BIO-RESORT

60-month primary endpoint results of an RCT comparing **Orsiro** DES and Synergy vs. Resolute Integrity

Conclusions

- In this 3,514-patient large, randomized, investigator initiated, all-comers trial, **Orsiro** DES demonstrates non-inferiority to Resolute Integrity while performing equally well as Synergy (primary endpoint Target Vessel Failure (TVF) at 12 months: **Orsiro** 4.7%, Synergy 4.7%, Resolute Integrity 5.4%, p non-inferiority < 0.0001).
- At 36 months, in this highly complex patient population, **Orsiro** DES shows favorable outcomes with numerically lower event rates in TVF compared to both Synergy and Resolute Integrity.
- At 60 months, **Orsiro** DES, Synergy, and Resolute Integrity show similar 5-year outcomes of safety and efficacy, including all cause mortality.

Study design

All-comers, multi-center, assessor and patient-blinded, randomized, non-inferiority trial

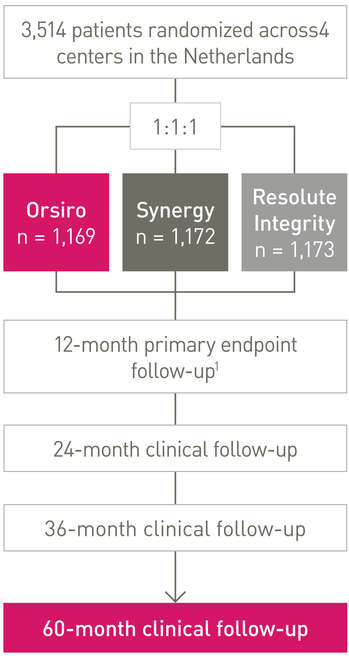
Endpoints

Primary endpoint

- TVF at 12 months defined as the composite of cardiac death, TV-MI or TVR

Secondary endpoints

- Individual components of the primary endpoint
  - All-cause mortality
  - Any MI
  - Target Lesion Failure (TLF) Clinically indicated Target Lesion Revascularization (CI-TLR)
  - Stent Thrombosis (ST)

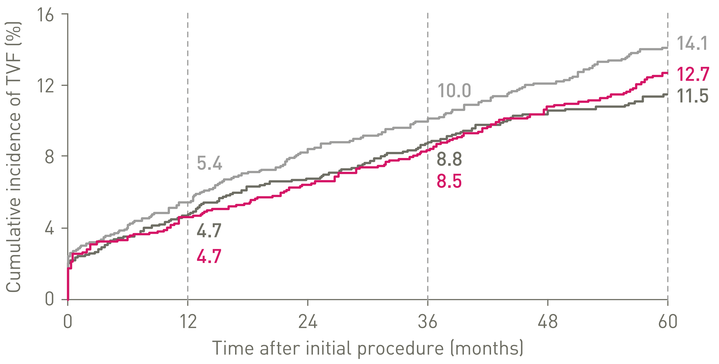


Patient characteristics[1]	Orsiro n = 1,169	Synergy n = 1,172	Resolute Integrity n = 1,173
Age, yrs‡	64.2 ± 10.7	64.0 ± 10.7	63.6 ± 10.9
Male	73%	72%	72%
Smoking	30%	30%	31%
Diabetes mellitus	18%	17%	18%
Previous MI	17%	16%	21%
Previous PCI	18%	18%	17%
Previous CABG	7%	8%	8%
Clinical indication			
ST-Elevation MI (STEMI)	32%	32%	28%
Non-ST-Elevation MI (NSTEMI)	20%	21%	23%
Unstable angina	18%	16%	19%

