EDITORIAL COMMENT

Chronic Total Coronary Occlusion Percutaneous Intervention

The Case for Randomized Trials*

Patrick L. Whitlow, MD, Kamran I. Muhammad, MD
Cleveland, Ohio

Chronic total coronary occlusions (CTO) are encountered frequently, found in up to 50% of patients with coronary artery disease (CAD) referred for elective angiography. Treatment strategy for an individual patient is often changed on the basis of the presence or absence of a CTO (1). Percutaneous coronary intervention (PCI) of CTO remains challenging, with observed success rates that are significantly lower than those for non-occluded lesions (2,3). Therefore, it is not surprising that in randomized trials from the BARI (Bypass Angioplasty Revascularization Investigation) trial to the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) study, CTO has endured as the strongest predictor for referral to coronary artery bypass surgery (CABG) rather than randomization.

An analysis of more than 15,000 patients from the New York State PCI registry demonstrated that incomplete revascularization (IR) was related to lower rates of survival when compared with complete revascularization (12). Chronic total coronary occlusion was frequently encountered in the IR cohort and conferred a greater hazard for death when compared with IR due to subtotal stenoses. Additionally, van der Schaaf et al. (13) demonstrated that the presence of a noninfarct-related artery CTO at the time of primary PCI for ST-segment elevation myocardial infarction is an independent predictor of future mortality. In addition to this indirect evidence, 7 observational studies have demonstrated significant reductions in mortality with successful PCI for CTO, compared with unsuccessful attempts (Table 1)(2,3,5–8,10). In addition, a recent meta-analysis of 13 observational trials also demonstrated a significant reduction in long-term mortality associated with successful CTO PCI, compared with failed attempts (14).

A major limitation of these studies is their observational design, with limited information with regard to potential baseline differences between the successful versus unsuccessful cohorts. The lack of a true randomized, medically treated control group brings up the persistent question of whether the survival benefit demonstrated with successful PCI is, in fact, related to the beneficial effects of opening a chronically occluded vessel versus potential harm conferred to those with failed CTO PCI. Furthermore, it has been hypothesized that failure of CTO PCI is simply a marker for increasing baseline patient and lesion complexity, and therefore the poorer outcomes seen in this group are related to the baseline burden of disease rather than any beneficial effect of CTO recanalization.

In this issue of JACC: Cardiovascular Interventions, Mehran et al. (15) report the results of a multicenter observational study examining long-term clinical outcomes of 1,791 patients after PCI for CTO. This was a large well-executed study conducted between 1998 and 2007 with expert CTO operators at highly regarded institutions. An overall procedural success rate of 68% was reported, with success as high as 81% at 1 site. After multivariate adjustment, successful CTO PCI was an independent predictor of reduced cardiac mortality with a strong trend toward lower all-cause mortality. These survival data reinforce the findings of multiple previous observational studies and emphasize that current aggressive PCI attempts and re-attempts with stiff wires and multiple drug-eluting stents provide excellent long-term results. Safety and efficacy endpoints with drug-eluting stents for CTOs in this trial demonstrated low rates of stent thrombosis and significantly reduced target vessel revascularization, compared with bare-metal stents.

With the existing mature body of observational, “real-world” registry data and a meta-analysis suggesting that successful CTO might prolong life, randomized data are now necessary to further clarify this important issue. A
positive randomized trial comparing optimal medical therapy (OMT) with OMT plus CTO PCI using contemporary techniques would complement existing data and raise the level of evidence favoring aggressive treatment of CTOs with PCI. Ideally, this trial would include patients with a CTO of the proximal or mid left anterior descending coronary artery or CTO of a large dominant right or circumflex artery with a moderate-to-large ischemic burden who have an acceptable amount of angina on medications to minimize crossovers. After baseline data collection and consent, patients would be randomized and followed for >5 years to tabulate survival and cardiovascular outcomes.

Undoubtedly such a trial will be difficult to conduct for multiple reasons. Randomization to a therapy with average success rates in the 75% range will pose a challenge for intention-to-treat analysis. By selecting sites with expert CTO operators performing >75 CTO PCIs/year, this issue could potentially be minimized. Conversely, selection bias directing patients with anatomically favorable CTOs with large ischemic burdens directly to PCI rather than randomization will also have to be monitored and minimized.

The fact that the addition of PCI to OMT for stable CAD has not previously been shown to improve survival in randomized trials is an important consideration. However, CTO has been excluded from these previous trials, and there is evidence from the COURAGE (Clinical Outcomes Utilizing revascularization and Aggressive Drug Evaluation) trial of incremental benefit with PCI with increasing ischemic burden in stable CAD patients (16). Substudies assessing ischemic burden, left ventricular function, and quality of life should be planned, in addition to the evaluation of the effect of CTO PCI on cardiac and total mortality, myocardial infarction, stroke, target vessel revascularization, and CABG. We feel strongly that a randomized trial of this nature would contribute significantly to our understanding of the importance of CTO and refine our treatment approach for CTO patients. Unfortunately, a single randomized trial with 80% power to show a 25% improvement in the expected approximately 8% 5-year mortality with OMT would require randomization of >5,000 patients. If patient-level data were available and entry criteria were consistent, survival data could potentially be pooled from multiple smaller randomized trials separately underpowered for survival analysis.

Currently, the DECISION-CTO (Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients with Chronic Total Occlusion) trial—a randomized trial of PCI versus medical therapy for CTO with a noninferiority, composite end-point design and planned enrollment of 1,100 patients—is being conducted in Asia and will provide us with the first randomized data on CTO PCI. More data from randomized trials are clearly needed to establish the proper positioning of CTO PCI in our treatment strategy.

Reprint requests and correspondence: Dr. Patrick L. Whitlow, Cleveland Clinic, Cardiovascular Medicine, 9500 Euclid Avenue, Desk J2-3, Cleveland, Ohio 44195. E-mail: whitlop@ccf.org.

REFERENCES


Key Words: chronic total coronary occlusions • percutaneous coronary intervention • randomized trial.