Orsiro Mission®

BIOFLOW-DAPT - Biodegradable-Polymer or Durable-Polymer Stents in Patients at High Bleeding Risk - A randomized, open-label clinical trial to assess the safety of HBR patients undergoing PCI with implantation of a drug-eluting stent and treated with DAPT for 1 month

Prof. Marco Valgimigli, Instituto Cardiocentro Ticino, Lugano, Switzerland

1. Based on primary and secondary outcomes from the BIOFLOW-DAPT RCT, Valgimigli M et al., Circulation 2023.

BIOFLOW-DAPT

BIOFLOW-DAPT

A randomized, open-label clinical trial to assess the safety of HBR patients undergoing PCI with implantation of a drug-eluting stent and treated with DAPT for 1 month

Design

International, randomized, open-label trial conducted at 52 centers in 18 countries from February 24, 2020, through September 20, 2021

Principal Investigators

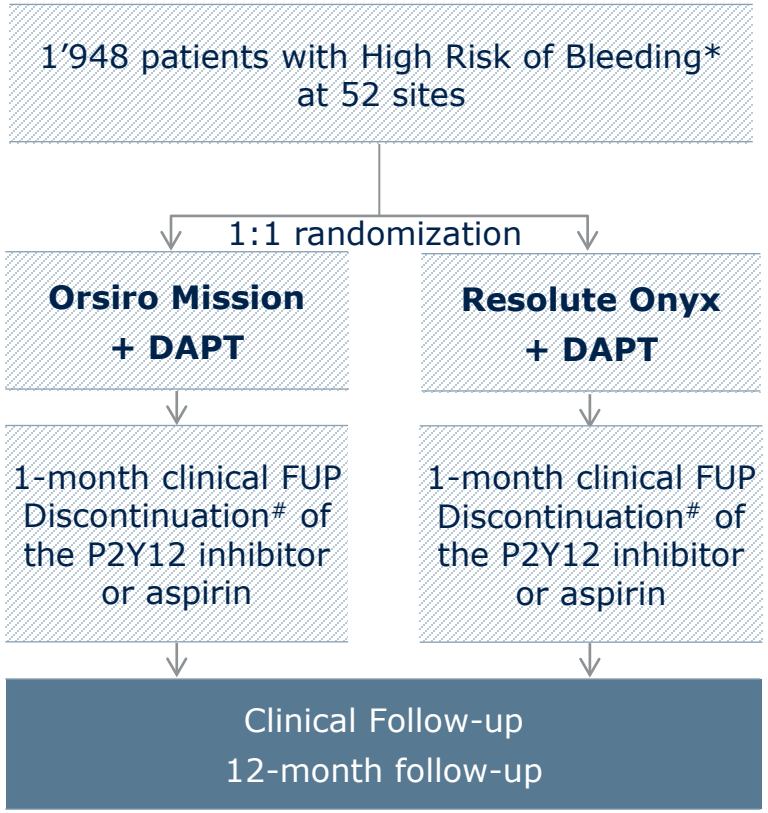
Prof. Marco Valgimigli, Instituto Cardiocentro Ticino, Lugano, Switzerland

Primary Endpoint

A composite of death from cardiac causes, myocardial infarction, or stent thrombosis at 1 year, and was powered for noninferiority, with an absolute margin of 4.1% at 1-sided 5% alpha.

Main Secondary Endpoints

- MACCE and MACE
- Clinically-indicated Target Lesion Revascularization (TLR)
- Target Vessel Failure (TVF)
- Target lesion failure (TLF)
- Bleeding according to BARC definition



*meeting at least 1 of the pre-defined HBR criteria
#Subjects not eligible for DAPT discontinuation not excluded from study

Sources: Valgimigli M et al. Biodegradable-Polymer or Durable-Polymer Stents in Patients at High Bleeding Risk: A Randomized, Open-Label Clinical Trial, Circulation, Aug. 2023

Endpoints

BIOFLOW-DAPT

Primary Endpoint

A composite of:

- Death from cardiac causes,
- Myocardial infarction,
- Stent thrombosis at 12 months,
- Powered for non-inferiority, with an absolute margin of 4.1% at 1-sided 5% alpha

Secondary Endpoints

- Definite/probable stent thrombosis according to the ARC definition
- MACCE
- MACE
- Cardiac death or MI
- All-cause death, cardiac, non-cardiac
- Stroke, ischemic and hemorrhagic
- Clinically-indicated TVR
- Clinically-indicated Target Lesion Revascularization (TLR)
- Target Vessel Failure (TVF)
- Target lesion failure (TLF)
- Bleeding according to BARC definition
- Device success
- Procedure success

Source: Valgimigli M et al. Biodegradable-Polymer or Durable-Polymer Stents in Patients at High Bleeding Risk: A Randomized, Open-Label Clinical Trial, Circulation, Aug. 2023

Inclusion/Exclusion

BIOFLOW-DAPT

Main Inclusion Criteria

- Acceptable candidate for treatment with a drug-eluting stent
- At least one high bleeding risk criterion as defined in the box above
- Age ≥18 years or the minimum age required for legal adult consent in the country of enrollment
- Capable of providing written informed consent
- Able to comply with all protocol and follow-up requirements, including agreement to discontinue dual antiplatelet therapy at 1 month
- Eligible for treatment with dual antiplatelet therapy (aspirin plus a P2Y12 inhibitor agent) for 1-month post index procedure