Lesion characteristics[2]	Orsiro n = 1,551§	Synergy n = 1,532§	Resolute Integrity n = 1,580§
De novo lesion	96.8%	97.1%	96.8%
Bifurcated lesion	28.6%	29.1%	27.7%
Severe calcification	20.4%	19.3%	20.7%
ACC-AHA lesion class (n)	1,545	1,527	1,573
A/B1	26.3%	29.0%	27.8%
B2/C	73.7%	71.0%	72.2%
Median lesion length (mm)	14.63	14.59	14.74
Minimum lumen diameter (mm)	0.71	0.71	0.70
Reference vessel diameter (mm)‡	2.75 ± 0.56	2.76 ± 0.56	2.76 ± 0.59
Stenosis (lumen diameter %)	72.8	73.8	72.5

§ Number of lesions
‡ Data shown as mean ± SD

Primary Endpoint



— Orsiro
— Resolute Integrity
— Synergy

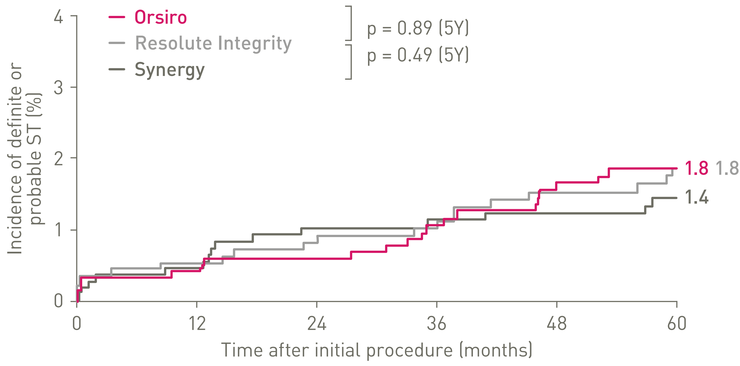
p non-inferiority <0.001 (1Y), p = 0.22 (3Y), p = 0.31 (5Y)

p non-inferiority <0.001 (1Y), p = 0.32 (3Y), p = 0.08 (5Y)

Orsiro DES showed similar 5-year safety and efficacy to Synergy and Resolute Integrity.*

Secondary Endpoints at 5 years[1]

Definite/Probable Stent Thrombosis[1,2]



Antithrombotic and Anticoagulant Therapy at 5-year follow-up

	All patients n = 2,950	Orsiro n = 994	Synergy n = 982	Resolute Integrity n = 974	p-value
Aspirin	2,288 77.6%	96.8%	97.1%	96.8%	97.1%
DAPT	28.6%	28.6%	29.1%	27.7%	29.1%
With clopidogrel	26.3%	26.3%	29.0%	96.8%	96.8%
With prasugrel or ticagrelor	73.7%	73.7%	71.0%	96.8%	96.8%

Principal investigator

Prof. Clemens von Birgelen, Enschede, the Netherlands

RCT: Randomized Controlled Trial, TVF: Target Vessel Failure, TV-MI: Target Vessel Myocardial Infarction, TVR: Target Vessel Revascularization, MI: Myocardial Infarction, TLF: Target Lesion Failure; CI-TLR: Clinically-Indicated-Target Lesion Revascularization, ST: Stent Thrombosis.

*Based on 5-year outcomes of the BIO-RESORT trial. 1. von Birgelen C et al. The Lancet. 2016;388(10060):2607-17; 2. Ploumen, Presented: BIO RESORT : 5 Year Outcomes From a Randomized Trial of 3 Drug Eluting Stents in Patients With Coronary Artery Disease.

Clinical data conducted with Orsiro, Orsiro Mission's predecessor device can be used to illustrate Orsiro Mission clinical outcomes.

