Randomised study of a bioabsorbable polymer-coated sirolimus-eluting stent: results of the DESSOLVE II trial

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Abstract

Aims: To compare the efficacy and safety of the MiStent absorbable polymer sirolimus-eluting stent (APSES) with a zotarolimus-eluting stent (ZES).

Methods and results: The trial was a 2:1 randomisation at 26 sites of 184 patients implanted with an APSES (n=123) versus a ZES (n=61). Following stent implantation, all patients underwent quantitative coronary angiography at baseline and at nine months of follow-up, while a select subgroup also underwent optical coherence tomography (OCT). The primary efficacy hypothesis was superiority of in-stent late lumen loss (LLL) of APSES compared to ZES. At nine months, the primary endpoint was met, with a mean in-stent LLL of 0.27±0.46 mm in 103 APSES patients versus 0.58±0.41 mm in 52 ZES patients (p<0.001). The proportion of uncovered stent struts by OCT at nine months was very low in both groups. The mean neointimal thickness of covered struts (p=0.002) and percent net volume obstruction (p≤0.003) were significantly lower in the APSES than in the ZES group. Major adverse cardiac event and stent thrombosis rates were low and comparable between groups.

Conclusions: The DESSOLVE II trial demonstrated superiority in the primary efficacy endpoint of nine-month mean LLL for APSES compared to ZES. Strut coverage by OCT was high with both stents and the clinical safety endpoints including stent thrombosis were equally low in both groups. ClinicalTrials.gov Identifier: NCT01294748

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Introduction

Drug-eluting stents (DES) were designed to prevent the development of coronary restenosis caused by the proliferation of neointimal tissue following stented angioplasty. The first generation of DES consisted of bare metal stents (BMS) coated with a permanent polymer, which eluted a drug that inhibited the growth of excessive luminal tissue. However, the presence of these durable polymers may contribute to the undesirable long-term effects on vessel healing potentially associated with (very) late stent thrombosis (ST)[1,2].

In an effort to enhance safety and efficacy, current DES focus has shifted to developing strategies to eliminate the potential harm associated with permanent polymer-based DES. One of these solutions is the use of bioabsorbable polymers. The MiStent® Sirolimus Eluting Absorbable Polymer Coronary Stent System (MiStent SES®; Micell Technologies, Durham, NC, USA) was developed using a thin-strut cobalt-chromium (CoCr) stent platform with a fully absorbable polymer coating uniquely containing a crystalline form of sirolimus. This next-generation sirolimus-eluting stent (SES) elutes and delivers sirolimus at a controlled rate from a recognised absorbable polymer (AP) and is intended to combine the long-term safety and stability characteristics of a BMS with the demonstrated clinical advantages of a DES.

We present the angiographic and the optical coherence tomography (OCT) evaluations along with clinical outcomes at nine months.

Study design and objectives

DESSOLVE II was a prospective, single-blind, 2:1 unbalanced, randomised, multicentre, superiority trial designed to compare the MiStent absorbable polymer sirolimus-eluting stent (APSES) to the control Endeavor® zotarolimus-eluting stent (ZES) system (Medtronic Vascular, Inc., Santa Rosa, CA, USA) using in-stent late lumen loss (LLL) at nine months as the primary study efficacy endpoint[3]. Investigational sites in Europe and New Zealand **(Online Appendix A)** participated in the trial.

Following implant of the DES, all patients underwent quantitative coronary angiography (QCA) and a subgroup underwent OCT at baseline and nine-month follow-up.

Patient population and methods

Patients included in this trial were required to be between the ages of 18 and 85 years, who presented with: a) stable or class I-IV unstable angina pectoris, or documented overt or silent myocardial ischaemia, and b) a single, *de novo*, type A, B1 or B2, >50% coronary stenosis (by visual estimate) in a 2.5 to 3.5 mm diameter (by visual estimate) native coronary artery that could be covered with a ≤30 mm long stent. Total occlusions, in-stent restenosis, highly calcified or thrombotic lesions and lesions located at major bifurcations or in highly tortuous vessels were excluded from the study. Direct stenting was not allowed. Patients could be enrolled ≥72 hrs after the onset of an acute myocardial infarction (MI), if the serum cardiac enzyme concentrations had returned to within normal ranges. All patients granted informed consent to participate in the study, which was approved by the ethics committees of the enrolling medical centres. The main study exclusion criteria are listed in **Online Appendix B**.

Study endpoints

PRIMARY

The primary efficacy endpoint of the study was in-stent LLL at nine-month follow-up by an independent angiographic core laboratory **(Online Appendix A)**, defined as the difference between the post-procedural minimal luminal diameter (MLD) and the follow-up MLD. The safety endpoint was the rate of major adverse cardiac events (MACE), defined as all-cause death, Q-wave or non-Q-wave MI and clinically driven target vessel revascularisation (TVR) at nine-month follow-up.

