. NOTE. Should unusual resistance be felt at any time during either lesion access or removal of delivery system post-stent implantation, the entire system should be removed as a single unit. See Precautions 5.11 Stent/System Removal Precautions for specific delivery system removal instructions.
4	Tighten the rotating hemostatic valve.
5	Repeat angiography to assess stented area. If necessary, post-dilate within stent. Balloon inflations should utilize balloon of size closely matching vessel.
6	Final stent diameter should match reference vessel. **ASSURE THAT THE STENT IS NOT UNDERDILATED.**

11.7. *In-Vitro* Information

Pressure [atm]	2.00 mm	2.25 mm	2.50 mm	2.75 mm	3.00 mm	3.50 mm	4.00 mm	4.50 mm
8	2.02	2.23	2.46	2.69	2.92	3.27	3.86	4.28
9	2.06	2.27	2.48	2.73	2.97	3.32	3.92	4.34
10	2.10	2.30	2.50	2.76	3.02	3.37	3.97	4.41
11	2.13	2.33	2.52	2.78	3.05	3.50	4.01	4.50
12	2.16	2.35	2.53	2.81	3.09	3.56	4.05	4.56
13	2.18	2.37	2.55	2.83	3.13	3.61	4.08	4.62
14	2.20	2.39	2.57	2.86	3.16	3.65	4.12	4.68
15	2.23	2.43	2.60	2.89	3.19	3.69	4.16	4.72
16	2.26	2.45	2.63	2.93	3.22	3.72	4.18	4.75

Nominal= 8 atm, for 2.00 mm to 2.25 mm, 10 atm for 2.50 mm to 3.00 mm, 11 atm for 3.50 to 4.50 mm
RBP=16 atm for all sizes

1atm=1.01bar=101.33kpa

12.0 Patient Information

In addition to these instructions for Use booklet, the following patient specific information regarding the **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent is available:

- Evaluation Form that includes both patient and **SUPRAFLEX CRUZ™** Sirolimus-eluting coronary stent specific information. All patients will be expected to keep this card in their possession at all times for procedure/stent identification.

13.0 Disclaimer of Warranty and Limitation of Remedy

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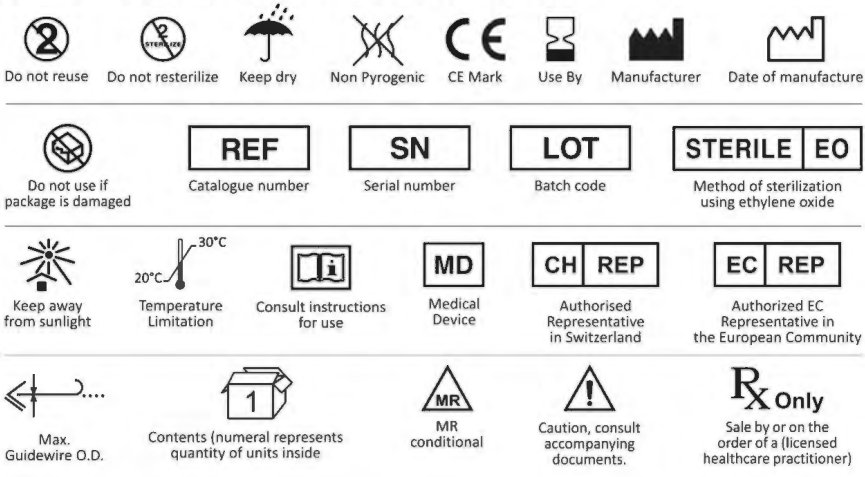
14.0 Explanation of symbols as per MDD 93/42/EEC & BS EN ISO 15223



SAHAJANAND MEDICAL
TECHNOLOGIES LIMITED

Registered Office / Corporate Office :
"Sahajanand Estate", Wakharia Wadi, Near Dabholi Char Rasta, Ved Road, Surat
395004, Gujarat, INDIA Tel.: +91 261 6112800 Fax: +91 261 6112801
Factory :
Plot No: 33, 34, 35, 52, 53 & 54, Surat Special Economic Zone, Sachin,
Surat - 394230, Gujarat, INDIA. Tel: +91 261 6112999 Fax: +91 261 6112801
Email : contact@smtpl.com Visit us at : www.smtpl.com

Consumer Care Helpline +91 261 6112820 contact@smtpl.com
State Consumer Helpline 1800 233 0222

ISO 13485 Certified Company

EC REP

Obelis s.a
Boulevard Général Wahis 53
1030 Brussels, BELGIUM
Tel: +(32) 2. 732.59.54
Fax: +(32) 2.732.60.03
E-Mail : mail@obelis.net

Swiss Authorized Representative

CH REP

OBELIS SWISS GmbH
Ruessenstrasse 12,
6340 Baar/ZG Switzerland
Tel: 041 544 15 26
Fax: 041 544 15 27
E-mail: info@obelis.ch

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Physiology-guided Complete vs. Culprit-Only Revascularization in Older MI Patients with HBR status: Insights from the FIRE TRIAL

Simone Biscaglia, MD
Ferrara University Hospital, Italy

CRF TCT

Disclosure of Relevant Financial Relationships

Within the prior 24 months, I have had a relevant financial relationship with a company producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients:

Nature of Financial Relationship	Ineligible Company
Grant/Research Support	Medis, SMT, Siemens, Insight Lifetech, GE
Consultant Fees/Honoraria	SMT, Siemens, Medis, Abbott and Insight Lifetech

All relevant financial relationships have been mitigated.
Faculty disclosure information can be found on the app

Background

- HBR status correlates with an increased risk of bleeding and ischemic complications [1].
- Enhancement of HBR patients outcomes have predominantly centered on identification of HBR status, radial access, optimization of antithrombotic regimens (intensity and length modulation) and selection of new-generation drug-eluting platforms [2].
- The FIRE study population represents a unique opportunity to generate evidence regarding the optimal revascularization strategy for HBR patients [3].

1. Circulation. 2019;140:240-261. 2. Nat Rev Cardiol. 2022;19:117-132. 3. N Engl J Med. 2023:389:889-898.

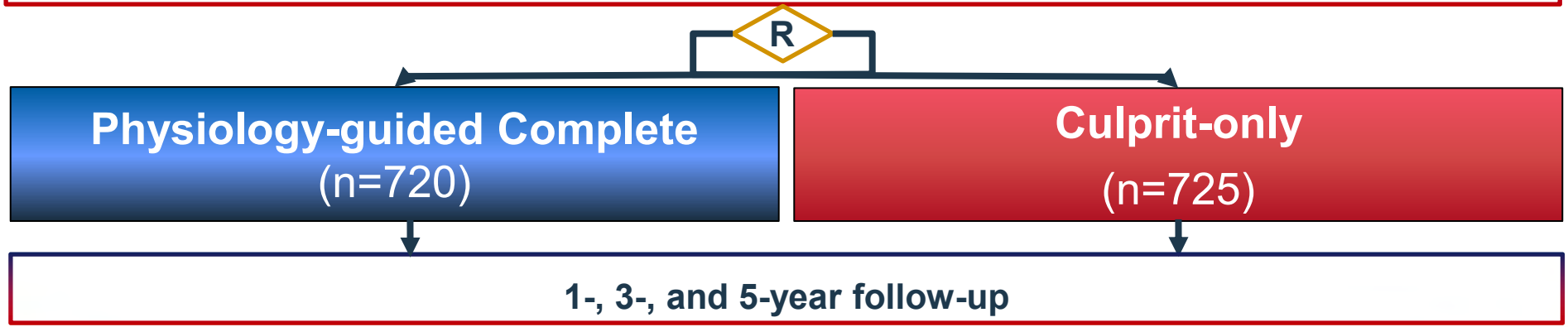
Design

All comers, prospective, randomized, multicenter, open-label trial with blinded adjudicated evaluation of outcomes (PROBE).

Pts ≥75 ys hospitalized for MI (STE or NSTE) with indication to invasive management

Multivessel disease at coronary artery angiography

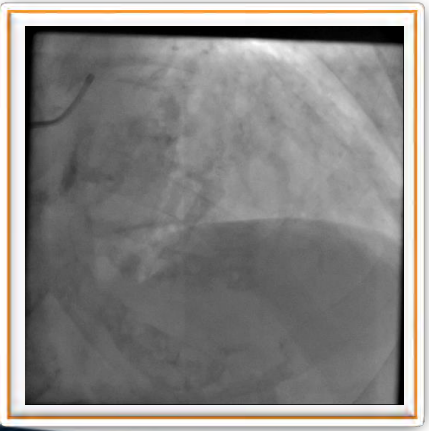
Culprit lesion clearly identifiable and successfully treated



1-, 3-, and 5-year follow-up

Coronary Physiology & Stents

- Non-culprit lesions were assessed with either wire-based FFR, resting index or angiography-derived FFR
- Flow-limiting lesions (FFR≤0.80, resting ≤0.89) had to be revascularized with biodegradable-polymer sirolimus ultra-thin stent(s)



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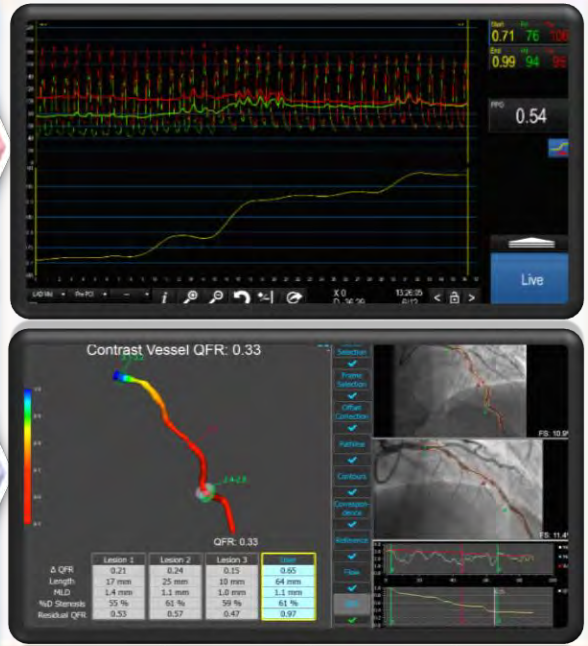

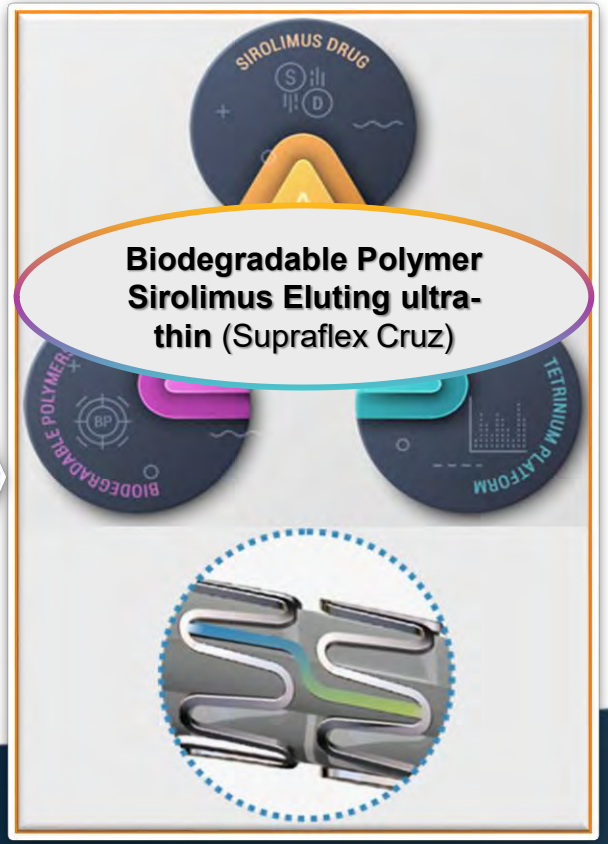

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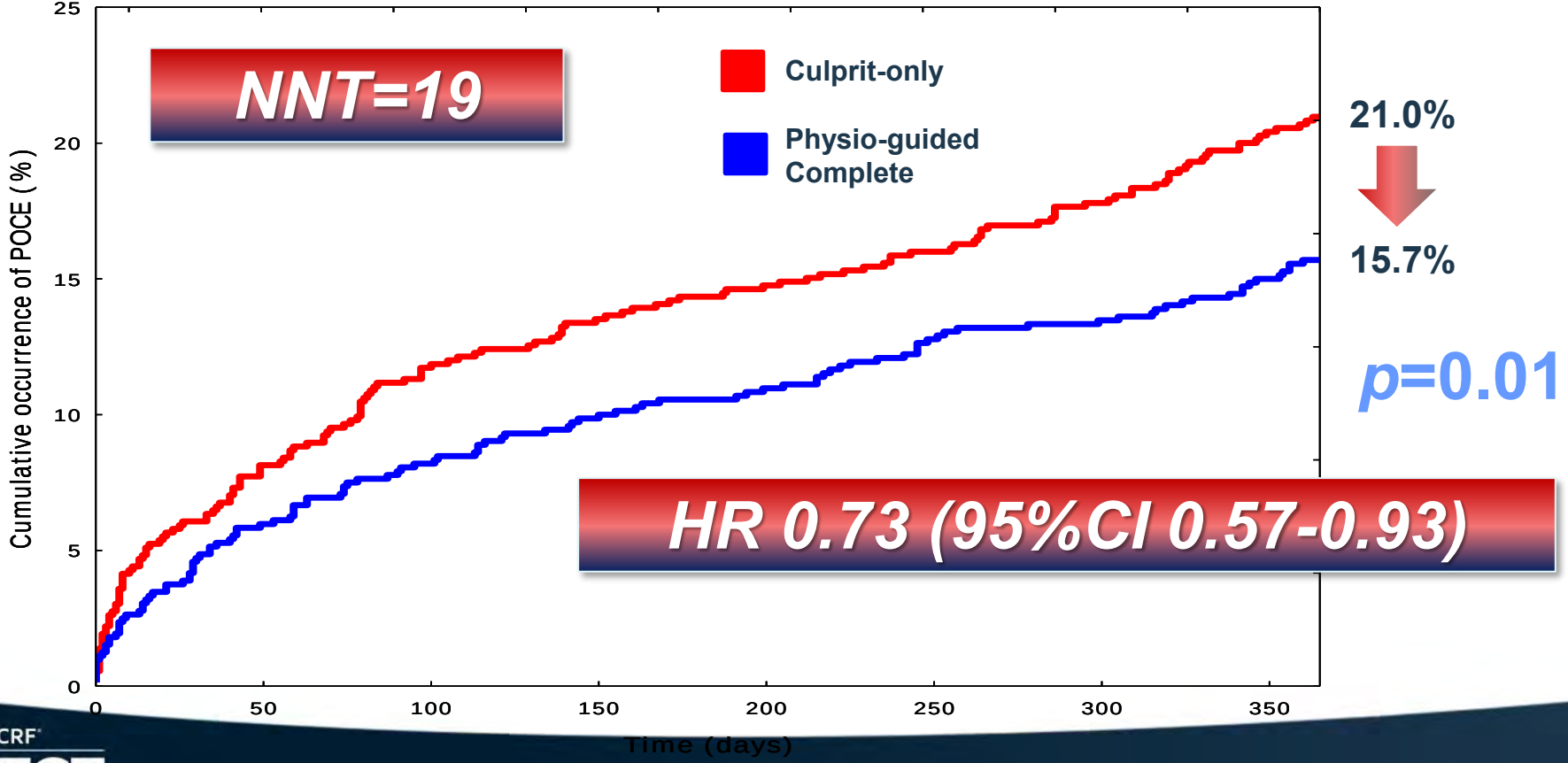
Primary endpoint

All-cause death, any MI, stroke, or ID-revascularization



Biscaglia S, et al. N Engl J Med. 2023 Sep 7;389(10):889-898.

Prespecified HBR analysis - Aims

i. To describe the *prognostic impact* of HBR status

ii. To investigate the efficacy and safety across HBR status of *physiology-guided complete* versus culprit-only strategy

iii. To explore outcomes of HBR patients treated with *≤1 m* vs. >1 m *DAPT* regimen with biodegradable polymer sirolimus eluting ultra-thin stent

Endpoints

Primary

Death, any MI, any stroke, or ID-revascularization

Key secondary

Cardiovascular death or MI

Safety

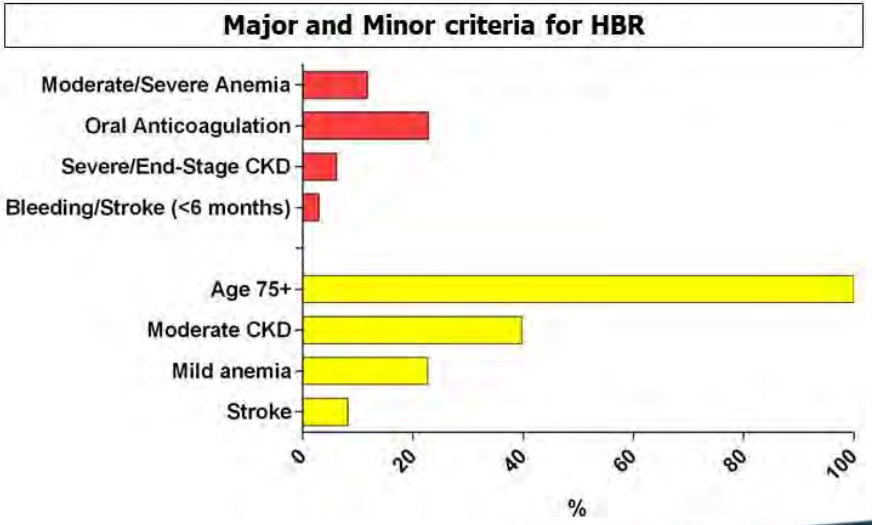
BARC type 3-5 bleeding

Baseline Characteristics

No differences between complete and culprit-only in HBR and non-HBR patients

Characteristic	non-HBR (n=420)	HBR (n=1025)	p
Age – years	79.6±4	81.5±4	<0.001
Female sex	140 (33)	388 (38)	0.118
Medical history			
Hypertension	323 (77)	862 (84)	<0.001
Diabetes	120 (28)	343 (33)	0.089
Prior MI	40 (10)	180 (17)	<0.001
History of AF	4 (1)	196 (19)	<0.001
eGFR<60 ml/min	0 (0)	662 (65)	<0.001
PAD	49 (12)	200 (19)	<0.001
CVA	0 (0)	119 (12)	<0.001
Killip ≥2	75 (18)	337 (33)	<0.001
LVEF – %	51.1±10	48.4±11	<0.001

1025/1445 (71%) fell within the HBR category, as defined by the ARC-HBR criteria



Baseline Characteristics

No differences between complete and culprit-only in HBR and non-HBR patients

Characteristic	non-HBR (n=420)	HBR (n=1025)	p
Antithrombotic drugs at discharge – no. (%) *			
Aspirin	419 (99)	956 (93)	<0.001
Clopidogrel	103 (25)	626 (61)	
Ticagrelor	297 (71)	366 (36)	<0.001
Prasugrel	19 (4.5)	13 (1)	
Vitamin K antagonist	0 (0)	63 (6)	<0.001
NOAC	0 (0)	266 (26)	<0.001
DAPT	419 (99)	676 (66)	<0.001
DAT	0 (0)	53 (5)	<0.001
TAT	0 (0)	276 (27)	<0.001

Characteristic	non-HBR (n=420)	HBR (n=1025)	p
Culprit vessel – no. (%)			
LM	8 (2)	68 (7)	
LAD	186 (44)	473 (46)	
LCX	95 (23)	174 (17)	<0.001
RCA	120 (28)	293 (28)	
RI	11 (3)	17 (2)	

Study Endpoints

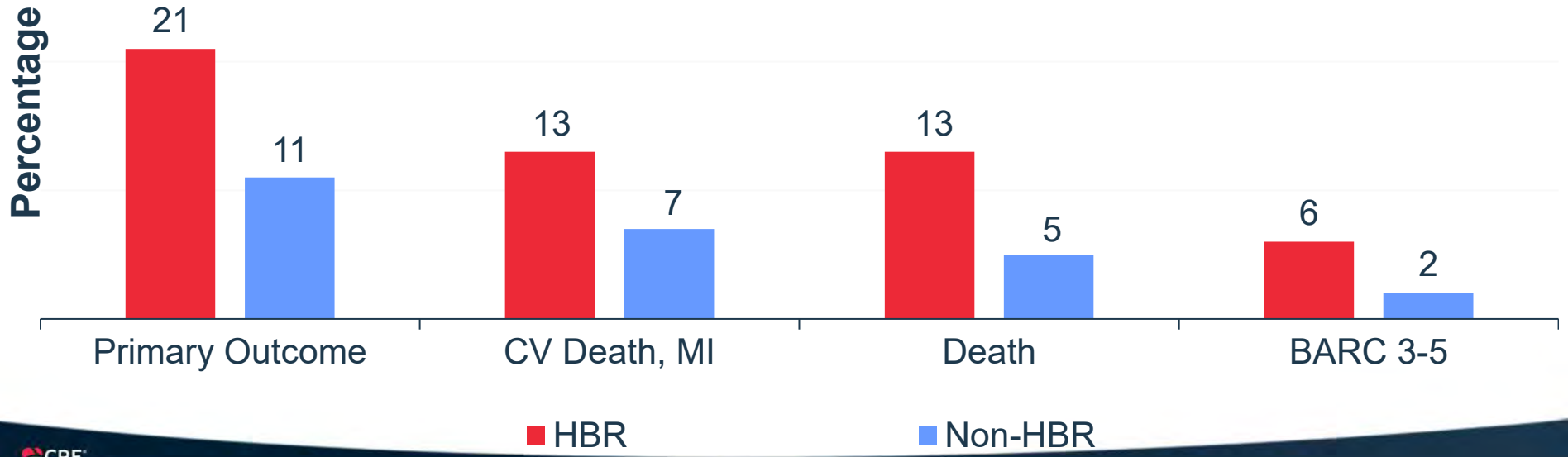
HBR vs non-HBR patients

HR 2.01, 95%CI 1.47-2.76, p<0.001

HR 1.89, 95%CI 1.26-2.83, p=0.001

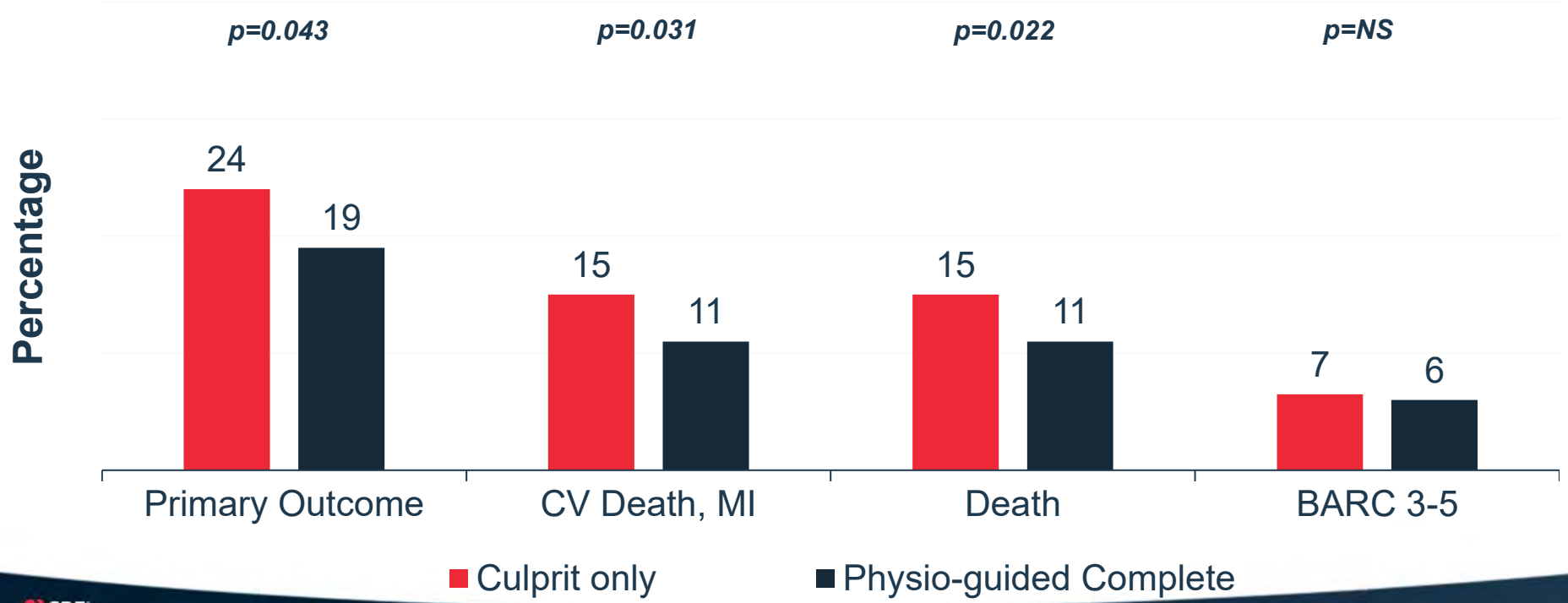
HR 2.53, 95%CI 1.63-3.94, p<0.001

HR 3.28, 95%CI 1.40-7.64, p=0.006

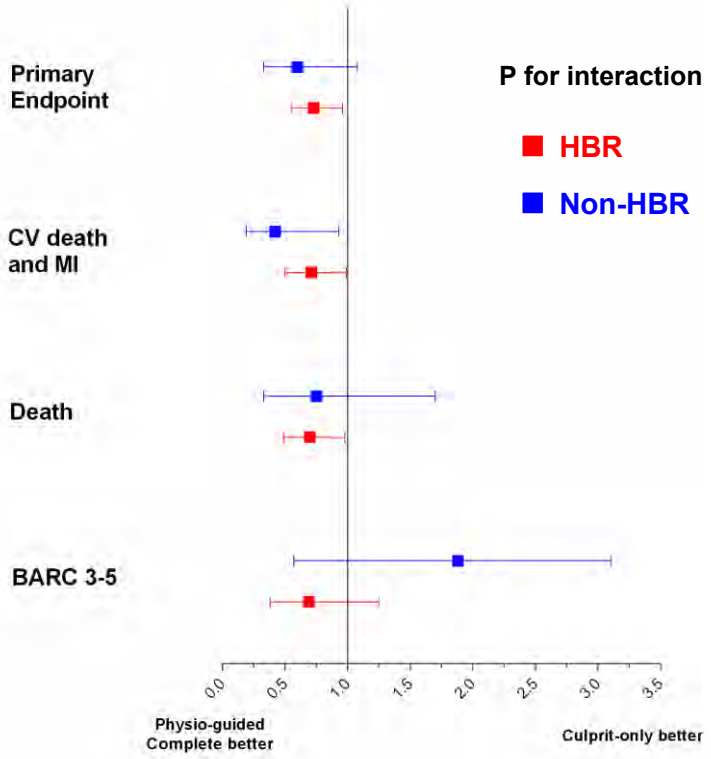


Study Endpoints

HBR patients / Culprit vs Physio-Complete



HBR vs non-HBR patients



P for interaction P=0.554

HBR

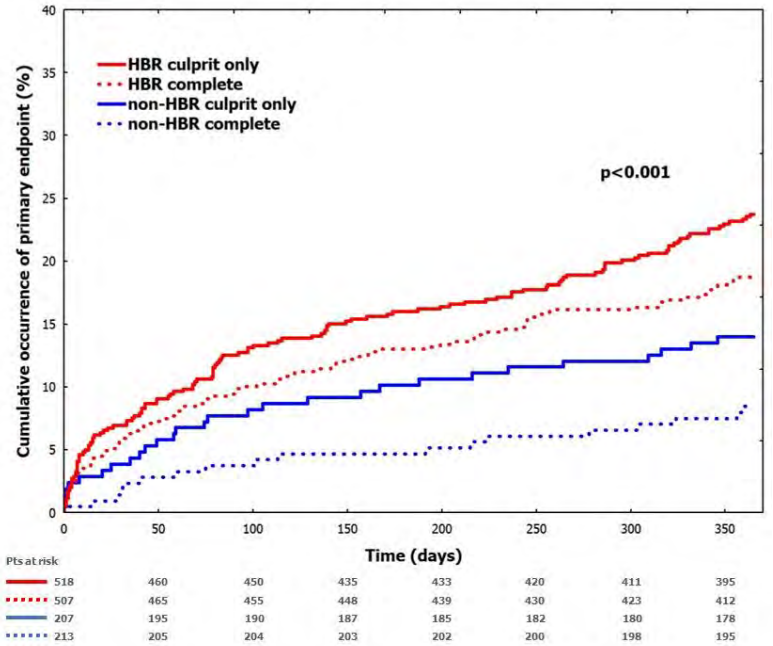
Non-HBR

P=0.236

P=0.878

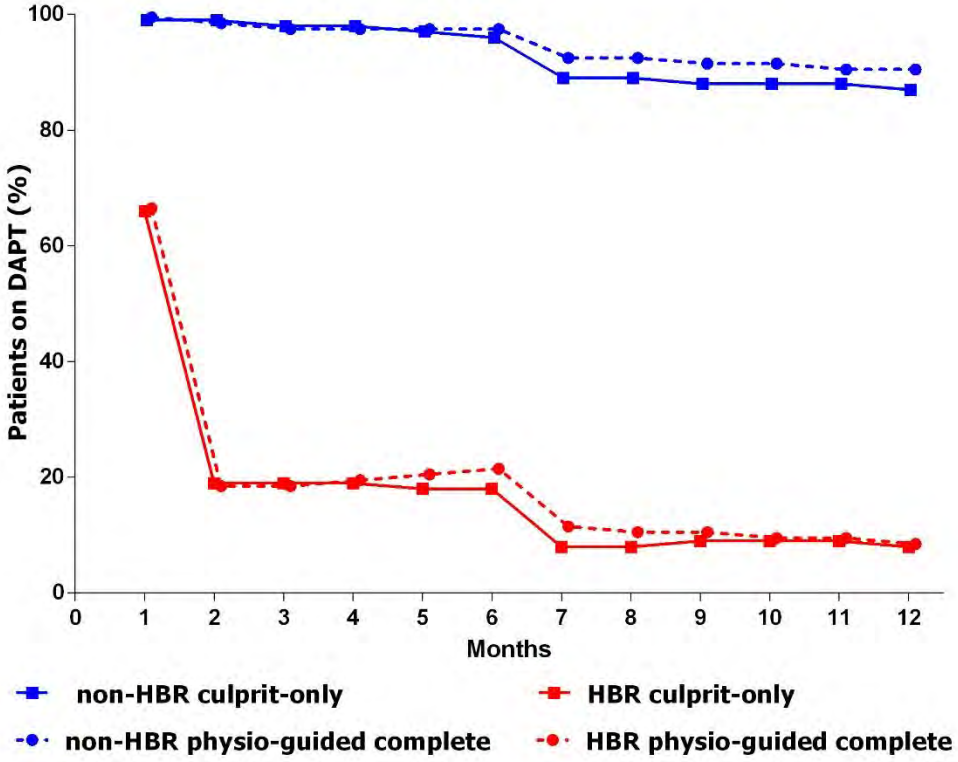
P=0.081

Primary Endpoint



DAPT in HBR patients in the FIRE trial

- In HBR patients DAPT was suggested for one month [1].
- In presence of OAT, the protocol suggested DAT (i.e., clopidogrel plus NOAC).
- If the physician opted for TAT (i.e., aspirin, clopidogrel plus NOAC), such a regimen was recommended for a maximum period of 30 days.

