Unrestricted randomised use of two new generation drug-eluting coronary stents: 2-year patient-related versus stent-related outcomes from the RESOLUTE All Comers trial

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Summary

Background In the RESOLUTE All Comers trial, the Resolute zotarolimus-eluting stent was non-inferior to the Xience V everolimus-eluting stent for the primary stent-related endpoint of target lesion failure (cardiac death, target vessel myocardial infarction, and ischaemia-driven target lesion revascularisation) at 1 year. However, data for long-term safety and efficacy from randomised studies of new generation drug-eluting coronary stents in patients treated in routine clinical practice are scarce. We report the prespecified 2-year clinical outcomes from the RESOLUTE All Comers trial.

Methods In 2008, patients with at least one coronary lesion 2·25–4·0 mm in diameter, with greater than 50% stenosis, were randomly assigned to a Resolute zotarolimus-eluting stent or a Xience V everolimus-eluting stent at 17 centres in Europe and Israel. Randomisation was by an interactive voice response system stratified by centre. Study investigators were not masked to treatment allocation; but those who did data management and analysis, and patients were masked. There were no restrictions as to the number of vessels or lesions treated, or the number of stents implanted. We assessed prespecified safety and efficacy outcomes at 2 years with specific focus on patient-related composite (all death, all myocardial infarction, all revascularisation) and stent-related composite outcomes. Analyses were by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00617084.

Findings 1140 patients were assigned to the zotarolimus-eluting stent and 1152 to the everolimus-eluting stent; 1121 and 1128 patients, respectively, completed 2-year follow-up. The patient-related outcome (231 [20·6%] zotarolimus *vs* 231 [20·5%] everolimus; difference 0·1%, 95% CI −3·2 to 3·5; p=0·958) and stent-related outcome (126 [11·2%] *vs* 121 [10·7%]; difference 0·5%, −2·1 to 3·1; p=0·736) did not differ between groups, although rates of the stent-related outcome were substantially lower than were those for the patient-related outcome. Three patients in each group (0·3%) had very late (after 1 year) stent thrombosis.

Interpretation Similar safety and efficacy outcomes were sustained between two new generation drug-eluting stents at 2-year follow-up. The greater number of patient-related than stent-related events in patients with complex clinical and lesion characteristics emphasises that during long-term follow-up, the optimisation of secondary prevention is at least as important as the selection of which new generation drug-eluting stent to implant in a specific lesion.

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Introduction

Early generation drug-eluting stents were better than bare-metal stents in reducing the need for repeat revascularisation for the treatment of obstructive coronary artery disease.[1,2] However, much of this initial evidence was based on patients with single, uncomplicated lesions and without serious comorbidities.[1–3] Over time, their use extended to patients with more complex lesions and clinical characteristics.[3] In 2006, after concerns about late (after 30 days) and very late (after 1 year) safety outcomes, the US Food and Drug Administration convened a special assembly of the Circulatory System Device Panel and concluded that the use of drug-eluting stents in study-defined patient cohorts did not increase risk of death or myocardial infarction.[4] Additionally, the Panel noted that data were insufficient in patients with more complex lesions and recommended that trials of drug-eluting stents should study patients with characteristics more likely to be encountered in routine clinical practice.[3,4] These patients often have an increased risk of adverse events when presenting with acute coronary syndromes in the presence of complex comorbidities such as diabetes mellitus and renal failure. Therefore, study endpoints should focus not only on stent-related parameters but also measure patient-related events to improve assessment of overall cardiovascular outcomes.[5]

At the same time, new stent technologies were developed with modified stent designs, improved delivery systems, altered polymers, and new drugs,[6] subsequently leading to the use of these new generation drug-eluting stents in patients with more challenging characteristics who more closely resemble those treated in routine clinical practice.

RESOLUTE All Comers was a randomised controlled trial to compare two new generation drug-eluting stents

in an unrestricted patient population. The Resolute zotarolimus-eluting stent (Medtronic, Santa Rosa, CA, USA) was non-inferior to the Xience V everolimus-eluting stent (Abbott Vascular, Santa Clara, CA, USA) for the primary composite stent-related endpoint of target lesion failure at 1 year.[7] Whether the similarity between these two stents is sustained beyond 1 year is unknown. We report the prespecified 2-year clinical outcomes from the RESOLUTE All Comers trial with specific focus on patient-related and stent-related outcomes.

