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Review Article

Revascularization of patients with chronic total occlusion and left ventricular systolic dysfunction

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ABSTRACT

Heart failure (HF) due to left ventricular systolic dysfunction (LVSD) remains a major clinical challenge, particularly among patients with chronic total occlusions (CTO). CTO are present in up to 30% of patients with LVSD undergoing coronary angiography and are independently associated with worse outcomes. Although advances in interventional techniques have increased success rates of CTO percutaneous coronary intervention (CTO-PCI), high-quality evidence supporting this procedure in patients with LVSD remains limited. Observational studies report potential benefits, including improved survival, alleviation of HF symptoms, and recovery of left ventricular ejection fraction (LVEF). However, randomized controlled trials (RCTs) have largely excluded patients with LVEF <35% and those with advanced, complex coronary artery disease (CAD), including CTO, thereby restricting generalizability. Assessment of myocardial viability remains central to patient select for CTO-PCI, its prognostic value for hard clinical endpoints has not been definitively established. The use of mechanical circulatory support (MCS) during high-risk CTO-PCI is increasing, particularly in patients with reduced LVEF and complex coronary anatomy; available data provides inconsistent evidence regarding its impact on clinical outcomes and appears to be largely influenced by individual patient characteristics. Finally, in the setting of acute coronary syndromes (ACS), the effect of CTO revascularization on clinical endpoints and arrhythmic risk is unclear, with conflicting observational data. Future research should prioritize this underrepresented high-risk cohort and be conducted in experienced centers within an integrated multidisciplinary care framework.

Abbreviations: ACS, acute coronary syndromes; CMR-LGE, cardiac magnetic resonance with late gadolinium enhancement; CTO, chronic total occlusion; DSE, dobutamine stress echocardiography; HF, heart failure; HFmrEF, heart failure with mildly-reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LVSD, left ventricular systolic dysfunction; LVEF, left ventricular ejection fraction; MACE/MACCE, major adverse cardiovascular (and cerebrovascular) events; MCS, mechanical circulatory support; NSTEMI, non-ST-elevation myocardial infarction; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; PET, positron emission tomography; RCT, randomized controlled trial(s); STEMI, ST-segment elevation myocardial infarction; VA-ECMO, venoarterial extracorporeal membrane oxygenation; VTA, ventricular tachyarrhythmia.

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Introduction

Coronary artery disease (CAD), including the presence of chronic total occlusions (CTO), remains the leading cause of heart failure (HF).[1,2] Among patients with ischemic heart disease, left ventricular systolic dysfunction (LVSD) is the primary driver of HF progression and clinical manifestation.[3,4] The severity of LVSD correlates inversely with prognosis, whereby greater dysfunction predicts poorer patient outcomes during follow-up.[3] Despite the increasing prevalence of CTO with greater LVSD severity and its association with higher cardiovascular risk, CTO-PCI volumes in these patients do not reflect this trend.[4,5] Managing patients with CTO and LVSD, particularly the decision whether to revascularize the chronically occluded vessel, is challenging owing to the greater technical complexity and higher complication rates associated with CTO-PCI compared to non CTO-PCI.[6,7] Moreover, it remains controversial whether successful CTO-PCI consistently improves ventricular function and other relevant clinical outcomes. Importantly, when left ventricular ejection fraction (LVEF) falls below 35%, surgical revascularization carries an elevated procedural mortality risk that is independent of other comorbidities.[8] Consequently, choosing the optimal revascularization approach, surgical versus percutaneous, for this patient population remains vital.[9–11]

Epidemiology

Across various studies, the reported prevalence of CTO in patients with LVSD undergoing coronary revascularization ranges from 10% to 30%.[12,13] Analysis of contemporary registries evaluating patients undergoing CTO-PCI indicates that LVSD is present in approximately 20–30% of patients, with LVEF<35% found in 7–10%.[14,15] The ERCTO registry reported that LVEF<35% was more frequent among males than females undergoing CTO-PCI (28.2% vs. 24.1%; $p < 0.001$).[16] In patients with heart failure and mildly reduced ejection fraction (HFmrEF), defined as LVEF between 41 and 49%, coronary CTO was present in 17%.[17] Furthermore, a CTO was found in up to 13–24% of those presenting with Non-ST-Elevation Myocardial Infarction (NSTEMI) and 8–12% with ST-Elevation Myocardial Infarction (STEMI),[18,19] and only 6% of patients undergoing CTO-PCI present with acute coronary syndrome (ACS).[20] Finally, among patients with cardiogenic shock undergoing coronary angiography, the prevalence of CTO rises to approximately 24%.[18]

Impact of CTO PCI revascularization on patients' outcomes

Table 1 summarizes clinical studies on CTO across different clinical scenarios, including LVSD. The two most relevant RCTs that investigated the impact of revascularization of patients with LVEF≤35% are the Surgical Treatment for Ischemic Heart Failure (STICH) trial and the Randomized Evaluation of Vascularized versus Ischemic myocardium in Ventricular Dysfunction – British Cardiovascular Intervention Society 2 (REVIVED-BCIS2).[12,13] However, these studies did not include only CTO patients and did not compare specifically CTO revascularization vs no CTO revascularization.

The extended STICH trial revealed that coronary artery bypass grafting (CABG) significantly decreased all-cause mortality compared to medical therapy alone at median follow-up of 9.8 years in patients with ischemic cardiomyopathy and LVSD (58.9% vs. 66.1%; HR 0.84, 95% CI 0.73–0.97).[12,21] Of course, in this study CTO lesions were included as target of revascularization.

In contrast, the REVIVED-BCIS2 trial showed no reduction in the primary composite endpoint of all-cause death or hospitalization for HF with PCI compared with optimal medical therapy (OMT) (37.2% vs. 38.0%; hazard ratio 0.99, 95% CI 0.78–1.27; $P = 0.96$), despite improved quality of life (Kansas City Cardiomyopathy Questionnaire difference + 6.5 and + 4.5 points, respectively).[13] A pooled individual patient data analysis of REVIVED-BCIS2 and STICHES suggested lower rates of all-cause death or HF hospitalization in patients enrolled in REVIVED-BCIS2 compared with STICHES, including those treated with PCI versus CABG (adjusted HR 0.61, 95% CI 0.43–0.87), although these findings are hypothesis-generating due to the observational nature of between-trial comparisons.[22]

Most CTO-PCI RCTs have focused on patients with preserved systolic function, or with mild LVSD, generally excluding those with LVEF≤35%.[23–27] For example, the Randomized Trial to Assess Regional Left Ventricular Function After Stent Implantation in Chronic Total Occlusion (REVASC Trial) found no significant improvement in global LVEF after CTO-PCI compared to OMT, but the median LVEF was 56%[27] Similarly, the EXPLORE trial, which studied STEMI patients with concurrent non-culprit CTO, showed no benefit of CTO-PCI on global LVEF or major adverse cardiovascular events (MACE) (median LVEF was 44.1 ± 12.2%).[28] However, in this trial, baseline LVEF was measured shortly after the index STEMI, and therefore the observed lack of improvement in global LVEF after CTO-PCI may have been influenced by myocardial stunning, which could recover over time.

