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# Letters

RESEARCH CORRESPONDENCE

## The Presence of a CTO in a Non–Infarct-Related Artery During a STEMI Treated With Contemporary Primary PCI Is Associated With Increased Rates of Early and Late Cardiovascular Morbidity and Mortality

### The CTO-TOTAL Substudy

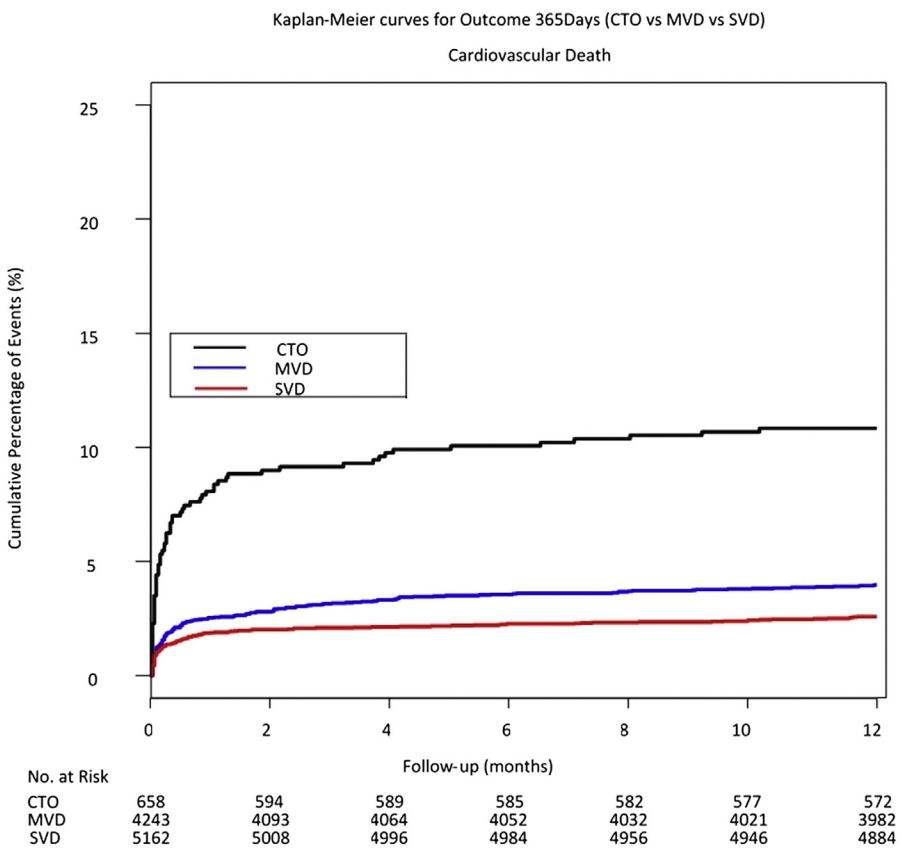
In patients with a ST-segment elevation myocardial infarction (STEMI), the prevalence of chronic total occlusion (CTO) in a non-infarct-related artery (non-IRA) is 8% to 15% (1) with 2-fold greater morbidity and mortality than in those with single-vessel disease (SVD) (2). The TOTAL (Thrombectomy Versus PCI Alone) trial was an international, multicenter, randomized trial of routine manual thrombectomy compared with percutaneous coronary intervention (PCI) alone in 10,732 STEMI patients treated with primary PCI (3). We sought to determine whether the presence of a CTO imparts a poorer prognosis above that of concurrent multivessel disease (MVD) at 365 days. A landmark analysis was also conducted, excluding those patients who had had a primary event within the first 30 days. For the CTO substudy, patients were divided into 3 groups based on the operator's angiographic assessment: 1) SVD, defined as <50% diameter stenosis in all non-IRAs; 2) MVD without a CTO, defined by at least 1 lesion with diameter stenosis 50% to 99% in 1 or more major non-IRA, and no lesions with 100% stenosis (1); and 3) CTO, defined as the presence of a 100% occlusion of a non-IRA.

