ORIGINAL ARTICLE

Impact of overlapping newer generation drug-eluting stents on clinical and angiographic outcomes: pooled analysis of five trials from the international Global RESOLUTE Program

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ABSTRACT

Background Overlapping first generation sirolimus- and paclitaxel-eluting stents are associated with persistent inflammation, fibrin deposition and delayed endothelialisation in preclinical models, and adverse angiographic and clinical outcomes—including death and myocardial infarction (MI)—in clinical studies.

Objectives To establish as to whether there are any safety concerns with newer generation drug-eluting stents (DES).

Design Propensity score adjustment of baseline anatomical and clinical characteristics were used to compare clinical outcomes (Kaplan–Meier estimates) between patients implanted with overlapping DES (Resolute zotarolimus-eluting stent (R-ZES) or R-ZES/other DES) against no overlapping DES. Additionally, angiographic outcomes for overlapping R-ZES and everolimus-eluting stents were evaluated in the randomised RESOLUTE All-Comers Trial.

Setting Patient level data from five controlled studies of the RESOLUTE Global Clinical Program evaluating the R-ZES were pooled. Enrolment criteria were generally unrestrictive.

Patients 5130 patients.

Main outcome measures 2-year clinical outcomes and 13-month angiographic outcomes.

Results 644 of 5130 patients (12.6%) in the RESOLUTE Global Clinical Program underwent overlapping DES implantation. Implantation of overlapping DES was associated with an increased frequency of MI and more complex/calcified lesion types at baseline. Adjusted in-hospital, 30-day and 2-year clinical outcomes indicated comparable cardiac death (2-year overlap vs non-overlap: 3.0% vs 2.1%, p=0.36), major adverse cardiac events (13.3% vs 10.7%, p=0.19), target-vessel MI (3.9% vs 3.4%, p=0.40), clinically driven target vessel revascularisation (7.7% vs 6.5%, p=0.32), and definite/probable stent thrombosis (1.4% vs 0.9%, p=0.28). 13-month adjusted angiographic outcomes were comparable between overlapping and non-overlapping DES.

Conclusions Overlapping newer generation DES are safe and effective, with comparable angiographic and clinical outcomes—including repeat revascularisation—to non-overlapping DES.

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INTRODUCTION

Overlapping first generation sirolimus- (SES) and paclitaxel- (PES) eluting stents have been associated with a persistent inflammatory response, fibrin deposition and delayed endothelialisation in preclinical models.[1] Although several,[2–4] predominantly small scale,[2 3] registries have shown the potential safety of overlapping first generation drug eluting stents (DES), a post hoc analysis of the randomised SIRTAX (Sirolimus-Eluting versus Paclitaxel-Eluting Stents for Coronary Revascularization) trial (n=1012) associated the implantation of overlapping SES or PES with impaired angiographic (8-month) and adverse 3-year clinical outcomes, including death or myocardial infarction (MI).[5] In addition, optical coherence tomography (OCT) sub-studies in principally first generation DES have shown the vascular response to be greater at the overlap compared to the non-overlap, with a resultant greater percentage volume obstruction at 6 months' follow-up.[6 7] These latter studies were however not adequately powered to assess clinical outcomes.

Preclinical models of overlapping newer generation DES (namely overlapping everolimus-eluting stents (EES) (Xience V, Abbott Vascular, Santa Clara, California, USA) in a healthy porcine model,[8] have shown that issues pertaining to first generation DES are potentially no longer present, with strut coverage and endothelialisation being complete within 30 days (equivalent to approximately 6 months in humans[9]). The purpose of this study is to examine the efficacy and safety of overlapping next generation DES, to establish whether the findings from preclinical models of the potential safety of overlapping newer generation DES are applicable to clinical practice.

METHODS

Patient level data from five controlled studies of the Global RESOLUTE Program evaluating the Resolute zotarolimus-eluting stent (R-ZES; Medtronic, Santa Rosa, California, USA) were pooled (RESOLUTE

First-in-Man, RESOLUTE All-Comers, RESOLUTE International, RESOLUTE US, RESOLUTE Japan) (n=5130).[10–15] All studies were prospectively designed with similar methods, clinical documentation forms, endpoint definitions, adjudication procedures, and statistical programming algorithms and datasets to allow database pooling.

