Percutaneous Recanalization of Chronically Occluded Coronary Arteries

A Consensus Document

Part I

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Remarkable progress in the percutaneous management of coronary artery disease has been achieved over the last decade. The scaffolding properties of coronary stents have resulted in percutaneous coronary intervention (PCI) becoming a predictable procedure, with reduced rates of acute closure and late restenosis compared with balloon angioplasty alone.[1,2] More recently, the site-specific delivery of antiproliferative agents from drug-eluting stents has been demonstrated to markedly attenuate vascular responses leading to neointimal hyperplasia, further reducing the occurrence of clinical and angiographic restenosis to <10% in most patients.[3,4] PCI in patients with acute coronary syndromes and acute myocardial infarction (AMI) has also been proven to save lives, reduce rates of myocardial infarction (MI), and enhance quality of life compared with alternative treatment modalities.[5–7]

With these advances in perspective, it is often stated that successful recanalization of chronic total occlusions (CTOs) of native coronary arteries represents the "last frontier" of PCI. This statement is made in deference to the fact that CTOs represent the most technically challenging lesion subset that interventional cardiologists face, with procedural success rates considerably lower than those achieved in nonoccluded coronary vessels or acutely occluded arteries. Moreover, no consensus exists with regard to the definition of CTO, the factors related to procedural failure and/or complications, and the optimal technical approach. Indeed, until recently, the clinical benefits of PCI in CTOs had not been demonstrated.

An international panel of 47 physicians from 9 countries was therefore convened in New York City for 2 days in January 2004, the purpose of which was to reach consensus on the current state of the art of CTO angioplasty (see Appendix in the online-only Data Supplement for a complete participant list). This goal was approached through a series of didactic lectures, roundtable discussions, breakout focus groups, and the performance of 14 live case demonstrations of CTO angioplasty by many of the world's most skilled operators in this subspecialty. The present report represents a synthesis of the findings from this meeting and also incorporates a literature review from the field of CTO intervention. Topics covered in Part I of this review include definitions, prevalence, and clinical presentation of CTOs; the anatomy and histopathology of coronary occlusions; experimental CTO models; and the clinical relevance and rationale for CTO revascularization. Part II will review the technical approach to and clinical outcomes after percutaneous intervention of CTOs and describe the novel devices and drugs approved and undergoing investigation for CTO recanalization.

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Definitions, Prevalence, and Clinical Presentation of Chronic Total Coronary Occlusion

Definitions

Any definition of coronary CTO must consider the degree of lumen narrowing, antegrade blood flow grade, and age of the occlusion. CTOs are characterized by significant atherosclerotic vessel narrowing with lumen compromise that results in either complete interruption of antegrade blood flow as assessed by coronary arteriography (Thrombolysis in Myocardial Infarction [TIMI] grade 0 flow), also known as "true" total occlusions, or with minimal contrast penetration though the lesion without distal vessel opacification (TIMI grade 1 flow), frequently referred to as "functional" total occlusions. In the absence of serial angiograms, the duration of coronary occlusion is difficult to specify with certainty and instead must be estimated from available clinical information related to the timing of the event that caused the occlusion, eg, acute MI or sudden change in angina pattern with ECG changes consistent with the location of the occlusion. However, in many patients the age of the CTO cannot be determined with confidence. Furthermore, the temporal criterion used to define a CTO has varied widely in prior reports, typically ranging from >2 weeks[8,9] to >3 months,[10] which in part explains interstudy differences in lesion characteristics and procedural success. In general, a total occlusion of duration >3 months may be considered "chronic."

Prevalence in the Population and in Patients Undergoing Angioplasty

The true prevalence of CTO in the general population is unknown because a certain proportion of patients with CTO are either asymptomatic or minimally symptomatic and never undergo diagnostic coronary arteriography. However, among patients with known or suspected coronary artery disease undergoing coronary angiography during a 1-year period, Kahn[11] documented 1 or more CTOs in approximately one third of cases during a 1-year period, 46% of which were judged suitable for coronary angioplasty in 1992.

