Safety and Effectiveness of Everolimus-Eluting Stents in Chronic Total Coronary Occlusion Revascularization

Results From the EXPERT CTO Multicenter Trial
(Evaluation of the XIENCE Coronary Stent, Performance, and Technique in Chronic Total Occlusions)

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ABSTRACT

OBJECTIVES This study sought to evaluate procedural and clinical outcomes among patients undergoing chronic total occlusion (CTO) percutaneous coronary intervention (PCI) using contemporary methods and everolimus-eluting stents (EES).

BACKGROUND Limited studies have detailed the procedural and late-term safety and efficacy of CTO revascularization among multiple centers applying modern techniques and with newer-generation drug-eluting stents.

METHODS Among 20 centers, 250 consecutive patients were enrolled for attempted CTO PCI. Procedural and in-hospital clinical outcomes were examined in addition to the 1-year primary endpoint of death, myocardial infarction, and target lesion revascularization (major adverse cardiac events [MACE]).

RESULTS Demographic, lesion, and procedural characteristics included prior bypass surgery: 9.9%; diabetes: 40.1%; lesion length: 36.1 ± 18.5 mm; and stent length: 51.7 ± 27.2 mm. Procedural success, defined as guidewire recanalization with no in-hospital MACE, was 96.4%. Success with antegrade-only methods was 97.9% and 86.2% by retrograde/combined methods, respectively. Compared with a pre-specified performance goal derived from 6 prior CTO drug-eluting stent trials (1-year MACE: 24.4%), treatment with EES was associated with significantly lower composite adverse events for both intent-to-treat (18.5%, 1-sided upper confidence interval: 23.4%, p = 0.025) and per-protocol populations (8.2%, 1-sided upper confidence interval: 12.3%, p < 0.0001). Target lesion revascularization at 1 year was 6.3%. Dual antiplatelet therapy adherence was 53.9% at 1 year, yet subacute definite stent thrombosis occurred in only 2 patients (0.9%), and late probable stent thrombosis occurred in 1 patient (0.5%).

CONCLUSIONS In a multicenter registration trial representing contemporary technique and EES, favorable procedural success and late-term clinical outcomes support CTO PCI in a patient population with high lesion complexity. (EXPERT CTO: Evaluation of the XIENCE PRIME LL and XIENCE Nano Everolimus Eluting Coronary Stent Coronary Stents, Performance, and Technique in Chronic Total Occlusions; NCT01435031) (J Am Coll Cardiol Intv 2015;8:761–9) © 2015 by the American College of Cardiology Foundation.
The potential merits of chronic total occlusion (CTO) percutaneous coronary intervention (PCI) are challenged by uncertainties related to procedural outcome, clinical indication, and durability of late-term vessel patency. Although a CTO is identified in approximately 1 in every 3 to 5 coronary angiograms (1,2), the disparity between prevalence and treatment underscores the procedural and clinical dilemmas presented by these complex lesions. Compared with treatment of nonocclusive coronary disease that is associated with a predictably high likelihood of procedural success, guidewire recanalization of a CTO is challenging and remains the principal cause of failure that, by historical standards, may approach 40% (3,4). Accordingly, treatment decisions (bypass surgery, attempted percutaneous revascularization, or continued medical therapy alone) are commonly derived by default rather than by decision given the limited therapeutic options and a less predictable risk/benefit balance for symptomatic CTO patients.

Unlike catheter-based revascularization of nonocclusive coronary disease, much of our understanding regarding total occlusions has been further limited by the fact that there are relatively few studies with rigorously detailed procedural and clinical results with contemporary methods and advanced-generation drug-eluting stents (DES). Until recently, many of the technologies and techniques promoted for the treatment of total occlusions were modeled after devices and methods applied to less complex, nonocclusive disease, erroneously assuming that the procedural and clinical outcomes between these lesion subsets were similar. Moreover, these investigations were often limited by their retrospective, observational design, variability in operator skills, inconsistencies regarding the definition of total occlusions, and bias regarding patient selection.

Recently, considerable progress has been achieved in CTO PCI, with procedural and clinical outcomes that represent a clinically significant and meaningful advancement beyond historically discouraging results. Innovative guidewire methods, including retrograde and dissection re-entry techniques (5,6), in addition to DES following recanalization (7–11), have furthered clinical success with safety similar to conventional PCI (12–14). To better characterize the incremental benefit of these advances, we performed a prospective, multicenter registration trial examining procedural and clinical outcomes following attempted CTO PCI with contemporary methods and newergeneration DES.