Main Exclusion Criteria

- Previous stent thrombosis in any coronary vessel
- Known allergy to all types of P2Y12 inhibitor, aspirin, heparin, bivalirudin
- Any TVR within 9 months prior to the index procedure or previous before PCI of any non-target vessel within 72 hours prior to or during the index procedure
- LVEF <30% as evaluated by the most recent imaging exam (within 90 days pre/procedure or during the index procedure)
- Unable for DAPT discontinuation at 1 month, due to another condition
- Planned procedure necessitating P2Y12 inhibitor and/or ASA discontinuation
- Active bleeding

Source: Valgimigli M et al. Biodegradable-Polymer or Durable-Polymer Stents in Patients at High Bleeding Risk: A Randomized, Open-Label Clinical Trial, Circulation, Aug. 2023

Countries and Centers

BIOFLOW-DAPT

- 17 Countries, 52 centers around the world
- Leading enrollment Sites:

Institution	Country	Number Enrolled
UZ Leuven-Campus Gasthuisberg	Poland	201
Segeberger Kliniken	Germany	182
University of Semmelweis	Hungary	152
Fondazione Cardiocentro Ticino	Switzerland	132
Sjaellands Universitets Hospital, Roskilde	Denmark	126
CHU Nîmes	France	100
Krakowski Szpital Specjalistyczny / John Paul II Hospital	Poland	98
Centro Cardiologico Monzino	Italy	82
Clinique Saint Hilaire	France	69
Medizinische Universitaet Graz	Austria	65
Clinique Pasteur, Toulouse	France	58
Hôpital Rangueil - Center Hospitalier de Toulouse	France	58
Stadtspital Triemli	Suisse	50
Ziekenhuis Oost Limburg Genk (ZOL Genk)	Belgium	44
Hopital Pitie-Salpetriere	France	43

Source: Valgimigli M et al. Biodegradable-Polymer or Durable-Polymer Stents in Patients at High Bleeding Risk: A Randomized, Open-Label Clinical Trial, Circulation, Aug. 2023

High Bleeding Risk Definition (1 or more criteria)

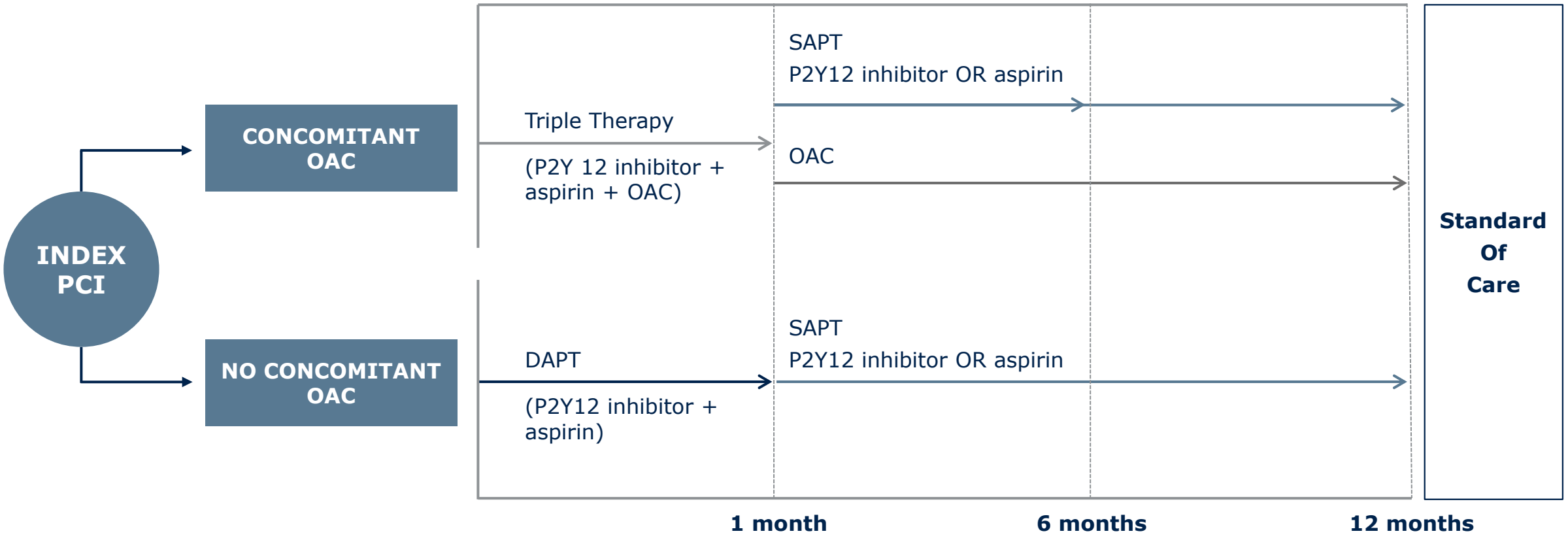
BIOFLOW-DAPT

a. ≥ 75 years of age
b. Moderate or severe chronic kidney disease or failure
c. Advanced liver disease
d. Cancer diagnosed or treated within the previous 12 months or actively treated
e. Anemia with hemoglobin < 11.0 g/dL or requiring transfusion within 4 weeks before randomization
f. Baseline thrombocytopenia
g. History of stroke, previous intracerebral hemorrhage (ICH) or presence of a brain arteriovenous malformation
h. History of hospitalization for bleeding within previous 12 months
i. Chronic clinically significant bleeding diathesis
j. Clinical indication for chronic or lifelong oral anticoagulation (OAC)
k. Clinical indication for chronic steroid or oral non-steroidal anti-inflammatory drug(s) other than aspirin
l. Non-deferrable major surgery on DAPT
m. Recent major surgery or major trauma within 30 days before PCI
n. PRECISE DAPT score ≥ 25

