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Percutaneous Coronary Intervention of Chronic Total Occlusions in Patients with Diabetes Mellitus: a Treatment-Risk Paradox

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Abstract

Purpose of Review Diabetes mellitus (DM) is highly prevalent among patients undergoing percutaneous coronary intervention (PCI) for chronic total occlusions (CTOs). This review aims to summarize the available evidence on CTO recanalization in patients with DM.

Recent Findings Coronary artery bypass grafting (CABG) surgery is the recommended revascularization modality for patients with DM and multivessel coronary artery disease (CAD). However, the optimal management strategy in diabetic patients with CTO and single-vessel disease or prior CABG remains a clinical dilemma. Contemporary, large-scale, observational registries support the notion that CTO PCI, if performed at high-volume CTO PCI centers by highly experienced operators, conveys similar high procedural success and low complication rates in patients with and without DM. Although DM patients have more frequently CTOs and may derive greater benefit from complete revascularization, they are less frequently exposed to CTO PCI than non-DM patients (*treatment-risk paradox*).

Summary CTO PCI performed by highly experienced operators constitutes a safe and effective treatment option for selected diabetic CTO patients who are not candidates for CABG. Randomized studies are warranted to compare long-term outcomes of CTO PCI and medical therapy in this high-risk subset.

Keywords Chronic total occlusion · Percutaneous coronary intervention · Diabetes mellitus · Coronary revascularization

Abbreviations

CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CTO	Chronic total occlusion
DES	Drug-eluting stent
DM	Diabetes mellitus
MACE	Major adverse cardiac events
MI	Myocardial infarction
PCI	Percutaneous coronary intervention
RCT	Randomized controlled trial
TLR	Target lesion revascularization
TVR	Target vessel revascularization

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Introduction

Percutaneous coronary intervention (PCI) for chronic total occlusions (CTOs) is a rapidly evolving area of interventional cardiology. If performed at high-volume CTO PCI centers and by highly experienced operators, the latest refinements in CTO PCI equipment and techniques, including the recent introduction of the *hybrid* approach which entails a tailored strategy based on angiographic characteristics (i.e., antegrade vs. retrograde approach and wire escalation vs. dissection re-entry crossing techniques) [1], enabled high procedural success rates (85–90%) while maintaining acceptable low major

complications rates (~3%) [2–5]. These results have contributed to a renewed interest for CTO PCI and the increase in the number of CTO recanalizations, as well as in the patient and lesion complexity approached [3–6].

Diabetes mellitus (DM) is highly prevalent among patients with coronary artery disease (CAD) [7] and is associated with greater atherosclerotic burden, including diffuse, small-vessel, and multivessel disease, coronary artery calcifications, and higher rates of left main coronary stenoses and CTOs [7–10]. The presence of DM is considered as a major determinant when selecting the optimal myocardial revascularization strategy (i.e., PCI vs. coronary artery bypass grafting [CABG]) in patients with multivessel CAD [11, 12•, 13]. Compared with individuals without DM, diabetic patients undergoing PCI with newer-generation drug-eluting stents (DES) have increased long-term major adverse cardiac events (MACE) rates, driven by higher rates of repeat revascularization, irrespective of the underlying CAD complexity [14–16]. Although, even with CABG surgery, DM is associated with an increased risk of complications [17, 18], current evidence from dedicated randomized controlled trials (RCTs), subgroup analyses of RCTs, and observational data consistently favors CABG as the revascularization modality of choice for patients with DM and multivessel CAD [11, 12•]. Nevertheless, PCI remains an established alternative treatment for selected diabetic patients with CTO and single-vessel disease or prior CABG [11, 12•]. This review aims to provide an overview of the currently available evidence on CTO recanalization in patients with DM, with a special emphasis on procedural success, periprocedural complications, and long-term MACE rates.