Conversely, observational studies, which focused mostly on patients with more pronounced LVSD, showed a positive impact of CTO-PCI on patients' hard outcomes.

For example, COMMIT-HF has linked CTO presence in patients with LVEF ≤35% to higher 12-month mortality.[2] Pinto et al. reported improved survival after successful CTO-PCI in patients with LVEF≤45%.[29] Galassi et al. reported a significant improvement in left ventricular ejection fraction in patients with severely reduced systolic function (LVEF≤35%) following successful CTO-PCI, with LVEF increasing from 29.1 ± 3.4% at baseline to 41.6 ± 7.9% at 6-month follow-up ($p < 0.001$). Despite baseline differences in ventricular function, MACCE-free survival at 2 years was comparable across LVEF strata (86% for LVEF≥50%, 82.8% for LVEF 35–50%, and 75.2% for LVEF≤35%; p = NS).[10] Recently, Behnes et al., reported that CTO patients with HFmrEF (mean LVEF was 45% [45–47]) have a higher rate of long-term MACCE compared to non-CTO patients (60% versus 32%, $P = 0.001$).[17] In this study, long-term mortality was lower after successful CTO-PCI compared with unsuccessful CTO-PCI or OMT (21% vs 38%; hazard ratio 0.49, 95% CI 0.24–0.99; $P = 0.046$).[17]

In conclusion, observational studies and subgroup analyses suggest that CTO-PCI may provide clinical and prognostic benefits, especially in symptomatic patients with more pronounced LVSD; conversely, RCTs, in which this subset of patients is definitely underrepresented, have not consistently confirmed these findings. **(Fig. 1).**

Aspects related to the management of patients with LVSD

Therapeutic options for patients with LVSD and CTO have expanded considerably. Nevertheless, this population remains clinically and procedurally complex, often demonstrating extensive myocardial damage, impaired hemodynamic reserve, and elevated procedural risk. Optimal management demands thorough patient selection and should take into consideration many factors at play. **(Central Illustration).**

As such, a multidisciplinary collaboration, including interventional and clinical cardiologists, imaging experts, and cardiac surgeons, at high-volume centers with dedicated Heart Team is strongly recommended to improve procedural success and long-term outcomes.[7]

Myocardial viability assessment

Myocardial viability evaluation remains pivotal in selecting candidates for CTO-PCI, despite debates on its predictive accuracy for clinical benefit. Identifying viable myocardium maximizes revascularization gains and minimizes procedural risks.[30] Different imaging modalities interrogate specific pathophysiological features. **(Fig. 2).**

Cardiac magnetic resonance imaging (CMR) with late gadolinium enhancement (LGE) is the gold standard for viability, precisely defining scar burden and transmurality, though with limited sensitivity when

Table 1
Summary of clinical studies evaluating coronary revascularization strategies (including CTO) in patients with LVSD.

First Author	Year	Name of Study	Study type	Aim	Primary Outcome	Follow-up	Study Population	LVEF	Results	Limitations
(1) LVSD										
Velazquez	2011	STICH Trial	multicenter, nonblinded, randomized study at 127 clinical sites in 26 countries	To assess whether coronary artery bypass grafting (CABG) plus optimal medical therapy reduces mortality compared with medical therapy alone in patients with ischemic cardiomyopathy and LVSD	All-cause mortality (primary) Secondary: CV mortality, death or hospitalization for cardiovascular causes	Median ~ 56 months (≈4.7 years) in primary analysis Extended follow-up analyses available up to ~10 years (STICHES)	1212 patients with ischemic cardiomyopathy and multivessel CAD amenable to CABG.	≤35%	Primary outcome (all-cause death): No statistically significant reduction with CABG + medical therapy vs medical therapy alone (HR 0.86; 95% CI 0.72–1.04; $P = 0.12$). Cardiovascular death was lower with CABG (HR 0.81; $P = 0.05$). Death or CV hospitalization significantly lower with CABG (HR 0.74; P < 0.001)	Not blinded Crossovers to CABG in medical therapy arm (typical for surgical strategy trials) Surgical risk variability across centers May not generalize to populations with different comorbidity profiles
Perera	2022	REVIVED-BCIS2	RCT	To demonstrate that revascularization with PCI in addition to OMT for HF, as compared with OMT alone, improves event-free survival in patients with severe ischemic left ventricular systolic dysfunction and demonstrable myocardial viability.	Death from any cause or hospitalization for heart failure	3.4 years	700 patients	27.0 ± 6.6%	Revascularization by PCI did not result in a lower incidence of death from any cause or hospitalization for heart failure	Most patients had little or no angina at enrollment lower number of events
Ezad	2024	REVIVED-BCIS2	prespecified analysis of RCT REVIVED-BCIS2	To identify the impact of complete revascularization in patients with severe LV dysfunction	death or hospi-talization for heart failure	6 years	670 patients	31.9 ± 9.9%	This study does not show a difference in event-free survival or frequency of improved left ventricular function in patients with stable coronary disease and severe impairment of left ventricular function who were assigned to PCI and subsequently underwent complete revascularization compared with patients who were assigned to PCI but underwent incomplete revascularization or patients who were	Not randomize to a strategy of complete revascularization vs incom-plete revascularization, The analysis included only revascularization with percutaneous coronary intervention (PCI).

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Table 1 (*continued*)