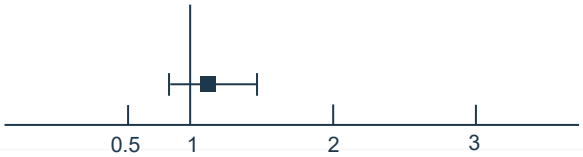


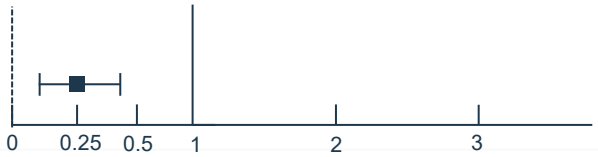
1. Circulation. 2023;147(25):1933-1944

Study Endpoints

DAPT ≤1-month 611 (61%)

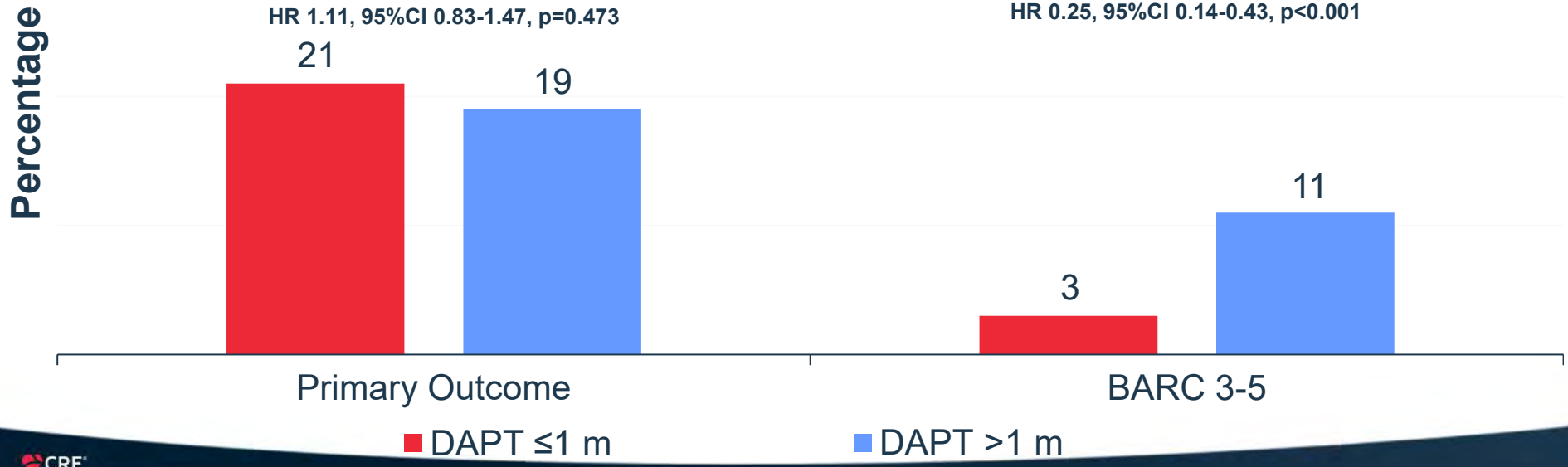
DAPT >1-month 398 (39%)





HR 1.11, 95%CI 0.83-1.47, p=0.473

HR 0.25, 95%CI 0.14-0.43, p<0.001



*The baseline characteristics of these 2 subgroups did not differ except for diabetes that was less frequent in HBR patients treated with DAPT regimen ≤1-month

Limitations

- To investigate the effect of physiology-guided complete revascularization in HBR patients was not the primary aim of the FIRE trial
- Findings on secondary endpoints should be considered with caution
- It remains uncertain whether our study's outcomes can be extrapolated to patients managed with different strategies and stent platforms

Conclusions

1. HBR status *amplifies* the risk of adverse events in a group of older MI patients with MVD
2. In HBR patients *Physio-guided complete* revascularization reduced primary and key secondary endpoint and should be pursued
3. *Short DAPT* regimen was safe regarding ischemic events and effective in major bleeding reduction in HBR patients treated with Supraflex Cruz

FIRE trial – Editorial Comment

Hector M. Garcia-Garcia, MD, PhD

Professor of Medicine, Georgetown University

Washington Hospital Center

Disclosure of Relevant Financial Relationships

Within the prior 24 months, I have had a relevant financial relationship with a company producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients:

Nature of Financial Relationship	Ineligible Company
Grant/Research Support	Phillips, Boston Scientific, Abbott, MedAlliance, Medis, Corflow, Chiesi, ACIST, Medtronic,
Consultant Fees/Honoraria	Boston Scientific, Abbott, MedAlliance, Medis, ACIST

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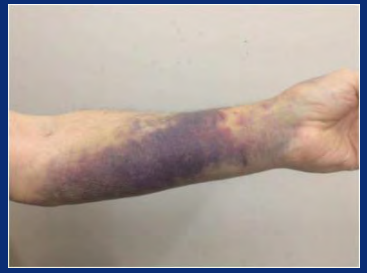
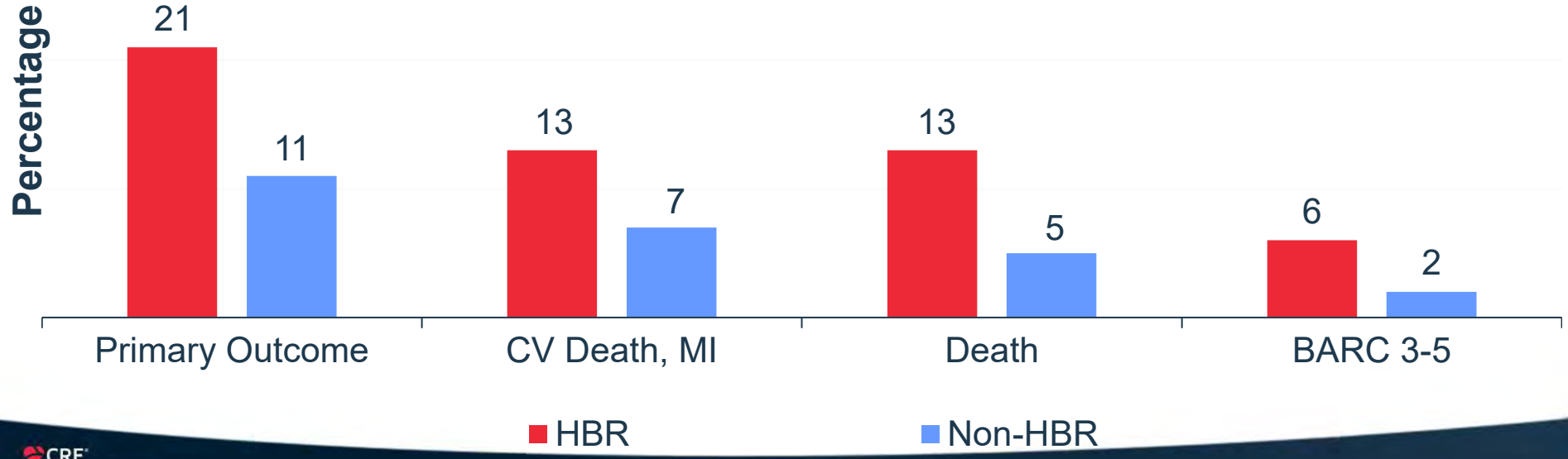
Study Endpoints



LESSON #1

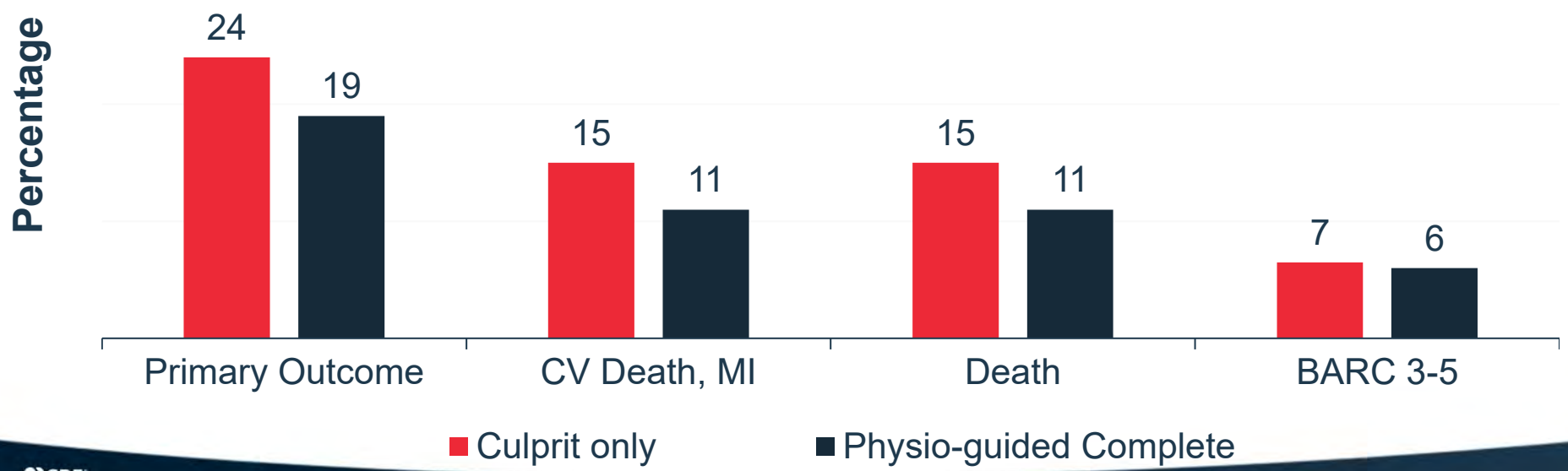
HBR = HIGH ISCHEMIC RISK



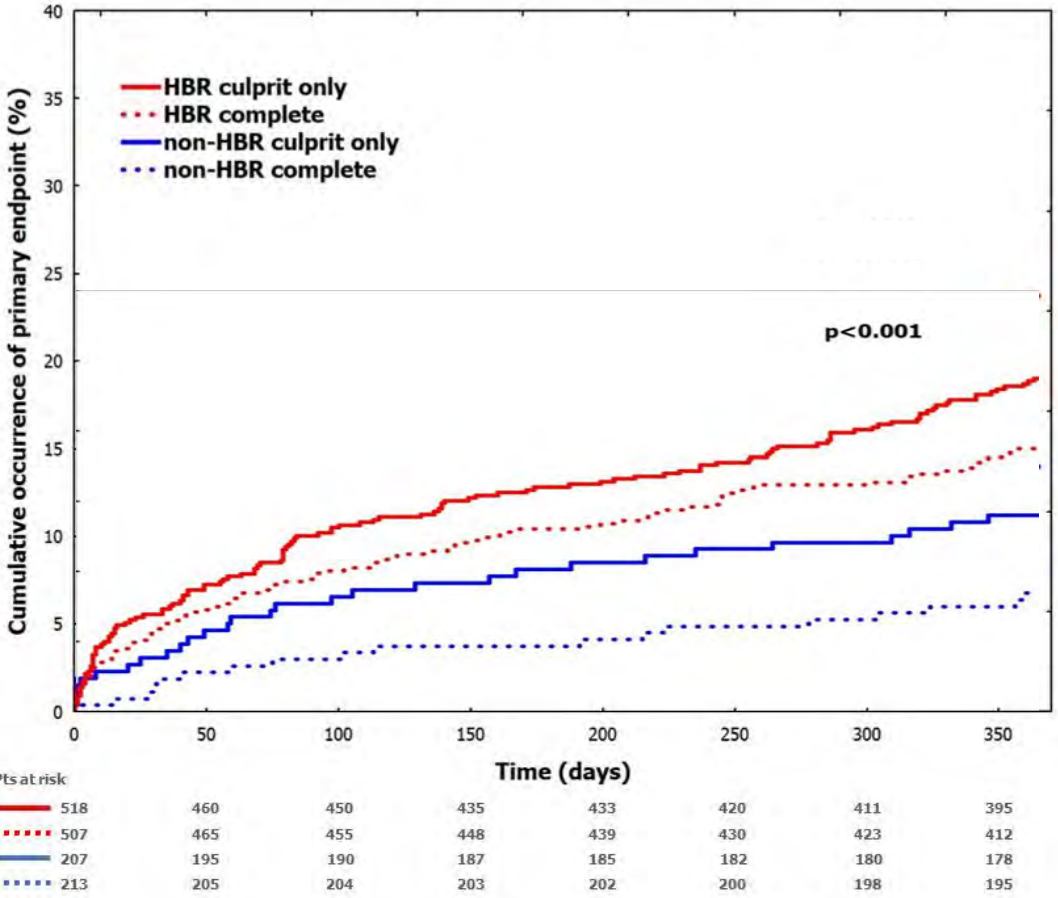
Study Endpoints

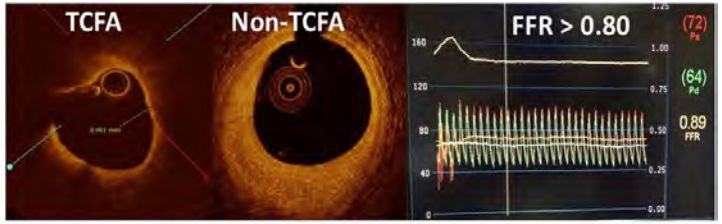
LESSON #2

FFR/QFR ⬇ ISCHEMIC RISK in AMI



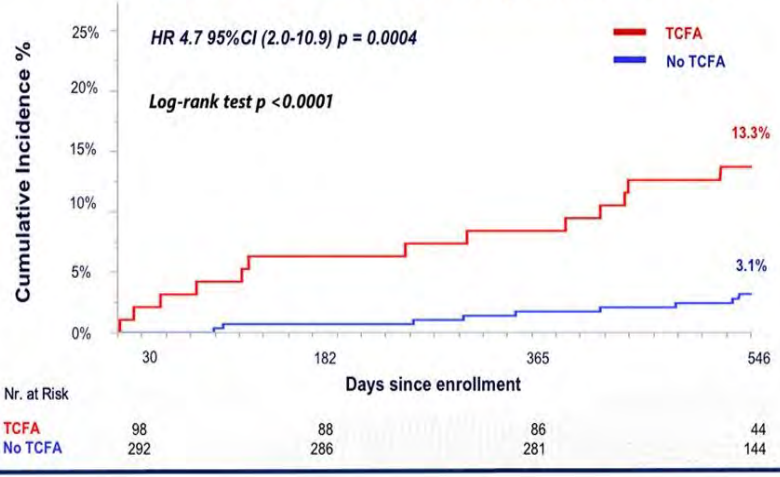
Primary Endpoint Met, but there is a VERY high residual risk





Conclusions: In DM patients, TCFA represents 25% of

Primary Endpoint
(CD, TVMI, CD-TLR, or Hospitalization UAP)



Eur Heart J, Volume 42, Issue 45, 1 December 2021, Pages 4671–4679

ORIGINAL ARTICLE

Complete or Culprit-Only PCI in Older Patients with Myocardial Infarction

S. Biscaglia, V. Guiducci, J. Escaned, R. Moreno, V. Lanzilotti, A. Santarelli, E. Cerrato, G. Sacchetta, A. Jurado-Roman, A. Menozzi, I. Amat Santos, J.L. Díez Gil, M. Ruozzi, M. Barbierato, L. Fileti, A. Picchi, V. Lodolini, G. Biondi-Zoccai, E. Maietti,* R. Pavasini, P. Cimaglia, C. Tumscitz, A. Erriquez, C. Penzo, I. Colaiori, G. Pignatelli, G. Casella, G. Iannopollo, M. Menozzi, F. Varbella, G. Caretta, D. Dudek, E. Barbato, M. Tebaldi, and G. Campo, for the FIRE Trial Investigators†

ABSTRACT

BACKGROUND

The benefit of complete revascularization in older patients (≥75 years of age) with myocardial infarction and multivessel disease remains unclear.

METHODS

In this multicenter, randomized trial, we assigned older patients with myocardial infarction and multivessel disease who were undergoing percutaneous coronary intervention (PCI) of the culprit lesion to receive either physiology-guided complete revascularization of nonculprit lesions or to receive no further revascularization. Functionally significant nonculprit lesions were identified either by pressure wire or angiography. The primary outcome was a composite of death, myocardial infarction, stroke, or any revascularization at 1 year. The key secondary outcome was a composite of cardiovascular death or myocardial infarction. Safety was assessed as a composite of contrast-associated acute kidney injury, stroke, or bleeding.

RESULTS

A total of 1445 patients underwent randomization (720 to receive complete revascularization and 725 to receive culprit-only revascularization). The median age of the patients was 80 years (interquartile range, 77 to 84); 528 patients (36.5%) were women, and 509 (35.2%) were admitted for ST-segment elevation myocardial infarction. A primary-outcome event occurred in 113 patients (15.7%) in the complete-revascularization group and in 152 patients (21.0%) in the culprit-only group (hazard ratio, 0.73; 95% confidence interval [CI], 0.57 to 0.93; P=0.01). Cardiovascular death or myocardial infarction occurred in 64 patients (8.9%) in the complete-revascularization group and in 98 patients (13.5%) in the culprit-only group (hazard ratio, 0.64; 95% CI, 0.47 to 0.88). The safety outcome did not appear to differ between the groups (22.5% vs. 20.4%; P=0.37).

CONCLUSIONS

Among patients who were 75 years of age or older with myocardial infarction and multivessel disease, those who underwent physiology-guided complete revascularization had a lower risk of a composite of death, myocardial infarction, stroke, or ischemia-driven revascularization at 1 year than those who received culprit-lesion–only PCI. (Funded by Consorzio Futuro in Ricerca and others; FIRE ClinicalTrials.gov number, NCT03772743.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Biscaglia can be contacted at bscsmn@unife.it or at the Cardiology Unit, Azienda Ospedaliera Universitaria S. Anna, Via Aldo Moro 8, 44124 Cona, Italy.

*Deceased.

†A list of the FIRE trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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An increasing proportion of older patients (≥75 years of age) are being admitted to hospitals with myocardial infarction. Although increasing age is a known predictor of a poor outcome after myocardial infarction, patients in this older age group are often excluded or underrepresented in clinical trials, and many are treated conservatively or suboptimally.[1,2] Clinicians often face challenges in medical and procedural treatment of older patients with myocardial infarction because of a lack of robust evidence in this age group, concerns about complications, perceptions of poor outcomes, and low success rates.[3,4]

One such challenge is the decision regarding whether to pursue complete coronary-artery revascularization by treating nonculprit lesions with percutaneous coronary intervention (PCI).[5,6] Although the benefits of complete revascularization are well established in younger patients with myocardial infarction who have multivessel coronary artery disease,[7,8] such benefits in older patients with myocardial infarction who are at higher risk for complications are uncertain.[9,10] To address this knowledge gap, we conducted a multicenter, randomized trial involving older patients with myocardial infarction and multivessel disease to investigate whether complete revascularization that is performed on the basis of coronary physiology is superior to culprit-only PCI.

Methods

Trial Design and Oversight

The Functional Assessment in Elderly MI Patients with Multivessel Disease (FIRE) trial was an investigator-initiated, multicenter, prospective, superiority, randomized trial that was designed to evaluate a strategy of physiology-guided complete myocardial revascularization as compared with a culprit-only strategy in older patients (≥75 years of age) who had either ST-segment elevation myocardial infarction (STEMI) or non–ST-segment elevation myocardial infarction (NSTEMI) and multivessel disease. The executive committee was responsible for the protocol design and for the conduct and oversight of the trial. The protocol (available with the full text of this article at NEJM.org) was approved by the institutional review board at each participating center.

The nonprofit organization Consorzio Futuro in Ricerca served as the trial sponsor and received unrestricted funding from Sahajanand Medical Technologies, Medis Medical Imaging Systems, Eukon, Siemens Healthineers, General Electric Healthcare, and Insight Lifetech. The companies that provided funds had no involvement in the trial design; in the collection, analysis, or interpretation of the data; or in the writing of the manuscript.

The authors attest to the accuracy and completeness of the data and adherence of the trial to the protocol. A data and safety monitoring committee provided oversight and assessed the safety profile of the trial. Independent contract research organizations were responsible for site monitoring and data collection (see the Supplementary Appendix, available at NEJM.org).

Patients

Patients were eligible for inclusion in the trial if they were at least 75 years of age, had been admitted to the hospital with either STEMI or NSTEMI, had undergone successful PCI of the culprit lesion, and had multivessel disease with at least one lesion in a nonculprit coronary artery that had a minimum vessel diameter of 2.5 mm and a visually estimated diameter stenosis of 50 to 99%. Exclusion criteria included an inability to identify a clear culprit lesion (on the basis of clinical history, electrocardiography, echocardiography, and angiography), localization of the nonculprit lesion in the left main coronary artery, planned or previous surgical revascularization, or life expectancy of less than 1 year. Detailed lists of inclusion and exclusion criteria have been published previously[11] and are provided in the Supplementary Appendix. All the patients provided written informed consent to participate in the trial.

Randomization

After successful treatment of the culprit lesion, the patients underwent randomization either immediately or within 48 hours. With the use of a central randomization system, patients were assigned in a 1:1 ratio to receive either physiology-guided complete revascularization or culprit-only revascularization. Randomization was concealed with the use of a Web-based system (Integrated Clinical Trial Environment, AdvicePharma), and treatment assignment was determined by a computer-generated randomization list stratified according to center, sex, and clinical presentation with STEMI or NSTEMI.

TREATMENTS AND FOLLOW-UP

Patients who had been randomly assigned to receive physiology-guided complete revascularization underwent PCI of all functionally significant nonculprit lesions.[11] Both physiological assessment and PCI of nonculprit lesions were allowed during either the index intervention or in a staged procedure within the index hospitalization.

Physiological assessment was conducted by means of wire-based methods (hyperemic or nonhyperemic) and angiography-based (quantitative flow ratio) measurements (Medis QFR, Medis Medical Imaging Systems).[11] A functionally significant nonculprit lesion was defined as a lesion with a hyperemic, nonhyperemic, or angiography-based threshold ratio of 0.80, 0.89, and 0.80 or less, respectively. Patients who had been randomly assigned to undergo culprit-only revascularization did not undergo any physiological assessment or revascularization of nonculprit lesions.[11]

The use of sirolimus-eluting, biodegradable polymer, ultrathin stents (Supraflex Cruz, Sahajanand Medical Technologies) was strongly suggested.[11] Guideline-based medical therapy was indicated for both treatment groups. Dual antiplatelet therapy for a minimum of 1 year was recommended, except for patients at high risk for bleeding.[11] Follow-up visits occurred at 1 month and 12 months and were then scheduled annually for up to 5 years after randomization.

OUTCOMES

The primary outcome was a composite of death, myocardial infarction, stroke, or ischemia-driven coronary revascularization occurring within 1 year after randomization.[11] A key secondary outcome was a composite of cardiovascular death or myocardial infarction at 1 year. Other secondary outcomes were the individual components of the primary outcome.[11]

The safety outcome was a composite of contrast-associated acute kidney injury, stroke, or bleeding defined as type 3, 4, or 5 by the Bleeding Academic Research Consortium (BARC) at 1 year.[11] Outcome events were adjudicated according to definitions of the Academic Research Consortium and BARC consensus documents.[12,13] A detailed description of outcome definitions is provided in the Supplementary Appendix. All events were reported by investigators and analyzed and adjudicated by an independent clinical evaluation committee whose members were unaware of group assignments.

STATISTICAL ANALYSIS

We assumed that a primary-outcome event would occur in 15% of the patients in the culprit-only group, with an anticipated relative risk reduction of at least 30% in the complete-revascularization group.[11] On the basis of these assumptions, we determined that the enrollment of 1358 patients would provide the trial with 80% power to show the superiority of complete revascularization over culprit-only revascularization at an alpha level of 5%. All hypothesis tests were two-sided, and a P value of less than 0.05 was considered to indicate statistical significance. To account for an anticipated 2% attrition, the final sample size was increased to 1385.[11] All the analyses were performed on an intention-to-treat basis.[11]

The two treatment groups were compared for baseline characteristics to ensure that the randomization process had minimized any differences between groups. Time-to-event plots were constructed for clinical events. A primary event was defined as the first occurrence of any outcome in the composite. Cox proportional-hazard models were fitted to estimate hazard ratios with 95% confidence intervals for treatment comparisons with respect to the primary outcome and the overall risk of death. Estimates and confidence intervals for the outcomes that included cardiovascular death were adjusted for the competing risk of noncardiovascular death. Other secondary and safety outcomes were adjusted for the competing risk of death.[14] The widths of the confidence intervals have not been adjusted for multiplicity, so the confidence intervals should not be used for hypothesis testing. The expected amount of missing data was minimal, and no imputation of missing values was performed for the outcomes. However, imputation of missing values with the use of multiple imputation techniques could be performed in case of any missing data for covariates (e.g., baseline characteristics and laboratory results).

Additional details about the statistical analysis are provided in the trial protocol document. All the analyses were performed with the use of R statistical software (Foundation for Statistical Computing).

RESULTS

PATIENTS

From July 18, 2019, to October 25, 2021, a total of 1898 patients at 34 sites in Italy, Spain, and Poland were screened for the trial (Fig. S1 in the Supplementary Appendix). Of these patients, 1445 were randomly assigned to receive either physiology-guided complete revascularization (720 patients) or culprit-only revascularization (725 patients). Randomization occurred at the time of the index procedure in 877 patients (60.7%) and within 48 hours after the index procedure in 568 patients (39.3%).

The characteristics of the patients at baseline and procedural data are provided in Table 1 and Table 2, respectively. Details regarding the representativeness of the patient sample with respect to race, ethnic background, age, and sex of the broader population affected by myocardial infarction are provided in Table S1. The median age of the patients was 80 years (interquartile range, 77 to 84), 528 patients (36.5%) were women, and 509 (35.2%) were admitted for STEMI. The assigned treatment was performed in 693 patients (96.2%) in the complete-revascularization group and in 706 patients (97.4%) in the culprit-only group (Fig. S1). In the complete-revascularization group, physiological assessment of at least one nonculprit vessel was performed in 700 patients (97.2%); this assessment identified 357 patients (49.6%) with at least one functionally significant nonculprit vessel. Revascularization of at least one nonculprit vessel was performed in 361 patients (50.1%); of these patients, 346 had a functionally significant nonculprit vessel, 4 had a negative physiological assessment, and 11 did not receive physiological assessment before PCI. A detailed description of the physiology-guided management according to patient and according to nonculprit vessel is shown in Figure S2. The median length of hospital stay was 5 days (interquartile range, 4 to 8) and appeared to be longer in the complete-revascularization group than in the culprit-only group (6 days [interquartile range, 4 to 8] and 5 days [interquartile range, 3 to 7], respectively) (Table 1).

PRIMARY OUTCOME

One-year follow-up data were complete for 1444 of 1445 patients (99.9%) (Fig. S1). A primary-outcome event occurred in 113 patients (15.7%) in the complete-revascularization group and in 152 patients (21.0%) in the culprit-only group (hazard ratio, 0.73; 95% confidence interval [CI], 0.57 to 0.93; P=0.01) (Table 3 and Fig. 1A). The number needed to treat to prevent the occurrence of one primary-outcome event was 19 patients.

SECONDARY OUTCOMES

Secondary outcomes are summarized in Table 3. The incidence of the composite outcome consisting of cardiovascular death or myocardial infarction appeared to be lower in the complete-revascularization group (hazard ratio, 0.64; 95% CI, 0.47 to 0.88) (Fig. 1B). The number needed to treat to prevent cardiovascular death or myocardial infarction from occurring in 1 patient was 22 patients.

With the exception of stroke, the incidence of the individual components of the primary outcome appeared to be lower in the complete-revascularization group, including death from any cause (hazard ratio, 0.70; 95% CI, 0.51 to 0.96) (Figs. S3 through S6); the number needed to treat to prevent one death from occurring was 27 patients. Subgroup analyses showed that the effect of complete revascularization on the primary outcome appeared to be consistent across prespecified subgroups (Fig. 2).

SAFETY

There was no apparent difference between the two treatment groups in the incidence of the composite safety outcome consisting of contrast-associated acute kidney injury, stroke, or bleeding (as defined as BARC type 3, 4, or 5), with 22.5% in the complete-revascularization group and 20.4% in the culprit-only group (hazard ratio, 1.11; 95% CI, 0.89 to 1.37; P=0.37) (Table 3).

DISCUSSION

In the FIRE trial, we evaluated the efficacy of physiology-guided complete revascularization as compared with a strategy of culprit-only PCI in patients who were at least 75 years of age with myocardial infarction and multivessel disease. Results showed that physiology-guided complete revascularization resulted in a 27% lower relative risk of a composite of death, myocardial infarction, stroke, or ischemia-driven revascularization than culprit-only revascularization. The benefit was driven by a reduction in each indi-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Culprit-Only Revascularization (N = 725)	Complete Revascularization (N = 720)
Median age (IQR) — yr	80 (77–84)	81 (77–84)
Female sex — no. (%)	265 (36.6)	263 (36.5)
Coexisting illness — no. (%)		
Hypertension	592 (81.7)	593 (82.4)
Dyslipidemia	375 (51.7)	384 (53.3)
Diabetes	233 (32.1)	230 (31.9)
Current smoker	62 (8.6)	61 (8.5)
Previous myocardial infarction	116 (16.0)	104 (14.4)
Previous percutaneous coronary intervention	136 (18.8)	121 (16.8)
Atrial fibrillation	109 (15.0)	91 (12.6)
Estimated glomerular filtration rate of <60 ml/min†	332 (45.8)	330 (45.8)
Peripheral artery disease	127 (17.5)	122 (16.9)
Stroke	63 (8.7)	56 (7.8)
Clinical presentation — no. (%)		
ST-segment elevation myocardial infarction	256 (35.3)	253 (35.1)
Non–ST-segment elevation myocardial infarction	469 (64.7)	467 (64.9)
Killip class ≥II‡	208 (28.7)	204 (28.3)
Left ventricular ejection fraction — %	49.0±10.9	49.4±10.5
Median length of hospital stay (IQR) — days	5 (3–7)	6 (4–8)
Medication at discharge — no. (%)		
Aspirin	683 (94.2)	692 (96.1)
Clopidogrel	358 (49.4)	371 (51.5)
Ticagrelor	337 (46.5)	326 (45.3)
Prasugrel	16 (2.2)	16 (2.2)
Vitamin K antagonist	36 (5.0)	27 (3.8)
Non–vitamin K antagonist oral anticoagulant	129 (17.8)	137 (19.0)
Angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker	552 (76.1)	556 (77.2)
Beta-blocker	541 (74.6)	556 (77.2)
Statin	661 (91.2)	680 (94.4)

* Plus–minus values are means ±SD. IQR denotes interquartile range.
† The estimated glomerular filtration rate was calculated by means of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.
‡ Killip class II indicates findings consistent with mild-to-moderate heart failure, class III the presence of overt pulmonary edema, and class IV the presence of cardiogenic shock.

vidual component of the composite outcome, with the exception of stroke. In addition, physiology-guided complete revascularization was associated with a 36% relative reduction in the composite outcome consisting of cardiovascular death or myocardial infarction.

The daily treatment of older patients with myocardial infarction is becoming increasingly challenging from therapeutic, organizational, and economic perspectives.[6,15,16] The debate concerns the resource-intensive nature of invasive procedures and hospitalizations, along with the lack of strong evidence from randomized trials to support such treatment in this patient population.[6] Studies have

Table 2. Procedural Characteristics.*

Characteristic	Culprit-Only Revascularization (N=725)	Complete Revascularization (N=720)
Procedure		
Total performed — no.	725	961
Index — no.		
All	725	720
With PCI of nonculprit vessels	19†	232
Staged — no.		
All	—	241
With PCI of nonculprit vessels	—	129
Interval between index and staged procedure (IQR) — days	—	3 (2–4)
Radial access — no./total no. of procedures (%)	672/725 (92.7)	911/961 (94.8)
Culprit vessel — no. (%)		
Left main coronary artery	41 (5.7)	35 (4.9)
Left anterior descending artery	330 (45.5)	329 (45.7)
Circumflex artery	133 (18.3)	136 (18.9)
Right coronary artery	209 (28.8)	204 (28.3)
Ramus intermedius artery	12 (1.7)	16 (2.2)
Number of nonculprit vessels per patient — no. (%)		
1	510 (70.3)	503 (69.9)
≥2	215 (29.7)	217 (30.1)
Location of nonculprit vessel — no./total no. (%)		
Left anterior descending artery	291/951 (30.6)	296/948 (31.2)
Circumflex artery	319/951 (33.5)	308/948 (32.5)
Right coronary artery	320/951 (33.6)	310/948 (32.7)
Ramus intermedius artery	21/951 (2.2)	34/948 (3.6)
Reference vessel diameter (IQR) — mm	3.0 (2.5–3.0)	3.0 (2.5–3.0)
Stenosis		
Diameter (IQR) — (%)	70 (60–80)	70 (60–80)
Percent diameter — no./total no. of nonculprit vessels (%)		
50–69%	401/951 (42.2)	390/948 (41.1)
70–89%	378/951 (39.7)	380/948 (40.1)
90–99%	172/951 (18.1)	178/948 (18.8)
Physiological assessment — no./total no. of nonculprit vessels (%)	—	909/948 (95.9)
Type of physiological assessment — no./total no. of nonculprit vessels tested (%)		
Wire-based hyperemic index	—	451/909 (49.6)
Wire-based nonhyperemic index	—	138/909 (15.2)
Angiography-based index	—	320/909 (35.2)
Functionally significant nonculprit vessels — no./total no. of nonculprit vessels (%)	—	425/948 (44.8)
Nonculprit vessel treated with PCI — no./total no. of nonculprit vessels (%)	—	431/948 (45.5)

* Because of rounding, the percentages may not total 100. PCI denotes percutaneous coronary intervention.
† These revascularizations were protocol violations. Details regarding these procedures are provided in Figure S1 in the Supplementary Appendix.