Specificities of Coronary Artery Disease in Diabetes Mellitus

DM is present in 20 to 30% of patients undergoing myocardial revascularization [11, 12•]. The accelerated atherosclerotic burden observed in diabetic individuals is believed to result from the combination of prothrombotic and proinflammatory states, systemic endothelial dysfunction, and metabolic disorders, including hyperglycemia, dyslipidemia, obesity, insulin resistance, and oxidative stress [7]. Compared with non-diabetic individuals, patients with DM have more extensive and complex coronary atherosclerotic disease, including multivessel, diffuse, and small-vessel CAD and coronary artery calcifications, and a twofold higher rate of CTOs [8–10]. The greater burden of anatomical coronary complexity observed in patients with DM as compared with non-DM individuals results in more challenging myocardial revascularization and higher degrees of residual jeopardized myocardium by the means of both PCI and CABG surgery [7, 19].

Complete myocardial revascularization was consistently associated with favorable long-term clinical outcomes, including lower mortality, myocardial infarction (MI), and repeat revascularization rates among patients with complex or multivessel CAD undergoing both PCI and CABG surgery [20, 21]. This was found to be true also for DM patients, as incomplete revascularization was associated with a higher risk of long-term MACE including death, MI, stroke, or repeat revascularization, among patients with DM compared with diabetic individuals completely revascularized, irrespective of the revascularization modality [19, 22]. In a post hoc analysis of the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial including 751 diabetic patients undergoing myocardial revascularization by the means of PCI using bare-metal stents or first-generation DES ($n = 487$), or CABG surgery ($n = 264$) [19], complete revascularization was achieved in only 38% of patients, whereas mildly and moderately to severely incomplete revascularization occurred in 47% and 15% of patients, respectively. Compared with patients incompletely revascularized, complete anatomical revascularization was associated with lower rates of the composite outcome of death, MI, or stroke, as well as repeat revascularization, irrespective of the revascularization strategy (PCI or CABG) [19]. Previous studies suggest that complete revascularization among patients with multivessel CAD is more commonly achieved with CABG surgery than with PCI [19, 20, 23•]. In the Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) trial, the significantly lower rates of complete revascularization observed among patients who underwent PCI compared with CABG surgery (34.3% vs. 64.8%, $p < 0.001$, respectively) resulted from extremely low CTO PCI procedural success rates achieved with PCI as compared with CABG surgery (49.4% vs. 68.1%, respectively) [23•]. The presence of a CTO was shown to be the strongest independent predictor of incomplete revascularization among patients with complex or multivessel CAD treated by PCI (hazard ratio (HR) 2.70, 95% CI 1.98–3.67, $p < 0.001$) [23•]. Among CTO patients undergoing PCI, heavy coronary artery calcifications and long lesions, which are observed more frequently among patients with DM than in non-diabetic individuals [8–10], were also independent predictors of incomplete myocardial revascularization [23•].

Current evidence supports CABG surgery over PCI as the preferred revascularization modality for diabetic patients with multivessel CAD [11, 12•, 13, 24, 25]. In the SYNTAX trial [24], PCI with first-generation DES in patients with complex multivessel CAD resulted in significantly higher rates of MACE, including all-cause death, MI, or stroke, as well as repeat revascularization, at 5 years compared with CABG. More recently, CABG surgery was found to be superior to PCI with mostly first-generation DES on the background of optimal medical therapy with respect to the composite

outcome of all-cause death, nonfatal MI, or stroke at 5 years in the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial [25]. Notwithstanding, the optimal revascularization strategy for selected diabetic patients with single-vessel CTO or recurrent disease after CABG remains a clinical dilemma, and PCI is frequently proposed to this high-risk patient subset.