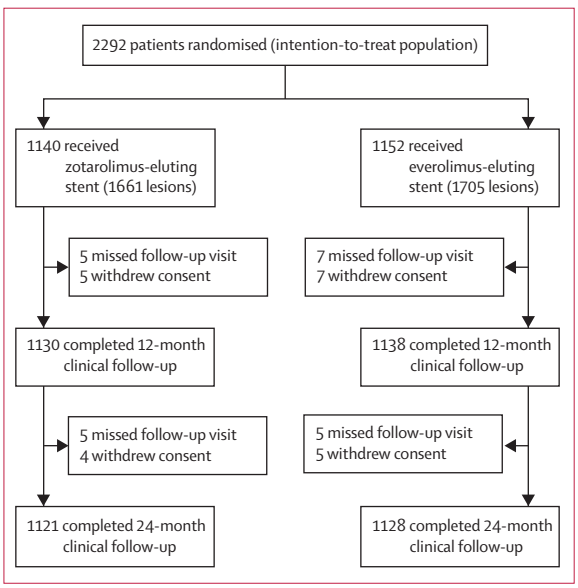


Figure 1: **Trial profile**

See Online for webappendix

	Zotarolimus-eluting stent (N=1140)	Everolimus-eluting stent (N=1152)
Age (years)	64·4 (10·9)	64·2 (10·8)
Men	874 (76·7%)	889 (77·2%)
Diabetes mellitus	268 (23·5%)	270 (23·4%)
Insulin treated	96 (8·4%)	82 (7·1%)
Hypertension	811 (71·1%)	821 (71·3%)
Hyperlipidaemia	730 (64·0%)	780 (67·7%)
Current smoker	302 (26·5%)	305 (26·5%)
Previous myocardial infarction*	323 (28·8%)	341 (30·4%)
Acute myocardial infarction (within 72 h)	330 (28·9%)	332 (28·8%)
Stable angina	382 (33·5%)	416 (36·1%)
Unstable angina	221 (19·4%)	218 (18·9%)
Left ventricular ejection fraction <30%†	17 (2·8%)	13 (2·1%)
SYNTAX score‡	14·8 (9·3)	14·6 (9·2)
Complex§	764 (67·0%)	756 (65·6%)
Target vessel		
Left main	25 (2·2%)	29 (2·5%)
Left anterior descending	600 (52·6%)	560 (48·6%)
Left circumflex	376 (33·0%)	379 (32·9%)
Right coronary	425 (37·3%)	476 (41·3%)
Bypass graft	28 (2·5%)	28 (2·4%)
Stents per patient¶	1·9 (1·2)	2·0 (1·3)
Total stent length (mm)¶	34·4 (24·5)	37·0 (26·5)
Reference vessel diameter (mm)	2·63 (0·57)	2·63 (0·58)

Data are mean (SD) or number (%). *Data available for 1122 patients in the zotarolimus group and 1120 in the everolimus group. †Data available for 610 patients in the zotarolimus group and 608 in the everolimus group. ‡Data available for 1008 patients in the zotarolimus group and 1025 in the everolimus group. §See methods section for definition. ¶Patient level.

Table 1: **Baseline patient and lesion characteristics at 2 years**

Methods

Study design and patients

The design, detailed methods, and endpoint definitions of the RESOLUTE All Comers trial have been previously described.[7] Briefly, the RESOLUTE All Comers trial is a prospective, randomised, single-blind, non-inferiority study in which patients with chronic stable angina, or acute coronary syndromes who qualified for percutaneous coronary intervention, were recruited from 17 centres in Europe and Israel (webappendix). Patients were enrolled between April 30, 2008, and Oct 28, 2008. Final 5-year follow-up is expected in November, 2013, with available data anticipated from January, 2014. Eligible patients had at least one coronary artery stenosis greater than 50% with a reference diameter of 2·25–4·0 mm by visual estimation. Key exclusion criteria were limited to study medication intolerance, stent component allergies, or necessary surgery within the 6 months after the index procedure. There were no restrictions as to the number, severity, or location of lesions, or number of stents used. Patients who met all eligibility criteria, and for whom written informed consent was obtained, were randomly assigned to receive either the Resolute zotarolimus-eluting stent or the Xience V everolimus-eluting stent. Randomisation was by an interactive voice response system stratified by centre. Study investigators were not masked to treatment allocation; however, those who did data management and analysis, and patients were masked.