Source: Valgimigli M et al. Biodegradable-Polymer or Durable-Polymer Stents in Patients at High Bleeding Risk: A Randomized, Open-Label Clinical Trial, Circulation, Aug. 2023

Medication Chart

BIOFLOW-DAPT



Source: Landi A et al. 2023. J Cardiovasc Transl Res. doi: 10.1007/s12265-023-10400-x

BIOTRONIK excellence for life

Patient Characteristics

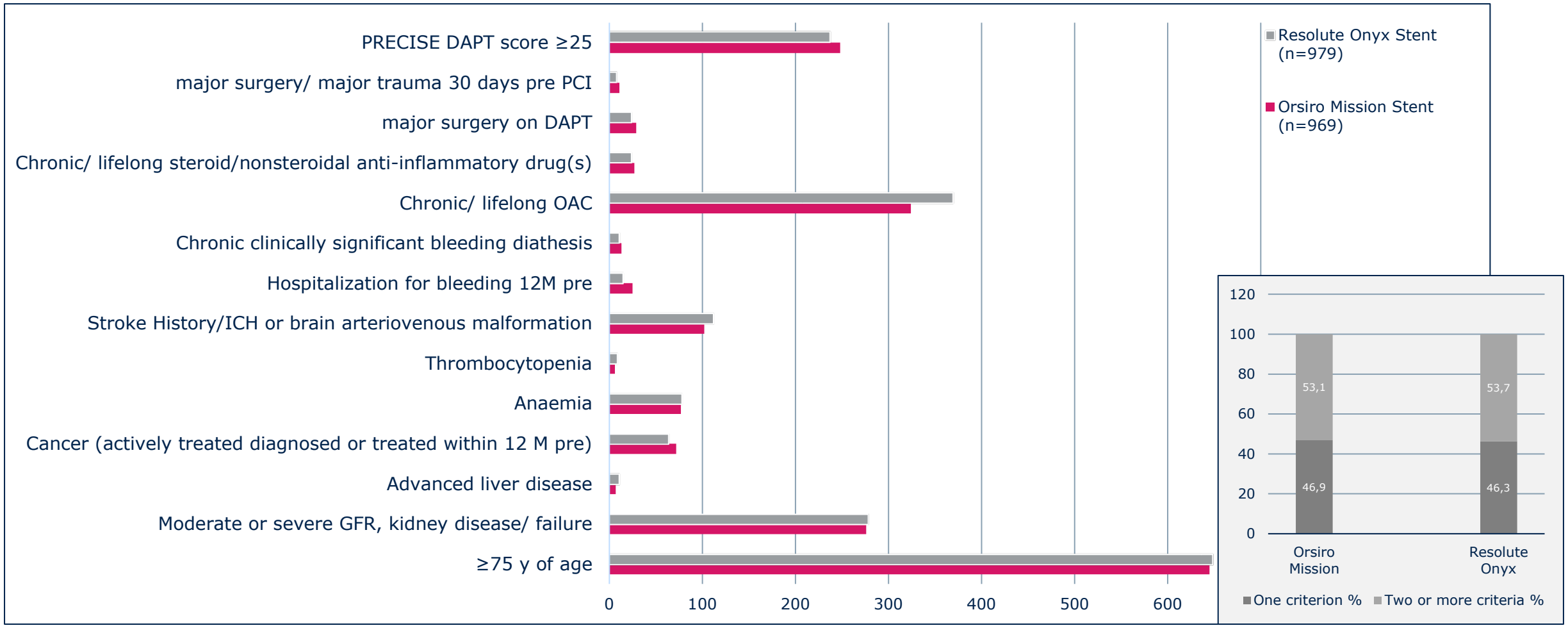
BIOFLOW-DAPT

	Orsiro Mission (n=969 Patients)	Resolute Onyx (n=979 Patients)
Age [years] Mean ± SD	76.0 ± 8.5	75.6 ± 8.2
Male	658 (67.9)	679 (69.4)
Renal disease	321 (33.1)	323 (33.0)
Hepatic disease	30 (3.1)	32 (3.3)
Respiratory disease	142 (14.7)	136 (13.9)
Hypertension	787 (81.2)	804 (82.1)
Hypercholesterolemia	659 (68.0)	678 (69.3)
Diabetes	301 (31.1)	311 (31.8)
Smoking History		
Ex-smoker	317 (32.7)	324 (33.1)
Current smoker	131 (13.5)	120 (12.3)
Congestive heart failure	215 (22.2)	202 (20.6)
Oral anticoagulant	324 (33.4)	369 (37.8)
Stable angina	477 (49.6)	495 (50.9)
Silent ischemia	190 (19.8)	197 (20.3)
Non–ST-elevation myocardial infarction	182 (19.0)	180 (18.5)
ST-elevation myocardial infarction	16 (1.7)	17 (1.7)

