Chronic total coronary occlusions (CTOs) represent one of the final frontiers in the evolution of revascularization with percutaneous coronary intervention (PCI). Although CTO revascularization relieves symptoms, reduces ischemic burden, improves left ventricular systolic function, and attenuates remodeling, convincing proof of improved survival remains elusive (1–3). Ongoing randomized trials such as EXPLORE (Evaluating XIENCE V and Left Ventricular Function in PCI on Occlusions After STEMI; NTR1108) (4), DECISION-CTO (Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients With Chronic Total Occlusion; NCT01078051), and EuroCTO (European Study on the Utilization of Revascularization Versus Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions; NCT01760083) will augment our understanding of long-term CTO outcomes (5), but none of these trials is statistically designed to detect mortality differences. Estimates of the mortality risks associated with CTO and the potential survival benefits of CTO PCI therefore remain founded in estimates from robust observational series (6–11).

In this issue of JACC: Cardiovascular Interventions, Råmunddal et al. (12) report the long-term outcomes of Swedish patients with CTOs undergoing angiography between 2005 and 2012. The SCAAR (Swedish Coronary Angiography and Angioplasty Registry) analysis of 14,441 patients with CTO (identified from 276,931 angiograms in 30 hospitals) integrates a robust prospective national cardiovascular registry with vital status records. By collecting information regarding the age of a coronary occlusion at both diagnostic angiography and at the time of PCI, the identification and definition of CTOs within the registry are harmonized. Although angiograms were not independently adjudicated by a core laboratory, the CTO definition was internally validated in a subgroup of 955 subjects identified at random from 4 of the 30 hospitals.

The analysis evaluated the value of CTO as a prognostic marker for subsequent cardiovascular events, adjusting for interactions often associated with advanced atherosclerotic coronary artery disease: number of diseased vessels, presence of acute coronary syndrome, age, sex, and diabetes. A propensity score-based sensitivity analysis achieved similar results to the Cox regression models reported as the primary analysis. The presence of a CTO increased the subsequent mortality risk, which was further augmented in patients with ST-segment elevation myocardial infarction, proximal CTOs, or age <60 years. The presence of diabetes, extent of coronary artery disease, and sex had no interaction with CTO, suggesting that these characteristics did not modify the underlying mortality risk attributable to the CTO. The lack of an interaction with diabetes contrasts with the findings of Suero et al. (9), who reported an increased mortality rate in this subgroup.

As with any large-scale data registry, the SCAAR dataset contains subjects with missing data elements.
despite error-checking routines and random monitoring visits. The investigators do not report the number of data elements that are missing in their analysis. Logistic regression analyses suggested that the missing data were not completely random, prompting the application of a multiple imputation method to estimate the missing data. Reassuringly, results using the imputed values are concordant with sensitivity results using only cases with complete records.

The association of CTO lesions with increased mortality still leaves an important information gap as to whether CTO revascularization alters that risk. During the study period, 6,442 patients underwent CTO PCI, with a procedural success rate of 54.2%. This success rate is lower than observed in other registry series (7–9), which reported rates >70% in the stent era. SCAAR patients with successful CTO PCI had a lower risk for death compared with unsuccessful revascularization (hazard ratio [HR]: 0.85; 95% confidence interval [CI]: 0.73 to 0.98; \( p < 0.034 \)).

These Swedish findings affirm an analysis of 14,439 CTO PCI procedures in the UK Central Cardiac Audit Database (8), in which CTO PCI was successful in 70.6% of cases. In the UK series, successful CTO PCI was associated with improved survival (HR: 0.72; 95% CI: 0.62 to 0.83; \( p < 0.001 \)), and complete revascularization had a mortality benefit over partial revascularization (HR: 0.70; 95% CI: 0.56 to 0.87; \( p = 0.002 \)) or failed revascularization (HR: 0.61; 95% CI: 0.50 to 0.74; \( p < 0.001 \)). An analysis of the New York State PCI database (10) reported a survival advantage for patients with complete revascularization (defined as successful PCI for all epicardial stenoses ≥70%). In 11,294 patients with multivessel coronary artery disease, there was progressively lower 18-month mortality with increasing extent of revascularization. Patients with 1 unopened CTO were 35% more likely to die. Patients with incomplete revascularization and 2 CTOs had the highest 18-month mortality. The principal vulnerability for each of these observational analyses is that the residual lesions were left unirevascularized either from operator discretion or ill fate (procedural failure).

The most important randomized trial to test the open-artery hypothesis remains OAT (Occluded Artery Trial) (13), which failed to detect a benefit for revascularization 3 to 28 days after acute coronary occlusion in the post-acute coronary syndrome setting. The population and lesion characteristics studied in OAT differ in important ways from the large-scale observational CTO experience. For example, CTOs in non-infarct-related arteries may have an additional contribution to mortality (14). Nevertheless, the equivocal mortality outcomes of the 2,166 randomized OAT subjects (HR: 1.03; 95% CI: 0.77 to 1.40) leave a lingering burden to prove that the mortality differences detected in more than 33,000 observational patients (6,8,12) is not a figment of selection bias.

For fans of angiographic gladiatorial spectacle, the dramatic antegrade reperfusion of a large coronary territory is exhilarating, particularly when a positive viability study (and perhaps a note from a demurring surgeon) lines the operator’s pocket. Those dedicated to evidence-based outcomes, however, will still clamor for dedicated randomized trials to demonstrate that relief of the CTO improves survival. Despite the efforts of a growing cadre of interventional cardiologists, CTO remains the most powerful predictor of referral to coronary bypass surgery (2). A broader view is the continuing affirmation that complete revascularization (including those areas subtended by CTOs) is more effective than incomplete revascularization. We have already recognized that the number of diseased vessels and the quantity of jeopardized territory affects long-term survival estimates, so it is not surprising that CTO outcomes have a similar influence (15).

There has been considerable progress made in the percutaneous revascularization techniques of CTO over the past decade. The popularization of retrograde access, the addition of dissection and reentry strategies, and improvement in specialty equipment is now christened as “the hybrid approach to CTO” (2,5). As robust observational and randomized data accrue in this area, it is now time to adopt a “hybrid approach” to CTO data interpretation. Rational assessments of the entire body of evidence for percutaneous CTO revascularization strategies and technologies will undoubtedly make complete revascularization more accessible to capable operators and ischemic patients. Although ongoing randomized trials will undoubtedly inform appropriate selection of patients with CTOs for complex PCI procedures, these very large observational series collectively suggest a vital role for the open artery in modifying future mortality.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. E. Magnus Ohman, Duke Clinical Research Institute, DUMC Box 3126, Durham, North Carolina 27710. E-mail: ohman001@mc.duke.edu.
REFERENCES


KEY WORDS mortality, PCI