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Vascular Intervention // Coronary // **Orsiro**

BIO-RESORT

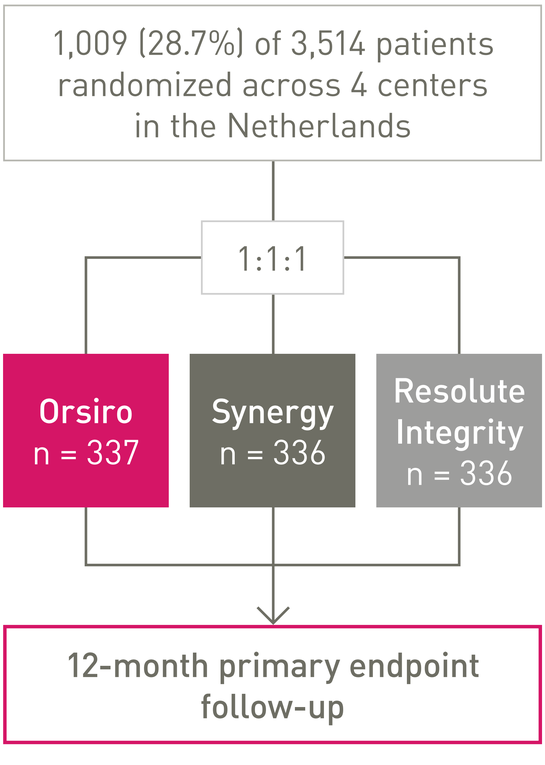
12-month High-Bleeding Risk (HBR) subgroup analysis of the BIO-RESORT trial, RCT **Orsiro** DES and Synergy vs. Resolute Integrity

Conclusions

- Almost 29% of the BIO-RESORT all-comers had a High-Bleeding Risk (HBR).
- In this subanalysis (n = 1,009), the Bioabsorbable Polymer DES (BP-DES) arm, including **Orsiro** DES, showed numerically lower event rates of the primary composite endpoint Target Vessel Failure (TVF) compared to Durable Polymer DES (DP-DES).
- On a product level, **Orsiro** DES alone demonstrated a numerically lower TVF rate (6.0%) than Synergy (6.9%), and Resolute Integrity (7.3%) in HBR patients, respectively. The differences did not reach statistical significance.

Study design

HBR patient stratification of an all-comers, multi-center, assessor and patient-blinded, randomized, non-inferiority trial according to defined established HBR criteria



Endpoints

Primary endpoint

- TVF at 12 months defined as the composite of cardiac death, Target Vessel-related Myocardial Infarction (TV-MI), Target Vessel Revascularization (TVR) or Target Lesion Failure (TLF)

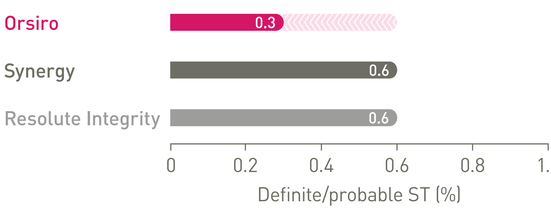
Secondary endpoints

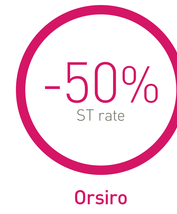
- Components of the primary endpoint
- All-cause mortality
- Any MI
- Clinically indicated Target Lesion Revascularization (TLR)
- Stent Thrombosis (ST)

12-month clinical endpoints in HBR patients[1]

Clinical endpoints	Orsiro n = 337	Synergy n = 336	Resolute Integrity n = 336
TVF¤	6.0%	6.9%	7.3%
Cardiac death	1.5%	2.1%	2.1%
TV-MI	2.4%	3.0%	3.3%
TVR	2.4%	2.2%	3.0%
TLF	5.7%	6.6%	5.7%
Major adverse cardiac events	6.8%	8.4%	8.1%
Patient-oriented composite endpoint[2]§	10.1%	9.3%	10.5%
Definite or probable ST	0.3%	0.6%	0.6%
Major bleeding	3.0%	3.7%	3.1%