Enrolment criteria were generally unrestrictive and encompassed more complex patients, including acute MI, long lesions, unprotected left main coronary artery disease, bifurcations, total occlusions, bypass grafts and visible thrombus. The overlap of the R-ZES was permitted with any DES type (R-ZES/DES), and incorporated subjects with overlapping R-ZES/R-ZES or R-ZES/other DES type. Overlapping R-ZES was however encouraged. The position of the DES in relation to the previous implanted R-ZES during the index procedure was reported by the study site as 'separate' (ie, implanted in the same vessel with no overlap), 'abutting' (ie, stent implantation side by side in the same vessel, with no overlap) or 'overlapping' (clear overlapping of stents). Clinical outcomes of subjects implanted with at least one overlapping R-ZES/DES were compared against subjects implanted with no overlapping DES (ie, single implanted R-ZES). Additionally, comparisons of clinical outcomes were made between subjects implanted with 'separate', 'abutting' or 'overlapping' R-ZES/DES. Comparisons of clinical outcomes were undertaken using unadjusted and adjusted p values (propensity score matching of baseline anatomical/clinical characteristics), between the overlap and non-overlap.

All RESOLUTE trials required the same dual antiplatelet therapy. A daily dose of at least 75 mg aspirin was prescribed indefinitely, and 75 mg of clopidogrel daily for at least 6 months. An independent Clinical Events Committee reviewed all serious adverse events, details of which have previously been described.[16 17] All studies were conducted according to the Declaration of Helsinki. All study protocols were approved by local ethics committees.

Definitions of the clinical outcome parameters

All clinical endpoint definitions have been previously described in detail and are consistent among the five studies.[10–15 18] The extended historical definition of MI is used for all the composite endpoints.[19 20] The primary outcome in all trials was target vessel failure, a composite of cardiac death, target vessel myocardial infarction (TVMI) and ischaemia-driven target vessel revascularisation. The secondary outcomes in all trials included: (1) major adverse cardiac events (MACE); a composite of any death, any MI, emergent coronary artery bypass and ischaemia-driven revascularisation by any method; and (2) target lesion failure (TLF); a composite of cardiac death, TVMI and ischemia-driven target lesion revascularisation. Any death was considered cardiac unless a non-cardiac cause could be confirmed. Any MI for which a clear ascription to a target vessel could not be determined was counted as a TVMI. Definite and probable stent thrombosis were adjudicated according to the Academic Research Consortium (ARC) criteria.[21]

RESOLUTE All-Comers Trial

Reasons for overlap were recorded in the electronic case records (eCRF) of the randomised RESOLUTE All-Comers Trial.[15] A subgroup of patients (20%) in the RESOLUTE All-Comers Trial (n=2292) were randomly assigned to undergo angiographic follow-up at 13 months. This subgroup included patients who underwent implantation with overlapping R-ZES or overlapping EES (Xience V). Overlapping of the same device was mandated. Quantitative coronary angiography (QCA) was performed with the use of the Cardiovascular Angiography Analysis System II (Pie Medical Imaging) and centrally assessed by an independent core laboratory (Cardialysis, Rotterdam, The Netherlands).[22] All angiographic measurements of the target lesion were obtained in the 'in-stent' and 'in-segment' zone. The 'in-segment' zone was defined as within the in-stent zone and 5 mm proximal and distal to each stent edge. All available QCA data for independent variables such as percentage diameter stenosis and binary restenosis were calculated using unmatched data, while matched paired QCA data was used in the analysis of serial angiographic endpoints.

Statistical methodology

All data were analysed by a dedicated independent statistician. For baseline comparisons, data are presented as percentages or mean±SD. A two-sample t test was used to compare continuous variables. Differences in discrete variables were assessed with the χ^2 or Fisher exact test as appropriate. Time-to-event analyses are reported using the Kaplan–Meier method, with comparisons made with the log-rank test. Non-adjusted and adjusted p values (to the propensity score) are reported. The propensity score was calculated with the overlapping stent vessel as dependent variable, and the following baseline variables as independent variables: age, gender, current smoker, prior percutaneous coronary intervention, hyperlipidaemia, diabetes, hypertension, prior MI, prior coronary artery bypass graft surgery, unstable angina or MI, left anterior descending coronary artery involvement, American College of Cardiology/American Heart Association (ACC/AHA) B2/C lesion,[23] moderate/severe calcification, vessel bend >45°, Thrombolysis In Myocardial Infarction flow 3, reference vessel diameter, lesion length and percentage diameter stenosis. A two-sided p value of <0.05 was considered statistically significant. All statistical analyses were performed using SAS V.9.1 or higher.