According to data from the 1997–1999 National Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry, CTOs are most prevalent in the right coronary artery and least common in the circumflex artery and increase with advancing patient age.[12] Total occlusion of the right coronary artery was identified in 18.2%, 21.3%, and 22.8% of patients aged <65 years, 65 to 79 years, and ≥80 years, respectively ($P<0.05$). The influence of patient age on the rate of total occlusion was even more prominent in the left anterior descending artery (13.8%, 19.1%, and 21.5%, respectively; $P<0.001$) but not in the circumflex artery (11.0%, 13.2%, and 12.7%, respectively; P=NS). Nevertheless, despite presenting more often with CTO, older patients were significantly less likely to undergo attempted percutaneous CTO revascularization than younger patients (15.5%, 10.5%, and 10.4% in patients aged <65, 65 to 79, and ≥80 years, respectively; $P<0.001$).[12]

The National Cardiovascular Registry of the American College of Cardiology reported that angioplasty for CTO was attempted in 12% of 100 292 patients at 139 US hospitals undergoing PCI from January 1998 through September 2000.[13] The proportion of patients undergoing PCI for CTO was even higher (15.6%) in the 1997–1998 NHLBI Dynamic Registry report.[14]

A significant proportion of patients after AMI will develop a persistently occluded infarct-related artery, with the frequency of total occlusion depending on the timing and type of reperfusion therapy (thrombolysis versus primary angioplasty versus none), as well as the time interval to patency assessment.[15] In patients with ST-segment elevation AMI not treated with reperfusion therapy, an occluded infarct-related artery has been found in 87% of patients within 4 hours, 65% within 12 to 24 hours, 53% at 15 days, and 45% at 1 month.[16–18] As many as 30% of patients treated with thrombolytic therapy followed by conservative care have a chronically occluded artery 3 to 6 months after AMI.[19] In patients treated with primary balloon angioplasty or stenting during evolving AMI, chronic occlusion of an infarct-related artery due to either initial treatment failure or subsequent vessel reocclusion is found in 5% to 10% of patients at 6 to 7 months.[20,21]

Clinical Presentation

Patients with CTO undergoing PCI usually have symptomatic angina; in several large databases, only 11% to 15% of patients undergoing angioplasty for CTO were asymptomatic.[22,23] Conversely, the proportion of patients presenting with unstable angina due to a CTO is also fairly low (9% to 18%).[22–25] Thus, the majority of patients undergoing PCI for CTO have stable or progressive angina, whereas many asymptomatic patients with CTO are managed medically. A history of prior MI has been reported in 42% to 68% of patients with an angiographically demonstrated CTO.[22–26]

Stress-induced ischemia can typically be elicited in patients with CTO, especially in the absence of a history of prior MI. He et al[27] found reversible perfusion defects using stress myocardial single-photon emission CT (SPECT) in 83% of 71 patients without prior MI with single-vessel disease and CTO of a single coronary artery. Similarly, Aboul-Enein et al[28] documented severe and extensive stress perfusion defects in 56 patients with no prior MI and single-vessel CTO with the presence of collaterals. Adenosine SPECT imaging may be even more sensitive than exercise-induced stress imaging to detect perfusion defects in patients with CTO.[29]

Anatomy and Histopathology of CTOs

Percutaneous revascularization of CTOs is often complicated by the inability to cross or dilate the lesion, as well as a high incidence of restenosis and reocclusion. Understanding the anatomy and histopathology of these lesions may not only explain these occurrences but also provide insight to aid development of new revascularization therapies.

The histopathology of the chronically occluded coronary artery has been comprehensively described by Srivatsa and colleagues.[30] Chronic coronary occlusions most often arise from thrombotic occlusion, followed by thrombus organization and tissue aging.[31] Particularly relevant to PCI strategies for CTO recanalization is the histological finding that approximately half of all CTOs are <99% stenotic when observed