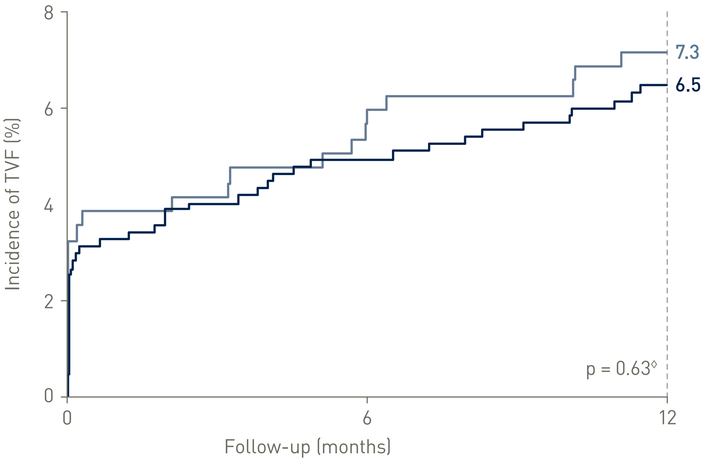
No significant difference: p >0.05





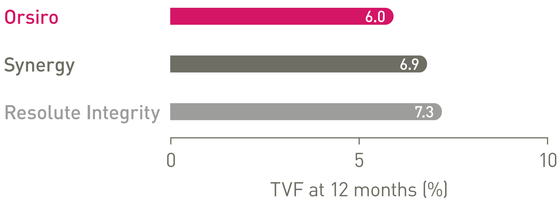
BP-DES showed numerically lower event rates in HBR patients

Primary endpoint TVF – at 12 months[1]



Orsiro demonstrated a numerically lower TVF[1]

Product level comparison



Differences did not reach statistical significance (Orsiro vs. Synergy p = 0.60◊, Orsiro vs. Resolute Integrity p = 0.49◊, Synergy vs. Resolute Integrity p = 0.87◊)

¤ Primary endpoint; Myocardial infarction and stent thrombosis classified according to Academic Research Consortium (ARC) criteria; Major bleeding = BARC 3 or 5 bleeding, or TIMI major bleeding. Values are n (%).
§ A composite of any death, any MI, or any revascularization.
◊ Logrank statistical method

Principal investigator

Prof. Clemens von Birgelen, Enschede, the Netherlands

1. von Birgelen C et al. High-Bleeding Risk Analysis of the BIO-RESORT Randomized Trial, Comparing 12-Month Clinical Outcome of All comer Patients Treated With Very Thin-Strut Biodegradable Polymer Versus Thin-strut Durable Polymer Drug-Eluting Stents; Presented at: CRT18; March 03, 2018 Washington DC, USA; ClinicalTrials.gov : NCT01674803; 2. Zocca P, Kok MM, von Birgelen C, et al. High Bleeding Risk Patients Treated with Very Thin-Strut Biodegradable Polymer or Thin-Strut Durable Polymer Drug-Eluting Stents in the BIO-RESORT Trial. Cardiovascular drugs and therapy. 2018 Aug 24:1-0.

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BIO-RESORT

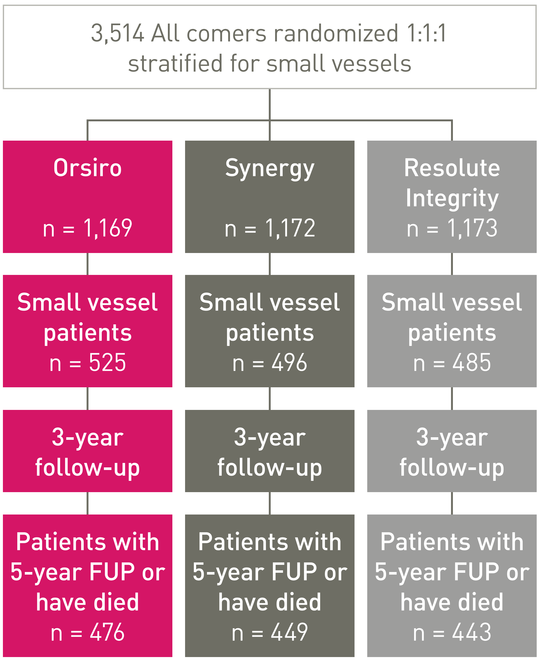
5-year outcome of patients with small coronary vessels treated with ultrathin, very thin or thin strut drug-eluting stents in the randomized BIO-RESORT trial[1]

Conclusions

- **Orsiro** DES shows a trend towards better efficacy and a similar safety to Synergy and Resolute Integrity in small vessels (<2.5mm) at 5-year follow-up.
- **Orsiro** DES shows a numerically lower cardiac death event rate in small vessels as well as a numerically lower definite or probable stent thrombosis in small vessels at long term follow-up compared to Resolute Integrity and Synergy.

