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Evaluation of a crystalline sirolimus-eluting coronary stent with a bioabsorbable polymer designed for rapid dissolution: two-year outcomes from the DESSOLVE I and II trials

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KEYWORDS

- bioabsorbable polymer
- drug-eluting coronary stent
- sirolimus

Abstract

Aims: Our aim was to evaluate the two-year clinical results of a new sirolimus-eluting stent (MiStent SES) with a bioabsorbable coating designed for rapid polymer dissolution but sustained drug delivery.

Methods and results: Major adverse cardiac events (MACE), target lesion failure (TLF), target vessel failure (TVF), and stent thrombosis (ST) at two-year follow-up are reported for the DESSOLVE I and II trials. In DESSOLVE I, the MiStent SES (n=29) demonstrated a 3.4% two-year MACE rate without TLF or TVF. In DESSOLVE II, the MiStent group had a 6.7% (8/120) two-year MACE rate compared to 13.3% (8/60) for Endeavor (p=0.167). TLF was 5.0% in the MiStent and Endeavor groups (p=1.00). TVF was 5.0% for MiStent versus 11.7% for Endeavor (p=0.129). No probable or definite ST was reported with the MiStent up to two years. The median duration of dual antiplatelet therapy (DAPT) in DESSOLVE I and II was 364 and 366 days, respectively.

Conclusions: The MiStent SES demonstrated good long-term safety and effectiveness with low two-year MACE, TLF, and TVF rates. ClinicalTrials.gov Identifiers: NCT01247428 and NCT01294748

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Introduction

Permanent polymers on drug-eluting stents (DES) can produce an inflammatory response causing late stent thrombosis (ST) and DES failure[1]. In order to enhance their long-term safety and efficacy, biodegradable polymer-based DES were developed with results supporting their use as safe and efficacious alternatives to permanent polymer DES[2,3].

The MiStent® Sirolimus-Eluting Absorbable Polymer Coronary Stent System (MiStent SES) (Micell Technologies, Durham, NC, USA) combines sirolimus, polylactide-co-glycolic acid (PLGA) and a cobalt-chromium stent platform **(Online Table 1)**. PLGA carries a crystalline form of sirolimus. The PLGA/sirolimus combination is cleared from the stent within 45-60 days and PLGA is fully absorbed within 90 days. The crystalline sirolimus remains in the tissue and continues to elute the drug into the surrounding tissue for up to nine months, a unique feature among DES[4,5].

Methods

STUDY DESIGNS

The MiStent results are derived from the DESSOLVE I first-in-human, single-arm trial, and from the DESSOLVE II 2:1 randomised trial comparing MiStent to Endeavor® Sprint DES (Medtronic, Santa Rosa, CA, USA)[6,7]. These studies enrolled subjects with symptomatic ischaemic heart disease due to *de novo* lesions in native coronary arteries with >50% diameter stenosis (**Online Table 2** for inclusion criteria).

The DESSOLVE I first-in-human trial provided an initial assessment of safety and efficacy and investigated early and long-term neointimal hyperplasia (NIH) and vessel healing (n=30)[6]. The DESSOLVE II trial showed superiority (p<0.001) for in-stent late lumen loss (LLL) at nine months for the MiStent (0.27±0.46 mm, n=123) when compared to the Endeavor (0.58±0.41 mm, n=61)[7].

Patients in both trials were contacted for clinical follow-up and reporting of adverse events at one and two years post index procedure. The minimum and maximum duration of dual antiplatelet therapy (DAPT) was per the country and/or study hospital standard-of-care recommendations.

CLINICAL ENDPOINT DEFINITIONS

Clinical endpoint definitions were identical in both DESSOLVE I and DESSOLVE II[6,7]. MACE was a composite of any death, myocardial infarction (MI) (Q-wave or non-Q-wave) or clinically driven target vessel revascularisation (TVR). Target lesion failure (TLF) was defined as cardiac death, MI, or clinically driven target lesion revascularisation (TLR). Target vessel failure (TVF) was defined as cardiac death, MI, or TVR.