Every centre's ethics committee approved the study protocol, all patients signed informed consent before intervention, and this study complied with the declaration of Helsinki. All case report forms were verified at the study site by an independent monitoring provider (Premier Research Group, Yverdon, Switzerland).

Study endpoints and procedures

The primary trial endpoint was stent-related target lesion failure, a composite of cardiac death, target vessel myocardial infarction, or ischaemia-driven target lesion revascularisation at 1 year. Any death of unknown cause was classified as cardiac. Secondary endpoints included the 2-year outcomes for the composite endpoints of target lesion failure, and the patient-related endpoint, including all deaths, all myocardial infarctions (Q wave or non-Q wave), and any revascularisation. Any revascularisation included all target lesion revascularisation (ischaemia-driven and non-ischaemia-driven), all target vessel revascularisation (ischaemia-driven and non-ischaemia-driven), and any non-target vessel

revascularisation by percutaneous or surgical means. Additional secondary endpoints included the composite major adverse cardiac events (any death, any myocardial infarction, emergent coronary bypass surgery, and any target lesion revascularisation); and definite, probable, possible, and overall stent thrombosis. Stent thrombosis was classified according to the Academic Research Consortium (ARC) definition.[5]

Patients with complex lesions were defined as having at least one of the following characteristics: serum creatinine concentration of 140 µmol/L or more; left ventricular ejection fraction less than 30%; an acute myocardial infarction within the previous 72 h; more than one lesion per vessel; two or more vessels treated with a stent; a lesion longer than 27 mm; or bifurcation, bypass graft, in-stent restenosis, unprotected left main coronary artery, presence of thrombus, or total occlusion. A complete list of study-related definitions has been previously published.[7]

All patients were prescribed lifelong daily aspirin (≥75 mg) and daily clopidogrel (75 mg) for at least 6 months. Follow-up was done in clinic at 30 days and 1 year, and by telephone at 2 years, which will be repeated every year for 5 years. An independent Clinical Events Committee, consisting of members masked to treatment assignments for the duration of the trial, adjudicated all clinical events for analysis.

Statistical analysis

All analyses were done by intention to treat. Published studies[8,9] that included an unrestricted patient population provided the basis for a predicted 1-year rate for the stent-related endpoint (target lesion failure) of 8% for both treatment groups. On the basis of a non-inferiority margin of 0·035 (3·5%) as the acceptable difference between the two groups to declare the zotarolimus-eluting stent to be non-inferior to the everolimus-eluting stent, and with a one-sided type I error of 0·05, 2300 patients (1150 patients in each group) would yield at least 90% power to detect non-inferiority.[10]

Categorical variables were reported as numbers and percentages of patients, and continuous variables as means and SD. Differences between treatment groups with 95% CIs and p values, on the basis of the Fisher's exact test for categorical outcomes, and two-sample *t* test for continuous outcomes are reported. Time-to-event analysis was assessed with the Kaplan-Meier method, with differences between groups compared with the log-rank test. A two-sided p value of less than 0·05 was regarded as significant.

This study is registered with ClinicalTrials.gov, number NCT00617084.