First Author	Year	Name of Study	Study type	Aim	Primary Outcome	Follow-up	Study Population	LVEF	Results	Limitations
									assigned to OMT alone.	
(2) CTO-PCI + LVSD										
Henriques	2016	EXPLORE Trial	investigator-initiated, prospective, multi-center, international, randomized, 2-arm trial with blinded evaluation of endpoints	To evaluate whether patients with STEMI and concurrent CTO in a non–infarct-related artery bene t from additional percutaneous coronary intervention (PCI) of CTO shortly after primary PCI.	Left ventricular ejection fraction (LVEF) and left ventricular end diastolic volume (LVEDV) on cardiac magnetic resonance imaging	4 months	304 patients	41 ± 11%	Additional CTO PCI within 1 week after primary PCI for STEMI was feasible and safe. In patients with STEMI and con-current CTO, we did not nd an overall bene t for CTO PCI in terms of LVEF or LVEDV.	Not hard clinical endpoints such as death, myocardial infarction, and stroke The results of our study apply only to patients who are hemodynami-cally stable during the rst week after primary PCI the study was not blinded
Tajstra	2016	COMMIT-HF registry	single-center, observational study	To assess the impact of CTO on long-term prognosis in patients with ischemic cardiomyopathy	all-cause mortality	12 months	675 patients	26.8 ± 5.5%	In patients with ischemic heart failure the presence of the CTO is related to worse long-term prognosis compared with patients without CTO	Retrospective nature
Toma	2017	Comparison of Benefit of Successful Percutaneous Coronary Intervention for Chronic Total Occlusion in Patients With Versus Without Reduced (≤40%) Left Ventricular Ejection Fraction	Retrospective multicenter observational study (pooled data from 5 centers)	To evaluate whether successful CTO PCI is associated with improved long-term survival in patients with reduced LVEF (≤40%) versus preserved LVEF (>40%)	All-cause mortality	Median 2.6 years (1.1. to 3.1 years)	2002 patients (348 with LVD)	Stratified: ≤40% vs. >40%	All-cause mortality was higher in patients with LV dysfunc-tion than in those with normal LV function. Successful CTO recanalization was independently associated with reduced all-cause mortality, with similar relative risk reductions in both the preserved and the reduced LV function groups	Large cohort of patients undergoing elective con-temporary CTO PCI by experienced operators; single-center observational design; retrospective design, no randomization, potential confounding, lack of viability assessment or ischemia burden stratification
Galassi	2017	Percutaneous Coronary Intervention of Chronic Total Occlusions in Patients With Low Left Ventricular Ejection Fraction	Prospective longitudinal multicenter study	outcome of percutaneous coronary intervention (PCI) of chronic total occlusions (CTOs) in patients with low left ventricular ejection fraction (LVEF) (<35%).	MACCE	8–12 months	839 (100%) 72 with LVEF <35%	<35%	PCI could represent a safe and efficient man-agement strategy able to improve LVEF and symptoms, and to ensure good midterm outcome in patients with LVEF <35%	Small sample size CTO expert operators no angiographic follow-up data were collected in LVEF groups (>50% and 35–50%)
Mashayekhi	2018	REVASC Trial	Pro-spective, randomized, single-center trial	To investigate whether percutaneous coronary intervention (PCI) of chronic total occlusions (CTOs) improves left ventricular function	The change in segmental wall thickening (SWT) in the CTO territory	12 months	205 patients	54.7% (42.9 to 65.1) at CMR	No benefit was seen for CTO PCI in terms of the primary endpoint, SWT, or other indexes of left ventricular function. CTO PCI resulted in clinical bene t over no CTO PCI, as evidenced	Not hard clinical endpoints, such as death or myocardial infarction study was not blinded the inclusion of CTO patients was not based on prior cMRI

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Table 1 (*continued*)

First Author	Year	Name of Study	Study type	Aim	Primary Outcome	Follow-up	Study Population	LVEF	Results	Limitations
									by reduced major adverse coronary event rates at 12 months.	perfusion deficiency and viability
Lopes	2020	Insights From the ISCHEMIA Trial	subgroup analysis of RCT	To compare cardiovascular outcomes between invasive and conservative treatment strategies among participants in the ISCHEMIA trial with left ventricular ejection fraction ≥35%, stratified by the presence or absence of a history of heart failure or left ventricular dysfunction at baseline.	Composite of cardiovascular death, MI, resuscitated cardiac arrest, or hospitalization for unstable angina or HF	3.2 years	398 (7.7%)	LVEF ≥35% and < 45%	ISCHEMIA participants with stable ischemic heart disease and at least moderate ischemia with a history of HF or LVD were at increased risk for the primary outcome.	small number of patients with clinical events LVEF recorded at trial inclusion may have varied around the somewhat arbitrary cut point of >35% Revascularization in the invasive strategy was a mixture of CABG and PCI
Pinto	2020	Long-term clinical effects of recanalization of chronic coronary total occlusions in patients with left ventricular systolic dysfunction	Retrospective analysis of consecutive patients	To evaluate the clinical impact of CTOs,recanalization in patients with left ventricular (LV) systolic dysfunction	Total mortality	2006 ± 1349 days	2421 patients at 436 patients with LVEF≤45%	37.9 ± 6.8%	In patients with systolic LV dysfunction (EF ≤ 45%), CTO revascularization was associated with significant lower rate of total and cardiac mortality compared to those with nonrevascularized CTO	Retrospective data analys
Kook	2021	Differential clinical impact of chronic total occlusion revascularization based on left ventricular systolic function	Retrospective multicenter observational cohort study	To assess the impact of successful CTO PCI on clinical outcomes according to baseline left ventricular systolic function	Composite of all-cause death or non-fatal myocardial infarction.	The median follow-up duration was 1138 days.	2173 CTO patients divided into either a PLVS (n = 1661; EF > 50%) or RLVSF (n = 512, EF < 50%)	Pts with RLVSF had a mean of 37% of EF and 19% had EF < 30%.	SCR was associated with better survival benefit than OMT regardless of LVSF. The benefit was greater and became more significant over time in patients with RLVSF versus PLVSF.	Retrospective design, observational nature precludes causality, potential residual confounders despite adjustment, no randomization of PCI strategy
Lesizza	2023	Heart Failure-Related Outcomes in Patients with Left Ventricular Dysfunction Undergoing Percutaneous Chronic Total Occlusion Revascularization	prospective multicenter study	To examine the success rate and complication rate of PCIs for CTOs in patients with an LV ejection fraction ≤40% at baseline	Success rate and complication rate	18 months	132 (9.2%)	31.41 ± 8.13%	In patients with reduced LV systolic function (LVEF ≤ 40%), CTO PCI is a safe and effective procedure and successful CTO PCI is independently associated with a lower risk of HFH during follow-up.	Patients with unsuccessful CTO PCIs as a control group. The patients in the unsuccessful PCI group were possibly more complex than the patients in the successful PCI group
Moliner-Abós	2025	RevascHeart study	Retrospective multicenter study	To compare long-term mortality between revascularization and	all-cause or cardiovascular mortality	44.6 months	408 patients	30%[24,35]	Revascularization did not outperform GDMT in ischaemic LV	Retrospective nature alloca-

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Table 1 (*continued*)