Table 3. Efficacy and Safety Outcomes.*

Outcome	Culprit-Only Revascularization (N=725)	Complete Revascularization (N=720)	Hazard Ratio (95% CI)†	P Value
	number of patients (percent)			
Primary outcome				
Composite of death, myocardial infarction, stroke, or ischemia-driven revascularization	152 (21.0)	113 (15.7)	0.73 (0.57–0.93)	0.01
Key secondary outcomes				
Cardiovascular death or myocardial infarction	98 (13.5)	64 (8.9)	0.64 (0.47–0.88)	
Other secondary outcomes				
Death				
From any cause	93 (12.8)	66 (9.2)	0.70 (0.51–0.96)	
From cardiovascular cause	56 (7.7)	36 (5.0)	0.64 (0.42–0.97)	
Myocardial infarction	51 (7.0)	32 (4.4)	0.62 (0.40–0.97)	
Death or myocardial infarction	133 (18.3)	93 (12.9)	0.68 (0.52–0.88)	
Stroke	7 (1.0)	12 (1.7)	1.73 (0.68–4.40)	
Ischemia-driven coronary revascularization	49 (6.8)	31 (4.3)	0.63 (0.40–0.98)	
Other outcomes				
Noncardiovascular death	37 (5.1)	30 (4.2)	0.82 (0.50–1.32)	
Cerebrovascular accident‡	9 (1.2)	18 (2.5)	2.03 (0.91–4.52)	
Transient ischemic attack	2 (0.3)	6 (0.8)	3.06 (0.62–15.1)	
Stent thrombosis				
Definite	5 (0.7)	6 (0.8)	1.21 (0.37–3.96)	
Probable	3 (0.4)	1 (0.1)	0.34 (0.04–3.22)	
Safety outcome				
Composite of contrast-associated acute kidney injury, stroke, or BARC type 3, 4, or 5 bleeding	148 (20.4)	162 (22.5)	1.11 (0.89–1.37)	0.37
Contrast-associated acute kidney injury	116 (16.0)	129 (17.9)	1.11 (0.87–1.42)	
BARC type 3, 4, or 5 bleeding	36 (5.0)	34 (4.7)	0.95 (0.59–1.53)	

* BARC denotes Bleeding Academic Research Consortium.
† The widths of the confidence intervals have not been adjusted for multiplicity, so the confidence intervals should not be used for hypothesis testing.
‡ Cerebrovascular accident includes stroke and transient ischemic attack.

shown that complete revascularization that is guided by angiography or physiological assessment is superior to the culprit-only strategy in younger and low-risk patients with STEMI.[8,10] This benefit is mainly driven by the reduction of recurrence of myocardial infarction or the need for repeated revascularization.[7,8] However, older patients with myocardial infarction have unique clinical, anatomic, and procedural characteristics that were not captured by these studies, such as the burden of coexisting illnesses, frailty, more complex coronary anatomy, more frequent presentation with NSTEMI, higher risk of complications, and side effects associated with a multidrug treatment regimen. Thus, there is a need for targeted evidence to guide the management and treatment of older patients with myocardial infarction.[3,6]

The FIRE trial addressed the lack of evidence for a revascularization strategy beyond culprit-lesion–only treatment of older patients with myocardial infarction and multivessel disease. The patients who were enrolled in the trial had a median age of 80 years, which is approximately 20 years older than that in earlier pivotal trials in the field.[8] Because patients in this age group have a high incidence of coexisting illnesses such as

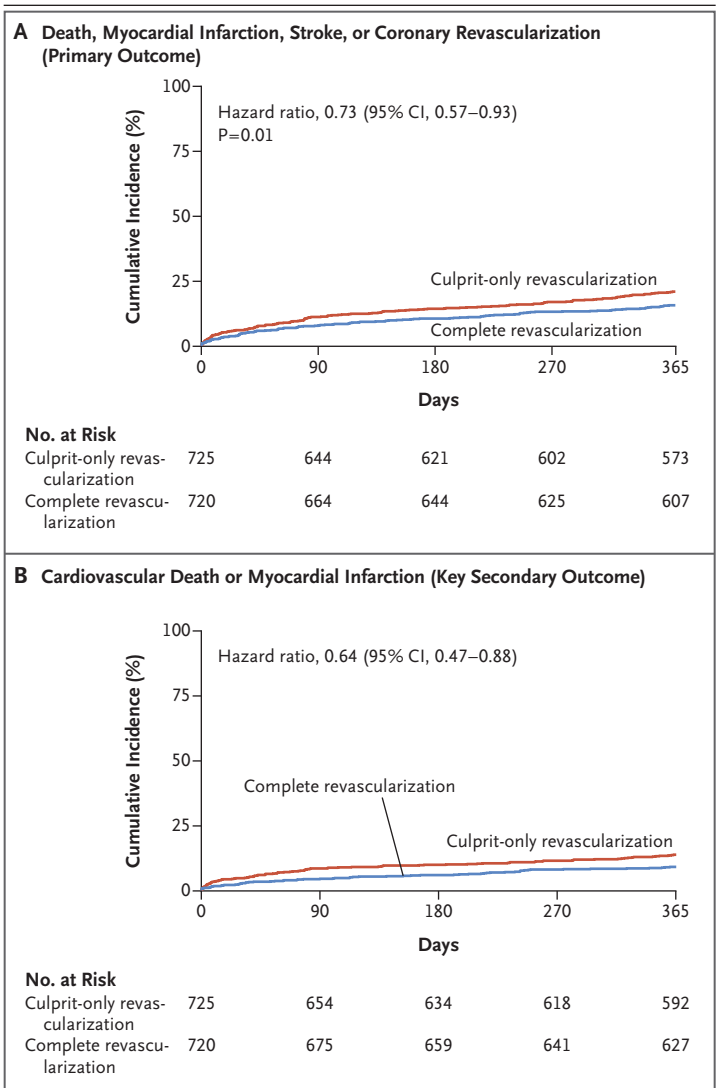

Figure 1. Cumulative Incidence of the Primary and Key Secondary Outcomes.

Shown is the composite primary outcome consisting of death, myocardial infarction, stroke, or ischemia-driven coronary revascularization (Panel A) and the key secondary outcome, a composite of cardiovascular death or myocardial infarction (Panel B). The widths of the confidence intervals have not been adjusted for multiplicity, so the confidence intervals should not be used for hypothesis testing.

diabetes, peripheral artery disease, and chronic kidney disease, the observed frequency of adverse events was also markedly higher than the frequency in previous trials.[7,8] This increase in adverse events was driven mainly by death and myocardial infarction. Elective invasive coronary procedures are less likely to be performed in older patients than in younger patients. However, in our trial, the risk reduction associated with physiology-guided complete revascularization among older patients was consistent with what has been observed in previous trials.[10] Furthermore, the benefit of complete revascularization was observed to accrue over time with continued divergence of the Kaplan–Meier curves during the first year.

In contrast to previous trials, patients with both STEMI and NSTEMI were enrolled in our trial. In patients with myocardial infarction, the safety of physiology-guided revascularization relies on clearly differentiating the culprit lesion from nonculprit lesions.[11] We found that physiology-guided complete revascularization was feasible and safe in patients with either STEMI or NSTEMI as long as the culprit lesion was clearly identifiable on the basis of electrocardiography, echocardiography, and angiography; this was mandated in the trial protocol.

The rationale behind the use of the coronary physiology in older patients is to decrease the number of interventions by treating only the prognostically determined nonculprit vessels at the time of the culprit-vessel treatment and by minimizing the occurrence of complications that portend a worse prognosis. The potential advantage is not limited to periprocedural complications, such as stroke, contrast-associated acute kidney injury, and periprocedural myocardial infarction. The number of treated vessels and implanted stents is a major driver of a prolonged duration of dual-antiplatelet therapy, which is associated with major bleeding and death in patients at risk for increased bleeding. This category includes patients who are at least 75 years of age, which is one of the minor criteria of the Academic Research Consortium for high bleeding risk. In that regard, it is relevant that 483 nonculprit vessels (50.9%) were not treated with PCI on the basis of physiological measurements that did not indicate the need for revascularization at the time of functional testing. The occurrence of the composite safety outcome consisting of contrast-induced acute kidney injury, stroke, or BARC type 3, 4, or 5 bleeding did not appear to be different between the groups, even though there was a numerical increase in the individual components of the composite safety outcome in the complete-revascularization group.

Our trial has several limitations. Because of the open-label design, knowledge of the angiographic results may have resulted in bias among both patients and physicians toward subsequent

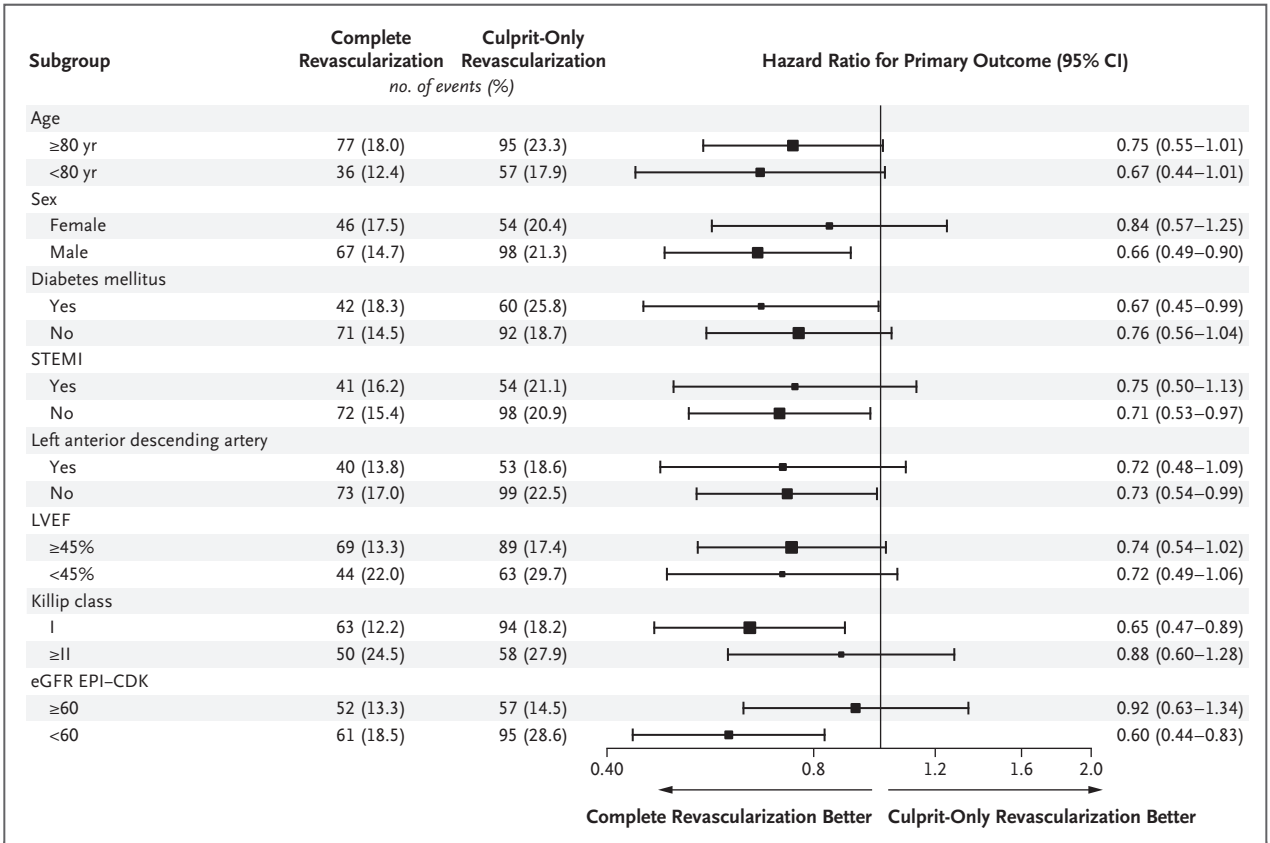

Figure 2. Subgroup Analysis of the Primary Outcome.

Shown are the results of subgroup analyses of the primary outcome, a composite of death, myocardial infarction, stroke, or any revascularization at 1 year. The size of the squares is proportional to the number of patients in each subgroup. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to evaluate treatment effects. The estimated glomerular filtration rate (eGFR) was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. LVEF denotes left ventricular ejection fraction, and STEMI ST-segment elevation myocardial infarction.

revascularization in the culprit-only treatment group. However, it should be noted that events related to ischemia-driven revascularization represented a small portion of the overall primary-outcome events, whereas hard clinical outcomes (e.g., myocardial infarction and death) accounted for the majority of events. Because complete revascularization was guided by coronary physiological assessment, the transferability of the results to angiography-guided complete revascularization should be considered with caution on the basis of the unique characteristics of the trial population. In addition, revascularization was completed during the index hospitalization and with the implantation of sirolimus-eluting, biodegradable-polymer, ultrathin stents. Therefore, it is not known whether the results of our trial may apply to patients who are receiving different management strategies and stent platforms.

Among patients aged 75 years or older with myocardial infarction and multivessel disease, physiology-guided complete revascularization was associated with a lower occurrence of the composite of death, myocardial infarction, stroke, or ischemia-driven revascularization than culprit-only revascularization.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

This article is dedicated to the memory of Dr. Elisa Maietti.

APPENDIX

The authors' full names and academic degrees are as follows: Simone Biscaglia, M.D., Vincenzo Guiducci, M.D., Javier Escaned, M.D., Raul Moreno, M.D., Valerio Lanzilotti, M.D., Andrea Santarelli, M.D., Enrico Cerrato, M.D., Giorgio Sacchetta, M.D., Alfonso Jurado-Roman, M.D., Alberto Menozzi, M.D., Ignacio Amat Santos, M.D., José Luis Díez Gil, M.D., Marco Ruozzi, M.D., Marco Barbierato, M.D., Luca Fileti, M.D., Andrea Picchi, M.D., Veronica Lodolini, B.Sc., Giuseppe Biondi-Zoccai, M.D., Elisa Maietti, Ph.D., Rita Pavasini, M.D., Paolo Cimaglia, M.D., Carlo Tumscitz, M.D., Andrea Erriquez, M.D., Carlo Penzo, M.D., Iginio Colaiori, M.D., Gianluca Pignatelli, M.D., Gianni Casella, M.D., Gianmarco Iannopollo, M.D., Mila Menozzi, M.D., Ferdinando Varbella, M.D., Giorgio Caretta, M.D., Dariusz Dudek, M.D., Emanuele Barbato, M.D., Matteo Tebaldi, M.D., and Gianluca Campo, M.D.

The authors' affiliations are as follows: the Cardiology Unit, Azienda Ospedaliero Universitaria di Ferrara, Ferrara (S.B., V. Lodolini, R.P., P.C., C.T., A.E., C.P., G. Campo), the Cardiology Unit, Azienda Unità Sanitaria Locale (USL) IRCCS Reggio Emilia, S. Maria Nuova Hospital, Reggio Emilia (V.G., G.P.), the Cardiology Unit, Ospedale Maggiore (V. Lanzilotti, G. Casella, G.I.), and the Department of Biomedical and Neuromotor Sciences, University of Bologna (E.M.), Bologna, the Cardiovascular Department, Infermi Hospital, Rimini (A.S., M.M.), the Interventional Cardiology Unit, San Luigi Gonzaga University Hospital, Orbassano, and Rivoli Infermi Hospital ASL TO3, Turin (E.C., F.V.), the Cardiology Unit, Umberto I Hospital, ASP Siracusa, Siracusa (G.S.), S.C. Cardiologia, Ospedale Sant'Andrea, ASL5 Liguria, La Spezia (A.M., G. Caretta), the Cardiology Unit, Ospedale Civile di Baggiovara, Baggiovara (M.R.), Interventional Cardiology, Department of Cardio-Thoracic and Vascular Sciences, Ospedale dell'Angelo, Venice (M.B.), the Department of Cardiology, S. Maria delle Croci Hospital, Ravenna (L.F.), the Cardiovascular Department, Azienda USL Toscana Sud-Est, Misericordia Hospital, Grosseto (A.P.), the Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome (G.B.-Z.), and the Cardiology Unit, Ospedale Santa Maria Goretti, Latina (I.C.), Mediterranea Cardiocentro, Naples (G.B.-Z.), Maria Cecilia Hospital, Cotignola (P.C., D.D.), the Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome (E.B.), and the Interventional Cardiology Unit, Presidio Ospedaliero San Salvatore di Pesaro, Pesaro (M.T.) — all in Italy; Hospital Clínico San Carlos, Complutense University of Madrid (J.E.), Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), and Instituto de Investigación Hospital La Paz, University Hospital La Paz (R.M., A.J.-R.), Madrid, CIBERCV, Department of Cardiology, Hospital Clínico Universitario, Valladolid (I.A.S.), and CIBERCV, Cardiology Department, H. Universitario y Politécnico La Fe, Valencia (J.L.D.G.) — all in Spain; and the Institute of Cardiology, Jagiellonian University Medical College, Krakow, Poland (D.D.).

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JAMA Cardiology | Original Investigation

Complete vs Culprit-Only Revascularization in Older Patients With Myocardial Infarction and High Bleeding Risk
A Randomized Clinical Trial

Andrea Erriquez, MD; Gianluca Campo, MD; Vincenzo Guiducci, MD; Javier Escaned, MD; Raul Moreno, MD; Gianni Casella, MD; Mila Menozzi, MD; Enrico Cerrato, MD; Giorgio Sacchetta, MD; Alberto Menozzi, MD; Ignacio Amat Santos, MD; Enrique Gutiérrez Ibañes, MD; Roberto Scarsini, MD; Giuseppe Vadalà, MD; Giuseppe Andò, MD; José Luis Díez-Gil, MD; Sergio Musto d'Amore, MD; Alessandro Capecchi, MD; Iginio Colaiori, MD; Francesco Gallo, MD; Rita Pavasini, MD; Andrea Marrone, MD; Graziella Pompei, MD; Valerio Lanzilotti, MD; Dariusz Dudek, MD; Emanuele Barbato, MD; Matteo Tebaldi, MD; Simone Biscaglia, MD

IMPORTANCE Patients with high bleeding risk (HBR) have a poor prognosis, and it is not known if they may benefit from complete revascularization after myocardial infarction (MI).

OBJECTIVE To investigate the benefit of physiology-guided complete revascularization vs a culprit-only strategy in patients with HBR, MI, and multivessel disease.

DESIGN, SETTING, AND PARTICIPANTS This was a prespecified analysis of the Functional Assessment in Elderly MI Patients With Multivessel Disease (FIRE) randomized clinical trial data. FIRE was an investigator-initiated, open-label, multicenter trial. Patients 75 years or older with MI and multivessel disease were enrolled at 34 European centers from July 2019 through October 2021. Physiology treatment was performed either by angiography- or wire-based assessment. Patients were divided into HBR or non-HBR categories in accordance with the Academic Research Consortium HBR document.

INTERVENTIONS Patients were randomized to either physiology-guided complete revascularization or culprit-only strategy.

MAIN OUTCOMES AND MEASURES The primary outcome comprised a composite of death, MI, stroke, or revascularization at 1 year. Secondary outcomes included a composite of cardiovascular death or MI and Bleeding Academic Research Consortium (BARC) types 3 to 5.

RESULTS Among 1445 patients (mean [SD] age, 81 [5] years; 917 male [63%]), 1025 (71%) met HBR criteria. Patients with HBR were at higher risk for the primary end point (hazard ratio [HR], 2.01; 95% CI, 1.47-2.76), cardiovascular death or MI (HR, 1.89; 95% CI, 1.26-2.83), and BARC types 3 to 5 (HR, 3.28; 95% CI, 1.40-7.64). The primary end point was significantly reduced with physiology-guided complete revascularization as compared with culprit-only strategy in patients with HBR (HR, 0.73; 95% CI, 0.55-0.96). No indication of interaction was noted between revascularization strategy and HBR status for primary and secondary end points.

CONCLUSIONS AND RELEVANCE HBR status is prevalent among older patients with MI, significantly increasing the likelihood of adverse events. Physiology-guided complete revascularization emerges as an effective strategy, in comparison with culprit-only revascularization, for mitigating ischemic adverse events, including cardiovascular death and MI.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03772743

Visual Abstract

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Simone Biscaglia, MD, Cardiology Unit, Azienda Ospedaliera Universitaria S. Anna, Via Aldo Moro 8, 44124 Cona (FE), Italy (bscsmn@unife.it).

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High bleeding risk (HBR) status represents a heterogenous condition that encompasses advanced age and/or severe comorbid conditions (anemia, chronic kidney disease, other hematological disorders, etc) and/or ongoing oral anticoagulant therapy.[1-4] Irrespective of these factors, HBR status unequivocally correlates with an increased risk of bleeding and ischemic complications.[1-4] To date, endeavors to enhance the outcomes of patients with HBR have predominantly centered on prompt identification of HBR status, choice of the radial artery as preferred vascular access for invasive procedures, optimization of antithrombotic regimens (intensity and length modulation), and selection of new-generation drug-eluting platforms.[5-9] To our knowledge, no data are available regarding the best revascularization strategy. Consensus documents suggest following the appropriate criteria and avoiding unnecessary revascularizations.[9] Randomized clinical trials and meta-analyses have clearly shown that complete revascularization in patients with myocardial infarction (MI) and multivessel disease is associated with a better clinical outcome, but whether this can be extrapolated to patients with HBR, MI, and multivessel disease is unclear.[10-13] The Functional Assessment in Elderly MI Patients With Multivessel Disease (FIRE) randomized clinical trial enrolled patients 75 years or older with MI and multivessel disease and showed a benefit in terms of ischemic adverse events in those randomized to physiology-guided complete revascularization.[12,13] As advanced age is one of the determinants of HBR status, including the fact that comorbidities associated with HBR are more frequent in older patients, the FIRE study population represents a unique opportunity to generate evidence regarding the optimal revascularization strategy for patients with HBR.

Key Points

Question Can patients with high bleeding risk (HBR) and myocardial infarction (MI) benefit from complete revascularization as compared with a culprit-only strategy?

Findings In this prespecified analysis of the Functional Assessment in Elderly MI Patients With Multivessel Disease (FIRE) randomized clinical trial including 1445 patients, HBR status was common in older patients with MI and correlated with a significant increase in the risk of ischemic and bleeding complications. Physiology-guided complete revascularization effectively improves outcomes and decreases complication rate, irrespective of HBR status.

Meaning HBR status alone should not be a deterrent to applying physiology-guided complete revascularization in older patients with MI and multivessel disease.

Methods

The FIRE study was a multicenter, investigator-initiated, randomized clinical trial comparing the efficacy of physiology-guided complete myocardial revascularization vs a culprit-only strategy in older patients with MI and multivessel disease.[12,13] The design, baseline characteristics, and primary results of the trial have been detailed in previous publications.[12,13] All enrolled patients provided written informed consent, and the trial protocol was approved by the institutional review board at each participating center (Supplement 1 and Supplement 2). The present study is a prespecified analysis of the FIRE trial aiming to (1) describe the frequency and prognostic impact of HBR status and (2) investigate the comparative efficacy and safety outcomes across HBR status of physiology-guided complete revascularization vs culprit-only strategy. For the present study, we followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Study Patients

Eligible patients were individuals aged 75 years or older who had been admitted to the hospital with either ST-segment–elevation MI (STEMI) or non–ST-segment–elevation MI (NSTEMI).[9,10] Furthermore, they were required to have undergone successful percutaneous coronary intervention (PCI) of the culprit lesion and needed to present at least 1 nonculprit coronary artery lesion with a minimum diameter of 2.5 mm and a diameter stenosis of 50% to 99%.[12,13] All patients were enrolled in Europe in centers where race and ethnicity heterogeneity is low. The vast majority of patients included in the study were White, therefore, no specific data regarding race and ethnicity were gathered for this study. Exclusion criteria included the inability to distinctly identify a culprit lesion based on clinical history, electrocardiogram, echocardiography, and angiography; presence of the nonculprit lesion in the left main, planned, or prior surgical revascularization; and a life expectancy of less than 1 year.[12,13]

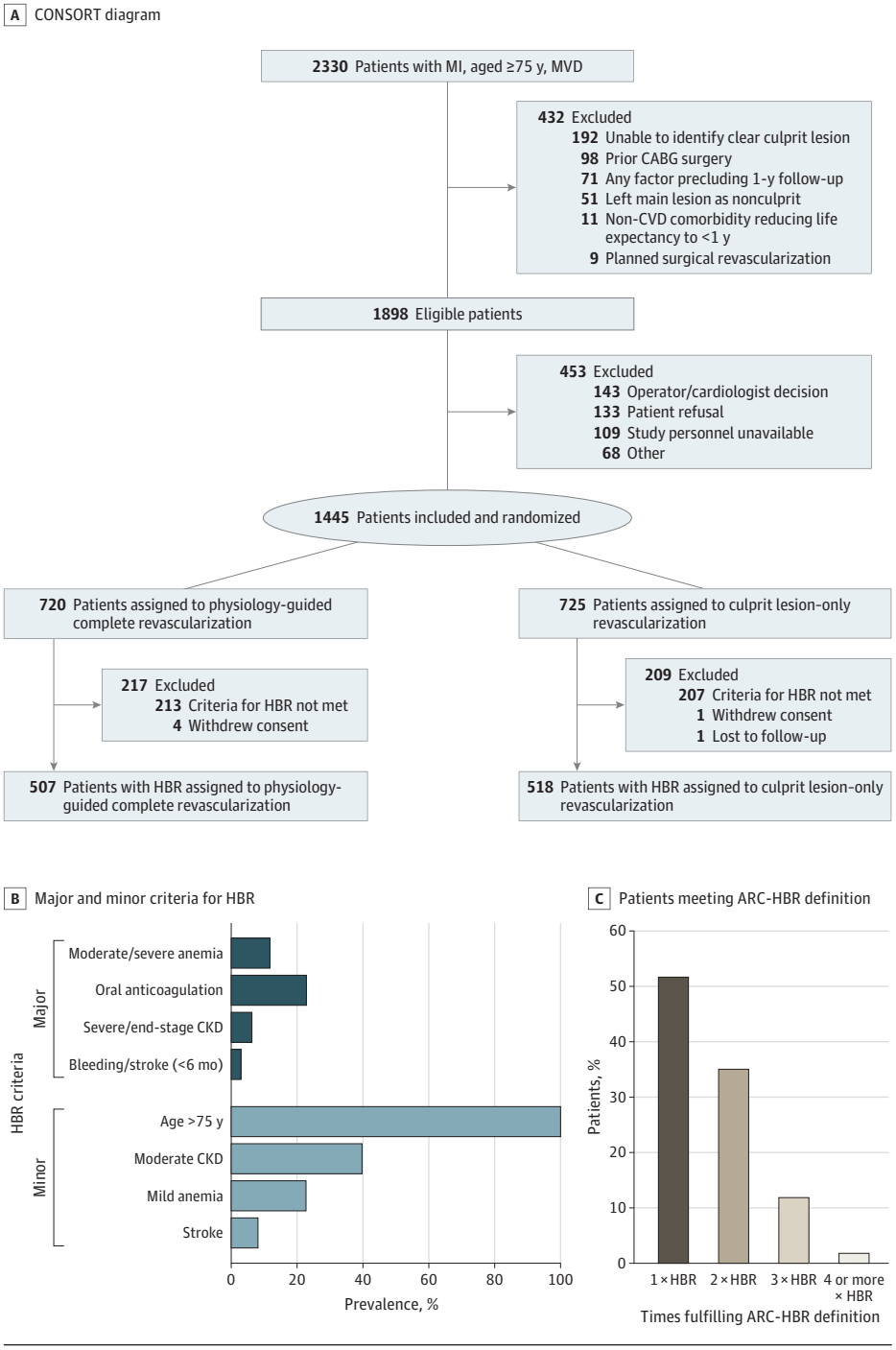
Study Procedures

Patients were randomized between July 18, 2019, and October 25, 2021. Patients who had been randomly assigned to physiology-guided complete revascularization received physiological assessment of nonculprit lesions using wire-based (hyperemic or nonhyperemic) and/or angiography-based (quantitative flow ratio [Medis Medical Imaging Systems B.V.]) measurements. All nonculprit lesions deemed functionally significant were subjected to PCI with subsequent stent implantation.[12,13] Conversely, patients assigned to culprit-only revascularization did not receive revascularization for nonculprit lesions.[12,13] In both treatment groups, the implantation of sirolimus-eluting biodegradable-polymer ultrathin stents (Supraflex Cruz [Sahajanand Medical Technologies]) was strongly recommended.[12,13] All individuals within both treatment arms received optimal medical therapy in accordance with established guidelines.

Study End Points

The primary outcome was a composite end point of death, MI, stroke, or ischemia-driven coronary revascularization occurring within 1 year of randomization.[12,13] A key secondary outcome was the 1-year composite end point of cardiovascular death or MI. Other secondary outcomes comprised the individual components of the primary outcome and bleeding defined by the Bleeding Academic Research Consortium (BARC) types 3, 4, or 5. Outcome events were adjudicated according to definitions of the ARC and BARC consensus documents.[14,15]

Figure 1. Patient Flow Diagram, Prevalence of Academic Research Consortium (ARC)–High Bleeding Risk (HBR) Criteria, and ARC-HBR Definition in the HBR Group



A, Consolidated Standards of Reporting Trials (CONSORT) diagram. B, Prevalence of major and minor ARC-HBR criteria. C, Percentage of patients with HBR meeting 1, 2, 3, or 4 or more times the ARC-HBR definition. CABG indicates coronary artery bypass graft; CKD, chronic kidney disease; CVD, cardiovascular disease; MI, myocardial infarction; MVD, multivessel disease.

All events were reported by investigators and analyzed and adjudicated by an independent clinical evaluation committee, blinded to the randomization arm.

HBR Definition

The criteria for HBR were established in accordance with the ARC-HBR document, and both major and minor HBR criteria were systematically collected within the electronic case report form by the investigators.[3] Patients were categorized as having HBR if they fulfilled at least 1 major criterion or 2 minor criteria. Conversely, individuals not meeting any ARC-HBR criterion or patients with only 1 minor criterion were considered part of the non-HBR group. The study protocol recommended dual antiplatelet therapy (DAPT) for a minimum of 1 year, except for patients with HBR.[12,13] In patients with HBR, in agreement with available consensus document,[16]

Table 1. Baseline Characteristics According to High Bleeding Risk (HBR) Status and Randomization Arm

Characteristic	Non-HBR (n = 420)	HBR (n = 1025)	*P* value	Non-HBR			HBR		
				Culprit only (n = 207)	Physiology-guided complete (n = 213)	*P* value	Culprit only (n = 518)	Physiology-guided complete (n = 507)	*P* value
Age, mean (SD), y	79.6 (4)	81.5 (4)	<.001	79.3 (4)	79.8 (4)	.13	81.6 (5)	81.4 (4)	.62
Sex, No. (%)									
Female	140 (33)	388 (38)	.12	71 (34)	69 (32)	.76	194 (37)	194 (38)	.84
Male	280 (66)	637 (62)		136 (66)	144 (68)		324 (63)	313 (62)	
Medical history, No. (%)									
Hypertension	323 (77)	862 (84)	<.001	49 (24)	48 (22)	.87	434 (84)	428 (84)	.85
Dyslipidemia	232 (55)	527 (51)	.21	117 (56)	115 (54)	.67	258 (50)	269 (53)	.33
Diabetes	120 (28)	343 (33)	.09	56 (27)	64 (30)	.57	177 (34)	166 (33)	.68
Current smoker	46 (11)	77 (8)	.04	16 (8)	30 (14)	.07	46 (9)	31 (6)	.12
Prior MI	40 (10)	180 (17)	<.001	18 (9)	22 (10)	.69	98 (19)	82 (16)	.28
Prior PCI	52 (12)	205 (20)	<.001	26 (12)	26 (12)	.97	110 (21)	95 (19)	.36
History of AF	4 (1)	196 (19)	<.001	2 (1)	2 (1)	.64	107 (21)	89 (17)	.24
eGFR <60[a]	0	662 (65)	<.001	207 (100)	213 (100)	.81	332 (64)	330 (65)	.79
PAD	49 (12)	200 (19)	<.001	22 (11)	27 (13)	.62	105 (20)	95 (19)	.59
CVA	0	119 (12)	<.001	0	0	.81	63 (12)	56 (11)	.65
Clinical presentation, No. (%)									
STEMI	164 (39)	345 (34)	.07	87 (42)	77 (37)	.26	169 (33)	176 (35)	.52
NSTEMI	256 (61)	680 (66)		120 (58)	136 (63)		349 (67)	331 (65)	
Killip ≥2	75 (18)	337 (33)	<.001	34 (16)	41 (19)	.80	177 (34)	163 (32)	.80
LVEF, mean (SD), %	51.1 (10)	48.4 (11)	<.001	51.1 (10)	50.9 (10)	.79	48.2 (11)	48.7 (10)	.41
Culprit vessel, No. (%)									
Left main coronary artery	8 (2)	68 (7)	<.001	4 (2)	4 (2)	.46	37 (7)	31 (6)	.63
Left anterior descending artery	186 (44)	473 (46)		86 (41)	100 (47)		244 (47)	229 (45)	
Circumflex artery	95 (23)	174 (17)		54 (26)	41 (19)		79 (15)	95 (19)	
Right coronary artery	120 (28)	293 (28)		59 (28)	61 (29)		150 (29)	143 (28)	
Ramus intermedius artery	11 (3)	17 (2)		4 (2)	7 (3)		8 (2)	9 (2)	
Antithrombotic drugs at discharge, No. (%)[b]									
Aspirin	419 (99)	956 (93)	<.001	206 (99)	213 (100)	.77	477 (92)	479 (94)	.42
Clopidogrel	103 (25)	626 (61)	<.001	50 (24)	53 (25)	.59	308 (59)	318 (63)	.64
Ticagrelor	297 (71)	366 (36)		149 (72)	148 (69)		188 (36)	178 (35)	
Prasugrel	19 (4.5)	13 (1)		7 (3)	12 (5)		9 (2)	4 (1)	
Vitamin K antagonist	0	63 (6)	<.001	0	0	.77	36 (7)	27 (5)	.34
NOAC	0	266 (26)	<.001	0	0	.77	129 (25)	137 (27)	.48
Dual antiplatelet therapy	419 (99)	676 (66)	<.001	206 (99)	213 (100)	.77	341 (66)	335 (66)	.91
Dual antithrombotic therapy	0	53 (5)	<.001	0	0	>.99	31 (6)	22 (4)	.27
Triple antithrombotic therapy	0	276 (27)	<.001	0	0	>.99	134 (26)	142 (28)	.55

Abbreviations: AF, atrial fibrillation; CVA, cerebrovascular accident; eGFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NOAC, non–vitamin K antagonist oral anticoagulant; NSTEMI, non–ST-segment–elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.