STUDY CONDUCT

All patients provided written informed consent in accordance with the local site's ethics committee. Participating sites and the study organisation are shown in **Online Table 3** and **Online Table 4**. SAS, version 9.1.3 SP2 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

Results

In DESSOLVE I, MACE was 0.0% (0/30) at 30 days, and 3.4% (1/29) at two years. The single event was a non-target vessel non-Q-wave MI. No patients experienced death, TVR, TLR, TVF, TLF or ST over two years. The median duration of DAPT in DESSOLVE I was 364 days (interquartile range: 328-542 days).

In DESSOLVE II, follow-up at two years was available for 97.6% in the MiStent group and 98.4% in the Endeavor group. The overall MACE rate up to two years **(Figure 1)** was 6.7% (8/120) for MiStent and 13.3% (8/60) for Endeavor (p=0.167). Death occurred in 2.5% of the MiStent patients and 1.7% of the

Table 1. Adjudicated MACE composite endpoints, TVF, TLF, and ST at two years in DESSOLVE II.

Cumulative for all follow-up	MiStent® (n=123 patients)	Endeavor® (n=61 patients)	Difference [95% CI]	*p*-value
MACE (Death, MI, TVR)	6.7% (8/120)	13.3% (8/60)	–6.7% [–18.0%,2.1%]	0.17
Death	2.5% (3/120)	1.7% (1/60)	0.8% [–6.5%,5.6%]	1.00
Cardiac death	1.7% (2/120)	1.7% (1/60)	0.0% [–7.3%,4.4%]	1.00
Non-cardiac death	0.8% (1/120)	0.0% (0/60)	0.8% [–5.2%,4.6%]	1.00
MI (Q-wave or non-Q-wave)	2.5% (3/120)	5.0% (3/60)	–2.5% [–11.4%,3.1%]	0.40
Target vessel Q-wave MI	0.0% (0/120)	0.0% (0/60)	0.0% [–6.0%,3.1%]	--
Non-target vessel Q-wave MI	0.8% (1/120)	0.0% (0/60)	0.8% [–5.2%,4.6%]	1.00
Target vessel non-Q-wave MI	1.7% (2/120)	3.3% (2/60)	–1.7% [–9.8%,3.2%]	0.60
Non-target vessel non-Q-wave MI	0.0% (0/120)	1.7% (1/60)	–1.7% [–8.9%,1.7%]	0.33
Clinically driven target vessel revascularisation	1.7% (2/120)	8.3% (5/60)	–6.7% [–16.5%,–0.3%]	0.04
Clinically driven target lesion revascularisation	1.7% (2/120)	1.7% (1/60)	0.0% [–7.3%,4.4%]	1.00
Target vessel failure	5.0% (6/120)	11.7% (7/60)	–6.7% [–17.5%,1.4%]	0.13
Target lesion failure	5.0% (6/120)	5.0% (3/60)	0.0% [–9.1%,6.4%]	1.00
Stent thrombosis--ARC defined - probable/definite	0.0% (1/120)	1.7% (1/60)	–1.7% [–8.9%,1.7%]	0.33

	0	90	180	270	360	450	540	630	720
MiStent									
# Entered	123	121	116	116	115	114	113	113	112
% Survived	98.37%	96.71%	96.71%	95.87%	95.04%	94.21%	94.21%	93.37%	93.37%
SE	1.14%	1.62%	1.62%	1.81%	1.97%	2.13%	2.13%	2.26%	2.26%
Endeavor									
# Entered	61	59	58	58	56	55	54	54	53
% Survived	96.72%	95.08%	95.08%	93.41%	91.75%	90.08%	90.08%	88.41%	86.74%
SE	2.28%	2.77%	2.77%	3.18%	3.54%	3.85%	3.85%	4.12%	4.37%