RESULTS

Within the international Global RESOLUTE Program (n=5130), 644 patients underwent overlapping R-ZES/DES implantation (1044 lesions), and 4486 patients (5814 lesions) non-overlapping (single implanted) R-ZES implantation. Baseline characteristics (table 1) indicated that the implantation of overlapping DES was associated with an increased frequency of MI, implantation in the right coronary artery, more complex lesion classification types (type C ACC/AHA classification[23]), more calcified and longer lesion types, and greater vessel tortuosity. Reasons for overlapping DES implantation in the randomised, All-Comers RESOLUTE Trial (n=2292) are illustrated in figure 1. Planned overlap, or bailout due to insufficient lesion coverage, were the most common reasons for overlap.

Clinical outcomes

In keeping with the adverse clinical co-morbidity and anatomical coronary complexity associated with patients implanted with overlapping R-ZES/DES, unadjusted clinical outcomes indicated greater in-hospital (p=0.068), 30-day (p=0.023) and 2-year (p=0.055) mortality in overlapping R-ZES/DES patients, compared to non-overlap (single implanted R-ZES) patients (table 2). Adjusted data (based on propensity score matching) indicated no significant differences in in-hospital (p=0.25), 30-day (p=0.22) and 2-year (p=0.13) mortality.

Similar findings of an increase in MACE were seen at 30 days (p=0.086) and 2 years (p=0.057), which was not evident after propensity score matching (p=0.25 and p=0.19, respectively). Notably there was no significant increase in MACE (adjusted

Table 1 Baseline demographic and lesion characteristics of overlapping resolute zotarolimus-eluting stent (R-ZES)/DES versus non-overlapping R-ZES in the International Global RESOLUTE Program (n=5130)

Baseline characteristics	Overlapping R-ZES/DES (n=644 patients, n=1044 lesions)	Non-overlapping R-ZES (n=4486 patients, n=5814 lesions)	p Value
Age (years)	64.0±10.9 (644)	63.8±11.0 (4486)	0.70
Men	76.6% (493/644)	74.7% (3349/4486)	0.31
History of smoking	60.9% (392/644)	58.7% (2633/4486)	0.30
Current smoker	24.2% (156/644)	23.6% (1059/4486)	0.73
Hyperlipidaemia	68.6% (442/644)	72.0% (3228/4486)	0.084
Diabetes mellitus	28.1% (181/644)	30.2% (1354/4486)	0.29
Insulin dependent	8.9% (57/644)	8.9% (398/4486)	1.00
History of hypertension	74.7% (481/644)	73.2% (3282/4486)	0.45
Prior MI	25.2% (160/635)	26.6% (1185/4453)	0.47
History of premature CAD in first degree relative	33.3% (171/513)	37.8% (1368/3622)	0.057
Prior CABG	8.7% (56/644)	8.5% (383/4486)	0.88
Reason for revascularisation			<0.001
Stable angina	35.9% (231/644)	38.9% (1745/4486)	
Unstable angina	22.7% (146/644)	26.4% (1183/4486)	
MI	28.6% (184/644)	21.6% (969/4486)	
Silent ischaemia	4.3% (28/644)	3.0% (133/4486)	
Left ventricular ejection fraction (%)			0.33
<30%	2.6% (11/427)	1.9% (58/3084)	
30–40%	9.8% (42/427)	8.3% (255/3084)	
>40%	87.6% (374/427)	89.9% (2771/3084)	
Serum creatinine (μmol/l)	88.2±36.8 (566)	88.2±37.5 (4036)	0.99
Vessel location (patient level)			
Left anterior descending	50.6% (326/644)	49.3% (2210/4486)	0.53
Left circumflex	31.4% (202/644)	29.7% (1334/4486)	0.41
Right coronary artery	42.1% (271/644)	32.3% (1447/4486)	<0.001
Left main coronary artery	2.2% (14/644)	1.8% (81/4486)	0.53
Saphenous vein graft	0.9% (6/644)	1.3% (58/4486)	0.57
Left internal mammary artery	0.0% (0/644)	0.2% (7/4486)	0.61
Lesion classification ACC/AHA			<0.001
A	4.3% (42/969)	7.6% (427/5628)	
B1	22.3% (216/969)	26.6% (1498/5628)	
B2	29.5% (286/969)	31.8% (1789/5628)	
C	43.9% (425/969)	34.0% (1914/5628)	
Moderate/severe calcification	40.8% (392/961)	30.5% (1707/5599)	<0.001
Bend			<0.001
<45°	71.1% (657/924)	80.5% (4411/5478)	
≥45° to <90°	25.9% (239/924)	17.9% (979/5478)	
≥90°	3.0% (28/924)	1.6% (88/5478)	
TIMI flow			<0.001
0	13.5% (131/968)	7.4% (416/5628)	
1	5.2% (50/968)	4.7% (262/5628)	
2	7.1% (69/968)	8.3% (469/5628)	
3	74.2% (718/968)	79.6% (4481/5628)	
Pre-procedure angiogram			
RVD (mm)	2.80±0.55 (903)	2.78±0.51 (5417)	0.23
MLD (mm)	0.59±0.47 (964)	0.68±0.46 (5605)	<0.001
Diameter stenosis (%)	78.2±17.0 (964)	75.1±16.3 (5605)	<0.001
Lesion length (mm)	22.88±15.12 (897)	14.54±7.49 (5398)	<0.001