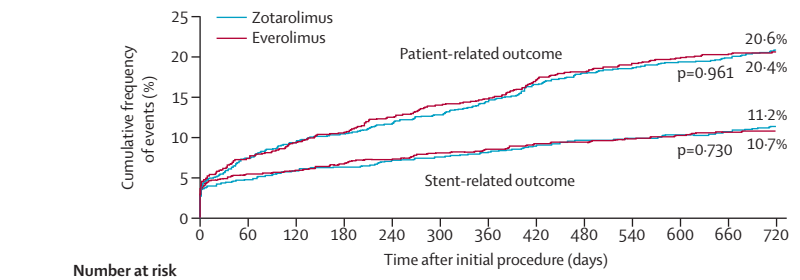
	Zotarolimus-eluting stent (N=1121)	Everolimus-eluting stent (N=1128)	Difference (95% CI)	p value
Patient-related outcome*	231 (20·6%)	231 (20·5%)	0·1% (–3·2 to 3·5)	0·958
Stent-related outcome†	126 (11·2%)	121 (10·7%)	0·5% (–2·1 to 3·1)	0·736
Any death	36 (3·2%)	45 (4·0%)	–0·8% (–2·3 to 0·8)	0·366
Cardiac death	29 (2·6%)	25 (2·2%)	0·4% (–0·9 to 1·6)	0·584
Any MI‡	62 (5·5%)	56 (5·0%)	0·6% (–1·3 to 2·4)	0·571
Q wave	15 (1·3%)	7 (0·6%)	0·7% (–0·1 to 1·5)	0·091
Non-Q wave	48 (4·3%)	49 (4·3%)	–0·1% (–1·7 to 1·6)	1·000
Target-vessel MI‡	53 (4·7%)	51 (4·5%)	0·2% (–1·5 to 1·9)	0·841
Q wave	11 (1·0%)	6 (0·5%)	0·4% (–0·3 to 1·2)	0·235
Non-Q wave	43 (3·8%)	45 (4·0%)	–0·2% (–1·8 to 1·4)	0·914
Non-target-vessel MI‡	10 (0·9%)	5 (0·4%)	0·4% (–0·2 to 1·1)	0·207
Q wave	4 (0·4%)	1 (0·1%)	0·3% (–0·1 to 0·7)	0·217
Non-Q wave	6 (0·5%)	4 (0·4%)	0·2% (–0·4 to 0·7)	0·547
Cardiac death or target-vessel MI‡	78 (7·0%)	71 (6·3%)	0·7% (–1·4 to 2·7)	0·553
Any death or any MI‡	93 (8·3%)	95 (8·4%)	–0·1% (–2·4 to 2·2)	0·939
All revascularisations	174 (15·5%)	156 (13·8%)	1·7% (–1·2 to 4·6)	0·258
Re-PCI	156 (13·9%)	139 (12·3%)	1·6% (–1·2 to 4·4)	0·288
CABG	27 (2·4%)	22 (2·0%)	0·5% (–0·7 to 1·7)	0·474
Ischaemia-driven TLR	64 (5·7%)	58 (5·1%)	0·6% (–1·3 to 2·4)	0·577
Re-PCI	56 (5·0%)	48 (4·3%)	0·7% (–1·0 to 2·5)	0·423
CABG	12 (1·1%)	12 (1·1%)	0·0% (–0·8 to 0·9)	1·000
Non-ischaemia-driven TLR	26 (2·3%)	25 (2·2%)	0·1% (–1·1 to 1·3)	0·888
Re-PCI	22 (2·0%)	23 (2·0%)	–0·1% (–1·2 to 1·1)	1·000
CABG	4 (0·4%)	2 (0·2%)	0·2% (–0·2 to 0·6)	0·451
Target-vessel revascularisation	112 (10·0%)	103 (9·1%)	0·9% (–1·6 to 3·3)	0·519
Re-PCI	99 (8·8%)	90 (8·0%)	0·9% (–1·4 to 3·1)	0·494
CABG	18 (1·6%)	18 (1·6%)	0·0% (–1·0 to 1·0)	1·000
Non-target-vessel revascularisation	87 (7·8%)	84 (7·4%)	0·3% (–1·9 to 2·5)	0·812
Re-PCI	73 (6·5%)	68 (6·0%)	0·5% (–1·5 to 2·5)	0·664
CABG	19 (1·7%)	17 (1·5%)	0·2% (–0·8 to 1·2)	0·740
Target-vessel failure§	141 (12·6%)	138 (12·2%)	0·3% (–2·4 to 3·1)	0·848
Major adverse cardiac events¶	140 (12·5%)	146 (12·9%)	–0·5% (–3·2 to 2·3)	0·752
ARC definite and probable stent thrombosis	21 (1·9%)	11 (1·0%)	0·9% (–0·1 to 1·9)	0·077
Early (0–30 days)‖**	12 (1·1%)	6 (0·5%)	0·5% (–0·2 to 1·3)	0·164
Late (31–360 days)**	7 (0·6%)	2 (0·2%)	0·4% (–0·1 to 1·0)	0·108
Very late (361–720 days)	3 (0·3%)	3 (0·3%)	0·0% (–0·4 to 0·4)	1·000
ARC definite and probable stent thrombosis and any death	53 (4·7%)	52 (4·6%)	0·1% (–1·6 to 1·9)	0·921