[a] eGFR measured as milliliters per minute per 1.73 m^2 and calculated by Chronic Kidney Disease Epidemiology Collaboration formula.

[b] The analysis considers only patients discharged alive (n = 1009).

DAPT was suggested for 1 month. In the presence of oral anticoagulant therapy, the protocol suggested dual antithrombotic therapy (ie, clopidogrel plus novel oral anticoagulant). If the physician opted for triple antithrombotic therapy (ie, aspirin, clopidogrel, and novel oral anticoagulant), such a regimen was recommended for a maximum period of 30 days.

Statistical Analysis

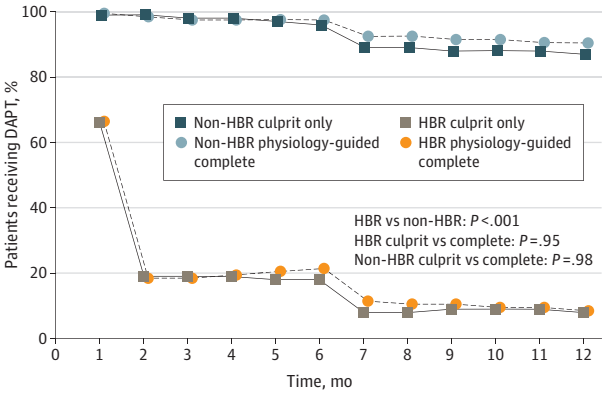
In the present analysis, patients were divided according to HBR status and their assigned randomization arm. Statistical analysis was conducted in accordance with the intention-to-treat principle, where all patients were assessed based on their designated treatment group. The normal distribution of continuous

variables was assessed through the Shapiro-Wilk test. Continuous variables were summarized with means (SD) or median (IQR), and comparisons were executed using the *t* test or Wilcoxon test, as appropriate. Categorical variables were presented as frequencies and percentages, and comparative analyses were conducted using either the Pearson χ^2 or Fisher exact test, in alignment with appropriateness. The pattern over time of patients with DAPT between patients with and without HBR (**Figure 1**) was analyzed with the χ^2 Cochran-Armitage test. Time-to-event data were evaluated with the use of Kaplan-Meier estimates and Cox proportional hazards models, dividing the study population according to HBR status and/or randomization arm. The proportionality assumption was tested by Schoenfeld residuals and was met ($P > .05$ for all outcomes). Estimates and CIs for the outcomes that included cardiovascular death were adjusted for the competing risk of noncardiovascular death. Other secondary and safety outcomes were adjusted for the competing risk of death. Subsequently, we conducted a Cox regression analysis with interaction testing to determine whether the effect of revascularization strategy on the prespecified end points was consistent across both patients with and without HBR. The interaction test was carried out with likelihood ratio tests of the null hypothesis that the interaction coefficient was zero. The statistical analyses were performed using R statistical software, version 4.2 (R Foundation for Statistical Computing). All *P* values were 2-sided, and a *P* value <.05 was considered statistically significant.

Results

Of the total 1445 patients (mean [SD] age, 81 [5] years; 917 male [63%]; 528 female [37%]) enrolled in the FIRE trial, 1025 (71%) fell within the HBR category, as defined by the ARC-HBR criteria (Figure 1A). The prevalence of each major and minor criterion within the HBR group is shown in Figure 1B. Specifically, 511 patients (49.8%) exhibited at least 1 major criterion. Further examination within the HBR group revealed that 528 patients (51.5%) fulfilled the ARC-HBR definition on a singular occasion, 358 (34.9%) met it 2 times, 121 (11.8%) met it 3 times, and 18 (1.8%) met it 4 times or more (Figure 1C). Significant disparities in baseline characteristics emerged between patients with and without HBR (**Table 1**). Compared with patients without HBR, patients in the HBR group were older (mean [SD] age, 81.5 [4] years vs 79.6 [4] years) and had a greater burden of comorbidities (eg, hypertension: 862 of 1025 [84%] vs 323 of 420 [77%]) (Table 1). At hospital admission, Killip class was worse in patients with HBR than those without HBR (337 of 1025 [33%] vs 75 of 420 [18%]) (Table 1). At hospital discharge, patients with HBR had lower left ventricle ejection fraction than those without HBR (mean [SD], 48.4% [11%] vs 51.1% [10%]), with clopidogrel being the most frequently prescribed P2Y12 inhibitor (626 of 1025 [61%] vs 103 of 420 [25%]); conversely, the prescription of DAPT was less common in this group (676 of 1025 [66%] vs 419 of 420 [99%]) (Table 1). DAPT prescription over time was lower in patients with HBR compared with patients in the non-HBR group (*P* for trend < .001) (**Figure 2**). After the first month, fewer than one-fifth of patients with HBR continued taking DAPT (Figure 2). In contrast, the non-HBR and HBR subgroups allocated to physiology-guided complete revascularization vs a culprit-only strategy exhibited a notable alignment in terms of demographics, medical history, clinical presentation, and medications on discharge (Table 1). Analyzing DAPT prescription over time, we observed that it was not associated with randomization arms (Figure 2).

Figure 2. Percentage of Patients Receiving Dual Antiplatelet Therapy (DAPT) Over Time According to High Bleeding Risk (HBR) Status and Randomization Arm



Clinical Outcomes of Patients With and Without HBR

The occurrence of the primary end point was higher in patients with HBR (21% [218 of 1025] vs 11% [47 of 420]; $P < .001$; hazard ratio [HR], 2.01; 95% CI, 1.47-2.76). Similarly, patients with HBR were at increased risk of cardiovascular death or MI (13% [133 of 1025] vs 7% [29 of 420]; $P = .001$; HR, 1.89; 95% CI, 1.26-2.83), death (13% [136 of 1025] vs 5% [23 of 420]; $P < .001$; HR, 2.53; 95% CI, 1.63-3.94), and cardiovascular death (8% [78 of 1025] vs 3% [14 of 420]; $P = .003$; HR, 2.33; 95% CI, 1.32-4.12). As expected, the cumulative occurrence of BARC types 3 to 5 was higher in patients with HBR than in those without HBR (6% [63 of 1025] vs 2% [7 of 420]; $P = .006$; HR, 3.28; 95% CI, 1.40-7.64).

Clinical Outcomes of Physiology-Guided Complete Revascularization vs Culprit-Only According to HBR Status

In the FIRE trial, physiology-guided revascularization was obtained by either angiography- or wire-based assessment (35% [320 of 909 vessels] vs 65% [589 of 909 vessels]). Angiography-based physiology was used both in patients with STEMI and NSTEMI (34% [86 of 249] vs 66% [163 of 249]). The most frequently interrogated vessels by angiography-based physiology were the left anterior descending and right coronary arteries (32% [103 of 320] and 37% [118 of 320], respectively). No significant interaction was noted between revascularization strategy and HBR status with respect to both primary and secondary end points (**Table 2** and **Figure 3**A). The primary end

Table 2. Clinical Outcomes According to Randomization Arm and High Bleeding Risk (HBR) Status

Outcome	Non-HBR (n = 420)			HBR (n = 1025)			
	Culprit only (n = 207)	Physiology-guided complete (n = 213)	*P* value	Culprit only (n = 518)	Physiology-guided complete (n = 507)	*P* value	*P* value for interaction
Primary outcome							
Composite of death, myocardial infarction, stroke, or ischemia-driven revascularization							
No. (%)	29 (14)	18 (8.5)	.07	123 (24)	95 (19)	.04	.55
HR (95% CI)	0.60 (0.33-1.08)			0.73 (0.55-0.96)			
Secondary outcomes							
Cardiovascular death, myocardial infarction							
No. (%)	20 (10)	9 (4)	.03	78 (15)	55 (11)	.047	.24
HR (95% CI)	0.42 (0.19-0.93)			0.71 (0.50-0.99)			
Death							
No. (%)	13 (6)	10 (5)	.49	80 (15)	56 (11)	.04	.88
HR (95% CI)	0.75 (0.33-1.70)			0.70 (0.49-0.98)			
Cardiovascular death							
No. (%)	8 (4)	6 (3)	.56	48 (9)	30 (6)	.04	.72
HR (95% CI)	0.73 (0.25-2.12)			0.62 (0.40-0.98)			
Myocardial infarction							
No. (%)	15 (7)	4 (2)	.01	36 (7)	28 (5.5)	.31	.07
HR (95% CI)	0.24 (0.07-0.83)			0.88 (0.51-1.51)			
Stroke							
No. (%)	2 (1)	2 (1)	.98	5 (1)	10 (2)	.19	.40
HR (95% CI)	0.98 (0.14-6.92)			2.73 (.73-1.31)			
Ischemia-driven coronary revascularization							
No. (%)	10 (5)	5 (2)	.16	39 (7.5)	26 (5)	.10	.76
HR (95% CI)	0.52 (0.18-1.54)			0.64 (0.37-1.09)			
Definite stent thrombosis							
No. (%)	0	0	NA	5 (1)	6 (1)	NA	NA
HR (95% CI)	NA			NA			
Probable stent thrombosis							
No. (%)	0	1 (0.5)	NA	3 (0.5)	0	NA	NA
HR (95% CI)	NA			NA			
BARC type 3, 4, or 5 bleeding							
No. (%)	2 (1)	5 (2)	.29	34 (6.5)	29 (6)	.53	.08
HR (95% CI)	4.88 (0.57-41.98)			0.69 (0.38-1.25)			

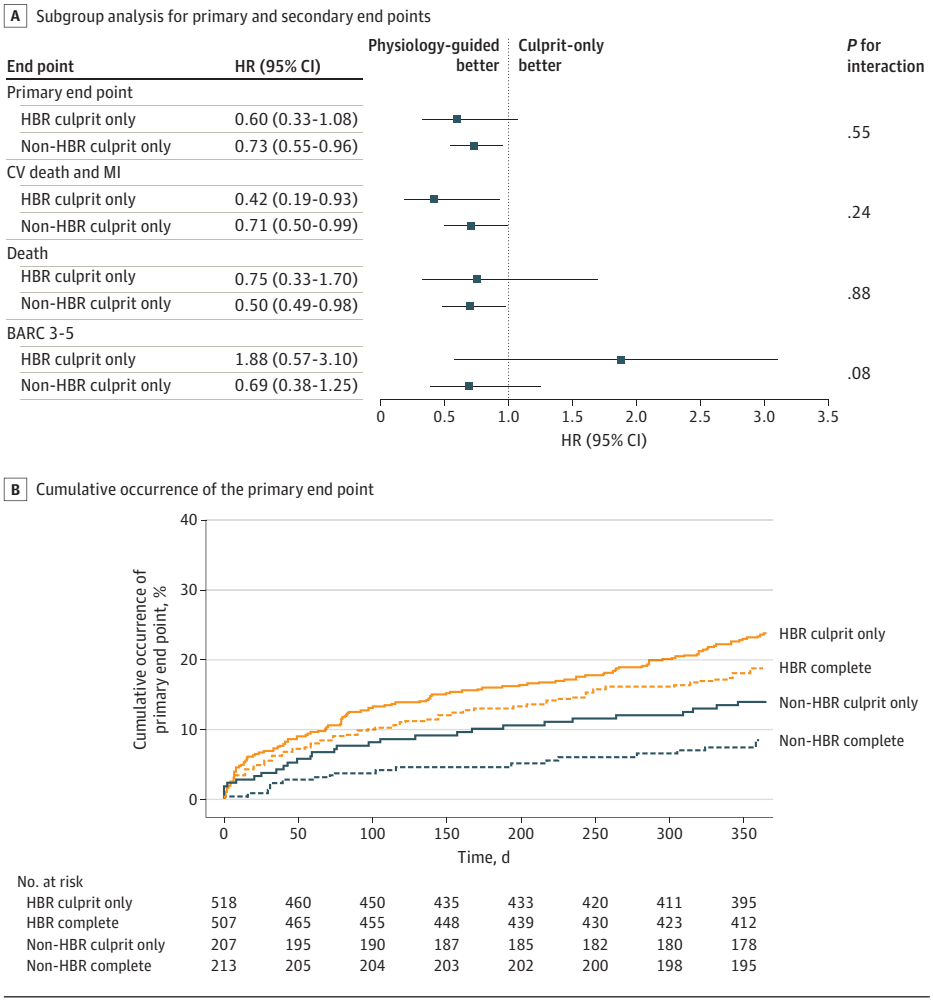
Abbreviations: BARC, Bleeding Academic Research Consortium; HR, hazard ratio; NA, not assessed.

point was significantly reduced with physiology-guided complete revascularization as compared with culprit-only strategy in patients with HBR (19% [95 of 507] vs 24% [123 of 518]; *P* = .04; HR, 0.73; 95% CI, 0.55-0.96), without significant interaction in patients without HBR (8.5% [18 of 213] vs 14% [29 of 207]; *P* = .07; HR, 0.60; 95% CI, 0.33-1.08; *P* for interaction =.55) (Table 2 and Figure 3B). Physiology-guided complete revascularization was consistently associated with lower cardiovascular death or MI in both non-HBR and HBR groups (non-HBR: HR, 0.42; 95% CI, 0.19-0.93; HBR: HR, 0.71; 95% CI, 0.50-0.99; *P* for interaction = .24) (Table 2 and Figure 3A). At further analysis, no indication of interaction was noted between revascularization strategy and HBR status for other secondary end points, including BARC types 3 to 5 (Table 2 and Figure 3A).

Discussion

The primary findings of this study are summarized as follows. First, HBR status was common within a predominantly unselected group of older patients with MI and multivessel disease, with a notable occurrence of 71% (95% CI, 68%-73%). Second, HBR status substantially amplified the risk of adverse events. This is not limited to bleeding complications, but it includes hard ischemic end points such as death and cardiovascular death or MI. Third, physiology-guided complete revascularization led to a meaningful decrease in both primary end point and occurrence of cardiovascular death or MI, independent of HBR status. This underscores the fact that the ex-

Figure 3. Subgroup Analysis for the Primary and Secondary End Points Stratifying Patients in High Bleeding Risk (HBR) and Non-HBR Groups and Cumulative Occurrence of the Primary End Point in Patients According to HBR Status and Randomization Arm



A, Subgroup analysis. B, Kaplan-Meier curve of the cumulative occurrence of the primary end point. BARC indicates Bleeding Academic Research Consortium; CV, cardiovascular; HR, hazard ratio.

pected benefits of complete revascularization remain intact for patients with HBR, despite potential challenges.

PCI stands as the primary approach to address obstructive coronary artery disease, yet clinicians encounter the intricate task of balancing bleeding and ischemia risks. In the past, the focal concern was avoiding periprocedural bleeding complications. Cardiologists commonly used femoral access for PCI, concurrently administering heparin along with glycoprotein IIb/IIIa inhibitors during the procedure. Subsequent studies underscored the fact that radial access and alternative drug protocols, like bivalirudin, notably decreased in-hospital major bleeding incidents.[17,18] This subsequently shifted the spotlight toward averting bleeding after discharge. In 2019, the ARC-HBR established a consensus definition of HBR based on existing evidence.[3] HBR status involves approximately 30% to 40% of the general population of patients undergoing PCI, and it is associated with a significant increase in the risk of bleeding complications and all-cause mortality.[1-4] Trying to generate evidence for the optimization of the outcomes of patients with HBR, many randomized clinical trials have been conducted on vascular access, antithrombotic regimens, and stent platforms.[4-9] Growing evidence supported the benefit of an antithrombotic strategy consisting of antiplatelet monotherapy after a shortened DAPT vs conventional DAPT. Additionally, the safety profile of present stent platforms with shortened DAPT regimen was corroborated.[4-9] However, no investigations have directly tackled the optimal revascularization approach for multivessel disease in patients with HBR presenting with MI.

Available data highlighted that complete revascularization is frequently underused in patients with HBR.[19,20] This observation, although not unexpected, is rooted in clinical practice, where the count of implanted stents and the extensive coronary treatment often dictate prolonged DAPT. In addition, patients with HBR frequently show a more complex coronary anatomy, severe calcifications, 3-vessel disease, all factors that may discourage pursuing complete revascularization due to concerns of periprocedural complications.[21,22] Finally, each procedure carries inherent risks of bleeding that are independent of the revascularization strategy.

Building on this foundation, the clinical implications of our analysis are transformative. We confirmed that HBR status is a common clinical pattern in older patients with MI, undeniably associated with poor prognoses. Allocating resources to a physiology-guided complete revascularization presents a formidable avenue for enhancing prognostic outcomes by significantly curbing the incidences of death, MI, and revascularization.

However, realizing these promising outcomes necessitated meticulous consideration of several pivotal factors. First, the revascularization of nonculprit lesions was guided by coronary physiology. This strategic approach channels efforts toward ischemia-generating lesions, where the prospect of achieving clinical benefits is higher. Coronary physiology guidance results in fewer unnecessary procedures and stents, simplifies the management of 3-vessel disease, and then minimizes the risk of periprocedural complications.[23] Second, the implantation of last generation drug-eluting stents reduced the risk of stent-related adverse events. Finally, in agreement with current standards, patients with HBR who participated in the FIRE trial were treated with short DAPT regimens. This stands as a noteworthy point because the enrolled patients exhibited substantial ischemic risks due to their advanced age, multiple comorbidities, and multivessel disease. Research has demonstrated that in the presence of HBR status, using a prolonged DAPT regimen is not the most effective approach to reduce ischemic risk.[24] The possible advantages of this approach are overshadowed by a higher chance of bleeding complications and their impact on mortality. In these cases, physicians should identify alternative strategies, and our data indicate that a physiology-guided complete revascularization with latest generation drug-eluting stent and short DAPT regimen could be a more suitable option.

Limitations

The present prespecified analysis has certain limitations that should be taken into consideration. Although prespecified, to investigate the effect of physiology-guided complete revascularization in patients with HBR was not the primary aim of the FIRE trial. Second, the FIRE trial was powered for the composite end point of death, MI, stroke, and ischemia-driven revascularization. Findings on secondary end points should be considered with caution. Furthermore, it should be noted that complete revascularization was guided by coronary physiology and with the implantation of sirolimus-eluting biodegradable-polymer ultrathin stents. As such, it remains uncertain whether our study's outcomes can be extrapolated to patients managed with different strategies and stent platforms. Lastly, it is essential to recognize that our findings pertain to the specific context of this trial, in which the majority of participating centers possessed extensive expertise in coronary physiology.

Conclusions

The present prespecified analysis of the FIRE randomized clinical trial suggests that HBR status was common in older patients with MI and was associated with a higher risk of ischemic and bleeding complications, including death. Physiology-guided complete revascularization emerged as an effective method to reduce ischemic complications, including cardiovascular death and MI, and should be considered in the treatment of patients with HBR.

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Author Affiliations: Cardiology Unit, Azienda Ospedaliero Universitaria di Ferrara, Ferrara, Italy (Erriquez, Campo, Pavasini, Marrone, Pompei, Biscaglia); Cardiology Unit, Azienda USL-IRCCS Reggio Emilia, S. Maria Nuova Hospital, Reggio Emilia, Italy (Guiducci, d'Amore); Hospital Clínico San Carlos IDISCC, Complutense University of Madrid, Calle del Prof Martin Lagos s/n, Madrid, Spain (Escaned); Centro de Investigación Biomédica en Red en Enfermedades Cardiovasculares, Madrid, Spain, Instituto de Investigación Hospital La Paz, University Hospital La Paz, Madrid, Spain (Moreno); Cardiology Unit, Ospedale Maggiore, Largo Nigrisoli 2, Bologna, Italy (Casella, Capecchi, Lanzilotti); Cardiovascular Department, Infermi Hospital, Rimini, Italy (M. Menozzi); Interventional Cardiology Unit, San Luigi Gonzaga University Hospital, Orbassano, and Rivoli Infermi Hospital ASLTO3, Rivoli, Turin, Italy (Cerrato); Cardiology Unit, Umberto I Hospital, ASP Siracusa, Siracusa, Italy (Sacchetta); S. C. Cardiologia, Ospedale Sant'Andrea, ASL5 Liguria, La Spezia, Italy (A. Menozzi); Centro de Investigación Biomédica en Red en Enfermedades Cardiovasculares, Cardiology Department, Hospital Clínico Universitario, Valladolid, Spain (Santos); Centro de Investigation Biomedica end Red en Enfermedades Cardiovasculares, Cardiology Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain (Ibañes); Azienda Ospedaliero Universitaria Integrata di Verona, Verona, Italy (Scarsini); Azienda Ospedaliero Universitaria Policlinico Paolo Giaccone, Palermo, Italy (Vadalà); Azienda Ospedaliero Universitaria Policlinico Gaetano Martino, Messina, Italy (Andò); Centro de Investigation Biomedica en Red en Enfermedades Cardiovasculares, Cardiology Department, H. Universitario y Politécnico La Fe, Valencia, Spain (Díez-Gil); Cardiology Unit, Ospedale Santa Maria Goretti, Via Lucia Scaravelli, Latina, Italy (Colaiori); Interventional Cardiology, Department of Cardio-Thoracic and Vascular Sciences, Ospedale dell'Angelo, Via Paccagnella, Venice, Italy (Gallo); Institute of Cardiology, Jagiellonian University Medical College, Krakow, Poland (Dudek); Department of Clinical and Molecular Medicine, Sapienza University of Rome, Roma, Italy (Barbato); Interventional Cardiology Unit, Presidio Ospedaliero San Salvatore di Pesaro, Pesaro, Italy (Tebaldi).

Author Contributions: Drs Campo and Biscaglia had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Erriquez, Campo, Guiducci, Amat-Santos, Pavasini, Marrone, Tebaldi, Biscaglia.
Acquisition, analysis, or interpretation of data: Erriquez, Campo, Escaned, Moreno, Casella, M. Menozzi, Cerrato, Sacchetta, A. Menozzi, Amat-Santos, Gutiérrez Ibañes, Scarsini, Vadalà, Andò, Díez-Gil, Musto d'Amore, Capecchi, Colaiori, Gallo, Pavasini, Marrone, Pompei, Lanzilotti, Dudek, Barbato, Biscaglia.
Drafting of the manuscript: Erriquez, Campo, Guiducci, Sacchetta, Díez-Gil, Musto d'Amore, Pavasini, Marrone, Biscaglia.
Critical review of the manuscript for important intellectual content: Erriquez, Campo, Escaned, Moreno, Casella, M. Menozzi, Cerrato, A. Menozzi, Amat-Santos, Gutiérrez Ibañes, Scarsini, Vadalà, Andò, Díez-Gil, Capecchi, Colaiori, Gallo, Pavasini, Marrone, Pompei, Lanzilotti, Dudek, Barbato, Tebaldi, Biscaglia.
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Safety and efficacy of a sirolimus-eluting coronary stent with ultra-thin strut for treatment of atherosclerotic lesions (TALENT): a prospective multicentre randomised controlled trial

Azfar Zaman, Robbert J de Winter*, Norihiro Kogame, Chun Chin Chang, Rodrigo Modolo, Ernest Spitzer, Pim Tonino, Sjoerd Hofma, Aleksander Zurakowski, Pieter C Smits, Janusz Prokopczuk, Raul Moreno, Anirban Choudhury, Ivo Petrov, Angel Cequier, Neville Kukreja, Angela Hoye, Andrés Iniguez, Imre Ungi, Antonio Serra, Robert J Gil, Simon Walsh, Gincho Tonev, Anthony Mathur, Bela Merkely, Antonio Colombo, Sander Ijsselmuiden, Osama Soliman, Upendra Kaul, Yoshinobu Onuma, Patrick W Serruys, on behalf of the TALENT trial investigators*

Summary

Background **Supraflex is a sirolimus-eluting stent with a biodegradable polymer coating and ultra-thin struts. We aimed to compare Supraflex with the standard of care, Xience, an everolimus-eluting stent with a durable polymer coating, regarding clinical outcomes with a randomised trial in an all-comer population.**

Methods **We did a prospective, randomised, single-blind, multicentre study (TALENT) across 23 centres in Europe (the Netherlands, Poland, the UK, Spain, Bulgaria, Hungary, and Italy). Eligible participants were aged 18 years or older, had one or more coronary artery stenosis of 50% or greater in a native coronary artery, saphenous venous graft, or arterial bypass conduit, and had a reference vessel diameter of 2·25–4·50 mm. Patients underwent percutaneous coronary intervention in an all-comer manner. We randomly assigned patients (1:1) to implantation of either a sirolimus-eluting stent with a biodegradable polymer coating and ultra-thin struts (Supraflex) or an everolimus-eluting stent with a durable polymer coating (Xience). Randomisation was done by local investigators by use of a web-based software with random blocks according to centre. The primary endpoint was a non-inferiority comparison of a device-oriented composite endpoint—cardiac death, target-vessel myocardial infarction, or clinically indicated target lesion revascularisation—between groups at 12 months after the procedure, assessed in an intention-to-treat population. On assumption of 1-year composite endpoint prevalence of 8·3%, a margin of 4·0% was defined for non-inferiority of the Supraflex group compared with the Xience group. This trial is registered with ClinicalTrials.gov, number NCT 02870140.**

Findings **Between Oct 21, 2016, and July 3, 2017, 1435 patients with 1046 lesions were randomly assigned to Supraflex, of whom 720 received the index procedure, and 715 patients with 1030 lesions were assigned to Xience, all receiving the index procedure. At 12 months, the primary endpoint had occurred in 35 patients (4·9 %) in the Supraflex group and in 37 patients (5·3%) in the Xience group (absolute difference –0·3% [one-sided 95% upper confidence bound 1·6%], $p_{non\text{-}inferiority}$<0·0001). Definite or probable stent thrombosis prevalence, a safety indicator, was low in both groups and did not differ between them.**

Interpretation **The Supraflex stent was non-inferior to the Xience stent for a device-oriented composite clinical endpoint at 12 months in an all-comer population. Supraflex seems a safe and effective alternative drug-eluting stent to other stents in clinical practice.**

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*Contributed equally

Freeman Hospital, Newcastle University, and Newcastle upon Tyne Hospitals NHS Trust, Newcastle, UK (Prof A Zaman MD); **Department of Cardiology, Amsterdam University Medical Center, Amsterdam, Netherlands** (Prof R J de Winter MD, N Kogame MD, R Modolo MD); **Department of Cardiology, Toho University Medical Centre Ohashi Hospital, Tokyo, Japan** (N Kogame); **Thoraxcenter, Erasmus University Medical Centre, Rotterdam, Netherlands** (C C Chang MD, E Spitzer MD, O Soliman MD, Y Onuma MD); **Cardiology Division, Department of Internal Medicine, Taipei Veterans General Hospital, Taiwan** (C C Chang); **Cardiology Division, Department of Internal Medicine, University of Campinas, Campinas, SP, Brazil** (R Modolo); **Cardialysis Clinical Trials Management and Core Laboratories, Rotterdam, Netherlands** (E Spitzer, O Soliman, Y Onuma); **Department of Cardiology, Catharina Hospital, Eindhoven, Netherlands** (P Tonino MD); **Medical Centre Leeuwarden, Leeuwarden, Netherlands** (S Hofma MD); **Małopolskie Centrum Sercowo-Naczyniowe PAKS, Chrzanow, Poland** (A Zurakowski MD); **Maasstad Ziekenhuis, Rotterdam, Netherlands** (P C Smits MD); **PAKS Kędzierzyn, Koźle, Poland**

Introduction

The evolution of coronary stent technologies has led to reduced adverse outcomes in patients who undergo percutaneous coronary intervention. These technological developments stem from reductions in strut and polymer thickness, improvements in metal alloys and biocompatibility of coating, and optimisation of the kinetics of drug release. The second generation of drug-eluting stents was introduced with thin struts (80–90 µm), new antiproliferative drugs with better elution profiles, and biocompatible polymers. These new stents had lower rates of restenosis coupled with adequate strut coverage,[1,2] resulting in significantly lower rates of thrombotic complications compared with those of first-generation, drug-eluting stents and bare metal stents.[3,4] Subsequently, biodegradable polymers were developed to disappear after drug release, thereby leaving a bare metal stent-like platform. The efficacy of

(J Prokopczuk MD); **Cardiology Department, La Paz University Hospital, Madrid, Spain** (R Moreno MD); **Department of Cardiology, University Hospital of Wales, Cardiff, UK** (A Choudhury MD); **Acibadem City Clinic Cardiovascular Center, Sofia, Bulgaria** (Prof I Petrov MD); **University Hospital of Bellvitge, Barcelona, Spain** (A Cequier MD); **Department of Cardiology, East and North Hertfordshire NHS Trust, Hertfordshire, UK** (N Kukreja MD); **Department of Academic Cardiology, University of Hull, Castle Hill Hospital, UK** (A Hoye MD); **Hospital do Meixoeiro, Vigo, Spain** (A Iniguez MD); **Division of Invasive Cardiology, Second Department of Internal Medicine and Cardiology Center, University of Szeged, Szeged, Hungary** (I Ungi MD); **Unidad de Cardiología Intervencionista, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain** (A Serra MD); **Department of Invasive Cardiology, Central Clinical Hospital of the Ministry of Interior, Warsaw, Poland** (Prof R J Gil MD); **Mossakowski Medical Research Centre, Polish Academy of Science, Warsaw, Poland** (Prof R J Gil); **Department of Cardiology Belfast Health & Social Care Trust, Belfast, UK** (S Walsh MD); **Multi-profile Hospital for Active Treatment, St George's University, Plovdiv, Bulgaria** (G Tonev MD); **Department of Cardiology, Barts Heart Centre, Barts Health NHS Trust, London, UK** (Prof A Mathur MD); **Heart and Vascular Center, Semmelweis University, Budapest, Hungary** (Prof B Merkely MD); **Division of Interventional Cardiology, Cardio-Thoracic-Vascular Department, San Raffaele Scientific Institute, Milan, Italy** (Prof A Colombo MD); **Amphia Ziekenhuis, Breda, Netherlands** (S Ijsselmuiden MD); **Academics and Research, Batra Hospital and Medical Research Center, New Delhi, India** (Prof U Kaul DM); **and International Centre for Circulatory Health, Imperial College London, London, UK** (Prof P W Serruys MD)

Research in context

Evidence before this study

We searched PubMed and checked the listings of the EuroPCR, European Society of Cardiology, Transcatheter Cardiovascular Therapeutics, and American College of Cardiology conferences for complete reports of clinical studies comparing Supraflex, a sirolimus-eluting coronary stent with biodegradable polymer coating, with any other drug-eluting stents. We used the search terms "Supraflex" AND "all-comers" for reports published in English up to Aug 29, 2018. We identified one multicentre, single-group, observational registry—the FLEX Registry. At 12 months, the primary device-oriented composite endpoint occurred in 36 (3·7%) of 980 patients who received Supraflex implantation. However, this registry, which had site-reported events without central adjudication, was a non-randomised trial.

Added value of this study

To our knowledge, this is the first randomised trial with a clinical primary endpoint comparing Supraflex with a contemporary drug-eluting stent in an all-comer population. The Supraflex stent was non-inferior to Xience, an everolimus-eluting stent with durable polymer coating, for the device-oriented composite endpoint of cardiac death, target-vessel myocardial infarction, or clinically indicated target lesion revascularisation at 12 months. Per-protocol analysis showed a significantly lower clinically indicated target lesion revascularisation in the Supraflex group than in the Xience group.

Implications of all the available evidence

The sirolimus-eluting Supraflex coronary stent with absorbable polymer coating was non-inferior to a currently best-in-class drug-eluting stent at 12 months and further benefits might emerge in long-term follow-up.

drug-eluting stents with biodegradable polymer coating was shown to be non-inferior to that of stents with durable polymer coating in several studies.[5–7] A study[8] published in 2017 showed that a drug-eluting stent with a biodegradable polymer coating and ultra-thin struts was superior to a stent with durable polymer coating, achieving a lower rate of target lesion failure at 12 months than that of the stent with durable coating. Additionally, a meta-analysis[9] published in 2018 showed that drug-eluting stents with ultra-thin struts (strut thickness <70 μm) reduced the incidence of target lesion failure compared with that of contemporary stents with thicker struts. Because clinical outcomes of contemporary stents are reaching a safety plateau, it is probable that cost-effectiveness might influence the decision on which stent to use.

The Supraflex is a sirolimus-eluting coronary stent made with a cobalt chromium alloy that has a biodegradable polymer technology and an ultra-thin strut thickness of 60 μm. With this stent, the drug is released over a short period of 48 days. Provided that clinical outcomes are comparable with market-leading stents, the introduction of Supraflex in the European market will increase competition and might drive down healthcare costs.[10] In the FLEX-Registry,[11] Supraflex showed a low incidence of major adverse cardiac events at 12 months of follow-up (3·7%) and excellent strut coverage at 6 months of follow-up in 995 unselected real-world patients. Although the ultra-thin strut stent with biodegradable polymer might have an important role in patients' outcomes,[7] the Supraflex has not yet been tested in the context of a randomised clinical trial.

We therefore did a trial to investigate non-inferiority of clinical outcomes after implantation of the Supraflex stent compared with the standard of care for atherosclerotic lesions (Xience, an everolimus-eluting stent with durable polymer coating) in broad patient and lesion scenarios from an all-comer European population.

