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Three-Year Clinical Outcome After Treatment of Chronic Total Occlusions with Second-Generation Drug-Eluting Stents in the TWENTE Trial

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Objective: To compare long-term outcome of patients treated for chronic total occlusion (CTO) lesions versus patients treated for non-CTO lesions only. Background: Percutaneous coronary interventions (PCI) for CTO lesions generally have a higher adverse event risk than PCI for non-CTO lesions. However, long-term outcome data from prospective studies with second-generation drug-eluting stent (DES) use in CTO lesions is scarce. Methods: We analyzed in this substudy of the TWENTE trial the data of 674 patients, who had stable angina and were electively treated with second-generation DES (Resolute zotarolimus-eluting or Xience V everolimus-eluting stents). Main outcome parameter was target lesion failure (TLF), a composite of cardiac death, target vessel-related myocardial infarction (MI), or target lesion revascularization (TLR). Results: Patients with CTO lesions ($n = 59$, 8.8%) were more often treated for lesions in small vessels (94.9% vs. 63.1%, $P < 0.001$), long lesions (52.5% vs. 17.7%, $P < 0.001$) and multiple vessels (42.4% vs. 22.4%, $P < 0.001$), and were less often males (62.7% vs. 74.6%, $P < 0.05$) than patients with non-CTO lesions ($n = 615$, 91.2%). J-CTO scores ≥ 2 were present in 56% of CTO lesions. Despite significant differences in characteristics of patients, lesions, and interventional procedures, the TLF rate at 3-year follow-up was similar for both groups (13.6% vs. 12.9%, $P = 0.89$). In addition, a patient-oriented composite endpoint (any death, MI or revascularization) did not differ between groups (18.6% vs. 18.8%, $P = 0.97$). Conclusion: Patients treated with second-generation DES for CTO lesions showed at 3-year follow-up an incidence of adverse clinical events that was low and similar to patients with non-CTO lesions only.

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Contributors: KGvH, HS, MKL, KT, MML, CJD, CvB developed the concept of the study. KGvH, HS, MKL, KT, MML, FHAFdM, JWL, MGS, MH, GCML, CvB acquired data. HS, CJMD performed the statistical analyses. KGvH, HS, MKL, KT, CvB interpreted the data. KGvH, HS, CvB drafted the manuscript. MKL, KT, MML, FHAFdM, JWL, MGS, MH, GCML, CD revised the manuscript for important intellectual content. CvB, CJD supervised the study. KGvH, HS, MKL, KT, MML, CJD, CvB had full access to all of the study data and take responsibility for the integrity of the data and the accuracy of the analysis.

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INTRODUCTION

As much as 6 to 10% of all patients who undergo percutaneous coronary interventions (PCI) require treatment of chronic total occlusion (CTO) lesions [1–3]. Following successful recanalization and treatment with bare metal stents, CTO lesions previously showed an increased risk of adverse clinical events as compared to non-CTO lesions [2]. First-generation drug-eluting stents (DES) that had been developed to reduce the need for repeat revascularization [4,5], lowered the rate of adverse clinical events in CTO lesions [6–8]. More recently, second-generation DES with more biocompatible, durable coatings have been developed [9–11] to reduce the risk of (very) late stent thrombosis, which was increased in first-generation DES [12–15]. The zotarolimus-eluting Resolute stent (Medtronic, Minneapolis, MN) and the everolimus-eluting Xience V stent (Abbott Vascular, Santa Clara, CA) are two such second-generation DES that have shown favorable results in the broad patient population of the prospective, randomized TWENTE trial [16].

Data to compare long-term outcome of patients treated with second-generation DES for CTO lesions versus non-CTO lesions are scarce. Available data are generally derived from registries that comprise mostly first-generation DES [17,18]. As treatment of a CTO lesion was traditionally a criterion for off-label DES use, only limited data on CTO treatment are available from prospective randomized studies. More recently, several investigator-initiated, randomized DES studies in broad patient populations and in all-comers liberally enrolled patients with various lesion types, including CTO lesions. Nevertheless, up to now, long-term data from prospective studies with second-generation DES use in CTO lesions are scarce.

We therefore analyzed in the present substudy of the TWENTE trial the data of 674 patients with stable angina, who underwent elective PCI with implantation of second-generation DES, and compared post hoc the 3-year clinical outcome of patients with treatment of at least one CTO lesion versus patients with treatment of non-CTO lesions only.