Data are number (%), unless otherwise indicated. MI=myocardial infarction. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. TLR=target lesion revascularisation. ARC=Academic Research Consortium. *Patient-related outcome included any death, any MI, or any revascularisation. †Stent-related outcome (target lesion failure) included cardiac death, target-vessel MI, or ischaemia-driven TLR. ‡Medtronic extended historical definition. §Target-vessel failure included cardiac death, target vessel MI, or ischaemia-driven target-vessel revascularisation. ¶Major adverse cardiac events included any death, Q wave or non-Q wave MI, emergent coronary bypass surgery, or repeat TLR (ischaemia-driven) by percutaneous or surgical methods. ‖One patient in the zotarolimus group had a probable stent thrombosis event on day 0 and a definite stent thrombosis event on day 5. **One patient in the zotarolimus group had a definite stent thrombosis event on day 4 and day 31.

Table 2: **Overall patient-related and stent-related composite and detailed clinical outcomes at 2 years**

Role of the funding source

The sponsor of the study participated in the trial design and aided in the management of data collection. The sponsor funded an independent data management and analysis centre (Cardialysis, Rotterdam, Netherlands) for database management and all statistical analyses, and an independent provider to perform study site monitoring (Premier Research Group, Yverdon,



Number at risk													
Patient-related outcome													
Zotarolimus	1140	1109	1049	1025	1014	998	987	966	936	921	913	904	898
Everolimus	1152	1118	1059	1038	1023	997	979	967	935	923	911	903	898
Stent-related outcome													
Zotarolimus	1140	1110	1076	1062	1058	1046	1041	1033	1016	1008	1004	998	992
Everolimus	1152	1121	1079	1073	1061	1048	1036	1026	1009	1005	998	992	986

***Figure 2*: Cumulative frequency of patient-related and stent-related* outcomes up to 2 years**
The difference between patient-related and stent-related outcomes continues to diverge over time. *Target lesion failure.

	Days after procedure	Clinical event	Antiplatelet drug at event
Zotarolimus-eluting stent			
Probable	376	MI	Aspirin; clopidogrel stopped same month as event
Definite	572	MI, TLR	Aspirin and clopidogrel
Definite	656	Q-wave MI, TLR	Aspirin; clopidogrel stopped 16 months before event
Everolimus-eluting stent			
Definite	408	TLR	Aspirin and clopidogrel
Definite	486	TLR	Aspirin; clopidogrel stopped 3 months before event
Definite	613	MI, TLR	Aspirin; clopidogrel stopped 7 months before event

ARC=Academic Research Consortium. MI=myocardial infarction. TLR=target lesion revascularisation.

***Table 3*: Timing and event details for the six patients who had an ARC definite or probable stent thrombosis event in year 2**

Switzerland). All authors had full access to the study data. The corresponding author had full responsibility for the decision to submit the report for publication.

Results

2292 patients were enrolled and randomly assigned to treatment with the zotarolimus-eluting stent (n=1140) or the everolimus-eluting stent (n=1152). 1121 (98·3%) of zotarolimus patients and 1128 (97·9%) of everolimus patients completed follow-up at 2 years (figure 1). Table 1 summarises the baseline demographics and the clinical and angiographic characteristics of all patients.

At 2 years, a patient-related outcome occurred in 231 patients in each group (table 2); the number of stent-related outcomes events was substantially lower, but did not differ between groups (table 2). Kaplan-Meier analyses showed no differences between the two groups in the incidence of patient-related or stent-related endpoints (figure 2). Furthermore, we noted no differences between the two stent groups for any major clinical event (table 2).