CTO and Diabetes Mellitus

CTOs are observed in 16 to 52% of patients undergoing coronary angiography [26••]. Despite the lack of definitive randomized evidence on the beneficial effects of CTO PCI compared with optimal medical therapy, observational cohort studies demonstrated that successful CTO PCI, as opposed to a failed procedure, is associated with improved clinical outcomes including lower risk of mortality, MACE, residual angina, and the need for CABG surgery [26••, 27]. Nonetheless, CTO PCI remains widely underused worldwide with the exception of dedicated high-volume CTO PCI centers [26••], as the majority of CTO patients are currently treated with either CABG surgery or medical therapy alone [26••, 28]. The probable explanation for this finding is that, compared with non-CTO PCI, CTO recanalization is a complex procedure requiring dedicated skillset and equipment, which is associated with lower procedural success rates, higher major complications risk, and increased radiation exposure to patient and operator [29]. Among patients undergoing CTO recanalization, DM is common with a prevalence ranging from 27 to 45% in large contemporary registries [30••, 31••, 32••]. Among patients with complex or multivessel CAD undergoing PCI, the presence of CTO was shown to negatively impact the degree of revascularization completeness and long-term clinical outcomes, including mortality, repeat revascularization, or stent thrombosis [23•]. These findings do apply more to DM patients because of the twofold higher prevalence of CTOs observed in patients with DM compared with non-diabetic individuals [8]. Whereas DM confers per se significantly worse prognosis in CAD patients undergoing coronary revascularization compared with non-diabetic individuals, additional cardiovascular risk factors and comorbidities that individually negatively impact cardiovascular outcomes are also more prevalent in DM patients. Baseline clinical and angiographic characteristics of patients with and without DM included in most contemporary large-scale CTO PCI registries are summarized in Table 1. Overall, diabetic patients undergoing CTO PCI had a higher baseline cardiovascular risk profile than non-diabetic individuals. Importantly, patients with DM were more likely to have a history of prior CABG, which has been invariably associated with lower success rates following CTO PCI [33–35].

CTO PCI and Diabetes Mellitus

Although, as mentioned, CTOs are more prevalent among patients with DM [8], CTO PCI is performed less commonly in diabetic patients compared with non-diabetic individuals [36, 37]. The fact that high-risk patients are less frequently treated than lower risk individuals, a so-called *treatment-risk paradox*, is not new in the field of PCI [7]. Diabetic patients remain at increased risk for long-term MACE following PCI even with newer-generation DES, driven by higher rates of target lesion revascularization (TLR), irrespective of the underlying CAD complexity [16]. However, data concerning the impact of DM on long-term clinical outcomes after CTO PCI in patients with DM in the DES era are scant. In the absence of dedicated trials, the evidence is limited to subgroup analyses of large-scale, prospective, observational studies [30••, 31••, 32••, 38–44]. Notwithstanding, interpretation of these data is limited by the number of diabetic patients included, the low proportion of patients with more advanced DM such as insulin-dependent diabetic subjects, and the short-term follow-up period, precluding therefore any definitive conclusion with respect to longer-term clinical outcomes after CTO PCI in diabetic patients.

Early Studies

Early evidence reporting on the clinical outcomes of patients with DM undergoing CTO PCI was mostly limited to small single-center, observational studies and demonstrated conflicting results. In a single-center registry, clinical outcomes of 506 diabetic patients who underwent CTO PCI were compared with 506 patients with DM undergoing PCI of a non-CTO using propensity score matching [38]. Whereas angiographic success rates were significantly lower in diabetic CTO patients (75% vs. 93%, $p < 0.001$), rates of in-hospital MACE, a composite of death, urgent CABG, Q wave MI, or target vessel revascularization (TVR) were similar between CTO and non-CTO diabetic patients (3.2% vs. 2.6%, $p = 0.57$) [38]. Five-year survival rates were not different between CTO and non-CTO diabetic subjects (75% vs. 79%, $p = 0.20$) and there were no significant differences with respect to in-hospital (success 1.6% vs. failure 2.4%, $p = 0.70$) or 1-year mortality (success 22.2% vs. failure 26.8%, $p = 0.30$) among diabetic CTO patients according to angiographic CTO PCI success [38]. In a single-center registry including 163 patients (diabetics, $n = 34$; non-diabetics, $n = 129$) who underwent successful CTO PCI [39], rates of in-hospital MACE, a composite of death, Q wave, or urgent TVR were significantly higher among diabetic patients compared with patients without DM (23.5% vs. 7.8%, $p = 0.02$), mainly driven by a significantly increased risk of repeat revascularization (20.6% vs. 7%, $p = 0.04$) in subjects with DM [39]. However, long-term MACE rates were not statistically different between

Table 1 Baseline characteristics of patients with and without diabetes mellitus included in recent large contemporary CTO PCI registries