Methods

Study design and participants

The TALENT trial was a prospective, randomised, controlled, single-blind, multicentre study in an all-comers population across 23 hospitals or specialised centres in Europe (the Netherlands, Poland, the UK, Spain, Bulgaria, Hungary, and Italy). There were few inclusion and exclusion criteria (appendix).[12] Briefly, patients aged at least 18 years, with one or more coronary artery stenosis of 50% or greater in a native coronary artery, saphenous venous graft, or arterial bypass conduit with a reference vessel diameter of 2·25–4·50 mm, who were suitable for coronary stent implantation were eligible for inclusion. Any type of coronary artery lesions and anatomical locations were included. The number of stents, treated lesions, and vessels and the length of lesions was unrestricted. All patients signed informed consent, which was approved by the ethics committee of each enrolling centre.

Randomisation and masking

Patients who met the enrolment criteria were randomly assigned (1:1) to implantation of either the Supraflex or the Xience stent. Randomisation was done by local investigators by use of a web-based software with random blocks according to centre. Clinical data were adjudicated by an independent clinical event committee, which was masked to the type of stent allocated to the patient.

Procedures

The Supraflex is a new generation metallic stent (Sahajanand Medical Technologies, Surat, India) consisting of an L605 cobalt–chromium alloy platform with ultra-thin struts (60 µm) across all stent diameters, highly flexible S-link connectors, and a biodegradable polymeric matrix coating (poly L-lactide, 50:50 mixture poly D,L-lactide-co-glycolide and polyvinyl pyrrolidone). Sirolimus, at a concentration of 1·4 µg/mm² and together with the polymeric matrix, is coated on the conformal surface of the stent. The average thickness of coating ranged from 4 µm to 5 µm. The drug is 70% released within 7 days, and the remainder is released over a period of 48 days.[11] The polymer gradually degrades over 9–12 months. Available stent diameters for this trial were between 2·25 mm and 4·0 mm, and available stent lengths were 8–48 mm. The crossing profile of Supraflex is 0·99 mm, whereas the crossing profile of the newest Xience Alpine is 1·10 mm and of Xience Sierra is 0·99 mm.

The control stent with durable polymer coating, Xience (Abbot Vascular, Santa Clara, CA, USA), is a cobalt–chromium alloy device with a strut thickness of 81 µm and an 8 µm-thick durable polymer coating. This polymer is made of polyvinylidene fluoride–hexafluoropropylene loaded with everolimus.[13] We used only Xience stents with similar diameter and length to those of Supraflex, thus Xience stents up to 48 mm in length and with diameters between 2·25 mm and 4·0 mm were allowed for implantation.

Investigators determined lesion parameters by visual estimation with angiography or online quantitative coronary angiography. Patients with stable coronary artery disease received dual antiplatelet therapy for at least 6 months after percutaneous coronary intervention, followed by aspirin monotherapy indefinitely. Patients with acute coronary syndrome received dual antiplatelet therapy for at least 12 months after percutaneous coronary intervention, followed by aspirin monotherapy indefinitely. For patients with acute coronary syndrome, the order of preference for P2Y12 (P2Y purinoceptor 12) inhibitors was ticagrelor, followed by prasugrel (or clopidogrel), according to local practice and drug availability.

Cardiac biomarkers (creatine kinase, creatine kinase-myocardial band, and troponin I or T) were measured within 24 h before percutaneous coronary intervention and 3–8 h after the procedure (appendix). Patients were followed up by hospital visit at 1 month and 12 months and by phone contact at 6 months to assess clinical status and adverse events. All information was recorded for data collection at each visit.

Outcomes

The primary endpoint of the study was a non-inferiority comparison at 12 months between the Supraflex group and the Xience group regarding a device-oriented composite endpoint of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularisation. The composite secondary endpoints were a patient-oriented composite endpoint of all-cause death, any myocardial infarction, and any revascularisation, a target vessel failure of cardiac death, target vessel myocardial infarction, and clinically indicated target vessel revascularisation. Other secondary endpoints of the study included individual components of composite endpoints and stent thrombosis (appendix).

Definite and probable stent thrombosis, which are safety indicators, were adjudicated according to the definition of the Academic Research Consortium (ARC).[14] Myocardial infarction was defined according to the Society for Cardiovascular Angiography and Interventions consensus for periprocedural myocardial infarction (when occurring 48 h or earlier after the index procedure) or according to the Third Universal Definition for myocardial infarction (when occurring later than 48 h after the index procedure).[15,16] Device success was defined as successful delivery and deployment of (only) the assigned device at the intended target lesion and successful withdrawal of

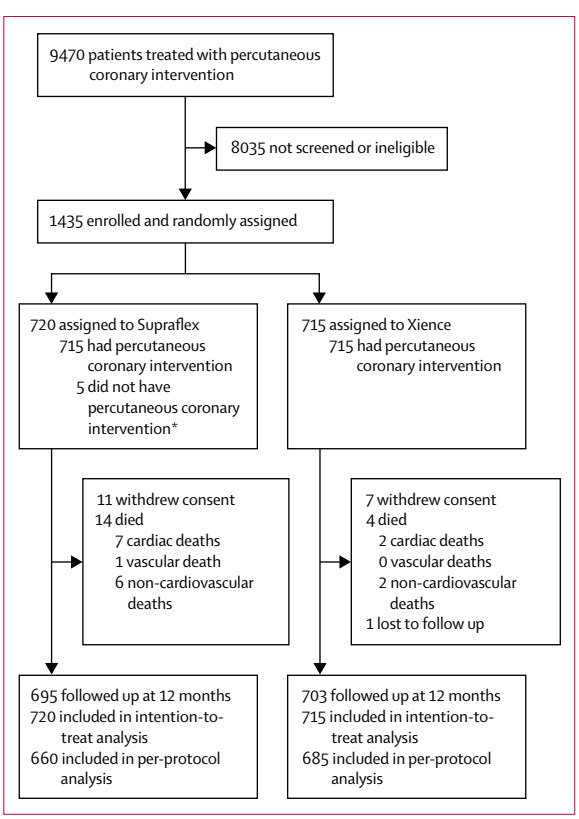

Figure 1: **Study profile**

*Percutaneous intervention was cancelled in two patients on the basis of intravascular ultrasound finding. In one patient, vasospastic stenosis observed during diagnostic angiography was not confirmed at the time of planned coronary intervention; therefore the procedure was not done. One patient was referred after randomisation to surgery because of concomitant mitral regurgitation. One patient did not receive percutaneous intervention because of a randomisation error.

Correspondence to:
Prof Patrick W Serruys, International Centre for Circulatory Health, Imperial College London, London SW7 2AZ, UK
patrick.w.j.c.serruys@pwserruys.com

or

Dr Yoshinobu Onuma, Thoraxcenter, Erasmus University Medical Center, 3015 GD Rotterdam, Netherlands
yonuma@cardialysis.nl

See Online for appendix

	Supraflex (n=720)	Xience (n=715)
Median age (IQR), years	66 (58–72)	65 (58–72)
Sex		
Men	546 (75·8%)	547 (76·5%)
Women		
Body-mass index (kg/m^2)	28·3 (4·8; n=719)	28·3 (4·6)
Smoking status		
Current	176 (24·5%; n=719)	172 (24·1%)
Previous	286 (39·8%; n=719)	311 (43·5%)
Never	257 (35·7%; n=719)	232 (32·4%)
Diabetes	157 (21·8%)	178 (24·9%)
Insulin-dependent	48 (6·7%)	67 (9·4%)
Non-insulin-dependent	109 (15·1%)	111 (15·5%)
Hypertension	470 (65·3%)	472 (66·1%; n=714)
Hypercholesterolaemia	444 (61·8%; n=718)	428 (60·2%; n=711)
Family history of coronary artery disease	311 (46·3%; n=671)	303 (45·2%; n=671)
Previous myocardial infarction	136 (18·9%)	128 (17·9%)
Established peripheral vascular disease	51 (7·1%)	64 (9·0%)
Previous PCI	175 (24·3%)	153 (21·4%)
Previous CABG	33 (4·6%)	55 (7·7%)
Heart failure	34 (4·7%)	49 (6·9%)
Renal insufficiency*	20 (2·8%)	14 (2·0%)
Indication		
Stable angina	291 (40·4%)	310 (43·4%)
Acute coronary syndrome	429 (59·6%)	405 (56·6%)
Unstable angina	116 (16·1%)	99 (13·8%)
Non-ST elevation myocardial infarction	194 (26·9%)	189 (26·4%)
ST elevation myocardial infarction	119 (16·5%)	117 (16·4%)

Data are mean (SD) or n (%). PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft. *Defined as serum creatinine concentration >2·5 mg/dL or creatinine clearance ≤30 mL/min.

Table 1: **Patient baseline characteristics**

the delivery system with attainment of final in-stent residual stenosis of less than 30% (preferably by online quantitative coronary angiography).

Statistical analysis

The trial was powered for testing of non-inferiority for the primary endpoint at 12 months after the procedure. After reviewing event rates from published data, we expected the composite endpoint prevalences at 12 months for both treatment groups to be 8·3%.[17] A margin of 4% (50% of the expected event rate) was defined for the non-inferiority margin of the Supraflex group compared with the Xience group. On the basis of this margin and a one-sided type I error of 0·05, a total of 1386 patients (693 patients in each group) would have at least 85% power to detect non-inferiority. Accounting for approximately 3% of patients lost to follow-up, we randomly assigned a total of 1435 patients. The primary analyses were based on an intention-to-treat population. For the primary endpoint analysis, we used a standard normal distribution to create a one-sided 95% upper confidence bound for the difference in Kaplan-Meier rates for the device-oriented composite endpoints of the Supraflex group and the Xience group. If the one-sided 95% upper confidence bound was less than or equal to the non-inferiority margin of 4·0%, Supraflex was declared to be non-inferior to Xience. This testing implied a 5·0% one-sided significance level. A secondary analysis of the primary endpoint and all secondary clinical endpoints was done in the per-protocol population, which consisted of patients who had received only the assigned study stent. Continuous variables were presented as mean (SD) and compared with the use of t test. Categorical variables were reported as n (%). Categorical variables with more than two categories were assessed by Mantel-Haenszel rank score test, and dichotomous variables were assessed by Fisher's exact test. Composite endpoints were calculated by use of time-to-first of any of the composite events per patient. Patients started being at risk on the day of index percutaneous coronary intervention or, if no procedure was done, on the day of randomisation. Survival curves were constructed with use of Kaplan-Meier estimates and the log-rank test was used to compare between-group differences. We pre-specified stratified analyses of the primary endpoint at 12 months for subgroups of patients with diabetes, ST-segment elevation myocardial infarction, small vessels (≤2·75 mm), multivessel treatment, long lesions (>18 mm), in-stent restenosis, bypass graft, left main treatment, bifurcation treatment, or overlapping stents. We calculated the interaction p value for the subgroup analysis. Unless otherwise specified, a two-sided p value of less than 0·05 was considered to indicate statistical significance. All statistical analyses were done using SAS software version 9.3. An independent data safety and monitoring board monitored the individual and collective safety of the patients in the study during the enrolment phase. This trial is registered with ClinicalTrials.gov, number NCT 02870140.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report, and did not participate in the decision to submit the manuscript for publication. The executive committee (AZa, RJdW, UK, and PWS) had full access to all the data in the study, and the corresponding authors (YO and PWS) had full responsibility for the decision to submit for publication.

Results

Between Oct 21, 2016 and July 3, 2017, we randomly assigned 1435 patients with a total of 2076 lesions to

either the Supraflex group (720 patients with 1046 lesions) or the Xience group (715 patients with 1030 lesions; figure 1). Five patients in the Supraflex group did not undergo percutaneous coronary intervention. 11 patients (1·5%) in the Supraflex group and seven patients (1·0%) in the Xience group withdrew consent within 12 months of the procedure. Baseline clinical characteristics were similar in the two study groups (table 1). 429 patients (59·6%) in the Supraflex group and 405 (56·6%) in the Xience group presented with acute coronary syndrome. To enable a timely report of the primary endpoint, the steering committee decided to encourage patients who were randomly assigned between June 3 and July 3, 2017 (last month of enrolment) to undergo the 1-year follow-up visit before 360 days had passed, with a minimum of 330 days after the index procedure. 720 patients from the Supraflex group and 715 from the Xience group were included in the intention-to-treat population.

Overall, lesion characteristics were similar between the two groups (table 2). Mean pre-dilatation balloon diameter was larger in the Supraflex group than in the Xience group. Mean stent length and diameter per stent were similar between groups. The number of stents used was not different between both groups. Mean post-dilatation balloon length was greater in the Xience group than in the Supraflex group. The device success proportion was analysed in 2000 lesions in which investigators attempted to implant the allocated stent. The detailed reasons for not using the allocated stent are provided in the appendix. The device success proportion per lesion in both groups was high, but there was significant difference between the Supraflex and the Xience group (973 [97·6%] of 997 lesions *vs* 998 [99·5%] of 1003; difference –1·9%, 95% CI –3·0 to –0·9; p=0·0003; appendix). This difference was mainly driven by increased crossover to non-allocated stent in the Supraflex group compared with that in the Xience group. There were no differences in the residual in-stent stenosis of 30% or greater between groups. This difference in device success did not affect in-hospital patient outcomes (in-hospital device-oriented composite endpoint 11 [1·5%] of 720 patients *vs* 10 [1·4%] of 715; difference 0·1%, 95% CI –1·2 to 1·5; p=0·837).

The primary device-oriented composite endpoint occurred in 35 (4·9%) of 720 patients in the Supraflex group and in 37 (5·3%) of 715 in the Xience group (table 3, figure 2A). Non-inferiority of the Supraflex stent compared with the Xience stent was shown, with an absolute difference of –0·3% and one-sided 95% upper confidence bound of 1·6% ($p_{non\text{-}inferiority}$ <0·0001, $p_{superiority}$=0·801). The frequencies of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularisation were similar for both stent types (table 3, figure 2). The details of cardiac deaths are described in the appendix. Results of the device-oriented composite endpoint from the per-protocol analysis, including 1345 patients, also showed non-inferiority of Supraflex compared with Xience (23 [3·5%] of 660 patients in the Supraflex group *vs* 30 [4·4%] of 685 in the Xience group; difference –0·9%, 95% CI –3·0 to 1·2; $p_{non\text{-}inferiority}$ <0·0001, $p_{superiority}$=0·41), with a significantly lower clinically indicated target

	Supraflex (1046 lesions)	Xience (1030 lesions)
Vessel location		
LAD	468 (44·7%)	432 (41·9%)
LCX	220 (21·0%)	237 (23·0%)
RCA	338 (32·3%)	328 (31·8%)
Left main	15 (1·4%)	16 (1·6%)
Bypass graft	5 (0·5%)	17 (1·7%)
Number of lesions treated per patient	1·45 (0·77; n=720)	1·44 (0·74; n=715)
Total stent length per patient (mm)	37·2 (27·4; n=709)	37·2 (27·0; n=710)
Index PCI undertaken	715 (99·3%; n=720)	715 (100%; n=715)
Reason PCI not undertaken		
Medical treatment only	3 (0·4%; n=720)	0
Other	2 (0·3%; n=720)	0
TIMI flow pre-procedure		
Flow 0	143 (13·7%)	112 (10·9%)
Flow 1	40 (3·8%)	42 (4·1%)
Flow 2	66 (6·3%)	84 (8·2%)
Flow 3	758 (72·5%)	744 (72·2%)
Assessment not done	39 (3·7%)	48 (4·7%)
Restenotic lesion	44 (4·2%)	42 (4·1%)
Small vessel (≤2·75 mm)	420 (40·2%)	414 (40·2%)
Long lesion (>18 mm)	518 (49·7%; n=1042)	511 (49·6%)
Bifurcation involved	167 (16·0%)	157 (15·2%)
Thrombus aspiration	40 (3·8%)	39 (3·8%)
Pre-dilatation	807 (77·2%)	782 (75·9%)
Maximum pressure (atm)	13·6 (4·3; n=801)	13·5 (4·1; n=777)
Maximum balloon length (mm)	15·75 (4·77; n=805)	15·40 (4·50; n=782)
Maximum balloon diameter (mm)	2·52 (0·43; n=805)	2·46 (0·43; n=782)
Stent characteristics		
Number of stents used per lesion	1·2 (0·5; n=1046)	1·2 (0·5; n=1030)
Total stent length per lesion (mm)	25·7 (14·5; n=1028)	26·0 (14·5; n=1015)
Overlapping stents per lesion	221 (21·1%)	201 (19·5%)
Stent length per stent (mm)	21·3 (8·3; n=1239)	21·8 (8·8; n=1208)
Stent diameter per stent (mm)	3·0 (0·5; n=1239)	3·0 (0·5; n=1208)
Post-stenting balloon dilatation	544 (52·0%)	538 (52·2%)
Maximum pressure (atm)	17·1 (4·3; n=543)	17·5 (3·9; n=532)
Maximum balloon length (mm)	13·79 (4·83; n=544)	14·39 (4·88; n=537)
Maximum balloon diameter (mm)	3·30 (0·58; n=544)	3·29 (0·60; n=538)
TIMI flow post-procedure		
Flow 0	7 (0·7%)	1 (0·1%)
Flow 1	2 (0·2%)	3 (0·3%)
Flow 2	11 (1·1%)	9 (0·9%)
Flow 3	995 (95·1%)	975 (94·7%)
Assessment not done	31 (3·0%)	42 (4·1%)

(Table 2 continues on next page)

	Supraflex (1046 lesions)	Xience (1030 lesions)
(Continued from previous page)		
Any periprocedural complication	48 (6·7%; n=715)	40 (5·6%; n=715)
Dissection	20 (2·8%; n=715)	16 (2·2%; n=715)
Occlusion	7 (1·0%; n=715)	9 (1·3%; n=715)
Coronary spasm	0 (0·0%; n=715)	0 (0·0%; n=715)
Coronary embolism	3 (0·4%; n=715)	2 (0·3%; n=715)
Coronary perforation	3 (0·4%; n=715)	2 (0·3%; n=715)
Thrombi at stented site	1 (0·1%; n=715)	1 (0·1%; n=715)
Other	17 (2·4%; n=715)	14 (2·0%; n=715)

Data are n (%) or mean (SD). LAD=left anterior descending artery. LCX=left circumflex artery. RCA=right coronary artery. PCI=percutaneous coronary intervention. TIMI=thrombolysis in myocardial infarction.

Table 2: **Angiographic and procedural characteristics**

lesion revascularisation in the Supraflex group (8 [1·2%] patients in Supraflex *vs* 21 [3·1%] in Xience; difference –1·9%, –3·5 to –0·3; p=0·021; appendix).

At 12 months, definite or probable stent thrombosis did not differ between groups (table 3). In the Supraflex group, there were two unexplained and unwitnessed deaths attributed to possible stent thrombosis according to ARC-1 definition. Frequency of any stent thrombosis (definite, probable, or possible) also did not differ between groups (table 3).

The patient-oriented composite endpoint was similar between the Supraflex group and the Xience group (table 3). There were 18 all-cause deaths in the trial and, as described previously, cardiac death was not statistically different between groups (table 3). Seven deaths in the Supraflex group were related to non-cardiac conditions (eg, cancer, sepsis, and pneumonia), compared with two deaths in the Xience group. The treatment effect of Supraflex against Xience was consistent across subgroups, except for patients with small vessels (≤2·75 mm; figure 3). In the per-protocol analysis of our study (appendix), Supraflex showed a 20% relative risk reduction in device-oriented composite endpoint at 1 year, mainly driven by a 61% reduction in clinically indicated target lesion revascularisation.

The proportion of patients on dual antiplatelet therapy did not differ between the two groups at 6 and 12 months (626 [89·9%] of 696 patients in the Supraflex group *vs* 642 [91·3%] of 703 in the Xience group, p=0·376 at 6 months, and 552 [80·2%] of 688 in the Supraflex group *vs* 575 [81·8%] of 703 in the Xience group, p=0·458 at 12 months).

Discussion

In the TALENT study, we showed that Supraflex, a sirolimus-eluting coronary stent with biodegradable polymer coating and ultra-thin struts, was non-inferior to the standard of care, an everolimus-eluting stent with durable polymer coating, for a device-oriented composite endpoint of cardiac death, target-vessel myocardial infarction, or clinically indicated target lesion revascularisation at 12 months, in an all-comer European population.

Although device success was high in our study, we found a significant difference that favoured Xience over Supraflex (appendix). This difference was mainly due to a crossover to the comparator that has been on the market for over a decade and with which the investigators are very familiar. When resistance in crossing a lesion was found, some investigators (in seven of 23 centres) tended to quickly crossover to a familiar stent technology. Despite the slight difference in device success proportions between the groups, the success proportions of Supraflex are similar or even superior to other drug-eluting stents in all-comer trials (appendix).[17–19] For instance, device success proportion in the TARGET all-comer trial[18] was 92·4% in the FIREHAWK group and 94·8% in the Xience group, whereas in the BIOFLOW V trial,[8] a non-all-comer trial, it was 98% in the Orsiro group and 97% in the Xience group.

Supraflex, in line with current generation drug-eluting stents with a biodegradable polymer coating and an ultra-thin strut thickness (60 µm), was designed to overcome the limitations of the second-generation drug-eluting stents with durable polymer coating, which have been reported with 2–3% annual increased rate for the device-oriented composite endpoint 1 year after the procedure.[20] By contrast with the Orsiro stent, all Supraflex stents have the same strut thickness, irrespective of their diameter (from 2·00 mm to 4·50 mm). In our study, visual assessment or quantitative coronary angiography online by the operator showed absence of recoil, supporting findings already documented in a previous study.[21] Regarding the MiStent stent, there is a fundamental difference between the drug release kinetics of MiStent and Supraflex. Drug release is completed in 48 days, with a burst elution of 70% within the first 7 days, with the Supraflex stent, whereas MiStent has no drug release within the first 3 days and its polymer is fully biodegraded and resorbed within 3 months after implantation, but microcrystalline sirolimus is impacted and embedded in the vessel wall, acting as a tissue reservoir for 270 days. The arterial sirolimus concentrations still reach more than 2 ng/mg at 270 days. Additionally, the clinical outcome of Supraflex in our study is similar to Orsiro and MiStent in their pivotal trials (appendix).[5,6,8,22]

A meta-analysis[9] published in 2018, of ten randomised trials including 11 658 patients, compared the performance of three drug-eluting stents with ultra-thin struts (Orsiro, MiStent, and BioMime) with that of three second-generation drug-eluting stents with thicker struts (Xience, Resolute, and Nobori). The results showed that newer generation stents with ultra-thin struts were associated with a 16% relative risk

	Supraflex (n=720)	Xience (n=715)	Difference, % (95% CI)	p value
Primary outcome				
Device-oriented composite endpoint*	35 (4·9%)	37 (5·3%)	−0·3% (−2·6 to 2·0)	0·801†
Separate endpoints for the primary outcome				
Cardiac death	7 (1·0%)	2 (0·3%)	0·7% (−0·1 to 1·5)	0·097
Target-vessel myocardial infarction‡	18 (2·5%)	20 (2·8%)	−0·3% (−2·0 to 1·4)	0·734
Clinically indicated target lesion revascularisation	19 (2·7%)	28 (4·0%)	−1·3% (−3·2 to 0·6)	0·183
Secondary outcomes				
Patient-oriented composite endpoint§	70 (9·9%)	61 (8·7%)	1·2% (−1·8 to 4·3)	0·434
Target-vessel failure¶	38 (5·4%)	43 (6·1%)	−0·8% (−3·2 to 1·7)	0·565
Any death	14 (2·0%)	4 (0·6%)	1·4% (0·3 to 2·6)	0·019
Cardiac death	7 (1·0%)	2 (0·3%)	0·7% (−0·1 to 1·5)	0·097
Any myocardial infarction‡	22 (3·1%)	26 (3·7%)	−0·6% (−2·5 to 1·3)	0·551
Q wave	3 (0·4%)	3 (0·4%)	0·0% (−0·7 to 0·7)	0·996
Non-Q wave	19 (2·7%)	24 (3·4%)	−0·7% (−2·5 to 1·1)	0·435
Target-vessel myocardial infarction‡	18 (2·5%)	20 (2·8%)	−0·3% (−2·0 to 1·4)	0·734
Q wave	2 (0·3%)	3 (0·4%)	−0·1% (−0·8 to 0·5)	0·651
Non-Q wave	16 (2·3%)	18 (2·6%)	−0·3% (−1·9 to 1·3)	0·721
Non-target-vessel myocardial infarction‡	4 (0·6%)	6 (0·9%)	−0·3% (−1·2 to 0·6)	0·523
Q wave	1 (0·1%)	0 (0·0%)	0·1% (−0·1 to 0·4)	0·317
Non-Q wave	3 (0·4%)	6 (0·9%)	−0·4% (−1·3 to 0·4)	0·314
Periprocedural myocardial infarction‡	5 (0·7%)	6 (0·8%)	−0·1% (−1·0 to 0·8)	0·755
Any revascularisation	51 (7·3%)	52 (7·4%)	−0·2% (−2·9 to 2·6)	0·914
Target lesion revascularisation	25 (3·5%)	30 (4·3%)	−0·7% (−2·8 to 1·3)	0·494
Clinically indicated	19 (2·7%)	28 (4·0%)	−1·3% (−3·2 to 0·6)	0·183
Non-clinically indicated	7 (1·0%)	6 (0·8%)	0·1% (−0·9 to 1·1)	0·788
Target vessel revascularisation	29 (4·1%)	38 (5·4%)	−1·3% (−3·6 to 0·9)	0·263
Clinically indicated	23 (3·3%)	35 (5·0%)	−1·7% (−3·8 to 0·3)	0·109
Non-clinically indicated	7 (1·0%)	10 (1·4%)	−0·4% (−1·6 to 0·7)	0·459
Non-target vessel revascularisation	33 (4·7%)	21 (3·0%)	1·7% (−0·3 to 3·7)	0·098
Thrombosis endpoints				
Definite stent thrombosis	5 (0·7%)	5 (0·7%)	0·0% (−0·9 to 0·9)	0·996
Acute (0–1 days)	1 (0·1%)	0 (0·0%)	0·1% (−0·1 to 0·4)	0·319
Subacute (2–30 days)	1 (0·1%)	2 (0·3%)	−0·1% (−0·6 to 0·3)	0·562
Late (31–360 days)	3 (0·4%)	3 (0·4%)	0·0% (−0·7 to 0·7)	0·997
Definite or probable stent thrombosis	6 (0·8%)	6 (0·9%)	0·0% (−1·0 to 1·0)	0·996
Acute (0–1 days)	1 (0·1%)	0 (0·0%)	0·1% (−0·1 to 0·4)	0·319
Subacute (2–30 days)	2 (0·3%)	2 (0·3%)	0·0% (−0·6 to 0·5)	0·998
Late (31–360 days)	3 (0·4%)	4 (0·6%)	−0·1% (−0·9 to 0·6)	0·701
Possible stent thrombosis	2 (0·3%)	0 (0·0%)	0·3% (−0·1 to 0·7)	0·159
Any stent thrombosis	8 (1·1%)	6 (0·9%)	0·3% (−0·8 to 1·3)	0·597

Data are n (%). *Cardiac death, target-vessel myocardial infarction, or clinically indicated target lesion revascularisation. †p value for non-inferiority was <0·0001; one-sided 95% upper confidence bound was 1·6%. ‡Determined on the basis of the Society for Cardiovascular Angiography and Interventions 2013 definition within 48 h post procedure or the third universal definition after 48 h post procedure. §All-cause death, any myocardial infarction, or any revascularisation. ¶Cardiac death, target-vessel myocardial infarction, or clinically indicated target vessel revascularisation.

Table 3: **Clinical outcomes at 12 months after stent implantation, by intention to treat**

reduction in device-oriented composite endpoint at 1 year. Additionally, in that meta-analysis, ultra-thin strut stents had numerically, but not significantly, lower prevalences of stent thrombosis.[9] One theoretical disadvantage of thicker struts compared with ultra-thin struts is that thick, protruding struts disrupt the laminar flow and induce flow disturbance, which could further activate a platelet-signalling procoagulation pathway.[23,24] Whether the benefit of drug-eluting stents with thin struts could improve clinical outcomes remains to be assessed by studies with longer follow-up periods.

Supraflex has both thinner total thickness (strut plus coating is 68–70 μm) and shorter duration of drug

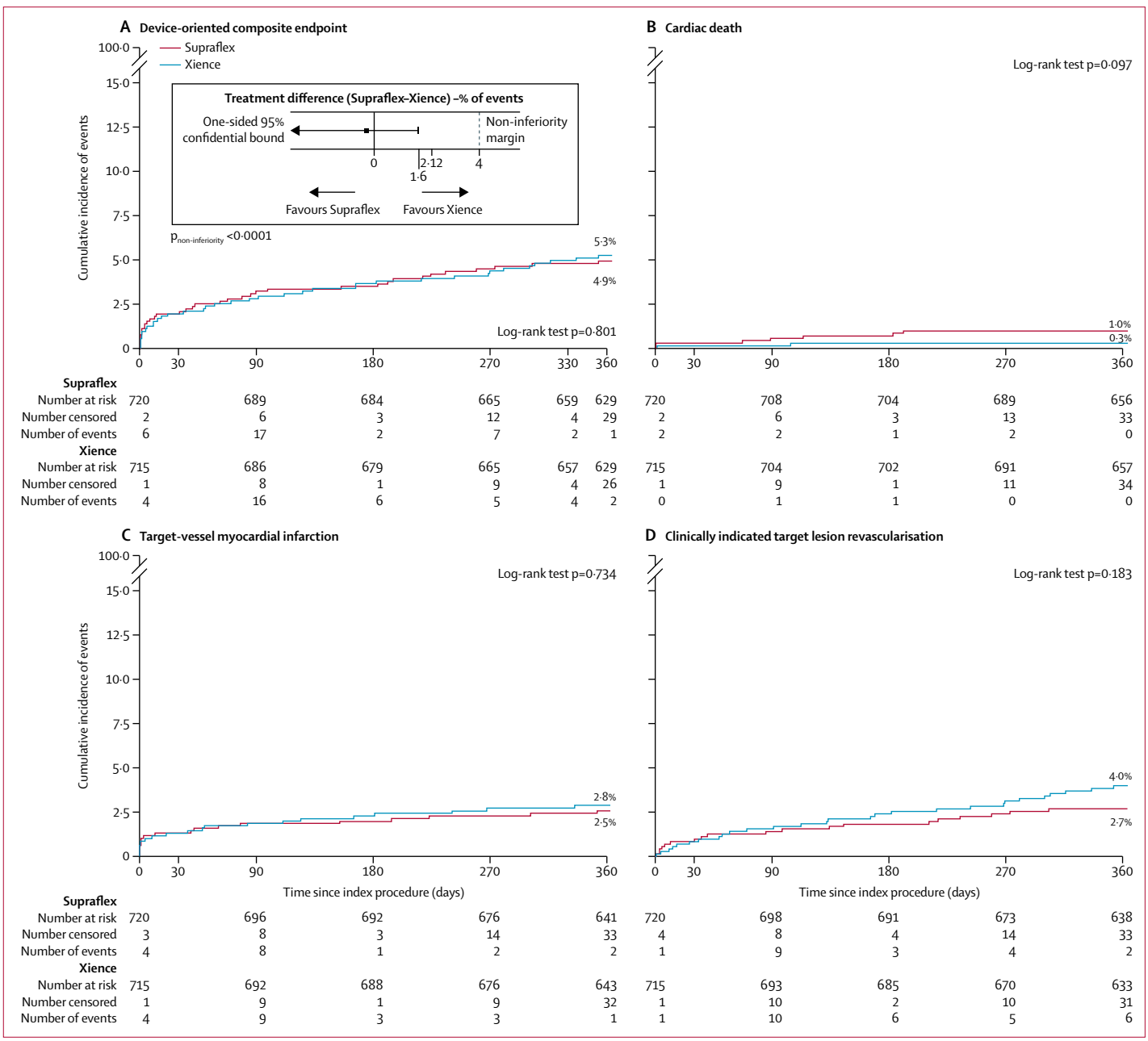

Figure 2: **Kaplan-Meier plot for primary endpoint and its components over 360 days of follow-up**
Kaplan-Meier curves show the cumulative incidence of device-oriented composite endpoint (primary endpoint; A) and of its components: cardiac death (B), target-vessel myocardial infarction (C), and clinically indicated target lesion revascularisation (D).

release (48 days) than those of Xience. In an optical coherence tomography subanalysis in the FLEX registry,[11] Supraflex showed excellent strut coverage of 98·1% at 6 months, whereas strut coverage of Xience was 94·1% in a previous study.[25] Moreover, Supraflex had a favourable healing score in the FLEX registry, which might be attributed to its ultra-thin strut thickness and shorter duration of drug release. The early healing process of Supraflex might allow shorter duration of dual antiplatelet therapy, although further study is needed to assess this.