Of 10,063 patients with complete angiographic reporting of all non-IRA, 658 (6.6%) had a CTO, 5,162 (51.3%) had SVD, and 4,243 (42.1%) had MVD. The relative frequencies of the location of the CTOs were right coronary artery (39%), left circumflex coronary artery (31%), left anterior descending coronary artery (23%), and double CTO (7%). CTO patients were older, more likely to be male, have greater rates of established cardiovascular risk factors, and worse hemodynamic profiles at presentation compared with SVD or MVD.

The presence of a CTO was associated with a significantly higher rate of cardiovascular death (10.8%) compared with SVD (2.6%; hazard ratio [HR]: 4.4, 95% confidence interval [CI]: 3.3 to 5.9; $p < 0.001$) or MVD (4%; HR: 2.85, 95% CI: 2.2 to 3.8; $p < 0.001$) (**Figure 1**). Patients with a CTO also had significantly higher rates of recurrent AMI, cardiogenic shock, major bleeding, and stroke (**Table 1**). Rates of target vessel revascularization were higher in those with a CTO (8.5%) as compared with SVD (3%; $p < 0.001$), but not compared with those with MVD (7.5%; $p = 0.2$). In multivariate analysis, the presence of a CTO was an independent predictor of cardiovascular death (HR: 2.0, 95% CI: 1.5 to 2.7; $p < 0.001$). In the landmark analysis, there were 605 patients with CTO, 5,065 patients with SVD and 4,132 with MVD. The presence of a CTO remained associated with greater rates of cardiovascular death compared with SVD and MVD (3% vs. 0.7% vs. 1.5%; $p < 0.001$ respectively). This represented a 4-fold greater risk of cardiovascular mortality compared with SVD ($p < 0.001$).

The present study demonstrated that with contemporary primary PCI techniques and optimal medical therapy, the presence of a CTO in a non-IRA remains a strong predictor of cardiovascular morbidity and mortality in both the short and long term following a STEMI. These results are in keeping with the findings of other trials (1). In particular, the presence of a CTO significantly increases the risk of cardiovascular death, above that of MVD, suggesting that this is not a reflection of a greater burden of coronary disease, but may in fact confer independent prognostic risk. These patients, with the so-called "double jeopardy" of a non-IRA CTO in the context of a STEMI, intuitively have a poorer early prognosis, owing to larger ischemic territories and, consequently, higher rates of cardiogenic shock at presentation. In the landmark analysis, even after excluding those patients, the presence of a CTO

**FIGURE 1 Cardiovascular Mortality at 365 Days**




Kaplan-Meier curves of rates of cardiovascular mortality within 365 days in chronic total occlusion (CTO), single-vessel disease (SVD), and multivessel disease (MVD).

significantly increased the risk of cardiovascular mortality, illustrating that the adverse effect of a CTO persists beyond the index presentation. The rates of target vessel revascularization were almost 3 times higher in the CTO group than in the SVD group, although there was no difference between the CTO and MVD group. Although data on revascularization of the CTO was not prospectively

**TABLE 1 Clinical Outcomes at 365 Days**

| | CTO (n = 658) | SVD (n = 5,162) | MVD (n = 4,243) | HR (95% CI) CTO vs. SVD | p Value | HR (95% CI) CTO vs. MVD | p Value |
|---|---|---|---|---|---|---|---|
| Primary outcome | 129 (19.6) | 297 (5.8) | 363 (8.6) | 3.71 (3.0–4.6) | <0.001 | 2.47 (2.0–3.0) | <0.001 |
| Cardiovascular death | 71 (10.8) | 132 (2.6) | 168 (4.0) | 4.42 (3.3–5.9) | <0.001 | 2.85 (2.2–3.8) | <0.001 |
| Recurrent MI | 36 (5.5) | 90 (1.7) | 117 (2.8) | 3.34 (2.3–4.9) | <0.001 | 2.10 (1.4–3.0) | <0.001 |
| Cardiogenic shock | 37 (5.6) | 69 (1.3) | 94 (2.2) | 4.39 (2.9–6.6) | <0.001 | 2.64 (1.8–3.9) | <0.001 |
| NYHA functional class IV heart failure | 34 (5.2) | 76 (1.5) | 92 (2.2) | 3.70 (2.5–5.5) | <0.001 | 2.51 (1.7–3.7) | <0.001 |
| Target vessel revascularization | 56 (8.5) | 156 (3.0) | 320 (7.5) | 3.07 (2.3–4.2) | <0.001 | 1.20 (0.9–1.6) | 0.218 |
| Major bleeding | 15 (2.3) | 65 (1.3) | 102 (2.4) | 1.90 (1.1–3.3) | 0.026 | 0.98 (0.6–1.7) | 0.951 |
| Stroke | 13 (2.0) | 32 (0.6) | 51 (1.2) | 3.39 (1.8–6.5) | <0.001 | 1.73 (0.9–3.2) | 0.077 |
| All-cause death | 77 (11.7) | 162 (3.1) | 199 (4.7) | 3.93 (3.0–5.2) | <0.001 | 2.62 (2.0–3.4) | <0.001 |