Characteristics	PROGRESS CTO registry [32••]			Sanguinetti et al. [33]			OPEN-CTO registry [34]		
	Diabetes ($n = 584$)	No diabetes ($n = 724$)	p value	Diabetes ($n = 362$)	No diabetes ($n = 958$)	p value	Diabetes ($n = 412$)	No diabetes ($n = 588$)	p value
Age (years)	65.3 ± 9.6	65.7 ± 10.6	0.26	65.5 ± 10.4	62.2 ± 11.6	< 0.0001	65.5 ± 9.9	65.3 ± 10.6	0.79
Male gender (%)	82.5	85.5	0.13	82.3	86.7	0.04	76.5	83.2	0.008
BMI (kg/m^2)	31.3 ± 6.4	29.2 ± 5.7	0.001	28.7 ± 4.6	26.7 ± 4.0	< 0.0001	32.2 ± 6.4	29.2 ± 5.4	< 0.001
Hypercholesterolemia (%)	96.4	92.8	0.005	63.3	63.5	0.94	NR	NR	NR
Hypertension (%)	NR	NR	NR	72.8	54.0	< 0.0001	NR	NR	NR
Current smoker (%)	26.3	29.6	0.29	21.8	28.6	0.01	12.3	14.3	0.37
Prior MI (%)	41.9	42.2	0.92	22.7	21.8	0.74	53.6	44.7	0.005
Prior PCI (%)	65.4	64.4	0.69	NR	NR	NR	68.9	63.4	0.07
Prior CABG (%)	38.1	31.0	0.007	10.2	6.4	0.01	42.2	32.5	0.001
PAD (%)	18.9	12.8	0.003	NR	NR	NR	21.6	14.6	0.004
LVEF (%)	NR	NR	NR	55.7 ± 9.0	57.0 ± 9.6	0.04	49.8 ± 13.7	51.8 ± 13.8	0.06
J-CTO score	2.6 ± 1.2	2.5 ± 1.2	0.82	1.5 ± 0.8	1.3 ± 0.9	0.02	2.4 ± 1.3	2.3 ± 1.2	0.03
CTO length (mm)	NR	NR	NR	18.3 ± 13.4	18.2 ± 14.9	1.00	63.7 ± 29.1	59.1 ± 27.9	0.01
CTO vessel (%)			0.34						0.48
Left anterior descending artery	22.8	23.6		31.2	31.1	0.97	19.2	21.9	
Left circumflex artery	21.6	18.3		25.4	21.6	0.14	17.2	16.7	
Right coronary artery	55.6	58.1		42.8	47.2	0.16	62.4	60.9	

Values are mean ± standard deviation. *NR* not reported, *BMI* body mass index, *CABG* coronary artery bypass grafting, *CTO* chronic total occlusion, *J-CTO* Japan chronic total occlusion, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *PAD* peripheral artery disease, *PCI* percutaneous coronary intervention

both groups at a mean follow-up of 15 months (35.3% vs. 28.5%) [39].