**METHODS**

**TRIAL OVERVIEW AND STUDY POPULATION.**

EXPERT CTO (Evaluation of the XIENCE Coronary Stent, Performance, and Technique in Chronic Total Occlusions) was a prospective, nonrandomized, multicenter trial evaluating the safety and efficacy of treatment with everolimus-eluting stents (EES) (XIENCE V and XIENCE PRIME, Abbott Vascular, Santa Clara, California) in patients undergoing elective percutaneous CTO revascularization at 20 hospitals in the United States (Online Appendix). The study was approved by the institutional review board at each site. Eligible patients signed written informed consent before the interventional procedure. Eligible patients were ≥18 years of age with symptomatic ischemic heart disease and undergoing clinically driven nonemergent percutaneous recanalization of a de novo occlusive coronary lesion, which exhibited Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 or 1 and was...
estimated to be at least 3 months duration by clinical, angiographic, or electrocardiographic criteria. Patients who provided consent were considered to be enrolled upon introduction of the coronary guidewire into the guiding catheter. Principal angiographic exclusion criteria were in-stent total occlusions and excessive vessel angulation that was deemed by the operator as likely to prohibit stent delivery. There were no restrictions regarding lesion length. Clinical exclusion criteria were recent (<72 h) myocardial infarction (MI), prior stent placement within the target vessel or any other vessel within 90 days of the index procedure, or any general contraindication to the revascularization procedure and routine pharmacological therapies. There were no restrictions regarding lesion length or treatment strategy (e.g., antegrade, retrograde, or dissection re-entry technique).

**STUDY ENDPOINTS AND DEFINITIONS.** The primary endpoint of this study was to evaluate the 1-year occurrence of major adverse cardiac events (MACE) (composite of all-cause death, MI, and target lesion revascularization [TLR]) among patients undergoing successful CTO PCI, and to compare these events with a performance goal established from 6 CTO DES trials reporting at least 1-year MACE (8,15-19). Two analysis populations were pre-specified: 1) intent-to-treat, representing all enrolled patients for whom recanalization and pre-dilation of CTO were achieved and EES were inserted into the guiding catheter; and 2) per protocol, indicating procedural success with EES with follow-up data available and no major protocol deviations.

Additional key objectives of this study were to determine guidewire (HT Progress and HT Pilot guidewires, Abbott Vascular) and angioplasty (Mini-Trek, Abbott Vascular) pre-dilation safety and effectiveness. The guidewire endpoint was procedural success, defined as angiographic confirmation of guidewire placement in the target vessel true lumen and absence of in-hospital MACE, and was compared with a performance goal established from pooled analysis of 3 studies reporting procedural success in CTO PCI (20-22). The guidewire endpoint was analyzed from the initial 138 patients undergoing attempted CTO PCI. Although a Progress or Pilot guidewire must have been used during attempted crossing of the CTO, use of additional guidewires were permitted. The cohort for the balloon angioplasty endpoint included the initial 88 patients with successful guidewire crossing of the CTO and examined catheter delivery, performance, and occurrence of catheter-related angiographic or clinical complications. Results of this descriptive endpoint have been previously reported (23).

Additional secondary endpoints included the individual components of the composite endpoint in addition to target lesion failure (cardiovascular death, target vessel-related MI, and TLR), device success (achievement of <50% diameter stenosis with assigned study stent), procedural success according to crossing technique, and measures of resource utilization. Clinical safety outcomes included all-cause and cardiac death, MI, and stent thrombosis (ST) through 1-year follow-up. Cardiac death was considered as any fatal event not attributable to a noncardiac cause. Both MI and ST were determined per Academic Research Consortium (ARC) definition criteria (24). Periprocedural MI was defined as an increase in creatine kinase (CK) myocardial band fraction or troponin >3× the upper normal limit within 48 h of the index procedure. In contrast, MI per protocol was determined as development of new pathologic Q waves by electrocardiography, or CK elevation that exceeded 2× the upper normal limit in association with elevated CK myocardial band fraction. An independent clinical events committee (Harvard Clinical Research Institute, Boston, Massachusetts) adjudicated all clinical endpoints. Coronary angiograms performed at baseline and follow-up, if clinically indicated, were reviewed by an independent angiographic core laboratory (Beth Israel Deaconess Angiographic Core Laboratory, Boston, Massachusetts).