1520 of 2292 (66·3%) patients were classified as complex (table 1). At 2 years, the zotarolimus and everolimus patient groups had similar outcomes irrespective of complexity. For the complex group, a patient-related outcome occurred in 162 of 752 (21·5%) patients in the zotarolimus group versus 166 of 738 (22·5%) in the everolimus group (difference –1·0%, 95% CI –5·2 to 3·3; p=0·662) and stent-related outcomes in 91 of 752 (12·1%) versus 93 of 738 (12·6%) patients (difference –0·5, –3·8 to 2·8; p=0·813). For the simple group (patients not meeting complex criteria), patient-related outcomes occurred in 69 of 369 (18·7%) patients in the zotarolimus group versus 65 of 390 (16·7%) in the everolimus group (difference 2·0%, –3·4 to 7·4%; p=0·505) and stent-related outcomes in 35 of 369 (9·5%) versus 28 of 390 (7·2%) patients (difference 2·3%, –1·6 to 6·2; p=0·293).

At 1 year, 933 of 1110 (84·1%) patients in the zotarolimus group and 929 of 1108 (83·8%) in the everolimus group were taking dual antiplatelet therapy (p=0·908). After 2 years, 201 of 1080 (18·6%) zotarolimus patients and 195 of 1076 (18·1%) everolimus patients were still on dual antiplatelet therapy (p=0·781). Three patients in each group (0·3% for both) had an ARC definite or probable stent thrombosis event during the second year (ie, very late stent thrombosis), with no associated mortality (table 3, figure 3).

Discussion

The RESOLUTE All Comers trial compared two new generation drug-eluting stents: the Resolute zotarolimus-eluting and the Xience V everolimus-eluting stents. The safety and efficacy of these two drug-eluting stents are clinically equivalent, even after 2 years in a mostly complex population. Our results accord with two post-hoc analyses[11,12] showing similar clinical outcomes between the two stents irrespective of complexity. Between year 1 and 2, six patients (three in each group) had an ARC definite or probable stent thrombosis, representing a very late stent thrombosis rate of 0·3% for each stent group (figure 3, tables 2 and 3).

The multicentre LEADERS trial[13,14] showed that over 3 years there is an increasing divergence in outcomes between early generation and new generation drug-eluting stents, in favour of the new stent. The same finding was detected in the single-centre COMPARE trial[15] that also compared a new generation drug-eluting stent with an early generation drug-eluting stent. Thus, LEADERS, COMPARE, and now the RESOLUTE All Comers trials suggest that new generation drug-eluting stents help to improve clinically important outcomes, especially in complex patient and lesion subsets (panel).[13–16] Our results are not comparable with the SORT OUT III study,[17] which compared an earlier generation zotarolimus-eluting stent (Endeavor, Medtronic) with an

early generation sirolimus-eluting stent, although as in our study the patient population was unrestricted. The Resolute zotarolimus-eluting stent is similar to its predecessor (Endeavor), but the drug release is sustained over a longer period (180 days *vs* 14 days).[18,19]

Composite endpoints in cardiovascular trials include a wide range of events, from patient-related death from any cause to so-called pure stent-related events, such as stent thrombosis. Comparison of composite endpoints can be difficult because of the lack of consensus definitions, and overlap between composite endpoint components. The difference between the patient-related and stent-related outcomes from the RESOLUTE All Comers trial included any non-cardiac death, any myocardial infarction not related to the target vessel, and any revascularisations not related to the target vessel. The differences between stent-related and patient-related events can be regarded as more indicative of the patients' underlying global disease,[20] rather than related to the specific localised coronary obstruction treated with the study stents. One example of the differences between patient-related and stent-related outcomes is shown by analysis of the mortality rates from our study: of 16 non-cardiovascular deaths, 13 were due to various carcinomas (three in zotarolimus group; ten in everolimus group), contributing to a substantial difference between patient-related and stent-related outcomes (table 2, figure 2). Any death of unknown cause was by default classified as a cardiac death, even if it was a non-cardiac death.