In the Multinational CTO Registry including 1742 patients (diabetics, $n = 395$; 23%; insulin-dependent diabetics, $n = 164$, 42% of the diabetic population) [40], the procedural success rates were similar in patients with versus without DM (69.6% vs. 67.9%, $p = 0.53$). Among diabetic patients, successful CTO PCI was associated with lower long-term mortality rates (10.4% vs. 13.0%, $p < 0.05$) and reduced need for CABG (2.4% vs. 15.7%, $p < 0.01$) at a median follow-up of 3 years [40]. Multivariate analysis identified insulin-dependent DM as an independent predictor of all-cause mortality among patients with DM (HR 2.25, 95% CI 1.04–4.87, $p = 0.04$) [40]. In a subanalysis of the multicenter, randomized CIBELES trial including 207 patients (diabetics, $n = 75$; insulin-dependent diabetics, 21%) undergoing successful CTO PCI with DES [41], the cumulative survival rates free from MACE (86.3% vs. 87.5%, $p = 0.80$), death (97.3% vs. 99.2%, $p = 0.27$), MI (100% vs. 97.7%, $p = 0.19$), and TVR (88.7% vs. 88.2%, $p = 0.90$) were similar between patients with and without DM at 12 months follow-up. Conversely, in a large-scale Korean multicenter CTO registry including 2865 patients (977 diabetic patients, 34%) who underwent CTO PCI with DES [42], successful CTO PCI (83% of the overall patient population), defined as reduction in angiographic minimum diameter stenosis to < 30% in presence of thrombolysis in myocardial infarction (TIMI) grade 2 flow, was associated with significantly the higher crude rates of TLR (6.1% vs. 3.9%, $p = 0.02$), TVR (7.2% vs. 4.8%, $p = 0.02$), MACE (10.3% vs. 7.7%, $p = 0.01$), and the combined endpoint of cardiac death, MI, or TLR (7.7% vs. 5.5%, $p = 0.02$) among patients with DM compared with non-diabetic individuals. Among diabetic patients, the all-cause mortality (6.1% vs. 1.9%, $p = 0.02$), TLR (11.3% vs. 4.6%, $p = 0.007$), TVR (12.2% vs. 5.9%, $p = 0.025$), MACE (17.4% vs. 9.2%, $p = 0.012$), and combined endpoints of cardiac death, MI, or TLR (8.0% vs. 5.9%, $p = 0.003$) and cardiac death, MI, or TVR (16.5% vs. 8.0%, $p = 0.008$) rates were significantly more frequent in patients with insulin-dependent than non-insulin-dependent DM [42]. In a multivariate analysis, DM was an independent predictor for the 1-year TLR (odds ratio (OR) 2.20, $p = 0.001$) and MACE (OR 1.68, $p = 0.002$), whereas insulin-dependent DM was an independent predictor for the 1-year all-cause death (OR 3.19, $p = 0.04$), TLR (OR 2.93, $p = 0.005$), TVR (OR 2.44, $p = 0.02$), MACE (OR 2.21, $p = 0.01$), and combined endpoints of cardiac death, MI, or TLR (OR 2.91, $p = 0.003$) and cardiac death, MI, or TVR (OR 2.35, $p = 0.009$) [42]. These findings persisted after

propensity score-matched analysis to account for differences in baseline demographic and lesion characteristics. The results of CTO registries reporting the initial experience of CTO PCI in diabetic versus non-diabetic patients were pooled in a recent meta-analysis of 7 trials (one randomized trial, 6 observational studies) including a total of 4571 patients (1915 subjects with type 2 DM) undergoing CTO PCI [43]. While acute procedural results were not reported, the all-cause mortality (OR 1.56, 95% CI 1.05–2.31, $p = 0.03$), MACE (OR 1.30, 95% CI 1.06–1.58, $p = 0.01$), and repeat revascularization (OR 1.30, 95% CI 1.06–1.59, $p = 0.01$) were significantly higher in CTO diabetic patients at long-term follow-up (≥ 1 year) [43].

Recent Studies

Recently, several studies reported the outcome results of contemporary cohorts of diabetic patients undergoing CTO PCI in high-volume centers by experienced operators using mostly the *hybrid* approach (Table 2). In a recent analysis of the large-scale, multicenter Prospective Global Registry for the Study of Chronic Total Occlusion Intervention (PROGRESS CTO) registry [30••] including 1308 patients (mean age 65.5 years) with ($n = 584$, number of insulin-dependent DM patients not reported) and without DM ($n = 724$) undergoing CTO PCI at 11 US high-volume centers, both technical (90.7% vs. 90.3%, $p = 0.80$) and procedural (89.3% vs. 89.1%, $p = 0.90$) success rates were similar among subjects with and without DM, despite adverse angiographic characteristics among diabetic patients (moderate-to-severe coronary calcifications, 61% vs. 56%, $p = 0.12$; proximal cap ambiguity, 33% vs. 30%, $p = 0.27$; Japan chronic total occlusion (J-CTO) score, 2.6 vs. 2.5, $p = 0.82$). The final successful crossing strategy was similar irrespective of the diabetic status (retrograde, 30% vs 27.7%; antegrade wire escalation, 45.8% vs. 47.2%; antegrade dissection re-entry, 24% vs. 25%, $p = 0.66$) [30••]. The CTO procedure duration and fluoroscopy time and fluoroscopy time were similar in both groups, but the radiation dose was higher, whereas contrast volume was lower, among diabetic subjects [30••]. Importantly, the in-hospital MACE (2.2% vs. 2.5%, $p = 0.61$), mortality (0.4% vs. 0.3%, $p = 0.51$), MI (1.3% vs 0.5%, $p = 0.11$), stroke (0.4% vs 0.1%, $p = 0.40$), emergency PCI (0.3% vs 0.3%, $p = 0.82$) or need for CABG surgery (0% vs. 0%), and emergency pericardiocentesis (0.6% vs 0.6%, $p = 0.99$) rates were similarly low in patients with and without DM [30••].