Study design

Small vessel subgroup (<2,5mm diameter) of an all-comers, multi-center, assessor and patient-blinded, randomized, non-inferiority trial.



Endpoints

Primary endpoint

- Target Lesion Failure (TLF): composite of cardiac death, target vessel-related myocardial infarction or target lesion revascularisation

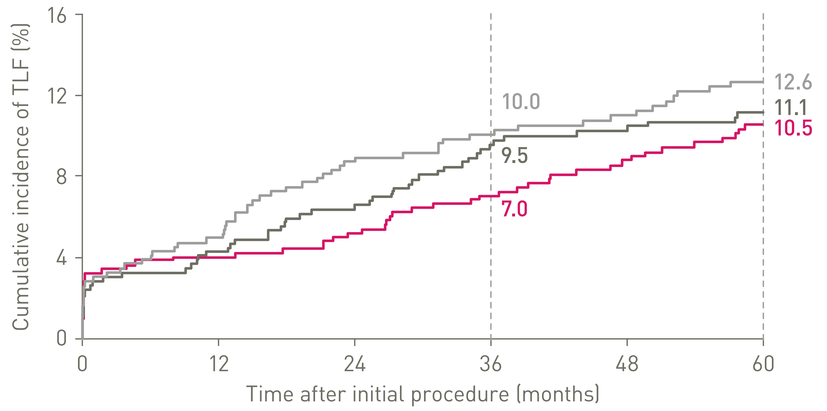
Secondary endpoints

- Cardiac death
- Target Vessel related Myocardial Infarction (TV-MI)
- Target Lesion Revascularisation (TLR)
- Stent Thrombosis (ST)

Patient characteristics[1]	Orsiro n = 525		Synergy n = 496		Resolute Integrity n = 485		p-value Orsiro vs. Resolute Integrity	p-value Synergy vs. Resolute Integrity
Age, yrs	64.9 ± 10.2		66.7 ± 9.6		65.5 ± 10.9		0.19	0.91
Female	158	30.1%	142	28.6%	149	30.7%	0.83	0.47
Diabetes mellitus	101	19.2%	106	21.4%	102	21.0%	0.48	0.90
Current smoker	133[a]	25.9%	128[b]	26.8%	129[c]	27.2%	0.63	0.90
Previous myocardial infarction	95	18.1%	87	17.5%	109	22.5%	0.08	**0.05**
Previous PCI	103	19.6%	93	18.8%	86	17.7%	0.44	0.68
Previous CABG	33	6.3%	42	8.5%	35	7.2%	0.56	0.47
Lesion characteristics (n = 1,1819)	**n = 636**		**n = 581**		**n = 602**			
Complex lesion (type B2 or C)	452	**71.4%**	399	68.7%	380	63.3%	0.002	0.053
CTO	24	3.8%	21	3.6%	26	4.3%	0.63	0.54
Severe calcification	113	17.8%	111	19.1%	126	20.9%	0.16	0.43
In-stent restenosis	3	**0.5%**	12	2.1%	13	**2.2%**	**0.009**	0.91

[a] Orsiro n = 514; [b] Synergy n = 477; [c] Resolute Integrity n = 475

Primary Endpoint[1,2]