SECONDARY

The secondary procedural/angiographic endpoints of the study were device, lesion and procedural success, in-segment LLL, percent diameter stenosis (%DS), MLD, and binary restenosis rates at nine-month follow-up. The secondary clinical endpoints of the study ascertained immediately after the index procedure and at each subsequent follow-up were all-cause mortality, rates of Q-wave and non-Q-wave MI, rates of clinically driven target lesion revascularisation (TLR) and TVR, rates of target lesion failure (TLF) and target vessel failure (TVF), and rates of ST according to the Academic Research Consortium (ARC) definitions[4] and adjudicated by an independent clinical events committee.

Device characteristics

APSES

The design of the rapid exchange delivery catheter of the MiStent APSES is compatible with guidewires ≤0.014 inch in diameter and 6 Fr guide catheters. The BMS platform of the APSES is a thin, laser-cut and electro-polished L605 cobalt-chromium alloy tube. The <10 μm thick (biased to the abluminal surface) stent coating consists of poly-lactide-co-glycolic acid (PLGA) loaded with

Figure 1. *MiStent SES utilises crystalline sirolimus in a polymer coating (scanning electron microscopy).*

crystalline particles of sirolimus **(Figure 1)**[5]. The drug load on the MiStent SES is similar to the CYPHER stent (Cordis, Miami Lakes, FL, USA) with a nominal sirolimus drug density of 2.44 µg/mm². PLGA, a biodegradable and biocompatible polymer, releases the crystalline drug in a controlled manner post implant and throughout the stented region. Based on observations made in animals, all of the polymer coating of the APSES is expected to be off the stent in 45-60 days, leaving a BMS within the artery. The drug continues to elute from the crystals into the tissue up to nine months.

ZES
The control Endeavor ZES combines the Driver® chromium-cobalt-nickel alloy coronary stent system with 91 µm stent struts coated with a durable phosphorylcholine polymer and 10 µg per 1 mm stent length of the antiproliferative agent zotarolimus[6,7].

Antithrombotic therapy
All patients were treated with DAPT for a minimum duration concordant with local practice guidelines. A loading dose of aspirin was recommended before the procedure, followed by an oral maintenance dose daily, indefinitely. A loading dose of clopidogrel was recommended within 24 hrs before the procedure, followed by a maintenance dose for 6-12 months. Prasugrel could also be used for patients who were intolerant of clopidogrel.

Patient follow-up
Between the index DES implantation procedure and their return at nine months to undergo follow-up QCA, the patients were contacted at 30 days and six months to review their medication regimen and ascertain their clinical status and the possible incidence of interim adverse events. The patients will be contacted annually through five years.

Follow-up imaging at nine months
All available patients were seen at nine months for recording of an ECG, assessment of clinical status, drug regimen and possible interim adverse events, and repeat invasive angiography for QCA of the stented lesion by independent core laboratory analysis. OCT studies were conducted in a subgroup of 38 patients (24 APSES and 14 ZES). Sequential measurements were made during the index procedure, after DES deployment, and at nine months after administration of intracoronary nitrates. OCT images were acquired with a commercially available system (C7-XR™ OCT Intravascular Imaging System; St. Jude Medical, St. Paul, MN, USA) without proximal balloon occlusion after intracoronary administration of 200 µg of nitroglycerine through conventional guiding catheters. A 0.014 inch guidewire was positioned distally and the OCT catheter (C7 Dragonfly™; St. Jude Medical) was advanced distal to the region of interest, which was scanned using the integrated automated pullback device at 20 mm/s and acquiring images at 100 frames/s. During image acquisition, coronary blood flow was replaced by contrast dye infusion delivered with an injection pump at 3-5 ml/s via the guiding catheter.

Study monitoring
All sites and data were monitored during the trial and the co-principal investigators reviewed the final trial results. A clinical events committee met regularly to adjudicate pre-specified events including all deaths, MI, TVR and ST. The data safety monitoring board was responsible for the overall safety of the study.

Core laboratory analysis
QCA was performed as previously described[8] using validated software (Medis version 7.2; Medis, Leiden, The Netherlands). Measurements included LLL, the primary study endpoint, as well as %DS, MLD, and binary restenosis (reduction in the %DS of 50% or more) of the treated lesion and vessel.