In a prospective, single-center, high-volume CTO PCI registry including 1320 consecutive patients (diabetics, $n = 362$; insulin-dependent DM patients not reported) [31••], the procedural success rates were numerically lower, despite statistically not significant, among subjects with DM compared with non-diabetic patients (69.8% vs. 75%, $p = 0.07$) despite a higher prevalence of multivessel CAD (64.4% vs. 59.4%, $p = 0.09$), prior CABG (10.2% vs. 6.4%, $p = 0.01$), and significantly more complex disease (J-CTO score, 1.45 vs. 1.34, $p = 0.02$) in the diabetic subgroup. Cardiac tamponade occurred similarly in both diabetic and non-diabetic groups (0.8% vs. 1.4%, $p = 0.43$) [31••]. Whereas all-cause (23.1% vs. 22.2%, $p = 0.16$) and cardiac (11.3% vs. 10.7%, $p = 0.08$) mortality rates did not significantly differ between successful and failed CTO PCIs among non-diabetic patients, unsuccessful CTO PCI was associated with significantly higher risk of all-cause (54.9% vs. 23.2%, $p < 0.001$) and cardiac (31.0% vs. 13.1%, $p < 0.001$) mortality in patients with DM at a median follow-up of 4.2 years [31••]. These findings suggest superior clinical benefits of successful CTO PCI in diabetic patients compared with non-diabetic subjects and a *treatment-risk paradox* (i.e., higher risk patients, more benefit from the procedure but the procedure is less frequently performed). By multivariate analysis, the presence of DM (HR 2.44, 95% CI 1.52–3.83, $p < 0.001$), decreased left ventricular ejection fraction (HR 0.96, 95% CI 0.94–0.99, per percent decrease, $p = 0.004$), and increased age (HR 1.06, 95% CI 1.03–1.08, per year increment, $p < 0.0001$) were found independent predictors of cardiac death at follow-up [31••]. Interestingly, the authors found a significant interaction between the presence of DM and procedural outcomes with lower cardiac mortality rates after failed PCI between diabetic and non-diabetic patients (24.7% vs. 9.3%, $p < 0.0001$), suggesting a preferential benefit of complete revascularization in the diabetic population [31••].

In the large-scale, the multicenter Outcomes, Patient Health Status, and Efficiency in Chronic Total Occlusion (OPEN-CTO) registry including 1000 consecutive patients (diabetics, $n = 412$; insulin-dependent diabetics, $n = 154$) undergoing CTO PCI using the *hybrid* algorithm at 12 US high-volume centers [32••], crude technical success rates were significantly lower in patients with DM compared with non-diabetic subjects (83.5% vs. 88.1%, $p = 0.04$), but both lesion length (63.7 vs. 59.1 mm, $p = 0.01$) and CTO complexity (J-CTO score 2.4 vs. 2.3, $p = 0.03$) were significantly greater among diabetic patients compared with non-diabetics. After adjustment for differences in baseline clinical and angiographic characteristics, technical success rates were not statistically significant between diabetics and non-diabetics (relative risk [RR] 0.96, 95% CI 0.91–1.01, $p = 0.12$), resulting from adjustment for prior CABG, which was more prevalent among diabetic patients and was independently associated with lower technical success ($p < 0.001$) [32••]. These findings extend previous knowledge suggesting the negative impact of prior CABG, rather than the DM status itself, on CTO PCI technical success rates and clinical outcomes [33, 34], even when performed by experienced operators using the *hybrid* algorithm [35]. CTOs are present in ~ 50% of post-CABG patients undergoing coronary angiography and prior CABG further increases the complexity of CTOs, thus representing a technically highly challenging CTO patient subset [33–35]. These concerns are