— Orsiro
— Resolute Integrity
— Synergy

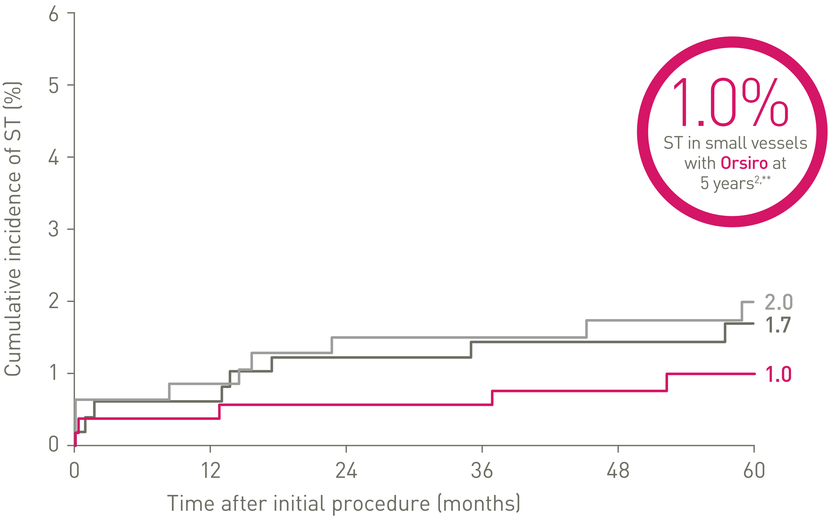
p = 0.08 (3Y), p = 0.25 (5Y)
p = 0.72 (3Y), p = 0.46 (5Y)

Orsiro DES shows a trend towards better efficacy in small vessels (<2.5mm)*,[2].

Secondary Endpoints[2]

TLF components at 5-years[2]	Orsiro n = 525	Synergy n = 496	Resolute Integrity n = 485	p-value Orsiro vs. Resolute Integrity	p-value Synergy vs. Resolute Integrity
TLF	10.5%	11.1%	12.6%	0.25	0.46
TLR	4.4%	4.7%	6.8%	0.08	0.18
Cardiac death	2.8%	3.4%	4.2%	0.27	0.57
TV-MI	4.9%	4.4%	4.4%	0.86	0.94

Definite or probable Stent Thrombosis[2]



— **Orsiro vs. Resolute Integrity, HR 0.51, 95% CI 0.17-1.53; p = 0.22**
— **Synergy vs. Resolute Integrity, HR 0.87, 95% CI 0.34-2.25; p = 0.77**
— Resolute Integrity

Principal investigator

Eline H. Ploumen MD PhD, Thoraxcentrum Twente, Enschede, the Netherlands

DES: Drug Eluting Stent, RCT: Randomized Controlled Trial, TLR: Target Lesion Revascularization, TV-MI: Target Vessel Myocardial Infarction, MI: Myocardial Infarction, ST: Stent Thrombosis.

*Based on TLF and TLR rates, compared to Synergy DES and Resolute Integrity DES, at 5 years, BIO-RESORT 5Y small-vessels subgroup, Presented by E.Ploumen at euroPCR 2022. **Compared to Resolute Integrity and Synergy, based on the 5-year outcomes from the BIO-RESORT small-vessels subgroup. 1. von Birgelen C. et al. The Lancet. 2016;388(10060): 2607-17; 2. Ploumen E. H., Five-year outcome of patients with small coronary vessels treated with ultrathin, very thin or thin strut drug-eluting stents in the randomized BIO-RESORT trial Presented at euroPCR 2022, Paris.

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BIO-RESORT

60-month primary endpoint results of an RCT comparing **Orsiro** DES and Synergy vs. Resolute Integrity - Diabetic Subgroup Analysis

Conclusions

- The prespecified sub-group analysis in patients with diabetes revealed no difference in the main clinical endpoint, yet cardiac mortality was found to be lower with **Orsiro** DES vs. Resolute Integrity.
- At 5 years, **Orsiro** DES shows significantly lower cardiac death events in diabetic patients in comparison to Resolute Integrity (p-value = 0.03).

Study design

All-comers, multi-center, assessor and patient-blinded, randomized, non-inferiority trial.