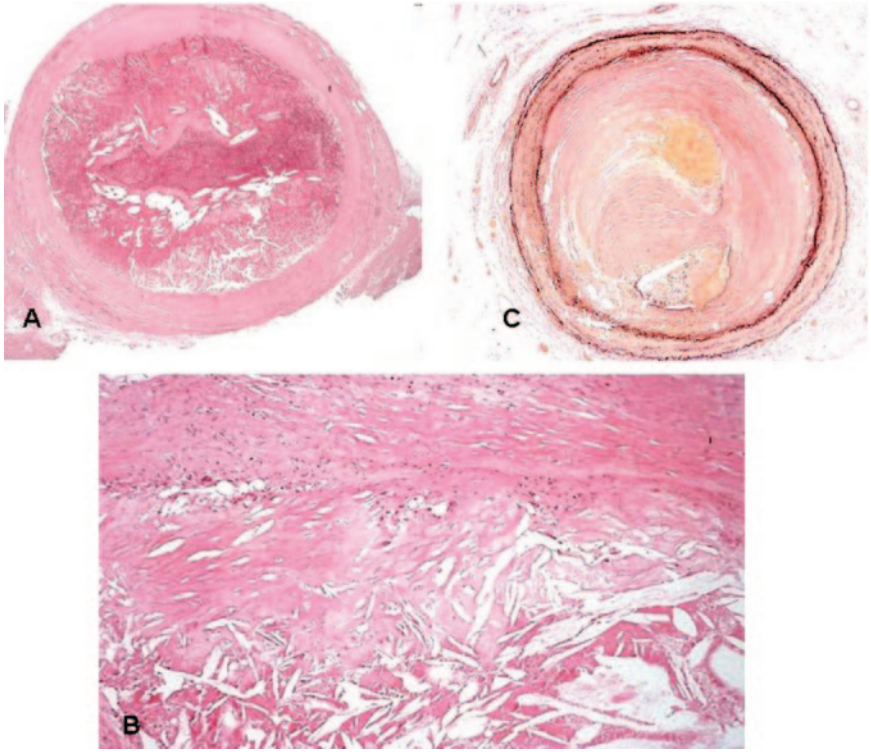

Figure 1. A, CTO, soft plaque (hematoxylin-eosin stain; magnification ×1). B, Magnified view of A, showing cholesterol clefts and loose fibrous tissue (hematoxylin-eosin stain; magnification ×10). C, CTO, hard plaque, dense fibrous tissue, and calcium (6 o'clock location). Note that the internal elastic lamina is intact (elastic van Gieson stain; magnification ×1).

by histopathology, despite the angiographic appearance of total occlusion with TIMI grade 0 antegrade flow. Moreover, little to no relationship exists between the severity of the histopathological lumen stenosis and either plaque composition or lesion age.

The typical atherosclerotic plaque of CTO consists of intracellular and extracellular lipids, smooth muscle cells, extracellular matrix, and calcium.[32] Collagens are the major structural components of the extracellular matrix,[33,34] with predominance of types I and III (and minor amounts of IV, V, and VI) in the fibrous stroma of atherosclerotic plaques.[35,36] The concentration of collagen-rich fibrous tissue is particularly dense at the proximal and distal ends of the lesion, contributing to a columnlike lesion of calcified, resistant fibrous tissue surrounding a softer core of organized thrombus and lipids.

Key histopathological attributes of CTO are calcification extent, inflammation, and neovascularization. The typical CTO may be classified as "soft," "hard," or a mixture of both (Figure 1). Soft plaque consists of cholesterol-laden cells and foam cells with loose fibrous tissue and neovascular channels and is more frequent in younger occlusions (<1 year old). Soft plaque is more likely to allow wire passage either directly through tissue planes or via neovascular channels into the distal lumen. Conversely, hard plaques are characterized by dense fibrous tissue and often contain large fibrocalcific regions without neovascular channels. These occlusions are thus more likely to deflect guidewires into the subintimal area, creating dissection planes. Hard plaques are more prevalent with increasing CTO age (>1 year old). Of note, however, areas of calcification frequently occur even in CTOs <3 months of age, although the extent and severity of calcification increase with occlusion duration. This age-related increase in calcium and collagen content of CTOs in part underlies the progressive difficulty during PCI in crossing older occlusions.

Inflammatory cell infiltrates in CTOs consist of macrophages, foam cells, and lymphocytes. Inflammation may exist in the intima, media, and adventitia of CTOs, although it is most predominant in the intima, regardless of lesion age. As fibrotic CTO lesions age, the vessels typically undergo negative remodeling with decreasing dimension of the external elastic membrane, a phenomenon due to adventitial vascular responses. Occasionally, though, plaque hemorrhage and inflammation may result in positive remodeling.[37]

Another hallmark of CTOs is extensive neovascularization, which occurs throughout the extent of the vessel wall (Figure 2). Capillary density and angiogenesis increase with increasing occlusion age. In CTOs <1 year old, new capillary formation is greatest in the adventitia. In CTOs >1 year old, the number and size of capillaries in the intima have increased to a similar or greater extent than those present in the adventitia. Relatively large (>250 μm) capillaries are frequently (47% to 67%) present throughout the CTO vessel wall, even in young occlusions, suggesting that angiogenesis within the CTO is an early event. Frequent colocalization of inflammation and neovascularization within the intimal plaque and adventitia suggests that these findings are closely related, although it is unclear whether inflammation is a cause or an effect of neovascularization in CTOs (Figure 2). Lymphocytes and monocytes/macrophages may play an active role in both angiogenesis and atherosclerotic lesion progression by producing a variety of mitogenic and angiogenic factors.[38]