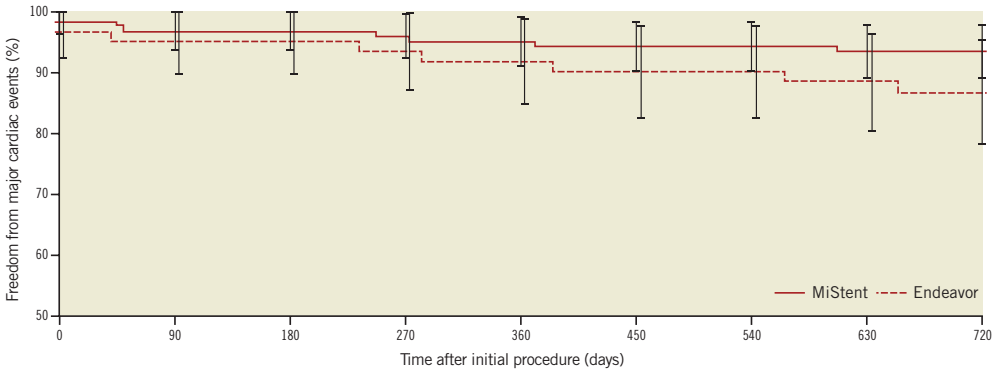

Figure 1. *Survival curve - major adverse cardiac events (MACE) at two years.*

Endeavor patients, with all deaths occurring later than 30 days post implantation **(Table 1)**. The largest difference between the two stents (p=0.042) was TVR, at 1.7% with MiStent and 8.3% with Endeavor, with identical TLR at 1.7%. Probable/definite ST occurred only with the Endeavor (1.7%; 1/60). The median duration of DAPT in DESSOLVE II was 366 days (interquartile range: 341-565 days), without difference between MiStent and Endeavor (median 366 days for both arms).

Discussion

First-generation DES with permanent polymers have been associated with adverse long-term consequences[8]. This led to the development of second-generation DES with more biocompatible, durable coatings[9,10], and third-generation DES with fully absorbable polymer coatings[4].

Determination of DES efficacy is evaluated by measuring LLL, in-stent LLL ≤0.5 mm resulting in TLR <5%[11]. Paired angiographic results from DESSOLVE I and II revealed a plateau of NIH at 0.09 mm from six/eight to 18 months[6,7]. No TVR or TLR have been reported in DESSOLVE I. Low TLR rates (1.7%) have been maintained in DESSOLVE II up to two years.

Long-term DES safety requires tissue coverage of the stent struts, rapid endothelialisation and sufficient healing. Optical coherence tomography in DESSOLVE II revealed high mean rates of stent coverage (97.9%) at nine months[7], and the endothelial function studies demonstrated preserved vasomotion both proximally and distally to the stent[12].

Limitations

Similar to other DES trials, investigators could not be blinded to study device, and the study size does not permit comparative analysis of safety outcomes such as ST. Longer-term follow-up of the DESSOLVE I and II, in addition to larger trials and real-world experience including more complex patient populations, will provide additional insights into the performance of the MiStent SES.

Conclusion

DESSOLVE I and II have revealed a good safety profile for the MiStent SES, with limited MACE events and no ST reported up to two years. These trials were not powered to compare clinical outcomes between DES; further studies in larger populations are ongoing (DESSOLVE III).

Impact on daily practice

The sirolimus-eluting MiStent is designed for drug delivery for up to nine months while the bioresorbable polymer undergoes rapid dissolution. Clinical follow-up at two years in 152 patients shows good medium-term safety and effectiveness with low event rates, supporting clinical implementation. On the basis of these results, further evaluation in complex patient and lesion subsets is ongoing in the all-comers DESSOLVE III randomised trial.

Funding

This trial is sponsored by Micell Technologies, Durham, NC, USA.

Conflict of interest statement

W. Wijns reports institutional grants from several device companies, including Micell Technologies and Medtronic; he is co-founder, shareholder and non-executive board member of Argonauts Partners, Cardio3 BioSciences and Genae. D. Donohoe is a

consultant and C. Knape is an employee of Micell Technologies. The other authors have no conflicts of interest to declare.

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Supplementary data

Online Table 1. MiStent sirolimus-eluting stent system: product description.