ACC/AHA, American College of Cardiology/American Heart Association lesion characteristics[23]; CAD, coronary artery disease; CABG, coronary artery bypass graft surgery; DES, drug eluting stents; MI, myocardial infarction; MLD, minimum lumen diameter; RVD, reference vessel diameter; TIMI, thrombolysis in myocardial infarction.

p value=0.38) or TVMI (adjusted p value=0.66), during hospitalisation for the index procedure (table 2).

Revascularisation rates and stent thrombosis (ARC definite/probable)[21] were comparable between overlapping R-ZES/DES and non-overlap (single implanted R-ZES) patients following propensity score matching at up to 2 years (table 2).

Clinical outcomes relating the position of the DES to the previous implanted R-ZES, indicated comparable clinical outcomes between overlapping (n=635), abutting (n=139) and separate (n=121) R-ZES/DES, during in-hospital (MACE: 3.9% vs 3.6% vs 4.1%, p=0.96), 30-day (MACE: 4.6% vs 4.3% vs 5.0%, p=0.97) and 2-year (MACE:

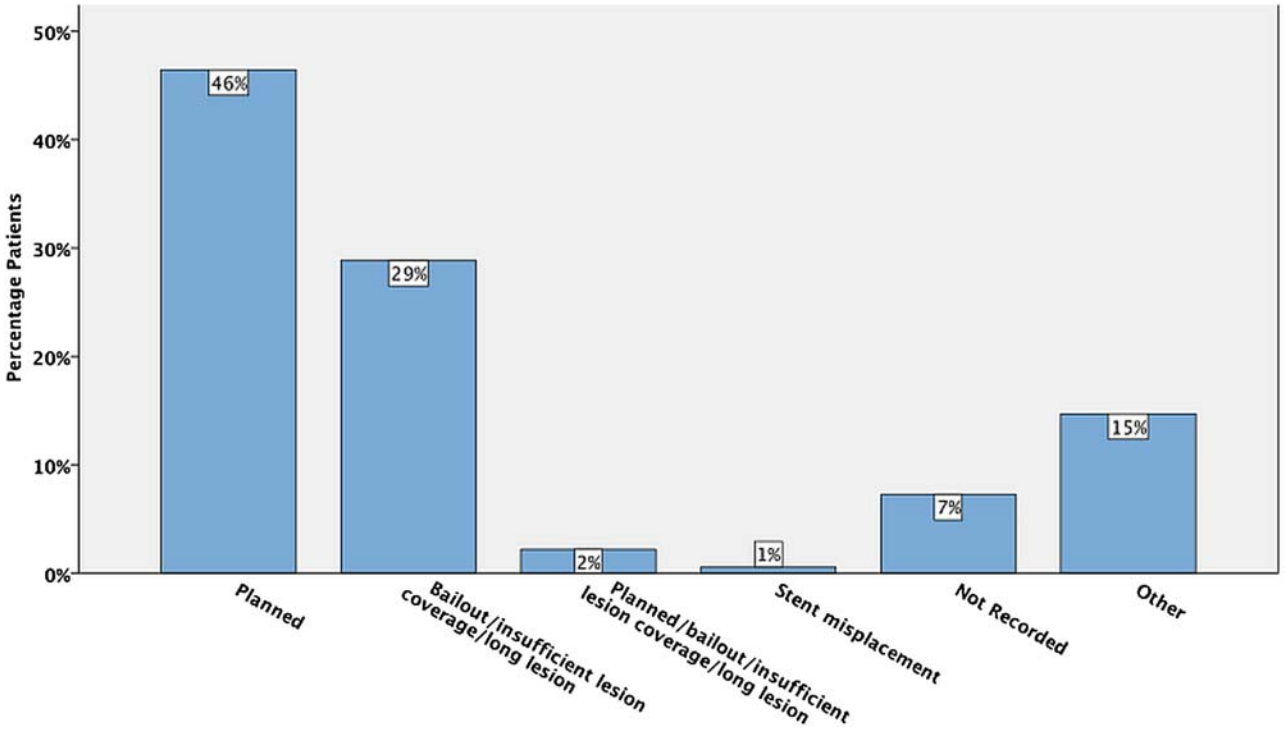

Figure 1 Reasons for overlap as documented in the electronic case records of the randomised, All-Comers Resolute Trial (n=2292).

13.6% vs 12.9% vs 16.1%, p=0.96) follow-up (see online supplementary appendix).

Angiographic outcomes in the RESOLUTE All-Comers randomised Trial

Within the RESOLUTE randomised All-Comers Trial,[15] 504 of 2292 patients (22.0%) underwent overlapping DES implantation (551 lesions). In the angiographic substudy of the RESOLUTE randomised All-Comers Trial, 92 of 459 lesions (20.0%) underwent overlapping DES implantation. Thirteen-month angiographic outcomes indicated that overlapping DES (R-ZES/R-ZES or EES/EES) (n=92 lesions) were associated with a greater percentage diameter stenosis within the in-stent (p=0.006) zone, and proximal (p=0.033) and distal (p=0.007) stent edges, compared to non-overlapping DES (single implanted R-ZES