A rich neovasculature network often traverses the CTO vessel wall, arising from the adventitial vasa vasorum across

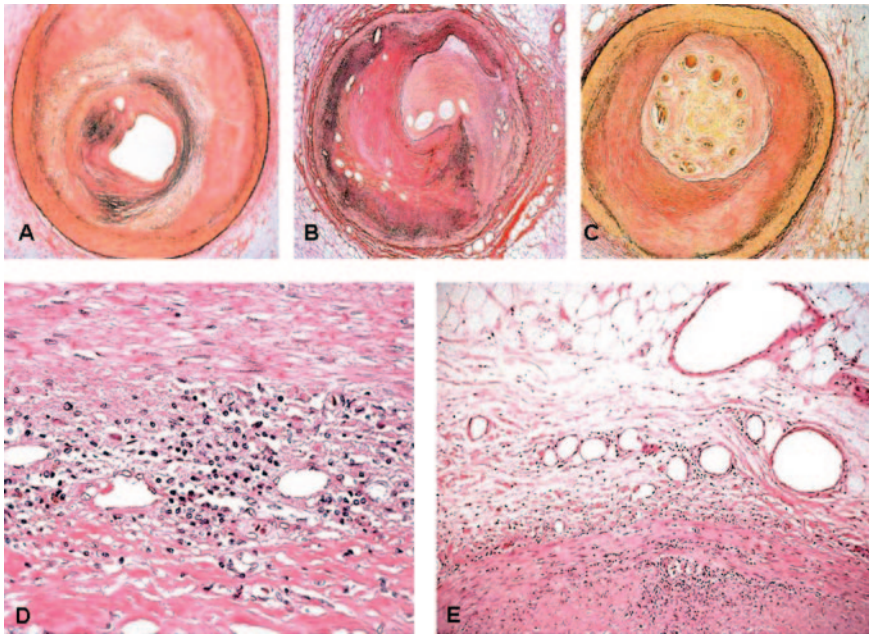

Figure 2. A, A single large channel is seen in this CTO. The area stenosis of this vessel is actually <90% (elastic van Gieson stain; magnification ×1). B, Traversing capillaries connect with the small recanalization channels in the center of this CTO (elastic van Gieson stain; magnification ×1). C, Small recanalization vascular channels are seen in the center of this CTO (elastic van Gieson stain; magnification ×1). D, Inflammation is found adjacent to vascular channels of the adventitia in this vessel (hematoxylin-eosin stain; magnification ×25). E, Adventitial capillaries have grown to large size in this CTO (hematoxylin-eosin stain; magnification ×40).

the media and into the lesion intima, suggesting that vessel ingrowth proceeds from the adventitia in younger lesions (Figure 3). An autopsy study of subtotal atherosclerotic lesions[39] demonstrated that new intimal vessels originate in the adventitial vasa vasorum of lesions with >70% stenosis but rarely from the coronary lumen. Such microchannels, which can recanalize the distal lumen, may result from thrombus-derived angiogenic stimuli[40] and are suggested on an angiogram of an old CTO without a well-defined stump. In this regard, the distinction should be made between ipsilateral epicardial angiographic "bridging" collateral vessels and true microvascular collaterals. Neochannels may also develop with organization of thrombus, connecting the proximal and distal lumens; this is suggested by a tapered CTO on an angiogram. Such channels may serve as a route for a guidewire to reach the distal vessel and hence may have therapeutic value.

Preclinical Models of CTOs

Spontaneous atherosclerotic plaque rupture and subsequent arterial occlusion do not occur naturally in any animal model, even among those models that have been genetically engineered to have increased atheroma formation. Recently, researchers have developed CTO models to guide therapeutic investigations and device development. The initial method of producing a total occlusion utilized external ligature or ameroid constriction, as developed by Elzinga[41] in 1969 and subsequently refined by Bredee et al.[42] A mechanical external occlusive device, however, does not replicate the histopathology of human occlusions or permit evaluation of the coronary