First Author	Year	Name of Study	Study type	Aim	Primary Outcome	Follow-up	Study Population	LVEF	Results	Limitations
				GDMT in patients with ischaemic LV dysfunction following admission for HF					dysfunction following HF admission	tion to REVASC or GDMT was based on clinical grounds ARNI and SGLT2i were not part of GDMT during the entire study period
Behnes	2025	HARMER (Heart Failure with Mildly Reduced Ejection Fraction Registry.	single-center observational and retrospective registry-based analysis	to investigate the prevalence and prognostic impact of coronary CTO in patients with heart failure with mildly reduced ejection fraction (HFmrEF).	long-term all-cause mortality	30 months	836 patients	45 (45–47)	Coronary CTO are common in HFmrEF with a significant impact on long-term prognosis.	retrospective and single-center study design the number of patients with CTO undergoing PCI procedures was small the presence of myocardial scarring or viability could not be routinely assessed selection bias toward patients with a higher pretest probability of CAD causes of death beyond index hospitalization were unavailable
(3) Viability imaging										
Allman	2002	Myocardial Viability Testing and Impact of Revascularization on Prognosis in Patients With Coronary Artery Disease and Left Ventricular Dysfunction	Meta-Analysis	To compare mortality rates in patients with/without viability treated by either revascularization/medical therapy	All-cause Death	NA	3088 patients (CTO patients not specified)	32 ± 8%	A strong association between myocardial viability on noninvasive testing and improved survival after revascularization in patients with chronic CAD and LV dysfunction	Observational, non-randomized, unblinded studies little information in the reports on background medical therapy The individual studies did not report late EF, so the relationship between any improvement in LV function and potential prognostic benefit could not be explored
Perera	2023	REVIVED-BCIS2 subanalysis	Prespecified Secondary Analysis of the REVIVED-BCIS2 Trial	To determine the effect of the extent of viable and nonviable myocardium on the effectiveness of PCI, prognosis, and improvement in left ventricular function.	The composite of all-cause death or hospitalization for heart failure.	3.4 years	610 patients	32 (10)	Viability testing does not identify patients with ischemic cardiomyopathy who benefit from PCI. The extent of nonviable myocardium, but not the extent of viable myocardium, is associated with event-free survival and likelihood of improvement of left ventricular function.	Data from Only 87% of the trial population. Enrollment in the REVIVED-BCIS2 trial required participants to have at least four segments of viable myocardium, as determined by local adjudication. Consequently, the exclusion of patients without myocardial

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Table 1 (*continued*)

First Author	Year	Name of Study	Study type	Aim	Primary Outcome	Follow-up	Study Population	LVEF	Results	Limitations
										viability limits the generalizability of the results across the full viability spectrum. Participants for whom viability was assessed with positron emission tomography or single-photon Emission computed tomography were excluded
(4) MCS										
Abaunza	2015	Incidence and prognosis of vascular complications after percutaneous placement of left ventricular assist device.	Retrospective cohort / Prospective database	Assessment of the incidence of vascular complications and associated morbidity and mortality that can occur with Impella placement.	Major vascular complication rate	30 days	90 patients (15 vascular complications)	30%	17% had major vascular complications; increased mortality and hospital stay	Single center, retrospective, small sample
Danek	2018	Mechanical Circulatory Support in Chronic Total Occlusion Percutaneous Coronary Intervention: Insights From a Multicenter U. S. Registry	Multicenter observational registry	Current use and clinical outcomes associated with percutaneous mechanical circulatory support (MCS) in CTO PCI	Procedural success and complication rates	In-hospital	1598 patients undergoing CTO-PCI	NR	Procedural success in 85.5%; high rates of in-hospital MACE (19.3%) and bleeding (11.3%)	Observational, no comparison group, selection bias
Riley	2018	Impella-assisted chronic total occlusion percutaneous coronary interventions: A multicenter retrospective analysis	Multicenter retrospective study	To describe the types of patients, procedural characteristics, and acute clinical outcomes of these patients in an effort to improve our understanding of the poten-tial role for these devices during higher-risk and indicated procedures.	In-Hospital Complications and Death during Impella-assisted CTO PCI	NA	57 patients	20% (15%, 30%)	Impella-assisted CTO PCI can be performed with high technical success rates	Retrospective nature Procedures were also performed at high-volume tertiary referral institutions with high-volume p-VAD use and CTO PCI volumes
Flaherty	2019	The Global cVAD Renal Protection Study	Observational, prospective, multicenter, single-cohort study	To address the impact of Impella support on renal function during nonemergent High Risk-PCI	Reduction in the development of the acute kidney injury network (AKIN) definition of AKI postprocedurally at 48 h (and up to 72 h) relative to the	48 h	223 patients CTO patients (N = 30; 14.42%)	30.83 ± 15.92	In high-risk patients, Impella support was associated with a significantly reduced risk of AKI when compared to the calculated predicted Mehran risk score of AKI and	observational analy-sis No randomization Operators were not blinded Mehran score may overestimate the risk of AKI Only in-hospital outcomes

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Table 1 (*continued*)

First Author	Year	Name of Study	Study type	Aim	Primary Outcome	Follow-up	Study Population	LVEF	Results	Limitations
					patient's predicted risk of AKI				eliminated the need for hemodialyis.	
Claessen	2009	Evaluation of the Effect of a Concurrent Chronic Total Occlusion on Long-Term Mortality and Left Ventricular Function in Patients After Primary PCI	Observational cohort study	Evaluate the effect of a concurrent chronic total occlusion (CTO) in patients with ST-segment elevation myocardial infarction (STEMI) on long-term mortality and left ventricular ejection fraction (LVEF).	Long-term mortality and left ventricular ejection fraction (LVEF)	5 years; landmark analysis at 30 days	3277 STEMI patients undergoing primary PCI; 420 with a CTO in a non-IRA	Reduced (<40%) in 28% of patients with CTO; further deterioration during follow-up (OR 3.5)	The presence of a CTO was an independent predictor of both early (HR 3.6) and late (HR 1.9) mortality. CTO was associated with lower LVEF immediately post-STEMI (OR 1.9) and further LVEF decline over time	Observational design, non-invasive LVEF assessment, partial data missing, possible overestimation of non-culprit stenoses
(5) Cardiogenic Shock										
Braik	2021	Impact of chronic total occlusion and revascularization strategy in patients with infarct-related cardiogenic shock: A subanalysis of the CULPRIT-SHOCK trial	Prespecified analysis of the CULPRIT-SHOCK Trial	To investigate the impact of chronic total occlusion (CTO) and revascularization strategy (culprit-lesion only vs. multivessel PCI) on clinical outcomes in patients with STEMI and cardiogenic shock	30-day all-cause mortality and need for renal replacement therapy	30 days and 1 year	667 patients with acute MI, cardiogenic shock, and multivessel CAD; 157 (23.5%) had at least one CTO in a non-infarct-related artery	Median LVEF: 29% in patients with CTO vs. 35% without CTO ($p = 0.002$)	In patients with MI-related CS and multivessel disease, the presence of CTO is associated with adverse outcomes while a strategy of culprit-lesion-only PCI seems beneficial regardless of the presence of CTO.	Post-hoc subanalysis, no randomization for CTO treatment, limited power to detect CTO-specific treatment effects, lack of viability testing
Goyal	2024	The impact of chronic total occlusion in non-infarct related arteries on patient outcomes following PCI for STEMI with cardiogenic shock	Systematic review and meta-analysis	To assess the impact of chronic total occlusion (CTO) in non-infarct-related arteries (NIRA) on short- and long-term outcomes in STEMI patients with cardiogenic shock (CS) undergoing PCI.	30-day mortality	30 days	5186 patients with STEMI and CS undergoing PCI (1031 with CTO in NIRA and 4155 without CTO in NIRA)	Varied across studies; mean LVEF ranged from ~21% to ~50% depending on subgroup and study	Presence of CTO in the NIRA serves as an independent indicator of unfavorable clinical outcomes including increased risk of 30-day mortality and all-cause mortality. The risk of repeat MI was comparable between the two groups.	- Only 5 observational studies included – No RCTs available - High heterogeneity in some outcomes - Lack of long-term follow-up data on stroke or CV mortality.
Behnes	2025	Cardiogenic Shock Registry Mannheim" (CARESMA-registry)	Prospective single-center study	to investigate the prognostic impact of CTO in patients with Cardiogenic shock irrespective of the underlying Cardiogenic shock etiology.	all-cause mortality at 30 days	30 days	192 patients	LVEF <30% (92 patients, 48%)	Coronary CTO are common in patients with Cardiogenic shock and represent an independent predictor of all-cause mortality at 30 days.	modest sample size no further risk stratification was performed according to CS etiology single-center study design we cannot proportion of patients undergoing CTO-PCI was modest ($n = 9$)
(6) VTA										
Behnes	2020	Coronary chronic total occlusions and mortality in patients with ventricular tachyarrhythmias	Retrospective single-center cohort study	To assess the prognostic impact of coronary chronic total occlusions (CTO) in patients presenting with ventricular	All-cause mortality	Median 3.0 years (IQR 1.3–4.4)	1461 consecutive patients admitted with ventricular tachyarrhythmias (20% had at least one CTO)	Median LVEF was significantly lower in patients with CTO (35% vs. 45%, $p < 0.001$)	The presence of a CTO was associated with an increase of midterm all-cause mortality, in-hospital all cause mortality and composite endpoint.	Retrospective observational design, single-center data, lack of randomization, potential selection bias and confounding factors, absence of long-term