OCT measurements were obtained with a dedicated semi-automated contour-detection system (OCT system software B.0.1; St. Jude Medical). All cross-sectional images (frames) were initially screened for quality assessment and excluded from analysis if any portion of the image was out of the screen or the image had poor quality caused by residual blood or sew-up artefact[9]. Side branches occupying >45° of the cross-section were excluded from the analysis. Strut-level analysis was performed considering every three frames (0.6 mm interval) along the entire target segment. Lumen, stent, and neointimal hyperplasia areas and volumes were calculated[9-11]. The centre of the luminal surface of the strut blooming was determined for each strut and its distance to the lumen contour was calculated automatically to determine strut-level intimal thickness. Strut malapposition was determined when the negative value of strut-level intimal thickness was higher than the strut thickness, according to the stent manufacturer's specifications, with the addition of a compensation factor of 20 µm to correct for strut blooming[12]. The blooming compensation factor was determined based on analysis of 2,250 struts. Highly reproducible measurements for strut apposition and coverage using the described methodology have been reported[13]. The following OCT variables were collected: percentage of stent struts uncovered/malapposed, percentage of frames with more than 30% of uncovered struts, maximum length of segments with uncovered/malapposed struts, maximum malapposition distance, percent net volume obstruction, frequency of abnormal intra-stent tissue, stent volume, and lumen volume. Qualitative imaging assessment was performed in every frame for the presence of abnormal intra-stent tissue which was defined as any mass protruding beyond the stent struts into the lumen, with irregular surface and a sharp intensity gap between mass and neointimal tissue[14,15].

Statistical analysis
The primary efficacy hypothesis of the trial was superiority of in-stent LLL associated with APSES compared to ZES at nine months. A total of 184 patients were randomised in a 2:1 manner to APSES versus ZES. This sample size provided 90% power to demonstrate a >50% reduction in LLL with APSES with a two-sided alpha of 0.05, assuming a control LLL for ZES of 0.50 mm±0.48 mm and 20% loss to follow-up. For safety, the difference in nine-month rates of MACE between the APSES and ZES arms was estimated

using a difference in sample proportions with a corresponding 95% confidence interval. Continuous variables were expressed as mean ±SD and categorical variables were expressed as counts and percentages. For per-patient analysis, the difference between the two stent types was evaluated by non-parametric Mann-Whitney U test for optical coherence tomography measurements, and Student's t-test for quantitative coronary angiographic continuous variables and Fisher's exact test for categorical variables. All statistical analyses were performed by Harvard Clinical Research Institute, Boston, MA, USA, using the Statistical Analysis Software, version 9.1.3 SP2 (SAS Corporation, Cary, NC, USA). Statistical significance was declared when the two-sided p-value was <0.05.

Results

Between February and July 2011 a total of 184 patients were randomised in DESSOLVE II: 123 were assigned to receive APSES and 61 to receive ZES. The mean age of the APSES patients (69% men) was 65.0±10.4 and that of the ZES patients (74% men) was 65.1±10.5 years. The baseline characteristics of the two study groups are shown in **Table 1**. Three patients did not correctly receive the assigned stent, including two patients assigned to APSES and one patient assigned to ZES, leaving 181 patients (121 APSES, 60 ZES) treated per protocol **(Figure 2)**. However, the analysis is reported for the intention-to-treat group.

Procedural and lesion characteristics

The angiographic lesion and procedural characteristics are shown in **Table 2**. Except for a minimally greater mean post-procedural %DS in the APSES group favouring the ZES group, all between-group differences were well balanced, including vascular lesion distribution, lesion length, amount of calcification, lesion complexity and mean post-procedural MLD.

Table 1. Baseline characteristics - percentage of each study group (intention-to-treat population).

		APSES n=123	ZES n=61
Age (mean)		65.0±10.4	65.1±10.5
Male		69.1	73.8
Medical history			
Myocardial infarction		23.1	16.4
Percutaneous coronary intervention	of non-target vessel	26.8	18.0
	of target vessel	4.1	4.9
Coronary artery bypass graft		4.1	3.3
Diabetes		19.0	19.7
Hypertension		70.5	68.9
Hypercholesterolaemia		72.7	81.7
Smoking	Current smoker	21.5	25.4
	Former smoker	38.0	40.7
Atrial fibrillation		6.6	10.0
Cancer		5.7	8.2
Angina	Stable	78.0	80.0
	Unstable	14.6	13.3

Values are means±standard deviation or numbers (%) of observations; the differences between APSES and ZES groups are all statistically non-significant.