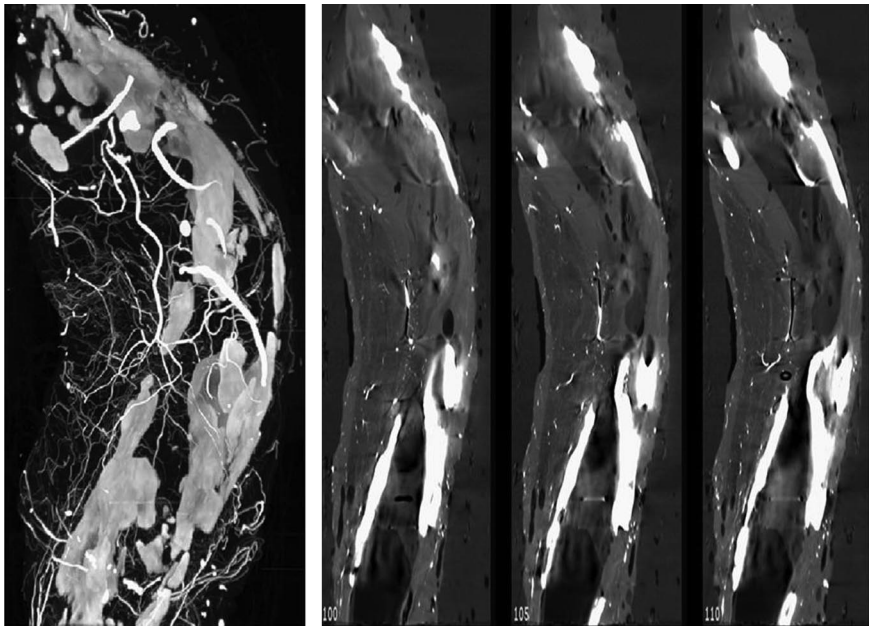

Figure 3. Microscopic CT images of a CTO. Left, The vasculature is filled with contrast in this 3-dimensional image of a chronic coronary occlusion. Bridging capillaries are readily seen connecting the adventitia with the interior of this lesion. The diffuse white areas are calcification. Right, Sequential sagittal sections of this lesion, showing the complete occlusion, bridging channels, and calcification.

TABLE 1. Long-Term Survival After Attempted Revascularization of CTOs in Unselected Patients Undergoing PCI, Stratified by Procedural Outcome

Study	No. of Patients	Success	Duration of Follow-up, y	Mortality, %		
				PCI Success	PCI Failure	*P*
Mid America Heart Institute[58]	2007	1491 (74.4%)	10	26.6	35.0	0.001
British Columbia Cardiac Registry[59]	1458	1118 (76.7%)	1	10.0	19.0	<0.001
TOAST-GISE[22]	369	286 (77.5%)	6	1.1	3.6	0.13

artery remodeling process and as such is unable to facilitate the development of devices to recanalize CTOs.

Subsequent techniques for endoluminal formation of CTOs in coronary and peripheral arteries have differed in their fundamental approach. Murphy et al[43] evaluated 4 methods in a rabbit iliac model for developing peripheral arterial thrombosis obliterans: (1) drying the endothelium with carbon dioxide gas; (2) gas-drying the artery plus mechanical injury; (3) gas-drying plus induced thrombosis of the treated segment with the use of thrombin; and (4) gas-drying, mechanical injury, and induced thrombosis followed by a high-cholesterol diet. Of these, gas-drying with thrombin and a high-cholesterol diet was the most efficacious. Strauss et al[44] subsequently modified the thrombin injection model by infusing collagenase before wire passage. Several characteristics of human CTOs were evident in this model, including mature fibrous tissue, multiple small intraluminal vascular channels, occasional extracellular lipid deposits, and disruption of the internal elastic lamina. Yoon and colleagues[45] developed a CTO model in rabbit and porcine superficial femoral arteries by creating a stenosis and then injecting autologous blood clot above the stenosis. Organization of these initially thrombotic occlusions into mature, fibrotic CTOs was evident at 4 weeks in the porcine model and by 10 weeks in the rabbit model. Other CTO models have included stents with occluded outflow[46] and even direct alcohol injection[47] to promote thrombosis.