METHODS

Study Population, Design, and Procedures

We analyzed all 674 patients in the TWENTE trial (investigator-initiated, patient-blinded, randomized TWENTE trial (ClinicalTrial.gov NCT01066650), who (1) had stable angina and (2) underwent the PCI procedure in an elective setting. In this study population, target lesions were classified as CTO lesions in the presence of a total luminal obstruction with TIMI flow grade 0 within the occluded segment and a duration of the occlusion >3 months [19]. Details of the randomized TWENTE trial, which enrolled patients between June 18, 2008 and August 26, 2010 at Thoraxcentrum Twente in Enschede, the Netherlands, have previously been reported [16]. Interventional procedures with implantation of second-generation DES (Resolute zotarolimus-eluting or Xience V everolimus-eluting stents) were performed according to routine clinical protocols and current guidelines [16].

Dual anti-platelet therapy was prescribed for 12 months following PCI. The TWENTE trial complied with the Declaration of Helsinki for investigation in human beings and was approved by the institutional ethics committee. All patients provided written, informed consent for participation in the trial.

Monitoring, processing of adverse clinical event data, and the adjudication of adverse clinical events were independently performed by two Dutch contract research organizations (CRO Cardialysis, Rotterdam, and CRO Diagram, Zwolle). Angiographic analyses were performed offline at Thoraxcentrum Twente. An experienced interventional cardiologist and a clinical researcher (KGvH, HS) determined the J-CTO score, as previously described [20]. The J-CTO score predicts successful crossing of a guide wire within 30 min through a CTO lesion in a native coronary artery and classifies lesions into four groups with increasing difficulty of treatment: 0 = easy; 1 = intermediate; 2 = difficult; ≥3 = very difficult.

Definition of Clinical Endpoints

The definitions of clinical endpoints, which have previously been described [16], followed suggestions of the Academic Research Consortium (ARC) [21,22]. In brief, the main outcome parameter target lesion failure (TLF) was defined as a composite of cardiac death, target vessel-related myocardial infarction (MI), or clinically indicated target lesion revascularization (TLR). Death was considered cardiac, unless an unequivocal non-cardiac cause could be established. MI was defined by any creatine kinase concentration of more than double the upper limit of normal with

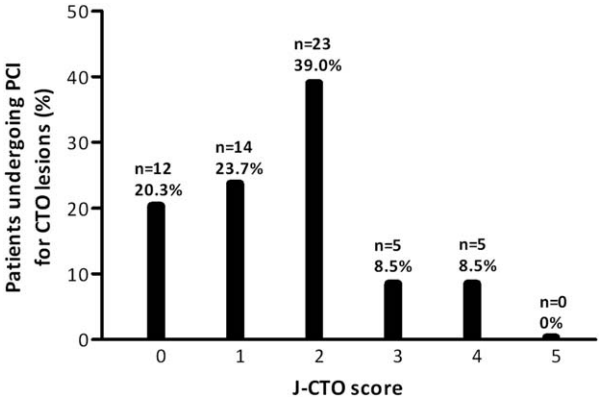

Fig. 1. J-CTO score of patients treated for CTO lesions. The J-CTO score predicts successful crossing of a guide wire within 30 minutes through a CTO lesion in a native coronary artery; lesions are classified into four groups with increasing difficulty of treatment (0 = easy; 1 = intermediate; 2 = difficult; ≥3 = very difficult) [20].

elevated confirmatory cardiac biomarker [22]. A target vessel-related MI was related to the target vessel or could not be related to another vessel. Target vessel revascularization (TVR) and TLR were considered clinically indicated if the angiographic diameter stenosis was ≥70%, or ≥50% in the presence of ischemic signs or symptoms [21]. Stent thrombosis was classified according to the ARC definitions [21]. In addition, we assessed these composite clinical endpoints: target vessel failure (TVF: cardiac death, target vessel-related MI, or clinically indicated TVR); major adverse cardiac events (MACE: all-cause death, any MI, emergent coronary bypass surgery, or clinically indicated TLR); patient-oriented composite endpoint (POCE: all-cause mortality, any MI, or any revascularization).

Statistical Analysis

Data were reported as frequencies and percentages for dichotomous and categorical variables and as mean ± SD for continuous variables. Chi-square and Fisher's exact tests were used to compare dichotomous and categorical variables. Student's *t*-test was used to compare continuous variables. The Kaplan–Meier method was used to calculate the time to clinical endpoints and the Log-rank test to compare between-group differences. Two-sided *P*-values <0.05 were considered significant. Data analysis was performed with SPSS (version 17, SPSS, Chicago, IL)

RESULTS

Characteristics of Patients, Lesions, and PCI Procedures

Among the study population of 674 patients, 59 (8.8%) patients were treated for at least one CTO lesion (mean length 31.3 ± 20.3 mm) of which the majority had J-CTO scores ≥2 (56%) (Fig. 1), indicating that most CTO lesions were classified as difficult to cross. All CTO interventions were performed with antegrade wire crossing technique only, of which 14 patients were treated with complex antegrade wire techniques (with use of sliding and/or aggressive wires (six times), kissing balloons (two times), rotablation (two times), over-the-wire balloon dilatation, Culotte stenting, or aspiration catheters, as well as treatment of an in-stent lesion CTO).