Our study had some limitations. The observed device-oriented composite endpoint in the control group was lower than the estimated event rate in the sample size calculation. This was mainly due to lower prevalence of target vessel myocardial infarction in the Xience group than in the referenced trial, RESOLUTE.[17] This difference might be caused by different definitions of periprocedural

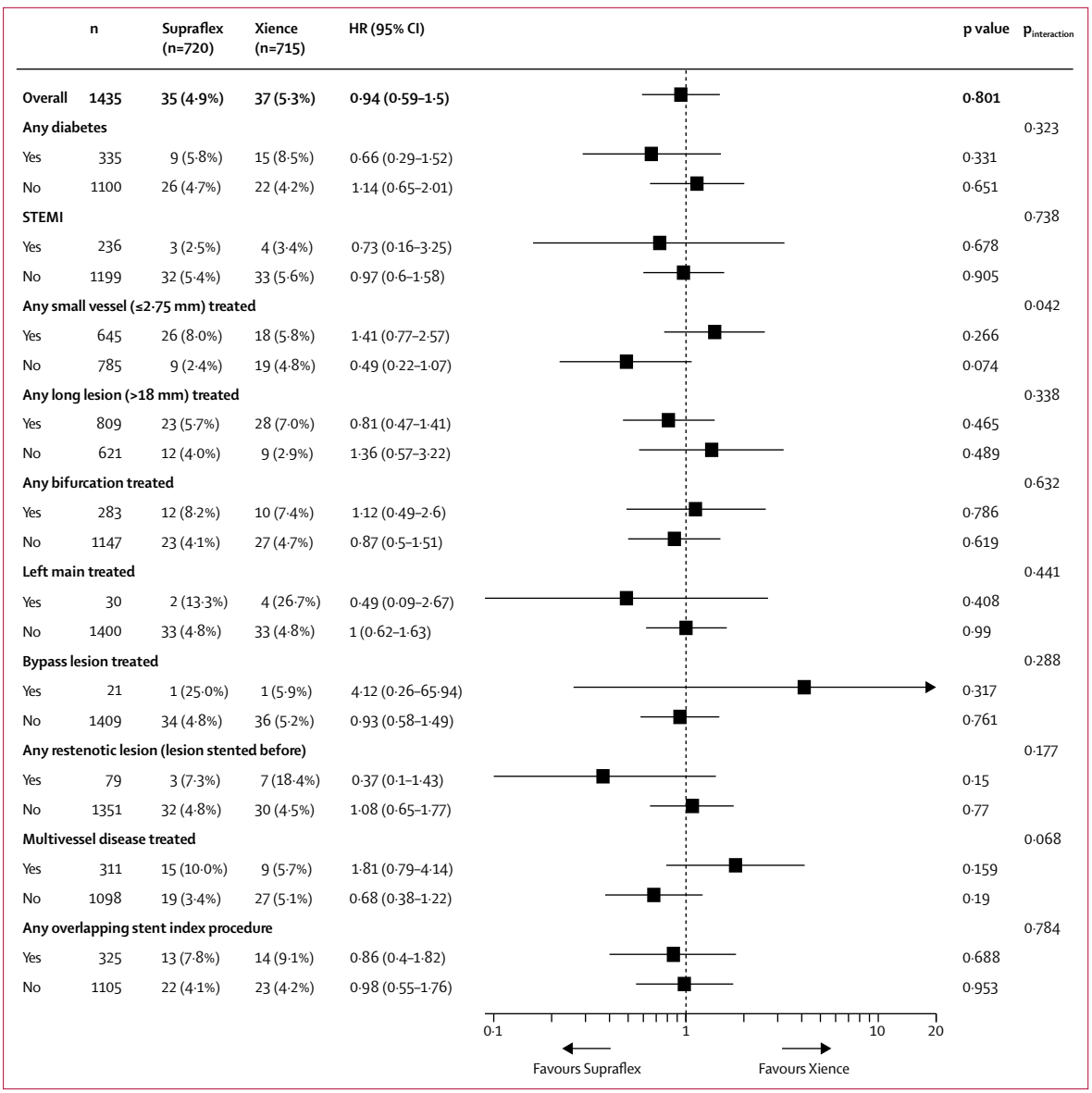

Figure 3: **Stratified analyses of the device-oriented composite endpoint at 12 months across subgroups**
Hazard ratio (HR) with 95% CI and p value results were from Cox proportional hazards analysis. STEMI=ST-segment elevation myocardial infarction.

myocardial infarction. In the TALENT study, the Society for Cardiovascular Angiography and Interventions consensus, which is more clinically relevant in terms of prognosis, was adopted for defining periprocedural myocardial infarction.[15]

The predefined non-inferiority margin might be considered, in retrospect, to be too wide. The original non-inferiority margin of 4·0% was determined as half of the device-oriented clinical endpoint prevalence of 8·3% in the Xience group of the RESOLUTE trial.[17] However, with a post-hoc non-inferiority margin of 2·1%, which corresponds to a hazard ratio of 1·4 based on the observed device-oriented composite endpoint prevalence in the Xience group, non-inferiority would still be met (post-hoc $p_{non\text{-}inferiority}$=0·019).

Although the trial was not powered for all-cause mortality, we found a significant difference in all-cause death between the two groups. The all-cause mortality (0·6%) of the TALENT trial was lower than that observed in the other all-comer trials, such as TARGET,[18] BIOSCIENCE,[6] TWENTE,[26] and RESOLUTE[17] (2·2–2·8%), suggesting the play of chance (appendix).

This trial was single-blinded, although the effect of this approach on event reporting is minimal because of the adjudication by an independent blinded clinical event committee.

1-year follow-up visits were done up to 30 days earlier than 360 days in 55 patients, although the effect of this early follow-up on primary endpoint measurement would be minimal with the Kaplan-Meier method. Finally, our report was limited to a short follow-up of 12 months. The protocol specifies that the follow-up of patients will continue for up to 3 years to assess the long-term benefits of biodegradable polymer coating (NCT02870140).

In conclusion, the Supraflex sirolimus-eluting stent with biodegradable polymer coating and ultra-thin strut was non-inferior to the Xience everolimus-eluting stent with durable polymer coating for a device oriented composite clinical endpoint at 12 months in an all-comer population.

Contributors

AZa, RJdW, UK, YO, and PWS contributed to the conception and design of the study. PT, SH, AZu, PCS, JP, RMor, ACh, IP, ACe, NKu, AH, AI, IU, AS, RJG, SW, GT, AM, BM, ACo, and SI contributed to data collection. AZa, RJdW, NKo, CCC, RMod, ES, OS, UK, YO, and PWS analysed and interpreted the data. NKo, CCC, RMod, YO, and PWS drafted the report, which was critically revised for important intellectual content by AZa, RJdW, UK, YO, and PWS. All authors approved the final version of the report.

Declaration of interests

AZa reports speaker fees from SMT and speaker and consulting fees from Abbott Vascular. ES received institutional grants from European Cardiovascular Research Institute during the conduct of the study. SH reports unrestricted research grant to institution by Abbott Vascular. PCS reports grants and personal fees from Abbott Vascular, St Jude Medical, and personal fees from Terumo and AstraZeneca, during the conduct of the study. NKu reports grants from DalCor Pharmaceuticals, Hamilton Health Sciences Corporation, Population Health Research Institute, and Bayer, and personal fees from Pfizer and AstraZeneca, outside the submitted work. SW reports grants and personal fees from Abbott Vascular, outside the submitted work. AM reports grants from Cardialysis, during the conduct of the study. BM reports grants from Abbott Vascular, Medtronic, Biotronik, and Boston Scientific, outside the submitted work. YO is a member of the Advisory Board of Abbott Vascular. PWS reports personal fees from Abbot Laboratories, AstraZeneca, Biotronik, Cardialysis, GLG Research, Medtronic, Sino Medical Sciences Technology, Société Europa Digital Publishing, Stentys France, Svelte Medical Systems, Philips/Volcano, St Jude Medical, Qualimed, and Xeltis, outside the submitted work. All other authors declare no competing interests.

Data sharing

All data, including study participant data, data dictionary, statistical analysis plan, and informed consent, will not be shared. The protocol is available online.

For the **study protocol** see https://clinicaltrials.gov/ct2/show/NCT02870140

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Circulation: Cardiovascular Interventions

RESEARCH LETTER

Prospective Multicenter Randomized All-Comers Trial to Assess the Safety and Effectiveness of the Ultra-Thin Strut Sirolimus-Eluting Coronary Stent Supraflex

Two-Year Outcomes of the TALENT Trial

Chao Gao, MD; Norihiro Kogame, MD; Faisal Sharif, MD, PhD; Pieter C. Smits, MD, PhD; Pim Tonino MD, PhD; Sjoerd Hofma, MD, PhD; Raul Moreno, MD; Anirban Choudhury, MD; Ivo Petrov, MD; Angel Cequier, MD; Antonio Colombo, MD; Upendra Kaul, MD, PhD; Azfar Zaman, MD; Robbert J. de Winter, MD, PhD; Yoshinobu Onuma, MD, PhD; Patrick W. Serruys, MD, PhD

Outcomes with the current second-generation drug eluting stents, although outstanding, have plateaued and remained steady over the past decade.[1] To further improve event-free survival, drug eluting stents with ultra-thin struts have been introduced. Compared with the thin strut drug eluting stents, stents with ultra-thin struts have the theoretical advantages of accelerating endothelialization, reducing vascular injury, and improving device deliverability.[2]

The Supraflex is a sirolimus-eluting metallic stent (Sahajanand Medical Technologies, Surat, India) with biodegradable polymeric matrix coating. The novelty of the Supraflex is its uniformly 60 μm strut thickness, irrespective of the diameter of the stents, ranging from 2.0 to 4.5 mm.[3] This is at variance with the Orsiro stent, which has a strut thickness of 60 μm in the small stent size platform (2.25–3.0 mm) but 80 μm in the large stent size platform (3.5–4.0 mm).

The TALENT trial (Thin Strut Sirolimus-Eluting Stent in All Comers Population vs Everolimus-Eluting Stent)[4] is a prospective, multicenter, single-blinded, all-comers, randomized controlled trial, allocating patients in a 1:1 ratio to either Supraflex or Xience everolimus-eluting stent (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02870140). Twenty-three sites in Europe enrolled patients from October 21, 2016, to July 3, 2017. Previously, the TALENT trial has showed noninferiority of Supraflex as compared with Xience in terms of device-oriented composite end point (a composite of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularization [CI-TLR]) at 12 months. However, it is still unknown whether these outcome results persisted in the long term. We here present the 2-year results of the TALENT trial.

All patients provided written informed consent to participate in the study. The study protocol of TALENT trial was approved by institutional ethics committees of participating institutions and central regulatory bodies for each of the center and was conducted according to the Declaration of Helsinki and Good Clinical Practice. The data that support the findings of this study are available from the corresponding author upon reasonable request. Time-to-event outcomes are compared using the log-rank test. A 2-sided P value <0.05 was considered as statistically significant.

Two-year follow-up information was available in 97.8% (704/720) of patients in the Supraflex arm and in 98.6% (705/715) of patients in the Xience arm. Comparisons of the clinical end points are presented in the Table. At 2 years, in the intention to treat data set, device-oriented composite end point occurred in 49 (6.9%) patients treated with

Key Words: death ■ drug-eluting stent ■ sirolimus ■ stents

Correspondence to: Patrick W. Serruys, MD, PhD, National University of Ireland, Galway (NUIG), PO University Rd, Galway, H91 TK33, Ireland. Email patrick.w.j.c.serruys@gmail.com

For Sources of Funding and Disclosures, see page 368.

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Nonstandard Abbreviations and Acronyms

CI-TLR	clinically indicated target lesion revascularization

Supraflex and 56 (7.9%) patients treated with Xience (*P*=0.491). Frequencies of cardiac death (9 [1.3%] versus 11 [1.6%], *P*=0.659), target vessel myocardial infarction (21 [3.0%] versus 27 [3.8%], *P*=0.382), and CI-TLR (33 [4.7%] versus 37 [5.3%], *P*=0.627) were not significantly different for both stent type. The rate of definite/probable ST was also not different between the Supraflex and XIENCE arms (8 [1.1%] versus 9 [1.3%], *P*=0.813).

The per-protocol population set consists of all patients who have been randomized to a treatment group, and who have received only the assigned study stent. Because the per-protocol analysis comparing the 1-year results showed a significantly lower CI-TLR rate in the Supraflex arm (1.2%) than in the Xience arm (3.1%), we investigated whether this difference persisted or accrued beyond 1 year. At 2-year follow-up, in the per-protocol data set, device-oriented composite end point occurred in 36 (5.5%) patients treated with Supraflex and 49 (7.2%) patients treated with Xience (*P*=0.223). Frequencies of cardiac death (9 [1.4%] versus 11 [1.6%], *P*=0.736), target vessel myocardial infarction (17 [2.6%] versus 26 [3.8%], *P*=0.216), and CI-TLR (21 [3.3%] versus 30 [4.5%], *P*=0.267) were all numerically lower in the Supraflex arm, but without reaching statistically significant differences compared with the Xience arm.

The main finding of our analyses is that the use of the Supraflex showed sustained efficacy and safety at 2-year, as compared with the Xience.

The fact that the rate of nontarget vessel revascularization is numerically lower in the Xience arm at 2-year has to be acknowledged. On one hand, nontarget vessel revascularization is not directly related to the allocated study device, and on the other hand, the study did not have the adequate sample size for any secondary end points. Therefore, we believe this observation is largely due to play of chance. In the second-year outcome, although in the per-protocol data set, the rate of CI-TLR was still numerically lower in the Supraflex arm than in the Xience arm, it did not reach a statistical significance. A longer-term follow-up is still needed to investigate whether Supraflex might show a lower CI-TLR rate as compared with Xience.

The current analyses have limitations. First, the study did not have the adequate statistical power for any itemized end points due to the relatively small sample size. Moreover, taking into account the observational nature of the analysis, there was no formal correction for multiple testing.[5] Therefore, these results should be interpreted cautiously and as hypothesis-generating only.

ARTICLE INFORMATION

Affiliations

Department of Cardiology, Xijing hospital, Xi'an, China (C.G.). Department of Cardiology, Radboud University, Nijmegen, the Netherlands (C.G.). Department of Cardiology, National University of Ireland Galway (C.G., F.S., Y.O., P.W.S.). Amsterdam UMC, University of Amsterdam, the Netherlands (N.K., R.J.d.W.). Maasstad Ziekenhuis, Rotterdam, the Netherlands (P.C.S.). Department of Cardiology, Catharina Hospital, Eindhoven, the Netherlands (P.T.). Medical Centre Leeuwarden, the Netherlands (S.H.). Cardiology Department, La Paz University Hospital, Madrid, Spain (R.M.). Department of Cardiology, University Hospital of Wales, Cardiff, United Kingdom (A. Choudhury). Acibadem City Clinic Cardiovascular Center, Sofia, Bulgaria (I.P.). University Hospital of Bellvitge, Barcelona, Spain (A. Cequier). Division of Interventional Cardiology, Cardio-Thoracic-Vascular Department, San Raffaele Scientific Institute, Milan, Italy (A. Colombo). Academics and Research, Batra Hospital and Medical Research Center, New Delhi, India (U.K.). Freeman Hospital, Newcastle University, and Newcastle upon Tyne Hospitals NHS Trust, Newcastle, United Kingdom (A.Z.). NHLI, Imperial College London, United Kingdom (P.W.S.).

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Table. Clinical Outcomes at 24 Months After Stent Implantation (Intention-to-Treat Basis)

Outcome	Supraflex SES (N=720)	Xience EES (N=715)	Difference (95% CI)	*P* value
TLF (DoCE)	6.9% (49)	7.9% (56)	−1.0% (−3.7% to 1.7%)	0.49
PoCE	15.5% (110)	13.1% (93)	2.4% (−1.3% to 6.0%)	0.20
TVF	8.3% (59)	8.9% (63)	−0.6% (−3.5% to 2.4%)	0.71
Components of composite end points				
Death	2.5% (18)	3.0% (21)	−0.4% (−2.1% to 1.3%)	0.64
Cardiac death	1.3% (9)	1.6% (11)	−0.3% (−1.5% to 0.9%)	0.66
MI	4.4% (31)	5.0% (35)	−0.6% (−2.8% to 1.6%)	0.62
Q-wave	0.7% (5)	0.9% (6)	−0.1% (−1.1% to 0.8%)	0.77
Non-Q-wave	3.8% (27)	4.2% (30)	−0.4% (−2.5% to 1.6%)	0.69
TV-MI	3.0% (21)	3.8% (27)	−0.9% (−2.8% to 1.0%)	0.38
Q-wave	0.6% (4)	0.9% (6)	−0.3% (−1.2% to 0.6%)	0.53
Non-Q-wave	2.5% (18)	3.1% (22)	−0.6% (−2.3% to 1.1%)	0.52
Non-TV MI	1.4% (10)	1.1% (8)	0.3% (−0.9% to 1.5%)	0.63
Q-wave	0.1% (1)	0.0% (0)	0.1% (−0.1% to 0.4%)	0.32
Non-Q-wave	1.3% (9)	1.1% (8)	0.2% (−1.0% to 1.3%)	0.80
All revascularization	12.4% (87)	9.7% (68)	2.7% (−0.5% to 6.0%)	0.11
TL revascularization	6.1% (43)	5.7% (40)	0.4% (−2.0% to 2.9%)	0.73
Clinically indicated	4.7% (33)	5.3% (37)	−0.6% (−2.8% to 1.7%)	0.63
nonclinically indicated	1.7% (12)	1.0% (7)	0.7% (−0.5% to 1.9%)	0.25
TV revascularization	7.4% (52)	7.0% (49)	0.4% (−2.3% to 3.1%)	0.77
Clinically indicated	6.3% (44)	6.4% (45)	−0.1% (−2.7% to 2.4%)	0.90
Nonclinically indicated	1.7% (12)	1.6% (11)	0.2% (−1.2% to 1.5%)	0.84
Non-TV revascularization	7.9% (55)	4.4% (31)	3.5% (0.9% to 6.0%)	0.01
Stent thrombosis				
Definite	1.0% (7)	1.1% (8)	−0.1% (−1.2% to 0.9%)	0.80
Acute (0–1 days)	0.1% (1)	0.0% (0)	0.1% (−0.1% to 0.4%)	0.32
Subacute (2–30 days)	0.1% (1)	0.3% (2)	−0.1% (−0.6% to 0.3%)	0.56
Late (31–360 days)	0.4% (3)	0.4% (3)	0.0% (−0.7% to 0.7%)	0.99
Very late stent thrombosis (after 360 days)	0.3% (2)	0.4% (3)	−0.1% (−0.8% to 0.5%)	0.66
Definite or probable	1.1% (8)	1.3% (9)	−0.1% (−1.3% to 1.0%)	0.81
Acute (0–1 days)	0.1% (1)	0.0% (0)	0.1% (−0.1% to 0.4%)	0.32
Subacute (2–30 days)	0.3% (2)	0.3% (2)	−0.0% (−0.6% to 0.5%)	0.99
Late (31–360 days)	0.4% (3)	0.6% (4)	−0.1% (−0.9% to 0.6%)	0.70
Very late stent thrombosis (after 360 days)	0.3% (2)	0.4% (3)	−0.1% (−0.8% to 0.5%)	0.66

DoCE indicates device-oriented composite end point; EES, everolimus-eluting stent; MI, myocardial infarction; PoCE, patient-oriented composite end point; SES, sirolimus-eluting stent; TLF, target lesion failure; TVF, target vessel failure; and TV-MI, target vessel myocardial infarction.

Sirolimus-eluting stents with ultrathin struts versus everolimus-eluting stents for patients undergoing percutaneous coronary intervention: final three-year results of the TALENT trial

Robbert J. de Winter[1], MD, PhD; Azfar Zaman[2], MD; Hironori Hara[1,3], MD; Chao Gao[3,4], MD; Masafumi Ono[1,3], MD; Scot Garg[5], MD, PhD; Pieter C. Smits[6], MD, PhD; Pim A.L. Tonino[7], MD, PhD; Sjoerd H. Hofma[8], MD, PhD; Raul Moreno[9], MD, PhD; Anirban Choudhury[10], MD; Ivo Petrov[11], MD; Angel Cequier[12], MD; Antonio Colombo[13,14], MD; Upendra Kaul[15], MD, PhD; Yoshinobu Onuma[3]*, MD, PhD; Patrick W. Serruys[3,16], MD, PhD

1. Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands; 2. Newcastle Freeman Hospital, Newcastle University, and Newcastle upon Tyne Hospitals NHS Trust, Newcastle, United Kingdom; 3. Department of Cardiology, National University of Ireland Galway, Galway, Ireland; 4. Department of Cardiology, Radboud University, Nijmegen, the Netherlands; 5. Department of Cardiology, Royal Blackburn Hospital, Blackburn, United Kingdom; 6. Maasstad Ziekenhuis, Rotterdam, the Netherlands; 7. Department of Cardiology, Catharina Hospital, Eindhoven, the Netherlands; 8. Medical Centre Leeuwarden, Leeuwarden, the Netherlands; 9. Cardiology Department, La Paz University Hospital, Madrid, Spain; 10. Department of Cardiology, University Hospital of Wales, Cardiff, United Kingdom; 11. Acibadem City Clinic Cardiovascular Center, Sofia, Bulgaria; 12. Bellvitge University Hospital, University of Barcelona, IDIBELL, Barcelona, Spain; 13. Invasive Cardiology Unit, Humanitas Clinical and Research Center, IRCCS, Rozzano, Milan, Italy; 14. Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; 15. Academics and Research, Batra Hospital and Medical Research Center, New Delhi, India; 16. NHLI, Imperial College London, London, United Kingdom on behalf of the TALENT Investigators

R.J. de Winter, A. Zaman and H. Hara contributed equally to this paper.

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KEYWORDS

- clinical trials
- drug-eluting stent
- innovation

Abstract

Background: In the TALENT study, the sirolimus-eluting ultrathin strut Supraflex stent was non-inferior to the XIENCE stent for a device-oriented composite endpoint (DoCE: defined as cardiac death, target-vessel myocardial infarction [TV-MI], or clinically indicated target lesion revascularisation [CI-TLR]) at 12 months.

Aims: This study investigated the 3-year outcomes of the TALENT trial and long-term impact of ultrathin drug-eluting stents (DES), compared to the XIENCE everolimus-eluting thin stent.

Methods: The TALENT trial is a prospective, multicentre, randomised all-comers trial comparing the Supraflex sirolimus-eluting stent with the XIENCE everolimus-eluting stent, with planned follow-up for 3 years.

Results: The TALENT trial enrolled 1,435 patients (Supraflex n=720, XIENCE n=715) with 3-year follow-up data available in 97.8% in the Supraflex group, and in 98.9% in the XIENCE group. At 3 years, DoCE occurred in 57 patients (8.1%) in the Supraflex group, and in 66 patients (9.4%) in the XIENCE group (p=0.406). There were no significant between-group differences in rates of cardiac death, TV-MI or CI-TLR. The rates of definite or probable stent thrombosis were low and similar between groups (1.1% vs 1.4%; p=0.640). In a meta-analysis of long-term follow-up (3-5 years), ultrathin strut DES tended to reduce DoCE (relative risk 0.89 [0.79-1.01]; p=0.068), compared to thicker strut DES. The risks for cardiac death and definite or probable stent thrombosis were similar between ultrathin strut DES and thicker strut DES.

Conclusions: At 3-year follow-up, the use of the Supraflex stent was at least as safe and efficacious as the XIENCE stent in an all-comers population. ClinicalTrials.gov: NCT02870140

**Corresponding author: Professor of Interventional Cardiology, National University of Ireland, Galway (NUIG), University Road, Galway H91 TK33, Ireland. E-mail: yoshinobuonuma@gmail.com*

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Abbreviations

CI	confidence interval
CI-TLR	clinically indicated target lesion revascularisation
DES	drug-eluting stent
DoCE	device-oriented composite endpoint
EES	everolimus-eluting stent
ITT	intention-to-treat
MI	myocardial infarction
PP	per protocol
PoCE	patient-oriented composite endpoint
RR	relative risk
SES	sirolimus-eluting stent
TV	target vessel

Introduction

Stents with thinner struts have been shown to reduce acute thrombogenicity and promote faster endothelialisation, compared to stents with thicker struts[1-3]. One hypothesis behind this is that protruding thicker struts disrupt laminar flow, inducing flow disturbances, which can activate a platelet-signalling procoagulation pathway[1,4]. The physiological benefits and improved fluid dynamics with thinner struts may be partly responsible for the reduced rates of restenosis, stent thrombosis, and myocardial infarction (MI) observed with contemporary second-generation drug eluting stents (DES), which all have strut thicknesses of <100 µm, when compared to first-generation DES, which had strut thicknesses of >132 µm. The development of ultrathin strut stents, with strut thicknesses of <70 µm may further improve event-free survival compared to thin strut DES (second-generation DES).

The Supraflex stent (Sahajanand Medical Technologies) is a sirolimus-eluting stent (SES) with a biodegradable polymeric coating and 60 µm ultrathin struts. In the TALENT study, the Supraflex SES was non-inferior to the XIENCE durable polymer everolimus-eluting stent (EES; Abbot Vascular), for a device-oriented composite endpoint (DoCE) of cardiac death, target-vessel myocardial infarction (TV-MI), or clinically indicated target lesion revascularisation (CI-TLR) at 12 months[5,6]. The longer-term outcomes with ultrathin DES are currently limited, and therefore we investigated the final 3-year outcomes after implantation of the Supraflex SES as compared to the XIENCE EES in the TALENT all-comers trial.

Methods

STUDY DESIGN AND POPULATION

The design and 2-year results of the TALENT trial have been reported previously[5-7]. In brief, the TALENT trial is a prospective, multicentre, single-blinded, all-comers, randomised controlled trial, allocating patients in a 1:1 ratio to either the Supraflex SES or XIENCE EES. Twenty-three sites in Europe enrolled patients from October 2016 to July 2017. The primary endpoint of the study was a non-inferiority comparison at 12 months of a DoCE, defined as a composite of cardiac death, TV-MI, and CI-TLR. The composite secondary endpoints were a patient-oriented composite endpoint (PoCE) of all-cause death, any MI, and any revascularisation, and target vessel failure (TVF), a composite of cardiac death, TV-MI, and clinically indicated target vessel revascularisation (CI-TVR). Stent thrombosis – a safety indicator – was defined as per the Academic Research Consortium definition[8]. MI was defined according to the Society for Cardiovascular Angiography and Interventions consensus for periprocedural MI (when occurring 48 hrs or less after the index procedure) or according to the Third Universal Definition for MI[9,10]. Clinical data were adjudicated by an independent clinical event committee, blinded to stent allocation.

Patients with stable coronary artery disease received dual antiplatelet therapy (DAPT) for >6 months after percutaneous coronary intervention (PCI), followed by aspirin monotherapy indefinitely. Patients with acute coronary syndrome received DAPT for >12 months after PCI, followed by aspirin monotherapy indefinitely. The protocol prespecified patient follow-up up to 3 years.

All patients provided written informed consent to participate in the study. The study protocol of the TALENT trial was approved by institutional ethics committees of participating institutions and central regulatory bodies for each country, and was conducted according to the Declaration of Helsinki and Good Clinical Practice.

STUDY STENTS

Supraflex is a new-generation metallic stent consisting of an L605 cobalt-chromium alloy platform with ultrathin struts (60 µm) across all stent diameters, flexible S-link connectors, and a biodegradable polymeric matrix coating. Sirolimus, at a concentration of 1.4 µg/mm², together with the polymeric matrix, is coated on the conformal surface of the stent, with an average coating thickness of 4-5 µm. Seventy percent of the sirolimus is eluted in the first 7 days, with the remainder released over the following 48 days. The polymer gradually degrades over 9-12 months. The crossing profile of the Supraflex is 0.99 mm (the crossing profile of the newest XIENCE Alpine EES is 1.10 mm and of the XIENCE Sierra EES is 0.99 mm).

The control stent used in the study was the XIENCE EES, which has a cobalt chromium alloy platform and a strut thickness of 81 µm. It has an 8 µm thick durable polymer coated with everolimus at a dose of 1 µg/mm², which is completed eluted over 120 days.

META-ANALYSIS

Randomised clinical trials comparing ultrathin strut DES (strut thickness <70 µm) and thicker strut DES (strut thickness ≥81 µm) with at least 3-year outcomes were searched from PubMed, EMBASE, and abstracts and presentations from major cardiovascular meetings between January 2010 and October 2021 **(Supplementary Table 1)**. The meta-analytic summary estimates (relative risk [RR] with 95% confidence interval [CI]) for the ultrathin strut DES versus thicker strut DES in terms of DoCE, its individual components, definite or probable stent thrombosis, and

all-cause death at the time of last available follow-up were evaluated using results reported in intention-to-treat (ITT) analyses. All outcomes were calculated using both the fixed-effects model and the random-effects model of DerSimonian and Laird[11]. This was done to compare the fixed- and random-effects estimates of the intervention as recommended by the Cochrane Collaboration, given that we anticipated some heterogeneity ($I^2>0$). If the estimates are similar, then any small-study effects have little impact on the intervention effect estimate. Heterogeneity was assessed using the I^2 statistic, with $I^2<25\%$ considered low, $I^2\geq25\%$ and $\leq75\%$ considered moderate, and $I^2>75\%$ considered high[12,13]. When heterogeneity was moderate or high, the L'Abbé plot was demonstrated. Publication bias was visually inspected using a funnel plot. Risk of bias was assessed according to the Cochrane Collaboration's tool[14].

STATISTICAL ANALYSIS

All patients in the ITT analysis were analysed according to their assigned treatment group, regardless of the actual treatment received. Patients who were randomised to a treatment group and only received that assigned study stent, were included in the per protocol (PP) analysis.

Prespecified subgroup analyses were performed for the primary endpoint, DoCE, with respect to diabetes, ST-segment elevation MI (STEMI), small vessels (≤2.75 mm), multivessel treatment, long lesions (>18 mm), in-stent restenosis, bypass graft, left main treatment, bifurcation treatment, or overlapping stents.

The cumulative event rates were estimated using the Kaplan-Meier method and comparisons of outcomes were performed with the log-rank test. Hazard ratios were calculated using the Cox proportional hazards model. P values are for the superiority and a two-sided p-value <0.05 was considered statistically significant. Analyses were performed using SAS software, version 9.3 (SAS Institute Inc.) and R version 3.6.0 (R Foundation for Statistical Computing).

Results

STUDY POPULATION

The TALENT trial enrolled 1,435 patients with 2,076 lesions; 720 patients with 1,046 lesions were randomly assigned to Supraflex, and 715 patients with 1,030 lesions to XIENCE **(Figure 1)**. Baseline clinical, angiographic, and procedural characteristics were comparable between the two groups, as previously reported[15]. Three-year follow-up data were available for 97.8% (704/720) of patients in the Supraflex group and for 98.9% (707/715) of patients in the XIENCE group **(Figure 1)**.

CLINICAL OUTCOMES AT 3 YEARS (ITT ANALYSIS)

At 3 years DoCE occurred in 57 patients (8.1%) in the Supraflex group, and in 66 patients (9.4%) in the XIENCE group (difference −1.3% [95% CI: −4.3% to 1.6%]; p=0.406) **(Table 1, Figure 2A)**. There were no significant between-group differences in rates of cardiac death, TV-MI, and CI-TLR **(Table 1, Figure 2B-Figure 2D)**.

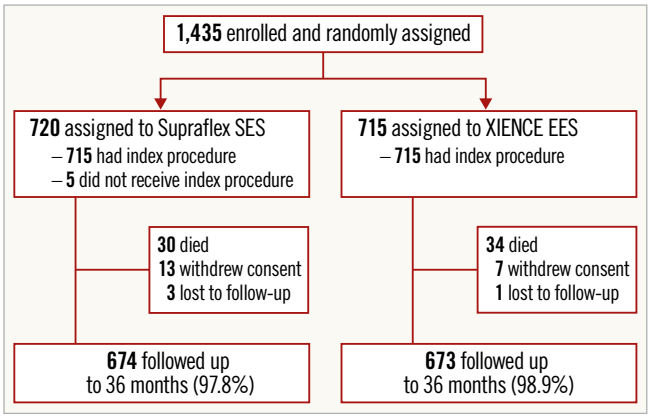


Figure 1. *Study follow chart. EES: everolimus-eluting stent; SES: sirolimus-eluting stent.*

There were also no significant differences in the groups between 1 and 3 years **(Supplementary Figure 1)**. The percentages of patients with DAPT at 6 and 12 months were similar **(Supplementary Table 2)**, and the rates of definite or probable stent thrombosis were low and comparable (Supraflex 1.1% vs XIENCE 1.4%, difference −0.4% [95% CI: −1.5% to 0.7%]; p=0.640) **(Table 1, Figure 2E)**. The rates of other clinical events are presented in **Table 1**. Non-TV revascularisation was significantly lower in the XIENCE group (5.7%), compared to the Supraflex group (8.6%) (difference 2.9% [95% CI: 0.2% to 5.6%]; p=0.035), although these events were not associated with lesions treated with study stents.

PER PROTOCOL (PP) ANALYSIS

In the PP analysis at 3 years DoCE occurred in 43 (6.6%) patients treated with Supraflex and 59 (8.7%) patients treated with XIENCE (difference −2.1% [95% CI: −5.0% to 0.8%], p=0.165) **(Supplementary Table 3, Supplementary Figure 2A)**. The rates of cardiac death, TV-MI and CI-TLR were all numerically lower, but not statistically different with Supraflex compared with XIENCE. Notably the significantly lower rate of CI-TLR observed with Supraflex in the PP analysis at 1-year (1.2% vs 3.1%, difference −1.9% [95% CI: −3.5% to 0.3%], p=0.021)[6] was no longer evident at 3 years (3.6% vs 5.1%, difference −1.5%, [95% CI: −3.7 to 0.7], p=0.192) **(Supplementary Table 3, Supplementary Figure 2B-Supplementary Figure 2D)**. There were no significant differences between stents in rates of non-TV revascularisation (Supraflex 7.8% vs XIENCE 5.8%, difference 2.0% [95% CI: −0.7% to 4.7%], p=0.143).