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Table 1 (*continued*)

First Author	Year	Name of Study	Study type	Aim	Primary Outcome	Follow-up	Study Population	LVEF	Results	Limitations
				tachyarrhythmias on admission.						ischemia testing or viability assessment
Behnes	2021	Prognostic impact of coronary chronic total occlusion on recurrences of ventricular tachyarrhythmias and ICD therapies	Retrospective single-center observational cohort study	To investigate the impact of coronary chronic total occlusion (CTO) on the recurrence of ventricular tachyarrhythmias and on the occurrence of appropriate implantable cardioverter-defibrillator (ICD) therapies	Recurrence of ventricular tachyarrhythmias (VT/VF) and appropriate ICD interventions	5 years	422 consecutive ICD recipients (CTO present in 25%)	Median LVEF significantly lower in CTO group	A coronary CTO even in the presence of less developed collaterals and more complex CTO category is associated with increasing risk of recurrent ventricular tachyarrhythmias at 5 years in consecutive ICD recipients.	Retrospective design, single-center data, lack of randomization, no invasive electrophysiological assessment, and potential confounders due to selection bias
Iannaccone	2022	VACTO PCI Study (Ventricular Arrhythmias and Chronic Total Occlusion Percutaneous Coronary Intervention)	Multicenter retrospective observational cohort study	Evaluate the impact of CTOs percutaneous coronary interventions (PCI) on arrhythmic events.	Appropriate ICD therapy	Median 2.9 (range 1.1–5 years)	Total 622 patients (CTO-PCI patients = 113; CTO-OMT = 86; no-CTO patients = 223)	Mean LVEF: 36 ± 11%; all patients had ischemic cardiomyopathy with reduced ejection fraction	CTO receiving PCI had lower arrhythmic event rates and lower mortality compared to the CTO-OMT group, while showing an event rate similar to no-CTO patients.	Retrospective design, relatively small sample size, potential confounding due to non-randomized treatment allocation, absence of systematic invasive arrhythmic substrate characterization
Lurz	2022	Relevance of Chronic Total Occlusion for Outcome of Ventricular Tachycardia Ablation in Ischemic Cardiomyopathy	Retrospective single-center observational study	To identify the impact of CTO, revascularized,or not revascularized,on the outcome of VT ablation	Composite of VT recurrence and all-cause mortality at 12 months	Median of 557 days	385 consecutive subjects with ICM-VT (108 without CTO; 198 with CTO)	Mean LVEF was 28.6 ± 8.9% (no significant difference between CTO and non-CTO groups)	In ICM patients with and without CTO, VT ablation was associated with equal effectiveness with regard to VT recurrence. However, in revascularizedCTO patients, the risk of recurrence of VT after ablation was significantly increased.	Retrospective single-center design, absence of systematic revascularization assessment, potential unmeasured confounding variables
Van Veelen	2024	Impact of a Chronic Total Coronary Occlusion on the Incidence of Appropriate Implantable Cardioverter-Defibrillator Shocks and Mortality: A Substudy of the Dutch Outcome in ICD Therapy (DO-IT) Registry	Prospective registry-based cohort study (substudy of DO-IT)	To assess whether the presence of a chronic total occlusion (CTO) is associated with higher incidence of appropriate ICD shocks and all-cause mortality in patients undergoing ICD implantation	Appropriate ICD shock and all-cause mortality	2 years (median of 27 months)	633 patients from the DO-IT registry who underwent ICD implantation; 415 had a CTO	Mean LVEF: 27% in CTO group vs. 32% in non-CTO group ($p < 0.001$); all patients had LVEF ≤35% as inclusion criterion	Within this nationwide prospective registry of primary prevention ICD recipients, the presence of an unrevas-cularized CTO was an independent predictor for the composite outcome of all-- cause mortality and appropriate ICD shocks.	Observational study design, no randomization of CTO treatment, CTO location not specified, limited imaging data for myocardial viability or ischemia
Assaf	2024	VACTOR study (Ventricular Arrhythmias and Chronic Total Occlusion Registry)	Prospective, multicenter, observational pilot study	To investigate the incidence of sustained VA in CTO patients after successful CTO revascularization and in patients with	Incidence of ventricular tachyarrhythmias (VT/VF) during follow-up	Median follow-up: 26 months	90 patients	LVEF 55 ± 8%	Patients with an CTO, who do not qualify for an ICD, have a substantial risk of sustained VA. In this study the incidence was	Observational design, lack of a control group without CTO, limited generalizability due to ICD prevalence in study cohort, and absence of

(*continued on next page*)

Table 1 (*continued*)