Online Table 2. Inclusion criteria.

Online Table 3. Investigators, institutions and core laboratories participating in DESSOLVE I and II.

Online Table 4. Study conduct and organisation.

Online Figure 1. Major adverse cardiac events (MACE) at two years.

The supplementary data are published online at: http://www.pcronline.com/eurointervention/100th_issue/56

Supplementary data

Online Table 1. MiStent sirolimus-eluting stent system: product description.

Available stent lengths (mm)	9, 13, 15, 19, 23, 27, 30
Available stent diameters (mm)	2.5, 2.75, 3.0, 3.5
Stent material	A medical grade L-605 cobalt-chromium (CoCr) alloy coronary stent.
Drug component	A conformal coating of an absorbable polymer and sirolimus is applied to the entire stent surface at a drug loading of 9-11 µg/mm stent length, with a maximum nominal drug content of 327 µg on a 3.5×30 mm stent.
Delivery system working length	140 cm
Delivery system design	Single access port to inflation lumen. Guidewire exit notch is located 25 cm from the tip. Designed for guidewires ≤0.36 mm (0.014 inch).
Stent delivery system balloon	A semi-compliant balloon with two radiopaque markers located on the catheter shaft to indicate balloon positioning and expanded stent length.
Balloon inflation pressure	Nominal inflation pressure: – 9 atm (912 kPa) for 2.5, 2.75, and 3.0 mm diameters – 10 atm (1,013 kPa) for 3.5 mm diameter – Rated burst pressure (RBP): 16 atm (1,621 kPa) for all sizes.
Guiding catheter inner diameter	6 Fr, ≥1.6 mm I.D. (0.063 inch)
Guidewire diameter	0.36 mm (0.014 inch) maximum diameter ×175 cm minimum length
Catheter shaft outer diameter (nominal)	Proximal: 1.8 Fr (0.59 mm) Distal: 2.6 Fr (0.87 mm)

Online Table 2. Inclusion criteria.

The study designs and inclusion criteria of DESSOLVE I and DESSOLVE II have been described previously in detail[6,7].
These studies enrolled subjects with symptomatic ischaemic heart disease due to *de novo* lesions in native coronary arteries with >50% diameter stenosis.
Patients presented with stable or unstable angina pectoris (Class I-IV), documented ischaemia, or documented silent ischaemia.
Patients with recent myocardial infarct (MI) less than 72 hours or elevated cardiac biomarkers were excluded.
Vessel diameter and lesion length were suitable for a 2.5-3.5 mm diameter x 9-23 mm or 30 mm (30 mm inclusion for DESSOLVE II only) length stent.
Patients were excluded if the lesion was highly calcified, tortuous, ostial, at a proximal angulation, at a side branch >2.5 mm, if thrombus was present, or if located within a previously treated vessel.
The treatment of a non-target lesion was allowed before the target lesion; if no procedural complications occurred, the patient was treated with the assigned study stent.

Online Table 3. Investigators, institutions and core laboratories participating in DESSOLVE I and II.

Co-principal Investigators for DESSOLVE I and DESSOLVE II

– William Wijns, Cardiovascular Research Center Aalst, Aalst, Belgium;
– John Ormiston, Mercy Angiography, Mercy Hospital, Auckland, New Zealand.

DESSOLVE I Investigators

– William Wijns, Cardiovascular Center Aalst, Aalst, Belgium;
– Mathias Vrolix, ZOL (Ziekenhuis Oost-Limburg), Genk, Belgium;
– Jim Stewart, Mercy Angiography Unit, Auckland, New Zealand;
– Mark Webster, Auckland City Hospital, Auckland, New Zealand;
– Robert Whitbourn, St. Vincent's Hospital, Melbourne, Australia.