Source: Valgimigli M et al. Biodegradable-Polymer or Durable-Polymer Stents in Patients at High Bleeding Risk: A Randomized, Open-Label Clinical Trial, Circulation, Aug. 2023

High-Bleeding Risk Criteria

BIOFLOW-DAPT



Sources: Valgimigli M et al. Biodegradable-Polymer or Durable-Polymer Stents in Patients at High Bleeding Risk: A Randomized, Open-Label Clinical Trial, Circulation, Aug. 2023

BIOTRONIK excellence for life

Procedural Characteristics at Patient Level (1)

BIOFLOW-DAPT

	Orsiro Mission (n=969 Patients)	Resolute Onyx (n=979 Patients)
Access[a], no. (%)		
Radial	815 (84.1)	834 (85.2)
Femoral	137 (14.1)	130 (13.3)
Brachial	10 (1.0)	9 (0.9)
Lesion location[c], no. (%) (at least 1 lesion)		
Left main	45 (3.7)	38 (3.9)
Left anterior descending	529 (55.2)	541 (55.6)
Left circumflex	270 (28.2)	264 (27.1)
Right coronary artery	310 (32.3)	299 (30.7)
Bypass graft	16 (1.7)	15 (1.5)
At least one B2/C lesion class[c], no. (%)	583 (60.9)	614 (63.5)
At least one lesion with moderate or severe calcification, no. (%)	339 (35.3)	335 (34.5)
At least one lesion with bifurcationc, no. (%)	290 (30.2)	308 (31.7)

a. Unknown for 7 patients in biodegradable-polymer stent group and 6 patients in the zotarolimus-eluting stent group.

b. Unknown for 10 patients in biodegradable-polymer stent group and 6 patients in the zotarolimus-eluting stent group (percentages were calculated using a total of 959 patients in the biodegradable-polymer stent group and 973 patients in the zotarolimus-eluting stent group).

Sources: Valgimigli M et al. Biodegradable-Polymer or Durable-Polymer Stents in Patients at High Bleeding Risk: A Randomized, Open-Label Clinical Trial, Circulation, Aug. 2023

Procedural Characteristics at Patient Level (2)

BIOFLOW-DAPT

	Orsiro Mission (n=969 Patients)	Resolute Onyx (n=979 Patients)
≥ 1 lesion with chronic total occlusion[b], no. (%)	24 (2.5)	22 (2.3)
≥ 1 lesion with in-stent restenosis[b], no. (%)	47 (4.9)	50 (5.1)
Mean reference vessel diameter per subject[b], mm	3.1 ± 0.5	3.1 ± 0.5
Mean diameter stenosis per subject[b], %	82.0 ± 11.8	82.2 ± 13.0
Mean lesion length per subject[b], mm	20.8 ± 11.1	21.3 ± 12.2
Multivessel intervention, no. (%)	210 (21.9)	181 (18.6)
Number of vessels treated per patient[c], no. (%)		
One	738 (77.0)	779 (80.1)
Two	173 (18.0)	150 (15.4)
Three	33 (3.4)	24 (2.5)
Number of stents per patient[a]	1.7 ± 1.0	1.7 ± 1.0
Total stent length per patient[a]	37.2 ± 25.4	36.7 ± 24.4
Any overlapping stenting, no. (%)	174 (18.0)	212 (21.7)

a. Plus–minus values are means ± SD.

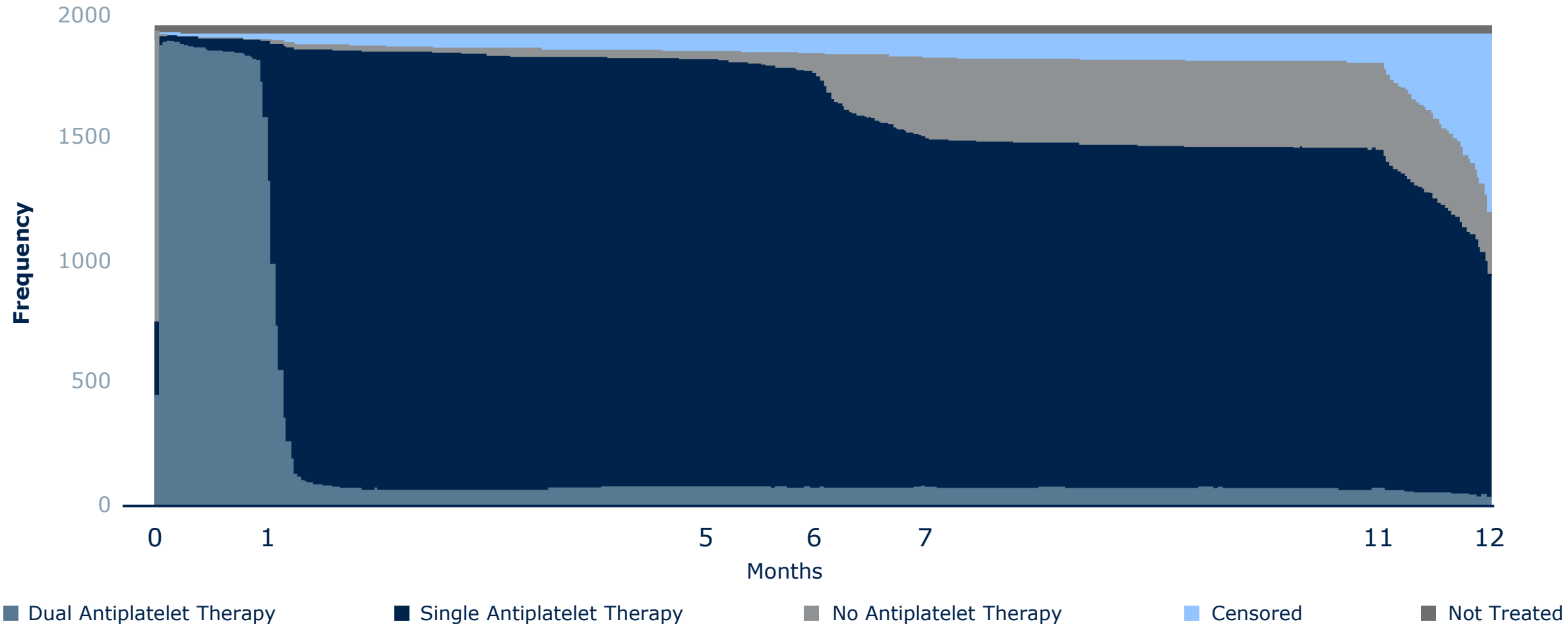
b. Unknown for 10 patients in biodegradable-polymer stent group and 6 patients in the zotarolimus-eluting stent group (percentages were calculated using a total of 959 patients in the biodegradable-polymer stent group and 973 patients in the zotarolimus-eluting stent group).