Table 2 Recent large contemporary studies comparing clinical outcomes after CTO PCI in patients with and without diabetes mellitus

Study	Design	Number of patients			Success rates						Clinical outcomes
					Technical success rate			Procedural success rate			
		Total number of patients (*n*)	Diabetes (*n*, %)	Insulin-dependent diabetes (*n*, %)	Diabetes (%)	No diabetes (%)	*p* value	Diabetes (%)	No diabetes (%)	*p* value	
PROGRESS CTO [32••]	Prospective, multicenter, registry, 11 US centers (2012–2015)	1308	584 (44.6)	NR	90.7	90.3	0.80	89.3	89.1	0.93	• In-hospital MACE (composite of all-cause death, MI, recurrent symptoms requiring urgent TVR with PCI or CABG surgery, tamponade requiring either pericardiocentesis or surgery, or stroke prior to hospital discharge): 2.2% in diabetics vs. 2.5% in non-diabetics ($p = 0.61$) • In-hospital all-cause death (0.4% vs. 0.3%, $p = 0.51$), MI (1.3% vs. 0.5%, $p = 0.11$), stroke (0.4% vs. 0.1%, $p = 0.40$), emergency PCI (0.3% vs. 0.3%, $p = 0.82$), emergency CABG surgery (0%), and emergency pericardiocentesis (0.6% vs. 0.6%, p = 0.99) rates were similar between diabetics and non-diabetics, respectively.
Sanguinetti et al. [33]	Prospective single-center registry, one center in France (2004–2012)	1320	362 (27.4)	NR	NR	NR	NR	71.5	76.3	0.07	• Periprocedural major complications, including cardiac tamponade (1.4% vs. 0.8%, $p = 0.43$), were similar between diabetics and non-diabetics undergoing CTO PCI. • Among *diabetics*, all-cause death (54.9% vs. 23.2%, $p < 0.001$) and cardiac death (31.0% vs. 13.1%, $p < 0.001$), but not TLR (4.8% vs. 14.2%, $p = 0.23$), TVR (19.8% vs. 20.9%, $p = 0.78$), MI (5.2% vs. 3.0%, $p = 0.18$), and MACE (35.4% vs. 28.1%, $p = 0.13$) rates, were significantly higher in patients with failed as compared with successful CTO PCI at a median follow-up of 4.2 years, respectively. • Among *non-diabetics*, all-cause death (23.1% vs. 22.2%, $p = 0.16$), cardiac death (11.3% vs. 10.7%, $p = 0.08$), TLR (10.4% vs. 14.1%, $p = 0.63$), TVR (20.2% vs. 23.1%, $p = 0.77$), MI (11.4% vs. 5.1%, $p = 0.71$), and MACE (32.7% vs. 31.6%, $p = 0.08$) rates were similar between patients with failed and successful CTO PCI at a median follow-up of 4.2 years, respectively.
OPEN-CTO [34]	Prospective, multicenter registry, 12 US centers (2014–2015)	1000	412 (41.2)	154 (37.4)	83.5*	88.1*	0.04#	NR	NR	NR	• MACE (composite of all-cause death, periprocedural MI, emergency CABG surgery, stroke, or clinically significant perforation): 6.8% in diabetics vs. 7.1% in non-diabetics ($p = 0.832$). • In-hospital mortality (0.7% vs. 1.0%, $p = 0.743$), periprocedural mortality (0.2% vs. 0.7%, $p = 0.654$), periprocedural MI (2.7% vs. 2.6%, $p = 0.907$), and

Table 2 (continued)