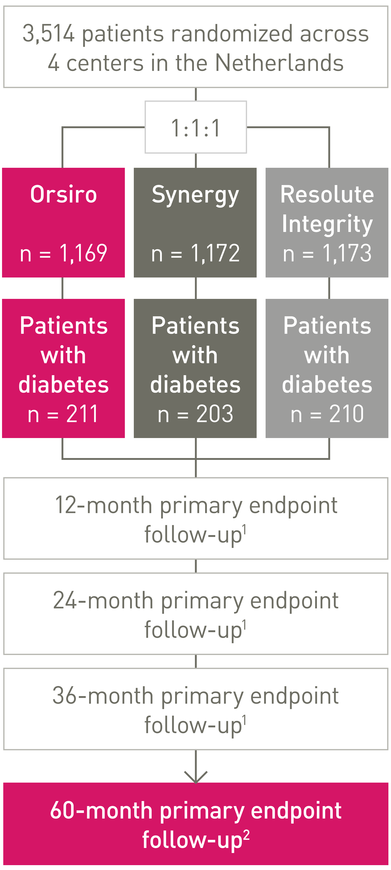
Endpoints

Primary endpoint

- Target Vessel Failure (TVF) at 12 months defined as the composite of:
  - Cardiac Death
  - Target Vessel-Myocardial Infarction (TV-MI)
  - Target Vessel Revascularisation (TVR)

Secondary endpoints

- Death
- Myocardial Infarction (MI)
- Revascularisation rate
- Stent Thrombosis (ST)
- Target Lesion Failure (TLF)
- Major Adverse Cardiac Events (MACE)
- Patient-Oriented Composite Endpoint (POCE)



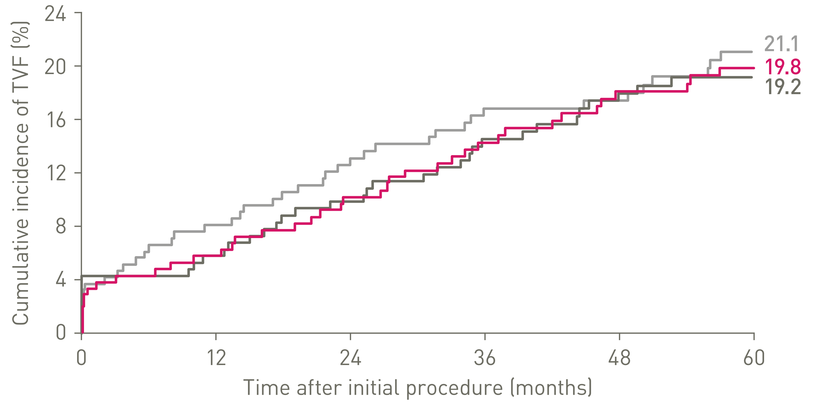
Patient characteristics with Diabetes

	All patients n = 624	Orsiro n = 211	Synergy n = 203	Resolute Integrity n = 210	p-value
Age, yrs	66.5 ± 10.1	67.1 ± 9.6	66.7 ± 9.6	66.5 ± 10.9	0.25
Female	200 32.1%	65 30.8%	61 30.0%	74 35.2%	0.47
Body mass index (kg/m²)	29.3 ± 4.7	29.7 ± 4.4	29.3 ± 4.9	29.1 ± 4.7	0.41
Medical history					
Previous MI	147 23.9%	54 25.6%	40 19.7%	55 26.2%	0.23
Previous PCI	157 25.2%	56 26.5%	57 28.1%	44 21.0%	0.21
Previous CABG	81 13.0%	129 61.1%	127 62.6%	124 59.0%	0.76
Acute coronary syndrome	113 17.8%	111 19.1%	126 20.9%	0.16	0.43