The remaining 615 (91.2%) patients were treated for non-CTO lesions only (Table I). Patients with CTO lesions were more often treated for lesions in small vessels (94.9% vs. 63.1%, $P < 0.001$) and long lesions (52.5% vs. 17.7%, $P < 0.001$), and were less often male (62.7% vs. 74.6%, $P < 0.05$). In addition, patients of the CTO group underwent significantly more often multivessel treatment (42.4% vs. 22.4%, $P < 0.001$). The target lesion location differed significantly between groups, as patients in the CTO lesion group showed more involvement of the right (55.9% vs. 34.0%, $P <= 0.001$) and left circumflex (49.2% vs. 31.1%, $P < 0.01$) coronary arteries than patients with non-CTO lesions only. Moreover, there was a trend toward more stent postdilatation in patients with treatment of CTO lesions (96.6 % vs. 88.7%, $P = 0.06$). In patients in the CTO group, significantly more stents were implanted (2.97 vs. 1.98, $P < 0.001$) and subsequently the total stent length (66.3 mm vs. 39.6 mm, $P < 0.001$) per patient was longer than patients with non-CTO lesions.

Three-Year Clinical Outcome

Three-year follow-up was available in 670 out of 674 (99.7%) patients. The incidence of the main outcome parameter TLF was similar for patients with treatment of CTO lesions and patients with non-CTO lesions only (13.6% vs. 12.9%, $P = 0.89$). Figure 2 shows similar Kaplan–Meier curves for TLF in both groups (HR 1.1, 95% CI: 0.5–2.2, $P = 0.85$).

Other composite clinical endpoints, such as TVF, MACE, and the most global patient-oriented endpoint (POCE) (18.6% vs. 18.8%, $P = 0.97$), also showed no differences between the two groups (Table II). In addition, the rates of various individual clinical endpoints, such as MI or TVR, were low and did not significantly differ between groups either (Table II). Peri-procedural MI (i.e., MI within the first 48 hr of treatment) occurred numerically more often in the CTO lesion group (8.5% vs. 4.1%, $P = 0.17$), but a maximum creatine kinase level >5x the upper limit of normal was only found in 1.7% patients with treatment of CTO lesions. Among the patients with treatment of CTO lesions, 26 patients were treated with Xience V stents and 33 patients with Resolute stents. Between the two stent-

TABLE I. Characteristics of Patients, Lesions, and Interventional Procedures

	Patients treated for CTO lesions *N=59*	Patients treated for non-CTO lesions only *N=615*	*P*
Age (yrs), mean (SD)	63.3 ± 9.9	64.5 ± 9.7	0.37
Men	37 (62.7%)	459 (74.6%)	<0.05
BMI (kg/m^2)	27.9 ± 3.7	27.9 ± 4.1	0.97
Diabetes mellitus (any)	10 (16.9%)	133 (21.6%)	0.40
Chronic renal failure[a]	2 (3.4%)	18 (2.9%)	0.69
Arterial hypertension	32 (54.2%)	378 (61.5%)	0.28
Hypercholesterolemia	33/57 (57.9%)	390/605 (64.5%)	0.32
Current smoker	12 (20.3%)	126 (20.5%)	0.98
Family history of CAD	29 (49.2%)	360 (58.5%)	0.16
Previous MI	14 (23.7%)	146 (23.7%)	1.00
Previous PCI	13 (22.0%)	128 (20.8%)	0.83
Previous CABG	7 (11.9%)	76 (12.4%)	0.91
Left ventricular ejection fraction < 30%[b]	1/44 (2.3%)	17/452 (3.8%)	1.000
Multivessel treatment	25 (42.4%)	138 (22.4%)	<0.001
Total no. of lesions treated per patient			0.02
One lesion treated	27 (45.8%)	394 (64.1%)	
Two lesions treated	23 (39.0%)	156 (25.4%)	
Three of more lesions treated	9 (15.3%)	65 (10.6%)	
Severe calcification	13 (22.0%)	129 (21.0%)	0.85
Aorta-ostial lesion	10 (16.9%)	69 (11.2%)	0.19
At least one bifurcation	17 (28.8%)	154 (25.0%)	0.53
At least one bifurcation with side branch treatment	10 (16.9%)	94 (15.3%)	0.74
At least one small-vessel (RVD< 2.75 mm)	56 (94.9%)	388 (63.1%)	<0.001
At least one lesion length > 27mm	31 (52.5%)	109 (17.7%)	<0.001
Target vessel			
Left main stem	1 (1.7%)	35 (5.7%)	0.36
Left anterior descending artery	24 (40.7%)	316 (51.4%)	0.12
Left circumflex coronary artery	29 (49.2%)	191 (31.1%)	<0.01
Right coronary artery	33 (55.9%)	209 (34.0%)	0.001
ACC-AHA lesion class[c]			–
A	–	35 (5.7%)	
B1	–	112 (18.2%)	
B2	–	181 (29.4%)	
C	59 (100%)	287 (46.7%)	
Postdilatation	57 (96.6%)	546 (88.8%)	0.06
No. of stents implanted per patient, mean (SD)	2.97 ± 1.43	1.98 ± 1.18	<0.001
Total stent length (mm) per patient, mean (SD)	66.3 ± 34.9	39.6 ± 26.4	<0.001