Study	Design	Number of patients			Success rates						Clinical outcomes
					Technical success rate			Procedural success rate			
		Total number of patients (*n*)	Diabetes (*n*, %)	Insulin-dependent diabetes (*n*, %)	Diabetes (%)	No diabetes (%)	*p* value	Diabetes (%)	No diabetes (%)	*p* value	
											periprocedural stroke (0% in both groups), were similar between diabetics and non-diabetics, respectively. • Major procedural complications rates, including any perforation (9.5% vs. 8.3%, $p = 0.533$), pericardial effusion (2.2% vs. 2.9%, $p = 0.489$), hemodynamically significant pericardial effusion (44.4% vs. 52.9%, $p = 1.0$), emergent CABG (0.2% vs. 0.9%, $p = 0.409$), contrast nephropathy (1.2% vs. 0.2%, $p = 0.085$), and access site hematoma (3.9% vs. 4.6%, $p = 0.586$), were similar in patients with and without DM, respectively. • Adjusted SAQ AF (87.59 ± 1.68 vs. 88.05 ± 1.84, $p = 0.64$), SAQ QoL (74.50 ± 2.13 vs. 73.80 ± 2.33, $p = 0.58$), SAQ SS (83.01 ± 1.54 vs. 82.70 ± 1.68, $p = 0.73$), RDS (1.46 ± 0.14 vs. 1.46 ± 0.13, $p = 0.92$) through a follow-up period (30 days, 6 months or 12 months) were similar between diabetics and non-diabetics, respectively.

NR not reported. *Unadjusted rates. # Relative risk 0.96; 95% confidence interval 0.91 to 1.01; $p = 0.12$ after adjustment for clinical and angiographic characteristics (primarily driven by adjustment for prior CABG, which was independently associated with lower technical success, $p < 0.001$). *AF* angina frequency, *CTO* chronic total occlusion, *CABG* coronary artery bypass grafting, *MACE* major adverse cardiovascular events, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *QoL* quality of life, *RDS* Rose Dyspnea Scale, *SAQ* Seattle Angina Questionnaire, *SS* summary score, *TLR* target lesion revascularization, *TVR* target vessel revascularization

of utmost importance considering that CABG remains the revascularization strategy of choice in patients with DM and multivessel CAD. Importantly, technical success rates were similar in diabetic patients requiring or not requiring insulin, suggesting that similar high technical success rates may be achieved from CTO PCI among non-diabetic, insulin-dependent diabetic, and non-insulin-dependent diabetic patients [32••]. Overall, there was no significant differences with respect to major procedural complications rates, including any perforation (9.5% vs. 8.3%), pericardial effusion (2.2% vs. 2.9%, of which nearly half were hemodynamically relevant in both groups), emergent CABG (0.2% vs. 0.9%), contrast nephropathy (1.2% vs. 0.2%), and access site hematoma (3.9% vs. 4.6%) in patients with and without DM, respectively [32••]. In-hospital MACE rates (6.8% vs. 7.1%, $p = 0.83$) were not different among patients with or without DM [32••]. Importantly, whereas the main indication to perform CTO PCI remains a relief of anginal symptoms [11, 12•], data reporting the impact of CTO PCI in diabetic patients with respect to short- and long-term health status outcomes compared with non-diabetic individuals are limited. Data from the OPEN-CTO registry demonstrate similar large and sustained symptom improvements with respect to angina burden, quality of life, and overall health status scores following CTO PCI over 1-year follow-up among patients with and without DM, even after adjustment for technical success, comorbidities, medications, and completeness of revascularization, including in the subgroup of diabetics requiring insulin [32••]. These results highlight the potential clinical impact of CTO PCI procedures among both diabetic and non-diabetic patients and support the use of CTO PCI with appropriate clinical indications irrespective of the DM status [44].

Conclusion

Evidence from contemporary, large-scale, observational registries supports the notion that CTO PCI, when performed at high-volume CTO PCI centers and by highly experienced operators, is a safe and effective treatment alternative to provide complete myocardial revascularization in selected CTO patients with DM. Importantly, in these studies, the degree of success of CTO PCI does not differ between DM and non-DM patients. Whereas CTO DM patients treated conservatively are at higher risk of adverse events compared with non-DM individuals, and incomplete revascularization negatively affects specifically DM patients, diabetic patients are less frequently exposed to CTO PCI. This *treatment-risk* paradox is concerning and deserves attention. Further randomized research is warranted to compare long-term outcomes of CTO PCI with newer-generation DES, CABG, and optimal medical therapy for the management of CTO patients with DM.

Compliance with Ethical Standards

Conflict of Interest Fabio Rigamont and Stéphane Noble declare that they have no conflict of interest.

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- • Of importance
- •• Of major importance

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