We recorded a substantial and surprisingly high numerical difference between patient-related and stent-related outcomes, with an approximate doubling of event rates for patient-related outcomes (table 2, figure 2). This finding emphasises the importance of stent-independent comorbidities in consideration of the prognosis of patients indicated for percutaneous coronary intervention with stenting, because these comorbidities exacerbate the underlying lesion-related coronary artery disease over time. Drug-eluting stents are able to perform the function for which they are designed; however, the patient's underlying disease affects long-term outcomes to a greater extent than does the need for repeat revascularisation or stent thrombosis of the initially treated lesion (figure 2). Thus, optimisation of secondary prevention and overall medical management during long-term follow-up seems to be more important than the initial choice between advanced, new generation drug-eluting stents. However, we should note that any comparisons between the stent-related and patient-related outcomes are hypothesis generating and were not prespecified. Our finding could be attributable to the pathophysiology of coronary artery disease, such that about half of the coronary events are attributable to so-called non-culprit lesions.[21]

Although drug-eluting stents do not generally increase mortality,[22] valid concerns about early (less than 30 days), late (31 days to 1 year), and very late (after 1 year) stent thrombosis persist. In our study, two patients (one in each group) with very late stent thrombosis were still on dual antiplatelet therapy (table 3). Overall, 18% of our patients were still on dual antiplatelet therapy after 2 years, compared with 13% from COMPARE[16] and 23% from LEADERS trials.[14] Although the rate of very late stent thrombosis of 0·3% recorded in our study is lower than the 0·6% per year described for early generation drug-eluting stents,[23] each very late stent thrombosis is a crucial event with potentially high mortality.[24] In our study, none of the six patients with very late stent thrombosis events died (table 3). We did not record any differences at 2 years between the two stent groups for any myocardial infarction or cardiac death (table 2). Despite the abundance of evidence supporting drug-eluting stents, whether prolonged dual antiplatelet use (beyond 12 months) can reduce the likelihood of very late stent thrombosis is unclear.[25]

Our analysis was limited to 2 years. This study's powered primary endpoint of stent-related target lesion failure outcome was at 1 year; however, the prespecified secondary endpoints included yearly reporting up to 5 years of all clinical outcomes, with each event adjudicated by the independent Clinical Events Committee. Since results of safety and efficacy of randomised trials can change substantially during long-term follow-up,[14,16,26] randomised trials of drug-eluting stents should report long-term follow-up results up to 5 years.[27]

An ideal study should include all patients presenting for percutaneous coronary intervention at the investigational

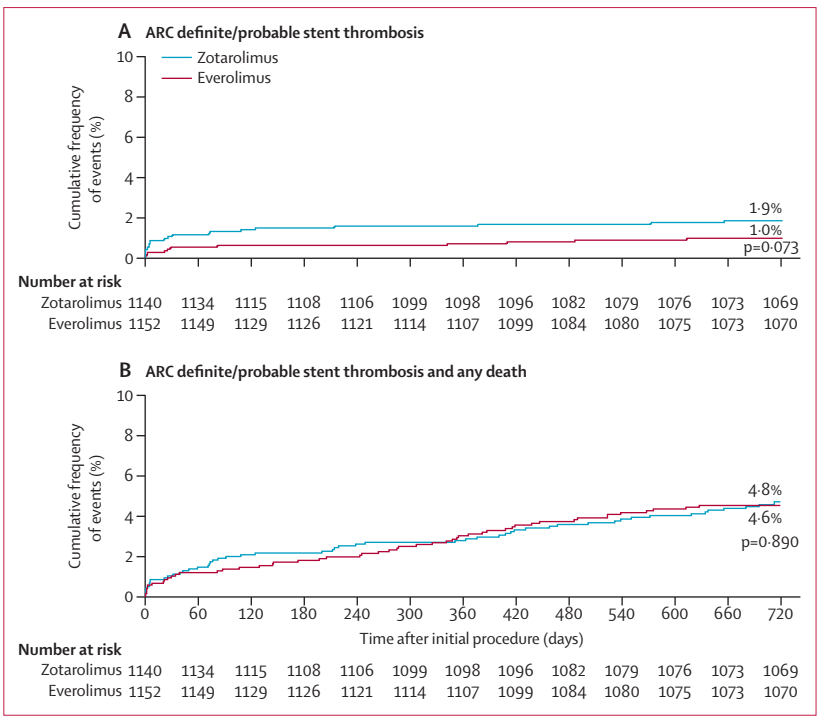


Figure 3: **Cumulative frequency of ARC definite and probable stent thrombosis (A), and composite of ARC definite and probable stent thrombosis and any death (B), up to 2 years**
ARC=Academic Research Consortium.

Panel: Research in context

Systematic review

We searched PubMed from January, 2007, to January, 2011, for complete reports of randomised trials comparing new generation drug-eluting stents with unrestricted use in all patient populations. We identified only the LEADERS and the COMPARE trials, which compared different generations of drug-eluting stents.