**STATISTICAL METHODS.** Patients were analyzed for all safety and efficacy endpoints on the basis of the intent-to-treat principle as well as per protocol criteria. Baseline characteristics of study patients were summarized in terms of frequencies and percentages for categorical variables and by mean ± SD for continuous variables. The primary analysis for the binary outcome against the performance goal was performed through the binomial distribution. To develop the performance goal for the primary endpoint of 1-year MACE, data from 6 CTO DES trials (8,15-19) were used (Online Table 1). Because some studies constituting the performance goal utilized a less conservative definition of MI not according to ARC criteria, an upward adjustment in the 1-year MI rate was necessary. To accommodate for this difference, data from treatment of long lesions from additional EES databases (SPIRIT PRIME long lesion registry, unpublished data, Abbott Vascular, August 2010; and SPIRIT IV long lesion subset, unpublished data, Abbott Vascular, March 2011) were used as a surrogate for CTO PCI given that these 2 indications are representative of similar, complex treatments. The average difference in 1-year MI between ARC and
coronary revascularization. The average lesion and occlusion lengths were 36.1 ± 18.5 mm and 14.0 ± 10.6 mm, respectively. Bridging collaterals and moderate/severe calcification were present in the majority of occlusions. More than one-half of the target lesions were located in the right coronary artery.

In the entire study population with guidewire recanalization, procedure success was achieved in 89.6% (198 of 221) of patients using the ARC MI definition, and 96.4% (213 of 221) when the protocol MI definition was applied (Table 2). Antegrade-only methods (including dissection re-entry techniques) were performed in approximately 80% (174 of 221) of cases followed by combined antegrade/retrograde and retrograde-only techniques. Procedural success rates according to guidewire strategy are detailed in Table 2. For the guidewire endpoint, among a
pre-specified cohort of 138 initial patients undergoing attempted CTO PCI, successful guidewire crossing was achieved in 89.9% of patients. Compared with the guidewire performance goal endpoint of 62.5% for procedural success, statistical superiority was achieved by both primary (ARC: 79%; 95% CI: 71.2 to 85.5; p < 0.0001) and per-protocol analyses (87.7%; 95% CI: 81.0 to 92.7; p < 0.0001). The average number of guidewires per case was 5.7 (range 1 to 18).

All patients with successful guidewire recanalization received treatment with EES. At 1 year, MACE occurred in 18.5% of patients (n = 222; upper 95% confidence limit: 23.4%; p = 0.025 compared with pre-specified performance goal) by ITT analysis, and 8.2% of patients by per-protocol analysis (n = 183; upper 95% confidence limit: 12.3%; p < 0.0001) (Table 3). The difference in endpoints was principally driven by assessment and definition of MI (13.9% by ITT and 3.4% per protocol). Elevation of CK myocardial band >10× the upper normal limit occurred in only 1.8% (4 of 220) of patients (Figure 1).

At 1 year, clinically driven target lesion revascularization was 6.3% (13 of 207), and cardiac death occurred in 1.9% (2 of 208) of patients (Table 3). Definite subacute ST was identified in 2 patients (0.9%), with no definite events observed after 30 days. Late probable ST was identified in 1 patient (0.5%). Notably, adherence to dual antiplatelet therapy at 1 year was 53.9%. All definite and probable ST events occurred while patients reported compliance with dual antiplatelet therapy.

**DISCUSSION**

In a multicenter registration trial representing contemporary technique, broad operator experience, and newer-generation EES, favorable procedural success and late-term clinical outcomes support CTO PCI.

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**Table 2** Procedural Results for the Everolimus Stent Group (n = 222)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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<tbody>
<tr>
<td>Stents/lesion</td>
<td>1.95 ± 0.98</td>
</tr>
<tr>
<td>Stent length, mm</td>
<td>51.72 ± 27.16</td>
</tr>
<tr>
<td>Stent diameter, mm</td>
<td>2.85 ± 0.36</td>
</tr>
<tr>
<td>Inflation pressure, atm</td>
<td>13.38 ± 3.14</td>
</tr>
<tr>
<td>≥2 stents implanted</td>
<td>61.7</td>
</tr>
<tr>
<td>Overlapping stents</td>
<td>60.8</td>
</tr>
</tbody>
</table>

**Table 3** 1-Year Clinical Outcomes for the Everolimus Stent Group (n = 222)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1.9</td>
</tr>
<tr>
<td>MI</td>
<td>13.9</td>
</tr>
<tr>
<td>Protocol MI definition</td>
<td>3.4</td>
</tr>
<tr>
<td>Clinically driven TLR</td>
<td>6.3</td>
</tr>
<tr>
<td>Percutaneous</td>
<td>5.8</td>
</tr>
<tr>
<td>Surgical</td>
<td>0.5</td>
</tr>
<tr>
<td>MACE</td>
<td>18.5</td>
</tr>
<tr>
<td>Protocol MI definition</td>
<td>10.0</td>
</tr>
<tr>
<td>TLF</td>
<td>15.8</td>
</tr>
<tr>
<td>Protocol MI definition</td>
<td>9.1</td>
</tr>
<tr>
<td>TVF</td>
<td>16.7</td>
</tr>
<tr>
<td>Protocol MI definition</td>
<td>10.0</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>0</td>
</tr>
<tr>
<td>Subacute</td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>0.9</td>
</tr>
<tr>
<td>Probable</td>
<td>0</td>
</tr>
<tr>
<td>Late</td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>0</td>
</tr>
<tr>
<td>Probable</td>
<td>0.5</td>
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</tbody>
</table>