First Author	Year	Name of Study	Study type	Aim	Primary Outcome	Follow-up	Study Population	LVEF	Results	Limitations
				untreated CTO or failed CTO revascularization.					not different between patients with revascularized and those with untreated CTO.	longitudinal imaging for ischemia assessment

viable and non-viable tissue coexist.[31,32] Dobutamine stress echocardiography evaluates contractile reserve; nuclear imaging techniques such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) assess perfusion and metabolic activity. Meta-analyses demonstrate that viability assessment predicts survival and functional recovery post-revascularization, with an estimated 80% mortality reduction versus OMT.[32] However, the STICH trial viability sub-study found that CABG benefits were independent of viability status.[30,33] Likewise, the REVIVED-BCIS2 trial showed that, regardless of treatment strategy, the extent of viable myocardium was not associated with improved outcomes, whereas the presence of extensive myocardial scarring predicted a worse prognosis.[34,35] This study did not specifically report CTO outcomes, **either** CTO PCI rates; therefore, their results should be considered cautiously in the setting of patient with LVSD and CTO. The REVASC trial reported a 99% CTO-PCI success rate and high viability prevalence (77% with infarct transmurality <50%). No overall improvement in wall thickening or LVEF at six-months was found, except in patients with low SYNTAX scores (≤13).[27] In conclusion, predicting LVEF recovery after CTO-PCI is often informed by myocardial viability assessment, though contemporary RCTs (e.g. STICH, REVIVED-BCIS2, REVASC) questioned its independent predictive value; viability assessment should be integrated with clinical, anatomical and ischemia data rather than used alone.[12,13,27,36,37]

When using mechanical circulatory support devices

Overall, MCS use during CTO PCI is low, under 1% in the ERCTO registry and 2–4% in the PROGRESS registry.[14,38] However, Mechanical circulatory support (MCS) devices have gained increasing relevance in complex coronary revascularization, including CTO-PCI of patients with LVSD.[39] In fact, patients with LVSD carry increased risk of hemodynamic compromise during revascularization, especially with complex anatomy or where collateral flow is jeopardized.[38,40–42] LVEF is a consistent predictor of periprocedural and long-term morbidity and mortality during CTO-PCI, with an LVEF≤35% commonly used as a threshold for prophylactic MCS consideration.[43–45] In this situation, elective MCS deployment can reduce hemodynamic instability and improve procedural safety compared with emergency implantation.[46] However, a prophylactic MCS use has not been definitively shown to increase CTO-PCI technical success versus unsupported PCI.[47] Furthermore, higher bleeding rates, linked primarily to large-bore vascular access, remain a concern; ultrasound-guided femoral artery puncture on adequately sized vessels (>6 mm) helps mitigate risk.[48–51]

Finally, in ACS settings, CTO presence in a non-infarct-related artery independently elevates mortality and reduces postprocedural LVEF.[52] In such contexts, early MCS may be warranted, particularly when donor arteries to CTO territory are involved.

Ongoing RCTs such as PROTECT IV and CHIP-BCIS3, including CTO patients, will clarify MCS safety and efficacy in this population.[53]

Fig. 3 depicts an expert opinion-based flow-chart to candidate patient for elective use of MCS. It considers different clinical, anatomical, and hemodynamic variables to facilitate the selection of candidates to MCS CTO-PCI.[43–45,54–56] For example, a patient with a severe LVSD undergoing a planned retrograde CTO approach or anticipated atherectomy should be considered for prophylactic MCS, because these strategies might jeopardize donor collaterals or increase no-reflow risk. Conversely, a patient with mild LVSD undergoing straightforward antegrade wiring typically would not require MCS. However, beyond patient factors, operator experience with large-bore access, centre volume of MCS-supported PCI, and availability of escalation (RV support or ECMO) can influence MCS outcomes.[51,52] As such, clinical decisions must integrate vessel territory, collateral dependence, access suitability, and team experience.

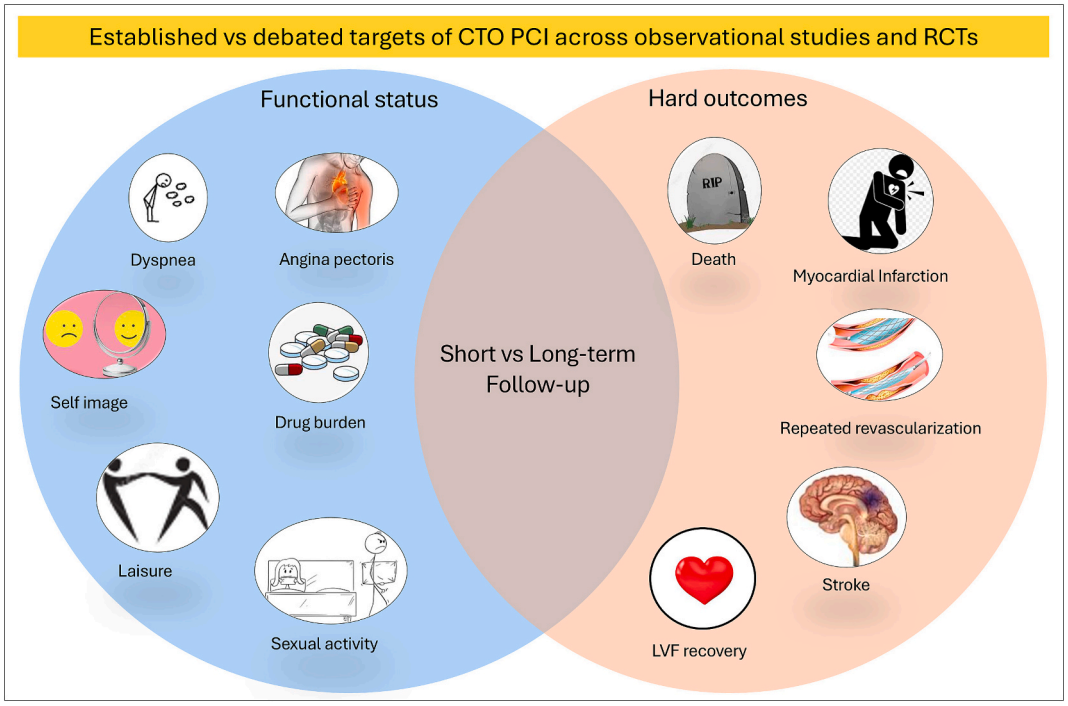

Fig. 1. Evidence from observational studies and randomized controlled trials (RCTs) consistently shows that CTO-PCI relieves symptoms such as angina and dyspnea and improves quality of life, as reflected by multiple clinical indicators (left panel). By contrast, the impact of CTO-PCI on hard clinical outcomes remains uncertain due to conflicting results from observational studies and RCTs (right panel).
Abbreviations: CTO = chronic Total occlusion; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; PCI = percutaneous coronary intervention; RCTs = randomized controlled trials.