SUBGROUP ANALYSIS

The treatment effect in DoCE was no different across the prespecified subgroup analyses for diabetes, STEMI, multivessel treatment, long lesions, in-stent restenosis, bypass graft, left main treatment, bifurcation treatment, or overlapping stents, although Supraflex resulted in better outcomes in patients without small vessels treated **(Figure 3)**.

Table 1. Clinical outcomes at 36 months after stent implantation.

Clinical outcomes (ITT)	Supraflex SES (n=720)	XIENCE EES (n=715)	Difference (95% confidence interval)	*p*-value
DoCE	8.1 (57)	9.4 (66)	–1.3 (–4.3-1.6)	0.406
PoCE	18.0 (128)	16.5 (117)	1.5 (–2.5-5.4)	0.424
TVF	9.8 (69)	10.6 (75)	–0.9 (–4.0-2.3)	0.604
Components of composite endpoints				
Death	4.2 (30)	4.8 (34)	–0.6 (–2.7-1.6)	0.619
Cardiac death	1.8 (13)	2.1 (15)	–0.3 (–1.8-1.2)	0.707
MI	5.3 (37)	6.0 (42)	–0.7 (–3.1-1.7)	0.563
Q-wave	0.9 (6)	1.0 (7)	–0.1 (–1.2-0.9)	0.785
Non-Q-wave	4.6 (32)	5.3 (37)	–0.7 (–3.0-1.5)	0.536
TV-MI	3.3 (23)	4.6 (32)	–1.3 (–3.3-0.7)	0.219
Q-wave	0.6 (4)	0.9 (6)	–0.3 (–1.2-0.6)	0.529
Non-Q-wave	2.8 (20)	3.9 (27)	–1.0 (–2.9-0.9)	0.300
Non-TV-MI	2.0 (14)	1.6 (11)	0.4 (–1.0-1.8)	0.545
Q-wave	0.3 (2)	0.1 (1)	0.1 (–0.4-0.6)	0.563
Non-Q-wave	1.7 (12)	1.6 (11)	0.2 (–1.2-1.5)	0.833
All revascularisation	13.3 (93)	11.6 (81)	1.7 (–1.8-5.2)	0.325
TL revascularisation	6.3 (44)	6.3 (44)	–0.0 (–2.5-2.5)	0.993
Clinically indicated	5.0 (35)	5.9 (41)	–0.9 (–3.2-1.5)	0.483
Non-clinically indicated	1.6 (11)	1.4 (10)	0.1 (–1.1-1.4)	0.827
TV revascularisation	8.0 (56)	8.2 (57)	–0.2 (–3.0-2.7)	0.922
Clinically indicated	6.9 (48)	7.6 (53)	–0.7 (–3.4-2.0)	0.603
Non-clinically indicated	1.6 (11)	2.0 (14)	–0.4 (–1.8-1.0)	0.543
Non-TV revascularisation	8.6 (60)	5.7 (40)	2.9 (0.2-5.6)	0.035
Stent thrombosis				
Definite	1.0 (7)	1.3 (9)	–0.3 (–1.4-0.8)	0.620
Definite (very late, >360 days)	0.3 (2)	0.6 (4)	–0.3 (–1.0-0.4)	0.419
Definite or probable	1.1 (8)	1.4 (10)	–0.3 (–1.5-0.9)	0.640
Definite or probable (very late, >360 days)	0.3 (2)	0.6 (4)	–0.3 (–1.0-0.4)	0.419

Data are presented as percentages (numbers). DoCE: device-oriented composite endpoint; ITT: intention-to-treat; MI: myocardial infarction; PoCE: patient-oriented composite endpoint; TL: target lesion; TV: target-vessel; TVF: target vessel failure

META-ANALYSIS

Including the TALENT trial, there were 11 randomised trials (15,370 patients) with at least 3-year results comparing outcomes between ultrathin strut DES with thicker strut DES **(Table 2, Supplementary Table 4, Supplementary Figure 3)**. Overall, ultrathin strut DES resulted in a 11% reduction in DoCE compared to thicker strut DES (RR 0.89, 95% CI: 0.79-1.01; p=0.068), although the effect was not statistically significant **(Figure 4)**. Ultrathin strut DES and thicker strut DES had similar risks for definite or probable stent thrombosis and mortality **(Figure 4)**. Moderate heterogeneity was observed for DoCE and death, thus the L'Abbé plots are presented in **Supplementary Figure 4**. The funnel plots and risk of bias are shown in **Supplementary Figure 5** and **Supplementary Table 4**.

In patients with diabetes or small vessel treated, there were no statistically significant differences in DoCE between ultrathin strut DES and the thicker strut DES **(Supplementary Figure 6)**.

Discussion

At 3-year follow-up of the randomised all-comers TALENT trial, there were no significant differences in rates of DoCE, its individual components, or stent thrombosis between patients assigned to the Supraflex or XIENCE groups (**Central illustration**, panel A).

IMPACT OF THE SUPRAFLEX STENT ON REPEAT REVASCULARISATION

At 1-year follow-up in the PP analysis, the Supraflex stent resulted in a significantly lower rate of CI-TLR, compared to XIENCE. At 3-year follow-up, whilst the rate of CI-TLR was still numerically lower with Supraflex, the difference was no longer statistically significant (5.0% vs 5.9%; p=0.483 [ITT analysis]; 3.6% vs 5.1%; p=0.192 [PP analysis]). Longer follow-up and/or a larger sample size are certainly needed to fully examine how this early difference could be more durable.

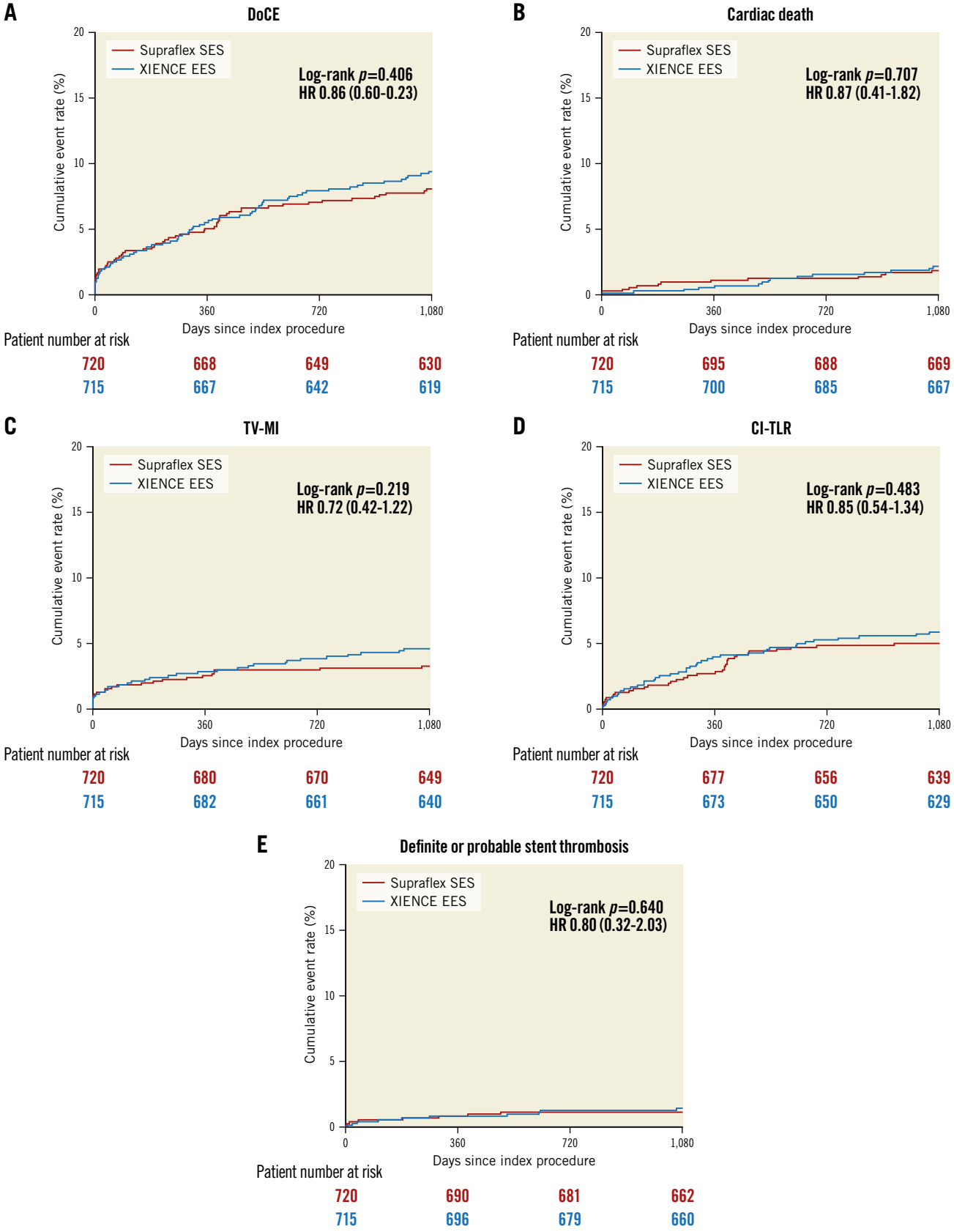


Figure 2. *Kaplan-Meier estimates for the device-oriented composite endpoint (DoCE) and its components at 3 years (intention-to-treat [ITT] basis). A) DoCE, B) cardiac death, C) target vessel myocardial infarction (TV-MI), D) clinically indicated target lesion revascularisation (CI-TLR), and E) definite or probable stent thrombosis. HR: hazard ratio.*

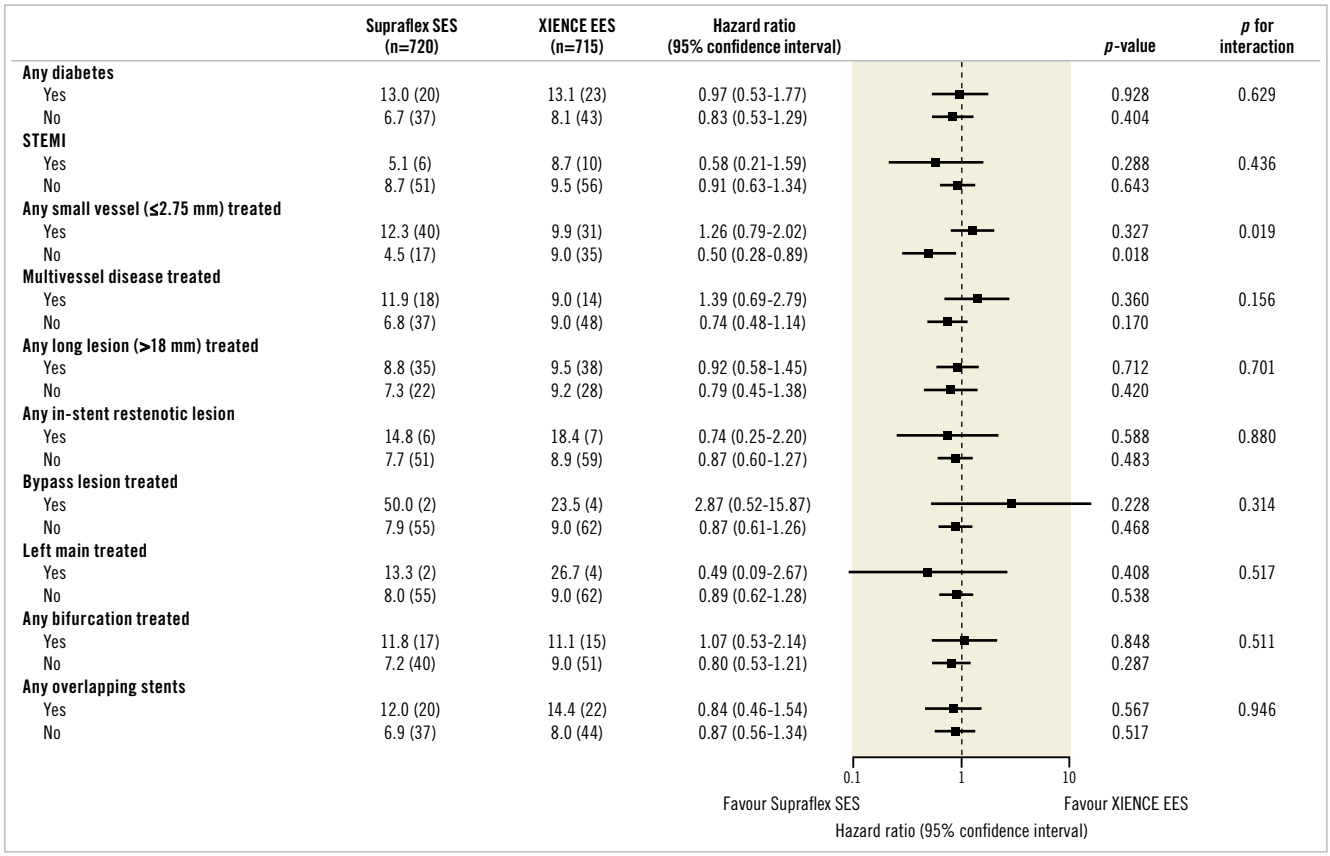


Figure 3. *Subgroup analysis for DoCE (ITT basis). STEMI: ST-elevation myocardial infarction*

IMPACT OF ULTRATHIN STRUT POLYMERS

A meta-analysis of 10 randomised trials including 11,658 patients by Bangalore et al demonstrated that at 1-year ultrathin strut DES (Orsiro, MiStent, and BioMime) resulted in a 16% RR reduction in DoCE (RR 0.84, 95% CI: 0.72-0.99), compared to second-generation DES with thicker struts (XIENCE, Resolute, and Nobori)[16]. Recently, another meta-analysis at a mean follow-up of 2.5 years demonstrated that ultrathin strut DES reduced the risk of DoCE (RR

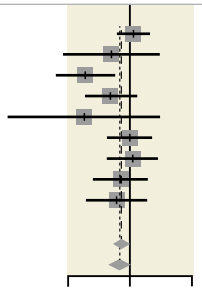
Table 2. Clinical randomised trials for a meta-analysis.

Study	Publi-cation	Follow-up	Comparisons	Population	Number of patients	DoCE	Cardiac death	TV-MI	CI-TLR	Definite or probable stent thrombosis
BIOSCIENCE[18]	2018	5 years	Orsiro vs XIENCE	All-comers	1,063 vs 1,056	20.2% vs 18.8%	8.6% vs 7.5%	6.3% vs 7.1%	10.8% vs 10.0%	6.3% vs 7.7%
BIOFLOW II[19]	2018	5 years	Orsiro vs XIENCE	All-comers	298 vs 154	10.4% vs 12.7%	1.7% vs 2.8%	3.4% vs 3.3%	6.3% vs 6.7%	0.0% vs 0.7%
BIOFLOW IV	2019	4 years	Orsiro vs XIENCE	All-comers	385 vs 190	NA	NA	NA	NA	0.8% vs 0.0%
BIOFLOW V[20]	2020	3 years	Orsiro vs XIENCE	Non-all-comers	884 vs 450	8.2% vs 13.6%	1.1% vs 1.2%	5.0% vs 9.2%	3.2% vs 6.7%	0.5% vs 1.5%
BIO-RESORT[21]	2019	3 years	Orsiro vs Resolute Integrity	All-comers	1,169 vs 1,173	6.7% vs 8.3%	2.1% vs 2.3%	3.0% vs 3.5%	2.9% vs 3.8%	1.1% vs 0.9%
PRISON-IV[22]	2019	3 years	Orsiro vs XIENCE	Chronic total occlusion	165 vs 165	NA	1.2% vs 1.8%	NA	NA	NA
ORIENT[23]	2020	3 years	Orsiro vs Resolute Integrity	All-comers	250 vs 122	4.7% vs 7.8%	0.8% vs 2.6%	NA	3.8% vs 5.2%	0.0% vs 1.6%
SORT OUT VII[24]	2020	3 years	Orsiro vs Nobori	All-comers	1,261 vs 1,264	9.0% vs 9.1%*	3.0% vs 2.6%	3.1% vs 2.9%*	5.2% vs 5.9%	1.5% vs 2.1%
BIONYX[25]	2021	3 years	Orsiro vs Resolute Onyx	All-comers	1,245 vs 1,243	7.5% vs 7.2%	1.9% vs 1.1%	3.1% vs 3.2%	4.6% vs 4.7%	1.2% vs 0.6%
DESSOLVE III[26]	2020	3 years	MiStent vs XIENCE	All-comers	703 vs 695	10.5% vs 11.5%*	3.9% vs 3.8%	3.2% vs 2.5%*	5.2% vs 6.5%	1.2% vs 1.5%
TALENT	2021	3 years	Supraflex vs XIENCE	All-comers	720 vs 715	8.1% vs 9.4%	1.8% vs 2.1%	3.3% vs 4.6%	5.0% vs 5.9%	1.1% vs 1.4%

*In the SORT OUT VII and DESSOLVE III trials, MI not clearly attributable to a non-target vessel was used, instead of TV-MI. CI-TLR: clinical indicated target lesion revascularisation

A DoCE

Sent	Study	Publication	Follow-up	Ultrathin Events	Ultrathin Number	Thicker Events	Thicker Number	Risk ratio (95% CI)	Weight (fixed)	Weight (random)
Orsiro	BIOSCIENCE	2018	5 years	198	1,063	189	1,056	1.04 (0.87-1.25)	25.3%	21.4%
	BIOFLOW II	2018	5 years	30	298	19	154	0.82 (0.48-1.40)	3.3%	4.5%
	BIOFLOW V	2020	3 years	70	884	59	450	0.60 (0.44-0.84)	10.4%	10.3%
	BIO-RESORT	2019	3 years	77	1,169	96	1,173	0.80 (0.60-1.07)	12.8%	12.4%
	ORIENT	2020	3 years	11	250	9	122	0.60 (0.25-1.40)	1.6%	2.0%
	SORT OUT VII	2020	3 years	114	1,261	115	1,264	0.99 (0.78-1.27)	15.3%	15.2%
	BIONYX	2021	3 years	91	1,245	88	1,243	1.03 (0.78-1.37)	11.8%	12.8%
MiStent	DESSOLVE III	2020	3 years	72	703	79	695	0.90 (0.67-1.22)	10.6%	11.6%
Supraflex	TALENT	2021	3 years	57	720	66	715	0.86 (0.61-1.20)	8.8%	9.8%
	Fixed effect model				7,593		6,872	0.91 (0.83-1.004)	100.00%	
	Random effects model							0.89 (0.79-1.01)		100.00%
	Heterogeneity: I^2=23%, p=0.18									



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B Cardiac death

Sent	Study	Publication	Follow-up	Ultrathin Events	Ultrathin Number	Thicker Events	Thicker Number	Risk ratio (95% CI)	Weight (fixed)	Weight (random)
Orsiro	BIOSCIENCE	2018	5 years	81	1,063	76	1,056	1.06 (0.78-1.43)	36.6%	38.3%
	BIOFLOW II	2018	5 years	5	298	4	154	0.65 (0.18-2.37)	2.5%	2.1%
	BIOFLOW V	2020	3 years	9	884	5	450	0.92 (0.31-2.72)	3.2%	2.9%
	BIO-RESORT	2019	3 years	24	1,169	26	1,173	0.93 (0.54-1.60)	12.5%	11.5%
	PRISON IV	2019	3 years	2	165	3	165	0.67 (0.11-3.94)	1.4%	1.1%
	ORIENT	2020	3 years	2	250	3	122	0.33 (0.06-1.92)	1.9%	1.1%
	SORT OUT VII	2020	3 years	38	1,261	33	1,264	1.15 (0.73-1.83)	15.8%	16.4%
	BIONYX	2021	3 years	23	1,245	13	1,243	1.77 (0.90-3.47)	6.2%	7.6%
MiStent	DESSOLVE III	2020	3 years	27	703	26	695	1.03 (0.61-1.74)	12.6%	12.5%
Supraflex	TALENT	2021	3 years	13	720	15	715	0.86 (0.41-1.80)	7.2%	6.4%
	Fixed effect model				7,758		7,037	1.05 (0.87-1.26)	100.00%	
	Random effects model							1.05 (0.87-1.26)		100.00%
	Heterogeneity: I^2=0%, p=0.79									

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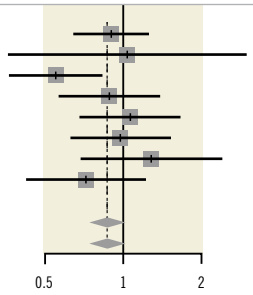
C TV-MI

Sent	Study	Publication	Follow-up	Ultrathin Events	Ultrathin Number	Thicker Events	Thicker Number	Risk ratio (95% CI)	Weight (fixed)	Weight (random)
Orsiro	BIOSCIENCE	2018	5 years	62	1,063	69	1,056	0.89 (0.64-1.24)	23.4%	22.1%
	BIOFLOW II	2018	5 years	10	298	5	154	1.03 (0.36-2.97)	2.2%	2.8%
	BIOFLOW V	2020	3 years	44	884	41	450	0.55 (0.36-0.82)	18.4%	15.8%
	BIO-RESORT	2019	3 years	35	1,169	40	1,173	0.88 (0.56-1.37)	13.5%	13.7%
	SORT OUT VII	2020	3 years	39	1,261	37	1,264	1.06 (0.68-1.65)	12.5%	13.8%
	BIONYX	2021	3 years	38	1,245	39	1,243	0.97 (0.63-1.51)	13.2%	14.0%
MiStent	DESSOLVE III	2020	3 years	22	703	17	695	1.28 (0.69-2.39)	5.8%	7.5%
Supraflex	TALENT	2021	3 years	23	720	32	715	0.71 (0.42-1.21)	10.9%	10.3%
	Fixed effect model				7,343		6,750	0.86 (0.73-1.02)	100.00%	
	Random effects model							0.86 (0.72-1.03)		100.00%
	Heterogeneity: I^2=13%, p=0.33									



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D CI-TLR

Sent	Study	Publication	Follow-up	Ultrathin Events	Ultrathin Number	Thicker Events	Thicker Number	Risk ratio (95% CI)	Weight (fixed)	Weight (random)
Orsiro	BIOSCIENCE	2018	5 years	103	1,063	97	1,056	1.05 (0.81-1.37)	23.5%	26.7%
	BIOFLOW II	2018	5 years	18	298	10	154	0.93 (0.44-1.97)	3.2%	3.3%
	BIOFLOW V	2020	3 years	27	884	28	450	0.49 (0.29-0.82)	8.9%	7.0%
	BIO-RESORT	2019	3 years	33	1,169	43	1,173	0.77 (0.49-1.20)	10.3%	9.3%
	ORIENT	2020	3 years	9	250	6	122	0.73 (0.27-2.01)	1.9%	1.8%
	SORT OUT VII	2020	3 years	66	1,261	74	1,264	0.89 (0.65-1.23)	17.8%	17.9%
	BIONYX	2021	3 years	55	1,245	57	1,243	0.96 (0.67-1.38)	13.7%	14.2%
MiStent	DESSOLVE III	2020	3 years	35	703	44	695	0.78 (0.51-1.21)	10.7%	10.0%
Supraflex	TALENT	2021	3 years	35	720	41	715	0.85 (0.55-1.31)	9.9%	9.7%
	Fixed effect model				7,593		6,872	0.87 (0.76-1.001)	100.00%	
	Random effects model							0.88 (0.76-1.003)		100.00%
	Heterogeneity: I^2=0%, p=0.46									

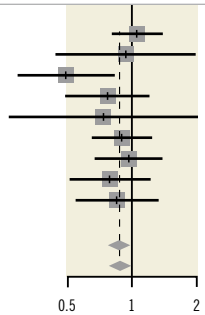

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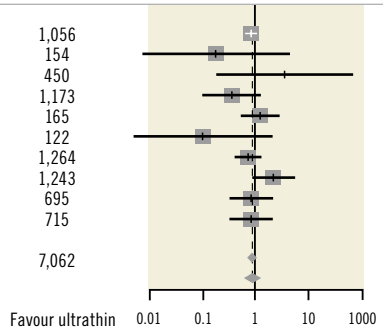
Figure 4. *Long-term outcomes of ultrathin strut DES vs thicker strut DES. A) DoCE, B) cardiac death, C) TV-MI, D) CI-TLR, E) definite or probable stent thrombosis, and F) death. In the BIOFLOW V trial, DoCE was defined as cardiovascular death, TV-MI, or ischaemia-driven TLR. In the SORT OUT VII and DESSOLVE III trials, MI not clearly attributable to a non-target vessel was used, instead of TV-MI. CI: confidence interval; CI-TLR: clinically indicated target lesion revascularisation; DoCE: device-oriented composite endpoint; TV-MI: target-vessel myocardial infarction*

E **Definite or probable stent thrombosis**

Sent	Study	Publication	Follow-up	Ultrathin Events	Ultrathin Number	Thicker Events	Thicker Number	Risk ratio (95% CI)	Weight (fixed)	Weight (random)
Orsiro	BIOSCIENCE	2018	5 years	62	1,063	76	1,056	0.81 (0.59-1.12)	49.4%	34.5%
	BIOFLOW II	2018	5 years	0	298	1	154	0.17 (0.01-4.21)	1.3%	0.9%
	BIOFLOW IV	2020	3 years	3	884	0	450	3.46 (0.18-66.63)	0.4%	1.0%
	BIOFLOW V	2019	3 years	4	1,169	6	1,173	0.34 (0.10-1.20)	5.2%	5.3%
	BIO-RESORT	2019	3 years	12	165	10	165	1.20 (0.52-2.78)	6.5%	10.8%
	ORIENT	2020	3 years	0	250	2	122	0.10 (0.00-2.02)	2.2%	1.0%
	SORT OUT VII	2020	3 years	19	1,261	27	1,264	0.71 (0.39-1.26)	17.5%	18.5%
	BIONYX	2021	3 years	15	1,245	7	1,243	2.14 (0.88-5.23)	4.5%	9.7%
MiStent	DESSOLVE III	2020	3 years	8	703	10	695	0.79 (0.31-1.99)	6.5%	9.1%
Supraflex	TALENT	2021	3 years	8	720	10	715	0.79 (0.32-2.00)	6.5%	9.1%
	Fixed effect model				7,978		7,062	0.84 (0.67-1.05)	100.00%	
	Random effects model							0.84 (0.62-1.15)		100.00%
	Heterogeneity: I^2=19%, p=0.27									



F **Death**

Sent	Study	Publication	Follow-up	Ultrathin Events	Ultrathin Number	Thicker Events	Thicker Number	Risk ratio (95% CI)	Weight (fixed)	Weight (random)
Orsiro	BIOSCIENCE	2018	5 years	139	1,063	105	1,056	1.32 (1.04-1.67)	25.1%	19.8%
	BIOFLOW II	2018	5 years	14	298	14	154	0.52 (0.25-1.06)	4.4%	4.9%
	BIOFLOW IV	2020	3 years	26	884	17	450	0.78 (0.43-1.42)	5.4%	6.6%
	BIO-RESORT	2019	3 years	53	1,169	57	1,173	0.93 (0.65-1.34)	13.6%	13.2%
	PRISON IV	2019	3 years	4	165	8	165	0.50 (0.15-1.63)	1.9%	2.0%
	ORIENT	2020	3 years	9	250	4	122	1.10 (0.34-3.49)	1.3%	2.1%
	SORT OUT VII	2020	3 years	88	1,261	74	1,264	1.19 (0.88-1.61)	17.6%	16.3%
	BIONYX	2021	3 years	67	1,245	45	1,243	1.49 (1.03-2.15)	10.7%	10.0%
MiStent	DESSOLVE III	2020	3 years	55	703	49	695	1.11 (0.77-1.61)	11.8%	12.9%
Supraflex	TALENT	2021	3 years	30	720	34	715	0.88 (0.54-1.42)	8.1%	9.2%
	Fixed effect model				7,758		7,037	1.12 (0.98-1.27)	100.00%	
	Random effects model							1.07 (0.90-1.27)		100.00%
	Heterogeneity: I^2=35%, p=0.13									

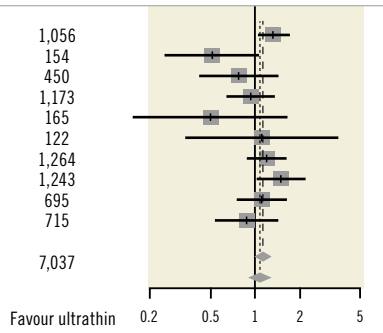
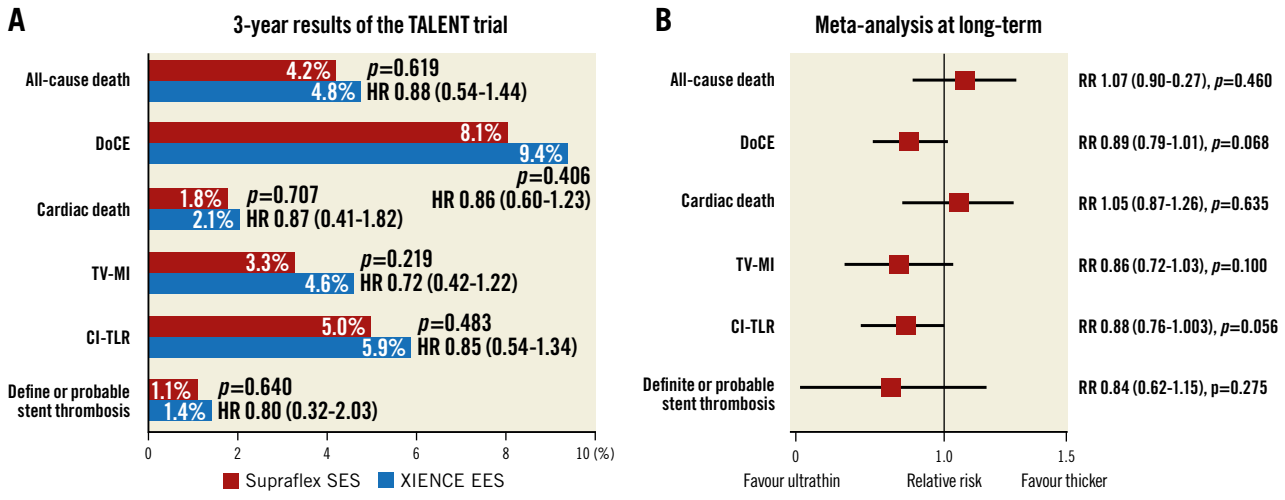


Figure 4. (cont'd) *Long-term outcomes of ultrathin strut DES vs thicker strut DES. A) DoCE, B) cardiac death, C) TV-MI, D) CI-TLR, E) definite or probable stent thrombosis, and F) death. In the BIOFLOW V trial, DoCE was defined as cardiovascular death, TV-MI, or ischaemia-driven TLR. In the SORT OUT VII and DESSOLVE III trials, MI not clearly attributable to a non-target vessel was used, instead of TV-MI. CI: confidence interval; CI-TLR: clinically indicated target lesion revascularisation; DoCE: device-oriented composite endpoint; TV-MI: target-vessel myocardial infarction*

0.85, 95% CI: 0.76-0.96), driven by less CI-TLR (RR 0.75, 95% CI: 0.62-0.92) compared with second-generation DES with thicker struts, with similar risks of cardiac death, and all-cause death[17].

In the TALENT trial, the ultrathin strut Supraflex stent reduced DoCE at 1 year by 6%, compared to the thin strut XIENCE stent in the ITT analysis[6]. The effect of the ultrathin strut Supraflex



Central illustration. *Results of the TALENT trial and a long-term meta-analysis. A) Three-year results of the TALENT trial. B) Long-term (3-5 years) results of a meta-analysis. CI: confidence interval; CI-TLR: clinically indicated target lesion revascularisation; EES: everolimus-eluting stent; DoCE: device-oriented composite endpoint; HR: hazard ratio; RR: relative risk; SES: sirolimus-eluting stent; TV-MI: target vessel myocardial infarction*

stent was retained at 3 years with 14% risk reductions in DoCE, although the effect was not statistically significant.

To date, long-term follow-up data with at least 3-year results of ultrathin strut stents (strut thickness <70 µm) versus thicker strut stents (strut thickness ≥81 µm) are available in the BIOSCIENCE[18], BIOFLOW II[19], BIOFLOW V[20], BIO-RESORT[21], PRISON-IV[22], ORIENT[23], SORT OUT VII[24], BIONYX[25] (Orsiro), DESOLVE III[26] (MiStent), and TALENT (Supraflex) randomised trials. The 4-year results of BIOFLOW-IV have not been published, but have been presented in Slagboom et al. TCT-43 A Prospective Randomized Multicenter Study to Assess the Safety and Effectiveness of the Orsiro Sirolimus-Eluting Stent in the Treatment of Subjects With Up to 2 *De Novo* Coronary Artery Lesions–BIOFLOW IV: 4-Year Clinical Results. J Am Coll Cardiol. 2019;74:B43. The characteristics of these ultrathin strut stents are shown in **Table 3**[16,27,28].