or EES, n=367 lesions). After propensity score adjustment, these findings no longer remained relevant (in-stent zone (p=0.75) and proximal (p=0.88) and distal (p=0.98) stent edges). In addition, overlapping DES (compared to non-overlapping DES) were associated with a comparable late lumen loss and binary restenosis within the in-stent zone and proximal and distal edges (adjusted and non-adjusted data) (table 3).

DISCUSSION

The main findings of this study are that the implantation of overlapping newer generation DES: (1) is safe and effective; (2) is associated with comparable clinical outcomes—including mortality, MI, MACE, target vessel or lesion revascularisation, and stent thrombosis—during in-hospital stay, at 30-day and 2-year follow-up, compared to non-overlapping DES after adjustment for baseline characteristics; (3) is associated with comparable 13-month angiographic outcomes (to non-overlapping DES), after adjustment for baseline characteristics; and (4) that the most common reason for overlapping DES was either planned for long lesions, or as bail-out stenting due to insufficient lesion coverage.

The present study is similar to the randomised SIRTAX Study[5] investigating first generation DES overlap, where adjustments for baseline characteristics were undertaken when comparing outcomes between overlapping and non-overlapping DES. The main difference is that the association of adverse angiographic and clinical outcomes reported with overlapping first generation DES in the SIRTAX Study did not transpire in the present study. In addition, first generation DES have been implicated to lead to an increase in the risk of peri-procedural necrosis, secondary to side branch compromise and occlusion at implantation.[2 24–27] These findings again were not apparent within the present study, where comparable incidences of in-hospital MI and MACE were evident (table 2).

