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Clinical Endpoints and Key Data Elements in Percutaneous Coronary Intervention of Coronary Chronic Total Occlusion Studies

A Call to the Academic Research Consortium for Standardized Definitions

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Several investigators have published studies on clinical outcomes after coronary chronic total occlusion (CTO) percutaneous coronary intervention (PCI) (1–10). These studies, however, are characterized by significant heterogeneity in the definition of clinical endpoints and key data elements (**Table 1**), limiting interpretation and comparisons among studies. For example, some investigators included both technical and procedural success, whereas others reported only procedural or technical success. Moreover, the definition of technical success and by extension procedural success differs widely among studies. Also, the definition of major adverse cardiovascular and cerebrovascular events differs among studies. A compelling justification for standardized definitions specific to CTO studies is the absence of perforation from the definition of major adverse cardiovascular and cerebrovascular events in most studies. The interest in standardizing techniques and reporting practices led groups and organizations to create specific statements and guidelines for CTO PCI (11–14). Our purpose here is to highlight this heterogeneity, create awareness of the challenges associated with clinically assessing CTO PCI, and, more important, call for consistency among endpoint and procedural definitions used for reporting the results of CTO PCI.

How are we to proceed? To make the best use of empirical knowledge, we can learn from the Academic Research Consortium, which developed a set of consensus definitions for regular coronary stent trials (15). This informal collaboration between organizations in the United States and Europe acknowledged the mixed perspectives of physicians, regulatory bodies, and manufacturers. Therefore, the consortium enlisted academics, clinical trialists, device manufacturers, and representatives of the U.S. Food and Drug Administration. Two aspects of the group's effort are noteworthy: first, it was suggested that endpoint definitions should relate to overall device safety and effectiveness. Specifically, safety endpoints were meant to include any adverse event, whether device-related or not, and effectiveness was related to the effects of early and late relief of coronary obstruction (pathophysiological mechanism of action). Second, patient-oriented composite endpoints (e.g., all-cause mortality, any myocardial infarction, and need for repeat revascularization) were contrasted with device-oriented endpoints (cardiac death, target vessel myocardial infarction, or target lesion revascularization) to highlight the patient's perspective and capture the complex interplay among patient baseline characteristics, procedural factors, device performance, and possibly unrecognized factors affecting

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TABLE 1 Heterogeneity in Definitions and Endpoint Analysis Among Various Coronary Chronic Total Occlusion Percutaneous Intervention Outcome Studies

Study (Ref. #)	CTO Definition	Procedure/Technical Success Definition	MACCE	MI
J-CTO Registry (1)	Occlusion with no antegrade filling of the distal vessel other than via collateral vessels with duration >30 days	Residual stenosis <50%	Not reported (only individual components)	Q-wave MI or non-Q-wave MI (defined as post-procedural CK rise ≥3 × UNL)
Expert CTO (2)	TIMI flow grade 0 or 1 with duration >3 months	Residual stenosis <50% within the target lesion segment and absence of in-hospital MACE	All-cause death, MI (Q-wave and non-Q-wave), and clinically driven TLR	• ARC definition • Periprocedural MI: increase in CK-MB or troponin rise >3 × UNL within 48 h • MI per protocol: development of new pathologic Q waves by ECG or CK rise >2 × UNL associated with elevated CK-MB
PRISON III trial (3)	TIMI flow grade 0 with duration >3 months	NA	Death, MI, or TLR	Presence of new significant Q waves or an elevation of CK or CK-MB >2 × UNL
Explore trial (4)	100% occlusion without antegrade flow or with antegrade or retrograde filling through collateral vessels	Residual stenosis <30% and TIMI flow ≤2 to at least 50% of the territory supplied by the CTO	Cardiac death, MI, or any repeat coronary intervention	ARC and third universal definition of periprocedural MI
Progress CTO (5)	TIMI flow grade 0 with duration estimated >3 months	Residual stenosis <30% within the stented segment and TIMI flow grade 3	Death, MI, recurrent symptoms requiring urgent TVR with PCI or coronary artery bypass graft surgery, tamponade requiring either pericardiocentesis or surgery, and stroke	MI: third universal definition of myocardial infarction (type 4 MI)
Recharge registry (6)	TIMI flow grade 0 with duration >3 months	Residual stenosis <30% within the stented segment and TIMI flow grade 3	Death, periprocedural MI, target vessel failure (followed by urgent repeat TVR with PCI or coronary artery bypass graft surgery), and stroke	Ongoing chest pain, changes on ECG, and positive cardiac enzymes
DECISION-CTO (7)	TIMI flow grade 0 with duration >3 months	NA	All-cause death, MI, stroke, and any revascularization	• Periprocedural MI: CK-MB >5 × UNL • Spontaneous MI: any cardiac enzyme elevation
EuroCTO (8)	NA	NA	All-cause death, nonfatal MI	NA
VA CART program (9)	100% stenosis presumed to be occluded for >3 months and not related to an acute clinical event prompting the procedure	Luminal diameter stenosis <50% in the CTO segment and no major adverse events (death, CABG surgery, or MI)	Not reported (only individual components)	• Periprocedural MI: NA • Rehospitalization for MI: third universal definition
OPEN CTO study (10)	100% occlusion with TIMI flow grade 0 with duration >3 months	Technical success: restoration of TIMI flow grade 2 or 3 and residual stenosis <50%, without occlusion of a significant side branch; procedural success: technical success and no MACCE	Long-term: death, MI, TVR, or target vessel reocclusion Procedural: in-hospital death, procedure-related MI, emergent coronary artery bypass grafting, stroke, or clinical perforation	Periprocedural MI: third universal definition types 4a and 5

ARC = Academic Research Consortium; CABG = coronary artery bypass graft; CK = creatine kinase; CTO = chronic total occlusion; ECG = electrocardiography; MACE = major adverse cardiovascular event(s); MACCE = major adverse cardiovascular and cerebrovascular event(s); MI = myocardial infarction; NA = not available; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction; TLR = target lesion revascularization; TVR = target vessel revascularization; UNL = upper normal limit.

outcomes. Such a collaboration is timely and necessary to guide the design and execution of subsequent studies on CTO PCI.

We may face as great or even greater challenges developing standardized reporting for CTO PCI. Some common ground for clinical endpoint reporting would be required to allow valid treatment comparisons between CTO PCI and optimal medical therapy or coronary artery bypass graft. The vast body of data of optimal medical therapy in the field of stable coronary disease cannot be overstated.

Recently, Galassi et al. (12) published an overview on appropriateness of CTO PCI. The investigators included key experts in the field of interventional cardiology. Their updated document was intended to facilitate the analysis, reporting, and comparison of clinical studies of various approaches to CTO. A closer examination of the studies' methodology would suggest that well-accepted definitions, such as of total coronary occlusion, would need reconsideration to properly compare studies (**Table 1**).

Standardized definitions of data elements and clinical endpoints of CTO PCI will allow effective communication among all interested parties, including patients, and allow comparisons. They would serve both clinical and regulatory purposes. Standardized definitions, however, would need to find a sensible balance between being too liberal or too strict, being overly focused on the long-term consequences or on the immediate results. Furthermore, they should be flexible enough to accommodate the rapidly changing technology and practice paradigms.

We call for a Chronic Total Occlusion Academic Research Consortium.

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