Interpretation

Our study showed that the two new generation Xience V and Resolute drug-eluting stents were clinically equivalent in all outcomes in a diverse patient population. When comparing the results from the RESOLUTE All Comers trial and the LEADERS and COMPARE trials, caution is needed. Nevertheless, we viewed target lesion revascularisation as representative of stent-related efficacy, and definite stent thrombosis as representative of stent-related safety (table 4). Keeping in mind the limitations of underpowered secondary endpoints of low frequency and of comparisons between studies, rates of stent thrombosis seem to be lower for the Xience V everolimus-eluting and the Resolute zotarolimus-eluting stents than for the other drug-eluting stents (table 4).[14,16] Furthermore, our study was unique in reporting patient-related versus stent-related outcomes, and draws attention to the importance of comprehensive patient management in the treatment of patients with drug-eluting stents for symptomatic coronary artery disease, especially after stenting procedures.

	Cypher sirolimus-eluting sent	Taxus paclitaxel-eluting stent	BioMatrix biolimus-eluting stent	Xience V everolimus-eluting stent	Resolute zotarolimus-eluting stent
TLR at 2 years	7·1%	5·9%	6·3%	5·1%	5·7%
Definite stent thrombosis at 2 years	2·5%	2·7%	2·2%	0·5%	1·3%

TLR represents stent-related efficacy; and definite (early, late, and very late) stent thrombosis represents stent-related safety. Data are from LEADERS,[14] COMPARE,[16] and RESOLUTE All Comers trials. TLR=target lesion revascularisation.

Table 4: **Stent-related efficacy and safety of early and new generation drug-eluting stents from randomised trials in unrestricted populations at 2 years**

sites; yet in our study, a mean of 44% of patients treated at the 17 centres were enrolled. This finding is consistent with enrolment percentages from the LEADERS study of 46%. There are many reasons why studies including unrestricted patient populations do not include all consecutive patients: many patients seen in routine practice are often too ill to be able to provide consent, are unable to fully comprehend the protocol within the given time, or refuse to participate. Furthermore, our patient group was probably not highly complex, as represented by a mean SYNTAX score of 15 compared with a mean score of 26 in the SYNTAX trial;[28] however, our patients were similar to those studied in the LEADERS study with a mean score of 14.[29]

Randomised trials are powered for their primary endpoints. Rare events such as very late stent thrombosis or death are clinically important events, yet to power studies for such rare events the number of patients needed to show even non-inferiority is unrealistic. Although the p value might be regarded as significant, the reported differences might still be a chance finding because of insufficient power. The difference in the rates of definite and probable stent thrombosis between the two stents at 1 year (zotarolimus 1·6%; everolimus 0·7%) was unchanged at 2 years (table 2, figure 3). Similarly, any differences in the rate of any death in year 1 (zotarolimus 1·6%; everolimus 2·8%) were balanced in year 2 (table 2). The cumulative incidence of the combined two rare events of definite and probable stent thrombosis and any death was 4·8% for the zotarolimus-eluting stent and 4·6% for the everolimus-eluting stent (table 2, figure 3).

Another limitation of this study was that we did not collect data for cardiovascular drugs, such as statin use, apart from dual antiplatelet therapy after the first year of follow-up; therefore we are not able to draw any associations between this important aspect of cardiac medical management and patient-related outcome. Therefore, more intense secondary prevention and overall medical management are at least as important as the device; and only stent-oriented pharmacological therapy might be insufficient for these complex patients.

Contributors

S Silber, P W Serruys, and S Windecker (the RESOLUTE All Comers Steering Committee) contributed to the design and execution of the trial. S Silber drafted the report, which was critically revised by S Windecker and P W Serruys. P Vranckx served as the chair of the Clinical Events Committee and critically revised this report. All authors approved the final report.

Conflicts of interest

S Silber has received research grants and lecture fees from Abbott Vascular, Boston Scientific, and Medtronic. S Windecker has received research grants, consultancy fees, and payment for lectures from Abbott, Biosensors, Boston Scientific, Cordis, and Medtronic. P Vranckx and P W Serruys declare that they have no conflicts of interest.

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