DESSOLVE II Investigators

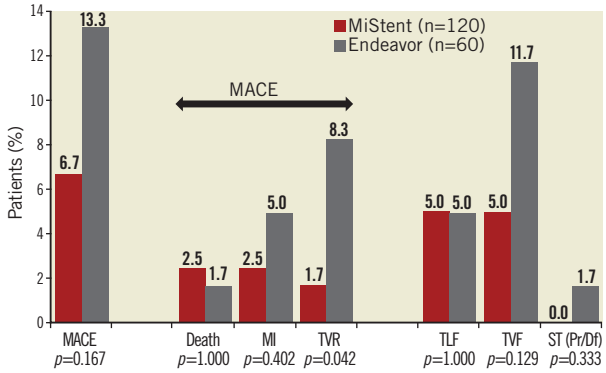
– William Wijns, Cardiovascular Center Aalst, Aalst, Belgium;
– Mathias Vrolix, ZOL (Ziekenhuis Oost-Limburg), Genk, Belgium;
– Stefan Verheye, Antwerp Cardiovascular Center, ZNA Middelheim, Antwerp, Belgium;
– Danny Schoors, Brussels University Hospital - UZ Brussel, Brussels, Belgium;
– Ton Slagboom, OLV, Amsterdam, The Netherlands;
– Marcel Gosselink, Isala Klinieken-Wezenland Zwolle, The Netherlands;
– Edouard Benit, Heart Center Hasselt, Jessaziekenhuis, Hasselt, Belgium;
– Walter Desmet, KUL Cardiology Gasthuisberg, Leuven, Belgium;
– Saqib Chowdhary, University Hospital South Manchester, Manchester, United Kingdom;
– Maarten Jan Suttorp, St. Antonius Ziekenhuis, Nieuwegein, The Netherlands;
– Leszek Zagozdzon, Orebro University Hospital, Orebro, Sweden;
– Marie-Claude Morice, Institut Hospitalier Jacques Cartier – Institut Cardiologique Paris Sud, Massy, France;
– Carlo Di Mario, Royal Brompton or Imperial College, London, United Kingdom;
– Jean Fajadet, CHU Rangueil, Clinique Pasteur, Toulouse, France;
– Dougal McClean, Christchurch Hospital, Christchurch, New Zealand;
– Pieter Stella, University Medical Center (UMC) Utrecht, Utrecht, The Netherlands;
– Phillipe Garot, Claude Galien Hospital, Quincy, France;
– Alisdair Ryding, Norfolk and Norwich University Hospital, Norwich, United Kingdom;
– Iain Simpson, Southampton University Hospital, Southampton, United Kingdom;
– Wilbert Aarnoudse, TweeSteden Ziekenhuis, Tilburg, The Netherlands;
– Per Albertsson, Sahlgrenska University Hospital, Goteborg, Sweden;
– Cameron Densem, Papworth Hospital, Cambridge, United Kingdom;
– Scott Harding, Wellington Hospital, Wellington, New Zealand;
– David Hildick-Smith, Royal Sussex County Hospital, Brighton, United Kingdom;
– Jim Stewart, Mercy Angiography Unit, Mercy Hospital, Auckland, New Zealand;
– Jim Stewart, Auckland City Hospital, Auckland, New Zealand;
– Robert Whitbourn, St. Vincent's Hospital, Melbourne, Australia

Core laboratories

– Angiography core laboratory: Alexandra J. Lansky, MD, Yale University School of Medicine, New Haven, CT, USA.
– Optical Coherence Tomography core laboratory: Marco Costa, MD, PhD, and Hiram Bezerra, MD, PhD, Case Western Medical Center, Cleveland, OH, USA.

Online Table 4. Study conduct and organisation.

Competent authority notification and medical ethical committee (EC) approval for the protocol and an informed consent form were completed for each investigator as required prior to participation in the trials.
Primary data collection, using source-documented hospital chart reviews, was performed by research coordinators at each investigative site and entered into the database via electronic data capture (EDC). Data were monitored with 100% source verification and site compliance to the protocol.
An independent clinical events committee (CEC) was responsible for adjudication of events that required review from the study.
The Data and Safety Monitoring Board (DSMB) was an independent panel of specialists not participating in the clinical trial and responsible for review of the safety data from the studies.



Online Figure 1. *Major adverse cardiac events (MACE) at two years.*