Values are %. MACE = major adverse cardiac events; MI = myocardial infarction; TLF = target lesion failure; TLR = target lesion revascularization; TVF = target vessel failure; other abbreviations as in Table 2.
in a patient population with high lesion complexity. Specifically, CTO PCI employing advanced guidewire technique, dissection re-entry methods, and antegrade and retrograde strategies was associated with successful recanalization that approached 90%, representing a substantial improvement above historical standards. Further, despite high lesion complexity and extensive stent length, treatment with EES was associated with rates of repeat revascularization and ST similar to outcomes observed in less complex disease and clinical indications. These findings challenge common perceptions in CTO PCI regarding likelihood of procedural success and durability of late-term vessel patency.

Against the background of outcomes data indicating benefit following CTO recanalization and the successes of DES in maintaining target vessel patency is the stark reality that any potential advantage of CTO PCI is handicapped from the outset by the commonality of procedural failure. As an example, despite the frequency of attempted CTO PCI within the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial, procedural success was only achieved in 49% of lesions (3). As a prospective, multicenter trial, the present study represents 1 of the most comprehensive examinations of procedural methods, resource utilization, and outcomes in contemporary CTO PCI, representing a generally unrestricted CTO patient population and broad operator experience and technique. Despite extensive lesion length and complexity, a high level of procedural success was achieved through application of antegrade and retrograde guidewire maneuvers and with favorable safety. Indeed, the procedural success endpoint was most influenced by the inclusion and definition of MI; when periprocedural MI was adjudicated according to the conservative ARC criteria (24), its frequency was more common than guidewire failure. Alternatively, nearly all MI events were characterized by biomarker elevation that fell below thresholds proposed as a clinically relevant standard (25), and its occurrence did not translate to adverse events through 1-year post-revascularization. Also, given that the pooled analyses of previous CTO studies to establish both the guidewire and stent performance goals were based on broader and less conservative definitions of MI than in the current study, these historical endpoints represented an even more conservative comparison that might have biased against the study cohort.

Apart from a variety of novel but often disappointing technologies for crossing occluded coronary segments, specialized coronary guidewires remain the mainstay instrument for CTO recanalization. Although CTO-specific guidewire technology itself has evolved considerably, a more revolutionary advancement has related to the technical skills and strategies regarding how these tools are used. Overall, guidewire crossing of the occlusion was demonstrated in 89% of enrolled patients, and in a pre-specified subgroup powered for comparison with prior CTO studies that largely represented more conventional antegrade guidewire methods (20–22), application of antegrade, retrograde, and dissection re-entry techniques resulted in statistically and clinically superior rates of procedural success. An average of 6 guidewires/case reflected both lesion complexity and technique, in the latter instance leveraging different guidewire features for differing aspects of lesion crossing (e.g., proximal cap penetration, traversing body of occlusion, distal lumen re-entry).

Similar to coronary guidewires, no previous study has been designed and completed as a registration trial with Food and Drug Administration oversight for newer-generation DES approval in an expanded indication of CTO percutaneous revascularization. In general, our understanding of procedural and clinical effectiveness of DES following CTO recanalization has been limited by the routine exclusion or under-representation of such patients in most major interventional cardiology clinical trials. Further, unlike the widespread evaluation of DES beyond

<table>
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<tr>
<th>MI According to Biomarker Elevation *</th>
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<tbody>
<tr>
<td>&gt;3X to 5X ULN</td>
<td>5.4%</td>
</tr>
<tr>
<td>&gt;5X to 10X ULN</td>
<td>3.6%</td>
</tr>
<tr>
<td>&gt;10X ULN</td>
<td>1.8%</td>
</tr>
</tbody>
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Determination of myocardial infarction (MI) according to creatine kinase-myocardial band elevation. *2MI events diagnosed by troponin only. ULN = upper limit of normal.