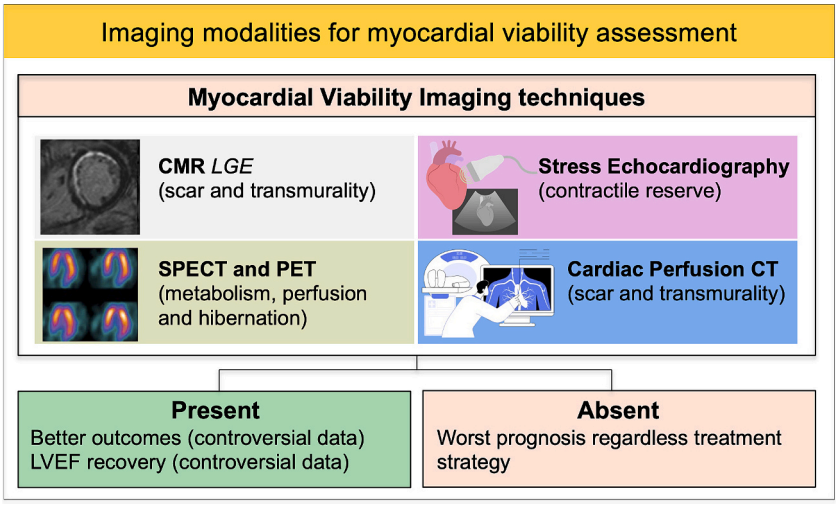

Fig. 2. Imaging modalities for myocardial viability assessment. Choice depends on local availability and expertise. Upper panel: principal techniques; lower panel: clinical implications and conflicting prognostic data.
Abbreviations: CT = computed tomography; CMR = cardiac magnetic resonance; CTO = chronic Total occlusion; LGE = late gadolinium enhancement; LV = left ventricle; LVEF = left ventricular ejection fraction; PET = positron emission tomography; SPECT = single photon emission computed tomography.

CTO-PCI of patients with LVSD and ACS

The impact of CTO revascularization in patients presenting with ACS and concomitant LVSD remains controversial. Several observational studies have suggested that successful CTO-PCI in the setting of ACS, as part of a complete revascularization strategy, may improve clinical outcomes, including reduction in mortality and HF hospitalizations. However, these data are largely derived from retrospective analyses and registries with inherent selection biases, and RCTs data are lacking.[39,47,57]

The EXPLORE trial investigated the effect of CTO-PCI performed within 7 days after primary PCI in patients with STEMI and a concurrent CTO in a non-culprit vessel. While no significant differences were observed in global LVEF, LV volumes, or MACE at 4-month follow-up, a prespecified subgroup analysis showed a higher LVEF in patients with a CTO located in the left anterior descending (LAD) artery who underwent CTO-PCI compared with conservative management (47.2 ± 12.3% vs. 40.4 ± 11.9%; p = 0.02), indicating a possible role for CTO

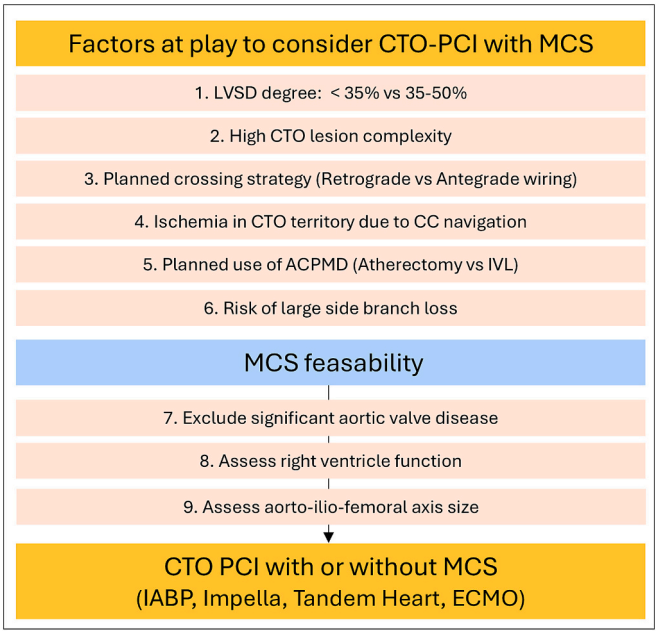

Fig. 3. 'Expert-opinion decision aid to select candidates for CTO-PCI and elective use of MCS. Beyond LVSD degree (1), other lesions, and procedural-related factors should be considered for MCS use. Examples include: high lesion complexity (2); the need for retrograde approach (3) which may cause ischemia in CTO territory during CC navigation (4); severe calcification requiring the use of ACPMD (5), and risk of a large side branch loss when using antegrade dissection and re-entry (ADR) techniques (6). If MCS use is indicated, its feasibility must be assessed by excluding: (7) significant aortic valve disease, (8) significant right ventricular dysfunction, and (9) unsuitable aorto-ilio-femoral anatomy for large-bore sheath placement.
Abbreviations: ACPMD = advanced calcium plaque modification devices; ADR = antegrade dissection and *re*-entry; CC = Collateral Channel; CTO = chronic Total occlusion; ECMO = extracorporeal membrane oxygenation; IABP = intra-aortic balloon pump; IVL = intravascular lithotripsy; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; PCI = percutaneous coronary intervention; MCS = mechanical circulatory support.

revascularization in select ACS patients.[28]

Moreover, in ACS complicated by cardiogenic shock, the presence of a CTO was associated with increased mortality (adjusted odds ratio 1.63, 95% CI 1.01–2.60). In these high-risk patients, the timing and indication for CTO-PCI should be carefully assessed on a case-by-case basis, balancing procedural risks with potential advantages, ideally within multidisciplinary Heart Team discussions.[18,46]

Given these considerations, the role of CTO-PCI in ACS patients with LVSD, the identification of patients who may derive survival and symptomatic benefit from CTO revascularization in the acute setting, and the optimal timing of CTO-PCI relative to non-CTO PCI require further investigation.

Arrhythmias and ventricular tachyarrhythmia substrate

The incidence of ventricular tachyarrhythmia (VTA) in patients with CTO and ischaemic cardiomyopathy, and the impact of CTO revascularization on arrhythmogenic substrate for life-threatening arrythmias are two relevant aspects, often underestimated. Among patients with VTA at hospital admission, the presence of a coronary CTO is independently associated with increased midterm all-cause mortality (40% vs. 27% at 18 months; hazard ratio [HR] 1.56, 95% CI 1.26–1.93; p = 0.001), as well as higher in-hospital mortality (29% vs. 20%; HR 1.33, p = 0.027).[58,59]

Patients with a combination of multivessel disease (MVD), CTO, and LVSD, have an increased arrhythmic risk, which is closely related to the extent of residual myocardial ischemia.[59] Furthermore, among patients with ischemic cardiomyopathy and implantable cardioverter defibrillator (ICD) for secondary prevention of sudden cardiac death (SCD), the presence of an angiographically documented CTO is an independent predictor of appropriate ICD therapy.[60]

Different studies suggest that reperfusion of ischemic but viable myocardium in CTO territories may reduce the burden of VTA and contribute to reverse remodelling in ACS patients with LVSD, although such potential benefits need confirmation in dedicated RCTs.[43,44] Within the recently published RACE-IT registry (Registry of Malignant Arrhythmias and Sudden Cardiac Death-Influence of Diagnostics and Interventions) including consecutive patients with a history of VTA undergoing coronary angiography (n = 1461), CTO prevalence was 20%, raising up to 40% among patients with LVEF<35%.[58] At 18 months follow-up, CTO patients with a history of VTA had higher rates of all-cause mortality (40% versus 27%) and the composite of early cardiac death at 24 h, recurrent VTA and ICD therapies (28% versus 20%).[61]

A couple of observational studies have investigated whether CTO revascularization can reduce arrhythmic events in patients with ischemic heart disease who already have an ICD.