Mechanisms to explain the safety of newer generation DES are fourfold. First, is the more biocompatible, biostable polymer coatings of newer generation DES, leading to a substantially attenuated arterial inflammatory response of a shorter duration compared to first generation DES.[1 28 29] Within the overlap of first generation DES, the increased density of polymer has been implicated in exacerbating this inflammatory response and subsequent risk of delayed endothelialisation.[1 29] Subsequent animal and clinical studies have associated newer generation DES with a limited, transient inflammatory response, and a considerably lower rate of uncovered struts, with consequent improved clinical outcomes when compared to first generation DES.[8 30–33]

Second, is the introduction of limus-based drugs, and the adaption of the antiproliferative drug dose and polymer drug release kinetics leading to the appropriate balance between adequate neointimal suppression and strut coverage.[34–37] Specifically for the R-ZES device, the 'BioLinx' polymer (Medtronic, Santa Rosa, California, USA) comprises three different polymers that allows for a slow, sustained release of the antiproliferative drug zotarolimus (85% of drug within 60 days and the remainder within 180 days), substantially improved biocompatibility which minimises fibrin deposition and stent thrombogenicity, and

Table 2 In-hospital, 30-day and 2-year clinical outcomes of overlapping R-ZES/DES versus non-overlapping R-ZES in the International Global RESOLUTE Program (n=5130)

Safety and effectiveness endpoints	Overlapping R-ZES/DES (n=644 patients, n=1044 lesions)	Non-overlapping R-ZES (n=4486 patients, n=5814 lesions)	Unadjusted p value	Adjusted p value*
In-hospital clinical outcomes (n=5130)				
Target lesion failure (TLF)†	3.4% (22/644)	2.4% (107/4486)	0.14	0.32
Target vessel failure (TVF)‡	3.4% (22/644)	2.4% (108/4486)	0.14	0.33
Major adverse cardiac events (MACE)§	3.4% (22/644)	2.5% (110/4486)	0.14	0.38
Cardiac death or target vessel myocardial infarction (TVMI)	3.0% (19/644)	2.2% (97/4486)	0.20	0.41
Death or TVMI	3.0% (19/644)	2.2% (98/4486)	0.26	0.42
Death	0.5% (3/644)	0.1% (5/4486)	0.068	0.25
Cardiac death	0.5% (3/644)	0.1% (4/4486)	0.047	0.23
Non-cardiac death	0.0% (0/644)	0.0% (1/4486)	1.00	0.39
Target vessel myocardial infarction (TVMI)	2.5% (16/644)	2.1% (94/4486)	0.56	0.66
Clinically driven target lesion revascularisation (TLR)	0.5% (3/644)	0.4% (17/4486)	0.73	0.99
Clinically driven target vessel revascularisation (TVR)	0.5% (3/644)	0.4% (19/4486)	0.75	0.91
Stent thrombosis (ARC definite/probable)	0.6% (4/644)	0.3% (12/4486)	0.13	0.31
30-day clinical outcomes (n=5130)				
Target lesion failure (TLF)†	4.2% (27/642)	2.8% (126/4473)	0.062	0.21
Target vessel failure (TVF)‡	4.7% (30/642)	2.9% (130/4473)	0.021	0.099
Major adverse cardiac events (MACE)§	4.2% (27/642)	2.9% (130/4473)	0.086	0.25
Cardiac death or target vessel myocardial infarction (TVMI)	3.6% (23/642)	2.5% (111/4473)	0.11	0.24
Death or TVMI	3.6% (23/642)	2.5% (112/4473)	0.11	0.24
Death	0.8% (5/642)	0.2% (9/4473)	0.023	0.22
Cardiac death	0.8% (5/642)	0.2% (8/4473)	0.017	0.21
Non-cardiac death	0.0% (0/642)	0.0% (1/4473)	1.00	0.39
Target vessel myocardial infarction (TVMI)	3.0% (19/642)	2.3% (105/4473)	0.34	0.37
Clinically driven target lesion revascularisation (TLR)	1.2% (8/642)	0.6% (29/4473)	0.13	0.21
Clinically driven target vessel revascularisation (TVR)	1.7% (11/642)	0.8% (35/4473)	0.040	0.078
Stent thrombosis (ARC definite/probable)	1.1% (7/642)	0.5% (23/4473)	0.091	0.24
2-year clinical outcomes (n=5130)				
Target lesion failure (TLF)†	10.9% (69/633)	9.0% (396/4381)	0.14	0.41
Target vessel failure (TVF)‡	12.8% (81/633)	10.6% (466/4381)	0.12	0.25
Major adverse cardiac events (MACE)§	13.3% (84/633)	10.7% (469/4381)	0.057	0.19
Cardiac death or TVMI	6.6% (42/633)	5.2% (228/4381)	0.16	0.25
Death or TVMI	8.7% (55/633)	6.6% (287/4381)	0.052	0.10
Death	5.1% (32/633)	3.5% (153/4381)	0.055	0.13
Cardiac death	3.0% (19/633)	2.1% (93/4381)	0.19	0.36
Non-cardiac death	2.1% (13/633)	1.4% (60/4381)	0.21	0.21
TVMI (extended historical definition)	3.9% (25/633)	3.4% (148/4381)	0.48	0.40
Clinically driven TLR	5.7% (36/633)	4.6% (201/4381)	0.23	0.48
Clinically driven TVR	7.7% (49/633)	6.5% (285/4381)	0.23	0.32
Stent thrombosis (ARC definite/probable)	1.4% (9/633)	0.9% (38/4381)	0.18	0.28