Quantitative coronary angiography and primary study endpoint analysis

The nine-month mean in-stent LLL was 0.27±0.46 mm in the APSES arm (n=103), versus 0.58±0.41 mm in the ZES arm (n=52) **(Table 3)**. This -0.31 mm difference (95% CI: -0.45 to -0.16) between the two groups was statistically significant (p<0.001) in favour of APSES, confirming the primary efficacy hypothesis of
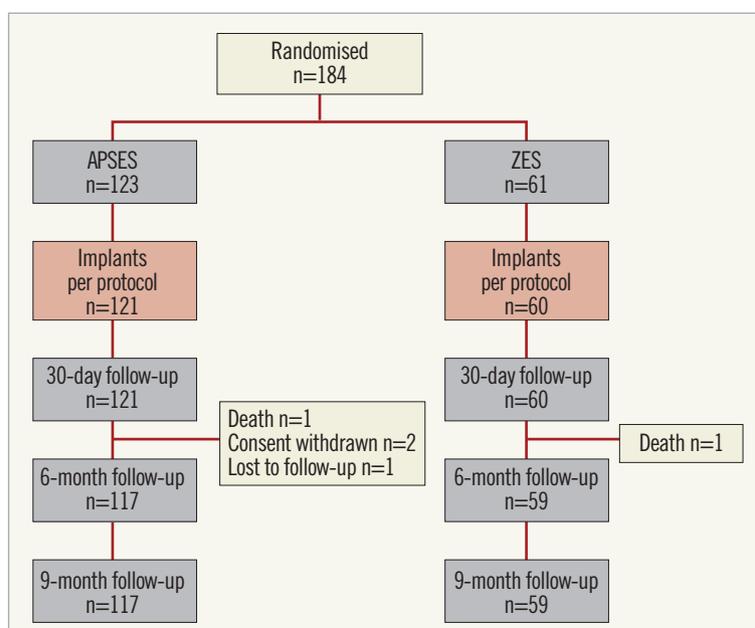

Figure 2. *Patient randomisation and follow-up through 9 months.*

Table 2. Angiographic observations and procedural characteristics per study group.

|		APSES n=123	ZES n=61
Target artery location	Left anterior descending	44.3	36.1
	Left circumflex	21.3	37.7
	Right coronary artery	34.4	26.2
Reference vessel diameter, mm		2.9±0.4	2.8±0.4
Lesion length, mm		13.6±5.0	13.4±6.2
Moderate to severe calcification		27.9	31.1
Thrombosis In Myocardial Infarction flow grade 3		91.8	91.8
ACC/AHA classification	A	8.2	9.8
	B1	45.9	45.9
	B2	29.5	26.2
	C	16.4	18.0
Maximum stent deployment pressure, atm		14.3±2.8	14.0±2.4
Post-dilatation		43.1	34.4
Lesion success		100	100
Device success		100	100
Procedure success		98.4	96.7
Minimum lumen diameter, mm	Pre-procedure	0.8±0.2	0.8±0.3
	Post procedure (in-stent)	2.8±0.4	2.9±0.4
	Post procedure (in-lesion)	2.5±0.4	2.5±0.4
Percent diameter stenosis	Pre-procedure	70.8±7.8	71.1±9.5
	Post procedure (in-stent)	3.4±7.3	−0.8±7.2*
	Post procedure (in-lesion)	13.5±7.6	14.1±6.8
Length of hospitalisation, days		1.2±1.5	1.3±1.1

Values are means±SD or numbers (%) of observations; *p<0.001 versus APSES; all other differences between APSES and ZES groups are statistically non-significant. ACC/AHA: American College of Cardiology/American Heart Association

the trial **(Figure 3)**. Concordantly, mean in-stent and in-lesion MLD was significantly smaller, and mean in-stent and in-lesion %DS significantly greater in the ZES than in the APSES group **(Table 3)**. Binary restenosis was similar in both groups.

Table 3. Quantitative coronary angiographic measurements at 9 months of follow-up in each study group.

		APSES n=103	ZES n=52	p
Reference vessel diameter, mm		2.94±0.4	2.84±0.4	0.174
Late lumen loss, mm	In-stent	0.27±0.46	0.58±0.41	<0.001
	In-lesion	0.19±0.43	0.34±0.36	0.029
Minimum lumen diameter, mm	In-stent	2.58±0.53	2.28±0.51	0.001
	In-lesion	2.37±0.51	2.11±0.49	0.003
Percent diameter stenosis	In-stent	12.11±16.10	19.34±15.62	0.008
	In-lesion	19.34±14.29	25.87±12.54	0.006
Binary restenosis, %	In-stent	4.9	1.9	0.664
	In-lesion	4.9	3.8	1.000

Values are means±SD or numbers (%) of observations.

Distribution of in-stent late lumen loss
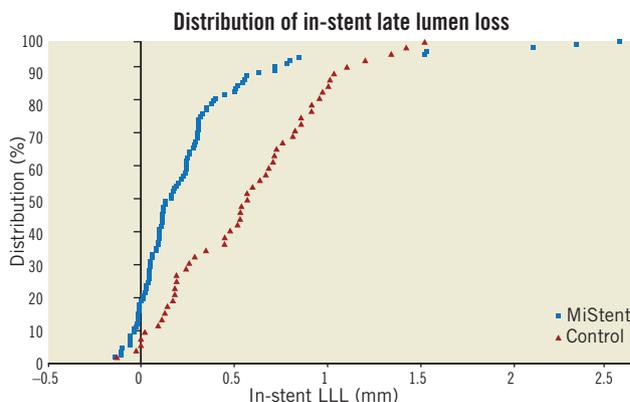
Figure 3. *Cumulative distribution curves of the in-stent late lumen loss between groups (primary study endpoint).*

Optical coherence tomography

The results of OCT studies, performed at procedure and nine-month follow-up in 24 APSES and 14 ZES patients, are shown in **Table 4**. The proportion of uncovered stent struts was marginally higher in the APSES (2.1±4.0%) group compared with the ZES (0.5±1.5%) group (p=0.048). The mean neointimal thickness of covered struts was 0.16±0.13 μm in the APSES versus 0.22±0.08 μm in the ZES group (p=0.002). Percent net volume obstruction (17.2±13.0% versus 26.3±8.7%) was also significantly lower in the APSES than in the ZES group (p=0.003). No other significant difference in OCT measurements was observed between the two groups **(Table 4)**.