Our updated meta-analysis of these trials, including results from the current study, demonstrate the safety of ultrathin strut DES compared to thicker strut DES at a minimum of 3 years follow-up (**Central illustration**, panel B). Although moderate heterogeneity was observed between studies and the difference was not statistically significant, ultrathin strut DES reduced DocE by 11%, compared to thicker strut DES (RR 0.89, 95% CI: 0.79-1.01; p=0.068). The risks for cardiac death and definite or probable stent thrombosis were similar between ultrathin strut DES and thicker strut DES. Theoretically, thinner struts could have some advantages: such as less stent-induced vessel injury and subsequent inflammation; faster re-endothelialisation; and less flow disturbance and fewer areas of low shear stress behind struts, resulting in reduced thrombogenicity[1-4,29]. The stent strut thickness of Orsiro is 80 µm for stent diameters ≥3.5 mm, which was similar to the stent strut thickness of XIENCE stent (81 µm for all sizes) and Resolute Onyx stent (81 µm for stent diameters ≤4.0 mm). The patients treated with Orsiro with a stent diameter ≥3.5 mm may dilute the impact of stent strut thickness. At least, in the BIOSCIENCE trial, 244 patients (23.0%) were treated with stents ≥3.5 mm in the Orsiro group. Thus, the meta-analysis may underestimate the impact of stent strut thickness, and the analysis using individual patient data is mandatory to investigate the impact of ultrathin strut DES precisely.

COMPARISON BETWEEN NEWER-GENERATION ULTRATHIN STRUT DES

There are notable differences in stent profiles amongst the ultrathin strut Orsiro, MiStent, and Supraflex DES. The Supraflex and MiStent DES have a fixed strut thickness of 60 and 64 µm, respectively, irrespective of the stent diameter, which is at variance with the Orsiro stent, which has a strut thickness of 60 µm for stents 2.25 to 3.0 mm in diameter and 80 µm for stents with a diameter of 3.5 to 4.0 mm. Moreover, whilst these ultrathin strut stents all have biodegradable polymers and elute sirolimus, there are fundamental differences in their drug release kinetics. In the Supraflex stent, 70% of the sirolimus is eluted in the first 7 days during an initial burst, followed by sustained release which is completed by day 48; the polymer gradually degrades over 9-12 months. In the MiStent, no drug release occurs in the first 3 days, and whilst the polymer is fully biodegraded and resorbed within 3 months of implantation, microcrystalline sirolimus is impacted and embedded in the vessel wall, acting as a tissue reservoir for 270 days, such that arterial concentrations of sirolimus still reach more than 2 ng/ml at day 270. In the Orsiro stent, sirolimus is slowly released over 12-14 weeks, whilst its polymer completely degrades within 12-24 months. Although the rate of DoCE at 3 years with the MiStent in the all-comers DESSOLVE III trial was 10.2% (72 patients out of 703 patients, Kaplan-Meier estimated rate 10.5%), the rate of DoCE at 3 years were lower in all-comers population treated with the Supraflex stents (57 patients [7.9%; Kaplan-Meier estimated rate 8.1%] out of 720 patients in the TALENT trial) **(Table 2)**. The rate of DoCE at 3 years in all-comers population treated with the Orsiro was available in the BIO-RESORT, ORIENT, SORT OUT VII, and BIONYX trials, and was 7.5% (293 patients out of 3,925 patients).

Table 3. Characteristics of stents.

	Orsiro	MiStent	Supraflex	XIENCE	Resolute Integrity	Resolute Onyx	Nobori
Platform material	Cobalt chromium	Cobalt chromium	Cobalt chromium	Cobalt chromium	Cobalt chromium	Cobalt chromium, platinum-iridium core wire	Stainless steel
Strut thickness	60/80 µm*	64 µm	60 µm	81 µm	91 µm	81/91 µm**	120 µm
Polymer thickness	7.4 µm abluminal 3.5 µm luminal	15 µm abluminal 5 µm luminal	4-5 µm abluminal 4-5 µm luminal	7.6 µm for both sides	5.3 µm for both sides	5.6 µm for both sides	10 µm abluminal
Polymer coating	Biodegradable	Biodegradable	Biodegradable	Durable	Durable	Durable	Biodegradable
Biodegradation of polymer	12-24 months	3 months	9-12 months	NA	NA	NA	6-9 months
Drug eluted	Sirolimus	Sirolimus	Sirolimus	Everolimus	Zotarolimus	Zotarolimus	Biolimus A9
Drug dose	1.4 µg/mm^2	2.4 µg/mm^2	1.4 µg/mm^2	100 µg/cm^2	1.6 µg/mm^2	1.6 µg/mm^2	15.6 µg/mm^2
Drug release	3 months	9 months	48 days	4 months	6 months	6 months	30 days

*60 µm for stents ≤3.0 mm and 80 µm for stents ≥3.5 mm; **81 µm for stents ≤4.0 mm and 91 µm for stents ≥4.5 mm

Limitations

The TALENT trial was single-blinded, although the effect of this approach on event reporting is minimal because of the adjudication by an independent blinded clinical event committee. The study did not have adequate statistical power for any individual endpoints due to its relatively small sample size.

In terms of meta-analysis, the definitions of DoCE were not the same in each trial (e.g., TV-MI or MI not clearly attributable to a non-target vessel, etc). The definition of MI was not consistent across trials (e.g., SCAI definition, universal definition of myocardial infarction, WHO's extended definition, criteria of cardiac biomarkers, etc). Furthermore, long-term results of DoCE were not available for the BIOFLOW-IV and PRISON IV trials. Longer-term follow-up and large-scale individual data are necessary to investigate long-term benefits of ultrathin strut DES.

Conclusions

In the present final report of the TALENT trial, the use of the Supraflex ultrathin strut stent was at least as safe and efficacious as the XIENCE stent at 3 years in an all-comers population.

Impact on daily practice

Supraflex ultrathin strut stent was at least as safe and efficacious as the XIENCE stent at 3 years in an all-comers population. In a meta-analysis of long-term follow-up (3-5 years), ultrathin strut DES was also as safe and efficacious as thicker strut DES. Ultrathin strut DES can be considered for PCI.

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Role of the Funder/Sponsor

The study funders had no role in trial design, data collection, analysis, interpretation of the data, preparation, approval, or making a decision to submit the manuscript or publication.

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Conflict of interest statement

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Supplementary data

Supplementary Table 1. Search syntax.

Supplementary Table 2. Patients with DAPT.

Supplementary Table 3. Clinical outcomes at 36 months after stent implantation (per protocol [PP] basis).

Supplementary Table 4. Risk of bias.

Supplementary Figure 1. Kaplan-Meier estimates for the device-oriented composite endpoint (DoCE) and its components between 1 and 3 years (intention-to-treat [ITT] basis).

Supplementary Figure 2. Kaplan-Meier estimates for the DOCE and its components at 3 years (per protocol [PP] basis).

Supplementary Figure 3. Flow chart for randomised control trials included in the meta-analysis.

Supplementary Figure 4. L'Abbé plots for the meta-analysis comparing ultrathin strut DES and thicker strut DES.

Supplementary Figure 5. Funnel plots for long-term meta-analysis.

Supplementary Figure 6. Long-term outcomes of ultrathin strut DES vs thicker strut DES in patients with diabetes and small vessel treated.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-00766

Supplementary data

Supplementary Table 1. Search syntax.

Database	Search term
PubMed	Filter: 2010-2021 (“ultra-thin”[Title/Abstract] OR “ultrathin”[Title/Abstract] OR “very thin”[Title/Abstract] OR “Orsiro”[Title/Abstract] OR “Mistent”[Title/Abstract] OR “Supraflex”[Title/Abstract] OR “Supralimus”[Title/Abstract] OR “BioMime”[Title/Abstract]) AND (“DES”[Title/Abstract] OR “stents”[Title/Abstract] OR “stent”[Title/Abstract])
EMBASE	ultra thin':ab,ti OR ultrathin:ab,ti OR 'very thin':ab,ti OR orsiro:ab,ti OR mistent:ab,ti OR supraflex:ab,ti OR supralimus:ab,ti OR biomime:ab,ti) AND ('des':ab,ti OR 'stent':ab,ti OR 'stents':ab,ti) AND [randomized controlled trial]/lim AND [2010-2021]/py

Supplementary Table 2. Patients with DAPT.

		Supraflex SES (n=720)	XIENCE EES (n=715)	Difference (95% confidence interval)	p-value
6 months	Patients with stable CAD	85.8% (242/282)	86.5% (262/303)	-0.7% (-6.3%, 5.0%)	0.905
	Patients with ACS	90.1% (372/413)	92.2% (367/398)	-2.1% (-6.0%, 1.8%)	0.324
12 months	Patients with stable CAD	83.7% (231/276)	85.1% (257/302)	-1.4% (-7.3%, 4.5%)	0.648
	Patients with ACS	79.7% (325/408)	81.2% (320/394)	-1.6% (-7.1%, 3.9%)	0.594

ACS: acute coronary syndrome; CAD: coronary artery disease; DAPT: dual antiplatelet therapy

Supplementary Table 3. Clinical outcomes at 36 months after stent implantation (per protocol [PP] basis).

Clinical outcomes (PP)	Supraflex SES (n=660)	XIENCE EES (n=685)	Difference (95% confidence interval)	p-value
DoCE	6.6% (43)	8.7% (59)	-2.1% (-5.0%,0.8%)	0.165
PoCE	16.5% (107)	15.5% (105)	1.0% (-3.0%,4.9%)	0.588
TVF	8.4% (54)	9.9% (67)	-1.6% (-4.7%,1.5%)	0.336
Components of composite endpoints				
Death	4.2% (27)	4.6% (31)	-0.4% (-2.6%,1.8%)	0.728
Cardiac death	1.9% (12)	2.2% (15)	-0.4% (-1.9%,1.1%)	0.649
MI	5.1% (33)	5.8% (39)	-0.7% (-3.1%,1.8%)	0.596
Q-wave	0.8% (5)	0.9% (6)	-0.1% (-1.1%,0.9%)	0.825
Non-Q-wave	4.5% (29)	5.1% (34)	-0.5% (-2.9%,1.8%)	0.644
TV-MI	2.9% (19)	4.6% (31)	-1.7% (-3.7%,0.4%)	0.119
Q-wave	0.5% (3)	0.9% (6)	-0.4% (-1.3%,0.5%)	0.353
Non-Q-wave	2.6% (17)	3.9% (26)	-1.2% (-3.1%,0.7%)	0.214
Non-TV-MI	2.2% (14)	1.4% (9)	0.9% (-0.6%,2.3%)	0.243
Q-wave	0.3% (2)	0.0% (0)	0.3% (-0.1%,0.8%)	0.147
Non-Q-wave	1.9% (12)	1.4% (9)	0.5% (-0.8%,1.9%)	0.441
All revascularisation	11.9% (76)	10.7% (72)	1.1% (-2.3%,4.6%)	0.502
TL revascularisation	4.8% (31)	5.4% (36)	-0.5% (-2.9%,1.9%)	0.677
clinically indicated	3.6% (23)	5.1% (34)	-1.5% (-3.7%,0.7%)	0.192
non-clinically indicated	1.6% (10)	1.0% (7)	0.5% (-0.7%,1.7%)	0.407
TV revascularisation	6.6% (42)	7.2% (48)	-0.6% (-3.3%,2.1%)	0.675
clinically indicated	5.5% (35)	6.7% (45)	-1.2% (-3.8%,1.3%)	0.346

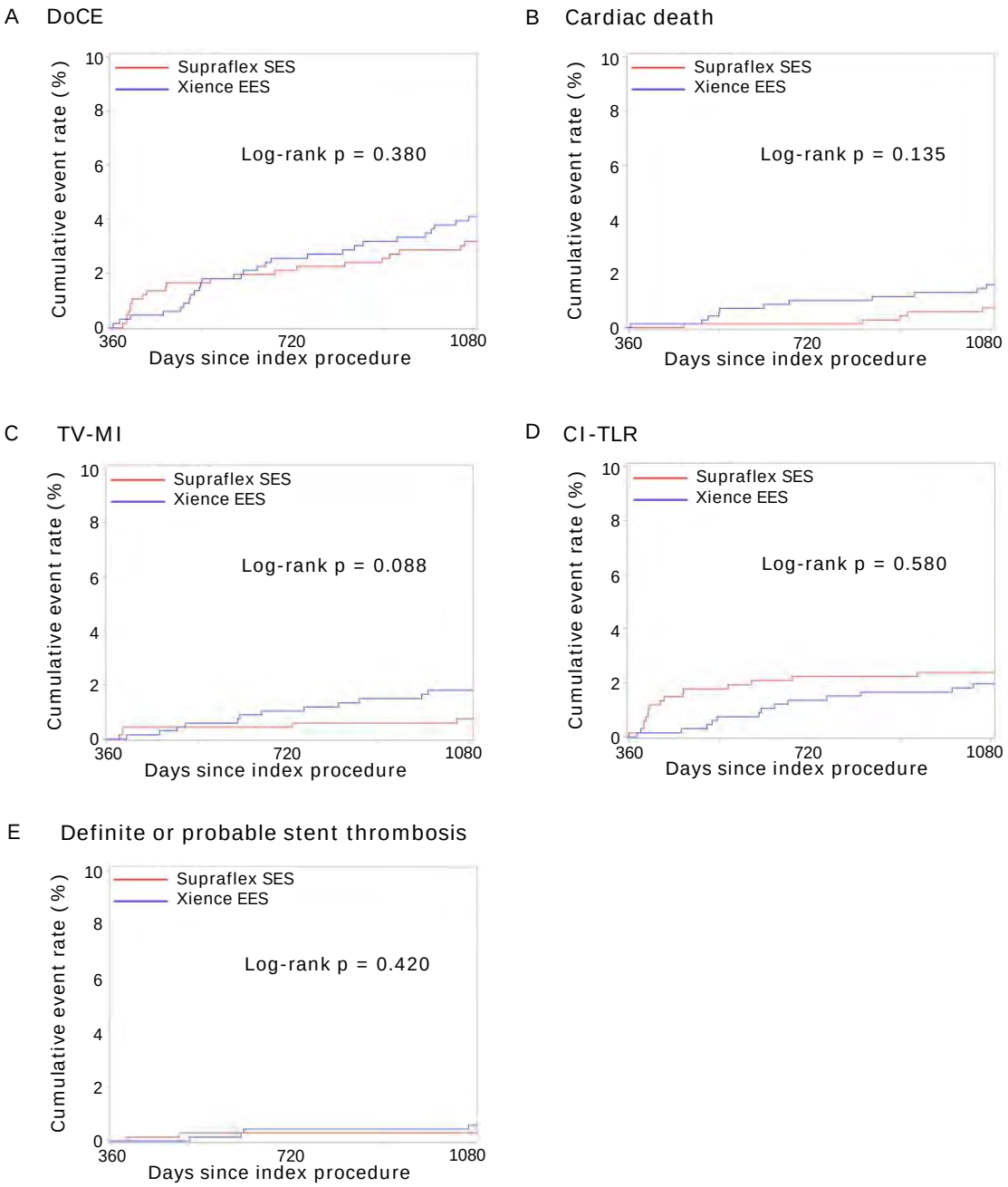
non-clinically indicated	1.6% (10)	1.5% (10)	0.1% (-1.3%,1.4%)	0.915
Non-TV revascularisation	7.8% (50)	5.8% (39)	2.0% (-0.7%,4.7%)	0.143
Stent thrombosis				
Definite	0.8% (5)	1.2% (8)	-0.4% (-1.5%,0.7%)	0.455
Definite (very late, >360 days)	0.3% (2)	0.5% (3)	-0.1% (-0.8%,0.5%)	0.699
Definite or probable	0.9% (6)	1.3% (9)	-0.4% (-1.5%,0.7%)	0.495
Definite or probable (very late, >360 days)	0.3% (2)	0.5% (3)	-0.1% (-0.8%,0.5%)	0.699

Data are presented as percentage (number).

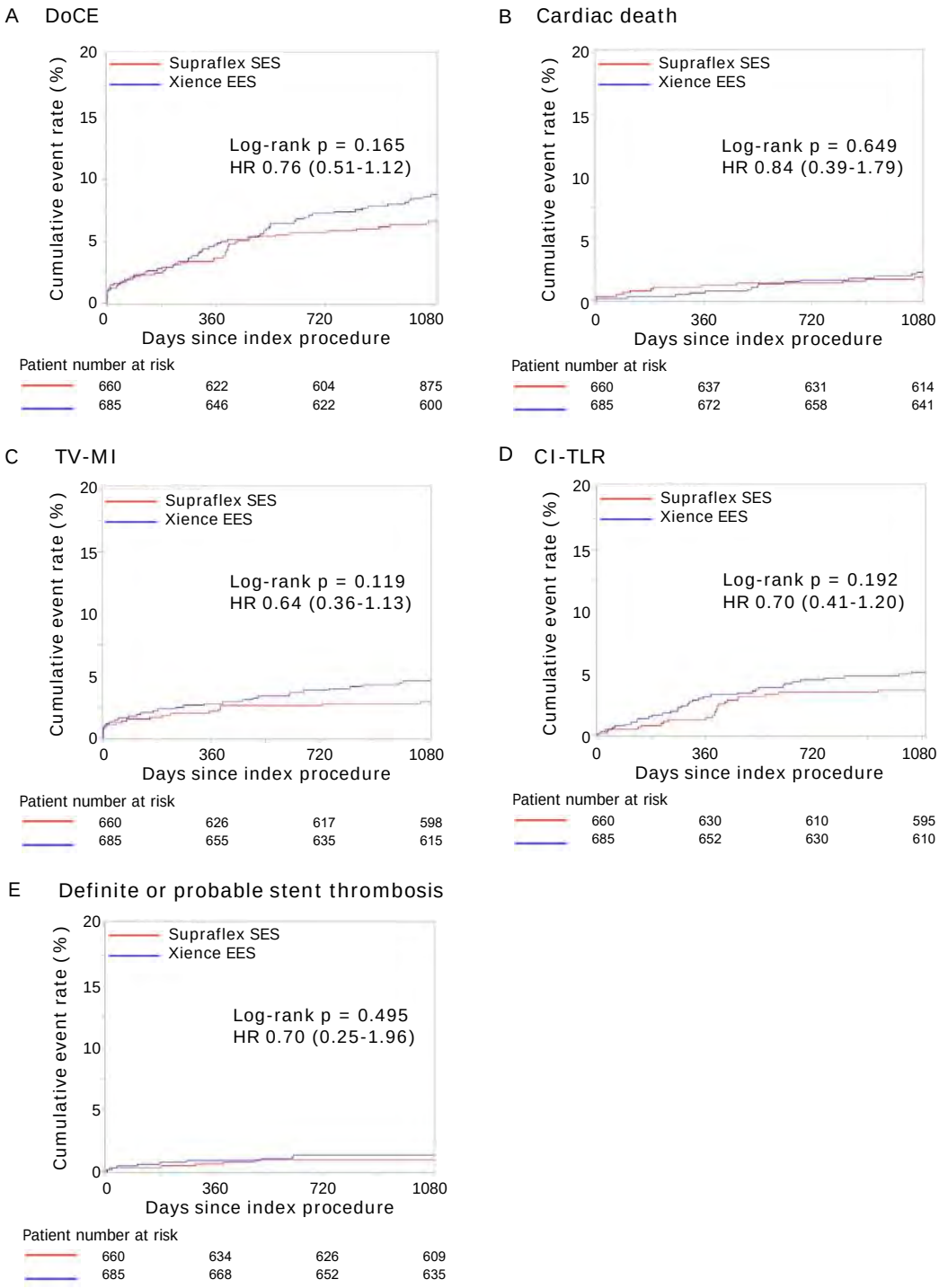
DoCE: device-oriented composite endpoint; MI: myocardial infarction; PoCE: patient-oriented composite endpoint; TL: target lesion; TV: target-vessel; TVF: target vessel failure

Supplementary Table 4. Risk of bias.

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
BIOSCIENCE	Low	Low	High	Low	Low	Low
BIOFLOW II	Low	Low	High	Low	Low	Low
BIOFLOW IV	Low	Low	High	High	Low	High
BIOFLOW V	Low	Low	High	Low	Low	Low
BIO-RESORT	Low	Low	Low	Low	Low	Low
PRISON-IV	Low	Low	Low	Low	Low	High
ORIENT	Low	Low	High	Low	Low	Low
SORT OUT VII	Low	Low	High	Low	Low	Low
BIONYX	Low	Low	Low	Low	Low	Low
DESSOLVE III	Low	Low	Low	Low	Low	Low
TALENT	Low	Low	Low	Low	Low	Low

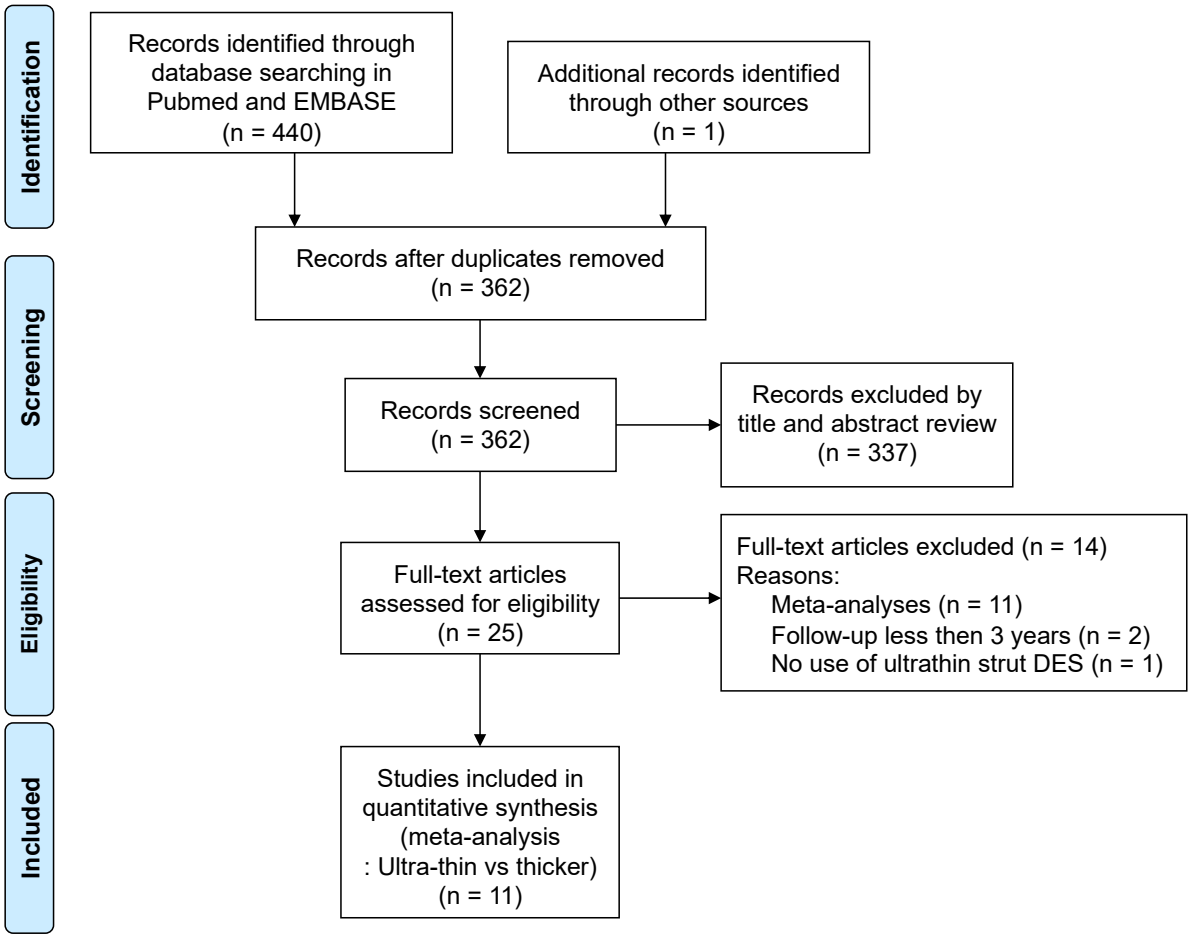


Supplementary Figure 1. Kaplan-Meier estimates for the device-oriented composite endpoint (DoCE) and its components between 1 and 3 years (intention-to-treat [ITT] basis). (A) DoCE, (B) cardiac death, (C) target vessel myocardial infarction (TV-MI), (D) clinical indicated target lesion revascularisation (CI-TLR), and (E) definite or probable stent thrombosis.

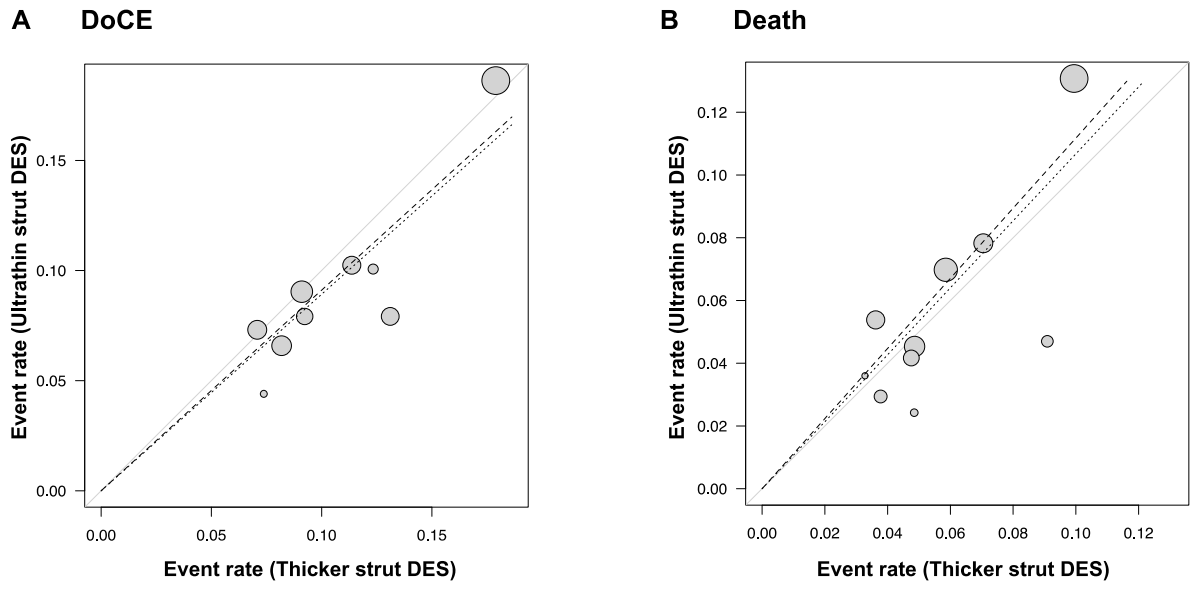


Supplementary Figure 2. Kaplan-Meier estimates for the DOCE and its components at 3 years (per protocol [PP] basis).

(A) DoCE, (B) cardiac death, (C) TV-MI, (D) CI-TLR, and (E) definite or probable stent thrombosis. HR: hazard ratio

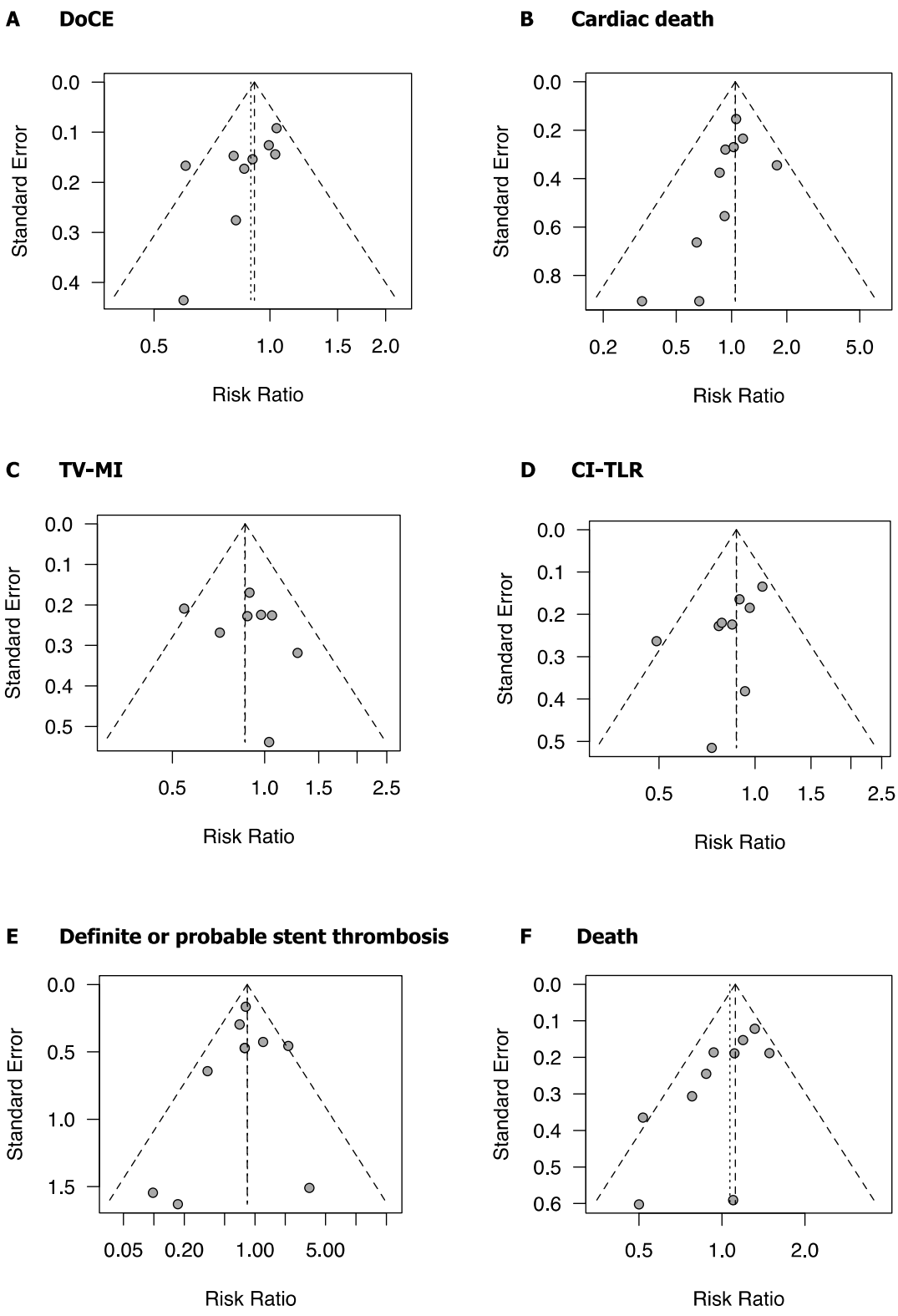


Supplementary Figure 3. Flow chart for randomised control trials included in the meta-analysis.

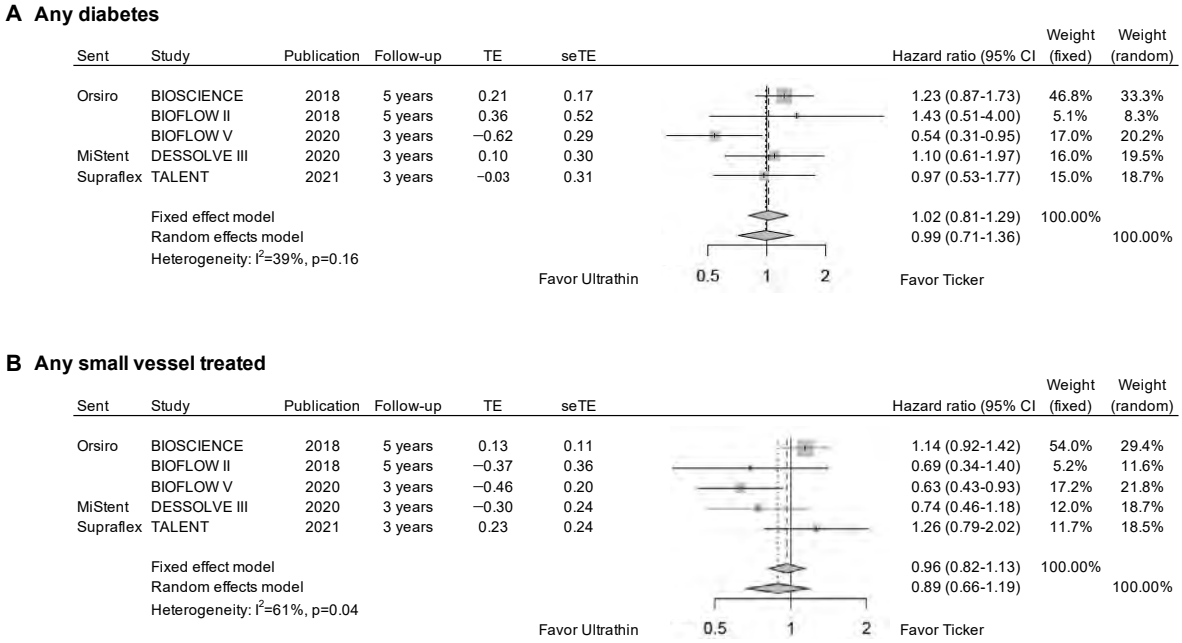


Supplementary Figure 4. L'Abbé plots for the meta-analysis comparing ultrathin strut DES and thicker strut DES.

(A) DoCE, and (B) death. DES: drug-eluting stent



Supplementary Figure 5. Funnel plots for long-term meta-analysis.
(A) DoCE, (B) cardiac death, (C) TV-MI, (D) CI-TLR, (E) definite or probable stent thrombosis, and (F) death.



Supplementary Figure 6. Long-term outcomes of ultrathin strut DES vs thicker strut DES in patients with diabetes and small vessel treated.

Long-term meta-analysis in patients with (A) diabetes, and (B) small vessel treated.