Developing an accurate and reproducible humanlike coronary CTO model has been a complex undertaking because (1) coronary vessels are less amenable to a direct surgical approach; (2) simulating luminal and medial pathology, including microcalcification, has been difficult; and (3) an inflammatory component must be present to mimic human CTO lesions.[30,31] Balloon angioplasty and stent implantation in animal coronary arteries, both standard methods of denuding the vessel and engendering neointimal proliferation, rarely result in CTO development. More aggressive measures that have been tried involved the use of thermal injury and copper stent implantation.[48,49] The vascular response to injury differs between these 2 methods, with neither perfectly replicating the human CTO; copper stents result in a dense inflammatory response with neointimal proliferation, whereas thermal injury induces adventitial remodeling with a decrease in vessel size and limited neointimal proliferation.

Polymers have also been used to invoke chronic coronary occlusions. Early polymeric implants were abandoned as stent platforms because they induced severe inflammatory responses and vessel occlusion.[50] Bailey et al[51] reported placement of a microporous poly L-lactic acid polymer into pig and dog coronary arteries; the polymer is absorbed by 28 days, resulting in a microchanneled occlusion histologically similar to a human CTO. These and other animal models may contribute to a deeper understanding of the biology of human CTOs and enable new device and pharmacological investigation to improve recanalization success in these challenging lesions.

Clinical Relevance and Rationale for CTO Revascularization

Although 1 or more totally occluded coronary vessels is identified in as many as one third of diagnostic coronary angiograms, recanalization of a CTO is attempted in only 8% to 15% of patients undergoing PCI.[12–14,52] In the Emory Angioplasty versus Surgery Trial (EAST), the presence of a CTO was the most common reason for referral to bypass surgery.[53] Similarly, in the Bypass Angioplasty Revascularization Investigation (BARI) trial, of 12 530 patients who were clinically eligible for randomization to angioplasty versus bypass graft surgery, 8000 patients were deemed angiographically ineligible, with the most common reason being the presence of 1 or more CTOs (68% of patients).[54] The disparity between the frequency of CTO and percutaneous treatment underscores not only the technical and procedural complexities of this lesion subtype but also the clinical uncertainties with regard to which patients benefit from CTO revascularization.

In addition to relief of symptomatic ischemia and angina, theoretical benefits of CTO revascularization include enhanced left ventricular function, reduced predisposition to ventricular arrhythmias, and improved tolerance of contralateral coronary occlusion. The Survival and Ventricular Enlargement (SAVE) Investigators noted that persistent occlusion of the infarct-related artery after AMI was associated with a relative risk of 1.47 in adjusted 4-year mortality,[55] implying that successful restoration of late infarct artery patency may improve long-term outcomes. Until recently, however, few studies have examined the clinical benefits of CTO recanalization.[56,57]

Three retrospective observational studies have now reported the clinical impact of successful percutaneous CTO revascularization on long-term survival (Table 1). In a consecutive series of 2007 patients undergoing intended PCI of a nonacute coronary occlusion at the Mid America Heart Institute between 1980 and 1999, technical success was achieved in 74.4% and procedural success in 69.9% of cases.[58] Compared with those patients in whom the procedure was successful, the in-hospital occurrence of major adverse cardiac events was significantly higher among patients with

TABLE 2. Outcomes of Randomized Trials of PCI vs Medical Therapy in Patients With Occluded Coronary Arteries After MI

Trial Acronym	No. of Randomized Patients	Time From MI to Randomization	PCI Success	Duration of Follow-up	Major Findings
TAMI-6[68]	71	24 h	81%	6 mo	LV function was improved at 1 mo, but no clinical differences were present by 6 mo.
TOMIIS[65]	44	24±13 d	72%	4 mo	Reocclusion was found in 40% of patients at 4 mo randomized to balloon angioplasty. LVEF was significantly greater in patients with a patent infarct artery. Clinical events occurred with similar frequency in both groups.
Horie et al[69]	83 (all LAD)	8±10 d	93.2%	50±24 mo	At 6 mo LVEF and infarct zone regional wall motion were similar in both groups, though LVEDV was smaller in the PCI group. At late follow-up, death tended to be reduced in the PCI arm (2.3% vs 12.9%; $P=0.06$), and PCI reduced the composite incidence of death, reinfarction, and CHF (9.1% vs 48.7%; $P<0.0001$).
TOAT[66]	66 (all LAD)	26±18 d	94%	12 mo	LVEDV and LVESV at 12 mo were greater in the PCI group. Exercise duration from 6 wk to 12 mo increased to a greater degree in the PCI group. At 12 mo, significantly less functional impairment and better quality of life were present in the PCI group.
DECOPI[67]	212 (83% non-LAD)	8 d (median)	96%	34 mo (mean)	The infarct artery at 6 mo was patent in 82.8% of the PCI group vs in 34.2% of those treated medically ($P<0.0001$). LVEF was greater, however, by 3.5% in the PCI arm ($P=0.025$). The primary clinical end point of death, nonfatal reinfarction, and ventricular tachyarrhythmias at 34 mo occurred in 8.7% of medically treated patients vs 7.3% undergoing PCI ($P=0.64$).