Adverse clinical events

The incidence of in-hospital and long-term adverse clinical events was similar in both groups **(Table 5)**. The overall MACE rate at nine months was 4.3% (5/117) in the APSES and 6.7% (4/60) in the ZES arm; a single cardiac death was observed in each study group and two patients in each group sustained a non-Q-wave MI.

Table 4. Results of OCT imaging substudy at 9 months of follow-up.

	APSES n=24	ZES n=14	p
Uncovered stent struts, %	2.1±4.0	0.5±1.5	0.048
Longest uncovered strut segments, mm	0.9±1.1	0.5±1.3	0.072
Malapposed stent struts, %	1.0±2.5	0.2±0.9	0.126
Longest malapposed strut segments, mm	0.4±1.0	0.17±0.6	0.149
Stent volume, mm³	157.9±54.9	131.4±50.7	0.169
Mean neointimal thickness of covered struts, μm	0.16±0.13	0.22±0.08	0.002
Neointimal hyperplasia volume, mm³	26.2±21.0	33.8±18.8	0.112
Net volume obstruction, %	17.2±13.0	26.3±8.7	0.003

Values are means±SD. The variable thickness of coverage by OCT shows a non-Gaussian distribution; therefore it may not be representative to report a mean±SD. Median values showed similar findings.

Table 5. Cumulative incidence of adverse clinical events up to 9 months.

Measure	APSES (MiStent®) n=117 patients	ZES (Endeavor®) n=60 patients
MACE¶ (Death, MI, TVR)	4.3	6.7
Death	0.9	1.7
Cardiac death	0.9	1.7
Non-cardiac death	0.0	0.0
MI (Q-wave or non-Q-wave)	2.6	3.3
Target vessel Q-wave MI	0.0	0.0
Non-target vessel Q-wave MI	0.9	0.0
Target vessel non-Q-wave MI	1.7	3.3
Non-target vessel non-Q-wave MI	0.0	0.0
Clinically driven target vessel revascularisation	0.9	3.3
Clinically driven target lesion revascularisation	0.9	1.7
Target vessel failure*	3.4	6.7
Target lesion failure**	3.4	5.0
Stent thrombosis--ARC defined#	0.9	1.7
Early	0.0	1.7
Acute	0.0	1.7
Subacute	0.0	0.0
Late	0.9	0.0

Values are numbers (%) of observations. ¶Death, Q- or non-Q-wave MI, and percutaneous or surgical TVR following stent implantation; *Cardiac death, Q-wave or non-Q-wave target vessel MI and clinically driven TVR; **Cardiac death, Q-wave or non-Q-wave target lesion MI, and clinically driven TLR; #Definite, probable and possible ST

The difference in MACE between the two arms was –2.4% with a two-tailed 95% CI from –12.0% to 4.3%. A single definite ST occurred in the ZES group and a single possible ST in the APSES group. These results suggest that the safety profiles of the two study devices are comparable.

Compliance with dual antiplatelet therapy
At six months, 110/119 patients (92.4%) and 47/59 (79.7%) in the APSES and ZES groups, respectively, remained on DAPT. At nine months, the proportions of patients treated with DAPT (83.2% in the APSES versus 79.7% in the ZES groups) were similar.

Discussion
APSES incorporates a proprietary surface modification technology to provide a unique drug delivery system. Compared with previous processes, the drug component is never dissolved during the coating process, thus retaining its crystalline properties. The crystalline sirolimus mitigates an initial burst release of drug and is simultaneously released into the surrounding tissue with the polymer[5]. The rapid-absorbing polymer formulation is intended to deliver drug into the surrounding tissue, control drug elution and limit the duration of polymer exposure. The drug remains in the tissue well after the polymer is absorbed to moderate any inflammation from the polymer degradation and provides for continued and predictable elution of sirolimus up to nine months. This provides a sustained, long-term inhibition of neointimal proliferation even after the polymer is absorbed, with the potential to avoid the long-term safety concerns and late failures that are associated with durable polymer DES[16].