Data are number (%) or mean (SD).

[a]Chronic renal failure was defined by a serum creatinine level ≥ 130 μmol/L.

[b]Left ventricular ejection fraction was assessed with ultrasound, MRI, or LV angiography.

[c]ACC-AHA lesion class = highest morphology type.

CTO = chronic total occlusion. BMI = body mass index. CAD = coronary artery disease. MI = myocardial infarction. PCI = percutaneous coronary intervention. CABG = coronary artery bypass grafting. RVD = reference vessel diameter. ACC = American College of Cardiology. AHA = American Heart Association.

subgroups, there was no significant difference in the incidence of the main outcome parameter TLF (15.4% vs. 12.1%, $P = 0.72$). In addition, within 14 patients in whom complex antegrade techniques were applied, the incidence of TLF was nonsignificantly higher than in patients without additional complex techniques (21.4% vs. 11.1%, $P = 0.38$).

DISCUSSION

To compare the long-term outcome of patients who were treated with second-generation DES implantation for at least one CTO lesion versus patients who were treated for non-CTO lesions only, we analyzed in the present substudy of the prospective TWENTE trial the data of 674 patients, who had undergone elective PCI for stable angina. Despite various significant differences in patient, lesion, and procedure-related characteristics, 3-year clinical outcome was similar and favorable for both patient groups.

Study Population

In the total patient population of the TWENTE trial, 6.8% patients underwent stenting for at least one CTO lesion [16], which is similar to rates (3.0 to 8.0%) in

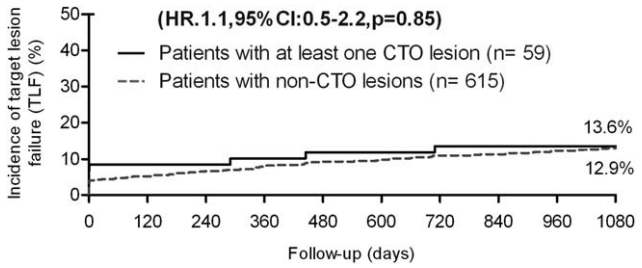

Fig. 2. TLF during 3-year follow-up. Kaplan–Meier cumulative event curves for the main outcome parameter TLF in patients treated for at least one CTO lesion versus non-CTO lesions only.

TABLE II. Clinical Outcome at 3-Year Follow-Up

	Patients treated for CTO lesions *N = 59*	Patients treated for non-CTO lesions only *N = 611*	*P*
Target lesion failure (TLF)	8 (13.6%)	79 (12.9%)	0.89
Target vessel failure (TVF)	9 (15.3%)	89 (14.6%)	0.89
Major adverse cardiac events (MACE)	9 (15.3%)	96 (15.7%)	0.93
Patient-oriented composite end-point (POCE)	11 (18.6%)	115 (18.8%)	0.97
Death, any cause	1 (1.7%)	39 (6.4%)	0.25
Death, cardiac cause	0	22 (3.6%)	0.24
MI, any	6 (10.2%)	35 (5.7%)	0.16
MI, target vessel related	6 (10.2%)	34 (5.6%)	0.15
MI, periprocedural	5 (8.5%)	25 (4.1%)	0.17
Revascularization, any	4 (6.8%)	62 (10.1%)	0.41
TVR, clinically indicated	3 (5.1%)	51 (8.3%)	0.61
TLR, clinically indicated	2 (3.4%)	34 (5.6%)	0.76
ST, definite or probable (0–1080 days)	1 (1.7%)	9 (1.5%)	0.89
ST, definite	1 (1.7%)	3 (0.5%)	0.25

Data are number (%).
CTO = chronic total occlusion. MI = myocardial Infarction. TVR = target vessel revascularization. TLR = target lesion revascularization. ST = stent thrombosis.

several other randomized DES trials that enrolled broad patient populations [23–26].