FIGURE 1
approved patient and lesion indications, relatively few investigations have been performed to support the clinical benefit of DES in total occlusion revascularization, especially with more recent-generation DES that may convey clinical benefit over first-generation DES. This latter issue is especially relevant given that failure to achieve or sustain patency after CTO recanalization has been associated with impairment in regional and global left ventricular systolic function, recurrent angina and target vessel revascularization, and a greater need for late bypass surgery (26).

Among patients enrolled in this study, lesion and stent length assessed by an independent core laboratory were among the most extensive described in contemporary DES reports, and to our knowledge, more than any other DES indication approval study. Despite this complexity, 1-year outcomes of TLR (6.3%) and definite ST (1%) were comparable with observations of EES in less complex, nonoclusive coronary disease. Further, compared with MACE rates derived from a pooled analysis of first-generation CTO DES trials, treatment with EES was associated with a significant reduction in adverse events at 1 year. In part attributed to thinner strut design, enhanced stent geometry, and polymer biocompatibility, these latter findings are consistent with prior comparative studies demonstrating the superiority of EES over first-generation DES in simple to moderate complexity disease (27–30). Depending upon endpoint definitions as previously described, the relative reduction in MACE ranged from one- to two-thirds with newer-generation EES. Notably, the low ST rate is observed despite approximately one-half of patients remaining adherent to dual antiplatelet therapy over this time period. Compared with prior studies of EES in CTO revascularization, outcomes in this study were similar if not improved; in prior studies of EES in CTO PCI (9,10,31), rates of repeat revascularization ranged from 8% to 11%, and ST was inconsistently reported. Despite similar lesion and stent length in the present study, rates of repeat revascularization were somewhat lower, likely due to the absence of mandatory angiographic surveillance.

STUDY LIMITATIONS. In the absence of randomization, a limitation to this analysis is that the possibility that measured or unmeasured confounders may have affected the comparison of these results with a performance goal derived from a pooled analysis of prior CTO DES trials cannot be excluded. As previously described, however, application of a less-conservative definition of MI would be expected to bias against the EES cohort, even despite statistical adjustment for differences in MI ascertainment. In addition, this study did not include mandatory angiographic surveillance that may inform rates of restenosis and reocclusion and also exaggerate estimates of repeat revascularization. Angiographic outcomes with EES in CTO PCI have been previously described. Instead, the intent of the current trial was to systematically detail patient-oriented procedural and clinical outcomes. Also regarding procedural outcomes, in comparison with some prior studies of occluded arteries, all CTOs were estimated as “chronic,” a characteristic that historically has been negatively related to technical success of recanalization, reflects lesion complexity, and underscores the capabilities of CTO PCI using contemporary methods and technologies.

CONCLUSIONS

In a multicenter registration trial representing contemporary technique, broad operator experience, and newer-generation DES, favorable procedural success and late-term clinical outcomes support CTO PCI in a patient population with high lesion complexity. Specifically, CTO PCI employing an advanced procedural technique and newer-generation DES was associated with favorably high rates of both procedural and 1-year clinical success, representing a substantial improvement above historical benchmarks. Despite high lesion complexity and extensive stent length, treatment with EES was associated with rates of repeat revascularization and ST similar to outcomes observed in less complex disease and clinical indications. These results challenge common perceptions in CTO PCI regarding the likelihood of procedural effectiveness and durability of late-term clinical success. Dedicated long-term follow-up will further clarify the late safety and efficacy of EES treatment in this complex lesion subset. Even so, the results suggest that treatment with EES should be favored for percutaneous revascularization in chronically occluded native coronary arteries.

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PERSPECTIVES

WHAT IS KNOWN? CTO PCI has been associated with reduced angina, improved left ventricular function, and enhanced survival. However, technical challenges and uncertainties regarding clinical outcome challenge more widespread consideration of PCI for this indication.

WHAT IS NEW? Application of contemporary procedural technique and newer-generation DES suggest improved early and late-term outcomes among patients undergoing attempted CTO PCI. Among operators with broad CTO experience, PCI of total coronary occlusions is associated with high procedural success and favorable clinical outcomes that are similar to those observed in less-complex PCI populations.

WHAT IS NEXT? CTO PCI employing advanced procedural technique and newer-generation DES represents a substantial improvement above historical benchmarks and should be considered when clinically appropriate. These results challenge common perceptions of CTO PCI regarding the likelihood of procedural effectiveness and durability of late-term clinical success.

REFERENCES

23. Kini AS, Karmpaliotis D, Tummal PE, et al. MINI TREK Coronary dilatation catheter in


**KEY WORDS** chronic total occlusion, drug-eluting stent, everolimus, percutaneous coronary intervention

**APPENDIX** For a list of the study sites, investigators, and enrollment as well as a supplemental table, please see the online version of this article.