Further to the results of the first-in-human investigation of the APSES[8,10,11], this randomised study has confirmed the superior effectiveness of APSES through greater inhibition of neointimal proliferation resulting in a late lumen loss of about half that of ZES. In this trial, while LLL was significantly less for APSES, the TLR rates were similar. In low- to moderate-risk lesions, ZES has also demonstrated comparable TLR rates to TAXUS and CYPHER even though ZES LLL was significantly higher[17-19]. However, in more complex lesions, high-risk patients or all-comer trials, the TLR rate for ZES is significantly higher than for DES with lower LLL[19-22]. The DESSOLVE II study design was effective for defining the performance profile of APSES with an LLL value that compares favourably with other clinically effective sirolimus-eluting, zotarolimus-eluting and everolimus-eluting stents which use durable polymers[23].

The post-procedure in-stent %DS was the only significant difference at baseline with mean %DS of –0.8% for ZES and 3.4% for APSES (p<0.001). Post-procedure in-lesion %DS was identical in both groups. The mean post-procedure MLD was not different for ZES at 2.9 mm versus 2.8 mm for APSES (p=0.57). There may have been some overexpansion of the ZES stent portending greater LLL. However, mean LLL of 0.58 mm for ZES is very consistent with the 0.58-0.68 mm LLL found in other ZES trials[7,17].

While ZES does not strongly inhibit neointimal proliferation, it has been considered a safer DES than TAXUS and CYPHER, providing better vessel "healing" with return of endothelial function[24], less acquired incomplete stent apposition and positive remodelling[25].

In this study OCT was used in a subgroup of patients to compare in greater detail the vessel response between APSES and ZES. Specific sites were identified to participate in this substudy with enrolled randomised patients consenting to OCT evaluations. For all OCT measurements the two groups were similar except for a significantly lower mean neointimal thickness covering the struts and lower net volume obstruction with APSES. While the percent of uncovered struts was lower for ZES, 2.1% vs 0.5%, both stents had a low percent of uncovered struts. Strut coverage with APSES is at least comparable, if not numerically higher than with other DES evaluated by the same core laboratory[26,27].

Study limitations
DESSOLVE II was designed as a single-blind RCT, blinding the patient to treatment assignment. Not blinding the operator could have influenced the operator's decision about the need for revascularisation. Adverse events were collected at each follow-up visit. At the nine-month visit an ECG was also performed in addition to an assessment of clinical status prior to the angiographic evaluation. To minimise potential bias, an independent CEC was used to adjudicate clinically driven revascularisations.

The results of OCT analysis were reported on per-patient summaries rather than per-strut. While this approach to OCT data analysis may have limitations, this method is commonly used in reporting OCT results and allows comparability with previously reported studies[26,27]. The main limitation is that lesions with uncovered areas of exactly the same size will weight differently in the analysis depending on the total stented length. Other per-patient approaches, such as the assessment of clusters of malapposed and uncovered struts, can potentially help elucidate better the entire spectrum of stent-vessel interactions[12,28,29].

While not evaluated in the DESSOLVE II trial, the rapid absorption of the polymer coating may allow for a reduction in the duration of dual antiplatelet therapy. Whether shortening the device-mandated indication period for DAPT would provide equivalent imaging and clinical results remains to be investigated in larger trials.

Conclusion

The DESSOLVE II randomised clinical trial confirmed the safety and improved efficacy of the APSES compared to a durable polymer-based DES. The primary efficacy endpoint of mean LLL at nine-month angiographic follow-up was superior for APSES compared to ZES, and accompanied by low major adverse cardiac event rates and stent thrombosis in both groups. Long-term clinical outcomes will be followed to five years and an additional larger trial powered for clinical endpoints will be conducted to build on the DESSOLVE II data.

Impact on daily practice

Based on its unique design features, the MiStent absorbable polymer sirolimus-eluting stent shows high antiproliferative properties along with timely vessel healing, both contributing to its demonstrated favourable short-term efficacy/safety profile. Potential for superior long-term biocompatibility of DES with absorbable polymer, hence reduced late failure rates, should be evaluated by long-term follow-up (from 3 to 5 years). In the meantime, further studies should test the clinical performance of the MiStent in various real-life patient and lesion subsets. Opportunities for shortening the duration of mandated DAPT treatment equally deserve further investigation.

Conflict of interest statement

G. Attizani receives consultant fees from St. Jude Medical. D. Donohoe is a consultant and C. Knape is an employee of Micell Technologies. W. Wijns reports institutional grants from several device companies, including Micell Technologies and Medtronic. The other authors have no conflicts of interest to declare.

References

1. Nebeker JR, Virmani R, Bennett CL, Hoffman JM, Samore MH, Alvarez J, Davidson CJ, McKoy JM, Raisch DW, Whisenant BK, Yarnold PR, Belknap SM, West DP, Gage JE, Morse RE, Gligoric G, Davidson L, Feldman MD. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol.* 2006;47:175-81.

2. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. *Circulation.* 2007;115:1440-5.