TAMI indicates Thrombolysis and Myocardial Infarction; TOMIIS, Total Occlusion Post-Myocardial Infarction Intervention Study; TOAT, The Open Artery Trial; DECOPI, Deobstruction Coronaire en Post-Infarctus; LV, left ventricular; LVEF, left ventricular ejection fraction; LAD, left anterior descending artery; LVEDV, left ventricular end-diastolic volume; CHF, congestive heart failure; and LVESV, left ventricular end-systolic volume.

procedural failure (3.2% versus 5.4%; $P=0.02$). Long-term survival was similar in patients with successful CTO recanalization compared with a matched cohort of patients undergoing successful angioplasty of nonoccluded lesions and significantly greater than in patients in whom attempted CTO revascularization failed (10-year survival 73.5% with CTO success versus 65.0% with CTO failure; $P=0.001$). By multivariate analysis, failure to successfully recanalize the CTO was an independent predictor of reduced survival (hazard ratio 1.4; $P<0.0003$).

Similarly, a time-independent benefit of total occlusion recanalization has been observed in the British Columbia Cardiac Registry, in which attempted revascularization of CTO lesions accounted for >15% of all PCI procedures.[59] Among 1458 patients with CTOs, successful percutaneous revascularization was associated with increased survival and a reduced need for surgical revascularization over a 7-year follow-up period (both $P<0.001$). CTO success was associated with a 56% relative reduction in late mortality (hazard ratio 0.44; 95% CI, 0.30 to 0.64).

Finally, in the prospective Total Occlusion Angioplasty Study–Società Italiana di Cardiologia Invasiva (TOAST-GISE), successful PCI of a CTO (attempted in 390 lesions in 369 patients) was associated with a reduced 12-month incidence of cardiac death or MI (1.1% versus 7.2%; $P=0.005$), a reduced need for coronary artery bypass surgery (2.5% versus 15.7%; $P<0.0001$), and greater freedom from angina (88.7% versus 75.0%; $P=0.008$).[22] In the overall study population, the only factor associated with enhanced 1-year event-free survival was successful CTO recanalization (odds ratio 0.24; $P=0.018$).

Other studies have demonstrated statistically significant improvements in left ventricular function and regional wall motion with successful CTO recanalization.[60–63] Importantly, improved left ventricular function in this setting may be conditional on revascularization of total occlusions of younger age (≤6 weeks) and sustained vessel patency at follow-up.[60,61] Moreover, contrast MRI may identify viable and ischemic myocardium subtended by a CTO that may benefit from revascularization. In a study by Kim et al,[64] 37 of 44 patients with 58 CTO segments and fixed SPECT perfusion defects had only subendocardial infarction involving <50% of the thickness of the left ventricle by MRI, including 12 patients (21%) in whom no evidence of infarction was present. Territories without extensive infarction at baseline demonstrated significant regional wall motion improvement after PCI, with subsequent resolution of ischemia demonstrated by adenosine stress MRI.

In contrast to these studies examining the outcomes of PCI in unselected patients with CTO (most of whom were symptomatic and had viable myocardium), 5 modest-sized randomized trials have examined the benefits of routine recanalization of occluded coronary arteries after AMI, irrespective of left ventricular function and clinical status (Table 2). The results of these trials in regard to the benefits of routine PCI in improving late remodeling, exercise duration,

freedom from symptoms, and adverse events have varied, possibly reflecting differences in study design, angioplasty technique (balloon angioplasty versus stents), adjunctive pharmacology, follow-up duration, and end points.[65–69] The definitive answer about the benefits of routinely recanalizing totally occluded vessels in the convalescent phase of MI should be provided from the Occluded Artery Trial (OAT), an ongoing investigation sponsored by the National Institutes of Health in which 3200 patients with an occluded vessel within 3 to 28 days after AMI are being randomized to PCI versus medical therapy, with follow-up continued for 2.5 years.[15]

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Disclosure

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KEY WORDS: angioplasty ■ coronary disease ■ occlusion ■ prognosis ■ revascularization

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