The VACTO trial (Ventricular arrhythmias among implantable cardioverter-defibrillator recipients for primary prevention: impact of chronic total coronary occlusion) showed that patients undergoing successful CTO-PCI had fewer arrhythmic events and (20.4% vs. 56.4%; adjusted HR 0.45, 95% CI 0.29–0.71; $p < 0.001$) lower all-cause mortality (8.8% vs. 23.0%; adjusted HR 0.43, 95% CI 0.22–0.85; $p = 0.005$) compared to those treated with OMT. Furthermore, arrhythmic risk and mortality were comparable between patients who underwent successful CTO-PCI and those without a CTO (20.4% vs. 17.1%, $p = 0.61$; mortality: 8.8% vs. 13.5%, $p = 0.28$).[62] Similarly, in the Dutch outcome in implantable cardioverter-defibrillator therapy (DO-IT) registry, the presence of an unrevascularized CTO was independently associated with a higher risk of the composite outcome of all-cause mortality and appropriate ICD shocks. During a median follow-up of 27 months, the primary endpoint occurred in 21.1% of patients with CTO versus 11.9% of those without CTO (hazard ratio [HR] 1.83, 95% confidence interval [CI] 1.05–3.19, $p = 0.034$). After adjustment for baseline characteristics, including LVEF, unrevascularized CTO remained an independent predictor of the composite outcome (adjusted HR 1.82, 95% CI 1.03–3.22, $p = 0.038$)[63] Conversely, another study showed that in patients with severely reduced LVEF (mean LVEF 33 ± 12%) undergoing VTA ablation after prior MI, those who had undergone CTO-PCI had a higher risk of VTA recurrence compared to patients with untreated CTO.[64] The authors hypothesized that revascularization may result in viable but denervated myocardium which exhibits denervation hypersensitivity, potentially increasing the risk of malignant arrhythmias.[64] Similarly, the VACTOR study (Incidence of ventricular arrhythmias in patients with chronic total coronary occlusion) found no benefit in reducing the risk of sustained VTA, all-cause mortality and MACE, during a median follow-up of 26 months, in patients undergoing CTO-PCI who were not ICD candidates [3-year cumulative incidence of sustained VTA: 8.8% vs. 4.5%, respectively; $p = 0.71$; all-cause mortality (4.7% vs. 6.7%, $p = 0.63$) and MACE (17.8% vs. 15.9%, $p = 0.90$)].[65] However, the VACTOR study enrolled a low-arrhythmic-risk population (no prior ventricular arrhythmia and LVEF >35%), which likely resulted in low event rates and limited the ability to detect between-group differences. In conclusion, based on the current literature, if CTO revascularization can reduce the arrhythmic risk remains uncertain.

Future perspectives

In next future the following research priorities should focus on[1]: clarifying the prognostic impact of CTO-PCI as part of a complete versus incomplete revascularization strategy in ACS setting[2]; comparing anatomy-guided versus viability/ischemia-guided revascularization

strategies[3]; establishing thresholds of ischemic and scar burden for clinical benefit[4]; characterizing myocardial hibernation and its reversibility.

Probably, the integration of advanced imaging, biomarkers, and artificial intelligence tools may refine patient selection.[66–68]

The ongoing CTO-PCI in Systolic Heart Failure (CTO-HF) trial (clinicaltrials.gov ID: NCT05632653) is designed to evaluate the effect of CTO-PCI on composite outcomes of all-cause mortality and HF rehospitalization over three years in patients with LVEF<50%. Prior to randomization, patients undergo an 8–12 weeks run-in phase including OMT, complete revascularization of non-CTO lesions, and adjustment of HF therapies such as cardiac implantable electronic devices and valvular interventions. This trial is expected to provide critical evidence addressing the current knowledge gap.

Furthermore, the STICH3 consortium trials (ISRCTN29654606, NCT05427370, and NCT05584280) are anticipated to provide contemporary insights into the comparative outcomes of CABG versus PCI in HF populations, including CTO prevalence and management data.

Lastly, the unresolved issues regarding safety and efficacy of mechanical circulatory support during complex PCI, including CTO cases, and criteria for patient selection are expected to be addressed by upcoming RCTs such as PROTECT IV (NCT04763200) and CHIP-BCIS3 (NCT05003817).[53] The PROTECT IV trial is evaluating whether Impella-supported high-risk PCI improves long-term clinical outcomes compared with PCI without MCS in patients with complex CAD (including CTO) and reduced LVEF, while the CHIP-BCIS3 trial is designed to determine the clinical benefit and cost-effectiveness of percutaneous left ventricular unloading during high-risk PCI (including CTO).

Conclusions

The management of patients with CTO and LVSD remains complex and continues to evolve. Despite CTO-PCI success and safety increased consistently over the last two decades, robust evidence demonstrating significant clinical benefits in LVSD is lacking. To date, no RCTs have specifically investigated the prognostic impact of coronary CTO revascularization in patients with severe LVSD. Consequently, current conclusions rely largely on large observational studies, as well as on randomized trials that either included predominantly patients with preserved LVEF or applied heterogeneous LVEF inclusion criteria with a low and non-representative prevalence of CTO. These methodological constraints significantly limit the applicability of existing RCTs results to the specific CTO population, and underscore the need for dedicated, adequately powered RCTs conducted in experienced centers. In this scenario, an optimal patient selection based on a multidisciplinary approach remains a pillar to guide CTO-PCI decision, and some procedural aspects like the selective use of MCS.

CRediT authorship contribution statement

Giuseppe Vadalà: Writing – original draft, Conceptualization. **Kambis Mashayekhi:** Writing – original draft, Conceptualization. **Cristina Madaudo:** Writing – review & editing, Writing – original draft, Conceptualization. **Michael Behnes:** Writing – review & editing, Writing – original draft, Validation. **Alice Moroni:** Writing – original draft, Visualization. **Davide Tomasello:** Writing – original draft, Conceptualization. **Gianluca Campo:** Writing – original draft, Conceptualization. **Emmanouil Brilakis:** Writing – review & editing, Supervision, Conceptualization. **Alfredo Ruggero Galassi:** Writing – review & editing, Methodology, Conceptualization.

Declaration of competing interest

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All Authors certify that they have made substantive contributions that justify being named as co-authors of the present manuscript.

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