Unadjusted and adjusted p values are shown.
*p Value adjusted to propensity score.
†TLF: cardiac death, TVMI (Q wave and non Q wave) or clinically driven target lesion revascularisation (TLR) by percutaneous or surgical methods.
‡TVF: cardiac death, target vessel myocardial infarction or clinically driven target vessel revascularisation.
§MACE: death, myocardial infarction (Q wave and non Q-wave), emergent coronary bypass surgery, or repeat target lesion revascularisation (TLR) (clinically driven/clinically indicated) by percutaneous or surgical methods.
ARC, Academic Research Consortium (ARC) criteria[21]; ACC/AHA, American College of Cardiology/American Heart Association lesion characteristics[23]; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; DES, drug eluting stent; MI, myocardial infarction; MLD, minimum lumen diameter; RVD, reference vessel diameter; TIMI, thrombolysis in myocardial infarction; TVMI, target vessel myocardial infarction; ZES, zotarolimus-eluting stent.

thereby allows for a substantial reduction in the inflammatory reaction and a faster neointimal healing response.[33 38]

Third, is the reduced strut thickness of newer generation DES. For example, the R-ZES has a strut thickness of 97 μm, compared to the first generation DES of approximately 150 μm (TAXUS Express ~148 μm, CYPHER ~154 μm). Reduced strut thickness has not only been implicated in reduced incidence of restenosis in the bare metal stent (BMS) and DES era,[34 39–41] but also in more rapid strut coverage, particularly in overlapping devices, probably in part related to the role of wall shear stress in modulating the neointimal response.[8 42] Further evidence to support these findings comes from a preclinical (porcine) study[8] comparing overlapping bioresorbable scaffolds[43 44] against overlapping Xience V EES. The increased strut thickness of the bioresorbable scaffold (approximately 150 μm) was implicated in delaying coverage in overlapping devices at 28 days but not 90 days (equivalent to approximately 6

Table 3 Thirteen-month angiographic outcomes of overlapping drug eluting stents (DES) compared to non-overlapping DES (resolute zotarolimus-eluting stent and everolimus-eluting stents) in the RESOLUTE All-Comers Trial; lesion level data is shown (n=459)

	Overlapping DES† (n=92 lesions)	Non-overlapping DES† (n=367 lesions)	Unadjusted p value	Adjusted p value*
In segment				
RVD (mm)	2.54±0.60 (64)	2.76±0.54 (308)	0.004	0.94
MLD (mm)	1.83±0.69 (66)	2.05±0.55 (311)	0.005	0.93
% Diameter stenosis‡	28.4±17.7 (66)	25.5±13.7 (311)	0.14	0.96
In stent				
MLD (mm)	1.98±0.69 (66)	2.26±0.57 (311)	<0.001	0.84
% Diameter stenosis‡	25.2±17.4 (66)	19.8±13.7 (311)	0.006	0.75
Proximal edge				
MLD (mm)	2.27±0.85 (46)	2.48±0.65 (226)	0.061	0.78
% Diameter stenosis‡	22.3±22.0 (46)	16.5±15.8 (226)	0.033	0.88
Distal edge				
MLD (mm)	1.96±0.67 (65)	2.25±0.61 (301)	<0.001	0.92
% Diameter stenosis‡	22.7±17.3 (65)	17.6±12.9 (301)	0.007	0.98
Binary restenosis§				
In-segment	9.1% (6/66)	5.1% (16/311)	0.24	0.73
In-stent	6.1% (4/66)	3.5% (11/311)	0.31	0.78
Proximal edge	8.7% (4/46)	3.5% (8/226)	0.13	0.82
Distal edge	3.1% (2/65)	1.3% (4/301)	0.29	0.82
Late lumen loss¶ (mm)				
In-segment	0.12±0.50 (64)	0.10±0.40 (296)	0.74	0.97
In-stent	0.29±0.51 (64)	0.21±0.39 (296)	0.16	1.00
Proximal edge	0.15±0.56 (42)	0.07±0.42 (208)	0.26	0.99
Distal edge	0.06±0.48 (63)	−0.01±0.38 (284)	0.19	0.82