Values are n (%) except as noted.

CI = confidence interval; CTO = chronic total occlusion; HR = hazard ratio; MI = myocardial infarction; MVD = multivessel disease; NYHA = New York Heart Association; SVD = single-vessel disease.

collected, this may be a confounder because routine complete revascularization was not mandated, and treating physicians were not blinded.

The CTO TOTAL substudy is the largest STEMI study to our knowledge and first landmark analysis assessing the impact of a non-IRA CTO in patients managed with contemporary therapies, illustrating the adverse prognostic impact of non-IRA CTO on both short- and long-term outcomes. The implications of these findings, including revascularization of CTOs requires further assessment.

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RESEARCH CORRESPONDENCE

# Morphological Patterns of In-Stent Chronic Total Occlusions

## An Intravascular Ultrasound Study

This was a retrospective intravascular ultrasound (IVUS) study of mechanisms of in-stent restenosis (ISR) chronic total occlusions (CTOs). ISR CTOs were defined as TIMI (Thrombolysis In Myocardial Infarction) flow grade 0 within a stented lesion (including 5-mm margins) with estimated occlusion duration >3 months by clinical symptoms (1). From February 2003 to May 2016, there were 77 ISR CTOs in 77 patients treated at NewYork-Presbyterian Hospital (n = 37) and Showa University Northern Yokohama Hospital (n = 40). The ethics committee at each site approved the protocol on the basis of prior written informed consent.

IVUS was performed after guidewire crossing and pre-dilation (if necessary) with a 1.5- to 2.0-mm balloon. In-stent calcium (superficial hyperintensity with acoustic shadow) or attenuated neointimal tissue (attenuation without calcium) was considered to represent neoatherosclerosis.

Primary morphological patterns were: 1) in-stent neointimal hyperplasia (NIH) (excessive NIH without stent underexpansion or neoatherosclerosis); 2) stent underexpansion (minimum stent area [MSA] <5 $mm^2$); 3) proximal new lesion progression (occlusion within 5 mm proximal to the stent edge without excessive in-stent NIH); or 4) in-stent neoatherosclerosis.

The mean patient age was 63.5 years, 91% were men, and 41% presented with unstable angina (the rest with stable angina [50%] or silent ischemia [9%]). In 64%, occluded length was ≥20 mm, with 63% having Rentrop's collateral grade ≥2. Lesions with grade ≥2 collateral vessels presented later (7.3 ± 4.3 years vs 5.4 ± 5.0 years, respectively, p = 0.08). The ISR CTO was crossed by wire escalation in 74% (n = 57) and dissection or re-entry in 26% (n = 20).

Morphological patterns of ISR CTO were: 1) NIH in 30% (n = 23); 2) stent underexpansion in 22% (n = 17); 3) proximal new lesion in 25% (n = 19); and 4) neoatherosclerosis in 23% (n = 18). In 23 cases in which the ISR CTO was due to NIH, MSA was large (7.0 ± 1.9 $mm^2$) compared with 17 cases with stent underexpansion (MSA 3.9 ± 0.8 $mm^2$) in a normally sized vessel at the site of the original lesion (peristent plaque burden 64.5 ± 11.0%). In 19 cases in which the ISR CTO was due to a