c. Four patients in the biodegradable-polymer stent group and 6 in the zotarolimus-eluting stent group had 4 treated vessels; 1 patient in the zotarolimus-eluting stent group had 5 treated vessels and 11 patient in biodegradable-polymer stent group and 13 in the zotarolimus-eluting stent group had only coronary artery bypass graft treatment.

Source: Valgimigli M et al. Biodegradable-Polymer or Durable-Polymer Stents in Patients at High Bleeding Risk: A Randomized, Open-Label Clinical Trial, Circulation, Aug. 2023

Adherence to Antiplatelet Therapy after PCI

BIOFLOW-DAPT



Source: Valgimigli M et al. Biodegradable-Polymer or Durable-Polymer Stents in Patients at High Bleeding Risk: A Randomized, Open-Label Clinical Trial, Circulation, Aug. 2023

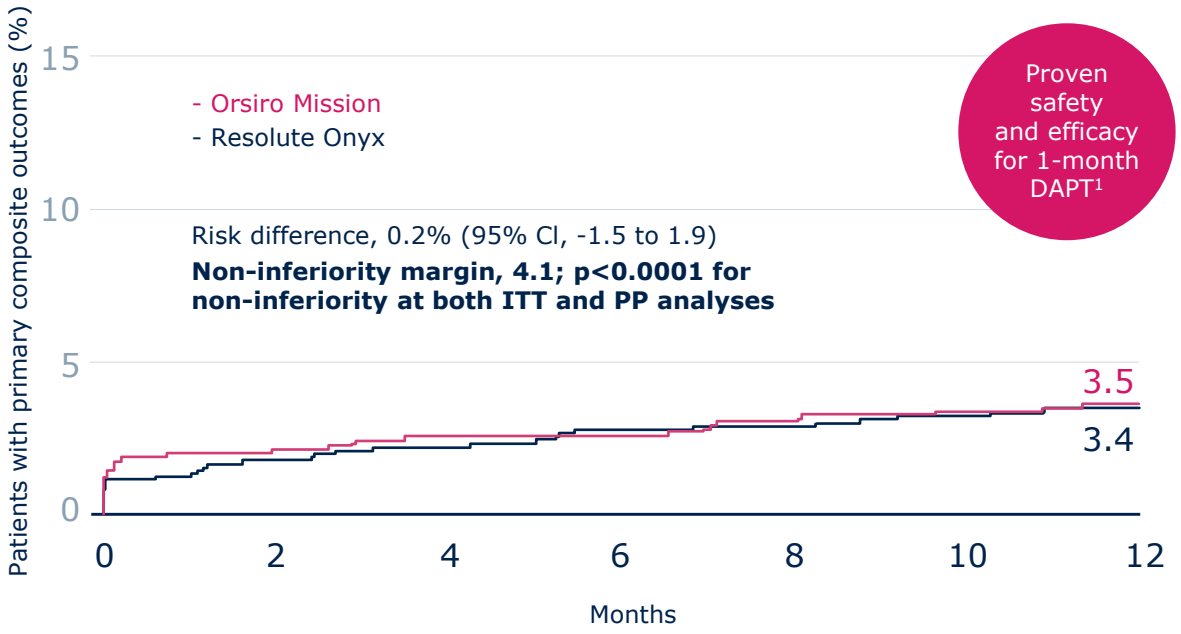
Primary Outcome: Cardiac Death, Myocardial Infarction, or Stent Thrombosis