*p Value adjusted to propensity score.
†Overlapping Resolute zotarolimus-eluting stent or overlapping everolimus-eluting stent.
‡Percentage diameter stenosis: difference between the reference vessel diameter and minimal lumen diameter/reference vessel diameter ×100).
§Binary restenosis: 50% or greater stenosis in the target lesion or segment at angiographic follow-up.
¶Late lumen loss: difference between the post-procedure and follow-up minimal lumen diameter.
MLD, minimum lumen diameter; PCI, percutaneous coronary intervention; RVD, reference vessel diameter.

and 18 months, respectively, in humans[9]). Conversely complete coverage was seen with the overlapping Xience V EES (strut thickness approximately 89 μm) at 28 days. These findings were likely to be related to the increased strut thickness of the bioresorbable scaffold, since it has a biocompatible polymer and drug release kinetics that are similar to the Xience V EES.[8]

Fourth, that first generation DES—namely PES—have previously been demonstrated to be an independent predictor of small side branch occlusion in two post hoc angiographic studies comparing PES implantation to the thinner strut ZES (previous generation to the R-ZES) and EES.[45 46] The mechanism is likely to be related to the increased strut thickness of the PES (approximately 148 μm), whereas the thinner strut R-ZES or EES were not associated with any increase risk of peri-procedural MACE or MI.[45 46] This phenomenon has also been reported with the thicker strut bioresorbable scaffold, where a higher incidence of post-procedural small side branch occlusion was reported, compared to the Xience V EES.[47]

Clinical implications

Achieving the balance between avoiding excessive stenting and leaving a flow-limiting edge dissection after stenting is an issue the interventional cardiologist is often faced with.[48 49] The results of this study imply that overlapping newer generation DES is safe and effective, contrary to findings with first generation DES where it was shown to lead to adverse angiographic and clinical outcomes (including mortality).[5] This may therefore potentially allow the interventional cardiologist to judge to limit stent length in order to cover a lesion, with the knowledge that overlapping the device if needed for bailout purposes, would not have a negative impact on clinical and angiographic outcomes.

LIMITATIONS

Although statistical adjustments (propensity score matching) were used to ensure optimal control of significant confounding factors in the present study, the small potential remains for any unmeasured confounders to have influenced the study findings. The study protocol and eCRF in the Global RESOLUTE Program did not specify the type of DES the R-ZES could be overlapped with. Consequently, the possibility of the R-ZES being overlapped with a first generation DES cannot be excluded. Since clinical outcomes were comparable between overlapping R-ZES/DES and the non-overlap, the clinical effects of this limitation are negligible.

The other limitation of the study is the lack of intravascular imaging. Consequently, the possibility of an increase in arterial/neointimal response at the overlap with newer generation DES cannot be excluded. Within the OCT substudy of the RESOLUTE All-Comers Trial,[33] overlapping segments of R-ZES (n=11 lesions) were associated with a numerically higher percentage volume obstruction compared to non-overlap (n=50 lesions) segments (% volume obstruction 16.0±12.3% vs 12.5±7.9%, respectively). This however did not translate into any increase in clinical events—including repeat revascularisation—at the overlap, as shown in the present study.

CONCLUSION

Overlapping newer generation DES are safe and effective, with comparable angiographic and clinical outcomes—including repeat revascularisation—to non-overlapping DES. Although the possibility of an increased neointimal response at the overlap

cannot be excluded in the present study, this was not clinically relevant at up to 2 years' follow-up.

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Heart

Impact of overlapping newer generation drug-eluting stents on clinical and angiographic outcomes: pooled analysis of five trials from the international Global RESOLUTE Program

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