Lesion characteristics with Diabetes

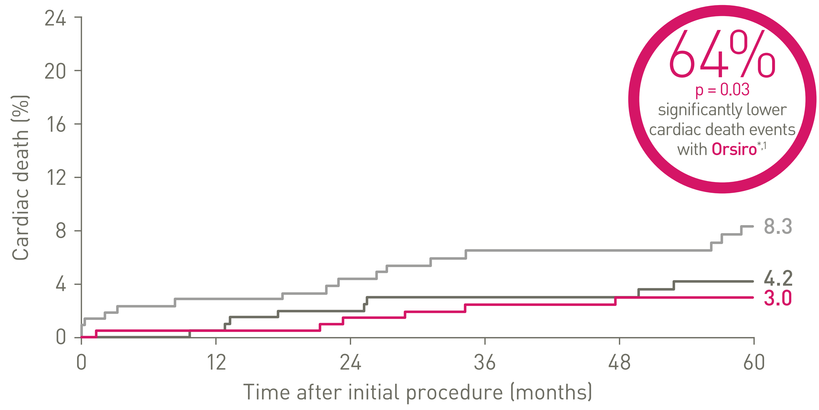
	All patients n = 624	Orsiro n = 211	Synergy n = 203	Resolute Integrity n = 210	p-value
At least 1 complex lesion	493 79.0%	174 82.5%	151 74.4%	168 80.0%	0.12
At least 1 CTO	33 5.3%	13 6.2%	12 5.9%	8 3.8%	0.50
At least 1 bypass graft lesion	19 3.0%	5 2.4%	5 2.5%	9 4.3%	0.44
At least 1 severely calcified lesion	162 26.0%	54 25.6%	53 26.1%	55 26.2%	0.99

Primary Endpoint – Target Vessel Failure[1]



— Orsiro
— Resolute Integrity — p = 0.69 (5Y)
— Synergy — p = 0.63 (5Y)

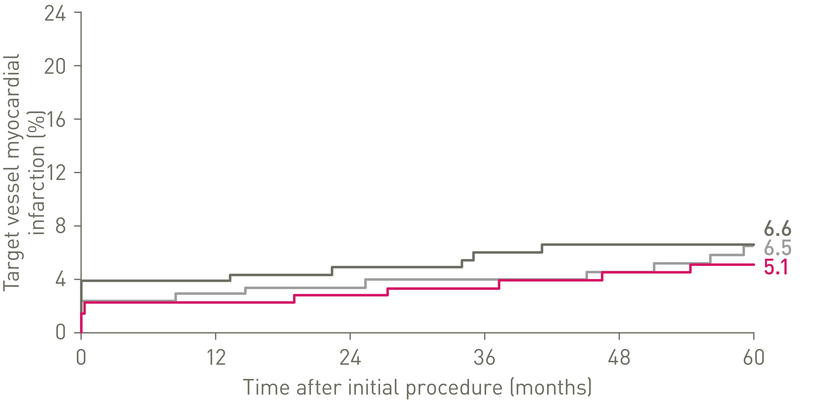
Secondary Endpoint – Cardiac Death[1]



64%
p = 0.03
significantly lower cardiac death events with Orsiro*[1]

— Orsiro
— Resolute Integrity — **p = 0.030** (5Y)
— Synergy — p = 0.10 (5Y)

Primary Endpoint[1,2]



— Orsiro
— Resolute Integrity — p = 0.060 (5Y)
— Synergy — p = 0.82 (5Y)

Orsiro DES shows numerically lower TV-MI events in diabetic patients at 5 years.[1]

Principal investigator

Eline H. Ploumen MD PhD, Thoraxcentrum Twente, Enschede, the Netherlands

TVF: Target Vessel Failure, TV-MI: Target Vessel-Myocardial Infarction, TVR: Target Vessel Revascularisation, MI: Myocardial Infarction, ST: Stent Thrombosis, TLF: Target Lesion Failure, MACE: Major Adverse Cardiac Events.

* In comparison to Resolute Integrity in diabetic patients at 5 years, based on the 5-year outcomes of the BIO-RESORT trial.

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