3. Mauri L, Orav EJ, O'Malley AJ, Moses JW, Leon MB, Holmes DR Jr, Teirstein PS, Schofer J, Breithardt G, Cutlip DE, Kereiakes DJ, Shi C, Firth BG, Donohoe DJ, Kuntz RE. Relationship of late loss in lumen diameter to coronary restenosis in sirolimus-eluting stents. *Circulation.* 2005;111:321-7.

4. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344-51.

5. Carlyle WC, McClain JB, Tzafriri AR, Bailey L, Zani BG, Markham PM, Stanley JR, Edelman ER. Enhanced drug delivery capabilities from stents coated with absorbable polymer and crystalline drug. *J Control Release.* 2012;162:561-7.

6. Meredith IT, Ormiston J, Whitbourn R, Kay IP, Muller D, Bonan R, Popma JJ, Cutlip DE, Fitzgerald P, Prpic R, Kuntz RE. First-in-human study of the Endeavor ABT-578-eluting phosphorylcholine-encapsulated stent system in de novo native coronary lesions: Endeavor I Trial. *EuroIntervention.* 2005;1:157-64.

7. Gershlick A, Kandzari DE, Leon MB, Wijns W, Meredith IT, Fajadet J, Popma JJ, Fitzgerald PJ, Kuntz RE; ENDEAVOR Investigators. Zotarolimus-eluting stents in patients with native coronary artery disease: clinical and angiographic outcomes in 1,317 patients. *Am J Cardiol.* 2007;100:45M-55M.

8. Ormiston J, Webster M, Stewart J, Vrolix M, Whitbourn R, Donohoe D, Knape C, Lansky A, Attizzani GF, Fitzgerald P, Kandzari DE, Wijns W. First-in-human evaluation of a bioabsorbable polymer-coated sirolimus-eluting stent: imaging and clinical results of the DESSOLVE I Trial (DES with sirolimus and a bioabsorbable polymer for the treatment of patients with de novo lesion in the native coronary arteries). *JACC Cardiovasc Interv.* 2013;6:1026-34.

9. Bezerra HG, Costa MA, Guagliumi G, Rollins AM, Simon DI. Intracoronary optical coherence tomography: a comprehensive review. *JACC Cardiovasc Interv.* 2009;2:1035-46.

10. Attizzani GF, Bezerra HG, Chamié D, Fujino Y, Spognardi AM, Stanley JR, Yamamoto H, Mehanna E, Wang W, Carlyle WC, McClain JB, Costa MA. Serial Evaluation of Vascular Response After Implantation of a New Sirolimus-Eluting Stent With Bioabsorbable Polymer (MISTENT): an optical coherence tomography and histopathological study. *J Invasive Cardiol.* 2012;24:560-8.

11. Attizzani GF, Bezerra HG, Ormiston J, Wang W, Donohoe D, Wijns W, Costa MA. Serial assessment by optical coherence tomography of early and late vascular responses after implantation of an absorbable-coating Sirolimus-Eluting stent (from the first-in-human DESSOLVE I trial). *Am J Cardiol.* 2013;112:1557-64.

12. Mehanna EA, Attizzani GF, Kyono H, Hake M, Bezerra HG. Assessment of coronary stent by optical coherence tomography, methodology and definitions. *Int J Cardiovasc Imaging.* 2011;27: 259-69.

13. Gonzalo N, Garcia-Garcia HM, Serruys PW, Commissaris KH, Bezerra H, Gobbens P, Costa M, Regar E. Reproducibility of quantitative optical coherence tomography for stent analysis. *EuroIntervention.* 2009;5:224-32.

14. Kume T, Akasaka T, Kawamoto T, Ogasawara Y, Watanabe N, Toyota E, Neishi Y, Sukmawan R, Sadahira Y, Yoshida K. Assessment of coronary arterial thrombus by optical coherence tomography. *Am J Cardiol.* 2006;97:1713-7.

15. Kume T, Okura H, Kawamoto T, Akasaka T, Toyota E, Watanabe N, Neishi Y, Sadahira Y, Yoshida K. Images in cardiovascular medicine. Fibrin clot visualized by optical coherence tomography. *Circulation.* 2008;118:426-7.

16. Park SJ, Kang SJ, Virmani R, Nakano M, Ueda Y. In-stent neoatherosclerosis: a final common pathway of late stent failure. *J Am Coll Cardiol.* 2012;59:2051-7.

17. Kandzari DE, Leon MB, Meredith I, Fajadet J, Wijns W, Mauri L. Final 5-year outcomes from the Endeavor zotarolimus-eluting stent clinical trial program: comparison of safety and efficacy with first-generation drug-eluting and bare-metal stents. *JACC Cardiovasc Interv.* 2013;6:504-12.