ARC-2 definition vs Third Universal MI definition

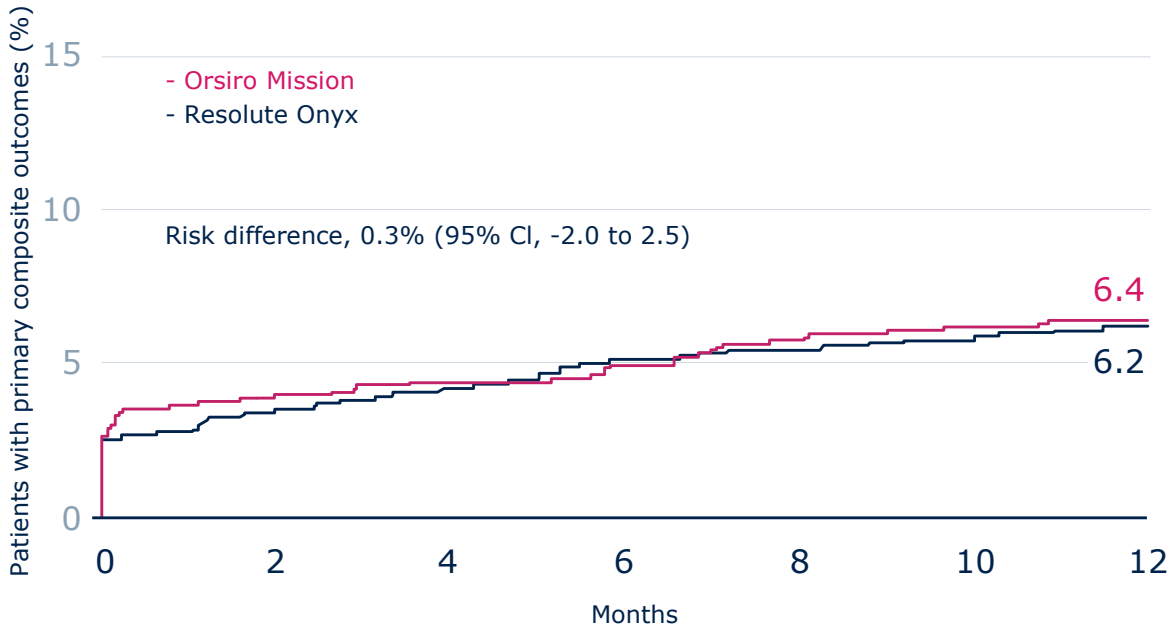
BIOFLOW-DAPT

Orsiro Mission is non-inferior to the Resolute Onyx for 1-month DAPT in HBR patients with regard to cardiac death, myocardial infarction or stent thrombosis (composite primary endpoint outcomes at 12-month).