The population of the present substudy consisted of TWENTE patients, who had undergone elective treatment for stable angina and included 59 (8.8%) patients in whom stents were implanted in CTO lesions. For our present study, we did not consider TWENTE patients with non-ST-elevation acute coronary syndromes (Non-ST-ACS) at presentation because in such patients the level of certainty about the duration of an occlusion (> 3 months) is much more often debatable. In clinical practice, lesions will often be labeled as CTO based on (1) the patient-reported course of stable angina symptoms during the last few months prior to the Non-ST-ACS, (2) the operator's tactile perception of the lesion, and (3) the response of the lesion to the guide wire. In addition, in patients with Non-ST-ACS, event rates may be mostly driven by unstable coronary lesions other than the CTO lesion, and it may be more difficult to prove the occurrence of certain clinical endpoints, such as periprocedural MI.

Comparison with Results of Previous Studies

In previous stent studies, treatment of CTO lesions with (mostly) first-generation DES was associated with lower MACE rates than after use of bare metal stents, mainly driven by lower revascularization rates. The randomized PRISON II trial showed favorable results and lower TLR rates after 5 years in CTO patients treated with sirolimus-eluting Cypher stents (Cordis, Warren, NJ) versus bare metal stents (12.0% vs. 30.0%, $P < 0.001$) [27]. Siek and coworkers assessed the outcome of 137 patients with CTO lesions who were treated with first and second-generation DES to compare the outcome with 208 CTO lesion patients treated with bare metal stents. In patients treated with DES the incidence of TLR was lower after 1 year (5.1% vs. 14.4%, $P < 0.01$) and after a median follow-up of 23 ± 3 months (7.3% vs. 14.4%, $P = 0.04$) [6]. A large registry, reported by Kato and coworkers, confirmed the relative safety of first-generation sirolimus-eluting Cypher stents in 1210 patients who were treated with CTO lesions; nevertheless, these CTO lesion patients still had a higher TLF rate than patients who were treated with the same DES for non-CTO lesions [18]. In addition, the CATOS trial showed the efficacy of zotarolimus-eluting Endeavor stents (Medtronic) for the treatment of CTO lesions with a numerically lower TVF rate as compared to the Cypher stent (10.0% vs. 17.5%; $P = 0.17$) [28].

Analyses of long-term clinical outcome following treatment of CTO lesions with second-generation DES are scarce, as most studies reported only 1-year follow-up data. The randomized CIBELES trial found in 207 patients with CTO lesions no difference in 1-year MACE rate between patients treated with first-generation Cypher sirolimus-eluting stents versus second-generation everolimus-eluting Xience V stents (15.9% vs. 11.1%, $P = 0.34$). The TVR rate, however, was lower following the use of Xience V stents (11.6% vs. 7.9%, $P = 0.53$) [29]. The XIENCE V CTO study, which followed 53 patients with CTO lesion treatment for 1 year, showed a TLR rate (6%) that was somewhat higher than in our study after 3-year follow-up (3.4%), which might be related to differences in patient populations, such as a higher prevalence of diabetes in the XIENCE V CTO population (28% vs. 17%) [11].

Clinical Perspective

This study assures our present clinical practice as it suggests that the use of second-generation DES for

CTO treatment is associated with high and sustained long-term efficacy and safety. The numerically higher rate of periprocedural MI following treatment of CTO lesions could be explained by the occasionally subintimal route of guide wires during the process of CTO recanalization, which may, to some extent, increase the likelihood of occluding minor side branches during the often challenging interventional procedures.

Limitations

Because of the post-hoc nature of the present analysis, the results should only be considered as hypothesis generating. The limited number of patients in the CTO lesion group and the relatively low event rates did not permit meaningful analyses of smaller subgroups, such as a detailed stent-level analysis. However, the similarity of both DES in clinical outcome until the most recent 3-year follow-up [30] justifies the present pooled analysis. However, our data cannot be generalized to patient populations that are treated with more complex CTO recanalization techniques than used in the present study.

CONCLUSIONS

Patients treated with second-generation DES for CTO lesions showed at 3-year follow-up an incidence of adverse clinical events that was low and similar to patients with non-CTO lesions only.

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