18. Maeng M, Tilsted HH, Jensen LO, Kaltoft A, Kelbæk H, Abildgaard U, Villadsen AB, Krusell LR, Ravkilde J, Hansen KN, Christiansen EH, Aarøe J, Jensen JS, Kristensen SD, Bøtker HE, Madsen M, Thayssen P, Sørensen HT, Thuesen L, Lassen JF. 3-Year clinical outcomes in the randomized SORT OUT III superiority trial comparing zotarolimus- and sirolimus-eluting coronary stents. *JACC Cardiovasc Interv.* 2012;5:812-8.

19. Ellis SG, Popma JJ, Lasala JM, Koglin JJ, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Stone GW. Relationship between angiographic late loss and target lesion revascularization after coronary stent implantation: analysis from the TAXUS-IV trial. *J Am Coll Cardiol.* 2005;45:1193-200.

20. Cassese S, Ndrepepa G, King LA, Tada T, Fusaro M, Kastrati A. Two zotarolimus-eluting stent generations: a meta-analysis of 12 randomised trials versus other limus-eluting stents and an adjusted indirect comparison. *Heart.* 2012;98:1632-40.

21. Maeng M, Jensen LO, Tilsted HH, Kaltoft A, Kelbaek H, Abildgaard U, Villadsen A, Aarøe J, Thayssen P, Krusell LR, Christiansen EH, Bøtker HE, Kristensen SD, Ravkilde J, Madsen M, Sørensen HT, Rasmussen K, Thuesen L, Lassen JF. Outcome of sirolimus-eluting versus zotarolimus-eluting coronary stent implantation in patients with and without diabetes mellitus (a SORT OUT III Substudy). *Am J Cardiol.* 2011;108:1232-7.

22. Hannan EL, Zhong Y, Wu C, Walford G, Holmes DR Jr, Jacobs AK, Stamato NJ, Venditti FJ, Sharma S, Fergus I, King SB 3rd. Everolimus-eluting stents and zotarolimus-eluting stents for percutaneous coronary interventions: two-year outcomes in New York State. *Catheter Cardiovasc Interv.* 2013;81:1097-105.

23. Bangalore S, Toklu B, Amoroso N, Fusaro M, Kumar S, Hannan EL, Faxon DP, Feit F. Bare metal stents, durable polymer drug eluting stents, and biodegradable polymer drug eluting stents for coronary artery disease: mixed treatment comparison meta-analysis. *BMJ.* 2013;347:f6625.

24. Hamilos M, Sarma J, Ostojic M, Cuisset T, Sarno G, Melikian N, Ntalianis A, Muller O, Barbato E, Beleslin B, Sagic D, De Bruyne B, Bartunek J, Wijns W. Interference of drug-eluting stents with endothelium-dependent coronary vasomotion: evidence for device-specific responses. *Circ Cardiovasc Interv.* 2008;1:193-200.

25. Guagliumi G, Ikejima H, Sirbu V, Bezerra H, Musumeci G, Lortkipanidze N, Fiocca L, Tahara S, Vassileva A, Matiashvili A, Valsecchi O, Costa M. Impact of drug release kinetics on vascular response to different zotarolimus-eluting stents implanted in patients with long coronary stenoses: the LongOCT study (Optical Coherence Tomography in Long Lesions). *JACC Cardiovasc Interv.* 2011;4:778-85.

26. Guagliumi G, Bezerra HG, Sirbu V, Ikejima H, Musumeci G, Biondi-Zoccai G, Lortkipanidze N, Fiocca L, Capodanno D, Wang W, Tahara S, Vassileva A, Matiashvili A, Valsecchi O, Costa MA. Serial assessment of coronary artery response to paclitaxel-eluting stents using optical coherence tomography. *Circ Cardiovasc Interv.* 2012;5:30-8.

27. Guagliumi G, Capodanno D, Ikejima H, Bezerra HG, Sirbu V, Musumeci G, Fiocca L, Lortkipanidze N, Vassileva A, Tahara S, Valsecchi O, Costa MA. Impact of different stent alloys on human vascular response to everolimus-eluting stent: an optical coherence tomography study: the OCTEVEREST. *Catheter Cardiovasc Interv.* 2013;81:510-8.

28. Guagliumi G1, Sirbu V, Musumeci G, Gerber R, Biondi-Zoccai G, Ikejima H, Ladich E, Lortkipanidze N, Matiashvili A, Valsecchi O, Virmani R, Stone GW. Examination of the in vivo mechanisms of late drug-eluting stent thrombosis: findings from optical coherence tomography and intravascular ultrasound imaging. *JACC Cardiovasc Interv.* 2012;5:12-20.

29. Attizzani GF, Capodanno D, Ohno Y, Tamburino C. Mechanisms, Pathophysiology, and Clinical Aspects of Incomplete Stent Apposition. *J Am Coll Cardiol.* 2014;63:1355-67.

Online data supplement

Online Appendix A. Investigators and institutions that participated in DESSOLVE II.
Online Appendix B. Main study exclusion criteria.