ARC-2 Definition



Third Universal MI Definition

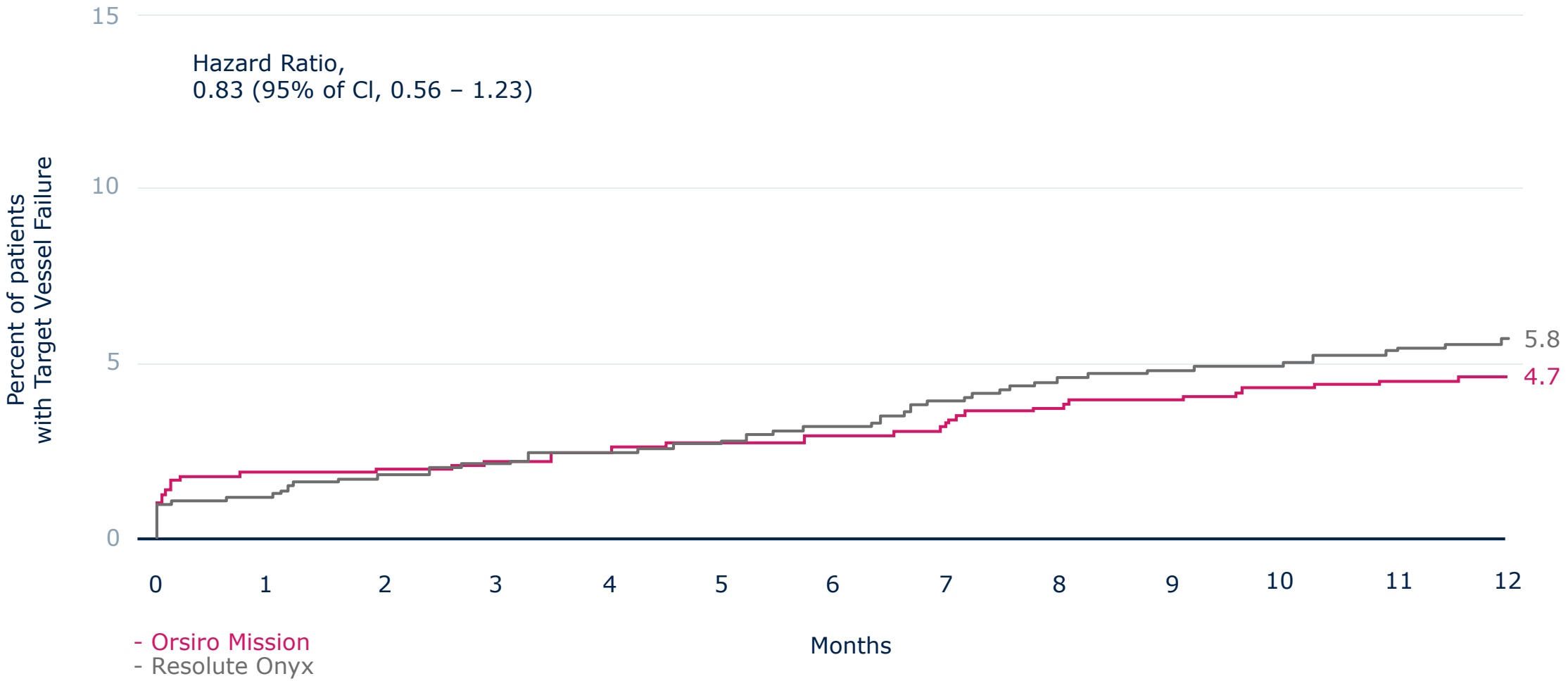


1. Based on primary and secondary outcomes from the BIOFLOW-DAPT RCT. Source: Valgimigli M et al. Biodegradable-Polymer or Durable-Polymer Stents in Patients at High Bleeding Risk: A Randomized, Open-Label Clinical Trial, Circulation, Aug. 2023

BIOTRONIK excellence for life

Target Vessel Failure

BIOFLOW-DAPT

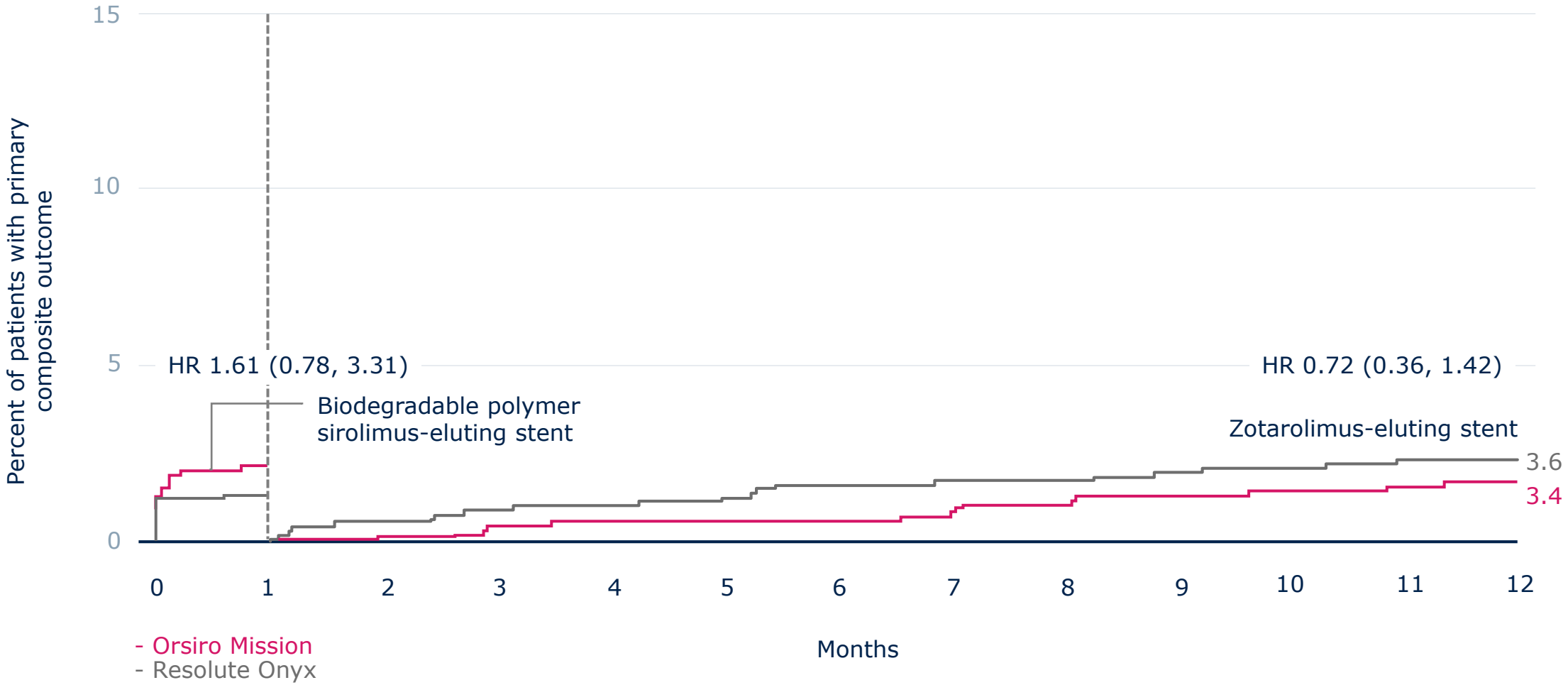


Source: Valgimigli M et al. Biodegradable-Polymer or Durable-Polymer Stents in Patients at High Bleeding Risk: A Randomized, Open-Label Clinical Trial, Circulation, Aug. 2023

Prespecified Landmark Analysis at 30 Days

Primary endpoint ARC-2 definition

BIOFLOW-DAPT

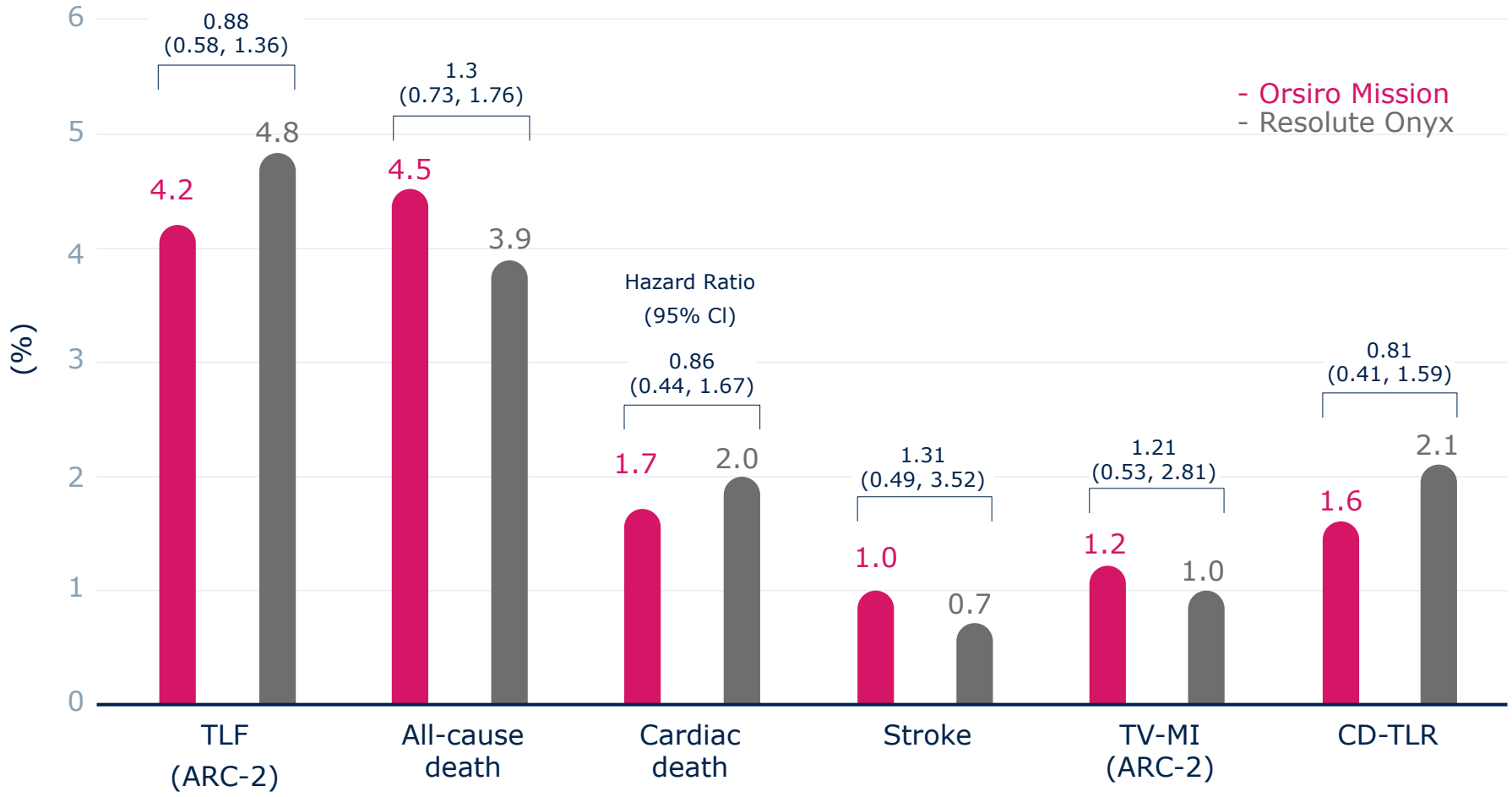


Source: Valgimigli M et al. Biodegradable-Polymer or Durable-Polymer Stents in Patients at High Bleeding Risk: A Randomized, Open-Label Clinical Trial, Circulation, Aug. 2023

Secondary Endpoints

BIOFLOW-DAPT

Orsiro Mission showed similarly low event rates to Resolute Onyx for short-DAPT in HBR patients*



*Based on primary and secondary outcomes in BIOFLOW-DAPT RCT including 1-month DAPT after PCI (Valgimigli M et al. Circulation 2023 Aug 25).
Source: Valgimigli M et al. Biodegradable-Polymer or Durable-Polymer Stents in Patients at High Bleeding Risk: A Randomized, Open-Label Clinical Trial, Circulation, Aug. 2023

BIOTRONIK excellence for life

Limitations

BIOFLOW-DAPT

- Incidences of outcome events at 1 year were lower than expected
- Treatments were open label
- Decision to continue aspirin or a $P2Y_{12}$ inhibitor was at the discretion of the physicians (Rx was stratified accordingly)
- Complete SDV was implemented in a random cohort of 28.2% of the patients
- Angiograms were not assessed by an independent core-laboratory

Source: Valgimigli M et al. Biodegradable-Polymer or Durable-Polymer Stents in Patients at High Bleeding Risk: A Randomized, Open-Label Clinical Trial, Circulation, Aug. 2023

Conclusions

1. In patients at high risk for bleeding, a strategy of PCI with Orsiro Mission followed by 30 days of DAPT therapy was non-inferior to Resolute Onyx with respect to the incidence of death from cardiac causes, myocardial infarction, or stent thrombosis.

2. Orsiro Mission showed safety and efficacy for short-DAPT in the BIOFLOW-DAPT trial.

Source: Valgimigli M et al. Biodegradable-Polymer or Durable-Polymer Stents in Patients at High Bleeding Risk: A Randomized, Open-Label Clinical Trial, Circulation, Aug. 2023